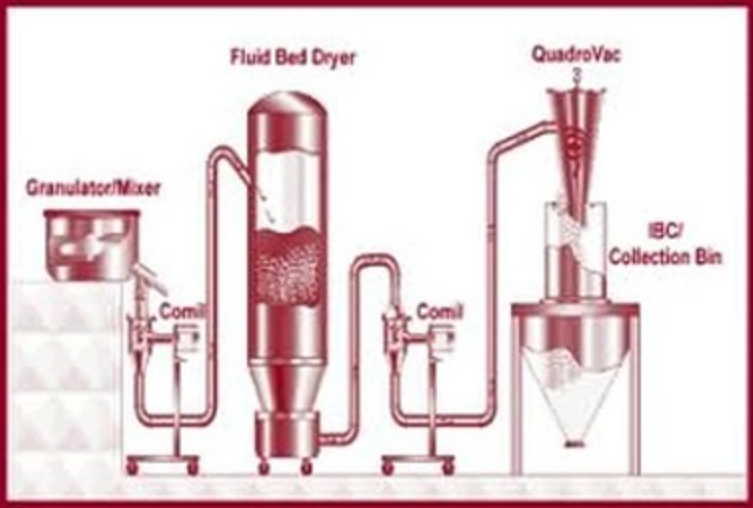
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 198

THIRD EDITION

Handbook of Pharmaceutical Granulation Technology



edited by
Dilip M. Parikh

informa
healthcare

Handbook of Pharmaceutical Granulation Technology

DRUGS AND THE PHARMACEUTICAL SCIENCES
A Series of Textbooks and Monographs

Executive Editor

Advisory Board

For information on volumes 1–151 in the *Drugs and Pharmaceutical Science* Series, please visit www.informahealthcare.com

152. Preclinical Drug Development, *edited by Mark C. Rogge and David R. Taft*
153. Pharmaceutical Stress Testing: Predicting Drug Degradation, *edited by Steven W. Baertschi*
154. Handbook of Pharmaceutical Granulation Technology: Second Edition, *edited by Dilip M. Parikh*
155. Percutaneous Absorption: Drugs–Cosmetics–Mechanisms–Methodology, Fourth Edition, *edited by Robert L. Bronaugh and Howard I. Maibach*
156. Pharmacogenomics: Second Edition, *edited by Werner Kalow, Urs A. Meyer and Rachel F. Tyndale*
157. Pharmaceutical Process Scale-Up, Second Edition, *edited by Michael Levin*
158. Microencapsulation: Methods and Industrial Applications, Second Edition, *edited by Simon Benita*
159. Nanoparticle Technology for Drug Delivery, *edited by Ram B. Gupta and Uday B. Kompella*
160. Spectroscopy of Pharmaceutical Solids, *edited by Harry G. Brittain*
161. Dose Optimization in Drug Development, *edited by Rajesh Krishna*
162. Herbal Supplements-Drug Interactions: Scientific and Regulatory Perspectives, *edited by Y. W. Francis Lam, Shiew-Mei Huang, and Stephen D. Hall*
163. Pharmaceutical Photostability and Stabilization Technology, *edited by Joseph T. Piechocki and Karl Thoma*
164. Environmental Monitoring for Cleanrooms and Controlled Environments, *edited by Anne Marie Dixon*
165. Pharmaceutical Product Development: In Vitro-In Vivo Correlation, *edited by Dakshina Murthy Chilukuri, Gangadhar Sunkara, and David Young*
166. Nanoparticulate Drug Delivery Systems, *edited by Deepak Thassu, Michel Deleers, and Yashwant Pathak*
167. Endotoxins: Pyrogens, LAL Testing and Depyrogenation, Third Edition, *edited by Kevin L. Williams*
168. Good Laboratory Practice Regulations, Fourth Edition, *edited by Anne Sandy Weinberg*
169. Good Manufacturing Practices for Pharmaceuticals, Sixth Edition, *edited by Joseph D. Nally*
170. Oral-Lipid Based Formulations: Enhancing the Bioavailability of Poorly Water-soluble Drugs, *edited by David J. Hauss*
171. Handbook of Bioequivalence Testing, *edited by Sarfaraz K. Niazi*
172. Advanced Drug Formulation Design to Optimize Therapeutic Outcomes, *edited by Robert O. Williams III, David R. Taft, and Jason T. McConville*
173. Clean-in-Place for Biopharmaceutical Processes, *edited by Dale A. Seiberling*
174. Filtration and Purification in the Biopharmaceutical Industry, Second Edition, *edited by Maik W. Jornitz and Theodore H. Meltzer*
175. Protein Formulation and Delivery, Second Edition, *edited by Eugene J. McNally and Jayne E. Hastedt*
176. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, Third Edition, *edited by James McGinity and Linda A. Felton*
177. Dermal Absorption and Toxicity Assessment, Second Edition, *edited by Michael S. Roberts and Kenneth A. Walters*

178. Preformulation Solid Dosage Form Development, *edited by Moji C. Adeyeye and Harry G. Brittain*
179. Drug-Drug Interactions, Second Edition, *edited by A. David Rodrigues*
180. Generic Drug Product Development: Bioequivalence Issues, *edited by Isadore Kanfer and Leon Shargel*
181. Pharmaceutical Pre-Approval Inspections: A Guide to Regulatory Success, Second Edition, *edited by Martin D. Hynes III*
182. Pharmaceutical Project Management, Second Edition, *edited by Anthony Kennedy*
183. Modified Release Drug Delivery Technology, Second Edition, Volume 1, *edited by Michael J. Rathbone, Jonathan Hadgraft, Michael S. Roberts, and Majella E. Lane*
184. Modified-Release Drug Delivery Technology, Second Edition, Volume 2, *edited by Michael J. Rathbone, Jonathan Hadgraft, Michael S. Roberts, and Majella E. Lane*
185. The Pharmaceutical Regulatory Process, Second Edition, *edited by Ira R. Berry and Robert P. Martin*
186. Handbook of Drug Metabolism, Second Edition, *edited by Paul G. Pearson and Larry C. Wienkers*
187. Preclinical Drug Development, Second Edition, *edited by Mark Rogge and David R. Taft*
188. Modern Pharmaceutics, Fifth Edition, Volume 1: Basic Principles and Systems, *edited by Alexander T. Florence and Jürgen Siepmann*
189. Modern Pharmaceutics, Fifth Edition, Volume 2: Applications and Advances, *edited by Alexander T. Florence and Jürgen Siepmann*
190. New Drug Approval Process, Fifth Edition, *edited by Richard A.Guarino*
191. Drug Delivery Nanoparticulate Formulation and Characterization, *edited by Yashwant Pathak and Deepak Thassu*
192. Polymorphism of Pharmaceutical Solids, Second Edition, *edited by Harry G. Brittain*
193. Oral Drug Absorption: Prediction and Assessment, Second Edition, *edited by Jennifer J. Dressman, Hans Lennernas, and Christos Reppas*
194. Biodrug Delivery Systems: Fundamentals, Applications, and Clinical Development, *edited by Mariko Morishita and Kinam Park*
195. Pharmaceutical Process Engineering, Second Edition, *edited by Anthony J. Hickey and David Ganderton*
196. Handbook of Drug Screening, Second Edition, *edited by Ramakrishna Seethala and Litao Zhang*
197. Pharmaceutical Powder Compaction Technology, Second Edition, *edited by Metin Celik*
198. Handbook of Pharmaceutical Granulation Technology, Third Edition, *edited by Dilip M. Parikh*

THIRD EDITION

Handbook of Pharmaceutical Granulation Technology

edited by
Dilip M. Parikh
DPharma Group Inc.
Ellicott City, Maryland, USA

informa
healthcare
New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 1-4398-0789-2 (Hardcover)
International Standard Book Number-13: 978-1-4398-0789-7 (Hardcover)

Library of Congress Cataloging-in-Publication Data

Handbook of pharmaceutical granulation technology / edited by Dilip M. Parikh.—3rd ed.

p. ; cm.—(Drugs and the pharmaceutical sciences ; 198)

Includes bibliographical references and index.

ISBN-13: 978-1-4398-0789-7 (hardcover : alk. paper)

ISBN-10: 1-4398-0789-2 (hardcover : alk. paper)

1. Drugs—Granulation—Handbooks, manuals, etc. I. Parikh, Dilip M., 1945- II. Series: Drugs and the pharmaceutical sciences ; v. 198.

[DNLM: 1. Technology, Pharmaceutical—Handbooks. 2. Powders—Handbooks. W1 DR893B v.198 2009 / QV 735 H2361 2009]

RS199.G73H36 2009

615′.19—dc22

2009038625

For Corporate Sales and Reprint Permissions call 212-520-2700 or write to: Sales Department, 52 Vanderbilt Avenue, 7th floor, New York, NY 10017.

Visit the Informa Web site at
www.informa.com

and the Informa Healthcare Web site at
www.informahealthcare.com

To my wife Leena, son Neehar, and my friends, who never left my side during the good times and tough times. Their love, dedication, and support will remain with me always.

Preface

Since the *Handbook of Pharmaceutical Granulation Technology,* first and second editions, were published, there have been rapid developments in the science of granulation, particle engineering, and process controls, requiring the publication of this third edition. The concepts of design space, process optimization, and harmonization of regulations by the global health authorities are being implemented in the industry. The U.S. and International regulatory bodies are restructuring their oversight of pharmaceutical quality regulation by developing a product quality regulatory system, which provides a framework for implementing quality by design, continuous improvement, and risk management. This edition addresses topics generated by these technological as well as regulatory changes in unit operation of particle generation and granulation.

Current advances in the field have led us to include new chapters on subjects such as supercritical fluids, nanoparticulate technology, nutraceuticals, biotechnology, controlled-release granulation, process control, and expert systems to bring the reader up to date with the key new drivers in the field. All classic and standard bearer chapters such as fluid bed, roller compaction, continuous granulation, process modeling, spray-drying, and effervescent and rapid-release granulation have been thoroughly revised to meet the current state of the art.

Within particle generation technologies, research and application of supercritical fluids and nanotechnology-based processes for particle production have proved suitable for controlling solid-state morphology and particle size of pharmaceuticals. Supercritical fluids have emerged as the basis of a system that optimizes the physicochemical properties of pharmaceutical powders. Supercritical fluids should be considered in a prominent position in the development processes of drug products for the 21st century. Nanoparticulate technology offers a potential path to rapid preclinical assessment of poorly soluble drugs. It offers increased bioavailability, improved absorption, reduced toxicity, and the potential for drug targeting. Nanoparticulate technology may thus allow for the successful development of poorly water-soluble discovery compounds, as well as the revitalization of marketed products through improvements in dosing. These particle generation technologies have been included in new chapters titled "Supercritical Fluid Technology" and "Pharmaceutical Applications of Nanoengineering."

As the nutraceuticals industry is growing worldwide, a new chapter for "Granulation of Plant Products and Nutraceuticals" is included in this edition. These herbal and mineral products pose unique challenges when preparing a solid dose. These products are normally formulated with numerous ingredients with varying particle sizes, morphology, hydrophobic or hydrophilic attributes, along with unique granulating and compressing challenges. Approaches to overcome these difficulties using various granulation techniques described in this chapter will be helpful to the professionals in dietary supplement industry. Regulatory approaches taken by different world regulatory authorities are highlighted in this chapter, and impact of recent implementation of U.S. FDA Good Manufacturing Practices regulation for nutraceutical industry is discussed in this chapter as well.

As the biotechnology industry grows worldwide, formulation efforts to formulate large molecules for oral dosage forms have accelerated. Research and application of classical granulation technologies have been investigated and presented in the chapter titled "Granulation Approaches in Biotech Industry," which will provide much needed knowledge of the current status and challenges inherent in this effort.

Controlled-release technology to produce matrix granulation is widely practiced. To prolong the life cycle of a product or to offer better patient compliance, controlled-release

granulation is a critical unit operation. A new chapter titled "Granulation Approaches for Modified-Release Products" specifically addresses the approaches that can be taken to produce granulation that can provide modified-release attributes.

With advent of high-throughput screening and combinatorial chemistry, evaluation of potential molecules with therapeutic activity is on the increase. However, majority of these new chemical entities have low aqueous solubility. Hence, a new chapter that presents current approaches for various techniques to improve the solubility of difficult to dissolve molecules titled "Granulation for Poorly Water-Soluble Drugs" is included.

End-point determination of a granulation process is the most prominent concern of any practicing industry professional as well as academician. Significant progress has been achieved to determine the process control and the end-point determination for various processes utilized in particle generation and formation of granular products. For example, torque and power measurements in high-shear granulation, online techniques to monitor and control processes using technologies such as near infrared (NIR), focused beam reflectance measurement (FBRM®), particle video microscope (PVM®), Fourier transform infrared spectroscopy (FTIR), etc., are being used routinely. A new chapter devoted to "Advances in Process Control and End-Point Determination" discusses this very important topic and provides helpful guidance.

It is common in most formulation development studies that the formulation scientist may have extensive knowledge of the active ingredients and yet needs to know which excipients to select and their proportions. At this stage, a knowledge-based, so-called "expert system," can be helpful to the scientist in selecting suitable excipients. Another case where such an expert system could be of use in formulation studies is the determination of the design space for manufacturing conditions. There are various researchers who are developing applications of expert system in unit operations such as granulation. A new chapter on "Expert Systems and Their Use in Pharmaceutical Application" discusses developments in this emerging field.

Granulation is a major unit operation in solid dosage manufacturing. It is generally capital intensive, requires more manpower, and is subject to costly batch rejection possibilities if improper techniques are used. It is the objective of every company management to have the most efficient and thus cost-effective product development and manufacturing operation in the current competitive environment. A revised chapter titled "Quality by Design and Process Technology in Granulation" includes current understanding of process analytical technology (PAT) and the subject of "quality by design" (QbD) and provides how industry is applying principles of PAT and how QbD helps integrated, systematic, and scientific approach to design, development, and delivery of performance attributes that ensure consistent delivery of specific quality, safety, and efficacy objectives.

As a complement to the most recent U.S. FDA regulations for Good Manufacturing Practices, "The Pharmaceutical Quality for the 21st Century—A Risk-Based Approach," a completely revised chapter titled "Regulatory Issues in Granulation: The Pharmaceutical Quality for the 21st century—A Risk-Based Approach" is presented in this edition to reflect the impact of these new regulations. It includes International Conference on Harmonization (ICH) guidelines and harmonization as it pertains to the process of granulation. This important topic is critical in building in and maintaining the desired quality in pharmaceutical product.

Besides these new chapters, chapters on high- and low-shear granulation from the second edition are combined into one, titled "Wet Granulation in Low- and High-Shear Mixers," to present a comprehensive treatment of these approaches. All other chapters are completely revised and updated with the information that is helpful to the reader.

This book is designed to give readers comprehensive knowledge of the subject. As in the earlier editions, all chapters include appropriate level of theory on the fundamentals of powder characterization, practical granulation approaches, state-of-the-art technologies, and regulation compliant manufacturing optimization.

Pharmaceutical professionals such as research and development scientists, manufacturing management professionals, process engineers, validation specialists, process specialists, quality assurance, quality control, and regulatory professionals, and graduate students in industrial pharmacy and chemical engineering programs will find the level of theory appropriate and the wealth of practical information from renowned pharmaceutical professionals from industry and academia invaluable. The knowledge provided will be

helpful in selecting the appropriate granulation technology while keeping in mind regulatory requirements and cost-effectiveness.

I would like to extend special thanks to all the contributors for their support and cooperation to make this edition of the book most comprehensive on this technical subject. I would like to extend my sincere thanks to Sandra Beberman of Informa Healthcare for her guidance and to Sherri Niziolek of Informa Healthcare for her help.

Dilip M. Parikh
Ellicott City, Maryland, U.S.A.

Contents

PART III: PRODUCT ORIENTED GRANULATIONS

PART IV: CHARACTERIZATION AND SCALE-UP

PART V: OPTIMIZATION STRATEGIES, TOOLS AND REGULATORY CONSIDERATIONS

Contributors

Guia Bertuzzi IMA SPA ACTIVE Division, Bologna, Italy

Albert W. Brzeczko Acura Pharmaceuticals, Inc., Baltimore, Maryland, U.S.A.

Ian T. Cameron School of Chemical Engineering, The University of Queensland, Queensland, Australia

M. Teresa Carvajal Department of Industrial and Physical Pharmacy, School of Pharmacy and Pharmaceutical Sciences, Purdue University, West Lafayette, Indiana, U.S.A.

Metin Çelik Pharmaceutical Technologies International, Inc., Belle Mead, New Jersey, U.S.A. and School of Pharmacy, Near East University, Nicosia, Turkish Republic of Northern Cyprus

Lai Wah Chan Department of Pharmacy, National University of Singapore, Singapore

Thomas Dürig Ashland Aqualon Functional Ingredients, Ashland Inc., Wilmington, Delaware, U.S.A.

Michel Deleers Global Pharmaceutical Technology and Analytical Development, UCB, Braine l'Alleud, Belgium

Bryan J. Ennis E&G Associates, Inc., Nashville, Tennessee, U.S.A.

David F. Erkoboni Cedar Consulting Corporation, Pennington, New Jersey, U.S.A.

Rajeev Gokhale Abbott, Abbott Park, Illinois, U.S.A.

Yinghe He School of Engineering and Physical Sciences, James Cook University, Queensland, Australia

Paul W. S. Heng Department of Pharmacy, National University of Singapore, Singapore

Sunil S. Jambhekar Department of Pharmaceutical Sciences, Lecom-Bradenton School of Pharmacy, Bradenton, Florida, U.S.A.

Tuo Jin School of Pharmacy, Shanghai Jiaotong University, Shanghai, P.R. China

David M. Jones OWI Consulting Inc., Ramsey, New Jersey, U.S.A.

Prasad Kanneganti Genentech Singapore Pte Ltd., Tuas Baylink, Singapore

Defne Kayrak-Talay School of Chemical Engineering, Purdue University, West Lafayette, Indiana, U.S.A.

Xiang Kou Department of Pharmacy, National University of Singapore, Singapore

Hui Li School of Pharmacy, Shanghai Jiaotong University, Shanghai, P.R. China

James D. Litster School of Chemical Engineering and Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, Indiana, U.S.A.

Lian X. Liu Particle & Systems Design Centre, School of Chemical Engineering, The University of Queensland, Queensland, Australia

Kevin A. Macias Department of Industrial and Physical Pharmacy, School of Pharmacy and Pharmaceutical Sciences, Purdue University, West Lafayette, Indiana, U.S.A.

Ronald W. Miller Miller Pharmaceutical Technology Consulting, Travelers Rest, South Carolina, U.S.A.

Sree Nadkarni FibroGen Inc., San Francisco, California, U.S.A.

Dilip M. Parikh DPharma Group Inc., Ellicott City, Maryland, U.S.A.

Yashwant Pathak Sullivan University, Louisville, Kentucky, U.S.A.

Neelima Phadnis Independent Pharma Consultant, Brisbane, California, U.S.A.

Cecil W. Propst SPI Pharma, Grand Haven, Michigan, U.S.A.

Gurvinder Singh Rekhi Elan Drug Technologies, Gainesville, Georgia, U.S.A.

Stanley Rodgers Sanofi-Aventis US LLC, Bridgewater, New Jersey, U.S.A.

Jean Paul Remon Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium

Firas El Saleh ISP Global Technologies Deutschland GmbH, Cologne, Germany

Richard Sidwell Elan Drug Technologies, Gainesville, Georgia, U.S.A.

John E. Simmons Simmons FDA Consulting, Chapin, South Carolina, U.S.A.

Harald Stahl GEA Pharma Systems, Hürth, Germany

Deepak Thassu PharmaNova Inc., Victor, New York, U.S.A.

Namrata R. Trivedi Covidien, Webster Groves, Missouri, U.S.A.

Griet Van Vaerenbergh GEA Pharma Systems nv - Collette™, Wommelgem, Belgium

Gopi Venkatesh Eurand, Inc., Vandalia, Ohio, U.S.A.

Chris Vervaet Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium

Gopi Vudathala Sanofi-Aventis US LLC, Malvern, Pennsylvania, U.S.A.

Martin A. Wahl Pharmaceutical Technology and Biopharmacy, Institute of Pharmaceutical Sciences, Eberhard-Karls-University Tübingen, Tübingen, Germany

Fu Y. Wang School of Chemical Engineering, The University of Queensland, Queensland, Australia

Susan C. Wendell Johnson & Johnson, Raritan, New Jersey, U.S.A.

Jiao Yang ISP Pharma Technologies, Inc., Columbia, Maryland, U.S.A.

Weien Yuan School of Pharmacy, Shanghai Jiaotong University, Shanghai, P.R. China

1 Introduction

Dilip M. Parikh
DPharma Group Inc., Ellicott City, Maryland, U.S.A.

BACKGROUND

The term "granulated" material is derived from the Latin word "granulatum," meaning grained. The practice of delivering medicinal powder by hand rolling into a pill by using honey or sugar has been used for centuries. It is still the practice to deliver the botanical and herbal extracts in homeopathic and ayurvedic branches of medicine, which are still practiced in India along with allopathic medicine.

Thomas Skinner, a physician in his article in 1862 (1), describes earlier mention of granulating medicine cited in 1773 in Duncan's *Elements of Therapeutics*, as follows: "by the application of art, it is intended that medicines should be rendered more agreeable, more convenient, more safe and more efficacious than they are in their natural state. To obtain these ends is the intention of pharmacy." Skinner further describes the earlier method of making granules by French pharmacists who had a form of medication that they call "*poudres granules*." The process of preparing these granules consisted in enveloping the particles of medicines in syrup by means of heat and constant stirring, as in the art of making comfits. This method was further modified to make granules with very little heat or moisture, which can be placed on the tongue and washed over with water, which was a modification of the method of granulating gunpowder.

Perry's *Chemical Engineer's Handbook* (2) defines the granulation process as "any process whereby small particles are gathered into larger, permanent masses in which the original particles can still be identified." This definition is, of course, particularly appropriate to a pharmaceutical granulation where the rapid breakdown of agglomerates is important to maximize the available surface area and aid in solution of the active drug. The granulated material can be obtained by direct size enlargement of primary particles or size reduction from dry, compacted material.

In modern times, granulation technology has been widely used by a wide range of industries, such as chemical, coal, mining, metallurgy, ceramic, and agrochemical. These industries employ agglomeration techniques to reduce dust, provide ease of handling, and enhance the material's ultimate utility.

The development of pharmaceutical granulation was driven by the invention of the tablet press by W. Brockedon in 1843. Subsequent improvements in the tablet machinery were patented in the United States by J. A. McFerran (1874), T. J. Young (1874), and J. Dunton (1876). The demands on the granulation properties were further enhanced in the 1970s as high-speed tablet and capsule-filling machines with automated controls were introduced. The continuous refinements in the regulatory requirements such as low-dose products requiring blend uniformity/content uniformity necessitated knowledge and technology to produce the required granule characteristics. The high-speed compression and capsule-filling machines require a uniform flow of material to the dies or filling stations that produce pharmaceutical dosage form.

Direct Compression

The processing of drug substance with the excipients can be achieved without employing the process of granulation. By simply mixing in a blender, a directly compressible formulation can be processed and compressed in tablets or filled in the hard gelatin capsules. In the 1970s, microcrystalline cellulose, as a directly compressible vehicle, was introduced. The compressible formulation containing microcrystalline cellulose is suitable for a number of products. This has several obvious advantages, such as lower equipment cost, faster process time, and efficient operation involving only two process steps. Sometimes, excipient costs may have to be compared against the savings in the processing steps and equipment by using alternate methods.

There are, however, a number of products that cannot be directly compressed because of low dosage, or flow properties of the drug and excipient mixture. Blend uniformity and the content uniformity in the drug product are critical attributes with low dose drug formulation. Other than content uniformity of a low-dose drug substance, there are a number of reasons why direct compression may not be suitable for a wide array of products. These include the required flow properties; the amount of drug substance in a dosage form may require it to be densified to reduce the size of the drug product, obtain the required hardness, friability, disintegration/dissolution, and other attributes.

Current Granulation Techniques and Research

The classical granulation process using either wet or dry methods is employed in the process industries. Pharmaceutical granulation process is used for tablet, capsule, and spherical granules for the modified-release indications or to prepare granules as sprinkles to be used by pediatric patients. In some countries like Japan, having granulated product in a "sachet" is acceptable where a large dose of the drug product is not suitable for swallowing. The reasons for granulating a pharmaceutical compound are well documented in the literature.

Many researchers studied the influence of material properties of the granulating powders and process conditions on the granulation process in a rather empirical way. In the 1990s, fundamental approach to research was started on various topics in the granulation process, looking into more detailed aspects of particle wetting, mechanism of granulation, material properties, and influence of mixing apparatus on the product. The overall hypothesis suggested that the granulation can be predicted from the raw material properties and the processing conditions of the granulation process. One of the major difficulties encountered in granulation technology is the incomplete description of the behavior of powders in general. The ongoing fundamental research on mixing, segregation mechanisms of powder, surface chemistry, and material science is necessary to develop the theoretical framework of granulation technology. An excellent review of the wet granulation process was presented by Iveson et al. (3). The authors have advanced the understanding of the granulation process by stating that there are three fundamental sets of rate processes, which are important in determining wet granulation behavior. These are wetting and nucleation, consolidation and growth; and breakage and attrition. Once these processes are sufficiently understood, then it will be possible to predict the effect of formulation properties, equipment type, and operating conditions of granulation behavior, provided these can be adequately characterized according to the reviewers.

Five primary methods exist to form an agglomerated granule. They are formation of solid bridges, sintering, chemical reaction, crystallization, and deposition of colloidal particles. Binding can also be achieved through adhesion and cohesion forces in highly viscous binders.

Successful processing for the agglomeration of primary particles depends on proper control of the adhesional forces between particles, which encourage agglomerate formation and growth and provide adequate mechanical strength in the product. Furthermore, the rheology of the particulate system can be critical to the rearrangement of particles necessary to permit densification of the agglomerate and the development of an agglomerate structure appropriate for the end-use requirements. If the particles are close enough, then the surface forces such as van der Waals forces (short range) and electrostatic forces can interact to bond particles. Decreasing particle size increases surface-mass ratio and favors the bonding. van der Waals forces are sevenfold stronger than electrostatic forces and increase substantially when the distance between them is reduced, which can be achieved by applying pressure as in dry granulation method. The cohesive forces that operate during the moist agglomerates are mainly due to the liquid bridges that develop between the solid particles. Electrostatic forces keep particles in contact long enough for another mechanism to govern the agglomeration process.

Dry compaction technique like roller compaction is experiencing renewed interest in the industry. There are a number of drug substances that are moisture sensitive and cannot be directly compressed. The roller compaction provides suitable alternative technology for processing these products. Early stages of wet granulation technology development employed low-shear mixers or the mixers/blenders normally used for dry blending such as ribbon mixers. There are a number of products currently manufactured using these low-shear

Table 1 Frequently Used Granulation Techniques and Subsequent Processing

	Process	Subsequent processing
Dry granulation	Direct compression	Blend—process further
	Slugging (double compression)	Mill slugs/recompress/mill/ blend—process further
	Roller compaction	Mill/blend—process further
Wet granulation	Low-shear mixer	Tray or fluid-bed dry, mill, blend—process further
	High-shear mixer	Tray or fluid-bed dry, mill, blend—process further
	High-shear mixer	Vacuum/gas stripping/microwave assist—mill, blend—process further
	Fluid-bed granulator dryer	After drying—mill, blend—process further
	Extrusion/spheronization	Tray or fluid-bed dryer—mill, blend—process further
	Spray dryer	Spray dryer—process further
	Continuous mixer granulator—mechanical	Continuous fluid bed—mill, blend—process further
	Continuous fluid-bed granulator/dryer	Dried product—mill, blend—process further

granulators. The process control and efficiency have increased over the years; however, the industry has embraced high-shear granulators for wet granulation because of its efficient process reproducibility and modern process control capabilities. The high-shear mixers have also facilitated new technologies, such as one-pot processing, that use the mixer to granulate and then dry using vacuum, gas stripping/vacuum, or microwave assist vacuum drying.

Fluid-bed processors have been used in the pharmaceutical industry for the last 40 years, initially only as a dryer and now as a multiprocessor to granulate, dry, pelletize, and coat particles. The most preferred method of granulation is to use the high-shear mixer to granulate and use the fluid bed as a dryer in an integrated equipment setup. This provides the best of both technologies: efficient controllable dense wet granules and a fast-drying cycle using fluid-bed dryer. Here again, the choice of this approach will be dependent on the product being processed and its desired properties at the end of the granulation process. Extrusion/spheronization is used to produce granulation for the tabletting or pelletizing, which involves mixing, extruding, spheronizing, and drying unit operations. These pellets can be produced as matrix pellets with the appropriate polymer or are coated in fluid-bed unit to produce modified-release dosage forms. Other techniques have been used by researchers such as steam granulation, using foam binder in place of liquid binders or moisture-activated dry granulation (MADG) where a small amount of moisture is added to the blend containing certain binders under constant mixing in high-shear mixer. This process eliminates the need for processing of the granulation however, essentially suffers from the same shortcomings as would be encountered with direct compression blend. Table 1 lists the most common techniques to granulate a pharmaceutical compound in the industry.

Granulation and Particle Design

Granulation is an example of particle design. The desired attributes of the granule are controlled by a combination of the formulation and the process.

Spray drying technique is now routinely used to prepare particles for inhalation dosage forms or to create solid dispersions of poorly soluble drugs. Recent interest in nanotechnology research has opened up a number of avenues for creating newer drugs. Various development groups are working to enhance traditional oral delivery systems with nano-engineered improvements. There are some areas where nano-enhanced drugs could make a big difference in increasing oral bioavailability and reducing undesirable side effects. By increasing bioavailability, nanoparticles can increase the yield in drug development and, more importantly, may help treat previously untreatable conditions. Another approach in the 1990s was to use supercritical fluid technology to produce uniform particles to replace crystallization. Even though supercritical fluids were discovered over 100 years ago and the commercial plant was built over 20 years ago in the United States, it is only now that the technology is used for a number of pharmaceutical applications (4–7) so as to produce aspirin, caffeine, ibuprofen, acetaminophen, etc. One of the major areas on which the research and

development of supercritical fluids is focused is particle design. There are different concepts such as "rapid expansion of supercritical solution," "gas antisolvent recrystallization," and "supercritical antisolvent" to generate particles, microspheres, microcapsules, liposomes, or other dispersed materials. When the supercritical fluid and drug solution make contact, a volume expansion occurs, leading to a reduction in solvent capacity, increase in solute saturation, and then supersaturation with associated nucleation and particle formation. A number of advantages are claimed by using this platform technology such as particle formation from nanometers to tens of micrometers, low residual solvent levels in products, preparation of polymorphic forms of drug, etc. (8). Attempts to make solid dosage forms of large molecules are under way even though there are numerous challenges.

Current Industry Status and Challenges

Efficient and cost-effective manufacturing of pharmaceutical products is being evaluated by the scientists, engineers, and operational managers of pharmaceutical companies worldwide. In the United States, where 49% of the world pharmaceutical market is, pharmaceutical companies are under tremendous pressure from the managed care organizations, politicians, and consumers. The pharmaceutical industry, worldwide in general and in the United States in particular, faces a unique paradox to drive future innovation through substantial R&D investments and return competitive margin to shareholders while providing access to pharmaceutical products at low cost. The industry has reached a critical juncture in its 100+ years of history. The industry is impacted simultaneously by growing competition, declining market performance, increasing regulation, escalating pricing pressures, and rapidly evolving innovations for improving people's health and quality of life. Recently published reports (9, 10) into pharmaceutical R&D and pharmaceutical manufacturing questioned the existing industry business model and has identified an emerging trend favoring outsourcing of discovery, research, clinical trials, and manufacturing of dosage forms, providing relief from the consistent, high-growth financial return expectations faced by the majority of pharmaceutical companies. Outsourcing allows these companies to pursue potential new revenue streams outside of their core focus areas and to benefit from improved productivity, emerging technologies, in-licensing opportunities, and increased growth. Consumers and local governments in the United States are pressuring the FDA authorities and politicians to allow importation of the drugs from other countries where costs are generally lower than in the United States. Demands for price control also extend to Europe; government-backed pharmaceutical payment plans in Germany and Italy, for example, have cut back reimbursements. Other European countries have controls on the drug prices. As a result of these pricing pressures and to enhance the drugs in the pipeline, mergers and acquisitions have accelerated. Acquisitions remain the preferred route to quickly enhance a product portfolio.

This trend of merging of equals or takeover of the significant biotechnological and technological companies will continue. Major pharmaceutical companies are witnessing the end of traditional research and development. This has created emergence of small niche technology companies as well. Drug delivery companies are becoming potential targets for mergers or strategic alliances.

Because biologics are less susceptible to generic competition, big pharmaceutical companies are acquiring biotech companies as well.

Table 2 lists the 12 biggest mergers that have taken place in 2008–2009 alone which shows how the industry is accelerating the acquisition approach.

During all of the upheaval that the industry is going through, it is becoming obvious that the cost of development, production, and goods must be controlled. The efficiencies in the research, development, and manufacturing, which were not necessarily sought after, are becoming the first priority of the pharmaceutical companies however small they may be in comparison to the final cost of the product to the consumer. The manufacturing of solid dosage product is no exception.

The significant advances that have taken place in the pharmaceutical granulation technology are presented in this book to provide the readers with choices that are available. The various techniques presented in this book will further help the scientists in their understanding and selection of the granulation process most appropriate for the drug substance. There is no substitute for good science. The characterization of the drug substance

Table 2 Top Twelve mergers in 2008–2009

Number	Merger/acquisition partners	Value in billion dollars
1	Novartis and Alcon	39
2	Takeda and Millenium	8.8
3	Teva and Barr	7.46
4	Eli Lilly and Imclone	6.5
5	Daiichi and Ranbaxy	4.6
6	Roche and Vatana	3.4
7	GSK and Actelion	3.2
8	Sanofi and Zentiva	2.6
9	Genzyme and Isis	1.9
10	Lily and Covance	1.6
11	Pfizer and Wyeth (2009)	$68.0
12	Merck and Schering-Plough (2009)	$41.0

Source: From Refs. 11–13.

along with the knowledge of granulation theory, identifying the critical process parameters, process modeling capability, in-line or on-line process analytical tools (PAT), process scale-up approaches, and a good definition of the end product required will prepare the reader to explore the various options presented in this book. Each drug substance poses a unique challenge that must be taken into consideration at the process selection stage by the scientists. The optimization techniques due to availability of state of the art computers, process control, and mathematical techniques to model the granulation process will advance the traditional granulation technology.

For production engineering, validation, and quality professionals in the industry, this book is intended to provide the fundamental understanding of the technique of granulation and the rationale behind the selection of each particular technique. This will further enhance the ability to design the production plant, carry out the technology transfer, scale up, troubleshoot, and maintain the pharmaceutical granulation operation in accordance with regulatory compliance.

REFERENCES

1. Skinner T. The Granulation of medicines. Br Med J 1862; 1(59):172–175.
2. Ennis BJ, Litster JD. Particle enlargement. In: Perry RH, Greens D, eds. Perry's Chemical Engineer's Handbook. 7th ed. New York:McGraw Hill, 1997:20-56–20-89.
3. Iveson SM, Litster JD, Hopgood K, et al. Nucleation, growth, and breakage phenomenon in agitated wet granulation process: a review. Powder Technol 2001; 117:3–39.
4. Charoenchaitrakool M, Dehghani F, Foster NR. Micronization by RESS to enhance the dissolution rates of poorly water soluble pharmaceuticals. Proceedings of the 5th International Symposium on Supercritical Fluids, Atlanta, GA, April 8–12, 2000.
5. Matson DW, Fulton JL, Petersen RC, et al. Rapid expansion of supercritical fluid solutions: solute formation of powders, thin films, and fibers. Ind Eng Chem Res 1987; 26:2298–2306.
6. Subra P, Boissinot P, Benzaghou S. Precipitation of pure and mixed caffeine and anthracene by rapid expansion of supercritical solutions. Proceedings of the 5th Meeting on Supercritical Fluids, Tome I, Nice, France, March 23–25, 1998.
7. Gilbert DJ, Palakodaty S, Sloan R, et al. Particle engineering for pharmaceutical applications—a process scale up. Proceedings of the 5th International Symposium on Supercritical Fluids, Atlanta, GA, April 8–12, 2000.
8. Baldyga J, Henczka M, Shekunov BY. Fluid dynamics, mass transfer and particle formation in super critical fluids. In: York P, Kompella UB, Shekunov BY, eds. Super Critical Fluid Technology for Drug Product Development. Marcel Dekker, 2004; 91–158.
9. Cambridge Healthcare Advisors (CHA) Report. Report identifies increasing outsourcing by pharma. September 29, 2004. Available at: http://www.outsourcing-pharma.com/Clinical-Development/Report-identifies-increasing-outsourcing-by-pharma.
10. PriceWaterhouseCoopers. Pharma 2020: Virtual R & D Which Path will you take? Available at: http://www.pwc.com/gx/en/pharma-life-sciences/index.jhtml
11. Top 10 Deals of 2008. Available at: http://www.fiercebiotech.com/special-reports/top-10-deals-2008.
12. Pfizer to pay $60 billion for Wyeth-Wall Street Journal, January 26, 2009.
13. Merck to buy rival for $41 Billion-Wall street Journal, March 10, 2009.

2 Theory of Granulation: An Engineering Perspective

Bryan J. Ennis
E&G Associates, Inc., Nashville, Tennessee, U.S.A.

INTRODUCTION

Overview

Wet granulation is a subset of size enlargement (1–6), which involves any process whereby small particles are agglomerated, compacted, or otherwise brought together into larger, relatively permanent structures in which the original particles can still be distinguished. Granulation technology and size enlargement processes have been used by a wide range of industries, ranging from the pharmaceutical industry to fertilizer or detergent production to the mineral processing industries. *Size enlargement* generally encompasses a variety of unit operations or processing techniques dedicated to particle agglomeration. These processes can be loosely broken down into *agitation* and *compression* methods.

Although terminology is industry specific, *agglomeration by agitation* will be referred to as *granulation*. A particulate feed is introduced to a process vessel and is agglomerated, either batch-wise and continuously, to form a granulated product. Agitative processes include fluid bed, pan (or disk), drum, and mixer granulators. Such processes are also used as coating operations for controlled release, taste masking, and cases where solid cores may act as a carrier for a drug coating. The feed typically consists of a mixture of solid ingredients, referred to as a formulation, which includes an active or key ingredient, binders, diluents, flow aids, surfactants, wetting agents, lubricants, fillers, or end-use aids (e.g., sintering aids, colors or dyes, taste modifiers). A closely related process of spray drying is also included here, but discussed in detail elsewhere (See Ref. 7 and chap. 5). Product forms generally include agglomerated or layered granules, coated carrier cores, or spray dried product consisting of agglomerated solidified drops.

An alternative approach to size enlargement is by *agglomeration by compression*, or *compaction*, where the mixture of particulate matter is fed to a compression device, which promotes agglomeration due to pressure. Either continuous sheets of solid material are produced or some solid form such as a briquette or tablet. Compaction processes range from confined compression devices, such as tabletting, to continuous devices, such as roll presses (chap. 8), briquetting machines and extrusion (chap. 12). Some processes operate in a semicontinuous fashion such as ram extrusion. Capsule filling operations would be considered a low-pressure compaction process.

At the level of a manufacturing plant, the size enlargement process involves several peripheral, unit operations such as milling, blending, drying or cooling, and classification, referred to generically as an agglomeration circuit (Fig. 1). In addition, more than one agglomeration step may be present. In the case of pharmaceutical granulation, granulated material is almost exclusively an intermediate product form, which is then followed by tabletting. In the context of granulation, therefore, it is important to understand compaction processes to establish desirable granule properties for tabletting performance.

Numerous benefits result from size enlargement processes as summarized in Table 1. A wide variety of size enlargement methods are available; a classification of available equipment and initial criteria of process selection is given in Tables 2 and 3. A primary purpose of wet granulation, in the case of pharmaceutical processing, is to create free flowing, nonsegregating blends of ingredients of controlled strength, which may be reproducibly metered in subsequent tabletting or for vial or capsule filling operations. The wet granulation process must generally achieve desired granule properties within some prescribed range. These

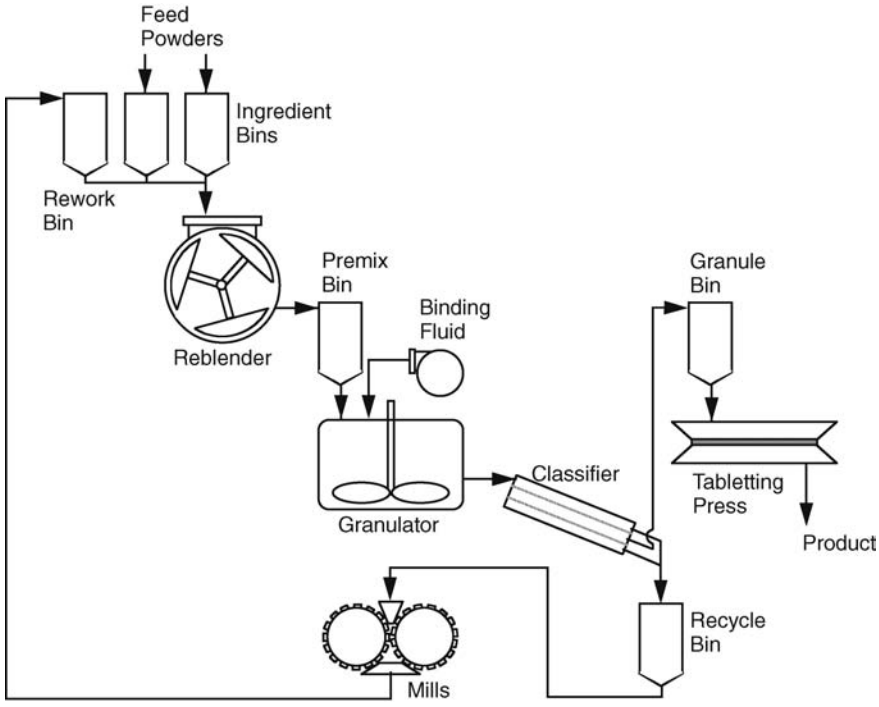


Figure 1 A typical agglomeration circuit utilized in the processing of pharmaceuticals involving both granulation and compression techniques. *Source*: From Refs. 1–6.

Table 1 Objectives of Size Enlargement

Production of useful structural form
Provision of a defined quantity for dispensing, with improved flow properties for metering and tabletting
Improved product appearance
Reduced propensity to caking
Increased bulk density for storage and tabletting feeds.
Creation of nonsegregating blends with ideally uniform distribution of key ingredients.
Control of solubility, and dissolution profiles.
Control of porosity, hardness and surface to volume ratio and particle size

Source: From Refs. 1–6.

attributes clearly depend on the application at hand. However, common to most processes is a specific granule size distribution and granule voidage. Size distribution affects flow and segregation properties, as well as compaction behavior. Granule voidage controls strength, and impacts capsule and tablet dissolution behavior, as well as compaction behavior and tablet hardness.

Control of granule size and voidage will be discussed in detail throughout this chapter. The approach taken here relies heavily on attempting to understand interactions at a particle level, and scaling to bulk effects. Developing an understanding of these microlevel processes of agglomeration allows a rational approach to the design, scale-up, and control of agglomeration processes (Figs. 2 and 3). Although the approach is difficult, qualitative trends are uncovered along the way, which aid in formulation development and process optimization, and which emphasize powder characterization as an integral part of product development and process design work.

Table 2 Process Selection Considerations for Wet Granulation Equipment

Product appearance attributes							Acceptable feed			Process characteristics							
	Attribute																
Process	Product details	Production		Product details						Product details					Product details			Product details
Batch fluid bed	L–M	100–900	0.2–1	M	SG	M–H	✘	✔	✔	L	✔	✘	✔	✘	L	H	✔	C
Continuous fluid bed	L–M	50	0.1–3	M	SG	M–H	✘	✔	✔	L	✔	✘	✔	✘	L–M	H	✔	C, R
Continuous disk	M	0.5–800	0.5–20	L	VSG	VH	✘	✘	✔	L	✔	?	✘	✘	L	L	✘	B, D, C, R
Continuous drum	M	0.5–800	2–20	M	SG	M–H	✘	?	✔	L	✔	?	✔	✘	H	L	✘	B, D, C, G, R
Batch mixer	M–H	100–500	0.1–3	M–H	IG	M	✔	✔	?	M	✘	✔	✔	✔	L–M	H	✔	D, C
Continuous mixer	M–H	50	0.1–3	M–H	IG	M	✔[a]	?[a]	?	M	✘	✔	✔	✔	L–M	H	✔	D, C, T

Binder required. Either solvent required, or in some cases, heat activated binder. Maximum feed of 500 μm, smaller preferred. Moisture no more than 80% pore saturation. Able to process brittle, abrasive, elastic, most plastic materials.

Abbreviations: ✔, yes; ✘, no; ?, possible; L, low; M, medium; H, high; V, very; G, granular; S, spherical; I, irregular; T, tablet form; C, cylindrical processing; C, classification; R, recycle; B, blending; D, drying; G, grinding; T, two-stage.

[a]Dependent on contact time.

Table 3 Process Selection Considerations for Compaction Equipment

Product appearance attributes							Acceptable feed			Process characteristics							
	Attribute																
Process	Product details	Production		Product details			Product details			Product details						Product details	
Roll pressing (smooth)	H	50	0.2—5	M–H	IG	M	✘	✔	✘	VH	✘	✘	✘	M–H	H	M	B, G, C, R, T
Roll pressing (pattern)[†]	H	50	5–50	VL	B	M	✔	?	✘	H	✘	✘	✘	L–M	M	M	T, B
Tabletting	H–VH	1	5–10	0	T	M	✔	✘	✘	H	✘	✘	✘	0	L	H	T, B
Ram/piston extrusion	H–VH	5	5–10	0	IT	M	✔	✘	✘	VH	✘	✘	✘	0	H	H	T, B
Pelleting mills	H–VH	10	0.5–3	L	C–SG	M	✘	✔	✔	VH	✘	✔	✘	L	L	M–H	B, C, D, R
Radial extrusion	M–H	5	0.5–3	L	C–SG	M	?	✔	✔	H	✔	✔	✔	L	H	H	B, C, D, R
Axial extrusion	VH	5	0.5–3	L	C–SG	M	?	✔	✔	VH	✔	✔	✔	L	H	H	B, C, D, R

Binder not required except for some hard materials. Small levels of moisture common; must be low or compaction arrested. Minimum feed of 100 μm, unless deaeration/vacuum provided. Moisture no more than 80% pore saturation. Nonwettable material acceptable.

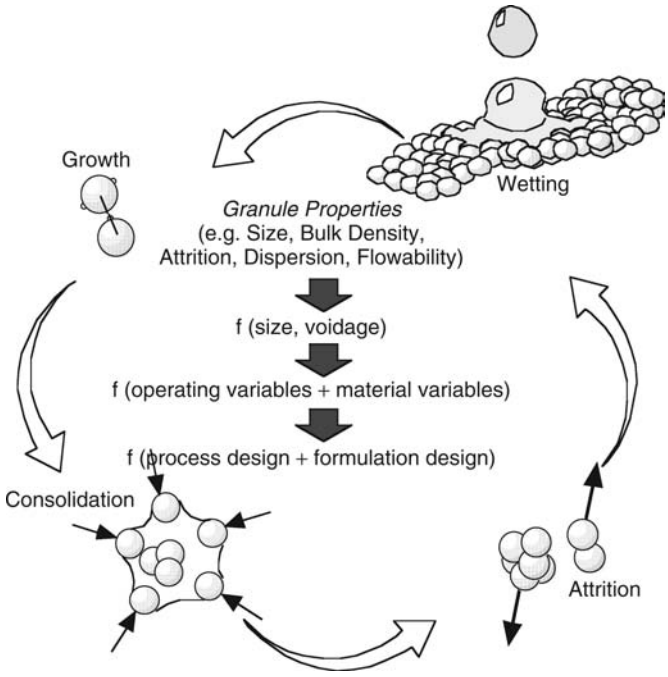


Figure 2 The mechanisms or micro-level processes of compressive agglomeration or compaction. These processes combined control compact strength, hardness, and porosity. *Source*: From Ref. 4.

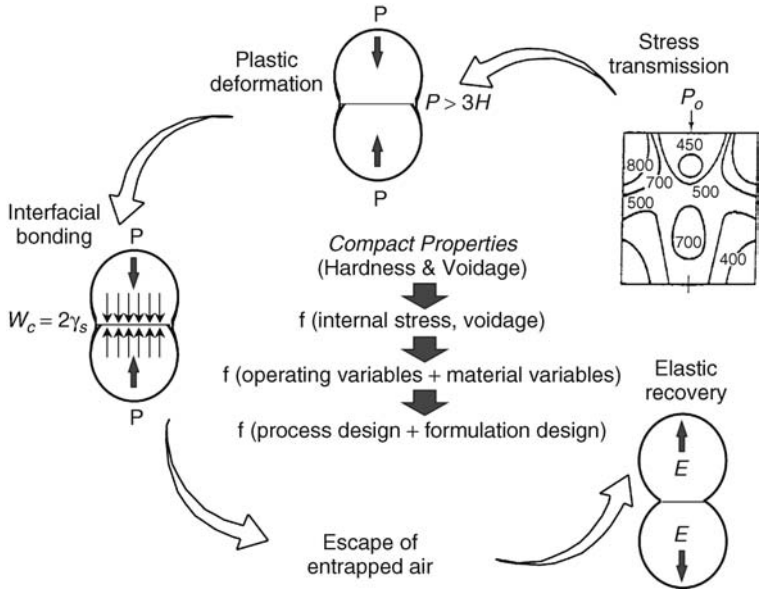


Figure 3 The mechanisms or rate processes of agitative agglomeration, or granulation, which include powder wetting, granule growth, granule consolidation, and granule attrition. These processes combine to control granule size and porosity, and they may be influenced by formulation or process design changes. *Source*: From Ref. 5.

Granulation Mechanisms

Four key mechanisms or *rate processes* contribute to granulation, as originally outlined by Ennis (4,5), and later developed further by Litster and Ennis (6). These include *wetting* and nucleation, *coalescence* or growth, *consolidation*, and *attrition* or breakage (Fig. 3). Initial *wetting* of the feed powder and existing granules by the binding fluid is strongly influenced by spray rate or fluid distribution, as well as feed formulation properties, in comparison with

mechanical mixing. Wetting promotes *nucleation* of fine powders, or coating in the case of feed particle size in excess of drop size. In the *coalescence* or *growth* stage, partially wetted primary particles and larger nuclei coalesce to form granules composed of several particles. The term *nucleation* is typically applied to the initial coalescence of primary particles in the immediate vicinity of the larger wetting drop, whereas the more general term of *coalescence* refers to the successful collision of two granules to form a new larger granule. In addition, the term of *layering* is applied to the coalescence of granules with primary feed powder. Nucleation is promoted from some initial distribution of moisture, such as a drop or from the homogenization of a fluid feed to the bed, as with high-shear mixing. As granules grow, they are consolidated by compaction forces due to bed agitation. This *consolidation* stage strongly influences *internal* granule voidage or granule porosity, and therefore end-use properties such as granule strength, hardness, or dissolution. Formed granules may be particularly susceptible to *attrition* if they are inherently weak or if flaws develop during drying.

These rate mechanisms can occur simultaneously in all processes. However, certain mechanisms may dominate. For example, fluidized-bed granulators are strongly influenced by the wetting process, whereas mechanical redispersion of binding fluid by impellers and particularly high-intensity choppers diminish the wetting contributions to granule size in high-shear mixing. On the other hand, granule consolidation is far more pronounced in high-shear mixing than fluidized-bed granulation. These simultaneous rate processes taken as a whole—and sometimes competing against one another—determine the final granule size distribution and granule structure and voidage resulting from the process and, therefore, the final end-use or product quality attributes of the granulated product.

Compaction Mechanisms

Compaction is a forming process controlled by mechanical properties of the feed in relationship to applied stresses and strains, as well as interstitial gas interactions. Microlevel processes are controlled by particle properties such as friction, hardness, size, shape, surface energy, elastic modulus, and permeability. Key steps, in any compaction process, include (*i*) powder filling, (*ii*) stress application and removal, and (*iii*) compact ejection. Powder filling and compact weight variability is strongly influenced by bulk density and powder flowability (2,3), as well as any contributing segregation tendencies of the feed. The steps of stress application and removal consist of several competing mechanisms, as depicted in Figure 2. Powders do not transmit stress uniformly. Wall friction impedes the applied load, causing a drop in stress as one moves away from the point of the applied load (e.g., a punch face in tabletting or roll surface in roll pressing). Therefore, the applied load and resulting density is not uniform throughout the compact, and powder frictional properties control the *stress transmission and distribution* in the compact (8). The general area of study relating compaction and stress transmission is referred to as *powder mechanics* (2,3,8–10). For a local level of applied stress, particles deform at their point contacts, including plastic deformation for forces in excess of the particle surface *hardness*. This allows intimate contact at surface point contacts, allowing cohesion/adhesion to develop between particles, and therefore interfacial bonding, which is a function of their *interfacial surface energy*. During the short timescale of the applied load, any *entrapped air* must escape, which is a function of feed permeability, and a portion of the elastic strain energy is converted into permanent plastic deformation. Upon stress removal, the compact expands because of remaining elastic recovery of the matrix, which is a function of elastic modulus, as well as any expansion of remaining entrapped air. This can result is loss of particle bonding, and flaw development, and this is exacerbated for cases of wide distributions in compact stress because of poor stress transmission. The final step of stress removal involves compact ejection, where any remaining radial elastic stresses are removed. If recovery is substantial, it can lead to capping or delamination of the compact.

These microlevel processes of compaction control the final flaw and density distribution throughout the compact, whether it is a roll pressed, extruded or tabletted product, and as such, control compact strength, hardness, and dissolution behavior. Compaction processes will not be discussed further here, with the remainder of the chapter focussing on wet granulation and agitative processes (for further discussion regarding compaction, see chap. 8 and Refs. 2,3,10, and 11).

Formulation Vs. Process Design

The *end-use properties* of granulated material are controlled by granule *size* and internal granule *voidage* or *porosity*. Internal granule voidage (or porosity) $\varepsilon_{granule}$ and bed voidage ε_{bed}, or voidage between granules, are related by:

$$\rho_{bulk} = \rho_{granule}(1 - \varepsilon_{bed}) = \rho_s(1 - \varepsilon_{bed})(1 - \varepsilon_{granule}) \quad (1)$$

where ρ_{bulk}, $\rho_{granule}$, and ρ_s are bulk, granule, and skeletal or envelop primary particle density, respectively. Here, granule voidage and granule porosity will be used interchangeably. Granule structure may also influence properties. To achieve a desired product quality as defined by metrics of end-use properties, granule size and voidage may be manipulated by changes in either process *operating variables* or product *material variables*, which effect the underlying granulation and compaction mechanisms, as initially outlined by Ennis (4,5), and later developed further by Ennis and Litster (2,3,6). The first approach is the realm of traditional *process engineering*, whereas the second is *product engineering*. Both approaches are critical and must be integrated to achieve a desired end-point in product quality. *Operating variables* are defined by the chosen granulation technique and peripheral processing equipment, as listed for typical pharmaceutical processes in Figure 4. In addition, the choice of agglomeration technique dictates the *mixing pattern* of the vessel. *Material variables* include parameters such as binder viscosity or wet mass rheology, surface tension, feed particle size distribution, powder friction, and the adhesive properties of the solidified binder. Material variables are specified by the choice of ingredients, or *product formulation*. Both operating and material variables together define the *kinetic mechanisms* and *rate constants* of wetting, growth, consolidation, and attrition. Overcoming a given size enlargement problem often requires changes in both processing conditions and in product formulation.

The importance of granule voidage to final product quality is illustrated in Figures 5 and 6 for a variety of formulations. Here, bulk density is observed to decrease, and granule attrition to increase. Similarly, dissolution rate is known to increase with an increase in the granule voidage (1). Bulk density is clearly a function of both granule size distribution, which controls bed voidage, and the voidage or porosity within the granule itself. The data of Figure 5 is normalized with respect to its zero intercept, or its effective bulk density at zero-granule voidage. The granule attrition results of Figure 6 are based on a CIPAC test method, which is effectively the percentage of fines passing a fine mesh size following attrition in a tumbling apparatus. Granules weaken with increased voidage. All industries have their own specific quality and in-process evaluation tests. However, what they have in common are the important contributing effects of granule size and granule voidage in controlling granule quality.

The importance of distinguishing the effects of process versus formulation changes can be illustrated with the help of Figure 6. Let us assume the particular formulation and current process conditions produce a granulated material with a given attrition resistance and dissolution behavior (indicted as "current product"). If one desires instead to reach a given "target," either the formulation or process variable may be changed. Changes to the process, or operating variables, generally readily alter granule voidage. Examples to decrease voidage might include increased bed height, increased processing time, or increased peak bed

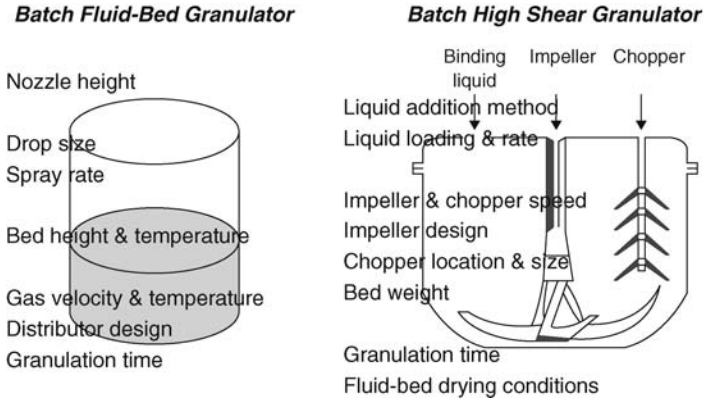


Figure 4 Typical operating variable for pharmaceutical granulation processes. *Source*: From Ref. 5.

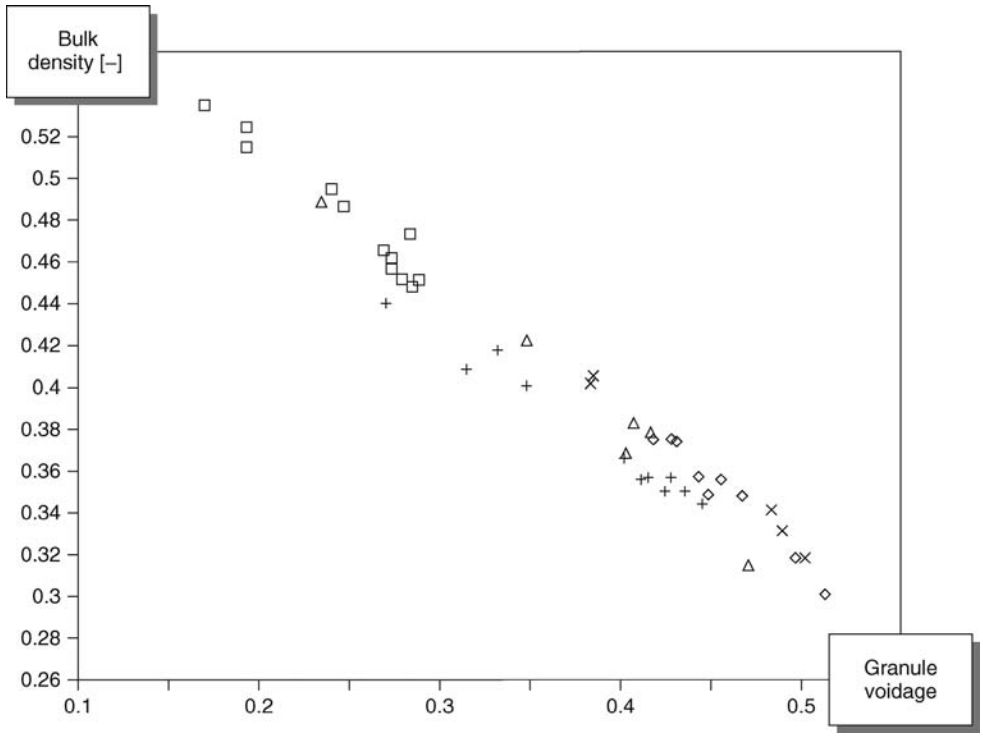


Figure 5 Impact of granule density on bulk density. Normalized bulk density as a function of granule voidage. *Source*: From Ref. 5.

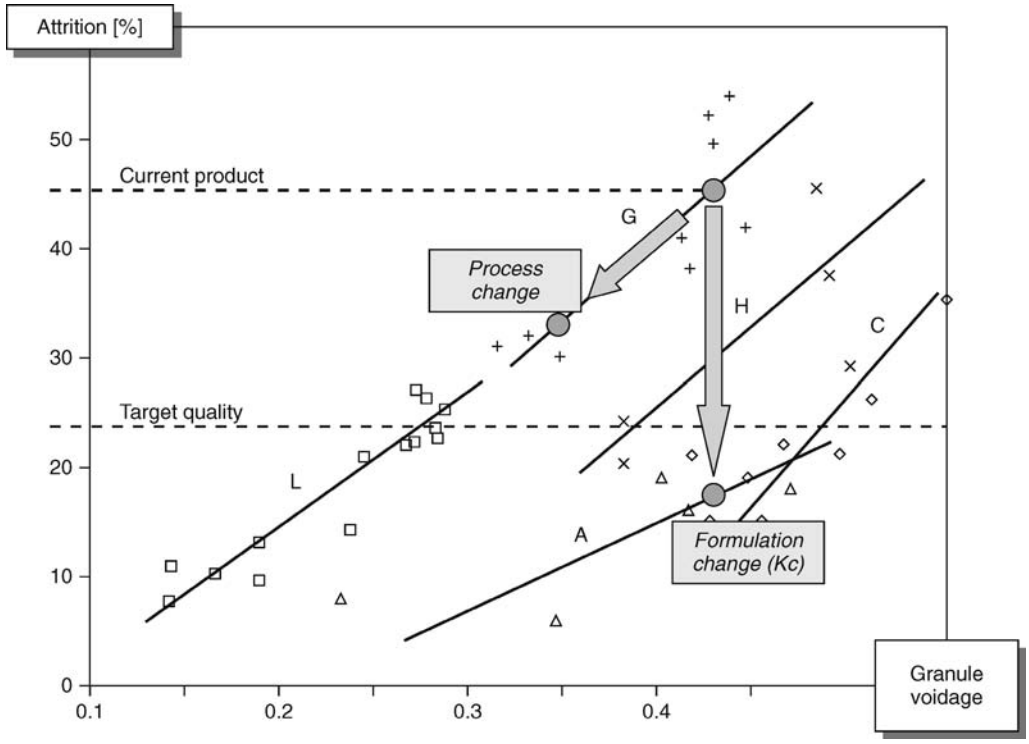


Figure 6 Impact of granule density on strength and attrition. Illustration of process changes versus formulation changes. *Source*: From Ref. 5.

moisture. However, only a range of such changes in voidage is possible. The various curves are due to changes in formulation properties. Therefore, it may not be possible to reach a target change in granule properties without changes in formulation, or material variables. Examples of key material variable effecting voidage would include feed primary particle size, inherent formulation bond strength, and binder solution viscosity, as discussed in detail in following sections. This crucial interaction between operating and material variables is crucial for successful formulation, and requires substantial collaboration between processing and formulation groups, and a clear knowledge of the effect of scale-up on this interaction.

Key Historical Investigations

A range of historical investigations has been undertaken involving the impact of operating variables on granulation behavior (4–6,12–14). Typical variables have included the effects of bed hydrodynamics and agitation intensity, pan angle and speed, fluid-bed excess gas velocity, mixer impeller and chopper speeds, drum rotation speed, spray method, drop size, nozzle location, and binder and solvent feed rates. While such studies are important, their general application and utility to studies beyond the cited formulations and process conditions can be severely limited. Often the state of mixing, moisture distribution and rates, and material properties such as formulation size distribution, powder frictional properties, and solution viscosity is insufficiently defined. As such, these results should be used judiciously and with care. Often even the directions of the impact of operating variables on granule properties are altered by formulation changes.

Two key pieces of historical investigation require mention, as the approach developed here stems heavily from this work. The first involves growth and breakage mechanisms that control the evolution of the granule size distribution (15) (Fig. 7). There are strong interactions between these mechanisms. In addition, various forms have been incorporated into population balances modeling to predict granule size in the work of Sastry and Kapur (15–19) See chapter 24 for details. Given the progress made in connecting rate constants to formulation properties, the utility of population balance modeling has increased substantially.

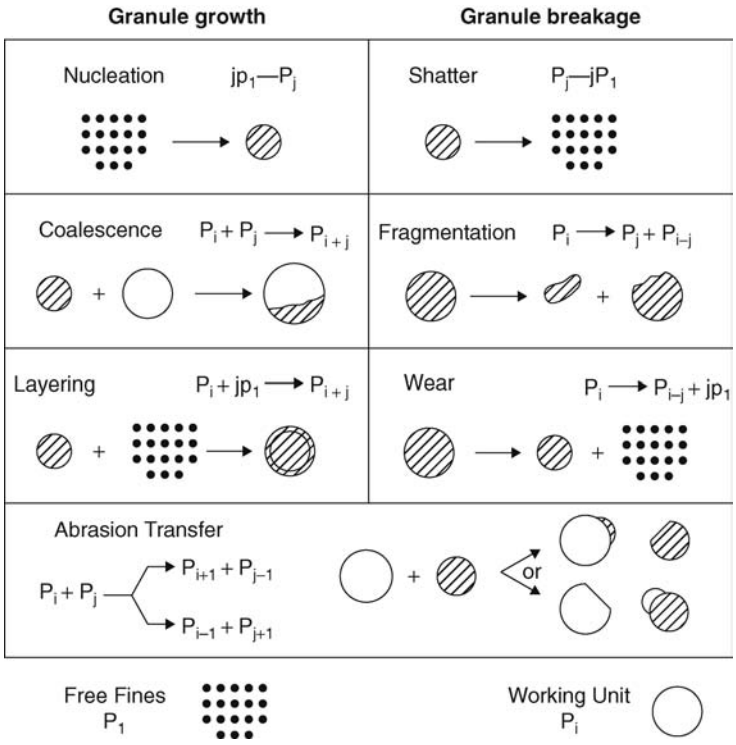


Figure 7 Growth and breakage mechanisms in granulation processes. *Source*: From Ref. 15.

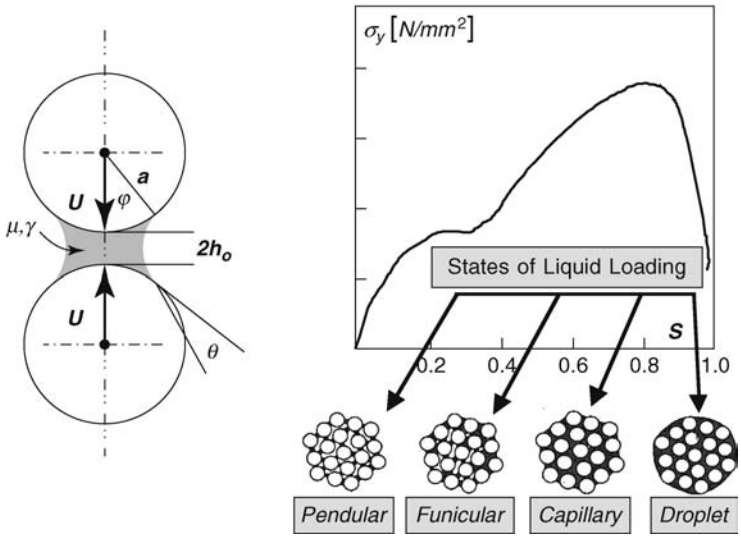


Figure 8 Static yield strength of wet agglomerates versus pore saturation. *Source*: From Refs. 19,20.

The second important area of contribution involves the work of Rumpf and colleagues (20–22), who studied the impact of interparticle force H, and in detail for capillary forces, on granule static tensile strength, or:

$$\sigma_T = \frac{9}{8}\left(\frac{1-\varepsilon}{\varepsilon}\right)\frac{H}{a^2} = A\left(\frac{1-\varepsilon}{\varepsilon}\right)\frac{\gamma\cos\theta}{a} \quad \text{with} \quad \begin{cases} A = 9/4 & \text{for pendular state} \\ A = 6 & \text{for capillary state} \end{cases} \tag{2}$$

Forces of a variety of forms were studied, including viscous, semisolid, solid, electrostatic, and van der Waals forces.

Of particular importance was the contribution of pendular bridge force arising from surface tension to granule tensile strength. Capillary pressure deficiency due to the curvature of the pendular bridge in addition to a contact line force results in an interparticle force, as highlighted in Figure 8 (here, interparticle velocity $U = 0$). This force summed over the granule area results in a granule static strength, which is a function of pore saturation S. The states of pore filling have been defined as pendular (single bridges), funicular (partial complete filling and single bridges), capillary (nearly complete filling $S \sim 80\%$ to 100%), followed by drop formation and loss of static strength. This approach will be extended in subsequent sections to include viscous forces and dynamic strength behavior ($U \neq 0$). The approach taken in this chapter follows this same vein of research as originally established by Rumpf and Kapur, namely, relating granule and particle level interactions to bulk behavior through the development of the rate processes of wetting and nucleation, granule growth and consolidation, and granule breakage and attrition. Each of these will now be dealt with in the subsequent sections.

WETTING

Overview

The initial distribution of binding fluid can have a pronounced influence on the size distribution of seed granules, or *nuclei*, which are formed from fine powder. Both the final *extent* of and the *rate* at which the fluid wets the particulate phase are important. Poor wetting results in drop coalescence, fewer larger nuclei with ungranulated powder, and over-wetted masses, leading to broad nuclei distributions. Granulation can retain a memory, with nuclei size distribution impacting final granule size distribution. Therefore, initial wetting can be critical to uniform nuclei formation and often a narrow, uniform product. Wide nuclei distributions can lead to a wide granule size distribution. When the size of a particulate feed material is larger than drop size, wetting dynamics controls the distribution of coating

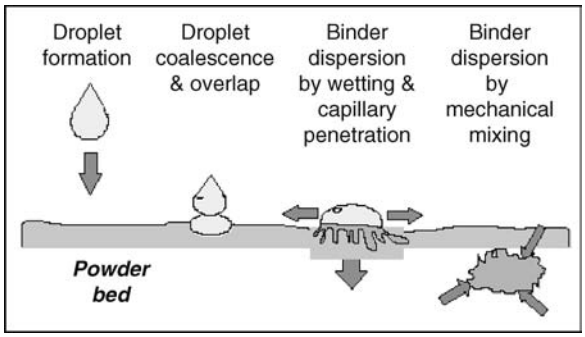


Figure 9 Stages of wetting for fine powder compared with drop size. *Source*: From Refs. 5, 6, and 24.

material, which has a strong influence on the later stages of growth. Wetting phenomena also influence redistribution of individual ingredients within a granule, drying processes, and redispersion of granules in a fluid phase. Other granule properties such as voidage, strength, and attrition resistance may be influenced as well. Preferential wetting of certain formulation ingredients can cause component segregation across granule size classes. An extensive review of wetting research may be found in Parfitt (23), Litster and Ennis (6), and Hapgood (24).

Mechanics of the Wetting Rate Process

Wetting is the first stage in wet granulation involving liquid binder distribution onto the feed powder. There are two extremes: (*i*) liquid drop size is large as compared to feed particle or granule size, and (*ii*) particle size is large as compared to the drop size. In the first case, the wetting process consists of several important steps (Fig. 9). First, droplets are formed related to spray distribution, or spray flux defined as the wetting area of the bed per unit time. Both atomization and the rate of drops are critical. In addition to binder viscosity and rheology, important operating variables include nozzle position, spray area, spray rate, and drop size. Second, droplets impact and coalesce on the powder bed surface if mixing or wet-in time is slow, or the spray flux is low. Third, droplets spread and penetrate into the moving powder bed to form loose nuclei, again coalescing if wet-in is slow or mixing is slow. In the case of high-shear processes, shear forces breakdown over-wet clumps, also producing nuclei.

For the second case of small drop size compared with the primary particle size, the liquid will coat the particles. Coating is produced by collisions between the drop and the particle followed by spreading of the liquid over the particle surface. If the particle is porous, then liquid will also be sucked into its pores by capillary action, lowering the effective moisture content promoting growth (25). Wetting dynamics control the distribution of coating material on large particles or formed granules, which has a strong influence on the later stages of growth as well as coating quality.

Methods of Measurement

Methods of characterizing wetting consist of four possible approaches: (*i*) drop spreading on powder compacts, (*ii*) penetration of fluid into powder beds, (*iii*) particle penetration into fluids, and (*iv*) interfacial characterization of powder surfaces (2,5,6). In first approach, the ability of a drop to spread is considered (23,26), and it involves the measurement of a *contact angle* θ of a drop on a powder compact, given by the Young-Dupré equation, or

$$\gamma^{sv} - \gamma^{sl} = \gamma^{lv} \cos\theta \tag{3}$$

where γ^{sv}, γ^{sl}, γ^{lv} are the solid-vapor, solid-liquid, and liquid-vapor interfacial energies, respectively, and θ is measured through the liquid. In the limit of $\gamma^{sv} - \gamma^{sl} \geq \gamma^{lv}$, the contact angle equals 0° and the fluid *spreads* on the solid, and is often referred to as the spreading coefficient. The extent of wetting is controlled by the group $\gamma^{lv} \cos\theta$, which is referred to as *adhesion tension*. Sessile drop studies of contact angle can be performed on powder compacts in the same way as on planar surfaces. Methods involve (*i*) the direct measurement of the contact angle from the tangent to the air-binder interface, (*ii*) solution of the Laplace-Young equation involving the

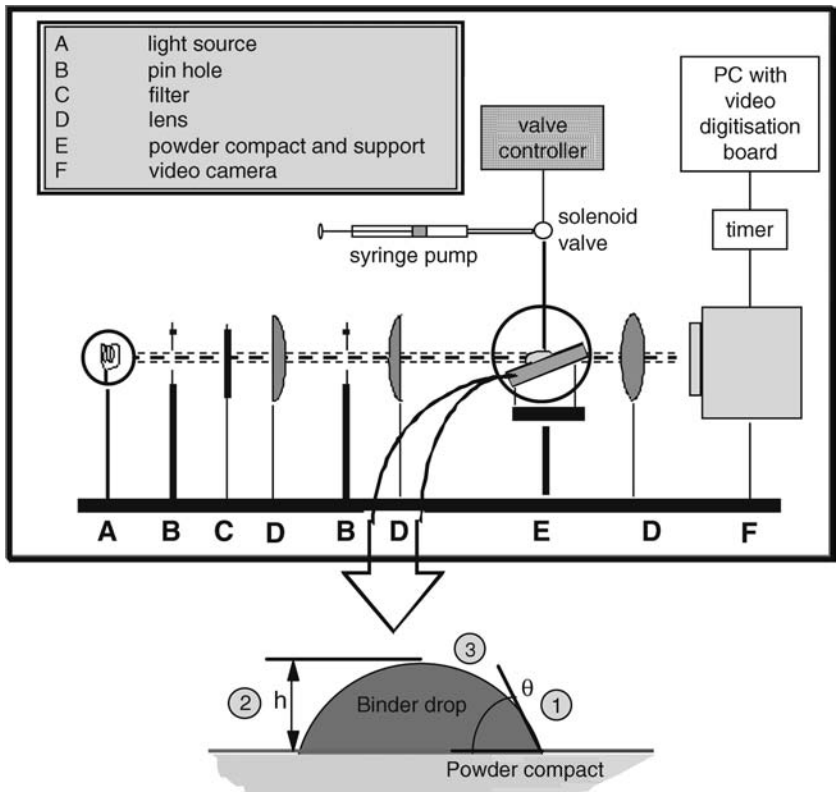


Figure 10 Characterizing wetting by dynamic contact angle goniometry. *Source*: From Refs. 5, 26, and 27.

contact angle as a boundary condition, or (*iii*) indirect calculations of the contact angle from measurements of, for example, drop height. The compact can either be saturated with the fluid for static measurements, or dynamic measurements may be made through a computer imaging goniometer (Fig. 10). For granulation processes, the dynamics of wetting are often crucial, requiring that powders be compared on the basis of a short timescale, *dynamic contact angle*. In addition, spreading velocity can be measured. Important factors are the physical nature of the powder surface (particle size, pore size, porosity, environment, roughness, pretreatment). The dynamic wetting process is, therefore, influenced by the rates of ingredient dissolution and surfactant adsorption and desorption kinetics (27).

The second approach to characterize wetting considers the ability of the fluid to penetrate into a powder bed (Fig. 11). It involves the measurement of the extent and rate of fluid rise by capillary suction into a column of powder, better known as the *Washburn* test or the Bartell cell variant (28,29). Considering the powder to consist of capillaries of radius R, the equilibrium height of rise h_e is determined by equating capillary and gravimetric pressures, or:

$$h_e = \frac{2\gamma^{lv}\cos\theta}{\Delta\rho g R} \tag{4}$$

where $\Delta\rho$ is the fluid density with respect to air, and g is gravity. In addition to the equilibrium height of rise, the dynamics of penetration are particularly important. Ignoring gravity and equating viscous losses with the capillary pressure, the rate (dh/dt) and dynamic height of rise h are given by:

$$\frac{dh}{dt} = \frac{R\gamma^{lv}\cos\theta}{4\mu h}, \quad \text{or} \quad h = \sqrt{\left[\frac{R\gamma^{lv}\cos\theta}{2\mu}\right]t} \tag{5}$$

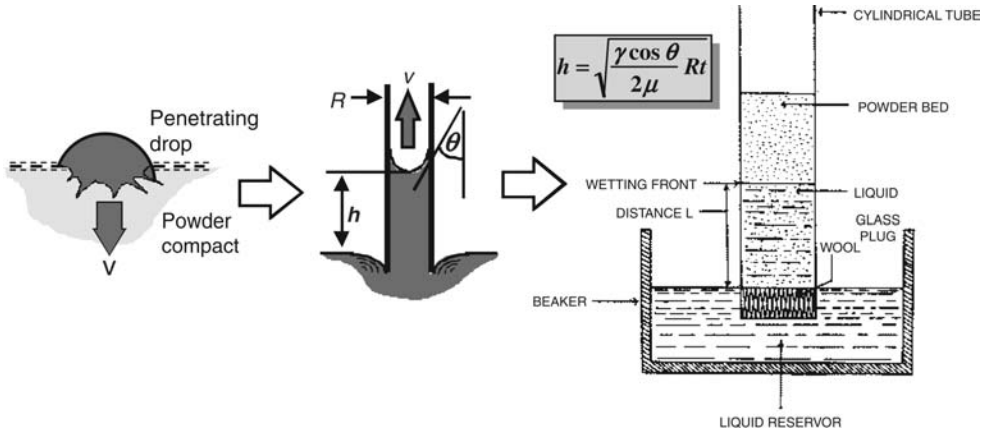


Figure 11 Characterizing wetting by Washburn test and capillary rise. *Source*: From Refs. 5 and 28.

where t is time and μ is binder fluid viscosity (28). The grouping of terms in brackets involve the material properties that control the dynamics of fluid penetration, namely average pore radius, or *tortuosity R* (related to particle size and void distribution of the powder), adhesion tension, and binder viscosity. The rate of capillary fluid rise, or the rate of binding fluid penetration in wet granulation, increases with increasing pore radius (generally coarser powders with larger surface-volume average particle size), increasing adhesion tension (increased surface tension and decreased contact angle), and decreased binder viscosity.

The contact angle of a binder-particle system itself is not a primary thermodynamic quantity, but rather a reflection of individual interfacial energies, which are a function of the molecular interactions of each phase with respect to one another. An interfacial energy may be broken down into its *dispersion* and *polar* components. These components reflect the chemical character of the interface, with the polar component due to hydrogen bonding and other polar interactions and the dispersion component due to van der Waals interactions. These components may be determined by the wetting tests described here, where a variety of solvents are chosen as the wetting fluids to probe specific molecular interactions (30). Interfacial energy is strongly influenced by trace impurities that arise in crystallization of the active ingredient, or other forms of processing such as grinding. It may be modified by judicious selection of surfactants (30,31).

Charges can also exist at interfaces, as characterized by electrokinetic studies (32). The total solid-fluid interfacial energy (i.e., both dispersion and polar components) is also referred to as the *critical solid surface energy* of the particulate phase. It is equal to the surface tension of a fluid, which *just* wets the solid with zero contact angle. This property of the particle feed may be determined by a third approach to characterize wetting, involving the penetration of particles into a series of fluids of varying surface tension (31,33), or by the variation of sediment height (34).

The last approach to characterizing wetting involves chemical probing of properties, which control surface energy (32,35). As just described, these methods include electrokinetic and surfactant adsorption studies. Additional methods are moisture or solvent adsorption studies and *inverse gas chromatography* (IGC). A distinct advantage of IGC is reproducible measurements of physical and chemical surface properties that control adhesion tension. IGC uses the same principles and equipment as standard gas chromatography (36), however, the mobile phase is comprised of probe gas molecules that move through a column packed with the powder of interest, which is the stationary phase. As the probe molecules travel through the column, they adsorb onto and desorb off the powder. The rate and degree of this interaction is determined by the surface chemistry of the powder and the probe molecules. Since the surface chemistry of the probe molecules is known, this allows calculation of the surface energies of the powder with the help of a series of plots of alkane and various polar

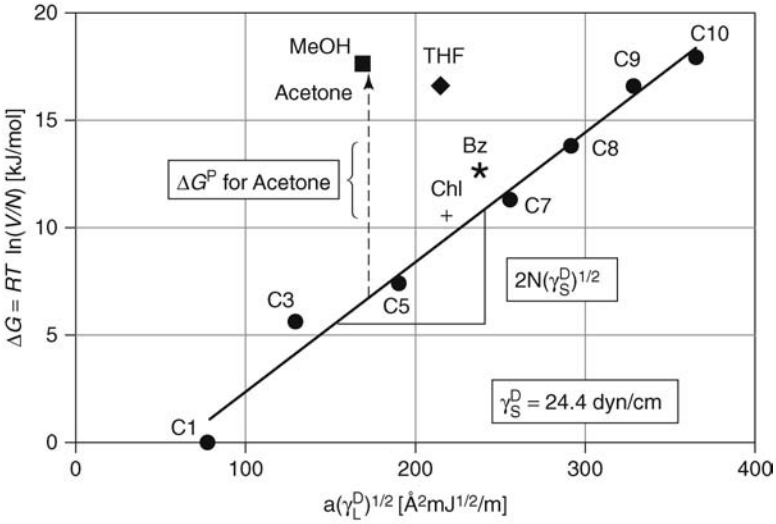


Figure 12 Characterizing wetting by inverse gas chromatography. *Source*: From Ref. 5.

probes. The strength of the solid/liquid interactions determines the average retention time of a probe, which is converted into net retention volume V_N. The free energy of desorption is then given by:

$$\Delta G = RT \ln V_N + c = 2Na\left(\sqrt{\gamma_S^D \gamma_L^D} + \sqrt{\gamma_S^P \gamma_L^P}\right) + c \tag{6}$$

where R is the universal gas constant, T is the column temperature, c is a system constant, N is Avagadro's number, and a is the surface area of a probe molecule. As illustrated in Figure 12, a plot of $RT \ln V_N$ versus $a\sqrt{\gamma_L^D}$ should give a straight line for a series of alkanes, the slope of which allows determination of the solid's dispersive surface energy γ_S^D. Plotting $RT \ln V_N$ versus $a\sqrt{\gamma_L^D}$ for the polar probes will give a point that is generally somewhere above the alkane reference line. The polar solid energy γ_S^P is then found from a plot of these deviations.

Granulation Examples of Wetting

Wetting dynamics has a pronounced influence on initial nuclei distribution formed from fine powder. As an example, initial nuclei size in fluid-bed granulation is shown to increase with decreasing contact angle, and therefore increasing adhesion tension (Fig. 13). Water contact angle was varied by changing the percentages of hydrophilic lactose and hydrophobic salicylic acid (37). Aulton et al. (38) also demonstrated the influence of surfactant concentration on shifting nuclei size due to changes in adhesion tension.

Figure 14A illustrates an example of dynamic wetting, where a time series of drop profiles are imaged as a drop wets in to a formulation tablet. Note that the timescale of wetting in this case is two seconds, with nearly complete wet-in occurring in one second. This particular formulation was granulated on a continuous pan system in excess of 2 ton/hr. Figure 14B compares differences in lots of the formulation. Note that a second lot—referred to as problem active—experiences significantly degraded granule strength and required production rates to be substantially reduced. This is associated with nearly twice the initial contact angle (120°) and a slower spreading velocity when compared with the good active. Poor wetting in practice can translate into reduced production rates to compensate for increased time for drops to work into the powder bed surface. Weaker granules are also often observed, since poor wet phase interfacial behavior translates, in part, to poor solid bond strength and high granule voidage. Note that differences in the lots are only observed

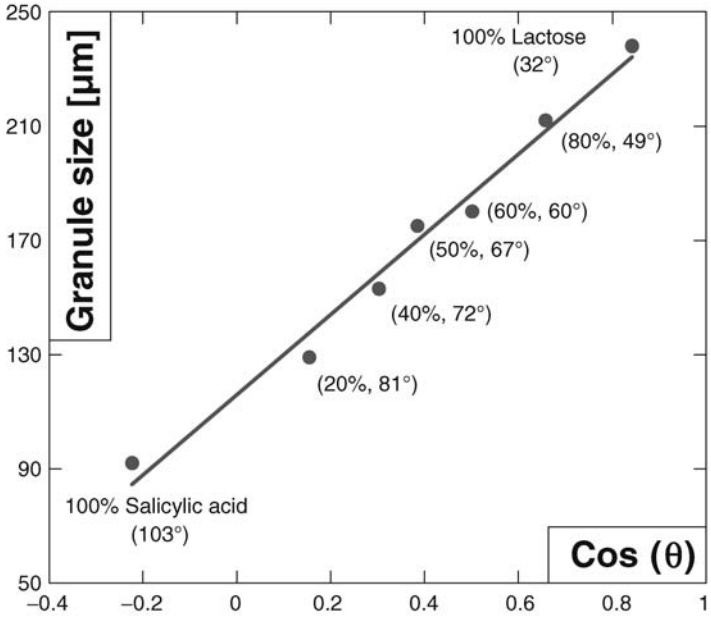


Figure 13 The influence of contact angle on nuclei size formed in fluid-bed granulation of lactose/salicylic acid mixtures. Powder contact angle determined by goniometry and percent lactose of each formulation are given in parentheses. *Source*: From Ref. 37.

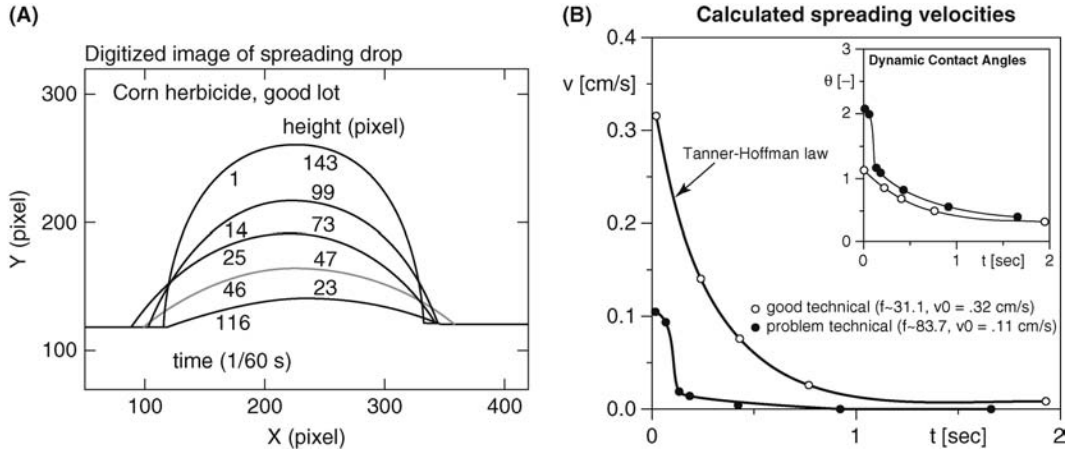


Figure 14 Dynamic imaging of drop wetting and its impact on continuous pan granulation. (**A**) Dynamic image of a drop wetting into a formulation with good active ingredient. (**B**) Comparison of surface spreading velocity and dynamic contact angle versus time for good and problem active ingredients or technical. Problem active required reduced production rates. *Source*: From Ref. 5.

over the first one-fourth to half a second, illustrating the importance of comparing dynamic behavior of formulations, after which time surfactant adsorption/desorption reduces contact angle.

As an example of Washburn approaches, the effect of fluid penetration rate and the extent of penetration on granule size distribution for drum granulation were shown by Gluba (39). Increasing penetration rate, as reflected by equation (5) increased granule size and decreased asymmetry of the granule size distribution (Fig. 15).

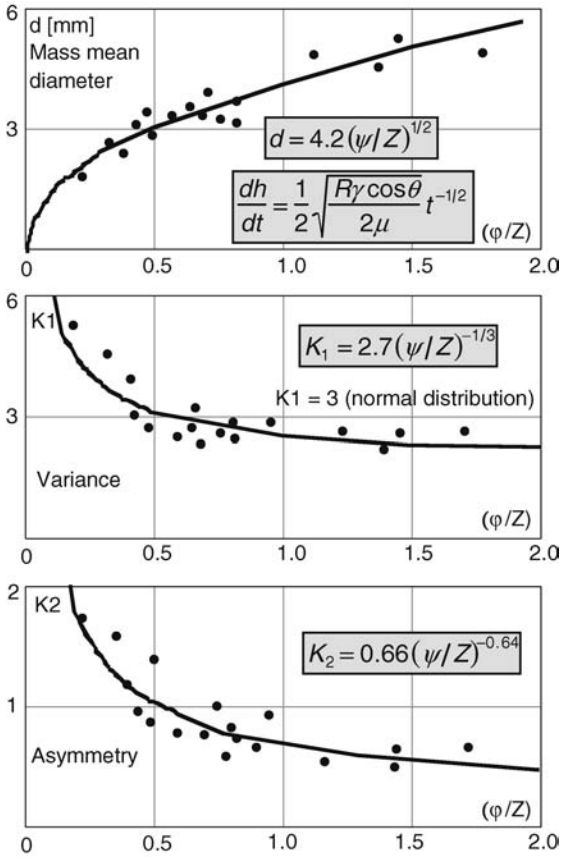


Figure 15 Influence of capillary penetration on drum granule size. Increasing penetration rate, as reflected by equation (5) increases granule size and decreases asymmetry of the granule size distribution. *Source*: From Ref. 39.

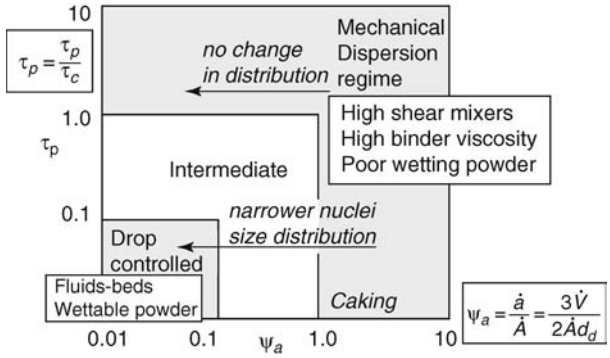


Figure 16 A possible regime map of nucleation, relating spray flux, solids mixing (solids flux and circulation time), and formulation properties. *Source*: From Refs. 5, 6, and 24.

Regimes of Nucleation and Wetting

The mechanisms of nucleation and wetting may be determined from a wetting regime map (Fig. 16), and is controlled by two key parameters. The first is the time required for a drop to wet in to the moving powder bed, in comparison to circulation time of the process. As discussed previously, this wet-in time is strongly influenced by formulation properties [Eq. (5)]. The second parameter is the actual spray rate or spray flux, in comparison with solids flux moving through the spray zones. Spray flux is strongly influenced by process design and operation. If wet-in is rapid and spray fluxes are low, individual drops will form discrete nuclei somewhat larger than the drop size in a *droplet-controlled regime*. At the other extreme, if drop penetration is slow and spray flux is large, drop coalescence and pooling of binder

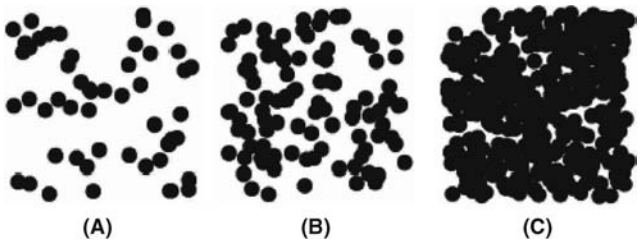


Figure 17 Monte-Carlo simulations of drop coverage on a powder bed: (**A**) $\Psi_d = 0.26$, (**B**) $\Psi_d = 0.59$, and (**C**) $\Psi_d = 2.4$. *Source*: From Refs. 6 and 24.

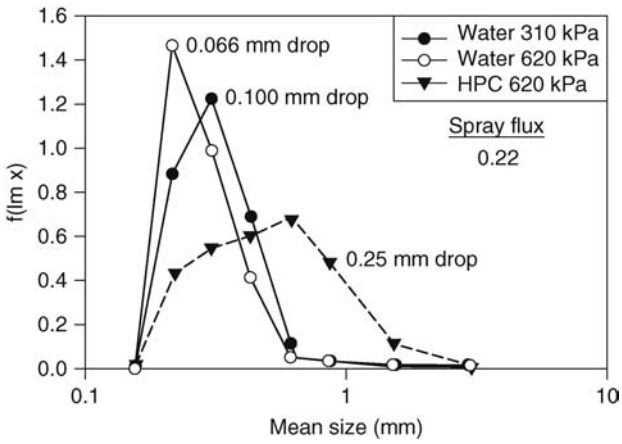


Figure 18 Effect of spray drop distribution at low spray flux on nuclei distribution. Lactose feed powder in spinning granulator. *Source*: From Ref. 31.

material will occur throughout the powder bed. Shear forces due to solids mixing must then breakdown over-wet masses or clumps in a *mechanical dispersion regime*, independent of drop distribution. Drop overlap and coalescence occur to varying extents in a *transitional intermediate regime*, with an increasingly wider nucleation distribution being formed for increasing spray flux and decreasing wet-in time.

To better understand the impact of process design and scale-up, we will consider drop penetration time and spray flux in greater detail. Small penetration time is desirable for droplet-controlled nucleation. Dimensionless drop penetration time T_p is given by Hapgood (24):

$$T_p = \frac{t_p}{t_c} \quad \text{where} \quad t_p = 1.35 \frac{V_d^{2/3}}{\varepsilon_{eff}^2} \left[\frac{\mu}{R_{eff} \gamma \cos \theta} \right] \tag{7}$$

Note the similarity with the Washburn relation equation (5). Dimensionless drop wet-in time decreases with increasing pore radius R_{eff}, decreasing binder viscosity μ, increasing adhesion tension $\gamma \cos\theta$, decreasing drop volume V_d, increasing bed porosity ε_{eff}, and increasing process circulation time t_c. Circulation time is a function of mixing and bed weight, and can change with scale-up. Effective pore radius R_{eff} is related to the surface-volume average particle size d_{32}, particle shape ϕ, bed porosity ε, tapped porosity ε_{tap}, and effective porosity ε_{eff} by:

$$R_{eff} = \frac{\varphi d_{32}}{3} \left(\frac{\varepsilon_{eff}}{1 - \varepsilon_{eff}} \right) \quad \varepsilon_{eff} = \varepsilon_{tap}(1 - \varepsilon + \varepsilon_{tap}) \tag{8}$$

To remain within a droplet-controlled regime of nucleation, the penetration time t_p should be less than the characteristic circulation time t_c of the granulator in question.

Now turning attention to spray distribution, the dimensionless spray flux Ψ_d is the ratio of the rate at which drops cover a given spray area ψ_d to the rate at which solids move through this same zone ψ_s and is a measure of the density of drops falling on the powder surface. The

volumetric spray rate V' and drop size d_d determine the number of drops formed per unit time, and, therefore, both the area occupied by a single drop and the total drop coverage area per unit time, or $\psi_d = 3V'/2d_d$. The dimensionless spray flux is then given by:

$$\Psi_d = \frac{\psi_d}{\psi_s} = \frac{3}{2}\frac{V'}{d_d\psi_s} \tag{9}$$

As with drop penetration time, spray flux plays a role in defining the regimes of nucleation (Figs. 16 and 17) (5,6,24). For small spray flux ($\Psi_d < 0.1$), drops will not overlap on contact and will form separate discrete nuclei if the drops *also* have fast penetration time. For large spray flux ($\Psi_d > .5$), however, significant drop overlap occurs, forming nuclei much larger than drop size, and in the limit, independent of drop size. Spray flux is strongly influenced by process design.

For the case of random drop deposition described by a Poisson's distribution (Fig. 18), Hapgood (24) showed the fraction of surface covered by spray as given by:

$$f_{single} = 1 - \exp(-\Psi_d) \tag{10}$$

In addition, the fraction of single drops forming individual nuclei (assuming rapid drop penetration) versus the number of agglomerates formed was given by:

$$f_{single} = \exp(-4\Psi_d) \tag{11}$$

and

$$f_{agglom} = 1 - \exp(-4\Psi_d) \tag{12}$$

Examples of the above as applied to nucleation are described by Litster et al. (40). Here, nuclei distribution was studied as a function of drop size and spray flux. For a moderate, intermediate spray flux of $\Psi_d = 0.22$, a clear relationship is seen between nuclei size and spray distribution, with nuclei formed somewhat larger than the drop size (Fig. 18). In addition, the nuclei distribution widens with the increasing formation of agglomerates for increasing spray flux (Fig. 19), as given by equation (12), for the case of rapid drop penetration.

The spray flux captures the impact of equipment operating variables on nucleation and wetting, and as such is very useful for scale-up if nucleation rates and nuclei sizes are to be maintained constant (Fig. 16). A *droplet-controlled nucleation regime* occurs when there is both low spray flux—relatively few drops overlap; and fast droplet penetration—drops wet into the bed completely before bed mixing allows further drop contact. Nuclei will be formed of

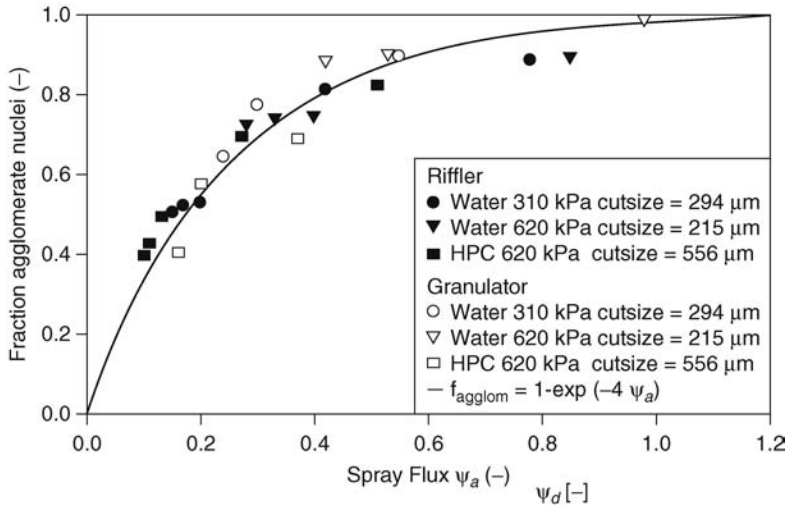


Figure 19 Agglomerate formation with lactose, water, and HPLC spray solutions. *Source*: From Refs. 6 and 25.

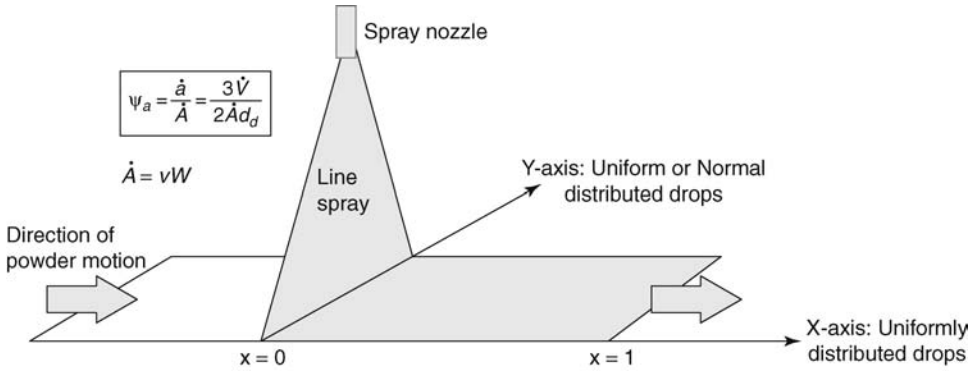


Figure 20 Idealized flat spray zone in a spinning riffle granulator. *Source*: From Refs. 6 and 24.

somewhat larger than the drop size. A *mechanical dispersion regime* occurs at the other extreme of high spray flux—giving large drop overlap and coalescence, and large drop penetration times, promoted by poor wet-in rates and slow circulation times and poor mixing. In this regime, nucleation and binder dispersion occurs by mechanical agitation. Viscous, poorly wetting binders are slow to flow through pores in the powder bed in the case of poor penetration time. Drop coalescence on the powder surface occurs (also known as "pooling") creating very broad nuclei size distributions. Binder solution delivery method (drop size, nozzle height) typically has minimal effect on the nuclei size distribution, though interfacial properties may affect nuclei and final granule strength. An *intermediate regime* exists for moderate drop penetration times and moderate spray flux, with the resulting nuclei regime narrowing with decreases in both.

There are several implications with regard to the nucleation regime map in trouble shooting of wetting and nucleation problems. If drop penetration times are large, making adjustments to spray may not be sufficient to narrower granule size distributions if remaining in the mechanical regime. Significant changes to wetting and nucleation occur only if changes take the system across a regime boundary. This can occur in an undesirable way if processes are not scaled with due attention to remaining in the drop controlled regime, or alternatively, within the mechanical dispersion regime. For example, scale-up may cause a granulation process to move from one regime on wetting to another, resulting in unexpected behavior and an entirely different dependence of atomization method and mixing.

Example of Wetting Regime Calculation

As an example of wetting calculations, consider an idealized powder bed shown in Fig. 20 of width $B = 0.10$ m, moving past a flat spray of spray rate $dV/dt = 100$ mL/min as a solids velocity of $w = 1.0$ m/sec. For a given spray rate, the number of drops is determined by drop volume or diameter $d_d = 100$ μm, which in turn defines the drop area a per unit time, which will be covered by the spray, giving a spray flux ψ_d of:

$$\psi_d = \frac{da}{dt} = \frac{dV/dt}{V_d}\left(\frac{\pi d_d^2}{4}\right) = \frac{3}{2}\frac{(dV/dt)}{d_d} = \frac{3}{2}\frac{(100 \times 10^{-6}/60\,\text{m/s})}{(100 \times 10^{-6}\,\text{m})} = 0.025\,\text{m}^2/\text{s} \tag{13}$$

As droplets contact the powder bed at a certain rate, the powder moves past the spray zone at its own velocity, or at solids flux ψ_s given for this simple example by:

$$\psi_s = \frac{dA}{dt} = B_w = 0.1\,\text{m} \times 1.0\,\text{m/s} = 0.1\,\text{m}^2/\text{sec} \tag{14}$$

This gives a dimensionless spray flux of:

$$\Psi_d = \frac{\psi_d}{\psi_s} = \frac{0.025\,\text{m}^2/\text{sec}}{0.1\,\text{m}^2/\text{sec}} = 0.25 \tag{15}$$

This is at the limit of allowable spray flux to remain within a droplet-controlled regime. If double the spray rate is required, wetting and nucleation would occur within the mechanical dispersion regime, diminishing the need for spray nozzles. To lower the spray rate by a factor of two, as a safety for droplet-controlled nucleation, either two nozzles spread well apart, double the solids velocity, or half the spray rate would be needed (e.g., doubling the spray cycle time). Alternately, smaller drops might prove helpful.

The last requirement for droplet-controlled growth would be a short drop penetration time. For a lactose powder of $d_{32} = 20$ μm, and loose and tapped voidage of ε=0.60 and ε_{tap}=0.40, the effective voidage and pore radius are given by:

$$\varepsilon_{eff} = \varepsilon_{tap}(1 - \varepsilon + \varepsilon_{tap}) = 0.4(1 - 0.6 + 0.4) = 0.32 \tag{16}$$

$$R_{eff} = \frac{\varphi d_{32}}{3}\left(\frac{\varepsilon_{eff}}{1-\varepsilon_{eff}}\right) = \frac{0.9 \times 20}{3}\left(\frac{0.32}{1-0.32}\right) = 2.8\,\mu m \tag{17}$$

The penetration time should be no more than 10% of the circulation time. For water with a viscosity of $\mu = 1$, *cp* =0.001 Pa/sec, and adhesion tension of $\gamma \cos\theta$ =.033 N/m, we obtain a penetration time of

$$t_p = 1.35\frac{V_d^{2/3}}{\varepsilon_{eff}^2}\left[\frac{\mu}{R_{eff}\gamma\cos\theta}\right] = 1.35\frac{(100 \times 10^{-6}\pi/6)^{2/3}}{0.32^2}\left[\frac{0.001}{2.8 \times 10^{-6} \times 0.033}\right] = 0.0009\,\text{sec} \tag{18}$$

Note that the penetration time is a strong function of drop size ($\propto d_d^2$) and viscosity. For a 100-fold increase in viscosity representative of a typical binding solution and twice the drop size, the penetration time would increase to 0.4 seconds. This time could, in fact, be short when compared with the circulation times of high-shear systems, suggesting a move toward mechanical dispersion.

GRANULE GROWTH AND CONSOLIDATION

Mechanics of Growth and Consolidation

The evolution of the granule size distribution is controlled by several mechanisms. Nucleation of fine powders and coating of existing granules by the fluid phase have been discussed in the previous section. Breakage mechanisms will be treated in the following. Here, we focus particularly on growth and consolidation mechanisms. Granule growth includes the *coalescence* of existing granules as well as the *layering* of fine powder onto previously formed nuclei or granules. The breakdown of wet clumps into a stable nuclei distribution can also be included among coalescence mechanisms. As granules grow by coalescence, they are simultaneously compacted by *consolidation* mechanisms, which reduce internal granule voidage or porosity, which impacts granule strength and breakage.

There are strong interactions between growth and consolidation, as illustrated in Figure 21. For fine powder feed, granule size often progresses through rapid, exponential growth in the initial *nucleation* stage, followed by linear growth in the *transition* stage, finishing with very slow growth in a final *balling* stage. Simultaneously with growth, granule porosity is seen to decrease with time as the granules are compacted. Granule growth and consolidation are intimately connected; increases in granule size are shown here to be associated with a decrease in granule porosity. This is a dominant theme in wet granulation.

As originally outlined in Ennis (4), these growth patterns are common throughout fluidized bed, drum, pan, and high-shear mixer processes for a variety of formulations. Specific mechanisms of growth may dominate for a process—sometimes to the exclusion of others, with the prevailing mechanisms dictated by the interaction of formulation properties, which control granule deformability, and operating variables, which control the local level of shear, or bed agitation intensity.

For two colliding granules to coalesce rather than breakup, the collisional kinetic energy must first be dissipated to prevent rebound as illustrated in Figure 22. In addition, the strength of the bond must resist any subsequent breakup forces in the process. The ability of the granules to deform during processing may be referred to as the formulation's *deformability*, and

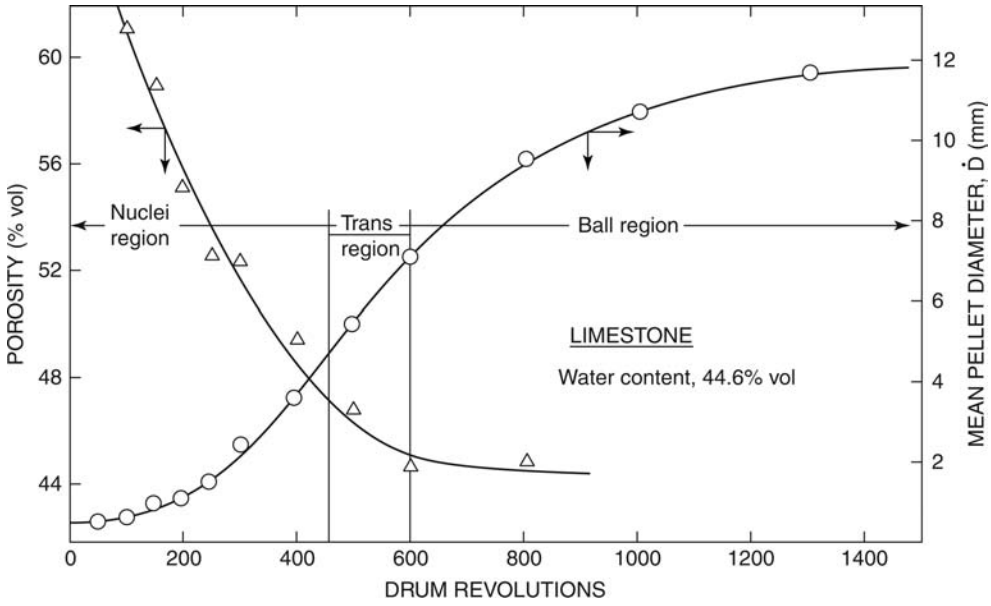


Figure 21 Granule porosity and mean (pellet) size. Typical regimes of granule growth and consolidation, shown for drum granulation of fine limestone. *Source*: From Refs. 16–19.

deformability has a large effect on growth rate, as well as granule consolidation. Increases in deformability increase the bonding or contact area, thereby dissipating and resisting breakup forces. From a balance of binding and separating forces and torque acting within the area of granule contact, Ouchiyama and Tanaka (41) derived a critical limit of size above which coalescence becomes impossible, or a maximum growth limit given by:

$$D_c = \begin{cases} (AQ^{3/2}K^{3/2}\sigma_T)^{1/4} & \text{plastic deformation } (K \propto 1/H) \\ (AQK^{3/2}\sigma_T)^{1/3} & \text{elastic deformation } (K \propto 1/E^{2/3}) \end{cases} \tag{19}$$

Here, K is *deformability*, a proportionality constant relating the maximum compressive force Q to the deformed contact area, A is a constant with units of $[L^3/F]$ and σ_T is the *tensile strength* of the granule bond. Depending on the type of collision, deformability K is a function of either hardness H, or reduced elastic modulus E^*. Granules are compacted as they collide. This expels pore fluid to the granule surface, thereby increasing local liquid saturation in the contact area of colliding granules. This surface fluid (*i*) increases the tensile strength of the liquid bond σ_T, and (*ii*) increases surface plasticity and deformability K.

The degree of granule deformation taking place during granule collisions defines possible growth mechanisms (Fig. 22). If little deformation takes place, the system is referred to as a *low-deformability/low-shear* process. This generally includes fluid bed, drum, and pan granulators. Growth is largely controlled by the extent of any surface fluid layer and surface deformability, which act to dissipate collisional kinetic energy and allow permanent coalescence. Growth generally occurs at a faster timescale than overall granule deformation and consolidation. This is depicted in Figure 22, where smaller granules can still be distinguished as part of a larger granule structure, or a popcorn-type appearance as often occurs in fluid-bed granulation. Note that such a structure may not be observed if layering or nucleation alone dominates. Granules may also be compacted, becoming smoother over time because of the longer-timescale process of consolidation. Granule coalescence and consolidation have less interaction than they do with high deformability systems, making low-deformability/low-shear systems easier to scale-up and control, for systems without high recycle.

For high-shear rates, large granule deformation occurs during collisions, and granule growth and consolidation occur on the same timescale. Such a system is referred to as a

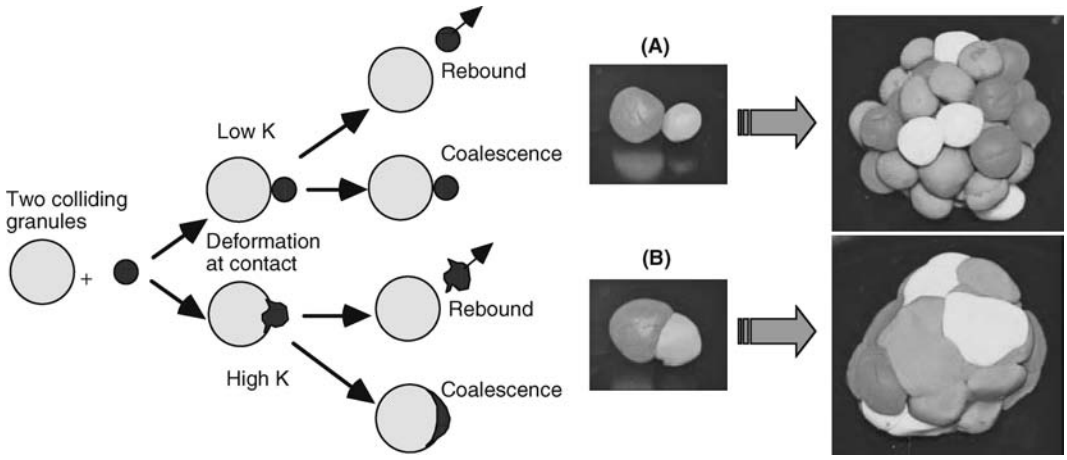


Figure 22 Mechanisms of granule coalescence for low and high deformability systems. Rebound occurs for average granule sizes greater than the critical granule size D_c. K = deformability. Granule structures resulting from (**A**) low and (**B**) high deformability systems, typical for fluid-bed and high-shear mixer granulators, respectively. *Source*: From Refs. 1, 2, and 4.

deformable/high-shear process, and includes continuous pin and plow shear type mixers, as well as batch high-shear pharmaceutical mixers. In these cases, kinetic energy is dissipated through deformation of the wet mass composing the granule. Rather than the *sticking* together mechanism of low-deformability processes such as a fluid-bed, granules are *smashed* or *kneaded* together, and smaller granules are not distinguishable within the granule structure (Fig. 22). High-shear and high-deformable processes generally produce denser granules than their low-deformability counterpart. In addition, the combined and competing effects of granule coalescence and consolidation make high-shear processes difficult to scale-up.

Although these extremes of growth are still the subject of much research investigation, a general model has emerged to help process engineers unravel the impact of operating variables and process selection. Two key dimensionless groups control growth. As originally defined by Ennis (4) and Tardos and Khan (42), these are the viscous and deformation Stokes numbers given, respectively, by:

$$\mathrm{St_v} = \frac{4\rho u_o d}{9\mu} \tag{20}$$

$$\mathrm{St_{def}} = \frac{\rho u_o^2}{\sigma_y}(\text{impact}) \quad \text{or} \quad \frac{\rho(\mathrm{d}u/\mathrm{d}x)^2 d^2}{\sigma_y}(\text{shear}) \tag{21}$$

The viscous Stokes number $\mathrm{St_v}$ is the ratio of kinetic energy to viscous work due to binding fluid occurring during granule/particle collisions. Low $\mathrm{St_v}$ or low granule energy represents increased likelihood of granule coalescence and growth, and this occurs for small granule or particle size (d is the harmonic average of granule diameter), low relative collision velocity u_o or granule density ρ, and high binder phase viscosity μ. The deformation Stokes number represents the amount of granule deformation taking place during collisions, and is similarly a ratio of kinetic energy to wet mass yield stress, a measure of granule deformability.

Bed agitation intensity is controlled by mechanical variables of the process such as fluid-bed excess gas velocity or mixer impeller and chopper speed. Agitation intensity controls the relative collisional and shear velocities of granules within the process and therefore growth, breakage, consolidation, and final product density. Figure 23 summarizes typical characteristic velocities, agitation intensities and compaction pressures, and product relative densities achieved for a variety of size enlargement processes.

Note that the process or formulation itself *cannot* define whether it falls into a low or high agitation intensity process. As discussed more fully below, it is a function of *both* the level of

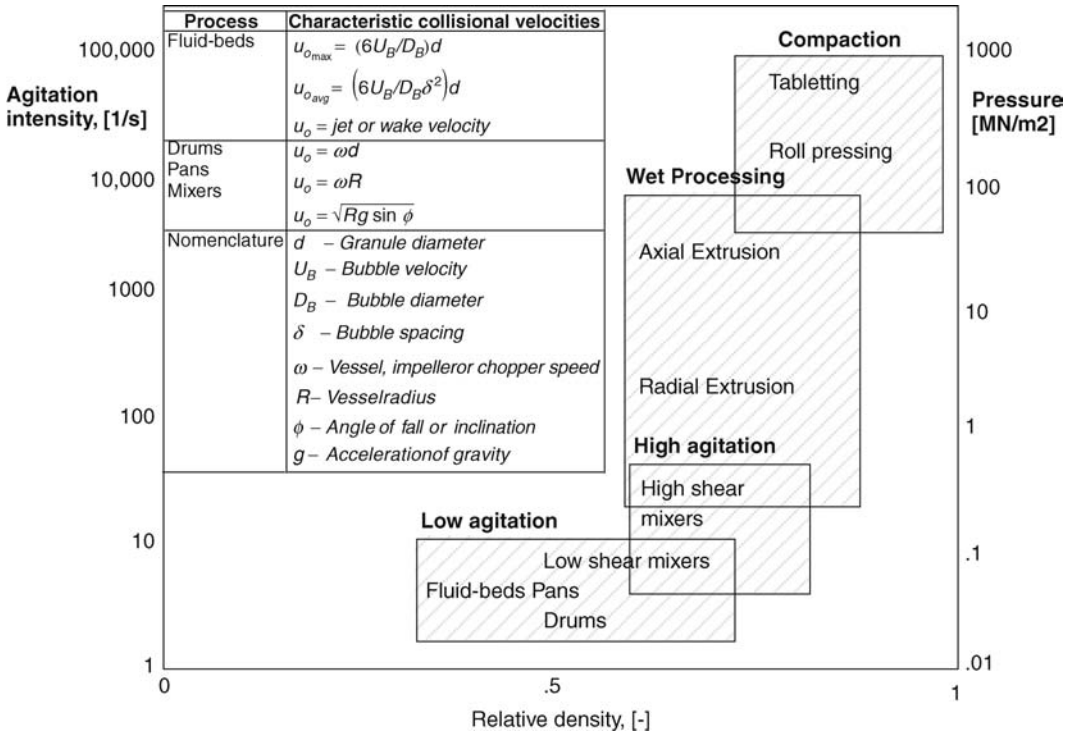


Figure 23 Classification of agglomeration processes by agitation intensity and compaction pressure. *Source*: From Refs. 1, 3, and 5.

shear as well as the formulation deformability. A very stiff formulation with low deformability may behave as a low-deformability system in a high-shear mixer, or a very pliable formulation may act as a high-deformable system in a fluid-bed granulator.

Granule consolidation or densification is also controlled by Stokes numbers, and typically increases for all processes with increasing residence time, shear levels, bed height, bed moisture or granule saturation, particle feed size or pore radius, surface tension, and decreasing binding fluid viscosity. Simultaneous drying or reaction usually acts to arrest granule densification.

Interparticle Forces

Interstitial fluid and resulting pendular bridges play a large role in both, granule growth and granule deformability. As shown previously, they control the static yield stress of wet agglomerates [Fig. 8, Eq. (2)]. Pendular bridges between particles of which a granule is composed give rise to capillary and viscous interparticle forces, which allows friction to act between point contacts (Fig. 24). Interparticle forces due to pendular bridges and their impact on deformability warrant further attention. Note that capillary forces for small contact angle attract particles (but repel for $\theta > 90^\circ$), whereas viscous and frictional forces always act to resist the direction of motion.

Consider two spherical particles of radius a separated by a gap distance $2h_o$ approaching one another at a velocity U (Fig. 24). The particles could represent two primary particles within the granule, in which case we are concerned about the contribution of interparticle forces on granule strength and deformability. Or they could represent two colliding granules, in which case we are concerned with the ability of the pendular bridge to dissipate granule kinetic energy and resist breakup forces in the granulation process. The two particles are bound by a pendular bridge of viscosity μ, density ρ, and surface tension γ. The pendular bridge consists of the binding fluid in the process, which includes the added solvent and any solubilized components. In some cases, it may also be desirable to also include very fine solid components

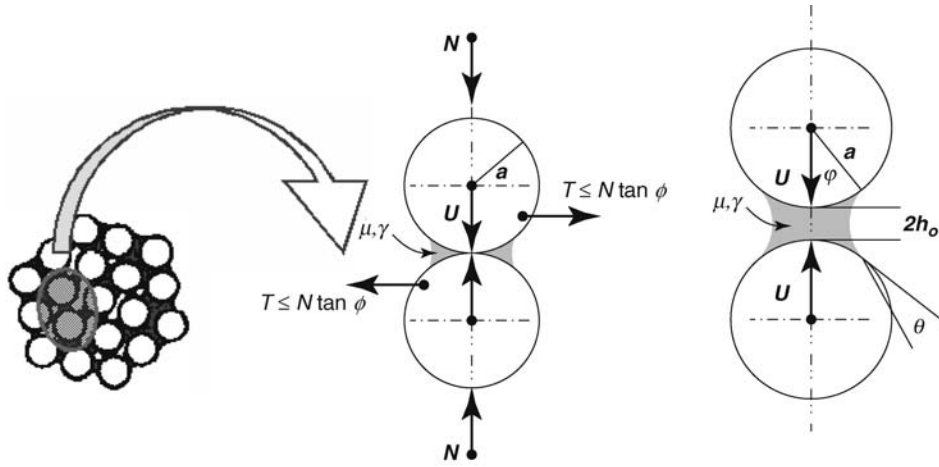


Figure 24 Interparticle forces and granule deformability. Interparticle forces include capillary forces, viscous lubrication forces, and frictional forces. *Source*: From Ref. 4.

within the definition of the binding fluid, and, therefore, consider instead a suspension viscosity and surface tension. These material parameters vary on a local level throughout the process, and are also time dependent and a function of drying conditions.

For the case of a static liquid bridge (i.e., $U = 0$) with perfect wetting, surface tension induces an attractive capillary force between the two particles due to a three-phase contact line force and a pressure deficiency arising from interfacial curvature. (For a poorly wetting fluid, the capillary pressure can be positive leading to a repulsive force.) The impact of this static pendular bridge force on static granule strength has been studied and reported extensively (3,20–22). It is important to recognize that in most processes, however, the particles are moving relative to one another and, therefore, the bridge liquid is in motion. This gives rise to viscous resistance forces, which can contribute significantly to the total bridge strength. The strengths of both Newtonian and non-Newtonian pendular bridges have been studied extensively (4,43,44). For Newtonian fluids (36), the dimensionless dynamic strength was shown to be given by:

$$\frac{F}{\pi\gamma a} = F_{\text{cap}} + F_{\text{vis}} = F_{\text{o}} + 3\text{Ca}/\varepsilon \quad \text{where} \quad \begin{cases} F_{\text{cap}} = (2 - 2H_{\text{o}})\sin^2\varphi \\ F_{\text{vis}} = 3\text{Ca}/\varepsilon \\ \text{Ca} = \mu U/\gamma \end{cases} \tag{22}$$

Forces have been made dimensionless with respect to a measure of the capillary force, or $\pi\gamma a$. F_{cap} is the strength of a static capillary bridge, which is a function of air-fluid interfacial curvature H_{o} and the filling angle φ. In dimensional form, it is given by:

$$F^*_{\text{cap}} = \pi\gamma a(2 - 2H_{\text{o}})\sin^2\varphi \tag{23}$$

F_{vis} is the strength of a viscous, dynamic bridge, and is equivalent to the force between two spheres approaching one another in an infinite fluid. This force is a function of binder viscosity μ, and the collision velocity U. Here, $\varepsilon = 2h_{\text{o}}/a$ is gap distance, and not granule voidage. In dimensional form, the viscous force is given by:

$$F^*_{\text{vis}} = 6\pi\mu Ua/\varepsilon \tag{24}$$

From equation (22), one finds that the dynamic bridge force begins with the static bridge strength, which is a constant independent of velocity (or Ca), and then increases linearly with Ca, which is a capillary number representing the ratio of viscous (μUa) to capillary (γa) forces, and is proportional to velocity. This is confirmed experimentally as illustrated in Figure 25 for the case of two spheres approaching axially. Extensions of the theory have also been conducted for non-Newtonian fluids (shear thinning), shearing motions, particle roughness, wettability, and time-dependent drying binders. The reader is referred to Ennis (4,43) for additional details.

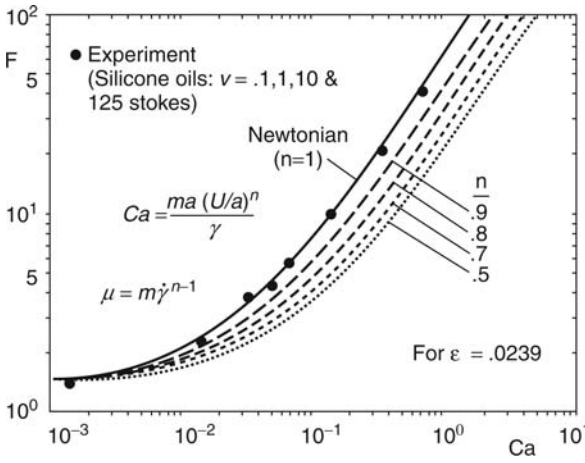


Figure 25 Maximum strength of a liquid bridge between two axial moving particles as a function of Ca for Newtonian and shear thinning fluids. *Source*: From Ref. 4.

For small velocities, small binder viscosity, and large gap distances, the strength of the bridge will approximate a static pendular bridge, or F_{cap}, which is proportional to and increases with increasing surface tension. This force is equivalent to the static pendular force previously given in equation (23) as studied by Rumpf (20–22). On the other hand, for large binder viscosities and velocities, or small gap distances, the bridge strength will approximately be equal to F_{vis}, which increases with increasing binder viscosity and velocity. This viscous force is singular in the gap distance and increases dramatically for small separation of the particles. It is important to note that as granules are consolidated, resulting in decreases in effective interparticle gap distance, and binders dry, resulting in large increases in binder viscosity, that the dynamic bridge strength can exceed the static strength by orders of magnitude.

Lastly, the role of interpacticle friction can be large, though rigorous experimental studies of the interaction between particle friction, granule porosity and binder viscosity, and surface tension in controlling bulk dynamic yield stress have not been undertaken.

Dynamic Wet Mass Rheology and Granule Deformability

Granule deformability and the maximum critical size D_c are strong functions of moisture. Figure 26A illustrates the low-shear rate, stress-strain behavior of agglomerates during

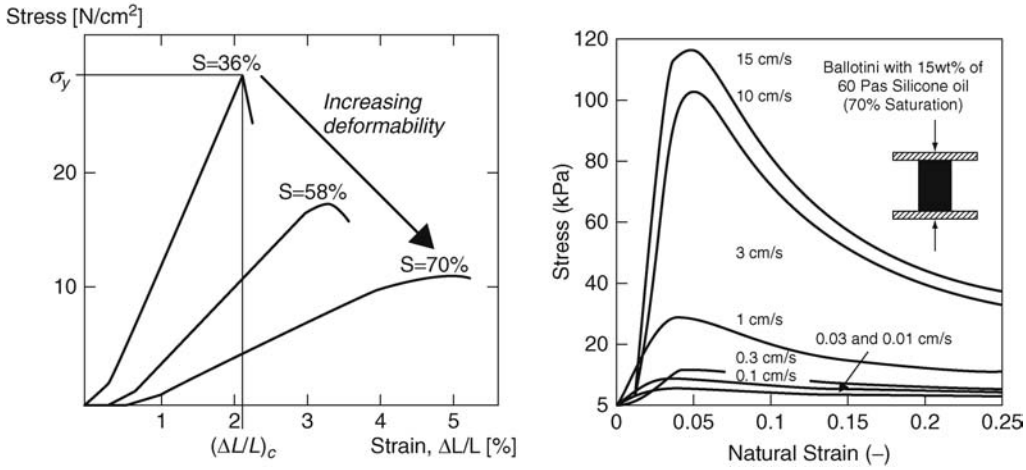


Figure 26 (**A**) The influence of sample saturation *S* on deformation strain ($\Delta L/L$) and yield strength σ_y. Dicalcium phosphate with 15 weight percent binding solution of PVP/PVA Kollidon® VA64. Fifty percent compact porosity. (**B**) Typical compact stress response for fast compression versus crosshead compression velocity for glass ballotini ($d_{32} = 35$ μm). *Source*: From Refs. 45 and 46.

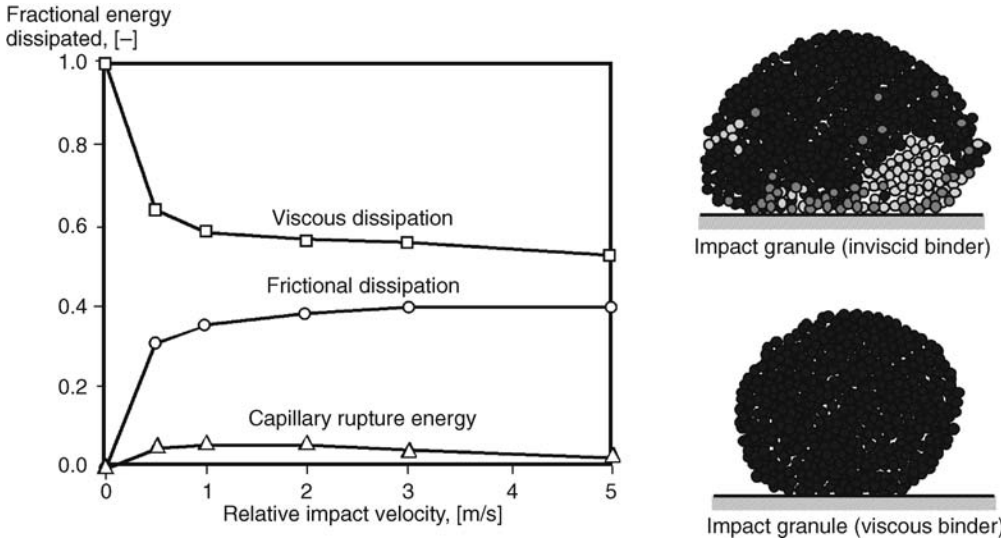


Figure 27 Distribution of energy dissipation during agglomerate collisions, with granular simulations of wall impact for 128 μsec duration for inviscid and viscous binder agglomerates. *Source*: From Refs. 2 and 47.

compression as a function of liquid saturation. Deformability K is related to both the *yield strength* of the material σ_y, that is, the ability of the material to resist stresses, and the ability of the surface to be strained without degradation or rupture of the granule, with this maximum allowable *critical deformation strain* denoted by $(\Delta L/L)_c$. In general, high deformability K requires low yield strength σ_y and high critical strain $(\Delta L/L)_c$, which is a measure of plastic versus brittle deformation. Increasing granule saturation increases deformability by lowering interparticle frictional. In most cases, granule deformability increases with increasing moisture (or granule saturation to be more precise), decreasing binder viscosity, decreasing surface tension, decreasing interparticle friction, and increasing average particle size (specifically d_{sv}, or the surface-volume mean size), as well as increasing bed agitation intensity.

The important contributions of binder viscosity and friction to granule deformability and growth are illustrated by fractions of energy dissipated during a granule collision as depicted in Figure 27. Note that 60% of the energy is dissipated through viscous losses, with the majority of the remainder through interparticle friction. Very little is lost because of capillary forces controlled by surface tension. Therefore, modern approaches to granule coalescence rest in understanding the impact of granule deformability on growth, rather than the original framework put for by Rumpf (20–22) regarding pendular and funicular liquid bridge forces alone.

Figure 26A illustrates yield stress behavior for slow yielding. However, the dependence of interparticle forces on *shear rate* clearly impacts *wet mass rheology* and, therefore, deformability. Figure 26B demonstrates that the peak flow or *dynamic* yield stress increases proportionally with compression velocity (45). In fact, in a similar fashion to dynamic liquid bridge forces, the peak flow stress of wet unsaturated compacts is seen to also increase with Ca (Fig. 28):

$$\frac{\sigma_y^{\text{Peak}}}{\gamma/a} = \sigma_o + A\,\overline{\text{Ca}}^{B} \quad \text{where} \quad \begin{cases} \sigma_o = 5.0 - 5.3 \\ A = 280 - 320\,, \quad B = 0.58 - 0.64 \\ \overline{\text{Ca}} = \mu\dot{\varepsilon}\,a/\gamma \end{cases} \tag{25}$$

There are several important points worth noting. First is the similarity between the yield strength of the compact [Eq. (25)] and the strength of the individual dynamic pendular bridge [Eq. (22)]; both curves are similar in shape with a capillary number dependency. As with the pendular bridge, two regions may be defined. In region 1, for a bulk capillary number of $\text{Ca} < 10^{-4}$, the strength or yield stress of the compact depends on the static pendular bridge,

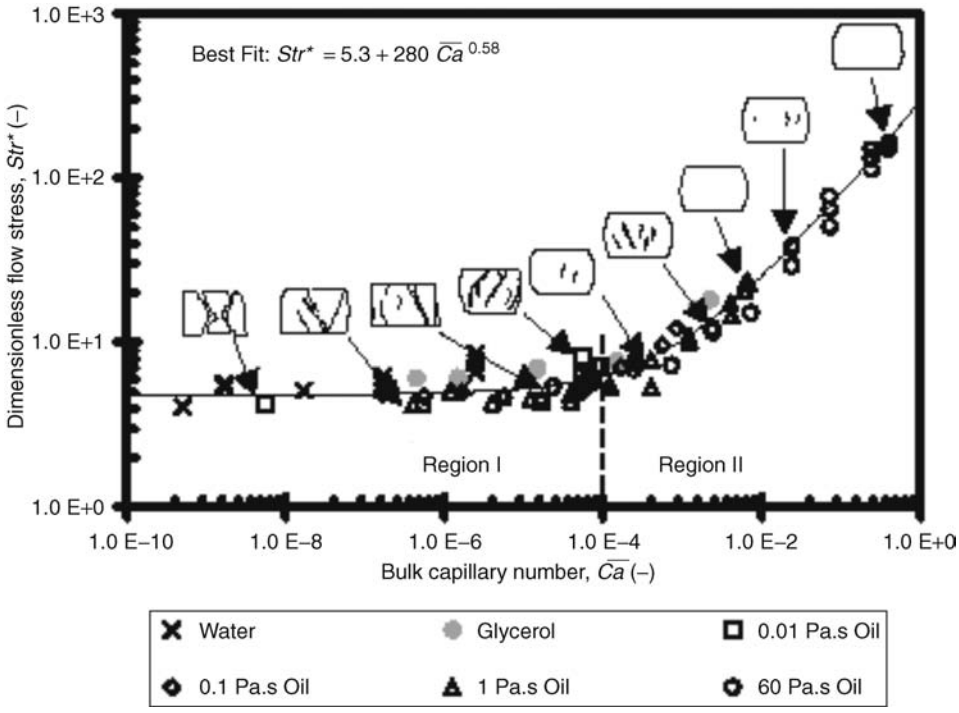


Figure 28 Dimensionless peak flow stress of Figure 26B versus bulk capillary number, for various binder solutions. *Source*: From Ref. 38.

and therefore on surface tension, particle size, and liquid loading. In region 2, for $\mathrm{Ca} > 10^{-4}$, the strength depends on the dynamic pendular bridge, and therefore on binder viscosity and strain rate, in addition to particle size.

Second, Figure 28 does not explicitly depict the role of saturation and compact porosity, these properties are known to affect strength. Decrease in compact porosity generally increases compact yield stress through increases in interparticle friction, whereas increases in saturation lowers yield stress (Fig. 26) (46,48). Hence, the curve of Figure 28 should be expected to shift with these variables.

Third, the static granule or assembly strength [Eq. (1.2)] as originally developed by Rumpf (20–22) is captured by the constant, low Ca value of the yield stress, with this yield stress depending linearly on $\sigma_y^{\mathrm{Peak}} \propto (\gamma/a)$ or:

$$\sigma_y^{\mathrm{Peak}} \approx \sigma_o(\gamma/a) \approx \frac{9}{8}\left(\frac{1-\varepsilon}{\varepsilon}\right)\frac{F_{\mathrm{cap}}}{a^2} \approx \left[\frac{9}{4}\left(\frac{1-\varepsilon}{\varepsilon}\right)\cos\theta\right](\gamma/a) \quad \text{for} \quad \mathrm{Ca} < 10^{-4} \tag{26}$$

Fourth, the mechanism of compact failure depends on strain rate and allowable critical strain rate $(\Delta L/L)_c$. Figure 28 illustrates schematically the crack behavior observed in compacts as a function of capillary number. At low Ca, compacts fail by brittle fracture with macroscopic crack propagation, whereas at high Ca, compacts fail by plastic flow. Large critical strain helps promote plastic flow without rupture, referred to as the *squish test* among process operators.

Within the context of granulation, small yield stresses at low Ca may result in unsuccessful growth when these yield stresses are small compared with breakup forces. With increased yield stress not only comes stronger granules but also decreased deformability. Therefore, high strength might imply a low-deformability growth mechanism for low-shear processes such as a fluid bed. On the other hand, it might imply smaller growth rates for high-shear processes that are able to overcome this yield stress and bring about kneading action and plastic flow in the process. Therefore, it is important to bear in mind that increased liquid

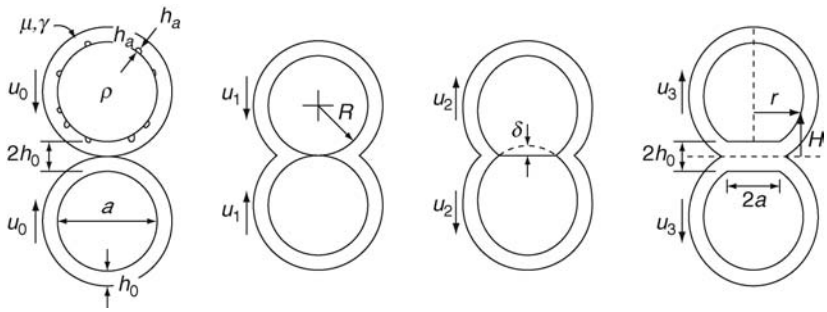


Figure 29 Collisions between surface wet granules, beginning with approach, and ending with separation. Note that no plastic deformation takes place in the original Stokes model. *Source*: From Refs. 4, 49, and 50.

saturation may initially lower yield stress, allowing more plastic deformation during granules collisions. However, as granules grow and consolidate and decrease in voidage, they also strengthen and rise in yield stress, becoming less deformable with time and withstanding shear forces in the granulator. Hence, the desired granule strength and deformability is linked in a complex way to granulator shear forces and consolidation behavior.

Low-Shear, Low-Deformability Growth

For those low-shear processes or formulations that allow little granule deformation during granule collisions, consolidation of the granules occurs at a much slower rate than growth, and granule deformation can be ignored to a first approximation. The growth process can be modeled by the collision of two nearly stiff granules, each coated by a liquid layer of thickness h, as illustrated in Figure 29. For the case of zero plastic deformation as developed by Ennis (4,49), successful coalescence requires that the viscous *Stokes number* $\mathrm{St_v}$ be less than St*, or:

$$\mathrm{St_v} = \frac{4\rho u_0 a}{9\mu} < \mathrm{St}^* \quad \text{where} \quad \mathrm{St}^* = \left(1 + \frac{1}{e_r}\right) \ln(h/h_a) \tag{27}$$

where St* is a critical Stokes number representing the energy required for rebound, u_0 is the relative collisional velocity of the granules, and a is the harmonic average of granule diameter. The Stokes number is one measure of normalized bed agitation energy, representing the ratio of granule collisional kinetic energy to viscous binder dissipation. The binder layer thickness h is related to liquid loading, e_r is the coefficient of restitution of the granules, and h_a is a measure of surface roughness or asperities. This critical condition, given by equation (27), controls the growth of low-deformability systems. This criteria has also been extended to capillary coalescence (4), and for cases of small plastic deformation (50).

Binder viscosity, μ, is a function of local temperature, strain rate (for non-Newtonian binders) and binder concentration dictated by drying rate and local mass transfer and local-bed moisture. It can be controlled as discussed above through judicious selection of binding and surfactant agents and measured by standard rheological techniques (51). The collisional velocity is a function of process design and operating variables, and is related to bed agitation intensity and mixing. Possible choices of u_0 are summarized in Figure 23 and discussed more fully regarding scale-up in chapter 25 and Ref. 52. Note that u_0 is an interparticle *collisional* velocity, not necessarily the local average flow velocity. Three regimes of granule growth may be identified for low-shear/low-deformability processes (4,49), as show for fluid-bed granulation in Figure 30.

Noninertial Regime

For small granules or high binder viscosity lying within a *noninertial regime* of granulation, all values of $\mathrm{St_v}$ will lie below the critical value St* and all granule collisions result in successful growth *provided* binder is present. Growth rate is independent of granule kinetic energy, particle size, and binder viscosity (provided other rate processes are constant). *Distribution of*

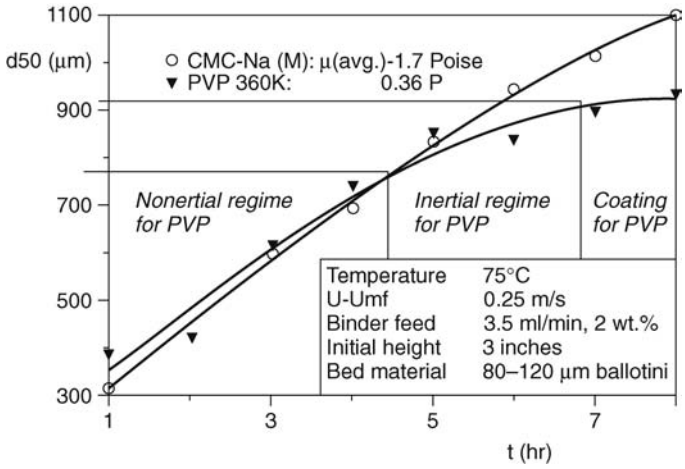


Figure 30 Median granule diameter for fluid-bed granulation of ballotini with binders of different viscosity indicating regimes of growth. *Source*: From Refs. 4 and 49.

binding fluid and *degree of mixing* then control growth, and this is strongly coupled with the rate process of wetting described in the previous section. As shown in Figure 30, both binders have the same initial growth rate for similar spray rates, independent of binder viscosity. (Note that binder viscosity can effect atomization and therefore nuclei distribution through the wetting process.) Increases in bed moisture (e.g., spray rate, drop rate) and increases in granule collisions in the presence of binder will increase the overall rate of growth. Bear in mind, however, that there is a 100% success of these collisions, since dissipation of energy far exceeds the collisional kinetic energy required for breakup/rebound.

Inertial Regime

As granules grow in size, their momentum increases, leading to localized regions in the process where St_v exceeds St*. In this *inertial regime of granulation*, granule size, binder viscosity, and collision velocity determine the proportion of the bed in which granule rebound is possible. Increases in binder viscosity and decreases in agitation intensity increase the *extent of granule growth*—that is, the largest granule that can be grown [D_c of Eq. (19)]. This is confirmed in Figure 30 with the CMC binder continuing to grow whereas the PVP system with lower viscosity slows in growth. Note that the *rate* of growth, however, is controlled by binder distribution and mixing, and not binder viscosity. Increasing binder viscosity will not effect growth rate or initial granule size, but will result in an increased growth limit.

Coating Regime

When the spatial average of St_v exceeds St*, growth is balanced by granule disruption or breakup, leading to the *coating regime of granulation*. Growth continues by coating of granules by binding fluid alone. The PVP system with lower viscosity is seen to reach its growth limit and therefore coating regime in Figure 30.

The exact transitions between granulation regimes depend on bed hydrodynamics. As demonstrated by Ennis et al. (4,5,49), granulation of an initially fine powder may exhibit characteristics of all three granulation regimes as time progresses, since St_v increases with increasing granule size. Implications and additional examples regarding the regime analysis are highlighted by Ennis (4,5,49). Increases in fluid-bed excess gas velocity exhibits a similar but opposite effect on growth rate to binder viscosity; namely, it is observed to not effect growth rate in the initial inertial regime of growth, but instead lowers the growth limit in the inertial regime.

Example: Extent of Noninertial Growth

Growth by coalescence in granulation processes can be modeled by population balances (see chap. 24), where one specifies the mechanism and kernel of growth. For fine powders within the noninertial regime of growth, all collisions result in successful coalescence *provided*

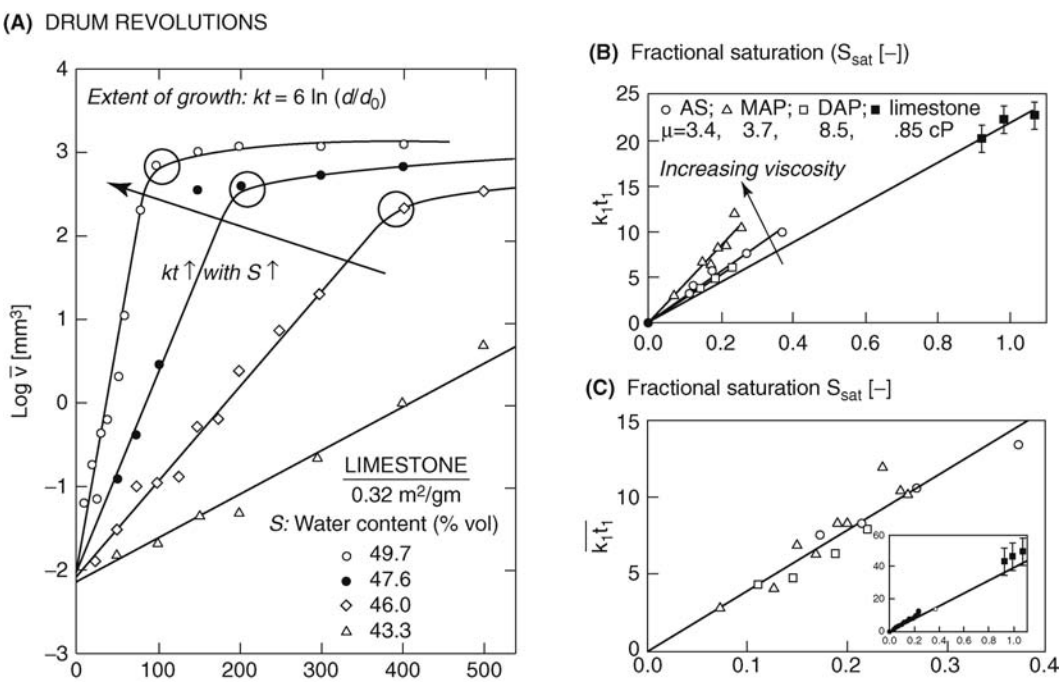


Figure 31 (**A**) Exponential growth in drum granulation reaching a growth limit d_{max}, or maximum extent of growth kt_{max}, which are functions of moisture saturation, (**B**) maximum extent of noninertial growth kt_{max} as a linear function of saturation of the powder feed and binder viscosity, and (**C**) maximum extent normalized for differences in binder viscosity, drum speed, granule density by Stokes number. *Source*: From Refs. 16–19 and 53.

binder is present. Coalescence occurs via a random, size independent kernel $\beta(u, v) = k$ that is only a function of liquid loading y and mixing. In the presence of sufficient binding fluid, it may be rigorously proven that the average granule size increases exponentially with time, or:

$$d = d_0 e^{\mathrm{kt}} \quad \text{where} \quad k = k^* f(y, \text{mixing}) \tag{28}$$

This exponential increase in size with time is confirmed experimentally in Figure 31, where increases in liquid loading increase growth rate. (Note that granule saturation S is connected to liquid loading y and porosity.) On the basis of regime analysis work above, growth will continue in a process while the conditions of equation (27) are met, that is, dissipation exceeds collisional kinetic energy or $\mathrm{St_v} < \mathrm{St}^*$. Examples of these growth limits are seen in fluid beds, drums (16–19), and mixers (Figs. 30–32). Combining Eqs. (27) and (28), the *maximum extent* of granulation kt_{max} occurring within the noninertial regime is given by (53):

$$\ln(d_{\max}) = (\mathrm{kt})_{\max} = 6\ln(\mathrm{St}^*/\mathrm{St}_0) f(y) \propto \ln\left(\frac{\mu}{\rho u_0 d_0}\right) \tag{29}$$

St_0 is the Stokes number based on initial nuclei diameter d_0. Extent kt_{max} is taken as the logarithim of the growth limit in the first random stage of growth, or d_{max}. The maximum diameters (Fig. 31A) are replotted as extents in Figure 31B, which is observed to depend linearly on liquid loading y. Therefore, the maximum granule size depends exponentially on liquid loading, as observed experimentally (Figs. 8 and 31C).

From equation (29), it is possible to scale or normalize a variety of drum granulation data to a common drum speed and binder viscosity. Maximum granule size d_{max} and extent kt_{max} depend linearly and logarithmically, respectively, on binder viscosity and the inverse of agitation velocity. Figure 31C illustrates the normalization of extent kt_{max} for the drum granulation of limestone and fertilizers, correcting for differences in binder viscosity, granule density, and drum rotation speed, with the data collapsing onto a common line following normalization.

High-Shear, Deformable Growth

For high agitation processes involving high-shear mixing or for readily deformable formulations, granule deformability, plastic deformation, and granule consolidation can no longer be neglected as they occur at the same rate as granule growth. Typical growth profiles for high-shear mixers are illustrated in Figure 32. Two stages of growth are evident, which reveal the possible effects of binder viscosity and impeller speed, as shown for data replotted versus impeller speed in Figure 33. The *initial, nonequilibrium stage of growth* is controlled by

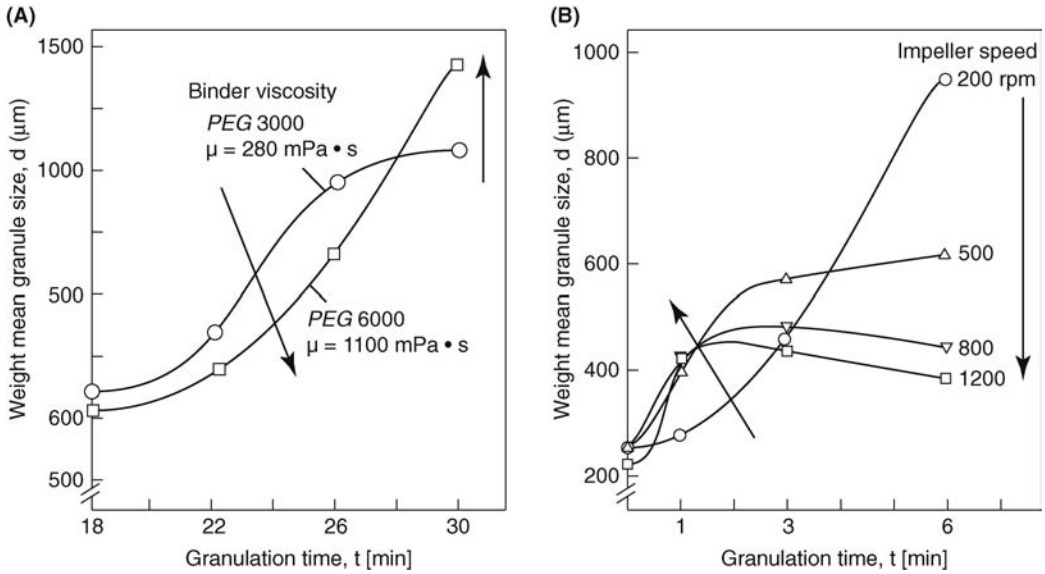


Figure 32 High-shear mixer granulation, illustrating the influence of deformability on growth. Increasing binder viscosity and impeller speed indicated by arrows. (**A**) Ten-liter melt granulation, lactose, 15 weight percent binder, 1400 rpm impeller speed, two different viscosity grades of polyethylene glycol binders. (**B**) Ten-liter wet granulation, dicalcium phosphate, 15 weight percent binder solution of PVP/PVA Kollidon® VA64, liquid loading of 16.8 weight percent and chopper speed of 1000 rpm for varying impeller speed. *Source*: From Refs. 56 and 57.

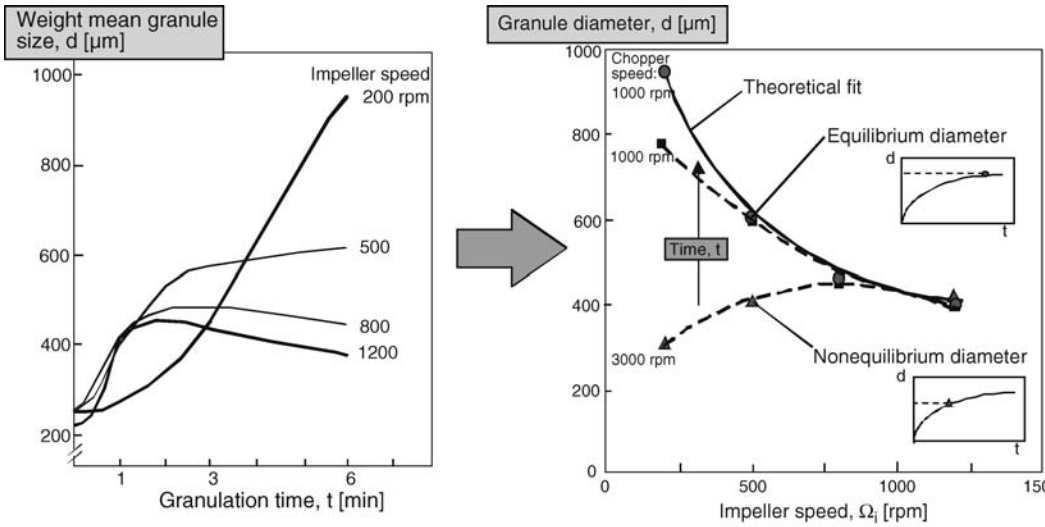


Figure 33 Granule diameter versus impeller speed for both initial nonequilibrium and final equilibrium growth limit for high-shear mixer granulation. *Source*: From Ref. 12.

granule deformability, and is of most practical significance in manufacturing for high-shear mixers. Increases in St due to lower viscosity or higher impeller speed increase the rate of growth, since the system becomes more deformable and easier to kneed into larger granule structures. These effects are contrary to what is predicted from the viscous Stokes analysis based on rigid, low-deformability granules, where high viscosity and low velocity increase the growth limit.

Growth continues until disruptive and growth forces are balanced in the process. This last *equilibrium stage of growth* represents a balance between dissipation and collisional kinetic energy, and so increases in St decrease the final granule size. Note that the equilibrium granule diameter decreases with the inverse square root of the impeller speed, as it should based on $St_v = St^*$, with $u_0 = a(du/dx) = \omega a$.

The viscous Stokes analysis is used to determine the effect of operating variables and binder viscosity on *equilibrium* growth, where disruptive and growth forces are balanced. In the early stages of growth for high-shear mixers, the Stokes analysis, in its present form, is inapplicable. Freshly formed, uncompacted granules are easily deformed, and as growth proceeds and consolidation of granules occur, they will surface harden and become more resistant to deformation. This increases the importance of the elasticity of the granule assembly. Therefore, in later stages of growth, older granules approach the ideal Stokes model of rigid collisions. In addition, the Stokes number controls, in part, the degree of deformation occurring during a collision since it represents the importance of collision kinetic energy in relation to viscous dissipation, although the exact dependence of deformation on St_v is presently unknown.

The Stokes coalescence criteria of equation (27) must be generalized to account for substantial plastic deformation occurring during the initial nonequilibrium stages of growth in high-shear systems. In this case, granule growth and deformation are controlled by a generalization of St_v, or a deformation Stokes number St_{def}, as originally defined by Tardos and colleagues (42,54):

$$St_{def} = \frac{\rho u_o^2}{\sigma_y}\,(\text{impact}) \quad \text{or} \quad \frac{\rho(du/dx)^2 d^2}{\sigma_y}\,(\text{shear}) \tag{30}$$

Viscosity has been replaced by a generalized form of plastic deformation controlled by the yield stress σ_y, which may be determined by compression experiments. As shown previously, yield stress is related to deformability of the wet mass, and is a function of shear rate, binder viscosity and surface tension, primary particle size and friction, and saturation and granule porosity. Critical conditions required for granule coalescence may be defined in terms of the viscous and deformation Stokes number, or St_v and St_{def}, respectively. These represent a complex generalization of the critical Stokes number given by equation (27), and are discussed in detail elsewhere (6,50). In general terms, as the yield stress of a material decreases, there is a relative increase in St_{def}, which leads to an increase in the critical Stokes number St* required for granule rebound, leading to an increase in maximum achievable granule size D_c.

An overall view of the impact of deformability of growth behavior may be gained from Figure 34, where types of granule growth are plotted versus deformability in a regime map, and yield stress has been measured by compression experiments (55). Growth mechanism depends on the competing effects of high-shear promoting growth by deformation on one hand, and the breakup of granules giving a growth limit on the other. For high velocities and low yield stress (high St_{def}), growth is not possible by deformation due to high shear, and the material remains in a crumb state. For low pore saturation, growth is only possible by initial wetting and nucleation, with surrounding powder remaining ungranulated. At intermediate levels of moisture, growth occurs at a steady rate for moderate deformability, but has a delay in growth for low deformability. This delay or *induction time* is related to the time required to work moisture to the surface to promote growth. For high moisture, very rapid, potentially unstable growth occurs. The current regime map, as presented, requires considerable development. Overall growth depends on the mechanics of local growth, as well as the overall mixing pattern and local/overall moisture distribution. Levels of shear are poorly understood in high-shear processes. In addition, growth by both deformation and the rigid

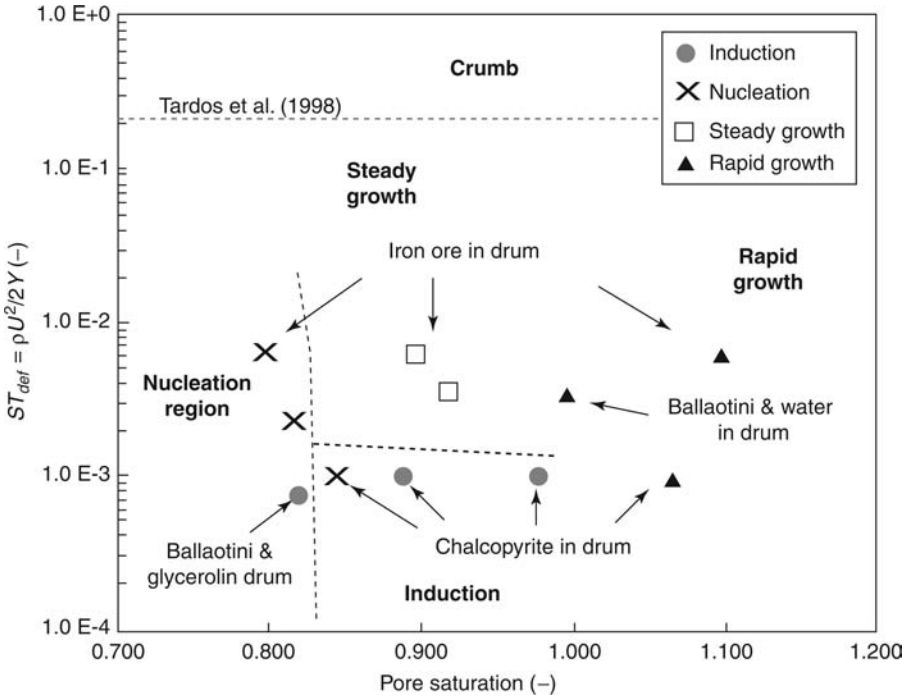


Figure 34 Regime map of growth mechanisms, based on moisture level and deformability of formulations. *Source*: From Ref. 55.

growth model are possible. Lastly, deformability is intimately linked to both granule porosity and moisture. They are not constant for a formation, but depend on time and the growth process itself through the interplay of growth and consolidation. Nevertheless, the map provides a starting point, and is discussed in additional detail in chapter 25.

Example: High-Shear Mixer Growth

An important case study for high deformability growth was conducted by Holm et al. (48) for high-shear mixer granulation. Lactose, dicalcium phosphate, and dicalcium phosphate/starch mixtures (15% and 45% starch) were granulated in a Fielder PMAT 25 VG laboratory scale mixer. Granule size, porosity, power level, temperature rise, and fines disappearance were monitored during liquid addition and wet massing phases. Impeller and chopper speeds were kept constant at 250 and 3500 rpm, respectively, with 7.0 to 7.5 kg starting material. Liquid flow rates and amount of binder added were varied according to the formulation. Power profiles and resulting granule size and porosity are depicted in Figures 35 and 36, respectively. Note that wet massing time (as opposed to total process time) is defined as the amount of time following the end of liquid addition, and the beginning of massing time is indicated in Figure 35.

Clear connections may be drawn between granule growth, consolidation, power consumption, and granule deformability. Noting from Figures 35 and 36 for lactose, there is no further rise in power following the end of water addition (beginning of wet massing), and this corresponds to no further changes in granule size and porosity. In contrast, dicalcium phosphate continues to grow through the wet massing stage, with corresponding continual increases in granule size and porosity. Lastly, the starch formulations have power increases for approximately two minutes into the wet massing stage, corresponding to the two minutes of growth; however, growth ceased when power consumption levels off. Therefore, power clearly tracks growth and consolidation behavior. Lastly, power levels and granule size also tracked temperature rise of the bowl and the level of remaining ungranulated fine powder.

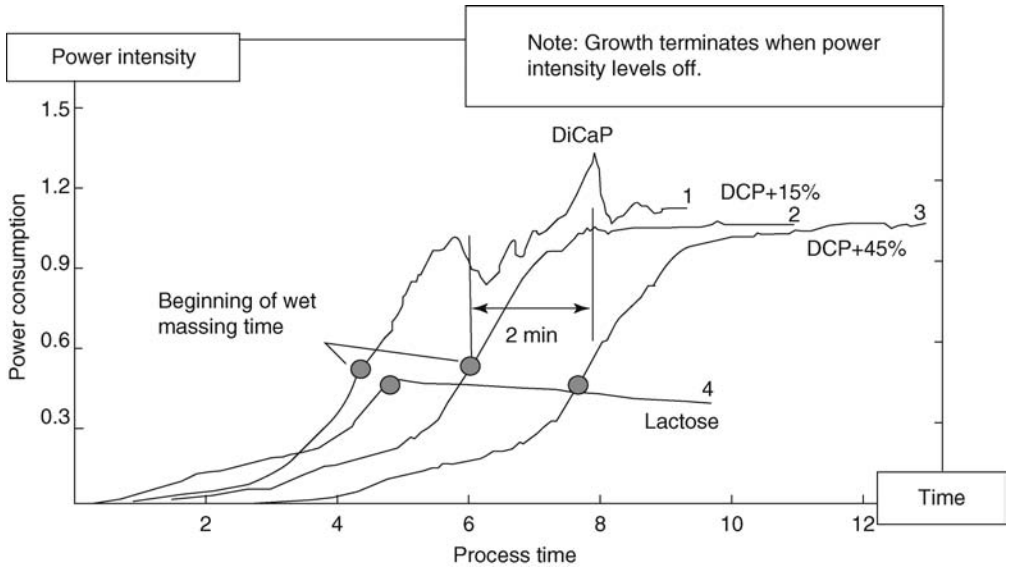


Figure 35 Power consumption for lactose, dicalcium phosphate, and dicalcium phosphate/starch mixtures (15% and 45% starch) granulated in a Fielder PMAT 25 VG. *Source*: From Ref. 48.

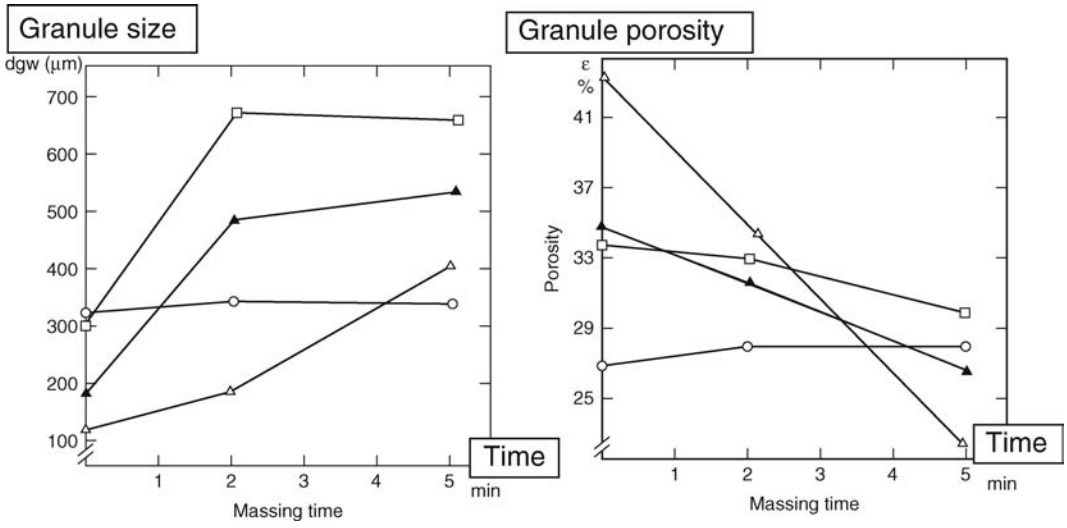


Figure 36 Granule size and porosity versus wet massing time for lactose, dicalcium phosphate and dicalcium phosphate/starch mixtures (15% and 45% starch) granulated in a Fielder PMAT 25 VG. *Source*: From Ref. 48.

Further results connecting power and growth to compact deformability and rheology are provided in Holm (48). The deformability of lactose compacts, as a function of saturation and porosity, is shown to increase with moisture in a stable fashion toward reaching a large critical strain $(\Delta L/L)_c$ required for plastic deformation. Therefore, growth rates and power rise do not lag behind spray addition, and growth ceases with the end of spraying. Dicalcium phosphate compacts, on the other hand, remain undeformable until a critical moisture is reached, after which they become extremely deformable and plastic. This unstable behavior is reflected by an *inductive lag* in growth and power after the end of spray addition, ending with unstable growth and bowl sticking as moisture is finally worked to the surface.

Power, Deformability, and Scale-Up of Growth

In the work of Holm (48), split lots of lactose and dicalcium phosphate exhibited reproducible power curves, suggesting the use of power as a control variable. While it is true that the power is reflective of the growth process, it is a dependent variable in many respects. For *small* variations in physical feed properties, specific power may be used for batch control, or for scale-up, to the extent that the entire bowl is activated. In practice, however, different lots of a formulation can possess different yield properties and deformability, and a different dependence on moisture. Therefore, there may not be a unique relationship between power and growth, or more specifically, unique enough to use power level to compensate for physical property variations of the feed that the control rate processes. *Specific* power is required for scale-up, where power is normalized by the active portion of the powder bed. The impact of scale-up on mixing and distribution of power in a wet mass, however, is only partly understood at this point. In many commercial, vertical high-shear designs, the active portion of the bowl changes greatly with scale, and geometric similarity is not maintained with scale-up. This is much less of a concern with horizontal plow shear designs.

Growth by a high-deformable mechanism requires deformation of wet mass, and therefore work input. Work provides a more natural variable than time, demonstrated in Figure 37, for plant scale wet granulation of a NSAID product with power curves versus time

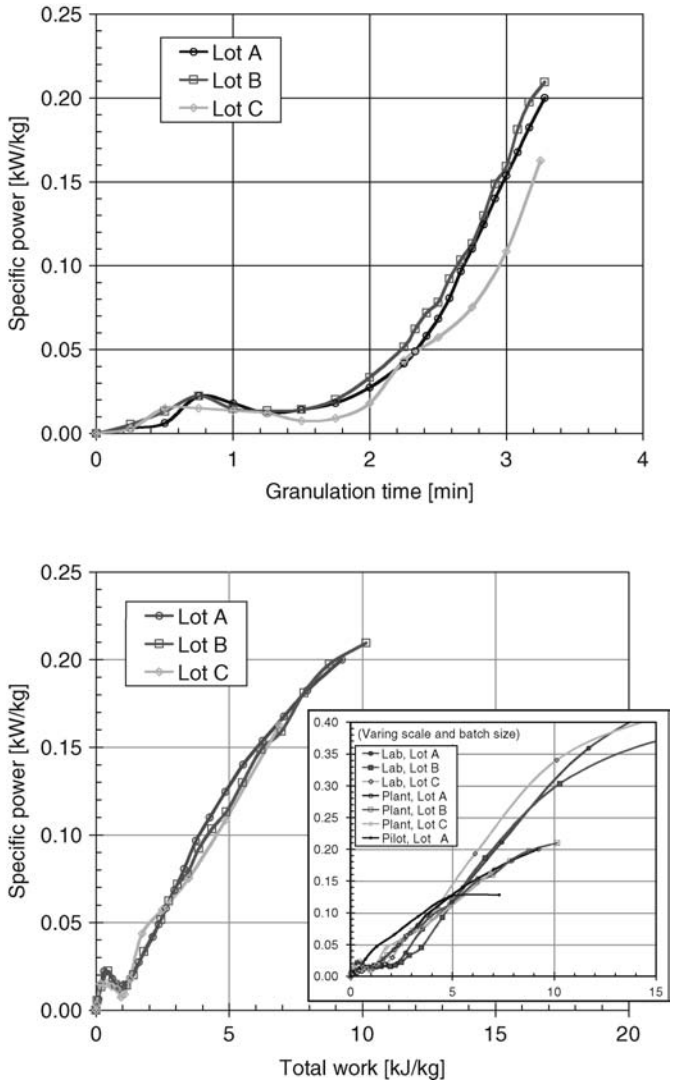


Figure 37 High-shear mixer granulation of NSAID product, plant scale, nominal 300 kg batches, 1000 L. Impeller power versus (**A**) wet mass time, and (**B**) total work input (*inset*: varying batch size and scale, 1 to 1000 L).

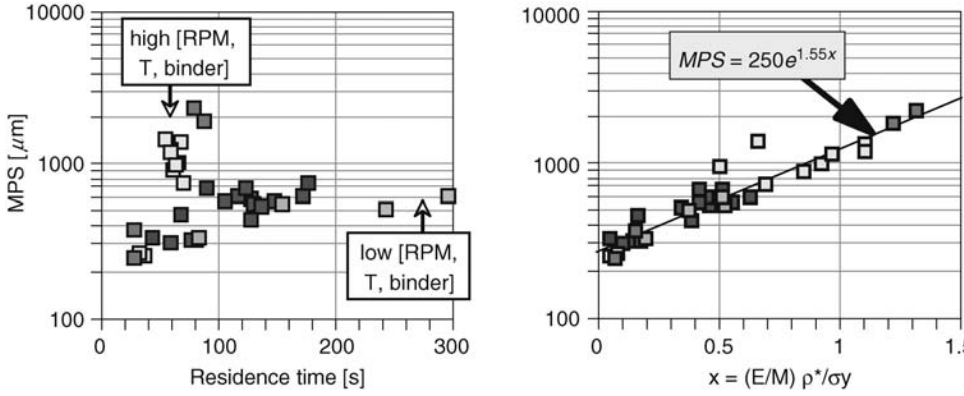


Figure 38 High-shear horizontal mixer granulation. Varying binder content, mixer speed, and temperature. Initial mean particle size 200 μm. (**A**) Mean particle size versus residence time, and (**B**) mean particle size versus normalized specific work. *E*/*M*, specific energy input; σ_y, yield stress. Figure courtesy of Paul Mort.

are replotted versus work input. Power curves from mixer scales of 1 to 1000 l also collapse onto one curve when replotted versus *specific work*. This is consistent with the work of Holm (49), where granule size tracked thermodynamic temperature rise of the mixer bowl, a measure of work input.

The work concept is taken a step further by Cuitino and Bridgwater (58), by plotting growth curves versus specific energy (or work) normalized by yield stress of each formulation, again with growth profiles collapsing onto a common line (Fig. 38). These trials used a high-shear horizontal pin mixer, of varying mixer speed, temperature, and moisture content. Note the equivalence between this normalized energy or work input, and the deformation number of Tardos, or $St_{def} = \rho u_o^2/\sigma_y \sim \rho(E/M)/\sigma_y$.

Determination of St*

The extent of growth is controlled by some limit of granule size, either reflected by the critical Stokes number, St*, or by the critical limit of granule size, D_c. There are several possible methods to determine this critical limit. The first involves measuring the critical rotation speed for the survival of a series of liquid binder drops during drum granulation (5). A second refined version involves measuring the survival of granules in a couette-fluidized shear device (42,54). Both, the onset of granule deformation and complete granule rupture are determined from the dependence of granule shape and the number of surviving granules, respectively, on shear rate. The critical shear rate describing complete granule rupture defines St*, whereas the onset of deformation and the beginning of granule breakdown defines an additional critical value. The third approach is to measure the deviation in the growth rate curve from random exponential growth (59). The deviation from random growth indicates a value of w^*, or the *critical granule diameter* at which noninertial growth ends. This value is related to D_c (Fig. 39). (See chap. 24 regarding modeling for further discussion.) The last approach is through the direct measurement of the yield stress through compression experiments.

Summary of Growth Patterns

Figure 40 summarizes possible *ideal* profiles of the evolution of the granule size distribution, and the impact of the discussed growth mechanisms. For nondeformable growth typical of a fluid-bed or drum granulation, there is an increase in granule size, which is independent of energy and viscous dissipation, and primarily a function of spray rate and contacting (e.g., mixing frequency). For fluid beds, this increase is often linear, whereas for drums, exponential growth is possible on the basis of contact frequency. The demarcation between linear and exponential growth likely depends on spray rate versus mixing rate. Here, attrition has been neglected. In addition, bimodal distributions are possible, with part of the distribution related to ungranulated powder, and the other portion to the granule phase.

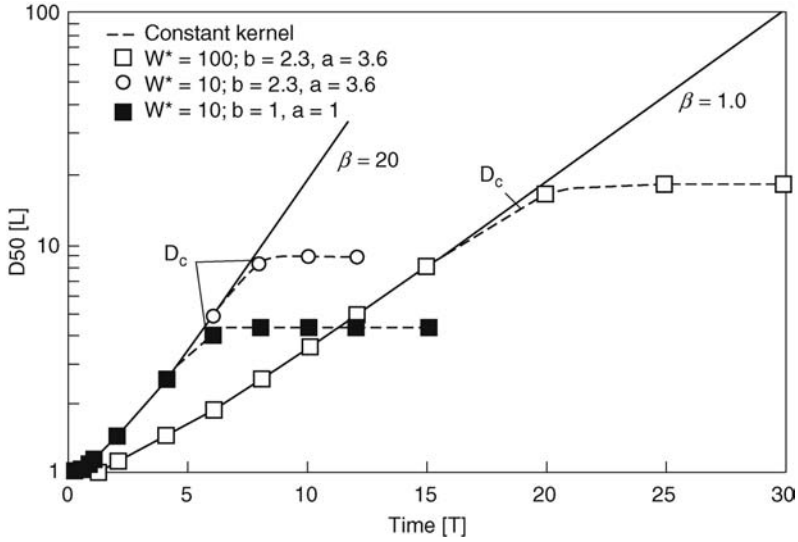


Figure 39 Determination of critical granule growth limit from evolution granule size. *Source*: From Ref. 59.

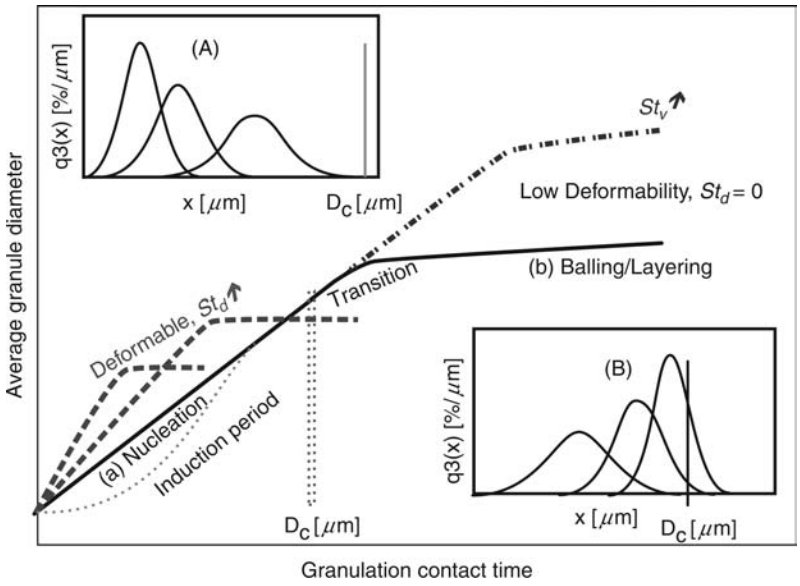


Figure 40 Typical evolution of mean granule size and variance for different growth mechanisms in batch or ideal plug flow systems.

For nuclei less than D_c, the granule size distribution starts at some nuclei distribution, which is a function of the wetting regime, and then widens with time in the nucleation regime. Variance increasing in proportion to average granule diameter under the conditions of self-preserving growth, as shown in the inset Figure 40A (60,61). When the largest granules reach the limiting granule size D_c [Eqs. (27) and (29)], they slow down substantially in their rate of growth as a balling regime is reached, now only able to grow by sticking to the smallest granules of the distribution (based on a harmonic average granule size less than D_c). However, the smaller size portions of granules may grow with all granule size classes. The distribution, therefore, narrows, as it pushes up against D_c, as shown in the inset Figure 40B. The limit of growth increases with lowering shear rates and collisional velocities, or raising binder

viscosity, or increasing bed moisture in this nondeformable growth regime governed by the viscous Stokes number St_v. (Here, we have assumed $St_{def} = 0$.)

As the yield stress of materials decrease, for example, by the introduction of more moisture, or shear rates increase, the deformation Stokes number St_{def} increases as we enter deformable growth. Growth rate increases as St_{def} increases, as illustrated in Figure 40. However, two features remain for this growth mechanism. First, a growth limit is to expected, depending on the yield properties of the formulation. Second, both widening and narrowing regions for the granule variance are possible, depending on the critical growth limit for the process. Lastly, for very stiff formulation, an induction period of no growth is possible, as discussed previously.

Granule Consolidation

Consolidation of granules determines *granule porosity or voidage*, and hence *granule density*. Granules may consolidate over extended times and achieve high densities, if there is no simultaneous drying to stop the consolidation process. The extent and rate of consolidation are determined by the balance between the collision energy and the granule resistance to deformation. The voidage ε may be shown to depend on time as follows:

$$\frac{\varepsilon - \varepsilon_{min}}{\varepsilon_0 - \varepsilon_{min}} = \exp(-\beta t) \quad \text{where} \quad \beta = fn(y, St, St_{def}) \tag{31}$$

Here, y is liquid loading, ε_0 and ε_{min} are, respectively, the beginning and final minimum porosity (62).

The effect of binder viscosity and liquid content are complex and interrelated. For low-viscosity binders, consolidation *increases* with liquid content as shown in Figure 41 (63). This is the predominant effect for the majority of granulation systems, with liquid content related to peak bed moisture on average. Increased drop size and spray flux are also known to increase consolidation. Drying effects peak bed moisture and consolidation by varying moisture level as well as binder viscosity. For very viscous binders, consolidation *decreases* with increasing liquid content (not shown, see ref. 62). As a second important effect, decreasing feed particle size decreases the rate of consolidation because of the high specific surface area and low permeability of fine powders, thereby decreasing granule voidage. Lastly, increasing agitation intensity and process residence time increases the degree of consolidation by increasing the energy of collision and compaction. The exact combined effect of formulation properties is determined by the balance between viscous dissipation and particle frictional losses, and, therefore, the rate is expected to depend on the viscous and deformation Stokes numbers (62).

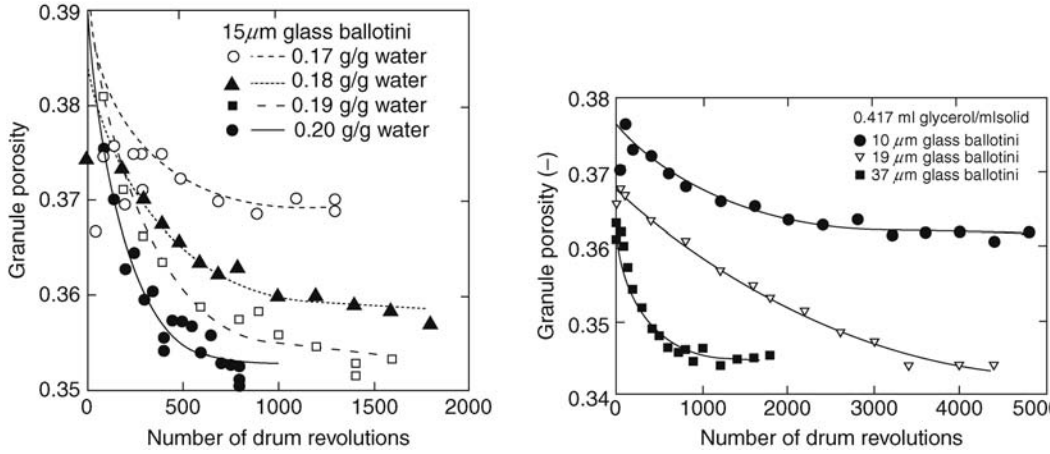


Figure 41 Effect of binder liquid content and primary feed particle size on granule porosity for the drum granulation of glass ballotini. Decreasing granule porosity corresponds to increasing extent of granule consolidation. *Source*: From Ref. 62.

GRANULE STRENGTH AND BREAKAGE

Overview

Dry granule strength impacts three key areas of pharmaceutical processing. These include physical attrition or breakage of granules during the granulation and drying processes, breakage of granule in subsequent material handling steps, such as conveying or feeding, and lastly, deformation and breakdown of granules in compaction processes, such as tabletting. Modern approaches to granule strength rely on *fracture mechanics* (63). In this context, a granule is viewed as a nonuniform physical composite possessing certain macroscopic mechanical properties, such as a generally anisotropic yield stress, as well as an inherent flaw distribution. Hard materials may fail in tension, with the breaking strength being much less than the inherent tensile strength of bonds because of the existence of flaws, which act to concentrate stress.

Bulk breakage tests of granule strength measure *both* inherent bond strength and granule flaw distribution and voidage (3,4,64). Figure 6, presented previously, illustrates granule attrition results for a variety of formulations. Granule attrition clearly increases with increasing voidage; note that this voidage is a function of granule consolidation discussed previously. Different formulations fall on different curves, because of inherently differing interparticle bond strengths. It is often important to separate the impact of bond strength versus voidage on attrition and granule strength. Processing influences flaw distribution and granule voidage, whereas inherent bond strength is controlled by formulation properties.

The mechanism of granule breakage is a strong function of material properties of the granule itself, as well as the type of loading imposed by the test conditions (65). Ranking of the product breakage resistance by ad hoc tests may be test specific, and in the worst case differ from actual process conditions. Instead, material properties should be measured by standardized mechanical property tests that *minimize* the effect of flaws and loading conditions under well-defined geometries of internal stress, as described in the below section.

Mechanics of the Breakage

Fracture toughness, K_c, defines the stress distribution in the body just before fracture and is given by:

$$K_c = Y\sigma_f\sqrt{\pi c} \tag{32}$$

where σ_f is the applied fracture stress, c is the length of the crack in the body, and Y is a calibration factor introduced to account for different body geometries (Fig. 42). The elastic stress increases dramatically as the crack tip is approached. In practice, however, the elastic stress cannot exceed the *yield stress* of the material, implying a region of local yielding at the

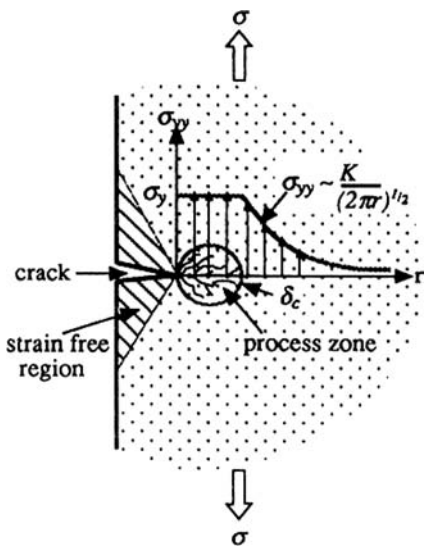


Figure 42 Fracture of a brittle material by crack propagation. *Source*: From Ref. 64.

crack tip. Irwin (66) proposed that this *process zone size*, r_p, be treated as an *effective* increase in crack length δc. Fracture toughness is then given by:

$$K_c = Y\sigma_f\sqrt{\pi(c+\delta c)} \quad \text{with} \quad \delta c \sim r_p \tag{33}$$

The process zone is a measure of the yield stress or plasticity of the material in comparison with its brittleness. Yielding within the process zone may take place either plastically or by diffuse microcracking, depending on the brittleness of the material. For plastic yielding, r_p is also referred to as the *plastic zone size*. The *critical strain energy release rate* $G_c = K_c^2/E$ is the energy equivalent to fracture toughness, first proposed by Griffith (67).

Fracture Measurements

To ascertain fracture properties in any reproducible fashion, specific test geometries must be used as it is necessary to know the stress distribution at predefined, induced cracks of known length. Three traditional methods are: (*i*) the three-point bend test, (*ii*) indentation fracture testing, and (*iii*) Hertzian contact compression between two spheres of the material. Figures 43 and 44 illustrate a typical geometry and force response for the case of a three-point bend test. By breaking a series of dried formulation bars under three-point bend loading of varying crack length, fracture toughness is determined from the variance of fracture stress on crack length, as given by equation (33) (64).

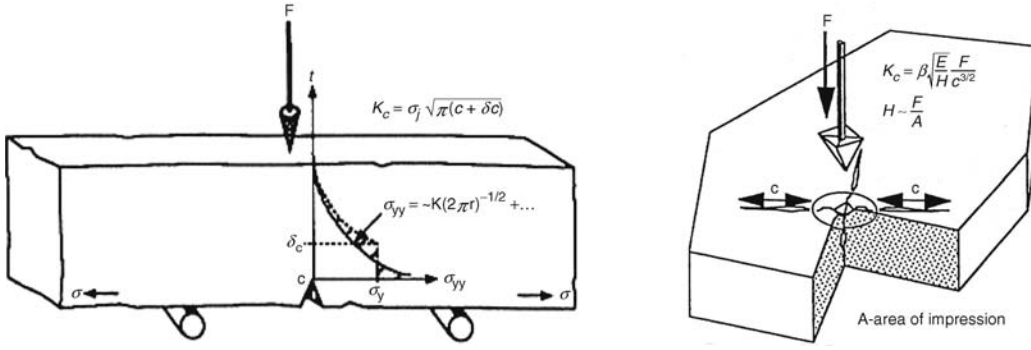


Figure 43 Three-point bend and indentation testing for fracture properties. *Source*: From Ref. 64.

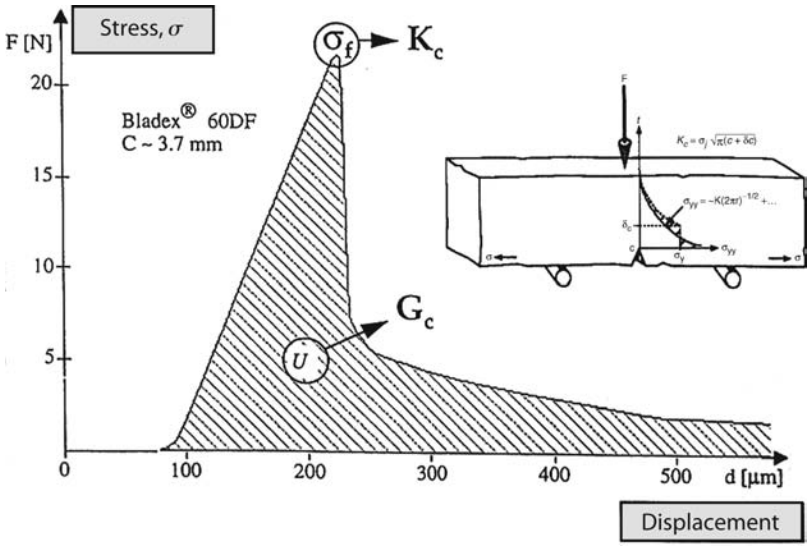


Figure 44 Typical force-displacement curve for three-point bend semistable failure. *Source*: From Ref. 4.

Table 4 Fracture Properties of Agglomerated Materials

Material	Id	K_c (Mpa/m$^{1/2}$)	G_c (J/m^2)	δ_c (μm)	E (MPa)	G_c/E (m)
Bladex 60®[a]	B60	0.070	3.0	340	567	5.29e–09
Bladex 90®[a]	B90	0.014	0.96	82.7	191	5.00e–09
Glean®[a]	G	0.035	2.9	787	261	1.10e–08
Glean® Aged[a]	GA	0.045	3.2	3510	465	6.98e–09
CMC-Na (M)[b]	CMC	0.157	117.0	641	266	4.39e–07
Klucel GF[b]	KGF	0.106	59.6	703	441	1.35e–07
PVP 360K[b]	PVP	0.585	199.0	1450	1201	1.66e–07
CMC 2% 1KN[b]	C2/1	0.097	16.8	1360	410	4.10e–08
CMC 2% 5KN[b]	C2/5	0.087	21.1	1260	399	5.28e–08
CMC 5% 1KN[b]	C5/1	0.068	15.9	231	317	5.02e–08

[a]DuPont corn herbicides.
[b]50 μm glass beads with polymer binder.
Source: From Ref. 64.

In the case of indentation fracture, one determines *hardness*, H, from the area of the residual plastic impression and fracture toughness from the lengths of cracks propagating from the indent as a function of indentation load, F (68). Hardness is a measure of the yield strength of the material. Toughness and hardness in the case of indentation are given by:

$$K_c = \beta\sqrt{\frac{E}{H}}\frac{F}{c^{3/2}} \quad \text{and} \quad H \sim \frac{E}{A} \tag{34}$$

Table 4 compares typical fracture properties of agglomerated materials. Fracture toughness, K_c, is seen to range from 0.01 to 0.06 MPa/m$^{1/2}$, less than that typical for polymers and ceramics, presumably due to the high agglomerate voidage. Critical strain energy release rates G_c from 1 to 200 J/m^2, typical for ceramics but less than that for polymers. Process zone sizes, δc, are seen to be large and of the order of 0.1 to 1 mm, values typical for polymers. Ceramics, on the other hand, typically have process zone sizes less than 1 μm. Critical displacements required for fracture may be estimated by G_c/E, which is an indication of the *brittleness* of the material. This value was of the order of 10^{-7} to 10^{-8} mm for polymer-glass agglomerates, similar to polymers, and of the order of 10^{-9} mm for herbicide bars, similar to ceramics. In summary, granulated materials behave similar to brittle ceramics that not only have small critical displacements and yield strains, but also are similar to ductile polymers that have large process or plastic zone sizes.

Mechanisms of Breakage

The process zone plays a large role in determining the mechanism of granule breakage (64), with such mechanisms previously presented in Figure 7. Agglomerates with process zones smaller in comparison with granule size break by a brittle fracture mechanism into smaller fragments, or *fragmentation* or *fracture*. On the other hand, for agglomerates with process zones of the order of their size, there is insufficient volume of agglomerates to concentrate enough elastic energy to propagate gross fracture during a collision. The mechanism of breakage for these materials is one of *wear*, *erosion*, or *attrition* brought about by diffuse microcracking. In the limit of very weak bonds, agglomerates may also *shatter* into small fragments or primary particles.

Each mechanism of breakage implies a different functional dependence of breakage rate on material properties. Granules generally have been found to have large process zones, which suggests granule wear as a dominant mechanism or breakage or attrition. For the case of *abrasive wear* of ceramics due to surface scratching by loaded indentors, Evans and Wilshaw (69) determined a volumetric wear rate, V, of:

$$V = \frac{d_i^{1/2}}{A^{1/4}K_c^{3/4}H^{1/2}}P^{5/4}l \tag{35}$$

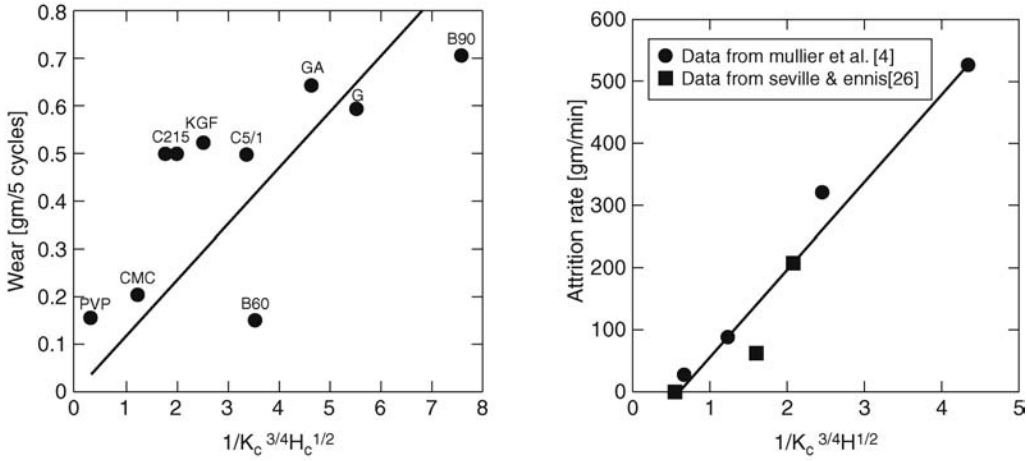


Figure 45 Bar wear rate and fluid-bed erosion rate as a function of granule material properties. K_c is fracture toughness and H is hardness. *Source*: From Ref. 64.

where d_i is indentor diameter, P is applied load, l is wear displacement of the indentor and A is apparent area of contact of the indentor with the surface. Therefore, wear rate depends inversely on fracture toughness.

For the case of fragmentation, Yuregir et al. (70) have shown that the fragmentation rate of organic and inorganic crystals is given by:

$$V \sim \frac{H}{K_c^2} \rho u^2 a \tag{36}$$

where a is crystal length, ρ is crystal density, and u is impact velocity. Note that hardness plays an opposite role for fragmentation than for wear, since it acts to concentrate stress for fracture. Fragmentation rate is a stronger function of toughness as well.

Drawing on analogies with this work, the breakage rates by wear, B_w, and fragmentation, B_f, for the case of fluid-bed granulation and drying processes should be of the form:

$$B_w = \frac{d_0^{1/2}}{K_c^{3/4} H^{1/2}} h_b^{5/4} (U - U_{mf}) \tag{37}$$

$$B_f \sim \frac{H}{K_c^2} \rho (U - U_{mf})^2 a \tag{38}$$

where d is granule diameter, d_0 is primary particle diameter, $(U-U\text{mf})$ is fluid-bed excess gas velocity, and h_b is bed height. Figure 45 illustrates the dependence of erosion rate on material properties for bars and granules undergoing a wear mechanism of breakage, as governed by Eqs. (33) and (37), respectively.

CONTROLLING GRANULATION PROCESSES

An Engineering Approach to Granulation Processes

Future advances in our understanding of granulation phenomena rest heavily on engineering process design. A change in granule size or voidage is akin to a change in chemical species, and so analogies exist between granulation growth kinetics and chemical kinetics and the unit operations of size enlargement and chemical reaction. These analogies are highlighted in Figure 46, where several scales of analysis must be considered for successful process design. Let us begin by considering a small volume element of material A within a mixing process as shown in Figure 47, and consider either the molecular or the primary particle/single granule scale. On the *granule scale of scrutiny*, the design of chemical reactors and granulation processes differ conceptually in that the former deals with chemical transformations whereas the latter

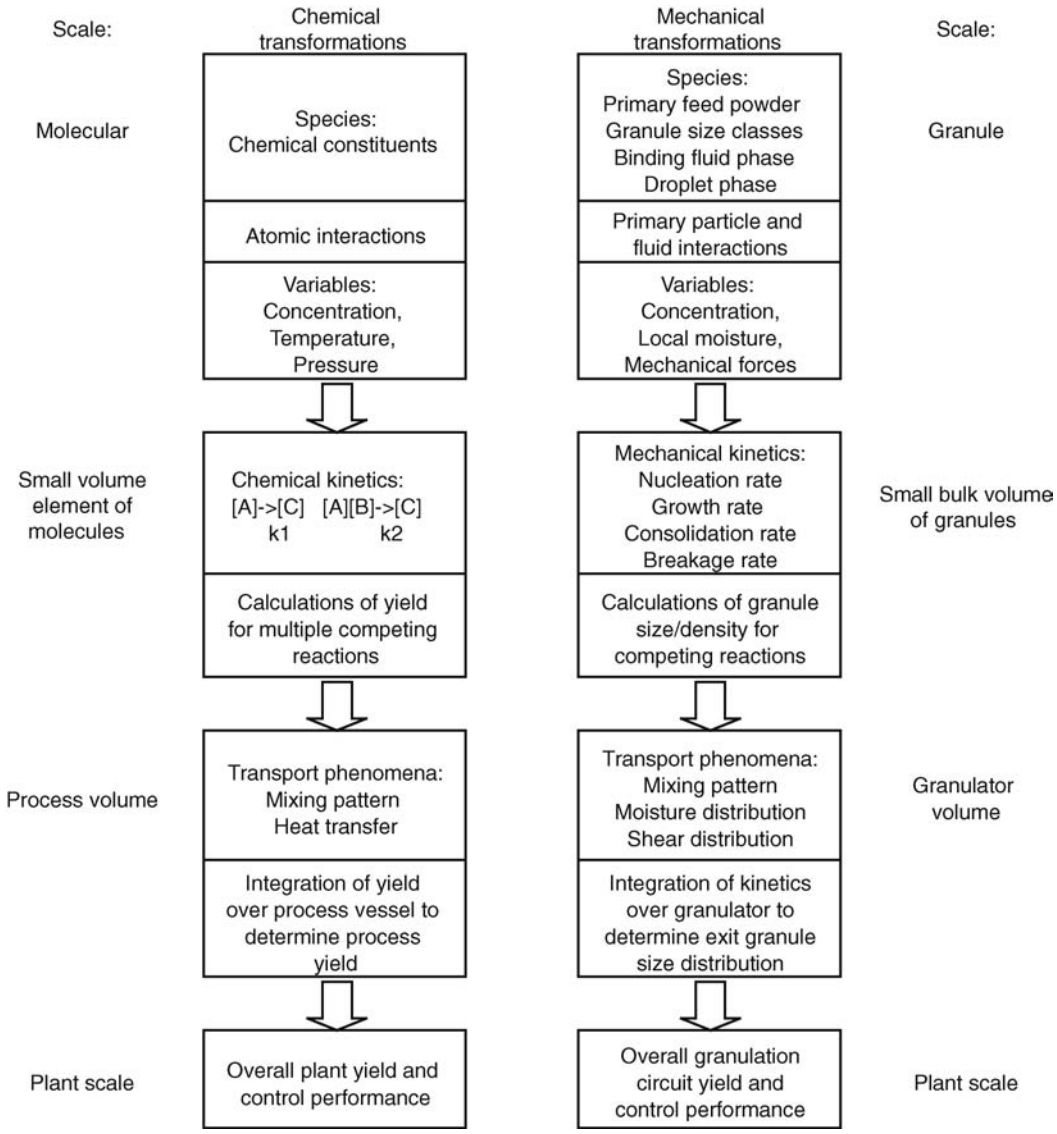


Figure 46 Changes in state as applied to granulator kinetics and design.

deals primarily with *physical transformations* controlled by *mechanical processing*[1] (71–73). Here, the rate processes of granulation are controlled by a set of key *physicochemical interactions*. These rate processes have been defined in the proceeding sections, including wetting and nucleation, granule growth and consolidation, and granule attrition and breakage.

We now consider a *granule volume scale of scrutiny*, returning to our small volume element of material *A* of Figure 47. Within this small volume for the case of chemical kinetics, we generally are concerned with the rate at which one or more chemical species is converted into a product. This is generally dictated by a *reaction rate constant* or *kinetic constant*, which is in turn

[1]This approach was pioneered by Rumpf and others in the early 1960s at the Universität Karlsruhe, leading to development of mechanical process technology within chemical engineering in Germany, or Mechanische Verfahrenstechnik. This was key to the founding of powder technology as a discipline.

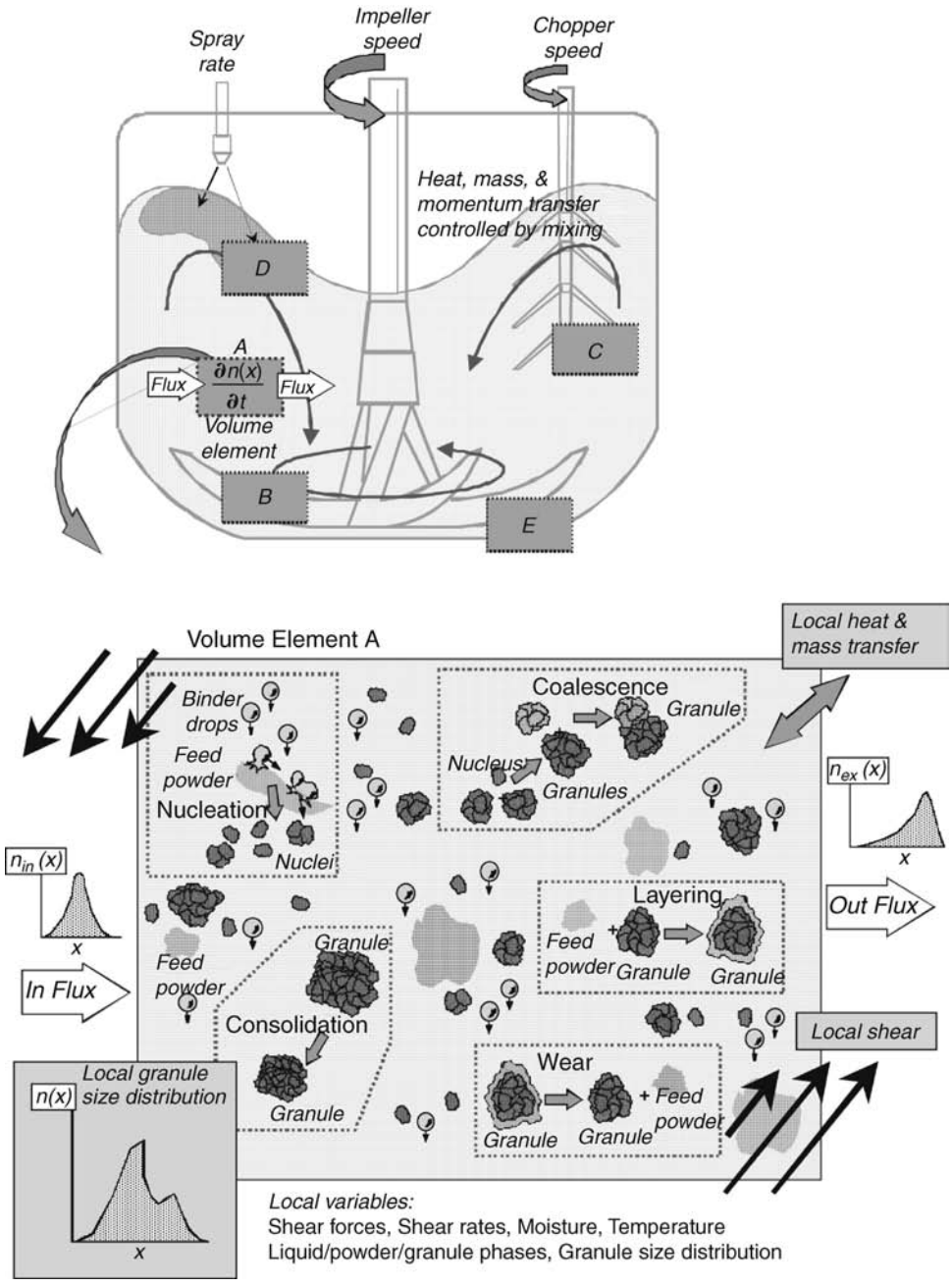


Figure 47 Granulation within a local volume element, as a subvolume of a process granulator volume, which controls local size distribution.

a local function of temperature, pressure, and the concentration of feed species, as was established from previous physicochemical considerations. These local variables are in turn a function of overall heat, mass, and momentum transfer of the vessel controlled by mixing and heating/cooling. The chemical conversion occurring within a local volume element may be integrated over the entire vessel to determine the chemical yield or extent of conversion for the reactor vessel; the impact of mixing and heat transfer is generally considered in this step at the *process volume scale of scrutiny*. In the case of a granulation process, an identical mechanistic

approach exists for design, where chemical kinetics is replaced by granulation kinetics. The performance of a *granulator* may be described by the *extent of granulation* of a species. Let $(x_1, x_2, \ldots, x_n)$ represent a list of attributes such as average granule size, porosity, strength, and any other generic quality metric and associated variances. Alternatively, $(x_1, x_2, \ldots, x_n)$ might represent the concentrations or numbers of certain granule size or density classes, just as in the case of chemical reactors. The proper design of a chemical reactor or a *granulator* then relies on understanding and controlling the evolution (both *time* and *spatial*) of the feed vector X to the desired product vector Y. Inevitably, the reactor or granulator is contained within a larger plant scale process chain, or *manufacturing circuit*, with overall plant performance being dictated by the interaction between individual unit operations. At the *plant scale of scrutiny*, understanding interactions between unit operation can be critical to plant performance and product quality. These interactions are far more substantial with solids processing, than with liquid-gas processing. Ignoring these interactions often leads processing personnel to misdiagnose sources of poor plant performance. Tabletting is often affected by segregation or poor mixing. Segregation becomes vital for preferential wetting and drug assay variation per size class, which can be influenced by trace impurities in the production of drug or excipients.

There are several important points worth noting with regard to this approach. First, the engineering approach to the design of chemical reactors is well developed and an integral part of traditional chemical engineering education (74). At present, only the most rudimentary elements of reaction kinetics have been applied to granulator design. Much more is expected to be gleaned from this approach over the coming decade. Examples might include staged addition of ingredients, micronization of processes, and tailored process designs based on specific formulation properties. Second, an appreciation of this engineering approach is absolutely vital to properly scale-up granulation processes for difficult formulations. Lastly, this perspective provides a logical framework with which to approach and unravel complex processing problems, which often involve several competing phenomena. Significant progress had been made with this approach in crystallization (75) and grinding (76).

Many complexities arise when applying the results of the previous sections detailing granulation mechanisms to granulation processing. The purpose of this section is to summarize approaches to controlling these rate processes by placing them within the context of actual granulation systems and granulator design. Additional details of modeling and granulator design can be found in chapters 24–26.

Scale of a Granule Size and Primary Feed Particles

When considering a scale of scrutiny of the order of granules, we ask what controls the rate processes, as presented in detail in the previous sections. This key step links formulation or material variables to the process operating variables, and successful granulator design hinges on this understanding. Two key local variables of the volume element, A, include the *local-bed moisture* and the local level of shear (both *shear rate* and *shear forces*). These variables play an analogous role of species concentration and temperature in controlling kinetics in chemical reaction, with the caveat that granulation mechanisms are primarily path functions in the thermodynamic sense, with work input as opposed to time controlling deformation mechanisms. In the case of chemical reaction, increased temperature or concentration of a feed species generally increases reaction rate. For the case of granulation considered here, increases in shear rate and moisture result in increased granule/powder collisions in the presence of binding fluid, resulting in an increased frequency of successful growth events and increases in granule growth rate. Increases in shear forces also increase the granule consolidation rate and aid growth for deformable formulations. In the limit of very high shear (e.g., due to choppers), they promote wet and dry granule breakage, or limit the growth at the least. Lastly, in the case of simultaneous drying, bed and gas phase moisture, temperature control heat and mass transfer, and the resulting drying kinetics.

Scale of a Granule Volume Element

Next consider a scale of scrutiny of the level of a small bulk volume of granules, or volume element of material, A, in Figure 46. This volume element has a particular granule size distribution controlled by the local granulation rate processes are shown pictorially in

Figure 47. In the wetting and nucleation rate process, droplets interact with fine powder to form initial nuclei, either directly of through mechanical breakdown of pooled over-wetted regions. It is generally useful to consider the initial *powder phase* and *drop phase* as independent feed phases to the *granule phase*. In addition, the granule phase can be broken down into separate *species*, each species corresponding to a particular granule mesh size cut. Nucleation, therefore, results in a loss of powder and drop phases, and the *birth* of granules. Granules and initial nuclei collide within this volume element with each other and with the surrounding powder phase, resulting in both granule growth and consolidation due to compaction forces. Granule growth by coalescence results in the discrete *birth* of granules to a new granule size class or species, as well as loss or *death* of granules from the originating size classes. This is a rapid, often exponential mechanism, with a widening of the distribution when below the limiting granule size. On the other hand, granule growth by layering and granule consolidation result in a slow differential increase and decrease in granule size, respectively. Granule breakage by fracture and attrition (or wear) act in a similar, but opposite, fashion to granule coalescence and layering, increasing the powder phase and species of smaller granules. Lastly, this volume element of granules interacts with surrounding material of the bed, as granulated, powder, and drop phases flow to and from surrounding volume elements. The rate processes of granulation and the flows or exchanges with surrounding elements combine to control the local granule size distribution and growth rate within this small volume element.

As illustrated in Figure 48, conducting an inventory of all granules entering and leaving a given size class $n(x)$ by all possible granulation mechanisms leads to a microlevel population balance over the volume element given by:

$$\frac{\partial n_{\mathrm{a}}}{\partial t} + \frac{\partial}{\partial x_i}(n_{\mathrm{a}} u_i) = G_{\mathrm{a}} = B_{\mathrm{a}} - D_{\mathrm{a}} \tag{39}$$

where $n(x,t)$ is the instantaneous granule size distribution, which varies with time and position. G, B, and D are growth, birth, and death rates due to granule coalescence and granule fracture. The second LHS term reflects contributions to the distribution from layering and

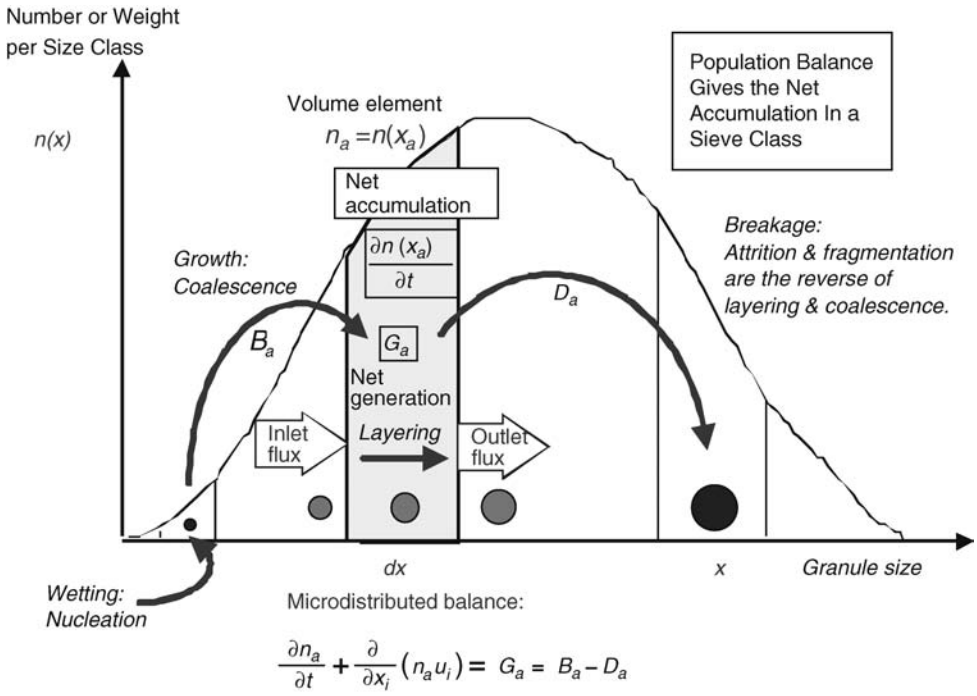


Figure 48 The population balance over a sieve class, or specific granule size class.

wear, as well as interchanges of granules from surrounding volume elements. Nucleation rate would be considered a boundary condition of equation (39), providing a source of initial granules. Equation (39) governs the local growth rate within volume element *A*.

Solutions to this population balance are described in greater detail in chapter 24, as well as in Refs. 6,75, and 76. Analytical solutions are only possible in the simplest of cases. Although actual processes would require specific examination, some general comments are warranted. Beginning with nucleation, in the case of fast drop penetration into fine powders and for small spray flux, new granules will be formed of the order of the drop size distribution, and contribute to those particular size cuts or granule species. If spray is stopped at low moisture levels, one will obtain a bimodel distribution of nuclei size superimposed on the original feed distribution. Very little growth may occur for these low moisture levels. This should not be confused with induction type growth, which is a result of low overall formulation deformability. In fact, the moisture level of the nuclei themselves will be found to be high and nearly saturated. Moisture, however, is locked up within these nuclei, surrounded by large amounts of fine powder. Therefore, it is important not to confuse granule moisture, local moisture, and the overall average peak bed moisture of the process; they are very much not the same but all are influenced by proper vessel design and operation. As moisture levels increase, and the concentration of the ungranulated powder phase decreases, the portion of the granule phase increases. As granules begin to interact more fully because of decreased surrounding powder and greater chances to achieve wet granule interaction, granule coalescence begins to occur. This, in turn, results in a decrease in granule number, and a rapid often exponential increase in granule size as previously demonstrated. Coalescence generally leads to an initial widening of the granule size distribution until the granule growth limit is reached, discussed in detail in section "Summary of Growth Patterns" (Fig. 40). As larger granules begin to exceed this growth limit, they can no longer coalesce with granules of similar size. Their growth rate drops substantially as they can only continue to grow by coalescence with fine granules or by layering with any remaining fine powder. At this point, the granule size distribution generally narrows with time. This provides a local description of growth, whereas the overall growth rate of the process depends greatly on mixing described next, as controlled by process design.

Scale of the Granulator Vessel

The local variables of moisture and shear level vary with volume element, or position in the granulator, which leads to the kinetics of nucleation, growth, consolidation, and breakage being dependent on position in the vessel, leading to a scale of scrutiny of the vessel size. As shown in Figure 47, moisture levels and drop phase concentration and nucleation will be high at position D. Significant growth will occur at position B because of increased shear forces and granule deformation, as well as increased contacting. Significant breakage can occur at position C in the vicinity of choppers. Each of these positions or volume elements will have their own specific, local granule size distribution at any moment in time.

Solids mixing (3,77) impacts overall granulation in several ways. First, it controls the local shear. Local shear rates and forces are a function of shear-stress transfer through the powder bed, which is in turn a function of mixer design and bed bulk density, granule size distribution, and frictional properties. Local shear rates determine granule collisional velocities. This first area is possibly one of the least understood areas of powder processing, and requires additional research to establish the connection between operating variables and local shear rates and forces. It is also a very important scale-up consideration, as discussed in chapter 25 (3,6,77).

Second, solids mixing controls the interchange of moisture, powder phase, and droplet phases among the local volume elements. Third, it controls the interchange of the granulated phase. Within the context of reaction kinetics (74), one generally considers extremes of mixing between well-mixed continuous, plug flow continuous or well-mixed batch processes. The impact of mixing on reaction kinetics is well understood, and similar implications exist for the impact of mixing on granulation growth kinetics. In particular, well-mixed continuous processes would be expected to provide the widest granule size distribution (deep continuous fluidized beds are an example), whereas plug flow or well-mixed batch processes should result

in narrower distributions.[2] In addition, it is possible to narrow the distribution further by purposely segregating the bed by granule size,[3] or staging the addition of ingredients, though this is a less explored area of granulator design. Lastly, it should be possible to predict effects of dispersion, back-mixing, and dead/stagnant zones on granule size distribution on the basis of previous work regarding chemical reaction kinetics.

Equation (39) reflects the evolution of granule size distribution for a particular volume element. When integrating this equation over the entire vessel, one is able to predict the granule size distribution versus time and position within the granulator. Lastly, it is important to understand the complexities of scaling rate processes on a local level to overall growth rate of the granulator. If such considerations are not made, misleading conclusions with regard to granulation behavior may be drawn. Wide distributions in moisture and shear level, as well as granule size, and how this interacts with scale-up must be kept in mind when applying the detailed description of rate processes discussed in the previous sections. With this phenomenological description of granulation in place, we will now discuss controlling wetting, growth and consolidation, and breakage in practice, as well as the implications for two of the more common pharmaceutical granulation processes, namely fluid-bed and high-shear mixer granulation.

Controlling Processing in Practice

Table 5 summarizes operating variables and their impact on fluid-bed and high-shear mixer granulation. From a processing perspective, we begin with the uniformity of the process in terms of solids mixing. Approaching a uniform state of mixing as previously described will ensure equal moisture and shear levels and, therefore, uniform granulation kinetics throughout the bed; on the other hand, poor mixing will lead to differences in local kinetics. If not accounted for in design, these local differences will lead to a wider distribution in granule size distribution and properties than is necessary, and often in unpredictable fashions—particularly with scale-up.

Increasing fluid-bed excess gas velocity ($U - U_{mf}$) will increase solids flux and decrease circulation time. This can potentially narrow nuclei distribution for intermediate drop penetration times. Growth rates will be minimally affected because of increased contacting, however, the growth limit will decrease. There will be some increase in granule consolidation, and potentially a large increase in attrition. Lastly, initial drying kinetics will increase. Impeller speed in mixers will play a similar role in increasing solids flux. However, initial growth rates and granule consolidation are likely to increase substantially with an increase in impeller speed. The growth limit will decrease, partly controlled by chopper speed.

Fluidized beds can be one of the most uniform processes in terms of mixing and temperature. Powder frictional forces are overcome as drag forces of the fluidizing gas support bed weight, and gas bubbles promote rapid and intensive mixing. In the case of mixers, impeller speed, in comparison with bed mass, promote mixing, with choppers eliminating any gross maldistribution of moisture and over growth.

With regard to bed weight, forces in fluid beds and, therefore, consolidation and granule density generally scale with bed height. As a gross rule of thumb, ideally the power input per unit mass should be maintained with mixer scale-up, related, in part, to swept volume per unit time, as studied by Kristensen and coworkers. However, cohesive powders can be ineffective in transmitting stress, meaning that only a portion of the bed may be activated with shear at large scale, whereas the entire bowl may be in motion at a lab scale. Therefore, mixing may not be as uniform in mixers as it is in fluidized beds. Equipment design also plays a large role, including air distributor and impeller/chopper design for fluid bed and mixers, respectively.

---

[2]*All else being equal*, plug-flow continuous and batch well-mixed processes should produce identical size distributions in the absence of back-mixing. It is very difficult to achieve uniform mixing in practice, with properly operating fluidized bed possibly coming the closest.

[3]Pan granulation is a specific process promoting segregation by granule size. Since large granules interact less with smaller granule size classes, layering can be promoted at the expense of coalescence, thereby narrowing the granule size distribution.

Table 5 Impact of Key Operating Variables in Pharmaceutical Granulation

Effect of changing key process variables	Fluidized beds (including coating and drying)	High-shear mixers
Increasing solids mixing, solids flux, and bed agitation	Increasing excess gas velocity: improves bed uniformity, increases solids flux, decreases solids circulation time, potentially improves nucleation, no effect on noninertial growth rate, lowers growth limit, some increase in granule consolidation, increases granule attrition, increases initial drying kinetics.	Increasing impeller/chopper speed: improves bed uniformity, increases solids flux, decreases solids circulation time, potentially improves nucleation, increases growth rate, lowers growth limit, increases granule consolidation, increases granule attrition.
	Distributor design: impacts attrition and defluidization.	Impeller/chopper design: improvements needed to improve shear transmission for cohesive powders.
Increasing bed weight	Increasing bed height: increases granule consolidation, density and strength.	Increasing bed weight: generally lowers power per unit mass in most mixers, lowering growth rate. Also increasing nonuniformity of cohesive powders, and lowers solids flux and increases circulation time.
Increasing bed moisture (*note*: increasing bed temperature normally acts to lower bed moisture due to drying), increasing residence time	Increases rates of nucleation, growth and consolidation giving larger, denser granules with generally a wider distribution. Distribution can narrow if growth limit is reached. Increases chances of defluidization.	Increases rates of nucleation, growth and consolidation giving larger, denser granules with generally a wider distribution. Distribution can narrow if growth limit is reached. Increases chances of overmassing and bowl buildup.
Increasing spray distribution: lower liquid feed or spray rate, lower drop size, increase number of nozzles, increase air pressure (two-fluid nozzles), increase solids mixing (above)	Largely effected: wettable powders and short penetration times generally required. For fast penetration: decreases growth rate, decreases spread of size distribution, decreases granule density and strength. For slow penetration: poor process choice and defluidization likely.	Less effected: poorly wetting powders and longer penetration time possible. For fast penetration: decreases growth rate, decreases spread of size distribution, decreases granule density and strength. For slow penetration: mechanical dispersion of fluid, little effect of distribution, however, slowing rate of addition minimizes lag in growth rate.
Increasing feed particle size (can be controlled by milling).	Requires increase in excess gas velocity, minimal effect of growth rate, increase in granule consolidation and density.	Increase in growth rate, increase in granule consolidation and density.

Increasing bed moisture and residence time increase overall growth and consolidation. However, it also increases the chances of bed defluidization or overmassing/bowl buildup in fluid beds and mixers, respectively. Increasing bed temperature normally acts to lower bed moisture due to drying. This acts to raise effective binder viscosity and lower granule consolidation and density, as well as initial growth rates for the case of high-shear mixers. This effect of temperature and drying generally offsets the inverse relationship between viscosity and temperature.

Spray distribution generally has a large effect in fluid beds, but in many cases, a small effect in mixers. In fact, fluid-bed granulation is only practical for wettable powders with short drop penetration time, since otherwise defluidization of the bed would be promoted by local pooling of fluid. Mechanical dispersion counteracts this in mixers. There may be benefit, however, to slowing spray rate in mixers for formulation with inductive growth behavior, as this will minimize the lag between spray and growth, as discussed previously.

In summary for the case of fluid-bed granulation, growth rate is largely controlled by spray rate and distribution and consolidation rate by bed height and peak bed moisture. For

the case of mixers, growth and consolidation are controlled by impeller and chopper speed. From a formulation perspective, we now turn to each rate process.

Controlling Wetting in Practice

Typical changes in material and operating variables that improve wetting uniformity are summarized in detail elsewhere (1,3). Improved wetting uniformity generally implies a tighter granule size distribution and improved product quality. Eqs. (7) and (9) provide basic trends of the impact of material variables on wetting dynamics and extent, as described by the dimensionless spray flux and drop penetration time.

Since drying occurs simultaneously with wetting, the effect of drying can substantially modify the expected impact of a given process variable and this should not be overlooked. In addition, simultaneously drying often implies that the *dynamics* of wetting are far more important than the *extent*.

Adhesion tension should be maximized to increase the rate and extent of both binder spreading and binder penetration. Maximizing adhesion tension is achieved by minimizing contact angle and maximizing surface tension of the binding solution. These two aspects work against one another as surfactant is added to a binding fluid, and in general, there is an optimum surfactant concentration for the formulation (31). Surfactant type influences adsorption and desorption kinetics at the three-phase contact line. Inappropriate surfactants can lead to Marangoni interfacial stresses, which slow the dynamics of wetting (28). Additional variables, which influence adhesion tension include (*i*) impurity profile and particle habit/morphology typically controlled in the particle formation stage such as crystallization, (*ii*) temperature of granulation, and (*iii*) technique of grinding, which is an additional source of impurity as well.

Decreases in binder viscosity enhance the rate of both binder spreading and binder penetration. The prime control over the viscosity of the binding solution is through binder concentration. Therefore, liquid loading and drying conditions strongly influence binder viscosity. For processes *without* simultaneous drying, binder viscosity generally decreases with increasing temperature. For processes *with* simultaneous drying, however, the dominant observed effect is that lowering temperature lowers binder viscosity and enhances wetting due to decreased rates of drying and increased liquid loading.

Changes in particle size distribution affect the pore distribution of the powder. Large pores between particles enhance the *rate* of binder penetration, whereas they decrease the final *extent*. In addition, the particle size distribution effects the ability of the particles to pack within the drop as well as the final degree of saturation (78).

The drop distribution and spray rate of binder fluid have a major influence on wetting. Generally, finer drops will enhance wetting, as well as the distribution of binding fluid. The more important question, however, is how large may the drops be or how high a spray rate is possible. The answer depends on the wetting propensity of the feed. If the liquid loading for a given spray rate exceeds the ability of the fluid to penetrate and spread on the powder, maldistribution in binding fluid will develop in the bed. This maldistribution increases with the increasing spray rate, increasing drop size, and decreasing spray area (due to, for example, bringing the nozzle closer to the bed or switching to fewer nozzles). The maldistribution will lead to large granules on one hand and fine ungranulated powder on the other. In general, the width of the granule size distribution will increase and generally the average size will decrease. Improved spray distribution can be aided by increases in agitation intensity (e.g., mixer impeller or chopper speed, drum rotation rate, or fluidization gas velocity) and by minimizing moisture losses due to spray entrainment, dripping nozzles, or powder caking on process walls.

Controlling Growth and Consolidation in Practice

Typical changes in material and operating variables, which maximize granule growth and consolidation, are summarized else in detail elsewhere (1,3). Also discussed are appropriate routes to achieve these changes in a given variable through changes in either the formulation or in processing. Growth and consolidation of granules are strongly influenced by rigid (especially fluid beds) and deformability (especially mixers) Stokes numbers. Increasing St increases

energy with respect to dissipation during deformation of granules. Therefore, the rate of growth for deformable systems (e.g., deformable formulation or high-shear mixing) and the rate of consolidation of granules generally increases with increasing St. St may be increased by decreasing binder viscosity or increasing agitation intensity. Changes in binder viscosity may be accomplished by formulation changes (e.g., the type or concentration of binder) or by operating temperature changes. In addition, simultaneous drying strongly influences the effective binder concentration and viscosity. The *maximum* extent of growth increases with decreasing St and increased liquid loading, as reflected by equation (29). See section "Summary of Growth Patterns" and Figure 40 for additional discussion. Increasing particle size also increases the rate of consolidation, and this can be modified by upstream milling or crystallization conditions.

Controlling Breakage in Practice

Typical changes in material and operating variables, which are necessary to minimize breakage are summarized in detail elsewhere (1,3). Also discussed are appropriate routes to achieve these changes in a given variable through changes in either the formulation or processing. Both fracture toughness and hardness are strongly influenced by the compatibility of the binder with the primary particles, as well as the elastic/plastic properties of the binder. In addition, hardness and toughness increase with decreasing voidage and are influenced by previous consolidation of the granules. While the direct effect of increasing gas velocity and bed height is to increase breakage of dried granules, increases in these variables may also act to increase consolidation of wet granules, lower voidage, and, therefore, lower the final breakage rate. Granule structure also influences breakage rate, for example, a layered structure is less prone to breakage than a raspberry shaped agglomerate. However, it may be impossible to compensate for extremely low toughness by changes in structure. Measurements of fracture properties help define expected breakage rates for a product and aid product development of formulations.

ACKNOWLEGEMENTS

This chapter is the result of many collaborative efforts. Support for initial granulation research was provided by the International Fine Particle Research Institute, G. Tardos and R. Pfeffer of The City College of the City University of New York, and E.I. du Pont de Nemours & Company. On the basis of earlier versions with A. Maraglou of Du Pont, the material was developed into a training course by E&G Associates, and later refined in collaboration with J. Litster of the University of Queensland. All of these collaborations, as well as discussions with P. Mort, A. Adetayo, J. Seville, S. Pratsinis, S. Iveson, K. Hapgood, J. Green, P.C. Kapur, T. Schaefer, and H. Kristensen are acknowledged with great appreciation. Lastly, to the countless granulation ad compaction course participants over the last two decades goes a special thank you.

REFERENCES

1. Ennis BJ. Theory of granulation. In: Parikh D, ed. Handbook of Pharmaceutical Granulation, 2005.
2. Ennis BJ, Litster J. Size enlargement and size reduction. In: Green D, Perry R, eds. Perry's Chemical Engineers' Handbook. Section 21 7th ed. New York: McGraw-Hill, 1994.
3. Ennis BJ, section ed. Solids-solids processing. In: Green D, Perry R, eds. Perry's Chemical Engineers' Handbook. Section 19 8th ed. New York: McGraw-Hill, 2005.
4. Ennis BJ. On the Mechanics of granulation, Ph.D. Thesis, The City College of the City University of New York, University Microfilms International (No.1416, Printed 1991), 1990.
5. Ennis BJ. Design & Optimization of Granulation Processes for Enhanced Product Performance. Nashville: E&G Associates, 1990–2004.
6. Litster J, Ennis BJ. The Science & Engineering of Granulation Processes. Dordrecht, The Netherlands: Kluwer Academic, 2004.
7. Masters K. Spray Drying Handbook. 3rd ed. Wiley, 1979; Spray Drying in Practice. ApS, Denmark: SprayDryConsult International, 2002.
8. Ennis BJ. Characterizing the impact of flow aids on flowability of pharmaceutical excipients by automated shear cell. AAPS Annual Meeting, Baltimore, MD, 2004.
9. Nederman R. Statics and Dynamics of Granular Material. Cambridge University Press, 1990.

10. Ennis BJ. Measuring Powder Flowability: Its Theory and Applications. E&G Associates, Inc., 2009.
11. Stanley-Wood N. Enlargement and Compaction of Particulate Solids. Butterworth & Company Limited, 1983.
12. Ennis BJ. Agglomeration and size enlargement session summary paper. Powder Technol 1996; 88:203.
13. Turton R, Tardos G, Ennis B. Fluidized Bed Coating and Granulation. Yang WC, ed. Westwood: Noyes Publications, 1999:331.
14. Pietsch W. Size Enlargement by Agglomeration. Chichester: Wiley, 1992.
15. Sastry K, Fuerstenau D. In: Sastry KVS, ed. Agglomeration 77. New York: AIME, 1977:381.
16. Kapur PC. Balling and granulation. Adv Chem Eng 1978; 10:55.
17. Kapur PC. Chem Eng Sci 1971; 26:1093.
18. Kapur PC, Fuerstenau DW. Size distributions and kinetic relationships in the nuclei region of wet pelletization. Ind Eng Chem Eng 1966; 5:5.
19. Kapur PC. Chem Eng Sci 1972; 27:1863.
20. Rumpf H. The strength of granules and agglomerates. In: Knepper WA, ed. Agglomeration. New York: Interscience, 1962:379–414.
21. Rumpf H. Particle adhesion. In: Sastry KVS, ed. Agglomeration 77. New York: AIME, 1977:97–129.
22. Augsburger L, Vuppala M. Theory of granulation. In: Parikh DM, ed. Handbook of Pharmaceutical Granulation Technology. New York: Marcel-Dekker, 1997:7–23.
23. Parfitt G. ed. Dispersion of Powders in Liquids. Elsevier Applied Science Publishers Limited, 1986.
24. Hapgood K. Nucleation and binder dispersion in wet granulation, Ph.D. thesis, University of Queensland, 2000.
25. Smith thesis
26. Kossen NWF, Heertjes PM. The determination of the contact angle for systems with a powder. Chem Eng Sci 1965; 20:593.
27. Pan et al. Dynamic Properties of Interfaces & Association Structure. American Oil Chemists' Society Press, 1995.
28. Washburn EW. Phys Rev 1921; 17:273.
29. Bartell FE, Osterhof HJ. Determination of the wettability of a solid by a liquid. Ind Eng Chem 1927; 19:1277.
30. Zisman WA. Relation of the equilibrium contact angle to liquid and solid construction. In: Fowkes FM, ed. Contact Angle, Wettability, & Adhesion, Advances in Chemistry Series, ACS, 43. Washington, DC: American Chemical Society, 1964:1.
31. Ayala R. Ph.D. Thesis, Chemical Engineering, Carnegie Mellon University, 1985.
32. Shaw DJ, Williams R. Introduction to Colloid & Surface Chemistry.London: Butterworths & Company Limited, 1980:273.
33. Fuerstaneau DW, Diao J, Williams MC. Colloids Surf 1991; 60:127.
34. Vargha-Butler EI, In: Botsaris GD, Glazman YM, eds. Interfacial Phenomena in Coal Technology.
35. Aveyard R, Haydon DA. An Introduction to the Principles of Surface Chemistry. London: Cambridge University Press, 1973:70.
36. Lloyd DR, Ward TC, Schreiber HP. eds. ACS Symposium Series 391. Washington DC: ACS, 1989.
37. Aulton ME, Banks M. Proceedings of Powder Technology in Pharmacy Conference, Powder Advisory Centre, Basel, Switzerland, 1979.
38. Aulton et al. J Pharm Pharmacol 1977; 29:59.
39. Gluba et al. Powder Hand Proc 1990; 2:323.
40. Litster et al. Powder Technol 2001; 124:272.
41. Ouchiyama N, Tanaka T. Ind Eng Chem Proc Des Dev 1982; 21:29.
42. Tardos G, Khan MI. AIChE Annual Meeting, Miami, 1995.
43. Ennis BJ, Li J, Tardos G, et al. The influence of viscosity on the strength of an axially strained pendular liquid bridge. Chem Eng Sci 1990; 45(10):3071.
44. Mazzone D, Tardos G, Pfeffer R. The effect of gravity on the shape and strength of a liquid bridge between 2 spheres. J Colloid Interface Sci 1986; 113:544.
45. Iveson SM, Breathe JA, Page NW. The dynamic strength of partially saturated powder compacts: the effect of liquid properties. Powder Technol 2002; 127:149.
46. Holm P et al. Granulation in high speed mixers. I. Effects of process variables during kneading. Powder Technol 1985; 43:213.
47. Adams M, Thornton C, Lian G. Agglomeration & Size Enlargement, Proc 1st Int Particle Technology Forum, Vol. 1, Denver, Co. AIChE, New York, 1994:155–286.
48. Holm P, Schaefer T, Kristensen HO. Parts V and VI. Powder Technol 1985; 43:213–233.
49. Ennis B, Tardos G, Pfeffer R. A microlevel-based characterization of granulation phenomena. Powder Technol 1991; 65:257.

50. Liu LX, Litster JD, Iveson SM, et al. Coalescence of deformable granules in wet granulation processes. AIChE J 2000; 46(3):529.
51. Bird RB, Armstrong RC, Hassager O. Dynamics of Polymeric Liquids, Vol.1. Wiley, 1977.
52. Forrest S, Bridgwater J, Mort PR, et al. Flow patterns in granulating systems. Proceedings of World Congress of Chemical Engineering, Melbourne, Australia, 2001.
53. Adetayo AA, Lister JD, Pratsinis SE, et al., Population balance modeling of drum granulation of materials with wide size distribution. Powder Technol 1995; 82:37.
54. Tardos GI, Khan MI, Mort PR. Critical parameters and limiting conditions in binder granulation of fine powders. Powder Technol 1997; 94:245.
55. Iveson SM, et al. Powder Technol 2001; 117:83.
56. Schaefer T, Holm P, Kristensen HG. Melt granulation in a laboratory scale high shear mixer. Drug Dev Ind Pharm 1990; 16(8):1249.
57. Schaefer T, Holm P, Kristensen G. Wet granulation in a laboratory scale high shear mixer. Pharm Ind 1990; 52(9):1147.
58. Cuitino, Bridgwater.
59. Adetayo A, Ennis B. A unifying approach to modeling granule coalescence mechanisms. AIChE J 1996; 43(4):927.
60. Sastry balling.
61. Pratsinis self preserving reference, or Friedlander.
62. Iveson S, Litster JD, Ennis BJ. Powder Technol 1996; 88:15.
63. Lawn B. Fracture of Brittle Solids. 2nd ed. Cambridge: Cambridge University Press, .
64. Ennis BJ, Sunshine G. On wear mechanism of granule attrition. Tribiol Int 1993; 26:319.
65. Bemros CR, Bridgwater J. A review of attrition and attrition test methods. Powder Technol 1987; 49:97.
66. Irwin GR. Analysis of stresses and strains near the end of a crack traversing a plate. J Appl Mech 1957; 24:361.
67. Griffith AA. The phenomena of rupture and flow in solids. Phil Trans Royal Soc 1920; A221:163.
68. Johnsson NL, Ennis DM. Proc First Int Part Technol Forum, Vol. 2, AIChE, Denver, 1994:178.
69. Evans AG, Wilshaw TR. Quasi-static solid particle damage in brittle solids. I. Observations analysis and implications. Acta Metal 1976; 24:939.
70. Yuregir KR, Ghadiri M, Clift R. Impact attrition of sodium chloride crystals. Chem Eng Sci 1987; 42:843.
71. Rumpf H. Translated Bull FA. Particle Technology. New York: Chapman & Hall, 1975.
72. Ennis BJ, Green J, Davies R. Particle technology: The US legacy of neglect. Chem Eng Prog 1994; 90 (4):32.
73. Ennis B, Green J. Visualizing Pharmaceutical Manufacturing as an Integrated Series of Particle Processes. New York: Interphex, 1995.
74. Levenspiel O. Chemical Reaction Engineering. 2nd ed. New York: Wiley, 1972.
75. Randolph AD, Larson MA. Theory of Particulate Processes. San Diego: Academic Press, Inc., 1988.
76. Prasher CL. Crushing and Grinding Process Handbook. New York: Wiley, 1987.
77. Weinekötter R,. Gericke H. Mixing of Solids. Dordrecht, The Netherlands: Kluwer Academic, 2000.
78. Waldie B. Growth mechanism and the dependence of granule size on drop size in fluidized-bed granulation. Chem Eng Sci 1991; 46:2781.

3 Drug Substance and Excipient Characterization

Lai Wah Chan, Xiang Kou, and Paul W. S. Heng
Department of Pharmacy, National University of Singapore, Singapore

INTRODUCTION

It is well established that the properties of granules, as well as the finished products, are significantly affected by certain properties of the raw materials employed. Characterization of drug substances and excipients is therefore an integral preformulation step. A good knowledge of different test methods is necessary to enable the selection of the most appropriate methods for the wide range of raw materials. The usefulness of the tests to give information on the properties of the raw materials and their effects on the manufacture, functionality, and esthetics of the granules and finished products should be carefully considered to avoid unnecessary testing and additional cost. This chapter aims to provide an overview of the more important properties of raw materials for granulation and the test methods that are available to evaluate these properties. Readers are strongly encouraged to refer to the appropriate references for in-depth discussion of the related scientific theories.

PARTICLE SIZE, SHAPE, AND SURFACE AREA

Particle size is an important physical characteristic of the raw material used in granulation. It has significant influence on the dissolution and bioavailability of the drug in the granules, as well as the flow, packing, and compaction behavior of the bulk powder in the production of granules (1). Segregation of different components in a powder mixture is often attributed to the variation in particle size between the components (2). Particle shape is another important parameter, which can have a significant effect on the bulk properties of a powder. It is well known that spherical particles flow better, pack better, and have a lower surface area to volume ratio than nonspherical particles. In recent years, increasing attention is paid to particle surface area because of its significant influence on drug-carrier interaction in dry-powder inhalation formulations. Particles of the same size may not have the same surface area if the roughness of their surfaces differs significantly. The extent of interaction between particles may not be adequately accounted for by the size of the particles as their surface area also plays an important role. In view of the above effects of particle size, shape, and surface area, it is easy to understand their significant influence on the granulation process and properties of granules produced.

Particle Size

Among the physical characteristics of particles, size is perhaps the most obvious descriptor. Also, particle size can influence many processing operations in product manufacture as well as end product quality. Thus, information on particle size of the raw material is important, and the various methods for assessment of particle size have been extensively studied.

Microscopy

One of the oldest methods for determining particle size involves the examination of the particles placed on a microscope slide using a light microscope with a calibrated scale in the eyepiece. The slide is moved in an orderly manner to avoid repetitive measurements of the same particles. Fine particles, which tend to aggregate, are usually dispersed in a nonsolvent liquid medium for measurement. Popular liquids used are silicone and paraffin oils. It is better to prepare the dispersion directly on the microscope slide used for measurement, and care should be taken to minimize any change to the particle shape and agglomeration in the preparation of the dispersion. The liquid medium used should not cause any dissolution of the particles as this will result in underestimation of the particle size. For small particles,

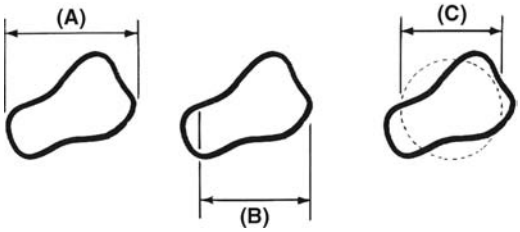


Figure 1 Commonly used particle diameters are the Feret's diameter (**A**), which is the longest horizontal dimension of the particle image; the Martin's diameter (**B**), which is the particle diameter that comprises a theoretical horizontal line that passes through the center of gravity of the particle image; and the projected area diameter (**C**), which is the diameter of a theoretical circle with the same projected area as the particle image.

especially those in the micron range, the scanning electron microscope may be employed to produce sharper images. In the latter method, the sample is prepared by dispersing the particles on double-sided tape and sputter coating with gold. Statistically, at least 625 particles should be measured for accurate results (3), but larger number of particles has been recommended (4). Thus, the microscopy method is tedious and less preferred unless it is used with an image analyzer capable of measuring the particle size from its projected image (5). Examples of projected dimensions are shown in Figure 1.

The microscopy method has several intrinsic drawbacks. There is a natural tendency for the operator to pay greater attention to large particles as they are less likely to be missed. In addition, small particles tend to clump, and this will cause an overestimation of particle size (6). Problem with clarity of image will occur as the particle size approaches the limits of the light microscope optics, which is about 1 μm. Depending on the quality of the lenses, particles may be oversized slightly because of fringe effects. Image resolution may, however, be improved by employing various microscope accessories and dyes to increase the contrast between the particle and its background. Besides the above, the measurement is taken from the top view of the particle, which normally rests in its most stable orientation. As such, it does not give an accurate assessment of the size of particles that deviate from spherical shape.

Recent advances in high-speed digital camera and computer technologies have enabled the development of automated image analysis instruments that are capable of capturing two-dimensional images of particles that are either stationary or mobile when presented in front of the detector. Particles in a dynamic image analysis are distributed within a finite depth defined by the design of the instrument. The test powder is placed in a vibratory chute and then accelerated to a high speed by a Venturi tube located in the sample dispersion line. Images of the particles are captured by a high-speed camera with a synchronized light source. For imaging with sufficient optical contrast, the aperture is modified for the imaging objective to allow only light rays that are parallel to the optical axis to reach the camera. Motion blurring during image acquisition is minimized by the use of a pulsed light source with very short exposure time, of approximately one nanosecond. The images captured are analyzed and converted to the corresponding particle size distributions.

Sieving

Sieving was initially employed for particle classification. Conceptually, particle sizing by sieving is easily understood as the different sieve meshes classify the particles to different weight-based size fractions, giving rise to the weight percent frequency distribution. The typical dry sieving process involves a nest of sieves, usually five to eight, arranged from the coarsest mesh at the top to the finest at the bottom, followed by a receiving pan. The sample is placed in the topmost sieve, which is covered with a lid. The whole assembly is then placed on a sieve shaker, which may gyrate, oscillate, or vibrate the sieves until there is no further change in the weight of material retained on each sieve. The amount of sample used should be sufficient so that the size fraction collected on each sieve can be accurately determined.

The introduction of high-quality standardized woven-wire sieves in a $\sqrt{2}$ progression starting from 75 μm has helped to establish sieving as a widely used particle sizing method, especially for larger particles. Various types of sieves with different aperture sizes are available. These include sieves with aperture size down to about 30 μm, electroformed micromesh sieves (100 μm to a few μm), and sieves with screens that have accurately drilled or

punched circular holes (about 500 μm and larger). Wet sieving is more suitable than the traditional dry sieving for sizing powders that are fine and cohesive. In this method, sieving of the sample starts with the finest mesh to remove the fines with a volume of liquid. The particles retained are resuspended in liquid and then classified using sieves with the largest to smallest aperture sizes. Wet sieving is very tedious as it requires additional drying of the size fractions collected. Air jet sieving is preferred for sizing particles below 75 μm. It involves the use of a vacuum pump to remove air from the underside of a sieve. Air current is also supplied from the underside of the sieve through a rotating arm of jets, which help to unclog the mesh. A collecting cyclone is usually attached in the vacuum line to collect the fines. The sample is sieved using a single mesh and the procedure is repeated using fresh samples of the powder and sieves with different aperture sizes to obtain different size fractions.

Size analysis using sieves has a number of limitations. It is a relatively slow process, and there may be problems with dust pollution. The safety of the operator has to be considered particularly when drug actives are used. In addition, particles tend to pass through the apertures via their narrower cross-sectional area. Hence, the aperture size of a given sieve is not an absolute cutoff value for particle sizing. Inaccurate results will be obtained if the wire mesh used is stretched because of repeated use, the sieve apertures are blanked because of inadequate washing, and small particles aggregate because of cohesive or electrostatic charge. Inadequate sieving time will also produce unreliable data, while too vigorous sieving may cause size reduction, especially with weak agglomerates.

A common point of discontent with size analysis using sieves is that the process requires quite a bit of preparatory work, weighing and subsequent washing. Because of limited availability of sieves of various aperture sizes, a typical analysis would yield seven to eight points on the size distribution plot. This may not be sufficiently discriminating for characterizing powders. Nevertheless, sieving is a straightforward and robust technique for classifying powders and is suitable for a wide variety of fine to very coarse powders.

Sedimentation

Sedimentation technique for particle sizing is based on the settling of particles in a fluid under the influence of gravity, as described by Stoke's law. For a particle of diameter d and density ρ_1, subjected to acceleration due to gravity g, in a fluid of viscosity η and density ρ_2, the gravitational force experienced at its terminal velocity, v, is balanced by the viscous drag and

$$v = \frac{d^2 g(\rho_1 - \rho_2)}{18\eta}$$

The Andreasen pipette introduced in the 1920s is commonly used for sampling from a sedimenting suspension of the test particles in a suitable liquid. Size determination is based on the following principle. As the terminal velocity of a particle varies with its size, the density of the sampled particle suspension will change with time, which enables the calculation of size distribution of the particles. As Stoke's law applies only to spherical particles, the particle size is expressed as Stoke's equivalent diameter. The typical size range measurable by this method is from 2 to 60 μm. The upper limit depends on the viscosity of liquid used, while the lower limit is due to the failure of very small particles to settle as these particles are kept suspended by Brownian motion.

Several innovations have been introduced to improve the speed and sensitivity of the sedimentation sizing method. These include the use of sedimentation onto sensitive weighing pan, turbidity measurements using light or X ray as well as centrifugation to enhance sedimentation of smaller particles. In general, sedimentation sizing method has limited use in pharmaceutical applications.

Electrical Sensing

The electrical sensing zone principle, which is more commonly known as the Coulter principle, is based on the phenomenon where the resistance at the aperture between two compartments containing an electrolyte is proportional to the electrical conducting area of the aperture (Fig. 2).

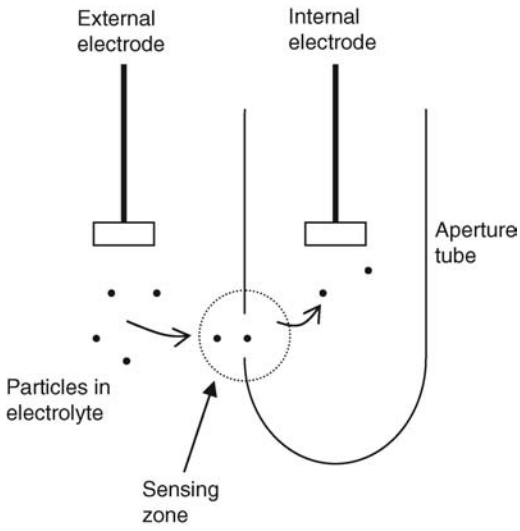


Figure 2 Electrical zone sensing sizer.

By drawing electrolyte from one compartment to the other, particles streaming through will decrease the conducting area of the aperture. Using fast time-based tracing of the resistance pulses, the number of particles passing through the aperture is obtained. The amplitude of the pulse is proportional to the volume of the particle. The electrical sensing zone sizer can analyze a large number of particles within a short time. Particle size range detectable depends on the aperture tube used. Each tube is effective over a size range of about 2% to 60% of its nominal aperture diameter. Apertures of sizes from 10 to 4000 μm are available. Before use, it is necessary to calibrate the equipment with standard latex containing monosized spherical particles of mean size within 5% to 20% of the aperture diameter.

Blockage of small apertures is commonly encountered. Settling of large particles in the electrolyte will give rise to sizing errors, thus setting the upper limit for coarse particles. It is important that the material for sizing is nonconductive and nonporous. The size of porous particles determined has been found to be much smaller than that derived by visual inspection. It is necessary to ensure a low background count of the electrolyte used. Care must be taken to ensure proper dispersion of the test particles, which should not flocculate or dissolve to any extent in the electrolyte (6). The concentration of particles must be within the acceptable range (up to 10,000 particles per second) for the instrument.

Laser Scattering, Light Obscuration, and Photon Correlation Spectroscopy

In recent years, light-scattering and light obscuration techniques have gained popularity as methods for determining particle size down to about 1 μm using Mie theory or Fraunhofer theory. The measurement of submicron particles had been difficult until the introduction of photon correlation spectroscopy for particle sizing. This latter technique enables particles from nanometers to a few microns to be measured.

As a small particle passes through a beam of light in a laser diffraction sizer, it will diffract light, which will be focused onto a diode array detector directly opposite the incident light (Fig. 3).

The detector has a series of photodiodes arranged outward from a central photodiode detector. Since the intensity of the light diffracted decreases as the scatter angle increases, photodiode elements are generally larger as they are further from the center. Calculations for particle size and size distribution involve rather complex mathematics. Simply put, the calculation is based on the angle of diffracted light, with smaller particles diffracting at wider angles than larger particles. Thus, from the scattered light angles and intensities, information on the size distribution of the particles can be obtained through a series of complex calculations.

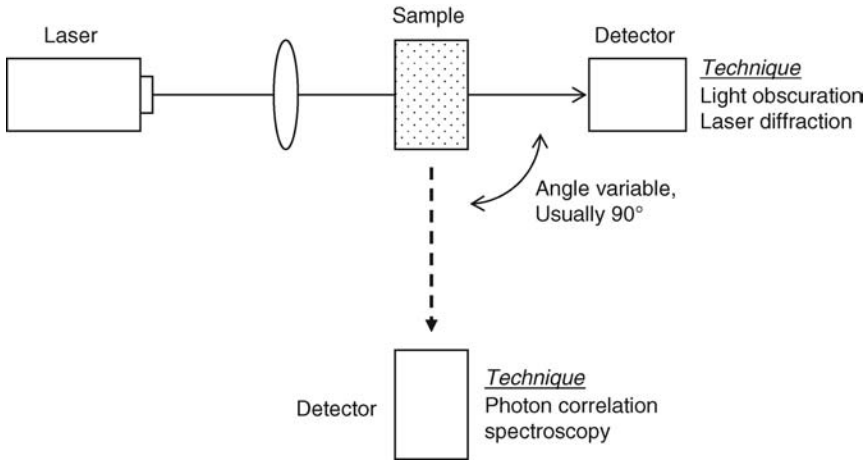


Figure 3 Schematic diagram for the light-scattering particle sizing.

In the light obscuration technique, the passage of each particle across the light beam reduces the amount of transmitted light, which is detected by a sensor directly opposite the incident light. The pulses are then classified to give the frequency of size distribution. The test sample in the light obscuration method is dispersed in an appropriate liquid medium for measurement.

Sizing by the laser diffraction technique may be carried out for powders using the dry-powder module or as dispersions using the wet module. The dry-powder module is used for free-flowing powders, while the wet module is recommended for cohesive powders. The powder sample for the dry module is fed by a vibrating tray and purged by an air jet prior to entering the chamber for measurement. The powder sample for the wet module is dispersed in an appropriate liquid medium, such as alcohol or oil, and is sonicated just prior to measurement (7,8). The complete dislodging of smaller particles adhering on larger ones can be an extremely difficult task, and with different dispersing efforts, different results may be obtained. Moreover, particulate interactive forces, including electrostatic, intermolecular, and capillary forces, could hold particles together, acting as soft aggregates. This would lead to overestimation of particle size and inaccurate size distribution measurement.

Alteration in shape and size of particles should be avoided for powders to be measured, and thus, they are best measured in their dry state. This advantage is particularly important in the case of powders made up of a combination of hydrophilic and lipophilic components, one of which is likely to dissolve partially in the liquid medium used when sizing is carried out with the wet module. However, as previously discussed, the sizing of powders dry with laser diffraction sizer can be fraught with problems. Possible causes of poor reproducibility are the poor control of ambient humidity, cohesive nature of the powder, powder particles breaking down, large size span of the particles, variable rate of feed powder introduction during the measurement period, possible segregation of powders during introduction, and stray powder particles depositing on the lens. The sizing of a powder composed of very large and very small particles can be problematic as a portion of the small particles will adhere onto the larger counterparts and will not be easily dislodged.

Detailed and reproducible particle size information can be obtained in a short measurement time for both the laser diffraction and light obscuration methods. Compared with the microscopy method, the laser diffraction method gives statistically more reliable data for the small particles, especially at the end of the size distribution curve (9), provided that there is little agglomeration or flocculation of particles in the liquid. However, it tends to overestimate the breadth of size distribution for nonspherical particles. On the other hand, the results obtained by the light obscuration method can be affected by the degree of light diffraction, opacity, and orientation of the particles as they pass the beam of light.

In photon correlation spectroscopy, fluctuations in the scattered light intensity are determined. These fluctuations are due to Brownian motion of the test particles suspended in a liquid medium. Larger particles will move more slowly than smaller ones, and therefore, the rate of decay in intensity of the scattered light at a particular measuring point will depend on the size of the particle. The particle size distribution is computed using complex calculations based on the different intensity of scattered light (normally at 90° to the incident beam) and rate of decay. Multiple angle measurements are sometimes applied to improve the quality of the size parameters obtainable.

Time of Flight

This is a relatively new method that is less widely used. The "aerosizer" has been around for quite some time. The test sample is dispersed in air to create an aerosol beam. The resulting individual suspended particles are then accelerated in an airflow. The time of flight (TOF), which refers to the time taken by the particle to travel a specific distance, is then measured by triggering two laser beams and converted to the corresponding particle size (10). The density should be taken into account when the size determined by TOF is converted to a geometric size. The results obtained have been reported to be affected by the feed rate and shear force exerted on the particles by the accelerating airflow. Thus, it is necessary to validate the measurement conditions employed (11).

There are many methods for measuring the size of particles. As discussed, the various methods are based on different principles, and each has its merits and limitations. A preliminary microscopic examination of the test sample is recommended as it will provide useful information, such as approximate particle size range and extent of cohesiveness, for the selection of a method that is appropriate for the test sample. Comparison of different methods is shown in Table 1.

Particle Shape

Despite the well-recognized importance of particle shape, the method of shape determination has not been clearly defined owing to the complexity and variability of the three-dimensional particles. In general, shape measurement methods are only able to define accurately the shape if the latter can be correctly predicted on the basis of a two-dimensional model. Shape of particles may be assessed descriptively by terms such as spherical, elongated, acicular, angular, and a host of other terms. These descriptive terms convey a general idea of the particle shape. Without a comparative quantitative measure, it may be difficult to assess the effects of particle shape on a process or product.

Table 1 Comparison of Different Sizing Methods

Method	Suitable shapes for measurement	Sizing range (μm)		Measurement condition	Particle concentration
		Lower	Upper		
Dynamic image analysis	Spherical, cubic, acicular	0.05	3,500	Wet and dry	Low
Electrical sensing	Spherical, cubic, acicular	0.4	1,600	Wet	Low
Laser diffraction	Spherical, cubic	0.01	5,000	Wet and dry	Low
Light obscuration	Spherical, cubic	0.5	5,000	Wet	Low
Photon correlation spectroscopy	Spherical, cubic, acicular, bladed, fibrous	0.001	10	Wet	Low
Sieve analysis	Spherical, cubic	5	10,000	Wet and dry	High
Scanning electron microscopy	Spherical, cubic, bladed, fibrous	0.001	1,000	Dry	Low
Light optical microscopy	Spherical, cubic, acicular, bladed, fibrous	1	10,000	Wet and dry	Low
Time of flight	Spherical, cubic, acicular, bladed	0.3	500	Wet and dry	Low

Shape has been quantified by the following parameters based on the length, L, breadth, B, projected area, A, perimeter, P, and diameter, d, of the particle (5,12–15) where

elongation ratio or aspect ratio $= L/B$,
circularity $= (4\pi A)/P^2$,
roundness $= P^2/(4\pi A)$ or $(\pi d^2)/4A$, and
bulkiness factor $= A/(L+B)$.

The elongation ratio or aspect ratio is very useful for assessing deviation from a spherical shape to an elongated form. The circularity, commonly also referred to as shape factor or form factor, gives a measure of sphericity, with a perfect sphere having a circularity value of unity. This shape descriptor provides the combined properties of surface roughness and shape. Roundness is the inverse of circularity. The bulkiness factor gives an indication of solidity, with large indentations on the particle giving rise to low values.

To date, particle shape is predominantly determined by image analysis. Indirect methods using techniques such as laser diffraction and photon sedimentation have been studied (16–19). However, these methods are seldom used in practice and hence will not be discussed here. Particle sizing by image analysis has already been discussed in an earlier section. Similar measurement procedures are employed to obtain the outlines of the particles for computing the various shape descriptors.

Particle Surface Area

Compared with particle size and shape, less attention has been paid to particle surface area. The methods for assessing this particle property are also relatively limited. Surface area measurement is usually carried out by either gas permeability or adsorption.

Gas Adsorption

Gas adsorption is carried out by placing a powder sample in a chamber and evacuating the air within. The latter process is commonly referred to as degassing. Upon achieving a very high vacuum, known volumes of an adsorbing gas are introduced. From the knowledge of pressure and temperature before and after introduction of the adsorbing gas, usually nitrogen, calculations of total sample surface area can be made. The surface area determination by gas adsorption is based on a simple principle. From Avogadro's number, a known volume of air at a certain temperature and pressure contains a determinable number of molecules. When various volumes of gas are introduced to a degassed sample, the small pressure changes in the chamber are recorded, and using a calculation technique known as the Brunauer, Emmett, and Teller (BET) method, the initial amount of gas molecules that are adsorbed onto the surface forming a monolayer can be calculated. Thus, the surface area covered by the gas molecules can be determined by multiplying the number of molecules needed with the surface area occupied per molecule. Samples are usually cooled to a low temperature using liquid nitrogen. There are variations in the technique for gas adsorption by different instrument manufacturers.

Gas Permeability

In the gas permeability method, the test powder is packed into a bed through which a gas, usually nitrogen, is passed. It is essential that the bed is uniformly packed. From the volumetric flow rate of the gas and the pressure drop across the bed, solid density, and packed bed porosity, the specific "envelope" surface area of the powder can be calculated using Kozeny-Carman equation. The measurement of specific surface area by gas permeability does not take into account the very small pores or fissures since the flow of gas is not hindered as it passes over them. More accurate measurements can be made by measuring gas flow under reduced pressure, but still, the accuracy cannot match that obtainable by gas adsorption if the total area to be determined includes those of the fine pores. Although gas permeability gives a lower specific area for a powder compared with gas adsorption, the value obtained is sometimes more useful in explaining factors like lubricity and flow, which would not involve

the pores present within the particles. This measurement may be variously referred to as the Blaine method or methods using Fisher sub-sieve sizer or Rigden apparatus.

DENSITY

Density is an important parameter because of its influence on particle mechanical properties (20), powder porosity (21), and powder fluidization (22). The bulk density of a mixed excipient powder used for tablet preparation has been found to affect the disintegration time of the tablet in the mouth (23). Similarly, it can affect the disintegration of granules. On the other hand, the true density can serve to assure the formulator of the identity of the material. Determination of particle density is not straightforward as it can be carried out by many different techniques, with differing interpretations.

Bulk Density

A graduated cylinder is filled with the test sample, followed by slight tapping. The filled volume of the sample is noted, and its mass is determined by weighing. It is a good practice to sieve in the powder when filling the cylinder. Bulk density is obtained by dividing the mass of the sample by its volume.

Tap Density

A graduated cylinder is filled with the test sample and tapped until the volume of the sample in the cylinder does not change. The mass of the sample is determined by weighing. Tap density is obtained by dividing the mass of the sample by its final tapped volume.

True Density

A calibrated pycnometer is used to determine the true volume of the test sample. The true density is obtained by dividing the mass of the sample by its true volume. Samples used for true density measurements should be very dry as vapor pressure of volatiles at low pressure can introduce measurement errors (24,25).

SOLUBILITY

The solubility of drugs and excipients constitutes an important physicochemical property as it affects the rate of drug release into the dissolution medium, bioavailability of the drug, and, consequently, the therapeutic efficacy of the pharmaceutical product. Factors affecting the solubility include nature of solvent, temperature, crystal characteristics, particle size and surface area of the material, pH, and presence of additives.

It must be borne in mind that a drug must first be in solution to be absorbed into the blood circulation. If the solubility of the drug is less than desirable, steps must be taken to improve its solubility or to use another more soluble drug form. Excipients that are poorly soluble in water might retard the release of a drug. Hence, the determination of drug and excipient solubility constitutes an important aspect of formulation study.

The solubility of a material is usually determined by the equilibrium solubility method, in which a saturated solution of the material is obtained by stirring an excess of the material in the solvent for a prolonged period of time at a constant temperature until equilibrium is attained. As a guide, stirring the dispersion overnight is usually adequate for achieving equilibrium solubility. The saturated solution can also be obtained by warming the solvent with an excess of the material and allowing the mixture to cool to the required temperature. This, however, may produce a supersaturated solution for some materials, and therefore, this method is less desirable. A portion of the saturated solution obtained by either method is then removed with the aid of a syringe through a membrane filter at different time intervals for assay. The determination is completed only if at least two successive samples produce the same results. The final value thus obtained is the solubility of the material. The sample may be assayed by a variety of methods, such as ultraviolet spectrophotometry, electrical conductivity measurement, gravimetric or volumetric analysis, and chromatographic methods.

The solution precipitation method is also employed to determine aqueous solubility. It is preferred when the amount of material available for use is low. In this method, a stock solution of the material in dimethylsulfoxide (DMSO) is prepared. The solution is diluted by an

aqueous medium until precipitation occurs. The material in the liquid mixture is then assayed. Precipitation is more accurately detected by the use of a nephelometer or polarized light microscope (26). Solubility values obtained by the solution precipitation method are often higher than the corresponding values obtained by the equilibrium solubility method. This could be attributed to the solubilization effect of DMSO and inadequate incubation time and effect of solid state in the equilibrium solubility method. Large discrepancy in the solubility values obtained is often due to the difference in the physical state of materials in the test. It was reported that the solubility of the crystalline state of a compound could be lower than that of the amorphous state by up to 100-fold (27), while the difference is 2- to 5-fold among crystal polymorphs (28).

CRYSTALLINITY AND POLYMORPHISM

Materials may occur as amorphous substances without any internally ordered structure or as crystalline particles with a definite structure and somewhat regular external shape. Some materials may exist in more than one crystalline form (polymorph) and are described as exhibiting polymorphism. The type of crystal formed depends on the conditions, such as temperature and type of solvent, under which crystallization is induced. At a specific temperature or pressure, more than one polymorph can exist, but only one will be thermodynamically stable. The less stable or metastable form will be converted to the stable form with time.

The different crystalline forms of a material generally differ in many physical characteristics, such as solubility, melting point, optical and electrical properties, density, hardness, and stability. The use of metastable polymorphs frequently results in higher solubility and dissolution rates, while the stable polymorphs are often more resistant to chemical degradation. It is obvious that any change in the crystalline form will affect the therapeutic efficacy of a pharmaceutical product. Drug polymorphism is especially important because it may affect the chemical stability, dissolution rate, bioavailability, efficacy, and safety of the drug. Therefore, knowledge of the crystalline form of the drug and changes to its crystalline form during processing is very important.

Dissolution Study

An amount of the material in excess of its solubility is added to the dissolution medium, and aliquot samples are removed and assayed at appropriate time intervals. The concentration of the material in solution as a function of time is then plotted. The crystalline form that constitutes the material is reflected by the shape of the dissolution curve (Fig. 4).

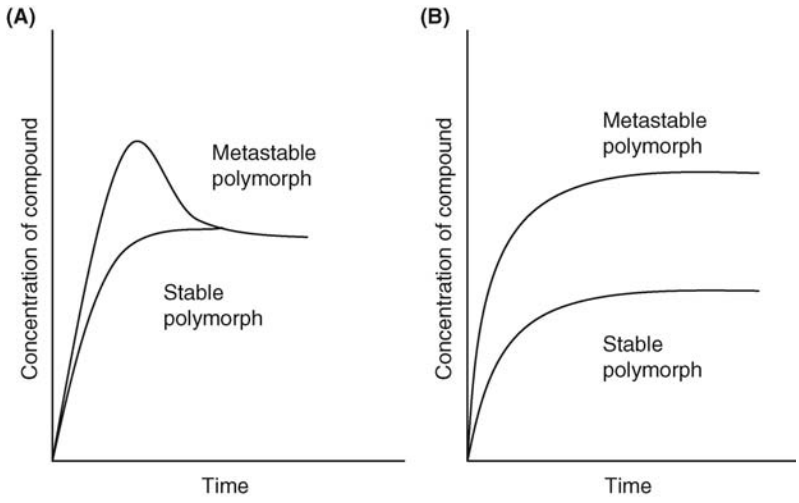


Figure 4 Typical dissolution profiles.

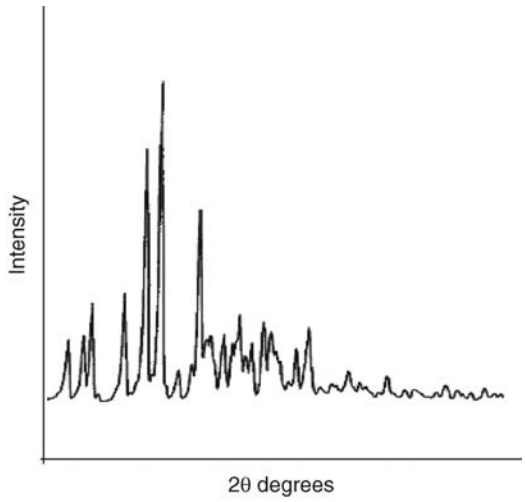


Figure 5 Typical X-ray diffractogram.

The concentration of the metastable polymorph typically increases much more rapidly in the initial period of the dissolution study and then drops to that of the stable polymorph. For the stable polymorph, the dissolution profile increases gradually to a plateau. The solubility of the metastable form is indicated by the peak of its dissolution curve. In some cases, the metastable polymorph does not revert readily to the stable form. The dissolution curve of such a metastable form lies above that of the stable form, indicating that the former is more soluble. The plateau of each curve indicates the solubility of the respective polymorph.

X-ray Diffractometry

X-ray diffractometry may be carried out using a powder X-ray or a single-crystal diffractometer. The latter is used to elucidate the crystal structure, while powder X-ray diffractometer is for general purpose. The polymorphs of a material have different crystal-packing arrangements and thus produce different X-ray diffractograms with characteristic peaks, which are related with lattice distances (Fig. 5).

The extent of conversion of a crystalline drug to the amorphous form during processing can be determined by comparing the magnitude of their characteristic peaks (29). A powder X-ray diffractometer is nondestructive and requires a very small sample of the material, which can be examined without further processing. For structural determination, good single crystals are used in a single-crystal diffractometer. Synchrotron sources have been employed to obtain high-resolution electron diffraction patterns for very small crystals or crystals of complex compounds. Very sensitive charge-coupled detectors have enabled electron diffraction patterns to be recorded in a few seconds using very low electron currents. In addition, microdiffractometers with two-dimensional area detectors have been developed for quick data acquisition (30).

Thermal Analysis

In this method, the polymorphs are identified by their thermal behaviors. The change in energy or related property of the polymorph as it undergoes transformation when it is heated is recorded as a thermogram (Fig. 6).

The thermogram consists of characteristic peaks, including melting point (T_m) and glass transition temperature (T_g). The peaks pointing downward indicate endothermic changes, such as melting, sublimation, and desolvation. The different polymorphs of a material will exhibit different thermograms, which allow them to be identified. Differential scanning calorimetry (DSC) and differential thermal analysis (DTA) are two methods of thermal analyses that are commonly used. The sample is sealed in an aluminum pan and placed inside the test chamber where it is subjected to different heating rates. In DSC, the change in heat

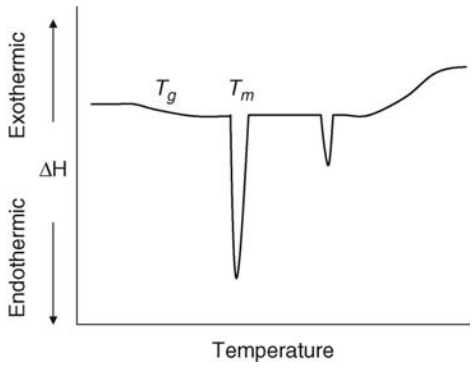


Figure 6 Example of a thermogram.

energy resulting from the crystalline transformation is recorded as a function of temperature. In DTA, the energy is expressed by differential temperature (sample vs. inert substance).

Conventional DSC has a major limitation; if a glass transition temperature occurs in the same temperature range as another transition, for example, water or solvent loss, the two events cannot be separated. This limitation may be overcome by employing modulated temperature DSC (MTDSC), where the measurements are conducted using sine wave temperature programs defined by underlying heating rate, amplitude, and period. The heat capacity change associated with the glass transition temperature can be separated from the heat flow changes caused by melting, drying, and solvent loss. By use of the phase angle curve produced from the MTDSC data analysis, very small changes in specific heat can be detected, thereby increasing the sensitivity of the method. On the basis of thermal behavior, MTDSC is able to differentiate the amorphous and polymorphic forms of a material with much greater clarity. One of the disadvantages of this method is that the data analysis and interpretation are more difficult than that for DSC. In addition, the experiment process can be much prolonged as much lower heating rates are used.

One of the latest techniques is hyperDSC (high-speed or high-performance DSC) where higher measurement sensitivity is achieved by using controlled fast heating and cooling rates of 50°C to 500°C. This is particularly useful for quantification of low levels of amorphous content (31). Microthermal analysis, which combines microscopy with thermal analysis, is another technique introduced recently. Mounted on a three-axis piezoelectric actuator, the microthermal analysis probe functions like an atomic force microscope probe in contact mode, scanning the surface of the sample to determine its topology. As the probe goes over the surface, changes in thermal properties will be recorded and converted to thermal conductivity images that are characteristic of the different polymorphs. The typical scanned surface is 100 μm by 100 μm because the z actuator only has a dynamic range of about 20 μm. As such, microthermal analysis requires relatively flat samples.

Vibrational Spectroscopy

Infrared Spectroscopy

As mentioned earlier, the polymorphs of a material show different crystal-packing arrangements and produce different X-ray diffractograms. The crystal-packing arrangement also affects the energy of molecular bonds and results in different infrared (IR) spectra that are characteristic of the polymorphs. IR analysis can be used for both qualitative and quantitative determinations, especially in the region of near infrared (NIR). It is based on the principle that the peaks in the IR spectrum arise from the stretching or bending vibrations of a particular functional group. The disappearance of a characteristic peak or the appearance of new peak in the IR spectrum of the mixture can be attributed to chemical interaction between the components of the mixture. It is important to use only materials in the solid form as the polymorphs of a material in solution have identical IR spectra.

A combination of NIR spectroscopy and digital imaging technologies allows identification and quantification of the components present in a sample using the spectroscopy element,

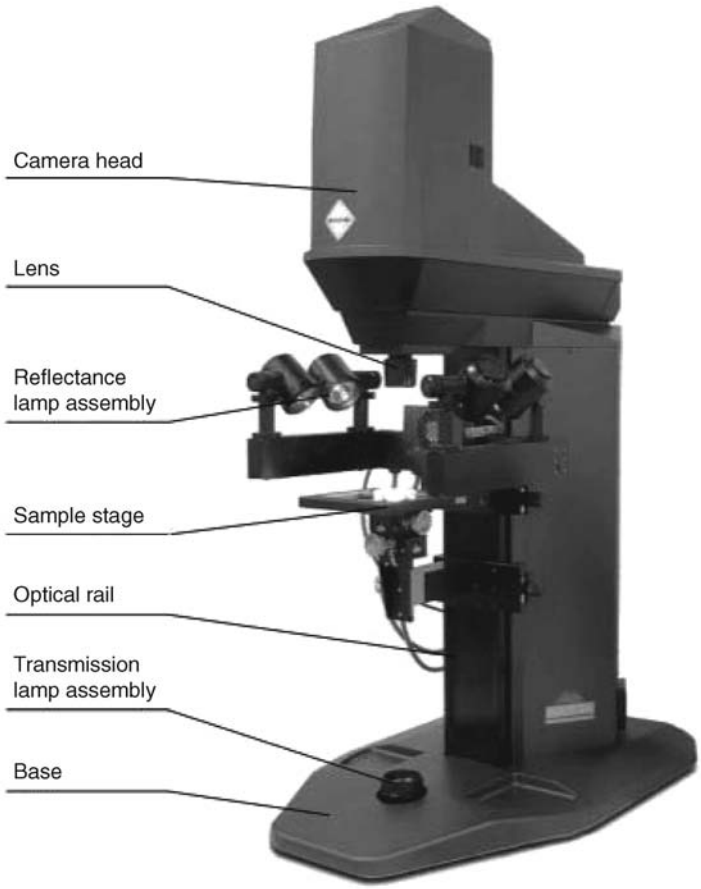


Figure 7 Near infrared chemical imaging instrument. *Source*: Courtesy of Malvern Instruments, Worcestershire, U.K.

but additionally, it is possible to visualize the distribution of the components using the imaging capability (Fig. 7).

The technique is used to investigate the heterogeneity of the distribution within solid samples, visualizing both pharmaceutical excipients and the active. Thus, it is not only possible to gain information about the morphology of the particles or component domains within a sample, but using the NIR spectroscopy element of the data, it is also possible to initially segregate the sample on the basis of chemical differences and then calculate the morphological information for the separate species. This provides numerical metrics for quantitative comparison of different samples (32,33).

Raman Spectroscopy

Raman spectroscopy provides molecular information about the crystalline as well as the amorphous forms of a material. In this method, the material is subjected to a laser beam and a spectrum of the scattered light obtained. The spectrum shows vibrational bands of the material at their characteristic frequencies. The amorphous and polymorphic forms of a material can be distinguished by their characteristic spectra.

Raman spectroscopy and IR spectroscopy complement each other. The former measures a change in polarization, whereas the latter measures a change in dipole moment. IR-inactive vibrations can be strong in Raman spectra, and vice versa. For example, vibrations in the wave number region of 10 to 400/cm are more easily studied by Raman than by IR spectroscopy.

One advantage of the Raman spectroscopy method is that no sample preparation is required, thus, the likelihood of inducing phase changes through sample preparation is avoided. However, representative sampling is critical for quantitative analysis. The results are affected by the particle size of the material. The use of Fourier transform Raman spectrometers with a longer wavelength laser of 1064 nm eliminates the problem of any fluorescent background. With the utilization of fiber optics, real-time crystallization can be monitored. Thus, this method is useful for in-line monitoring of pharmaceutical processes.

Solid-State Nuclear Magnetic Resonance

Solid-state nuclear magnetic resonance (SSNMR) spectroscopy is a more advanced method for differentiating the polymorphs of a material. The sample is placed in a strong magnetic field and subjected to radiofrequency radiation. The individual nuclei experience different magnetic environments and thus show different changes in resonant frequency characterized by chemical shifts. The polymorphs are differentiated by their characteristic spectra. This method is suitable for characterization of solid-state forms that cannot be crystallized and studied by the X-ray diffraction method. It is also useful for quantifying components of heterogeneous mixtures. In contrast to IR and Raman spectroscopy, the results are less affected by the particle size of the test material.

Moisture Sorption

Moisture sorption is performed in a climatic chamber. A balance measures weight changes of the sample exposed to a defined humidity program. In comparison with crystalline materials, the amorphous state is characterized by a higher potential to absorb moisture. This leads to a higher mass increase of amorphous materials in comparison with crystalline materials (34).

Hot-Stage Microscopy

The polarizing microscope fitted with a hot stage is very useful for identifying the crystalline forms of a material. In this method, the polymorph is heated to a temperature at which it undergoes a change in birefringence and/or appearance that is characteristic of the polymorph.

A wide range of methods can be employed to assess polymorphism of materials. In some cases, it is necessary to use a combination of methods to avoid erroneous conclusions obtained from the use of a single method. The detection limits of the different methods are 10% for DSC, 1% to 10% for X-ray diffraction, 1% for Raman spectroscopy, and 0.5% for SSNMR (35).

OTHER PHYSICAL PROPERTIES

It is undoubted that the type of physical characterization tests for a drug or excipient depends very much on the material concerned as well as the processing involved. Material testing can be broadly divided into two types, namely physical testing and functionality testing. Physical testing, which is used to determine properties, such as size, shape, surface area, solubility, and crystal form, is generally more direct, and the procedures are better established. Functionality testing, which evaluates properties, such as flowability, compressibility, and packing property, is less well established. However, such tests may yield useful information about the raw materials and their potential effects on the processing.

Flow Properties

Powder flowability is important for delivery of the powder from the hopper to the die during the tabletting process. Erratic flow of the powder will result in unacceptable variation in the weight of the tablets produced. In addition, uneven powder flow could lead to excess entrapped air within the powder, which, in some high-speed tabletting conditions, may promote capping or lamination. Similarly, powders with poor flowability will move with greater difficulty in the granulation chamber, and this will affect the granulation process and the properties of the granules produced. Knowledge of the flowability of powders, especially of the bulk excipients, is therefore important so that the necessary steps can be undertaken to avoid problems during processing. The Hausner ratio, Carr index, angle of repose, and angle

of slide are parameters that are commonly used to quantify flowability of powders. For poorly flowing powders, the Jenike-type shear test is used.

Hausner Ratio and Carr Index
The tapped density (ρ_t) and bulk density (ρ_b) of the test sample are determined by the methods described previously.

$$\text{Hausner ratio} = \rho_t/\rho_b$$
$$\text{Carr index} = (\rho_t - \rho_b)/\rho_t$$

A higher Hausner ratio (36) indicates poorer flow. On the other hand, a higher Carr index (37,38) indicates better flow. A Carr index value of 1.12 to 1.18 indicates very good flow; 1.19 to 1.25, fair flow; and 1.46 to 1.59, very poor flow.

Angle of Repose
A funnel is mounted vertically and at a distance from a horizontal plate. It is filled with the test sample, which is then allowed to flow down freely to form a conical heap on the plate. A metal tube may also be used in place of the funnel. The tube is placed vertically on the plate and filled with the test sample to a height of about 4 cm. It is then slowly lifted vertically, leaving a conical heap of powder on the plate (5). Using either method, the height of the heap (h) is determined by measuring the distance between the plate and the tip of the heap. The radius of the heap (r) is determined by dividing the diameter of its circular base by 2. The angle of repose is obtained from the inverse tangential of the ratio between h and r (5,39). A smaller angle of repose indicates better flow.

Angle of Slide
This is employed to quantify the flowability of a powder bed. A small amount (about 10 mg) of sample is placed on a stainless steel plane, which is then tilted by screwing a supporting spindle vertically upward until powder slide occurs. The angle of slide is equal to the angle between the tilted plane and the horizontal base at this point (5).

Flowability Determined by Annular Ring Shear Tester
The test powder is overfilled into a shear cell, and the excess is scrapped off with a spatula so that the powder surface is flushed with the upper edge of the shear cell. The powder bed is then subjected to a shear test. Failure of the powder bed is indicated by a sudden drop in shear stress, and the flowability of the powder is calculated using the instrument software (40).

Avalanche Behavior
A flow analyzer is used to study the avalanche behavior of powder. The behavior of a powder under dynamic conditions is a better indicator of its flowability during processing. The flow analyzer consists of a transparent acrylic drum that is rotated along its horizontal axis (Fig. 8).

The drum is partially filled with the test powder and programmed to rotate at different rates. By rotating the drum, the test powder bed is subjected to increased angles of inclination up to an unstable position from which it will avalanche. Detection of the sudden shifts brought about by powder avalanches is achieved by the degree of obliteration of a light source shone across the length of the drum onto an array of photocell located at the opposite end. A metal mesh collar is fitted onto the inner circumference of the drum to prevent the powder from sliding along the circumferential wall instead of avalanching along the free powder surface. The time periods between consecutive avalanches throughout the test duration are recorded, and the data are presented in the form of a discrete phase space map known as a strange attractor plot. The center of this plot is represented by the average time required for a complete avalanche. Spread of points around the center is denoted by the scatter, which refers to the standard deviation of the time between avalanches. The strange attractor plots provide a visual

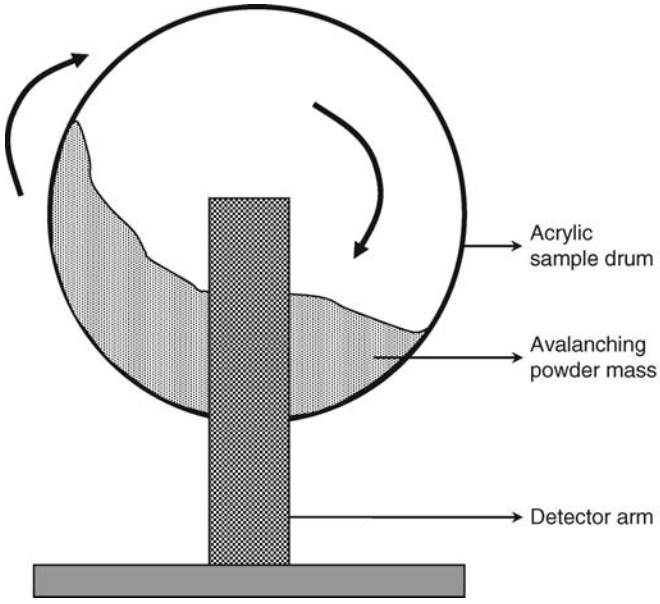


Figure 8 Avalanche powder flowability tester.

comparison of the flow properties of powders. The test is repeated at different drum speeds. From the data, the avalanche flow index (AFI) of the test powder is calculated as follows:

$$\mathrm{AFI} = 1/m$$

where m is the gradient of the graph for average time required for a complete avalanche against drum speed. A larger AFI value indicates better flow. Free-flowing powders generate strange attractor plots that are dense and closer to the origin, and their AFI values are correspondingly small (41).

Compatibility

Although excipients have traditionally been thought of as being inert, experience has shown that they can interact with a drug. Readers are encouraged to refer to the literature on drug-excipient interactions and their effects on drug absorption (42). Incompatibility may occur between drug and excipient, as well as between the excipients themselves, and affect the potency, stability, and, eventually, therapeutic efficacy of the product. It is therefore essential to avoid incompatibility, and this can be achieved by carrying out studies to detect potential chemical interactions between the different components used in the formulation.

Stability Study

This is the traditional method of detecting incompatibility. Mixtures of the drug and excipients are prepared and stored under exaggerated conditions of heat, light, and humidity. The mixtures are examined for any physical change, and aliquot samples are withdrawn for assay of the intact drug at varying time intervals. Incompatibility is reflected by various signs such as appearance of precipitate and decrease in the concentration of the intact drug.

Chromatography

Chromatography was first used for the separation of leaf pigments. The operation of chromatography is based on the distribution of a material between a stationary phase and a mobile phase. The stationary phase can be a solid or a liquid supported on a solid, while the mobile phase can be a gas or a liquid, which flows continuously around the stationary phase. As a result of differences in their affinity for the stationary phase, the different components in a mixture can be separated and identified.

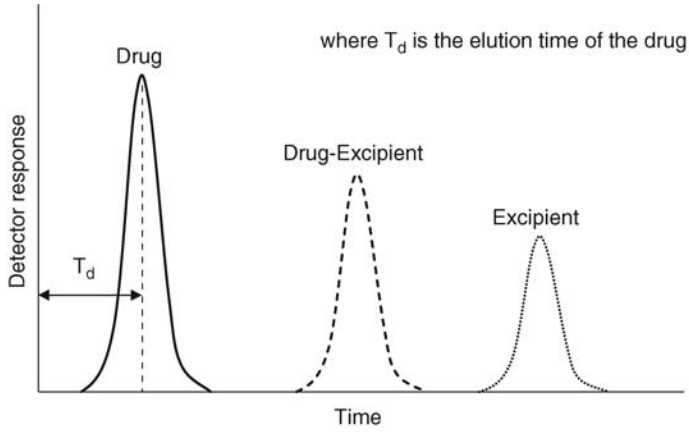


Figure 9 Chromatograms illustrating drug-excipient interaction.

In addition to its application in the separation and identification of materials, chromatography is also employed to detect potential interactions between materials. Both thin-layer chromatography and liquid chromatography are commonly employed for this purpose. In thin-layer chromatography, the stationary phase consists of a powder adhered onto a glass, plastic, or metal plate. The powders commonly used are silica, alumina, polyamides, celluloses, and ion exchange resins. Solutions of the drug, excipient, and drug-excipient mixture are prepared and spotted on the same baseline at one end of the plate. The plate is then placed upright in a closed chamber containing the solvent, which constitutes the mobile phase. As the solvent moves up the plate, it carries with it the materials. Materials that have a stronger affinity for the stationary phase will move at a slower rate. The material is identified by its R_f value, which is defined as the ratio of the distance traveled by the material to the distance traveled by the solvent front. The position of the material on the plate is indicated by spraying the plate with certain reagents or exposing the plate to ultraviolet radiation. If there is no interaction between the drug and excipient, the mixture will produce two spots whose R_f values are identical with those of the individual drug and excipient. If there is interaction, the complex formed will produce a spot whose R_f value is different from those of the individual components.

In liquid chromatography, the affinity of the material for the solid stationary phase in a column governs the time taken by the material to elute from the column. The time of elution is used to identify the material. Solutions of the drug, excipient, and drug-excipient mixture are prepared and injected separately into the column. The concentration of the material that elutes from the column is detected and plotted against time to give a chromatogram. If there is interaction between the drug and excipient, the complex formed will exhibit an elution time different from those of the individual components (Fig. 9). Similarly, gas chromatography may be used for volatile components.

Thermal Methods

DSC offers a relatively simple approach for the investigation of potential interaction between a drug and an excipient (43,44). The drug, individual excipients, and binary mixtures of the drug and excipient are separately scanned at a standard rate over a temperature range that encompasses all the thermal features of the drug and excipients. Each mixture consists of equal proportions of drug and excipient to maximize the likelihood of an interaction. The thermograms of the mixtures and the individual components are compared (Fig. 10).

Interaction is deduced by changes in the thermal features such as disappearance of characteristic peaks or appearance of a new peak in the thermogram of the mixture. Changes in shape, onset, and relative height of the peaks may also indicate interaction. However, it should be cautioned that these changes could also arise from physical mixing of the components or dissolution of components in the first molten substance.

A big advantage of the DSC method over the traditional stability test is the speed of determination. However, like all methods, DSC has its own limitations. It is not applicable

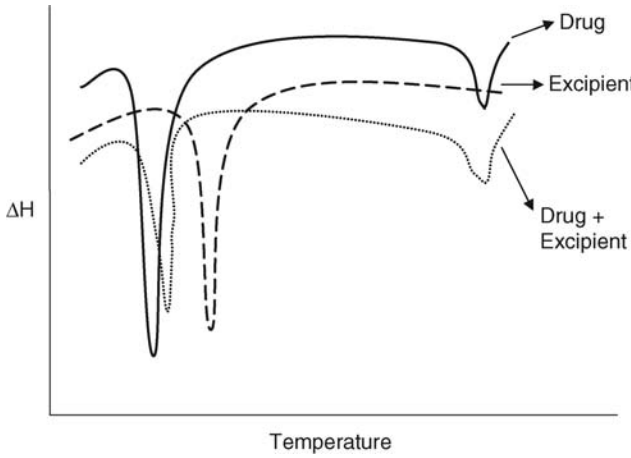


Figure 10 Thermograms indicating possible drug-excipient interaction.

if the test materials exhibit properties that make data interpretation difficult, such as formation of eutectic mixture, coincident melting, and dissolution of one component in the melt of the other. The DSC method has received specific criticism (44) that it subjects drug and excipient to elevated temperatures that are unrealistically high. In addition, the ratio of drug to excipient employed in the test mixture is not likely to be encountered in practice. Furthermore, DSC thermograms do not provide information about the nature of the interaction; they only indicate the likelihood of an interaction. It is therefore not advisable to rely on the DSC method alone to determine incompatibility. Instead, it should be used to supplement stability tests by eliminating the incompatible excipients and reducing the number of samples for stability testing.

Microthermal analysis has also been employed to study interaction. This method is a derivative of atomic force microscopy, whereby the probe is replaced with a miniaturized thermistor, allowing the temperature at the tip of the probe to be both controlled and measured. Different techniques have been employed to study interaction between two materials on the basis of microthermal analysis. In the nanosampling technique, the tip is placed on the surface of one of the test materials, which is heated to soften the surface so that the tip is partially covered with the material. The tip, which is then withdrawn, retains some of the material in the nanogram-to-picogram range. In another technique, known as thermally assisted particle manipulation, the tip is used to pick up a particle of one of the test materials that have been softened by heat. By employing either technique, the tip (laden with the first test material) is placed on the surface of the second test material, which is then subjected to a heating program. Interaction between these two test materials is deduced from the thermal profiles obtained (45).

Other Methods

IR, particularly Fourier transform IR spectrometry, can also be employed to study interaction (44). In the same way, modifications in the spectra obtained by Raman spectroscopy indicate that chemical interactions have occurred. The Raman spectra can be processed to give unambiguous identification of both drugs and excipients, and the relative intensity of the drug and excipient bands can be used for quantitative analysis. This method is very useful, but the equipment is expensive. More information about the different Raman techniques can be obtained from the literature (46).

Unlike most other methods, SSNMR is applicable to materials of varying complexity, from pure drugs and excipients to their solid dispersions (47). Selective investigation of the individual components of the solid dispersions does not usually require any chemical or physical treatment of the sample. However, the complexity and high cost of SSNMR restrict its application as a routine characterization method.

CONCLUSION

The greatest difficulty for any process technologist is to decide on the type and extent of material characterization to be undertaken. The methods used should be able to provide accurate results, easy to carry out and cost effective. Often, it is the problem from the production run that necessitates further material characterization to be carried out either for the purpose of resolving the problem or to prevent future occurrences. This chapter serves to identify the more common material characterization methods that can be carried out and the potentially useful information that can be inferred from the tests. It is hoped that the discussion of the many methods of material characterization can help in the choice of characterization methods for material testing.

REFERENCES

1. Patel S, Kaushal A, Bansal A. Effect of particle size and compression force on compaction behavior and derived mathematical parameters of compressibility. Pharm Res 2007; 24:111–124.
2. Tang P, Puri VM. Segregation quantification of two component particulate mixtures: effect of particle size, density, shape and surface texture. Part Sci Technol 2007; 25:571–588.
3. British Standard 3406, Part 4, 1963.
4. Jones MD, Harris H, Hooton JC, et al. An investigation into the relationship between carrier-based dry powder inhalation performance and formulation cohesive-adhesive force balances. Eur J Pharm Biopharm 2008; 69:496–507.
5. Zeng XM, Martin GP, Marriott C, et al. Crystallization of lactose from carbopol gels. Pharm Res 2000; 17:879–886.
6. Bosquillon C, Lombry C, Preat V, et al. Comparison of particle sizing techniques in the case of inhalation dry powders. J Pharm Sci 2001; 90:2032–2041.
7. Yang JZ, Young AL, Chiang PC, et al. Fluticasone and budesonide nanosuspensions for pulmonary delivery: preparation, characterization, and pharmacokinetic studies. J Pharm Sci 2008; 97:4869–4878.
8. Adi H, Larson I, Stewart P. Laser diffraction particle sizing of cohesive lactose powders. Powder Technol 2007; 179:90–94.
9. Stevens N, Shrimpton J, Palmer M, et al. Accuracy assessments for laser diffraction measurements of pharmaceutical lactose. Meas Sci Technol 2007; 18:3697–3707.
10. Laitinen N, Juppo AM. Measurement of pharmaceutical particles using a time-of-flight particle sizer. Eur J Pharm Biopharm 2003; 55:93–98.
11. Oskouie AK, Wang H-C, Mavliev R, et al. Calculated calibration curves for particle size determination based on time-of-flight (TOF). Aerosol Sci Technol 1998; 29:433–441.
12. Dickhoff BHJ, de Boer AH, Lambregts D, et al. The effect of carrier surface treatment on drug particle detachment from crystalline carriers in adhesive mixtures for inhalation. Int J Pharm 2006; 327:17–25.
13. Tee SK, Marriott C, Zeng XM, et al. The use of different sugars as fine and coarse carriers for aerosolised salbutamol sulphate. Int J Pharm 2000; 208:111–123.
14. Larhrib H, Martin GP, Prime D, et al. Characterisation and deposition studies of engineered lactose crystals with potential for use as a carrier for aerosolised salbutamol sulfate from dry powder inhalers. Eur J Pharm Sci 2003; 19:211–221.
15. Brewer E, Ramsland A. Particle size determination by automated microscopical imaging analysis with comparison to laser diffraction. J Pharm Sci 1995; 84:499–501.
16. Naito M, Hayakawa O, Nakahira K, et al. Effect of particle shape on the particle size distribution measured with commercial equipment. Powder Technol 1998; 100:52–60.
17. Ma Z, Merkus HG, de Smet JGAE, et al. New developments in particle characterization by laser diffraction: size and shape. Powder Technol 2000; 111:66–78.
18. Mulenweg H, Hirleman ED. Laser diffraction spectroscopy: influence of particle shape and a shape adaptation technique. Part Part Syst Char 1998; 15:163–169.
19. Borovoi A, Naats E, Oppel U, et al. Shape characterization of a large nonspherical particle by use of its Fraunhofer diffraction pattern. Appl Opt 2000; 39:1989–1997.
20. Sun C. Quantifying errors in tableting data analysis using the Ryshkewitch equation due to inaccurate true density. J Pharm Sci 2005; 94:2061–2068.
21. Sun C. True density of microcrystalline cellulose. J Pharm Sci 2005; 94:2132–2134.
22. Hedden DB, Brone DL, Clement S, et al. Development of an improved fluidization segregation tester for use with pharmaceutical powders. Pharm Technol 2006; 30:56–64.
23. Yamamoto Y, Fujii M, Watanabe K, et al. Effect of powder characteristics on oral tablet disintegration. Int J Pharm 2009; 365:116–120.
24. Sun C. A novel method for deriving true density of pharmaceutical solids including hydrates and water-containing powders. J Pharm Sci 2004; 93:646–653.

25. Imamura K, Maruyama Y, Tanaka K, et al. True density analysis of a freeze-dried amorphous sugar matrix. J Pharm Sci 2008; 97:2789–2797.
26. Sugano K, Kato T, Suzuki K, et al. High throughput solubility measurement with automated polarized light microscopy analysis. J Pharm Sci 2006; 95:2115–2122.
27. Hancock BC, Park M. What is the true solubility advantage for amorphous pharmaceuticals? Pharm Res 2000; 17:397–403.
28. Pudipeddi M, Serajuddin ATM. Trends in solubility of polymorphs. J Pharm Sci 2005; 94:929–939.
29. Dong W, Gilmore C, Barr G, et al. A quick method for the quantitative analysis of mixtures. 1. Powder x-ray diffraction. J Pharm Sci 2008; 97:2260–2276.
30. Yamada H, Suryanarayanan R. X-ray powder diffractometry of intact film coated tablets—an approach to monitor the physical form of the active pharmaceutical ingredient during processing and storage. J Pharm Sci 2007; 96:2029–2036.
31. Whiteside P, Luk S, Madden-Smith C, et al. Detection of low levels of amorphous lactose using H/D exchange and FT-Raman spectroscopy. Pharm Res 2008; 25:2650–2656.
32. Gombás A, Antal I, Szabó-Révész P, et al. Quantitative determination of crystallinity of alpha-lactose monohydrate by near infrared spectroscopy (NIRS). Int J Pharm 2003; 256:25–32.
33. Blanco M, Valdes D, Llorente I, et al. Application of NIR spectroscopy in polymorphic analysis: study of pseudo-polymorphs stability. J Pharm Sci 2005; 94:1336–1342.
34. Gorny M, Jakobs M, Mykhaylova V, et al. Quantifying the degree of disorder in micronized salbutamol sulfate using moisture sorption analysis. Drug Dev Ind Pharm 2007; 33:235–243.
35. Young PM, Chiou H, Tee T, et al. The use of organic vapor sorption to determine low levels of amorphous content in processed pharmaceutical powders. Drug Dev Ind Pharm 2007; 33:91–97.
36. Liu LX, Marziano I, Bentham AC, et al. Effect of particle properties on the flowability of ibuprofen powders. Int J Pharm 2008; 362:109–117.
37. Steckel H, Markefka P, teWierik H, et al. Effect of milling and sieving on functionality of dry powder inhalation products. Int J Pharm 2006; 309:51–59.
38. Chawla A, Taylor KMG, Newton JM, et al. Production of spray dried salbutamol sulphate for use in dry powder aerosol formulation. Int J Pharm 1994; 108:233–240.
39. Joshi M, Misra A. Dry powder inhalation of liposomal ketotifen fumarate: formulation and characterization. Int J Pharm 2001; 223:15–27.
40. Hou H, Sun CC. Quantifying effects of particulate properties on powder flow properties using a ring shear tester. J Pharm Sci 2008; 97:4030–4039.
41. Louey MD, Razia S, Stewart PJ. Influence of physico-chemical carrier properties on the in vitro aerosol deposition from interactive mixtures. Int J Pharm 2003; 252:87–98.
42. Jackson K, Young D, Pant S. Drug-excipient interactions and their affect on absorption. Pharm Sci Technol Today 2000; 3:336–345.
43. Marini A, Berbenni V, Pegoretti M, et al. Drug-excipient compatibility studies by physico-chemical techniques; the case of atenolol. J Therm Anal Calorim 2003; 73:547–561.
44. Hartauer KJ, Guillory JK. A comparison of diffuse reflectance FTIR spectroscopy and DSC in the characterization of a drug-excipient interaction. Drug Dev Ind Pharm 1991; 17:617–630.
45. Harding L, Qi S, Hill G, et al. The development of microthermal analysis and photothermal microspectroscopy as novel approaches to drug-excipient compatibility studies. Int J Pharm 2008; 354:149–157.
46. Zaru SCP, Pavel I, Leopold N, et al. Identification and characterization of pharmaceuticals using Raman and surface-enhanced Raman scattering. J Raman Spectrosc 2004; 35:338–346.
47. Geppi M, Mollia G, Borsacchi S, et al. Solid-state NMR studies of pharmaceutical systems. Appl Spectrosc Rev 2008; 43:202–302.

4 Binders in Pharmaceutical Granulation

Thomas Dürig
Ashland Aqualon Functional Ingredients, Ashland Inc., Wilmington, Delaware, U.S.A.

INTRODUCTION

Granulation processes are among the most widely practiced unit processes in pharmaceutical finished form manufacturing. Granulation (also referred to as agglomeration) can be used to improve powder flow properties and reduce fine dust through size enlargement and densification, thus improving tableting operations. Frequently, granulation provides the means to intimately combine a thermoplastic binder with other formulation components, thus improving compactibility of tablet formulations (1). Granulation is also used to prevent powder segregation, thereby ensuring uniform drug distribution. This is especially important in low-dose, high-potency drugs. Lastly, granulation is used to improve solubility and dispersibility of powders and tablets in water. This may also be referred to as "instantizing" or "hydrophilizing."

Granulation may be practiced by only adding a solvent as a binder fluid, but in the majority of cases, binders (usually polymeric) are also included, either by being "fully activated," that is, predissolved in a suitable granulating fluid, or by preblending ("dry addition") with the other formulation components. This step is followed by wet massing with a suitable granulation solvent. Dry binder addition is also the method of binder incorporation in dry granulation processes such as roller compaction and in the emerging field of hot melt granulation.

The general function of a binder is to promote bonding between the primary particles of the formulation, thereby assuring granule strength and density so that integrity is not compromised on further handling and processing. Additionally, for granules that are intended for compaction into tablets, it is equally important that the binder provides the necessary thermoplasticity and toughness to improve formulation compactibility without compromising tablet dissolution and disintegration times. Very frequently, drugs and other formulation components possess nonideal compaction properties, such as excessive brittleness and elasticity, leading to capping tendencies, high friability, and generally poor tablet performance. This is especially true when compressed at the high strain rates that are typical of commercial, high-speed tablet presses. The ideal tablet and granule binder will therefore provide the necessary thermoplastic character to overcome the unfavorable mechanical properties of the formulation yielding a dense compact, while minimizing the amount of applied force. The various modes of consolidation during tablet formation are shown in Figure 1.

While binder selection has traditionally been empirical and often dependent on formulator experience and preference, significant progress has been made over the last two decades in bringing quantitative and mechanistic particle engineering and materials sciences approaches to bear on this important aspect of pharmaceutical powder technology. The purpose of this chapter is therefore to review the major binders in current pharmaceutical use, and to discuss practical considerations in binder selection and use in the context of their key physical and chemical properties. Recent advances in the understanding of granulation technology and particle design will be discussed in detail, specifically the importance of selecting binders with a focus on end product stability, wetting and surface energetics of the granulation system, and thermomechanical properties.

COMMONLY USED BINDERS IN CURRENT PHARMACEUTICAL PRACTICE

Many different types of materials have been used as binders in the past, including natural polymers such as gelatin, gum acacia, gum tragacanth, starch, and sugars, such as sucrose and glucose. With exception of starch and acacia, these more traditional materials have for the most part been supplanted in current pharmaceutical practice by various derivatives of cellulose,

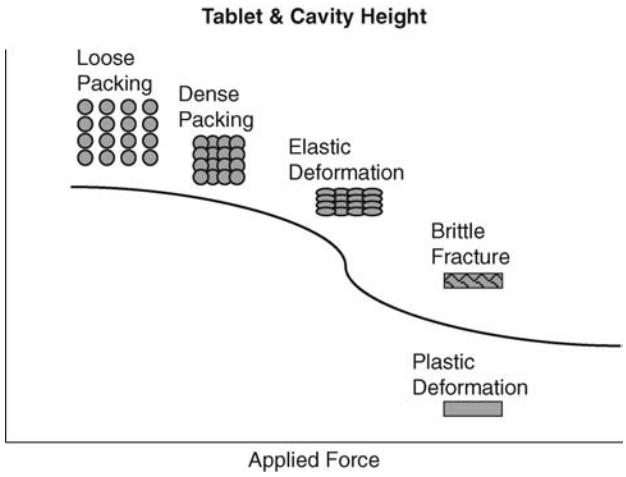


Figure 1 Mechanisms of consolidation for tableting materials. *Source*: Adapted from Ref. 1.

Table 1 Commonly Used Wet Binders

Binder	Typical use level	Comments
Hydroxypropylcellulose	2–6%	Used with water, hydroalcoholic and neat polar organic solvents; equally effective in wet and dry addition because of high plasticity and wetting.
Methyl cellulose	2–10%	Used with water or hydroalcoholic solvents; dry addition typically requires higher use levels than wet addition.
Hypromellose	2–10%	Used with water or hydroalcoholic solvents; dry addition requires higher use levels.
Ethyl cellulose	2–10%	Used with polar and nonpolar organic solvents; not soluble if water exceeds 20% of total solvent. Hydrophobic coating can slow down drug release for less soluble drugs; thus, it is best used for high-dose, highly soluble drugs and moisture-sensitive drugs.
Povidone	2–10%	Used with water, hydroalcoholic and neat polar organic solvents; dry addition requires higher use levels. Ultra low-viscosity grades allow high solution concentrations (20%).
Copovidone	2–8%	Used with water and hydroalcoholic solvents; more thermoplastic than PVP; dry addition requires higher use levels.
Pregelatinized starch	5–15%	Can only be used with water; also acts as a disintegrant; effective use levels are mostly higher than other binders (8–20%).

polyvinylpyrrolidone (PVP), and modified starch. These binders have found increasing favor as they tend to be less variable and have presented less aging issues than some of the more traditional materials.

Among the most frequently used binders are povidone (PVP) and copovidone (PVA-PVP), modified starches such as partially pregelatinized starch (PGS) and various cellulose ethers such as hydroxypropylcellulose (HPC), methyl cellulose (MC), hypromellose (HPMC), and less frequently ethyl cellulose (EC) and sodium carboxymethyl cellulose (NaCMC). These binders will be the focus of this chapter. Table 1 lists some of the most frequently used binders, typical use levels, and suitable solvents.

Hydroxypropylcellulose

HPC is manufactured by reacting alkali cellulose with propylene oxide at elevated pressure and temperature. It is a highly substituted cellulose ether, with 3.4 to 4.1 moles of hydroxypropyl substituent per mole of anhydroglucose backbone units (2). The hydroxypropyl substituent

Table 2 Selected Commercial Binder Grades

Binder	Trade name/grade/supplier	Nominal viscosity
Hydroxypropylcellulose	Klucel® hydroxypropylcellulose ELF, EF, and LF Pharm also available as fine particle grades EXF and LXF Pharm	2% viscosities at 5, 8, and 12 cps
	Nisso® HPC SL and L also available as fine grades	2% viscosities at 5 and 8 cps
Hypromellose	Methocel™ E3, E5, E6, and E15 Premium LV Hypromellose	2% viscosities at 3, 5, 6, and 15 cps
	Benecel® Hypromellose E3, E5, E6, and E15 Pharm	2% viscosities at 3, 5, 6, and 15 cps
	Pharmacoat® 603, 605, 606, and 615 hypromellose	2% viscosities at 3, 5, 6, and 15 cps
Methyl cellulose	Methocel A15 Premium LV methyl cellulose	2% at viscosity 15 cps
	Benecel A15 LV Pharm methyl cellulose	2% viscosity at 15 cps
Ethylcelluose	Aqualon® ethyl cellulose N7, N10, N14, and N22 Pharm	5% viscosities at 4, 7, 10, 14, and 22 cps
	Ethocel™ Standard Premium ethyl cellulose NF	5% viscosities at 4, 7, 10, and 20 cps
NaCMC	Aqualon NaCMC 7L2P and 7LF Pharm	2% viscosities at 20 and 50 cps
	Blanose® NaCMC 7L2P and 7LF Pharm	2% viscosities at 20 and 50 cps
Povidone	Kollidon® 25,30 and 90F Povidone	5% viscosities at 2, 2.5 and 55 cps
	Plasdone® K12, K17, K25, K29/32 and K90 povidone	5% viscosities 1, 1.8, 2.0, 2.5, and 55
Copovidone	Kolidon VA 64 copovidone	5% viscosity at 2.5 cps
	Plasdone S630 copovidone	5% viscosity at 2.5 cps
Pregelatinized starch	Starch 1500® partially pregelatinized starch	N/A
	Lycatab® pregelatinized starch partially pregelatinized starch	N/A

Abbreviation: NaCMC, sodium carboxymethyl cellulose.
Klucel®, Benecel®, Aqualon®, and Blanose® are registered trademarks of Ashland Aqualon Functional Ingredients. Nisso® is a registered trademark of Nippon Soda Company. Pharmacoat® is a registered trademark of Shin-Etsu Corporation. Methocel™ and Ethocel™ are trademarks of the Dow Chemical Company. Kollidon® is a registered trademark of BASF Corporation. Plasdone® is a registered trademark of ISP. Starch 1500® is a registered trademark of BPSI. Lycatab® is a registered trademark of Roquette Frères.

groups therefore comprise up to 80% of the weight of HPC. This high level of substitution renders HPC more thermoplastic and less hygroscopic than other water-soluble cellulose ethers. HPC has compendial status in the National Formulary (USP/NF), European Pharmacopoeia (Ph. Eur.), Japanese Pharmacopeia (JP), and Food Chemicals Codex (FCC). HPC is fully soluble in water and polar organic solvents such as methanol, ethanol, isopropyl alcohol, and acetone. Water solubility is temperature dependent with a cloud point around 45°C. HPC is a true thermoplastic polymer and has shown equivalent binder efficiency and good compactibility when added as a solution or in dry, powder form, before granulation (3). Various molecular weight (MW) grades are available ranging from 60 to 1000 kDa; however, low MW grades are most typically used as binders (Table 2). Moreover, for dry addition, fine particle size grades (60–80 μm mean diameter) are preferred because of faster hydration and uniform mixing and distribution. Coarse grades are preferred for solution addition as they disperse more easily without lumping than dry grades. Lump-free aqueous solutions are best prepared by dispersing the powder in 30% of the required final volume of water at 65°C. After 10 minutes of hydration the remaining water can then be added cold while continuing to stir. Because of its high binder efficiency, HPC tends to be particularly well suited for high-dose, difficult-to-compress tablets, where only small amounts of binder can be added. In general, use levels above 8% are not recommended as they tend to cause excessive slowing of disintegration and dissolution times. HPC is also frequently used in film coating and melt extrusion.

Methyl Cellulose

MC is the reaction product of methyl chloride and alkali cellulose. In contrast to HPC, it is less heavily substituted, with methoxy groups comprising 27% to 32% by weight of the polymer. MC is soluble in hot water up to about 55°C and will reversibly gel at elevated temperatures. This indicates slightly higher water solubility than HPC. MC is also soluble in polar organic solvents like ethanol, methanol, and isopropyl alcohol, as long as a small amount of water (10%) is added as a cosolvent. Like all cellulose ethers, MC is available in a wide range of MW grades, but almost exclusively the low MW grade with nominal viscosity of 15 cps at 2% concentration is used as a tablet binder (Table 2). Low –molecular weight MC is a versatile binder with good thermoplastic flow and wetting ability. It is also a good film former. While MC can be added dry to a granulation blend before wet massing, it is generally more effective when predissolved and added as a solution (3). Aqueous solutions can be prepared in analogous fashion as described above for HPC. MC is listed in the USP/NF, Ph. Eur., JP, and FCC.

Hypromellose

HPMC is one of the most widely used excipients in general and is also frequently used as a tablet binder. It is also known as hydroxypropyl methyl cellulose (HPMC) and is formed by reacting alkali cellulose with methyl chloride and propylene oxide to yield a mixed substitution cellulose ether. Various substitution ratios and MW grades are available. Primarily low-viscosity grades with substitution type "2910" (28–30% methoxy groups by weight and 4–12% hydroxypropyl groups) are used as tablet binders (Table 2). These grades are also very popular for film coating formulations. HPMC is listed in the USP/NF, Ph. Eur., JP, and FCC.

The properties of HPMC are largely similar to those of MC with the exception that HPMC is less thermoplastic and somewhat more hydrophilic. Although a good film former, unplasticized films are more brittle than MC and HPC and cloud points are higher. For example, HPMC type 2910 has a cloud point in the range of 65°C, which necessitates higher water temperatures for solution preparation. As with MC, HPMC is soluble in hydroalcoholic solvents with a minimum of 10% alcohol. It can be used in solution or added dry, but is less efficient in the latter form (3).

Povidone

Povidone, which is alternately referred to as PVP, is recognized as a versatile excipient that is used in complexation, solubilization, and film applications in addition to being one of the most widely used granulation and tablet binders. PVP is manufactured by radical polymerization of *N*-vinylpyrrolidone. PVP is available in multiple MW grades ranging from 2 to ~1500 kDA. The high MW grades have been reported to have very high binder efficiency, however, medium and low MW grades are most often used as granulation and tablet binders since high MW grades may impede dissolution behavior (Table 2). PVP is listed in the USP/NF, Ph. Eur., and JP (4). Much of its versatility derives from favorable solution behavior. Povidone is highly soluble in water and freely soluble in many polar organic solvents such as ethanol, methanol, isopropyl alcohol, and butanol. It is insoluble in nonpolar organic solvents. PVP is generally used in the form of a solution, where its low viscosity allows solids concentrations as high as 15% to 20%. PVP can also be added dry to a powder blend and then granulated with just the solvent, but as with MC and HPMC, binder efficiency is significantly lower in this case (3). Although use levels in the literature are reported as 2% to 5% (4), higher levels up to 10% may have to be used in challenging, poorly compactable formulations. PVP is highly hygroscopic, and at 50% RH, typical equilibrium moisture content exceeds 15% by weight (Fig. 2). It is therefore advisable to take precautions against uncontrolled and unnecessary exposure to atmospheric moisture.

Copovidone

Copovidone (PVA-PVP) is the 60:40, random, linear copolymer of *N*-vinyl-2-pyrrolidone and vinyl acetate. It is therefore a derivative of PVP. Vinyl acetate somewhat reduces the

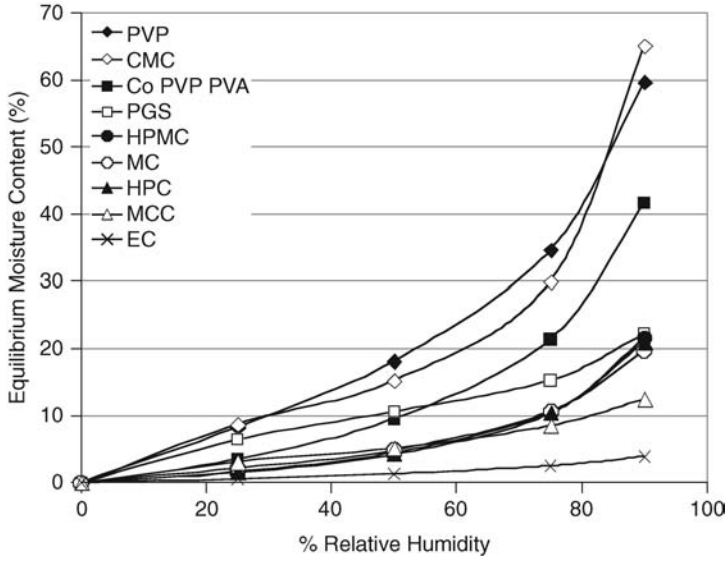


Figure 2 Equilibrium moisture contents at 25°C for selected polymeric binders.

hydrophilicity and hygroscopicity of the PVP homopolymer. At 50% RH, the typical equilibrium moisture content is approximately 10% (Fig. 2). The addition of vinyl acetate also increases the plasticity of the polymer, thus lowering the glass transition temperature and improving compactibility and adhesiveness. In addition to being used as a wet and dry binder, PVA-PVP can also be incorporated into film coating formulations together with HPMC (5). PVA-PVP can be used in wet granulation either in dissolved form or added dry to the powder blend, followed by wet massing. Binder effectiveness is approximately equivalent for these two methods of incorporation. Copovidone is soluble in water and polar organic solvents and is listed in USP/NF and Ph. Eur., and also has a monograph in the JPE.

Pregelatinized Starch

Pregelatinized starch (PGS) is classified as a modified starch. Chemical and mechanical treatment is used to rupture all or part of the native starch granules. Pregelatinization enhances starch cold-water solubility and also improves compactibility and flowability. PGS is marketed as a multifunctional excipient, providing binding, disintegration, good flow, and lubrication. PGS monographs can be found in the USP/NF, Ph. Eur., and JPE (6). It is typically used from solution in wet granulation; it can also be dry added, but this reduces efficiency significantly. Furthermore, at 15% to 20%, use levels are usually higher for PGS relative to other binders. PGS is not compatible with organic solvents and thus is used only in aqueous binder systems. While it tends to have high equilibrium moisture levels (Fig. 2), starch is known to hold water in different states, that is, only a portion of the sorbed water will be available as "free" water. This property can be exploited by using starch as a stabilizer or moisture sequestrant. Partially pregelatinized starch is the most frequently used form of PGS, but fully pregelatinized starch is also available. The degree of pregelatinization determines cold water solubility. Commercial, partially pregelatinized starch typically has around 20% pregelatinized or water-soluble content. The cold water–soluble part acts as a binder, while the remainder aids tablet disintegration. For this reason, fully pregelatinized starches tend to have higher binder efficiency, but not necessarily good disintegrant properties.

Starch

Starch has traditionally been one of the most widely used tablet binders, although today PGSs are often preferred. Starch is polysaccharide carbohydrate consisting of glucose monomers linked by glycosidic bonds. The main sources for excipient-grade starch are maize and potato

starch. References to wheat, rice, and tapioca starch can also be found in the literature. Starch is a GRAS-listed material with monographs in the USP/NF, Ph. Eur., and JP. Starch is not cold water or alcohol soluble; traditionally, it is used by gelatinizing in hot water to form a paste. Starch paste can be prepared by heating a starch suspension up to the boiling point with constant stirring. Binder use levels for starch are usually relatively high (5–25%). The high viscosity of starch paste can make granulation, efficient binder distribution, and substrate wetting somewhat problematic, however, an advantage of starch is that it tends to enhance tablet disintegration.

Gum Acacia

Gum acacia is also known as gum arabic; it is a natural material made of hardened exudate from *Acacia senegal* and *Acacia seyal*. Commercial gum arabic is largely harvested from wild trees in the Sahel region of Africa. It is a complex mixture of polysaccharides and glycoproteins that is today used primarily in the food industry as an emulsion stabilizer. Acacia is a highly functional binder, in that it is known to form strong tablets and granules; however, dissolution times are often impeded. Additional reasons why today this binder is used rarely with exception of nutritional supplement applications where organic origin is include solution susceptibility to enzymatic and bacterial degradation, large natural variability, and sporadic supply shortages.

PRACTICAL CONSIDERATIONS IN BINDER SELECTION AND USE

Use Levels and Binder Efficiency

While the binder use levels in Table 1 serve as a general guide, the reader will appreciate that use levels tend to be drug and formulation specific and may deviate significantly from the typical values cited. In general, increased binder concentration leads to an increase in mean granule size and strength, and decreased granule friability. An increase in binder concentration strengthens bonds between the substrate particles as there is more binder per bond (7). Binder efficiency may be defined as the minimum binder use level that is required to achieve a certain benchmark tablet crushing strength and friability. With regard to binder efficiency there is no absolute standard for these criteria. The strongest tablets and granulations may not always be the most desirable; rather the minimum amount of binder necessary to achieve a minimum acceptable strength or maximum acceptable friability is often chosen. This will minimize cost and tablet size because stronger granules and tablets tend to be correlated with slower drug release. In terms of maximum acceptable friability, as a general rule, friability needs to be low enough to allow handling and coating in commercial-scale tablet coating pans (e.g., 48- and 60-in diameter pans). The friability for smaller tablets (500 mg or less) should therefore be less than 0.8%. Larger tablets (1000 mg) should have friabilities below 0.3% to allow for problem- and blemish-free handling and commercial-scale coating.

Stability and Compatibility

It is well known that chemical or physical incompatibility between actives and excipients or their impurities can compromise drug stability and safety. Binders are brought into intimate contact with actives during mixing, wet massing, and codrying; therefore, final formulation stability is a primary consideration in binder selection. Like all excipients, binders are generally designed to be "inert;" thus, direct chemical reactions between the functional groups of binder and drug molecules are relatively rare. More frequently, the interaction involves impurities that can be introduced into the final drug product by the drug, excipients, or packaging materials (8). The majority of such impurity-induced incompatibilities in solid dosage forms can be attributed to a select group of small molecules including water, electrophiles such as aldehydes, and the often related carboxylic acids and peroxides.

Binder Hygroscopicity and Water Content

Water is well known as a major environmental destabilizing factor for drug products. The destabilizing interaction may be chemical such as hydrolysis. Examples of physical interactions involving water are plasticization (lowering glass transition temperatures),

triggering of recrystallization, tablet hardening or softening, and slower dissolution behavior (8–11). Water can be found in most drugs and excipients. Water may be associated with solids in various states including loosely held surface water, intermediate bound water, which is not freely available, as well as very tightly bound water of crystallization, which can only be released as part of transition in crystal structure. Water is also the most frequently used solvent in granulation processing and film coating. Finally adsorption of atmospheric moisture is a well-known pathway for water to enter finished dosage forms.

Binders with high equilibrium water content and high hygroscopicity (especially if used in quantities exceeding 5%) can therefore be problematic. The hygroscopicity of various binders is illustrated in Figure 2. Typically, manufacturing environments are humidity controlled to be at 50% relative humidity or less. At these levels PVP and NaCMC equilibrium moisture levels are approximately 18 and 15 weight percent, respectively. Copovidone and PGS have equilibrium moisture levels of 10%, whereas the remaining cellulose ethers, HPMC, MC, HPC, and EC are at 5% moisture content or less. Most notably, EC is the least hygroscopic binder.

Examples of where hygroscopic binders are a problem include reports of tablet softening and reduction in disintegration time due to excessive moisture uptake by ranitidine tablets comprising PVP as a wet granulation binder (9). It has been observed that PVP is predominately in the glassy state at room temperature and at relative humidity below 55°C. At higher humidities, the glass transition temperature is significantly reduced, resulting in conversion to the rubbery state where molecular mobility is increased, resulting in hardening of tablets prepared from glass ballotini and PVP (10). In a further example, Fitzpatrick et al. (11) reported a significant decrease in dissolution rate for a tablet formulation of a new chemical entity when wet granulated with PVP and stored at accelerated conditions (40°C and 75% relative humidity). Tablets stored at lower temperatures, for example, 30°C, and 60% relative humidity and tablets made with HPC as a wet binder remained stable and did not show the decreased dissolution rate. The change was correlated to a decrease in the glass transition temperature with increased moisture sorption.

Aldehydes and Carboxylic Acids

Low–molecular weight aldehydes and carboxylic acids are found in many excipients including sugars, polymers, and unsaturated fats (8). The most common reactive species of concern in solid dosage forms tend to be formaldehyde and its corresponding acid, formic acid. Table 3 lists typical levels of these impurities for various binders, granulation aids, and tableting excipients. Others include acetaldehyde, glyoxal, furfural, glyoxalic, and acetic acid. Carboxylic acids could be introduced because of not only carryover from manufacturing but also autoxidation of excipients, which, for example, leads to formation of formaldehyde, which

Table 3 Levels of Formic Acid and Formaldehyde in Selected Binders and Tableting Excipients

			Level (ppm)	
Excipient	Supplier	Lot	Formic acid	Formaldehyde
Lactose	A	1	1.0	<0.2
Microcrystalline cellulose, 50 μm average size	D	1	9.3	<0.2
Microcrystalline cellulose, 100 μm average size	D	2	23.9	0.9
Microcrystalline cellulose, 100 μm average size	D	3	11.8	1.0
Starch 1500®	E	1	3.0	<0.2
Povidone K-25	H	1	3080.3	<0.2
Povidone K-90	H	2	630.0	<0.2
Povidone K-25	I	1	1990.5	0.4
Hypromellose	J	1	58.3	11.1
Hypromellose	J	2	86.4	15.7
Polyethylene glycol 4000	N	3	14.0	3.6
Polyethylene glycol 400	O	2	469.0	85.8

Source: From Ref. 12.

Table 4 Total Peroxide Content in Selected Excipients

Excipient	Number of lots tested	Average level (nmol/g)
Povidone	5	7300
Polyethylene glycol 400	4	2200
Polysorbate 80	8	1500
Hydroxypropylcellulose	21	300
Polyethylene glycol solid	4	20
Microcrystalline cellulose	5	<10
Lactose	5	<10

Source: From Ref. 14.

is then further oxidized to form formic acid. The presence of these impurities needs to be considered in acid-labile drugs as well as drugs with nucleophilic functional groups, for example, primary and secondary amines and hydroxyl groups (8,12). Formaldehyde and formic acid have been identified as being of particular concern when using polysorbate, povidone, and polyethylene glycol (13).

Peroxides

Peroxides are oxidizing materials. They can be found in a number of excipients including binders. Peroxides occur as "organically" bound peroxide (ROOH), where R is a carbon atom, or hydrogen peroxide (H_2O_2), which is the more mobile, freely available, and volatile form. Peroxides can react directly with drugs sensitive to oxidation as well as generate radicals, which initiate radical chain reactions, or themselves react with the active ingredient (8,14).

Excipients most often associated with peroxide impurities can be divided into two general groups, although peroxides may be found in many other excipients, albeit usually at lower levels. The first group comprises polymeric ethers, including polyethylene glycols, polyethylene oxides, and polysorbates. In general, only high–molecular weight polyethylene glycol is occasionally used as a binder, although polysorbates are frequently used as wetting agents in binder solutions. These polymers frequently have some peroxide content as supplied, but can also form greater amounts because of autoxidation. Frequently, these materials are supplied with small amounts of antioxidants added as stabilizers.

The second group chiefly consists of PVP and PVP-related polymers, such crospovidone and copovidone. PVP-based excipients typically contain relatively high levels of peroxides. Table 4 lists total peroxide (hydrogen peroxide and organically bound peroxide) for a series of common tablet binders and related tableting excipients. PVP undergoes autoxidation, and greater amounts can form under high-shear conditions typical of granulation and tableting (8). A number of reports correlating drug-excipient incompatibilities to peroxide levels in PVP have been published (15,16). In the case of raloxifene, peroxide impurities associated with PVP resulted in the formation of high levels of an *N*-oxide derivative of raloxifene. Hartauer et al. (16) were able to identify the critical destabilizing levels of peroxide, thus allowing for a peroxide limit test that assures product stability. Additionally peroxides can also be formed, albeit at lower levels, in cellulose ethers such as HPC.

Wettability and Surface Energetics

The ability to wet the porous powder substrate, to penetrate rapidly into the powder bed and spread across the surfaces of the host particles, and to distribute uniformly throughout the powder bed is important in granulation process control. Poor wettability and spreadability of the binder are frequently associated with porous, weak, low-density granules with nonuniform binder distribution and broad particle size distributions. During the initial wetting and nucleation phase, the binder fluid disperses mainly by wetting and capillary action. This crucial stage of granule formation is therefore strongly dependent on formulation and binder selection. It is the binder fluid characteristics (surface tension, viscosity) and the substrate characteristics (surface free energy) that determine the interaction between the binder fluid and the substrate, which can be characterized by substrate surface wetting (contact angles),

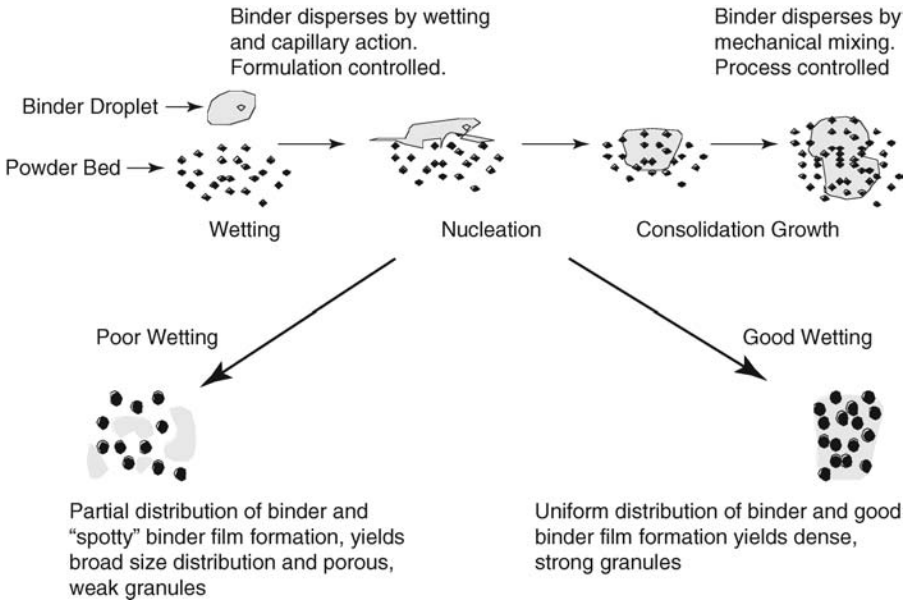


Figure 3 Schematic showing wetting, nucleation, consolidation, and granule growth processes. *Source*: Adapted from Ref. 19.

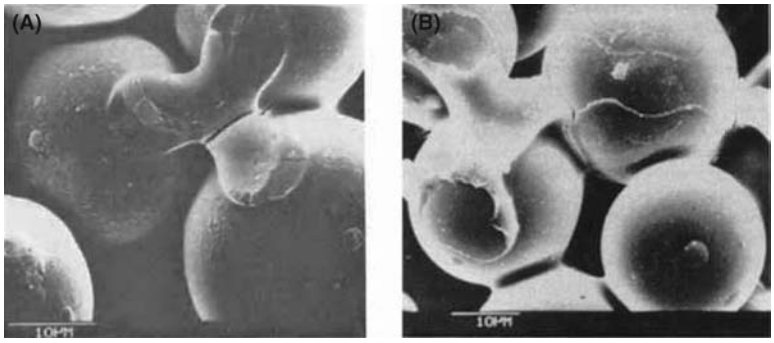


Figure 4 Broken PVP bonds within granules of (**A**) hydrophilic glass beads showing fracture within the PVP bonding film and (**B**) hydrophobic glass beads showing adhesive failure at the glass–PVP film interface. *Abbreviation*: PVP, polyvinylpyrrolidone. *Source*: Adapted from Ref. 7.

spreading ability (spreading coefficients) of the binder over substrate, and the resultant granule characteristics (17,18). Once nuclei are formed, the binder is predominantly dispersed by the mechanical shear forces of the mixer during the consolidation and growth phases of the granulation. This phase is mainly dependent on process parameters, the amount of binder fluid added, and the rheological characteristics of the wet mass (19,20). Depending on operating shear forces and strength and toughness of wet granules, granule break up and attrition can occur simultaneously with growth and consolidation in the later stages of a granulation process. Figure 3 depicts some of these key aspects.

The consequences of good and poor substrate wetting were highlighted in a seminal study by Cutt et al. (7) and further analyzed by Rowe (17), and are shown in Figure 4A, B. and Table 5. Aqueous PVP solutions were able to spread easily over hydrophilic glass beads (positive or high spreading coefficient of the binder over the substrate), resulting in a continuous and strongly adhering film, which led to strong and dense granules with binder film bonds at all contact points between substrate particles. In these granules with good adhesion

Table 5 Properties of Glass Granules with 2.72% Polyvinylpyrrolidone Binder

Glass bead type	Friability (%)	Strength (load at failure, g)
Hydrophilic	5.2	202
Hydrophobic	13.8	115

Source: From Ref. 7.

between binder and substrate, failure occurs within the binder film or bond (i.e., cohesive failure) (Fig. 4A). By contrast, in the case of hydrophobically modified glass beads, where the spreading coefficient of the binder solution over the substrate was negative, no continuous binder film was formed; rather the binder is distributed in discontinuous "patches" (17). This leads to a more open and porous granule structure and lower granule strength, as illustrated in Figure 3 and Table 4. The low binder-substrate adhesion in these weaker granules causes failure to occur at the interface between the substrate particles and the binder film as illustrated in Figure 4B.

Wetting Fundamentals

A number of techniques can be used to measure wetting and spreading abilities for binder solutions to ensure that an appropriate binder is chosen for a particular substrate.

Typically, this involves calculation of surface free energies and the works of cohesion, adhesion, and spreading (also referred to as spreading coefficient) from measurements of solution contact angles on the substrate of interest and measurement of the liquid-vapor surface energy of the wetting liquid, which is usually referred to as surface tension.

The contact angle, θ, is a measure of the affinity of the fluid for a solid as described in the Young's equation:

$$\gamma_{sv} - \gamma_{sl} = \gamma_{lv} \cos\theta$$

where γ_{sv} is the solid-vapor surface or interfacial energy, γ_{sl} is the solid-liquid surface energy, and γ_{lv} is the liquid-vapor surface energy, which is more commonly referred to as the surface tension of the liquid. A fluid is said to wet a solid when the contact angle is less than 90°; this occurs when solid-vapor surface energy exceeds the solid-liquid surface energy. The extent of wetting is, therefore, determined by $\gamma_{lv} \cos\theta$, the product of the binder solution surface tension and the contact angle, which is known as adhesion tension (18).

Knowledge of the surface energies is important as it allows calculation of the works of adhesion, cohesion, and spreading. The work of cohesion for a solid can be written as:

$$W_{c_s=2\gamma_{sv}}$$

Similarly for a liquid:

$$W_{c_l} = 2\gamma_{lv}$$

The work of adhesion for a solid-liquid interface can be written as:

$$W_a = \gamma_{sv} + \gamma_{lv} - \gamma_{sl} = \gamma_{lv}(1 + \cos\theta)$$

W_a represents the work that is done when a particle adheres to a liquid surface, in the process replacing air-particle and air-liquid interfaces with a particle-liquid interface.

The work of spreading, also known as spreading coefficient, can be calculated as:

$$W_s = W_a - W_{c_l} = \gamma_{lv}(\cos\theta - 1)$$

The work of spreading represents the work that is done by a liquid spreading over a particle surface, thereby replacing the particle-air interface with a liquid-air and particle-liquid interface. In addition, it is possible to divide the respective surface energies into their polar and dispersive components (17).

Finally, Hapgood et al. (19) introduced the concept of liquid binder drop penetration time, t_p, as a measure of wetting and powder penetration kinetics for a liquid of viscosity, η, where:

$$t_p \propto \frac{\eta}{\gamma_{lv} \cos\theta}$$

Binder fluid drop penetration time can therefore be decreased by ensuring lower solution viscosity and by maximizing adhesion tension of the binder fluid, which, in practice, requires selection of a low-viscosity fluid that yields a contact angle as close to 0 as possible. For drop-controlled nucleation, both a fast (small) drop penetration time and a relatively low spray flux are required (19). Readers who are interested in a more detailed review and treatment of the above topics are directed to Refs. 17 to 19 and 21.

Direct measurement of contact angles on nonporous substrate surfaces can be made using the sessile drop technique and a contact angle goinometer. An important aspect of this technique is that the substrate needs to be rendered into a nonporous form, which often is done by sintering, or melting, or alternately forming very hard and smooth compacts by compression.

Alternatively, the penetration kinetics of liquid into a powder bed can be measured using the Washburn method (22,23), which has the advantage of mimicking the binder penetration by capillary action and wetting processes that occur in wet granulation. In this technique, binder solution uptake by capillary action into a packed column of substrate powder is measured. The following equations describe this event:

$$t = Am^2, \quad A = \frac{\eta}{C\rho^2\gamma_{lv}\cos\theta}$$

where t is the time after the solid and the liquid are brought into contact, m is the mass of the liquid drawn into the solid, A is a constant dependent on the liquid properties (viscosity η, density ρ, the liquid/vapor interfacial surface tension γ_{lv}, and the solid-liquid contact angle θ), and C is a material constant dependent on the porous architecture of the powder bed.

Additional techniques include floatation tests where the penetration kinetics of the substrate into liquid is measured and inverse gas chromatography, which allows calculation of surface energies by measuring preferential adsorption of various well-characterized probe gases onto the substrate particles (18).

Wetting Studies as Formulation Tools

Krycer et al. (24) were among early workers to highlight the importance of binder fluid wetting and spreading abilities over the substrate in relation to granule friability and ultimately compressed tablet strength and capping tendencies. Studying relative binder efficiencies of HPMC, PVP, starch, acacia, and sugar for a model acetaminophen system, they concluded that important factors for optimum granulation included wetting of the substrate by the binder, binder-substrate adhesion, and binder cohesion. They also investigated the mechanical properties of binder films in detail. It is important to note that in addition to the surface interactions between binders and substrates, the mechanical properties of various binders will exert a strong influence on final granule and tablet strength. Granule and tablet characteristics are therefore a function of binder-substrate interactions and also mechanical properties of the binder and substrate mixture. The thermomechanical properties of binders will be discussed in more detail in the Thermal and Mechanical Properties section of this chapter. Table 6 shows the correlation between wetting characteristics and the acetaminophen granule friability and tablet crushing strength. In general, there is a good rank order correlation between the surface tensions, contact angles and spreading coefficients, and granule friability and tablet strength, the exception being the friability of sucrose granules, which may be attributable to the significant brittleness of sucrose, which could result in reduced granule toughness and abrasion resistance.

Using independently measured and calculated values for surface free energies, Rowe (17) was able to also show good correlation between spreading coefficient and the experimental data of Krycer et al. (24) (Fig. 5). A practical example where the spreading coefficients were

Table 6 Properties of 4% (w/v) Binder Solutions and Resultant Granule and Tablet Properties in a APAP Model System (24)

Binder solution	Surface tension (dyne/cm)	Contact angle on APAP (°)	Work of spreading (dyne/cm)	Granule friability index	Tablet strength (N)[a]
Hypromellose	45.2	27.4	−5.07	14.8	180
Acacia	50.6	30.3	−6.92	19.8	162
Sucrose	50.4	32.8	−8.01	87. 6	98
Polyvinylpyrrolidone	53.6	42.2	−13.9	26.5	57
Starch	58.7	47.3	−18.9	45.3	37
Water	70.3	59.6	−110	–	–

[a]Diametral crushing strength for tablets compressed at 120 MPa.
Abbreviation: APAP, acetaminophen.

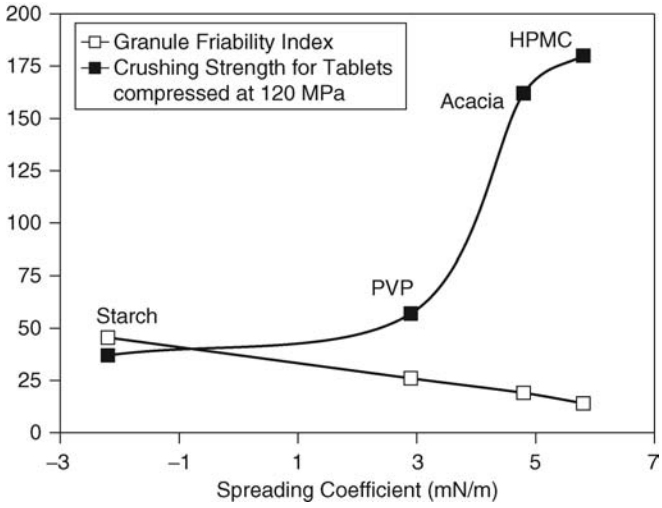


Figure 5 Relationship between spreading coefficients calculated by Rowe and tablet and granule strength data reported by Krycer et al. *Source*: Adapted from Refs. 17 and 24.

used to select optimal binder solutions for a particular granulation substrate is illustrated in Figure 6, which shows spreading coefficients and granule friabilities improving, for two experimental drug formulations, when PVP solutions are replaced with lower surface tension HPC solutions. Further improvements occur when water is replaced by a less polar hydroalcoholic solvent (25).

In a further example of the general applicability of wetting measurements to the selection of binder solutions, Lusvardi et al. (23) used the Washburn approach to study the wetting kinetics of selected binders on two low soluble drugs (ibuprofen and naproxen) and correlated these to final granulation and tablet characteristics. Figure 7 depicts the mass uptake of various binder solutions into a column packed with ibuprofen powder. The HPC solution rapidly wets the ibuprofen as shown by the fast rate of adsorption. HPMC solution has an intermediate adsorption rate while the PVP solution shows only a slight improvement over water, which was not absorbed at all.

On the basis of the slopes of the uptake profiles and the measured solution characteristics (viscosity, surface tension, density), the wetting contact angles were calculated for the various binder solutions. As shown in Table 7, HPC solutions provided the best wetting for both drugs, followed by HPMC and PVP. Naproxen was perfectly wetted by HPC solutions as indicated by the contact angle of 0.

Using Zisman's approach, one can estimate the surface energy of the solid from Young's equation and the contact angle data (26,27). Figure 8 illustrates this approach. Extrapolating to a cosine of 1 ($\cos 0^\circ$) provides an estimate of $\sim$40 mN/m for the surface energy of naproxen, which is consistent with the surface tension measured for HPC solutions. Extrapolating

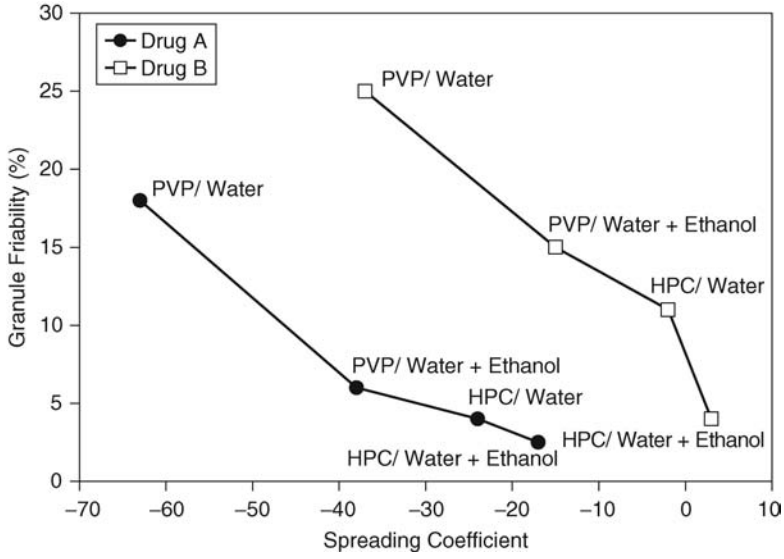


Figure 6 Effect of spreading coefficient on granule friabilities of two experimental drug formulations. *Source*: Adapted from Ref. 25.

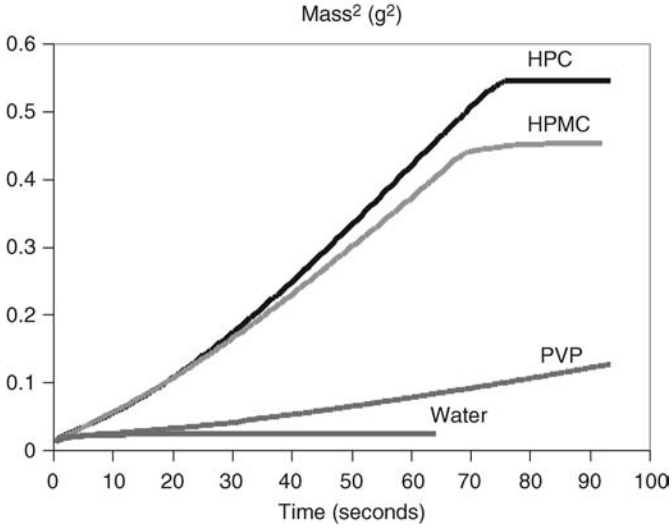


Figure 7 Binder solution uptake profiles into an ibuprofen powder bed. *Source*: Adapted from Ref. 23.

Table 7 Binder Solution Wetting Characteristics on Drugs with Different Degrees of Hydrophobicity, Ibuprofen, and Naproxen

Wetting solution	Surface tension (mN/m)	Viscosity (cps)	Contact angle on ibuprofen	Spreading coefficient for ibuprofen (mN/m)	Contact angle on naproxen	Spreading coefficient for naproxen (mN/m)
n-hexane	18.4	0.3	0°	0	0°	0
Hydroxypropylcellulose	40.0	2.3	68°	−25.0	0°	0
Hypromellose	48.4	1.9	81°	−40.8	37°	−9.7
Polyvinylpyrrolidone	53.6	1.5	88°	−51.7	63°	−29.3
Water	72.1	1.0	>90°	>72.1	85°	−65.0

Source: From Ref. 23.

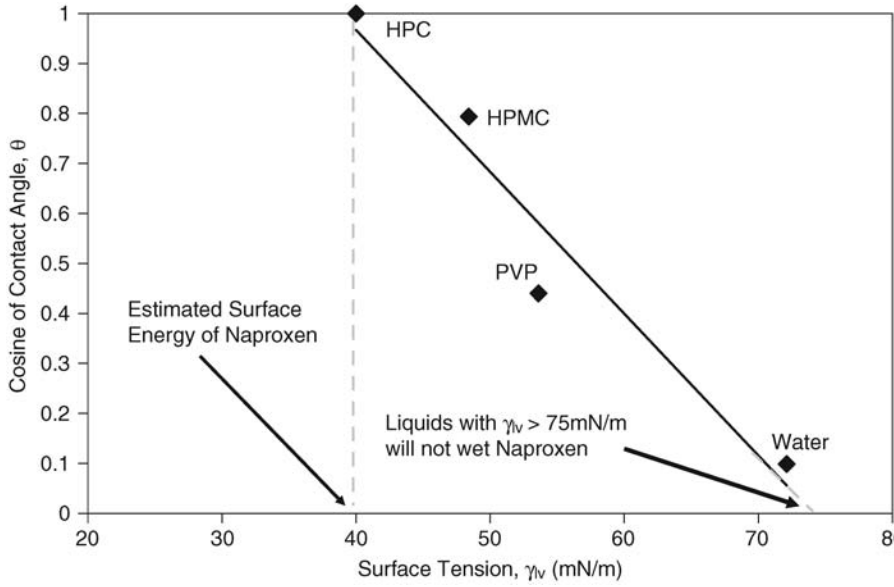


Figure 8 Zisman surface energy plot for naproxen. *Source*: Adapted from Ref. 23.

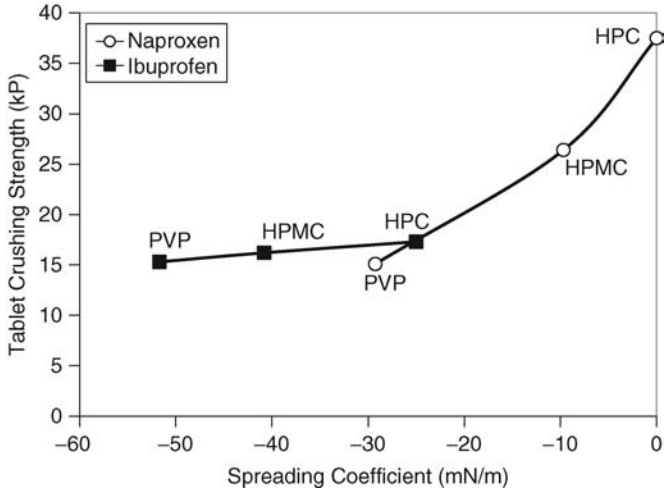


Figure 9 Relationship between spreading coefficients of binder solutions of HPC, HPMC, and PVP over ibuprofen and naproxen and tablet crushing strength. Ibuprofen and naproxen were granulated with HPC, HPMC, and PVP solutions and compressed at 15 kN compression force. Tablets weighed 600 mg and were compressed with 0.4375 inch standard concave tooling. *Abbreviations*: HPC, hydroxypropylcellulose; HPMC, hypromellose; PVP, polyvinylpyrrolidone. *Source*: Adapted from Ref. 23.

to 0 (cos 90°) indicates that liquids with surface tensions higher than ~75 mN/m can be expected to have contact angles greater than 90°, indicating that there will be no spontaneous wetting or penetration into the powder bed. Modification of the binder fluid through selection of a binder with lower surface tension or use of a less polar solvent or surfactants is therefore necessary to ensure good binder distribution.

The relevance of the wetting data to binder performance is shown in Figure 9, where the tablet strength of wet-granulated ibuprofen and naproxen tablets is plotted as a function of the calculated spreading coefficients.

The studies reviewed here allow the general conclusion that binder choice is an important tool in assuring optimal wetting for granulation. The polarity of the binder directly affects binder solution surface tension, which in turn affects adhesion tension and spread ability on the substrate. In general, better wetting is assured by choosing lower surface tension binder solutions. For reference, the surface tensions for common binder-water solutions are summarized in Tables 6 and 7.

THE ROLE OF SOLVENT

As indicated, a primary factor in good granulation is the wetting and spreading ability of the binder over the substrate. One of the obvious ways to modulate these properties is modification of the solvent composition to influence polarity and wetting properties in the desired direction. In addition to choosing binders with lower surface tensions, one may add surfactants to reduce surface tension or alternately add a less polar organic solvent to water or completely replace the aqueous solution with a less polar, organic solvent. The report of Krycer et al. (24) was among the first reports that showed improved granule properties by adding a surfactant to PVP. Their work showed that sodium lauryl sulfate (SLS) addition markedly improved the spreadability coefficient of the PVP solution and with it granule friability was also significantly decreased. However, tablet crushing strength was only modestly influenced (Table 8). Surfactants such as sodium lauryl sulfate or polysorbate are now frequently added to binder solutions as wetting agents; however, caution needs to be exercised as an excessive film of surfactant on the granule surface can lead to poor binding. Most surfactants generally have poor compressibility and binding characteristics.

An alternate approach to modify the surface energies of the binding solution is to incorporate less polar, organic solvents. Among the frequently used solvents for granulation are hydroalcoholic solutions of methanol, ethanol, IPA, and acetone.

Figure 6, shown earlier, illustrates the effect of the granulation solvent on the granule friabilities for two experimental drugs granulated using either PVP or HPC and water or ethanol/water combinations. It is clear that granule friability decreases markedly as the spreadability coefficient increases by switching from water to an ethanol:water blend. An obvious limitation of this approach to enhancing wetting is binder polymer solubility in the solvent system. For instance, starches and NaCMC are generally not soluble at all in organic solvents, and MC and HPMC require a minimum of about 10% to 15% water to be soluble in polar organic solvents such as methanol, ethanol, isopropyl alcohol, and acetone. HPC, PVP, PVA-PVP, and EC are fully soluble in these solvents. An additional complication that needs to be considered is that binder solutions with the same binder concentration may vary considerably in different solvent systems. Table 9 shows the variation in PVP solution viscosity

Table 8 Properties of 4% (w/v) Binder Solutions and Resultant Granule and Tablet Properties for a PVP-acetaminophen Model System

Binder solution	Surface tension (dyne/cm)	Contact angle on acetaminophen (°)	Work of spreading (dyne/cm)	Granule friability index	Tablet strength (N)[a]
PVP + sodium lauryl sulfate (90:10)	44.1	44.1	−0.9	20.8	58
PVP + glycerol (90:10)	43.8	40.1	−10.7	25.5	80
PVP	53.6	42.2	−13.9	26.5	48

[a]Diametral crushing strength for tablets compressed at 120 MPa.
Abbreviation: PVP, polyvinylpyrrolidone.
Source: From Ref. 24.

Table 9 Effect of Solvent Composition on PVP Binder Solution Properties and PVP Acetylsalicylic Acid Granulations and Tablet Strength

Binder solution	Viscosity (cps)	Surface tension (dyne/cm)	Wettability ($r \times \cos\theta \times 10^{-4}$)	Bulk density (g/mL)	Tablet strength (kP)	Tablet friability (%)
100% water	67	69.5	4.1	0.48	6.6	3.5
25% ethanol	194	42.6	12.16	0.44	6	4
50% ethanol	287	33.6	15.9	0.43	5.8	4.6
75% ethanol	240	30.1	18.68	0.425	8	3.4
100% ethanol	186	26.35	16.4	0.42	–	2.5

Abbreviation: PVP, polyvinylpyrrolidone.
Source: From Ref. 28.

when the water:alcohol ratio is varied. Similar behavior occurs for most polymers including HPC and HPMC.

Among the more detailed studies on solvent effects is the study by Wells and Walker (28). These workers studied the effect of solvent choice on PVP acetylsalicylic acid granulations by varying the ratios of ethanol and water in the granulation fluid. In somewhat contradictory fashion, granule bulk density was found to decrease with decreased surface tension (increased ethanol). However, tablet crushing strength and tablet friability were found to be correlated with lowest surface tension (100% ethanol). These results would indicate that a lower polarity and surface tension allow for stronger and denser tablets to be ultimately formed. The authors also pointed out that aspirin solubility is increased in this optimal solvent range, thus possibly contributing to bond formation through greater dissolution and recrystallization of aspirin.

THERMAL AND MECHANICAL PROPERTIES

As indicated in section "Stability and Compatibility," the characteristics of granules and their resultant tablets are dependent on not only the interaction and surface energies of the binder solution and the substrate, but also the mechanical properties of the binder films that are formed around and between the substrate particles. In their seminal study, Krycer et al. (24) concluded that in addition to having a favorable spreading coefficient on acetaminophen, HPMC also was a superior film former when compared with PVP, acacia, and starch in that it produced soft but tough films in relation to those materials. Reading and Spring (29) investigated these concepts further using MC, PVP, starch, and gelatin as film-forming wet binders and sand as a hydrophilic, but otherwise inert, substrate. As shown in Table 10, MC film strength and deformation ability are significantly greater than those of the other binders. Simultaneously, MC films are softer, showing the lowest Brinell (indentation) hardness. These properties correlate with significantly larger, less friable granules, and stronger tablets.

The studies of Krycer et al. and Reading and Spring therefore suggest that binders that have good wettability *and* also form films with high toughness (toughness is the work of failure as measured by the area under the stress-strain curve) and high percent elongation at break, which together are indicators of plastic flow, will likely produce more robust granules and tablets. However, these studies do not directly address the compaction behavior of tablet binders when subjected to high-speed, uniaxial compaction, which occurs in commercial tableting.

Figure 10 shows the deformation behavior of pure binder tablets (100% polymer) when subjected to diametral compression on a universal testing machine. These binder tablets were prepared by compressing the dry binder powders, of similar fine particle size, on a rotary press at high speed, thus replicating the strain rates typically encountered by the binder and other formulation components in commercial tableting presses. HPC exhibits significantly greater plasticity and toughness (area under the curve) as compared with the other binders, which uniformly show an increased tendency to undergo brittle fracture. PVA-PVP, MC, and microcrystalline cellulose (MCC) tablets achieve high peak loads during compression testing, but these tablets fracture at very low deformation (0.28–0.46 mm). In contrast, HPC tablets do not show this brittle behavior. The HPC tablets were deformed beyond 2.6 mm without

Table 10 Selected Free Film, Granule, and Tablet Properties for MC, PVP, Gelatin, and Starch Binders. Sand Was Used as the Binder Substrate. Films Were Dried at 60°C.

Property	MC	PVP	Gelatin	Starch
Film tensile strength (MPa)	70	18	27	33
Percent elongation at break	37	5.3	3.1	3.2
Film toughness ($J/m^3 \times 10^5$)	192	8	9	10
Film Brinell hardness, 12% RH (MPa)	7.5	9.17	18.7	15.6
Percent granule friability	5.0	11.0	14.6	20.4
Mean granule size (μm)	680	445	365	200
Tablet crushing strength[a] (kPa)	345	240	200	70

[a]Tablets compressed at 120 MPa compression force.
Abbreviations: MC, methyl cellulose; PVP, polyvinylpyrrolidone.
Source: Adapted from Ref. 29.

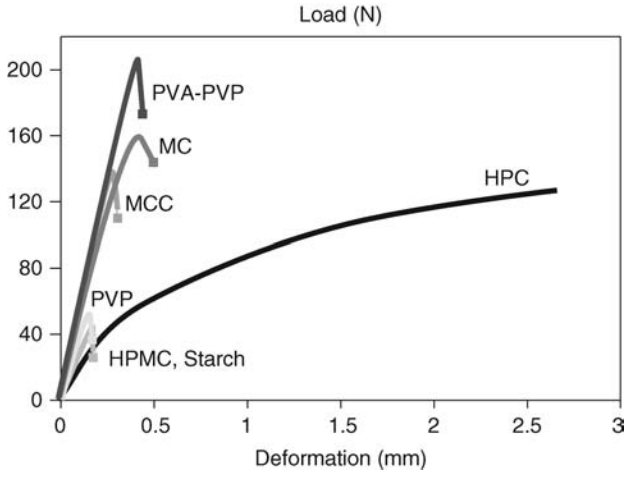


Figure 10 Load-deformation plots for pure polymer tablets subjected to diametral compression on a universal testing machine (0.5 in/min crosshead speed). The 100% polymer tablets were made on a rotary tablet press. *Source*: Adapted from Ref. 30.

Table 11 Glass Transition Temperature at Equilibrium Moisture Content as Received, Detected by Modulated Temperature Differential Scanning Calorimetry

Binder	Equilibrium moisture content (%)	Glass transition temperature (°C)
Hydroxypropylcellulose	3.2	−2.6
Methyl cellulose	4.7	145
Hypromellose (type 2910)	3.1	160
MCC	4.9	~105
Copovidone	4.8	101
Polyvinylpyrrolidone	8.0	164

Source: Adapted from Ref. 30.
Abbreviation: MCC, microcrystalline cellulose.

fracturing, while absorbing applied energy, providing much greater toughness. Relative to the other materials tested, the HPMC and PVP tablets were the least deformable and fractured at low peak loads.

The greater toughness and deformability of HPC also coincides with higher thermoplasticity as measured by thermal analysis. In contrast to other polymers, HPC at a typical equilibrium moisture content (~3%) exhibited a high-intensity glass transition in the low temperature range (−3–0°C) (Table 11) (30,31). Increased molecular mobility and plasticity are generally associated with lower glass transition. Overall, these results confirm a higher state of plasticization for HPC in relation to the other binders.

Consistent with the results for pure polymer tablets and the earlier reports on binder film mechanical properties, Joneja et al. (32) showed that for wet-granulated acetaminophen formulations, binder toughness and a high degree of plastic flow were key determinants in assuring robust tablets. They studied four binders, HPC, MC, PVP, and PGS, at 6% use levels. HPC yielded stronger, more deformable, and therefore tougher tablets. The differences in terms of tablet friability and strength were further accentuated when the tablet press speed was increased to simulate the speeds typically encountered in commercial production (Figs. 11 and 12). Further studies evaluated whether comparable properties could be achieved by varying the various binder levels.

It is notable that the results from this study are consistent with the studies of Krycer et al. (24), as also Lusvardi et al. (23) discussed in section "Stability and Compatibility," and also correlate with the results of Reading and Spring (29) indicating that binder performance rank order can be predicted on the basis of thermal and mechanical properties such as binder plasticity and toughness.

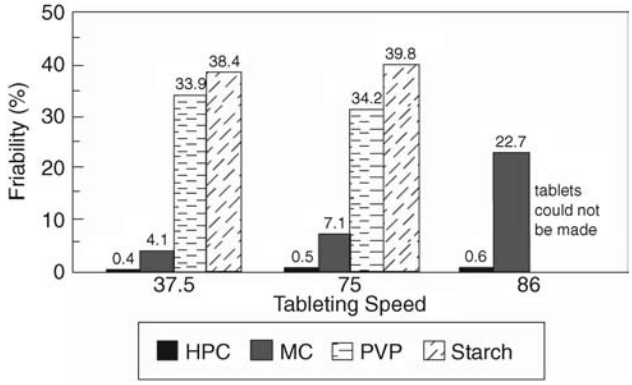


Figure 11 Friability for wet-granulated acetaminophen tablets containing 6% HPC, methyl cellulose, PVP, or starch as wet binders. 600-mg tablets (0.4375 inch standard round convex) were compressed on a Manesty Betapress at 15 kN at three different turret speeds. HPC comprising tablets showed only a negligible increase in friability. PVP- and starch-comprising tablets could not be made at 86 rpm because of excessive capping on ejection from the press. *Abbreviations*: HPC, hydroxypropylcellulose; PVP, polyvinylpyrrolidone. *Source*: Adapted from Ref. 32.

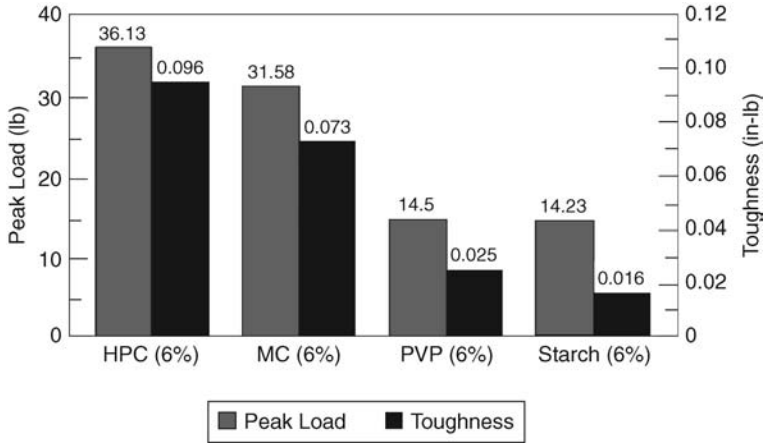


Figure 12 Tablet strength and toughness for wet-granulated acetaminophen tablets comprising 6% hydroxypropylcellulose, methyl cellulose, polyvinylpyrrolidone, or pregelatinized starch binder. Tablets were compressed on a Manesty Betapress at 37.5 rpm turret speed at 15 kN compression force. Tablet strength and toughness were assessed by diametral compression on a universal testing machine at 0.05 in/min crosshead speed. *Source*: Adapted from Ref. 32.

However, it is important to recognize that the results also correlate well with measures of binder wettability and spreading such as aqueous surface tensions, binder solution contact angles on the substrate, and spreading coefficients. It is not possible to easily separate the contributions of surface interaction from those of the inherent mechanical properties of the binders. However, on the basis of the consistent evidence from binder studies involving a variety of substrates, one can conclude that both binder solution-substrate wetting and the mechanical and compressive properties of the binder and binder films are key determinants of granule properties such as density and strength, as well as tablet strength and robustness. Furthermore, it is clear that significant differences exist among currently available binders in terms of functionality, in particular wettability and surface tension, plasticity, and toughness.

REGULATORY ACCEPTANCE AND SUPPLIER RELIABILITY

Formulators and scientists are generally well attuned to focusing on technical aspects of a formulation development project, but regulatory acceptance and supplier reliability for the binders and formulation components that one chooses to work with are just as important to assure project success.

It is sometimes not appreciated that most excipients including binder polymers are manufactured in large chemical plants, rather than pharmaceutical manufacturing

environments. Apart from the massive difference in scale compared with typical pharmaceutical manufacturing (a typical binder lot size may be 20–30,000 kg), it is also important to understand that similar polymer grades may also be manufactured for industrial use. Frequently, pharmaceutical grades represent only a small portion of the output of a typical polymer plant. When working with a particular binder or excipient in general, it is therefore important to ensure that the chosen supplier has the necessary excipient GMP manufacturing capabilities and has an audit history with the FDA or similar authorities. It should also be understood that excipient GMP differ from drug product manufacturing GMP or API manufacturing.

In terms of choice of binders it is important to work with materials that are well established as pharmaceutical excipients with established pharmacopeial monographs. Ideally the binder will be represented in all the major pharmacopeias, that is, USP/NF, Ph. Eur., and JP. For nutritional supplements it is also important that the binder has a monograph in the Food Chemicals Codex, or that the binder has GRAS status or is listed as a direct food additive by FDA or the relevant authorities in the country of interest. It is then also important for the formulator to ensure that the particular grade chosen to work is compliant with the relevant monographs and standards.

Last, to comply with the directives on quality by design, it will be important for the scientist to test the impact of varying the excipient quality parameters within and sometimes outside the specification limits. This is best accomplished by working with three to five lots of the chosen binder at an early stage to elucidate critical functional differences. Frequently, suppliers will also accommodate requests for samples made at the specification or process limits. Where possible and if available, it can also be useful to study multiyear lot histories for the various quality parameters.

REFERENCES

1. Rudnic E, Schwartz JB. Oral solid dosage forms. In: Genaro AR, ed. Remington: the Science and Practice of Pharmacy. 19th ed. Vol 2. Easton: Mack Publishing Company, 1995:1629.
2. Klucel® Hydroxypropyl Cellulose. Physical and Chemical Properties. Ashland Aqualon Functional Ingredients, Wilmington, DE 2001.
3. Skinner GW, Harcum WW. Evaluation of low-viscosity polymers in a model high-dose, acetaminophen formulation. Aqualon Pharmaceutical Technology Report PTR 11, 1998. Available at: http://www.herc.com/aqualon/product/data/ptr/ptr011. Accessed March 2009.
4. Soluble Kollidon® grades, Povidone Ph.Eur., USP, JP. Technical Information. August 2008. BASF SE, Care Chemicals Division, Limburgerhof.
5. Plasdone® S-630 Copovidone Product Guide. International Specialty Products, Wayne, NJ.
6. Starch 1500® Partially Pregelatinized Maize Starch. Product Brochure, 1999. Colorcon, Westpoint, PA.
7. Cutt T, Fell JT, Rue PJ, et al. Granulation and compaction of a model system. I. Granule properties. Int J Pharm 1986; 33:81–87.
8. Waterman KC, Adami RC, Hong J. Impurities in drug products. In: Ahuja S, Alsante KM, eds. Handbook of Isolation and Characterization of Impurities in Pharmaceuticals. Separation Science and Technology. Vol. 5. Amsterdam: Academic Press, 2003:75–88.
9. Uzunarslan K, Akbuga J. The effect of moisture on the physical characteristics of ranitidine hydrochloride tablets prepared by different binders and techniques. Drug Dev Ind Pharm 1991; 17(8): 1067–1081.
10. Kiekens F, Zelko R, Remon JP. Effect of the storage conditions on the tensile strength of tablets in relation to the enthalpy relaxation of the binder. Pharm Res 2000; 17(4):490–493.
11. Fitzpatrick, S, McCabe JF, Petts CR, et al. Effect of moisture on polyvinylpyrrolidone in accelerated stability testing. Int J Pharm 2002; 246:143–151.
12. del Barrio MA, Hu J, Zhou P, et al. Simultaneous determination of formic acid and formaldehyde in pharmaceutical excipients using headspace GC/MS. J Pharm Biomed Anal 2006; 41:738–743.
13. Nassar MN, Nesarikar VN, Lozano R, et al. Influence of formaldehyde impurity in polysorbate 80 and PEG-300 on the stability of a parenteral formulation of BMS-204352: identification and control of the degradation product. Pharm Dev Technol 2004; 9:189–195.
14. Wasylaschuk W, Harmon PA, Wagner G, et al. Evaluation of hydroperoxides in common pharmaceutical excipients. J Pharm Sci 2007; 96(1):106–116.
15. Huang T, Garceau ME, Gao P. Liquid chromatographic determination of residual hydrogen peroxide in pharmaceutical excipients using platinum and wired enzyme electrodes. J Pharm Biomed Anal 2003; 31:1203–1210.

16. Hartauer KJ, Arbuthnot GN, Baertschi SW, et al. Influence of peroxide impurities in povidone and crospovidone on the stability of raloxifene hydrochloride in tablets: Identification and control of an oxidative degradation product. Pharm Dev Tech 2000; 5(3):303–310.
17. Rowe RC. Correlation between predicted binder spreading coefficients and measured granule and tablet properties in the granulation of paracetamol. Int J Pharm 1990; 58:209–213.
18. Litster J, Ennis B. Wetting nucleation and binder distribution. In: Litster J, Ennis B, eds. The Science and Engineering of Granulation Processes. 1st ed. Dordrecht: Kluwer Academic Publishers, 2004:37–73.
19. Hapgood KP, Litster JD, Biggs SR, et al. Drop penetration into porous powder beds. J Colloid Interface Sci 2002; 253:353–366.
20. Ritala M, Jungersen O, Holm P, et al. A comparison between binders in the wet phase of granulation in a high shear mixer. Drug Dev Ind Pharm 1986; 12(11):1685–1700.
21. Wu S. Polar and non-polar interactions in adhesion. J Adhesion 1973; 5:39–55.
22. Washburn EW. The dynamics of capillary flow. Phys Rev 1921; 17:273–383.
23. Lusvardi KM, Dürig T, Skinner GW, et al. Fundamentals of hydroxypropylcellulose binders in wet granulation. Aqualon Pharmaceutical Technology Report PTR 26, 2003. Available at: http://www.herc.com/aqualon/product/data/ptr/ptr026. Accessed March 2009.
24. Krycer I, Pope DG, Hersey JA. An evaluation of tablet binding agents. I. Solution binders. Powder Technol 1983; 34:39–51.
25. Kaufman M. How physical properties translated into formulation design. Sino-American Pharmaceutical Professionals Association Pharmaceutical Symposium, East Hanover, NJ, May 2002.
26. Fox HW, Zisman WA. The spreading of liquids on low energy surfaces. I. Polytetrafluoroethylene. J Colloid Sci 1950; 5:514–531.
27. Zisman WA. Contact angle wettability and adhesion. In: Gould R F, ed. ACS Advances in Chemistry Series. Vol 43. Washington: American Chemical Society, 1964:1–50.
28. Wells J I, Walker CV. The influence of granulating fluids upon granule and tablet properties: the role of secondary binding. Int J Pharm 1983; 15:97–111.
29. Reading SJ, Spring MS. The effects of binder film characteristics on granule and tablet properties. J Pharm Pharmacol 1984; 36:421–426.
30. Skinner GW, Harcum WW, Lusvardi KM, et al. Evaluation of hydroxypropylcellulose as a direct compression binder. Aqualon Pharmaceutical Technology Report PTR 25, 2003. Available at: http://www.herc.com/aqualon/product/data/ptr/ptr025. Accessed March 2009.
31. Picker-Freyer KM, Dürig T. Physical mechanical and tablet formation properties of hydroxypropylcellulose: in pure form and in mixtures. AAPS Pharm Sci Tech 2007; 8(4):92. Available at: http://www.aapspharmscitech.org. Accessed March 2009.
32. Joneja SK, Harcum WW, Skinner GW, et al. Investigating the fundamental effects of binders on pharmaceutical tablet performance. Drug Dev Ind Pharm 1999; 25(10):1129–1135.

5 Spray Drying and Pharmaceutical Applications

Metin Çelik
Pharmaceutical Technologies International, Inc., Belle Mead, New Jersey, U.S.A. and School of Pharmacy, Near East University, Nicosia, Turkish Republic of Northern Cyprus

Susan C. Wendell
Johnson & Johnson, Raritan, New Jersey, U.S.A.

INTRODUCTION

Spray drying is one of the oldest forms of drying and one of the few technologies available for the conversion of a liquid, slurry, or low-viscosity paste to a dry solid (free-flowing powder) in one unit operation (1).

Figure 1 shows a general spray drying process schematically. The simplicity and flexibility of the spray drying process make it ideal for handling a wide variety of pharmaceutical products.

Background

The first detailed description of the drying of products in spray form was mentioned in a patent of 1872 entitled "Improvement of Drying and Concentration Liquid Substances by Atomizing" (2). However, this process found its first significant applications in the milk and detergent industries in the 1920s (3). In current times, spray drying is utilized extensively in many aspects of our daily life, from food products, cosmetics, and pharmaceuticals to chemicals, fabrics, and electronics. Typical pharmaceutical examples include spray-dried enzymes (such as amylase, protease, lipase, and trypsin), antibiotics (such as sulfathiazole, streptomycin, penicillin, and tetracycline) and many other active pharmaceutical ingredients, vitamins (such as ascorbic acid and vitamin B12), and excipients for direct compression (such as lactose, mannitol, and microcrystalline cellulose). A recent review article has reported the advances in spray drying technology and its applications (4).

Advantages and Limitation

There are several reasons why the technology of spray drying has found many applications in numerous industries. It is a continuous process. As long as liquid feed can continue to be supplied to the drying system, the spray-dried product will continue to be produced. In some instances, this process has been operated for months without interruption. The physical properties of the resulting product (such as particle size and shape, moisture content, and flow properties) can be controlled through the selection of equipment choices and the manipulation of process variables. The actual spray drying process is almost instantaneous as the major portion of the evaporation takes place in as short time as milliseconds or a few seconds, depending on the design of the equipment and process conditions. This makes spray drying well suited for heat-sensitive products. In addition, corrosive and abrasive materials can be readily accommodated because the contact between the mechanical parts and materials is minimal as compared with other granulation processes. Also, spray dryers have few moving parts. In fact, careful selection of various components can result in a system having no moving parts in direct contact with the product. Operation requirements of small and large dryers are the same. This makes spray drying a labor cost-effective process, especially for high-volume products. Last, the spray drying process can be fully automated. Commercial-scale spray dryers are controlled by programmable logic controllers (PLCs) or solid-state controllers. These control systems monitor exhaust air temperature or humidity and provide an input signal that, by way of a set point, modulates the energy supplied to the process (5).

Like all other granulation processes, spray drying also has some limitations. For example, it is not typically well suited for producing granules with mean particle size less than 200 μm as shown in Figure 2. It also has poor thermal efficiency at lower inlet temperatures, and the

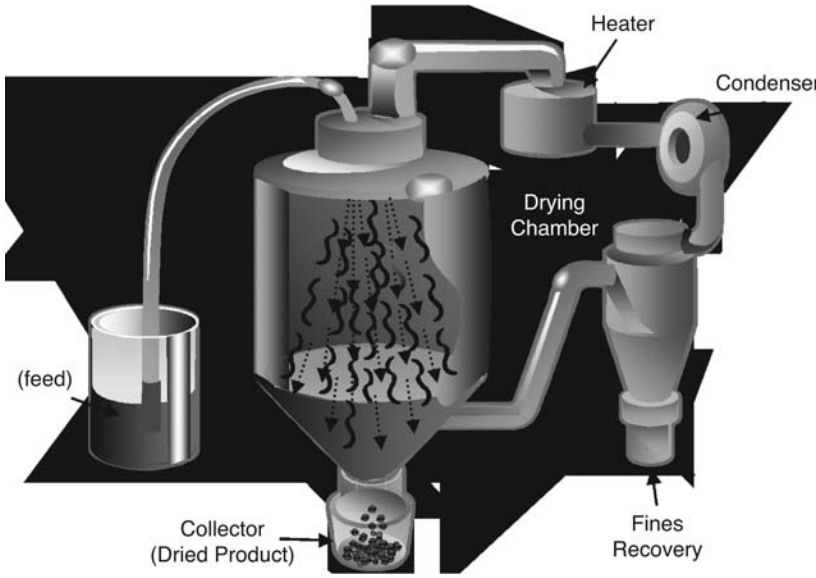


Figure 1 A schematic representation of a general spray drying process with primary and secondary product separations.

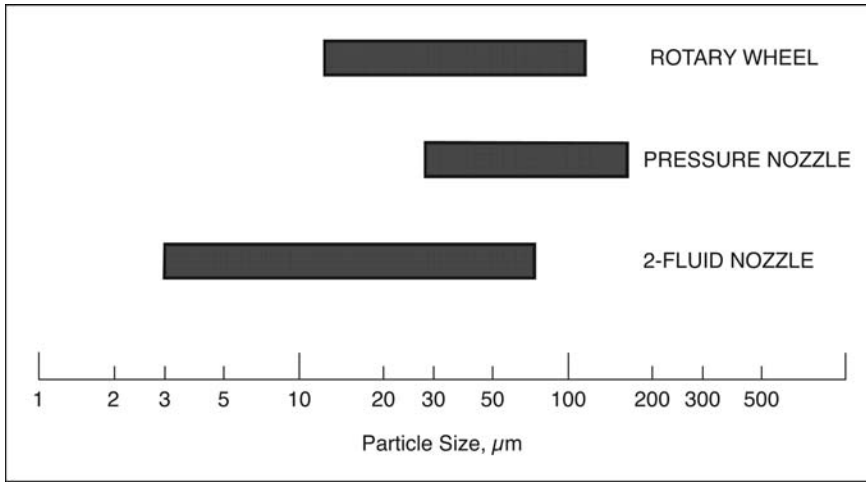


Figure 2 Range of mean particle sizes achievable by control of atomizer operation at low to medium feed rates.

exhaust air stream contains heat, which often requires sophisticated heat exchange equipment for removal.

SPRAY DRYING PROCESS STAGES

The spray drying process is carried out in three fundamental stages as shown schematically in Figure 3. The first stage is atomization of a liquid feed into fine droplets. In the second stage, spray droplets mix with a heated gas stream, and the dried particles are produced by the evaporation of the liquid from the droplets. The final stage involves the separation of the dried powder from the gas stream and collection of this powder in a chamber. The second stage (i.e., the mixing and drying step) has also been considered as separate steps (6). The following section details each of these stages, their process parameters, and related equipment details.

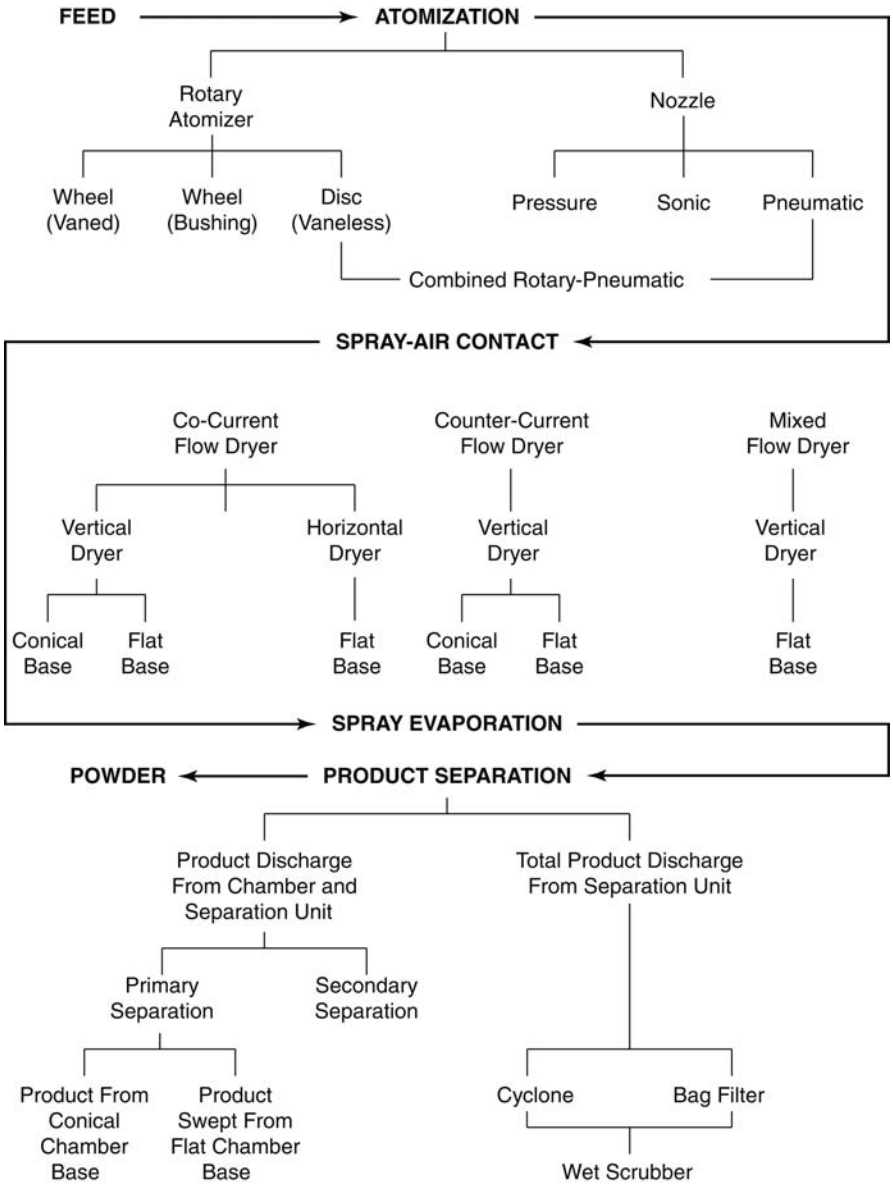


Figure 3 Schematic of spray drying process shown in stages: stage 1: atomization; stage II: spray-air contact and evaporation; and stage III: product separation. *Source*: Adapted from Ref. 6.

Atomization

Atomization is the process by which a liquid is disintegrated into many fine droplets. The formation of a spray with high surface/mass ratio is highly critical for optimum liquid evaporation conditions and, consequently, the desired properties of the resulting product. Although ideally the sizes of all droplets should be the same, in practical terms, formation of droplets with a narrow size distribution would be satisfactory.

Atomizer Types and Designs

Formation of the atomized spray requires application of a force. The commercially available systems employ one of the following in order to create an atomized spray: centrifugal energy, pressure energy, kinetic energy, or sonic energy and vibrations.

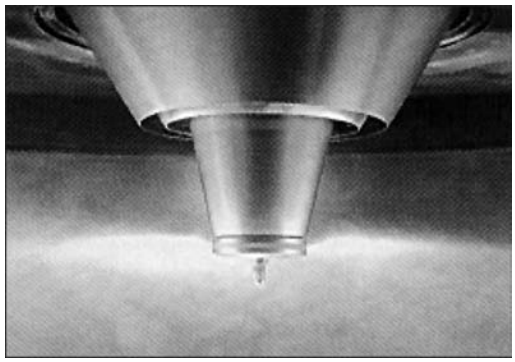


Figure 4 Common rotary atomizers (courtesy GEA Pharma Systems).

Centrifugal atomizers. Centrifugal atomizers utilize either a rotating disk or wheel to disintegrate the liquid stream into droplets (7). Examples of rotary atomizers are shown in Figure 4. These devices form a low-pressure system, and a wide variety of spray characteristics can be obtained for a given product through combinations of feed rate, atomizer speed, and atomizer design. The droplet size distribution is fairly narrow for a given method and process conditions but the mean droplet size can be varied from as small as 15 μm to as large as 250 μm, depending on the amount of energy transmitted to the liquid. Larger mean sizes require larger drying chamber diameters. Wheels are well suited for producing sprays in the fine to medium-coarse size range while disks are used to produce coarse sprays.

Rotary atomizers normally operate in the range of 5000 to 25,000 rpm with wheel diameter of 5 to 50 cm. The mean size of the droplet produced is inversely proportional to the wheel speed and directly proportional to the feed rate and its viscosity. Solid content and surface tension are other factors having minor effects on the droplet size. For example, an increase in feed rate may slightly increase the particle size, but the use of a variable-speed drive on the centrifugal atomizer facilitates correction to the specified size.

Centrifugal atomizer designs include wheels with vanes or bushings and vaneless disks. Vaned atomizer wheels produce sprays of high homogeneity and are the most commonly used as compared with other designs. In this type of atomizer, liquid fed onto a wheel moves across the surface until contained by the rotating vane. The liquid flows outward under the influence of centrifugal force and spreads over the vane, wetting the vane surface as a thin film. At very low liquid vane loadings, the thin film can split into streams. No liquid slippage occurs on a wheel once the liquid has contacted the vanes. Whether radial or curved, the vanes prevent transverse flow of liquid over the surface. Abrasive materials are best handled using atomizer wheels with bushings. Since the feed material is in direct contact with rotating parts, the bushings feature wear-resistant surfaces and require additional maintenance. Vaneless (disk) designs are often applied when coarse powders are required at high production rates.

Bulk pharmaceutical excipients and fine chemicals, such as antacids, are often produced using centrifugal atomizers. The particles produced by this technique are generally free

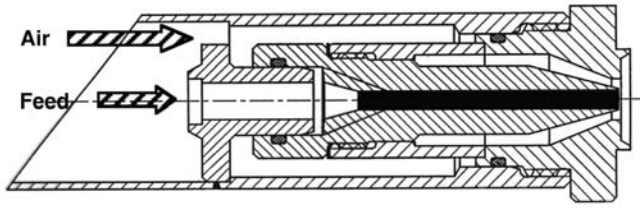


Figure 5 Schematic presentation of a typical two-fluid nozzle. *Source*: Courtesy of GEA Pharma Systems.

flowing and, unless intentionally produced with very fine atomization, dust free. The porous structure of the particles provides increased solubility, and the relatively low density and friability of these particles result in generally good compaction properties. Also, the batch-to-batch reproducibility and dryer-to-dryer transferability of this technique are excellent. As mentioned earlier, if larger spray-dried particles are desired, larger production drying chambers must be employed.

Kinetic energy nozzles. Kinetic energy is applied in the form of two-fluid or pneumatic atomization. This is the most commonly used atomization technique within the pharmaceutical industry. Here, atomization is accomplished by the interaction of the liquid with a second fluid, usually compressed air. High air velocities are generated within the nozzle for effective feed contact, which breaks up the feed into a spray of fine droplets. Neither the liquid nor the air requires very high pressure, with 200 to 350 kPa being typical. A typical two-fluid nozzle is shown in Figure 5. Particle size is controlled by varying the ratio of the compressed airflow to that of the liquid. The main advantage of this type of atomization is that the liquid has a relatively low velocity as it exits the nozzle; therefore, the droplets require a shorter flight path for drying. Because many pharmaceutical applications use relatively small spray dryers, pneumatic nozzles are often used. Another advantage is the simple design that lends itself to easy cleaning, sterile operation, and minimal contamination. Pneumatic nozzles can be designed to meet the most stringent requirements for sterile or aseptic applications. Special consideration must be given to supplying a sterile source of compressed air for atomization.

Another type of kinetic energy nozzle is the three-fluid nozzle. The spray characteristics obtained by two- and three-fluid nozzles are similar when atomizing low-viscosity feeds at up to intermediate feed rates. Use of the second air stream with three-fluid nozzles causes a waste of energy, except for high feed rates of low-viscosity feeds.

Pressure nozzles. The second most common form of atomization for pharmaceutical applications is hydraulic pressure nozzle atomization. Here the feed liquid is pressurized by a pump and forced through a nozzle orifice as a high-speed film that readily disintegrates into fine droplets. The feed is made to rotate within the nozzle, resulting in a cone-shaped spray pattern emerging from the nozzle orifice. Rotary motion within the nozzle can be achieved by use of swirl inserts or spiral grooved inserts (Fig. 6). The swirl inserts have comparatively larger flow passages and enable such nozzles to handle high-solid feeds without causing any wear or clogging.

Because the liquid spray exits the nozzle with a relatively high velocity, a spray drying chamber of at least 2.5 m in diameter and 3.0 m in cylinder height is usually required to operate with pressure nozzles.

The differential pressure across the orifice determines the mean droplet diameter. The distribution about the mean is similar to, but in most cases is narrower than, two-fluid atomization. In contrast, sprays from pressure nozzles handling high feed rates are generally less homogeneous and coarser than sprays from vaned wheels. At low feed rates, spray characteristics from nozzles and wheels are comparable. Mean size of spray is directly proportional to feed rate and inversely proportional to pressure.

Pressure nozzles are generally used to form coarse spray-dried particles (120 to 300 μm mean particle size) with good flow properties. Antibiotics are a typical application for such a dryer.

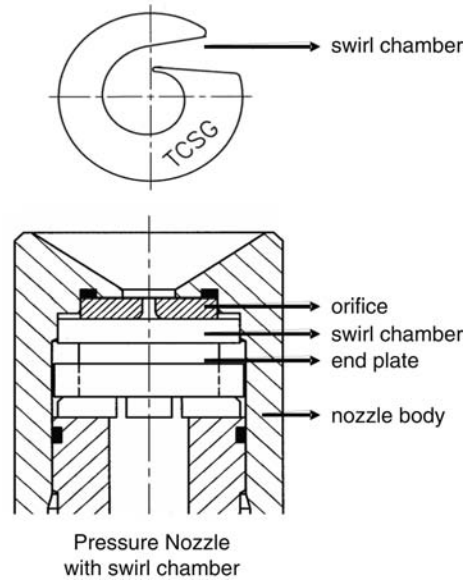


Figure 6 Schematic presentation of pressure nozzles. *Source*: Courtesy of GEA Pharma Systems.

Sonic energy atomizers. The use of sonic energy and vibrations for atomization in spray drying has found growing interest in the last two decades. However, this type of atomizer has not yet found significant commercial applications. The advantages of sonic nozzles operating at low pressure and having wide flow channels suggest they may be suitable for abrasive and corrosive materials, but it is most likely that sonic nozzles will continue to be developed as atomizers for special applications, such as very fine sprays of mean size 20 μm, where the nature of the spray angle and cone minimizes droplet coalescence (8).

Atomizer Selection

The function of any atomizer is to produce as homogeneous a spray as possible. The nature of the feed, the characteristics of the spray, and the desired properties of the resulting dried product play very important roles in the selection of the atomizer type. With proper design and operation, nozzles and rotary atomizers can produce sprays having similar droplet size distribution. In all atomizer types, the size of droplets can be altered by either increasing or decreasing the atomization energy (e.g., increased atomization energy results in smaller droplet size). For a given amount of energy, the viscosity and surface tension values of the feed influence the size of the droplet (e.g., higher values of these feed fluidity properties result in larger spray droplets).

In general, rotary atomizers are utilized to produce a fine to medium-coarse product with a mean size of 20 to 150 μm, although larger spray-dried particles can also be obtained if a very large drying chamber is used. Nozzle atomizers are used to produce spray-dried product with a coarse mean particle size of 150 to 300 μm (9).

For a given spray drying application, the selection between rotary and nozzle atomizers involves the following considerations (10):

1. The feed capacity range of the atomizer for which complete atomization is attained,
2. Atomization efficiency
3. The droplet size distribution at identical feed rates
4. Spray homogeneity
5. The operational flexibility
6. The suitability of dryer chamber design for atomizer operation
7. Feed properties
8. The atomizer experience available for the product in question

Spray-Air Contact and Evaporation

Once the liquid is atomized, it must be brought into intimate contact with the heated gas for evaporation to take place equally from the surface of all droplets. This contact step takes place within a vessel called the drying chamber. The heated gas is introduced into the chamber by an air dispenser, which ensures that the gas flows equally to all parts of the chamber.

Spray-Air Contact

The way in which spray contacts the drying air is a critical factor in spray drying operations. Spray-air contact is determined by the position of the atomizer in relation to the air inlet.

Inlet air is introduced to the drying chamber via an air disperser, which uses perforated plates, or vaned channels through which the gas is equalized in all directions. It is critical that the air entering the disperser is well mixed and has no temperature gradient across the duct leading into it; otherwise, the drying will not be even within the chamber. The air disperser is normally built into the roof of the drying chamber and the atomization device is placed in or adjacent to the air disperser. Thus, instant and complete mixing of the heated drying gas with the atomized clouds of droplets can be achieved.

Spray droplet movement is classified according to the dryer chamber layout and can be designated as cocurrent, countercurrent, or mixed flow, although this designation is not a true representation of actual conditions.

1. Cocurrent flow is the configuration in which the spray and drying air pass through the dryer in the same direction. This arrangement is widely used and is ideal for heat-sensitive products. Spray evaporation is rapid, the drying air cools accordingly, and overall evaporation times are short. The particles are not subject to heat degradation. In fact, low-temperature conditions are achieved throughout the entire chamber in spite of very hot air entering the chamber.
2. Countercurrent flow is the configuration in which the spray and air enter at the opposite ends of the dryer. This arrangement has excellent heat utilization. Countercurrent flow is used with nozzle atomization and is well suited for meeting the final spray-dried properties of non-heat-sensitive materials.
3. Mixed flow is the configuration in which both co- and countercurrent flows are incorporated. The advantage of this type of arrangement is that coarse free-flowing products can be produced in relatively small drying chambers. In mixed-flow systems the powder is subjected to higher particle temperature. A mixed-flow system can be integrated with a fluid-bed drying chamber when lower particle temperatures are necessary.

The spray-air contact design can be selected according to the required particle size and the temperature to which the dried particle can be subjected. For example, if a low product temperature must be maintained at all times, a cocurrent rotary atomizer is selected for producing fine particles while a countercurrent pressure atomizer is preferred for obtaining coarser particles. If coarse particles with predetermined porosity and bulk density properties are desired, a countercurrent pressure nozzle atomizer is well suited as high product temperature can be maintained for obtaining the desired porosity and bulk density of the resulting product. For obtaining coarse spray-dried particles of heat-sensitive materials, a mixed-flow nozzle system can be selected. Integration with a fluid bed is recommended for agglomerated or granulated powders.

Drying

The largest and most obvious part of a spray drying system is the drying chamber. This vessel can be tall and slender or have a large diameter with a short cylinder height. Selecting these dimensions is based on two-process criteria that must be met. First, the vessel must be of adequate volume to provide enough contact time between the atomized cloud and the heated gas. This volume is calculated by determining the mass of air required for evaporation and multiplying it by the gas residence time, which testing or experience dictates.

The second criterion is that all droplets must be sufficiently dried before they contact a surface. This is where the vessel shape comes into play. Centrifugal atomizers require larger diameters and shorter cylinder heights. In contrast, nozzle atomizer systems must have narrower and taller drying chambers. Most spray dryer manufacturers can estimate, for a given powder's mean particle size, what dimensions are needed to prevent wet deposits on the drying chamber walls.

Drying Gas

In pharmaceutical applications of spray drying, the feedstock can be prepared by suspending or dissolving the product to be spray-dried in water. However, the utilization of a wide variety of organic solvents in feedstock preparations is also common. Alcohols, such as ethanol, methanol, and isopropanol, are preferred organic solvents in spray drying of pharmaceuticals, although other organic solvents such as ketones are also used in other industries; often the synthesis process upstream from the drying step determines the solvent selection. The drying characteristics of the solvents are also important. For example, a solvent with a low boiling point may be the only choice for heat-sensitive materials.

Although evaporating organic solvents by a spray drying process is very efficient because of the resulting shorter residence time, as compared with the evaporation of water, the risk of explosion makes the use of these solvents very hazardous. Therefore, an inert gas, usually nitrogen, instead of air must be used as drying gas for the evaporation of the solvents. Use of inert gas requires the use of a closed-cycle system for spray drying to recover the solvent and to limit the gas usage. However, for small drying tests and laboratory work, the nitrogen can be used without recirculation, using a carbon bed on the exhaust gas to collect the solvent.

Dried Powder Separation

Powder separation from the drying air follows the drying stage. In almost every case, spray drying chambers have cone bottoms to facilitate the collection of the dried powder.

Two systems are utilized to collect the dried product. In the first type of system, when coarse powders are to be collected, they are usually discharged directly from the bottom of the cone through a suitable airlock, such as a rotary valve. The gas stream, now cool and containing all of the evaporated moisture, is drawn from the center of the cone above the cone bottom and discharged through a side outlet. In effect, the chamber bottom is acting as a cyclone separator. Because of the relatively low efficiency of collection, some fines are always carried with the gas stream. These must be separated in high-efficiency cyclones followed by a wet scrubber or in a fabric filter (bag collector). Fines collected in the dry state (bag collector) are often added to the larger powder stream or recycled. When very fine powders are being produced, the side outlet is often eliminated and the dried product together with the exhaust gas is transported from the chamber through a gooseneck at the bottom of the cone. The higher loading of entrained powder affects cyclone design but has little or no effect on the bag collector size.

In the second type of system, total recovery of dried products takes place in the separation equipment. This type of system does not need a product-conveying system; therefore, the separation efficiency of the equipment becomes very critical. Separation of dried product from air influences powder properties by virtue of the mechanical handling involved during the separation stage. Excessive mechanical handling can produce powders with a high percentage of fines.

PROCESS LAYOUTS

The most widely used spray drying process layout is open-cycle layout in which the air is drawn from the atmosphere, passed through the drying chamber, and exhausted back to the atmosphere. This layout is used for aqueous feedstock and employs air as the drying gas. There are numerous variations of open-cycle layout systems, two of which are common in pharmaceutical applications (Fig. 7) (11). The most common and cost-effective layout utilizes a high-efficiency cyclone and scrubber (Fig. 7A). In this layout, the loss of very fine particles to atmosphere cannot be prevented. If the desired particle size of the spray-dried product is too

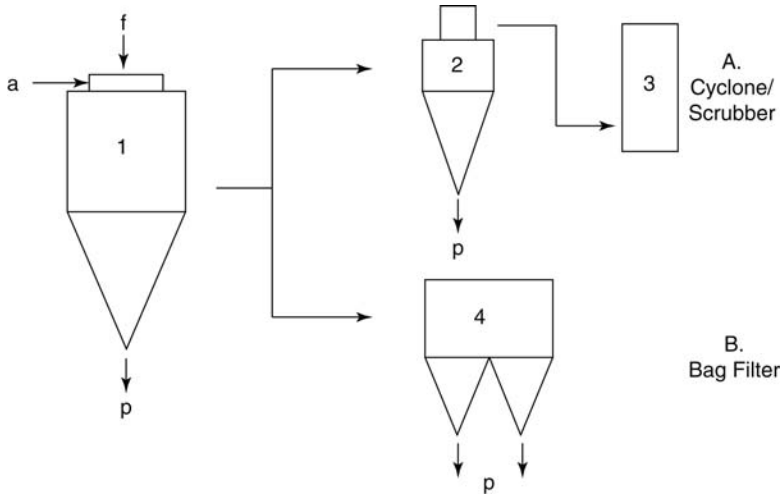


Figure 7 Typical layout of the open-cycle spray dryer system: (**A**) cyclone/scrubber and (**B**) bag filter. a, air; f, feed; p, spray-dried product. 1, spray dryer chamber; 2, cyclone; 3, wet scrubber; 4, bag filter/collector. *Source*: Adapted from Ref. 11.

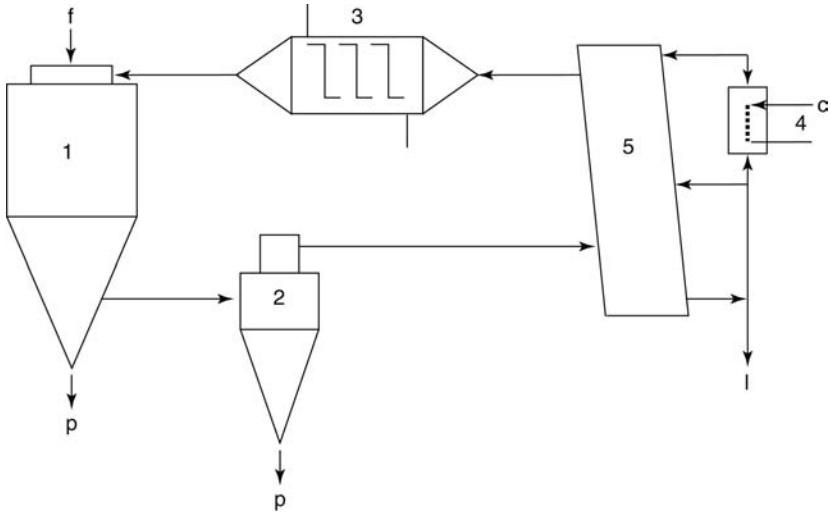


Figure 8 Typical layout of the closed-cycle spray dryer system. *Abbreviations*: c, coolant (diluent); f, feed; l, solvent recovery; p, spray-dried product; 1, dried powder; 2, cyclone; 3, liquid-phase indirect heater; 4, heat exchanger; 5, scrubber-condenser. *Source*: Adapted from Ref. 12.

small to be recovered by cyclone and scrubber systems, then the use of a layout employing a bag filter is recommended (Fig. 7B).

Closed-cycle layouts are mainly used for nonaqueous (i.e., organic solvents) feedstock and generally require the use of inert gas as the drying medium. They are also employed when flammable, explosive, or toxic products are used in the spray drying process or atmospheric pollution is not permitted. Figure 8 illustrates the flow diagram of a closed-cycle layout schematically (12). These systems require a good control of the scrubbing-condensing stage at precise temperatures.

In addition to open- and closed-cycle systems, there are semiclosed-cycle layouts that are not strict in terms of type of drying medium and are operated under slight vacuum conditions.

THEORY OF SPRAY DRYING FUNDAMENTALS

Droplet Formation

Rotary Atomizer

During rotary atomization, bulk liquid feed is accelerated to a high centrifugal velocity. During this acceleration, the liquid feed forms a thin film over the rotating surface. For smooth disk atomizers, the film or liquid feed disintegrates into droplets at the edge of the wheel by one of three mechanisms: (*i*) direct droplet formation, (*ii*) ligament formation, and (*iii*) sheet formation, as shown in Figure 9, respectively. The type of droplet formation mechanism that occurs during processing is a function of the surface tension and viscosity of the feed as well as the wheel speed and feed rate (13). Direct droplet formation occurs at low wheel speeds when surface tension and viscosity dominate the atomization mechanism. The other variables that could potentially affect direct droplet formation are inertia and air friction. However, because of liquid slippage on the surface of the wheel, inertia is limited and the low release velocities minimize air friction effects, so that the effect of these variables is minimized at low wheel speeds. As wheel speeds and feed rates increase, the amount of feed in each vane increases giving rise to ligaments instead of droplets on the periphery of the wheel. These ligaments disintegrate into droplets with larger droplets forming from feeds with higher viscosity and higher surface tension. While the first two atomization mechanisms are partially controlled by the physical properties of the feed, sheet formation is a result of inertial forces becoming predominant over these properties. At high wheel speeds and feed rates, the ligaments join to form a liquid sheet that extends beyond the edge of the wheel. The liquid sheet disintegrates into a broad droplet distribution as it extends from this edge. To produce a narrow droplet distribution from this mechanism, high wheel speeds are combined with low wheel loading, which is often achieved with a decreased feed rate.

In contrast, a vaned wheel directs the flow of the liquid feed across the surface of an inner liquid distributor in which liquid slippage over the surface of the distributor occurs until there is contact with the vane or channel. The feed then flows outward because of centrifugal force and forms a thin film across the surface of the vane. As the liquid film leaves the edge of the vane, droplet formation occurs as a result of the radial and tangential velocities experienced. Atomizer wheel characteristics that influence droplet size include speed of rotation, wheel diameter, and wheel design, for example, the number and geometry of the vanes.

Two-Fluid Nozzle

Using the two-fluid nozzle type, also referred to as a pneumatic nozzle, atomization is achieved by impacting the liquid feed with high-velocity air, which results in high frictional

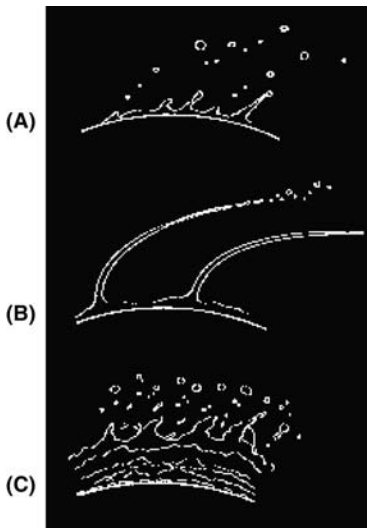


Figure 9 Smooth disk atomizer droplet formation mechanisms: (**A**) direct droplet formation, (**B**) ligament formation, and (**C**) sheet formation. *Source*: Adapted from Ref. 13.

forces that cause the feed to disintegrate into droplets. To achieve optimal frictional conditions, this high relative velocity between liquid and air can be accomplished by either expanding the air to sonic velocities or destabilizing the thin liquid film by rotating it within the nozzle prior to spray-air contact.

There are several two-fluid nozzle designs available to produce the conditions necessary for liquid-air contact. A common design is one in which the liquid and air come into contact outside the nozzle. This nozzle is often referred to as an external mixing nozzle and its main advantage is the greater control available over the atomization through the independent control of both the liquid and air streams. Other two-fluid nozzle designs include: (a) an internal mixing design with the air and liquid contacting within the nozzle head, (b) a combined internal-external mixing design created by using two airflows in the nozzle head (also called three-fluid), and (c) a pneumatic cup design with liquid-air contact occurring at the rim of a rotating nozzle head.

In general, two-fluid nozzles are capable of producing small droplet sizes over a wide range of feed rates. These droplets are then carried away from the nozzle by the momentum of the spray and the expanding atomizing air. The most important variable involved in the control of droplet size is the mass ratio of airflow to feed rate, which is also known as the air-to-feed ratio. An increase in this ratio causes a decrease in droplet size. This ratio generally ranges from 0.1 to 10. At ratios approaching 0.1, atomization is difficult even for low-viscosity feeds while a ratio of 10 approaches the limit above which atomization occurs using excess energy without an appreciable decrease in particle size (14).

Sprays formed by two-fluid nozzles are symmetrical with respect to the nozzle axis and have a cone-shaped pattern. The angle of this cone is called the spray angle and, for two-fluid nozzles, it is narrow and cannot be varied greatly by adjusting the air-to-feed ratio. The maximum spray angle available is 70° to 80°, which can be obtained by employing the maximum feed rate and airflow in a high-throughput nozzle. In general, an increase in air pressure will increase the spray angle if the feed rate is maintained at a constant level as long as the maximum angle has not been obtained. Spray angles are maintained if an increase in airflow is accompanied by an increase in feed rate resulting in a similar air-to-feed ratio.

Droplet Drying Mechanisms

Evaporation of water from a spray is often characterized using a curve that describes the change in drying rate as a function of time. This drying rate curve or evaporation history is a function of temperature, humidity, and the transport properties of the droplet formulation, as well as the air surrounding the droplet. However, many characteristics of droplet evaporation can be characterized using a general drying rate curve (Fig. 10).

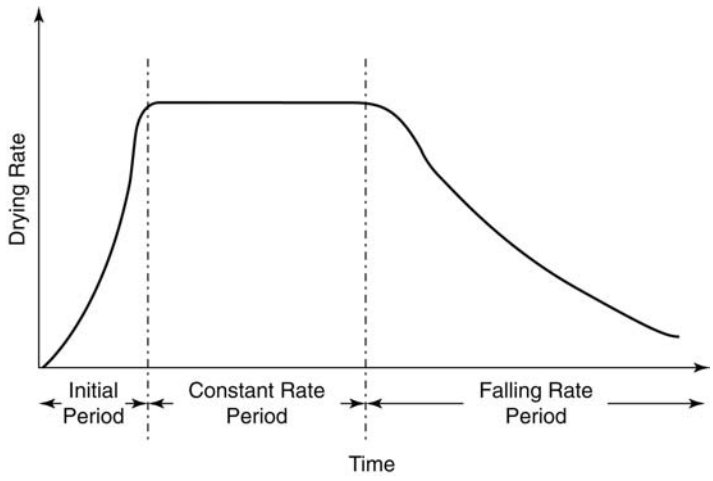


Figure 10 General drying rate curve. *Source*: Adapted from Ref. 16.

The general drying rate curve has three main phases: an initial drying phase, a phase in which the rate of drying is mainly constant, and a final phase during which the rate of drying decreases (falling-rate phase) (15). During the main phase, the removal of moisture from the droplet is at a near-constant rate representing the highest rate achieved during the evaporation history. This constant evaporation rate results in a near-constant droplet surface temperature with the wet bulb temperature representing the droplet temperature. During this phase, the majority of the droplet moisture is removed. The droplet surface is maintained at saturation by moisture migration from within the droplet to the surface. In contrast, during the falling-rate phase, the rate of moisture migration is rate-limiting to the drying rate causing a decrease in the overall rate of drying. The surface moisture content is no longer maintained and the droplet temperature rises.

The general drying rate curve is directly applicable to the spray drying process. The initial drying phase begins during the spray-air contact phase immediately upon contact of the droplet with the drying air. During this initial phase, as the drying rate increases toward equilibrium, a slight increase in droplet surface temperature occurs. The drying rate continues to increase until equilibrium across the droplet-air interface is established and the drying rate becomes constant. In the later phase, the solid layer of the spray-dried particle becomes rate limiting to mass transfer and drying rate decreases. The evaporation rate continues to decrease until the droplet reaches equilibrium moisture content with the surrounding air stream unless the product is removed from the spray dryer before equilibrium moisture content is reached. In addition, all evaporation histories, regardless of material type or spray dryer configuration, have two main points in common: the majority of the evaporation is completed in an extremely short time interval, usually less than 1.5 seconds, and the temperature of the drying air decreases rapidly during evaporation.

While the general evaporation history is representative of the processes occurring during spray drying, the actual rate of moisture migration is affected by several factors including the temperature of the surrounding air. If the inlet temperature is so high that the evaporation rate is higher than the moisture migration rate needed to maintain surface wetness, then the constant-rate drying phase is very short. This is because a dried layer forms instantaneously at the droplet surface that acts as a barrier to additional moisture transfer and retains moisture within the droplet causing the surface temperature to be much higher. In contrast, lower inlet temperatures actually yield a lower initial drying rate with a surface temperature equal to wet bulb temperature for a longer period of time.

It is important to note that the drying curve is only representative. In reality, there are no defined points during an evaporation history. Some phases may not even occur or will be very short depending on the process conditions. One example of this is a spray drying process for a heat-sensitive material where the inlet temperature is low. In this case, the initial phase may extend until a critical point where moisture migration becomes rate limiting, effectively eliminating the constant-rate drying period. In reality, the actual evaporation rate is dependent on several factors including the droplet shape, composition, physical structure, and solid concentration. The actual drying time is a sum of the constant-rate period and the falling-rate period until a desired moisture content is achieved.

Effect of Formulation on Droplet Drying Mechanisms

Droplet composition also plays a significant role in droplet evaporation history. Typically, sprays are differentiated into three main types: pure liquids, feeds containing undissolved solids, and feeds containing dissolved solids (17).

Pure Liquid Sprays

For sprays comprised of pure liquids, the droplet evaporates away completely. While this type of spray is not useful for pharmaceutical formulations, its behavior is representative of very dilute feed materials. The evaporation of pure liquids is dependent upon the dryer configuration. For low-velocity sprays in a low-velocity air stream (countercurrent dryer) or for low-velocity sprays in a high-velocity air stream (cocurrent dryer), the evaporation of the

pure liquid spray causes the air temperature and evaporation rate to decrease. Pure liquid sprays having a wide droplet distribution evaporate more quickly than narrow distributions having the same mean droplet size because of the smaller droplets in the wide distribution. In addition, the size distribution of the droplet changes during evaporation. If the initial spray is a homogeneous or very narrow distribution, the mean droplet diameter decreases during evaporation. In contrast, if the initial spray is nonhomogeneous or a wide distribution, then the mean droplet diameter initially increases prior to decreasing. In general, a distribution is the best representation of a spray since the mean of this distribution may not adequately describe all characteristics of the distribution. For dryer configurations of high relative velocities such as coarse atomization in cocurrent or fountain-type dryers, the droplets travel farther before a given fraction is evaporated. The relative velocity between droplet and drying air affects evaporation rates more significantly at higher velocities and higher drying temperatures.

Feeds Containing Insoluble Solids

For droplets containing insoluble solids, the droplet temperature is equal to the wet bulb temperature of the pure liquid droplet during the constant-rate phase since insoluble solids have negligible vapor pressure lowering effects. The total drying is the sum of the two drying periods. The drying time for the first period is short compared with the falling-rate period. The falling-rate period depends on the nature of the solid phase and can be estimated given the specific gravity of the feed slurry, the density of the dried product, and the thermal conductivity of the gaseous film around the droplet, where gaseous film temperature is the average between the exhaust temperature and droplet surface temperature. The droplet surface temperature is equal to the adiabatic saturation temperature of the suspension spray.

Feeds Containing Dissolved Solids

Droplets containing dissolved solids have lower evaporation rates than pure liquid droplets of equal size. The dissolved solids decrease the vapor pressure of the liquid, thus reducing the driving forces for mass transfer. Drying results in the formation of a solid crust on the droplet surface, which does not occur for pure liquid droplets. Vapor pressure lowering causes droplet temperature to increase over wet bulb temperature from the previous two examples. Formation of dried solid during evaporation has a significant effect on the subsequent evaporation history. During evaporation, spray-air contact and constant-rate period occur but may be shorter. The main effect of dissolved solids is seen when the first period of drying ends and droplet moisture content falls to critical value representing the formation of the solid phase on the surface. During the falling-rate period, the migration of moisture decreases because of resistance to mass transfer caused by increasing solid phase. Lastly, the heat transfer is greater than the mass transfer and the droplet temperature increases. Vaporization of the moisture within the droplet during this phase may occur if the transfer is sufficiently high.

The relationship between mass transfer and heat transfer for droplets containing dissolved solids can lead to the formation of many different particle morphologies depending on process conditions and material characteristics. Charlesworth and Marshall (18) have defined these morphologies as falling into two groups dependent on the temperature of the drying air relative to the boiling point of the droplet solution during the majority of the evaporation period (Fig. 11).

If the air temperature exceeds the boiling point of the droplet solution, then a vapor will be formed. As the solid crust forms around each droplet, vapor pressure within the droplet is formed and the resultant effect of this pressure is dependent on the nature of the crust. A porous crust will release the vapor, but a nonporous crust may rupture resulting in fractured particles or fines from disintegrated particles.

Alternately, the droplet temperature may not reach boiling point levels because of cocurrent airflow or because the residence time of droplets in the hottest regions of the dryer is often very short. In this case, moisture migration occurs through diffusion and capillary mechanisms.

In both cases, the porosity of the solid crust is often evident in the characteristics of the falling-rate period of the drying curve. If the film is highly nonporous, the rate will fall sharply

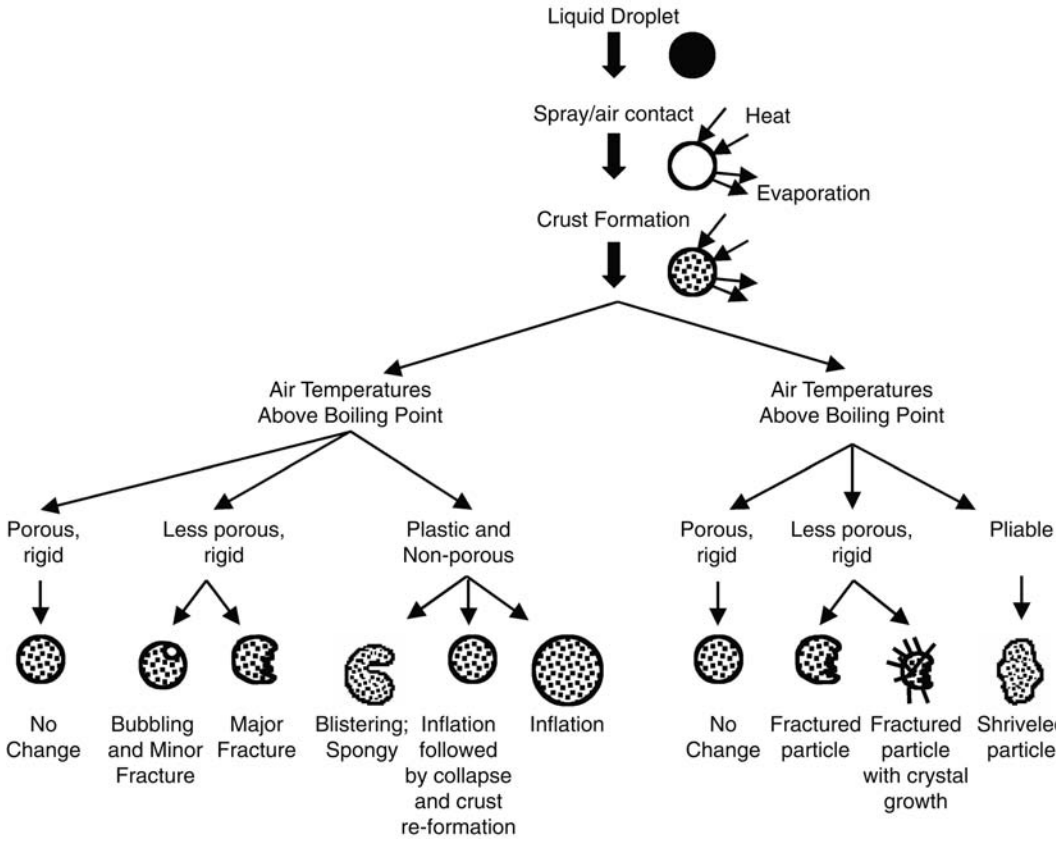


Figure 11 Potential spray-dried particle morphologies in relation to process conditions and material characteristics. *Source*: Adapted from Ref. 18.

and the evaporation time will be prolonged. However, if a highly porous film exists, then vapor is easily removed from the droplet-air interface and the drying rate is similar to that found during the first period of drying.

These drying mechanisms result in a range of particle shapes including solid, hollow, shriveled, and disintegrated, examples of which are shown in Figure 12. However, it is important to note that particle morphology is also dependent on several material characteristics including solubility, temperature of crystallization, melting point, and thermal conductivity since they will also impact the rate of crust formation, the porosity of the crust, and the subsequent drying rate.

It is also possible to influence particle density and size distribution through the modification of process parameter settings such as atomizer settings, temperature levels, and feed rates (19). For example, an increased feed rate while maintaining a constant inlet temperature results in particles that have higher moisture content and a resultant increased bulk density. By increasing the temperature of the feedstock, the ability of the feed to be atomized is often improved because of the reduction in ligament formation causing an increase in the bulk density of the dried particles. Also, an increase in the concentration of the feed solids often increases the bulk density of the dried particle as does the use of a rotary atomizer since many wheel designs reduce air entrapment. Alternatively, bulk density may be decreased through feed aeration or an increase in inlet temperature. Also, cocurrent spray-air contact is often effective for reduction in bulk density because the wettest droplets encounter the hottest air facilitating rapid evaporation and air entrapment. It is important to note that the outlined process modifications are generally applicable, but that exceptions to each can be found on the basis of material characteristics.

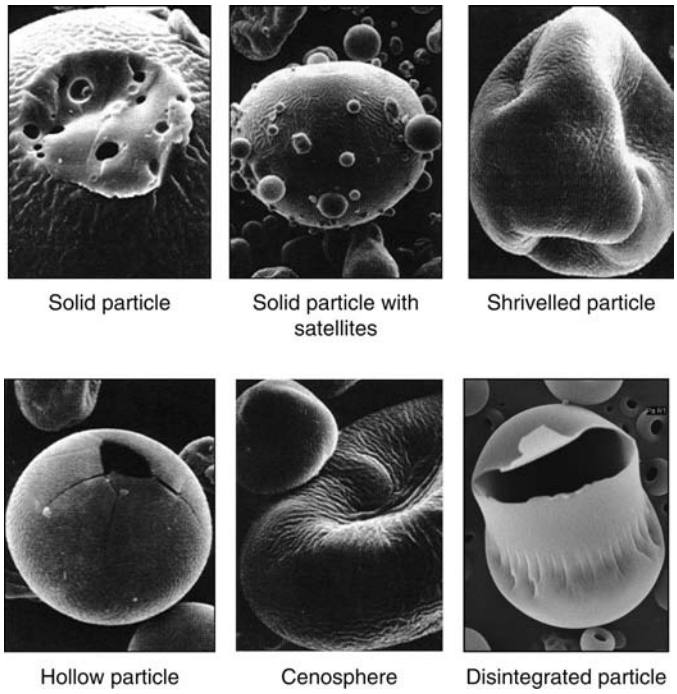


Figure 12 Various particle forms of skim milk powder. *Source*: Courtesy of GEA Pharma Systems.

In a similar manner, it is often possible to influence spray-dried particle size distribution by changing process parameter settings. As mentioned earlier, the size of the droplets formed during atomization is affected by process parameters such as atomization type, atomizer settings, feed solids concentration, feed physical properties, and drying temperatures. The size of the resultant particles following evaporation is a function of the initial droplet size as well as the material characteristics such as solid-state and film formation mechanisms.

The research on the properties droplet still continues. In a recent study, the surface stickiness of droplets, subjected to a spray drying environment, to their surface layer and powder recovery in spray dryers was investigated. A model was proposed by introducing a dimensionless time as an indicator of spray dryability and correlating this time parameter with the recovery of powders in practical spray drying. Droplets with initial diameters of 120 μm were subjected to simulated spray drying conditions, and their safe drying regime and dimensionless time values were generated. The model predicted the recovery in a pilot-scale spray dryer reasonably well (20).

SPRAY DRYING APPLICATIONS

Feasibility Assessments

Before any spray drying application work begins, it may be advantageous to conduct the following simple, qualitative tests at the laboratory bench using very little material to determine the feasibility of the application (21). A rheological profile of the solution or suspension should be evaluated or, alternatively, a small sample can be tested to see if droplets from a stirring rod can be readily formed. In the latter test, if the liquid strings from the surface or forms peaks, then high viscosity is indicated and the product may not be a candidate for spray drying without formulation changes. The behavior of non-Newtonian fluids (pseudo-plastic, thixotropic, dilatant, etc.) has been found to influence atomization and resultant droplet size (22). However, while it is expected that Newtonian and non-Newtonian fluids atomize differently, this difference was not found to be as important as the more significant effect of the wheel speed on droplet size. It is also important to note that highly viscous materials cannot be atomized by pressure nozzles.

Once the effect of viscosity has been evaluated, it may be advisable to dry a few drops of product on a glass slide using a heated air gun. During this bench drying test, the air temperature is recorded and the material is observed for the presence of stickiness, color changes, or other physical changes. If the dried powder is found to be suitable at the air temperature applied, it can be placed on a variable-temperature hot bench to determine the temperature at which the powder becomes tacky. For spray drying to be successful, this temperature must be higher than the outlet temperature of the dryer.

If the initial feasibility evaluation is successful, it is reasonable to commit additional materials for a spray drying trial. A laboratory dryer of at least 500 mm in diameter is recommended for such tests. Bench-scale spray dryers are available but limited in their ability to provide adequate atomization or sufficient process airflow for the successful production of dried particles. The laboratory unit, however, combined with very fine atomization (two-fluid or rotary) will often produce acceptable product for further testing. A series of tests can be performed at different inlet-outlet temperature combinations using small quantities of material and these samples can be tested for chemical stability to evaluate thermal effects from process air contact. The relationship between outlet temperature and final product moisture can also be established for this scale. While samples produced in a laboratory dryer are suitable for evaluating the effect of spray drying on the product, they are not suitable for use in downstream processing because the fine particle distribution produced as a result of the small drying chamber dimensions may not be representative of the final spray-dried product.

Production of coarser particles requires a larger, pilot-scale dryer, which in turn requires larger feed volumes. This pilot-scale work is often conducted at a spray drying development center since many companies have laboratory dryers but few have the sizes and variety of process types needed to fully develop a spray-dried product from pilot scale through one-tenth commercial scale and into final production. These facilities are usually found at spray drying manufacturers or custom processing companies. In addition to having the equipment, manufacturers and custom processors often have the expertise to more quickly optimize product characteristics.

Spray Drying to Produce a Specific Type of Particle

Because of its inherent costs, spray drying is not always considered as a processing option for many conventional formulations. However, when a specialized particle type is required by the active ingredient or dosage form, spray drying can become a feasible alternative to more conventional manufacturing processes. Such particle types include microcapsules, controlled-release particles, nanoparticles, and liposomes. The application of spray drying to pharmaceuticals has been extensively discussed in review articles (23,24).

Granulation

Spray drying is a unique process in several ways as compared with other granulation methods. The feedstock is a homogeneous liquid, which results in the uniform distribution of all components of the spray-dried product in the same ratio in each individual particle and eliminates the concerns of uniformly granulating dry components with a liquid. While granule characteristics may exhibit batch-to-batch variation, which in turn may influence the compaction behavior of the formulation and/or the postcompaction properties of the tablet, granules produced using spray drying are extremely consistent in terms of particle size, bulk density, and compaction behavior. These features make spray drying a suitable process for the production of directly compressible excipients such as lactose, microcrystalline cellulose, and mannitol. Spray-dried lactose is by far the most commonly encountered spray-dried excipient (23).

Many granulation methods utilize mechanical energy to transform very fine particles into granules. Although shear forces are employed in nozzle and centrifugal atomizer to create sprays, this form of energy will not destroy microencapsulated material as can happen in high-shear granulation. In spray drying, some trial and error is encountered in establishing the nozzle combinations and liquid pressures to obtain equivalent particle size distribution during scale-up; however, the resultant powder will have similar physical properties such as bulk

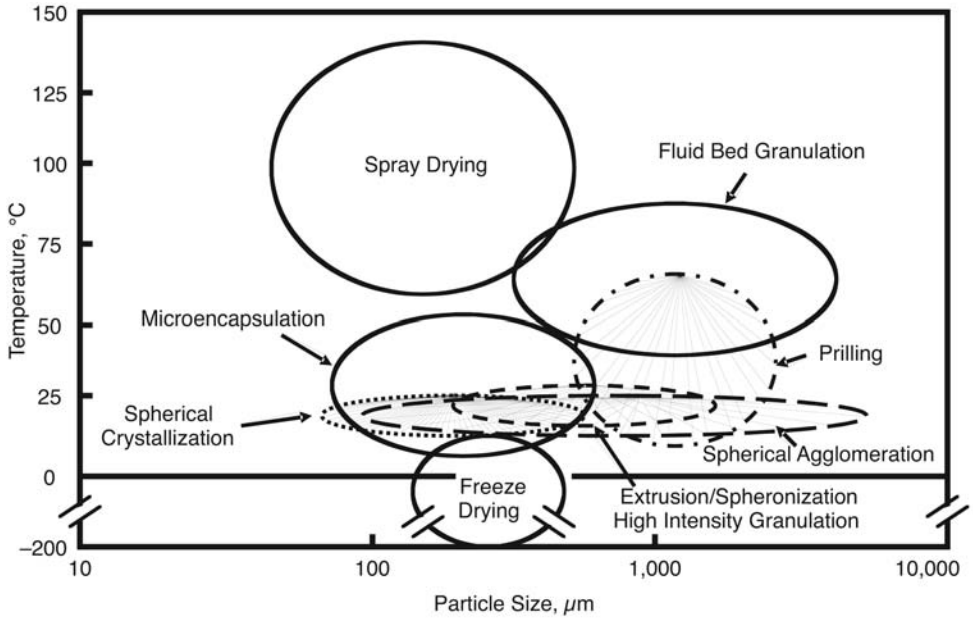


Figure 13 Particle size range of the methods utilized in particle growth. *Source*: Adapted from Ref. 25.

density and compaction. Also, it is important to note that, within the spray dryer, the product is never in contact with moving parts, which facilitates the proper cleaning process greatly.

If the granulation size is a critical criterion for a given formulation, then the selection of the granulation process may be determined on the basis of the desired particle size and feasible operating temperatures. Figure 13 compares the general particle size limitations of numerous granulations techniques.

As seen in this figure, the spray drying process results in smaller size particles as compared with some other granulation methods such as fluid-bed granulation or high-shear (high intensity) granulation. One option for producing larger agglomerates using spray drying technology is to employ fluidized spray drying, which combines the features of the spray drying process with fluid-bed granulation. The result of this process is particles similar to those obtained from a fluid-bed granulation operation, and yet the process is a continuous type in contrast to the batch operation of a fluid-bed granulator. In a fluidized spray drying system, the bottom cone of a conventional spray dryer has been modified to include an integral fluid bed (Fig. 14). When this process is implemented, atomization and spray-air contact occur as they do in a conventional spray dryer. However, when the partially dried particles reach the lower portion of the dryer, instead of undergoing product separation, the particles are fluidized by the

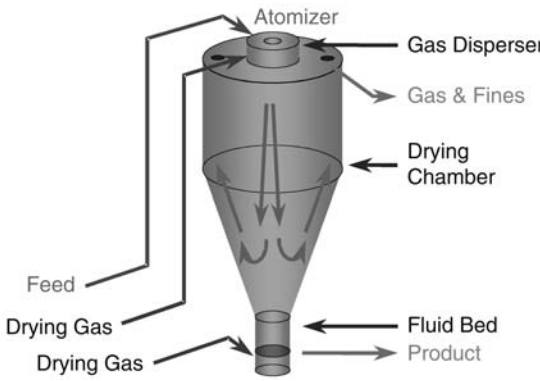


Figure 14 Schematic of fluidized spray drying system (FSD™). *Source*: Courtesy of GEA Pharma Systems.

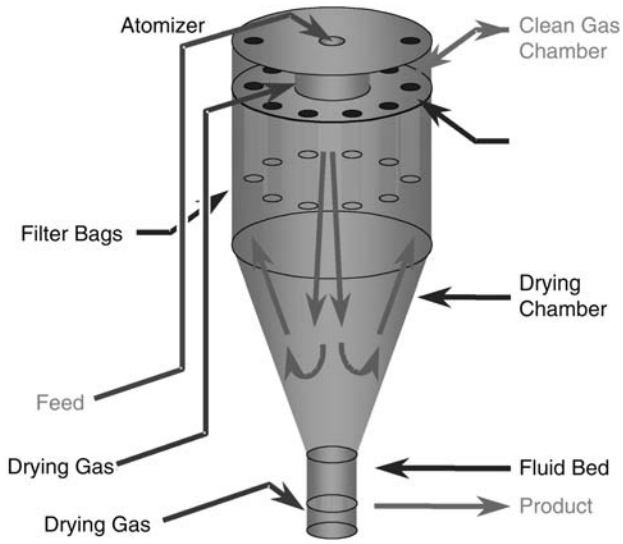


Figure 15 Schematic of an integrated fluid-bed dryer (IFD™). *Source*: Courtesy of GEA Pharma Systems.

second stream of drying gas. Controlled temperature and humidity of this fluid bed gas stream ensure that the particles retain enough moisture to be suitable for agglomeration. At the end of the process, each granule is an agglomerate of spray-dried droplets. Droplets that dry completely before agglomerating and granules that experience attrition during fluid-bed drying create fines, which are entrained in the gas stream and carried upward to the drying gas exhaust. As a result, these fines pass through the atomized spray, providing an additional opportunity for agglomeration. Fines that are carried through the exhaust are collected in cyclones or a bag collector and can be pneumatically recycled into the dryer.

A variation of this system is the integrated fluid-bed dryer (Fig. 15). This system includes integrated filter bags, which are suspended from the chamber roof. This roof is perforated and serves a dual purpose as a gas disperser. The chamber above the roof contains clean gas that supplies the inlet process drying air and also has an exhaust point for clean gas, as any remaining fines are entrapped in the filters.

Products produced using fluidized spray drying have a broader particle size distribution and lower bulk density than the particles produced by conventional spray dryers with a typical mean size particle size range of 150 to 400 μm. This process is not meant to replace conventional spray drying processes but instead is a feasible alternative for spray drying applications that require larger mean particle sizes.

Modification of Solid-State Properties

Characterization and modification of solid-state properties of drug substances are profoundly important in developing pharmaceutical products with desired drug release properties. The importance of the process understanding and improvement of the dissolution rate for poorly water-soluble drugs has been known for decades (26). Majority of the new drug entities have low aqueous solubility and potentially low bioavailability. Availability for absorption may decrease in magnitude or become more variable under the influence of factors such as poor wetting of the compound by gastrointestinal fluids, low solubility in relation to dose and permeability, slow dissolution in relation to gastrointestinal residence time, or precipitation of, for example, weak bases upon entry into the small intestine (27). Dispersion of the drug as very fine particles increases the surface area available for dissolution and thus dissolution rate.

Particle size reduction methods (such as grinding, micronization, and ball milling), precipitation, formation of inclusion compounds, making solid dispersions by quench cooling, melt extrusion, rotary vacuum evaporation, freeze drying, spray drying, and other process

techniques have been used extensively for improving the solubility and dissolution rate of poorly water-soluble materials (4,28–34). These processes generally impart a polymorphic change by transforming a low-energy crystalline form to amorphous form.

Particle size reduction may go to the nanoscale; however, this reduction will not lead to concentrations above the maximum solubility of drug in the intestinal fluids. Alternatively, solid dispersions can be used to increase the dissolution rate of poorly water-soluble drugs and they have proven to increase the amount of drug at the absorption site, sometimes to supersaturated concentrations and consequently improved bioavailability. Using spray drying to produce solid dispersions, which have high amorphous content, is one of the most efficient techniques. Because of the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. Moreover, the solid dispersions prepared by spray drying consist of particles, the size of which may be customized by changing the droplet size to meet the requirements for further processing or application such as for pulmonary delivery or for free-flowing particles suitable for direct compression (4). The hollow structure of the spray-dried particles also increases the solubility and subsequent dissolution rate of the drugs by several folds. For example, the dissolution rate of poorly water-soluble salicylic acid was found to be almost instantaneous and 60 times faster when spray-dried as compared with that of the original powder (28).

In addition, the energy of the amorphous state depends, to some extent, on the method of preparation (29). The dissolution behavior of solid dispersions must remain unchanged during the storage. However, solid dispersions, partially or fully amorphous, are thermodynamically unstable. For optimal stability, the molecular mobility should be as low as possible. However, the recrystallization of the solid dispersion is a challenge that has been documented in literature (30). The rapid nature of the spray drying process (i.e., short residence time of the droplets during drying) improves the stability of otherwise instable amorphous forms. The stabilization of the amorphous material can be accomplished by incorporating polymers with high glass transition temperature (Tg). The spray drying process is suitable for integration of these polymers as stability agents (such as PVP and PEG) into spray-dried particles. For example, spray drying of the poorly soluble drug with 50% PVP resulted in enhanced dissolution when compared with a physical mixture of micronized drug with PVP (31). A physically stable amorphous form of ibuprofen, which has a low melting point, was obtained when spray-dried in the presence of 50% to 75% PVP (32). In a study on the effect of spray drying varying lactose/PEG compositions, it was found that the most amorphous particles were obtained when PEG was present at 10% w/w concentration. Conversion to more crystalline materials occurred over time and the crystallization of lactose appeared to be retarded at low PEG concentrations (33). In another work, increased amount and molecular weight of PVP was found to have the potential to increase the physical stability of amorphous lactose (34).

Microencapsules

The preparation of microcapsules involves the coating of particles or liquid droplets with a biodegradable polymer. Applications for microspheres in the pharmaceutical industry include controlled release, particle coating, flavor stabilization, taste masking, and physical or chemical stabilization. Microencapsulation can be achieved through a number of processes, but, in general, an API is trapped within a reservoir or matrix. This process often begins with the preparation of a three-phase, immiscible system containing a liquid vehicle, a core particle, and a coating material or polymer. Several manufacturing techniques can be employed to deposit the polymer around the particle and cause this coating to become rigid. These methods include spray drying, Wurster fluid-bed coating, pan coating, coacervation, and emulsion evaporation. In the spray drying process, the encapsulation process is achieved in one step in which desolvation and thermal cross-linking occur concurrently and the particle is coated. A review of the main factors involved in the application of spray drying for achieving microencapsulation references many works that detail pharmaceutical applications, especially drug delivery systems (35).

Microencapsulation is a process that is often used for the purpose of providing controlled release of a protein or drug. Several authors have studied microencapsulation formulations manufactured from a spray drying process as a means to achieve controlled release. In one case, the effect of polymer hydrophilicity on API release was evaluated and the most hydrophilic polymer was found to gel faster and retard drug release the most (36). The size and cohesiveness of the resultant spray-dried particles were found to be a function of the polymer and also affected drug release with the smaller, more cohesive particles tending to agglomerate and delay drug release. In another case, release of a model drug was controlled using a spray-dried, water-activated, pH-controlled microsphere (37). Water influx into the microcapsule caused buffer to dissolve and adjusted the inner pH causing the fraction of unionized drug to increase, resulting in the increased release of the drug.

One specific polymer type that has been employed in the spray drying of microspheres to modify release is acrylic resin. A commercial blend of neutral methacrylic acid esters was used for the preparation of spray-dried controlled-release microcapsules containing model drugs (38). Dissolution results of tablets compressed from the microspheres showed successful controlled release with advantages over a matrix system. In a similar study, sustained-release and enteric tablets were prepared by directly compressing spray-dried microspheres produced using different types of acrylic resins (39). Complete enteric properties were observed for tablets made from pH-dependent, anionic acrylic polymers while a sustained-release profile was observed for tablets made from microspheres containing pH-dependent, cationic acrylic polymers.

Two common biodegradable polymers used in microencapsulation are polylactide (PLA) and polylactide-co-glycolide (PLGA). The efficacy of spray drying as a method for PLA and PLGA microsphere preparation was investigated using a model lipophilic drug (40). The spray drying process was tailored to each polymer and the microspheres obtained were evaluated for shape, size, drug content, and polymer influences on these characteristics. Polymer type, polymer molecular weight, and polymer concentration were shown to be the greatest contributing factors to these characteristics. In vitro dissolution testing revealed different release profiles depending on polymer type and microsphere morphology.

Inhalation Dosage Forms

For inhalation dosage forms to be clinically effective, the drug should deposit in the lower airways. In general, the site of drug deposition in the lungs depends on the particle size and size distribution of the drug particles or droplets, the inhaler device and formulation, the patient's breathing patterns, and airway geometry (41). Generally, the aerosol particles or droplets must be less than 5 μm aerodynamic diameter to be deposited into the lower respiratory tract.

Because of its known ability to produce fine microspherical powders with good flow properties, spray drying is a useful method of production for dry powder inhalers. Cospray drying for inhalation delivery appears to have advantages, in terms of powder particle size and flowability, as well as uniformity of the mix, In a study, cospray drying salbutamol sulfate, a widely used drug in inhaler products, with lactose, which is amorphous when spray-dried alone, resulted in amorphous composites. Cospray drying salbutamol sulfate with PEG 4000 and PEG 20,000, which do not form amorphous systems when spray-dried alone, resulted in systems of varying crystallinity, the crystallinity depending on the weight ratio of polymer to drug. Feed concentration was found to be an important factor determining the particle size of the resultant spray-dried powders. The formation and physical stability of amorphous composites formed by spray drying was shown to be dependent on whether the Tg of one of the components was high enough to result in a Tg of the mix components sufficiently high that the Kauzmann temperature of the mix is greater than the temperature of storage (42).

A formulation of mucoadhesive microspheres for nasal administration was examined through the preparation of microspheres containing active and one of two polymer types using a spray drying procedure (43). The mean diameter of the spray-dried particles was 3 to 5 μm and surface morphology was dependent on polymer type. Microspheres containing active and either polymer were more mucoadhesive than any of the starting materials alone, and the dissolution rate decreased with increasing polymer content.

The ability to control the particle size and density of particles for inhalation was investigated using lactose solutions atomized with a two-fluid nozzle and dried in a laboratory-scale dryer. It was found that droplet size during atomization was affected by nozzle orifice diameter and atomization airflow but not by feed concentration. However, dried particle size was influenced by feed concentration and it was suggested that the shell thickness of the hollow particles increased with increasing feed concentration (44).

An alternative method of atomization for the formation of respirable particles is the air blast atomizer. This type of two-fluid nozzle introduces a liquid feed pumped at a slow rate into a high-velocity gas stream via single or multiple jets. This atomizer type was utilized at laboratory scale to evaluate the effect of grounded versus electrostatically charged tower configurations on the median particle size of the spray-dried product (45). This study found significant differences between the two configurations, with the latter producing small particles but compromising collection efficiency.

Microparticles and Nanoparticles

Despite the availability of numerous crystal engineering techniques, generating drug-rich microparticles with a predetermined size, morphology, and crystallinity still represent a challenge. Amongst many techniques, spray drying, because of its ability to control the size, shape, and other properties of the resulting particles, has become a versatile technology for the preparation of microparticles and, more importantly, nanoparticles for the pharmaceutical/biotech applications. For example, in a recent study, it was shown that the adsorption of excipients onto micrometer-size drug substrates using spray drying process was found to be an attractive approach to engineer drug-rich microparticles with characteristics suitable for drug delivery (46). In another recent study, ***fast-dissolving mucoadhesive microparticulate delivery system was developed using spray drying method for piroxicam, which is a drug with low water solubility and high membrane permeability (47). It is known that such delivery systems intended for sublingual administration could be a suitable alternative to fast-dissolving tablets because the sublingual absorption can be improved as a consequence of prolonging residence time on the mucosa and reducing the amount of swallowed drug (48).

Attempts have been made to manufacture particles on the nanometer scale for applications such as controlled-release and intravenous delivery systems. A comparison evaluating the processability and solid dosage performance of spray-dried nanoparticles and microparticles was conducted (49). In this study, nanoparticle suspensions were prepared by wet comminution in the presence of stabilizers and converted into dried particles using a spray drying process and subsequently compressed. Compacts prepared from micro- and nano-particles were found to differ in their internal structure and micromechanical deformations.

In another study, solid and lipid nanoparticles were produced using high-pressure homogenization and loaded with drug using hot or cold methods for lipophilic or hydrophilic drugs, respectively (50). Surfactant addition was investigated, and stability and entrapment efficiency were evaluated. Long-term sterile storage of these dispersions was difficult, and spray drying was investigated as a potential, feasible technique.

The feasibility of developing nanoparticles for aerosol delivery has also been investigated (51). The spray-dried nanoparticles, produced using one carrier type, were found to be hollow while others had a continuous matrix. Particle size was measured before spray drying and after the spray-dried powder was redissolved. Both carrier types resulted in an increase in particle size after spray drying, although both were found to remain in the nanometer range after drying and were suitable for efficient lung delivery.

Liposomes

Another particle type capable of being produced by spray drying is liposomes. Traditional preparation of liposomes begins with the preparation of a solution containing the lipids to be used in a volatile organic solvent mixture. Following filtration of the solution, the solvent mixture is removed under conditions that ensure phase separation does not occur. The dry lipid mixture is then hydrated by an aqueous mixture containing the drug to be entrapped. Lastly, this mixture is dried. Spray drying is one method available for accomplishing one or

both of these drying steps. For example, lipid vesicles were produced using a spray drying process instead of the first step of the traditional process (52). Vesicles containing phosphatidylcholine (soybean lecithin) were produced by extruding the phospholipid through a 0.2-μm polycarbonate membrane followed by spray drying with 10% lactose. The particle size, vesicle size distribution, and stability of the multilamellar vesicles were measured. The mean particle diameter after spray drying with a rotary atomizer was 7 μm and the dry particles could be reconstituted in water to liposomes without any major change to the vesicle size distribution. In addition, the chemical stability of the liposomes was not significantly affected by the spray drying process. In subsequent work, the same authors utilized spray drying for the hydration step of the traditional process (53).

Peptides and Proteins

Recent advances in biotechnology have made it possible to use macromolecules such as peptides and proteins as therapeutic agents. Spray drying has been used for decades for processing antibiotics, vaccines, and, for the last few decades, macromolecular drugs.

The effect of spray drying process parameter settings on the activity of peptides and proteins is often difficult to study. Consequently, enzymes are frequently used as model protein drugs because of the ease with which their activity can be determined. Investigations of the application of spray drying for the production of some enzymes and proteins and the effects that processing parameters have on enzyme activity have been discussed in a review article (23).

Many proteins and peptides are susceptible to degradation upon spray drying because of relatively high temperatures. In a recent study, the effects of inlet and outlet temperatures on some spray-dried peptides and proteins were reported (54). In another study, enzyme activity was found to be susceptible to spray drying temperature, and only half of its activity remained after spray drying without additives at outlet temperatures below 50°C (55). In this study, it was found that the activity of a formulation comprised of enzyme and mannitol was maintained at outlet temperatures below 50°C and compromised above 50°C. Replacing mannitol with trehalose stabilized the spray-dried enzyme and its activity was maintained at 100% at an outlet temperature of 100°C.

The antigenic extract hot saline from *Brucella ovis* was microencapsulated by the spray drying technique with different polyesters and blends with poly-ε-caprolactone [PEC]) to obtain microparticles smaller than 5 μm. The microparticulated antigenic formulation containing the higher ratio of PEC was shown to be susceptible to be used in animal vaccination studies (56).

Another method of producing protein powders is spray freeze drying process. Spray freeze drying process involves spraying the solution into freezing air, causing the resultant droplets to freeze. The frozen droplets are subsequently sublimed under vacuum conditions producing a dry product. Spray drying and spray freeze drying were compared to produce protein inhalation powders and spray drying was found to be superior in scalability, operational cost, and product yield than spray freeze drying (57). Comparisons of freeze drying with spray drying to produce dry powder dispersions for nonviral gene delivery showed that spray drying produces stable, efficient, and potentially respirable particles (58).

A number of methods, including spray drying, lyophilization, pulverization, precipitation, and some other techniques, currently available for protein powder preparation were evaluated in a review article based on the following criteria: control on particle size and size distribution, efficiency (yield), powder flowability, scalability, and long-term protein biochemical stability (59). On the basis of these criteria, spray drying was found to be advantageous for its convenience and simplicity, as well as for controlling the particle size and shape and attaining fine (<5 μm) spherical particles of proteins.

Dry Elixirs and Emulsions

A dry elixir is a novel dosage form developed by spray drying actives and excipients dissolved or suspended in ethanol and water mixtures. One example is a dry elixir in which the feed solution contained active, dextrin, and sodium lauryl sulfate in a mixture of ethanol/water (60). The spray-dried product was spherical in shape with a smooth surface and a mean

diameter of 13 μm. A comparison with the active in powder form revealed a major decrease in dissolution time from over 60 to 2 minutes.

A dosage form similar to dry elixir is dry emulsion. In this case, the emulsified drug or oily drug solution with additives is spray-dried to produce dry emulsion particles. A dry emulsion of a water-insoluble nutrient was studied, and release from the spray-dried particle was found to be dependent on the type and amount of oily carrier and surfactant used (61). Differences in release among the different formulations were attributed to the differences in the physical state of the drug and surfactant in the dried particle.

Effervescent Products

Spray-dried particles have also been incorporated into effervescent products. In one study, spray drying was used to protect a degradation-sensitive active by coating fine particles of the drug with a sugar alcohol solution (62). In vivo results of tablets made using the spray-dried particles combined with coated citric acid and sodium bicarbonate revealed that the active was rapidly absorbed from the tablet.

Other Process Variations

Two variations of the spray drying process have been developed in response to product requirements. The first variation is spray congealing. In this process, solids such as wax or monoglycerides are melted. Other ingredients such as drugs, flavors, or fragrances are dissolved or suspended in the molten material. This molten feed is sprayed using the same basic spray drying equipment except that no heat source is required. Depending on the freezing point of the feed, ambient or chilled air may be used during the drying process. This process has been described in more detail and a comparison between particles produced by both the spray drying and spray congealing techniques has also been drawn (63). One study compared microcapsules produced using both methods and found that the solvent used, the lipid type, and the chain length were variables that influenced the surface properties of both particle types (64,65).

A second variation of the spray drying process is spray freeze drying. In this process, the feed is sprayed into freezing air causing the droplets to freeze. The frozen droplets are subsequently sublimed under vacuum conditions producing a dry product. One study investigated this method further by eliminating the use of vacuum conditions for sublimation (66). In this study, the feasibility of spraying pharmaceutical solutions at atmospheric pressure was investigated using very low air temperatures and desiccated air for the removal of the water from the frozen particles. The process resulted in fine, free-flowing powder with high surface area, good wetting, and good solubility characteristics.

Another type of atomization employed for pharmaceuticals is supercritical fluid nebulization. The process uses carbon dioxide as an aerosolization aid, which permits drying at lower temperatures than usually needed in conventional spray drying (67). Within the atomization system, supercritical carbon dioxide is intimately mixed with aqueous solutions containing API, often proteins or peptides. The outcome is the formation of microbubbles, which are rapidly dried in less than five seconds, resulting in dried particles predominately less than 3 μm in diameter (68,69). This method is generally applied for the production of materials for pulmonary use or to achieve increased bioavailability (70).

APPLICATION OF PAT TO SPRAY DRYING PROCESS

Process Analytical Technology (PAT) is defined as a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (71). It is important to note that the term "analytical" in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. As PAT will be the subject matter of entire chapter 29, the focus of discussion here is not what PAT is but how it applies to spray drying process.

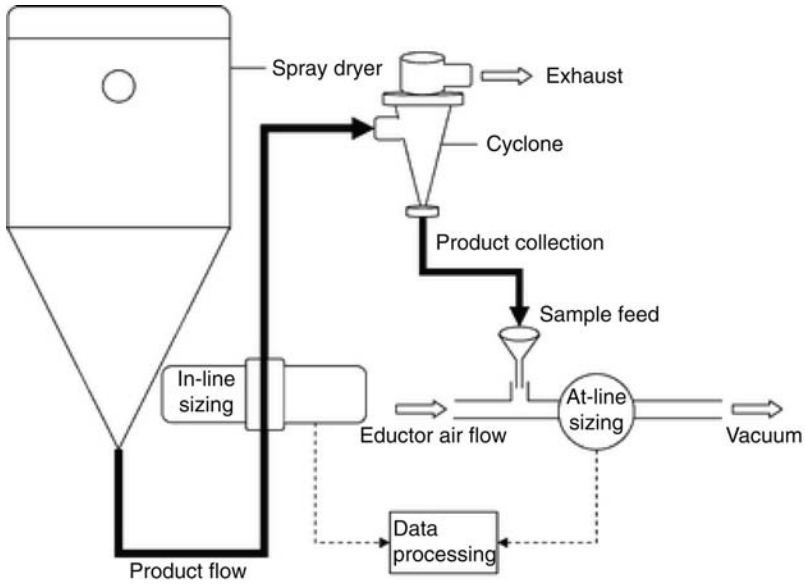


Figure 16 Layout of the spray dryer with the in-line and at-line laser diffraction setup. *Source*: Adapted from Ref. 72.

The specific application of this relative new initiative to spray drying is currently focused on the continuous real-time quality assurance aspect.

In a recent study, employing PAT for particle sizing during spray drying with the use of an in-line and at-line laser diffraction system was employed for monitoring the particle sizing during spray drying, and the particle size data were compared with those determined with off-line laser diffraction and light microscopy (72).

The in-line laser diffraction system comprised the optical head, interface box, computer, and data analysis software. The optical head was directly connected in-line to the process stream. The main components used for the at-line laser diffraction system were the same as those used in the in-line system, except that for the at-line system, the laser module was not physically connected to the product flow stream. Instead, it was positioned adjacent to the spray dryer and worked as a separate system. Sampling and sizing were performed after the product had left the process stream (Fig. 16).

The system was found to be a rapid and convenient method, which provided instantaneous information about the particle size distribution of the microspheres (of maltodextrin and modified starch) as they were made. The at-line setup was reported to be superior to the in-line setup in this particular application. The workers pointed out the need for taking into account the cohesiveness of material measured and cautioned about the importance of the judicious data management and interpretation of results from PAT-enabled instruments to make valid conclusions.

One must bear in mind that the goal of PAT is to understand and control the manufacturing process and quality cannot be tested into products but it should be built-in or should be by design. Therefore, the real-time monitoring (on-line or at-line measurements) or increase of process sample size or automated end product testing alone does not qualify as PAT. The critical issue is the understanding of the spray drying process by applying the science and not regarding that as an art. Otherwise, what will be monitored in real time will not necessarily ensure a quality product.

A process is generally considered well understood when all critical sources of variability are identified and explained, variability is managed by the process, and product quality attributes can be accurately and reliably predicted over the ranges of acceptance criteria established for materials used, process parameters, and manufacturing environmental and other conditions. The ability to predict reflects a high degree of process understanding.

In spray drying, some of the critical formulation and process factors are:

1. material and feed properties (such as melting point of the material, feed type, solid content in the feed, additives, etc.),
2. process variables (such as feed rate, atomizer type and speed, air pressure, inlet and outlet gas temperatures, etc.), and
3. product specifications (such as moisture content, particle size, particle density, flow characteristics, etc.).

The knowledge acquired for these factors during the structured product and process development studies can assure the quality of the spray-dried product as one would expect an inverse relationship between the level of process understanding and the risk of producing a poor-quality product. In this respect, there were studies conducted before the publication of the FDA's PAT guidelines. An example for such a study involved the use of experimental factorial designs to investigate the effects of a number of formulation and process parameters on production yields and moisture contents of spray-dried products. These factors concerned both the solution feed (drug concentration, colloidal silica concentration, and polymer/drug ratio) and the spray dryer (inlet temperature and feed rate). In this study, the optimal operating conditions were estimated by response surface methodology. Central rotational composite designs showed that quadratic models were found to be adequate. The results showed that the control of processing variables, especially inlet temperature and feed rate, allowed production of microparticles of low moisture content with high yields. Experimental factorial design was claimed to be necessary before new production runs to determine the values of the parameters to be used for the optimization of the spray drying process (73).

Another example will be the subject matter of chapter 27 on expert systems in which a knowledge-based expert system will be described in some detail.

CONCLUSION

Spray drying has found many applications in numerous industries despite its initial installation, training, and operation-related costs. The scale-up of the spray drying process is less troublesome as the operation requirements of small and large dryers are the same when compared with other conventional granulation processes such as high-shear granulation method.

Spray drying, being a continuous process, is well suited for the production of bulk drug substances and excipients. Using this process, the physical properties of the resulting product (such as particle size and shape, moisture content, and flow properties) can be controlled through the selection of equipment choices and manipulation of process variables; thus, the final spray-dried particulate matter may not need further processing (wet or dry granulations) before compaction. In addition, the spray drying process matches the directives outlined in the PAT initiative currently being guided and championed by the FDA.

Spray drying processes offer several advantages when solid-state properties of drug substances need to be modified. Using this process, solubility and dissolution rates of properties of poorly soluble materials can be increased by several folds and the stability of the amorphous form of the materials can be improved significantly.

Because of its initial inherent costs, spray drying is not always considered as a processing option for many conventional formulations, especially for small batch size operations. However, when a specialized particle type is required by the active ingredient or dosage form, spray drying can become a feasible alternative to more conventional manufacturing processes. Such particle types include microcapsules, controlled-release particles, nanoparticles, and liposomes.

ACKNOWLEDGMENT

We gratefully acknowledge the extensive contribution of Keith Masters whose handbook was referenced extensively as a leading text in the field.

REFERENCES

1. Traub DA. Spray dryers. Part 1. Process heating, August 2001. Available at: http://www.process-heating.com/CDA/ArticleInformation/Drying_Files_Item/0,3274,61137,00.html.
2. Percy SR. Improvement in drying and concentrating liquid substances by atomizing, U.S. Patent 125,406. 9 April 1872.
3. Masters K. Introduction. Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:1–20.
4. Parikh DM. Advances in spray drying technology: new applications for a proven process. Am Pharm Rev 2008; 11(1):34–41.
5. Traub DA. Spray dryers. Part 2. Process heating, September 2001. Available at: http://www.process-heating.com/CDA/ArticleInformation/Drying_Files_Item/0,3274,63175,00.html.
6. Masters K. Spray drying fundamentals: process stages and layouts. In: Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:24.
7. Masters K. Spray drying fundamentals: process stages and layouts. In: Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:26.
8. Masters K. The process stages of spray drying. In: Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:268.
9. Masters K. Spray drying fundamentals: process stages and layouts. In: Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:31.
10. Masters K. The process stages of spray drying. In: Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:271.
11. Masters K. Spray drying fundamentals: process stages and layouts. In: Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:43.
12. Masters K. Spray drying fundamentals: process stages and layouts. In: Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:47.
13. Masters K. The process stages of spray drying. In: Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:199.
14. Masters K. The process stages of spray drying. In: Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:255.
15. Masters K. Drying of droplets/sprays. In: Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:309.
16. Traub DA. The drying curve. Part 2. Process heating, October 2002. Available at: http://www.process-heating.com/CDA/ArticleInformation/Drying_Files_Item/0,3274,84744,00.html.
17. Masters K. Drying of droplets/sprays. Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:326.
18. Charlesworth DA, Marshall WR. Evaporation for drops containing dissolved solids. AIChE J 1960; 6(1): 9–23.
19. Masters K. Drying of droplets/sprays. Spray Drying Handbook. 5th ed. Essex: Longman Scientific Technical, 1991:345.
20. Adhikari B, Howes T, Lecomte D, et al. A glass transition temperature approach for the prediction of the surface stickiness of a drying droplet during spray drying. Powder Technol 2005; 149:168–179.
21. Shaw F. Spray drying as a granulation technique. In: Parikh DM, ed. Handbook of Pharmaceutical Granulation Technology. New York: Marcel Dekker, 1997:93–96.
22. Filkova I, Weberschinke J. Apparent viscosity of non-Newtonian droplet on the outlet of wheel atomizers. In: Mujumdar AS, ed. Drying '82. New York: McGrawHill, 1982:165–170.
23. Broadhead J, Rouan SK, Rhodes CT. The spray drying of pharmaceuticals. Drug Dev Ind Pharm 1992; 18(11–12):1169–1206.
24. Wendel SC, Çelik M. An overview of spray-drying applications. Pharm Technol 1997; 21(10):124–156.
25. Kadam KL. Granulation Technology for Bioproducts. Boca Raton: FL CRC Press, 1990.
26. Fincher JH. Particle size of drugs and its relationship to absorption and activity. J Pharm Sci 1968; 57(11):1825–1835.
27. Kostewicz ES, Wunderlich M, Brauns U, et al. Predicting the precipitation of poorly soluble weak bases upon entry in the small intestine. J Pharm Pharmacol 2004; 56:43–51.
28. Kawashima Y, Satio M, Takenaka H. Improvement of solubility and dissolution rate of poorly water-soluble salicylic acid by a spray-drying technique. J Pharm Pharmacol 1975; 27:1–5.
29. Pikal MJ, Lukes AL, Land JE, et al. Quantitative crystallinity determination for beta-lactam antibiotics by solution calorimetry: correlations with stability. J Pharm Sci 1978; 67:767–773.
30. Morris KR, Griesserb UJ, Eckhardt CJ, et al. Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes. Adv Drug Deliv Res 2001; 48: 91–114.
31. Junginger H, Wedler M. Acta Pharm Technol 1984; 30(1):68.

32. Corrigan OI, Holohan EM, Reilly MR. Physicochemical properties of indomethacin and related compounds co-spray dried with polyvinyl-pyrrolidone. Drug Dev Ind Pharm 1985; 11(2–3):677–695.
33. Corrigan DO, Healy AM, Corrigan OI. The effect of spray drying solutions of polyethylene glycol (PEG) and lactose/PEG on their physicochemical properties. Int J Pharm 2002; 235(1–2):193–205.
34. Berggren J, Alderborn G. Effect of polymer content and molecular weight on the morphology and heat- and moisture-induced transformations of spray-dried composite particles of amorphous lactose and poly(vinylpyrrolidone). Pharm Res 2003; 20:1039–1046.
35. Re MI. Microencapsulation by spray drying. Drying Technol 1998; 16(6):1195–1236.
36. Wan LS, Heng PW, Chia CG. Spray drying as a process for microencapsulation and the effect of different coating polymers. Drug Dev Ind Pharm 1992; 18(9):997–1011.
37. Sutinen R, Laasanen V, Paronen P, et al. pH-controlled silicone microspheres for controlled drug delivery. J Control Release 1995; 33:163–171.
38. Palmieri GF, Wehrle P, Stamm A. Evaluation of spray-drying as a method to prepare microparticles for controlled drug release. Drug Dev Ind Pharm 1994; 20(18):2859–2879.
39. Takeuchi H, Handa T, Kawashima Y. Controlled release theophylline with acrylic polymers prepared by spray drying technique. Drug Dev Ind Pharm 1989; 15(12):1999–2016.
40. Pavanetto F, Genta I, Giunchedi P, et al. Evaluation of spray drying as a method for polylactide and polylactide-co-glycolide microsphere preparation. J Microencapm 1993; 10(4):487–497.
41. Gonda I. Targeting by deposition. In: Hickey AJ, ed. Pharmaceutical Inhalation Aerosol Technology. New York: Marcel Dekker, Inc., 1992:61–82.
42. Corrigan DO, Corrigan OI, Healy AM. Predicting the physical state of spray dried composites: salbutamol sulphate/lactose and salbutamol sulphate/polyethylene glycol co-spray dried systems. Int J Pharm 2004; 273(1–2):171–182.
43. Vidgren P, Vidgren M, Aronen P, et al. Nasal distribution of radioactive drug administered using two dosage forms. Eur J Drug Metab Pharmacokinet 1991; 3:426–432.
44. Elversson J, Millqvist-Fureby A, Alderborn G, et al. Droplet and particle size relationship and shell thickness of inhalable lactose particles during spray drying. J Pharm Sci 2003; 92, 900–910.
45. Dunbar CA, Concessio NM, Hickey AJ. Evaluation of atomizer performance in production of respirable spray-dried particles. Pharm Dev Technol 1998; 3(4):433–441.
46. Buttinia F, Soltani A, Colombo P, et al. Multilayer PVA adsorption onto hydrophobic drug substrates to engineer drug-rich microparticles. Eur J Pharm Sci 2008; 33(1):20–28.
47. Cilurzo F, Selmin F, Minghetti P, et al. Fast-disolving mucoadhesive microparticulate delivery system containing piroxicam. Eur J Pharm Sci 2005; 24:355–361.
48. Ahuja A, Khar RP, Ali J. Muchoadhesive drug delivery systems. Drug Dev Ind Pharm 1997; 23: 489–515.
49. Lee J. Drug nano- and microparticles processed into solid dosage forms: physical properties. J Pharm Sci 2003; 92(10):2057–2068.
50. Muller-Mehnert RH, Lucks JS, Schwarz C, et al. Solid lipid nanoparticles (SLN)-alternative colloidal carrier system for controlled drug delivery. Eur J Pharm Biopharm 1995; 41(1):62–69.
51. Sham JO, Zhang Y, Finlay WH, et al. Formulation and characterization of spray-dried powders containing nanoparticles for aerosol delivery to the lung. Int J Pharm 2004; 269:457–467.
52. Goldbach P, Brochart H, Stamm A. Spray-drying of liposomes for a pulmonary administration. Part 1. Chemical stability of phospholipids. Drug Dev Ind Pharm 1993; 19(19):2611–2622.
53. Goldbach P, Brochart H, Stamm A. Spray-drying of liposomes for a pulmonary administration. Part 2. Retention of encapsulated materials. Drug Dev Ind Pharm 1993; 19(19):2623–2636.
54. Costantino HR, Andya JD, Nguyen PA, et al. Effect of mannitol crystallization on the stability and aerosol performance of a spray-dried pharmaceutical protein, recombinant humanized anti-IgE monoclonal antibody. J Pharm Sci 1998; 87:1406–1411.
55. Broadhead J, Ruan SK, Rhodes CT. The effect of process and formulation variables on the properties of spray dried β-galactosidase. J Pharm Pharmacol 1994; 46:458–467.
56. Murillo M, Gamazo C, Goñi MM, et al. Development of microparticles prepared by spray-drying as a vaccine delivery system against brucellosis. Int J Pharm 2002; 242(1–2):341–344.
57. Maa YF, Nguyen PA, Sweeny T, et al. Protein inhalation powders: spray drying vs. spray freeze drying. Pharm Res 1999; 16(2)249–254.
58. Sevelle PC, Kellay LW, Birchall JC. Preparation of dry powder dispersions for non-viral gene delivery by freeze-drying and spray-drying. J Gene Med 2002; 4:428–437.
59. Maa YF, Prestrelski SJ. Biopharmaceutical powders: particle formation and formulation considerations. Curr Pharm Biotechnol 2000; 1:283–302.
60. Kim CK, Soon YS. Development of digoxin dry elixir as a novel dosage form using a spray-drying technique. J Microencap 1995; 12(5):547–566.

61. Takeuchi H, Sasaki H, Niwa T, et al. Design of redispersible dry emulsion as an advanced dosage form of oily drug (vitamin E nicotinate) by spray-drying technique. Drug Dev Ind Pharm 1992; 18(9):919–937.
62. Timmington H. Improved aspirin. Chem Drug 1973; 482–483.
63. Killen MJ. Process of spray drying and spray congealing. Pharm Eng 1993; 13:58–62.
64. Eldem T, Speiser P, Altorfer H. Polymorphic behavior of sprayed lipid micropellets and its evaluation by differential scanning calorimetry and scanning electron microscopy. Pharm Res 1991; 8:178–184.
65. Eldem T, Speiser P, Hincal A. Optimization of spray-dried and -congealed lipid micropellets and characterization of the surface morphology by scanning electron microscopy. Pharm Res 1991; 8(1):47–54.
66. Mumenthaler M, Leuenberger H. Atmospheric spray-freeze drying: suitable alternative in freeze dry technology. Int J Pharm 1991; 72:97–110.
67. Sievers RE, Huang ETS, Villa JA, et al. Low-temperature manufacturing of fine pharmaceutical powders with supercritical fluid aerosolization in a bubble dryer. Appl Chem 2001; 73(8):1299–1303.
68. Sievers RE, Karst U. Methods for fine particle formation. U.S. Patent 5,639,441, June 1997.
69. Sievers RE, Karst U. Methods and apparatus for fine particle formation. U.S. Patent 6,095,134, August 2000.
70. Sievers RE, Karst U, Milewski PD, et al. Formation of aqueous small droplet aerosols assisted by supercritical carbon dioxide. Aerosol Sci Technol 1999; 30:3–15.
71. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), Office of Regulatory Affairs (ORA). Guidance for industry: PAT—a framework for innovative pharmaceutical development, manufacturing, and quality assurance. September 2004.
72. Chan L, Tan L, Heng P. Process analytical technology: application to particle sizing in spray drying. AAPS Pharm Sci Technol 2008; 9(1):259–266.
73. Billon A, Bataille B, Cassanas G, et al. Development of spray-dried acetaminophen microparticles using experimental designs. J Pharm Int 2000; 203(1–2):159–168.

6 Supercritical Fluid Technology

Martin A. Wahl

Pharmaceutical Technology and Biopharmacy, Institute of Pharmaceutical Sciences, Eberhard-Karls-University Tübingen, Tübingen, Germany

INTRODUCTION

Supercritical fluid (SCF) technology experienced a significant boost over the past years. Apart from the classical use in extraction, preparative techniques like particle design or functionalization of material grew up. Today, these techniques can be applied under GMP conditions, making them available for use in drug formulation or food industry. One must, however, admit that some of these techniques actually are rather in an experimental state, but because of increasing speed of scientific development, they may become available in a short time. It seems, therefore, important to present these techniques within the actual standards of granulation.

HISTORICAL VIEW ON THE USE OF SUPERCRITICAL FLUIDS IN PHARMACEUTICAL TECHNOLOGY

Formation of fine particles by a rapid release of the pressure was initially observed by Hannay and Hogarth in 1879 (1). This report is seen as the beginning of particle design by the use of SCF. It took, however, almost 100 years to understand the process and invent the technique to handle high-pressure fluids. From the 1960s, development of the use of SCF for extraction purpose was getting more popular, with decaffeination of coffee and tea being the most important industrial application in the 1980s with respect to the amount of material processed. In parallel, from the 1980s, the development of the different particle generating processes like the rapid expansion of supercritical solutions (RESS) process came up, early reports (2) followed by patents (3). Because of the fact that drugs frequently were rather insoluble than soluble in SCF, the antisolvent techniques were developed, starting with early reports in 1954 (4) and followed by numerous patents (5), a summary of the early patents was published by Jung and Perrut in 2001 (6). Industrial use of the techniques is so far mainly limited to extraction (coffee, tea, hops), but the presence of companies in the market supporting the development of particle and formulation techniques by the construction of pilot plants (e.g., SITEC AG, Zürich, Switzerland), by the offer of development or handling techniques (e.g., Natex, Ternitz, Austria; Phasex Corporation, Lawrence, MA; Separex, Champigneulles, France), or by the construction of large facilities (e.g., Uhde GmbH, Dortmund, Germany) clearly shows that SCF play a role in actual developments. Because of the fact, that modern drug development lasts for up to 20 years until the market is reached, one can assume that in the near future the first products based on SCF production technique will be approved.

SUPERCRITICAL FLUIDS

Gases or liquids, which were used under pressure and temperature above the critical point, reach an aggregate state, which is called the SCF state (Fig. 1). Under these conditions, which are typical for individual substances (Table 1), the fluid possesses properties that are unique and different from the liquid or gaseous state.

Fluid Properties

In many cases, the use of SCF is thought as a replacement for organic solvents. Comparing the properties of SCF with the properties of an organic solvent, however, shows, beside similarities, significant differences too. Similarities are lipophilicity or density; differences are seen in viscosity or volatility. CO_2, for example, above the critical point shows viscosities in the range of about 50 to 150 μPa sec (CO_2 at 273 K and 0.1 MPa: approx. 14 μPa sec), increasing with increasing pressure but decreasing with increasing temperature. The absolute values here are slightly above the viscosity of gases; pressure- and temperature-dependent changes are as

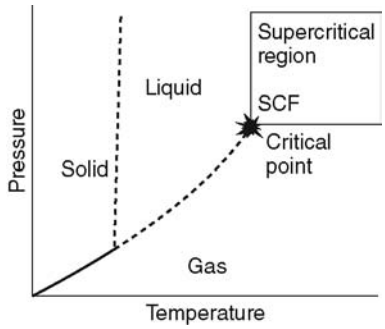


Figure 1 Schematic of P-T phase diagram indicating the supercritical state. The volume is assumed as constant.

Table 1 Critical Pressure and Temperature of Supercritical Fluids (Examples)

Type of fluid	P_c (MPa)	T_c (K)
Trifluoromethane	4.7	299
CO_2	7.4	304.1
Ethane	4.8	305.3
N_2O	7.2	309.6
Propane	4.2	369.8
Norflurane (R134a)	4.0	374.2
n-Hexane	3.0	507.5
Water	22.1	647.1

Abbreviations: P_c, critical pressure; T_c, critical temperature.
Source: From Refs. 7–10.

for liquids (7). The density of the SCF is dependent on temperature and pressure, the correlation subject to intense research (11). In addition, no surface tension is seen in SCF (8).

Because of the high pressure required for the existence of the supercritical state, supercritical solutions can easily be used for spray-expansion technologies. Chemistry and, at least for the most frequently used CO_2, moderate temperatures required make the use of SCF as solvents less dangerous for drug stability.

Fluids Used

In pharmaceutical technology, the primary choice of SCF is $scCO_2$, trifluoromethane, and norflurane. $scCO_2$ is the preferred fluid because of its inert behavior, easy-to-handle supercritical parameters, and nontoxicity. Here, even residues in the preparation will not be measurable. The supercritical conditions for the latter two are comparable to $scCO_2$ except the higher temperatures required for the work with norflurane.

Carbon Dioxide

The most preferred SCF is definitely $scCO_2$. Its rather low critical temperature and pressure make it an easy-to-handle tool for extraction and particle generation. Apart from the rapid disappearance of the "solute" at the end of the processes caused by depressurization, remaining residues in the product would not be seen as critical. The low reactivity, even under high pressure, makes it suitable to be used for sensible drug molecules. The lipophilicity of $scCO_2$ can be influenced by the addition of modifiers or cosolvents like methanol, ethanol, or acetone (12). These additives, if they do not reach their supercritical state under the conditions applied, must be removed separately at the end of the process from the product.

Water, Nitrous Oxide, Norflurane, Trifluoromethane

All other SCF actually play a minor role in pharmaceutical technology. Despite its important role in waste decomposition (13), supercritical water is rarely used in pharmaceutical

technology because of its high critical temperature and high reactivity; both can be expected to affect drug stability under these conditions, as it is expected to do in waste decomposition. N_2O, which has similar critical properties as CO_2, was sometimes used as SCF (14); a report about an explosion with this SCF (15), however, seemed to have terminated the use. Norflurane (HFA 134a) might be interesting because of its acceptance in the formulation of pharmaceutical products in the past; its relatively high critical temperature makes handling of drugs under these conditions critical (16), even though it is used in food chemistry (17). A SCF with less lipophilicity and higher polarity compared with $scCO_2$ is trifluoromethane (R23); this might be useful for treatment of compounds that do not dissolve sufficiently in $scCO_2$ because of their polarity, like griseofulvin (18).

Drug Solubility in Supercritical Fluid

SCF possess properties similar to those of organic solvents. The solubility of drugs in the SCF is strongly dependent on the type of SCF and the properties of the drug. For $scCO_2$, similarity with hydroalkane solvents can be seen. Apart from experimental data, which can be obtained by cloud-point determination in phase behavior experiments (19), knowledge of the chemical properties of the drug in the SCF can help to predict solubility. With regard to $scCO_2$, the presence of functional groups, which can interact with CO_2 as Lewis acid or base, would be beneficial. In addition, certain kind of polarity would improve the interaction with the quadrupole moment of CO_2. Free volume and flexibility of the molecule would also facilitate dissolution in the SCF; this may be seen by low glass transition temperature of polymers. In addition, a molecular weight above 500 seems to be critical (20).

For solubility of drugs in $scCO_2$, data for a broad variety of drugs are summarized by Gupta and Shim (21).

PARTICLE DESIGN TECHNIQUES

Solubility of drugs in water is a key element of the action. Drugs with high in vitro activity on the physiological target structure are frequently highly lipophilic, leading to poor water solubility. A common method to improve water solubility is the reduction of particle size, thereby increasing the dissolution speed according to the Noyes-Whitney equation. The production of small—mainly in the submicron or even nanoscale range—particles can be done by either milling or precipitation technologies. If the compound of interest is soluble in SCF, at least to an acceptable extent, precipitation of very small particles can be obtained by a release of the pressure and, therefore, high precipitation speed (e.g., in the RESS process). This will directly lead to solid particles in the expected size range. Another possibility is the removal of a solvent by the use of SCF, which will again lead to supersaturation of the solution followed by precipitation of small particles. This technique is applied in the antisolvent processes (e.g., the GAS process). Both techniques lead to free-floating particles at the end of the production process. Since handling of nanoscaled particles is difficult and the subsequent processing to formulations sometimes just impossible, techniques that deposit the particles directly in the formulation are useful, like the drying of aerogels or the impregnation techniques [e.g., the controlled particle deposition (CPD) process].

Direct Particle Production I: Solvent Techniques

The basic mechanisms of the solvent techniques is solubility of the drug in the SCF. This leads to a supercritical solution, which can, subsequently, be expanded. The expansion leads to supersaturation and particle precipitation.

Rapid Expansion of Supercritical Fluids

The RESS is the simplest process in SCF technology used for particle production. For this process, the drug has to be dissolved in the SCF. The hereby formed supercritical solution is then expanded through a nozzle into an expansion chamber (Fig. 2). This leads to particle precipitation (6). With the RESS process, care is taken that the drugs dissolving in the SCF do not melt. This may sometimes be difficult because of melting point depression under high pressure. Characteristics of the product obtained are dependent on the working conditions.

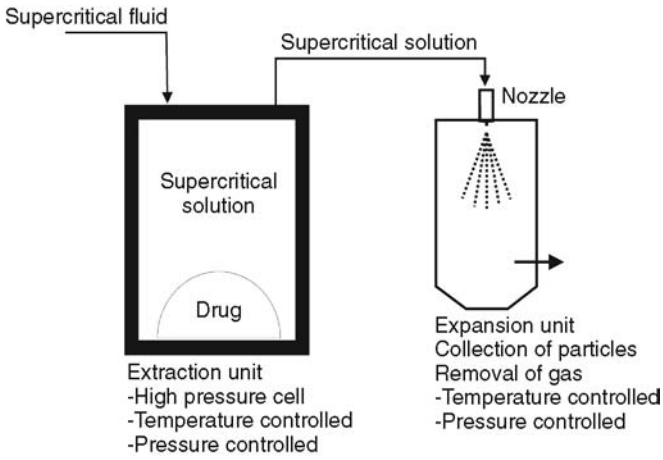


Figure 2 Function scheme of the rapid expansion of supercritical solutions process. The drug is dissolved in a high-pressure chamber. The resulting supercritical solution is afterward expanded through a nozzle into an expansion chamber.

Table 2 Examples of Drugs Processed by Supercritical Fluid Technology

Drug	Technique used	Reference
Acetylsalicylic acid	RESS	28
Beclometasone dipropionate	RESS	29
Carbamazepine	RESS	22
Cefpodoxime proxetil	ASES	30
Cefuroxime axetil	RESS	31
Cyclosporin	PGSS	32
Dexamethasone acetate	SAA	33
Dihydroartemisinin	RESS	34
Felodipine	RESS	35
Griseofulvin	RESS	18, 36
Hydrocortisone	SEDS	37
Insulin	ASES	38, 39
	GAS	40
Ibuprofen	RESS	41
Levofolxacin hydrochloride	SAA	42
Meloxicam	RESS	43
Naproxen	RESS	44
Nifedipine	PGSS	45
Tolbutamide	RESS	46

Abbreviations: RESS, rapid expansion of supercritical solutions; ASES, aerosol solvent extraction system; PGSS, particles from gas-saturated solutions/suspensions; SAA, supercritical assisted atomization; SEDS, solution-enhanced dispersion by supercritical fluid technique; GAS, gas antisolvent.

Particles may occur as amorphous or crystalline product, depending on the working conditions applied (22); however, most authors report the occurrence of crystalline products. Particle size normally appears to be in the range of about 20 to 200 nm, with a narrow distribution, because of the short time available for crystallization during expansion, based on the jet stream through the nozzle with ultrasonic speed range (23). Because of its simplicity, the process can be well modeled (24); a critical summary of modeling work is given by Türk (23), which helps to understand and predict the influence of the process parameters on product properties. Expansion of binary (25) or even ternary mixtures (26) containing drugs and excipients (Co-RESS) or expansion into dispersing media to stabilize particles have been reported and will be discussed later in this chapter. To overcome poor solubility of drugs in $scCO_2$, modifiers or cosolvents can be added; this is even possible with solid cosolvents (27). The technique has been employed with a significant number of drugs (Table 2); some more are listed by Jung and Perrut (6). In most studies reported, the dissolution velocity—and

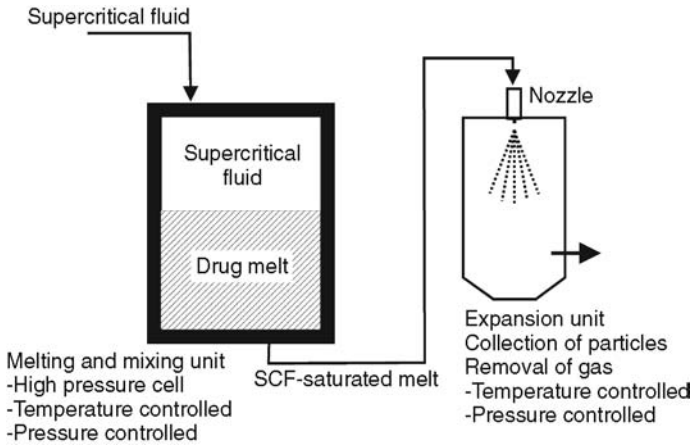


Figure 3 Function scheme of the particles from gas-saturated solutions/suspensions process. The drug is molten in a high-pressure melting chamber and saturated with the supercritical fluid. The mixture is then expanded through a nozzle into an expansion chamber.

sometimes even solubility—of RESS products is improved if compared with the untreated raw material or even micronized preparations (18,47).

Particles from Gas-Saturated Solution

A different technique, the particles from gas-saturated solutions/suspensions (PGSS, Fig. 3) technique, makes use of the fact that compressed gases sometimes show better solubility in liquid or dispersed drugs than these drugs in the compressed gases. Melts of drugs are, therefore, saturated with the SCF and this mixture is expanded through a nozzle.

The binary mixture of $scCO_2$ and some drugs/polymers show melting far below their glass transition temperature or their (normal pressure) melting point (6), in addition, their viscosity is significantly reduced. This leads to expanded droplets, which can be collected either as droplets or as solids, being formed because of the intense cooling produced by the expansion of the SCF (48). This method allows incorporating drug particles in polymers or in fat material, giving microcapsule-like formulations (49). It should, however, be kept in mind that many drugs decompose before they melt. This is also true under supercritical pressure and hereby reduced melting temperatures (32), and makes the PGSS process rarely suitable for pharmaceutical technology (50).

Direct Particle Production II: Antisolvent Techniques

If the drug of interest is insoluble in SCF, antisolvent techniques can help for the production of particles. Briefly, the drug must be dissolved in any kind of suitable solvent. Afterward, the solvent is removed by the SCF and particles are generated.

Antisolvent Techniques I: GAS/SAS

The gas antisolvent (GAS) or SCF antisolvent (SAS) process induces the formation of particles by removing the solvent from a drug solution using a SCF (51). The drug, which should be insoluble in the SCF, must, therefore, initially be dissolved in a suitable solvent, which has to be soluble in the SCF used. The solution is then mixed with the SCF. Because of the dissolution of the solvent in SCF and hereby reduced solvent strength, the drug particles will start to crystallize and precipitate and can be collected from the mixture (Fig. 4) (52).

With careful control of the working parameters, the morphology of the obtained product can be designed to either crystalline or amorphous (53), as can be the particle size and shape (54). The method is rather useful for the generation of pure particles, for composite particles only formulations containing drug and poly-L-lactic acid are reported (55).

Antisolvent Techniques II: ASES, SEDS, SAA

The aerosol solvent extraction system (ASES, Fig. 5, upper panel) uses antisolvent technique like the GAS/SAS process. Here, a solution of the drug in a suitable solvent is sprayed into an

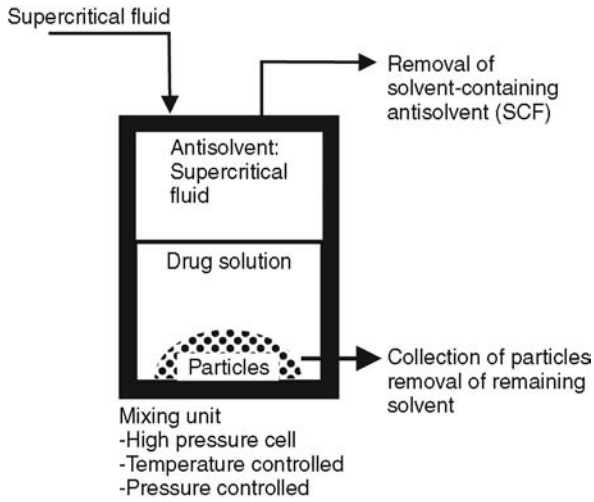


Figure 4 Function scheme of the gas antisolvent/supercritical fluid antisolvent process. A solution of the drug in an appropriate solvent. The solution is then sprayed in a supercritical fluid. The supercritical fluid dissolves the solvent; drug particles remain and can be collected.

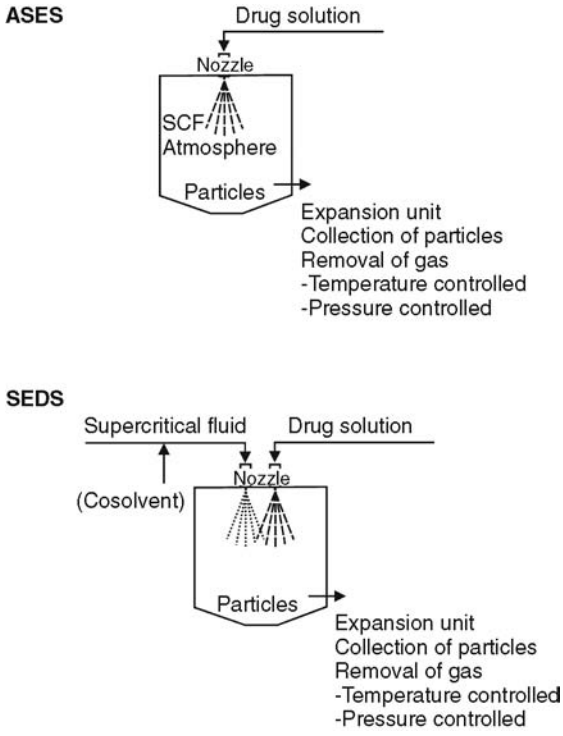


Figure 5 Function scheme of the ASES/SEDS process. ASES: A solution of the drug is sprayed into a supercritical atmosphere. SEDS/SAA: A solution of the drug is sprayed together with a supercritical fluid into the expansion chamber. The mixture is created either at the tip of the nozzle (SEDS) or before going through the nozzle (SAA). *Abbreviations*: ASES, aerosol solvent extraction system; SEDS, solution-enhanced dispersion by supercritical fluid technique; SAA, supercritical assisted atomization.

expansion vessel with a SCF atmosphere (56). With the solution-enhanced dispersion by SCF technique (SEDS), the drug solution is sprayed in parallel with a SCF into the expansion chamber (Fig. 5, lower panel), using coaxial nozzles (6,57). In both cases, the nucleation and crystal growth is induced by dissolving the drug's solvent in the SCF (atmosphere). Both methods are used for the preparation of insulin microparticles in the range of 1 to 5 μm (38,39). The supercritical assisted atomization (SAA) uses a drug solution that is mixed with the SCF and the mixture subsequently expanded through a nozzle into an expansion chamber. The difference in the SEDS process is the fact that in SEDS the mixture is created at the tip of the nozzle but in SAA before going through the nozzle. In SAA, the particle-forming principle is drying of droplets and simultaneously dispersion of the droplets to even smaller units (33).

Other Antisolvent Processes

On the basis of the ASES/SEDS technology, a couple of other processes are developed, which are different in some technical aspects. One of the main rationale for development of a variety of similar methods is the need to avoid violence of patents. A detailed overview on these process variations has been summarized by Jung and Perrut (6).

Impregnation Techniques

All methods with direct particle production suffer from the difficulty to collect, and sometime later to handle, the obtained very small particles. An alternative is to generate the particles within the final formulation or within carriers. This leads to the particle deposition or impregnation techniques. A premise is, of course, the possibility for the supercritical solution to penetrate into the carrier, either by pores or by swelling or amorphous parts of the carriers (58).

Controlled Particle Deposition

The CPD (Fig. 6) is intended to generate particles directly in the final formulation (e.g., tablets) or in a preformulated carrier (e.g., granules), which will then be postproduced to the final formulation. The process requires the drug to be dissolved in the SCF; this supercritical solution is then permeated into pores of the carrier. After rapid release of the pressure, because of drastic reduction of the solubility of the drug in the subcritical state, particles are formed within the pores, leading to preparations with rapid dissolution characteristics (59).

This method has been shown to be suitable for deposition of ibuprofen (as a model drug) in β-cyclodextrin powder (60), in granules prepared from microcrystalline cellulose (61) or in preformed, porous tablets (62). In all cases, the drug particles were crystalline and showed superior dissolution profiles compared with the raw drug material.

Supercritical Solvent Impregnation: Single-Stage Technique

With the supercritical solvent impregnation, the drug and the carrier are mixed, creating a physical mixture. Afterward, the mixture is brought into a high-pressure cell and kept for a certain time period in a SCF. This induces the formation of inclusion complexes, as reported with cyclodextrin (63); however, large amounts of uncomplexed physical mixture may remain in the material.

Supercritical Solvent Impregnation: Multiple-Stage Technique

A multistage flow-through system has been shown to be suitable for loading of carriers like cyclodextrin powders, too (64). Here, the drug is dissolved in a dissolution chamber and

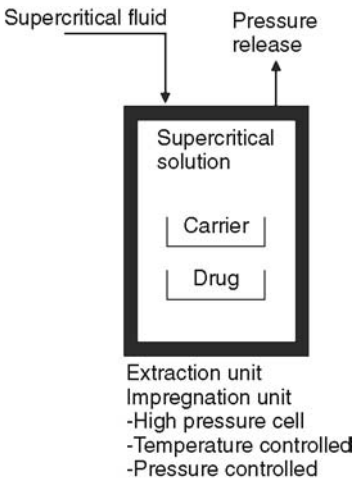


Figure 6 Function scheme of the controlled particle deposition process. The drug is dissolved in a high-pressure chamber. The supercritical solution diffuses in the pores of the carrier. Particles are generated during depressurization.

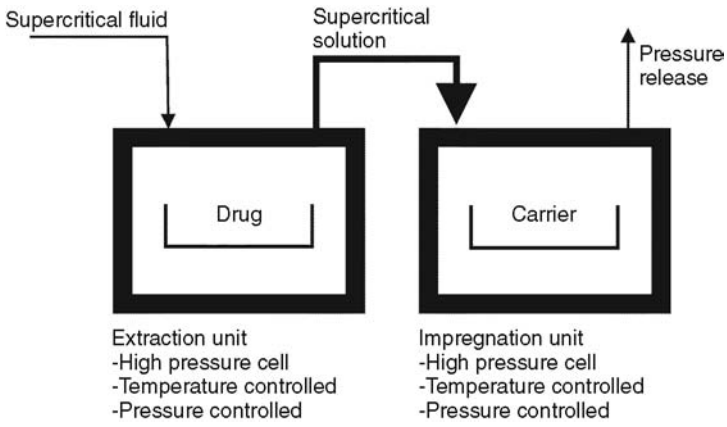


Figure 7 Function scheme of the dynamic impregnation process. The drug is dissolved in a high-pressure cell. The supercritical solution is pumped through a carrier bed in a loading cell. Particles are generated during depressurization.

subsequently pumped through a bed consisting of the carrier (Fig. 7). This technique, when used with methyl-β-cyclodextrin, showed a very high inclusion yield. One has, however, to take into account that under the working conditions applied, methyl-β-cyclodextrin was melting. The technique has also been shown to be suitable for the impregnation of methyl/ethyl cellulose microparticles with naproxen (65,66).

Concentrated Powder Form

The concentrated powder form (CPF) technique is a method to convert liquid material into free flowable powders. A supercritical solution of the liquid in SCF is expanded through a nozzle; the obtained spray is mixed with a solid carrier spray obtained with an inert gas. This leads to an intensive mixing and an agglomeration of the solid carrier by the liquid, resulting in a powder with a liquid content of up to 90 weight percent. A frequent use is the conversion of liquid extracts of essential oils to standardized powders (67).

DRYING TECHNIQUES

Drying of preparations like gels can also be used to prepare solid particles, mainly as composite material. These products are mainly developed for increased dissolution speed, but if suitable excipients are used, they may also show sustained or otherwise controlled release.

Aerogels

The production of free-flowing and ultrafast-dissolving powders is possible by drying of aerogels. Comparable to frozen smoke, these powders have a density about three times that of air and must be seen as a porous material consisting of 99.8% air. On the basis of a sol-gel transformation process with a subsequent drying step, highly porous structures can be generated. In a first step, the silica aerogels were prepared from tetramethoxysilane in a water and organic solvent containing medium. The aerogels are dried by the use of SCF to form a dry powder (68). The dry aerogel powder is then impregnated with the drug in a supercritical solution. These aerogels can be used for significantly improving the dissolution of rarely soluble drugs like griseofulvin (69).

Emulsion Drying

The extraction of organic solvents from emulsions by SCF (supercritical fluid extraction of emulsions, SFEE) was suggested to facilitate the production of drug microspheres based on polymers. With this technique, drugs were dissolved in the lipid phase of an emulsion, which can later be incorporated as inner (O/W) or outer phase (W/O) of the emulsion. In addition, the polymers like polymethacrylate, poly(lactide-co-glycolide) (PLGA), cholesterol acetate, or

lipids were added in the respective phase. The SCF is then applied to extract the lipid phase from the water-in-oil (70) or oil-in-water (71) emulsion, the drug remaining as microparticle composites with the polymer in the water phase. This technique is comparable to the antisolvent techniques and similar apparatuses are used (50).

FUNCTIONALIZATION OF PARTICLES

Apart from the size reduction of particles to the submicron- or nanoscale by SCF technology, functional modification of the particle surface is of major interest. Since handling, and therefore postprocessing, of very small particles is difficult, functionalization beneficially takes place during the particle formation process. A couple of techniques have been developed to combine micronization and functionalization in a single step. These techniques are based on the standard methods described above but are using mixtures of components rather than pure drugs.

Composites by Expansion Technique

An approach to the formation of functionalized particles is the particle formation from supercritical solutions of binary mixtures by the RESS process (so called Co-RESS process). Here, mixtures of a drug and an excipient/excipients like phytosterol and polymethacrylates (72) are dissolved in the SCF. The resulting supercritical solution is then expanded through a nozzle in an expansion chamber, forming particles in the submicron range, which contain both components and can be seen as composites. This technique can be used to control the dissolution of the drug, or to reach other goals. With the PGSS technique, incorporation of particles into melted polymers is also possible. Using polyethylene glycol, solid dispersion of drugs with improved dissolution properties can be produced (73).

Composites by Antisolvent Techniques

The antisolvent techniques, which are in use for pure drug processing, can also be employed for the preparation of composites. Here, however, again the solubility criteria are valid not only for the drug but for the functional excipients, too (48). If both are soluble in the same solvent, they can be precipitated by a SCF in a classical SAS process (58). This process, however, rarely results in the coprecipitation of nanoparticular crystalline material but rather in the formation of microparticles. No consistent data about the efficiency of the coating process are actually available; in addition, the morphology of the particles obtained seems to be quite different, because of experimental conditions (50). If the drug is present only as particles or particles are generated in the process, these can be used as nuclei for the excipient precipitation, resulting in an encapsulation of the drug particle by the excipient. The technique can be used by spraying a particle suspension into a supercritical solution, as done with hydrocortisone as drug particles and PLGA as the polymer excipient (74). If the drug and excipient are soluble in different solvents, both solutions may be sprayed into a supercritical atmosphere, as done with the ASES process and reported for insulin with macrogol/PLA (40).

SUMMARY AND FUTURE ASPECTS

The variety of methods to micronize particles by means of SCF is large. Compounds, which are soluble or insoluble in SCF can be handled by either solvent or antisolvent techniques, with good efficiency. Production methods for coated or functionalized particles are developed; however, their efficacy still lacks profound proof with regard to the properties (e.g., acid resistance, delayed/controlled release) obtained. All these methods suffer from the difficulties to collect and handle very small particles; separation, agglomeration, dust formation, or bad flowability cause problems. Solving these difficulties should open the way to marketed products for these techniques. One possible solution of these problems might be impregnation or controlled deposition, techniques that can help to generate or place particles directly in carriers or even the final formulation, avoiding the collection and handling difficulties. The actual state of acceptance of SCF technology in the industry is difficult to judge; according to the rumor, the first products employing SCF technology for production are supposed to be in phase II clinical studies. It is, however, clear that no company will show its technical head start at this stage. In addition, SCF technology is accepted as a green technology, at least as far as

nontoxic fluids are used, and residues will rarely be found in the final products. This could also help these techniques to find their way into the production lines of rather sophisticated (and somewhat more complex) drug formulations in the future.

REFERENCES

1. Hannay JB, Hogarth J. On the solubility of solids in gases. Proc Roy Soc Lond 1879; 29:1.
2. Krukonis V. Processing of polymers with supercritical fluids. Polym News 1985; 11(1):7–16.
3. Smith RD, inventor (Battelle Memorial Institute, U.S.A., assignee). Supercritical fluid molecular spray film deposition and powder formation. Application: US. US patent 83-528723 4582731. 1986 19830901.
4. Francis AW. Ternary systems of liquid carbon dioxide. J Phys Chem 1954; 58:1099–1114.
5. Mueller BW, Fischer W, inventors; (Schwarz Pharma GmbH, Fed Rep Ger, assignee). Manufacture of sterile sustained-release drug formulations using liquefied gases. Application: DE. DE patent 87-3744329 3744329. 1989 19871228.
6. Jung J, Perrut M. Particle design using supercritical fluids: literature and patent survey. J Supercrit Fluids 2001; 20(3):179–219.
7. Arai Y, Sako T, Takebayashi Y. Supercritical Fluids. Berlin, Heidelberg, New York: Springer, 2002: 71–126.
8. Martinez JL. Supercritical Fluid Extraction of Neutraceuticals and Bioactive Compounds. Boca Raton, London, New York: CRC Press, 2008:1–24.
9. Cabanas A, Renuncio JAR, Pando C. Thermodynamic study of the $N_2O + CO_2$ and $N_2O + CO_2 +$ cyclohexane systems in the near-critical and supercritical regions. Ind Eng Chem Res 2000; 39(10): 3566–3575.
10. Tillner-Roth R, Baehr HD. Measurement of liquid, near-critical, and supercritical (p, r, T) of 1,1,1,2-tetrafluoroethane (R 134a) and of 1,1-difluoroethane (R 152a). J Chem Thermodyn 1993; 25(2):277–292.
11. Saitow K, Kajiya D, Nishikawa K. Dynamics of density fluctuation of supercritical fluid mapped on phase diagram. J Am Chem Soc 2004; 126(2):422–423.
12. Ohgaki K, Katayama T. Isothermal vapor-liquid equilibrium data for binary systems containing carbon dioxide at high pressures: methanol-carbon dioxide, *n*-hexane-carbon dioxide, and benzene-carbon dioxide systems. J Chem Eng Data 1974; 21(1):3.
13. Chiu K-H, Yak HK, Wang JS, et al. Supercritical fluid extraction of mixed wastes. Green Chem 2004; 6 (10):502–506.
14. Subra P, Castellani S, Ksibi H, et al. Contribution to the determination of the solubility of beta-carotene in supercritical carbon dioxide and nitrous oxide: experimental data and modeling. Fluid Phase Equilibria 1997; 131(1–2):269–286.
15. Sievers RE, Hansen B. Supercritical fluid nitrous explosion. Chem Eng News 1991; 69:1.
16. Abbott AP, Eardley CA. Solvent properties of liquid and supercritical 1,1,1,2-tetrafluoroethane. J Phys Chem B 1998; 102(43):8574–8578.
17. Corr S. 1,1,1,2-tetrafluoroethane (R-134a): a selective solvent for the generation of flavor and fragrance ingredients. ACS Symp Ser 2005; 908:41–59.
18. Türk M, Hils P, Helfgen B, et al. Micronization of pharmaceutical substances by the Rapid Expansion of Supercritical Solutions (RESS): a promising method to improve bioavailability of poorly soluble pharmaceutical agents. J Supercrit Fluids 2002; 22(1):75–84.
19. Weinstein RD, Muske KR, Moriarty J, et al. The solubility of benzocaine, lidocaine, and procaine in liquid and supercritical carbon dioxide. J Chem Eng Data 2004; 49(3):547–552.
20. York P, Kompella UB, Shekunov BY. Supercritical Fluid Technology for Drug Product Development. New York, Basel: Marcel Dekker, 2004:1–27.
21. Gupta RB, Shim J-J. Solubility in Supercritical Carbon Dioxide. Boca Raton, London, New York: CRC Press, 2007.
22. Gosselin PM, Thibert R, Preda M, et al. Polymorphic properties of micronized carbamazepine produced by RESS. Int J Pharm 2003; 252(1–2):225–233.
23. Türk M. Manufacture of submicron drug particles with enhanced dissolution behaviour by rapid expansion processes. J Supercrit Fluids 2009; 47(3):537–545.
24. Helfgen B, Türk M, Schaber K. Hydrodynamic and aerosol modelling of the rapid expansion of supercritical solutions (RESS-process). J Supercrit Fluids 2003; 26(3):225–242.
25. Debenedetti PG, Tom JW, Yeo S, et al. Application of supercritical fluids for the production of sustained delivery devices. J Control Release 1993; 24(1–3):27–44.
26. Domingo C, Wubbolts FE, Rodriguez-Clemente R, et al. Solid crystallization by rapid expansion of supercritical ternary mixtures. J Cryst Growth 1999; 198/199 (pt 1):760–766.
27. Thakur R, Gupta RB. Formation of phenytoin nanoparticles using rapid expansion of supercritical solution with solid cosolvent (RESS-SC) process. Int J Pharm 2006; 308(1–2):190–199.

28. Bettini R, Rossi A, Lavezzini E, et al. Thermal and morphological characterization of micronized acetylsalicylic acid powders prepared by rapid expansion of a supercritical solution. J Therm Anal Calorim 2003; 73(2):487–497.
29. Charpentier Paul A, Jia M, Lucky Rahima A. Study of the RESS process for producing beclomethasone-17,21-dipropionate particles suitable for pulmonary delivery. AAPS Pharm Sci Tech 2008; 9(1):39–46.
30. Chu J, Li G, Row KH, et al. Preparation of cefpodoxime proxetil fine particles using supercritical fluids. Int J Pharm 2009; 369(1–2):85–91.
31. Varshosaz J, Hassanzadeh F, Mahmoudzadeh M, et al. Preparation of cefuroxime axetil nanoparticles by rapid expansion of supercritical fluid technology. Powder Technol 2009; 189(1):97–102.
32. Tandya A, Dehghani F, Foster NR. Micronization of cyclosporine using dense gas techniques. J Supercrit Fluids 2006; 37(3):272–278.
33. Della Porta G, Ercolino SF, Parente L, et al. Corticosteroid microparticles produced by supercritical-assisted atomization: process optimization, product characterization, and "in vitro" performance. J Pharm Sci 2006; 95(9):2062–2076.
34. Chingunpitak J, Puttipipatkhachorn S, Tozuka Y, et al. Micronization of dihydroartemisinin by rapid expansion of supercritical solutions. Drug Dev Ind Pharm 2008; 34(6):609–617.
35. Chiou AH-J, Cheng H-C, Wang D-P. Micronization and microencapsulation of felodipine by supercritical carbon dioxide. J Microencapsul 2006; 23(3):265–276.
36. Reverchon E, Della Porta G, Taddeo R, et al. Solubility and micronization of griseofulvin in supercritical CHF3. Ind Eng Chem Res 1995; 34(11):4087–4091.
37. Ghaderi R, Artursson P, Carlfors J. A new method for preparing biodegradable microparticles and entrapment of hydrocortisone in dl-PLG microparticles using supercritical fluids. Eur J Pharm Sci 2000; 10(1):1–9.
38. Snavely WK, Subramaniam B, Rajewski RA, et al. Micronization of insulin from halogenated alcohol solution using supercritical carbon dioxide as an antisolvent. J Pharm Sci 2002; 91(9):2026–2039.
39. Amidi M, Pellikaan HC, de Boer AH, et al. Preparation and physicochemical characterization of supercritically dried insulin-loaded microparticles for pulmonary delivery. Eur J Pharm Biopharm 2008; 68(2):191–200.
40. Elvassore N, Bertucco A, Caliceti P. Production of insulin-loaded poly(ethylene glycol)/poly (L-lactide) (PEG/PLA) nanoparticles by gas antisolvent techniques. J Pharm Sci 2001; 90(10):1628–1636.
41. Charoenchaitrakool M, Dehghani F, Foster NR, et al. Micronization by rapid expansion of supercritical solutions to enhance the dissolution rates of poorly water-soluble pharmaceuticals. Ind Eng Chem Res 2000; 39(12):4794–4802.
42. Cai M-Q, Guan Y-X, Yao S-J, et al. Supercritical fluid assisted atomization introduced by hydrodynamic cavitation mixer (SAA-HCM) for micronization of levofloxacin hydrochloride. J Supercrit Fluids 2008; 43(3):524–534.
43. Chiou AH-J, Yeh M-K, Chen C-Y, et al. Micronization of meloxicam using a supercritical fluids process. J Supercrit Fluids 2007; 42(1):120–128.
44. Kim J-H, Paxton TE, Tomasko DL. Microencapsulation of naproxen using rapid expansion of supercritical solutions. Biotechnol Prog 1996; 12(5):650–661.
45. Sencar-Bozic P, Srcic S, Knez Z, et al. Improvement of nifedipine dissolution characteristics using supercritical CO_2. Int J Pharm 1997; 148(2):123–130.
46. Shinozaki H, Oguchi T, Suzuki S, et al. Micronization and polymorphic conversion of tolbutamide and barbital by rapid expansion of supercritical solutions. Drug Dev Ind Pharm 2006; 32(7):877–891.
47. Perrut M, Jung J, Leboeuf F. Enhancement of dissolution rate of poorly-soluble active ingredients by supercritical fluid processes. Part I. Micronization of neat particles. Int J Pharm 2005; 288(1):3–10.
48. Cocero MJ, Martin A, Mattea F, et al. Encapsulation and co-precipitation processes with supercritical fluids: fundamentals and applications. J Supercrit Fluids 2009; 47(3):546–555.
49. Wendt T, Brandin G, Kilzer A, et al. Manufacture of powdered multiphase composite coatings by the methods of particles from gas saturated solutions (PGSS). Chem Ind Technol 2007; 79(3):287–295.
50. Reverchon E, Adami R, Cardea S, et al. Supercritical fluids processing of polymers for pharmaceutical and medical applications. J Supercrit Fluids 2009; 47(3):484–492.
51. Reverchon E, De Marco I, Torino E. Nanoparticles production by supercritical antisolvent precipitation: a general interpretation. J Supercrit Fluids 2007; 43(1):126–138.
52. Yeo SD, Debenedetti PG, Radosz M, et al. Supercritical antisolvent process for substituted para-linked aromatic polyamides: phase equilibrium and morphology study. Macromolecules 1993; 26(23): 6207–6210.
53. Martin A, Scholle K, Mattea F, et al. Production of polymorphs of ibuprofen sodium by supercritical antisolvent (SAS) precipitation. Cryst Growth Des 2009; 9(5):2504–2511.

54. Shekunov BY, York P, Baldyga J. Particle formation using supercritical antisolvent: influence of flow velocity and supersaturation. Int Symp Ind Cryst 1999; 1112–1126.
55. Song KH, Lee C-H, Lim JS, et al. Preparation of PLLA submicron particles by a continuous supercritical antisolvent precipitation process. Korean J Chem Eng 2002; 19(1):139–145.
56. Subra P, Jestin P. Screening design of experiment (DOE) applied to supercritical antisolvent process. Ind Eng Chem Res 2000; 39(11):4178–4184.
57. Huang J, Moriyoshi T. Fabrication of fine powders by RESS with a clearance nozzle. J Supercrit Fluids 2006; 37(3):292–297.
58. Tandya A, Mammucari R, Dehghani F, et al. Dense gas processing of polymeric controlled release formulations. Int J Pharm 2007; 328(1):1–11.
59. Türk M, Upper G, Steurenthaler M, et al. Complex formation of Ibuprofen and beta-cyclodextrin by controlled particle deposition (CPD) using SC-CO_2. J Supercrit Fluids 2007; 39(3):435–443.
60. Hussein K, Türk M, Wahl MA. Comparative evaluation of Ibuprofen/beta-cyclodextrin complexes obtained by supercritical carbon dioxide and other conventional methods. Pharm Res 2007; 24(3): 585–592.
61. Hussein K, Türk M, Wahl MA. Drug loading into beta-cyclodextrin granules using a supercritical fluid process for improved drug dissolution. Eur J Pharm Sci 2008; 33(3):306–312.
62. Wischumerski RS, Türk M, Wahl MA. Direct drug loading into preformed porous solid dosage units by the controlled particle deposition (CPD), a new concept for improved dissolution using SCF-technology. J Pharm Sci 2008; 97(10):4416–4424.
63. Van Hees T, Piel G, Evrard B, et al. Application of supercritical carbon dioxide for the preparation of a piroxicam-beta-cyclodextrin inclusion compound. Pharm Res 1999; 16(12):1864–1870.
64. Charoenchaitrakool M, Dehghani F, Foster NR. Utilization of supercritical carbon dioxide for complex formation of ibuprofen and methyl-beta-cyclodextrin. Int J Pharm 2002; 239(1–2):103–112.
65. Duarte Ana Rita C, Costa Mariana S, Simplicio Ana L, et al. Preparation of controlled release microspheres using supercritical fluid technology for delivery of anti-inflammatory drugs. Int J Pharm 2006; 308(1–2):168–174.
66. Kikic I, Sist P. Applications of supercritical fluids to pharmaceuticals: controlled drug release systems. NATO Sci Ser Ser E 2000; 366:291–306.
67. Weidner E. High pressure micronization for food applications. J Supercrit Fluids 2009; 47:9.
68. Smirnova I, Suttiruengwong S, Arlt W. Feasibility study of hydrophilic and hydrophobic silica aerogels as drug delivery systems. J Non-Cryst Solids 2004; 350:6.
69. Smirnova I, Türk M, Wischumerski R, et al. Comparison of different methods for enhancing the dissolution rate of poorly soluble drugs: case of griseofulvin. Eng Life Sci 2005; 5(3):277–280.
70. Chattopadhyay P, Shekunov BY. Supercritical fluid: new enabling technologies for drug delivery. Drug Delivery Technol 2006; 6(8):64–68.
71. Della Porta G, Reverchon E. Nanostructured microspheres produced by supercritical fluid extraction of emulsions. Biotechnol Bioeng 2008; 100(5):1020–1033.
72. Türk M. Studies of the coating of submicron particles by the CORESS process. Chem Ind Technol 2004; 76(6):835–838.
73. Weidner E, Steiner R, Knez Z. Powder generation from polyethylene glycols with compressible fluids. Process Technol Proc 1996; 12:223–228.
74. Wang Y, Wang Y, Yang J, et al. The application of a supercritical antisolvent process for sustained drug delivery. Powder Technol 2006; 164(2):94–102.

7 Pharmaceutical Applications of Nanoengineering

Deepak Thassu
PharmaNova Inc., Victor, New York, U.S.A.

Yashwant Pathak
Sullivan University, Louisville, Kentucky, U.S.A.

Michel Deleers
Global Pharmaceutical Technology and Analytical Development, UCB, Braine l'Alleud, Belgium

INTRODUCTION

Nanoengineering, or, as it is sometimes called, molecular engineering, is a field of science whose goal is to control individual atoms and molecules to create material that have a size of only a few nanometers. To fully understand the nanoscale, the prefix nano means ten to the minus ninth power, or one billionth, and is about a thousand times smaller than micron. Depending on the atom approximately three to six atoms can fit inside of a nanometer.

Similar to molecular engineering process, granulation is a process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using binding agent. There are wide varieties of techniques that are capable of creating nanostructures with various degrees of quality, speed, and cost. These approaches fall under two categories bottom up and top down. Both the processes, just like dry and wet granulations, generate materials with different properties. Bottom-up process has significant similarities with the granulation process, which includes building of nanostructures molecule by molecule. This can be accomplished by chemical synthesis, self-assembly, and positional assembly. These processes allow customized molecular granulation process to produce nanomaterial with surface-enhanced properties. This process is used heavily in the nature and has minimum wastage.

Top-down manufacturing requires a large piece of material and etching, milling or machining a nanostructure from it by removing material. Top-down methods offer reliability and device complexity. These processes are higher in energy usage, produce more waste than the bottom-up methods and limits surface modifications of nanomaterial.

Manufacturing Techniques Applied in Nanoengineering

Conventionally, two groups of manufacturing techniques have been reported for producing nanoparticles (NPs). The first involves polymerization of the monomers, whereas the second one is based on dispersion of the performed polymers. The salting out (1), emulsification-diffusion (2), and nanoprecipitation (3) can be cited as typical examples of the second method. NPs are a collective term used to describe the nanospheres and nanocapsules (NCs). The difference between these forms lies in the morphology and the architecture. NCs are composed of a liquid core (generally an oil) surrounded by polymeric membrane, whereas nanospheres are formed by a dense polymeric matrix (4). NCs are pharmaceutically attractive because of their oil-based central cavities, which allow a high encapsulation level for lipophilic substances, enabling improved drug delivery. It is possible to avoid drug precipitation during preparation and subsequent stability problems caused by the presence of the drug on the surface of the NPs. Two techniques are widely used to prepare a biodegradable NC.

Interfacial Polymerization of Alkyl Cyanoacrylate Monomers

In this process, the cyanoacrylate monomer and the lipophilic drug are dissolved in a mixture of oil and ethanol. This organic solution is then added slowly to water or a buffer solution (pH 3–9) containing surfactants such as poloxamers or phospholipids. NCs are formed

spontaneously by anionic polymerization of the cyanoacrylate in the oily phase after contact with hydroxyl ions, which act as initiators.

Interfacial Deposition of Performed Polymers

In this process, the lipophilic drug, oil polymer, and optionally phospholipids are dissolved in a water-miscible solvent (e.g., acetone). This solution is then poured while stirring into an aqueous solution containing a nonionic surfactant (e.g., poloxamer 188). NCs are instantly formed by the fast diffusion of solvent into water, which provokes the spontaneous emulsification of the oily solution in the form of nanodroplets, where the dissolved polymer will form a film around the droplets that contain the drug (5). The method of interfacial polymerization is not ideal for three reasons: (*i*) the probable presence of the residual, (*ii*) potentially toxic monomers or oligomers, and the possibility of cross-reaction with the drug, and (*iii*) the difficulty in predicting the molecular weight of the resulting polymer (6). The principal drawback of this method is the polymer aggregation that is frequently observed when working with high polymer concentration or low organic solvent/water ratio. Guerrero et al. (7) have described a new process based on an emulsification-diffusion technique, overcoming these drawbacks. This study demonstrated that the emulsification-diffusion technique represents a viable alternative for preparing biodegradable NCs starting from performed polymers. It is simple and versatile, and permits high efficiency of entrapment of lipophilic drugs (7).

It is important to note that a deeper understanding of the physicochemical phenomena involved during the NPs formation is also necessary. Specifically, the relationship between physicochemical parameters and their quantitative effects on NPs features could be an invaluable tool in the controlled engineering of particles. Knowledge of these fundamental relationships would allow NPs to be designed with defined size and surface characteristics for delivery to specific cells or organs without requiring exhaustive experimental procedures. Rodriguez et al. (8) studied the influence of certain physicochemical properties of the aqueous and organic phases used during NP preparation and the effects on the characteristics of NPs produced by salting out, emulsification-diffusion, and nanoprecipitation methods, and concluded that the mean size of the NPs could be narrowed, using different methods. For example, salting out offered NP mean size range between 123 and 710 nm. Emulsification method gave 110 to 715 nm mean size, whereas nanoprecipitation gave a very narrow size range distribution of 147 to 245 nm (8). The water-solvent interaction and diffusion motion of the solvent play an important role in explaining the variation of the NP size during NP preparation by the nanoprecipitation method. Common disadvantages of solid-lipid nanoparticles (SLNs) include: particle growing, unpredictable gelation tendency, unexpected dynamics of polymorphic transitions, and inherent low incorporation rates resulting from the crystalline structure of the solid lipids (9).

NANOPARTICULATE SYSTEMS

Nanoparticulate systems are being explored for the purpose of solving the challenges of drug delivery. Coming in many shapes and sizes, most carriers are less than 100 nm in diameter. The systems provide methods for targeting and releasing therapeutic compounds in very defined regions. These vehicles have the potential to eliminate or at least ameliorate many problems associated with drug distribution. As many drugs have a hydrophobic component, they often suffer from problems of precipitation in high concentration, and there are many examples of toxicity issues with excipients designed to prevent drug aggregation. To combat these issues, many nanoparticulate systems provide both hydrophobic and hydrophilic environments, which facilitate drug solubility. Alternatively, many drugs suffer from rapid breakdown and/or clearance in vivo. Encapsulating the drugs in a protective environment increases their bioavailability, thereby allowing the clinicians to prescribe lower doses. With recent advances in polymer and surface conjugation techniques, as well as microfabrication methods, perhaps the greatest focus in drug delivery technology is in the design and applications of nanoparticulate systems. Ranging from simple metal ceramic core structure to complex lipid polymer matrices, these submicron formulations (10) are being functionalized in numerous ways to act as therapeutic vehicles for a variety of conditions (Figs. 1 and 2).

Nanoparticulate drug delivery systems (NPDDSs) can be defined as the DDSs where nanotechnology is used to deliver the drug at nanoscale. Below 100 nm, materials exhibit

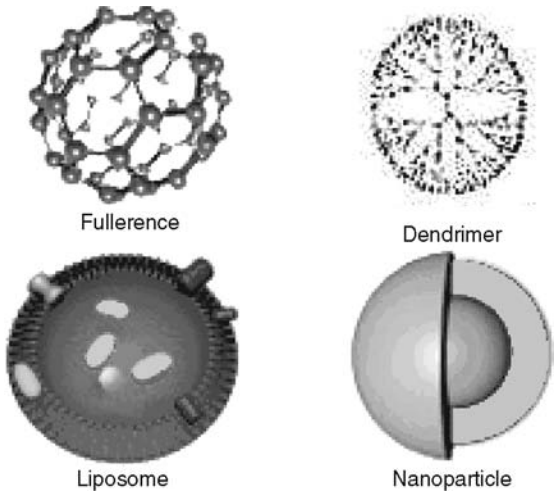


Figure 1 Different types of nanoparticulate structures.

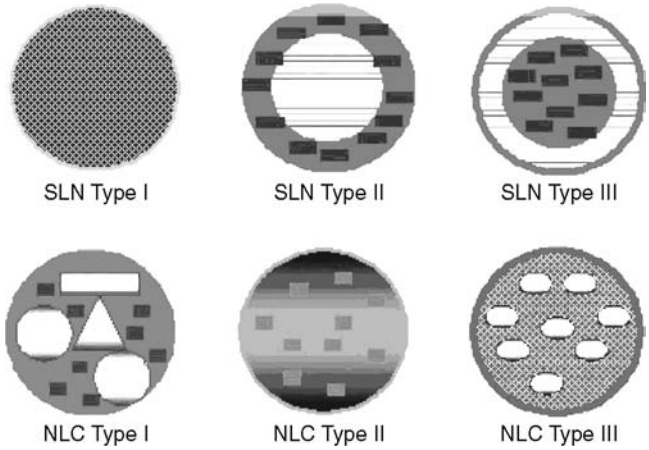


Figure 2 Basic types of solid nanoparticles and nanostructured lipid center. *Abbrevations*: NLC, nanostructured lipid carrier; SLN, solid-lipid nanoparticle. *Source*: From Ref. 43.

different, more desirable physical, chemical, and biological properties. Given the enormity and immediacy of the unmet needs of therapeutic areas such as CNS disorders, this can lead to drugs that can extend life and save untimely deaths (10).

Advantages of Nanoparticulate Drug Delivery Systems

The NPs may offer some advantages such as protection of drugs against degradation, targeting the drugs to specific sites of action, organ or tissues, and delivery of biological molecules such as proteins, peptides, and oligonucleotides.

A number of different strategies have been proposed to modify the physicochemical characteristics of the NPs, and thus their interactions within the biological systems. For example, it is possible to change the chemical nature of the polymeric matrix of the NPs and thereby alter certain biological phenomena, such as biorecognition, biodistribution, bioadhesion, biocompatibility, and/or biodegradation. Some polymeric materials used for this purpose are gelatin, chitosan (CS), sodium alginate, poly(alkyl)cynoacrylates, poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(ethylene glycol-co-(lactic-glycolic acid), poly(caprolactone), and polymethyl methacrylate (11,12). Another approach to modify the biological response is based on the incorporation of suitable adjuvants in the NPs, like proteins such as albumin, invasins, and lectins, and polymers such as poloxamers and poloxamines (13). Different manufacturing methods can also enable modifications of the physicochemical characteristics of NPs such as size, shape, structure, morphology, texture, and composition (8).

NANOPARTICULATE DRUG DELIVERY SYSTEM APPLICATIONS

NPDDSs have been utilized for their therapeutic applications over a wide range, from cancer treatments to some over the counter (OTC) preparations. Many drugs have been used as model drugs for specific spatial and temporal applications. Table 1 enumerates various drugs that have been used in NPDDSs. In the pharmaceutical formulations, NPDDSs can be used with advantages. Table 2 shows applications of NPDDSs to address various formulations issues.

Nanoparticulate Drug Delivery Systems for Proteins and Peptides

Large numbers of new therapeutic proteins and peptides are being discovered, thus protein drug delivery technologies are of ever increasing importance. Traditionally, the protein is delivered parenterally via solutions that are injected subcutaneously, intramuscularly, and intravenously. Although such injections benefit from high bioavailability, they fail to provide sustained plasma concentrations and suffer from poor patient compliance because of the required frequency of injections. NPDDSs are designed to provide the drug release over an extended period of time, thereby minimizing the need for frequent injections. These can be used for systemic or oral delivery, and the biodegradable nature of the nanoparticulate materials alleviates the need for surgical removal. Biodegradable nanoparticulate delivery for protein must satisfy several technical requirements. Among these, the proteins should be encapsulated with a high loading efficiency, and remain stable throughout the manufacturing process and the course of their intended dosing period. NPs need to be less than 125 nm in diameter and form a free-flowing powder so that they can be resuspended in an injectable vehicle and passed through a needle. The release profile of the drug needs to be reproducible and therapeutically effective, and pose no pharmacological or toxicological risks due to rapid early release or burst.

Macromolecules, such as proteins and DNA, play an increasingly important role in our arsenal of therapeutic agents. Delivery of these molecules to their site of action at the desired rate is a challenge because their transport through compartmental barriers, for example, endothelium and epithelium in the body, is inefficient and/or they are readily metabolized. For controlled release or site-specific delivery of such macromolecules, delivery systems are required, which need to be more sophisticated than our present-day strategies. These systems must be custom made, taking into account both size and specific characteristics of these molecules. One has to build a platform of different delivery strategies that use input from technical, pharmaceutical, and biomedical disciplines to meet these challenges.

The development of appropriate DDSs for new macromolecules coming out of the biotech industry is a meaningful challenge to pharmaceutical scientists. Proteins, peptides, oligonucleotides, and genes are very unstable compounds that need to be protected from degradation in the biological environment. Their efficacy is highly limited by their inability to cross biological barriers and to reach the target sites. They are vulnerable to harsh conditions in the gastrointestinal tract, leading to chemical and enzymatic degradation. The future of these molecules solely depends on the delivery systems and appropriate carriers.

There are three possible pathways for protein and peptide drug absorption through the GI tract. The first is via the M-cells of Payer's patches, the second via a transcellular route involving enterocytes, and the third via paracellular avenues through tight junctions (14,77). The nanosystems are providing a viable alternative for these drugs such as liposomes, polymeric micelles, and NPDDSs. One of the crucial and pervasive troubles in human therapy is to achieve a balance between toxicity and therapeutic effect of the drugs. Therefore, the site-specific delivery could reduce such side effects at nontarget sites and increase the efficacy. Rodrigues et al. (78) have reported an interesting work on lectin nanocarrier conjugate. They used dextran/poly(e-caprolactone) polyester polymers and conjugated with three different proteins, lectins from leaves of *Bauhinia monandra* and *Lens culinaris*, and bovine serum albumin (BSA). The NPs having a size around 200 nm could be used for delivering proteins (78).

A polypeptide hormone consisting of 32 amino acids plays a crucial role in both bone remodeling and calcium homeostasis. Yoo and Park (79) formulated salmon calcitonin (sCT) into biodegradable PLGA NPs using sCT oleate complexes. The sCT oleate complexes were prepared by hydrophobic ion pairing. SCT NPs were readily taken up by Caco-2 cells and sCT

Table 1 Drugs Used for Nanoparticulate Drug Delivery Systems

Name of the drug and reference numbers	Carrier
Aclacinomycin (14)	PBCA NPs
Adriamycin (15)	PBCA NPs
Antifungal drugs (16)	Submicronized emulsion
Atovaquone (17)	SLNs
Betamethasone (18)	$CaCO_3$ NPs
Bifonazole (19)	B-cyclodextrin NPs
Brimonidine (20)	Polyacrylic NPs
Budesonide (21)	Polylactic acid NPs nanosuspension
Camptothecin (22)	SLNs
Cephalosporin(23)	Nanoconjugates
Cisplatin (24)	Polymeric micelles
Clotrimazole (20)	B-cyclodextrin NPs
Clobetasol (25)	SLNs
Clozapine (26)	SLNs
Curdlan derivative: anticancer drugs (27)	SLNs
B-cyclodextrin (28)	Nanosphere
Cyclosporine (29)	SLNs
Cyclosporine (30)	Stearic acid NPs
Cyclosporine (31)	HPMCP
Cyclophosphamide (32)	PBCA NCs
Diclofenac (33–36)	Inorganic microparticles (33), polylactide (34), polylactide (35), caprolactone (36)
Danazol (34,37)	Lipid-based emulsion
Darodipine (35,38)	SLNs
Delargin (36)	PBCA NPs
Dexamethasone (37)	Supercritical carbon dioxide nanosphere poly(l-lactide-co-glycolide) (nPLGA)
Diminazine (38)	Lipid based
Diminazenediaceturate (39)	Lipid-drug conjugate
Gadolinium (40)	Lipid-based NPs
5-Fluouracil (41)	Colloidal NPs
Flurbiprofen (42)	Nanosuspension
Halofantrine (43)	Lipid-based emulsion
Heparin (44)	Methacrylate polymers
Hydrocortisone (45)	SLNs
Idarubicin (46)	SLNs
Indomethacin (47)	SLNs
Isoniazid (48)	PL glycolide polymer
Ketoprofen (49)	Polycaprolactone and Eudragit S100
Kytorphin (50)	PBCA NPs
Loperamide (51)	Polysorbate 80-coated PBCA NPs
Methotrexate (41)	Colloidal carriers
Mitoxantrone (52)	Magnetic NPs
Nifedipine (53,54)	SLN nanocrystals
Ontazolost (55)	Lipid-based delivery
Paclitaxel (56–59)	SLNs (56), cetyl alcohol/polysorbate NPs (57), gelatin NCs (58), PLGA (59)
Phenothiazine (53)	SLNs
Pilocarpine (60)	PLGA
Praziquantel (61)	PLGA NCs
Prednisolone (62)	SLNs
Porpofol (63)	Lipid-free NCs
Progesterone (44)	SLNs
Protamine phosphorothioate (64)	NP complexes
Pyrazinamide (47)	PL glycolide
Retinal (65)	SLNs
Rifabutine (17)	SLNs
Rifamycin (47)	PL glycolide
Tamoxifen (66)	Polycaprolactone NPs
Tarazepide (67)	Cyclodextrin
Thiamine (68)	Lipid
Tobramycin (69)	SLNs

(*continued*)

Table 1 Drugs Used for Nanoparticulate Drug Delivery Systems (*Continued*)

Name of the drug and reference numbers	Carrier
Tretinoin (70)	SLNs
Triclosan (71)	Submicron emulsion and NCs
Tubocurarine (72)	Polysorbate 80-coated PBCA NPs
Ubidecarone (73)	SLNs
UCB-35440-3 (74)	Nanocrystals
Vincristine (41)	Colloidal carriers
Vitamin A (75)	SLNs
Xanthone (76)	PLGA

Abbreviations: HPMCP, hydroxypropyl methyl cellulose phthalate; NCs, nanocapsules; NP, nanoparticle; PBCA; polybutylcyno acrylate; PLGA, polylactic-co-glycolic acid; SLN, solid-lipid nanoparticle.

Table 2 Nanoparticulate Drug Delivery Systems: Formulation Applications

Addressing the drug delivery problems

- Solving the issues related to solubility
- Overcoming the poor bioavailability of the drugs
- Issues with fed/fasted variability
- Pharmacokinetic variability

Finding solutions with nanoparticulate drugs

- Technology advances
- Reduction in particle size of the poorly water-soluble drugs
- Increased active agent surface area

Benefits for faster dissolution

- Greater bioavailability
- Smaller drug doses
- Diminished toxicity
- Decreased dosing variability

Pharmacodynamic factors: applicable to peptides and other drugs

- These can be formulated as receptor-specific
- These can be more resistant to unspecific degradation

They can deliver the drug in encapsulated form to delay the degradation, set a depot form for prolonged signaling, and increase the treatment efficacy as compared with substitution of the natural form of peptide.

was transported across the Caco-2 monolayer in vitro. In vivo experiments showed that sCT was orally absorbed.

A study by Alphandary et al. (80) has shown the crossing of insulin through the intestinal epithelial barrier to the blood compartment, where it was absorbed by portions of the M-cell-free epithelium. The insulin was incorporated in biodegradable poly(alkyl cynoacrylate) NCs (81).

An excellent review discusses the strategies of enhancing the immunostimulatory effects of CpG oligonucleotides and outlines the latest development in the application of liposomes and NPDDSs for the delivery of oligonucleotides with an extensive literature survey. Leach et al. (82) demonstrated that excipient-free protein NPs prepared by spray freezing into liquid technology (83) can be dispersed into PLGA and PLA microparticles and the burst effect can be prevented. The uniform encapsulation of the stable proteins at high loading was achieved with minimal burst effect. NPs based on hydrogels are being developed for the delivery of macromolecules.

An interesting mechanistic study reported by Mo and Lim (84) and Murakani et al. (85) exhibited uptake of wheat germ agglutinin-conjugated NPs by A549 cells. In this study, they prepared the PLGA NPs by solvent diffusion method (86) and later surface modified with

wheat germ agglutinin through a two-step carbodiimide method. Cellular uptake was studied using confluent A549 cells as an in vitro model of the type II alveolar epithelial cells. Uptake of the WGA-conjugated PLGA NPs was compared with that of NPs similarly modified with the BSA to demonstrate the specificity of the surface WGA in enhancing the cellular uptake of the NPs. The mechanism of uptake was studied by performing the uptake experiments under several inhibiting conditions. They concluded that the grafting of WGA on PLGA NPs has increased the uptake by five to eight times, hence this method can be exploited for the intracellular delivery of therapeutic and diagnostic agents (85).

Targeted delivery of proteins and DNA requires a carrier system in submicron size or nanosize. This carrier needs to be target site (cell or tissue)-specific. Often, the actual target site location is intracellular, and the delivery of the carrier payload at this intracellular target site is a prerequisite for therapeutic success. For example, plasmid DNA needs to be delivered inside the nucleus of the target cell before the cell can express the desired therapeutic protein. A very good example of this system is the immunoliposomes, where liposomes carrying the drug with monoclonal antibodies or monoclonal antibody fragments are covalently attached to the bilayer for targeting purposes. A selection of monoclonal antibodies, with induced endocytic uptake, can lead to the entrance of immunoliposomes (Fig. 3) into tumor cells (82,87). Another application of liposome-dependent drug is diphtheria toxin A (DTA) chain. Liposome dependent means that the drug as such cannot reach its target site of action inside the cell without a carrier, as it cannot pass the cytoplasmic membrane without help (a carrier). Such a drug will show neither the desired nor the undesired pharmacological effects. Diphtheria toxin, a protein consisting of an A chain coupled with a B chain, can readily enter cells through the transporter B chain.

Upon entering the cell, the A chain causes the cell kill with exceptional efficiency by blocking ribosomal activity. Thus, DTA (lacking B chain) alone needs a cell-specific transport system, that is, a system that transports it into the desired target cells, for example, tumor cells (88) (Fig. 4).

The design of a custom-made carrier at the nanometer level is a targeted delivery system for plasmid DNA to efficiently transfer only to target cells. The cationic polymer poly[2-(dimethylamino)ethyl methacrylate] (pDMAEMA) condenses plasmid DNA effectively into 100 nm NPs (polyplexes). In vitro transfection is very efficient but in vivo was ineffective. Polyplexes were subsequently coated with lipids yielding lipopolyplexes, which demonstrated target cell-specific binding characteristics, and were able to transfect the cells with hardly any cell toxicity (89).

Ocular Applications of Nanoparticulate Drug Delivery System

Topical ophthalmic drugs generally have poor absorption in the eye due to the cornea's low permeability to drugs and noncorneal factors such as rapid tear turnover, nasolacrimal drainage, and systemic absorption. One of the major problems in ocular delivery is providing and maintaining an adequate concentration of the therapeutic agent in the precorneal area. Topical drop administration of ophthalmic drugs in aqueous solutions results in extensive drug loss due to tear fluid and eyelid dynamics (21,90,91). Most noninvasive approaches for enhancing ocular drug absorption involve the use of prodrugs, the use of viscosity agents designed to prolong the drug residence time, and colloidal systems (92,93). Polymeric NPs are attractive colloidal systems because they demonstrate increased stability and have a longer elimination half-life in tear fluid (up to 20 minutes), than the conventional drugs applied topically to the eye, which have half-lives of just one to three minutes.

NPDDSs have been evaluated for ocular applications to enhance absorption of therapeutic drugs, improve bioavailability, reduce systemic side effects, and sustain intraocular drug levels (94). NPDDSs have shown potential in the treatment of external eye diseases (95). PLGA has been evaluated and proved to be a very useful biodegradable polymer for NPDDS formulation because of its medical use, biocompatibility, and safety (96). Qaddoumi et al. (93) have studied the characteristics and mechanism of uptake of PLGA-based NPDDSs for ophthalmic application.

They suggested that PLGA-based NPDDSs could be used for the enhancement of drug absorption in the eye and the controlled release of proteins and drugs. Some reports in ocular

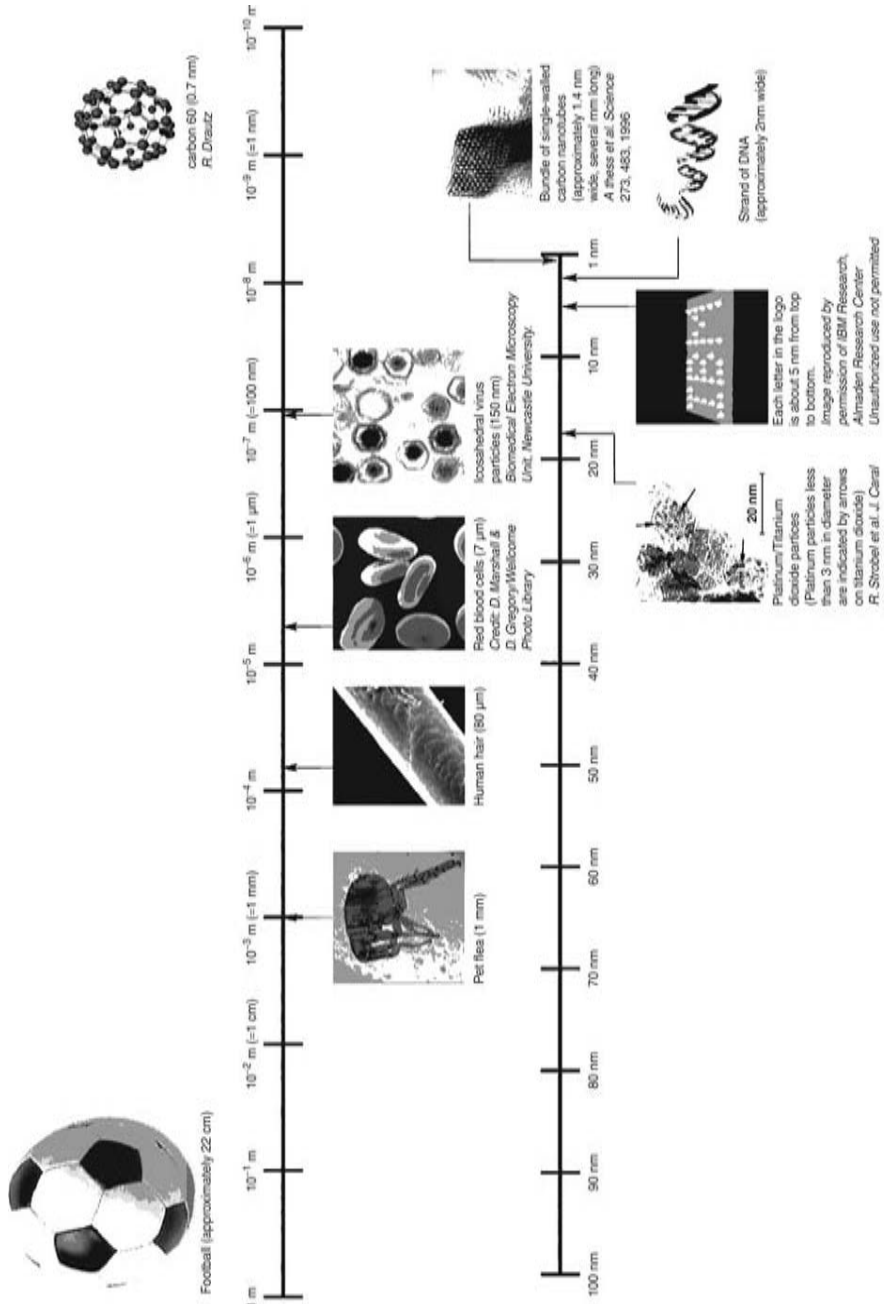


Figure 3 Length scale showing the nanometer in context, the length scale of interest for nanoscience and technologies is from the 100 nm down to the atomic scale approximately 0.2 nm. *Source*: From Ref. 1.

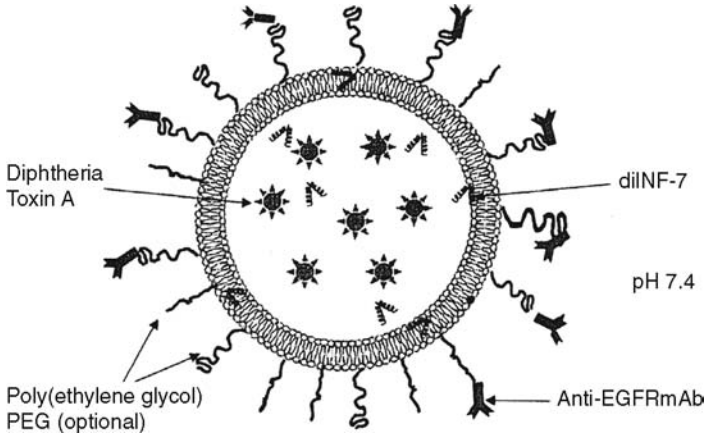


Figure 4 Immunoliposomes: the use of nanotechnology to build a carrier system for site-specific delivery of a protein. The anti-EGFR antibody permits endocytosis helping the immunoliposomes to enter the target cells after cell binding. The peptide dilNF-7 induces the release of liposome entrapped diphtheria toxin A chain from immunoliposomes. *Abbreviation*: EGFR, epidermal growth factor receptor. *Source*: From Ref. 86.

applications are very novel approaches involving periocular routes for retinal drug delivery of celecoxib and aldose reductase inhibitors (97–99). Salgueiro et al. (32) demonstrated ophthalmic application of cyclophosphamide-loaded polybutyl cyanoacrylate (PBCA) nanosphere as an immunosuppressive agent. The morphometrical properties such as average particle size and polydisparity index of these DDSs are adequate for ophthalmic application without induced corneal or conjunctival irritation (33).

Nanoparticulate Drug Delivery Systems for Pulmonary Treatment

Pulmonary drug delivery for both systemic and local treatments has many advantages over other delivery routes because the lungs have a large surface area (43–100 m^2), thin absorption barrier, and low enzymatic activity. In addition, the alveoli of the lungs have a slower mucociliary clearance than the airways, and the lung epithelia are thinner and more permeable. There is a potential for possible systemic absorption of the peptides and proteins through the alveolar region of the lungs. Several studies have exhibited the absorption of high–molecular weight drugs such as insulin, heparin, and GCSF (recombinant human granulocyte colony-stimulating factor) through pulmonary DDSs (100–102). As these peptides have a short life, the development of delivery systems with sustained pharmacological action would be very useful.

Innovative, noninvasive, inhalable DDSs for peptides are being explored for lung disease therapy with the vasoactive intestinal peptide (VIP) being used in the treatment of severe lung diseases. Owing to its known antiinflammatory and vasodilative properties, it has been demonstrated to possess a high therapeutic potential for other lung diseases, which are common in industrialized countries. VIP, unfortunately, reveals a variety of bifunctions mediated by at least two different receptors on the cell surface. The ways thought to deal with this situation are to develop a receptor-specific system to make it more specific in function. These need to be protected by licensing, and allow for superior treatment compared with natural VIP. It can be achieved by designing, engineering, and production of analog peptides, which will be very useful. By modifying the peptide, VIP in the amino acid sequence becomes more receptor-selective and more resistant to unspecific degradation. It can deliver the new peptides in nanoencapsulated form to delay the degradation, and to set in depot form for prolonged signaling, increasing the treatment efficacy as compared with substitution of the natural form of the peptide.

An enormous diversity of therapeutic agents is currently administered to the patients via aerosol inhalation, and the number of potential drug candidates for pulmonary application increases daily. The major areas of research and therapeutic applications are asthma (103), cystic fibrosis (104), lung cancer (105), tuberculosis (106,107), pulmonary hypertension (108), and diabetes (109). Nanostructured drug delivery and targeting systems are tools to overcome the limitations of lung delivery by stabilizing and protecting the release in the bronchi and make lung therapy through inhalation possible and effective. Some of the polymers such as PLGA, protamine, thiomer, and lipid-based particles can be loaded by VIP or new designed

analogs. The parameters, which need to be tested, will be improved by in vitro enzymatic stability, in vitro long-term drug release, and retarding properties and bioavailability of the carrier.

Insulin-loaded PBCA NPs were studied by Zhang et al. (110); they demonstrated that the pulmonary administration of these NPs could significantly prolong the hypoglycemic effect of insulin. It was reported that the bioavailability of insulin NPs was relatively higher than that of solution when administered by pulmonary route to normal rats, but when NPs were administered subcutaneously, the bioavailability was comparatively lower compared with solution administered the same way (110). Another study using PLGA NPs to deliver insulin by nebulization also showed the usefulness of NPDDSs for insulin (111). An interesting study was reported by Liu et al. (112,113) incorporating estradiol and colloidal gold NPs in PLGA NPs to be used as a model for the pulmonary DDSs. They proposed that large, porous NPs can be used as delivery systems for the pulmonary tract.

Several issues complicating the development of aerosol formulation include: compound loss during inhalation, dosing difficulties, enzymatic degradation within the lungs, and the high cost of production. Nanoparticulate-controlled release DDS has the potential to overcome many of these problems. Such formulation may be incorporated in aerosol form, remaining stable against forces of degradation during aerosolization. It can target a specific site or cell population in the lung, protect the drug-aggressive elements in the pulmonary tract, and release the compound in a predetermined manner concurrently. It can be inert to the surrounding tissues and contains no irritant or toxic additives, and degrade when applicable within an acceptable period of time, producing no toxic byproducts (114). Polymeric nanoparticulate systems show promise in fulfilling the stringent requirements of the pulmonary DDSs.

An interesting study is reported by Dailey et al. (114) using short-chain PLGA grafted onto an amine-substituted poly(vinyl alcohol) backbone (3-diethylamino-1-propylamine (8%)-poly(vinyl alcohol)-grafted poly(lactide-co-glycolide) (DEAPA-PVAL-g-PLGA) polymer. This polymer has amphiphilic properties and is highly suited for the pulmonary delivery system. It was also reported that by adding varying amounts of polyanion such as carboxymethyl cellulose, dextran sulfate, or even DNA to the polymer ring during NPs formation, NPs of variable physicochemical properties could be generated enable. This can increase the loading efficiency of various drugs along with a greater stability. However, these polymer derivatives were found to degrade from 24 hours to within a week. Some related studies have described these aspects in detail (112,115).

NPs may be very effective DDSs for various pulmonary therapeutic schemes. The study by Dailey et al. (116) investigated the effect of nebulization technology and NP characteristics on the features of aerosol generation. They concluded that biodegradable NPs contained in the suspensions did not affect the aerosol droplet size in a clinically relevant manner; however, both NP characteristics and the technique of aerosolization influence NP aggregation occurring during the aerosolization (116).

Vila et al. (117) have shown that polyethylene glycol (PEG) coating of the PLA NPs increased the absorption of drug in nasal mucosa. Pandey et al. (49) demonstrated the application of NPDDSs for the treatment of experimental tuberculosis using poly(D,L-lactide-co-glycolide) as a polymer. They used an inhalable system using the NPs and three anti-TB drugs rifampicin, isoniazid, and pyrazinamide (49).

Nanoparticulate Drug Delivery Systems for Central Nervous System

The entry of a drug molecule into the brain is limited by one of the most challenging barriers, the blood-brain barrier (BBB). The BBB consists of a continuous layer of endothelial cells joined together by tight junctions (zonula occludens), which severely restrict paracellular transport across the barrier. The BBB allows passive diffusion of small lipid-soluble molecules, whereas hydrophilic substances or molecules with high molecular weight have minimal passive permeation. The mechanism of permeability regulation includes macrovascular endothelial tight junctions, enzymatic regulation, and active brain efflux. Transport across BBB is additionally regulated by a number of transporters including very effective efflux transporters, such as multidrug resistance-associated protein or P-glycoprotein.

Several strategies have been tried to cross the BBB; one alternative strategy is to use drug carrier systems such as liposomes, antibodies, and NPs (118). Numerous studies have shown the applications of NPs for brain targeting (51,52,119,120).

Hexapeptide dalargin, a Leu-encephalin analog with no BBB permeability adsorbed to the surface of PBCA NPs, caused central analgesia after IV administration (121). Other drugs tubocurarine (72), doxorubicin (124), kytorphin (51), and loperamide (52) were also used as model drugs for these purposes. Brain uptake of NPs in these studies was suggested on the basis of the fact that the drugs adsorbed to PBCA NPs caused a resultant pharmacological effect in the CNS (51,71,121). Brain distribution of drugs delivered on the surface of NPs was also confirmed by quantification of the drug in the brain tissue itself (122). Studies have also shown the intact presence of NPs in brain cells in vivo (123). Koziara et al. (118) tried to quantify the presence of the NPs in brain in situ and studied the impact on BBB parameters (124).

Another study from the same laboratories showed the effectiveness of using microemulsions as precursors to engineer NPs. The advantages with the microemulsions were simplistic production of the NPs approximately 100 nm in diameter, possible incorporation of hydrophobic drugs in oil droplets, and inclusion of site-specific ligands. They also reported the kinetic modeling of brain uptake, and their data suggested the probable mechanism of brain entry (69).

Nanoparticulate Drug Delivery Systems for Enzymes

Many scientists attempted application of nanocarriers for delivery of therapeutic enzymes (125,126). A catalase delivery system seems to be an ideal testing model for evaluating the key aspects of enzyme delivery by nanocarriers. There is a fascinating study describing the loading and protection of an active enzyme catalase into a polynanocarrier composed of diblock PEG-PLGA copolymers (125). It showed nanocarriers in the size range of 200 to 500 nm protecting at least 25% of the loaded proteases. Figure 3 demonstrates the method of formulation of PLGA-PLA NPs carrying the enzymes (125). Nanocapsulation helps to lengthen the therapeutic window by designing biodegradable polymeric nanocarriers, which protect encapsulated catalase from lysosomal proteolysis, thus prolonging the duration of the desired effects (Fig. 5). They hypothesized that the polynanocarriers formation, sizing, and loading should a potential basis for a more general framework for the formulation of NPDDSs, especially for enzymes. Many enzymes using small substrates diffusing through polymer shells such as sugars, amino acids, and glutathione may be amenable to loading into protecting polynanocarriers. The study recommended testing of the delivery vehicles in cell culture and animal studies, as a new strategy for a prolonged protection against vascular oxidative stress (125).

Weissenbock et al. (127) showed the application of wheat germ agglutinin to enhance the absorption of PLGA NPs. The wheat germ agglutinin has cytoadhesive and cytoinvasive properties. This process of surface engineering the PLGA NPs by wheat germ agglutinin promises high versatility of application in the search for biorecognitive ligands enhancing the cytoadhesion, cytoinvasion, and probably transcellular transport of colloidal carriers after peroral administration (127). Gref et al. (128) and Lochner et al. (129) reported novel surface engineering of the NPDDS.

Proticles: Protamine Nanoparticles as Drug Delivery Systems

Proticles are novel NPs composed of protamine, a peptide used in many pharmaceutical formulations with DNA, proteins such as albumin and other therapeutically active substances. Junghans et al. (130) reported the use of proticles as delivery systems for oligonucleotides. The stability of the particles and the oligonucleotides bound to the particles was examined in fetal calf serum and cell culture medium.

Proticles significantly decreased cellular growth in a cell proliferation assay using oligonucleotides against the c-myc protooncogene. Proticles can also be used for diagnostics. NPs can bind large amounts of substances on their surface by adsorption, and so they can be used as an absorber. Proticles with ligand-specific as amyloid-β can bind the neurotoxic amyloid-β protein. The neuroprotective effects of this delivery system may find a novel therapy for Alzheimer's disease.

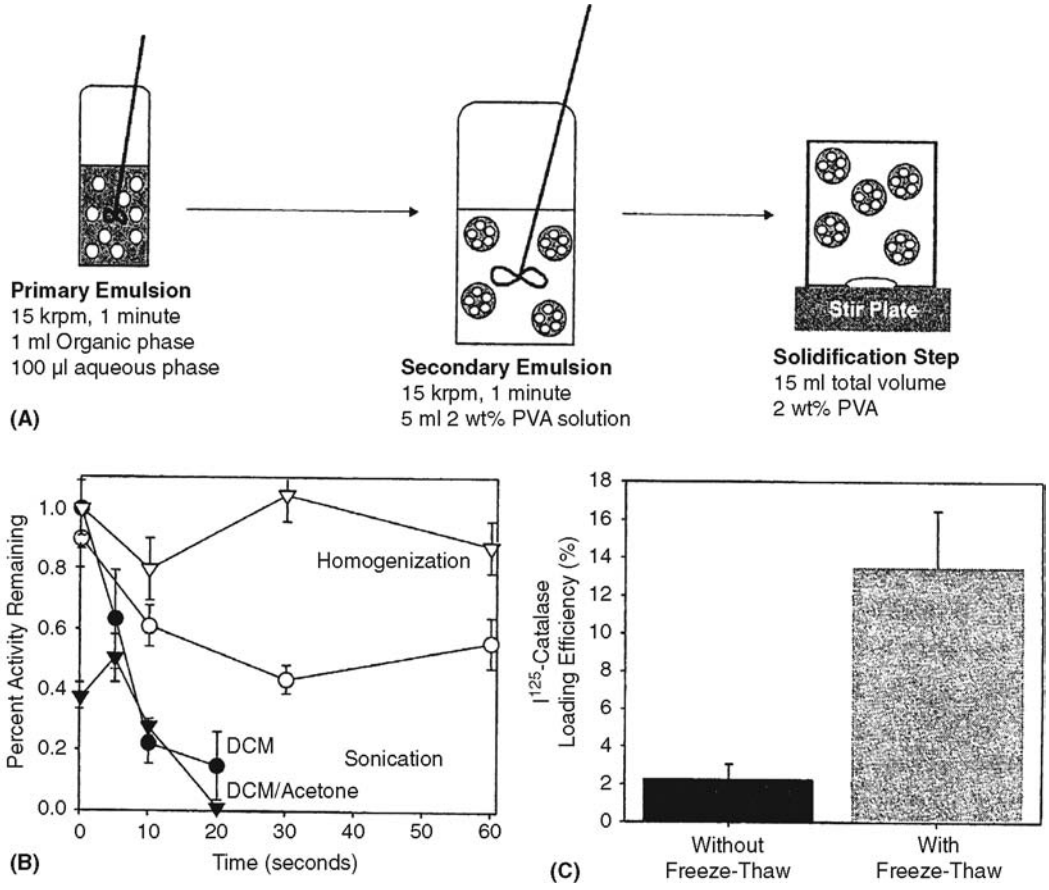


Figure 5 Formulation of poly(lactic-co-glycolic acid)–polyethylene glycol nanoparticles: (**A**) scheme with the double-emulsion synthesis procedure and (**B**) by sonication in DCM/acetone mixture. (**C**) The loading efficiency was determined by tracing the amount of radiolabeled catalases contained inside either the microparticles (i.e., pellet obtained after centrifuging for 15 minutes at 1000 × *g*) or nanoparticles fractions (second pellet obtained by centrifuging for 30 minutes at 22,000 × *g*). Loading efficiency was greatly enhanced (eight-fold) when a freeze-thaw cycle (*gray bar*) was included in the primary emulsion step. The data in this figure is presented as $M \pm$ SEM ($n = 3$). *Source*: From Ref. 124.

Amyloid-binding peptide depot system is aimed at developing therapy for Alzheimer's disease. Amyloid-binding peptides are substances that can disintegrate amyloid plaques. These are hidden in the interior of proticles to cross the BBB and for slow controlled release to achieve a high concentration of amyloid-binding peptides in the brain over a long period. This can be further studied using the MRI with gadolinium as a contrast substance. VIPs, which are used in the treatment of severe lung diseases, can be packaged in proticles and can be used to create a pulmonary depot for the treatment for 12 to 24 hours. Antigens are bound to the surface of proticles for efficient composition of the proticles that might further boost the immune response. Some recent reports show the application of proticles as DDSs (131–133).

Mucoadhesive Nanoparticulate Drug Delivery Systems

Mucosal surfaces are the most common and convenient routes for delivering drugs to the body. However, macromolecular drugs such as peptides and proteins are unable to overcome the mucosal barrier and are degraded before reaching the bloodstream. NPDDSs show a promising strategy for delivering drugs through mucosa. Polysaccharide CS is mucoadhesive, and CS NPs, CS-coated oil nanodroplets (nanocapsules), and CS-coated lipid NPs have shown

interesting possibilities for this purpose (134). CS-coated systems have exhibited an important capacity to enhance the intestinal absorption of the peptide sCT and in vivo, a long-lasting decrease in the calcemia levels observed in rats (135).

Takeuchi et al. (136) have written a review on mucoadhesive NPDDSs for peptide drugs. They discussed the preparation and methods for evaluation of mucoadhesive nanoparticulate systems. Mucoadhesive properties were conferred on the systems by coating with mucoadhesive polymers such as CS and carbapol. The feasibility of this surface adhesion was confirmed by measuring the zeta potential. They suggested that these delivery systems could be used for delivery of peptides by oral and pulmonary administration. Nanoprecipitation techniques using PLGA and PLA polymers were found to be useful for nanoparticulate delivery of proteins and have shown more versatility and flexibility in the formulation for protein delivery (137).

Takeuchi et al. (138) described mucoadhesive PLGA nanospheres prepared by surface modification with CS for oral peptide delivery. CS-modified nanospheres were applied to improve the pulmonary delivery of peptides by nebulization. The particle average diameter of 650 nm of the aqueous dispersion of the nanospheres was an important factor to enclose the particles in the aerosolized aqueous droplets produced with the nebulizer. The elimination rate of CS-modified nanospheres from the lungs was decreased significantly because of their mucoadhesive property after pulmonary administration compared with that of the unmodified nanospheres, and as a result the pharmacological action was significantly prolonged. It is also confirmed that the CS on the surface of the nanospheres enhanced the absorption by opening the intercellular tight junctions in the lung epithelium (102).

Nanoparticulate Drug Delivery in Cancer Treatment

Several NPDDSs are reported for the application in cancer therapy, transferring conjugated paclitaxel-loaded NPs (139), nanovaccines (140), adriamycin-loaded NPs for hepatoma treatment (141), magnetic PBCA nanospheres with aclacinomycin A in gastric cancer (15), near-infrared absorption nanospheres (142), polypropylenimine dendrimer NPs for oligonucleotides (143), lytic peptide–bound magnetite NPs for breast cancer treatment (144), ceramic-based NPs entrapping water-insoluble photosensitizing anticancer drugs (145), and poly(epsilon-caprolactone) NPs for the delivery of tamoxifen for breast cancer treatment (146,147).

Yoo and Park (148) have reported a study of folate receptor targeted anticancer therapy using doxorubicin-PEG folate nanoconjugates. Doxorubicin and folate were, respectively, conjugated to α and ω terminals of the PEG chain. The conjugates assisted formation of doxorubicin nanoaggregates with average size of 200 nm in diameter when combined with an excess amount of depronated doxorubicin in an aqueous phase. In vivo studies have shown significant reduction in the tumor volume in a human tumor xenograft nude mouse model. Controlled release of paclitaxel through submicroemulsion with particle size of 45 to 270 nm was evaluated in vitro and in vivo for their antitumor activity by Kang et al. (149).

They used PLGA polymer for formulating self-emulsifying DDSs and showed the effectiveness of the system.

Nanoparticles in the Treatment of Vascular Thrombosis

The formation of blood clots in the circulatory system is associated with a range of serious medical conditions, including heart attacks, pulmonary embolisms, strokes, and deep vein thrombosis. The main component of the clot is the insoluble protein fibrin. Treatment of vascular thrombosis involves the use of thrombolytic drugs that break up the fibrin, allowing the clot to disperse. Biocompatible NPs are used to develop such delivery systems, which can carry the thrombolytic drugs. Chellini (150) explained that the thrombolytic drugs are powerful agents, with serious side effects like causing hemorrhage if they are given systemically. However, orally they are less efficient. If they can be incorporated in NPs, they can be delivered directly to the specific site, using less drug materials, and the treatment will be cost-effective with less side effects. The drug will be released from the NPs by diffusion, degradation, or erosion. A sustained-release NP formulation may be more helpful (151).

Nanoparticulate Drug Delivery Systems for Gene Therapy

Intracellular gene delivery involves changing the expression of genes to prevent, cure, or treat a disorder or a disease. Therefore, this treatment method alters the expression of a gene and corrects a defective gene that may be the cause of a disease or a disorder. Nonviral vectors for gene therapy have inherent advantages of safety and flexibility over viral vectors, although they are less efficient. Serious issues of integration with the host genome to permanently alter its genetic structure, self-replication capability, recombination potential, and the possibility of complement activation (immunogenicity) of the otherwise transfection efficient viral vectors limit their use for gene delivery. In the last decade, the focus of development is on nonviral gene delivery systems. Specific characteristics that must be included in nonviral vectors include small size and stability against aggregation in blood, serum, and extracellular fluid, the ability to be efficiently internalized by the target cells, and the ability to disassemble and release the payload into the cell nucleus, once internalized.

Gene therapy has attracted considerable interest for the treatment of life-threatening diseases. Several viral and nonviral vectors (transporting devices) are under investigation (151,152). One of the common disadvantages of both types is rapid clearance from the blood circulation to first-pass organs such as liver and lungs. A frequently applied strategy to circumvent this rapid elimination is to coat the outer surface of the complexes with hydrophilic uncharged polymers by which the positive charge of these lipo/polyplexes is shielded (153–155). Several polymers such as poly-L-lysine, CS (156) polyamidoamine dendrimers (PAMAMs) (157), polyethylenimine (PEI) (158), poly(4-aminobutyl-L-glycolic acid) (159), poly-L-glutamic acid (160), poly(β-amino esters) (161), pDMAEMA, plasmid-lipid particles have been used for this purpose with PEG coating (159,160,162).

Funhoff et al. (163) have reported the use of PEG-shielded double-layered micelles for gene delivery. Zhang et al. (164) reported galactosylated ternary DNA/polyphosphoramidate NPs as hepatocyte-targeted gene carriers. Zhao et al. (165–168) wrote an excellent review on polyphosphoesters in drug and gene delivery. A report described the application of PLGA: poloxamer and PLGA:poloxamine blend NPs as new carriers for the gene delivery: plasmid DNA (169). They developed several formulations and found that all NP formulations provided continuous and controlled release of the plasmid with minimal burst effect. In addition, the release rate and duration were dependent on the composition of the particle matrix. Zahr et al. (71) have created a layer-by-layer stepwise self-assembly of the polyelectrolytes poly (allylamine hydrochloride). Poly(styrenesulfonate) was used to create a macromolecular nanoshell around drug NPs (approximately 150 nm in diameter).

Dexamethasone was chosen as a model drug. The polymeric nanoshell on the surface of the drug NPs provides a template on which surface modifications can be made to create stealth or targeted DDSs (170).

Kaul et al. (171), in their study, used PEG-modified gelatin NPs as long-circulating intracellular delivery systems with a mean particle size of 300 nm. They could efficiently encapsulate hydrophilic macromolecules including plasmid DNA. These particles were internalized by tumor cells and were found near the nucleus after 12 hours. The PEGylated gelatin NPs were also very efficient in expressing GEP. Drug loading and drug release rates from NPs are important parameters for the formulation of NPDDSs to optimize the therapeutic efficacy of the encapsulated drug (172–176).

Panyam et al. (176) showed that solid-state solubility of the drug in polymer could be an important determinant that could influence the drug loading in NPs, as well as release characteristics of the encapsulated drug. In a recent study by Kaul et al., plasmid DNA was formulated with gelatin and PEGylated gelatin with average diameter of 200 nm for targeted systemic delivery to solid tumors. The results showed 61% transfection efficiency, which was attributed to a biocompatible, biodegradable long-circulating carrier system (177).

Dendrimers are emerging as a new generation of nonviral vectors for gene delivery because of two distinctive features: their structures can be controlled and their chemistry can be adapted for various requirements, such as drug or gene delivery (178,179). They also belong to the polyamine group of nonviral vectors, which includes poly-L-lysine, polyethylenimine, and polyamidoamine. The versatility of these vectors has been exploited to attach various ligands such as transferrin, sugars, and antibodies for receptor-targeting dendrimers. A new

family of composite dendrimers with lipidic amino acids was synthesized by Bayele et al. (180) and used for transporting DNA both single- and double-stranded, as well as RNA. PAMAM represents one of the most efficient polymeric gene carriers.

Zhang et al. (181) have shown their utility for gene delivery. Xia et al. (175) report a novel DDS recently by preparing monodispersed NPs consisting of interpenetrating polymer networks (IPNs) of polyacrylic acid (PAAc) and isopropylacrylamide by a seed and feed method. The aqueous dispersion of IPN NPs was found to be a unique NPDDS because of its abrupt inverse thermoreversible gelation at around 33°C. IPN and drugs were thoroughly mixed as an aqueous solution at room temperature and formed a drug delivery gel at body temperature. The drug delivery model was found very useful because such a dispersion and drug were mixed without chemical reaction and the liquid can be injected into a body to form in situ a gelled drug depot to release the drug slowly (175).

Benita et al. (182) described the application of PLGA-PEI NPs for gene delivery to pulmonary epithelium. Diwan et al. (183) have shown that antigen delivery in biodegradable NPs can facilitate induction of strong T-cell response, particularly of the TH1 type, at an extremely low dose of CPG oligonucleotides. Such reduction in dose would be advantageous for minimizing the potential side effects of these novel adjuvants (183).

Rhaese et al. (184) reported NPs consisting of DNA, human serum albumin, and polyethylenimine to be a carrier for the nonviral gene delivery. They could achieve optimum transfection efficiency, and displayed a low cytotoxicity when tested in cell culture. They recommended these carriers for delivering DNA for IV administration.

An interesting strategy for the treatment of various vascular diseases uses poly (methylidene malonate 2.1.2) NPs, which is a biocompatible polymer that enhances the periadventitial adenoviral gene delivery (185).

Gene therapy strategies have been proposed for a vast and diverse range of disorders for which currently available treatments are deemed unsatisfactory.

Effective delivery of genes into cells has been considered a major hurdle in achieving successful gene therapy. A number of delivery systems based on viral (186) or nonviral vectors (187,188) have been devised; none of them have proven to be completely satisfactory. Viral vectors can only introduce genes, not other macromolecules such as siRNA or antisense nucleotide. Furthermore, side reactions such as host immune response and insertional mutagenesis leading to death, carcinogenesis, or germline alternations have led to serious concerns about the use of viruses as gene transfer vectors (189–192). Several analytical techniques were reported to be useful for characterizing and establishing the structure/function relationship of polyamidoamine/DNA dendrimers as nanoparticulate drug/gene delivery systems. Braun et al. (193) used dynamic and electrophoretic light-scattering technique for particle size, and phase analysis light scattering for zeta potential. Ethium bromide displacement assay has been utilized for determining the interaction between the dendrimer and DNA, and extent of gene uptake. Circular dichroism spectroscopy was used for characterizing helical structure of DNA within dendrimer DNA complexes. Fourier transform infrared spectroscopy was used as a complimentary technique to further investigate the secondary structure of DNA component complexes. Isothermal titration calorimetry was employed to investigate the thermodynamics of binding of dendrimers and DNA complexes. Differential scanning calorimetry was applied to evaluate the thermal stability of DNA/dendrimer complexes (193). Zaitsev et al. (194) used a strategy based on the formation of polyelectrolyte NPs and later deposition of negatively charged polyelectrolytes onto a DNA core. They showed that these negatively charged particles exhibited colloidal stability and high transfection efficiency in an in vivo model (194).

The mechanistic pathways for gene expression are limited by at least five major barriers: in vivo stability, cell entry, endosome escape, cytosolic transport, and nuclear entry. The nuclear membrane restricts the transport of the plasmid DNA and the efficiency of the DNA transfer from the cytoplasm to the nucleus has been estimated to be about 10 to 14 nm. To obtain high gene expression, the genes introduced into the cells must be reduced to a compact size so that they can pass through nuclear pores. The collapsing of the DNA into NPs of reduced negative or increased positive charges (i.e., DNA condensation) has received considerable interest because of its biological importance in DNA packaging in-virus heads (195).

Gene delivery usually takes advantage of the endocytic pathway of the cell. The cells continually ingest a part of their plasma membrane via endocytosis to form endocytic vesicles. The cells can take up solvent and solute by the endocytosis activity later. Endocytic vesicles incorporating DNA-bearing particles are transferred to endosomes and then to lysosomes, where liberation of DNA somehow takes place. However, the plasma membrane is directly linked to and functionally integrated with the underlying cytoskeleton; the endocytosis at the membrane would require the rearrangement of actin and tubulin.

Nonviral vectors hold several advantages over modified virus employed for gene delivery in terms of improved and predictable safety profile, a high DNA-carrying capacity, increased versatility, the ease of large-scale production, and quality control. Nevertheless, their efficiency lags behind that of viral systems. The nonviral vectors efficient in transfection are often toxic because of their nondegradable property (187). The gene transfer efficiency of nontoxic vectors, for example, biodegradable cationic polymers, is often not satisfactory (196). Li et al. have reported the synthesis, characterization of poly(D,L-lactide-co-4-hydroxy-L-porline) polymer for the purpose of gene delivery, and they studied degradation, cytotoxicity, as well as pDNA release kinetics and sustained gene expression of this polymer-based system. They showed the usefulness of these polymers with multiple advantages (188).

Gupta and Gupta (189) have shown the application of the pullulan, a water-soluble, neutral linear polysaccharide for gene delivery. They showed that these NPs had high transfection potential, could release DNA efficiently, and were stable against degradation by DNAse. As specific ligands can be bound to the NP surface, these particles offer the possibility for additional targeting strategies (Fig. 6).

Kabanov et al. (197) suggested an interesting approach using polymer genomics in their recent publication. Pluronic, the A-B-A amphiphilic block copolymers of poly(ethylene oxide), can upregulate the expression of selected genes in cells and alter the genetic response to antineoplastic agents in cancer. They reported that these block copolymers alone, as well as in combination with polyethylenimine, can upregulate the expression of the reporter genes in stably transfected cells. This underscores the ability of selected synthetic polymers to enhance transgene expression through a mechanism that augments improved DNA delivery into cell.

Pluronic is genetically benign when combined with an antineoplastic agent doxorubicin. It drastically alters pharmacogenomic responses to this agent and prevents the development of multidrug resistance in breast cancer cells. They proposed the need for a thorough assessment of pharmacogenomic effects of polymer therapeutics to maximize the clinical outcomes and

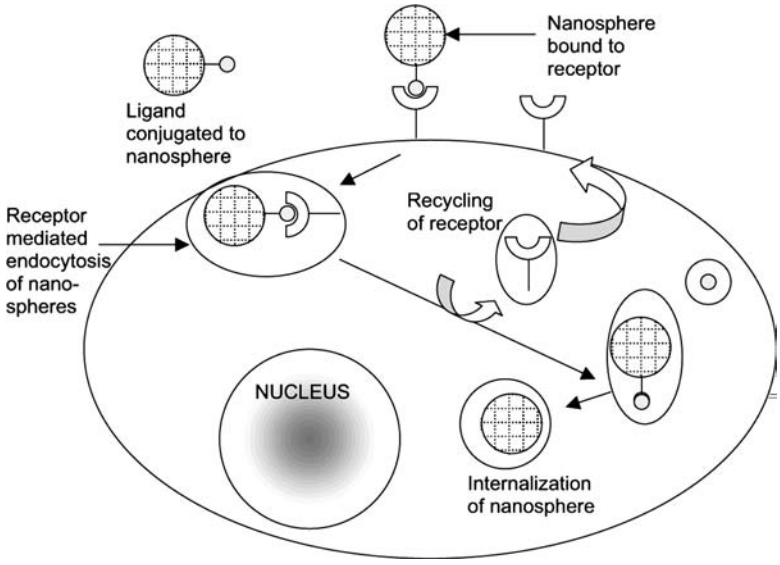


Figure 6 Schematic diagram of specific receptor targeting of nanospheres using ligands.

understand the pharmacological and toxicological effects of polymer-based drugs and delivery systems (197).

Tabatt et al. (198) compared the cationic SLN and liposomes for gene transfer as a carrier. They found that DNA binding differed only marginally in these two systems. They concluded that cationic lipid composition seems to be more dominant for the in vitro transfection performance than arranged colloidal structure.

Hence, cationic SLN extends the range of highly potent nonviral transfection agents by one with favorable and distinct technological properties (198). Wissing et al. (199) published a review, which describes the use of NPs based on solid lipid for the parenteral application of drugs. Different types of NPs based on solid lipids, such as SLNs, nanostructured lipid carriers, and lipid-drug nanoconjugates, are introduced and structural differences are pointed out. Different production methods including the suitability for large-scale production are described along with the stability issues, and drug-incorporation mechanisms into the particles are discussed in detail. The biological activity of parenterally applied SLNs and biopharmaceutical aspects, such as pharmacokinetic profiles, as well as toxicity aspects, are reviewed (199).

NANOPARTICULATE SYSTEMS: KNOWN AND UNKNOWN RISKS

An excellent review was recently published by Hoet et al. (200) with an extensive literature survey in which they suggested that the particles in the nanosize range could certainly enter into the human body through lungs, gastrointestinal system, mucosa, and the skin. It is possible that some particles penetrate deep in the dermis and gradually may be taken up by the body. The chances of penetration depend on the size and surface properties of the particles and also point of contact. The distribution of particles in the body systems is also a function of the surface characteristics of the NPs. There might be a critical size involved beyond which the movement of the particles might be restricted. The pharmacokinetic behavior of different types of the nanosystems requires a detailed investigation and a database of health risks associated with different NPs needs to be created. The increased risk of cardiopulmonary disease requires specific measures to be taken for every newly developed nanoparticulate product. There is no universal NP to fit all the cases; each NP system needs to be treated individually when a health risk is expected. The tests currently used to verify safety of materials should be applicable to identify hazardous NPs, and more stringent and efficient testing procedures are needed to evaluate the nanoparticulate systems, especially when used as a food component or as DDSs

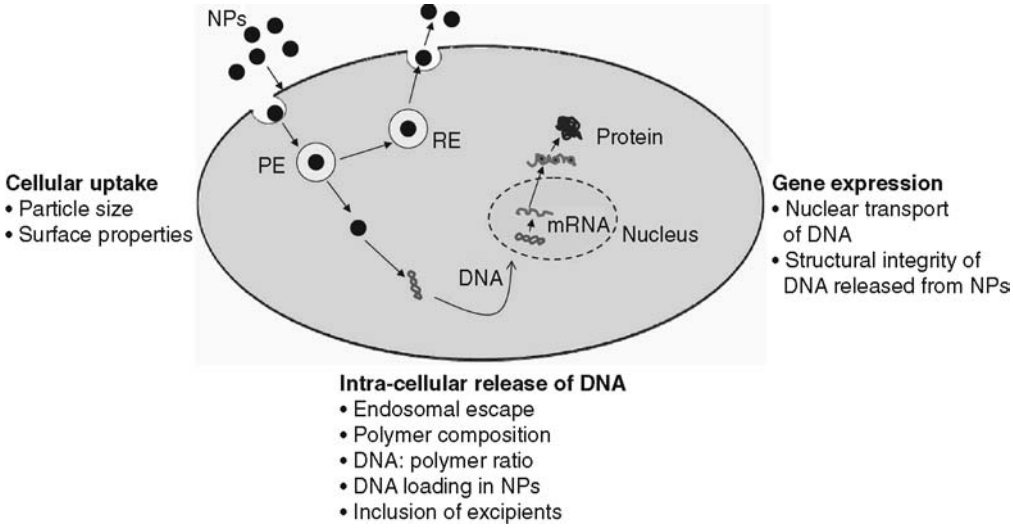


Figure 7 Formulation factors influencing nanoparticle-mediated gene expression. *Abbreviations*: NPs, nanoparticles; PE, primary endosomes; RE, recycling endosomes.

(117,201–204). A study reported by Bilati et al. (205) discussed the processing and formulation issues related to PLGA protein-loaded NPs prepared by double-emulsion method. They evaluated the effect of some typical formulation factors and processing conditions on the mean size and the drug entrapment efficiency of PLGA NPs. They found that the parameters that generally increase the entrapment efficiency are: (*i*) high molecular weight of the polymer, (*ii*) the presence of uncapped carboxylic end groups when PLGA is used, (*iii*) the use of methylene chloride instead of ethyl acetate, and (*iv*) an increased nominal drug loading. An interesting study regarding the GI uptake and transport of SLN to the lymphatic system was reported by Bargoni et al. (206). They showed that particle size is a critical determinant of the fate of NPs administered orally; larger particles may be retained for longer time in Peyer's patches, whereas smaller particles are transported to the thoracic duct. Another study by Passirani et al. (207) reported that NPs bearing heparin or dextran covalently bound to polymethyl methacrylate was found to be in circulation for a long time. The potent capacity for opsonization of the polymethyl methacrylate core was hidden by the protective effect of either polysaccharide. In the case of heparin NPs, the stealth effect was probably increased by its inhibiting properties against complement activation. Silveira et al. (208) reported a new type of NPs where they used polyisobutyl cyanoacrylate and cyclodextrin combination as polymeric carrier. Owing to the presence of many lipophilic sites belonging to the cyclodextrins, which were firmly anchored to the structure of the NPs, these type of carriers were very useful to enhance and increase the loading of the lipophilic drugs with probably less side effects. But, the risks involved need to be verified and established by appropriate sensitive methods to ensure the safety of the NPDDS (Fig. 7).

REFERENCES

1. Bindschaedler C, Gurny R, Doelker E. Process for preparing a powder of water insoluble polymer which can be redispersed in a liquid phase, the resulting powder and utilization thereof. Patent WO 88/08011, 1988.
2. Leroux JC, Allemann E, Doelker E, et al. New approach for the preparation of nanoparticles by an emulsification-diffusion method. Eur J Pharm Biopharm 1995; 41:14.
3. Fessi H, Puisieux F, Devissaguet JP, et al. Nanocapsule formation by interfacial polymer deposition following solvent displacement. Int J Pharm 1989; 55:R1.
4. Puglisi G, Fresta M, Giammona G, et al. Influence of the preparation conditions on polyethyl cyanoacrylate nanocapsule formation. Int J Pharm 1995; 125:283.
5. Kreuter J. Nanoparticles. In: Kreuter J, ed. Colloidal Drug Delivery Systems. New York: Marcel Dekker, 1994:219.
6. Guterres SS, Fessi H, Barratt G, et al. Poly(D,L-lactide) nanocapsules containing diclofenac. I. Formulation and stability studies. Int J Pharm 1995; 113:57.
7. Guerrero DQ, Allmann E, Doelker E, et al. Preparation and characterization of nanocapsules from performed polymers by a new process based on emulsification-diffusion technique. Pharm Res 1998; 15:1056.
8. Rodriguez SG, Allemann E, Fessi H, et al. Physicochemical parameters associated with nanoparticles formation in the salting out, emulsification-diffusion and nanoprecipitation methods. Pharm Res 2004; 21:1428.
9. Mehnert W, Mader K. Solid-lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev 2001; 40:165.
10. Willis RC. Good things in small packages. Modern Drug Discov 2004; 7:1.
11. Couvreur P, Barratt G, Fattal E, et al. Nanocapsule technology: a review. Crit Rev Ther Drug Carrier Syst 2002; 19:99.
12. Hans ML, Lowman AM. Biodegradable nanoparticles for drug delivery and targeting. Curr Opin Solid State Mater Sci 2002; 6:319.
13. Florence AT. The oral absorption of micro and nano particulates: neither exceptional nor unusual. Pharm Res 1997; 14:259.
14. Gao H, Wang JY, Shen XZ, et al. Preparation of magnetic polybutylcyanoacrylate nanospheres encapsulated with aclacinomycin A and its effect on gastric tumor. World J Gastroenterol 2004; 10:2010.
15. Chen JH, Ling R, Yao Q, et al. Enhanced antitumor efficacy on hepatoma bearing rats with adriamycin loaded nanoparticles administered into hepatic artery. World J Gastroenterol 2004; 10:1989.

16. Piemi MPY, Korner D, Benita S, et al. Positively and negatively charged submicron emulsions for enhanced topical delivery of antifungal drugs. J Control Release 1999; 58(2):177–187.
17. Dalencon F, Amjaud Y, Lafforgue C, et al. Atovaquone and Rifabutine loaded nanocapsules: formulation studies. Int J Pharm 1998; 153:127.
18. Ueno Y, Futagawa H, Takagi Y, et al. Drug incorporating calcium carbonate nanoparticles for a new delivery system. J Control Release 2005; 103:93.
19. Memisoglu E, Bochot A, Ozalp M, et al. Direct formation of nanospheres from amphiphilic beta cyclodextrin inclusion complexes. Pharm Res 2003; 20:117–125.
20. De TK, Rodman DJ, Holm BA, et al. Brimonidine formulation in poly-acrylic acid nanoparticles for ophthalmic delivery. J Microencapsul 2003; 20:361.
21. Jacobs C, Muller RH. Production and characterization of a Budesonide nanosuspension for pulmonary administration. Pharm Res 2002; 19:189.
22. Yang S, Zhu J, Lu Y, et al. Body distribution of camptothecin solid-lipid nanoparticles after oral administration. Pharm Res 1999; 16:751.
23. Cortez RV, Backmann N, Senter PD, et al. Efficient cancer therapy with a nanobody based conjugate. Cancer Res 2004; 15:2853.
24. Cabral H, Nishiyama N, Okazaki S, et al. Preparation and biological properties of dichloro(1,2-diaminocyclohexane) platinum (II) (DACHPt) loaded polymeric micelles. J Control Release 2005; 101:223.
25. Hu FQ, Yuan H, Zhang HH, et al. Preparation of solid-lipid nanoparticles with Clobetasol propionate by a novel solvent diffusion method in aqueous system anphysicochemical characterization. Int J Pharm 2002; 239:121.
26. Venkateswarlu V, Manjunath K. Preparation, characterization and in vitro release kinetics of Clozapine solid-lipid nanoparticles. J Control Release 2004; 95:627.
27. Kun N, Keun-Hong P, Sung WK, et al. Self assembled hydrogel nanoparticles from curdlan derivatives: characterization, anticancer drug release and interaction with a hepatoma cell line (Hep G2). J Control Release 2000; 69:225.
28. Geze A, Putaux JL, Choisnard L, et al. Long term shelf stability of amphiphilic B-cyclodextrin nanospheres suspensions monitored by dynamic light scattering and cryo-transmission electron microscopy. J Microencapsul 2004; 21:607.
29. Olbrich C, Kayser O, Muller RH. Lipase degradation of Dynasan 114 and 116 solid-lipid nano particles-effect of surfactants, storage time and crystallinity. Int J Pharm 2002; 237:119.
30. Zhang Q, Yie G, Li Y, et al. Studies on the cyclosporine A-loaded stearic acid nanoparticles. Int J Pharm 2000; 200:153.
31. Wang X, Dai J, Chen Z, et al. Bioavailability and pharmacokinetics of cyclosporine A-loaded pH sensitive nanoparticles for oral administration. J Control Release 2004; 97:421.
32. Salgueiro A, Egea MA, Espina M, et al. Stability and ocular tolerance of cyclophosphamide loaded nanospheres. J Microencapsul 2004; 21:213.
33. Beck RCR, Pohlman AR, Guterres SS. Nanoparticles-coated microparticles: preparation and characterization. J Microencapsul 2004; 21:499.
34. Porter CJH, Kaukonen AM, Boyd BJ, et al. Susceptibility to lipase mediated digestion reduces the oral bioavailability of Danazol after administration as a medium chain lipid based microemulsion formulation. Pharm Res 2004; 21:1405.
35. Hubert B, Atkinson J, Guerret M, et al. The preparation and acute antihypertensive effects of a nanoparticle form of Darodipine, a dihydropyridine calcium entry blocker. Pharm Res 1991; 8:734.
36. Schroeder U, Sommerfield P, Sabel BA. Efficacy of oral Delargin loaded nanoparticles delivery across blood-brain barrier. Peptides 1998; 19:777.
37. Thote AJ, Gupta RB. Formation of nanoparticles of a hydrophilic drug using super-critical carbon dioxide and microencapsulation for sustained release, nanomedicine: nanotechnology. Biol Med 2005; 1:85.
38. Olbrich C, Gessner A, Schroder W, et al. Lipid-drug conjugate nanoparticles of the hydrophilic drug diminazene-cytotoxicity testing and mouse serum absorption. J Control Release 2004; 96:425.
39. Olbrich C, Gessner A, Kayser O, et al. Lipid drug conjugate nanoparticles as novel carrier system for the hydrophilic antitrypanosomal drug diminazenediaceturate. J Drug Target 2002; 10:387.
40. Oyewumi MO, Yokel RA, Jay M, et al. Comparison of cell uptake, bio-distribution and tumor retention of folate coated and PEG coated Gadolinium nanoparticles in tumor bearing mice. J Control Release 2004; 95:613.
41. Moutardier V, Tosini F, Vlieghe P, et al. Colloidal anticancer drugs bioavailability in oral administration. Int J Pharm 2003; 260:23.
42. Castelli F, Messina C, Sarpietro MG, et al. Flurbiprofen release from Eudragit RS and RL aqueous nanosuspensions: a kinetic study by DSC and dialysis experiments. AAPS Pharm Sci Tech 2002; 3:9.

43. Khoo SM, Humberstone AJ, Porter CJH, et al. Formulation design and bioavailability assessment of lipidic self emulsifying formulations of Halofantrine. Int J Pharm 1998; 87:164.
44. Dufresne MH, Leroux JC. Study of the micellization behavior of different order amino block copolymers with heparin. Pharm Res 2004; 21:160.
45. Cavalli R, Peira E, Caputo O, et al. Solid-lipid nanoparticles as carriers of hydrocortisone and progesterone complexes with beta cyclodextrins. Int J Pharm 1999; 182:59.
46. Zara GP, Bargoni A, Cavelli R, et al. Pharmacokinetics and tissue distribution of Idarubicin loaded solid-lipid nanoparticles after duodenal administration to rats. J Pharm Sci 2002; 91:1324.
47. Calvo P, Alonso MJ, VilaJato JL, et al. Improved ocular bioavailability of Indomethacin by novel ocular drug carriers. J Pharm Pharmacol 1996; 48:1147.
48. Pandey R, Sharma A, Zahoor A, et al. Poly(D,L-lactide-co-glycolide) nanoparticles based inhalable sustained drug delivery system for experimental tuberculosis. J Antimicrob Chemother 2003; 10:1093.
49. Palmiri GF, Bonacucina G, Martino DP, et al. Gastroresistant microspheres containing Ketoprofen. J Microencapsul 2002; 19:111.
50. Schroder U, Sommerfield P, Urlich S, et al. Nanoparticle technology for delivery of drugs across the blood-brain barrier. J Pharm Sci 1998; 78:1305.
51. Alyautidin RN, Petrov VE, Langer K, et al. Delivery of loperamide across the blood-brain barrier with polysorbate 80 coated nanoparticles. Pharm Res 1997; 14:325.
52. Alexiou C, Jurgons R, Schmid RJ, et al. Magnetic drug targeting biodistribution of the magnetic carrier and the chemotherapeutic agent mitoxantrone after loco-regional cancer treatment. J Drug Target 2003; 11:139.
53. Cavalli R, Caputo O, Carlotti ME, et al. Study by X ray diffraction and differential scanning calorimetry of two model drugs, Phenothiazine and Nifedipine, incorporated into lipid nanoparticles. Eur J Pharm Biopharm 1995; 41:329.
54. Hecq J, Nollevaux G, Deleers M, et al. In vitro transport studies of nifedipine nanoparticles across caco-2 HT 29-5M21 culture and cocultures. Eur J Pharm Biopharm (in press).
55. Hauss DJ, Fogal SE, Ficorilli JV, et al. Lipid based delivery systems for improving the bioavailability and lymphatic transport of a poorly water soluble LTB4 inhibitor. J Pharm Sci 1998; 87:164.
56. Chen DB, Yang TZ, Lu WL, et al. In vitro and in vivo study of two types of long circulating solid-lipid nanoparticles containing Paclitaxel. Chem Pharm Bull 2001; 49(11):1444–1447.
57. Koziara JM, Lockman PR, Allen DD, et al. Paclitaxel nanoparticles for the potential treatment of brain tumors. J Control Release 2004; 99:259.
58. Yeh TK, Lu Z, Woentjes MG, et al. Formulating paclitaxel in nanoparticles alters its disposition. Pharm Res 2005; 22:867.
59. De S, Miller DW, Robinson DH. Effect of particle size of nanospheres and microspheres on the cellular association and cytotoxicity of paclitaxel in 4T1 cells. Pharm Res 2005; 22:766.
60. Yoncheva K, Vandervoort J, Ludwig A. Influence of process parameters of high pressure emulsification method on the properties of pilocarpine loaded nanoparticles. J Microencapsul 2003; 20:449.
61. Mainerdes RM, Evangelista RC. Praziquantel loaded PLGA nanoparticles: preparation and characterization. J Microencapsul 2005; 22:13.
62. Muhlen AZ, Mehenert W. Drug release and release mechanisms of prednisolone loaded solid-lipid nanoparticles. Pharmazie 1998; 53:552.
63. Chen H, Zhang Z, Almarsson O, et al. A novel lipid free nanodispersion formulation of propofol and its characterization. Pharm Res 2005; 22:356.
64. Lochmann D, Vogel V, Weyermann J, et al. Physicochemical characterization of protamine-phosphorothioate nanoparticles. J Microencapsul 2004; 21:625.
65. Muller RH, Dobrucki R, Radomska A. Solid-lipid nanoparticles as a new formulation for retinal. Acta Pol Pharm Drug Res 1999; 56:117.
66. Shenoy DB, Amiji MM. Poly(ethylene oxide)-modified poly(varepsilon-caprolactone) nanoparticles for targeted delivery of tamoxifen in breast cancer. Int J Pharm 2005; 293:261.
67. Jacobs C, Kayser O, Muller RH. Nanosuspensions as a new approach for the formulation for the poorly soluble drug tarazepide. Int J Pharm 2000; 196:161.
68. Lockman PR, Oyewumi MO, Kozira JM, et al. Brain uptake of thiamine coated nanoparticles. J Control Release 2003; 93:271.
69. Bargoni A, Cavalli R, Zara GP, et al. Transmucosal transport of tobramycin incorporated in solid-lipid nanoparticles after duodenal administration to rats. Part II. Tissue distribution. Pharmacol Res 2001; 43:497.
70. Maria M, Chiara S, Donatella V, et al. Niosomes as carriers for trentinoin: preparation and properties. Int J Pharm 2002; 234:237.
71. Maestrell F, Mura P, Alonso MJ. Formulation and characterization of triclosan submicron emulsions and nanocapsules. J Microencapsul 2004; 21:857.

72. Alyautidin RN, Tezikov EB, Ramage P, et al. Significant entry of tubocurarine into the brain of rats by adsorption to polysorbate 80 coated poly(butyl cyanoacrylate) nanoparticles: an in situ brain perfusion studies. J Microencapsul 1998; 15:67.
73. Bunjes H, Drechsler M, Koch MHJ, et al. Incorporation of the model drug ubidecarone into solid-lipid particles. Pharm Res 2001; 18:287.
74. Hecq J, Deleers M, Fanara D, et al. Preparation and in vitro/in vivo evaluation of nanosized crystals for dissolution rate enhancement of UCB-35440-3, a highly dosed poorly water soluble weak base. Eur J Pharm Biopharm 2006; 64:360.
75. Jennings V, Korting MS, Gohla S. Vitamin A loaded solid-lipid nanoparticles carrier system for topical use: drug release properties. J Control Release 2000; 66:115.
76. Teixeira M, Alonso MJ, Pinto MM, et al. Development and characterization of PLGA nanospheres and nanocapsules containing xanthone and 3-methoxy xanthone. Eur J Pharm Biopharm 2005; 59:491.
77. Delie F. Evaluation of nano and micro particles uptake by the gastrointestinal tract. Adv Drug Deliv Rev 1998; 34:221.
78. Rodrigues JS, Magalhaes NSS, Coelho LCBB, et al. Novel core (polyester)-shell (polysaccharide) nanoparticles: protein loading and surface modification with lectins. J Control Release 2003; 92:103.
79. Yoo HS, Park TG. Biodegradable nanoparticles containing protein-fatty acid complexes for oral delivery of salmon calcitonin. J Pharm Sci 2004; 93:488.
80. Alphandary HP, Aboubaker M, Jaillard D, et al. Visualization of insulin loaded nanocapsules: in vitro and in vivo studies after oral administration to rats. Pharm Res 2003; 20:1071.
81. Mutwiri GK, Nichani AK, Babiuk S, et al. Strategies for enhancing the immunostimulatory effects of CpG oligodeoxynucleotides. J Control Release 2004; 97:1.
82. Leach WT, Simpson DT, Val TN, et al. Uniform encapsulation of stable protein nanoparticles produced by spray freezing for the reduction of burst release. J Pharm Sci 2005; 94:56.
83. Yu Z, Rogers TL, Hu J, et al. Preparation and characterization of microparticles containing peptide produced by a novel process: spray freezing into liquid. Eur J Pharm Biopharm 2002; 54:221.
84. Mo Y, Lim LY. Mechanistic study of the uptake of wheat germ agglutinin-conjugated PLGA nano particles by A549 cells. J Pharm Sci 2004; 93:20.
85. Murakami H, Kobayashi M, Takeuchi H, et al. Preparation of poly(D,L-lactide-co-glycolide) nanoparticles by modified spontaneous emulsification solvent diffusion method. Int J Pharm 1999; 187:143.
86. Crommelin DJA, Storm G, Jiskoot W, et al. Nanotechnological approaches for the delivery of macromolecules. J Control Release 2003; 87:81.
87. Nassander UK, Steerenberg PA, Poppe H, et al. In vivo targeting of OV-TL3 immunoliposomes to ovarian carcinoma ascetic cells (OVCAR-3) in anthymic nude mice. Cancer Res 1992; 52:646.
88. Mastrobattista E, Kapel RHG, Eggenhuizen MH, et al. Lipid coated polyplexes for targeted gene delivery to ovarian carcinoma cells. Cancer Gene Ther 2001; 8:405.
89. De TK, Hoffman AS. A reverse microemulsion polymerization method for preparation of bioadhesive polyacrylic acid nanoparticles for mucosal drug delivery: loading and release of timolol maleate. Artif Cells Blood Subst Immobil Biotech 2001; 29:31.
90. De TK, Hoffman AS. An ophthalmic formulation of beta adrenoreceptor antagonist, levobetaxolol, using polyacrylic acid nanoparticles as carriers, loading and release studies. J Bioact Compat Polym 2001; 16:20.
91. Bourlais CL, Acar L, Zia H, et al. Ophthalmic drug delivery systems: recent advances. Prog Retin Eye Res 1998; 17:33.
92. Qaddoumi MG, Ueda H, Yang J, et al. The characteristics and mechanisms of uptake of PLGA nanoparticles in rabbit conjunctival epithelial cell layers. Pharm Res 2004; 21:641.
93. Zimmer A, Chetoni P, Saettone M, et al. Evaluation of pilocarpine loaded albumin nanoparticles as controlled drug delivery systems for the eye. II. Coadministration with bioadhesive and viscous polymers. J Control Release 1995; 33:31.
94. Diepold R, Kreuter J, Himber J, et al. Comparison of different models for the testing of pilocarpine eye drops using conventional eye drops and a novel depot nanoparticles formulation. Graefes Arch Clin Exp Ophthalmol 1989; 227:188.
95. Gilding DK, Reed AM. Biodegradable polymers for use in surgery: polyglycolic/polylactic acid homo and copolymers. Polymers 1979; 20:1459.
96. Raghava S, Hammond M, Kompella UB. Periocular routes for retinal drug delivery. Exp Opin Drug Deliv 2004; 1:99.
97. Ayalasomayajula SP, Kompella UB. Retinal delivery of celecoxib is several-fold higher following subconjunctival administration compared to systemic administration. Pharm Res 2004; 21:1797.
98. Sunkara G, Ayalasomayajula SP, Cheruku RS, et al. Systemic and ocular pharmacokinetics of N-4-benzoylaminophenylsulfonylglycine (BAPSG), a novel aldose reductase inhibitor. J Pharm Pharmacol 2004; 56:351.

99. Contreras LG, Morcol T, Bell SJ, et al. Evaluation of novel particles as pulmonary delivery systems for insulin in rats. AAPS Pharm Sci 2003; 5:E9.
100. Yamamoto A. Improvement of transmucosal absorption of biologically active peptide drugs. Yakugaku Zasshi 2001; 121:929.
101. Yamamoto H, Kuno Y, Sugimoto S, et al. Surface modified PLGA nanospheres with chitosan improved pulmonary delivery of calcitonin by mucoadhesion and opening of the intercellular tight junctions. J Control Release 2005; 102:373.
102. Courrier HM, Butz N, Vandamme TF. Pulmonary drug delivery systems: recent developments and prospects. Crit Rev Ther Drug Carrier Syst 2002; 19:425.
103. Pahl A, Szelenyi I. Asthma therapy in the new millennium. Inflamm Res 2002; 51:273.
104. Contreras LG, Hickey AJ. Pharmaceutical and biotechnological aerosols for cystic fibrosis in therapy. Adv Drug Deliv Rev 2002; 54:1491.
105. Sharma S, White D, Imondi AR, et al. Development of inhalational agents for oncological use. J Clin Oncol 2001; 19:1839.
106. Suarez S, O'Hara P, Kazantseva M, et al. Airways delivery of rifampicin microparticles for the treatment of tuberculosis. J Antimicrob Chemother 2001; 48:431.
107. Sharma R, Saxena D, Dwivedi AK, et al. Inhalable microparticles containing drug combinations to target alveolar macrophages for treatment of pulmonary tuberculosis. Pharm Res 2001; 18:1405.
108. Zwissler B. Inhaled vasodilators. Anaesthesist 2002; 51:603.
109. Owens DR. New horizons-alternative routes for insulin therapy. Nat Rev Drug Discov 2002; 1:529.
110. Zhang Q, Shen Z, Nagai T. Prolonged hypoglycemic effect of insulin loaded polybutylcyanoacrylate nanoparticles after pulmonary administration to normal rats. Int J Pharm 2001; 218:75.
111. Kawashima Y, Yamamoto H, Takeguchi H, et al. Pulmonary delivery of insulin with nebulized D,L-lactide/glycolide copolymer, nanospheres to prolong hypoglycemic effect. J Control Release 1999; 62:279.
112. Tsapis N, Bennett D, Jackson B, et al. Trojan particles: large porous carriers of nanoparticles for drug delivery. Proc Natl Acad Sci U S A 2002; 99:12001.
113. Liu Y, Tsapis N, Edwards DA. Investigating Sustained-Release Nanoparticles for Pulmonary Drug Delivery. Cambridge: Harvard University Press, 2003.
114. Dailey LA, Kleemann E, Wittmar M, et al. Surfactant free biodegradable nanoparticles for aerosol therapy based on the branched polyesters, DEAPA-PVAL-g-PLGA. Pharm Res 2003; 20:2011.
115. Jung T, Kamm W, Breitenbach A, et al. Loading of tetanus toxoid to biodegradable nanoparticles from branched poly (sulfobutyl-polyvinyl alcohol)-g-(lactide-co-glycolide) nanoparticles by protein adsorption: a mechanistic study. Pharm Res 2002; 19:1105.
116. Dailey LA, Schmehl T, Gessler T, et al. Nebulization of biodegradable nanoparticles: impact of nebulizer technology and nanoparticles characteristics on aerosol features. J Control Release 2003; 86:131.
117. Vila A, Gill H, McCallion O, et al. Transport of PLA-PEG particles across the nasal mucosa: effect of particle size and PEG coating density. J Control Release 2004; 98:231.
118. Koziara JM, Lockman PR, Alen DD, et al. In situ blood-brain barrier transport of nanoparticles. Pharm Res 2003; 20:1772.
119. Lockman PR, Mumper RJ, Khan MA, et al. Nanoparticle technology for drug delivery across the blood-brain barrier. Drug Dev Ind Pharm 2002; 28:1.
120. Kreuter J. Nanoparticulate systems for brain delivery of drugs. Adv Drug Deliv Rev 2001; 47:65.
121. Schroder U, Sable BA. Nanoparticles: a drug carrier system to pass the blood-brain barrier, permit central analgesic effects of i.v. dalargin injections. Brain Res 1996; 710:121.
122. Gulyaev A, Gelperina SE, Skidan IN, et al. Significant transport of Doxorubicin into the brain with polysorbate 80 coated nanoparticles. Pharm Res 1999; 16:1564.
123. Kreuter J, Alyautdin RN, Kharkevich DA, et al. Passage of peptides through the blood-brain barrier with colloidal polymer particles (nanoparticles). Brain Res 1995; 674:171.
124. Lockman PR, Koziara J, Roder KE, et al. In vivo and in vitro assessment of baseline blood-brain barrier parameters in the presence of novel nanoparticles. Pharm Res 2003; 20:705.
125. Dziubla TD, Karim A, Muzykantov VR. Polymer nanocarriers protecting active enzyme cargo against proteolysis. J Control Release 2005; 102:427.
126. Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. Science 2004; 303:1818.
127. Weissenbock A, Wirth M, Gabor F. WGA grafted PLGA nanospheres preparation and association with Caco-2 single cells. J Control Release 2004; 99:383.
128. Gref R, Couvreur P, Barratt G, et al. Surface engineered nanoparticles for multiple ligand binding. Biomaterials 2003; 24:4529.
129. Lochner N, Pittner F, Wirth M, et al. Wheat germ agglutinin binds to the epidermal growth factor of artificial Caco-2 membranes as detected by silver nanoparticles enhanced fluorescence. Pharm Res 2003; 20:833.

130. Junghans M, Kreuter J, Zimmer A. Antisense delivery using protamine-oligonucleotide particles. Nucleic Acid Res 2000; 28:e45.
131. Vogel V, Lochmann D, Weyermann J, et al. Oilgonucleotide-protamine albumin nanoparticles, preparation, physical properties and its distribution. J Control Release 2004; 103:99.
132. Mayer G, Vogel V, Weyermann J, et al. Oligonucleotide-protamine-albumin nanoparticles: protamine sulfate causes drastic size reduction. J Control Release 2005; 106:181.
133. Weyermann J, Lochmann D, Zimmer A. Comparison of antisense oligonucleotides drug delivery systems. J Control Release 2004; 100:411.
134. Vila A, Sanchez A, Tobio M, et al. Design of biodegradable particles for protein delivery. J Control Release 2002; 78:15.
135. Prego C, Garcia M, Torres D, et al. Transmucosal macromolecular drug delivery. J Control Release 2005; 101:151.
136. Takeuchi H, Yamamoto H, Kawashima Y. Mucoadhesive nanoparticulate systems for peptide drug delivery. J Control Release 2004; 98:1.
137. Bilati U, Allemann E, Doelker E. Development of a nanoprecipitation method intended for the entrapment of hydrophilic drugs into nanoparticles. Eur J Pharm 2005; 24:67.
138. Takeuchi H, Yamamoto H, Kawashima Y. Mucoadhesive nanoparticulate systems for peptide drug delivery. Adv Drug Deliv Rev 2001; 47:39.
139. Sahoo SK, Ma W, Labhasetwar V. Efficacy of transferring conjugated paclitaxel loaded nanoparticles in a murine model of prostate cancer. Int J Cancer 2004; 112:335.
140. Fifis T, Gamvrellis A, Crimeen-irwin B, et al. Size dependent immunogenicity: therapeutic and protective properties of nano vaccines against tumors. J Immunol 2004; 173:3148.
141. Chen JH, Wang L, Ling R, et al. Body distribution of nanoparticles containing adriamycin injected into the hepatic artery of hepatoma bearing mice. Dig Dis Sci 2004; 49:1170.
142. O'Neal DP, Hirsch LR, Halas NJ, et al. Photo thermal tumor ablation in mice using near infra red absorbing nanoparticles. Cancer Lett 2004; 23:2406.
143. Santhakumaran LM, Thomas T, Thomas TJ. Enhanced cellular uptake of a triplex-forming oligonucleotides by nanoparticles formation in the presence of polypropylenimine dendrimers. Nucleic Acid Res 2004; 15:2102.
144. Kumar CS, Leuschner C, Doomes EE, et al. Efficacy of lytic peptide bound magnetite nanoparticles in destroying breast cancer cells. J Nanosci Nanotechnol 2004; 4:245.
145. Roy I, Ohulchanskyy TY, Pudavar HE, et al. Ceramic based nanoparticles entrapping water soluble photosensitizing anticancer drugs a novel drug carrier system for photodynamic therapy. J Am Chem Soc 2003; 125:7860.
146. Chawla JS, Amiji MM. Cellular uptake and concentrations of tamoxifen upon administration in poly (epsilon-caprolactone) nanoparticles. AAPS Pharm Sci 2003; 5:E3.
147. Chawla JS, Amiji MM. Biodegradable poly(epsilon-caprolactone) nanoparticles for tumor targeted delivery of tamoxifen. Int J Pharm 2005; 249:127.
148. Yoo HS, Park TG. Folate receptor targeted delivery of doxorubicin nano aggregates stabilized by doxorubicin PEG-folate conjugate. J Control Release 2004; 100:247.
149. Kang BK, Chon SK, Kim SH, et al. Controlled release of paclitaxel from microemulsion containing PLGA and evaluation of anti tumor activity in vitro and in vivo. Int J Pharm 2004; 286:147.
150. Chellini E. Nanotechnologies and nanosciences, knowledge-based multifunctional materials and new production processes and devices. TATLYS project. University of Pisa, Italy, 2003.
151. Wagner E. Strategies to improve DNA polyplexes for in vivo gene transfer: will artificial viruses be the answer? Pharm Res 2004; 21:8.
152. Pichon C, Gonsalves C, Midoux P. Histidine rich peptides and polymers for nucleic acids delivery. Adv Drug Deliv Rev 2001; 53:75.
153. Verbaan FJ, Ousorren C, Snel CJ, et al. Steric stabilization of poly(2(dimethylamino)ethyl methacrylate) based polyplexes mediates prolonged circulation and tumor targeting in mice. J Gen Med 2004; 6:64.
154. Ogris M, Walker G, Blessing T, et al. Tumor targeted gene therapy: strategies for the preparation of ligand polyethylene glycol-polyethylenimine/DNA complexes. J Control Release 2003; 91:173.
155. Oupicky D, Ogris M, Howard PR, et al. Importance of lateral and steric stabilization of polyelectrolyte gene delivery vectors for extended systemic circulation. Mol Ther 2002; 5:463.
156. Borchard G. Chitosan for gene delivery. Adv Drug Deliv Rev 2001; 52:145.
157. Ohsaki M, Okuda T, Wada A. In vitro gene transfection using dendritic poly(L-lysine). Bioconjug Chem 2002; 13:510.
158. Forrest ML, Koerber JT, Pack DW. A degradable polyethylenimine derivative with low toxicity for highly efficient gene delivery. Bioconjug Chem 2003; 14:934.

159. Lim YB, Han SO, Kong HU. Biodegradable polyester, poly(alpha-(4-aminobutyl)-L-glycolic-acid) as a nontoxic gene carrier. Pharm Res 2000; 17:811.
160. Dekie L, Toncheva V, Dubruel P. Poly-L-glutamic acid derivatives as vectors for gene therapy. J Control Release 2000; 65:187.
161. Akinc A, Anderson DG, Lynn DM. Synthesis of poly-(beta-amino esters) optimized for highly effective gene delivery. J Am Chem Soc 2000; 122:10761.
162. Bettinger T, Remy JS, Erbacher P. Size reduction of galactosylated PEI/DNA complexes improves lectin mediated gene transfer into hepatocytes. Bioconjug Chem 1999; 10(4):558–561.
163. Funhoff AM, Monge S, Teeuwen R, et al. PEG shielded polymeric double layered micelles for gene delivery. J Control Release 2005; 102:711.
164. Zhang XQ, Wang XL, Zhang PC, et al. Galactosylated ternary DNA/polyphosphoramidate nano particles mediate high gene transfection efficiency in hepatocytes. J Control Release 2005; 102:749.
165. Zhao Z, Wang J, Mao HQ. Polyphosphoesters in drug and gene delivery. Adv Drug Deliv Rev 2003; 55:483.
166. Li Y, Wang J, Li CG. CNS gene transfer mediated by a novel controlled release system based on DNA complexes of degradable polycation PPE-EA: a comparison with polyethylenimine/DNA complexes. Gene Ther 2004; 11:109.
167. Wang J, Gao SJ, Zhang PC. Polyphosphoramidate gene carriers: effect of charge group on gene transfer efficiency. Gene Ther 2004; 11:1001.
168. Wang J, Zghang PC, Lu HF. New polyphosphoramidate with a spermidine side chain as a gene carrier. J Control Release 2002; 83:157.
169. Csaba N, Caamano P, Sanchez A, et al. PLGA: poloxamer and PLGA; poloxamine blend nanoparticles, new carriers for gene delivery. Biomacromolecules 2005; 10:271.
170. Zahr AS, deVillers M, Pishko MV. Encapsulation of drug nanoparticles in self assembled macromolecular nano-shells. Langmuir 2005; 21:403.
171. Kaul G, Parsons CL, Amiji M. Poly(ethylene glycol) modified gelatin nanoparticles for intracellular delivery. Pharm Eng 2003; 23:1.
172. Panyam J, Labhasetwar V. Biodegradable nanoparticles for drug and gene delivery to cells and tissues. Adv Drug Deliv Rev 2003; 55:329.
173. Panyam J, Labhasetwar V. Sustained cytoplasmic delivery of drugs with intracellular receptors using biodegradable nanoparticles. Mol Pharm 2004; 1:77.
174. Moghimi SM, Hunter AC, Murray JC. Long circulating and target specific nanoparticles, theory and practice. Pharmacol Rev 2001; 53:283.
175. Xia X, Hu Z, Marquez M. Physically bonded nanoparticles networks: a novel drug delivery system. J Control Release 2005; 103:21.
176. Panyam J, Williams D, Dash A, et al. Solid state solubility influences encapsulation and release of hydrophobic drugs from PLGA/PLA nanoparticles. J Pharm Sci 2004; 93:1804.
177. Kaul G, Amiji M. Tumor targeted gene delivery using poly(ethylene glycol) modified gelatin nano particles: in vitro and in vivo studies. Pharm Res 2005; 22:951.
178. Esfand R, Tomalia DA. Poly(amidoamine) PAMAM dendrimers: from biomimetic to drug delivery and biomedical applications. Drug Discov Today 2001; 6:427.
179. Toth I, Salthivel T, Wilderspin AF, et al. Novel cationic lipidic peptide dendrimer vectors: in vitro gene delivery. STP Pharm Sci 1999; 9:93.
180. Bayele HK, Salthivel T, O'Donnell M, et al. Versatile peptide dendrimers for nucleic acid delivery. J Pharm Sci 2005; 94:446.
181. Zhang XQ, Wang XL, Huang SW, et al. In vitro gene delivery using polyamidoamine dendrimers with a trimesyl core. Biomacromolecules 2005; 6:341.
182. Benita BM, Romejin S, Jungingger HE, et al. PLGA-PEI nanoparticles for gene delivery to pulmonary epithelium. Eur J Pharm Biopharm 2004; 85:1.
183. Diwan M, Elamanchilli P, Cao M, et al. Dose sparing of CpG oligodeoxynucleotide vaccine adjuvants by nanoparticles delivery. Curr Drug Deliv 2004; 1:405.
184. Rhaese S, Briesen HV, Waigmann HR, et al. Human serum albumin-polyethylenimine nanoparticles for gene delivery. J Control Release 2003; 92:199.
185. Quiang B, Segev A, Beliard I, et al. Poly(methylidene malonate 2.1.2) nanoparticles: a biocompatible polymer that enhances peri adventitial adenoviral gene delivery. J Control Release 2004; 98:447.
186. Lee HC, Kim S, Kim K, et al. Remission in models of type 1 diabetes by gene therapy using a single chain insulin analogue. Nature 2000; 408:483.
187. Godbey WT, Wu KK, Mikos AG. Tracking the intracellular path of poly(ethylenimine)/DNA complexes for gene delivery. Proc Natl Acad Sci U S A 1999; 96:5177.
188. Li Z, Huang L. Sustained delivery and expression of plasmid DNA based on biodegradable polyester, poly (D,L-lactide-co-4-hydroxy-L-proline). J Control Release 2004; 98:437.

189. Gupta M, Gupta AK. Hydrogel pullulan nanoparticles encapsulating pBUDLacZ plasmid as an efficient gene delivery carrier. J Control Release 2004; 99:157.
190. Marshall E. Gene therapy death prompts review of adenovirus vector. Science 2000; 286:2244.
191. Boyce N. Trial halted after gene shows up in semen. Nature 2001; 414:677.
192. Check E. Gene therapy, a tragic setback. Nature 2002; 420:116.
193. Braun CS, Vetro JA, Tomalia DA, et al. Structure/function relationships of polyamidoamine/DNA dendrimers as gene delivery vehicles. J Pharm Sci 2005; 94:423.
194. Zaitsev S, Cartier R, Vyborov O, et al. Polyelectrolyte nanoparticles mediate vascular gene delivery. Pharm Res 2004; 21:1656.
195. Montigny WJ, Houchens CR, Illenye S, et al. Condensation by DNA looping facilities transfer of large DNA molecules into mammalian cells. Nucleic Acid Res 2001; 29:1982. 212.
196. Lim Y, Kim C, Kim K, et al. Development of a safe gene delivery system using biodegradable polymer, poly(4-aminobutyl)-L-glycolic acid). J Am Chem Soc 2000; 122:6524.
197. Kabanov AV, Batrakova EV, Sriadibhatla S, et al. Polymer genomics: shifting the gene and drug delivery paradigms. J Control Release 2005; 101:259.
198. Tabatt K, Kneuer C, Sameti M, et al. Transfection with different colloidal systems: comparison of solid-lipid nanoparticles and liposomes. J Control Release 2004; 97:321.
199. Wissing SA, Kayser O, Muller RH. Solid-lipid nanoparticles for parenteral drug delivery. Drug Deliv Rev 2004; 56:1257.
200. Hoet P, Hohlfeld IB, Salata OV. Nanoparticles-known and unknown health risks. J Nanobiotechnol 2004; 2:12.
201. Service RF. Nanomaterials show signs of toxicity. Science 2003; 300:243.
202. Brown JS, Zeman KL, Bennett WD. Ultrafine particle deposition and clearance in the healthy and obstructed lung. Am J Respir Crit Care Med 2002; 166:1240.
203. Kreilgaard M. Influence of microemulsions on cutaneous drug delivery. Adv Drug Deliv Rev 2002; 54:S77.
204. Davda J, Labhasetwar V. Characterization of nanoparticles uptake by the endothelial cells. Int J Pharm 2002; 233:51.
205. Bilati U, Allemann E, Doelker E. Poly(D,L-lactide-co-glycolide) protein loaded nanoparticles prepared by the double emulsion method—processing and formulation issues for enhanced entrapment efficiency. J Microencapsul 2005; 22:205.
206. Bargoni A, Cavalli R, Caputo O, et al. Solid-lipid nanoparticles in lymph and plasma after duodenal administration to rats. Pharm Res 1998; 15:745.
207. Passirani C, Barratt G, Devissaguet JP, et al. Long circulating nanoparticles bearing heparin or dextran covalently bound to poly (methyl methacrylate). Pharm Res 1998; 15:1046.
208. Silveira AM, Ponchel G, Puisieux F, et al. Combined poly(isobutylcyanoacrylate) and cyclodextrins nanoparticles for enhancing the encapsulation of lipophilic drugs. Pharm Res 1998; 15:1051.

8 Roller Compaction Technology

Ronald W. Miller
Miller Pharmaceutical Technology Consulting, Travelers Rest, South Carolina, U.S.A.

INTRODUCTION

Since the publication of the *Handbook of Pharmaceutical Granulation Technology, Second Edition*, late 2005, the world's economy has slowed and capital expansion in worldwide pharmaceutical industry, particularly in oral solid dosage forms, has suffered (1). A number of pharmaceutical drug companies, large and small, have had and are still reducing staffs, selling manufacturing sites or merging. During the last three years, new drug development has slowed as well, as is evident for fewer new drug approvals by the U.S. Food and Drug Administration. In spite of the apparent pharmaceutical industry economic and the innovative drug downturn trends temporarily, I do believe, the important need for dry granulation technology keeps growing in the pharmaceutical industry, as well as in other industries.

The legacy pharmaceutical roller compaction technology and scale-up book chapters, by this author, previously published in *The Handbook of Pharmaceutical Granulation Technology, First and Second Editions*, *The Encyclopedia of Pharmaceutical Technology, and The Pharmaceutical Process Scale-Up, Second Edition* covered a very wide range of useful related topics (1–4). The learnings and findings expressed in these chapters reviewed and discussed roller compaction theory, equipment design features, for example, feed screw and specifically the importance of vacuum deaeration theory and equipment designs of different manufacturers. New findings by Guigon and his team were expressed about their advanced roll sensor instrumentation. The work showed that the pressure variance applied to powder across the roll surface was caused by the feed screw position.

Miller presented the first at-line near-infrared (NIR) roller compaction evaluations of compacts manufactured at different roll pressures, vacuum deaeration pressures, power consumptions and compared different processing effects. Later, he teamed with Purdue University Industrial Physical Pharmacy School faculty and graduate students, in a series of noninvasive real-time NIR dynamic-mode roller-compacted powder blend property (e.g., content uniformity, moisture content, compact density, tensile strength, and Young's modulus), evaluations that were published (5).

The beginning section of this book chapter describes the industrial perspective of the value of roller compaction technology, its importance and some technical aspects. While the primary focus of this chapter is related to the pharmaceutical industry, other industrial viewpoints are illustrated for comparison and reference.

ACTIVE PHARMACEUTICAL INGREDIENT POWDERS

In the pharmaceutical industry, brand name innovator companies aim to develop formulations and processes to convey new therapeutical benefits of active pharmaceutical ingredients (APIs), in oral solid dosage forms for patients.

Typically the morphology of newly invented synthesized API powders is very fine, with low density and nonuniform in shape; with powder particle physical attributes being nonfree flowing. Ultimately, the API is a poor actor regarding powder property behaviors for formulation and process development considerations and for downstream drug product manufacturing. Similar situations arise in the battery, beverage, cement, chemical, and food industries, where synthesized processes produce powders that have poor powder physical properties for next step downstream processing operations.

When manufacturing solid oral dosage forms, there must be successful powder rheology performance. This means, it is often necessary to modify the morphology characteristics of fine API powders, typically those powders that are less than 150 μm in size, to obtain better powder

properties for tableting, encapsulation, and powder for oral suspensions (PFOSs) drug product manufacturing.

Emphasizing the key considerations of powder technology properties for pharmaceutical oral solid dosage forms, which are given below, cannot be understated.

- Powder flowability
- Powder compactibility
- Chemical stability

Controlling these three key powder properties will assure achieving critical oral solid dosage form specifications and efficacy. Without the proper physical properties of powder flowability and powder compactibility, meeting worldwide pharmacopeia requirements such as tablet or capsule content uniformity, assay, dissolution, weight, and dosage form physical robustness: hardness and friability are virtually impossible.

The third powder property, chemical stability, is very important for any manufactured drug product. Effects of moisture and dry heat from processing powder granulations can be problematic and stressful for drug product manufactured by nondry granulation technologies. There is significantly less product stability risk from latent moisture and heat liable degradation products when manufacturing by a dry granulation processing method. The author admits that from a stability standpoint, it has been his observation that the most robust drug product granulation manufacturing is by roller compaction dry granulation technology. Anecdotal proof of this assertion can be surveyed online in the pharmaceutical "The Pink Sheets" or "The Pink Sheets Daily," publisher FDC Reports, where product recall information identifies which commercial oral solid dosage form product failed specifications, why it failed, and describes the general drug process method. Reviewing these two published resources since 2000, there have been no cited dry granulated recalled products (6).

GRANULATION TECHNOLOGIES

There are three key technology drug product processing methods that are most widely used to enable modifying API physical properties to formulate pharmaceutical oral solid dosage forms: direct compression, wet agglomeration, and dry agglomeration. Direct compression is a process by which tablets are compressed directly from powder blends containing the API and suitable excipients, for example, disintegrants, binders, glidants, and lubricants, without any preprocessing treatment. For some time now, many new API powder substances in the pharmaceutical industry cannot be directly compressed into tablets or encapsulated into hard gelatin capsules or even filled into PFOS bottles. Typically, a successful direct compression blend must be designed and developed to meet drug product specification requirements when operating high speed compression machines, for example, filling a die cavity in 12 msec; anecdotally, not a trivial task (7).

The majority of new active pharmaceutical powder ingredients are small, needle-like habit morphology that is very heterogeneous in size and very potent. Oral solids formulations of these drugs are usually low dosage strengths that are generally well under 100 mg per dose. Achieving active uniform distribution to guarantee correct drug product uniformity in each individual unit dose is paramount and not easy, requiring an optimal processing technology.

The demanding robustness of such formulations and drug product processes must imperatively withstand API and excipients' additional physical property variances, for example, lot-to-lot granulometry and morphology changes, which effect potential segregation of powder blend transfers from one manufacturing floor to another, or the transfer of the product's process to multiple drug product manufacturing sites. Illustrating the point, potential powder segregation can occur during the conveyance of a final blend from a holding vessel through a long tube or chute (possibly as long as two to four meters) from one processing floor to another where compressing or encapsulating machines are located. Variable API and excipient raw material physical properties and the potential rigorous handling of drug product blend throughout the drug product manufacturing process requires that the successful drug product be undisturbed by potential segregation mechanisms or influences. Thus, it is the author's

contention that it is less likely that brand name innovator companies will want to develop and manufacture new oral solid drug formulations via direct compression technology.

The increasingly important reason for pretreatment of active pharmaceutical powders is the necessity to attain acceptable powder flowability, powder compactibility, and minimize powder segregation after mixing during downstream process handling.

The wet granulation pretreatment technologies, low shear, high shear, and fluid bed have two common processing technology requirements: a liquid to granulate the batch and a drying cycle to dry the granulated mass. The author has observed that the new APIs developed today are more potent and much more sensitive to nondry preprocessing treatments and environments. The pharmaceutical risk is that in aqueous drug product manufacturing environments the API can be potentially modified and new degradants formed or a known degradant level abnormally increased.

Pharmaceutically, this is unacceptable for stability, efficacy, and potential safety reasons and can delay or doom a promising API for potential patient therapeutical use. It is the author's opinion that the risk is so great that it can over-ride all other attributes regarding wet agglomeration development and product manufacturing. Other issues that compare and illustrate additional wet granulation differences versus dry granulation roller compaction drug product technologies are given below.

- Typically, there are more machines and plant space requirements to maintain for aqueous granulation processes than dry granulation technology.
- Equipment sunken costs are greater for wet granulation equipment cross contamination issues than with dry granulation technology requirements.
- Variable operating costs are higher for wet granulator and dryer systems than with dry granulation technology.
- Cleaning cycles are more frequent with wet granulation equipment trains than dry granulation manufacturing equipment.
- Initial operating and recovery safety issues are very costly with solvent granulating systems, there are none with roller compaction.
- Scale-up is less complicated with dry granulation compared with wet granulation (4).
    - Wet granulation scale-up has many more major and minor variables to monitor during wet granulation and drying processes than a dry granulation roller compaction process (8).
    - Scale-up using wet granulation equipment requires larger bowl and batch sizes—manufacturing capacity is a function of bowl size volume and manufacturing time.
    - Scale-up using roller compaction can be accomplished with development sized equipment—it only requires longer equipment operating hours as manufacturing capacity is primarily a function of operating time providing more capacity and operational flexibility.
- Wet granulation end points can change as the granulator power consumption profile can change when manufacturing multiple consecutive batches during a shift or campaign-requiring more sensor controls to understand the process.
- The wetting of raw material is more influenced with raw material property changes, for example, particle size distribution (psd), and density than raw material changes affecting roller compaction.
- In the case of manufacturing a wet granulation batch, if an electrical outage occurs, the probability of losing the batch is high if there is no backup battery system to quickly start up and continue the process; this is not an issue with a roller compaction process.
- Massing effects and drying capacity issues are key concerns in scale-up for drying granulations produced in separate steps for high- or low-shear wet granulation technologies (8).

A word regarding solvent granulation processing technology: while the solvent granulation technology generally eliminates the issues and the pharmaceutical risks that are associated with aqueous drug product manufacturing environments as aforementioned; the

Figure 1 Dry agglomeration processing steps; API powder (*upper left*), compacted API blend (*lower left*), milled and blended compacts (*upper right*), and compressed tablets (*lower right*).

manufacturing equipment and ancillary supporting equipment costs, environmental, U.S. government, and OSHA safety issues, and public concerns with solvent manufacturing technologies have become significantly more intense, complex and costly, particularly for start-up. Lastly, it is highly questionable that this technology, in general, does not reduce pharmaceutical drug product manufacturing costs for the potential drug product manufacturing gains.

Summary

The above-mentioned concerns and issues, which are associated with the development of new APIs transformed into pharmaceutical drug product processes; direct compression, wet and solvent granulation technologies, and improved drug product granulation processes make use of dry granulation technology, roller compaction. A schematic picture depicts basic dry agglomeration processing stages (Fig. 1).

COMPACTION THEORY

The bonding forces in a dry aggregate are important for granulation properties such as granule integrity, flowability, friability, density, compressibility, and size for downstream manufacturing process steps. Pietsch and co-workers (9) described the bonding mechanisms occurring during dry granulation as a mixture of van der Waals forces, mechanical interlocking, a recombination of bonds established between freshly created surfaces, and solid bridges, created because of solidification during compression.

A general theory describes particle bonding related to roller compaction in the *Handbook of Pharmaceutical Granulation Technology* (2). The process of dry granulation relies on interparticulate bond formation. Granule bond formation is characterized in different stages, which usually occurs in the following order:

1. Particle rearrangement
2. Particle deformation
3. Particle fragmentation
4. Particle bonding

Particle rearrangement occurs initially as powder particles begin filling void spaces. Air begins to leave the powder blend's interstitial spaces, and particles begin to move closer together. This action increases the powder blend's density. Particle shape and size are key factors in the rearrangement process. Spherical particles will tend to move lesser than other-shaped particles because of their close initial packing to one another. Particle deformation occurs as compression forces are increased. This deformation increases the points of contact between particles where bonding occurs and is described as plastic deformation (2). Particle fragmentation follows as the next bonding stage. This occurs at increased compression force levels. At this stage, particle fracturing creates multiple new surface sites, additional contact points, and potential bonding sites. Particle bonding occurs when plastic deformation and fragmentation happen. It is generally accepted that bonding takes place at the molecular level, and that this is due to the effect of van der Waals forces (2).

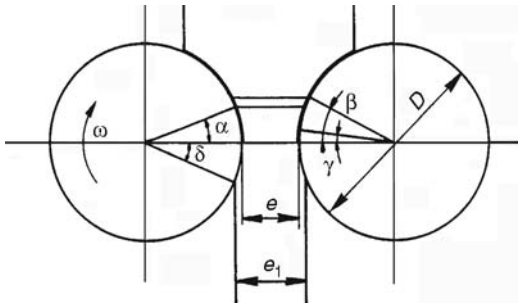


Figure 2 Front view of rolls in horizontal plain. *Source*: From Ref. 10.

When powder granules undergo an applied force or stress, a stress force is released from the granules. The granules attempt to return to their original shape or form; this is described as *elastic deformation*. A deformation that does not totally recover after the stress is released is a *plastic deformation*. Elastic and plastic deformations can occur simultaneously, but one effect usually predominates.

Dehont et al. provided a simplified approach to roller compaction theory. They described that powder granules move through stages in the feed area. The material is drawn into the gap by rubbing against the roll surfaces. The densification that occurs in this area is particle rearrangement. At this stage, the speed of the powder is slower than the peripheral speed of the rollers. Figure 2 represents compactor rolls in the horizontal plain; powder is pushed vertically downward into the compaction area (10).

Note that in Figure 2, α is the nip angle and β is the material in volume space. The material is located in the compaction area between α and the horizontal axis (Fig. 2). At this stage, the material undergoes additional compaction forces.

The particles undergo plastic deformation and are bonded. Dehont's team noted that nip angle varies according to the material characteristics of particle size and density and the angle is about 12° (10). They defined the neutral angle, γ, which corresponds to the point where the pressure applied by the rollers is the greatest on the material. They also defined elastic deformation, δ, and that occurs after the compact begins leaving the compression roll area. Compacted flakes may increase in size because of material elastic deformation and actually may have a larger thickness than the roll gap, e, (10). Dehont et al. developed equation (1) for the linear variation of flake thickness at a specific roll diameter (10).

$$e_1 = D\left(\frac{d_0}{d_1 - d_0}\right)(1 - \cos\alpha) \tag{1}$$

Equation (1) defined:

e_1 = flake thickness
D = roll diameter
d_0 = material density at angle α
d_1 = flake density

Dehont et al. assumed that the material in the compaction area remains horizontal and moves at the peripheral speed of the rollers. They also considered that the angle, α, is independent of the roller diameter size and noted that the flake thickness, e_1, depends on the roller speed, the roller surface, and the compaction pressure. All these parameters influence the density of the flake, d_1. Dehont et al. concluded that if the same flake thickness were obtained with different roller diameters, the flake density would be greater with larger diameter rollers (10). This is due to the greater nip angle formed with the larger rolls allowing more material to be compacted.

Johanson identified, through very comprehensive mathematical models and relationships, material properties, press dimensions, and operating conditions for roll compactors. For more information, the interested person should read the entire reference 11. In short, he

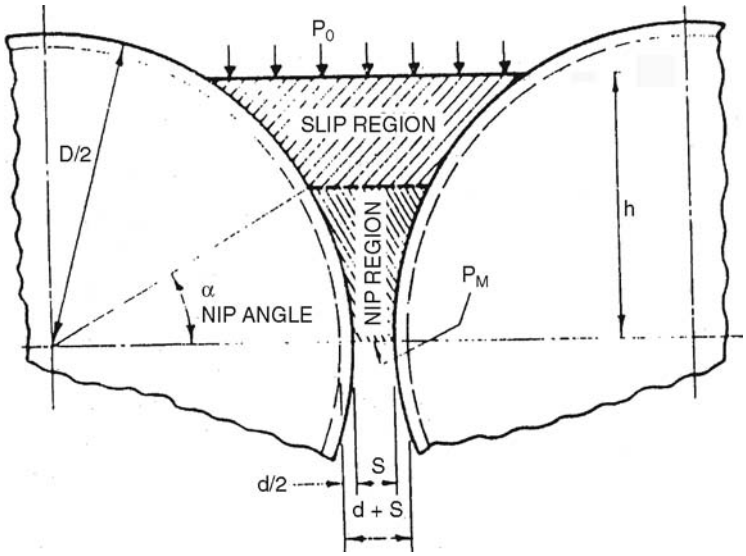


Figure 3 Front view of compactor rolls in horizontal plain depicting powder regions under different compaction forces. *Abbreviations*: P_o, horizontal pressure between rolls; θ, angular position of roll bite; α, nip angle; 2*d*, roll diameter *D*; *h*, height above the roll center line at which feed pressure P_o is applied; P_m, horizontal pressure at $\theta = 0$; *S*, roll gap. *Source*: From Ref. 11.

described that roller compaction involves a continuous shear deformation of the granules into a solid mass.

To satisfy the theory's assumption, it was postulated that the material be isotropic, frictional, cohesive and compressible. Figure 3 depicts material in a press that undergoes shear deformation into a solid mass (11).

Johanson pointed out that no roller compactor theories at that time determined the angle of the nip and the bulk density at $\theta = \alpha$, except by actually rolling the granular solid in a roll press. He also provided a method to calculate the nip angle and the pressure distribution between the rolls. His calculations determined the pressure distribution above the nip area and the pressure in that area (11).

He provided the technical rationale to calculate the nip pressures in the nip region. He showed that the material trapped in a volume, V_α, between arc-length segments ΔL, must be compressed to volume, V_θ, between the same arc-length segments. The relationship requires that the bulk densities, γ_α and γ_θ in volumes, V_α, and V_θ, be related by equation (2) (11).

$$\frac{\gamma_\alpha}{\gamma_\theta} = \frac{V_\theta}{V_\alpha} \tag{2}$$

Johanson stated that the pressure, σ_θ, at any $\theta < \alpha$ can be determined as a function of the pressure σ_α, at $\theta = \alpha$, by the pressure-density relationship. It was understood that, for increasing pressures, log density was a linear function of log pressure (12).

Johanson found that the nip angle does not depend on the magnitude of the roll force or the roll diameter. He demonstrated that the nip angle was affected very little by the geometry of the press or the cut grooves on the roll surface. It was mostly influenced by the nature of the materials that were compressed. The very compressible materials, with small *K* values, had very large nip angles. On the other hand, incompressible materials, with large *K* values, had very small nip angles. Ultimately, Johanson's results showed that material properties determine the maximum pressure that a roller press can apply to a material.

Note that further information from authorities, Heckel, Johanson, and Pietsch, on bonding and compaction theories is described for the readers' interest in *The Handbook of Pharmaceutical Granulation Technology, Second Edition* (1).

DESIGN FEATURES OF ROLLER COMPACTORS

Certainly, a key enhancement that highlights today's pharmaceutical industry state-of-the-art roller compactors, is programmable logic controllers (PLCs). They are used to control and monitor mechanical parts that regulate screw feed rate, roll speed, roll pressure, roll gap, vacuum deaeration, and mill speed. Operator interface screens allow online monitoring and controlling feed screw speed, roll gap and pressure, and sizing granulators. Diagnostic feature functions are displayed online, such as operation, maintenance and calibration. All functions are interfaced and adjustable through PLC for process control and report monitoring. The technical nature of this information and discussion is precluded in this chapter because of brevity requirements. The interested reader can contact roller compactor manufacturing vendors and get information on the same subject.

Briefly, a key machine innovation, vacuum deaeration, was a new important feature design added by some roller compactor vendors in the early-mid-1990s. The design feature has been shown to help premodify raw material density prior to compacting and increase throughput (13). Other equipment features, such as multiple horizontal or angled feed screws, assist manufacturing a uniform powder feed across the rolls (13,14).

Newly designed roll machine blocks, featuring cantilever roll systems, offer more efficient ways to clean, handle, facilitate product and equipment changeovers. Newly designed storage hoppers and various screw feeder designs have improved delivering poor powder flowing materials to the rolls. A history of hopper and feed screw designs showed that each design evolved to facilitate and improve powder flow to the compactor feed screw conveyance system. Innovatively designed feed screw systems are used commercially in roller compactors worldwide to improve powder feed to the rolls. These systems can be seen in reference (3). Sizing mills are now trimly fitted to the compactor body and controlled by variable-speed drives. Most compactors no longer require a second machine (mill) in tandem to size compacts as required by slugging technology. Roller compactors have clean-in-place (CIP) systems that offer environmental and safety features. These systems minimize human exposure to chemicals and improve cleaning efficiencies.

Compactor design features have evolved over the years. By the mid-1970s, research revealed a number of roll design improvements that increased compacting efficiency. Three key conditions were identified, at that time, which optimized the roll compact throughput and minimized leakage of noncompacted powder (15).

- Adequate powder supply must enter the gripping zone.
- Powder must be conveyed fully into the narrowest part of the roller gap.
- Compaction pressure must be distributed as uniformly as possible across the whole roller-gripped powder mass.

Equipment engineers and researchers worked on improving feeding-equipment systems and roll designs to satisfy and maximize the above conditions. Some of the key advances are identified in reference (13) and are reemphasized here.

Because of powder feed variability at the nip and in the roll gap regions, powder leakage is produced during the compaction process. This situation produces excessive fines and possible undesirable processed material. Usually, this problem is caused by uneven powder flow and compact formed when the powder is fed toward the middle of the roll width. Granules produced under these conditions are sometimes not optimal for further pharmaceutical processing.

This leads to some questions; What is the optimum roll speed for a compaction process? What factors does the formulating scientist or process engineer need to consider to maximize compact quality and compaction throughput? Johanson (16) attempted to answer these questions by predicting roll-limiting speeds for briquetting presses. He developed mathematical expressions considering even the gas and liquid effects as they can theoretically be squeezed from a solid mass. Solid properties, press dimensions, and operating conditions were evaluated to predict optimum roll speeds. The results necessary for a quality briquette are most critical for low-density fine particles. Johanson's work showed the relation between feed pressure and roll speed to essentially be proportional to the material's permeability (porosity). For additional information, the interested reader should peruse the reference list.

Sheskey and Hendren, in 1999, studied the effect of roll surface configuration on the drug release and physical properties of a HPMC matrix controlled-release dosage form (17). Smooth and axial-grooved roll surface designs were studied using a Vector Model TF-Mini roller compactor (Vector Corporation, Marion, IA). Their hypothesis was that the greater the depth of the roll concavity surface, the less evenly the powder would displace on the roll surface compared to a smooth non-concave roll surface. Thus, as with tablet-tooling design, the top of the crown area of the compacted ribbon would theoretically be softer than the rest of the ribbon. However, the results of a particle size distribution test performed on milled ribbons generated using both smooth and axial-grooved roll pairs, showed similarity between tested samples. In addition, results showed little difference in tablet-crushing strength values between samples manufactured using either type of (smooth or axial grooved) roll surface designs. Drug release profiles of tablets prepared from roller-compacted granulations using both roll surface configurations were also similar.

The consistency and evenness of the powder feed, largely determined by powder flow properties and by the feed screw conveyance into the roll pair determines to a large extent, how complete a compact is made and ultimately the success of a compaction process. Most roller compacting systems suffer the disadvantage of leakage, that is, 20% to 30% powder particles (depending on the formulation) that are not uniformly compacted. This primarily occurs because of uneven powder feed and powder slippage between individual loose particles and the roll surfaces. Under these conditions, it is usually necessary to recycle the uncompacted powder or fines. Recycling a compaction process is a significant drawback because of additional capital expenditure, labor costs, and increased throughput time.

Operationally, the key goal of a compactor is to maintain a range of pressure on the powder feedstock, independent of the fluctuating powder granulometry and powder flow fed to the rolls, so that a consistent compact is made. Historically, the compaction process was managed by controlling the input material, the quantity per unit of time, the roll speed, and the roll gap. Allowing the roll gap to float unchecked can influence the production rate and the compact quality. Therefore, it is important to control the compaction process by setting a constant powder feed rate during the compaction operation. Design innovations on the powder feed input side of the roller compactor are complex. It is suggested that the interested readers read Ref. 2 for additional details.

Deaeration Theory

A key factor limiting compaction throughput and quality is air entrapment in powder materials. During compression, air-occupying voids between particles are compressed and squeezed. The gas pushes through the powder causing powder fluidization and a nonuniform level of powder at the roll gap. It is best described in Figure 4A. This situation limits compact throughput and creates a nonuniform compact density. It also creates excess fines prior to sizing because of "spidering" compact edges (18).

The spidering condition occurs when gases rush across the inside of a compact to thinly and weakly formed flaked edges. The flake edges break apart perpendicular to the compaction direction. The compact edge breakage appears "saw tooth" in structure and varies in length depending on the nature of the powder binding properties, the amount of air entrainment and the roll dwell time.

Both Johanson and Pietsch reported that expanding gas in a compact is detrimental to the compaction process: by reducing the compaction throughput and increasing the amount of fine particles. The effects of roll speed and powder porosity on air pressure in a compacted sheet are illustrated in Figure 5 by Pietsch (19). This graphic shows a relatively larger roll speed operating range when compacting a permeable (porous) powder. Air entrainment does not limit roller speed for coarse granular powders. On the other hand, when compacting very fine powders, the operating roll speed range is significantly reduced because of air entrainment.

Miller indicated that the evenness of the powder feed into the rolls determines, to a large extent, the success of compaction. Roller compactor systems suffer from two disadvantages: as the powder feed bulk density approaches 0.3 g/cm^3 or less, the compaction throughput efficiency decreases. Secondly and concurrently, the uncompacted powder leakage generally

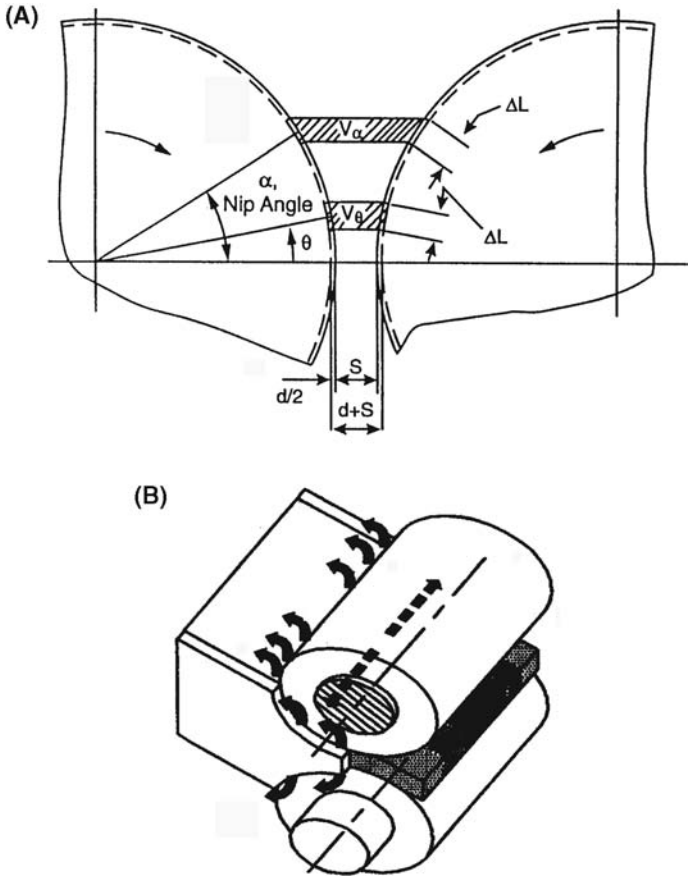


Figure 4 (**A**) Front view of compactor rolls in horizontal plain depicting nip angle. (**B**) Pattern of gas escape from roll nip region. *Abbreviations*: P_o, horizontal pressure between rolls; θ, angular position of roll bite; α, nip angle; 2*d*, roll diameter *D*; *h*, height above the roll center line at which feed pressure P_o is applied; P_m, horizontal pressure at $\theta = 0$; *S*, roll gap, ΔL, arc-length segments; V_α, material trapped in volume space described by arc lengths; V_θ, compressed volume space described by arc lengths; γ_α and γ_θ, respective powder bulk densities in volume spaces V_α and V_θ; *K*, a material property constant for a given moisture content, temperature, and time of compaction. *Source*: From Refs. 11 and 18.

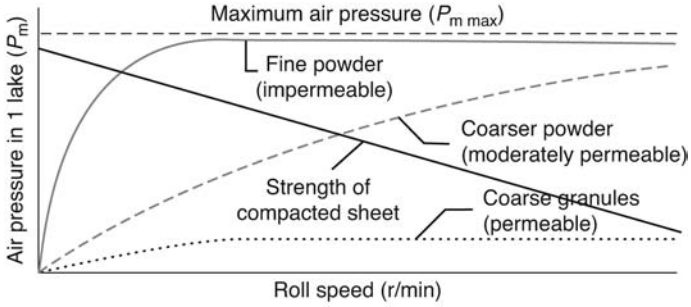


Figure 5 Effects of roll speed and permeability on air pressure in a compact. *Source*: From Ref. 19.

increases around the rolls (13). Miller, in 1994, described a new machine design improvement that used vacuum deaeration to remove air entrainment from the powder just prior to the nip angle during roller compaction. The multiple benefits of such an action are significant, and remarkable efficiency results have been observed when compacting low-density raw materials (13).

- More uniform powder feed to the rollers
- Less voltage and amperage variability for the roll pair
- More uniform and strong compact

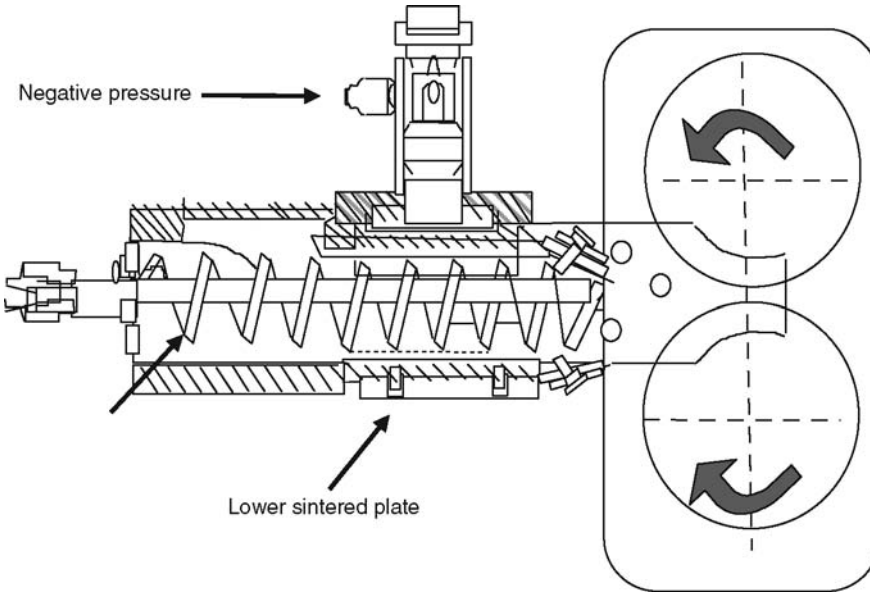


Figure 6 Side view of feed screw system and vacuum deaeration with sintered plate segments. *Source*: From Ref. 2.

- Less powder leakage
- Greater yield
- Less powder adhering to the compact prior to sizing
- Higher compact throughput
- Less airborne particles

The newly designed equipment involved a compactor fitted with two horizontal feed screws, which featured vacuum deaeration. Specifically, the roll compactor was equipped with a conical storage hopper containing a variable-speed agitator. Bulk powder was fed directly from the top of the hopper to the top of twin horizontal auger feed screws, which directly transported the powder to the nip roll area (2). A side view of the design features is shown in Figure 6.

The design is described as a novel stainless steel encasing that leads to the compactor rolls that enclose the variable-speed auger screws. Just before the nip area, a pair of sintered stainless steel segments are assembled within the horizontal auger feed system, which can operate under partial vacuum. A small, self-contained vacuum pump draws negative pressure through a dry filter and a stainless steel line to the sintered assembly plates. The partial vacuum is adjustable from -0.1 to -0.8 bars. The compaction rolls operate at different speeds and are supported on heavy-duty bearings in such a way that the lower roll is fixed and the upper roll is slightly movable in the vertical plane. The deaerated material passes through the roll pair, which is under infinitely variable hydraulic pressure. The deaeration, auger feed screws' design and speed, roll speed, and hydraulic roll pressures are the main factors in producing a compact with specified properties.

In several experiments, Miller studied the effects of using horizontal twin auger feed screws under partial vacuum (Alexanderwerk, Inc., Horsham, Pennsylvania, U.S., model 50/75 compactor). The powder feed was deaerated just before roller compaction. The experimental design showed that the compactor's deaeration feed system significantly increased compaction output and minimized powder leakage when compacting very low-density blends (<0.35 g/cm^3) (13).

In several other trials, Miller also studied the effects of using two different compactor's vacuum deaeration systems. His experiments evaluated the effects of powder density, screw

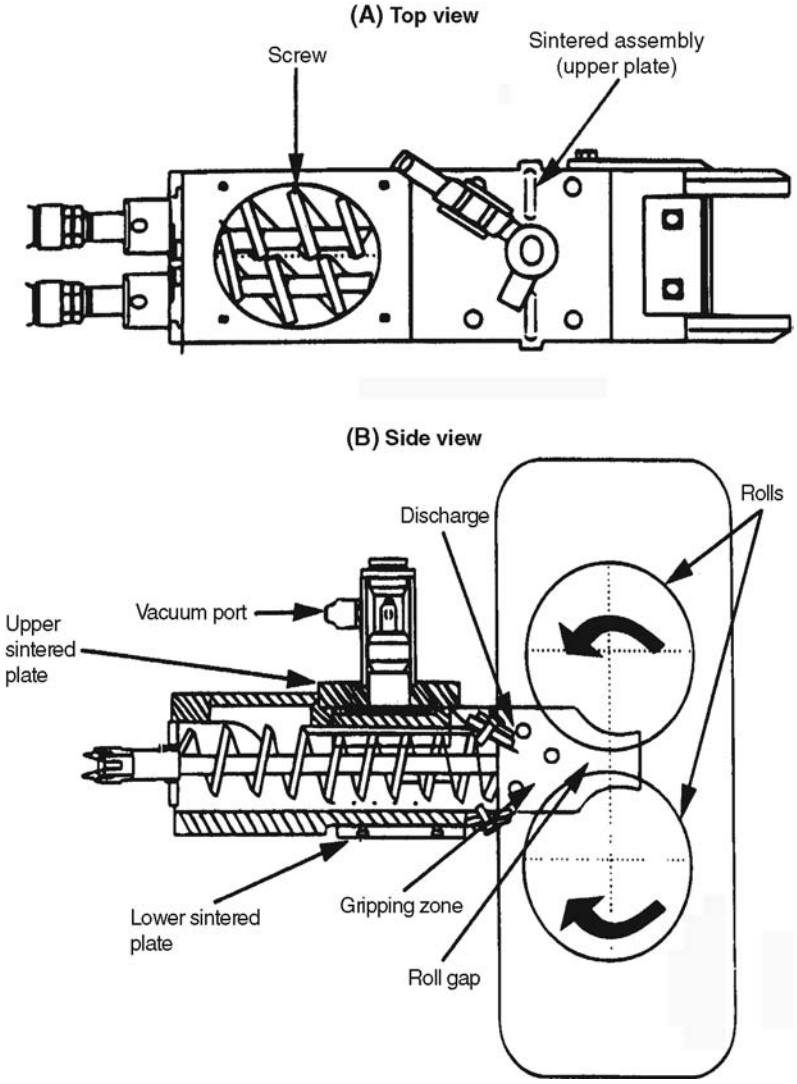


Figure 7 Horizontal twin-scew vacuum deaeration feed system. *Source*: From Ref. 20.

feed speed, roll speed, roll pressure, vacuum deaeration pressure, compaction rate, and compaction-leakage rate. Test results demonstrated that the first compactor's deaeration and feed system designs significantly increased compaction output. The new equipment design and process provided high compact yields and virtually eliminated powder leakage, obviating the need for expensive powder recirculation equipment. Vacuum deaeration design of the compactor 1 (Fig. 7) proved to be superior to the second compactor design (Fig. 8), when compacting an active bulk drug with a density of approximately 0.2 g/cm^3. In summary, a new critical condition, vacuum deaeration, had been identified in optimizing roller compacting effectiveness and efficiency (2,13).

Miller concluded that four key processing conditions must exist to optimize roller compaction throughput and minimize powder leakage around the rolls (2,13).

- Adequate powder supply must enter the gripping zone.
- Powder must be fully conveyed into the narrowest part of the roller gap.

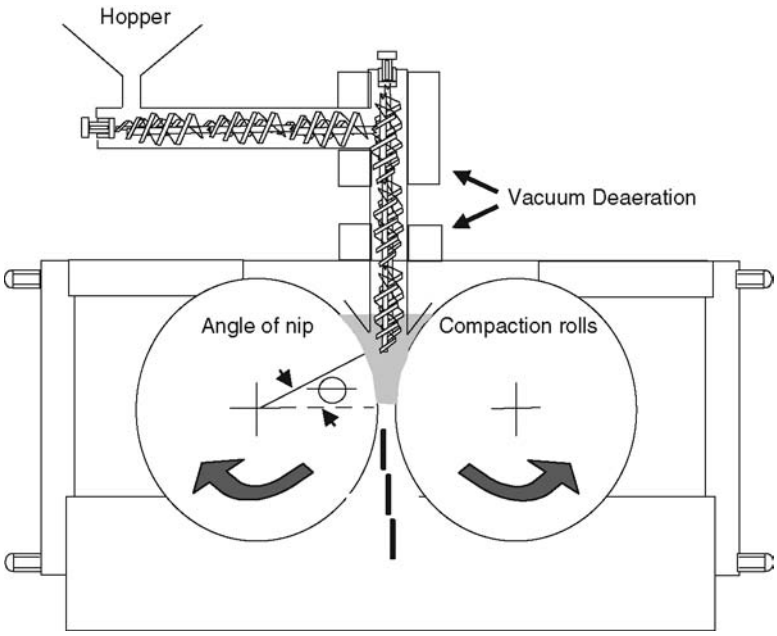


Figure 8 Compactor front view of vertical feed screw system with vacuum deaeration. *Source*: From Ref. 2.

- Compaction pressure must be distributed as uniformly as possible over the whole of the roller-gripped powder mass.
- Sufficient vacuum deaeration must be effectively distributed prior to the nip roll region, particularly for low bulk density powder feed stock.

Today most compactor companies have designed deaeration systems and have engineered improvements in their deaeration operational effectiveness.

FORMULATION CONSIDERATIONS

There has not been much published about which ingredients are typically used and at what percentages in the pharmaceutical industry as well as in other industries. This is a very sensitive subject as it goes to patentability, competitive business advantages, and privileged information. The author, while reviewing previous book chapters that he wrote, noted there was no mention of this subject matter and thus brief remarks are made here.

The nature of a dry granulated formulation is directly tied very closely to API, the intended therapeutical use and its physical characteristics. Looking at the intended drug use, we need to determine if the dosage form is for immediate- or extended-release therapy. Both dosage forms are uniquely different and require a different formulation approach in the selection of pharmaceutical excipients to make drug product.

The percentage of the API in a formulation is usually dependent on its potency and therapeutical effect, for example, a highly potent API, usually requires a smaller percentage of active drug substance, by weight, to be formulated. On the other hand, a lower potent API, usually requires a larger percentage of the active drug substance, by weight, to be formulated into a dosage form. Thus, the physical characteristics of the API generally come more into play when developing a roller compaction formulation when the API potency is low and the physical amount of the API is greater by weight.

The API physical property characteristics, cohesive/adhesive, particle size and distribution, low density—typically less than 0.4 g/cc, and morphology, are the keys to determine if the API powder property behavior is a good or bad actor. Generally, if the API powder has poor powder properties, then more or very specific excipients are needed to enhance powder flow to assist roller compaction processing. Typical pharmaceutical excipient selections for

roller compaction formulations are cited below. Specific ingredients and concentrations vary depending on the aforementioned drug product release discussion. Useful formulation starting points are noted below.

- Filler/diluents/binders—microcrystalline cellulose, mannitols, corn starch, povidone, tribasic calcium phosphate, lactose, HPC, HPMC ~10% to 90%.
- Disintegrants—sodium starch glycolate, (all; half intra and half extra), ~ 1% to 1.5%.
- Lubricants—magnesium stearate, PEGs, SSF, stearic acid, calcium stearate ~1%.
- Glidants—colloidal silicon dioxide ~0.5%.
- Surfactant—sodium lauryl sulfate ~ less than 0.5%.

Compaction Formulation Technology Needs

2001 survey findings concluded that companies manufactured less than 25% of their products worldwide using roller compaction. More pharmaceutical innovator companies used roller compaction for a larger percentage of their product line than other industry segments, Figure 9. It was speculated by the authors that the innovator industry may be more likely to prefer a granulation of one type versus another because of long lead times from discovery to market and to minimize the risk of the uncertainty of API chemical properties (21).

In the same survey, Table 1 illustrates the preferences for different polymer types used to roller compact immediate-release formulations. Pharmaceutical formulators in general appeared to have a similar formulating mindset when it came to developing solid dosage forms. The authors speculated that roller compaction, in the mind of a pharmaceutical

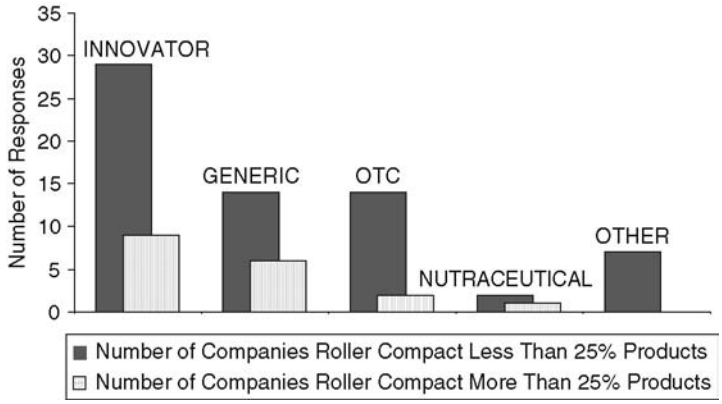


Figure 9 Companies' approximate percentage of products roller compacted worldwide. *Source*: From Ref. 21.

Table 1 Preferences for Polymer for Immediate-Release Roller Compaction Formulations

Polymer	Responses	Average rating
Microcrystalline cellulose, PH 101 or PH 102, USP	48	3.8
Polyvinylpyrrolidone, USP	41	3.7
Hydroxypropyl methylcellulose, NF	40	3.4
Starch, USP	45	3.2
Methylcellulose, USP	38	2.8
Hydroxypropyl cellulose, NF	36	2.8
Methacrylic acid copolymer, A, B, or C	20	2.3
Ammonio methacrylate copolymer, A or B	29	1.7
Wax	28	1.5
Others	8	1.9

5, high preference; 1, low preference.
Source: From Ref. 21.

Table 2 Preferences for Polymer for Extended-Release Roller Compaction Formulations

Polymer	Responses	Average rating
Hydroxypropyl methylcellulose, NF	46	4.5
Hydroxypropyl cellulose, NF	37	3.6
Ethylcellulose, USP	37	3.5
Methylcellulose, USP	38	3.0
Ammonio methacrylate copolymer, A or B	29	2.5
Methacrylic acid copolymer, A, B, or C	32	2.5
Aminoalkyl methacrylate copolymer, E	29	2.1
Others	9	2.3
Wax	27	2.1

5, high preference; 1, low preference.
Source: From Ref. 21.

Table 3 Excipient Class Preferences

Excipient class	Responses	Average rating
Binder	54	3.6
Disintegrant	51	3.2
Lubricant	53	3.0
Filler	53	2.9
Glidant	52	2.5

5, high preference; 1, low preference.
Source: From Ref. 21.

formulator, is a combination of a direct compression choice for a polymer (e.g., microcrystalline celluloses) and a granulation choice for a polymer (e.g., the wet granulation polymers chosen by formulators such as polyvinylpyrrolidone, hydroxypropyl methylcellulose, and starch) (21).

When developing an immediate-release tablet formulation, the tablet must release the drug quickly while maintaining good physical characteristics. To achieve fast drug dissolution properties, it is useful to incorporate a portion of the disintegrant excipient within the powder mix prior to roller compaction. A remaining portion of the disintegrant should be added extragranular to the final blend just before the lubricant addition. This intra- and extragranular disintegrant placement is quite important to maintain minimal tablet disintegration and fast dissolution times. This concept is described in U.S. patent 4609695 (Franz and Guyer). They described tablet disintegration and drug release of ibuprofen from a high dose drug formulation was enhanced through the use of intra- and extragranular placement of a disintegrant excipient.

Table 2 shows that hydroxypropyl methylcellulose is the preferred polymer for use in extended-release roller compaction formulations. Hydroxypropyl cellulose and ethylcellulose polymers are also significantly preferred, followed by methylcellulose and various methacrylate polymers. The polymer preferences for extended-release formulations, using roller compaction technology, appeared to reflect polymer usage that is associated with matrix extended-release systems.

Survey information ranked compaction formulations containing API and lubricant only versus compacting formulations containing API with small amounts of lubricant and excipients. The combination of API + lubricant + excipients was more preferred in formulations. This process preference may be due, in part, to improved efficiencies of technical operations, from minimizing subsequent processing and less cumbersome handling steps downstream prior to encapsulating and or tableting.

Table 3 indicates that the binder class is slightly more likely to be used than other excipient classes when a roller compaction formulation is developed. The preferred usage of the other excipient classes is about the same.

Table 4 Excipient Filler Preferences

Excipient filler	Responses	Average rating
Microcrystalline cellulose, PH 101	54	4.0
Microcrystalline cellulose, PH 102	53	3.6
Lactose	48	3.2
Lactose, anhydrous	43	3.1
Dibasic calcium phosphate	48	2.5
Starch	52	2.4
Others	6	2.7

5, high preference; 1, low preference.
Source: From Ref. 21.

Table 5 Disintegrant Preferences

Disintegrant	Responses	Average rating
Croscarmellose sodium	36	3.7
Sodium starch glycolate	44	3.4
Pregelatinized starch 1500	34	3.3
Crospovidone	30	2.8
Starch	37	2.5
Other	6	1.3

5, high preference; 1, low preference.
Source: From Ref. 21.

Table 4 shows that the most preferred excipient filler for pharmaceutical roller compaction is the microcrystalline celluloses followed by lactoses. Microcrystalline celluloses and lactoses are popular in solid-dose formulations because of their compactibility, compatibility, functionality, uniformity of supply, and their long withstanding use in the industry. A comment about the "other" excipient category is warranted; a number of survey write-ins included sucrose as an excipient filler of choice.

Regarding the use of disintegrants, Table 5 shows the most highly rated disintegrants used in roller compaction, croscarmellose sodium and sodium starch glycolate.

It is useful to incorporate half of the total lubricant in the powder mix before the roller compaction step and incorporate the remaining portion of the lubricant post granulation.

The idea is to have sufficient lubricity in the powder mix to adequately lubricate the surfaces of the roller compaction equipment (interior of the powder feed area, feed screws, and roll surfaces) and secondly, also for the tablet press tooling and dies. Figure 10 describes lubricant usage levels in roller-compacted formulations. Seventy-five percent of the roller-compacted formulations containing magnesium stearate are formulated at 0.5% to 1.0% level. Stearic acid, hydrogenated vegetable oil, and talc are formulated primarily at 1% or higher levels in roller compaction formulations. Sodium stearyl fumarate, at this time, appears to be used sparingly in roller compaction formulations (21).

Sheskey et al. conducted studies demonstrating the enhancement of material flow properties of niacinamide controlled-release matrix. The excipients used consisted of methylcellulose, hydroxypropyl methylcellulose, and magnesium stearate. Using roller compaction technology, the authors successfully demonstrated the processing of high molecular weight polymers with niacinamide into free-flowing granules that were compressed into controlled-release tablets (22).

They also roller-compacted powder blends at low, intermediate, and high pressure levels and selectively sized the compacts. The granule portions were evaluated for the following process attributes: recompactibility, content uniformity, and tablet characteristics. Evaluations of the selective granule portions indicated that the smaller granules were produced at lower compaction pressures and the larger granules were produced at higher compaction pressures. The relationship is explained by higher compactor pressures producing a stronger, more resilient powder mass,

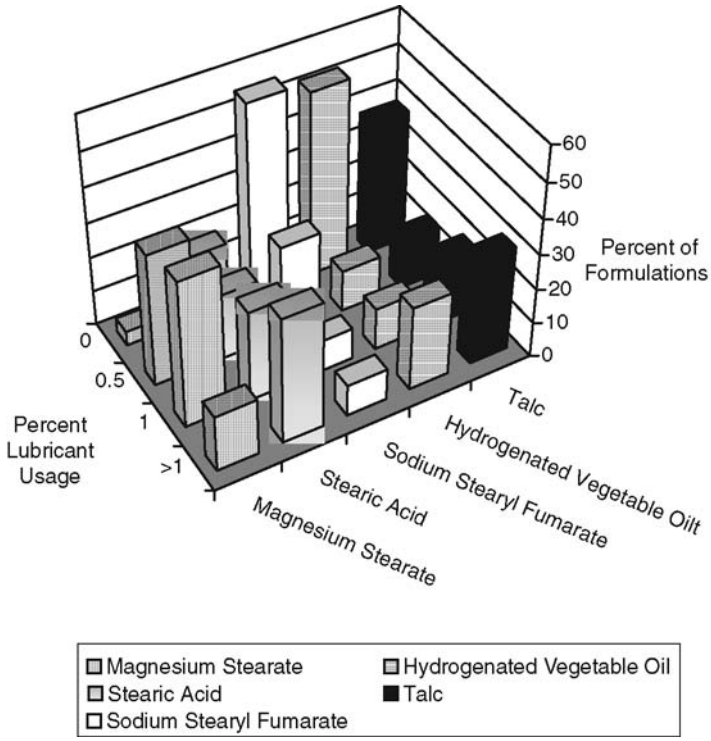


Figure 10 Lubricant usage in roller-compacted formulations. *Source*: From Ref. 21.

which, when subsequently milled, resists sizing. This, in turn, produced a coarser particle size distribution. Compressed tablets from the three different pressure compacts demonstrated consistently higher hardness values and lower friability results from granulations compacted at the lowest compaction pressures. These findings parallel other authors' results (23,24) pertaining to reworking compressed tablets into sized granules that were then recompressed into tablets.

Sheskey et al. (24) also found that extensive recycling of coarse and fine material with the original feedstock produced poor tablet content uniformity results. The subsequent tablet compression produced lower tablet hardness values than were observed in the original tablet compression. This situation is explained by the production of robust granules that exhibit increasing resistance to deformation during recompression. This effect is known as the work hardening principle. Sheskey and team found no apparent relationship between the compaction pressure level applied to the polymers in the matrix system and the resultant drug tablet dissolution. Also, no relationship was observed between the tablet hardness levels and the drug tablet dissolution. In their studies, they observed that the granulation densities increased because of roller compaction. The interested reader will find more information per the reference.

INSTRUMENTED ROLLER COMPACTOR TECHNOLOGY FOR PRODUCT DEVELOPMENT, DESIGN OF EXPERIMENTS, AND SCALE-UP

Some time ago in the mid-1990s, I mentioned, "There is no such thing as a standard approach to solve compactor scale-up or compactor equipment changes in the pharmaceutical production process" (2). At that time, it appeared that was very much the case history of roller compaction scale-up in the pharmaceutical industry. This understanding was based on the fact that there were no pharmaceutical industrial journal articles published at the time on the subject. On the other hand, it was also true that considerations, approaches, and examples presented in that chapter were experienced by others and were not all-inclusive.

The *Pharmaceutical Process Scale-Up, Second Edition*, roller compaction scale-up chapter, published in 2006 offers specific compaction process scale-up and equipment technology transfer concepts experienced by the author and others that were published since 1997. To those who contributed and are advancing roller compaction technology, it is gratifying to see a paradigm shift and an expansion to dry granulation roller compaction technology in our industry. Additionally, with process analytical technology tools, significant opportunities to standardize roller compaction design of experiments and scale-up exist. It is my view that process analytical technology tools will drive roller compaction scale-up for years to come.

Factors of scaling-up a pharmaceutical compaction process or equipment technology transfer involve a number of issues and technologies. Numerous considerations go beyond the specific process and technology that evolve from the pilot plant to the manufacturing technical operations center. Most of these concerns are centered on the plant's current operations, and its previous use or manufacture of dry granulations using roller compaction technology. See Ref. 21, which cites comparative study summary.

Some scale-up factors that go beyond specific formulation technical aspects follow: What type of equipment manufacturer support is expected? What is the reputation and reliability of the equipment manufacturer in the country where the start-up will occur? What is the equipment manufacturer's customer service record worldwide? How many days will it take to replace a broken or worn out part? Does the equipment manufacturer carry a reliable stock parts inventory? *Note*: A survey evaluated industrial practices and preferences that addressed some of these questions (21).

Professionals in pharmaceutical manufacturing science understand that no single written journal article could hope to provide universal guidance on roller compaction scale-up. On the one hand, the best way to solve these types of challenges is to attack them systematically. This usually can be achieved through appropriate process qualifications and validation efforts: trial and error approaches before start-up, knowledge of equipment processing capabilities and limitations, and understanding raw materials' variability. On the other hand, process analytical technology tools and approaches will offer different pathways to attack the scale-up and the validation process (25).

Discussion about roller compaction solid dosage form scale-up, specifically here, does not imply compliance with suggested scale-up and postapproval change (SUPAC) guidelines. The described approaches do not necessarily provide ideas/recommendations that meet tests and filing requirements for changes in manufacturing processes and equipment. Scale-up guidance for immediate-release solid dosage forms and postapproval changes have been published. Readers are suggested to familiarize themselves with the referenced material (26).

FDA CDER has issued significant new changes for good manufacturing practices for process validation when advanced pharmaceutical science and engineering principles and manufacturing control technologies provide a high level of process understanding and control capability (27,28). The Agency, for example, indicates that manufacturers using such procedures and controls may not necessarily have to manufacture multiple conformance batches to complete process validation (27). One can readily see how the times are changing and how I believe roller compaction technology for the pharmaceutical industry, because of its simplicity, is primed for additional manufacturing technology advancement.

Technology and Physics Understanding

The compacted ribbon characteristics emerging from a roller compactor depend on the *force-time* profile imparted to the entering powder by the rollers. A central key for drug product development and scale-up is, therefore, to quantitatively characterize the loading profile across the roller width that the powder is subjected to during the compaction process.

Knowing the force-time profile, the compact density can be determined and modeled in real time. Generating real-time compaction density provides not only a compact process footprint but the compactor vendor can initiate control with electronic signal to equilibrate compaction density, for example, adjusting feed screw speed, roll gap, and roll pressure. Also, important is that the sized-compacted granulate can be modeled from the force–time profile relationship to understand and predict the granulometry and particle size distribution.

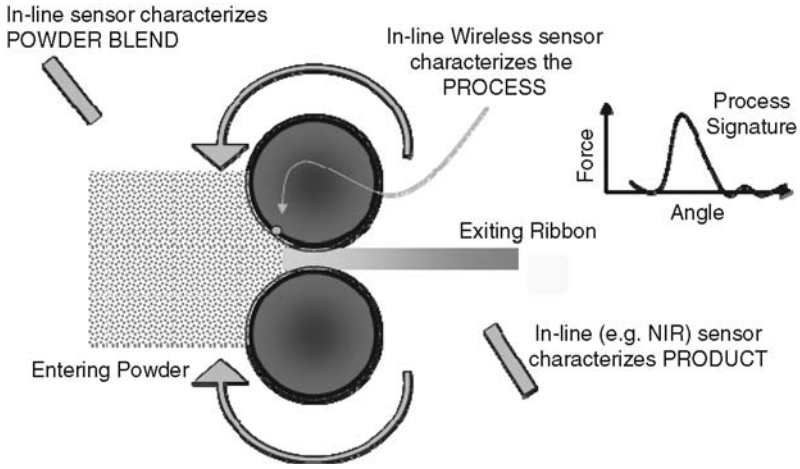


Figure 11 Schematic of roller compaction in-line sensor approach. Powder blend (input) and compacted ribbon properties (output) are monitored, as well as the force–time profile (process). This approach allows for control and optimization of the final product as a function of process and input materials. Details of the roll sensor technology are shown in Figure 12.

This temporal loading profile is a signature of the process that can be directly linked to the characteristics of the ribbon from the fed powder blend, as schematically described in Figure 11.

Three elements, powder blend, ribbon property, and final blend characterizations, are necessary to understand the process characterization. These sources of information are necessary to build an experimental database, which contains the information for the development of physically based models that link the properties of the input (powder blend) with the compactor output (compact ribbon and sized granules).

This type of model is desired for designing products attendant to the powder and process characteristic, and thus, central to the quality by design initiative. These models are also necessary for developing robust scaling-up guidelines using numerical simulations that account for the material characteristics as well as boundary and initial conditions, such as techniques that include discrete particle dynamics and finite element method. The predictive capabilities of these numerical techniques rest on the accuracy of the constitutive relations for the evolving properties, in this case, the roller-compacted material, which starts as a loose powder and is transformed into solid-ribbon compact and is then converted back to loose powder.

The instrumented roll provides a new dimension in the translation from R&D to scale-up and routine manufacturing, which is a model-independent approach. The central idea is to instrumentize two different rolls, one typically for R&D environments (small roll) and one for manufacturing environments (large roll). The strategy is that once a successful roller compaction process is achieved in the R&D lab, the load-time signature is recorded, as well as the sized granulometry measured. When in the manufacturing site, the conditions of the production compactor are tuned to produce the same load-time signature using the larger instrumented roll as the one obtained from the R&D compactor. From an operational point, there is no need for constant use of the instrumented roll in the laboratory or in the manufacturing plant after the specific process has been validated by this technology. The sensor-roll will be used only to develop and record the load-time profile during the design of experiments. Similarly, the sensor-roll on the production compactor will be used only during scale-up and validation. Process parameters are stored in the compactor's control memory for real-time process monitoring and control.

Figure 12 shows pictorially the development of an instrumented roll with small inserted load cells across the roll face that measure $F = P \times A$ on the compact in real time. Real-time information is generated by this device that enables the development of the design of

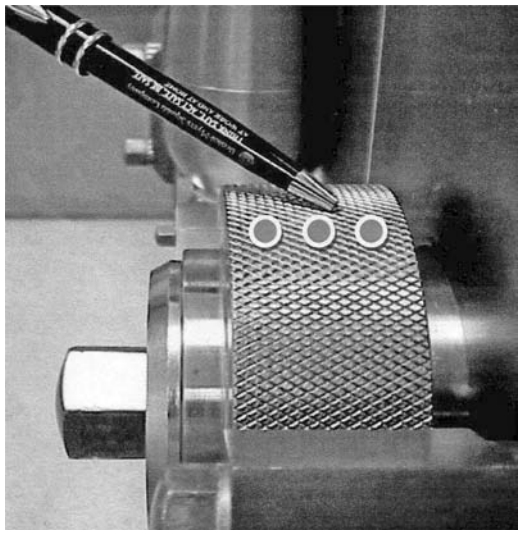


Figure 12 Using embedded load cells (red dots) the temporal force profile across the roll is measured in real time on an Alexanderwerk WP120 roll. Wireless technology transports signals to a control monitor where statistical analysis determines compact density in real time.

experiments, modeling, and scale-up strategies to larger roll compactors (with more of the same sensors on the larger roll).

Wireless communication instrumented from the roll facilitates the sensor information to software that statistically interprets the data real time. The scale-up and compaction control through real-time statistical feedback goes to a monitor where the information is processed, displayed, and stored.

This applied instrumented roll approach goes to the heart of *process analytical technology*, by providing real-time data to expand the processing knowledge, to shorten the drug product development time, to shorten drug product scale-up time, to reduce raw material loses, and to reduce drug product manufacturing risks due to processing failures that originate from non-controlled processes.

The author and an engineering firm are currently implementing this technology on two production scale drug product R&D compactors. A paper is planned later in the year.

REFERENCES

1. Miller RW. Roller compaction technology. In: Parikh DM, ed. Handbook of Pharmaceutical Granulation Technology. Vol 154. 2nd ed. Boca Raton: Taylor Francis Group, 2005:159–190.
2. Miller RW. Roller compaction technology. In: Parikh DM, ed. Handbook of Pharmaceutical Granulation Technology. Vol 81. 1st ed. New York: Marcel Dekker, Inc., 1997:99–150.
3. Miller RW. Roller Compaction Technology for the Pharmaceutical Industry. Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker, Inc., 2003 (online).
4. Miller RW, Morris KR, Gupta A. Roller compaction scale-up. In: Levin, M. Ed. Pharmaceutical Process Scale-Up. Vol 157. 2nd ed. Boca Raton: Taylor and Francis Group, 2006:237–266.
5. Gupta A, Peck G, Miller RW, et al. Real time NIR monitoring of content uniformity, moisture content, compact density, tensile strength and Young's modulus of roller compacted powder blends. February 2, 2005, published online Wiley InterScience, DOI 10.1002/ JPS 20375.
6. FDC Reports: the pink sheets. published online.
7. Pietsch W. Agglomeration in Industry. In: Pharmaceutical Applications. Vol 1. Weinheim: Wiley-VCH Verlag GmbH & Company, 2005.
8. Parikh D. In: Parikh DM, ed. Handbook of Pharmaceutical Granulation Technology. Vol 154. 2nd ed. Boca Raton: Taylor Francis Group, 2005:247–309.
9. Pietsch W. Roll Pressing. London: Heyden, 1976.
10. Dehont F R, Hervieu PM, Jerome E, et al. Briquetting and granulation by compaction: a new granulator-compactor. In: Wells J, Rubinstein M, eds. Pharmaceutical Technology, Tableting Technology. Vol 2 (Compression). London: Ellis Horwood, 1993:1–11.
11. Johanson JR. Rolling theory for granular solids. Trans Am Soc Mech Eng 1965; 842–848.
12. Jenike AW, Shield RT. Plastic flow of coulomb solids beyond original failure. J Appl Mech 1959; 26:599–602.

13. Miller RW. Advances in pharmaceutical roller compactor feed system designs. Pharm Technol 1994; 154–162.
14. Shileout G, Lammens R L, Kleinebudde P. Dry granulation with a roller compactor. Part 1. The function units and operational modes. Pharm Technol Eur 2000; 24–35.
15. Funakoshi Y, Asogawa T, Satake E. Use of a novel roller compactor with a concavo-convex roller pair to obtain uniform compacting pressure. Drug Dev Ind Pharm 1977; 3(6):555–573.
16. Johanson JR. Predicting limiting roll speed for briquetting presses. Proceedings of the 13th Institute for Briquetting and Agglomeration, 1975, 13:89–99.
17. Sheskey P J, Hendren J. The effects of roll compaction equipment variables, granulation technique, and HPMC polymer level on a controlled-release matrix model drug formulation. Pharm Technol 1999; 23(3):90–106.
18. Dec RT. Problems with processing of fine powders in roll press. Proceedings of the 24th Institute for Briquetting and Agglomeration, 1995, 24:199–210.
19. Pietsch W. Size enlargement by agglomeration. In: Fayed M, Otten L, eds. Handbook of Powder Science, and Technology. 2nd ed. New York: Chapman and Hall, 1997:347–364.
20. Miller RW. Using vacuum-deaeration feed system to minimize powder leakage during roll compaction. Powder Bulk Eng 1997; 11(2), 71–75.
21. Miller RW, Sheskey PJ. A survey of current industrial practices and preferences of roller compaction technology and excipients year 2000. Am Pharm Rev 2001; 4(1):24–35.
22. Sheskey PJ, Cabelka T, Robb R, et al. Use of roller compaction in preparation of controlled-release hydrophilic tablets containing methylcellulose and hydroxypropyl methylcellulose polymers. Pharm Technol 1994; 18:132–150.
23. Malkowska S, Khan K. Effect of recompression on the properties of tablets prepared by dry granulation. Drug Dev Ind Pharm 1983; 9:331–347.
24. Sheskey PJ, Cabelka T. Reworkability of sustained-release tablet formulation containing HPMC polymers. Pharm Technol 1992; 16:60–74.
25. Miller RW. Process Analytical Technologies (PAT). Part 2. Am Pharm Rev 2003; 6(2):52–61.
26. Guidance for industry immediate release solid oral dosage forms scale-up and post approval changes, SUPAC: chemistry, manufacturing, and controls in vitro dissolution testing and in vivo bioequivalence documentation. Coordinating Committee (CMC CC) of the Center for Drug Evaluation and Research at the Food and Drug Administration, November 1997.
27. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), and Office of Regulatory Affairs (ORA). PAT—a framework for innovative pharmaceutical development, manufacturing, and quality assurance. Available at: http://www.avarent.com/docs/pat.pdf.
28. wwwfdagov.com. Innovation and continuous improvement in pharmaceutical manufacturing pharmaceutical CGMPs for the 21st Century. September 29, 2004. Available at: http://www.fda.gov/cder/gmp/gmp2004GMP_final report2004.htm.

9 Wet Granulation in Low- and High-Shear Mixers

Rajeev Gokhale
Abbott, Abbott Park, Illinois, U.S.A.

Namrata R. Trivedi
Covidien, Webster Groves, Missouri, U.S.A.

INTRODUCTION

Granulation is the process of agglomeration of a dry powder mixture with a suitable binder. Enlargement of particles through the granulation process is often necessary for manufacturing solid dosage forms such as tablets. The materials, which are compressed into tablets, must possess adequate flowability, density, and compressibility. This is because the requisite amount of powder mixture required to compress each tablet is filled into the die cavity by volume and not by weight. This requirement of adequate flowability, density, and compressibility is particularly important during a high-speed tablet production where the dwell time is often short. For example, active pharmaceutical ingredients such as ibuprofen and acetaminophen, which have inadequate flow and compression properties, and a relative high dose, are often granulated prior to compression into tablets. Thus, the overall purpose of granulation is to improve the flowability and compressibility of the powder mixture. Besides improving the flowability and compressibility, the granulation process can also

- ensure uniform distribution of the drug in the powder mixture,
- narrow the particle size distribution of the powder mixture,
- densify the powder mixture and reduce dust, and
- improve the dissolution characteristics of the finished tablets.

The three commonly used granulation methods include wet granulation, dry granulation, and hot-melt granulation. These methods are categorized on the basis of the type of binder and the process employed during granulation. The equipment that is used during the granulation processes is classified into the following three major categories on the basis of the shearing strength it generates on the powder bed during the granulation process:

- Low-shear granulators
- Medium-shear granulators, for example, fluid-bed granulators with a rotogranulator attachment
- High-shear granulators

This chapter discusses in detail the equipment, process variables, formulation requirements, granulation end point determination, and scale-up considerations of wet granulation using both low- and high-shear granulation processes.

TYPES OF GRANULATORS

Types of Low-Shear Granulators

The low-shear granulators generate lesser shear than medium- or high-shear granulators, because of either agitator speed, sweep volume, or bed pressures on the powder bed. Examples of low-shear granulators include

1. ribbon and paddle blenders,
2. planetary mixer granulators,

3. orbiting screw granulators,
4. Sigma blade mixers, and
5. rotating-shape mixer/granulators.

Ribbon and Paddle Blenders

The ribbon blender consists of ribbon-shaped blades, which are attached to a drive shaft. The blades traverse the entire length of a U-shaped horizontal trough. It is top-loading equipment with a bottom discharge port. The ribbon blender is generally used for mixing either solids or liquids and solids. After loading the mixer with the desired quantities of powder, the top of the mixer is covered during mixing to prevent generation of dust during the dry-mixing process. The cover also prevents evaporation of the granulating solution or liquid during the wet granulation process. Despite being a good blender, one of the main disadvantages of the equipment is the dead spots at the end and in the corners of the mixer where some material may remain unmixed. To prevent the unmixed material from being trapped in the discharge spout, it is opened several times during blending and the discharged material is returned to the mixer.

The paddle blender consists of a fabricated paddle agitator with multiple paddles positioned to move materials in opposing lateral directions and radially through a U-shaped horizontal trough.

It is designed to scoop, lift, and tumble materials in a gentle and thorough mixing action. The material travels in a three-dimensional "Figure 8" pattern while being mixed. The most aggressive mixing takes place in the middle of "Figure 8," where the material is constantly being pulled from the ends of the mixer. This unique paddle design is ideal for mixing solids or liquids of various particle sizes, density, and viscosity. The gentle scooping action is ideal for blending fragile materials. Paddle blenders can be operated with as little as 20% of the rated capacity, thus allowing flexibility of batch sizes. Unlike ribbons, the paddles require less torque during mixing and have less sticking problems. Hence, the paddle blenders can handle wetter pastes. Moreover, the paddle style agitators allow easier access for cleaning between batches.

Planetary Mixers

The planetary mixer consists of a mixing bowl, a mixer blade attached to a mixing shaft. The mixing shaft is driven by a planetary gear train (Fig. 1). The mixer blade is rotated when the small planetary gear, which is attached to the mixing blade, is driven in the direction around the ring gear. Hence, in this mixer, both the mixing blade shaft and the mixing blade rotate

Figure 1 Planetary mixer MP2150. *Source*: Courtesy of GEA.

simultaneously. The planetary mixer can be operated at a variable speed. Generally, the slower speed is used to mix powders, and faster speeds are used for the kneading action required during the wet granulation process. The mixing bowl can be removed from the mixer either by lowering the mixing bowl underneath the blade or raising the blade above the mixing bowl. One of the advantages of the planetary mixers is that there are no dead spaces in the mixing bowl. However, one of the disadvantages is the limited batch size that can be prepared at one time. Hence, often, several sublots are prepared using this equipment and the final blend of the sublots is done in a large tumbling mixer.

There are several commercial manufacturers of the planetary mixers, and hence these mixers are often called by their manufacturer's name as Hobart mixer, kitchen aide mixer, Pony mixer, and AMF Glen granulators. All of these mixers have the same basic makeup, which includes: (a) planetary motion, (b) removable bowl, and (c) top-drive agitators.

Conical Screw Mixer Granulators

The conical screw mixer granulator is also called as an orbiting screw mixer granulator. Like the ribbon, paddle, and the planetary mixers, the orbiting screw granulator is also a stationary shell mixer. In this blender, the screw shaft rotates around the periphery of the cone and the screws turn in such a way that the pitch transfers the material from the bottom of the mixer to the top. The orbiting screw granulator is a very gentle granulator mixer.

The equipment can be adapted for wet granulation by fitting a nozzle for adding liquids through the center of the agitator. Also, the vessel can be jacketed for providing both heating and cooling. Drying can also be facilitated in the blender by placing a sintered metal plate that allows entry of compressed air through the skin of the mixer and exhaustion of the moisture from the wet granules. All of these added features, along with a chopper along the sidewall, allow this blender to be used as an effective granulator for powders, or for mixing slurries, suspensions, and pastes (Fig. 2).

Sigma Blade Mixer Granulators

The σ blade mixer is commonly used in the baking industry for dough mixing because of its kneading action created by the intermeshing blades. The mixer can be used for either blending solids, or liquids and solids. The mixer has a minimum of dead space in the bowl during mixing because of the close tolerances between the sidewalls and the bottom of the mixer shell. It is top-loading equipment and the granulated material is emptied by tilting the entire shell via rack and pinion drive assembly.

Rotating-Shape Mixer Granulators

In these types of mixer granulators, mixing of materials and granulation occurs because of rotation of the entire mixer shell or body. These vessels of the granulators are usually some

Figure 2 Conical (orbiting) screw mixer.

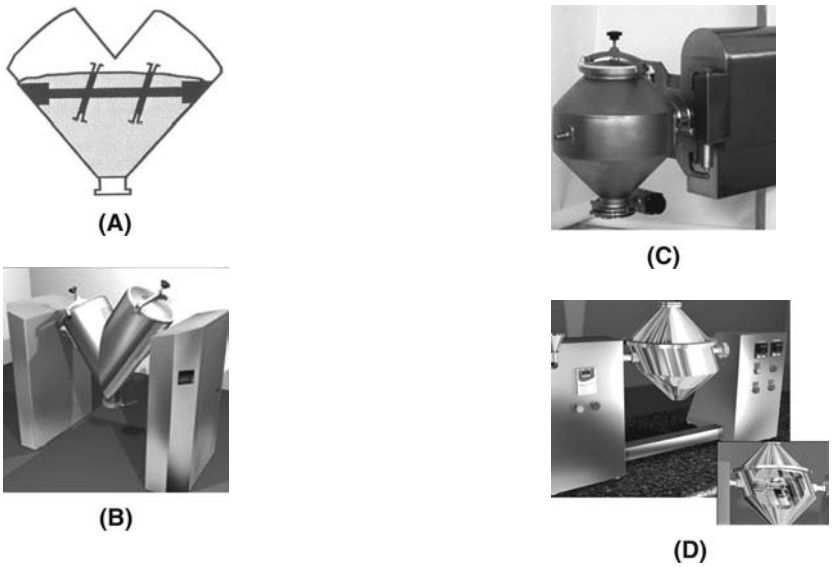


Figure 3 (**A**) V-blender with intesifier bar, (**B**) slant V-blender (cross flow), (**C**) double-cone mixer granultor, and (**D**) slant double-cone mixer granulator *Source*: Courtesy of Patterson Kelly Corporation and Gemco.

derivation of a cylinder, for example, a double cone or a V shape. The peripheral rotation speed of the vessel generally ranges from 72.2 to 106.7 m/min (250–350 ft/min), whereas, the rotation speed in rpm changes as vessel size grows (1). For example, a laboratory model may rotate at 25 to 30 rpm, whereas a larger production model may rotate at 4 to 8 rpm. The peripheral speed remains constant to maintain a scale-up relationship among vessel sizes (1) Examples of rotating-shape granulators include

a. V-shell mixer granulator (Fig. 3A),
b. slant V-blender (cross flow) (Fig. 3B),
c. double-cone mixer granulator (Fig. 3C), and
d. slant double-cone mixer granulator (Fig. 3D).

The slant-cone design eliminates the dead space that may occur in a double-cone vessel. The advantages of using the V-shell, double-cone, and the slant V-blender and double-cone mixer granulators are as follows:

a. Minimal shear and attrition during mixing.
b. Equipment is available in large capacity, thus allowing laboratory-scale formulation batches to be scaled up to production batches.
c. The materials can be easily loaded and discharged from the granulators.
d. The granulators are easy to clean.

To facilitate wet granulation after mixing of the powders in the vessel, a second high-speed rotating device (a bar) called an agitator or intensifier bar with disks is located on the same axis of the rotating shell. The bar is driven by an additional, larger motor that runs independently of the shell motor, and imparts substantially more energy to the system than that delivered by the rotating shell. The agitator or intensifier bar may also serve as a delivery device through the slits, for granulating fluid, such as binder solution or a binder activating liquid, during the granulation process. Alternatively, a separate liquid dispensing system can be installed in the vessel as well. The agitator or intensifier bar is either supported at both ends or is cantilevered, with support only at one end.

The vessel of the granulator may be jacketed for heating and cooling, if there is a need during the granulation process. In addition, the granulators may also have vacuum capabilities, thus making them ideal candidates for a single-pot processor for mixing, granulating, and drying in the same vessel.

TYPES OF HIGH-SHEAR MIXER GRANULATORS

Most of the conventionally used high-shear granulators consist of a mixing bowl, a three-bladed impeller, and an auxiliary chopper. The shape of the mixing bowl can be cylindrical or conical. The mixing bowl can be jacketed for heating or cooling the contents in the bowl, by circulating hot or cool liquid or steam through the jacket. An impeller is employed to mix the dry powder and to spread the granulating fluid. The impeller of the high-shear mixer granulator normally rotates at a speed ranging from 100 to 500 rpm. The function of the chopper is to break down the wet lumps into granules. The rotation speed of the chopper ranges from 1000 to 3000 rpm. The high-shear granulator could be termed as either vertical or horizontal, on the basis of the orientation and the position of the impeller. The vertical high-shear granulator could be either a top- or bottom-driven unit.

Figure 4 shows the schematic view of a top-driven vertical high-shear granulator, ULTIMAGRAL™/ULTIMAPRO™. Figure 5 shows GMX top-drive high-shear granulation/mixing system.

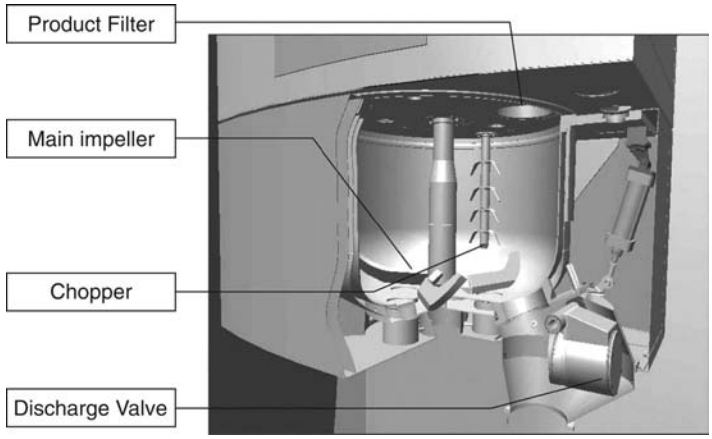


Figure 4 Schematic view of top-driven vertical high-shear granulator. *Source*: Courtesy of GEA (ULTIMAGRAL™/ULTIMAPRO™).

Figure 5 GMX 600 top-drive high-shear granulation/mixing system. *Source*: Courtesy of Vector Corporation.

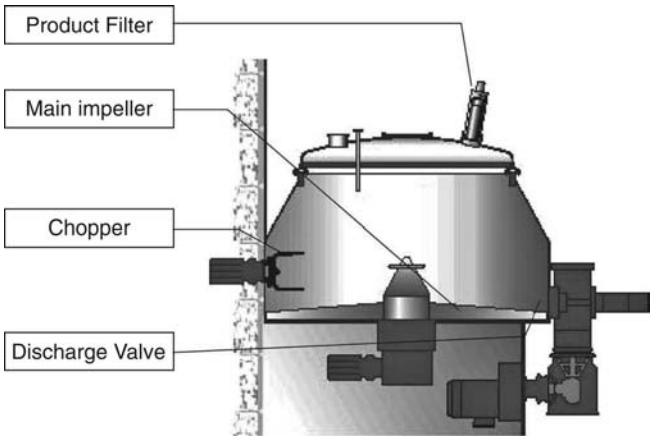


Figure 6 Schematic view of a bottom-driven vertical high-shear granulator with horizontal chopper shaft. *Source*: Courtesy of GEA.

Figure 7 (**A**) Glatt high-shear mixer VG 1200 with cylindrical working vessel for nonsticky products. (**B**) Glatt high-shear mixer VG 100 with conical working vessel for sticky products. *Source*: Courtesy of Glatt GmbH Binzen.

Figure 6 shows the schematic view of a bottom-driven vertical high-shear granulator, with a horizontal chopper shaft (PMA through-the-wall design). Figure 7A and B shows cylindrical and conical working vessels of bottom-driven vertical high-shear granulators. The cylindrical working vessel is generally used for nonsticky products, whereas the conical working vessel is used for sticky products. Figure 8 (A–C) shows photographs of impellers and choppers of high-shear granulators. Figure 9 shows the photograph of horizontal high shear mixer granulator.

Over the years, tray drying was employed to dry wet-granulated product, but now the preferred drying method for the wet granules obtained from the high-shear multiphase granulation process is fluid bed drying. However, a primary problem inherent in the two-step process of high-shear mixer granulation and fluid-bed drying is the possibility of exposure of the workers and the environment to potentially toxic materials during the transfer of the wet granules from the high-shear granulator to the fluid bed.

To avoid manual transfer of the granulation from the high-shear mixer to the fluid-bed unit, an integrated system that connects discharge from the high-shear mixer to the fluid bed is a very common set up that is used in the industry. The material handling and operator exposure problems of the multiphase granulation process can be remedied by a single-pot granulation process in which the high-shear wet granulation and drying processes are combined into a single step. This approach improves material handling, reduces the possibility of cross contamination and exposure of potentially toxic materials to the workers and the environment, and saves time since cleaning and validating a single bowl is inherently easier than tackling two or three units. Moreover, it is easy to maintain compliance with good manufacturing practices (GMP) with the single-pot granulation process.

The single-pot granulators consist of a double jacketed mixing bowl, an impeller and a chopper combined with a built-in dryer. However, the drying efficiency of single-pot dryer

(A)

(B)

(C)

Figure 8 (**A**) GRAL^{TM} top-driven impeller and chopper, (**B**) z-shaped rotor blade, and (**C**) chopper design of Glatt vertical granulator. *Source*: Courtesy of GEA and Glatt GmbH Binzen.

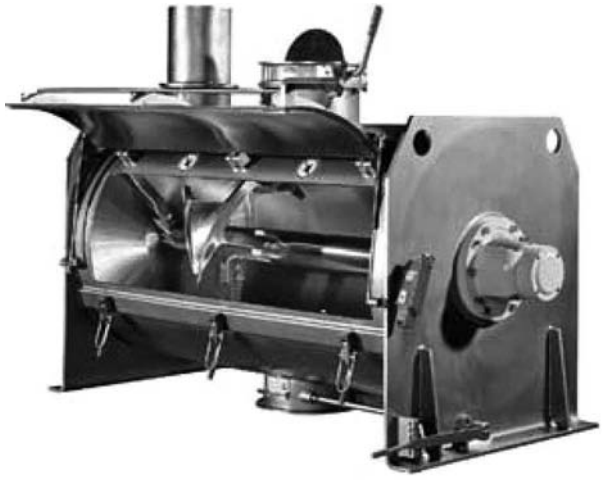


Figure 9 A horizontal high-shear mixer granulator (FKM-1200, Loedige) has been presented.

with just a heated jacket is inferior to conventional fluid-bed drying. Therefore, the options such as oscillating the bowl during drying, vacuum drying, gas-assisted vacuum drying, and microwave drying are also available to improve the drying efficiency, and to decrease the drying time. In addition, attention should also be given to particle over growth and lump formation since single-pot process does not involve any wet milling or sieving before the drying step. Figures 10 and 11 show the single-pot units manufactured by different suppliers.

The sizes of the high-shear granulators vary considerably from the small laboratory-scale models to large production-scale models, depending on the type of the model and end use.

Figure 10 Single-pot high-shear mixer granulator with vacuum drying capabilities UltimaPro^{TM} 600 swinging bowl. *Source*: Courtesy of GEA.

Figure 11 Single-pot high-shear mixer granulator VMA-70. *Source*: Courtesy of L. B. BOHLE LLC.

High-shear granulators are often equipped with granulation end point control devices, which are used to detect the end point of the granulation process. Some other features include clean-in-place (CIP) or wash-in-place (WIP) system, user-friendly modern operating panel, process monitoring through built-in camera, and NIR probe. High-shear granulators with CIP or WIP features can be cleaned easily, without removing the bowl, the impeller, and the chopper. This also helps to validate the cleaning process because of the automation. Process monitoring through NIR and built-in camera provide great promise as PAT tools for real-time process monitoring.

High-Shear Wet Granulation Process

A high-shear wet granulation process includes the following steps:

- Loading all the ingredients into the mixing bowl by either of the following methods: Manually charging the bowl, gravity feeding with manual or pneumatic valve, and vacuum feeding

- Mixing of dry ingredients such as API, other excipients, and disintegrant (optional), with an impeller and chopper at high-speed settings for a short period of time (2–5 minutes)
- Addition of a liquid binder (either binder solution or solvent) into the powder mixture, while both the impeller and the chopper are running at a low speed
- Wet massing with both the impeller and the chopper running at a high speed (this can vary depending on product)
- Wet milling and screening (most desirable)
- Removal of the resulting wet granules from the granulator bowl, and drying them using an appropriate drying technique such as fluid bed or tray drying
- Sieving the dried granules

The high-shear wet granulation process offers several advantages over the other granulation processes. These include

- short processing time,
- use of less binder solution,
- granulation of highly cohesive materials containing hydrophilic polymers, which is not achievable with low-shear granulation processes,
- greater densification and production of less friable granules than the low-shear granulated product,
- production of reproducible granules with a uniform particle size distribution,
- reduction of process dust, thus minimizing exposure to workers during the subsequent processing, and
- obtaining predictable granulation end point determination.

Despite the above advantages, the process is not immune to challenges such as

- overwet, harder granules could produce less compressible granules compared with low-shear granulation processes and
- narrow range of operating conditions.

FACTORS AFFECTING THE GRANULATION PROCESS

Factors affecting granulation process include process variable and formulation variables.

Effects of Process Variables

Process variables play a critical role in defining various granular properties of the final granules. Generally, formulations are developed in R&D scale granulators and then scaled up to production-scale granulators. Significant differences exist between laboratory and production models of granulators in terms of design, shape, size, speed, and geometry of the granulator bowl, impellers, and choppers. Even though the composition of the formulation is similar, the physical properties of the obtained granules could be dramatically different because of the differences between granulators used at the development scale and the production scale. These differences could significantly affect the physical properties of the granules, which in turn could affect the properties and performance of the final tablets. The understanding of various process factors is the key to successful tech transfer in product development process.

The following example illustrates how varying the aforementioned process variables influence the properties of the granules obtained using a high-shear wet granulation process. Processing variables, such as impeller speed, granulating solution addition rate, total amount of water added in the granulation step, wet massing time, etc., were evaluated using a Plackett-Burman experimental design in a study by Badawy et al. (2). The results showed that granule compressibility of the lactose-based formulation was extremely sensitive to the processing conditions. The granule particle size was increased by increasing the amount of added water, high impeller speed, and short wet massing time. The wet massing time and impeller speed

also had a significant impact on granulation compressibility. Increasing the impeller speed and/or wet massing time decreased granule porosity and fragmentation propensity, and resulted in decreased hardness of the finished tablets.

In a similar study, Wang et al. investigated the effect of impeller speed, chopper speed, and kneading time on granule properties. The authors found that process parameters also have a significant effect on MCC- and starch-based formulations (3).

Granulating Solution Addition Rate and Method

The optimal amount of liquid binder used for high-shear granulation is within a narrow range. If the optimal amount of binder solution is not used, there could be no growth or lump formation during the wet granulation process. In theory, the amount of liquid should be equal or just exceed the liquid content corresponding to 100% liquid saturation. However, some grades of lactose and dicalcium phosphate could be granulated by coalescence at liquid saturation far below 100% (4). It would be desirable to predict the required amount of liquid binder on the basis of the formulation composition. However, this is a challenging task, since the liquid binder required for high-shear granulation depends on a number of formulation and process factors, such as physicochemical properties of the starting materials (API and excipients), type of the binder used, impeller speed, wet massing time, etc.

The mode of addition of the liquid binder can affect the characteristics of the granules (5). When water used as a binder liquid was added to the powder mixture by atomization, granules with a slightly narrower particle size distribution were obtained. The droplet size would have a large effect on particle size distribution of the granules made in low-shear granulators compared with the high-shear granulator.

Effect of Granulator Size and Design

A variety of high-shear granulators are commercially available. The orientation of the mixing chamber in the granulators is either vertical or horizontal. The vertical granulators could be bottom or top driven. Besides, the configuration differences, a significant difference exists among the mixers in terms of the shapes of the mixing bowl and impeller blades. For example, the GRAL™ (vertical top drive) mixer utilizes a curved-blade design allowing the tips of the mixing blade to reach up the sidewall of the mixing bowl, which is curved in a similar shape. On the other hand, the Diosna (vertical bottom drive) mixers have a flat blade design, parallel to the lid and bowl bottom. Only a small portion of the impeller blade directly sweeps off the sidewall of the mixing bowl. However, the conical shape of the mixing bowl, which bends back toward the center, can fold back the powder mixture into the mixing blade. These differences in impeller blades and mixing bowl design are expected to result in different flow patterns and dynamics for powder mixture in the bowl.

During the wet granulation process, the impellers impact the powder mixture and keep the mixture moving. During this process, binder solution is distributed and the powder mixture is compacted and densified. Relative swept volume, the volume swept out per second by impeller and chopper divided by the volume of the mixer, is the indicator of the work input on the powder material inside the bowl of the granulator. Changes in the granulator design could affect the relative swept volume of the granulation process, which in turn could change the degree of densification of the wet agglomerates. As a result, the optimal amount of granulating liquid and the physical properties of the resulting granules may be altered. Therefore, the design of high-shear granulators must be taken into account during the granulation process.

Schaefer et al. (6) found that there was a difference between the horizontal (Lödige M5GR) and vertical (Fielder PMAT 25 VG) granulators in terms of granule growth for dicalcium phosphate. The degree of liquid saturation required was higher for the vertical (Fielder PMAT 25 VG) granulator to obtain the same granule size. Agglomeration of dicalcium phosphate began at lower degrees of liquid saturation in the horizontal (Lödige M5GR) granulator. This could be because the rolling motion of granules in the horizontal (Lödige M5GR) granulator facilitated agglomeration, whereas the stronger mechanical forces in vertical (Fielder PMAT 25 VG) granulator promoted the breakage of granules. A similar trend was observed for lactose granulation (7).

Load of the Granulator Bowl

The effect of granulation processing parameters, fill ratios, impeller speed, chopper speed, and wet massing time on granule size distribution of placebo formulations was studied by Bock and Kraas (8). High fill ratios in the bowl resulted in an increased proportion of fines in the obtained granules. Increasing the impeller speed and the massing time increased the granule size. The speed of the chopper did not affect the granule size distribution for the formulations that were tested. The fill level of 50% to 70% of the total size of the bowl is generally used. Overloading of the bowl can influence the mixing process and result in inadequate mixing and granulation. However, under-loading of material can affect the mechanical energy applied to powder bed and result in poor granulation. The type of the granulator vessel material can also affect the granule properties. Bouwman et al. (9) investigated the effect of different kinds of granulator vessel materials such as stainless steel, glass, polymethylmethacrylate (PMMA), and polytetrafluoroethylene (PTFE), and found that the granules made in glass and stainless steel vessels were different than those made in PMMA and PTFE vessels.

Impeller/Chopper Design and Speed

The movement of the powder bed inside the granulator vessels is dependent on the design and speed of the impeller, while the purpose of the chopper is to cut lumps into smaller pieces and help to distribute the binder. The different designs of impeller and chopper can have major impact on swept volume, product temperature, material adhesion, and attrition during the granulation process. The shear effects of the impeller on the properties of granules prepared from surface-treated sericite were investigated by Oulahna et al. (10). Surface-treated sericite was granulated with an alcoholic solution of polyethylene glycol 20000 using a high-shear granulator at three different impeller speeds (100, 500, 100 rpm). The properties of the granules produced under different impeller speeds were examined in terms of porosity, friability, and binder content. The results indicated that heterogeneous granules (in terms of binder concentration) with more fine particles and a wider particle size distribution were obtained at low impeller speed (100 rpm). However, at higher impeller speeds, homogenous granules with lesser fine particles, and a narrower size distribution were observed. Moreover, the porosity of the granules decreased with increasing impeller speeds. Therefore, mechanical energy brought to the powder bed by the impeller is as important as the physicochemical characteristics of the powder-binder pair to affect the granule properties.

The effects of impeller and chopper design on granule growth of dicalcium phosphate in a laboratory high-speed mixer (Fielder PMAT 25) were investigated by Holm (11). Three different changeable impeller blades with the same surface area were constructed. The angles of inclination were kept at 30°, 40°, and 50°. The granules with low porosity were obtained at high impeller speed for the inclination angles at 40° and 50°. The effects of the impeller design with respect to the blade inclination and impeller rotation speed can be explained in terms of the volume of powder mixture swept out by the impeller. The relative swept volumes for the impellers at three different inclination angles were 2.2, 2.82, and 3.36 at 400 rpm. A high swept volume causes high densification of the agglomerates and narrow granule size distributions. Chopper size and rotation speed had no effect in this case; on the granule size distribution because the primary function of the chopper is to disturb the uniform flow pattern of the mass.

Wet Massing Time

The effects of massing time on the properties of the granules of hydrophilic polymer based controlled-release formulations were studied by Timmins et al. (12). The formulations consisted of approximately 30% sodium alginate, 10% hydroxypropyl methylcellulose (HPMC), and approximately 50% of diltiazem hydrochloride or verapamil hydrochloride. The increase in massing time resulted in an increase in the mean granule size of the formulations. This could be true for all the matrix controlled-release formulations, which contain high concentration of hydrophilic polymers.

Microcrystalline cellulose (MCC) granules were prepared by wet granulation with water in a high-shear mixer granulator. Samples of wet granules were taken at different time points after the addition of water to examine the physical characteristics of the granules using near IR

spectrometry, thermogravimetry, and isothermal water vapor adsorption. The results indicated that the degree of interaction between MCC and water increased with granulation time because of change of physical structure of MCC during the granulation process (13).

Effect of Formulation Variables

Binders Classification and Characteristics

The binders used in wet granulation process can be broadly classified into three categories: binders derived from natural, semisynthetic, or synthetic origins, and polysaccharides and sugars.

Detailed information on the types of binders can be seen in chapter 4.

Binder Efficiency

In general, various physicochemical properties of drug, binders, and other excipients can have a strong influence over the binder efficiency. Primary particle size of drug or excipients affect granule strength, porosity, and consolidation rate during granulation. Smaller particles have more contact surfaces to allow formation of stronger granules. However, binder and solvent requirements increase, when the drug particle size is small.

Increasing the solubility of drug and excipients in the solvent reduces solvent requirements and friability, and produces granules with tighter particle size distributions. If the insoluble excipients such as MCC are added to lactose, the solvent, binder requirement increases with production of larger granule size (14). In a comparative study, PVP K90, PVP K25, PVP-PVA copolymer, Methocel E5, Methocel E15 were studied. The results demonstrated that binder solution with higher surface tension such as PVP solutions produced denser granules with larger mean particle diameter (15).

The film forming properties of binders determine the strength and deformation behavior of binder matrix. The results show that while acacia and PVP form weak films, gelatin produces films with higher tensile strengths (16). PVP is a more deformable and the most versatile binder.

Dense, nonfriable granules are expected when binder spreading coefficient is high, while a nonspreading binder produces porous granules. For low polarity substrates such as griseofulvin, PVP, and starch will be optimal binders, while for polar substrates such as theophylline, acacia or HPMC will be optimal binders (17). PVP and HPMC have higher spreading coefficients over lactose, acyclovir and pentoxyphylline substrates. Increasing the solvent viscosity and granule particle size decreases the amount of binder required. When the viscosity of the binder solution is increased, excessive spreading of the binder solution becomes an issue. Increasing the viscosity of PVP and HPMC is directly related to their molecular weight.

Binder Concentration and Liquid Addition Rates

Generally, increasing the amount of binder concentration could result in production of larger granules. However, starch paste behaves differently (18). In this case, increasing the binder concentration decreased the granule particle size. However, no differences in granule friabilities were observed. As the binder concentration of PVP was increased, the crushing strength of the granules also increased (19). Starch and gelatin produced much stronger granules with lower concentrations than those produced with acacia (20). High molecular weight PVP produces larger calcium hydrogen phosphate granules than hydrolyzed gelatin and low viscosity HPMC (21). PVP produced granules of lower friability than those produced with HPMC. Gelatin produced the strongest granules. In a formulation containing a model API, Avicel®, and lactose excipients, increasing the binder concentration with low viscosity HPMC, increased the wet mass consistency. Granule friability decreased with an increase in binder concentration. An inverse relationship was observed between granule friability and the amount of water added to formulation of lower drug concentration. In another study, the effect of different types of binders such as PVP K 30, HPMC (HP-M603), maltodextrin, pregelatinized starch, low substituted hydroxypropyl cellulose (L-HPC) was studied on the hardness of placebo and paracetamol tablets (19). The placebo granules only contained lactose and Avicel. The binders were added at 2%, 6%, and 10% in the dry form and water was used as a granulating liquid. The median particle size increased between 2% and 6% binder solutions

except when L-HPC was used as binder. The granule size and the hardness increased with increasing binder concentration. PVP K30 (6%) and HP-M603 (6%) appeared to be binders of choice for paracetamol. Concentrated starch paste produces lactose granules with a narrow particle size distribution in high-shear mixers. High impeller speed and longer processing times were required to cause deaggregation and better distribution of starch paste. Dilute starch paste produce stronger granules with better compressibility and longer disintegration times. When starch is dextrimized by the addition of α-amylase, the resultant paste produces stronger granules with better flowability and tablets with shorter disintegration times, lower friability, uniform weight, and hardness. Excessive dextrimization leads to poor binding capabilities (19).

In general, granules are finer when the amount of granulation liquid is decreased. For example, the mean particle size of lactose, glucose, and mannitol granules increased when the amount of granulation solution was increased. Besides the effect on the particle size of the granules, the amount of water added can also affect content uniformity. For water-soluble drug such as ascorbic acid, the content uniformity was not affected. However, for water-insoluble drug, ethenzamide, more drug was found in smaller granules. The drug content in the smaller size granules decreased as the amount of binder was increased (22).

Lower water addition rates improve PVP-PVA copolymer distribution and lowers liquid requirements for acceptable granulation (5,23). Slower PVP solution addition rate enhances granule growth and decreases porosity of the insoluble dicalcium phosphate. The hardness of MCC granules increases with granulation time and amount of water added. The specific surface area decreases during the granulation process. Crystallite size of cellulose decreased with granulation time, and increased amount of water added. Different binders affect granulation properties on the basis of liquid saturation rates (21). The granules prepared with PVP and gelatin produce larger particle size granules and thus lower intragranular porosity. This was attributed to higher densification of DCP. PVP-PVA copolymer, Methocel E5, and Methocel E 15 binder solutions behaved equally. Thus, it was concluded that granules had higher liquid saturation with lower volume of binder solution.

Granules of MCC or silicified microcrystalline cellulose (SMMC) were prepared in high-shear mixers (24). Increasing water level affected the granule particle size, increased granule density, and flow properties of the granules, and decreased porosity and compactibility. The compactibility of both materials was similar up to a water level of 40%. Both the materials showed poor compactibility at higher levels. No difference was observed between MCC and SMCC.

Increasing the impeller speed in high-shear granulation for PVP and PVP-PVA copolymer increased the granule size and bulk and tap density. In the wet addition method, different viscosity grades of HPMC and MC in lactose-cornstarch-MCC systems increases the percentage of binder rich oversize granules (7,25–28). In dry addition method, increasing the concentration of HPC, and low viscosity HPMC, increases medium granule size. Increasing the concentration of medium and relatively high viscosity HPMC and MC is accompanied by a decrease in medium size granule fraction and increase in oversized granules.

GRANULATION END POINT DETERMINATION AND CONTROL

The granule properties are a function of the process parameters such as the impeller speed, amount of granulating fluid, and granulation time (wet massing time). Therefore, the time to end the granulation process during a high-shear granulation process becomes critical. The properties of the granules produced determine, in part, the ultimate quality and performance of the finished dosage forms. Thus, the determination of the granulation end point becomes necessary. The ultimate goal of end point determination in a granulation process is to obtain an indication of formation of granules with the desired physical properties, such as acceptable mean particle size range and porosity. The advantages of using an appropriate method to determine the granulation end point are listed below:

- Process optimization
  Evaluate raw material
  Determine optimal end point

- Batch reproducibility
  Use end point to achieve batch to batch consistency
  Document adherence to batch protocol
- Process troubleshooting
  Detect mechanical problems
  Identify mixing irregularities

Several different approaches have been explored for granulation end point determination. These approaches can be classified into two major categories: indirect measurements and direct measurements. In the indirect measurements, the electrical and mechanical parameters of the motor are monitored since the changes of these parameters are related to the changes of the consistency of the powder mixture in the wet granulation process. Faure's study (29) has confirmed that there is a close relationship between the wet mass consistency/viscosity of samples prepared in a mixer granulator and physical properties of the dry granules produced from the wet mass. The physical properties of the dry granules include granule size distribution, bulk density, friability, and flow characteristics. Variations in the formulation affect the relationships between the wet mass consistency and dry granule properties, and the net power consumption of the mixer granulator.

In the direct measurements, the physicochemical properties of the powder mixture are monitored during the wet granulation process. These properties could be mass conductivity and granule size.

Indirect Measurements

In the indirect measurement, both electrical and mechanical characteristics of the motor are monitored to control the end point. The electrical characteristics of the motor are motor current and power consumption. The mechanical characteristics of the motor are torque and tachometry.

The power consumption of the granulator motor is related to the resistance of the mass mixture to the granulator blades, which varies with the consistency of the powder mixture. Power consumption used as granulation end point control has been related to the level of liquid saturation of the moist agglomerates (30), densification of wet mass (15,31,32) and granule growth (30). Leuenberger proposed that the liquid amount required for granulation corresponds to the plateau in the power consumption record profile (33).

High-shear granulators capable of monitoring the granulation end point using power consumption are commercially available. Figure 12 (33) shows a typical power consumption profile obtained from a commercially available high-shear granulator with an end point determination. It is evident that the profile consists of five phases during the wet granulation process.

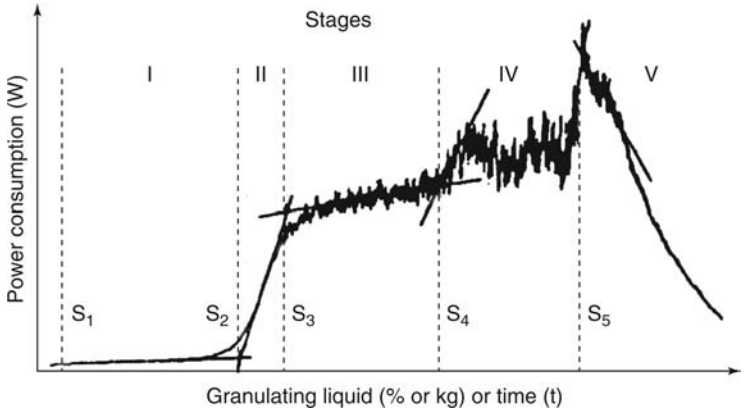


Figure 12 A typical power consumption profile obtained from a commercially available high-shear granulator. *Source*: From Ref. 33.

In phase I, the powder mixture is being moistened by adding granulation liquid. In this phase, there is no formation of liquid bridges between primary particles. Therefore, the power consumption does not increase. In phase II, liquid bridges begin to form among the primary particles; hence, this is the stage of granule formation. In this phase, the power consumption increases dramatically. In phase III, as more granulation liquid is added, the interparticular voids are filled by the granulation liquid and coarser granules are formed. The power consumption remains relatively constant in this phase. In phase IV, liquid saturation of the powder bed is reached and more coarse granules are formed. The power consumption increases. In phase V, as more granulation liquid is added, a suspension is formed, where particles are surrounded by liquid (droplet stage). The power consumption starts declining in this phase. It has been noticed that only the granules formed during phase III are usable for further dosage form development. Thus, the power consumption profile can be used to monitor the granulation process and to determine the end point.

The drawback of monitoring power consumption is that the signal is affected by a number of factors, such as product, equipment, or process variables. For example, the densification properties of the starting materials, type and amount of binder used, addition rate of binder solution, impeller speed, etc., influence the power consumption profile. Wear and tear of the granulator could also affect the power consumption signal. Thus, the power consumption profile for a granulation process is formulation and process specific.

The end point control of granulation by power consumption measurement in a 25-L high-shear mixer was investigated by Holm et al. (5). The effect of impeller design, impeller speed, liquid addition rate, type of binder, and mixing ratios between lactose and starch on the correlation between power consumption and granule growth was investigated in the liquid addition phase of the process using a fractional factorial experimental design. A linear correlation between power consumption and mean granule size was observed. The correlation was dependent on the impeller design, the impeller speed, and the type of binder. However, an end point control based on power consumption was not found to be sensitive to variations in the lactose:starch ratio. An end point control based on the peak detection method was not generally applicable, because a peak in the differentiated power consumption signal could not be identified in all the experiments.

Monitoring of power consumption was also explored for automating of wet granulation process (34). A vertical high-shear mixer (300 L Collette GRAL™) was instrumented with a control unit, which controls the continuous addition of granulating liquid in relation to the consistency of the powder mass by power consumption measurement. The instrumentation comprises an important approach for automated process control and online documentation of critical process parameters with respect to validation. Similarly, a signal analysis system with memory-programmable automatic process control for determining power consumption in a high-shear mixer was introduced by Laicher et al. (35). The signal analysis system makes it possible to perform gliding mean value calculations of the measuring signal and to evaluate the signal fluctuations. The granulation end point is determined by curve analysis. Using this system, granules with a reproducible particle size distribution are obtained from active ingredient/excipient mixtures, which either show a tendency to form lumps in the case of overwetting (paracetamol) or require a short granulation time because of low melting point (ibuprofen).

Since power consumption is related to both current and voltage of the motor, it would be logical to use motor current for end point control. However, the motors used in high-shear granulators are induction motors, which use alternating current that lags behind the voltage. Therefore, it is inappropriate to determine granulation end point by monitoring motor current or the simple combined product of current and voltage (32). The power consumption of induction motors can be expressed by the following equation:

$$\text{Power} = \sqrt{3}\,IV\cos\theta$$

where I = current, V = voltage, and θ = phase difference between current and voltage.

Alternative to power consumption is torque measurement (31). A high-shear mixer was instrumented with a new capacitive sensor, a wattmeter, and a strain-gauge torque sensor.

Placebo formulations containing dicalcium phosphate, MCC 101, MCC 102, and lactose were granulated in the high-shear granulator. A similar graph (profile of torque measurement or power consumption) of the granulation process was obtained for power consumption and torque measurement.

In another study (32), a high-shear vertical mixer/granulator was instrumented to monitor power consumption, direct torque (signal from impeller shaft) and reactive torque (signal from the motor). Of the three methods used, direct torque generated the most descriptive profile for the granulation process. Granules produced for the test formulations based on the end points determined using direct torque measurement resulted in tablets with acceptable hardness. Measurement of direct torque also could detail the granulation process of an overwetted formulation.

Torque profiles of granulation of MCC or lactose in a high-shear granulator with various operating conditions were studied by Kornchankul et al. (36). The torque measurement for each batch of granules obtained was correlated with the corresponding tablet characteristics. The scatter plots of tablet hardness indicated that hardness for tablets prepared with MCC granules was higher than 7 kP as long as end torque was less than 100 lb-in, granulation rate was less than 0.4 lb-in/sec, and granulation extent was less than 13,000 lb-in/sec.

The relevance of end point determination based on torque measurement in controlling performance characteristics of compressed tablets such as hardness, friability, disintegration time, and dissolution time was determined by Achanta et al. (37). The measurement of torque was used to determine the end point of the granulation process in a high-shear granulator. With increasing end point levels, tablets compressed with corresponding granules were found to be harder.

Direct Measurements

During high-shear wet granulation process, the binder liquid is dispersed in the powder mixture. At this point, the wetted powder becomes agglomerated and densified. Thus, the physical properties (particle size, density, consistency) of the powder mixture change with time during the granulation process. This change in the properties of the powder mixture can be used as an indication of the end point of the granulation process.

Consistency Measurement Using a Probe

One approach to determine the granulation end point is based on monitoring the change of the consistency or strength of the wet mass during granulation process. This approach was first developed by the Boots Company for Diosna high-shear mixers (4). The Diosna-Boots probe is designed to detect changes in momentum of granules in a constant velocity region of the mass with use of strain gauges instrumented on the probe. To avoid bias due to random events (e.g., large lumps due to inhomogeneous solution distribution), signal pulse heights, sampling times, and pulse density are all considered to attain the final signal. The signal is normalized over a calibrated range of forces 0% to 100%. The criterion for end point indication is that the signal obtained during granulation process must be greater than the preset value. When properly developed and calibrated for a given high-shear granulator, the probe can be successfully used to determine a repeatable granulation end point (similar particle size and density). However, the signal obtained from the probe is granulator and formulation dependent.

However, this approach is no longer used in the industry because of its intrusive approach.

Acoustic Emission

Acoustic emission monitoring detects and analyzes the sound produced by a process or system. During the wet granulation process, particle size, flow properties of the powder mixture, and degree of powder densification change with time because of the addition of binder and formation of agglomerates. The change of physical properties of the powder mixture could affect the acoustic emission signal. Thus, this technique can be used to map the granulation process and determine its end point. The technique is noninvasive, sensitive and relatively inexpensive.

The acoustic emissions during the wet granulation of a model formulation containing lactose and MCC were monitored using acoustic emission sensors (38). The sensors were attached to the outside of the high-shear mixer bowl. Undergranulated to overgranulated granules were prepared by varying the quantity of the binder solution. Average signal level increased with increasing the amount of binder solution added and wet massing time. A strong correlation between the acoustic emissions and the physical properties of the granules at the end of the granulation process was demonstrated. This technique was capable of monitoring changes in physical properties of powder material during granulation (particle size, flow properties, and compression properties).

Image Analysis

In the direct measurement techniques, one of the successful methods is monitoring the granulation processing on the basis of the particle size of the granules. A novel system to continuously monitor granule growth in a high-shear granulation has been developed by Watano et al. (39). The system consists of an image processing system and a particle image probe comprising a CCD camera, lighting unit, and air purge system. High-shear granulation was conducted using pharmaceutical powders and granule size, and product's yield of various size ranges were continuously measured by the developed system. Sieve analysis of the granules sampled out during the granulation was simultaneously conducted, and the data was compared with that of the in-line image processing system. A close relationship was found between both data, proving that the system could monitor the granule growth accurately and continuously throughout. Another approach to characterize the real-time growth of particles by measuring back scattered laser beams is offered by Lasentec as Focused Beam Reflectance Measurement (FBRM®) and Particle Vision Measurement (PVM®), which can be added to the existing equipment.

Such imaging process system was further developed to automatically control the wet granulation process by Watano et al. (40). Besides the image probe, a fuzzy control system using a linguistic algorithm employing if-then rules with a process lag element was developed to control granule growth accurately. The system consisted of an image processing and a fuzzy control system. An image probe continuously monitored granule images through the sidewall of the vessel. The images were digitized by the image processing system and granule median diameter and shape factor were calculated automatically. The difference between desired and measured granule diameters was used as input for fuzzy reasoning. The result of fuzzy reasoning was used to control the output power of liquid feed pump. The system could control granule growth with high accuracy, regardless of changes in operating conditions.

NIR Spectroscopy

In recent years more and more emphasis has been placed on real-time process monitoring as a part of the FDA's PAT initiative. The push for the in-line process monitoring and control has led the industry toward the nonconventional techniques such as NIR spectroscopy. The granulation power consumption and torque measurement have been conventionally used tools for process monitoring and end point determination. However, NIR spectroscopy, a PAT tool is gaining a lot of interest as *in situ* processing monitoring. NIR spectroscopy is a great technique that provides qualitative information in real-time process. NIR can detect the change in moisture and agglomeration behavior during the granulation process. Rantanen et al. (41,42) were able to find good correlation between NIR spectra and mean particle size, bulk density, and moisture content. Bjorn et al. (43) used NIR spectrums as in-line process monitoring tool to detect the changes in granulation process by changing the impeller speeds and quantity of MCC.

For additional reading on end point control, see chapters 26 and 29.

A COMPARISON OF AND DIFFERENCES BETWEEN LOW- AND HIGH-SHEAR GRANULATION PROCESSES

The process of wet granulation involves several steps including blending and mixing, liquid binder addition with or without dissolved binder and wet massing or distribution of the liquid, followed by granule formation, and determining the end point of liquid addition, wet sieving, drying, and finally dry sieving.

In general, the bulk densities of granulations produced by low shear are intermediate between high shear and fluid bed, with fluid bed being the lowest. In general, low-shear granulators produce fluffier, more porous granules than do high-shear granulators. Moreover, high-shear granulation requires 60% to 80% of the liquid as compared with low-shear granulation, because of higher densification. In the high-shear granulation, slower drug dissolution is frequently observed because of slower dissolution media penetration into the denser and less porous granules. The degree of granule fragmentation is related to granule porosity. A granule with high porosity has a higher fragmentation propensity. On the other hand, the tablet strength is correlated with fragmentation, the granules with higher fragmentation yield tablets of higher hardness. The high-shear granules have lower friability as compared with the one produced by low-shear granulation.

In the low-shear granulation, synergistic effects of less mechanical shear and low bed pressure allows for thicker deposits indicating uneven distribution of binder solution, especially when the binder is added as a bolus into the granulation instead of being sprayed as droplets. Use of dissolved solids binder addition method through an agitator bar in V-blender could be problematic. Any undissolved solid may clog the liquid evacuation spacing on the disk. Thus, droplet size becomes very important in low-shear granulation compared with high-shear granulation where the distribution of liquid is helped by the high mechanical energy in the mixer. Moreover, particle motion in low-shear granulator becomes complex creating difficulties to determine the optimum rate of liquid addition. Stamm and Paris (44) studied the effect of different liquid addition rates in a fixed shell, helicoidal mixer, and vertical bar and found that the slowest rate had the best results. Extremely rapid liquid addition overwhelms the blending capability of the system resulting in overwet granulation in certain areas and underwet granulation in other areas of the bed.

The thicker film often dries to a more effectively spreadable film during compression of these granules to form tablets. This increased plasticity is especially true for at the low compression forces. The tablets also have a much lower friability. The improved friability can be over a much broader range of compression forces. The fact that less amount of liquid can be used for high-shear granulation provides reduced drying time, thus increasing the overall efficiency of the granulation process.

SCALE-UP CONSIDERATION

The granulation process is a multiphase process with numerous formulations and process variables. The incomplete understanding of the main effect and the interaction effect of each variable often lands the scale-up process in the trial and error world. The formulation and process for a new API is normally optimized using laboratory-scale granulator owing to the limited amount of API. The formulation is generally fixed during the clinical trial studies. However, the production batches are manufactured with large-scale equipment. Therefore, scale-up of a solid dosage form, prepared using the wet granulation process in a high-shear granulator becomes challenging. This is because significant differences exist between laboratory and production models in terms of design, shape, size, speed, and geometry of the granulator bowl, impellers and choppers. Even though the composition of the formulation is similar, the physical properties of the obtained granules could be dramatically different because of the difference of granulators at development scale and the production scale. These differences in the physical properties of the granules could significantly affect the properties and performance of the final tablets.

The ultimate goal of product scale-up is to maintain the properties of the granules at similar level even after scale-up. Therefore, it is important to identify and monitor key-process parameters during the product development stage so that the tablets produced from the large-scale granulation batch perform similarly to those produced from the small scale batch.

Ideally, the amount of binder and granulation liquid will be scaled by linearly increasing the amount of water with batch size. If the time of binder solution addition was kept constant by increasing the rate of binder addition upon scale-up, then the variables, which needed to be controlled, can be narrowed down to impeller speed and wet massing time. Different approaches have been proposed to control the impeller speed, which includes the following: keep the tip speed of the impeller constant, keep relative swept volume constant, or keep

Froude number (dimensionless number) constant during scale-up. The wet massing time can be determined by end point determination such as power consumption. However, because of the size and shape differences of mixing bowl and impeller between laboratory and production-scale granulators, linear scale-up may not work.

A constant relative swept volume and a constant impeller tip speed during the granulation of lactose in three GRAL high-shear mixers (GRAL 10, 75, and 300 L), did not produce desirable results (45). Thus, even within the similar kind of high-shear granulators, compensatory changes in either volume of binder fluid, impeller speed, or wet massing time, to produce equivalent granules during scale-up may be required.

To achieve a linear scale-up for formulations that are sensitive to the changes due to scale-up, the two processes from laboratory scale to production scale have to be similar. The two processes may be considered similar if there is a geometrical, kinematic, and dynamic similarity (46). The two systems are considered geometrically similar if they have the same ratio of linear dimensions. Two geometrically similar systems are kinematically similar if they have the same ratio of velocities between corresponding points. Two kinematically similar systems are dynamically similar when they have the same ratio of forces between corresponding points. For any two dynamically similar systems, all the dimensionless numbers, necessary to describe the process, are the same (47).

An ideal scenario is that the granulation processes at laboratory- and production-scale granulators are geometrically, kinematically, and dynamically similar. However, the shape and size of granulators currently available vary from manufacturer-to-manufacturer. It is difficult for the processes to be geometrically, kinematically, and dynamically similar. For example, Collette GRAL 10, 75, and 300 are not geometrically similar (45). One relatively easier approach is to keep the processes from two different scales dynamically similar, which is defined by same dimensionless numbers. Therefore, dimensionless number such as Froude number can be used for scale-up. The matching Froude numbers for different size granulators provide the possibility of linear scale-up. However, some precautions are still needed for the geometric dissimilarity of mixing bowl vessels and the shape of the impellers in the granulators of different types and scales.

Nonlinear Scale-Up

If linear scale-up cannot be achieved, the amount of binder solution, impeller speed and the wet massing time should be optimized. For example, Kristensen attempted to compensate the less efficient mixing from large-scale granulation by increasing the relative amount (ratio between granulation liquid and starting materials) of granulation liquid used (48). Rekhi et al. (49) recommended maintaining the tip speed constant, scaling up the granulation liquid linearly, and adjusting the granulation time on the basis of the ratio of impeller speeds between the granulators used in the two scales.

Additional information on scaling up can be found in chapter 25.

Utilization of Optimization Techniques

Since scale-up of high-shear granulation is still a "trial and error" process due to the complexity of the granulation process and lacking standards for granulators of different types and sizes, methodology of design of experiment (DoE) can be useful.

CONCLUSIONS

Low- and high-shear wet granulation processes are important unit operations in the production of tablets. Various innovative approaches have been explored to simplify and control the granulation process, and improve the quality of the produced granules. Some of these novel approaches in the high-shear wet granulation process include using a one-pot granulation system, and end point measurement techniques. However, both the low- and high-shear wet granulation process and formulation parameters for each formulation still need to be individually optimized because of the complexity of the number of variables involved during the granulation process and uniqueness of the formulation. Moreover, the relationship between the properties of the finished tablets and unit operations for tableting, such as wet granulation, drying, milling, and tablet compression is inconclusive. Therefore, a systematic

evaluation of all formulation and process variables involved in the manufacturing of tablets is required for the optimization of production of tablets. Future advancement in the equipment and granulation techniques could further improve the granulation process, thus resulting in better quality of the granules.

REFERENCES

1. Chirkot T, Propst C. Low shear granulation. In: Parikh DM, ed. Handbook of Pharmaceutical Granulation Technology. 2nd ed. Boca Raton: Taylor & Francis Group, 2005:229–245.
2. Badawy SIF, Lee TJ, Menning MM. Effect of drug substance particle size on the characteristics of granulation manufactured in a high-shear mixer. AAPS Pharm Sci Tech 2001; 1(4):E33.
3. Wang S, Ye G, Heng PW, et al. Investigation of high shear wet granulation processes using different parameters and formulations. Chem Pharm Bull 2008; 56(1):22–27.
4. Kristensen HG, Schaefer T. Granulation. A review on pharmaceutical wet-granulation. Drug Dev Ind Pharm 1987; 13:803–872.
5. Holm P, Schaefer T, Larsen C. End point detection in a wet granulation process. Pharm Dev Technol 2001; 6:181–192.
6. Schaefer T, Holm P, Kristensen HG. Comparison between granule growth in a horizontal and a vertical high speed mixer. I. Granulation of dicalcium phosphate. Arch Pharm Chem, Sci Ed 1986; 14:1–16.
7. Schaefer T, Holm P, Kristensen HG. Comparison between granule growth in a horizontal and a vertical high speed mixer. II. Granulation of lactose. Arch Pharm Chem, Sci Ed 1986; 14:17–29.
8. Bock TK, Kraas U. Experience with the Diosna mini-granulator and assessment of process scalability. Eur J Pharm Biopharm 2001; 52:297–303.
9. Bouwman A, Visser MR, Eissens AC, et al. The effect of vessel material on granules produced in a high-shear mixer. Eur J Pharm Sci 2004; 23(2):169–179.
10. Oulahna D, Cordier F, Galet L, et al. Wet granulation: the effect of shear on granule properties. Powder Technol 2003; 130:238–246.
11. Holm P. Effect of impeller and chopper design on granulation in a high speed mixer. Drug Dev Ind Pharm 1987; 13:1675–1701.
12. Timmins P, Delargy AM, Minchom CM, et al. Influence of some process variables on product properties for a hydrophilic matrix controlled-release tablet. Eur J Pharm Biopharm 1992; 38:113–118.
13. Suzuki T, Kikuchi H, Yonemochi E, et al. Interaction of microcrystalline cellulose and water in granules prepared by a high-shear mixer. Chem Pharm Bull (Tokyo) 2001; 49:373–378.
14. Rohera BD, Zahir A. Granulation in a fluidized-bed: effect of binders and their concentrations on granule growth and modeling the relationship between granules size and binder concentration. Drug Dev Ind Pharm 1993; 19(7):773–792.
15. Ritala M, Holm P, Schafer T, et al. Influence of liquid bonding strength on power consumption during granulation in a high-shear mixer. Drug Dev Ind Pharm 1988; 14:1041–1060.
16. Healey JNC, Rubinstein MH, Walter V. The mechanical properties of some binders used in tableting. J Pharm Pharmac 1974; (suppl 26):41.
17. Rowe RC. Binder-substrate interactions in granulation: a theoretical approach based on surface free energy and polarity. Int J Pharm 1989; 52:149–154.
18. Visavarungroj N, Remon JP. Crosslinked starch as a binding agent. II. Granulation in a high-shear mixer. Int J Pharm 1990; 65:43–48.
19. Becker D, Rigassi T, Bauer Brandi A. Effectiveness of binders in wet granulation: a comparison using model formulations of different tablet ability. Drug Dev Ind Pharm 1997; 23:791–808.
20. Armstrong NA, March GA. Quantitative assessment of factors contributing to mottling of colored tablets. II. Formulation variables. J Pharm Sci 1976; 65(2):200–204.
21. Ritala M, Jungersen O, Holm P, et al. A comparison between binder in wet phase granulation in a high shear mixer. Drug Dev Ind Pharm 1986; 12(11–13):1685–1700.
22. Miyamoto Y, Rye A, Sugawara S, et al. Simultaneous optimization of wet granulation process involving factor of drug content dependency on granule size. Drug Dev Ind Pharm 1998; 24:1055–1065.
23. Lindeberg NO, Johnson C. Granulation of lactose in a recording high-speed mixer, Diosna P 25. Drug Dev Ind Pharm 1983; 9(6):959–970.
24. Habib YS, Abramonowitz R, Jerzewski RL, et al. Is silicified wet-granulated microcrystalline cellulose better than original wet granulated microcrystalline cellulose? Pharm Dev Technol 1999; 4:431–437.
25. Schaefer T, Holm P, Kristensen HG. Comparison between granule growth in a horizontal and vertical high speed mixer. I. Granulation of dicalcium phosphate. Arch Pharm Chem Sci Ed 1984; 14:1–16.
26. Lindeberg NO, Johnson C. Granulation of lactose and starch in a recording high-speed mixer, Diosna P 25. Drug Dev Ind Pharm 1985; 11(2,3):387–403.

27. Vojnovic D, Chicco D, El Zenary H. Doehlert experimental design applied to optimization and quality control of granulation process in a high shear mixer. Int J Pharm 1996; 145:203–213.
28. Badaway SIF, Mennning MM, Gorko MA, et al. Effect of process parameters on compressibility of granulation manufactured in a high-shear mixer. Int J Pharm 2000; 198:51–61.
29. Faure A, Grimsey IM, Rowe RC, et al. Process control in a high shear mixer-granulator using wet mass consistency: the effect of formulation variables. J Pharm Sci 1999; 88:191–195.
30. Holm P, Schaefer T, Kristensen HG. Granulation in high-speed mixers. Part VI. Effects of process conditions on power consumption and granule growth. Powder Technol 1985; 43:225–233.
31. Corvari V, Fry WC, Seibert WL, et al. Instrumentation of a high-shear mixer: evaluation and comparison of a new capacitive sensor, a watt meter, and a strain-gage torque sensor for wet granulation monitoring. Pharm Res 1992; 9:1525–1533.
32. Kopcha M, Roland E, Bubb G, et al. Monitoring the granulation process in a high shear mixer/granulator: an evaluation of three approaches to instrumentation. Drug Dev Ind Pharm 1992; 18:1945–1968.
33. Leuenberger H. Granulation, new techniques. Pharm Acta Helv 1982; 57:72–82.
34. Werani J. Production experience with end point control. Acta Pharm Suecica 1988; 25:247–266.
35. Laicher A, Profitlich T, Schwitzer K, et al. A modified signal analysis system for end-point control during granulation. Eur J Pharm Sci 1997; 5:7–14.
36. Kornchankul W, Parikh NH, Sakr A. Correlation between wet granulation kinetic parameters and tablet characteristics. Drugs Made Ger 2001; 44:78–87.
37. Achanta AS, Adusumilli PS, James KW. Endpoint determination and its relevance to physicochemical characteristics of solid dosage forms. Drug Dev Ind Pharm 1997; 23:539–546.
38. Whitaker M, Baker GR, Westrup J, et al. Application of acoustic emission to the monitoring and end point determination of a high shear granulation process. Int J Pharm 2000; 205:79–92.
39. Watano S, Numa E, Miyanami K, et al. On-line monitoring of granule growth in high shear granulation by an image processing system. Chem Pharm Bull (Tokyo) 2000; 48:1154–1159.
40. Watano S, Numa T, Miyanami K, et al. A fuzzy control system of high shear granulation using image processing. Powder Technol 2001; 115:124–130.
41. Rantanen J, Wikstrom H, Turner R, et al. Use of in-line near-infrared spectroscopy in combination with chemometrics for improved understanding of pharmaceutical processes. Anal Chem 2005; 77 (2):556–563.
42. Rasanen E, Rantanen J, Jørgensen A, et al. Novel identification of pseudopolymorphic changes of theophylline during wet granulation using near infrared spectroscopy. J Pharm Sci 2001; 90(3): 389–396.
43. Bjorn NI, Jansson A, Karlsson M, et al. Empirical to mechanistic modeling in high shear granulation. Chem Eng Sci 2005; 60(14):3795–3803.
44. Stamm A, Paris L. Influence of technological factors on the optimal granulation liquid requirement measured by power consumption. Drug Dev Ind Pharm 1985; 11(2–3):333–360.
45. Horsthuis GJB, van Laarhoven JAH, van Rooij RCBM, et al. Studies on upscaling parameters of the GRAL high-shear granulation process. Int J Pharm 1993; 92:143–150.
46. Leuenberger H. Scale-up of granulation processes with reference to process monitoring. Acta Pharm Technol 1983; 29:274–280.
47. Zlokarnik M. Problems in the application of dimensional analysis and scale-up of mixing operations. Chem Eng Sci 1998; 53:3023–3030.
48. Kristensen HG. Particle agglomeration in high shear mixers. Powder Technol 1996; 88:197–202.
49. Rekhi GS, Caricofe RB, Parikh DM, et al. A new approach to scale-up of high shear granulation process. Pharm Technol 1996; 20:58–67.

10 Batch Fluid Bed Granulation

Dilip M. Parikh
DPharma Group Inc., Ellicott City, Maryland, U.S.A.

David M. Jones
OWI Consulting Inc., Ramsey, New Jersey, U.S.A.

INTRODUCTION

The size enlargement of primary particles has been carried out in the pharmaceutical industry in a variety of ways. One of the most common unit operations used in the pharmaceutical industry is the fluid-bed processing where the granules are produced in a single piece of equipment by spraying a binder solution onto a fluidized powder bed. This process is sometimes classified as the one-pot system because granulation and drying are carried out in the same equipment. The batch fluid bed granulation process is a well-established unit operation in the pharmaceutical industry; however, other process industries, such as food, nutraceutical, agrochemical, dyestuffs, and other chemical industries, have adopted fluid-bed granulation process to address particle agglomeration, dust containment, ease of material handling, and modifying particle properties to provide dispersibility or solubility to products, among other product enhancements.

Fluidization is the unit operation by which fine solids are transformed into a fluid-like state through contact with a gas. At certain gas velocities, the gas will support the particles, giving them freedom of mobility without entrainment. Such a fluidized bed resembles a vigorously boiling fluid, with solid particles undergoing extremely turbulent motion, which increases with gas velocity. The smooth fluidization of gas-solid particles is the result of equilibrium between the hydrodynamic, gravitational, and interparticle forces.

The fluidization technique, as it is known today, began in 1942, with the work of the Standard Oil Company (now known as Exxon, in the United States) and M.W. Kellogg Company, in an effort to produce the first catalytic cracking plant on a commercial scale (1). Fluid-bed processing of pharmaceuticals was first reported by Wurster, when he used the air suspension technique to coat tablets (2,3). In 1960, he reported on granulating and drying a pharmaceutical granulation, suitable for the preparation of compressed tablets, using the air suspension technique. In 1964, Scott et al. (4) and Rankell et al. (5) reported on the theory and design considerations of the process using a fundamental engineering approach and employing mass and thermal energy balances. They expanded this application to the 30-kg capacity pilot plant model designed for both batch and continuous operation. Process variables, such as airflow rate, process air temperature, and liquid flow rate, were studied. Contini and Atasoy (6) later reported the processing details and advantages of the fluid-bed process in one continuous step.

Wolf (7) discussed the essential construction features of the various fluid-bed components, and Liske and Mobus (8) compared the fluidized bed and traditional granulation process. The overall results indicated that the material processed by the fluid-bed granulator was finer, more free-flowing, and had homogeneous granules that, after compression, produced stronger and faster disintegration of tablets than the materials processed by conventional wet granulation. Reviews by Sherrington and Oliver (9), Pietch (10), and a series published on the topic of "fluidization in the pharmaceutical industry" (11–17) provide an in-depth background on the fundamental aspects of the fluidized bed and other granulation technologies. Earlier application of fluid bed was for efficiently drying of granulated or wet material. With advent of newer technologies and drug delivery techniques, these units are now routinely used for granulation, particle coating by spraying binder, or polymer solution from top, bottom, and tangential location to produce granules or modified release particles or pellets. Because of this versatility, these units are normally classified as multiprocessor fluid-bed units.

The batch size increase using fluid-bed granulation requires a good understanding of the equipment functionality, theoretical aspect of fluidization, excipient interactions, and, most of all, identifying the critical variables that affect the process of agglomeration.

This chapter will provide the essential understanding of the fluidization theory, system description that makes up the fluid-bed processor, and will discuss the critical variables associated with equipment, product, and the process. Since this process involves large amount of air and fine powders and in some cases organic compounds as a binder solvents, understanding of safety precaution in installing and operating fluid-bed equipment will be discussed as well.

FLUIDIZATION THEORY

The van der Waals forces have been established to be dominant during powder handling and fluidization, but the electrostatic forces also have great influence on the behavior of the process. In fluid-bed process mixing effect is generally good for the particles between 50 and 200 μm. Fluidization behavior is a summation of various interaction and interparticle forces. When a packed bed of particles is subjected to a sufficient high upward flow of gas, the weight of particles is supported by the drag force exerted by the gas on the particles and particles become fluidized. At low gas velocities the bed of particles is practically a packed bed, and the pressure drop is proportional to the superficial velocity. As the gas velocity is increased, a point is reached at which the bed behavior changes from fixed particles to suspended particles. The superficial velocity required to first suspend the bed particles is known as minimum fluidization velocity (U_{mf}). The minimum fluidization velocity sets the lower limit of possible operating velocities and the approximate pressure drop can be used to approximate pumping energy requirements. The flow required to maintain a complete homogeneous bed of solids in which coarse particles will not separate from the fluidized portion is very different from the minimum fluidization velocity. After the bed has been fluidized and the velocity of gas increased, the pressure drop across the bed stays constant but the height of the bed continues to increase. When the rate of flow of gas increases, the pressure drop across the bed also increases until, at a certain rate of flow, the frictional drag on the particles equals the effective weight of the bed. These conditions and the velocity of gas corresponding to it are termed incipient fluidization and incipient velocity, respectively (18). The relationship between the air velocity and the pressure drop is as shown in Figure 1 (19).

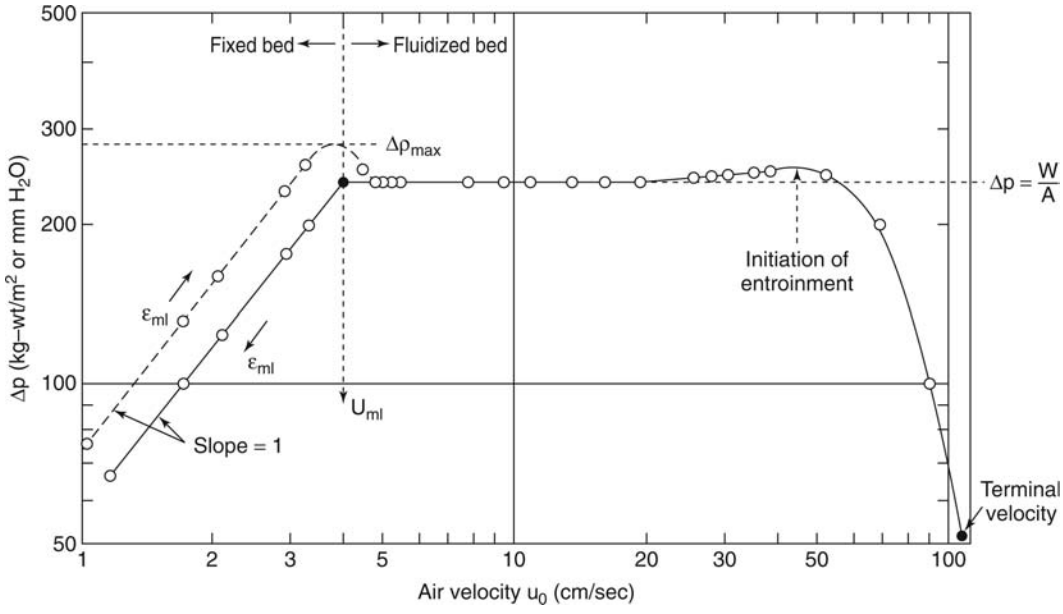


Figure 1 Relation between the air velocity and pressure drop. *Source*: From Ref. 19.

At the incipient point of fluidization, the pressure drop of the bed will be very close to the weight of the particles divided by the cross-sectional area of the bed (W/A). For the normal gas fluidized bed, the density of the gas is much less than the density of the solids and the balance of forces can be shown as

$$\Delta P_{\mathrm{mf}} = \frac{W}{A}$$

where

$$W = (1 - \varepsilon_{\mathrm{mf}})\rho_{\mathrm{p}} \times \frac{g}{g_{\mathrm{c}}}$$

where ΔP = pressure drop, $\varepsilon_{\mathrm{mf}}$ = minimum fluidization void fraction, A = cross-sectional area, W = weight of the particles, ρ_{p} = density of particles, and g/g_{c} = ratio of gravitational acceleration and gravitational conversion factor.

The fundamental phenomenon of fluidization was recently studied by the researchers (20) using small-scale fluid-bed unit. The purpose of the study was to compare experimental and computational minimum fluidizing velocities (U_{mf}) of pharmaceutical materials using miniaturized fluid-bed device. Using various materials, researchers found that experimental method was more capable of describing the fluidizing behavior of pharmaceutical materials than the computational approach. Computational models of fluidization are based on behavior of various model particles. Computational models do not take into account particle size and shape distributions, and cohesion and adhesion of pharmaceutical materials.

At gas flow rates above the point of minimum fluidization, a fluidized bed appears much like a vigorously boiling liquid; bubbles of gas rise rapidly and burst on the surface. The bubbles form very near the bottom of the bed, very close to the distributor plate, and as a result the design of the distributor plate has a significant effect on fluidized bed characteristics. The bubbles contain very small amount of solids. Each bubble of gas in a wake contains a significant amount of solids. As the bubble rises, it pulls up the wake with its solid behind it. As the velocity of the gas is increased further, the bed continues to expand and its height increases with only slight increase in the pressure drop. As the velocity of the gas is further increased, the bed continues to expand and its height increases, whereas the concentration of particles per unit volume of the bed decreases. At a certain velocity of the fluidizing medium, known as entrainment velocity, particles are carried over by the gas. This phenomenon is called entrainment. When the volumetric concentration of solid particles is uniform throughout the bed all the times, the fluidization is termed as the particular. When the concentration of solids is not uniform throughout the bed, and if the concentration keeps fluctuating with time, the fluidization is called aggregative fluidization. A slugging bed is a fluid bed in which the gas bubbles occupy entire cross sections of the product container and divide the bed into layers. A boiling bed is a fluid bed in which the gas bubbles are approximately the same size of the solid particles. A channeling bed is a fluid bed in which the gas forms channels in the bed through which most of the air passes. A spouting bed is a fluid bed in which the gas forms a single opening through which some particles flow and fall on the outside.

Figure 2 shows various types of fluid beds (21).

The mechanisms by which air affects fluidization have been discussed by various researchers (12,13,22–25). When the fluidizing velocity is greater than the incipient velocity, bubbles of air rise through the bed causing mixing of particles. It is the gas passing through the bed in the form of bubbles that determines the degree of mixing. The extent of mixing appears to vary with the particle size. As the mean size of particles approaches zero, mixing of particles less than 150 μm decreases. Different types of beds, described above, are formed depending upon the movement of bubbles through the bed. The pattern of movement of the gas phase in and out of bubbles depends on several factors, including minimum fluidization velocity and particle size. These movements affect heat transfer between air bubbles and particles. The air distributor at the bottom of the container has a controlling influence on the uniform distribution of gas, minimization of dead areas, and maximization of particle movement. The most common reason for mixing problems such as segregation in the fluid bed is the particle

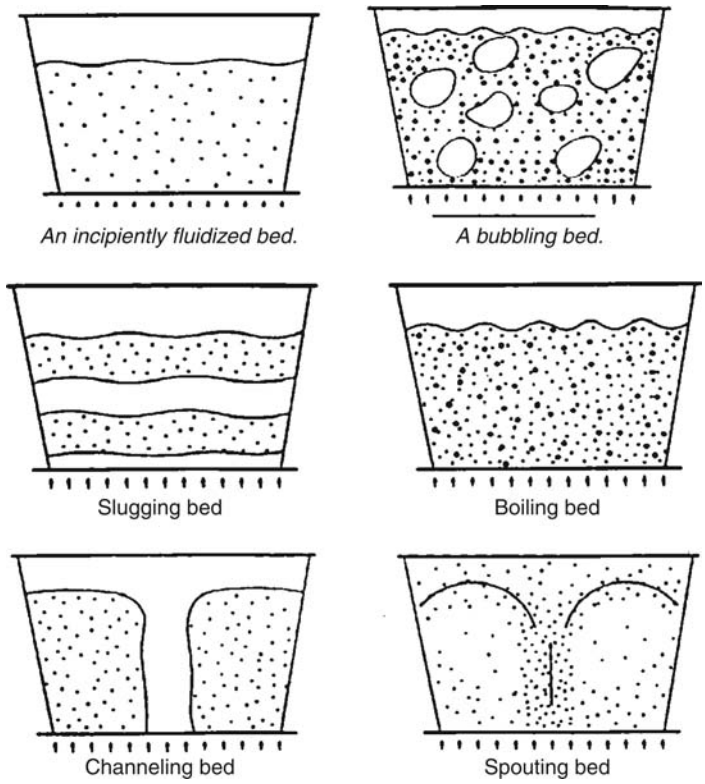


Figure 2 Various types of fluid beds. *Source*: From Ref. 21.

density differences. The main characteristic of the fluid bed is the relative velocity imparted to the particles, U_o, which is strong function of the size of the particles and the gas velocity in the bed, and was shown to be given by

$$U_o \approx a\gamma^o = 18\frac{U_b a}{D_b}\delta^2$$

where a is the average particle size, γ° is the interfacial energy, U_b is the bubble velocity, D_b is the bubble diameter, and δ is the dimensionless bubble spacing (26). The first expression on the right-hand side of equation applies to fluidized beds with no rotating parts where shear is induced by the motion of bubbles only. Recognizing the importance of particle size and density on the fluidization properties, Geldart has found four fluidization modes and determined a general particle classification chart (Fig. 3). For any particle of known density ρ_p and mean particle size dp, the Geldart chart indicates the type of fluidization to be expected (1).

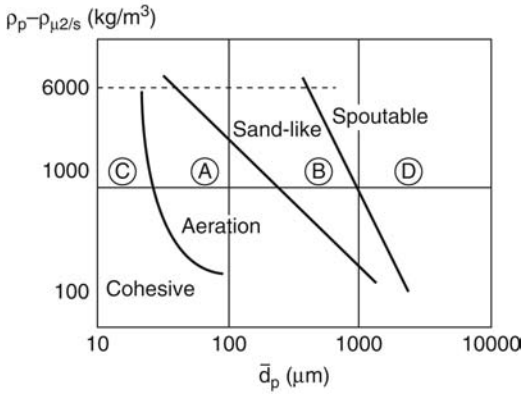


Figure 3 Geldart classifications of particles. *Source*: From Ref. 1.

The extent of segregation can be controlled in part by maintaining high fluidizing velocities and high bowl height to bowl diameter ratio. There are standard air velocities for various processes that can be used as guidelines. The standard velocities are based on the cross-sectional area at the bottom of the product container.

This is calculated by using the following formula for calculating the air velocity:

$$\text{Velocity (m/sec)} = \text{air flow [cubic meter per hour (CMH)]} \div \text{area(square meters)} \times 3600$$

where air flow in CMH = air flow [cubic feet per minute (CFM)] $\times$ 1.696.

Standard air velocities are based on the application. Airflow velocities are normally 1.0 to 2.0 m/sec. For agglomeration, air velocity required is normally five to six times the minimum fluidization velocity. Low air velocities such as 0.8 to 1.4 m/sec are required for drying. The higher velocity is required during the early stages of drying because of the wet mass present in the bowl, but is normally reduced when the product loses its moisture. The objective is to have good particle movement but to keep the material out of filters. Particle movement and quick drying are important during the agglomeration process. An indication of good fluidization is a free downward flow of the granulation at the sight glass of the product container. However, improper fluidization can also be detected by monitoring the outlet air temperature. Every product has a unique constant rate of drying in which the bed temperature remains relatively constant for significant length of time. Therefore, if the outlet temperature rises more rapidly than anticipated, it will indicate an improper fluidization and the process may have to be stopped and manual or mechanical intervention may be required to assist the fluidization.

SYSTEM DESCRIPTION

A fluid-bed processor is a system of unit operations involving conditioning of process air, a system to direct it through the material to be processed, and has the same air (usually laden with moisture) exit the unit void of the product. Figure 4 shows a typical fluid-bed processor with all the components. These components and its utility for the granulation will be reviewed in this section.

At the downstream end of the fluid-bed processor, an exhaust blower or a fan is situated to draw the air through the entire unit. This arrangement provides negative pressure in the fluid bed that is necessary to facilitate material loading, maintaining safe operation, preventing material escape, and carrying out the process under good manufacturing practices guidelines, all of which will be discussed later in the chapter.

Air Handling Unit

A typical air preparation system includes sections for prefiltering incoming air, heating the air dehumidification, clean steam generating unit for rehumidification when needed, and final high-efficiency particulate air (HEPA) filter. Generally, outside air is used as the fluidizing medium in a fluid-bed processor. For the air to be used for pharmaceutical products, it must be free of dust and contaminants. This is achieved by placing coarse dust filters (30–85%) in the air handling unit (AHU). Figure 5 shows the typical AHU.

Through years of experience and dealing with various types of materials and various climate conditions, it is known that incoming air must be controlled very closely. As an example it has been found that humidity of the incoming air can greatly affect the quality of spray granulation, drying, or coating. Therefore, air preparation systems are now designed to better control the conditions of the incoming air. After the installation of the coarse prefilters, distinct heating or cooling sections are installed in the air handler depending upon the geographical location of the plant. In an extremely cold climate, where cooling coils (needed in summer months for maintaining uniform dew point) can freeze in winter, a preheating section is placed ahead of the cooling coils. A typical range for the air after pretreatment that one should aim at achieving is 15°C to 30°C dry bulb and 3°C to 5°C wet bulb. If the unit is located in a tropical or humid climate, the humidity removal section is employed first. The dehumidification of the air is extremely important where the outside air moisture varies over a wide range. In summer, in some parts of the world, when the outside humidity is high,

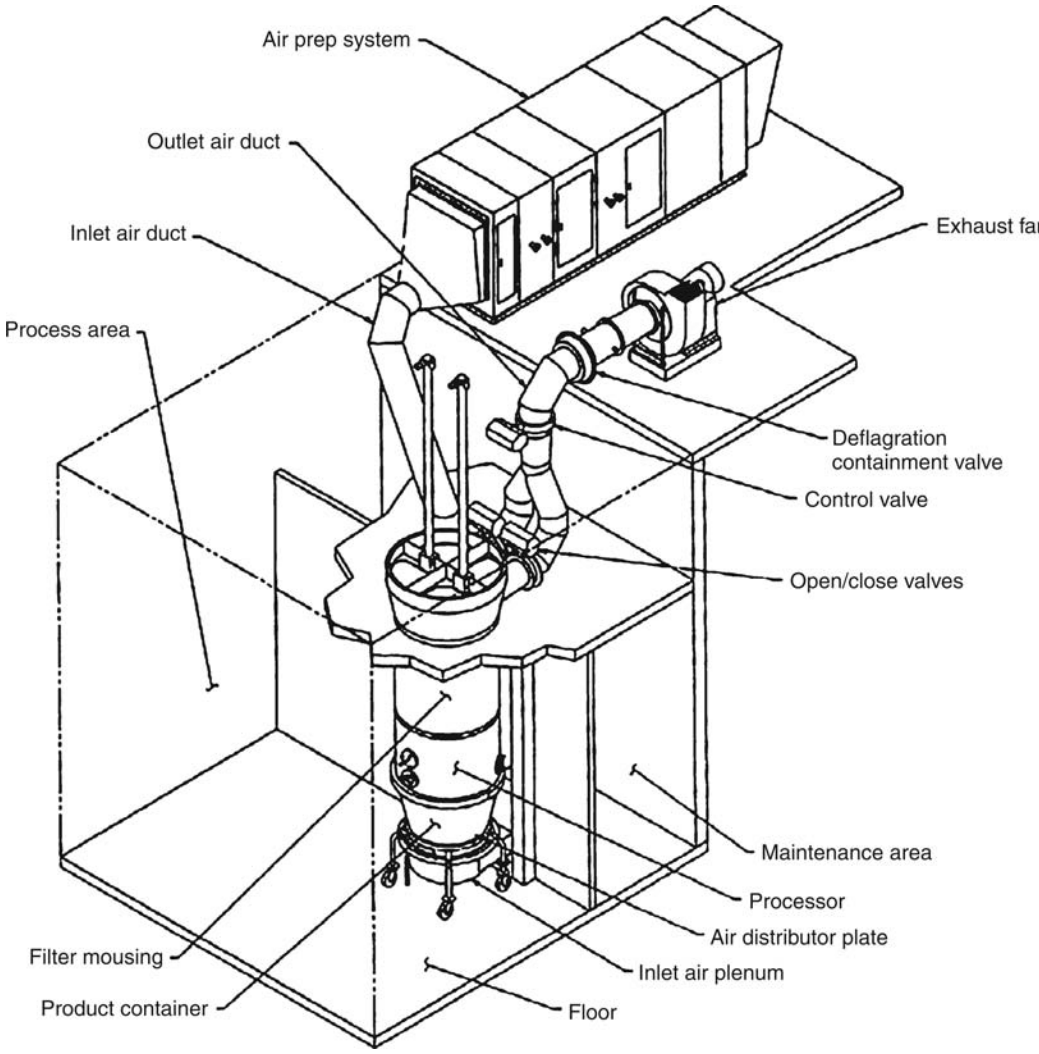


Figure 4 Fluid-bed processor installation with all components.

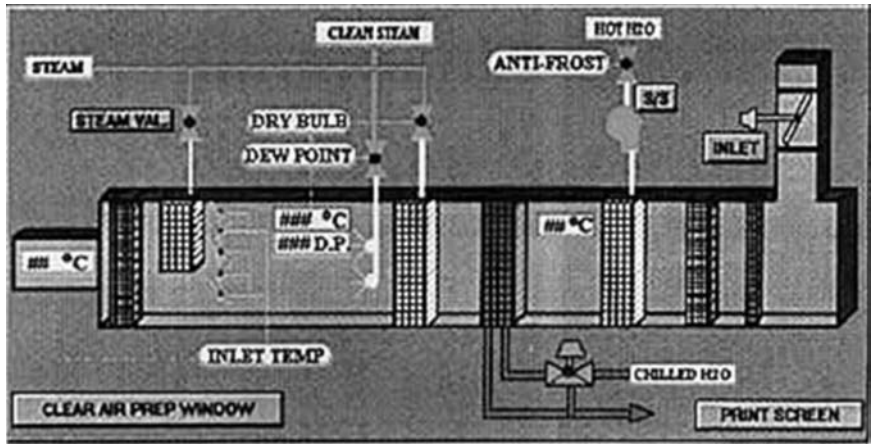


Figure 5 Typical air handling unit.

dehumidification of the process air is required to maintain specific dew point of the incoming air. On the other hand, during dry winter months, with a low humidity in the incoming air, rehumidification may be necessary in some regions. A clean steam injector is used for rehumidifying the dry air. Generally, process air with a lower dew point has higher affinity to entrain moisture reducing the process time. When granulating extremely fine powders, inlet air dew point of 15°C is beneficial to reduce static charges and facilitate uniform fluidization. In many processes, when preheating is required, a bypass loop can be used for preconditioning the air. This loop allows the required process temperature and humidity to be attained within the system ducts before the product is subjected to fluidization. After the conditioned air leaves humidification/dehumidification section of the AHU, it is finally heated to the desired process air temperature and then passed through a HEPA filter of about 99.90% to 99.99% capacity. As the process air is treated and filtered, it is transported by the inlet duct into the lower plenum of the fluid-bed unit.

Product Container and Air Distributor

With the air at the desired humidity and temperature it is ready to be passed through the bed of solids. Figure 6A, B shows typical product container with the air distributor. Another supplier offers single-air distributors where open area can be changed by adjusting the slots underneath without using different air distributor mainly used for bottom spraying.

The air must be introduced evenly at the bottom of the product container through an inlet air plenum. Proper air flow in the inlet air plenum is critical to ensure that equal air flow velocities occur at every point on the air-distributor plate. If the air is not properly distributed before it reaches the bottom of the container, uneven fluidization can occur. To facilitate the even flow of powder in the product container, the conditioned air is brought in the plenum at a various location by certain manufacturers.

To properly fluidize and mix the material in the container, correct choice of the container and air distributor must be made. The container volume should be chosen such that the container is filled to at least 35% to 40% of its total volume and no more than 90% of its total volume. Correct choice of the air distributor is important. These distributors are made of stainless steel and are available with a 2% to 30% open area. Typically, the distributor should be chosen so that the pressure drop across the product bed and air distributor is 200 to 300 mm of water column. Most common air distributors are covered with a 60 to 325 mesh fine screen to retain the product in the container. This type of sandwiched construction (Fig. 6A, B) has been used for the last 30 years in the fluid-bed processors.

Keeping the screen and air distributors clean has been challenging. Partially to address the cleaning problems and partially to provide the efficient processing, number of manufacturers

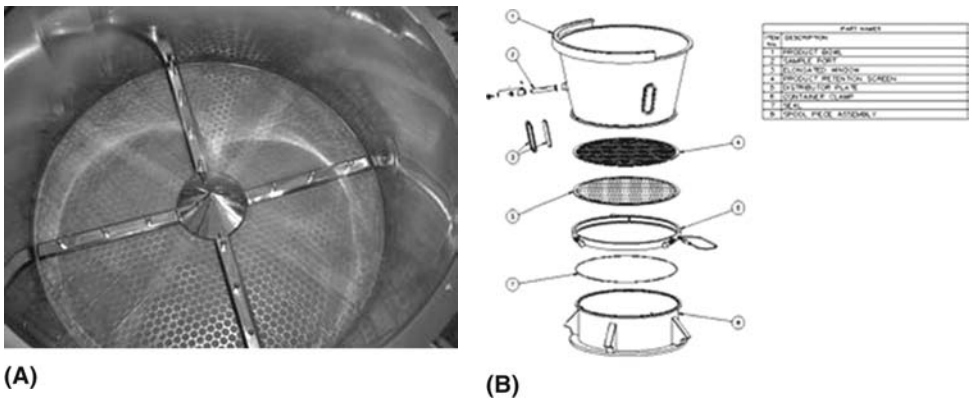
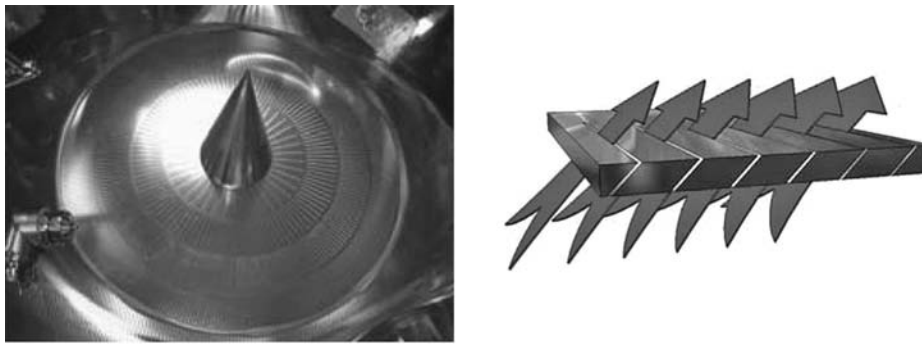
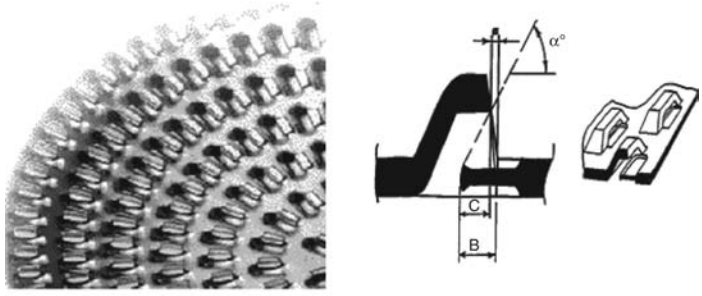


Figure 6 (**A**, **B**) Typical air distributors with different parts and retaining screen.



(A)



(B)

Figure 7 (**A**) Slotted air-distributor design. (**B**) Overlap gill plate air distributor. *Source*: Part A courtesy of LB Bohle, and part B courtesy of GEA Pharma Systems.

have introduced air distributors that eliminate the use of retaining screen. The overlap gill plate (Fig. 7B) or air distributor with slotted angle (Fig. 7A) are examples of newer designs available. The overlap gill plate was introduced in 1990 (27). These new air distributors eliminate the need for a fine screen and perform dual functions as the efficient air distributor and product retainer. Other advantages claimed by the manufacturer are ability to validate clean in place (CIP) system, controlled fluidization, and directional flow of air to discharge the processed product from the container. Because there is no fine screen, these types of air distributors sometimes sift very fine particles through the screen, thus loosing part of the batch in the plenum. This sifting of fine powder through these types of air distributors is of concern when a container containing product is moved around on the production floor, losing some product due to movement of the container. Before selecting these types of single-plate air distributors, sifting test for finer particles should be performed. However, these types of air distributors offer advantage for discharging product by providing the directional air flow to the dried product from the container (see sect. "Material Handling Options").

Spray Nozzle

A spray is a zone of liquid drops in a gas and spraying is the act of breaking up a liquid into a multitude of these droplets. The general purpose of spraying is to increase the surface area of a given mass of liquid to disperse it over the product area. The primary concern is with the increase of surface area per unit mass achieved by spraying. The nozzle is an orifice through which liquid is forced, normally by compressed air. This is done by three general methods: (*i*) liquid may be sucked up by a pressure drop created over the nozzle cap, after which compressed air atomizes the liquid stream by disintegrating it with air jets, or (*ii*) the

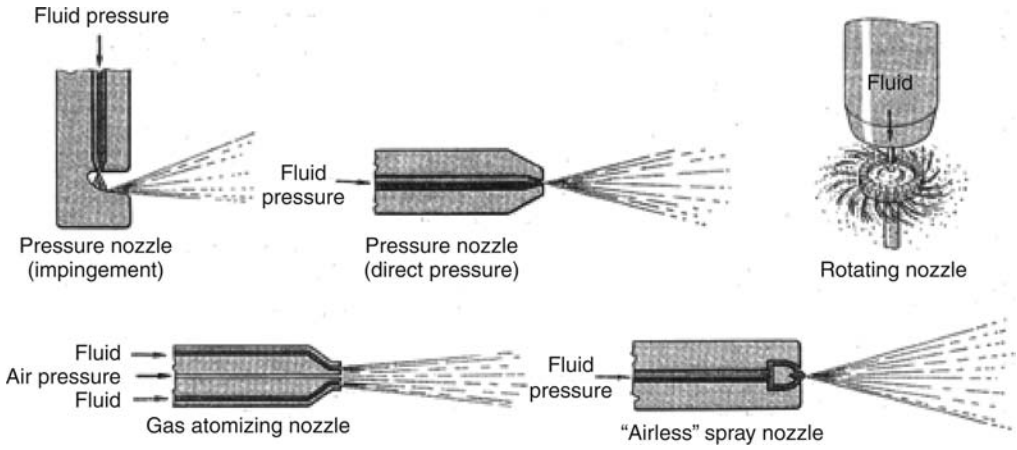


Figure 8 Types of nozzle. *Source*: From Ref. 28.

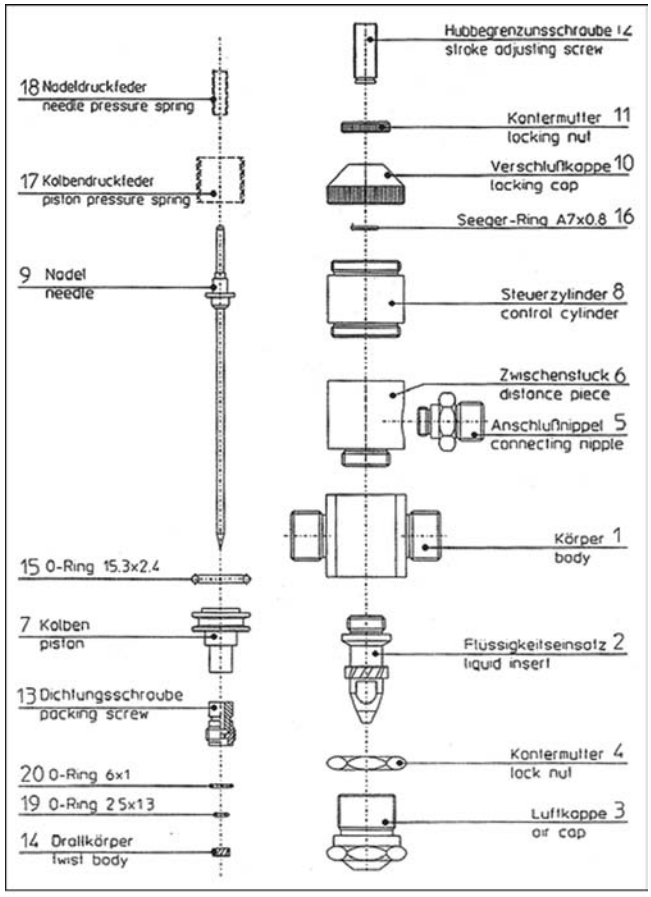
compressed air operates a piston arrangement that pushes the liquid through the orifice and then lets surface tension create droplet, or (*iii*) impinge two pressure streams of liquid upon each other, and so form a highly dispersed, uniform spray.

The type of spray system is usually characterized by one of the four nozzle designs (Fig. 8) (28).

1. *Pressure nozzle*: The fluid under pressure is broken up by its inherent instability and its impact on the atmosphere, on another jet, or on a fixed plate.
2. *Rotating nozzle* (rotary atomizer): Fluid is fed at low pressure to the center of a rapidly rotating disk and centrifugal force breaks up the fluid. These types of nozzles are used mainly in a spray drying application.
3. *Airless spray nozzle:* The fluid is separated into two streams that are brought back together at the nozzle orifice, where upon impingement, they form drops.
4. *Gas atomizing nozzle* (two-fluid nozzle): The two-fluid (binary) nozzle where the binder solution (one fluid) is atomized by compressed air (second fluid) is the most commonly used nozzle for the fluid-bed granulation (Fig. 9A).

These nozzles are available as a single-port or multiport design. Generally, the single-port nozzles are adequate up to 100-kg batch, but for larger size batches multiport nozzles such as either three-port (Fig. 9B) or six-port (Fig. 9C) nozzle is required. When these nozzles are air-atomized, the spray undergoes three distinct phases. In the first, the compressed air (gas) expands, essentially adiabatically, from the high pressure at the nozzle to that of the fluid-bed chamber. The gas undergoes a Joule–Thomson effect, and its temperature falls. In the second, the liquid forms into discrete drops. During this atomization, the liquid's specific surface area usually increases 1000 times. In the third, the drops travel after being formed, until they become completely dry or impinge on the product particles. During this phase the solvent evaporates and the diameter of the drops decreases. The energy required to form a drop is the product of the surface tension and the new surface area. About 0.1 cal/g is needed to subdivide 1 g of water into 1 μm droplets. The air pressure required to atomize the binder liquid is set by means of pressure regulator. The spray pattern and spray angle are adjusted by adjusting the air cap.

Optimum atomization is achieved by fine adjustment of the air cap and atomization air pressure measured at the nozzle. The binder solution is delivered to the nozzle port through a spray lance and tubing. The peristaltic or positive displacement pump is commonly used to pump the binder solution. The pneumatically controlled nozzle needle prevents the binder liquid from dripping, when the liquid flow is stopped. Nozzle port openings of 0.8 to 2.8 mm in diameter are most common and are interchangeable.



(A)

(B)

(C)

Figure 9 (**A**) Schematic nozzle showing different parts. (**B**) Three-port nozzle. (**C**) Six-port nozzle. *Source*: Part B courtesy of The Vector Corporation, and part C courtesy of The Glatt Group.

The two-fluid nozzle in its simplified model is based on energy transmission as shown below:

$$\text{Energy} + \text{Liquid} \rightarrow \text{Two} - \text{Fluid Nozzle} \rightarrow \text{Droplets} + \text{Heat}$$

The ratio of energy dissipation by heat and by the droplet-making process is difficult to measure. Masters (29) suggested that less than 0.5% of applied energy is utilized in liquid breakup. Virtually, the whole amount is imparted to the liquid and air as kinetic energy.

For top spray granulation in a production size unit, nozzles placement may be required to be placed at various heights depending on the bed coverage required. To provide location

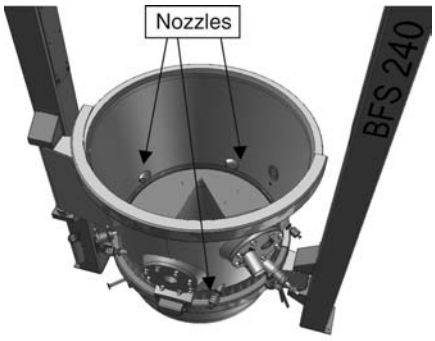
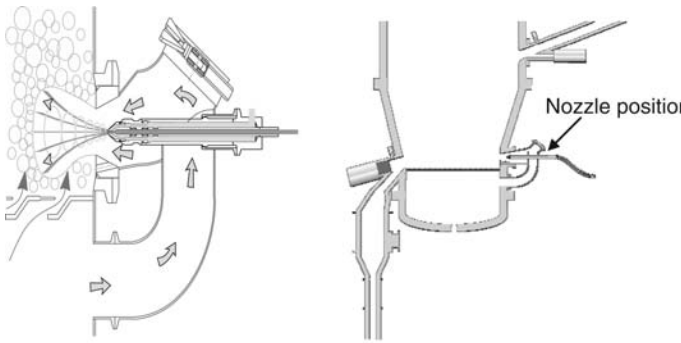
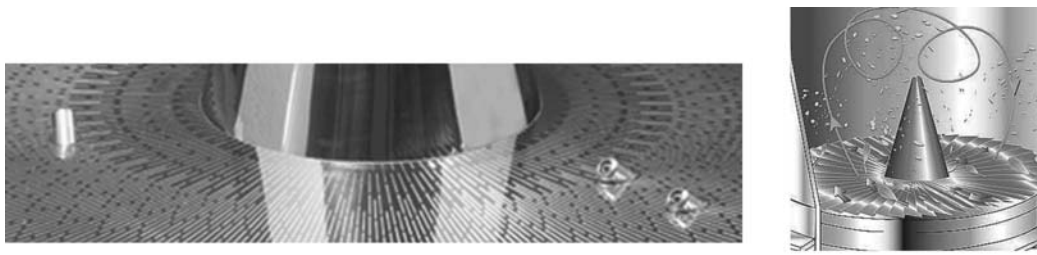


Figure 10 Nozzle position in the container. *Source*: Courtesy of LB Bohle.



(A)



(B)

Figure 11 (**A**) Nozzle location in the container of FlexStream™ system. (**B**) Three-fluid nozzle position within the air distributor for granulation and coating. *Source*: Part A courtesy of GEA Pharma Systems, and part B courtesy of OYSTAR-Hütlin, U.S. Web site.

flexibility for nozzle placement, some companies provide multiple ports to locate the nozzle. Some other companies provide nozzle extenders with only single port.

Since nozzles are placed in the cloud of powder flowing in opposite direction to the flow of liquid from the nozzle, clogging of nozzles, or building up of product on nozzles or nozzle arm, poses problems. To overcome this some companies have introduced the location of nozzle in the product container (Figs. 10 and 11), or in the air distributor (Fig. 11A) spraying tangentially to the flow of powder. In one version offered by LB Bohle (Pennsylvania, U.S.) (Fig. 10), the slotted air distributors where the nozzle placement is on the side of the product container provide spraying of the particles tangentially as they fluidize. According to the manufacturer, the need for tall units for disengagement of particles is not needed and thus the overall height of the unit can be reduced.

Similar approach with additional features is offered by GEA Pharma Systems (Wommelgem, Belgium) with their Flex Stream™ system. Here the nozzle is placed on the side of the container, surrounded by passage through which a low-pressure process air, diverted from the lower plenum, enters around the nozzle and creates an area of spray pattern eliminating the possibility of overwetting of particles and keeping the nozzles clean (Fig. 11). OYSTAR-Huttlin also has introduced the nozzle in the air distributor. The nozzle is patented three-fluid nozzle where the third fluid being the process air itself. The granulating fluid is sprayed where the speed of the product is highest, avoiding local overwetting.

By placing the nozzle accessible it is possible to remove nozzle during the processing. Flex Stream™ system claims to eliminate need for changing containers for spray granulation, drying, or particle coating, and offers linier scale-up possibility as long as the overlap gill plate is used as an air distributor.

This nozzle positioning approach away from traditional top or bottom spray is the most significant change in the fluid-bed technology. The effort here is to eliminate the different modules traditionally used for drying, granulating, or coating in the industry.

Disengagement Area and Process Filters

Once the air leaves the product bed, fine particles need to be separated from the air stream. Two zones are used in the fluid bed to separate particles from the air stream: the disengagement area and the exhaust filter. In the disengagement area larger particles lose momentum and fall back into the bed. The velocity of the process air is highest at the center of the processor and approaches zero at the sidewalls. A process air filter system removes the particles from the exhaust air. The process air is filtered by using bags or cartridges. The bag filters are widely used and are available as a single bag or with double-bag configuration, where one bag is mechanically shaking the particles while the other bag remains functional, thus facilitating uninterrupted fluidization. This alternate shaking of dual bags allows the process to be consistent from batch to batch. These filter bags are constructed out of nylon, polyester, polypropylene, and/or polytetrafluroethylene (PTFE) lined materials (Figs. 12, 13A–C). To dissipate the potential static charges from the product particles, conductive fabrics are also available and are recommended. Cartridge filters lined with PTFE were introduced to the industry in 1980s (30). Standard filtration system normally contains a multiple cartridge filter system with an alternating blowback pulse arrangement allowing continuous product fluidization. A cleanable polyester 2-μm material is utilized for processing water-soluble and nonsoluble materials, which has an electrical conductivity for static-free operation. Recently, cartridges made of stainless steel suitable for CIP system have been introduced (31). Various suppliers of the process equipment have filter arrangements. The vertical filter cartridge claimed to provide better cleaning, however, requires mechanical means to bring the filters down to replace them. Cartridge filters located at an angle do provide better access to take them out from the unit. They are equally effective. Figure 14A (a&b) and 14B shows the different cartridge filter arrangements in the fluid-bed processor. The stainless steel cartridge filters (Fig. 15) are expensive alternative to the cloth filter bags but provide possibility of cleaning using automated CIP system. For a potent compound processing, these stainless steel cartridge filters with a CIP system capability is normally recommended.

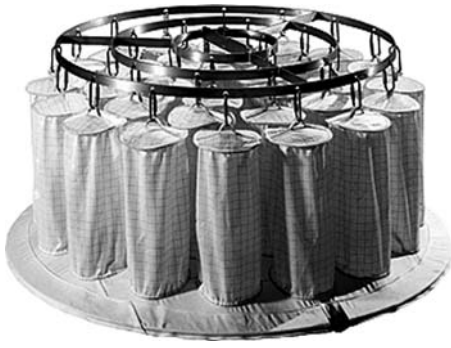


Figure 12 Conventional cloth filter bag with hanging arrangements. *Source*: Courtesy of The Vector Corporation.

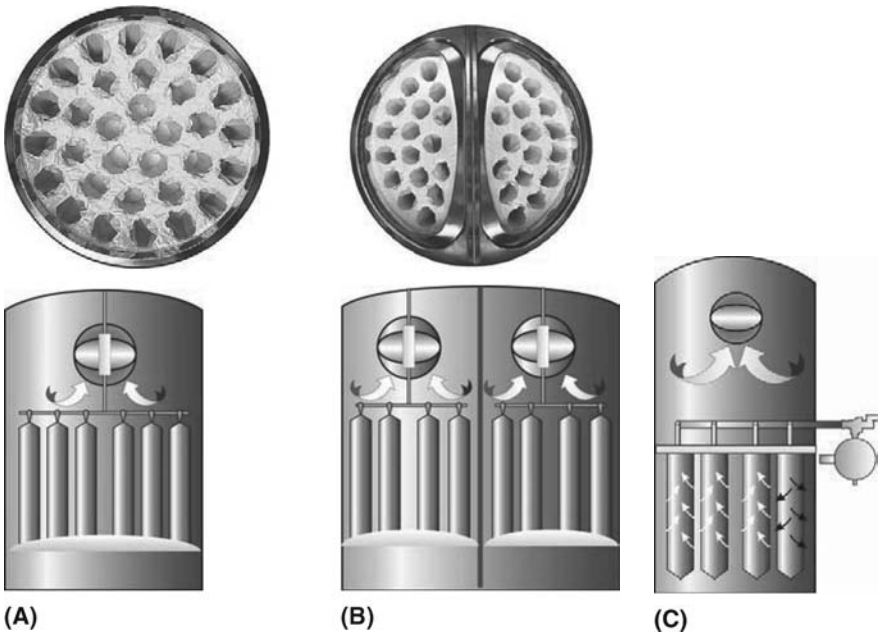


Figure 13 (**A**, **B**) Single shake and split shake filter bags. (**C**) Cartridge filters with low-pressure blow back system. *Source*: Part A and B courtesy of The Glatt Group Inc., and part C courtesy of The Glatt Group.

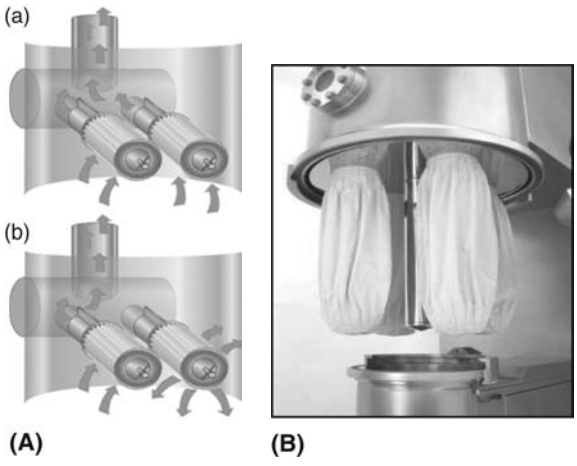


Figure 14 (**A**) Pleated Cartridge filters installed at an angle. In the processing (a) and cleaning (b) mode. (**B**) Cloth Cartridge filters. *Source*: Part A courtesy of The Vector Corporation and part B courtesy of L.B. Bohle.

During the granulation or drying process, cloth filters with socks are mechanically shaken to dislodge any product adhered, while cartridge or cloth filters use low-pressure compressed air blowback system to do the same.

Exhaust Blower or Fan

Once the air leaves the exhaust filters, it travels to the fan. The fan is on the outlet side of the system, which keeps the system at a lower pressure than the surrounding atmosphere. The airflow is controlled by a valve or damper installed just ahead or after the fan. Manufacturers of the fluid bed normally make the selection of the fan, based on the layout and the complexity of the system. Fan size is determined by calculating the pressure drop (ΔP) created by all the

Figure 15 Stainless steel Cartridge Filters. *Source:* The Glatt Group.

components that make up the fluid-bed processor including product at the highest design airflow volume.

Control System

A fluid-bed granulation process can be controlled by pneumatic analog control devices, or state of the art, programmable logic controllers (PLCs) or computers. The electronic-based control system offers not only reproducible batches according to the recipe but also a complete record and printout of all the process conditions. Process-control technology has changed very rapidly and it will continue to change as advances in computer technology take place and as the cost of control systems fall. The CFR Part 11 requirements (32) mandated by the U.S. FDA have created number of approaches to assure these control systems are complying with the current regulation.

Solution Delivery System

The liquid delivery systems operate at a low pressure. A peristaltic pump capable of delivering fluid at a controlled rate is desirable. The liquid is transported from the solution vessel through the tubing and atomized using a two-fluid (binary) nozzle in the fluid-bed processor.

PARTICLE AGGLOMERATION AND GRANULE GROWTH

Agglomeration can be defined as the size enlargement process, in which the starting material is fine particles and the final product is an aggregate in which primary particles can still be identified. The granules are held together with bonds formed by the binder used to agglomerate. Various mechanisms of granule formation have been described in the literature (33–35). The chapter on theory of granulation in this book discusses the theory of granule growth. To summarize, the researchers have suggested three mechanisms for granule formation. These are as follows:

1. Bridges because of immobile liquids form adhesional and cohesional bridging bonds. Thin adsorption layers are immobile and can contribute to the bonding of fine particles under certain circumstances.
2. Mobile liquids where interfacial and capillary forces are present.
3. Solid bridges formed due to crystallization of dissolved substances during drying.

   The type of bonds formed approaches through four transition states, described by Newitt and Conway-Jones (33) as (*i*) pendular, (*ii*) funicular, (*iii*) capillary, and (*iv*) droplet, which normally happens during spray drying.

Tardos et al. (36) investigated a comprehensive model of granulation. They developed a pendular bridge apparatus that can be used to test the bridge-forming characteristics of the binder and to determine binder penetration and spreading rates and the critical time of binder strengthening.

Iveson (37) worked to find a mathematical model for granule coalescence during granulation. He found that current models had one of the two limitations: either they only

consider whether a bond formed on impact is strong enough to survive subsequent impacts or they fail to consider the possibility of bond rupture after formation at all. He developed a new model that takes into account both the effects of bond strengthening with time, and the distribution of impact forces. He suggest that his models be combined with existing models that predict whether or not two granules stick initially on impact, to then be able to predict the probability of permanent coalescence.

Most of the fluid-bed granulated products require an amount of wetting much less than the high shear granulation or spray dryer processed product.

In the fluid-bed granulation process, the particles are suspended in the hot air stream and the atomized liquid is sprayed on it. The degree of bonding between these primary particles to form an agglomerated granule depends upon the binder used, physicochemical characteristics of the primary particles being agglomerated, and upon process parameters.

Schaefer et al. (38) and Smith and Nienow (39) have reported a description of the growth mechanisms in the fluid bed, where the bed particles are wetted by liquid droplets in the spray zone. Atomized liquid from the nozzle tends to spread over the particle surface, as long as there is an adequate wettability of the particle by the fluid (40). Wet particles on impact form a liquid bridge and solidify as the agglomerate circulates throughout the remainder of the bed. Solid bridges then hold particles together. The strength of the binder determines whether these particles stay as agglomerates. These binding forces should be larger than the breakup forces and in turn depend on the size of the solid bridge. The breakup forces arise from movement of the randomized particles colliding with each other and are related to the excess gas velocity and particle size.

If the binding forces are in excess of the breakup forces, either in the wet state or in the dry state, uncontrolled growth will proceed to an overwetted bed or production of excessive fines, respectively. If a more reasonable balance of forces is present, controlled agglomeration will occur, growth of which can be controlled. Maroglou and Nienow presented a granule growth mechanism in the fluid bed by the use of model materials and scanning electron microscope (41). Goldschmidt et al. (42) described the granule growth proportional to the collision frequency between the particles present in the granulator, and the fraction of collisions that are successful, that is, the fraction of collisions that lead to coalesce rather than rebound. For collision to be successful, two conditions must be met: (*i*) the particles must contact each other by a binder wet region, and (*ii*) the viscous binder layer in this region must be able to dissipate the kinetic energy of the particles. Thielmann et al. (43) investigated the assumption that "better wetting means better granulation." Their experimental study concluded that effect of surface properties resulted in having the hydrophilic particles resulting in smaller granules than hydrophobic ones and better wettability does not necessarily mean better granulation.

Figure 16 shows the various paths a liquid droplet can take and its consequences on the particle growth.

The mechanism of formation of a granule and subsequent growth primarily progresses through following three stages:

1. Nucleation
2. Transition
3. Ball growth

Figure 17 shows the growth of the granule relative to the liquid added. In the beginning of the spraying stage, primary particles form nuclei and are held together by liquid bridges in a pendular state. The size of these nuclei depends upon the droplet size of the binder solution. As the liquid addition continues, more and more nuclei agglomerate and continue the transition from the pendular state to the capillary state.

The uniqueness of the fluid-bed agglomeration process is how the liquid addition and drying (evaporation) steps are concurrently carried out. When the granulation liquid is sprayed into a fluidized bed, the primary particles are wetted and form together with the binder, relatively loose and very porous agglomerates. Agglomeration between two particles will take place if the particles collide with each other and at least one of them is wet enough to

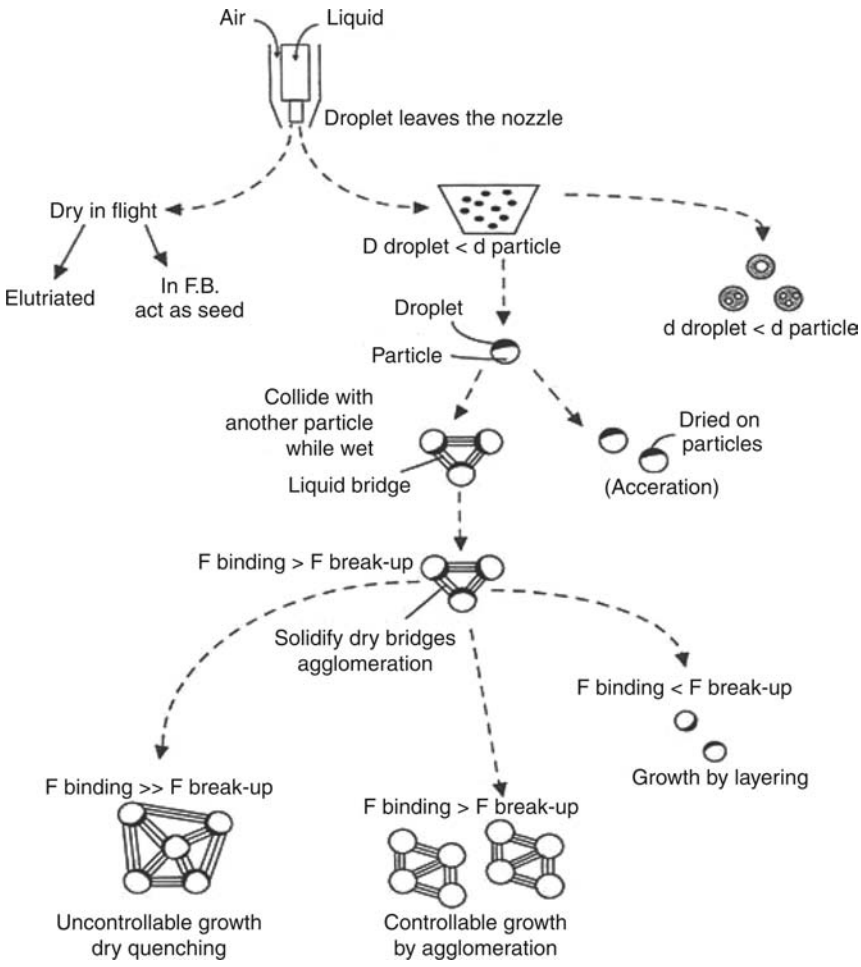


Figure 16 Mechanism of granulation in fluid bed.

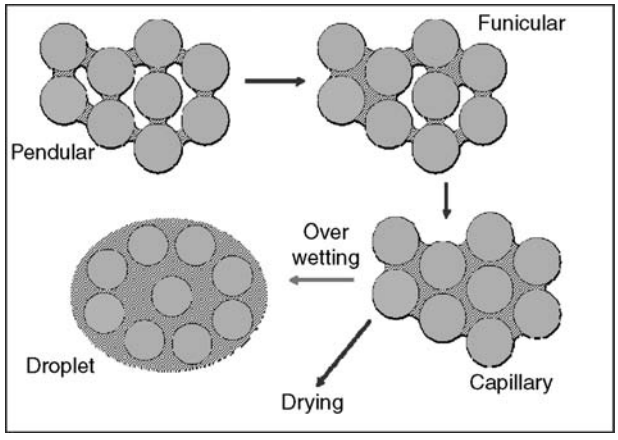


Figure 17 States of liquid saturation.

form a liquid bridge. A sufficiently high moisture content of one colliding particle depends on the wetting and drying processes. Densification of these agglomerates is brought about solely by the capillary forces present in the liquid bridges. It is therefore important that the quantity of liquid sprayed into the bed should be relatively larger compared with that used in high shear

granulation. Although wetting and nucleation step may be seen as a minor part of the granulation process it is nevertheless a vital part of the process, and spray rate conditions and particle flux in the spray zone have primary importance for the entire process and the resulting granule properties. Agglomerate can exist in a number of different spatial structures depending on the binder liquid saturation. It is the amount of liquid binder as well as the humidity conditions in the bed that determines the degree of saturation, which again determines the spatial structure of the final granule (44). Drying a wet product in a fluid bed is a separate topic but during the granulation process it becomes integral part of the process; hence, understanding fluid-bed drying is important before we review the agglomeration process.

FLUID-BED DRYING

Drying is usually understood to be removal of moisture or solvent. Drying involves heat transfer and mass transfer. Heat is transferred to the product to evaporate liquid, and mass is transferred as a vapor in the surrounding gas; hence, these two phenomena are interdependent. The drying rate is determined by the factors affecting the heat and mass transfer. The transfer of heat in the fluid bed takes place by convection. Convection is the transfer of heat from one point to another within a fluid (gas, solid, and liquid) by the mixing of one portion of the fluid with another. The removal of moisture from a product granulated in the fluid-bed granulator or in other equipment essentially removes the added water or solvent. This free moisture content is the amount of moisture that can be removed from the material by drying at a specified temperature and humidity. The amount of moisture that remains associated with the material under the drying conditions specified is called the equilibrium moisture content or EMC.

The evaporation rate of liquid film surrounding the granule being dried is related to the rate of heat transfer by the equation:

$$\frac{dw}{dt} = \frac{h \times A}{H} \times \delta T$$

where dw/dt is the mass transfer rate (drying rate), h is the heat transfer coefficient, A is the surface area, H is the latent heat of evaporation, and δT is the temperature difference between the air and the material surface.

Because fluid-bed processing involves drying of a product in suspended hot air, the heat transfer is extremely rapid. In a properly fluidized processor, product temperature and the exhaust air temperatures should reach equilibrium. Improper air distribution, hence poor heat transfer in fluidized bed, causes numerous problems such as caking, channeling, or sticking. The capacity of the air (gas) stream to absorb and carry away moisture determines the drying rate and establishes the duration of the drying cycle. Controlling this capacity is the key to controlling the drying process. The two elements essential to this control are inlet air temperature and air flow. The higher the temperature of the drying air, the greater is its vapor holding capacity. Since the temperature of the wet granules in a hot gas depends on the rate of evaporation, the key to analyzing the drying process is psychrometry (45–47).

Psychrometry is defined as the study of the relationships between the material and energy balances of water vapor–air mixture. Psychrometric charts (Fig. 18) simplify the crucial calculations of how much heat must be added and how much moisture can be added to the air or removed from the air. The process of drying involves both heat and mass transfers. For drying to occur, there must be a concentration gradient, which must exist between the moist granule and the surrounding environment. As in heat transfer, the maximum rate of mass transfer that occurs during drying is proportional to the surface area, turbulence of the drying air, the driving force between the solid and the air, and the drying rate. Because the heat of vaporization must be supplied to evaporate the moisture, the driving force for mass transfer is the same driving force required for heat transfer, which is the temperature difference between the air and the solid.

Schaefer and Worts (48) have shown that the higher the temperature differences between incoming air and the product, the faster is the drying rate. Therefore, product temperature should be monitored closely to control the fluidized bed drying process.

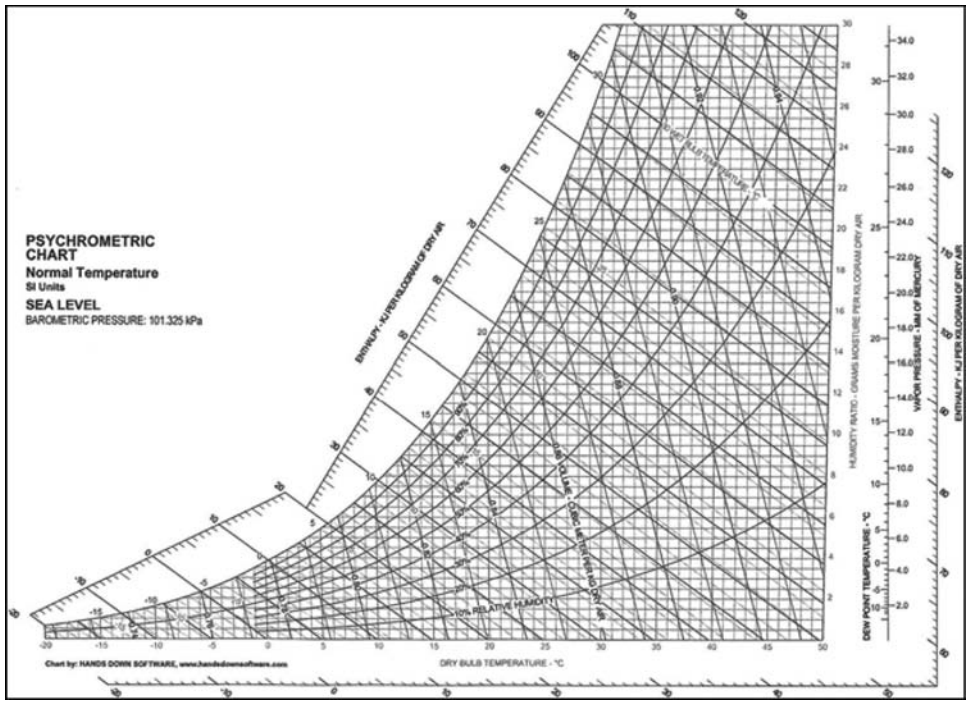


Figure 18 Psychrometric chart.

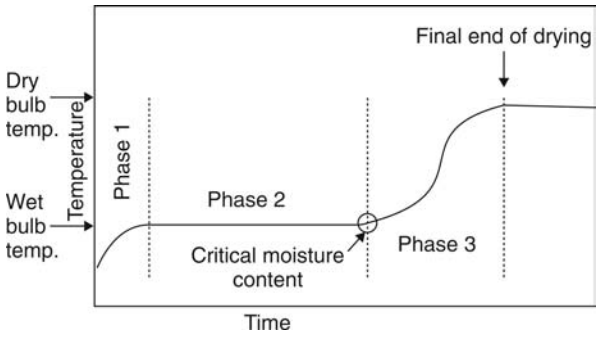


Figure 19 Product temperature changes during drying. *Source*: From Ref. 21.

During fluid-bed drying, the product passes through three distinct temperature phases (Fig. 19).

At the beginning of the drying process, the material heats up from the ambient temperature to approximately the wet-bulb temperature of the air in the dryer. This temperature is maintained until the granule moisture content is reduced to the critical level. At this point, the material holds no free surface water, and the temperature starts to rise further.

The drying capacity of the air depends upon the relative humidity (RH) of the incoming air. At 100% RH, the air is holding the maximum amount of water possible at a given temperature, but if the temperature of the air is raised, the RH drops and the air can hold more moisture. If air is saturated with water vapor at a given temperature, a drop in temperature will force the air mass to relinquish some of its moisture through condensation. The temperature at which moisture condenses is the dew point temperature. Thus, the drying capacity of the air varies significantly during processing. By dehumidifying the air to a preset dew point, incoming air can be maintained at a constant drying capacity (dew point) and hence provide reproducible process times.

Julia ZH Gao et al. (49) studied importance of inlet air velocity to dry product granulated in a high shear granulator and dried in a fluid-bed dryer. The manufacturing process involved granulating the dry components containing 63% water-insoluble, low-density drug in a high shear granulator, milling the wet mass, and drying in a fluid-bed dryer. The granules were dried at an inlet air temperature 60°C. Two different air velocities were examined for their effect on drying uniformity of the product. The authors observed that the excessive velocity indicated by the rapid rise in the exhaust air temperature resulted in nonuniform drying of the product besides resulting in an inefficient process. Granules exhibit an intrinsic breakage propensity during drying, which is dependent on water content and extent of stress exposed to the granules (50). Water content and granule size are critical process and quality parameters during drying process. Nieuwmeyer et al. (51) expanded on the concept that the larger granules contain more water than smaller granules and developed a model to determine the water content of granule based on near infrared (NIR) to monitor the drying process in fluid bed. This model provided median water content of granules and hence the drying end point. According to the authors, based on the amount of moisture in the granules, determined by the NIR technique, granule size determination can be made This approach provides faster way to determine the water content than the off-line measurement more commonly employed.

The combination of granulating solvent and drying conditions could result in conversion of some of the products to alternate crystalline forms during the drying process. Using NIR spectroscopy, knowing basic properties of the drug substance being granulated is critical during fluid-bed drying. Davis et al. (52) studied drying of glycine and microcrystalline cellulose (MCC) (1:1) aqueous granulation in a fluid-bed unit as well as in a tray dryer. Using NIR researcher concluded that the slower drying techniques, such as tray drying, resulted in significantly less formation of α-glycine a polymorph. The drying rate determined the overall polymorph content. The faster the granulation was dried, the more rapid the increase in supersaturation with respect to the metastable form and the greater the thermodynamic driving force for the nucleation and crystallization of the metastable form. The granulation rapidly dried by fluidized bed drying, resulted in more crystallization of α-glycine than the granulations that were tray dried. Drying a high shear wet granulated if not wet milled could be very cohesive. In case of cohesive materials in the fluid bed, the interparticle forces are considerable and they control the behavior of a bed. Thus, during the fluidization, the bed cracks into large portions and the gas tends to flow into the gap between the fissures. Then, channeling occurs in the bed, and eventually, the gas-solid contact is very low and heat and mass transfer operation is weakened. In such cases, a mechanical agitator as a part of the product container, for breaking up the cohesive granulation cake, is employed. Alternative is to pass the wet granulated product through a mill with four to eight mesh screen to break up the lumps.

PROCESS AND VARIABLES IN GRANULATION

Granulation Process

As with any granulating system, with fluid-bed granulation processing, the goal is to form agglomerated particles through the use of binder bridges between the particles. To achieve a good granulation, particles must be uniformly mixed, and liquid bridges between the particles must be strong and easy to dry. Therefore, this system is sensitive to the particle movement of the product in the unit, the addition of the liquid binder, and the drying capacity of the air. The granulation process in the fluid bed requires a binary nozzle, a solution delivery system, and compressed air to atomize the liquid binder. Figure 20 shows the equipment setup for granulation using the fluid-bed processor.

Thurn (53) in a 1970 thesis investigated details of the mixing, agglomerating, and drying operations, which take place in the fluid-bed process. Results indicated that the mixing stage was particularly influenced by airflow rate and air volume. It was suggested that the physical properties of the raw materials such as hydrophobicity might exert a strong influence upon the mixing stage. At the granulation stage, particular attention was paid to the nozzle and it was concluded that a binary design (two-fluid) nozzle gave a wide droplet size distribution yielding a homogeneous granule. The need for strong binders was recommended to aid granule formation and it was suggested that the wettability of the raw materials required particular attention. Several research papers have been published on the influence of raw

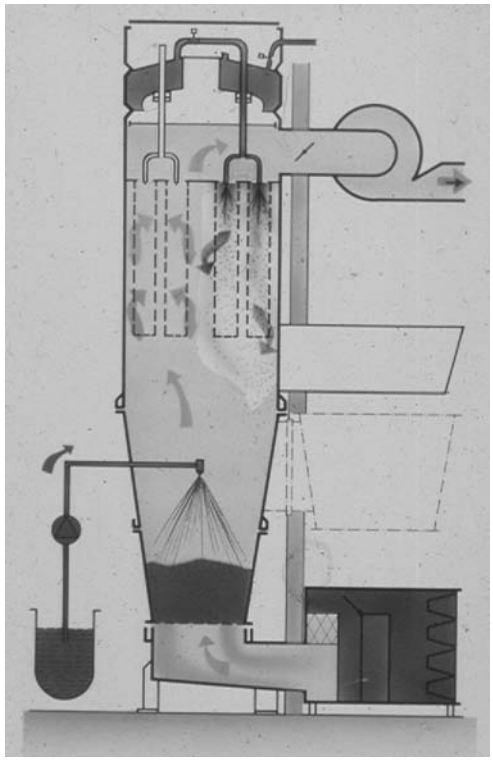


Figure 20 A typical fluid bed processor setup for fluid-bed granulation.

material (38,49,53–68), binder type (5,8,48,53,62,64,69–79), binder concentration, and binder quantity (8,55,60,64,66,71–73,80–96). Binder in the form of foam instead of liquid has been utilized by some pharmaceutical companies. Using foams of aqueous solutions of low molecular weight methocel hypromellose polymers (E3PLV and E6PLV) or conventional solution for fluid-bed granulation did not have effect on physical properties of granules or tablets compressed from these granules. However, they found that because of foam, the granule formation is achieved more efficiently. It was further claimed that variables associated with nozzles were eliminated by using foam and that the water requirement was reduced along with shorter production time (97).

Each phase of the granulation process must be controlled carefully to achieve process reproducibility. When binder liquid is sprayed into a fluidized bed, the primary particles are wetted and form together with the binder, relatively loose and very porous agglomerates. Densification of these agglomerates is brought about almost solely by the capillary forces present in the liquid bridges. A portion of the liquid is immediately lost by evaporation, it is therefore important that the liquid binder sprayed into the bed should be relatively large in quantity compared with that used in high or low shear granulation process. The particle size of the resulting granule can be controlled to some extent by adjusting the quantity of binder liquid and the rate at which it is fed, that is, the droplet size. The mechanical strength of the particles depends principally on the composition of the primary product being granulated and the type of the binder used. Aulton et al. (86) found that lower fluidizing air temperature, a dilute solution of binder fluid, and a greater spray rate produced better granulation for tableting.

Variables

Factors affecting the fluid-bed granulation process can be divided into three broad categories:

1. Formulation-related variables
2. Equipment-related variables
3. Process-related variables

Formulation-Related Variables

Properties of primary material. Ideally, the particle properties desired in the starting material include a low particle density, a small particle size, a narrow particle size range, the particle shape approaching spherical, a lack of particle cohesiveness, and a lack of stickiness during the processing. Properties such as cohesiveness, static charge, particle size distribution, crystalline or amorphous nature, and wettability are some of the properties that have impact on the properties of granules formed. The cohesiveness and static charges on particles present fluidization difficulty. The same difficulties were observed when the formulation contained hydrophobic material or a mixture of hydrophilic and hydrophobic materials. The influence of hydrophobicity of primary particles has been shown by Aulton and Banks (17), where they demonstrated that the mean particle size of the product was directly related to wettability of the primary particles expressed as cos θ (where θ is the contact angle of the particles). It was also reported that as the hydrophobicity of the mix is increased, a decrease in granule growth is observed. Aulton, Banks, and Smith in a later publication showed that addition of a surface-active agent such as sodium laurel sulfate improves the fluidized bed granulation (60). In a mixture containing hydrophobic and hydrophilic primary particles, granule growth of hydrophilic materials takes place selectively creating content uniformity problems. Formulating a controlled release granulation can be accomplished by using fluid-bed granulation. A controlled release matrix formulation of naproxen was successfully developed using fluid-bed granulation (98).

The change in granulation when a new active pharmaceutical ingredient (API) is introduced, even the same material with a different lot number, can be caused by several factors. Surface free-energy is considered as one of the material properties for successful outcome of the granulation process (43).

Low-dose drug content. Wan et al. (27) studied various methods of incorporating a low-dose drug such as cholrpheniramine maleate in lactose formulation with polyvinylpyrrolidone (PVP) as the granulating solution. They concluded that the randomized movement of particles in the fluid bed might cause segregation of the drug and that uniform drug distribution was best achieved by dissolving the drug in granulating solution. The mixing efficiency of drug particles with the bulk material was found to increase in the proportion of the granulating liquid used to dissolve the drug. The optimum nozzle atomizing pressure was deemed to be important to avoid spray drying the drug particles or overwetting, which creates uneven drug distribution. Higashide et al. (99) studied the fluidized-bed granulation using 5-fluorouracil in concentration of 0.3% in 1:1 mixture of starch and lactose. The hydroxypropyl cellulose (HPC) was used as the binder. The ratios of starch and lactose contained in the granules were measured gravimetrically. The researchers found that bigger amount of the drug and starch was found in larger granules than in smaller granules. The results were attributed to the hydrophobicity of the 5-fluorouracil, starch, and the hydrophilicity of lactose.

Binder. A more general discussion on the types of binders used in the pharmaceutical granulations and their influence on the final granule properties can be studied in chapter 4 of this book. Different binders have different binding properties, and the concentration of individual binder may have to be changed to obtain similar binding of primary particles. Thus, the type of binder, binder content in the formulation, and concentration of the binder have major influence on granule properties. These properties include friability, flow, bulk density, porosity, and size distribution.

Davies and Gloor (100,101) reported that the types of binder such as povidone, acacia, gelatin, and HPC all have different binding properties that affect the final granule properties mentioned above. Hontz (94) investigated MCC concentration, inlet air temperature, binder (PVP) concentration, and binder solution concentration effects on tablet properties. Binder and MCC concentrations were found to have significant effect on tablet properties. Alkan et al. (79) studied binder (PVP) addition in solution and as a dry powder in the powder mix. They found a larger mean granule size when the dry binder was granulated with ethanol. However, when the binder was in solution the granules produced were less friable and more free-flowing. Similar finding was confirmed by other researchers (95,96). Binder temperature affects the

Table 1 Heats of Vaporization for Commonly Used Solvents

Solvent	Solvent boiling point °C	Density (g/mL)	Heat of vaporization (kcal/g)
Methylene chloride	40.0	1.327	77
Acetone	56.2	0.790	123.5
Methanol	65.0	0.791	262.8
Ethanol	78.5	0.789	204.3
Isopropanol	82.4	0.786	175.0
Water	100.0	1.000	540.0

viscosity of the solution and in turn affects the droplet size. Increased temperature of the binder solution reduces the viscosity of the solution reducing the droplet size and hence producing smaller mean granule size. Binder solution viscosity and concentration affect the droplet size of the binder. Polymers, starches, and high molecular weight PVP cause increased viscosity, which in turn create larger droplet size and subsequently larger mean granule particle size (71).

Diluted binders are preferred because they facilitate finer atomization of the binder solution, provide the control of the particle size, reduce friability, and increase the bulk density even though the tackiness or binding strength may suffer (8,72,82,86,101).

Under conditions that optimal process parameters are selected, spreading of the binder over a substrate, binder-substrate adhesion, and binder cohesion are the main parameters that influence optimum granulation (102). Planinsek et al. (103) investigated and concluded that the surface free-energy of the formulation ingredients is important, and they found a good correlation between the spreading coefficient of binder over the substrate and the friability of the granules.

Binder solvent. In most instances water is used as a solvent. The selection of solvent such as aqueous or organic depends upon the solubility of the binder and the compatibility of product being granulated. Generally organic solvents, because of their rapid vaporization from the process, produce smaller granules than the aqueous solution. Different solvents have different heats of vaporization as shown in Table 1. Incorporating binder or mixture of binders of low melting point and incorporating it with the drug substance in the dry form can eliminate requirement of solvent for the binder. The temperature of the incoming air is sufficient to melt the binder and form the granules. Seo et al. (104) studied fluid-bed granulation using meltable polymers such as polyethylene glycol (PEG) 3000, or esters of PEG and glycerol (Gelucire 50/13). They showed that melt agglomeration by atomization of a melted binder in a fluid bed occurs by initial nucleation followed by coalescence between nuclei. The nuclei are formed by immersion of the solid particles in the binder droplets provided that the droplet size is larger than the size of the solid particles. The agglomerate growth rate is supposed to be practically independent of the droplet size if the binder viscosity is so low that the droplets are able to spread over the agglomerate surface. If the droplets are unable to spread because of high viscosity, the growth rate is supposed to be inversely proportional to the droplet size. These effects of droplet size are different from those seen in aqueous fluid-bed granulation, probably because the aqueous process is affected by evaporation of binder liquid.

Equipment-Related Variables

Design. To fluidize and thus granulate and dry the product, certain quantity of process air is required. The volume of the air required will vary based upon the amount of material that needs to be processed. The ratio of drying capacity of the process air and quantity of the product needs to be maintained constant throughout the scaling up process. Most of the fluid-bed units available are modular ones, where multiple processes such as drying, granulating, bottom (Wurster) coating, rotary fluid-bed granulating, or coating can be carried out by changing the container specially designed for individual process. The recent offerings by some manufacturers offer single unit with nozzle configuration such that all of these processes can be carried out without changing of the containers (105).

Air-distributor plate. The process of agglomeration and attrition because of random fluidization requires control of the particle during the granulation process. Optimization of the process requires control over fluidized particles. This is a complex phenomenon because of the prevailing fluidizing conditions and particle size distribution, which undergoes changes during the process. As the conditioned air is introduced through the lower plenum of the batch fluid bed, the fluidizing velocity of a given volume of air determines how fluidization will be achieved.

Perforated air-distributor plates, described previously, provide an appropriate means of supplying air to the product. These plates are identified by their percentage of open area. Air-distributor plates that have 4% to 30% open area are normally available. These interchangeable plates or plates with adjustable openings provide a range of loading capacities so that batches of various sizes can be produced efficiently and with uniform quality. To prevent channeling, an operator can select a plate with optimum lift properties. For example, a product with low bulk density requires low fluidizing velocity. A distributor plate having a small open area to give large enough pressure drop may provide uniform fluidization of such a product without reaching entraining velocity and impinging the process filters. Alternatively, a product with higher bulk density can be fluidized and processed using a plate with a larger open area.

Pressure drop (ΔP). The blower creates flow of air through the fluid-bed processor or a fan located downstream from the process chamber. This fan imparts motion and pressure to air using a paddle-wheel action. The moving air acquires a force or pressure component in its direction of motion because of its weight and inertia. This force is called velocity pressure and is measured in inches or millimeters of water column. In operating duct systems, a second pressure that is independent of air velocity or movement is always present. Known as static pressure, it acts equally in all directions. In exhaust systems such as fluid-bed processors, a negative static pressure exists on the inlet side of the fan. Total pressure is thus a combination of static and velocity pressures. Blower size is determined by calculating the pressure drop (ΔP) created by all the components of the fluid-bed processing system. Proper selection of blower is essential in fluid-bed design. A blower with appropriate ΔP will fluidize the process material adequately. However, a blower without enough ΔP will not allow proper fluidization of the product resulting in longer process time and improper granulation. A similar effect can be seen when a product with unusually high bulk density is processed in place of normal pharmaceutical materials, or an air-distributor plate offering high resistance because of its construction. This creates a pressure drop that the blower was not designed to handle. A proper sized blower or fan should develop sufficient ΔP so that the exhaust damper can be used in the 30% to 60% open position. Any additional components such as scrubbers, exhaust HEPA, police filters, catalytic thermal oxidizer, or overall length of the inlet or outlet duct and additional components in the AHU would require a larger blower/static pressure, which can be recommended by the supplier of the fluid-bed processor.

Shaker/blow back cycle mechanism. To retain entrained particles of a process material, process filters are used. To maintain these filters from building up layers of fine process material, and causing higher pressure drop and thus improper fluidization, these filters are cleaned during the granulation process. When bag filters are used mechanical means are used to clean them. This mechanical cleaning of the bag filters requires a cessation of air flow and thus the fluidization during the filter cleaning process. In units with a single-bag house, this results in a momentary dead bed, where no fluidization takes place. This interruption in the process extends the process time. To avoid process interruptions, a multishaking filter bag arrangement is desired, where granulation process is continuous. Using bag filters with a blowback or using cartridge filters, where air under pressure is pulsed through the filters, also achieves the continuous process. Generally, filters should be cleaned frequently during the granulation step, so as to incorporate the fines in the granulation. This is possible if the cleaning frequency is high and the period between the filter cleanings is short. Rowley (106) reported the effect of bag-shake/interval cycle. He discussed the possibility of improving

particles size distribution by optimizing the shake time and the corresponding interval between bag shakes.

Following general guidelines for filter cleaning frequency and duration are recommended.

Single-bag shaker unit

Frequency is 2 to 10 minutes between filter cleanings, and 5 to 10 seconds for shaking. This may vary as the fine powders form granules and the frequency between the shakes or duration of shaking interval can be extended. In any case, the occurrence of collapsed bed should be kept at a minimum in a single shaker unit.

Multiple-bag shaker unit

Since this is a continuous process, frequency of shaking for each section is approximately 15 to 30 seconds between filter cleanings, and about 5 seconds for shaking the filters. If a low-pressure blow back system is used for the bags, the frequency of cleaning is about 10 to 30 seconds.

Cartridge filters

These offer continuous processing and require cleaning frequency of 10 to 30 seconds.

The cleaning frequency and cleaning duration are now offered as an automated system where instead of having to base the cleaning frequency on time, the trigger point for filter cleaning is the buildup of a pressure drop across the filters. This automates the process and eliminates operator input.

Other miscellaneous equipment factors. Granulator bowl geometry is considered to be a factor that may have impact on the agglomeration process. The fluidization velocity must drop from bottom to the top rim of the bowl by more than half to prevent smaller, lighter particles being impinged into the filter creating segregation from heavier product components in the bowl. Generally, conical shape of the container and expansion chamber are preferred where ratio of cross-sectional diameter of the distributor plate to the top of the vessel is 1:2. Most of the suppliers of this equipment offer units with a multiprocessor concept where a single unit can be used for drying, agglomerating, air suspension coating, or rotary fluid-bed processing by changing the processing container while the rest of the unit is common. This approach does eliminate the concerns about the geometry of the processor because of the way these units are constructed.

Process-Related Variables

The agglomeration process is a dynamic process where a droplet is created by a two-fluid nozzle and deposited on the randomly fluidized particle. The binder solvent evaporates leaving behind the binder. Before all of the solvent is evaporated other randomized particles form bonds on the wet site. This process is repeated numerous times to produce desired agglomerated product. There are number of process variables that control the agglomeration. Process variables most important to consider are listed as follows:

1. Process inlet air temperature
2. Atomization air pressure
3. Fluidization air velocity and volume
4. Liquid spray rate
5. Nozzle position and number of spray heads
6. Product and exhaust air temperature
7. Filter porosity and cleaning frequency
8. Bowl capacity

These process parameters are interdependent and can produce desirable product if this interdependency is understood. Inlet process air temperature is determined by the choice of binder vehicle, whether aqueous or organic, and the heat sensitivity of the product being agglomerated. Generally, aqueous vehicles will enable the use of temperatures between 60°C

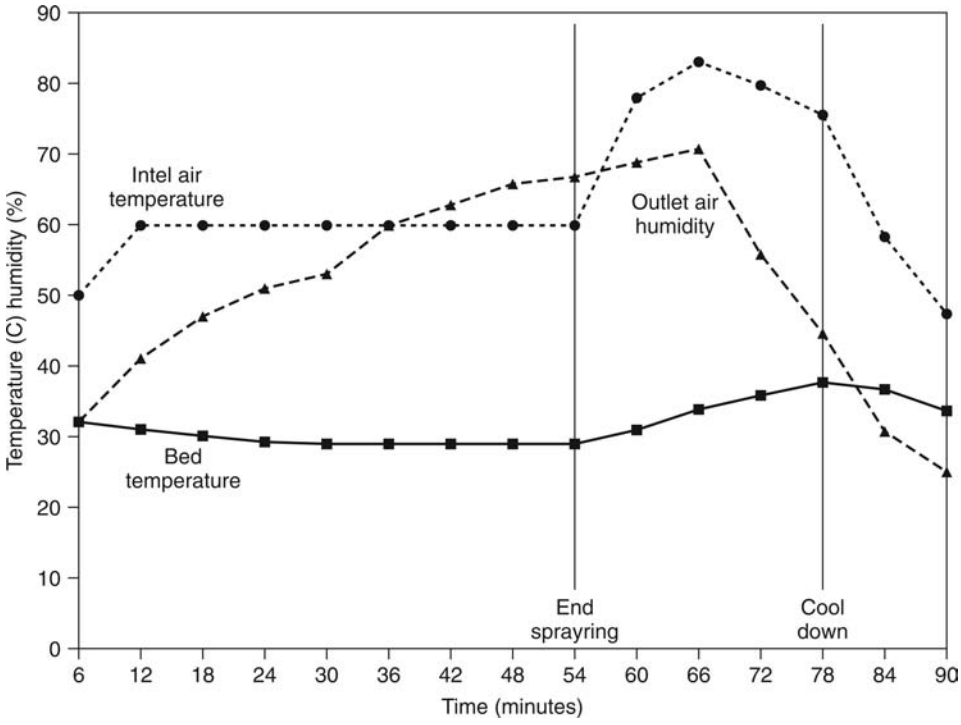


Figure 21 Temperature and humidity changes during the granulation process.

and 100°C. On the other hand organic vehicles will require the use of temperatures from 50°C to below room temperature. Higher temperature will produce rapid evaporation of the binder solution and will produce smaller, friable granules. On the other hand, lower temperature will produce larger and fluffy and denser granules.

Figure 21 shows the relationship of inlet and product air temperature, and outlet air humidity during the granulation process.

The process of drying while applying spraying solution is a critical unit operation. This mass transfer step was previously discussed. The temperature, humidity, and volume of the process air determine the drying capacity. If the drying capacity of the air is fixed from one batch to the next, then the spray rate can also be fixed. If the drying capacity of the air is too high, the binder solution will have a tendency to spray dry before it can effectively form bridges between the primary particles. If, on the other hand, the drying capacity of the air is too low, the bed moisture level will become too high and particle growth may become uncontrollable. This will result in unacceptable movement of the product bed.

As previously discussed, the appropriate process air volume, inlet air temperature, and binder spray rate are critical to achieving proper and consistent particle size distribution and granule characteristics. There are many ways to arrive at the proper operating parameters. The following procedure was found by the authors to be one of the ways one can set the operating parameters when granulating with fluid-bed processors.

1. Determine the proper volume of air to achieve adequate mixing and particle movement in the bowl. Avoid excessive volumetric air flow so as not to entrain the particles into the filters.
2. Choose an inlet air temperature that is high enough to negate weather effects (outside air humidity or inside room conditions). The air temperature should not be detrimental to the product being granulated. (To achieve consistent process year round, a dehumidification/humidification system is necessary, which provides the process air with constant dew point and hence constant drying capacity.)

Table 2 Calculation of Fluid-Bed Spray Rate

Given Process data

Air volume range:

Minimum (1.2 m/sec) _____m^3/hr

Maximum (1.8 m/sec) _____m^3/hr

Inlet air temperature and humidity to be used: _____°C_____%RH

% Solids in sprayed solution _____% solids

From psychrometic chart

Air density at point where air volume is measured: _____m^3/kg air

Inlet air absolute humidity (H): _____ g H_2O/kg air

Maximum outlet air absolute humidity (H): _____ g H_2O/kg air

(Follow line of constant adiabatic conditions)

Use 100% outlet RH for spray granulator or 30–60% RH (as required for column coating)

Calculations for spray rate

Step 1. Convert air volumetric rate to air mass rate

Minimum _____m^3/hr ÷ (60 × _____m^3/kg air) = _____kg air/min

Maximum_____ m^3/hr ÷ (60 × _____m^3/kg air) = _____kg air/min

Step 2. Subtract inlet air humidity from outlet air humidity:

_____(g H2O/kg air) H out − _____(g H2O/kg air) H in = _____g H_2O removed/kg air

Step 3. Calculate (minimum and maximum) spray rate of solution:

This will provide range of generally acceptable spray rates based on the airflow used in the unit

Step 1 (Minimum) _____ × step 2 _____ ÷ [1 − (_____% solids ÷100]
= _____ spray rate g/min) at minimum air flow

Step 2 (Maximum) _____ × step 2 _____ ÷ [1 − (_____% solids ÷ 100]
= _____ spray rate g/min) at minimum air flow

3. Achieve a binder solution spray rate that will not spray dry and will not overwet the bed. This rate should also allow the nozzle to atomize the binder solution to the required droplet size.
4. As stated earlier, a typical air velocity used for spray granulation is from 1.0 to 2.0 m/sec. Table 2 is based on the psychrometric chart, which gives a first guess at determining the proper spray rate for a spray granulation process in a fluid-bed processor.

Variables in the fluid-bed granulation process and their impact on the final granulation were summarized by Davies and Gloor (107), where they state that the physical properties of granulation are dependent on both the individual formulations and the various operational variables associated with the process. The solution spray rate increase and subsequent increase in average granule size resulted in a less friable granulation, higher bulk density, and a better flow property for a lactose/corn starch granulation. Similar results were obtained by an enhanced binder solution, decreasing nozzle air pressure, or lowering the inlet air temperature during the granulation cycle. The position of the binary nozzle with respect to the fluidized powders was also studied. It was concluded that by lowering the nozzle, binder efficiency is enhanced, resulting in average granule size increase and a corresponding decrease in granule friability.

Table 3 Significant Variables and their Impact on the Fluid-Bed Granulation Process

Process parameter	Impact on process	References
1. Inlet air temperature	Higher inlet temperature produces finer granules and lower temperature produces larger stronger granules	77,88
2. Humidity	Increase in air humidity causes larger granule size, longer drying times	38
3. Fluidizing air flow	Proper air flow should fluidize the bed without clogging the filters. Higher air flow will cause attrition and rapid evaporation, generating smaller granules and fines	17,20,77
4. Nozzle and position	A binary nozzle produces the finest droplets and is preferred. The size of the orifice has an insignificant effect except when binder suspensions are to be sprayed.Optimum nozzle height should cover the bed surface. Too close to the bed will wet the bed faster producing larger granules, while too high a position will spray-dry the binder, create finer granules, and increase granulation time.	62
5. Atomization air volume and pressure	Liquid is atomized by the compressed air. This mass-to-liquid ratio must be kept constant to control the droplet size and hence the granule size. Higher liquid flow rate will produce larger droplet and larger granule and the reverse will produce smaller granules. At a given pressure an increase in orifice size will increase droplet size	38,62 90,97
6. Binder spray rate	Droplet size is affected by liquid flow rate, and binder viscosity and atomizing air pressure and volume. The finer the droplet, the smaller the resulting average granules.	17,59,76 77,97

The significant process parameters and their effect on the granule properties are summarized in Table 3

Maroglou (108) listed various parameters affecting the type and rate of growth in batch fluidized granulation (Table 4) and showed the influence of process parameters and the material parameters on the product.

PROCESS CONTROLS AND AUTOMATION

The agglomeration process is a batch process, and accurate repeatable control of all critical process parameters (CPPs) is necessary for a robust system. At the same time, it is a good example of a multivariate process in which effective and reliable process-control tools are necessary to ensure end-product quality. The initial nucleation that takes place as droplet hits the particle surfaces in the fluidized powder bed is characterized by a fast agglomerate growth rate. This phase is followed by slower granule growth phase or a transition phase where amount of nongranulated fines has substantially decreased (52). In this transition region, the slower growth kinetics enable easier process control, and the process end point will most likely found in this place. Earlier designs of the fluid-bed processor used pneumatic controls, which provided safe operation in hazardous area but relied heavily on human actions to achieve repeatable product quality and accurate data acquisition. Current designs use PLCs and personal computers (PCs) to achieve sophisticated control and data acquisition. The operating conditions are controlled to satisfy parameters of multiple user-configured recipes and critical data is collected at selected time intervals for inclusion in an end-of-batch report. Security levels protect access to all user-configured data with passwords permitting access only to selected functions. With the appropriate security level not only are operating conditions configured, but also identification of each valid recipe and operator is entered. The identification is verified before any operator actions are permitted and is included with the end-of-run report. The use of computer-related hardware requires some additional validation, but with coordination between the control system provider and the end user, the validation of software can be managed. Figure 22 shows the pneumatic control panel and Figure 23A, B shows PLC-based control panel with a typical operator screen.

The most important sensors for control of the drying process are inlet and exhaust air temperature and sensor for air flow measurement, located in the air transport system. Other sensors for the spray agglomeration process are product bed temperature, atomization air pressure and volume, pressure drops (across the inlet filter, the product container with

Table 4 Influence of Operating and Material Parameters on the Granulated Product

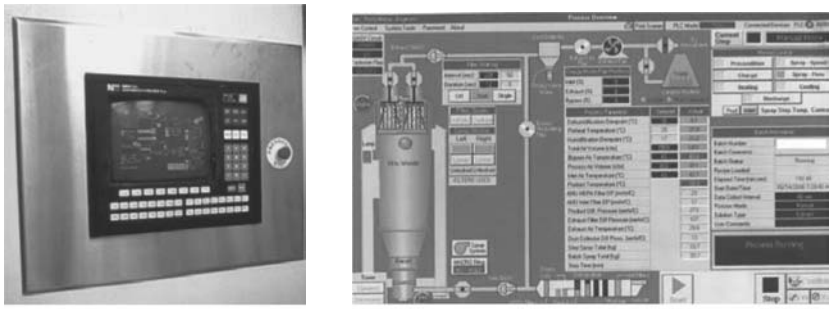
A. Operating parameters		
	Droplet size	NAR[a]
		Atomization air velocity
Rheology		
		Surface tension
		Nozzle position
		Nozzle type
	Bed moisture content	Solution type and feed rate
		Bed temperature
		Fluidization velocity
		Aspect ratio
		Nozzle position and atomization velocity
		Air distributor design
		Jet grinding
	Binder solution/suspension concentration	Bridge strength and size
		Rheology
B. Material parameters		
	Binder solution/suspension concentration	Bridge Strength and size
		Rheology
	Type of Binder	Molecular length and weight
	Wettability	Particle-solvent interaction
		Surface tension
		Viscosity
	Material to be granulated	Average particle size
		Size distribution[a]
		Shape and porosity
		Drying characteristics
		Density and density differences[b]

[a]NAR is the ratio of air-to-liquid flow rates through the nozzle of a twin fluid atomizer expressed either in mass units or in volume units (air at STP).
[b]Especially important relative to elutriation and segregation.

Figure 22 Pneumatic control panel. *Source*: Courtesy of The Glatt Group.

the product being processed and outlet process air filter), inlet air humidity or dew point, process filter cleaning frequency and duration, spray rate for the binder solution, and total process time.

All of these sensors provide constant feedback information to the computer. These electronic signals may then be stored in the computer's memory and then recalled as a batch report. With this ability to recall data analysis, a greater insight can be gained into the process.



(A) (B)

Figure 23 (**A**, **B**) PLC-based system. *Source*: Courtesy of The Glatt Group.

Advances in Process Control and Automation

The degree of the instrumentation of pharmaceutical unit operations has increased. This instrumentation provides information on the state of the process and can be used for both process control and research. A central part of optimizing production is increasing the level of automation. Besides monitoring the process parameters, numbers of approaches are being developed for measuring the moisture of the product to determine the end point of the process and consequently the in-process particle size analysis. Numbers of publications discuss on-line moisture measurement and process end-point determination using NIR.

Near Infrared

The nondestructive character of vibrational spectroscopy techniques, such as NIR, makes them novel tools for in-line quality assurance (109). NIR has been widely used for the measurement of water in various applications (110) NIR can be applied for both quantitative analysis of water and for determining the state of water in solid material. This gives a tool for understanding the physicochemical phenomena during manufacture of pharmaceutical granulation. Accurate NIR in-line particle size analysis of moving granules is challenging, because the scattering and absorptive properties of the granules vary. In addition, since particle size data are not directly obtained using NIR techniques, pretreatment of spectra and chemometric modeling are needed.

The pharmacopoeias have defined some characteristics of analysis with NIR (111,112). Developing a functional automation system requires new measuring techniques; new in-line measuring devices are needed (113–117). Solid-water interactions are one of the fundamental issues in the pharmaceutical technology. State of water in solid material may be characterized using X-ray diffraction, microscopic methods, thermal analysis, vibrational spectroscopy, and nuclear magnetic resonance spectroscopy (118). Traditionally, the control of fluidized bed granulation has based on indirect measurements. These control methods applied utilize the properties of process air by Schaefer and Worts (48). Frake et al. (119) demonstrated the use of NIR for in-line analysis of the moisture content in 0.05 to 0.07 mm pellets during spray granulation in fluid-bed processor. Rantanen et al. (120,121) described a similar approach for moisture content measurement using a rationing of three to four selected wavelengths. He and his coworkers reported that the critical part of in-line process was the sight glass for probe positioning that was continuously blown with heated air. They also reported spectra baselines caused by particle size and refractive properties of the in-line samples; they recurred to analyze several data pretreatments to eliminate these effects on their fixed wavelength setup. Solvents other than water have also been evaluated for real-time quantification. Nieuwmeyer et al. (51) determined the particle size and the drying end point of granules using NIR. Lipsanen et al. (122) evaluated the instrumentation system to determine the parameters expressing the changing conditions during the spraying phase of a fluid-bed process using in-line spatial filtering technique (SFT) probe to the variations in properties of product being processed. Vázquez recently provided comprehensive review of FT-NIR application in

measuring fluid-bed drying end (123). Rantanen et al. (124) used NIR to monitor the moisture as well as air flow. Using in-line multichannel NIR the multivariate process data collected was analyzed using principal component analysis (PCA). The authors showed that robust process control and measurement system combined with reliable historical data storage can be used for analyzing the fluid-bed granulation process. PCA modeling proved a promising tool to handle multidimensional data that was collected and for reduction of the dimensionality of process data. FT-NIR spectra gave useful information for understanding the phenomenon during granulation. Rantanen et al. (125) further studied the application of NIR for fluid-bed process analysis. The authors used NIR to study moisture measurement combined with temperature and humidity measurements. By controlling the water during the fluid-bed granulation the granulation process was controlled. They concluded that the varying behavior of formulations during processing can be identified in a real-time mode. Thus, they found that NIR spectroscopy offered unique information on granule moisture content during all phases of granulation.

Other Approaches for Process Control

Self-organizing maps. On-line process data is usually multidimensional, and is difficult to study with traditional trends and scatter plots. Rantanen et al. (126) has suggested new tool called "self-organizing maps" (SOM) for dimension reduction and process state monitoring. As a batch process, granulation traversed through a number of process states, which was visualized by SOM as a two-dimensional map. In addition, they demonstrated how the differences between granulation batches can be studied.

At-line measurement. Laitinen et al. presented a paper at a recent conference (127) proposing at-line optical technique to study particle size. Using CCD camera with optics and illumination units with stabilized collimated light beams, authors took two images of 36 granule samples by illuminating the samples alternatively. Two digital images with matrices of their gray scale values were obtained and the differences between two matrices were calculated. This method provided very rapid (1 min/sample) measurement of particle size with a very sample size (less than 0.5 g).

Focused beam reflectance measurement. This device uses a focused beam of laser light that scans, in a circular path across a particle or particle structure passing in front of the window. Upon hitting the particle, light is scattered in all directions. The light scattered back toward the probe is used to measure the chord length or the length between any two points on a particle. Such devices are supplied commercially and claim to be useful for monitoring on-line measurement of particle size in the fluid-bed granulation process.

Artificial neural network. Neural networks have been used by scientists for optimizing formulations as an alternative to statistical analysis because of its simplicity for use and potential to provide detailed information. The neural network builds a model of the data space that can be consulted to ask "what if" kinds of questions. Recently, there has been interest in using artificial neural network (ANN) for process control. Similar to the human brain, an ANN predicts events or information based upon learned pattern recognition. ANNs are computer systems developed to mimic the operations of human brain by mathematically modeling its neurophysiological structure (i.e., its nerve cells and the network of interconnections between them). In ANN, the nerve cells are replaced by computational units called neuron and the strengths of the interconnections are represented by weights (128). This unique arrangement can simulate some of the neurolocal processing abilities of the brain such as learning and drawing conclusions from experience (129). Using the process-control system, quality assurance results, or energy usage data, an ANN develops supervisory set points for the system. When ANN and process-control systems are used together they form a product control system. Product control occurs when a system measures defined product attributes in real time and uses the knowledge to adjust the control system. While process-control system runs the process (i.e., fans, motors, and heaters) the ANNs control the moisture level and consistency of

the product. The fluidized-bed processor process-control system includes an operator interface, sensing elements, and final control elements. The inputs in that case are inlet air temperature, outlet air temperature, airflow rate, and energy consumption. Additional contributing factors are fouling coefficient of the dryer bags, quantity of product in the processor, and the type of product with its unique characteristic. Watano et al. (130) described practical method for moisture control in fluid-bed granulation by means of neural network. Wet granulation of pharmaceutical powder was conducted using an agitation fluidized bed, and moisture content was continuously measured by IR moisture sensor. A neural network system for moisture control was developed using moisture content and its changing rate as input variables, and the moisture control characteristics were investigated by the neural network system with backpropagation learning. Good response and stability without overshoot were achieved by adopting the developed systems. This system also maintained favorable stability under various operating conditions. Several researchers have published papers detailing use of ANN for different applications (131–133).

Three-dimensional particle measurement. To address the issues with in-line measurement of particle size because of probes and windows are prone to coating, Närvänen et al. (134) used a camera described image analysis method to measure particle size in 3D and in color. In on-line application they were able to successfully retrieve images and were able to determine the median granule size trend.

Triboelectric probe for moisture measurement. Portoghese et al. (135) developed a method to measure moisture content in the fluid bed by using a triboelectric probe.

Fuzzy logic. Koerfer and Simutis (136) showed that fuzzy logic can be used to for simulated real-time observations of fluidized bed agglomeration process and in general eliminate number of trial and error approaches for the process. Watano and coworkers (137) have used fuzzy logic to control granulation processes in agitation fluid bed. Additional information on process control for granulation processes can be obtained in chapter 26 of this book.

PROCESS SCALE-UP

In fluid-bed granulation, the spreading of the binder liquid droplets in the powder bed is much more crucial, because it is the phenomenon that controls most of agglomeration. The process parameters are all interdependent, hence it is critical to obtain stable regime by fully balancing the different input variables as you scale up the process. Scale transfer in fluid-bed granulation involves similar equipment designs, parameters related to starting materials, input variables such as spraying conditions, amount of solvent energy input and efficiency and processing time. More detailed engineering treatment can be seen in chapter 25 of this book.

Scale-Up and Equipment Design

The scale-up from the laboratory equipment to production size units is dependent on equipment design. The importance of scalability is well-understood and accepted by the manufacturers of fluid-bed processors. Various sizes in their product line are logically designated and manufactured. The design and selection of the processor are very important for the laboratory and production unit. Because airflow is one of the components of the drying capacity of a fluid-bed system, ratio of air volume per kilogram or liter of the product is very critical to achieve scale-up that is linear. The other design feature is the cross-sectional area of the product container, and how it has been designed throughout the various sizes that a manufacturer supplies. The relationship between various sizes of the process containers can be utilized to calculate the scale-up of binder spray rate, and if the cross-sectional area is designed linearly, then the spray rate scale-up can be linear. Nozzle position should always be such that it should cover the powder bed, and hence the location and the number of nozzle ports are an important consideration as you scale up.

Scale-Up and Process Factors

The fluid-bed agglomeration process is a combination of three steps, namely, dry mixing, spray agglomeration, and drying to a desired moisture level. Granule size is directly proportional to the bed humidity during granulation (48), and hence control of this humidity during scale-up is essential.

Gore et al. (138) studied the factors affecting the fluid-bed process during scale-up. The authors found that processing factors that most affected granule characteristics were process air temperature, height of the spray nozzle from the bed, rate of binder addition, and the degree of atomization of the binder liquid.

The atomizing air pressure and the wetness of the bed are two of the most important elements of fluid-bed granulation. A higher atomizing air pressure yields a finer droplet of binder solution. Therefore, granule growth (as described earlier in this section) is affected by the atomizing air pressure. A major factor, which must be considered during the scale up of fluid-bed granulation process, is maintaining the same droplet size of the binder for assuring successful scale-up. Another study (139) confirmed the influence of spray nozzle setup parameters and drying capacity of the air. The study concluded that more attention should be to the easily overlooked nozzle atomizing air pressure and volume. When considering the atomizing air pressure, attention must be paid to ensure enough air is delivered to the nozzle tip. This can be assured by placing air pressure and volume measurement devices at the nozzle. The data also shows that the drying capacity of the process air influences the final granulated particle size.

Jones (140) has suggested various process-related factors that should be considered during the scale-up of a fluid-bed processing. Because of the higher degree of attrition in the larger unit compared with the smaller unit the bulk density of the granulation from the larger fluid bed is approximately 20% higher than the smaller unit. He also reemphasized the importance of keeping the bed moisture level below critical moisture level to prevent the formation of larger agglomerates. Since the higher air flow along with the temperature (drying capacity) in a larger unit provides higher evaporation rate, one must maintain the drying capacity in the larger unit such that the bed temperature is similar to the smaller unit bed temperature. This can be accomplished either by increased spray rate, increased air temperature, increased airflow, or by the combination of these variables to obtain suitable results. Since the ratio of bed depth to the air distributor increases with the size of the equipment, the fluidization air velocity is kept constant by increasing the air volume. In the past, the scale-up was carried out by selecting best guess process parameters. The recent trend is to employ the factorial and modified factorial designs and search methods. These statistically designed experimental plans can generate mathematical relationships between the independent variables such as process factors and dependent variables such as product properties. This approach still requires an effective laboratory/pilot scale development program and an understanding of the variables that affect the product properties.

In summary, when scaling up, following processing conditions should be similar to the pilot scale studies:

1. Fluidization velocity of the process air through the system
2. The ratio of granulation spray rate to drying capacity of fluidization air volume
3. Droplet size of the binder spray liquid

Each of these values must be calculated based on the results of the operation of the pilot size unit. Pilot size equipment studies should also be conducted in a wide range to determine the allowable operating range for the process.

Another chapter of this book provides fluidized-bed scale-up and should be reviewed. Matharu and Patel (141) presented a scale-up case study where low-dose multiple-strength product (0.5–5% w/w active) was spray granulated and scaled up from a pilot scale fluid-bed processor and scaled up to production size equipment. Their approach was based on matching air velocity between the two scales of operation. The impact of droplet size was determined by varying the independent parameters. On the basis of their study, authors have suggested an equation, which takes into account material and equipment parameters. Rambali (142) scaled

up granulation process from small (5 kg) to medium (30 kg) to large (120 kg) with an aim to obtain target geometric mean granule size of 400 μm. The scaling-up was based on the relative droplet size and the powder bed moisture content at the end of the spraying cycle. Authors found that the effect of the change in relative droplet size on the granule size was different for each fluid bed. They applied experimental design on the small- and medium-scale unit, and regression models for the granule size were proposed to scale up the granulation process on the small to medium scale. Using only the relative droplet size authors were able to scale up the process to the larger unit.

PROCESS TROUBLESHOOTING

In the life cycle of a product, troubleshooting is inevitable. Over the years a raw material vendor may stop supplying an ingredient, requiring a replacement. A producer may change the manufacturing process, and while the new material may meet the specifications on their certificate of analysis, it may have an unexpected and adverse impact on your product and/or process. A material for exhaust air filters may be discontinued affecting process air volume performance. Finding a new fabric and identifying a test that will quantify its equivalence is certainly a challenge, and the list goes on. With all of this in mind, when does process troubleshooting start? When a production batch fails? When the finished product attributes begin to drift toward the failure limits? When the process and equipment parameters begin to drift? Or does it start during formulation development? Process troubleshooting should be both proactive and reactive. A product that is formulated well and a process that has a broad operating window and is well characterized will be easier to troubleshoot once the inevitable occurs. The goal during the development process is this: for a well-designed product the raw materials and process variables and their impact on critical quality attributes (CQA) are generally well understood. Applying statistics, via design of experiments (DoE), will quantify the impact of the variables and the robustness of a product and its process. Continued use of DoE can confirm these findings during scale-up to pilot and production scale equipment, and this leads to the establishment of operating ranges that were derived experimentally rather than arbitrarily [such as applying operational qualification (OQ) limits for instance].

Metrics: Granule Properties and Tableting

The variables in fluidized bed processing have an impact on granule properties such as particle size distribution and bulk (and tap) density, two metrics that are valuable tools in product and process understanding as well as in retrospective (or reactive) troubleshooting. These in turn are likely to impact tablet attributes such as hardness, friability, disintegration, and possibly dissolution rate. Unfortunately, in too many instances, particle size distribution (both before and after any milling or sizing step) and bulk and tap densities are not routinely recorded as in-process parameters beyond the process validation activities. They may be taken under protocol up to that point, but to avoid the potential that a specification may eventually be required (possibly leading to granulation batch rejections on an arbitrary basis), these metrics are often eliminated from the batch records for routine production. This is unfortunate. If a production batch exhibits failures such as delamination of tablets or friability, the troubleshooter must work from the tablet press backward. Granulation machine parameters may give insight into the root cause and the properties of the granules themselves will likely help to confirm the findings. The fluid-bed spray granulation process should take place slowly and deliberately, building granules to the desired size range by the precise control of CPPs. A subsequent milling step should not substantively alter the particle size distribution of the dried granulation. It should merely shift the small fraction (typically less than 5%) of oversized granules into the size range of the aggregate. It should also not be of a type that is aggressive or milling may dramatically affect the performance of the granulation on a tablet press. By nature, fluid-bed granules are porous and friable in comparison with those made using a high shear granulator. They do not need the force of a high shear mill to break the oversize agglomerates. In fact, a high shear mill may do a considerable amount of damage to the granules, causing an unnecessary amount of fines, and this would almost certainly impact the tableting properties. A comparison of the particle size distributions taken before and after the milling step will expose the magnitude of impact of the mill.

A poorly functioning spray nozzle will typically cause a combination of fines and coarse, dense granules. It does so as a consequence of nonuniformity of droplets—the majority is a fine mist, but there is likely to be a component of very large droplets (exceeding 50 μm) that form granules with nearly liquid centers and the resulting particle size distribution may be bimodal. The consequent dense granules will result in nonuniformity of moisture distribution because there is little interstitial porosity. Internal moisture cannot move to the surface for evaporation. The surfaces may dry and "case harden" making it all the more likely that the moisture will become entrapped. In some cases, the wet granules will blind the screen during the final milling step, and in others the mill will grind them finer and mask their existence. In either case, there is a strong possibility that their presence will have an adverse impact on tableting properties. It may seem that taking the moisture content of granules of various sizes would be an effective metric for identifying this problem. However, by the time the batch has been tableted, the moisture will be equilibrated in the remaining granulation and the disparity shadowed. If the problem is seen in a particular granulation batch, moistures should be taken as soon as the batch has finished. In a dried granulation, the high density of these granules may be revealed in the particle size distribution as a rogue peak, and bulk and tap density numbers for the aggregate will likely increase.

Proactive Troubleshooting—Design of Experiments

A comment often heard when discussing formulation and product development is as follows: "DoE? We don't have the time or the resources to do it." A consequence is that all too often a product that is successful in the clinic is a menace on the manufacturing floor. When used effectively in small-scale batches, DoE is a learning tool—it helps identify and quantify CPPs. The selected response variables may extend well beyond the CQAs, sometimes teaching you things you didn't expect. At the pilot scale, successful experimentation in a broadened domain establishes the operating limits for the CPPs. A machine's operating limits are too often selected either arbitrarily or simply reflect the OQ ranges identified during the equipment qualification stage of the installation. Unfortunately, these values are generated from the data taken from an empty machine, and this will almost certainly not reflect the behavior during batch processing. Finally, a limited number of early production scale batches should confirm the results of the pilot scale DoE.

Figure 24 shows the particle size distributions for a series of batches produced in a pilot scale (220 L) top spray fluidized bed granulator for a domain screening study.

There is a significant response within the selected domain for the parameters being evaluated. Isolating the results by process parameters, the responses can be seen individually in Figures 25 to 27. In Figure 25, it is apparent that inlet air temperature has a significant impact on the average particle size, with the peak shifting from 250 μm (60 mesh) for the high inlet temperature experiment to 420 μm (40 mesh) for the low value. What is notable is that the size distribution is very narrow—in each batch, more than 50% is retained on one screen. It also

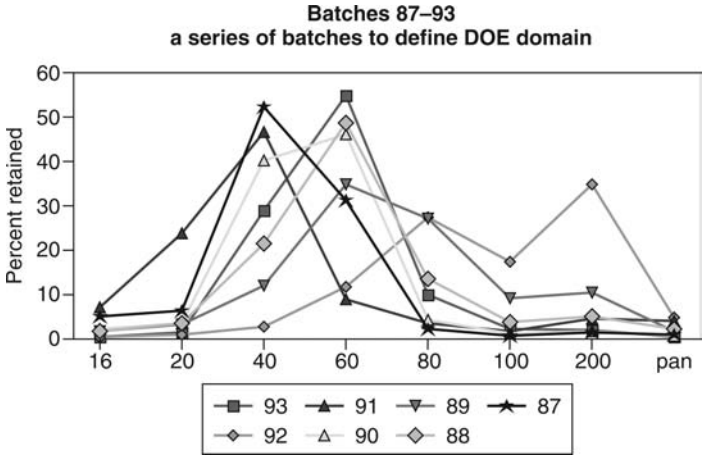


Figure 24 Particle size distribution for a fluid-bed spray granulation DoE. *Source*: Courtesy of Glatt Air Techniques Inc..

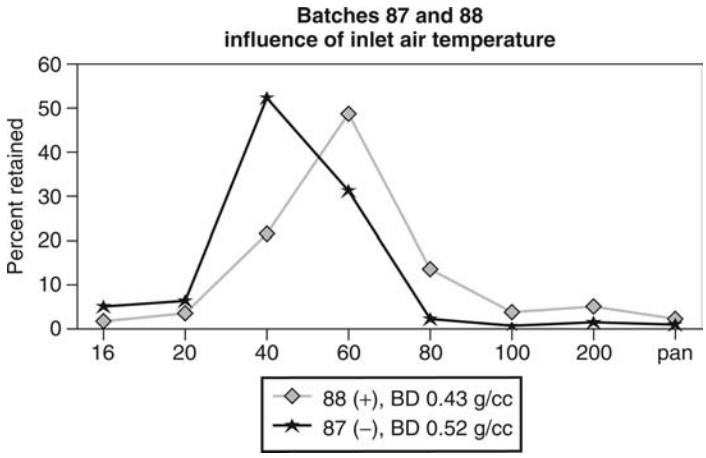


Figure 25 The influence of inlet air temperature on particle size and bulk density (high and low values). *Source*: Courtesy of Glatt Air Techniques Inc.

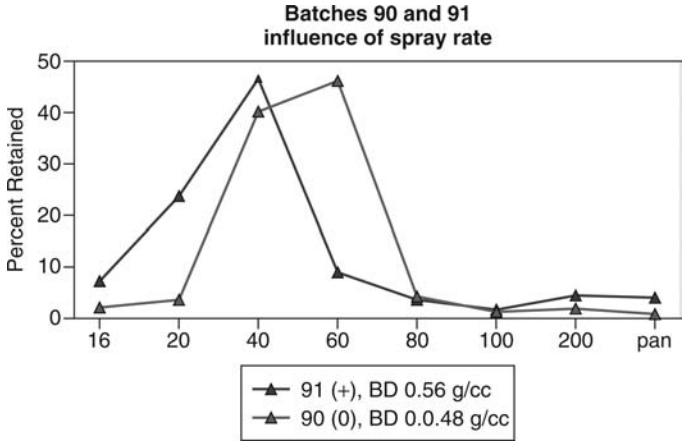


Figure 26 The influence of spray rate on particle size and bulk density (center point and high values). *Source*: Courtesy of Glatt Air Techniques Inc.

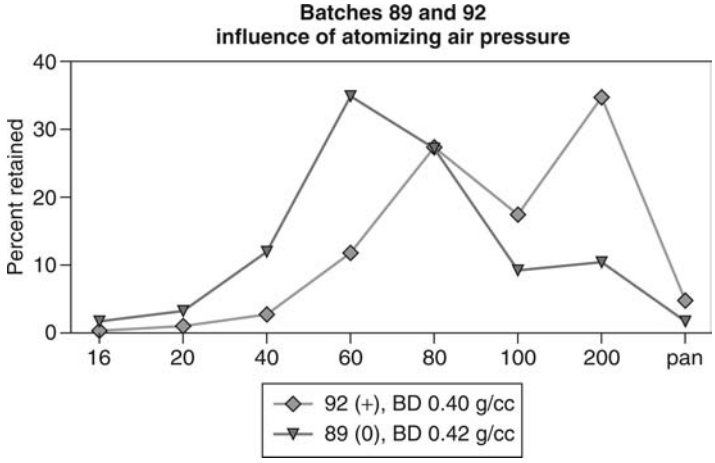


Figure 27 The influence of atomizing air pressure on particle size and bulk density (center point and high values). *Source*: Courtesy of Glatt Air Techniques Inc.

profoundly impacts the bulk density for the granulation—0.43 g/cc and 0.52 g/cc, a 20+% difference. This commonly has a considerable influence on tableting properties, particularly on the potential for delamination and tablet friability (commonly seen with low-density granulations).

In Figure 26, it is also apparent that spray rate has an impact, and in this case, the domain value selected as "high" was in fact too high.

The resulting granulation was coarse; though after milling, it was reasonable in particle size distribution. However, it took a considerable amount of time for the sizing step, and the difference before and after milling was notable. As a consequence, the domain was adjusted and the high value for spray rate was lowered. This particular batch teaches a valuable lesson—a goal of DoE is to quantify the impact of process parameters on the selected response variables. To gain the most knowledge about the robustness of a product, it is prudent to operate within a broad domain, but this exposes the process to the potential that a batch may fail, diminishing the power of the DoE to an extent. For this reason, it is suggested that the first batch or two processed for the study are intentionally (not randomly) selected as the candidates that have the greatest propensity to fail—the extremes of the DoE. If in fact a batch "fails" during processing, meaning that it cannot be produced successfully or dramatically impacts productivity or efficiency, the domain should be revisited. Complete randomization of a series of experiments may not be the best alternative because if a batch produced in the middle of the study is a disaster, some of the power of the study may be lost, or other batches may need to be added (such as edge points in a center composite design). As the figures demonstrate there is a notable response for particle size distribution and bulk density within the tested domain. Interestingly, all batches tableted successfully—hardness, friability, disintegration, and dissolution all met specification. The product and process are robust. What is also interesting is that the DoE revealed something unexpected—the response variables need not be limited to product considerations. A fluidized bed spray granulation process starts with raw materials that are small in particle size. The outlet air filter type must be selected with care to assure that the yield and potency of the finished product will be acceptable. Additionally, from a productivity perspective, it is best that multiple batches can be produced without the need for outlet air filter cleanings. The need to remove, replace, and clean an outlet filter after every batch is undesirable. Operators and the work area are exposed to airborne product, and the time for the exchange impedes productivity and increases the chances of damage to the filter because of excess handling and washing. In this series of experiments, it was seen that outlet filter differential pressure was strongly related to the moisture of the product during the spray granulation process. Figure 28 shows the filter pressure response for the first few minutes of processing.

Batch "C" shows a filter pressure peaking at 500 mm, and at this pressure, even for a short duration there is a possibility of catastrophic failure (rupture or separation of the filter

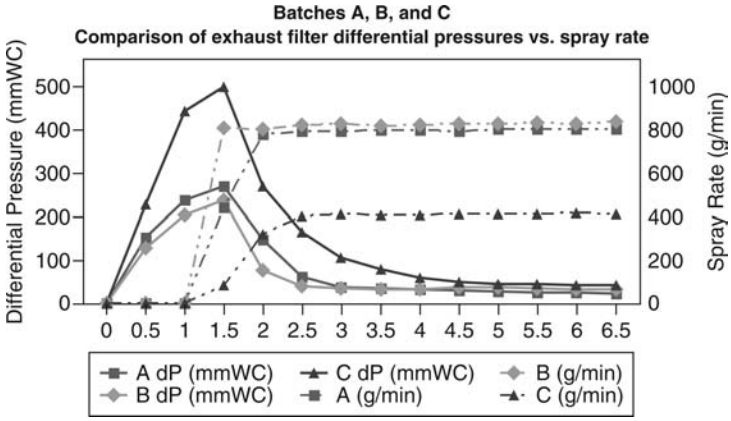


Figure 28 Filter differential pressure and spray rate for various batches. *Source*: Courtesy of Glatt Air Techniques Inc.

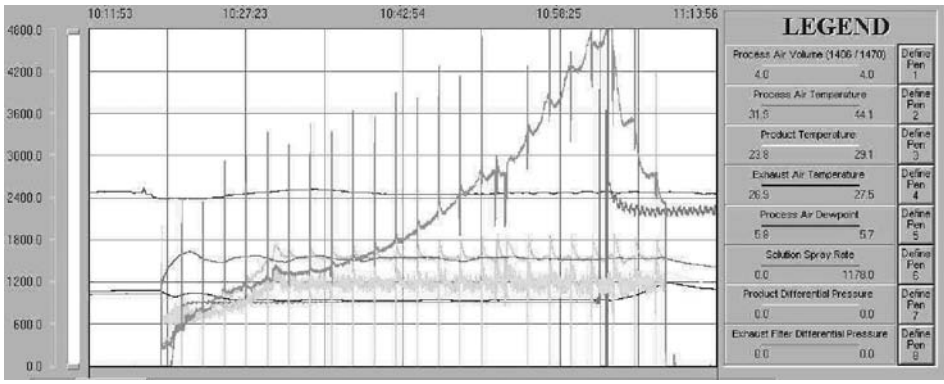


Figure 29 Historical trend display showing escalating outlet filter pressure as a consequence of low in-process moisture content. *Source*: Courtesy of Glatt Air Techniques Inc.

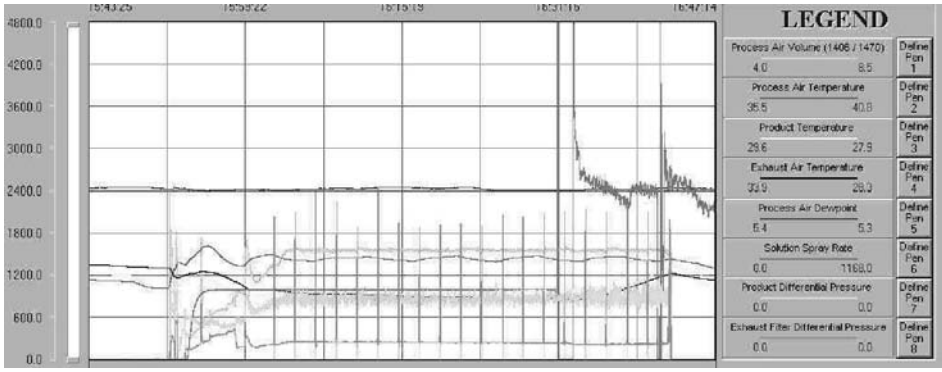


Figure 30 Historical trend display showing outlet filter pressure at a low and constant value as a consequence of higher in-process moisture content. *Source*: Courtesy of Glatt Air Techniques Inc.

from its "D" ring). Partial or complete loss of the batch is a possibility and should be avoided if at all possible. A process air volume "ramp" of about 10 minutes (rising from a lower value initially to the desired high air flow rate for the duration) was employed to eliminate the problem at the front end of the process. However, batches produced with low in-process moistures during spraying resulted in filter pressure building to a high level later as the batch progressed, and this too is undesirable. High spray rates kept the filter pressure low from beginning to end, and from a production perspective, this is far more attractive. Multiple batches can be produced, improving operating efficiency and keeping operator exposure to the API at a minimum. Tracings for filter differential pressure for dry and wetter batches are illustrated in Figures 29 and 30.

For commercialization, the scale-up (tech services) staff can select from a variety of process conditions. However, it is in the company's best interest to select a process that yields higher in-process moisture so that productivity is enhanced. Both the shorter process time and the opportunity to produce many batches between filter washings are strongly positive findings of the DoE study.

Reactive Trouble Shooting: Acquired Data as a Process Troubleshooting Tool

A significant number of companies continue to record in-process data by hand (via the process operators). The typical recording interval depends on the total process time but in general it is once every 10 to 15 minutes. Although it is an accurate representation of the process when the operator recorded the readings, it is of very little use for retrospective troubleshooting. A fluid-

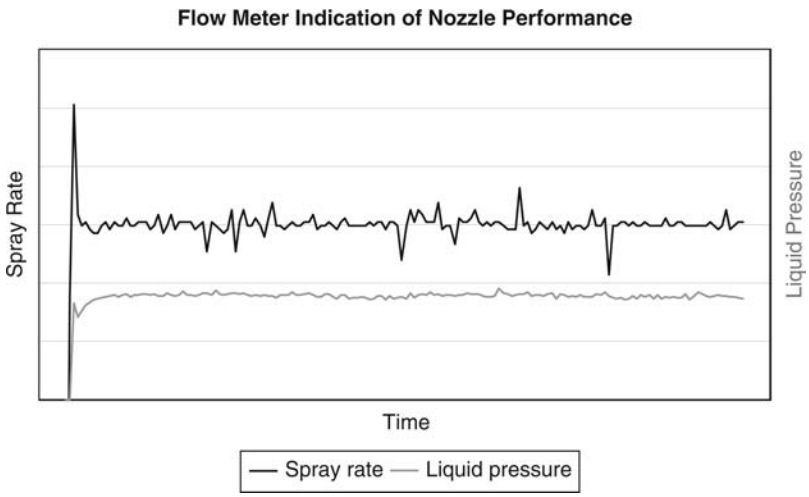


Figure 31 Tracing showing erratic spray nozzle performance. *Source*: Courtesy of Glatt Air Techniques Inc.

bed process is very dynamic and the "point in time" numbers do not reflect the intrinsic and rapid oscillation of parameters such as process air volume and product and filter differential pressure. Additionally, erratic variability in the spray rate, which would indicate a spray nozzle defect, would not be reflected at all in the hand written data. Electronically acquired data is superior from the perspective that it is recorded more frequently. The typical recording interval is 30 to 60 seconds, and as such, the resolution is improved by a factor of 10× to 30×. It is also not subjective, as is the operator collected data. The increased resolution affords the possibility that the root cause for the out of spec batch can be identified. Figure 8 shows a tracing for spray rate in which the erratic peaks and troughs are an indication of a defective spray nozzle. This type of behavior is a frequent reason for poor particle size distribution. A granulation produced under these conditions may exhibit a bimodal particle size distribution with the coarse fraction containing higher moisture content than the aggregate, as described earlier.

The benefit of historical data is illustrated in Figure 31, in which the data recording rate was 60 seconds.

However, some process variables, including spray rate, react much more quickly, and at this interval, much of the actual behavior is lost. By contrast, a historical trend utility in some control systems displays data in one second intervals, a 60-fold improvement in resolution. In a recent laboratory trial, a spray pump defect caused a one to three second surge or lag in spray rate. Subsequent to batch processing, the data acquired in one minute intervals were plotted and this behavior was seen only a few times in the hour long process, and the amplitude was not seen. However, on the historical trend screen, the defect was seen more than 30 times and the surge and lag amplitude was seen to be as much as 50% of the set point. Although the finished product did not exhibit negative consequences, the behavior of the pump was unacceptable and requires intervention to determine and repair the root cause. Resolution is "revelation," and the shorter the collection interval, the more effective acquired data will be as a troubleshooting tool.

The previous examples show the effectiveness of using acquired data as a reactive troubleshooting tool. In fact, when minor and/or major excursions for CPP occur or a batch outright fails, beyond inquiring of the operators to sort out the reasons, it is often the most independent and reliable source of information. It can confirm or refute the hypothesis. It may seem that the acquired data is only effective as a troubleshooting tool. However, it is extremely valuable for process understanding and anticipating a problem before it becomes sufficiently serious that a batch or series of batches is lost. As such, examination of the data for ALL batches is highly recommended.

Table 5 Summary of Trouble Shooting Process Challenges

Issue	Most likely root cause
1. Poor particle size distribution (coarse, wet granules mingled with acceptable granules and fines)	Spray nozzle performance
Proposed action	Prior to processing of any batch, conduct a functional test of the spray nozzle to assure that it is performing correctly. Poor particle size control and nonuniform distribution of moisture is most commonly the fault of a defective spray nozzle. An effective spray nozzle cleaning/maintenance and testing program is essential. A functional check of the spray nozzle at the anticipated spray rate and atomizing air pressure/volume must be conducted after a major cleaning. Replacement of the nozzle head (port and air cap assembly) between batches is generally sufficient as a minor clean to assure proper performance. The reason for this is that the o-rings and sealing from which the defects originate are in the nozzle body itself. If this component is not disturbed between batches, it is highly unlikely that the nozzle will malfunction during a subsequent batch.
2. Lumps/large aggregates	Coalescence of granules—transition into ball growth
Proposed action	Transition into ball growth is typically seen in the latter stages of the spraying process. Ball growth is indicated by the presence of a considerable number of very large lumps comprised of granules, not starting material. Resolution of the problem depends on discerning its onset. The progression of particle size growth is powder to nuclei to uniform agglomerates. As granule size grows, there is less overall surface area to accumulate the spray liquid. The velocity and pattern density also decrease and there is a tendency for the material in proximity to the spray nozzle to be overwetted. The excess surface moisture results in coalescence of granules and eventually ball growth. While this is not a common occurrence, it is undesirable and should be mitigated. This can be done either by an increase in fluidization air volume or a slight decrease in spray rate at the time the ball growth would usually begin. Because the resulting "balls" are comprised of porous agglomerates, they may dry reasonable well. However, their size typically leads to a slower moisture loss and consolidation at the base of the product container. As a consequence, they are not seen in the sample port and a final moisture cannot include their contents. After milling, it is not uncommon for the final moisture content to be higher than that taken at the end of the drying process.
3. Nonuniform distribution of potent insoluble API	Particle size incompatibility—API and excipients
Proposed action	The root cause for the nonuniformity must be identified. A particle size distribution should be conducted and assay can be performed on the various fractions (generally up to 6 sieve sizes). Often the cause is a particle size incompatibility between the API and the granulation excipients, and this will be seen as superpotency in one or more of the sieve fractions. The purpose of a binder is to immobilize the API in a matrix with the other materials. A relatively rigid granule structure at the end of drying and after milling is essential. Examination of the Certificate of Analysis for the API should reveal the particle size distribution, but it says nothing of its shape. Needle-like materials are problematic in that a particle size distribution (using sieve analysis) is a 2D test for a 3D material. Scanning Electron Microscopy (SEM) will reveal particle shape and subjectively the size distribution. If the material is found to be the root cause, either an additional step to bring it into compatibility with the excipients will be needed (such as milling) or the specification to the vendor must be narrowed. If the API particle size is very small but the material is cohesive, it is likely that small soft lumps of API remain in the finished granulation. In comparison to high shear granulation, there is far less mechanical stress in the fluidized-bed process. If the API is added as a dry material to other excipients in the product container, it is suggested that it be co-milled with one of the excipients prior to its addition with the remaining materials. The shear of the premilling process would be sufficient for delumping and would give the mixing process a head start.

Table 5 Summary of Trouble Shooting Process Challenges

Issue	Most likely root cause
	It is common practice at the end of a spray granulation process to shake filter fines into the product container. If this layer is substantial and contains principally very fine material, it should be assayed for potency. If the material is found to be superpotent, the mechanicals for the filter system must be checked. In alternating shaking types of processors, often a gas-tight flap has lost its ability to seal completely and it must be repaired. A consequence is that there is still air flowing past it during shaking, therefore fines cannot be released from the stiffened filter fabric. This may be externally manifested by a comparatively high filter differential pressure from start to finish in the process. In cartridge filter systems, the effect is similar—material adhering to the filter material cannot be released by the compressed air pulse while fluidization air continues through the cartridge. Release is only possible at the end of the batch when fluidization ceases. If this is an issue during process development and scale-up, irrespective of the type of filter shaking, it may be possible to mitigate by trying different types of filter materials. In any case, the problem should be addressed and solved before it is released to routine production.
4. Low potency of potent API	Poor initial distribution of API, demixing of API, preferential retention of API on machine surfaces (expansion chamber, outlet air filter)
Proposed action	Any residue in the machine tower should be assayed for potency and checked for particle size and distribution to ascertain if it is of primary size or wetted agglomerates. If the material is fine and dry, it is possible that it has demixed due to electrostatic charge. This can potentially occur during vacuum charging, or during a product warm-up step prior to spraying if the temperature is high or the step exceeds 1–2 min. In both cases the fluidization air is dry and the environment is fertile for electrostatic charge. If there is considerable residue and it is superpotent, the process can be adjusted such that fluidization forces the granular product into the upper reaches of the expansion chamber and into the outlet air filter to "sand" the residue from these surfaces (during the middle and latter stages of spraying).
	If the filter material that has been used to produce the product is no longer available, a replacement must be found. It should be noted that there is no standardized test for determining either porosity (the size of particle that can be retained) or permeability (quantity of air flow per unit time at a given pressure difference across the fabric). Essentially, one must rely on performance with the product for which it is intended to be used. A production batch (one or more) must be earmarked as "experimental" and processed using the current recipe. If the filter differential pressure is lower, there is some risk that yield will also be less. There is also potential for the API to be lost if it is small in particle size. If this is the case, yet another type of fabric should be tested—the fabric should not dictate process conditions, but must be selected to serve the product and process.
5. Poor process air temperature control at low process air volume settings	Operation of the machine at too close to the qualified lower limit for temperature and air flow.
Proposed action	This is an unfortunate characteristic when the process starts at low air volume and temperature. The air flow sensor accuracy is diminished at low air flows, and the ability of an air handler to control a low temperature at low air flow is an extreme challenge and should be avoided if possible. A higher air volume is recommended even if it results in material being captured in the outlet air filter. If the filter system functions correctly, these fines will be returned regularly to be exposed to the spray liquid, ultimately becoming agglomerates. Evidence of this is a steady decay in filter differential pressure during spraying.
6. Bed stalling (in regions of the product container)	High in-process and end-spray moisture content
Proposed action	Experimentation to determine the operating domain (design space) should identify an in-process moisture profile that reaches a failure limit. If this is done and in-process testing includes sampling for moisture, bed stalling would then be seen as a consequence of a breach of this moisture "threshold." A common cause for a sudden shift from success to failure in

(*Continued*)

Table 5 Summary of Trouble Shooting Process Challenges (*Continued*)

Issue	Most likely root cause
	routine production is calibration of the process air volume sensor. Many fluidized-bed spray granulations, particularly those with insoluble raw materials, have spraying conditions in which the air leaving the machine tower is saturated with moisture. The liquid spray rate slightly exceeds the drying capacity of the process air, therefore the bed builds in moisture. Routine (quarterly or semiannual) machine calibration always includes the process air volume sensor, and of all of the instruments on a fluid-bed processor, this is the most difficult to calibrate. Some companies conduct point checks in which the instrument and its transmitter are calibrated while disconnected. Others employ a loop check in which the testing instruments are installed in tandem with the sensor connected in the loop or a second instrument is used in the duct work to independently confirm the accuracy of the machine-indicated value. In either case, if a change is made to the sensor, the user of the processor will not likely see the impact in any of the readings. For example, assume that calibration found the air volume sensor to be indicating a reading that is 5% higher than the actual. When it is corrected, the first batch processed may be found to have in-process and end-spray moisture contents that are higher than usually seen. All of the operator interface terminal (OIT) indicated process parameters are the same as usual, but the batch outcome is different. The problem rests with the air volume sensor (its changed transmitter). If the process operates at saturation, the inlet and product temperature will not change—they represent the condition for each cubic meter or cubic foot of air entering and leaving the batch (at saturation). A sensor found to be off by 5% will mean that less water is being evaporated per unit time, therefore the bed is gaining moisture more quickly. If moisture gain is sufficiently rapid, the ball growth or bed stalling threshold may be reached and the batch will be at risk. It is strongly suggested that all calibration data, especially involving changes to any instrument be discussed with the equipment users so that the impact of these types of issues can be anticipated and are not "surprises."

Abbreviation: API, active pharmaceutical ingredient.

Process Trouble Shooting Summary

Table 5 addresses "frequently asked questions" with respect to process troubleshooting. For a number of issues, common root causes are listed. There are approaches to problem solving proposed as well. In general, the fluidized bed spray granulation process yields CQA via a selection of process variables that methodically and intentionally produce the granulation. Some form of troubleshooting is inevitable at some point during the life cycle of the product. However, a well-designed formulation and process as well as granule metrics and instrumentation should permit a satisfactory resolution to the problems commonly encountered.

SAFETY IN FLUID BED

For an explosion to occur three conditions must exist: an ignition source, a fuel, and oxygen. With an explosion oxygen reacts with the fuel releasing heat and gases. If a dust explosion occurs in free space, a fireball of considerable extent arises. If the dust explosion occurs in a closed container, then there is a sudden pressure rise that is mainly decided by the following factors: type of dust, size of the dust, dust/oxygen ratio, turbulence, precompression, temperature, shape of the container, and ignition source. In a container without precompression and with an organic dust of sufficient fineness, the pressure inside the container can rise to over 10-bar overpressure.

The fluid-bed process handles a large amount of air. This air in the presence of fine product dust poses potential for an explosion. This hazard can be enhanced when using flammable solvents. If sufficient ignition energy (static charge) is introduced, an explosion within the processor can take place. To contain these dust or flammable solvent-induced explosions, fluid-bed processors are normally constructed to withstand overpressure of 2.0 bars. Two-bar fluid-bed units are provided with explosion relief flaps, to release the

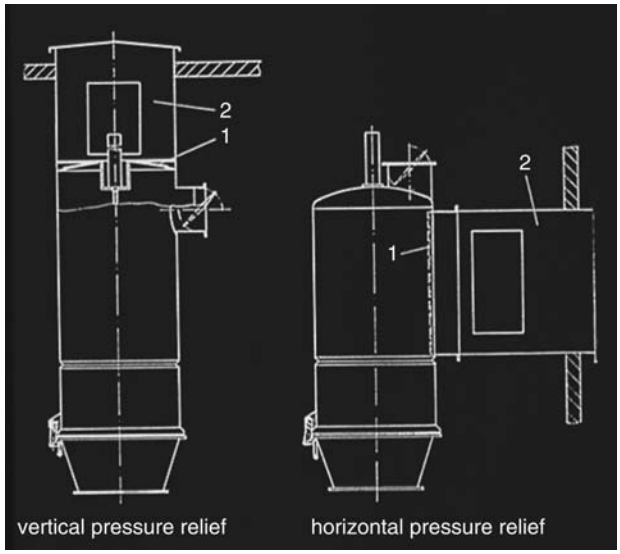


Figure 32 Processor with horizontal and vertical relief.

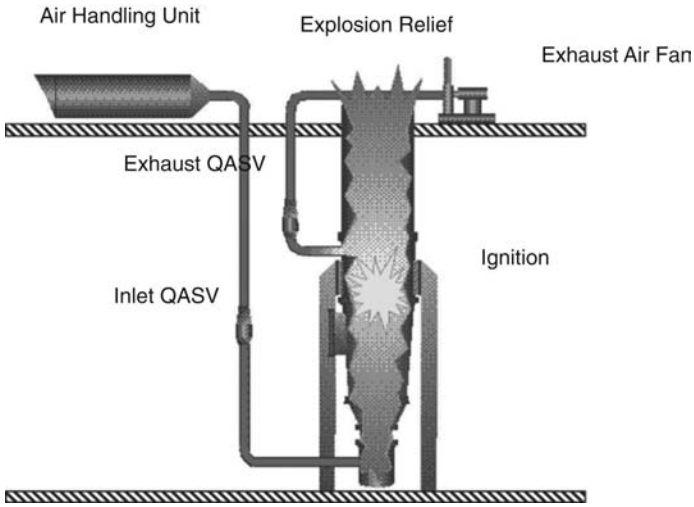


Figure 33 Two-bar unit vented design. *Source*: Courtesy of The Glatt Group.

pressure as soon as it starts to build up inside the processor. The explosion flaps mounted either horizontally or vertically (Fig. 32) are designed to vent the pressure buildup as low as 0.06 bar. The two-bar vented design shows the propagation of the overpressure (Fig. 33). The explosion flaps open up to the outside of the building. These panels are gasketed, and sealed so normal fluid-bed operation is not affected. It was an accepted practice to have production unit with two-bar pressure shock integrity; however, the cleaning of the gasket area around the flaps is always difficult. To avoid having the product be exposed to the outside during such an event, a suppression system is used to contain the possible overpressure front from leaving the unit (Fig. 34). The suppression system consists of low-pressure sensors located within the processor. These sensors are designed to trigger a series of fire extinguishers (containing ammonium phosphate), as soon as a preset level (generally 0.1 bar) of pressure is set within the processor.

With the introduction of potent and costly drug substances, the 2-bar design is being replaced with 10- or 12-bar designs. Most of the pharmaceutical dust explosions studied (143) show the overpressure reaching 9 bars with a K_{st} value (constant of explosion speed) of 200. An explosion in a 10- or 12-bar unit is contained within the unit. A 10- to 12-bar designed unit does not require any explosion relief panels, or gaskets. This eliminates the concerns about cleaning of the gaskets and flaps. Another advantage of a 10- to 12-bar unit is that, in case of explosion,

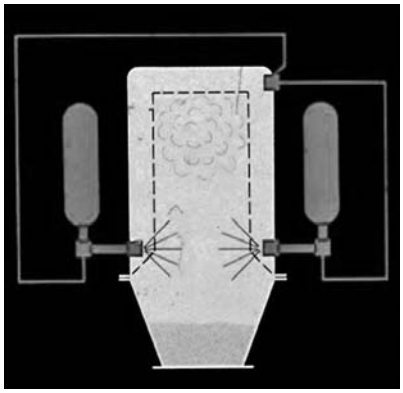


Figure 34 Explosion suppression system.

Figure 35 Ventex SEI valve (deflagration Valve).

the processor containing potent drug substance is contained inside the unit and explosion does not pose an environmental problem as with the 2.0-bar unit. Figure 35 shows the Ventex-ESI valve for passive control of the explosion.

The deflagration valve such as Ventex-ESI valve requires less maintenance than the active valve previously used in the industry. An explosion force (pressure wave) moving ahead of the flame front hurls the poppet forward to the valve seat providing an airtight seal. The poppet once seated is locked in by a mechanical shutoff device, which retains the seal until manually reset. The three basic versions of the standard mechanical Ventex valve are available with a set pressure of 1.5 psi and a maximum pressure of 150 psi. The Ventex-ESI valve closes by the explosion pressure wave, without external power for horizontal or vertical operation. Figure 36 shows how the Ventex valve closes. The pressure wave of an explosion pushes the closing device against a seal. When closed, the valve is locked and effectively prevents the spread of flames and pressure waves. The actual position of the valve is shown by a position indicator and can be transferred to a control unit via a switch.

In case of granulation requiring flammable solvents, process air, and nozzle, atomization air is replaced by an inert gas such as nitrogen and the system is designed as a closed cycle with the solvent recovery capability (144). Number of approaches can be taken to handle solvent from the process. Table 6 summarizes various methods for solvent emission control systems.

Kulling and Simon (18) reported the closed loop system shown in Figure 37. The inert gas used for fluidization circulates continuously. An adjustable volume of gas is diverted through the bypassed duct where solvent vapors are condensed and solvent collected. The circulating

Table 6 Comparison of Different Solvent Emission Control System

Considerations	Water scrubbing	Catalytic burning	Carbon absorption	Condensation
System	Open cycle	Open cycle	Open cycle	Open cycle with N_2
Capital cost	High	Low	Moderate	Low
Energy requirement	High	Low		
Installation	External	External	External	Internal
Space required	Medium	High	Moderate	Small
Flexibility	Medium	Medium	Low	Good
Waste treatment	Required	CO_2/H_2O emission treatment	Required	Concentrated

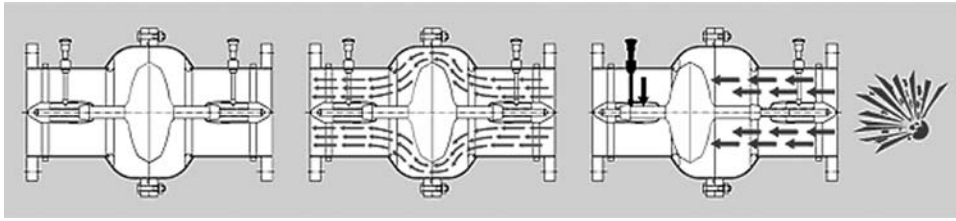


Figure 36 Explosion protection valve in action.

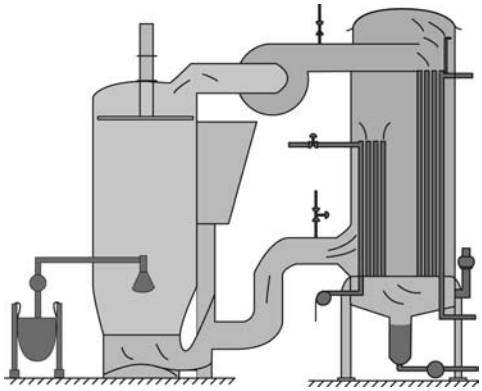


Figure 37 Schematic of a closed loop fluid-bed processor with solvent recovery.

gas passes through the heat exchanger to maintain the temperature necessary for evaporation of the solvent from the product bed. During the agglomeration and subsequent drying process, the solvent load in the gas stream does vary. The bypass valve controls the flow of the gas to the heat exchanger and the condenser. By controlling the gas stream in this manner, the drying action is continued until the desired level of drying is reached. Even though the cost of fluid-bed processor with the solvent recovery is generally double the cost of a regular single pass fluid-bed processor, such a system offers effective measure for both explosion hazard reduction and an air pollution control.

In 1994 European parliament issued ATEX directive (145) on the approximation of the laws of the Member States concerning equipment and protective systems intended for use in potentially explosive atmospheres. As of July 2006, organizations in EU must follow the directives to protect employees from explosion risk in areas with explosive atmospheres. There are two ATEX directives (one for the manufacturer and one for the user of the equipment):

- The ATEX 95 *equipment* directive 94/9/EC: Equipment and protective systems intended for use in potentially explosive atmospheres
- The ATEX 137 *workplace* directive 99/92/EC: Minimum requirements for improving the safety and health protection of workers potentially at risk from explosive atmospheres.

ATEX gets its name from the French title of the 94/9/EC directive: *Appareils destinés à être utilisés en* ***AT****mosphères* ***EX****plosibles*.

Employers must classify areas where hazardous explosive atmospheres may occur into zones. The classification given to a particular zone, and its size and location, depends on the likelihood of an explosive atmosphere occurring and its persistence if it does. Areas classified into zones (0, 1, 2 for gas-vapor-mist and 20, 21, 22 for dust) must be protected from effective sources of ignition. Equipment and protective systems intended to be used in zoned areas must meet the requirements of the directive. Zones 0 and 20 require category 1 marked equipment; zones 1 and 21 required category 2 marked equipment; and zones 2 and 22 required category 3 marked equipment. Zones 0 and 20 are the zones with the highest risk of an explosive atmosphere being present. All manufacturers of fluid-bed processors in Europe must comply with this directive.

MATERIAL HANDLING OPTIONS

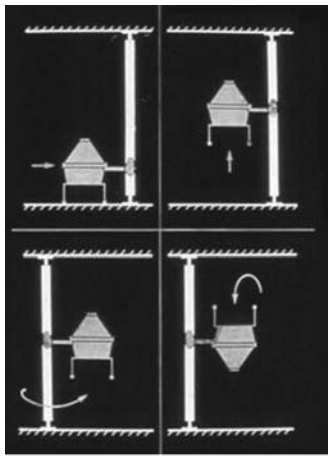
The transfer of materials to and from the fluid-bed processor is an important consideration. The loading and unloading of the processing bowl can be accomplished by manual mode or by automated methods.

Loading

The contemporary method for loading the unit is by removing the product bowl from the unit, charging the material into the bowl, and then placing the bowl back into the unit. This loading is simple and cost effective. Unfortunately, it has the potential of exposing the operators to the product and contaminating the working area. To avoid the product being a dust and cleaning hazard, a dust collection system should be installed to collect the dust before it spreads. A manual process also depends on the batch size and the operator's physical ability to handle the material and the container full of product. Furthermore, this can be time consuming since the material must be added to the product container, one material at a time.

The loading process can be automated and isolated to avoid worker exposure, minimize dust generation, and reduce loading time. There are two main types of loading systems. These systems are similar because both use the fluid bed's capability to create a vacuum inside the unit. Here the product enters the fluid bed through a product in-feed port on the side of the unit. This is done by having the fan running and the inlet air control flap set so that minimum air flow may pass through the product container and the outlet flap is almost fully open. Typically, when the high shear granulated material needs to be charged into the fluid bed this approach helps (Fig. 38). Once the material has been charged to the fluid bed, the product in-fed valve is closed and the granulating process started. This transfer method uses some amount of air to help the material move through the tube. Loading can be done either vertically from an overhead bin, or from the ground. Less air is required through the transfer pipe when the material is transferred vertically, because gravity is working to help the process. Vertical transfer methods do require greater available height in the process area. Loading by

Figure 38 Loading of fluid bed from high shear mixer. *Source*: Courtesy of The Glatt Group.



(A)

(B)

Figure 39 (**A**) Product discharge system. (**B**) Inverted product container with a cone mounted on top for in-line milling.

this method has the advantages of limited operator exposure to the product, allows the product to be fluidized as it enters the processor, and reduces the loading time. The disadvantage of this type of system is the cleaning required between different products.

Unloading

As with loading, the standard method for unloading is by removing the product bowl from the unit. Once the bowl is removed, the operator may scoop the material from the bowl, which is the most time consuming and impractical method, because of its potential of exposure to the product. Alternatively, the product can be vacuum-transferred to a secondary container or unloaded by placing the product bowl into bowl dumping device as shown in Figure 39A, B.

This hydraulic device is installed in the processing area. The mobile product container of the fluid-bed processor is pushed under the cone of the bowl dumper and coupled together by engaging the toggle locks. Subsequently, the container is lifted hydraulically, pivoted around the lifting column, and rotated 180° for discharging. Use of the bowl dumping device or vacuum unloading device still requires that the product bowl be removed from the unit. There are contained and automated methods for unloading the product while the product bowl is still in the fluid-bed processor. The product may either be unloaded out of the bottom of the product container or from the side. Until recently, the most common contained method is to unload the material from the bottom of the unit. This requires the ceiling height high enough to accommodate or the installation becomes a multistoried installation.

There are two types of bottom discharge options: gravity or pneumatic gravity discharge (Fig. 40) allows for collection of the product into container, which is located below the lower plenum. If the overall ceiling height limitation prevents from having the discharge by gravity, the gravity/pneumatic transfer combination can be considered. The gravity discharge poses cleaning problems, since the process air and the product discharge follow the same path; assurance of cleanliness is always of prime concern.

The desire to limit the processing area and development of the overlap gill air distributor mentioned earlier in the chapter has prompted the consideration of the side discharge as an option. The product bowl is fitted with the discharge gate, as shown in Figure 41A, B.

Most of the product being free-flowing granules flows through the side discharge into a container. The remainder of the product is then discharged by manipulation of the airflow through the overlap gill air distributor. The discharged product can be pneumatically transported to an overhead bin if the dry milling of the granulation is desired. The contained system for unloading the product helps to isolate the operator from the product. The isolation

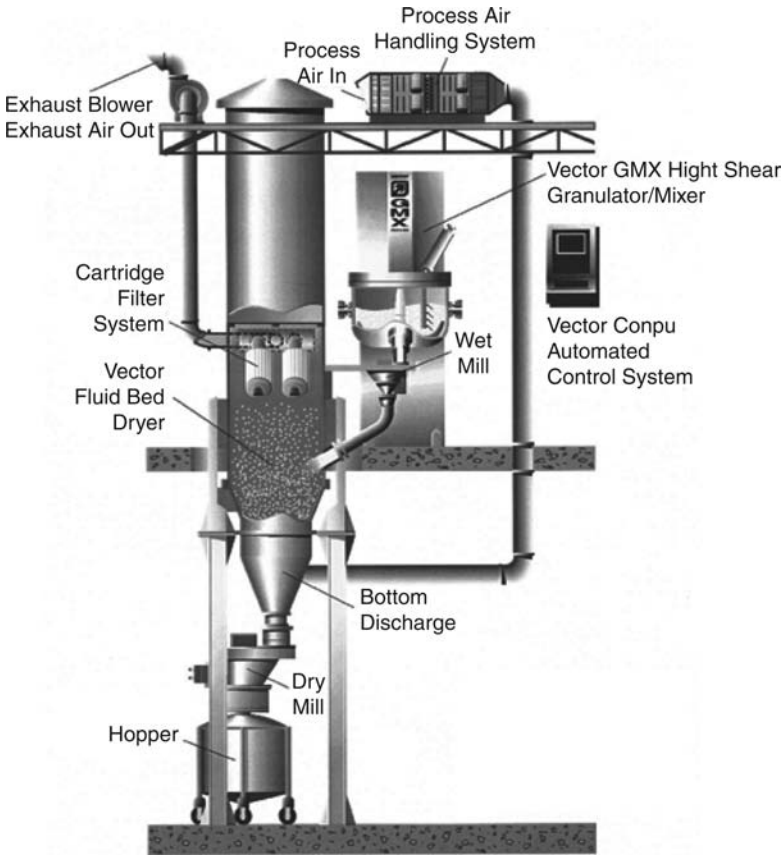


Figure 40 Loading and unloading setup with bottom discharge in an integrated system. *Source*: Courtesy of The Vector Corporation.

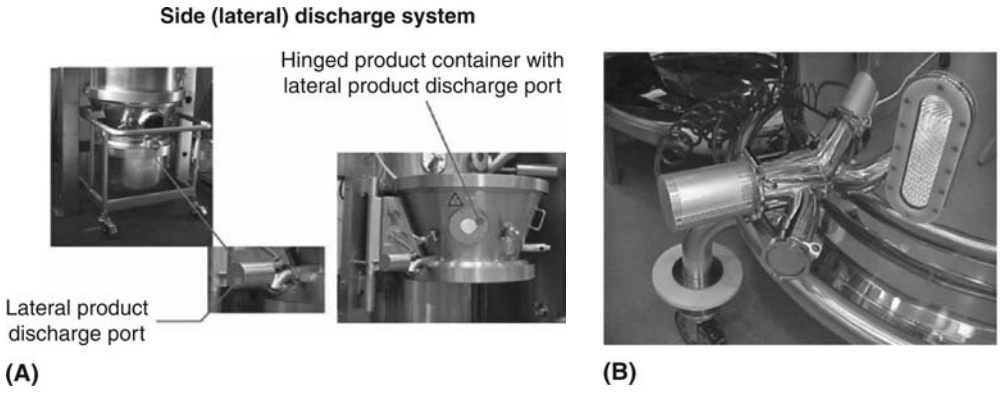


Figure 41 (**A**) Side discharge Glatt. (**B**) Side discharge. *Source*: Part A courtesy of The Glatt Group, and part B courtesy of GEA Pharma Systems.

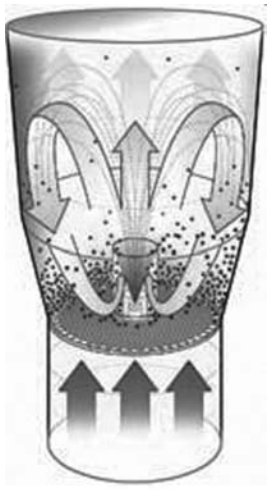
feature also prevents the product from being contaminated from being exposed to the working environment. Material handling consideration must be thought of, early in the equipment procurement process. Fluid-bed processing, whether used as an integral part of high shear mixer/fluid-bed dryer or as a granulating equipment option, production efficiency, and eventual automation can be enhanced by considering these loading and unloading options.

FLUID-BED TECHNOLOGY DEVELOPMENTS

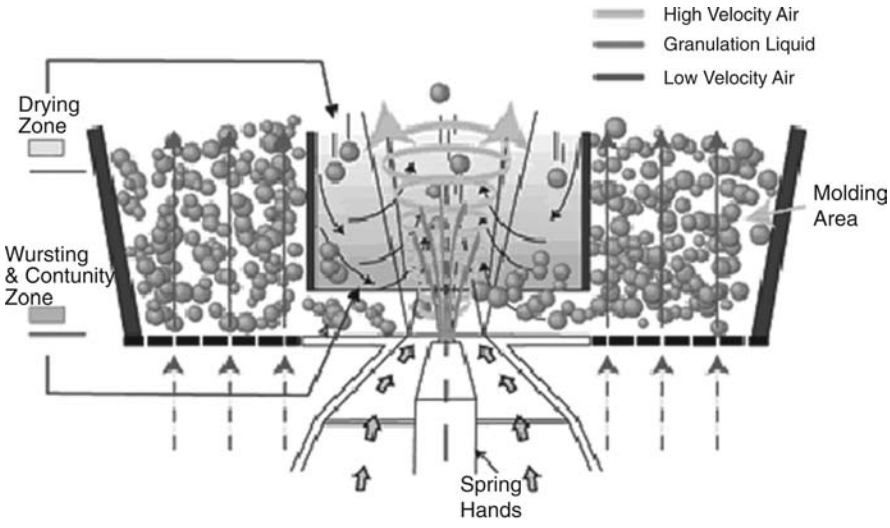
Parikh (146) has presented review of all of the fluid-bed equipment developments. Among various advances, development of production units that can withstand more than 12-bar pressure shock resistance is a very significant development. These units do not require pressure relief duct and associated cleaning problems. Units are now equipped with the air handler that can provide designated humidity and dew point air, throughout the year and at any geographical location. The fluid-bed cleaning in place (CIP) became a reality with the introduction of the overlap gill air distributors and the stainless steel cartridge filters described earlier in this chapter.

Bottom Spray Particle Coating/Agglomeration

The coating of the particles is carried out most frequently using Wurster column (Fig. 42A, B). The Wurster process is the most popular method for coating particles. The Wurster-based coating process does not contain any fluid-bed regions in the traditional sense, as it is a



(A)



(B)

Figure 42 (**A**) Typical Wurster coater. (**B**) Precision Coater®. *Source*: Part A courtesy of The Glatt Group, and part B courtesy of GEA Pharma Systems.

circulating fluid-bed process. Four different regions within the equipment can be identified: the upbed region, the expansion chamber, the downbed region, and the horizontal transport region. The coating process consists of three phases: the start up phase, the coating phase, and the drying and cooling phase. During the coating phase, several processes take place simultaneously. They are as follows: atomization of the coating solution or suspension, transport of the atomized droplets of the coating solution to the substrate, and the drying of the film. Even though particle coating with a bottom spray is preferred, numbers of products have been coated using top spray in fluid bed. Recently, Ehlers and coworkers (147) coated ibuprofen powder particles with HPMC using a top spray without agglomerating powders.

Bottom spray coating is also used for agglomeration as well as particle coating as it was developed originally. As seen earlier in this chapter, by placing the nozzles tangentially, most of the manufacturers have improved the operational difficulties encountered when nozzle plugging required that the process be stopped to pull the nozzle during the coating process. By placement of nozzles tangentially, some manufacturers claim that separate modules to carry out agglomeration, coating, and drying will not be needed. Of the modification of the basic Wurster Technique, a column within column (HS collar) was introduced by Glatt to minimize agglomeration during coating and enabling the higher spraying rate. Further modification of the Wurster was introduced by GEA Pharma systems as a coating as well as bottom spray granulating technique with an introduction of Precision Coater® as shown in Figure 42B.

Researchers have discussed the incorporation of microwave in the laboratory fluid-bed processor (148,149). Fluid-bed process using organic solvent requires inert gas such as nitrogen to replace the air used for fluidization as discussed earlier in the chapter. It is accompanied with the solvent recovery system.

Rotary Fluid Bed

The other advance of significance is the development of a rotary fluid bed, for producing denser granulation. Modules were introduced by various manufacturers and the technology is discussed below. The 1972 patent (150) for the rotor technology was awarded for the equipment and coating of the granular material. The subsequent patents (151,152) were awarded for the coating of the spherical granules. An advantage of rotary fluid-bed processing to produce granules was reported by Jager and Bauer over conventional top spray granulation technique (153). In this unit, the conventional air distributor is replaced by the rotating disk. The material to be granulated is loaded on the rotating disk. The binder solution is added through the atomization nozzle located tangentially to the wall of the bowl. The centrifugal force creates a dense, helical doughnut-shaped pattern. This type of motion is caused by the three directional forces.

The vertical movement is caused by the gap or slit air around the rotating disk, the gravitational force folds back the material to the center, and the centrifugal force caused by the rotating disk pushes the material away from the center. The granulation produced in the rotary fluid-bed processor shows less porosity compared with the conventionally agglomerated product in the fluid-bed processor. The rotary fluid bed (Fig. 43) does provide granules, which have less porosity and higher bulk density compared with the granulation produced by the typical top spray granulated fluid-bed process.

Türkoglu et al. produced theophylline granulation using a rotary fluid bed (154). The formulation contained lactose, starch, and MCC along with theophylline. They reported that the granules produced were spherical and dense. Three different drug level formulations were evaluated. The authors concluded that rotary fluid bed as a wet granulator has the potential to obtain a better drug content uniformity for tablets even at low active levels such as 1% in comparison with conventional fluidized beds. The use of rotary fluid bed to produce spherical granules for modified release application is reported by number of authors. Rotary fluid-bed technology was reviewed by Li et al. (155) and its usefulness was described to produce the pellets. The comparison of the rotary fluid-bed processing with the multiple step extrusion and spheronization was reported by Robinson et al (156). The authors manufactured acceptable immediate release acetaminophen pellets using both of these techniques. The quality of the pellet produced improved as the minimum quantity of product was increased in the rotary

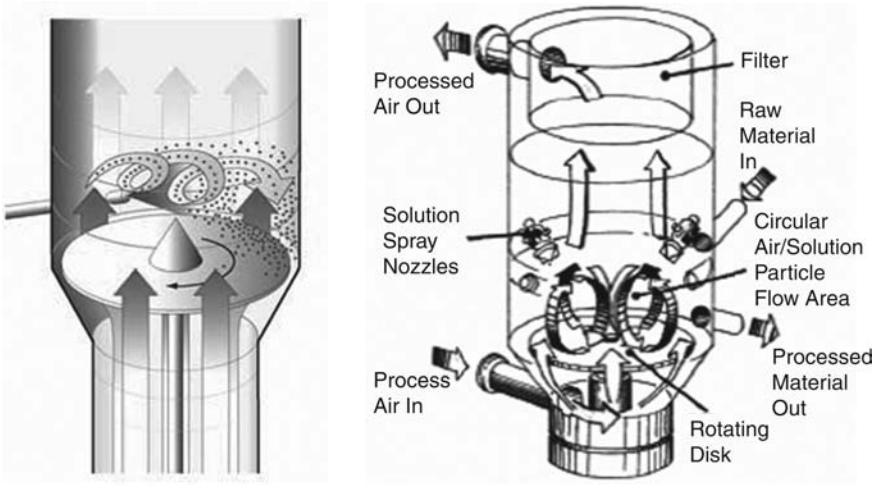


Figure 43 (**A**) Rotary fluid-bed processing modules. (**B**) SPIR—A flow design. *Source*: Part A courtesy of The Glatt Group, and part B courtesy of Vector Corporation Web site.

fluid-bed processor. The advantage of using a single unit such as rotary fluid bed over multiple unit process involving several pieces of equipment was described.

The rotary fluid bed is used for producing a pellet by layering the active drug suspension or solution onto nonpareil cores and subsequently coating them with polymers to impart modified release properties (157). Hileman et al. (158) reported manufacture of immediate spheres of a poorly water-soluble drug in a rotary fluid bed by layering the active drug suspension onto nonpareil cores. These immediate release spheres were then overcoated with an ethyl cellulose/HPMC hydroalcoholic solution in the same unit eliminating the need for additional process and handling steps. Iyer et al. evaluated layering of aqueous solution of phenylpropanolamine hydrochloride with different binders (159). The layered beads were coated in the rotoprocessor and the Wurster Coater to compare the utility of rotoprocessor as an equipment not only to produce pellets but to coat them as well. Various equipment manufacturers have promoted powder layering on the pellets, in a rotary fluid bed. In 1992, Jones et al. received patent for such a process (160). The process claims to have advantages of layering a drug substance with relatively small amount of liquid, thus making this layering process more efficient. The commercial application of this process has not been reported in the literature. Korakianiti et al. (161) studied the preparation of pellets using rotary fluid-bed granulator. Authors concluded that the rotor speed and amount of water significantly affected the geometric mean diameter of the pellets and they proposed an equation to show that correlation. Piśek et al. (162) studied the influence of rotational speed and surface of rotating disk on pellets produced by using rotary fluid bed. They used mixture of pentoxifylline and MCC to produce pellets using suspension of Eudragit® NE 30 D as a binder. The results showed that both surface and rotational speed of the disk have influence on shape, surface, and size of the pellets while there was less effect on the density, humidity content, and yield. They found the textured surface of the disk produced pellets with rougher surface when rotational speed was increased compared with the smooth surface, where increased rotational speed produced more spherical pellets with larger diameter.

Kristensen and Hansen (163) compared granulation prepared in the fluid bed with a top spray and rotary processor, and concluded that the rotary processor offers better maneuverability in terms of the obtainable granule size and was less influenced by the flow properties of the starting materials. Similar tablet characteristics were found in the investigated types of equipment. The applicable range of liquid addition rates was found to be similar in the rotary processor and in the top spray fluid-bed module. Generally, wet granulation in the rotary processor was found to be a good alternative to conventional fluid-bed granulation,

particularly when cohesive powders with poor flow properties or formulations with low drug content are to be granulated by a fluidizing air technique. Kristensen (164) in another study of granulation of binary mixtures of MCC and either lactose, calcium phosphate, acetaminophen, or theophylline, in a 1:3 ratio, using a 50% (w/w) aqueous solution of PEG and water as the binder liquid, demonstrated that up to 42.5% w/w PEG can be incorporated and may be an alternative process to the melt granulation with hydrophilic meltable binders.

Integrated Systems

The fluid-bed technology is used for drying, agglomerating, coating, and pelletization. However, the industry is using fluid-bed processor for drying in cases where higher bulk density, low drug content formulations of a hydrophobic drug substance that may have to be incorporated in a larger batch of excipients sizes, and granulation are carried out in high shear mixer and the fluid bed is used a dryer. To facilitate these two separate operations, an integrated system is set up in number of companies where the transfer of wet mass from high shear is passed through a mill prior to loading in the fluid bed.

Figures 44 and 45 shows typical integrated system where containment is considered for controlling dust and cross contamination. When these two-unit operations are integrated as a single unit, number of points must be considered. Following is the list of some of the questions reader may want to consider:

1. Engineering layout and the footprint, ceiling height requirements.
2. How will the high shear mixer be loaded by gravity, vacuum, or manually?
3. How will the binder solution be prepared and delivered to the mixer?
4. How will the granulation end point be determined and reproduced?

Figure 44 Integrated system showing high shear mixer next to fluid-bed unit. *Source*: Courtesy of LB Bohle.

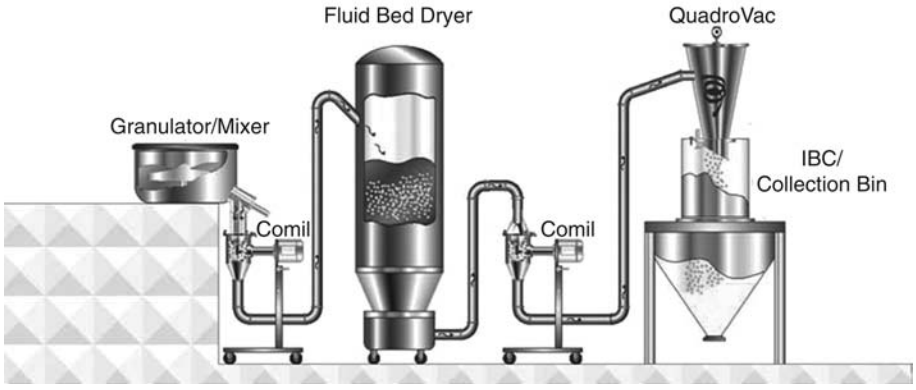


Figure 45 Integrated system with in-line conical mill at the discharge of high shear mixer. *Source*: Courtesy of Quadro Engineering.

5. How will the discharge from the high shear mixer be accomplished?
6. Are the process parameters for granulation and fluid-bed drying established and are reproducible, indicating a robust process?
7. How will the product discharged from the fluid-bed dryer be handled? Does it require sizing and blending with the lubricants?
8. Is this system dedicated for a single product or multiple products?
9. How will this system be cleaned?
10. Will the control of a process be done individually for each unit or by an integrated control system?

For the potent compound processing requiring high shear granulation and fluid-bed drying, some companies have introduced a lab size unit with isolators and glove box. For commercial scale, a totally contained unit is designed that minimize or eliminate the operator exposure to the potent compound. Such a system is costly and does require enormous amount of time for process and cleaning validation.

CONCLUSION

The fluid-bed dryer was used as an efficient way to dry a product because of suspension of wet particles in the hot air stream. However, over the last 40 years of development in the pharmaceutical industry and the proliferation of the batch fluid-bed processing technology in other industries such as food, polymer, detergent, etc., have provided the opportunity to use the batch fluid-bed processor for granulation, drying, particle coating, and pelletization. The advances in the fluid bed can be attributed to the several factors. The needs of formulators, the requirements of the regulators, and technological innovations from the manufacturers of this technology are responsible for these advances. The result of these changes provided units that are paint-free, modular, and safer, in compliance with the cGMPs, and are capable of performing various processes that were not thought of before.

The fluid-bed process like other granulation technique requires understanding the importance of characterization of the raw materials, especially of a drug substance, the process equipment, limitations of the selected process, establishment of an in-process control specifications, characterization of the finished product, and cleaning and process validation.

Over the last 10 years, process analytical technology has provided different approaches to understand this complicated unit operation. The interrelationship of process parameters is very critical as you establish the process parameters. We now have the modern computerized control panels and various on-line/in-line measurement options available for process control. If one reviews the history of innovation for this unit operation, the rate of equipment modification or improvement is relatively slow compared with the various process-control options being developed. The proper understanding of the process during the development stage will provide a robust process for the commercial application.

REFERENCES

1. Kunii D, Levenspiel O. Fluidization Engineering. New York: John Wiley & sons Inc., 1968.
2. Wurster DE. Preparation of compressed tablet granulations by the air-suspension technique. II. J Am Pharm Assoc 1960; 49:82.
3. Wurster DE. Air-suspension technique of coating drug particles; a preliminary report. J Am Pharm Assoc (Sci Edi) 1959; 48(8):451–454.
4. Scott MW, Liberman HA, Rankell AS, et al. Continuous production of tablet granulation in Fluid Bed I. Theory and design consideration. J Pharm Sci 1964; 53(3):314–319.
5. Rankell AS, Scott MW, Liberman H A, et al. Continuous production of tablet granulations in a fluidized bed. II. Operation and performance of equipment. Pharma Sci 1964; 53(3):320.
6. Contini S, Atasoy K. Fluid bed granulation, a modern economic method for tabletting and encapsulation. Pharm Ind 1966; 28:144–146.
7. Wolf G. Fluidized layer spray granulation. Drugs Made Germany 1968; 11:172–180.
8. Liske T, Mobus W. The manufacture and comparative aspects of fluidized layer spray granulation. Drugs Made Germany 1968; XI:182–189.
9. Sherrington PJ, Oliver R. Granulation monograph. In: Goldberg AS Sr., ed. Powder Science and Technology. London: Heyden, 1981.

10. Pietch WB. Fluidization phenomena and fluidized bed technology. In: Fayed ME, Otten L, eds. Handbook of Powder Science and Technology. New York: Van Nostrand Reinhold, 1984.
11. Hersey JA. Fluidized bed technology—an overview. Int J Pharm Tech Prod Manuf 1981; 2(3).
12. Thiel WJ. The theory of fluidization and application to the industrial processing of pharmaceutical products. Int J Pharm Tech Prod Manuf 1981; 2(5).
13. Thiel WJ. Solids mixing in gas fluidized beds. Int J Pharm Tech Prod Manuf 1981; 2(9).
14. Littman H. An overview of flow in fluidized beds. Pharm Technol 1985; 9(3):48.
15. Whitehead AB. Behavior of fluidized bed systems. Pharm Technol 1981; 2(13).
16. Story MJ. Granulation and film coating in the fluidized bed. Pharm Technol 1981; 2(19).
17. Aulton MJ, Banks M. Fluidized bed granulation, factors influencing the quality of the product. Pharm Technol 1981; 2(24).
18. Kulling W, Simon EL. Fluid bed Technology applied to pharmaceuticals. Pharm Technol 1980; 4(1).
19. Gomezplata A, Kugelman AM. Processing systems. In: Marchello JM, Gomezplata A, eds. Gas-Solid Handling in the Process Industries. Chemical Processing and Engineering. Vol. 8. New York: Marcel Dekker Inc., 1976.
20. Räsänen E. Rantanen J, Mannermaa JP, et al. The characterization of fluidized behavior using a novel multi-chamber microscale fluid bed. J Pharm Sci 2004; 93:780–791.
21. Parikh DM. Airflow in batch fluid-bed processing. Pharm Technol 1991; 15(3):100–110.
22. Row PN, et al. Trans Inst Chem Eng 1965; 32T:271.
23. Davis L, et al. Trans Inst Chem Eng 1966; 44T:293.
24. Gorrodnichev VI, et al. (English Translation). Pharm Chem J (USSR) 1974; 8:298.
25. Kirk-Othmer. Fluidization in Encyclopedia of Chemical Technology. Vol. 10, 3rd ed. New York: Wiley-Interscience, 1981:548–581.
26. Ennis BJ, Tardos GI, Pfeffer R. A micro-level–based characterization of granulation phenomena. Powder Technol 1991; 65:257–272.
27. Wan Lucy SC, Heng Paul WS, Muhuri G. Incorporation and distribution of a low dose drug in granules. Int J Pharm 1992; 88:159–163.
28. Long GE. Spraying theory and practice. Chem Eng 1978; PP73–PP77.
29. Masters K. Spray Drying: An Introduction to Principles, Operational Practice and Application. 2nd ed.New York: John Wiley & Sons Inc., 1976.
30. Japanese Patent Application 61-259696, 1986.
31. Swiss Patent 0176/93, 1993, US Patent 5,444,892, 1995, European Patent number 0572356A1.
32. Guidance for Industry, Part 11, Electronic Records; Electronic Signatures—Scope and application. 2003.
33. Newitt DM, Conway-Jones JM. A contribution to the theory and practice of granulation. Int J Pharm Tech Prod Manuf 1958; 36:422.
34. Record PC. A review of pharmaceutical granulation technology. Int J Pharm Tech Prod Manuf 1980; 1:32.
35. Rumpf H. The strength of granules and agglomerates. In: Krepper W, ed. Agglomeration. New York: Interscience, 1962:379–418.
36. Tardos GI, Khan MI, Mort PR. Critical parameters and limiting conditions in binder granulation of fine powders. Powder Technol 1997; 94:245–258.
37. Iveson SM. Granule coalescence modeling: including the effects of bond strengthening and distributed impact separation forces. Chem Eng Sci 2001; 56:2215–2220.
38. Schaefer T, Worts O. Control of fluidized bed granulation I effects of spray angle, nozzle height and starting materials on granule size and size distribution. Arch Pharm Chem Sci Ed 1977; 5:51–60.
39. Smith PJ, Nienow AW. Particle growth mechanism in fluidized bed granulation. Chem Eng Sci 1983; 38(8):1223–1231, 1323–1240.
40. Aulton ME, Banks M. Fluidized bed granulation-factors including the quality of the product. Int J Pharm Tech Prod Manuf 1981; 2(4):24–29.
41. Maroglou A, Nienow AW. Fourth Symposium on Agglomeration. Toronto, Canada: Iron & Steel Society Inc., 1985:465–470.
42. Goldschmidt MJV. Hydrodynamic modeling of fluidized bed spray granulation. PhD Thesis, Twente University, Enschede, The Netherlands, 2001.
43. Thielmann F, et al. The effect of primary particle surface free-energy on agglomeration rate in fluidized bed wet granulation. Powder Technol 2007; doi:10.1016/j.powtec.2006.12.015.
44. Jain K. Discrete characterization of cohesion in gas-solid flows. Master Thesis, School of Engineering, University of Pittsburg, 2002.
45. McCabe W L, Smith JC. Unit Operations of Chemical Engineering. New York, NY: McGraw-Hill, 1956.
46. Green Don W, ed. Perry's Chemical Engineer's Handbook, Section 20. New York, NY: McGraw-Hill, Inc., 1984.

47. Rankell RS, Liberman HA, Schiffman RF. Drying in the Theory and Practice of Industrial Pharmacy. 3rd ed. Philadelphia: Lea & Feabiger, 1986.
48. Schaefer T, Worts O. Control of fluidized granulation III, effects of the inlet air temperature, and liquid flow rate on granule size and size distribution. Control of moisture content of granules in the drying phase. Arch Pharm Chem Sci Ed 1978; 6(1):1–13.
49. Julia ZH Gao, Gary DB, Motheram R, et al. Importance of inlet velocity in fluid bed drying of a granulation prepared in a high shear mixer. AAPS PharmSciTech, 2000; 1(4).
50. Nieuwmeyer FJS, Vromans H. Granule breakage during drying processes. Int J Pharm 2007; 329:81–87.
51. Nieuwmeyer FJS, Damen M, Gerich A, et al. Granule characterization during fluid bed drying by development of a near infrared method to determine water content and median granule size. Pharm Res 2007; 24(10):1854–1861.
52. Davis TD, Peck GE, Stowell JG, et al. Modeling and monitoring of polymorphic transformations during the drying phase of wet granulation. Pharm Res 2004; 21(5).
53. Thurn U. Dissertation no. 4511, Eidgenossischen Technischen, Hochschule, Zurich, 1970.
54. Liske T, Mobus W. Drugs Made Germany 1968; 11(4):182–189.
55. Schaefer T, Worts O. Control of fluidized bed granulation V, factors affecting granule growth. Arch Pharm Chem Sci Ed 1978; 6:69–82.
56. Ormos Z, Pataki K. Hung J Indust Chem 1979; 7:89–103.
57. Ormos Z, Pataki K. Hung J Indust Chem 1979; 7:105–117.
58. Banks M. Ph.D. Thesis. C.N.A.A. Leicester Polytechnic, 1981.
59. Galmen MJ, Greer W. Fluid Technol Pharm Manuf International Conference, Paper 2, 1982.
60. Aulton ME. Fluid Technol Pharm Manuf International Conference, Paper 3, Powder Advisory Center, London, 1982.
61. Veillard M, et al. Int J Pharm Tech Prod Mfg 1982; 3(4):100–107.
62. Georgakopoulos PP, et al. The effects of using different grades of PVP and gelatin as binders in the fluidized bed granulation and tabletting of lactose. Pharmazie 1983; 38(4):240–243.
63. Jinot JC, et al. STP Pharma 1986; 2(13):126–131.
64. Shinoda A, et al. Yakuzaigaku 1976; 36(2):83–88.
65. Aulton ME, et al. The wettability of powders during fluidized bed granulation. J Pharm Pharmacol 1977; 59P(suppl)
66. Schepky G. Acta Pharm Technol 1978; 24(3):185–212.
67. Aulton ME, Banks E. Proc Intl Conf Powder Technol Pharm Basel, Switzerland: Powder Advisory Center, 1979.
68. Kocova El, Arini S, et al. Drugs Made Germany 1983; 26(4):205–211.
69. Davies W L, Gloor WT. Batch production of pharmaceutical granulations in a fluidized bed. II Effects of various binders and their concentrations on granulations and compressed tablets. J Pharm Sci 1972; 61(4):618–622.
70. Rouiller M, et al. Acta Pharm Technol 1975; 21(2):129–138.
71. Schaefer T, Worts O. Control of fluidized bed granulation II, estimation of droplet size of atomized binder solution. Arch Pharm Chem Sci Ed 1977; 5:178–193.
72. Ormos Z, Pataki K, Stefko B. Studies in granulation in a fluidized bed IX. Effects of concentration of various binders upon granule formation. Hung J Indust Chem 1979; 7:131–140.
73. Ormos Z, Pataki K, Stefko B. Studies in granulation in a fluidized bed X. Effects of the relative amounts of various binders upon granule formation. Hung J Indust Chem 1979; 7:141–151.
74. Ormos Z. Studies in granulation in a fluidized bed XI Approximate description of the particle size distribution. Hung J Indust Chem 1979; 7:153–163.
75. Ormos Z. Studies in granulation in a fluidized bed XII, Bed expansion of fluidized heterodisperse granule masses. Hung J Indust Chem 1979; 7: 221–235.
76. Kocova El-Arini S. Pharm Ind 1981; 43(7):674–679.
77. Jager KF, Bauer KH. Acta Pharm Technol 1984; 30(1):85–92.
78. Nouh ATI. Pharm Ind 1986; 48(6):670–673.
79. Alkan H, et al. Doga Tu J Med Pharm 1987; 11(1):1–7.
80. Bank A, et al. Proc Conf Appl Phys Chem 1971; 2:687–692.
81. Davies W L, Gloor WT. Batch production of pharmaceutical granulations in a fluidized bed. III Binder dilution effects on granulation. J Pharm Sci 1973; 62(1):170–172.
82. Ormos Z, Pataki K, Csukas B. Hung J Indust Chem 1973; 1:307–328.
83. Ormos Z, Pataki K, Csukas B. Hung J Indust Chem 1973; 1:463–474.
84. Johnson MCR, et al, J Pharm Pharmacol 1975; 80P(suppl).
85. Schaefer T, Worts O. Control of fluidized bed granulation IV. Effects of binder solution and atomization on granule size and size distribution. Arch Pharm Chem Sci Ed 1978; 6:14–25.
86. Aulton ME, et al. Mfg Chem Aerosol News 1978; 12:50–56.

87. Gorodnichev VI, et al. Pharm Chem J (USSR) 1980; 14(10):72–77.
88. Ceschel GC, et al. II Farmaco Ed Prat 1981; 36(6):281–293.
89. Rangnarsson G, et al. Int J Pharm 1982; 12:163–171.
90. Meshali M, El-Banna H M, El-Sabbagh H. Pharmazie 1983; 38(5):323–325.
91. Hajdu R, Ormos Z. Hung J Ind Chem 1983; 12:425–430.
92. Devay A, et al. Acta Pharm Technol 1984; 30(3):239–242.
93. Alkan MH, Yuksel A. Granulation in fluidized bed II-Effect of binder amount on the final granules. Drug Dev & Ind Pharm 1986; 12(10):1529–1543.
94. Hontz J. Assessment of Selected Formulation and Processing Variables in Fluid Bed Granulation. Ph.D. Thesis, University of Maryland at Baltimore, 1987. Dissertation Abs Int 1987; (6):1655-B.
95. Wan LSC, Lim KS. STP Pharm 1988; 4(7):560–571.
96. Wan LSC, Lim KS. Mode of action of polyvinylpyrrolidine as a binder on fluidized bed granulation of lactose and starch granules. STP Pharm 1989; 5(4):244–250.
97. Sheskey P, Keary C, Inbasekaran P, et al. Foam technology: the development of a novel technique for the delivery of aqueous binder systems in high shear and fluid-bed wet-granulation applications. Poster @ AAPS Annual Meeting, October 26–30, 2003.
98. Dahl TC, Bormeth AP. Naproxen controlled release matrix tablets: fluid bed granulation feasibility. Drug Dev Ind Pharm 1990; 16(4):581–590.
99. Higashide F, Miki Y, Nozawa Y, et al. Dependence of drug content uniformity on particle sizes in fluidized bed granulation. Pharm Ind 1985; 47(11):1202–1205.
100. Davies WL, Gloor WT Jr. Batch production of pharmaceutical granulation in fluidized bed II: effects of various binders and their concentrations on granulations and compressed tablets. J Pharm Sci 1972; 61:618.
101. Davies WL, Gloor WT Jr. Batch production of pharmaceutical granulation in fluidized bed III: binder dilution effects on granulation. J Pharm Sci 1973; 62:170.
102. Krycer I, Pope DG, Hersey JA. An evaluation of tablet binding agents: Part 1: solution binder. Powder Tech 1983; 34:39–51.
103. Planinsek O, Pisek, R, Trojak A, et al. The utilization of surface free-energy parameters for the selection of a suitable binder in fluidized bed granulation. Intl J Pharm 2000; 207:77–88.
104. Seo A, Holm, P, Schaefer T. Effects of droplet size and type of binder on the agglomerate growth mechanisms by melt agglomeration in a fluidized bed. Eur J Pharm Sci 2002; 16:95–105.
105. GEA Pharma Flexstream Brochure and Web site. Available at: http://www.GEApharma.com, and A Company Brochure and Web site. Available at: http://www.niro-pharma-systems.com.
106. Rowley FA. Effects of the bag shaking cycle on the particle size distribution of granulation. Pharm Technol 1989; 13(9):78–82.
107. Davies WL, Gloor WT Jr. Batch production of Pharmaceutical granulation in fluidized bed. I: Effects of process variables on physical properties of final granulation. J Pharm Sci 1971; 60(12):1869–1874.
108. Maroglou A, Nienow AW. Fluidized bed granulation technology and its application to tungsten carbide. Powder Metallurgy 1986; 29(4):15–25.
109. Workman J Jr. A review of process near infrared spectroscopy: 1980-1994. J Near Infrared Spectrosc 1993; 1:221–245.
110. Osborne BG, Fearn T, Hindle PH. In Practical NIR Spectroscopy with Applications in Food and Beverage Industry Analysis. 2nd ed. Harlow, UK: Longman, 1993:227.
111. USP XXVII 2004.
112. European Pharmacopoeia. Near Infra Red Spectrometry, 2004:59.
113. Callis J, Illman D, Kowalski B. Process analytical chemistry. Anal Chem 1987; 59:624A–637A.
114. Beebe K, Blaser W, Bredeweg R, et al. Process analytical chemistry. Anal Chem 1993; 65:199R–216R.
115. Blaser W, Bredeweg R, LaPack M, et al. Process analytical chemistry. Anal Chem 1995; 67:47R–70R.
116. Hassel D, Bowman E. Process analytical chemistry for spectroscopists. Appl. Spectrosc 1998; 52: 18A–29A.
117. Workman J Jr., Veltkamp D, Doherty S, et al. Process analytical chemistry. Anal Chem 1999. 71: 121R–180R.
118. Brittain H. Methods for the characterization of polymorphs and solvates in polymorphism in pharmaceutical solids. In: Brittain H, ed. Polymorphism in Pharmaceutical Solids. Vol. 95, 1st ed. New York: Marcel Dekker Inc., 1999:227–278.
119. Frake P, Greenhlgh D, Grierson SM, et al. Process control and end-point determination of fluid bed granulation by application of near-infrared spectroscopy. Int J Pharm 1997; 151:75–80.
120. Rantanen J, Antikanen O, Mannermaa JP, et al, Use of near-infrared reflectance method for measurement of moisture content during granulation. Pharm Dev Technol 2000; 5(2):209–217.
121. Rantanen J, Lehtola S, Rämet P, et al. On-line monitoring of moisture content in an instrumented fluidized bed granulator with multi-channel NIR moisture sensor. Powder Technol 1998; 99:163–170.

122. Lipsanen T, Närvänen T, Räikkönen H, et al. Particle size, moisture, and fluidization variations described by Indirect In-line physical measurements of fluid bed granulation. AAPS PharmSciTech 2008; 9(4):1070–1077.
123. Vazquz Elizabeth Rivera Master of Science Thesis. Optimization of Drying -End-Points Measurements for the Automation of a Fluidized-Bed Dryer Using FT-NIR Spectroscopy. University of Puerto Rico, 2004.
124. Rantanen J, Känsäkoski M, Tenhunen J, et al. Next generation fluidized bed granulator automation. AAPS PharmSciTech 2000; 1(2):article10.
125. Rantanen J, Jørgensen A, Räsänen E, et al. Process analysis of fluidized bed granulation. AAPS PharmSciTech 2001; 2(4):article 21.
126. Rantanen JT, Laine SJ, Antikainen OK, et al. Visualization of fluid bed granulation with self organizing maps. J Pharm Biomed Anal 2001; 24(3):2001:343–352.
127. Laitinen N, Antikainen O, Airaksinen S, et al. At-line particle size analysis with a novel optical technique during a fluidized-bed granulation process. Poster @AAPS Annual Meeting, 2002.
128. Jha BK, Tambe SS, Kulkarni BD. Estimating diffusion coefficients of a micellar system using an ANN. J Coloid Interface Sci 1995; 170:392—398.
129. Bourquin J, Schmidi H, Van Hoogevest P, et al. Basic concepts of ANN modeling in the application to pharmaceutical development. Pharm Dev Technol 1997; 2(2):95–109, 111—121.
130. Watano, S, Takashima H, Miyanami K. Control of moisture content in fluidized bed granulation by neural network. J Chem Eng 1997; 30(2):223–229.
131. Leane MM, Cumming I., Corrigan OI. The use of artificial neural networks for the selection of the most appropriate formulation and processing variables in order to predict the in vitro dissolution of sustained release minitabs. AAPS PharmSciTech 2003; 4(2):article 26.
132. Vandel D, Davari A, Famouri P. Modeling of fluidized bed neural networks. Proceedings of 32nd IEEE SSST. Florida: FAMU-FSU Tallahassee, 2000.
133. Quantrille TE, Liu YA. Artificial Intelligence in Chemical Engineering. San Diego: Academic Press, 1991.
134. Närvänen T, Seppälä K, Antikainen O, et al. A new rapid on-line imaging method to determine particle size distribution of granules. AAPS PharmSciTech 2008; 9(1):282–287.
135. Portoghese F, Berruti F, Briens C. Continuous on-line measurement of solid moisture content during fluidized bed drying using Triboelectric probes. Powder Technol 2007; doi:10.1016/j Powtec 2007.01.003.
136. Koerfer R, Simutis R. Advanced process control for fluidized bed agglomeration. Inf Technol Control 2008; 37(4):285–293.
137. Watano S, Sato Y, Miyanami K. Control of granule growth in fluidized bed granulation by an image processing system. Chem Pharm Bull 1996; 44:1556—1560.
138. Gore AY, McFarland DW, Batuyios NH. Fluid bed granulation: factors affecting the process in laboratory development and production scale-up. Pharm Technol 1985; 9(9):114.
139. Bonck JA. Spray granulation presented at the AIChE Annual Meeting, November, 1993.
140. Jones DM. Factors to consider in fluid bed processing. Pharm Technol 1985; 9(4):50.
141. Matharu AS, Patel MR. A new scale-up equation for fluid bed processing. Poster Presentation AAPS Annual Meeting, 2003.
142. Rambali B, Baert L, Massart DL. Scaling up of the fluidized bed granulation process. Int J Pharm 2003; 252(1–2):197–206.
143. Simon EJ. Fluid bed Processing of Bulk Solids. Paper presented at the Third International Powder Technology and Bulk Solids Conference, PowTech, Harrogate, England, Heyden & Sons, 1975:63–73.
144. Kulling W. Method and apparatus for removing a vaporized liquid from gas for use in a process based on the fluidized bed principle. US patent 4,145,818, March 27, 1979.
145. ATEX Directive 94/9/EC of the European Parliament and the council, March 23, 1994 and July 2006.
146. Parikh DM. Fluid bed processing in the 1990s. Tabletting and granulation year book. Pharm Tech 1996; (suppl):40–47.
147. Ehlers H, Räikkönen, H, Antikainen O, et al. Improving flow properties of ibuprofen by fluidized bed particle thin-coating. Intl J Pharm 2009; 368:165–170.
148. Doelling MK, Jones DM, Smith RA, et al. The development of a microwave fluid bed processor I: construction and qualification of a prototype laboratory unit. Pharm Res 1992; 9(11):1487–1492.
149. Doelling MK, Nash RA. The development of a microwave fluid bed processor II: drying performance and physical characteristics of typical pharmaceutical granulations. Pharm. Res 1992; 9(11):1493–1501.
150. Funakoshi Y, Kajiura T, Fujii K, et al. Process for coating granular materials. US Patent 3,671,296. June 20, 1977.

151. Funakoshi Y, Matsumura Y, Yamamoto M, et al. Process for coating granular materials. US Patent 4,034,126. July 5, 1977.
152. Abe E, Hirosue H. Method and apparatus for continuously coating discrete particles in turning fluidized bed. US Patent 4,542,043. Sept 17, 1985.
153. Jager KF, Bauer KH. Effect of material motion on agglomeration in the rotary fluidized -bed granulator. Drugs Made Germany 1982; 25:61–65.
154. Türkoglu M, He M, Sakr A. Evaluation of rotary fluidized-bed as a wet granulation equipment. Eur J Pharm Biopharm 1995; 41(6):388–394.
155. Li SP, Kowarski CR, Feld KW, et al. Recent advances in microencapsulation technology and equipment. Drug Dev Ind Pharm 1988; 14(2–3):353–376.
156. Robinson RL, Hollenbeck G. Manufacture of spherical acetaminophen pellets: comparison of rotary processing with multiple-step extrusion and spheronization. Pharm Technol 1991; 15(5):48–56.
157. Parikh DM. Layering in Rotary Fluid Bed a unique process for the production of spherical pellets for controlled release. Presented at Interphex-USA, New York, NY, 1991.
158. Hileman GA, Sarabia RE. Manufacture of Immediate and Controlled Release Spheres in a Single Unit Using Fluid Bed Rotor Insert. Presented at the Annual Meeting of The American Association of Pharmaceutical Scientists (AAPS), Poster PT 6167, 1992.
159. Iyer RM, Augsburger LL, Parikh DM. Evaluation of drug layering and coating: effect of process mode and binder level. Drug Dev Ind Pharm 1993; 19(9):9891–998.
160. U.S. patent 5, 132, and 142, 1992.
161. Korakianiti ES, Rekkas DM, Dallas PP, et al. Optimization of the pelletization process in a fluid bed rotor granulator using experimental design. AAPS PharmSciTech 2000; 1(4):article 35.
162. Piśek R, Planinśek O, Tuś M, et al. Influence of rotational speed and surface of rotating disc on pellets produced by direct rotor pelletization. Pharm Ind 2000; 62:312–319.
163. Kristensen J, Hansen VW. Wet granulation in rotary processor and fluid bed: comparison of granule and tablet properties. AAPS PharmSciTech 2006; (7):article 22 PPE1–PPE10.
164. Kristensen J. Investigation of a 2-step agglomeration process performed in a rotary processor using PEG solutions as the primary binder liquid. AAPS PharmSciTech 2006; 7(4):article 89.

11 Single-Pot Processing

Harald Stahl
GEA Pharma Systems, Hürth, Germany

Griet Van Vaerenbergh
GEA Pharma Systems nv - Collette™, Wommelgem, Belgium

INTRODUCTION

Single-pot processing was developed to provide the means for mixing, granulating, drying, and blending pharmaceutical granulations in a single apparatus. Although equipment design varies from manufacturer to manufacturer (Figs. 1–4), this category of processors is comprised of a high- or low-shear mixer granulator (similar to conventional granulators) outfitted with a variety of drying options. Initially, vacuum was combined with a heat-jacketed bowl to provide the means for drying in the single pot. Today, processors are available that provide vacuum drying with microwaves or that percolate gas under low pressure into the vacuum chamber (i.e., processing bowl). Another very interesting improvement is the use of swinging processing bowls (1).

Single-pot processors for the pharmaceutical industry have been available for years. They received renewed interest in the mid-1980s when microwaves were coupled with vacuum to enhance the drying operation. Microwaves applied to drying pharmaceutical granulations became synonymous with single-pot processing, and there was anticipation that this technology would eventually become the norm for granulation processing. Several major pharmaceutical companies purchased production-scale units following successful trials conducted at vendors' pilot facilities. In the ensuing years, when the technology did not become as popular as expected, there were rumors that microwave systems could not be validated and suffered from excessive regulatory hurdles. The reality is neither; single-pot technology has continued to evolve during the last decade. It has deemphasized its association with microwave drying while continuing to demonstrate its appropriate role in granulation technology (2).

In a production setting, single-pot processing may offer a number of advantages. By integrating granulating and drying capabilities into a single unit, capital investment in equipment, and good manufacturing practice (GMP) floor space may be lower than other alternatives. The number of material-handling steps is decreased; consequently, the total processing time may be shorter while maintaining a high yield and keeping production support to a minimum. Environmental variables, such as humidity, are eliminated from the manufacturing process, which may offer advantages for processing moisture-sensitive formulations. State of the art is to outfit a single-pot processor with clean-in-place systems, thereby enhancing operator safety by minimizing exposure to the product both during manufacturing and cleaning (3). Requirements for solvent recovery systems are lower for single-pot processors compared with fluid-bed dryers. Single-pot processors outfitted with vacuum are attractive for evaporating solvents that are explosive or for containing drug substances with low-exposure limits.

The versatility and compactness of small-scale (3- to 25-L) single-pot processors also make the technology attractive for development and pilot laboratory facilities. Within the last decade, equipment manufacturers began offering single-pot processors that can accommodate the batch sizes required during early development (0.3 g to 10 kg). The processors can be used as mixer blenders for direct compression formulations, or as mixer granulators to prepare wet granulations for fluid-bed drying, or utilized for their full range of capabilities as a single-processing unit for all the steps required for granulation preparation. Some vendors offer the option of upgrading their small-scale processors. For example, a user can initially purchase a single-pot processor with vacuum drying capabilities and add a microwave drying system at a

Figure 1 Ultimapro™ 75 microwave/vacuum single-pot processor with swinging bowl. *Source*: Courtesy of GEA Pharma Systems nv, Wommelgem, Belgium.

Figure 2 VMA70 microwave/vacuum single-pot processor. *Source*: Courtesy of L.B. Bohle Group, Ennigerloh, Germany.

later time. Consequently, single-pot processors should be given strong consideration when equipping a development laboratory or pilot plant intended to offer a variety of processing options to the pharmaceutical formulator.

The following text is intended to expose the reader to the drying methods, the capabilities, and the applications of single-pot processing to pharmaceutical granulations. Fluid-bed technology, which can also be used to mix, granulate, and dry granulate in a single unit, will not be addressed in this chapter because it is discussed elsewhere in this book.

TYPICAL SINGLE-POT PROCESS

The steps and sequence of manufacturing pharmaceutical granulations using single-pot processing are the same as those that use alternative technologies, except that several of the steps are performed in the same product chamber. The majority of production installations make use of its mixing, granulating, and drying capabilities during the processing of a single batch.

Figure 3 RotoCube single-pot granulator. *Source*: Courtesy of IMA Group, Lucca, Italy.

Figure 4 VAC 600 vacuum single-pot processor. *Source*: Courtesy of Diosna, Osnabrück, Germany.

Important to note is the absence of a milling steps in between granulation and drying. The advantage of a reduced number of process steps is obvious while the drawback is that there is no possibility of breaking lumps generated during granulation. Single-pot operations, therefore, require excellent control of the granulation to prevent the formation of oversized material.

Dry Mixing

Powders are loaded into the single pot either manually (for development- and pilot-scale units) or by a conveying system (for production-scale units). Vacuum pump(s) used for the drying operation can also be used to charge the processor. Pneumatic- and vacuum-conveying systems contribute to minimizing operator exposure to the drug product. The powders are mixed in the dry state until the desired degree of uniformity is obtained. Depending on the geometry of the processing bowl and the efficiency of its mixing blades, optimal mixing for

most processors generally occurs when the bowl is charged to 50% to 75% of capacity. Batch size, impeller speed, and mixing time are variables that affect the desired degree of blend homogeneity before the addition of the binder solution.

Addition of Binder Solution

Once dry mixing is completed, the binder solution is added through a spray lance connected to a solvent delivery system (such as a pressure pot or peristaltic pump). For highly viscous binder solutions, it is advantageous to use the vacuum system of the processor for sucking into the processor. Because the single-pot processor is operating as a granulator at this point, all variables considered during the manufacture of wet granulations in conventional high- or low-shear mixer granulators are applicable. Those variables include the rate of binder action, droplet size, and spray pattern (the latter two being determined by the selection of the spray nozzle and the distance between the nozzle tip and granulation bed). The speed of the main impeller and the granulating tool (e.g., high-intensity chopper bar), as well as the jacket temperature, should also be controlled during binder addition.

Wet Massing

Following binder addition, additional energy may be imparted to the granulation until the desired consistency is obtained. The speeds of the main impeller and granulating tool, wet massing time, and jacket temperature are variables that can affect the physical attributes of the granulation. Like the bowl shape, the impeller design will also affect the amount of shear imparted to the granulation. Granulation endpoint may be controlled by process time, temperature of the product bed, and the energy consumption, or torque of the main impeller.

Drying

After granulation, the material is dried using one of three approaches: (a) vacuum drying, (b) gas-assisted vacuum drying, or (c) microwave vacuum drying. Details of each drying method are summarized in section "Drying Methods for Single-Pot Processors." The product bed is usually stirred at low intensity during the drying process to facilitate solvent removal and promote uniform drying, as well as to prevent caking of the granulation on the chamber's walls. Agitation may be applied by slowly tilting the bowl or operating the impeller at low speed either continuously or intermittently throughout the drying stage. Caution must be exercised to avoid granule breakdown during drying, which may result in unfavorable compression characteristics (4). Variables for vacuum drying include the level of vacuum maintained in the bowl, the jacket temperature, and the degree of agitation. In addition to the parameters listed for vacuum drying, gas-assisted vacuum drying must also consider the type of drying gas used and its rate of delivery. When microwave vacuum drying is used, all of the variables used for vacuum drying are applicable, as well as the level of microwave power used to dry the granulation. If yield is of greater importance than the process time, a very interesting process option is to follow the product temperature very closely with the wall temperature and use as a source of drying energy only the introduced microwave energy. This mode of operation minimizes the amount of material sticking to the walls for the price of a prolonged drying operation resulting in a reduced throughput. This option is of special interest for the processing of highly expensive materials.

If required, cooling can be conducted at the conclusion of the drying operation. The heated water or steam in the bowl jacket, which supplied conductive heat during the drying process, can be replaced with a glycol-water solution to provide a contact surface as low as 10 °C. Another approach to cool the granulation is by purging a cooling gas into the single pot while agitating the granulation bed.

Sizing and Lubrication

Once the granulation is dried, it is usually necessary to size it. This may be accomplished by discharging the material through an in-line mill into a receiving vessel where it may be blended with any remaining excipients (e.g., lubricant and flavors). This process design maintains the containment benefits of the single-pot process. Alternatively, the remaining excipients may be added to the single-pot processor and blended with the granulation before

discharging and milling. This approach requires that the lubricant be adequately distributed during milling and material transfer during the compression operation.

DRYING METHODS FOR SINGLE-POT PROCESSORS

Conductive Drying

The bowls of single-pot processors are generally jacketed for temperature control, which minimizes condensation of the granulating solvent and assists in solvent evaporation during drying. As a result, conductive heating provided by the heat-jacketed lid and walls of the single pot contributes to the drying process. Its dependence on the transfer of heat through pharmaceutical powders, which are poor conductors of heat, prevents its use as the sole mode of drying in single-pot processors. Equation (1) addresses the conductive drying component for solvent removal.

Heat transfer from the vessel walls to the granulation bed is governed by

$$Q = hS\Delta T \tag{1}$$

where

Q = the energy exchange,
h = the exchange coefficient,
S = the contact surface of the heated wall, and
ΔT = the temperature difference between the contact wall and the granulation.

The rate of drying can be facilitated either by increasing the contact area between the granulation and the vessel walls (which can be achieved by agitating the product or utilizing a tilting bowl) or by maximizing the temperature difference between the vessel walls and product (either through increasing the jacket temperature or maintaining the temperature of the product as low as possible during processing).

Equation (2) is a simple relation that may be of some value for the scaling-up of processes using conductive heating (5).

$$\frac{t_b}{t_a} = \frac{(A/V)_a}{(A/V)_b} \tag{2}$$

where

t = drying time,
A = heat transfer surface (m^2),
V = vessel working volume (m^3),
a = refers to pilot scale, and
b = refers to production scale.

This relation accounts for the ratio of the surface area of the jacketed bowl and the volume of the product requiring drying.

Vacuum Drying

Single-pot processors using vacuum drying may be considered if the product must be dried at a low temperature (<40°C), if solvent recovery is required, or if the potential for explosion is high. A vacuum is maintained within the vessel, thereby lowering the temperature at which the granulating solvent evaporates. Because vapors are removed from the processing bowl, vacuum drying provides a convenient means for solvent recovery.

De Smet (6) has discussed the theory, advantages, and limitations of vacuum drying. Aqueous granulations require a large amount of energy during drying, which is generally supplied by the transfer of heat through conduction from the jacketed bowl to the product. The amount of energy required for water removal is dependent on the level of vacuum applied to the vessel and the osmotic pressure of dissolved substances. As additional material dissolves in the water, the osmotic pressure increases and additional energy is necessary to drive off the

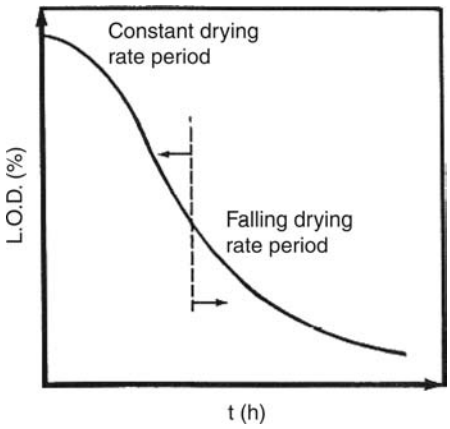


Figure 5 Typical curve for vacuum drying. *Source*: Courtesy of Manufacturing Chemist, London, United Kingdom.

water. Therefore, as the material becomes drier, the amount of energy necessary to evaporate the water increases, and the rate of evaporation slows. Processing times in vacuum dryers are often long, owing to the limited contact of the granulation with the heat from the jacketed walls, and the slow rate of evaporation of the solvent from the interior of the granules.

The drying rate of the vacuum component is dependent on the following relation:

$$V = ks\Delta P \tag{3}$$

where

V = evaporation rate,
k = rate coefficient,
s = total surface of granules, and
ΔP = the vapor pressure difference between the granules and the surrounding space.

The rate of drying can be facilitated by increasing the level of vacuum (i.e., decreasing the pressure within the bowl) to increase the differential between granule and bowl vapor pressure. Figure 5 is a typical drying curve for a vacuum drying process. When moisture content in the granulation is high, the rate of drying is constant because evaporation of solvent from the product surface readily occurs. As the level of moisture on the granule surface decreases, water must migrate from the interior of the granule before evaporation. As a result, the rate of evaporation progressively decreases.

During vacuum drying processes, one should be aware of various problems that could arise. For example, granule damage may occur owing to excessive attrition as the bed is agitated during drying. Vacuum systems should contain adequate filtering or blowback to prevent the loss of granulation "fines" through the vacuum line, which may compromise the drug uniformity within the processed batch.

A condenser positioned between the processor and vacuum pump should always be used, especially for granulations manufactured using organic solvents. The condensate must be sufficiently cooled to prevent it from being released into the atmosphere. Also, filters may become blocked owing to condensation forming on the filter or the entrapment of solid particles. Blockage of the filters reduces the level of vacuum that can be pulled on the bowl and excessively strains the pump itself.

Gas-Assisted Vacuum Drying

Accelerating the drying process in vacuum dryers is often limited by characteristics of the product or equipment. Bowl temperature is generally limited by the physicochemical stability of the product, which can limit the use of higher temperatures to expedite drying. Increasing the contact area between the product and the vessel is difficult without significantly altering the design of the equipment. Excessive agitation of the product can lead to considerable granule attrition, which can lead to poor granulation flow and compression properties.

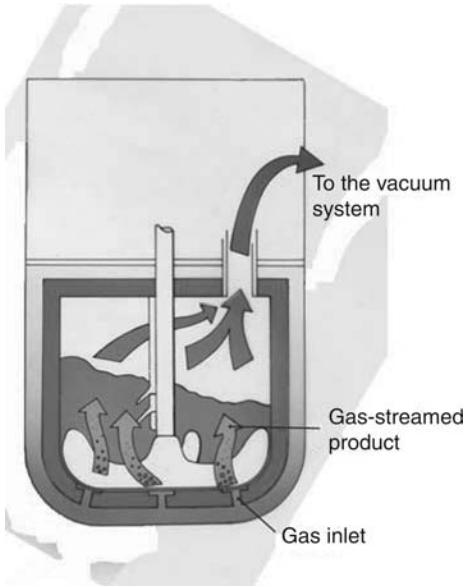


Figure 6 Gas-assisted vacuum drying principle. *Source*: Courtesy of GEA Pharma Systems nv, Wommelgem, Belgium.

Gas-assisted vacuum drying improves the efficiency of single-pot processors that use vacuum drying by continuously introducing a small stream of gas through the granulation to facilitate solvent removal. Drying continues to be performed at lower temperatures (compared with tray and fluid-bed drying), but at shorter processing times than vacuum drying alone and with the capability of reaching lower moisture contents.

The gas may be introduced into the unit through openings in the bottom of the vessel or through the mixing blades (Fig. 6). Compressed air or nitrogen (mixed with or without air) are commonly used gases for these units. The rate of gas flow and the level of vacuum applied to the bowl can be adjusted for a specific product to produce optimal drying conditions.

The introduction of gas into a vacuum chamber facilitates the drying process through several actions. The constant flow of gas through the product improves the transport of moisture from the product to the vacuum solvent recovery system (7). Introducing gas into the bowl also increases the vapor pressure driving force (8). The pressure gradient across the vessel is increased, resulting in a reduction in the rate at which water molecules recombine, producing a net increase in the rate of evaporation. This causes the product temperature to be reduced, which increases the temperature differential between the granules and the bowl wall. The gas also reduces drying time by increasing the heat transfer coefficient from the bowl to the bed. In addition to improving the heat transport through the bed, the gas can reduce or eliminate product sticking to the sides of the vessel walls because it improves flow and dries the particle surfaces more quickly. As the vessel wall is the only notable source of drying energy, this technology is best used in case of

- small batch sizes (good surface volume ratio),
- heat-insensitive materials (allows to operate at a higher wall temperature), and
- organic solvents (required only a fraction of the energy water needs for evaporation). Additionally the boiling temperature corresponding to the actual vacuum level is much lower for organic solvents than for water, generating a larger temperature difference between product bed and vessel.

Microwave Vacuum Drying

High-shear granulators with microwave vacuum drying capabilities provide the fastest drying rates in the family of single-pot processors. Microwave drying is based on the absorption of electromagnetic radiation by dielectric materials, the theory of which has been extensively

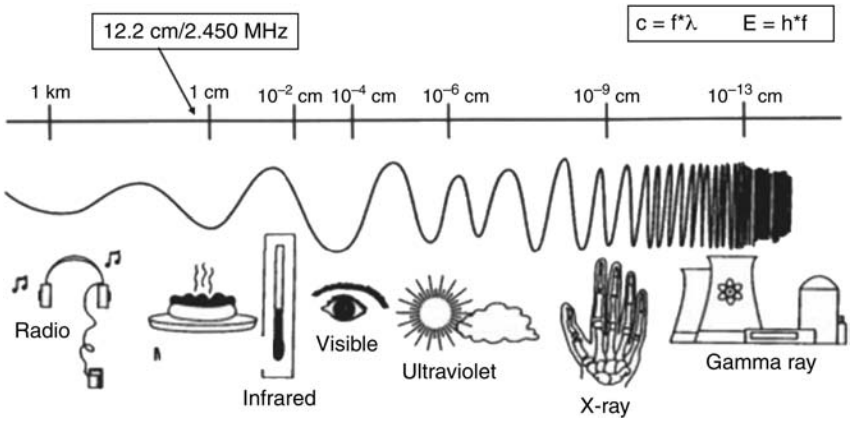


Figure 7 The electromagnetic spectrum.

described (9–11). Microwaves are a form of electromagnetic energy similar to radio waves, the frequencies of which fall between 300 and 3000 MHz (between radio and optical waves, see Fig. 7). The two frequencies allocated for domestic, scientific, medical, and industrial purposes are 915 and 2450 MHz. Pharmaceutical processors generally use 2450 MHz, because this frequency is more desirable when used in conjunction with vacuum. Single-pot processors incorporating microwave drying are constructed of stainless steel because metal is a common reflector of microwave energy and contains the energy within the processing chamber. Teflon is essentially inert to microwaves, making it a suitable material for components required in the processing bowl (e.g., spray lance and temperature probe).

Energy absorption of materials exposed to microwaves is described by equation (4) (10,11).

$$P = 2\pi f V^2 E_o E_r \tan \delta \tag{4}$$

where

P = the power density of the material (W/m^3),
f = frequency (Hz),
V = voltage gradient (V/m),
E_o = dielectric permissivity of free space (8.85×10^{-12} F/m), and
E_r = dielectric constant of the material, and tan δ = loss tangent.

For a constant electric field strength, V, the term $2\pi f V^2 E_o$ is constant. Therefore, the power absorbed is proportional to the term $E_r \tan \delta$, called the loss factor, which is a relative measure of how easily a material absorbs microwave energy.

Various materials commonly used in pharmaceutical formulations have low loss factors and only absorb microwave energy at high field strengths. Solvents used in the granulation process (water, ethanol, isopropanol, and such), however, possess high loss factors relative to the pharmaceutical powders (10). The dipolar component of the solvents couples with the high-frequency electromagnetic field producing high heating rates for the solvent, resulting in its evaporation and subsequent removal from the processing chamber. Table 1 lists the loss factors for various components in a typical pharmaceutical granulation (12).

Lucisano and Moss (13) performed a study in which a microwave drying process was conducted in two different processors, one using fixed-output magnetrons and the other using a variable-power magnetron. The unit using fixed-output magnetrons had difficulty obtaining low moisture levels (<0.3%) because the E-field safety set point was exceeded when the moisture went below 1%. This problem did not occur for the unit using the variable-power magnetron because forward power was reduced as the E-field increased. During the late stages of drying, the unit was primarily functioning as a vacuum dryer, as the amount of microwave

Table 1 Loss Factors for Typical Pharmaceutical Ingredients

Pharmaceutical ingredient	Loss factor at 20°C
Lactose	0.02
Mannitol	0.06
Microcrystalline cellulose	0.15
Corn starch	0.41
Isopropanol	2.9
Water	6.1
Ethanol	8.6

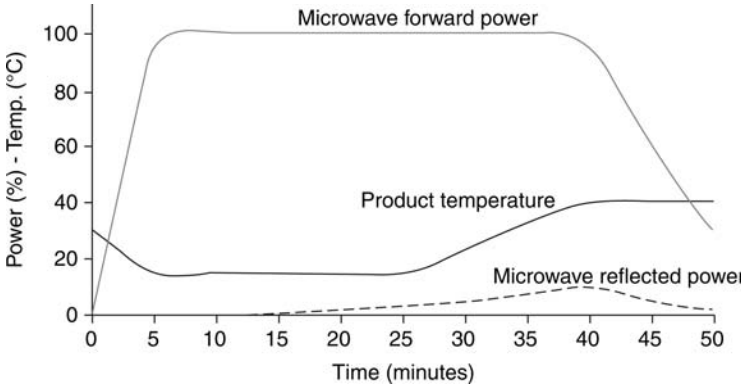


Figure 8 Relationship between microwave forward power, microwave reflected power and product temperature during microwave vacuum drying.

energy being introduced into the bowl was minimal. Nowadays, most microwave dryers use the variable output magnetrons.

The use of vacuum during microwave drying lowers the temperature at which the solvent volatilizes, thereby limiting the temperature to which the material is exposed. For example, at a vacuum of 45 mbar, water-based granulations will dry at approximately 31 °C. Once most of the water is removed from the process, the temperature of the material will rise as components in the mixture with lower loss factors start to absorb the microwaves. If too much vacuum is applied to the system, there is a potential for granule breakdown owing to the excessive pressure between the core and surface of the granules. Microwaves are typically applied in a vacuum range of 30 to 100 mbar. Introducing microwave into a vacuum less than 30 mbar risks ignition of the surrounding atmosphere, a condition known as "arcing."

Control of the drying process is achieved through the simultaneous measurement of product temperature, forward power and reflected power. Figure 8 depicts the level of microwave forward power, microwave reflected power, and product temperature at various times during the drying process. During the initial stage, the product temperature remains relatively constant as the free solvent is preferentially evaporated, and the reflected power remains relatively low. The amount of vacuum applied to the bowl, and to a lesser extent, the bowl jacket temperature, will affect the actual product temperature observed. As drying progresses at a constant rate of forward power, the amount of absorbed energy decreases as the material dries, thereby increasing the amount of free energy. As the free energy increases, a corresponding increase in the reflected power is also observed.

The rise in reflected power is accompanied by an increase in product temperature, which is simultaneously monitored while the magnetron output power is reduced. This is necessary because the loss factors for some pharmaceutical components are so small that very low moisture can be achieved before the temperature rises. For such materials, the reflected power can rise sharply, once most of the solvent has evaporated, resulting in significant temperature gains.

The rise in temperature and reflected power signifies that the end of the drying process is approaching. Several factors, such as the loss factors of the formulation components, microwave power, and the solvent retention properties of the solids, influence the point at which the previous relation will occur.

For example, lactose has a low loss factor and shows a sharp rise in reflected power, followed by a slow temperature rise. Conversely, starch has a high loss factor and demonstrates a fast temperature rise followed by a slow rise in reflected power.

OTHER PROCESSES AND APPLICATIONS

Because of the different technologies incorporated into a single-pot processor, it is capable of executing many different processes, apart from the standard wet granulation and drying process, while small modifications or additional options can extend the flexibility even further.

This chapter discusses some of the possible "special" processes and applications in a single-pot processor. Although many of these processes are used in the pharmaceutical industry, scientific literature about them is rare. The main reason for this is that many of these processes were developed by the pharmaceutical industry as product-specific solutions. This does not imply, however, that these processes cannot be used more widely.

Melt Granulation

Melt granulation is a process in which the binder solution of the standard wet granulation process is replaced with a meltable binder such as a wax or PEG, which is generally added in solid form, and melted during the process by adding the necessary energy. Chapter 20 of this book discusses various methods of producing melt granulation in details.

The most common production technique for melt granulation uses extruders, but melt granulation in a high-shear mixer has also been extensively described in literature.

In this process, the necessary energy to melt the binder is provided either by the mixer arm (mainly in laboratory scale equipment) or by a heated jacket (14–16).

If the meltable binder used absorbs microwaves (such as PEG), using a single-pot processor equipped with microwave drying, can present major time savings to the production process.

Providing the melting energy by the impeller or the heated jacket can be a very time-consuming process, especially in production-scale equipment. Microwaves are an instant source of energy that penetrates into the product and can provide the energy faster and immediately where needed.

In a comparison between the use of the heated jacket to melt the binder and the use of heated jacket supplemented with microwaves, the latter method not only proved to be more than twice faster in melting the binder used (PEG 3000), but also the granulation step was reduced threefold (17).

At this moment, there is no literature available about other meltable binders in combination with microwaves.

However, the results from the above-mentioned study show that it is worthwhile to consider a single-pot processor for the production of melt granulations.

Another step where a single-pot processor can present a major advantage compared with the standard production techniques, and especially compared with the process in a high-shear mixer, is the cooling step. To achieve a stable "dry" granule from a melt granulation process, the product needs to be cooled down to room temperature. In a high-shear mixer, the cooling process is done by circulating cold water or a glycol-water mixture in the bowl jacket. As the contact surface between the product and the jacket is limited, the cooling process generally takes a long time. If the process is executed in a single-pot processor equipped with a gas-assisted vacuum drying system, this system can be used to pass cold air or even liquid nitrogen through the product to aid the cooling process and reduce the cooling time considerably. If liquid nitrogen is used, even a fivefold reduction of the cooling time is achievable (17).

Pellet Production

For the production of spheres or pellets, in most cases an extrusion/spheronization process is used.

Figure 9 Example of a special pelletizing mixer arm. *Source*: Courtesy of GEA Pharma Systems nv, Wommelgem, Belgium.

There are, however, many references in scientific literature detailing the production of pellets using a high-shear mixer, most of which concern melt pelletization (15–21).

Taking into account the explanations above on melt granulation, a single-pot processor can, of course, also be used for this process for the same reasons.

Also for other pelletization processes, not using meltable binders, the use of a single-pot processor can be advantageous. In scientific literature, there are some references describing the use of a high-shear mixer for such processes (22,23), but so far none can be found about single-pot processors. Nevertheless, a standard pellet formulation often contains microcrystalline cellulose, which needs high water content to obtain a good granule/pellet quality. Drying the pellets is always a part of the production process. The advantage of a single-pot processor is that the whole process of pelletization and drying can be executed in the same equipment, making product transfers redundant and thereby reducing the risk of product loss and contamination and enhancing containment and operator safety.

To enhance the pelletization/spheronization process, many vendors of high-shear mixers/single-pot processors offer special mixing tools for producing pellet-like granules. Depending on the geometry of the equipment, this special mixing tool has either more (up to six) or less (2) mixing blades than a standard mixing tool, which generally has three mixing blades (Fig. 9). All special pellet-mixing tools have, however, the same purpose: so simulate the product behavior in a spheronizer and enhance the spheronization process that occurs in the mixer.

Effervescent Production

The production of effervescent tablets is first of all a conventional solid dosage form manufacturing process, which has to take into consideration some unusual features because of the special characteristics of the product.

For granulation of effervescent products, many different production techniques can be used, ranging from dry granulation methods over two-step granulation (granulating acid and alkali phase separately) to one-step granulation using water or organic solvents.

For the one-step granulation methods, the use of a single-pot processor offers many benefits. Apart from the overall benefit of eliminating product transfer between a granulator and a dryer, a single-pot processor allows easy solvent recovery by condensation in case organic solvents are used as granulation liquid, compared with the quite complex system for the exhaust gas treatment required for a fluid-bed dryer.

When water is used as granulation liquid for effervescents, the effervescent reaction will start and cause a chain reaction. The critical point in such a process is to stop this reaction at the correct time by evaporating the water created by this reaction. In a single-pot processor, this can be very easily and accurately achieved by switching on the vacuum drying system (possibly supplemented with gas-assisted drying or microwave drying) (24).

Crystallization

Although a high-shear mixer/single-pot processor is mainly intended for powder processing, there is a possibility to execute crystallization or re-crystallization processes in this type of equipment as well. Starting from either a solution or from a powder, which is dissolved in a suitable solvent, the speed of the drying process can be controlled to achieve a desired crystallization process. Using vacuum drying only, the drying process will be slow and gradual. Temperatures during this process will remain low, creating an environment for slow crystal growth. When microwaves are used for drying, the process will be considerably faster and the temperature of the product will most likely be higher than under "pure" vacuum conditions. The crystals that result from such a crystallization process will have different characteristics than those from the vacuum drying process. When choosing the appropriate settings for the drying/evaporation process, combining vacuum and microwave drying, crystals with specific properties can thus be obtained.

The main advantage of executing a (re-)crystallizing process in a single-pot processor is that the possibility exists to granulate the product at the same time by varying the mixer speed during the drying process. The resulting product will be suitable for tableting without the necessity of executing other processing steps (apart from lubrication).

SCALE-UP OF DRYING PROCESSES

Because the rate of solvent removal during vacuum drying is dependent on a favorable surface area/volume ratio, the drying time in a vacuum processor often increases substantially during scale-up like described by equation (2). Microwave vacuum drying is relatively insensitive to the surface area/volume ratio and does not suffer the same inefficiency as vacuum drying during transition from pilot to production scale. Pearlswig et al. (25) reported successfully scaling a microwave vacuum drying process for a moisture-sensitive formulation that required a drying endpoint of less than 0.2%. The drying time remained within a 30- to 45-minute range throughout the scale-up from 15 Kg (Vactron 75) to 300 Kg (Vactron 600), whereas the time for vacuum drying increased threefold. After additional scale-up to 600 Kg in a Vactron 1200, the drying time rose slightly to a 50- to 55-minute range. Poska (26) also reported attaining equivalent drying times when scaling-up in Spectrum processors ranging from 65- to 300-L bowl size. Figure 10 compares typical drying curves for a lactose-starch granulation prepared in single-pot processors using vacuum drying, gas-assisted vacuum drying, or microwave vacuum drying. Although not as rapid as microwave vacuum drying, gas-assisted vacuum drying can decrease the drying time by up to 50% compared with that of vacuum drying alone. As the wall of the vessel is the only source for drying energy also in this case the scale is of major importance for the drying time (27).

When performing feasibility trials on a development- or pilot-scale single-pot processor, it is important to be aware of the maximum energy input capacity of the corresponding, production-scale processor. In Figures 10 and 11, the drying times for each drying method in a

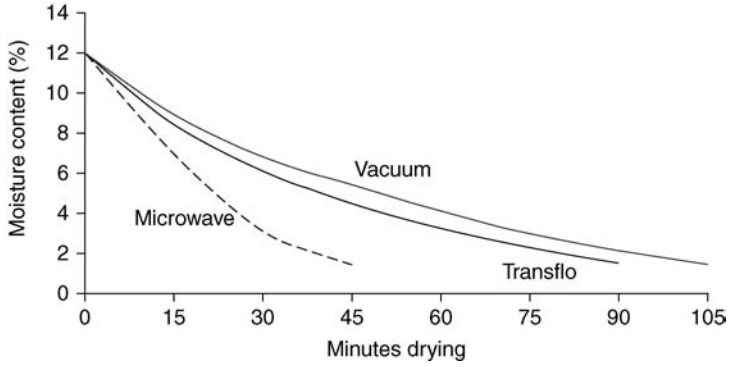


Figure 10 Comparison of drying curves for different modes of drying in a 75-L UltimaPro™. *Source*: Courtesy of GEA Pharma Systems nv, Wommelgem, Belgium.

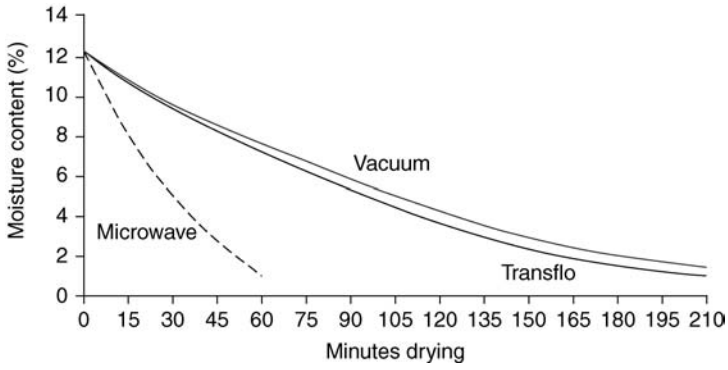


Figure 11 Comparison of drying curves for different modes of drying in a 600-L UltimaPro™. *Source*: Courtesy of GEA Pharma Systems nv, Wommelgem, Belgium.

pilot-scale and production-scale single-pot processors are shown. While for processors equipped with microwaves, the drying time is relatively independent of the scale, a significant increase in drying time is observed for vacuum and gas-assisted vacuum drying processes.

CONTAINMENT

One of the main drivers for the use of single-pot systems is the need of processing potent substances such as hormones. Reasons for this are the small surface area in contact with the product (compared for instance with a fluid bed), the tight execution of a single pot, and the processing under negative pressure.

As always, when dealing with potent substances, three main areas of concern exist, which are

- cleaning,
- loading and unloading the processor, and
- sampling.

As described in chapter 7, modern single pots are equipped with cleaning-in-place capabilities eliminating the risk of exposure during the cleaning operation.

For the loading and unloading of potent substances from and to up- and downstreaming processes, nowadays, in most cases, split butterfly valves are used. The functional principal of a split butterfly valve is shown in Figure 12.

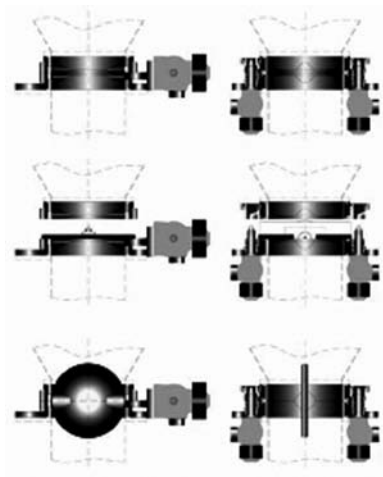


Figure 12 Functional principle of a split butterfly valve. *Source*: Courtesy of GEA Pharma Systems AG, Bubendorf, Switzerland.

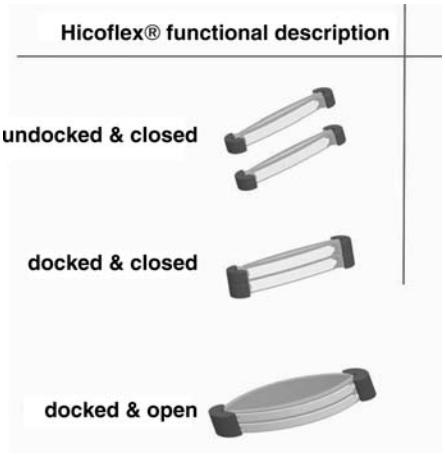


Figure 13 Functional principle of the Hicoflex® system. *Source*: Courtesy of GEA Pharma Systems AG, Bubendorf, Switzerland.

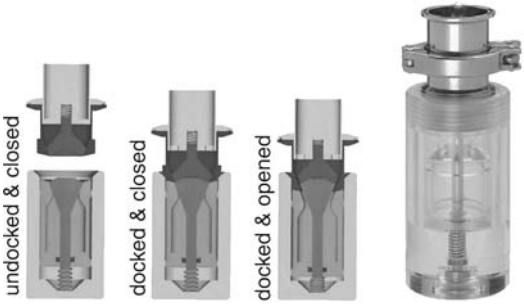


Figure 14 Principle of a contained sampler. *Source*: Courtesy of GEA Pharma Systems AG, Bubendorf, Switzerland.

Depending on their complexity, split butterfly valves offer containment performances down to 20 ng/m^3 of airborne particles. One of the most recent developments in the arena of split butterfly valves is the Buck MC valve, which has some unique features as for instance that it employs only passive valves or that the containment performance of the valve system can be upgraded at a later stage if required because of more potent substances (28).

An alternative, especially in smaller scale, is the use of flexible and disposable containment solutions. A prime example of this is the Hicoflex® technology, which is also based on the functional principle of the split valve combined with the locking principle of a snap ring. In Figure 13, the functional principal of Hicoflex is shown. Hicoflex offers a containment performance of significantly below 10 μg/m^3 of airborne particles.

While the use of PAT for the elimination of any need for sampling—as described in chapter 12—offers the most consequent approach when dealing with potent substances, it is also possible to sample in a contained manner. The Buck Sampler is based on the functional principle of split butterfly valves. Its functional principle is shown in Figure 14.

Alternatively, a special Hicoflex Sampling Bag, as shown in Figure 15, can also be used, allowing a contamination free sampling process.

CLEANING

As a single-pot processor is often used for highly potent products, or more general for contained production, it is also important that cleaning of the machine can be executed in a contained, automated fashion to eliminate the risk of operator exposure to the active product.

All single-pot processors on the market nowadays are equipped with a more or less extensive clean-in-place system. Vendors have made a great effort to optimize their design enabling easy cleaning in place, which can be validated (3). The focus has been to eliminate any dead spots in the equipment where the cleaning water cannot reach and to include cleaning spray balls in critical product contact areas such as the product filter and discharge valve.

Figure 15 Hicoflex® sampling bag. *Source*: Courtesy of GEA Pharma Systems AG, Bubendorf, Switzerland.

Drying of the single-pot processor after the cleaning cycle to prepare the equipment for a next batch can be done using the system's own vacuum drying system and jacketed bowl, making a separate drying unit redundant.

A nice case study of an evaluation of a clean-in-place system on a pilot-scale single-pot processor is given in Ref. 3. In this study, it has been proven that a complete change-over from one product to the next can take place in less than two hours.

PRODUCT STABILITY

The stability of pharmaceutical granulations dried by microwaves is comparable to that provided by alternative methods. Microwaves are nonionizing and do not possess the amount of energy required for the formation of free radicals or the liberation of bound-water conditions that foster product instability (Fig. 6).

Since the introduction of microwave drying at the end of the 1980s, numerous new and supplemental drug applications that include the use of microwave vacuum drying of wet granulations have been approved by the Food and Drug Administration (FDA). We are unaware of any instance in which the FDA required additional stability or analytical testing beyond that normally required for other methods of manufacture. Mandal (29), Moss (30), and others (26,31) have also published or presented data showing the comparability of the physicochemical characteristics of granulation dried in microwave processors versus tray dryers and fluid-bed driers.

When microwaves were first introduced, some authors (32) concluded that microwave drying could not be generally recommended because of the inability to control the microwaves after they enter the drying cavity and the risk of unacceptable thermal damage to active substances with high loss factors (i.e., high dielectric constants). The routine production of pharmaceutical products by several installations of single-pot processors using microwave vacuum drying indicates that their general concerns can be addressed by the proper selection of formulation components and process parameters.

REGULATORY CONSIDERATIONS

Single-pot processors combine established technologies into a single piece of equipment and, in general, deserve no special regulatory consideration when using them to develop a new product or to manufacture an approved product. Robin and colleagues (4) surveyed eight European regulatory agencies in 1992 to determine the implications of converting from fluid-bed drying to microwave vacuum drying within a single-pot processor. The majority of the agencies required only process validation data and three suggested limited stability data (up to six months of accelerated data). These requests were no different from those expected for similar types of manufacturing changes (i.e., change in process or equipment).

Manufacturers considering converting to a single-pot process for an immediate release, solid oral dosage form (tablets, capsules, or the like) with an approved manufacturing process should consult their appropriate regulatory agencies governing the practices they used to manufacture their products. For drug products sold in the United States, manufacturers should refer to FDA's SUPAC IR Guidance document (33) that addresses scale-up and postapproval changes for marketed products. This document describes the levels of change that may be made in a manufacturing process and equipment. It outlines the chemistry, manufacturing, and control tests and documentation for each level of change as well as the appropriate regulatory filing (Annual Report, Prior Approval Supplement, or other).

For example, a tablet formulation is currently granulated using a high-shear granulator and dried in a tray drier. A drug manufacturer wishes to replace this process with a single-pot processor that incorporates high-shear granulation and gas-assisted vacuum drying. This conversion would be viewed as a change in equipment to a different design and operating principles (defined as a level 2 equipment change in the SUPAC IR Guidance document). Such a change requires the manufacturer to submit a Prior Approval Supplement, with up to three batches with three-month accelerated stability data (depending on the duration of commercial experience with the product). The submission would also require updated batch records including the new equipment, and the generation of multipoint dissolution profiles.

The requirements for this conversion are, however, the same as those for a conversion of a tray drier to a fluid-bed drying process.

VALIDATION OF SINGLE-POT PROCESSORS

Because single-pot processors combine standard engineering approaches into a single processor, their validation should pose no special problems. Other sources adequately describe the validation of granulating and drying processes (34), although validation of the microwave drying system and the approach to process control of drying endpoint deserves special mention.

For operational qualification of microwave components, such as forward and reflected power, and arc detection, we suggest that customers contract the vendors because of the specialized nature of microwave systems. The cost associated with the calibration equipment is difficult to justify, and microwave systems should operate reliably following proper set-up and qualification and require no more periodic maintenance than other granulation approaches.

When microwave processors were first introduced, there was the expectation that E-field would be a reliable indicator of the drying endpoint. With experience, users found that the E-field tends to be too variable, and now view it primarily as a safety feature monitoring the microwave field within the drying cavity. Most microwave dryers on the market today do not even include E-field monitoring anymore, because of the difficulties with validation of this system.

Product temperature, time, cumulative forward power, and reflected power are proving more reliable indicators of drying endpoint with verification by some in-process control that directly measures moisture content of a product sample. The industrial processes in operation today all use one of these approaches for endpoint determination.

With the pharmaceutical industry moving toward the use of PAT technology however, the equipment vendors are also investigating the possibility of applying this technology to single-pot processors and thereby eliminating the necessity of taking product samples. The first single-pot processors with PAT technology will undoubtedly be introduced into the market shortly.

PROCESS ANALYTICAL TECHNOLOGY

As PAT will be discussed extensively in other chapters of this book, the main focus of this chapter is to outline the areas of application of PAT in a single-pot processor.

The goal of PAT is to gain better process understanding resulting in better process control and eventually real-time product release by online monitoring and measuring of critical product characteristics.

The product characteristics that are critical during a single-pot processing are

- homogeneity of the active in the powder mixture,
- particle size distribution of the granules, and
- moisture content of the product after drying.

Several online measuring techniques can be used to monitor and measure these characteristics.

Near infrared spectroscopy, for example, can be used during different stages of the single-pot process: during the dry mixing, NIR is used to monitor blend homogeneity, while during drying the same probe—using a different analysis algorithm—can be used to monitor moisture content.

For monitoring particle size distribution, focussed beam reflectance measurement (FBRM) offers promising results.

Also other techniques, such as Raman spectroscopy are under investigation for monitoring high-shear granulation and drying processes.

Some specific points of attention, if applying PAT measurements to single-pot processing, are as follows:

- The powders in a single-pot processor move at a high speed during the process. The chosen monitoring method should have the capability to meet this speed to make the necessary snapshots needed to show the changes taking place in the process.
- During the wet granulation process, the product goes through different degrees of wetness. Most products become sticky during one or more of these stages and this can obscure the optical sensors and lead to false measurements. An in-line cleanable system is advised for measurements in granulation.
- Containment is often a reason to go for single-pot processing. When applying NIR as PAT measurement tool, it is a good practice to take a baseline before every batch. As this is done by placing a white standard in front of the sensor, a problem may occur with containment unless a system is chosen that can take the white reference spectrum including the whole optical path without breaking containment.

To assist you with developing PAT on single-pot processors, many equipment vendors now have application labs where single-pot processors are equipped with PAT ports and tools and where specialists can assist.

CONTROL SYSTEMS AND DATA ACQUISITION SYSTEMS

Users of single-pot processors may use one or all of its processing features (mixing, granulating, drying, or others). The accompanying data acquisition system must collect, display, and record the relevant processing conditions and granulation behavior for each cycle. The degree of sophistication of the system may depend on the venue in which the processor is used (Fig. 16).

In a development setting, the sequence of cycles is often interrupted to collect samples for analysis, and the user is interested in capturing as much information as possible to assist in defining a suitable processor for a particular formulation. In many cases, the control system for a development environment can be limited to a manual control system. The data acquisition system, however, needs to be more sophisticated to allow registration of all relevant processing data.

In production, the manufacturing sequence and process parameters are predefined and validated, and information needs are reduced to monitoring critical parameters. In these settings, an automatic control system with recipes to reduce operator interventions is indispensable. The data acquisition system may or may not be as sophisticated as for the development settings, depending on the requirements for data in the batch records.

For the purposes of trouble-shooting and trend analysis of production operations, however, the information requirements of development and production converge, and data acquisition systems for single-pot processors should seek to address the needs of both types of users.

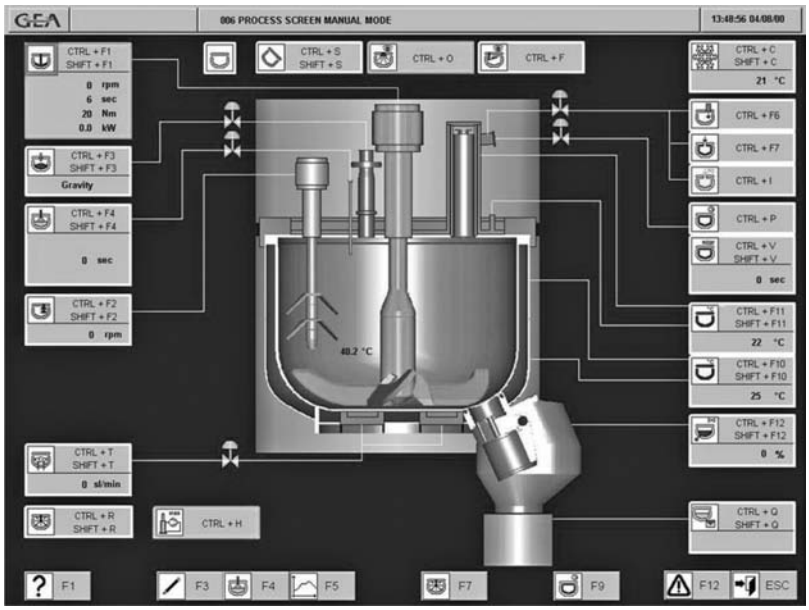


Figure 16 Screen of a typical control system for a single-pot processor. *Source*: Courtesy of GEA Pharma Systems nv, Wommelgem, Belgium.

All data acquisition systems are considered to generate electronic records. If these electronic records are used as batch documentation, the acquisition system needs to be compliant with FDA 21 CFR part 11.

Most vendors have addressed these issues by including password control, audit trails, and point verification systems.

SAFETY

The primary safety concern during the granulation and drying processes is the prevention of explosions. Bulk powder, dust clouds, and flammable vapors, all have the potential to explode. Adequate grounding and ventilation during loading and discharging the vessel and controlling the various processing conditions can reduce the risk of explosion.

In Europe, all equipment used in a potentially explosive atmosphere needs to be compliant with the ATEX guidelines (35).

Two approaches are generally taken toward explosion protection in single-pot processors.

One consists of removing oxygen from the processing chamber and replacing it with an inert gas (e.g., nitrogen) before any mixing action can take place. The removal of oxygen reduces the risk of explosion by eliminating one of the necessary elements to create an explosion.

The other approach is to design the equipment to contain the explosion. Executions of 10 or even up to 16 bar of high-shear granulators and single-pot processors are now readily available on the market.

Apart from the measures taken to avoid or contain explosions within the processing chamber, the electrical, electronic, and mechanical parts of single-pot processors that will be used in potentially explosive atmospheres also need to be explosion protected.

The leakage of microwave energy is a concern for single-pot processors that use this drying approach. Industrial microwave processors are expected to meet the guidelines for microwave leakage specified by the Center for Devices and Radiological Health within FDA and by the American National Standards Institute (36,37). The guideline is 1 mW/cm^2 maximum exposure at a frequency of 2450 MHz at a distance of 5 cm from any surface of the microwave cavity before purchase and 5 mW/cm^2 at any such point during its lifetime. Survey

meters for the detection of microwave leakage are relatively inexpensive and should be purchased by users of single-pot processors that incorporate microwave drying. The survey meters are calibrated before shipment and returned to the supplier for recalibration at periodic intervals. Their use should be incorporated in standard operating procedures for the equipment. Operator readings that exceed the guideline limit are often indicative of deteriorating seals around the lid cavity.

In addition to energy leakage standards, microwave processors are designed with safety interlocks to prevent accidental exposure. For example, the magnetrons can be activated only if the microwave cavity (i.e., bowl of the processor) is operating under vacuum, usually 30 to 100 mbar. If the vacuum falls outside this range, as in the unlikely event that an operator inadvertently tries to open the lid during microwave vacuum drying, the magnetrons are disabled. Vendors also incorporate additional safeguards to assure the microwave power is disabled with access to the bowl.

Because of popular misconceptions about the use of microwave ovens (e.g., stainless steel should not be used in a microwave cavity) and electromagnetic radiation (e.g., all types cause biological effects), a training program should be instituted in any facility that uses microwave drying. This will demystify any unfounded concerns about the technology and foster a rational approach to a sound safety and maintenance program.

CONCLUSION

Over the past 30 years since its introduction, single-pot processing has developed into a mature and generally accepted production technique.

Even if the technique, historically, was often used because of its specific advantages for effervescent production, potent compounds, organic solvents, or multiproduct facilities, practice has shown that single-pot processing is also attractive for standard pharmaceutical solid dosage production.

REFERENCES

1. Van Vaerenbergh G. The influence of a swinging bowl on granulate properties. Pharm Technol Eur 2001; 13(3):36–43.
2. Lucisano LJ, Poska RP. Microwave technology-fad or the future. Pharm Technol 1990; 14:38–42.
3. Van Vaerenbergh G. Cleaning validation practices using a one-pot processor. Pharm Technol 2004: 26–34.
4. Robin P, Lucisano LJ, Pearlswig DM. Rationale for the selection of a single pot manufacturing process using microwave/vacuum drying. Pharm Technol 1994; 18:28–36.
5. Bellini G, Pellegrini L. Non adiabatic drying. In: Goldberg E, ed. Handbook of Downstream Processing. London: Chapman & Hall, 1993.
6. De Smet P. Vacuum drying. Manuf Chem 1989; 37–39:37.
7. Technical Report. Granulation and drying with SYSTEM-VAGAS. Bristol, Pennsylvania, LB Bohle, Inc., 19007.
8. Technical Report. AEROVAC system, accelerated vacuum drying. Eastleigh, Hampshire, Niro-Fielder Ltd.
9. Metaxas AC, Meredith RJ. Industrial Microwave Heating. London: Peter Peregrines, 1983.
10. Doyle C, Cliff MJ. Microwave drying for highly active pharmaceutical granules. Manuf Chem 1987; 23–32.
11. Waldron MS. Microwave vacuum drying of pharmaceuticals: the development of a process. Pharm Eng 1988; 8:9–13.
12. Poska RP. Microwave processing: the development experience revisited. Proceedings of International Society of Pharmaceutical Engineers Congress, 1992.
13. Lucisano U, Moss RA. Vacuum drying vs. microwave-vacuum drying in three pilot-scale single pot processors using sodium acid pyrophosphate as the model granulation. AAPS Annual Meeting, San Antonio, Texas, 1992.
14. Schaefer T. Melt agglomeration with polyethylene glycols in high shear mixers. The Royal Danish School of Pharmacy, Copenhagen 1996—thesis for doctoral degree in pharmacy.
15. Schaefer T, Holm P, Kristensen HG. Melt pelletisation in a high shear mixer. I. Effects of process variables and binder. Acta Pharm Nord 1992; 4:133–140.
16. Schaefer T, Mathiesen C. Melt pelletisation in a high shear mixer. IX. Effects of binder particle size. Int J Pharm 1996; 139:139–148.

17. Van Vaerenbergh G. Melt granulation with polyethylene glycol in a one-pot processor. Internal document, GEA Pharma Systems, available upon request.
18. Heng PW, Wong TW, Chan LW. Influence of production variables on the sphericity of melt pellets. Chem Pharm Bull (Tokyo) 2000; 48:420–424.
19. Hamdani J, Moës AJ, Amighi K. Development and evaluation of prolonged release pellets obtained by the melt pelletization process. Int J Pharm 2002; 245:167–177.
20. Thies R, Kleinebudde P. Melt pelletisation of a hygroscopic drug in a high shear mixer. Part 1. Influence of process variables. Int J Pharm 1999; 188(2):131–143.
21. Voinovich D, Moneghini M, Perisutti B, et al. Melt pelletization in high shear mixer using a hydrophobic melt binder: influence of some apparatus and process variables. Eur J Pharm Biopharm 2001; 52(3):305–313.
22. Vonk P, Guillaume CPF, Ramaker JS, et al. Growth mechanisms of high-shear pelletisation. Int J Pharm 1997; 157(1):93–102.
23. Ramaker JS, Albada Jelgersma M, Vonk P, et al. Scale-down of a high-shear pelletisation process: flow profile and growth kinetics. Int J Pharm 1998; 166(1):89–97.
24. Stahl H. Manufacturing effervescent tablets. Pharm Technol 2003; 15(4):25–28.
25. Pearlswig DM, Robin P, Lucisano LJ. Simulation modeling applied to the development of a single-pot process using microwave/vacuum drying. Pharm Technol 1994; 18:44–60.
26. Poska R. Integrated mixing granulating and microwave drying: a development experience. Pharm Eng 1991; 11:9–13.
27. Stahl H. Single pot systems for drying pharmaceutical granules. Pharm Technol Eur 2000; 12(5):23–34.
28. Koch M, Stoye J, Stahl H. Flexible pharma containment solutions. Innov Pharm Technol 2007; 23:78–81.
29. Mandal TK. Evaluation of microwave drying for pharmaceutical granulations. Drug Dev Ind Pharm 1995; 21:1683–1688.
30. Moss RA. Demonstration-microwave/vacuum drying of pharmaceuticals. AAPS Annual Meeting, Washington DC, 1991.
31. Van Scoik K. Microwave vacuum processing in the Vactron 300. AAPS Annual Meeting, Washington DC, November 1991.
32. Duschler G, Carius W, Bauer KH. Single-step granulation method with microwaves: preliminary studies and pilot scale results. Drug Dev Ind Pharm 1995; 21:1599–1610.
33. FDA. Immediate release solid oral dosage forms: scale-up and postapproval changes: chemistry, manufacturing, and controls; in vitro dissolution testing; in vivo bioequivalence documentation; guidance. Fed Reg 1995; 60:61638–61643.
34. Berry IR, Nash RA, eds. Pharmaceutical Process Validation. New York: Marcel Dekker, 1993.
35. Directive 94/9/EC of The European Parliament and the Council of 23 March 1994 on the approximation of the laws of the Member States concerning equipment and protective systems intended for use in potentially explosive atmospheres.
36. Performance standards for microwave and radio frequency emitting products. 21 Code of Federal Regulations, Part 1030. General Services Administration, Washington, DC, April 1, 2008.
37. IEEE standard for safety levels with respect to human exposure to radio frequency electromagnetic fields, 3 kHz to 300 GH—supplement 1999 (IEEE C95.1-1999). Institute of Electrical and Electronics Engineers, New York.

12 Extrusion-Spheronization as a Granulation Technique

David F. Erkoboni
Cedar Consulting Corporation, Pennington, New Jersey, U.S.A.

INTRODUCTION

Extrusion-spheronization is a multiple-step process capable of producing uniformly sized spherical particles. This chapter will discuss the use of this process as a granulation method for use in producing free-flowing spherical granules. The initial edition and the second edition were written by Erkoboni (1) and Mehta et al. (2), respectively.

The process is now being widely utilized in the pharmaceutical industry. It is primarily used as a method of producing multiparticulates or multiple units for use in immediate- or controlled-release applications. In immediate-release applications, the multiple units in the dosage form can readily disperse throughout the GI tract upon administration as indicated by Dukieć-Ott et al. (3). In controlled-release applications, the release is typically controlled by the application of a rate controlling membrane or coating or by the use of polymer matrix demonstrated by Mehta et al. (4) and Thommes and Kleinbudde (5).

As pharmaceutical dosage units, pellets are defined as small, free-flowing, spherical, or semispherical particles made up of fine powders or granules of bulk drugs and excipients by variety of processes, extrusion-spheronization being one. The major advantage of extrusion-spheronization over other methods of producing drug loaded spheres, pellets, or granules is the ability to incorporate high levels of active components without producing excessively large particles. This is critical to the production of free-flowing spherical granules, as well as the pellets used for the more typical applications. Heilman et al. (6) showed that pellets having a drug loading level of 80% can be produced reproducibly.

Though the process is more efficient than other techniques for producing spheres or pellets for controlled-release dosage forms, it is more labor and time intensive than the more common granulation techniques. Therefore, it should be considered as a granulating technique when the desired particle properties are essential and cannot be produced using more conventional techniques. Pharmaceutical development scientists worldwide have been able to use this method more easily and reliably because of advances made in equipment, as well as material and process understanding. Extrusion-spheronization equipment engineering has made the equipment simpler to use. Formulation and process work conducted at academic institutions as well as in industry has progressed the understanding of the manufacturing process, thus making it simpler to use. Pellets offer scientists a great deal of development flexibility. Chemically incompatible ingredients, for instance, can be incorporated into single capsule using two pellet types, each containing one of the incompatible ingredients. Similarly, incompatible ingredients can be compressed into a tablet by coating spherical particles containing the ingredients with an immediate-release barrier coat prior to blending them with other ingredients. Pellets of different release characteristics can be combined to achieve the desired release pattern of the active ingredients. Pellets or spherical granules are characterized by a low surface area to volume ratio compared with powder or granules, which provides excellent coating substrate.

Typically, pellets range in diameter between 0.25 and 1.5 mm. They are normally filled into hard gelatin capsules, or eventually compressed into tablets, which can disintegrate into individual pellets after oral administration. Granules produced by the process can have a narrower size distribution, higher density, and more spherical shape than granules produced using conventional techniques. These properties, when needed, can have significant advantages over more typical granule properties. They can also have undesirable effects if,

for instance, the granules flow too well or the density is high enough to impede compression. These issues will be discussed below.

Spheronization is a process invented by Nakahara in 1964. The patent describes a "*Method and Apparatus for Making Spherical Granules*" from wet-powder mixtures (7). The equipment described in the patent was commercialized by Fuji Denki Kogyo Co. under the trade name Marumerizer®. The process went widely unnoticed in the pharmaceutical industry until 1970 when two articles were published by employees of Eli Lilly and Co. Conine and Hadley (8) described the steps involved in the process including: (*i*) dry blending, (*ii*) wet granulation, (*iii*) extrusion, (*iv*) spheronization, (*v*) drying, and (*vi*) screening (optional). Reynolds (9) went on to further describe the equipment and the mechanics of the process including the movement of the particles within the spheronizer. Both publications cite desirable product attributes that can be achieved, including good flow, low dusting, uniform size distribution, low friability, high hardness, ease of coating, and reproducible packing. Additionally, the resulting pellets offer not only technological advantages as mentioned before but also therapeutic advantages such as less irritation of the gastrointestinal (GI) tract and a lowered risk of side effects due to dose dumping and reproducibility of the drug blood levels as demonstrated by Mehta et al. (10). The interest in extrusion-spheronization has continued to grow from the time these articles were published till today. Interest was initially driven by academia and then industry. Today the process has become a common approach to producing spheres and pellets for multiparticulate applications. The increased popularity in recent years is, in part, due to a growing understanding of the effects of process parameters and material characteristics. Vervaet et al. presented a thorough review of the various aspects of extrusion-spheronization in an excellent article (11).

In recent times, hot-melt extrusion (HME) and subsequent spheronization has gained academic and to some degree industrial attention with both sectors working to evaluate and learn critical formulation and process variables to control the process and produce stable product. This process extension of extrusion-spheronization is being evaluated and in some cases used to solve some current issues, including solubilization of poorly soluble drugs. For pharmaceutical systems, this method has been used to prepare controlled-release granules, readily deformable granules, effervescent granules, taste-masked granules, and granules containing solid drug in polymer solutions or dispersion of drug facilitate solubilization. The bioavailability of the drug substance has been demonstrated to improve when it is dispersed at the molecular level using HME. Several examples of melt-extruded molecular dispersions were presented by Breitenbach and Mägerlein (12).

Fully rounded spheres or pellets having similar properties for multiparticulate delivery systems can likewise be prepared, as demonstrated by Young et al. (13). The advantage of HME is that it does not require the use of solvents and water and few processing steps are needed making the process somewhat simpler, efficient, and continuous. The disadvantage of HME is that it may use complicated know how and typically employs high temperatures around and over 100 °C as a processing requirement.

APPLICATIONS

Potential applications for spherical granules are many, including use in both immediate- (3) and controlled-release dosage forms. Almeida-Prieto et al. (14) discuss immediate and controlled release from pellets produced by extrusion-spheronization by adjusting the levels of various starches. Mehta et al. showed the use of polymer matrix systems prepared by extrusion-spheronization could be used to achieve zero-order release with poorly soluble drugs (15). Effervescent dosage forms for rapid delivery can be prepared, as well as taste-masked and chewable products. Repka et al. (16) reviewed articles describing the use of HME to form effervescent granules, as well as pelletization by spheronization. Kayumba et al. (17) discussed taste making of pediatric dosage forms using coated pellets prepared by extrusion-spheronization. Immediate and modified release of poorly soluble drugs can be achieved by preparing solid solutions, dispersion of drug in polymers, incorporating self-emulsifying systems, or solubility enhancers, such as emulsifiers, surfactants, pH modifiers in the formulation. Serratoni et al. demonstrated preparation of pellets containing drug dissolved in a self-emulsifying system results in improved dissolution. Further incorporation of a release

controlling membrane can modulate the release (18). Bioadhesive granules or pellets can be formulated to enhance absorption of drugs with a narrow absorption window. Awad et al. evaluated the use of bioadhesive pellets containing polyacrylic acids (19).

Regardless of application the spherical granules can be filled into capsules or compressed into tablets. Two or more actives can easily be combined in any ratio in the same dosage form. These combination products can contain actives that are incompatible or have varying release profiles. Spheres or spherical granules can be used as a method to limit drug migration. Physical characteristics of the active ingredients and excipients can be modified to improve physical properties and downstream processing. As an example, a low density, finely divided active can be pelletized to increase density, improve flow, and limit dusting as demonstrated by Jalal et al. (20). Dense multiparticulates disperse evenly within the GI tract and can be used to prolong GI transit times or improve tolerance of some compounds. The effect of density was investigated and discussed by Clarke et al. (21) and Devereus et al. (22). Regardless of the application, care must be taken to achieve the required sphere or granule properties.

Pellets or spheres for controlled-release coating applications will likely have significantly different physical requirements than granules for compression. A product to be coated for controlled release should have a uniform size distribution, good sphericity, and surface characteristics, as well as low friability. Once coated, the pellet should have the desired release characteristics. Additionally, if the coated pellets are to be compressed into tablets, they will require sufficient strength to withstand the forces of compression. Upon disintegration of the tablet, the individual spheres must retain their original release profile.

Physical properties such as flow, density, friability, porosity, and surface area are important for spherical granules intended for compression into tablets. The granules should have good deformation and bonding characteristics to form tablets having desirable physical properties. Drug release from the final dosage form must meet the target specification.

Product produced using extrusion-spheronization can range from barely shaped, irregular particles with physical properties similar to a conventional granulation to very spherical particles having properties that are drastically different. Woodruff and Nuessle (23) discuss the effect of process variables on the properties of particles produced by extrusion-spheronization. Tableting characteristics can be modified by altering either the composition of the spherical particles as indicated by Schwartz et al. (24), granulating fluid as discussed by Millili et al. (25), physical characteristics as discussed by Santos et al. (26), or the process conditions used to produce them as indicated by Malinowski and Smith (27). Compaction studies conducted on spheres similar to those used for controlled-release applications show the bonding and densification that occur during extrusion-spheronization can alter the deformation characteristics of some materials (25). Microcrystalline cellulose (MCC), which deforms plastically in the dry-powder state, exhibits elastic deformation followed by brittle fracture once spheronized (24). The deformation characteristics, coupled with the larger size particles result in reduced bonding sites and the production of weak compacts. A compaction profile of MCC and spheres prepared from MCC is shown in Figure 1.

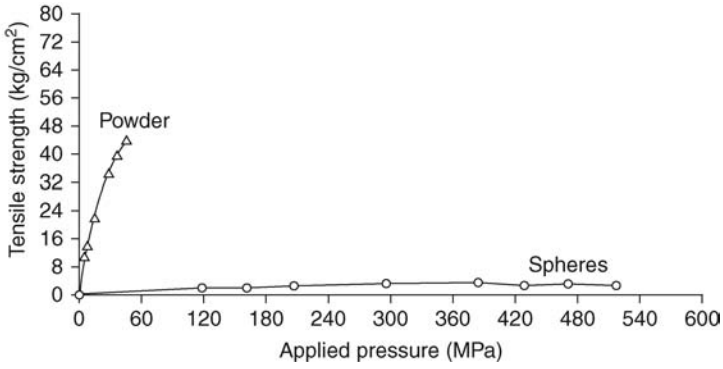


Figure 1 Compaction profiles of microcrystalline cellulose powder and spheres. *Source*: From Ref. 24.

The point is not to dwell on the properties required for each application, but rather to reinforce the fact that each application will have very specific requirements. One must first understand the properties required and then tailor the process to yield the desired effects. The effects of process and formulation variables will be discussed below.

A review of the literature shows that most investigators have tried to understand small components of this process isolated from other effects. They have focused on particular formulation or process parameters. It is valuable to have a detailed understanding of the main variables; however, this approach fails to take into consideration the high degree of interaction that exists between the variables. The use of statistical experimental design is a valuable tool to understand not only the main effects but also the interactions that can have a profound effect on the characteristics of the resulting particles. Malinowski and Smith (28) used a factorial design to evaluate granulations, Erkoboni et al. (29) determined the effect of process and formulation variable on sphere properties, and Chariot et al. used a factorial design to evaluate process variables (30). Additionally, these techniques are extremely useful during product/process development to understand the effect of variables and control them to produce product having desired attributes (6).

After pointing out the benefits of design methodology in this application, it should be understood that, for simplicity, much of the discussion to follow will address the various topics individually. In reality, however, they truly cannot be isolated from one another. This chapter will review and discuss the general process, equipment types and the effect of process and formulation variables on the properties of spherical granules.

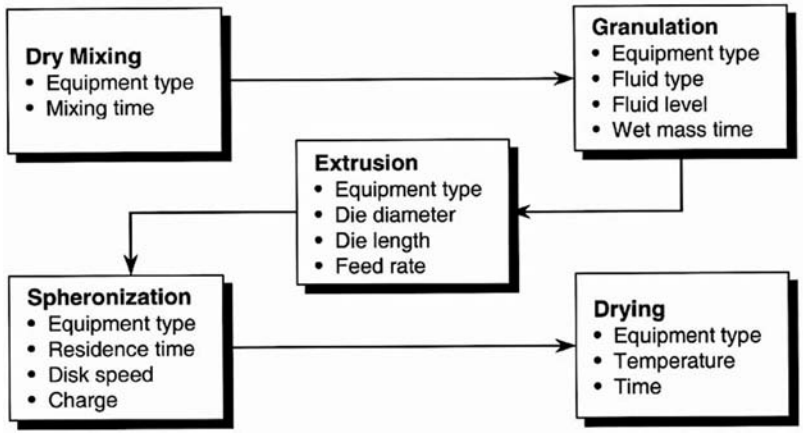


Figure 2 Process flow chart of the extrusion-spheronization process showing the process variables for each individual step. *Source*: From Ref. 31.

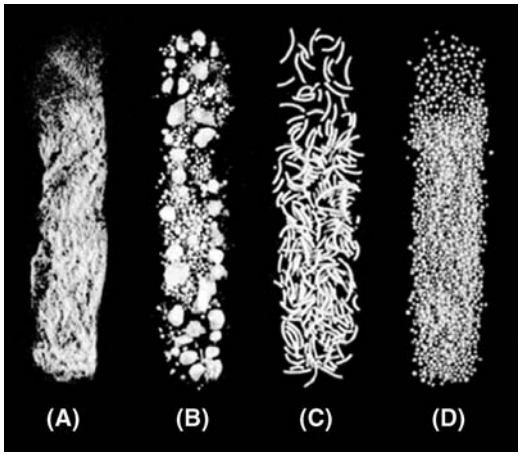


Figure 3 Product produced by the first four extrusion-spheronization process steps. (**A**) Powder from dry mixing, (**B**) granules from granulation, (**C**) extrudate from extrusion, and (**D**) spheres from spheronization.

GENERAL PROCESS DESCRIPTION

Extrusion-spheronization is a process requiring at least five units of operation with an optional sixth screening step. First, the materials are dry mixed (*i*) to achieve a homogeneous powder dispersion, and then wet granulated (*ii*) to produce a sufficiently plastic wet mass. The wet mass is extruded (*iii*) to form rod-shaped particles of uniform diameter that are charged into a spheronizer and rounded off (*iv*) into spherical particles. The spherical particles are then dried (*v*) to achieve the desired moisture content and optionally screened (*vi*) to achieve a targeted size distribution. The process flow diagram, shown in Figure 2, has been used by O'Conner et al. to show each of the process steps along with critical variables associated with them (31). The end product from each of the steps is shown in Figure 3.

EQUIPMENT DESCRIPTION AND PROCESS PARAMETERS

Dry Mixing

During the first step, powders are dry mixed to achieve a uniform dispersion prior to wet granulation. It is generally carried out in the same mixer used for the granulation; however, if a continuous granulator is used, a separate mixer is required for the dry mix. This step is typically taken for granted because wet massing follows. The uniformity of the dry mix, however, can have a significant effect on the quality of the granulation and, in turn, the spherical particles produced. An uneven distribution of materials having wide differences in properties such as size and solubility can result in localized over wetting, at least initially, during the granulation step. The more soluble and finely divided components can also dissolve and become part of the granulating fluid. The fluids, rich in soluble compounds, can either remain as overwet regions or, with continued wet massing, can be redistributed. Ojile et al. (32) discuss the effect of drug distribution during wet massing on granule uniformity. Sphere or granule uniformity (size and shape) is very much dependent on the uniform distribution and composition of the granulating fluid, which includes not only the solvent but any dissolved ingredients.

Granulation

The second step is granulation, during which a wet mass having the requisite plasticity or deformation characteristics is prepared. With a few exceptions, this step is similar to conventional granulation techniques used to produce product for compression. It is typically carried out in a batch-type mixer/granulator; however, any equipment capable of producing a wet mass, including the continuous type, can be used. Batch-type processors include planetary mixers, vertical or horizontal high-shear mixers, and σ blade mixers. Examples of continuous mixers include the Nica M6 instant mixer, as discussed by Hellén et al. (33) and high-shear twin-screw mixer/extruders, which was studied by Kleinebudde and Lindner (34) and Schmidt and Kleinebudde (35). The high-shear twin-screw mixer/extruders have mixer/feeders, which are capable of shearing and kneading the feed materials. Dry powders and fluids are fed in through separate ports and mixed by the action of the extruder blades and screws. The mixer/extruder is capable of being configured to customize the amount of shear and energy used in the process by changing the configuration of the mixing blades. This can have an impact on the properties of the extrudate produced as demonstrated by Lindberg et al. (36). As with the batch processors, it is critical to achieve a uniform level of fluid within the wet mass. The proper fluid/solids ratio is accomplished by maintaining a steady powder and fluid feed into the mixer/extruder. Both are critical, however, the powder feed is the most problematic. Small variations in feed rates can cause significant shifts in the moisture content of the granulation and, therefore, the quality of the spherical particles produced.

The two major differences in the granulation step, as compared with typical granulations for compression are the amount of granulating fluid required and the importance of achieving a uniform dispersion of the fluid. The amount of fluid needed to achieve pellets or spheres of uniform size and sphericity, using extrusion-spheronization, is likely to be greater than that for a conventional granulation intended for tableting. Instruments have been used to characterize the flow characteristics of granulations for use in extrusion-spheronization, such as a ram extruder as used by Harrison et al. (37) and a torque rheometer as used by Landín et al. (38). They are useful tools in quantifying the rheological effect of formulation and process variations

in the granulation. The ram extruder has been used to characterize the flow of wet masses through a die as shown by Baert et al. (39). Granulation flow has been divided into stages. They are: (*i*) compression, where the materials are consolidated under slight pressure, (*ii*) steady-state flow, where the pressure required to maintain the flow is constant, and (*iii*) forced flow, where an increase in force is required to maintain flow. The three stages are shown in the force versus displacement profile in Figure 4. The change from steady state to forced flow is caused by the movement of fluid under pressure. Extrusion in a ram extruder is continuous, and this phenomenon is less likely to be seen in extruders that are discontinuous such as gravity-fed models. A diagram of a ram extruder is shown in Figure 5.

Regardless of the mixer used, one must remember that the downstream process steps of extrusion and spheronization are very dependent on the level of water contained in the

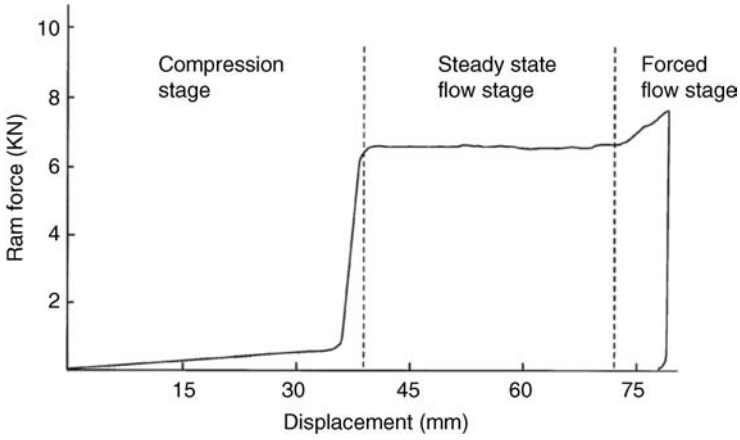


Figure 4 A force-displacement profile for a microcrystalline cellulose–lactose-water mixture showing the three stages of extrusion on a ram extruder: compression, steady-state flow, and forced flow (ram speed: 4 mm/sec; die diameter: 1.5 mm; *L*/*R* ratio: 12). *Source*: From Ref. 42.

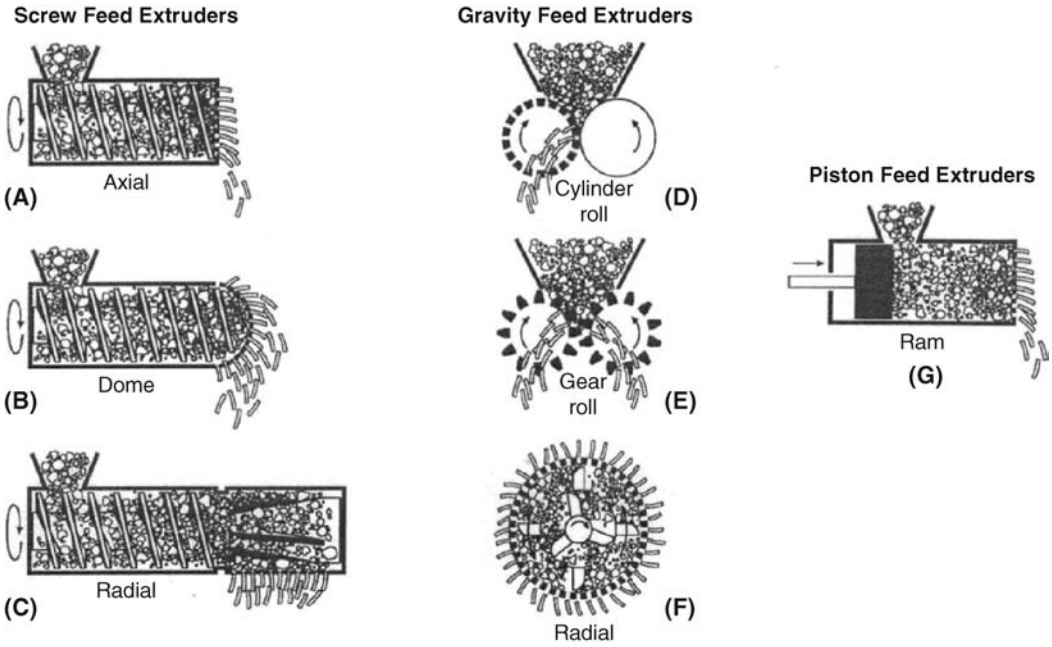


Figure 5 Schematic diagrams of extruder types used in extrusion-spheronization.

granulation and the quality of its dispersion. High-energy mixers such as high-shear mixers and high-shear twin-screw mixer/extruders can cause a significant rise in temperature. It may be necessary to use a jacket to guard against heat build-up. High temperatures can result in a greater than tolerable level of evaporation or an increase in the solubility of some of the solids as demonstrated by Baert et al. (40). A reduction in fluid will reduce the plasticity of the granulation. This will likely cause a finer, more porous, less dense, less uniform, and spherical granulation to be produced. The objective of downstream processing will determine whether some of these effects are desirable or not. If some of the effects are desirable, it is better to add lesser water and control the environmental conditions and mixing better. If the effects are undesirable, better control of the process is necessary.

An increase in the solubility of the drug due to an increase in temperature will increase the weight ratio of granulating fluid to solids since the solute is then part of that fluid. Ku et al. demonstrated that temperature of the granulating fluid had a significant effect on the size distribution of pellets or spherical granules produced (41). The water solubility of the drug in the granulation plays a key role in determining granulation end point for extrusion-spheronization process. A highly water soluble drug will dissolve in the granulation fluid whereas a highly insoluble drug will have wetting problems during the granulation step and remain part of the solid during granulating and wet massing.

Extrusion

The third step is the extrusion step that forms the wet mass into rod-shaped particles. The wet mass is forced through dies and shaped into small cylindrical particles having a uniform diameter. The extrudate particles break at similar lengths under their own weight. The extrudate must have enough plasticity to deform but not so much to adhere to other particles when collected or rolled in the spheronizer.

Extruders come in many varieties, but can generally be divided into three classes on the basis of their feed mechanism. They include those that rely on a screw, gravity, or a piston to feed the wet mass into the extrusion zone as described by Rowe (42). Examples of extruders from each class are shown in Figure 5. Screw-fed extruders include the (*i*) axial or end plate, (*ii*) dome, and (*iii*) radial types, while gravity-fed extruders include (*iv*) cylinder, (*v*) gear, and (*vi*) radial types. The screw- and gravity-fed types are used for developing and manufacturing with the radial varieties being the most popular for pharmaceutical applications. The piston feed or ram extruder is primarily used in research as an analytical tool.

Screw extruders have either one (single) or two (twin) augers that transport the wet mass from the feed area to the extrusion zone. During the transport process, the screws compress the wet mass removing most of the entrapped air. Studies have been conducted on the ram extruder to understand this compression or consolidation stage. They have shown the apparent density of the wet mass plug prior to extrusion is approximately equal to the theoretical apparent particle density, indicating that nearly all of the voids were eliminated as determined by Harrison et al. (43). Twin-screw extruders generally have a higher throughput than single-screw models, while single-screw extruders compress and increase the density of the extrudate more. Other features that can affect the density of the extrudate are the spacings of the turnings on the screw and the space between the end of the screw and the beginning of the die as described by Hicks and Freese (44). Turnings that are wide and regularly spaced minimize the amount of compression during material transport. Screws with closer or progressively closer spacing between the turnings will result in more compression and produce a denser extrudate. Space between the screw and the die result in a void into which material is deposited and compressed. The greater the space, the more the compression takes place prior to extrusion. As material builds up, pressure increases and causes the material to be forced, under hydraulic pressure, to flow through the die. When space between the screw and the die is at a minimum, extrusion takes place as material is compressed in the nip, between the extruder blade and the die.

The primary difference between the various types of screw extruders is in the extrusion zone. An axial or dome extruder transports and extrudes the wet mass in the same plane. Axial extruders force the wet mass through a flat, perforated endplate, typically prepared by drilling holes in a plate. The thickness of the plate can be more than four times the hole diameter,

Figure 6 Twin-screw axial extruder. *Source*: Courtesy of LCI Corporation.

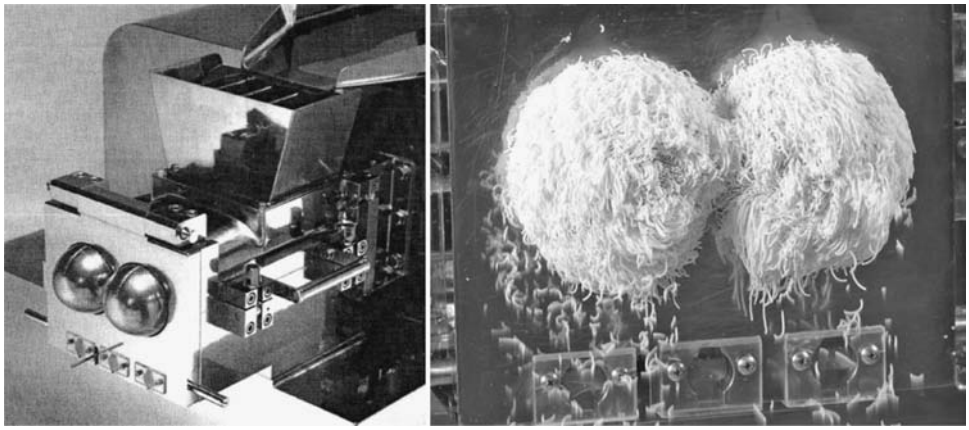


Figure 7 Dome extruder. *Source*: Courtesy of LCI Corporation.

resulting in high die length to radius (L/R) ratios. A twin-screw axial endplate extruder is shown in Figure 6.

Dome extruders use a dome or half sphere–shaped screen as the die. It is prepared by stamping holes in metal stock having a similar thickness as the hole diameter. This results in a die L/R ratio to about 2:1; however, variations in screen thickness are possible resulting in a slightly higher or lower ratio. A dome extruder is shown in Figure 7.

Unlike axial and dome extruders, radial extruders extrude the wet mass perpendicular to the plane of transport. Material is transported to the extrusion zone where it is wiped against the screen die by an extrusion blade. The mass is forced through the die by pressure generated at the nip. A screw-fed radial extruder is shown in Figure 8.

As with dome-type extruders the die is a stamped screen. Because of the shorter die lengths and the increased number of holes or dies, dome and radial extruders have the advantage of higher throughput as compared with the axial type.

As with almost every step in extrusion-spheronization, heat build-up during extrusion is a significant concern. This is especially true of the screw-fed extruders. Axial extruders generate heat because of their long die lengths. Radial extruders can have a significant heat differential over the width of the screen. Materials fed into the extrusion zone will have the lowest temperature. However, as material moves to the front of the zone, the temperature increases due to the longer residence time of material. Of the screw-fed extruders, the dome type has the highest rates and is least likely to generate significant heat over an extended period, since it allows for uniform extrusion and shear over the extrusion screen. Since radial

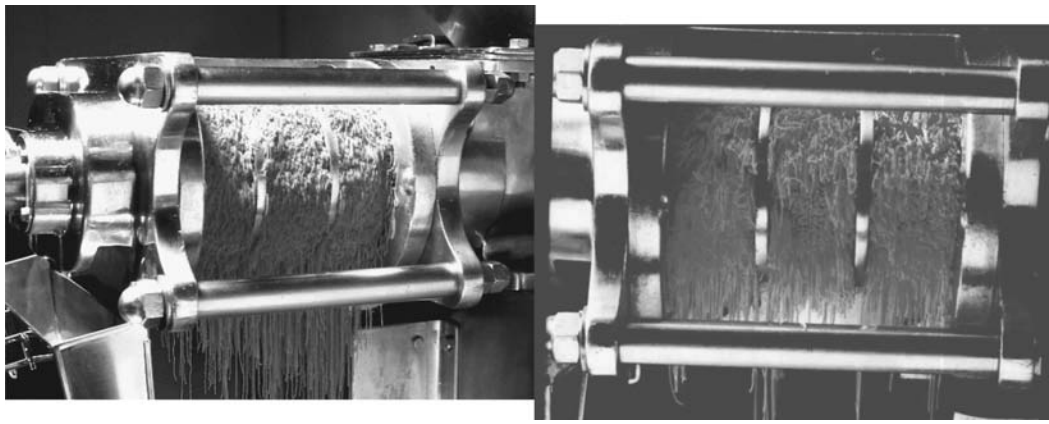


Figure 8 Side views of the extrusion zone of radial extruder. *Source*: Courtesy of LCI Corporation.

Figure 9 Gears of a gear-type extruder *Source*: Courtesy of AC Compacting Corporation.

and dome extruders use stamped dies or screens, they are the most fragile and susceptible to damage due to high forces. Care must be taken to minimize the force required by formulation and fluid optimization, which will be discussed later in the chapter.

Gravity-fed extruders include cylinder, gear, and radial types. The cylinder and gear both belong to a broader class referred to as roll extruders. Both use two rollers to exert force on the wet mass and form an extrudate. The cylinder extruder has rollers in the form of cylinders, one solid and one hollow with drilled holes to form the dies. The wet mass is fed by gravity into the nip area between the two cylinders and forced through the dies into the hollow of the cylinder. Gear-type extruders have rollers in the form of hollow gears. The dies are holes drilled at the base of each tooth. Wet mass is forced through the holes and collected in the hollow of the gears as the teeth and the base areas mesh. The gears of a gear extruder are shown in Figure 9 to illustrate the teeth.

The last type of gravity-fed extruder to be discussed is the radial type. Of the gravity-fed extruders, it is the most widely used. One or more arms rotate to stir the wet mass as it is fed by gravity. Rotating blades wipe the wet mass against the screen, creating localized forces sufficient to extrude at the nip. There is no compression prior to extrusion, which is the major difference between the gravity- and screw-fed radial extruders. A gravity-fed extruder is shown in Figure 10. Additionally, a schematic showing the extrusion zone and principle of operation are shown in Figure 11A and B, respectively.

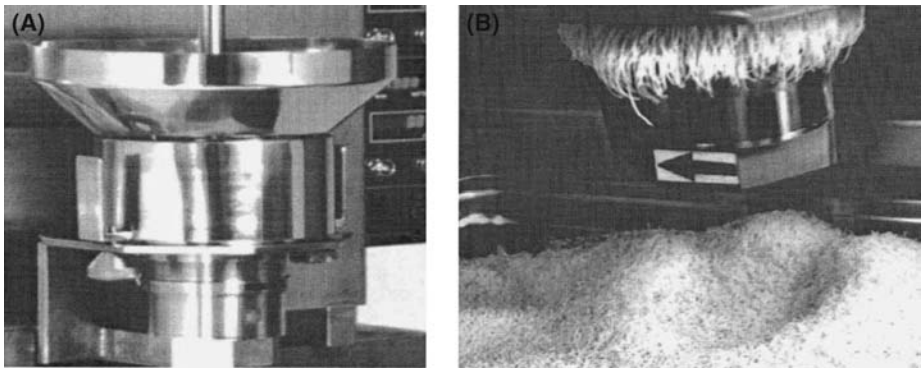


Figure 10 Gravity-fed rotary extruder (**A**) front view and (**B**) close-up showing extrusion zone. *Source*: Courtesy of Niro Pharma Systems.

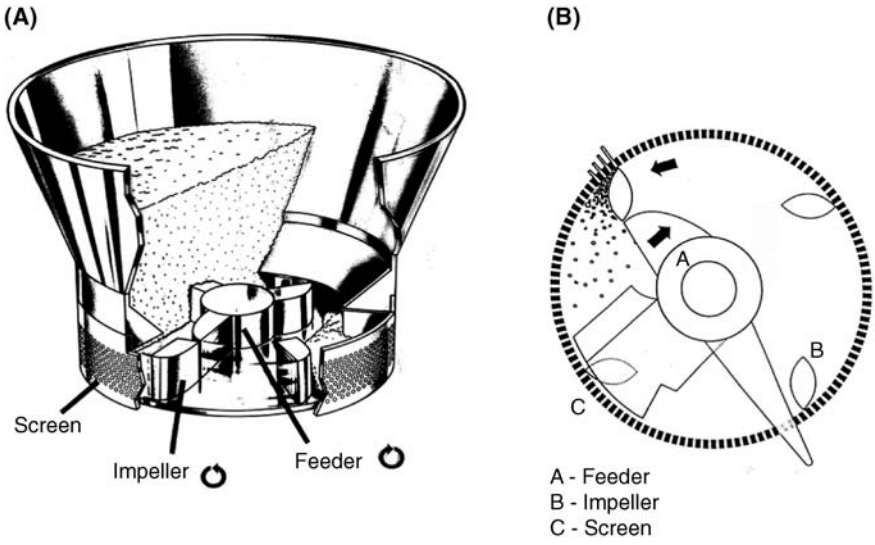


Figure 11 Gravity-fed rotary extruder (**A**) schematic of the extrusion zone and (**B**) principle of operation of gravity-fed extruder. *Source*: Courtesy of Niro Pharma Systems.

The primary extrusion process variables are the feed rate, die opening, and die length. The water content of the granulation is also very critical, since the properties of the extrudate and resulting spheres are very dependent on the plasticity and cohesiveness of the wet mass. The process variables and water content have been the focus of many studies. Harrison et al. (37,43,45,46) studied the flow of the wet mass as it is forced through a die. They determined steady-state flow (described above, Fig. 4) was essential to produce smooth extrudate that results in uniformly sized spherical particles having good sphericity and surface characteristics. Materials and processes that did not result in steady state, a condition referred to as forced flow, produced extrudate having surface impairments. In moderate cases, the surface is rough, while in more severe cases, a phenomenon commonly referred to as shark-skinning occurs. Examples of smooth extrudate and shark-skinned extrudate are shown in Figure 12. There continues to be differences of opinions regarding the value of smooth extrudate in the production of spherical particles, commonly referred to as spheres, beads, and pellets, intended for use in multiparticulate drug delivery systems. Spherical granules intended for applications such as tablet or capsule granules, as well as granules for filling into sachet-type units, do not require uniformity in size and therefore less care need to be taken in the extrusion step.

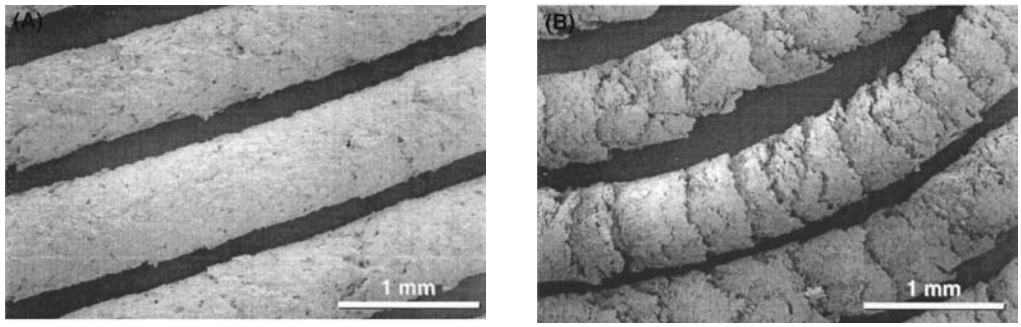


Figure 12 SEMs showing an example of (**A**) smooth extrudate and (**B**) extrudate having surface impairment, or shark-skinning.

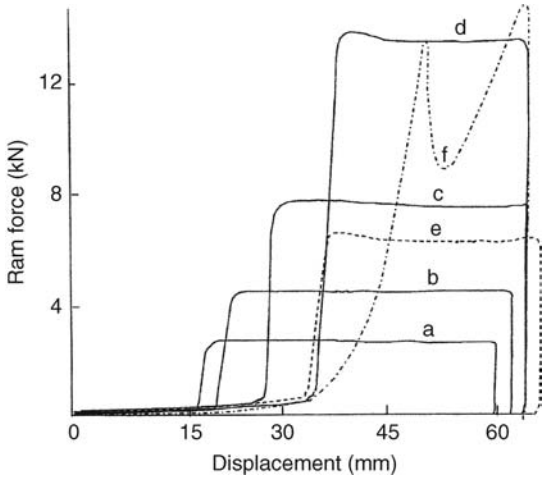


Figure 13 Force-displacement profiles at various moisture contents of mixtures of microcrystalline cellulose and water: (a–d) microcrystalline cellulose-lactose-water (5:5:6); (e) lactose-water (8:2); (f) at a ram speed of 4 mm/sec, die diameter of 1.0, and a length/radius ratio of 12. Percentage of moisture content of microcrystalline cellulose–water mixture: a, 59.4; b, 51.1; c, 45.0. *Source*: From Ref. 37.

Force-displacement profiles of MCC and water at various ratios, MCC, lactose, and water at a 5:5:6 ratio, and lactose and water at 8:2 ratio, developed by Harrison et al. (37), are shown in Figure 13. Steady state was possible with the MCC and MCC-lactose samples but not with lactose alone. As can be seen with the MCC samples, the duration of the compression stage was water level dependent with no effect seen on the steady-state stage. Additional studies indicated the effect of ram speed (extrusion speed) and die L/R ratio. An increase in ram speed increased duration of the steady-state stage with no effect on the compression stage. The L/R ratio had no effect on either compression or steady state. Wet mass composition, therefore, influenced the ability to achieve steady state while the water level and ram speed influenced duration. Higher water levels decreased the force to produce steady-state flow but increased the duration. Faster ram speeds (extrusion rates) increased the duration of steady state and increased the force. As discussed below, other investigators have reported the correlation between extrusion force and sphere quality.

Harrison et al. (37) also indicated that a uniform lubricating layer at the die wall interface must occur to eliminate the slip-stick phenomenon responsible for forced flow. Development of a lubricating layer was dependent on the length of the die (a minimum length required), wall shear stress, and upstream pressure loss. They represent the frictional forces at the die-wall interface and the estimated pressure loss at zero die length in the barrel of the ram extruder. The method for deriving these values is described in reference article. These parameters allow for a quantitative comparison between formulations and process; however, no specific values can be targeted since they vary with materials.

Pinto et al. (47) also showed that, at slow ram speeds, water moves toward the die wall interface and acts as a lubricant resulting in reduced extrusion forces. At higher speeds, water is unable to move rapidly through the mass resulting in higher forces. They indicated the water content and its distribution are critical in determining the particle size and sphericity of the product. Lower water content and higher speed will reduce the size and sphericity of the particles. The extrusion speed and water content should be adjusted to achieve the desired effect. Other researchers have investigated the effect of die length using gravity-fed radial extruder. Hellén et al. indicated that the extrudate became smoother and more bound as the L/R ratio of the die was increased (48). Vervaet et al. reported that a higher L/R ratio enables the use of lower water levels to achieve a more bound extrudate (49). This also increased the range (drug loading and water level) over which quality spheres could be produced. They attributed the increased latitude and capability to increased densification and resulting well-bound extrudate. The average pore diameter and bulk density reported for extrudate prepared from various MCC:DCP:water ratios at two L/R ratios are shown in Table 1.

Baert et al. (50) also indicated a similar increase in latitude when a cylinder extruder having a L/R ratio of 4 was compared with a twin-screw extruder having a L/R ratio of close to 1.8. Other studies have shown there is an optimal pressure range over which extrudate that is capable of yielding acceptable spheres can be produced. Shah et al. (51) demonstrated the correlation between screen pressure yield and density. A high yield of spheres within a targeted narrow size distribution was produced as long as the screen pressure was maintained within a given range. The relationship between yield and screen pressure is shown in Figure 14.

While many of the researchers have indicated a need for a more cohesive extrudate, few have expressed a need to remove all surface impairments. Some researchers have indicated that spheres having acceptable characteristic can be produced from extrudate having shark-skinning. O'Connor and Schwartz have found the presence of shark-skinning

Table 1 Average Pore Diameter and Bulk Density of Extrudate Composed of DCP–Avicel PH-101–Water Mixture, Extrudated Using Screens with a Different *L/R* Ratio

Composition DCP-Avicel-water (w/w)	*L/R* ratio of screen	Average pore diameter (μm)	Bulk density (g/mL)
150:380:470	4	0.982	1.132
150:400:450	4	0.992	1.211
150:380:470	2	1.249	0.949
150:400:450	2	1.292	0.947

Source: From Ref. 49.

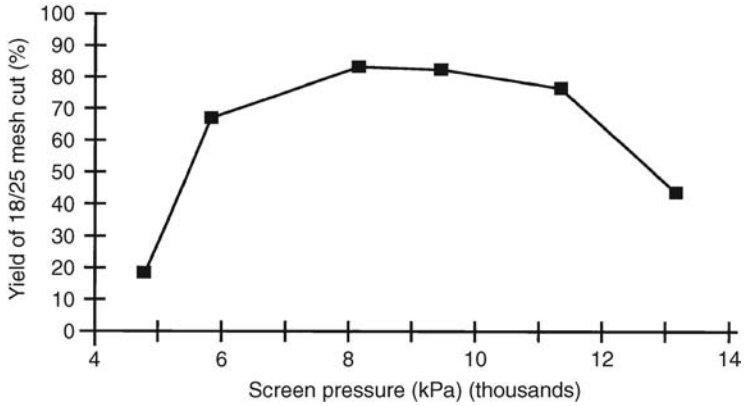


Figure 14 The effect of extruder screen pressure on the yield of particles within an acceptable distribution. *Source*: From Ref. 51.

to be advantageous in facilitating the breakage of the extrudate during the spheronization step (52).

Experimental design studies conducted to concurrently investigate the effect of extrusion, as well as other process and formulation variables, have indicated the extrusion variables to be less significant than granulating fluid level or variables of the spheronization step. Hasznos et al. (53) determined that extruder speed had little effect on the size distribution of the final product or moisture change during processing as compared with the spheronization variables. Hileman et al. (54) indicated that when water/MCC ratios are held constant, a change in screen size results in a significant change in the size distribution. However, in a study where water level was included as a variable, Erkoboni et al. showed the effect of screen size on size distribution to be small compared with the effect of a change in water level. A change in water level can shift the mean size and still result in an acceptable distribution (29). This is in agreement with earlier work by Jalal et al. who also showed that the mean particle size is typically smaller than the size of the screen itself because of shrinking during the drying step (20).

Spheronization

The fourth step in the extrusion-spheronization process is the spheronization step. It is carried out in a relatively simple piece of equipment. The working parts consist of a bowl having fixed sidewalls with a rapidly rotating bottom plate or disk. The rounding of the extrudate into spheres is dependent on frictional forces. The forces are generated by particle to particle and particle to equipment interaction. For this reason, the disk is generally machined to have a grooved surface, which increases the forces generated as particles move across its surface. Disks having two general geometric patterns are produced, a cross-hatched pattern with the groves running at right angles to one another and a radial pattern with the groves running radially from the center. The two varieties are shown graphically in Figure 15. Some studies have shown the rate of spheronization to be faster with the radial pattern; however, both plates will result in acceptable product (42).

During the spheronization step, extrudate is transformed from rod-shaped pellets into spherical particles. This transition occurs in various stages. Once charged into the spheronizer, the extrudate is drawn to the walls of the extruder because of centrifugal forces. From here what happens is very much dependent on the properties of the extrudate. Under ideal conditions, the extrudate breaks into smaller, more uniform pieces. Within a short period of time, the length of each piece is approximately equal to the diameter, because of attrition and rapid movement of the bottom plate or disk. The differential in particle velocity as they move outward to the walls, begin to climb the walls and fall back onto the rotating bed, along with the angular motion of the disk results in a rope like formation (9). A graphic representation of the spheronizer charge movement and rope like formation, as well as a running spheronizer showing the formation, is shown in Figure 16. This formation can be a critical indicator of the quality of the granulation or extrudate. The disk rotating without movement of the product indicates an overwet condition. The condition is caused either from a granulation that was initially overwet or migration of water or a fluid ingredient to the surface of the extrudate during extrusion or spheronization.

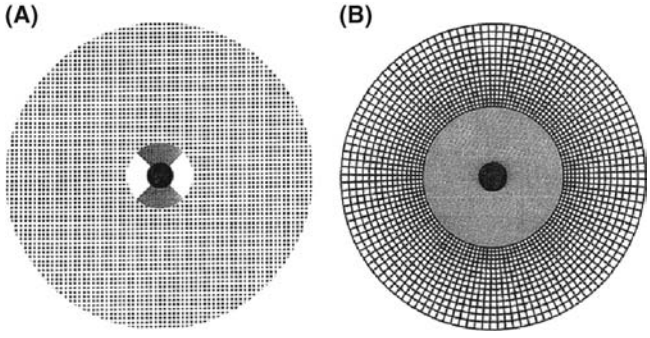


Figure 15 Spheronizer disks having two geometric patterns: (**A**) a cross-hatched pattern with the groves running at right angle to one another and (**B**) a radial pattern with the groves running radially from the center. *Source*: Courtesy of Niro Pharma Systems.

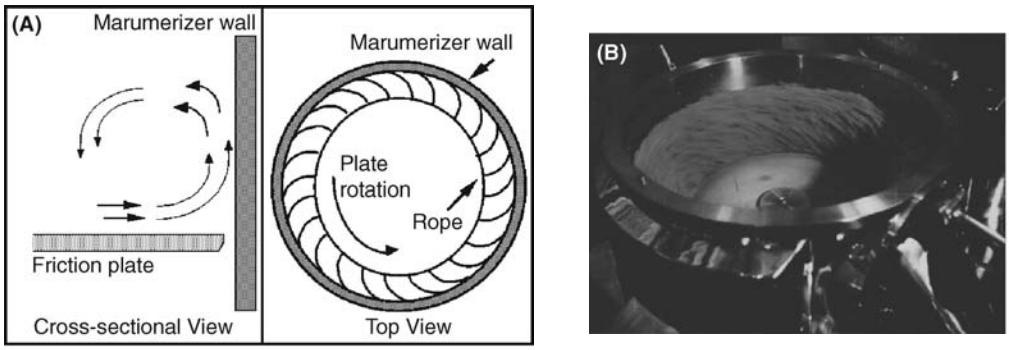


Figure 16 A graphic representation of (**A**) the characteristic rope like formation in a spheronizer bowl during operation, as well as (**B**) a running spheronizer. *Source*: Courtesy of Niro Pharma Systems and LCI Corporation.

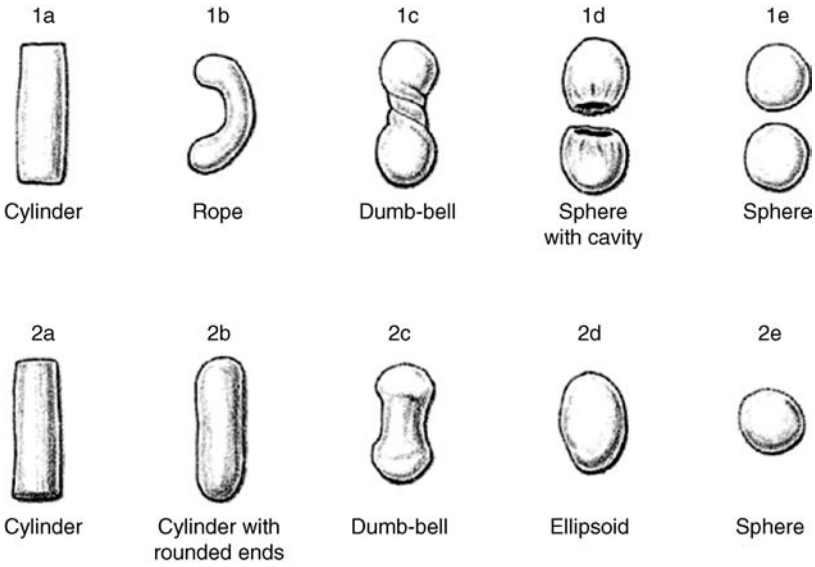


Figure 17 A graphic representation of the two models proposed to describe the mechanism of spheronization. The model proposed by Baert et al. (53) describes a transition from initial cylindrical particles (1a) into a bent rope (1b), dumbbell (1c), two spherical particles with a hollow cavity (1d), and spheres (1e). The model proposed by Rowe (41) describes a transition from cylindrical particles (2a) into cylindrical particles with rounded edges (2b), dumbbells (2c), ellipsoids (2d) and spheres (2e). *Source*: From Refs. 43 and 55.

The transformation from cylinder-shaped extrudate to a sphere occurs in various stages. Two models have been proposed to describe the mechanism and are shown graphically in Figure 17. The model proposed by Rowe (42) describes a transition whereby the cylindrical particles (2a) are first rounded off into cylindrical particles with rounded edges (2b), then form dumbbell-shaped particles (2c), ellipsoids (2d), and finally spheres (2e). The second model proposed by Baert et al. (50) suggests that the initial cylindrical particles (1a) are deformed into a bent rope–shaped particle (1b), then form a dumbbell with a twisted middle (1c). The twisting action eventually causes the dumbbell to break into two spherical particles with a flat side having a hollow cavity (1d). Continued action in the spheronizer causes the particles to round off into spheres (1e). When the sphere is fractured, a hollow particle is revealed (55). The exact mechanism is likely composition dependent. If the extrudate is overwet, particle growth will occur, resulting in a broad size distribution. Underwet extrudate will not have enough plasticity to further round off in the spheronizer; the result is the formation of dumbbells.

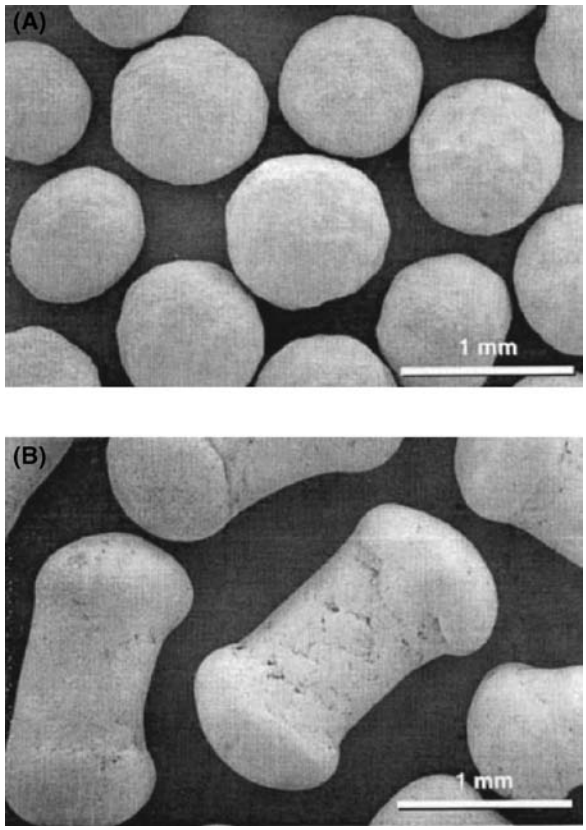


Figure 18 An example of (**A**) good spheres produced from a sufficiently plastic mass and (**B**) dumbbells that would not deform further produced from underwet extrudate.

The scanning electron micrographs (SEMs) in Figure 18 show an example of good spheres produced from a sufficiently plastic mass and dumbbells that would not deform further.

Of the two process steps unique to extrusion-spheronization, the first, extrusion, is a continuous process while the second, spheronization, is a batch process. To make the process viable for commercial operations, two systems have been developed to enable the extruder to continuously feed material to the spheronizer(s). The first system is a semicontinuous shuttle system and the second is a cascade system. The shuttle system is typically used when uniform particles are required, such as for controlled-release coating applications. The cascade system, however, can be used for applications where less size and shape uniformity is required, such as granulations intended for compression.

The shuttle system uses two spheronizers in parallel. It is designed to fill one spheronizer while the second is in the middle of its cycle, continue to collect extrudate in a shuttle receptacle while they are both full and operational, and fill the second after it empties and the first unit is in the middle of its cycle. The shuttle system operation is shown graphically in Figure 19. A picture of a spheronizing system having an extruder, a shuttle system to fill two spheronizers and twin spheronizers is also shown in Figure 20.

The cascade operation uses one or more spheronizers that are modified to have the disks some distance below the discharge chute (44). This results in a spheronization zone having a fixed volume. Product is continually fed from either the extruder or a previous spheronizer. As the charge volume grows from incoming material, some product is discharged. The residence time is dictated by the feed rate. The reduced size and shape distribution are due to the percentage of material that does not reside in the spheronization zone for the intended period of time. The number of spheronizers placed in sequence depends on the desired outcome. However, if only a slight rounding with minimal densification is required, one spheronizer with a short residence time will be sufficient. The cascade operation is shown graphically in Figure 21.

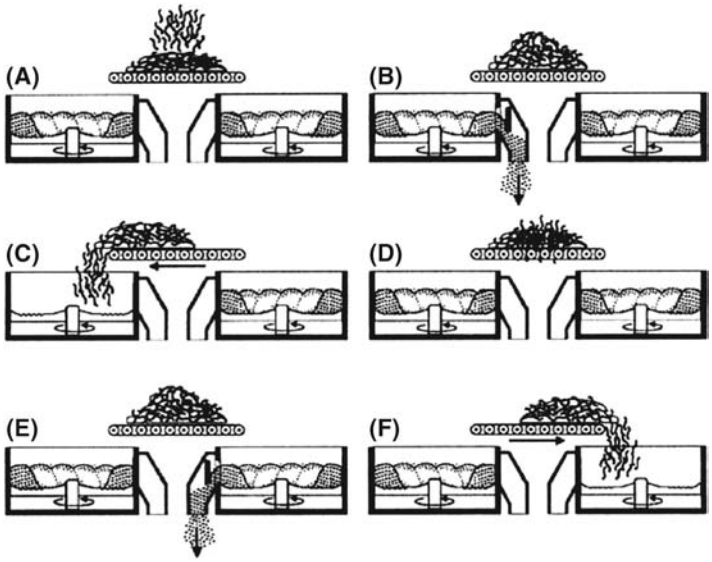


Figure 19 A graphic representation of twin-spheronizer shuttle system using two spheronizers in parallel and shuttle receptacle: (**A**) when both units are full, the shuttle receptacle collects extrudate; (**B**) after one empties; (**C**) the shuttle box fills it; (**D**–**F**) the cycle repeats itself for the second unit. *Source*: From Ref. 44.

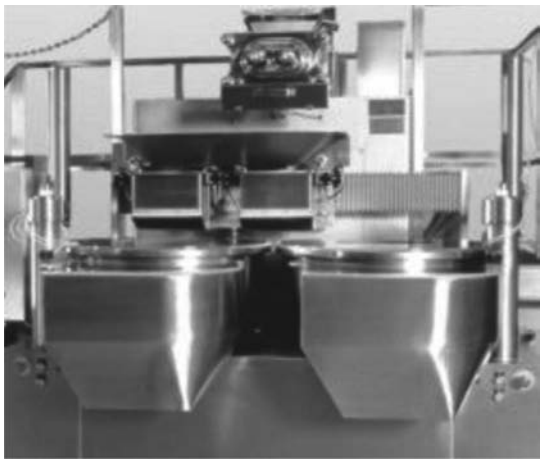


Figure 20 A spheronizer system having an extruder at the top, a shuttle system to fill two spheronizers in the middle of the picture and twin spheronizers at the bottom. *Source*: Courtesy of AC Compacting Corporation.

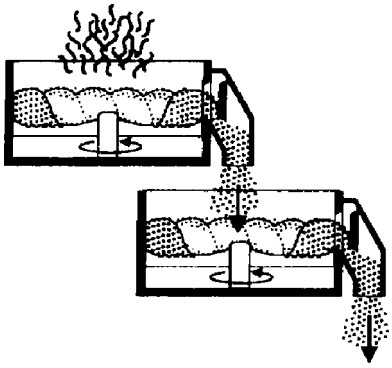


Figure 21 A graphic representation of a cascade spheronizer operation using two spheronizers. One of the spheronizers discharges into the second by overflow making the spheronization step continuous. *Source*: From Ref. 44.

Variables in the spheronization step include spheronizer size, charge, disk speed, and residence time. A number of studies have shown that each of the variables has the potential to play a significant role in influencing the physical characteristics of the resulting product. Hasznos et al. (53) showed that a higher disk speed and longer residence time increased the coarse fraction and mean diameter and decreased the fine fraction. The faster speed and longer time also increased the moisture loss during the process. Since the moisture loss can reduce the plasticity of the particle, it can have the same effect as an underwet granulation. The particles may not round off into spheres and stay as deformed cylinders or dumbbells. Higher spheronizer charges reduced the moisture loss. They also suggested that an interaction between spheronizer speed and residence time indicated the total number of revolutions of the disk was critical. A change in one of the variables could be offset by an opposite change of the other, as long as the total number of revolutions remained constant. Hellén et al. (33) showed a similar moisture loss during spheronization. In addition, they indicated that the major factors influencing the shape of the spheres were the disk speed and residence time. High speed and long time produced more spherical particles. Wan et al. (56) indicated that a minimum disk speed and residence time was required to round the cylinder-shaped extrudate. Furthermore, an increase in speed or time, up to a limit, increased the median diameter of the spheres while higher speeds and longer times caused a reduction in size. Short residence times at high-disk speeds resulted in small but round particles.

A number of investigators have reported the effect of disk speed and residence time on density. Woodruff and Neussle (23) reported the variables to have no effect on the density of the spheres as compared with the density of the granulation and extrudate. The results conflict with most of the other studies; however, they are likely due to the use of mineral oil in the formulation. The oil can reduce the frictional forces at the die wall during extrusion and between particles and equipment surfaces during spheronization. A number of investigators, including Malinowski and Smith, reported an increase in either disk speed or residence time resulted in an increase in density (28,29,33,54). Mehta et al. (4) studied the effect of spheronization time on the pellet hardness and drug release. Pellet hardness increased with spheronization time for an initial period after which no increase was observed. The increase is likely due to the densification that occurs during the spheronization step. In another study, Mehta et al. (57) showed the effect of spheronization time on the porosity parameters of the pellets. A residence time of 2 to 10 minutes increased the number of pores and the total pore surface area and decreased the pore diameter. Beyond this time, for up to 20 minutes of spheronization time, the porosity was unchanged. O'Connor et al. (31) indicated that the friability of placebo spheres decreased with increasing residence time while the mean particle diameter decreased. Erkoboni et al. showed an increase in extruder screen size resulted in reduced friability (29).

Drying

Drying is the final step in the process. This can be accomplished in any dryer that can be used for conventional-type granulations, including tray dryers, column-type fluid beds, and deck-type vibratory fluid beds. Each of the drying techniques has advantages; however, the major differences are based on the rate of water removal. Tray drying is the slowest of the processes. Fluidized-bed dryers result in a much more rapid drying rate because of the higher air volumes and the potential use of higher inlet temperatures. Column fluid beds are batch dryers, while the deck-type dryers offer the advantage of a continuous process. Both have been used successfully in drying product produced by extrusion-spheronization. The drying process must be chosen on the basis of the desired particle properties.

Pellets or granules to be dried in fluid-bed equipment will have to withstand fluidization process and resist attrition and maintain its integrity. The more rapid rate in a fluid bed will likely minimize the effects of migration. This phenomenon can have an effect on a number of particle properties. Tray drying is a slow process in a static bed. Because of this, it can offer the greatest opportunity for drug to migrate toward the surface and recrystallize as indicated by Dyer et al. (58). The increased active concentration at the surface of the particle can increase the rate of dissolution. This recrystallization, however, can cause a problem for applications requiring film coating since the smooth surfaces developed by the spheronization process

would be damaged. Additionally, the crushing strength of tray dried particles will likely be greater than their fluid-bed counterparts. The slow recrystallization in the static bed allows for crystal bridges to develop as the fluid is removed and the solute recrystallizes. The drying rate will also affect pellet or granule hardness. Slower rates will result in lower porosity and higher hardness.

FORMULATION VARIABLES

The composition of the wet mass is critical in determining the properties of the particles produced. This is clearly understood if we look at what material behaviors are required during each of the process steps. During the granulation step, a plastic mass is produced—a simple enough task if ended there. The materials must form a plastic mass, deform when extruded, and break off to form uniformly sized cylindrical particles. A minimal amount of granulating fluid should migrate to the surface during extrusion and the particles should stay discrete during collection. During spheronization, the particles must round off to form uniformly sized spheres. They must not dry out because of temperature or air volume or grow in size because of agglomeration. The fact is a lot is asked from materials used in this process. This is especially true of formulations containing high percentages of active where low levels of excipients are used to impart the desired properties to the mass.

The importance of using sphere-forming excipients was noted early on. Conine and Hadley (8) cited the necessity of using MCC. Reynolds (9) went on to indicate the need for either adhesive or capillary-type binders. He cited cellulose gums, natural gums, and synthetic polymers as adhesives and MCC, talc, and kaolin as capillary-type binders. Since then much work has been conducted in an attempt to understand the significance of material properties. Some of the studies are discussed below.

O'Connor et al. (31) studied the behavior of some common excipients in extrusion-spheronization. The materials were studied as single components using water as the granulating fluid in an attempt to understand their application in the process. Of the materials tested, only the MCC or MCC with sodium carboxymethyl cellulose (Na-CMC) was capable of being processed. Others including dicalcium phosphate, lactose, starch, and modified starch did not process adequately.

In an additional study, they investigated the effect of varying drug, excipient and excipient:drug ratios (59). At low drug levels, they found the spheronizing excipient(s) played the most significant role in determining sphere properties. They found that, for low dose applications, MCC was the best excipient to use, since it formed the most spherical particles. At moderate drug loading (50%), MCC, as well as the two products consisting of MCC coprocessed with Na-CMC (Avicel® RC-581 and Avicel CL-611), resulted in acceptable spheres. At higher loading levels, however, the MCC did not yield acceptable spheres and the coprocessed materials did. The spheres produced using Avicel CL-611 were the most spherical. In addition, they found dissolution to be dependent on the type of excipient used, the solubility and concentration of the active. Spheres containing MCC remained intact and behaved as an inert matrix systems, while those containing the coprocessed products formed a gel plug in the dissolution basket and were described as water-swellable hydrogel matrix systems. The release profiles for spheres containing each of the excipients and theophylline in a 50:50 ratio are shown in Figure 22. Release profiles for spheres containing different drug loads are shown in Figure 23. An increase in drug load resulted in an increased release rate. Release profiles for spheres containing actives having different solubilities, including chlorpheniramine maleate, quinidine sulfate, theophylline, and hydrochlorothiazide are shown in Figure 24. An increase in drug solubility resulted in an increased release rate.

Baert and Remon showed the effect of granulating fluid level on the release of drug from pellets (55). Two model drugs were used, theophyline, which has a solubility of 1 g in 125 mL and sulfametoxazole, which is practically insoluble. In each case, pellets were prepared using three granulating fluid levels. Dissolution rate was inversely proportional to the granulating fluid level with the higher levels resulting in slower release rates (Figs. 25 and 26).

Mehta et al. demonstrated the use of polymethacrylate polymers such as Eudragit L 100-55 and Eudragit S 100 in the development of controlled-release pellets (15,60) by extrusion-spheronization. The polymethacrylate polymers can be used as pellet-forming and release

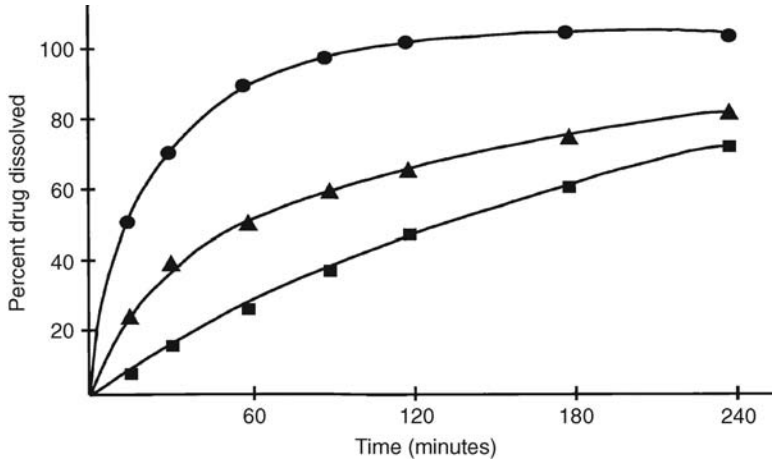


Figure 22 Dissolution profiles of spheres containing 50% theophylline in different Avicel MCC types: ●, Avicel PH-101; ▲, Avicel RC-581; ■, Avicel CL-611. *Source*: From Ref. 59.

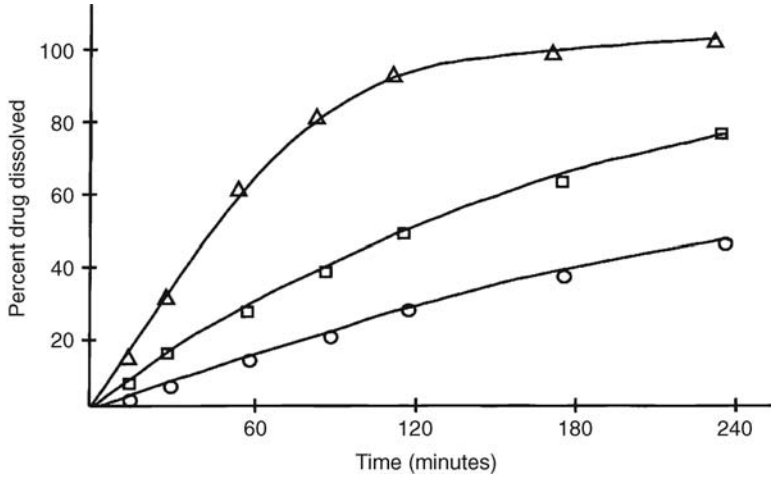


Figure 23 Dissolution profiles of spheres containing different concentrations of drug in Avicel CL-611: ○, 10%; □, 59%; △, 80%. *Source*: From Ref. 59.

rate–governing polymers for developing a controlled-release drug delivery system without the use of MCC in the matrix. An eroding matrix capable of controlling the release of insoluble actives is formed.

Zhou et al. produced matrix pellets by combining microcrystalline waxes, pregelatinized starches and hydrolyzed starches with model drugs such as ibuprofen, chloroquin phosphate, and others (61). They concluded the combination of microcrystalline waxes and pregelatinized starches or maltodextrins is a flexible system for the production of matrix pellets, even with a high drug concentration. Additionally, they concluded that the drug release with such a system could be modeled by varying the type and the concentration of the wax and the starch. Tapia et al. (62) described factors influencing the mechanism of release from sustained release matrix pellets, produced by extrusion-spheronization process. They demonstrated that the pellets that form a hydrogel during dissolution and sustain the release of drug without a coating can be prepared.

Kleinebudde et al. (63) concluded that during the extrusion process, water content in the extrudate and pellet porosity were increased as the degree of polymerization of MCC and

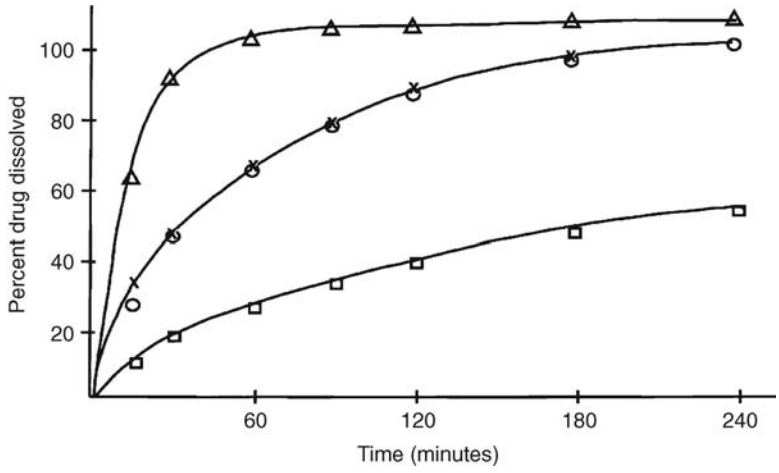


Figure 24 Dissolution profiles of spheres containing 10% drug in Avicel PH-101: △, chlorpheniramine maleate; ○, quinidine sulfate; ×, theophyline; □, hydrochlorothiazide. *Source*: From Ref. 59.

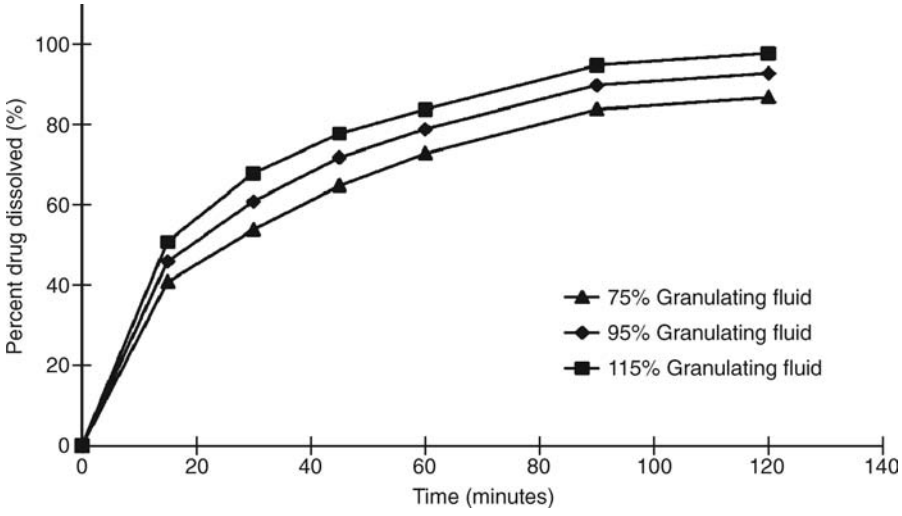


Figure 25 Dissolution profiles of pellets containing 80% Avicel PH-101, 20% theophylline monohydrate, and granulated with 115% (■), 95% (◆), and 75% (▲) of water expressed as dry weight. Each curve is the mean of three experiments. The coefficient of variation (CV) was always lower than 2%. *Source*: From Ref. 55.

powder cellulose in the matrix was increased. Millili and Schwartz demonstrated the effect of granulating with water and ethanol at various ratios. The physical properties of the spheres changed significantly as the ratio of the two fluids was varied. Spheres could not be formed with absolute ethanol but were possible with 5:95 water and ethanol. An increase in the water fraction resulted in a decrease in porosity, friability, dissolution, and compressibility, and an increase in density. The porosity of spheres granulated with 95% ethanol was 54%, while the water-granulated product had a porosity of 14%. When greater than 30% water was used, spheres remained intact throughout the dissolution test. As previously discussed, water-granulated spheres were very difficult to compress while spheres granulated with 95% ethanol were significantly more compressible than those prepared using water (24). A tablet hardness versus compression forces profile is shown in Figure 27. Millili et al. proposed a bonding mechanism, referred to as autohesion, to explain the differences in the properties of spheres granulated with water and ethanol (64). Autohesion is a term used to describe the strong

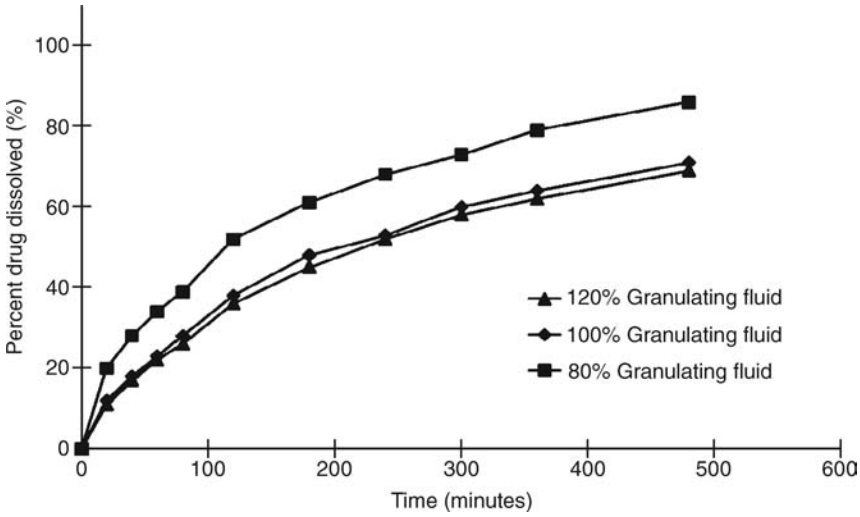


Figure 26 Dissolution profiles for pellets containing 90% Avicel PH-101, 10% sulfamethoxazole, and granulated with 120% theophylline monohydrate and granulated 120% (▲), 100% (◆), and 80% (■) of water expressed as dry weight. Each curve is the mean of three experiments. The CV was always lower than 2%. *Source*: From Ref. 55.

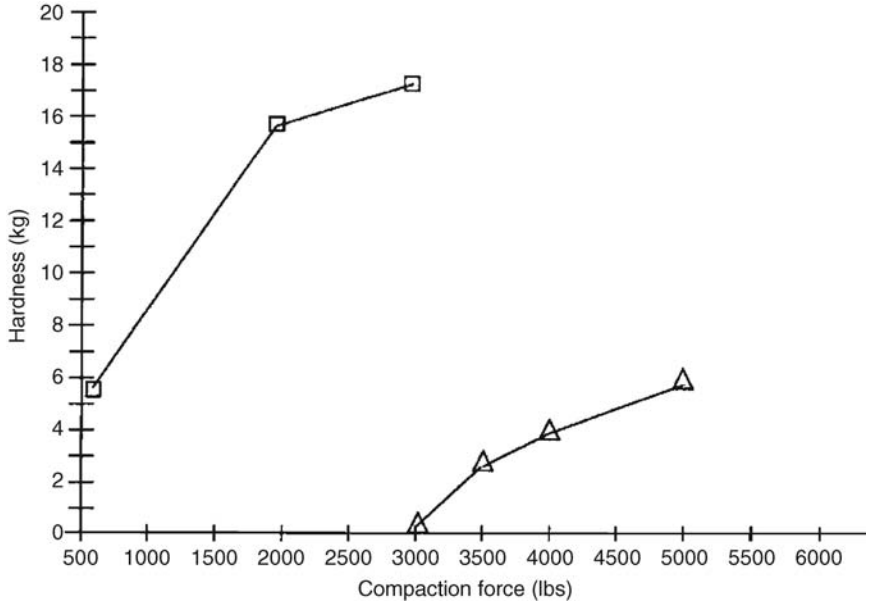


Figure 27 The effect of varying compression force on the hardness of compacted 16/30-mesh spheres of 10% theophylline–Avicel PH-101: △, spheres prepared by water; □, spheres prepared by 95% ethanol granulation. *Source*: From Ref. 24.

bonds formed by the interdiffusion of free polymer chain ends across particle-particle interfaces.

Using a ram extruder, Harrison et al. (37) demonstrated that steady-state flow could not be achieved with lactose. Additionally, they demonstrated the reduced sensitivity of MCC to small changes in moisture as determined by the force required to induce plug flow in a cylinder. Comparing MCC with a MCC/lactose blend and 100% lactose, they found that, with

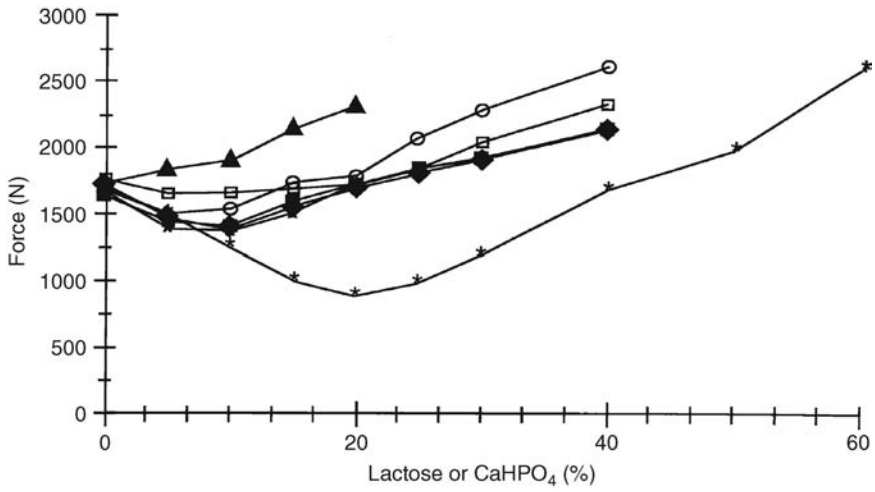


Figure 28 Influence of the amount of lactose or dicalcium phosphate dehydrate (% total weight) on the extrusion forces (*N*) for mixtures of lactose or dicalcium phosphate dehydrate–Avicel PH-101–water after granulation with a planetary mixer. Each end point is the mean of six value. The standard deviation (SD) is lower than 3% for each point. Six different types of lactose were used: α-lactose monohydrate 80 mesh (□); α-lactose monohydrate 200 mesh (○); α-lactose monohydrate 325 mesh (◆); spray-dried lactose DCL 11 (■); anhydrous β-lactose DCL 21 (×); anhydrous α-lactose DCL 30 (*); and one type of dicalcium phosphate dehydrate was used (▲). *Source*: From Ref. 40.

lactose, small changes in moisture caused large changes in force while with MCC, larger changes in moisture were required to have similar effects on the force.

Baert et al. (40) used mixtures of MCC and coexcipients at various ratios to demonstrate the effect of solubility and the total fluid on extrusion forces. They showed that if the coexcipient was insoluble, such as dicalcium phosphate, the force required to extrude increased with increasing levels of coexcipient. When a soluble excipient such as lactose was used, the force required to extrude decreased with the addition of the initial amounts of lactose. After a certain level, however, the reduction in force stopped and began to increase. This was due to the initial solubilization of lactose and the resulting increase in the total fluid level. Once the fluid was saturated, the remaining lactose was not soluble and the force began to increase. The increase began at about 10% lactose level for α-lactose and 20% for β-lactose. This was due to the difference in solubility between the two materials. The effects of dicalcium phosphate and various lactose grades on extrusion force are shown in Figure 28.

Funck et al. (65) showed that low levels of common binders could be used to produce high drug-loaded spheres with MCC. Materials such as carbomer, Na-CMC, hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), povidone (PVP) and pregelatinized starch were used. All materials were capable of producing spheres of acceptable quality. Dissolution testing showed spheres containing HPC and HPMC remained intact during testing while spheres containing starch, PVP, and Na-CMC disintegrated. Linder and Kleinebudde reported that spheres produced with powdered cellulose had higher porosity and faster dissolution than those made using MCC (66). Spheres could not be produced using only powdered cellulose and drug; a binder was required. The higher porosity of the spheres prepared from powdered cellulose may be beneficial for applications requiring compression.

Fielden et al. (67) showed that increasing the particle size of lactose resulted in forced flow and high-extrusion forces, which resulted in poor quality of extrudate and spheres having a wide-size distribution. This was attributed to the increased pore diameter of the mixture containing the coarse lactose, which allowed greater movement of water. Chien and Nuessle showed the use of a surfactant, such as sodium lauryl sulfate, reduced the migration of drug to the surface of the sphere during drying by reducing the surface tension of the granulating fluid

(68). The reduction in surface tension also made it difficult to produce a cohesive extrudate in some cases.

Some miscellaneous observations include the following. Reynolds (9) reported that excess extrudate friability can be overcome by incorporating more MCC, binder or water in the granulation. Erkoboni et al. (29) indicated that sphere hardness was most affected by the level of MCC in the formulation and the level of granulating fluid used. Hileman et al. (54) showed that MCC had a narrower water range over which quality spheres could be made than MCC coprocessed Na-CMC. Hellén et al. (33) showed that the surface characteristics were influenced by the water level with higher water levels giving smoother surfaces. Mehta et al. (4) showed that changing the concentrations of pellet-forming and release rate–controlling polymers in the matrix altered the dissolution kinetics of a poorly soluble drug.

COMRESSION OF SPHERICAL GRANULES OR PELLETS

Pellets produced by extrusion-spheronization are typically used in controlled-release applications. They are typically produced for filling into hard gelatin capsules or compression into a tablet dosage form without fracture or rupture of the pellet. The tablets are normally intended to disintegrate and the gelatin capsule shell to dissolve, releasing discrete, intact pellets into the GI tract. The dosage forms are generally intended to deliver the active content through a modified-release technique.

The properties of the spherical particles, however, can be advantageous in the compression of tablets, filling of capsules and production of other less common dosage forms such as sachets. Some of the granule properties that can be favorable to compression are improved flow, increase density, reduced friability, and low dusting. These properties were cited by a number of investigators including Conine and Hadley (8), Reynolds (9), Woodruff and Nuessle (23).

Care must be taken to tailor the process to maximize the desirable qualities, while minimizing any undesirable effects. In general, the spherical pellets produced for controlled-release or multiparticulate dosage forms are not suitable particles or granules for compression. They flow too freely, do not blend well with other compression aids such as lubricants and, depending on their composition, likely require excessive force to fracture (8). We have reviewed the factors affecting the properties of spherical multiparticulates produced by spheronization. Generally the more spherical and denser particles are not preferred for compression. Physical properties conducive to compression can be produced by reducing the forces that cause consolidation. This includes optimizing variable such as the granulating fluid level, wet mass mixing time, extrusion screen size, spheronizer disk speed, and residence time. Some of the factors will be discussed below relative to compression.

Spherical granules or pellets have been shown to react differently to compaction and consolidation than powders of the same material. Think of the process pathway that transforms the powders to pellets as a continuum. The extremes represent properties that are not desirable. There are process conditions along the path that result in desirable product that meets the needs of the product being produced.

Wang et al. reported compression of lactose/MCC compositions at various ratios in both powder and pellet forms (69). Compacts made from the pellets had a different compaction and consolidation mechanism than the similar powders. The powders show an increase in tensile strength with increase MCC levels while compacts prepared from the pellets showed and opposite trend. Schwartz et al. (24) also demonstrated the compaction characteristics of MCC processed into spheres are significantly different than the original powder. The powder material forms hard compacts at low-compression forces, while the spheres are not compressible and form soft compacts, even at high forces. They indicated that spheres prepared from MCC showed a high degree of viscoelasticity over the entire compression range. Inclusion of coexcipients such as lactose and dicalcium phosphate increase the compactability by decreasing the viscoelastic resistance or pressure range over which the spheres behave elastically. A reduction in viscoelastic resistance was seen with spheres containing both lactose and dicalcium phosphate; however, dicalcium phosphate had a greater effect. Compaction profiles of spheres containing 10% theophylline with either MCC, MCC/DCP or MCC/lactose in a 22.5/67.5 ratio are shown in Figure 29.

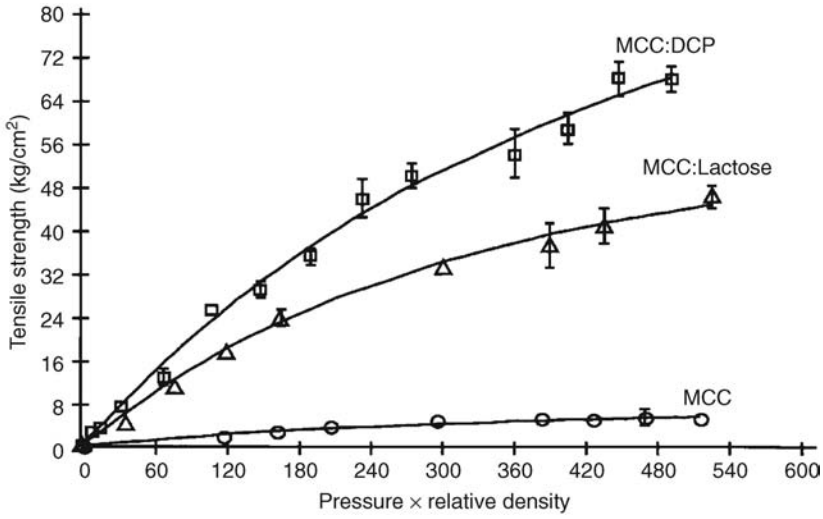


Figure 29 The effect of excipients on the compaction profile of spheres: Compaction profiles of spheres containing 10% theophylline with either MCC, MCC-DCP, or MCC-lactose in a 22.5:67.5 ratio using the Leunberger model. *Source*: From Ref. 24.

A similar phenomenon was reported by Maganti and Celik (70) when pellets produced by rotor granulation were compressed. They compared the compaction behavior of pellet formulations, mainly consisting of MCC, to that of the powders from which they were formed and also found significant differences. The powders examined were found to compact by plastic deformation and produced strong compacts, while the pellets exhibited elastic deformation and brittle fragmentation, resulting in compacts of lower tensile strength. This can be explained by the fact that the pellets, which are large and spherical in shape as compared with the small, irregular powder particles they are composed of, have a low surface to volume ratio, which might result in a decreased area of contact between the particles as they consolidate. Nicklasson et al. (71) investigated compression behavior of pellets consisting of MCC, with or without other excipients such as polyethylene glycol and DCP. Deformation of the aggregates was found to depend on three deformation characteristics, namely, the capacity for, the mode of and the resistance to deformation. High surface deformation refers to the great ability of the pellets to conform to the surface of the surrounding pellets. In pellets containing the soft component, the primary particles can reposition within the agglomerate and the ability to fill the intragranular pore space is increased. For pellets containing hard materials, the compaction stress may give local failure at pellet surfaces. Thus, the material properties of the primary particles constituting the pellets are important for the compression behavior of pellets. In number of studies, various soft materials have been incorporated in pellets to modify their deformability and compatibility. Iloañusi and Schwartz (72) investigated the effect of glyceryl behenate on the compaction of MCC beads or pellets containing acetaminophen. They found beads containing the waxy material required less force to form cohesive tablets. Salako et al. (73) found that pellets containing theophylline and MCC were hard and less brittle than the ones containing glyceryl monostearate, which were soft pellets. The soft pellets were found to fracture under low-compression pressures and were able to form a coherent network of deformable material in the tablets at higher pressures. The hard pellets were unable to form such a network at high pressures and found to reduce more in volume without bond formation than soft pellets. Nicklasson and Alderborn studied the modulation of the tableting behavior of pellets through the incorporation of polyethylene glycol and found that these soft pellets had an increased propensity to deform and altered mode of deformation to the relatively hard MCC pellets (74).

The size of the pellets can also have a bearing on their compression behavior. Small pellets have been shown to be less affected than larger ones by the compaction process as

shown by Haslam et al. (75) and Johansson et al. (76). Smaller beads were significantly stronger, relative to their size, than larger ones and larger pellets were much more readily deformed.

SUMMARY

Extrusion-spheronization is a versatile process capable of producing granules, pellets, or spheres having unique physical properties. Since it may be more labor and time intensive than the more common granulation techniques, it should be considered as a granulating technique when the desired properties cannot be produced using more conventional techniques. Potential applications are many including both immediate and controlled release. Regardless of the application, care must be taken to understand the desired properties and the formulation and process variables capable of achieving them. The use of statistical experimental design for formulation and process development is strongly recommended because of the high degree of interactions between the variables. Lastly, new technologies such as HME with spheronization are gaining considerable interest in the pharmaceutical drug delivery arena for solving specific problems such as enhancing taste masking, improving solubility and drug bioavailability and, in general, for controlled-release drug delivery. The extrudate formed by HME can be rounded as desired to achieve the desired size, shape, and other properties.

REFERENCES

1. Erkoboni D. Extrusion–spheronization for granulation. In: Parikh DM, ed. Handbook of Pharmaceutical Granulation Technology. New York: Marcel Dekker, 1997.
2. Mehta KA, Rekhi GS, Parikh DM. Extrusion–spheronization for granulation. In: Parikh DM, ed. Handbook of Pharmaceutical Granulation Technology. New York: Marcel Dekker, 2005.
3. Dukieć-Ott A, Remon JP, Forman P, et al. Immediate release of poorly soluble drug from starch-based pellets prepared via extrusion/speheronization, Eur J Pharm Biopharm 2007; 67:715–724.
4. Mehta KA, Kislalioglu MS, Phuapradit W, et al. Effect of formulation and process variables on matrix erosion and drug release from a multiunit erosion matrix of a poorly soluble drug. Pharm Tech 2002; 26–34.
5. Thommes M, Kleinbudde P. Properties of pellets manufactured by wet extrusion/spheronization process using K-carrageenan: effect of process parameters. AAPS Pharm Sci Tech 2007; 8(4):E1–E8.
6. Hileman GA, Goskonda SR, Spalitto AJ, et al. Response surface optimization of high dose pellets by extrusion spheronization, Int J Pharm 1993; 100:71–79.
7. Nakahara. U.S. Patent 3, 277, 520 (October 1966).
8. Conine JW, Hadley HR. Preparation of small solid pharmaceutical spheres. Drug Cosm Ind 1970; 106: 38–41.
9. Reynolds AD. A new technique for the production of spherical particles. Manuf Chem Aerosol News 1970; 41:40–43.
10. Mehta KA, Kislalioglu MS, Phuapradit W, et al. In vivo release performance of nifedipine in dogs from a novel Eudragit based multi-unit erosion matrix. Drug Deliv Technol 2002; 2(2):38–42.
11. Vervaet C, Baert L, Remon JP. Extrusion-spheronization a literature review. Int J Pharm 1995; 116:131–146.
12. Breitenbach J, Mägerlein M. Melt extruded molecular dispersions. In: Ghebre-Sellassie, ed. Pharmaceutical Extrusion Technology. New York: Marcel Dekker, 2003.
13. Young CR, Koleng JJ, McGinity JW. Production of spherical pellets by a hot-melt extrusion and spheronization process. Int J Pharm 2002; 242:87–92.
14. Almeida-Prieto S, de Sá Ferreira da Rocha CI, Blanco-Méndez J, et al. Fast and controlled release of triamcinolone acetonide from extrusion-spheronization pellets based on mixtures of native starch with dextrin or waxy maize starch. Drug Dev Ind Pharm 2007; 33:945–951.
15. Mehta KA, Kislalioglu MS, Phuapradit W, et al. Release performance of a poorly soluble drug from a novel Eudragit based multi-unit erosion matrix. Int J Pharm 2001; 213:7–12.
16. Repka MA, Battu SK, Upadhye SB, et al. Pharmaceutical applications of hot-melt extrusion. Part II. Drug Dev Ind Pharm 2007; 33:1043–1057.
17. Kayumba PC, Huyghebaert N, Cordella C, et al. Quinine sulfate pellets for flexible pediatric drug dosing: formulation development and evaluation of taste-masking efficiency using the electronic tongue. Eur J Pharm Biopharm 2007; 66(3):460–465.
18. Serratoni M, Newton M, Booth S, et al. Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system. Eur J Pharm Biopharm 2007; 65:94–98.
19. Awad GA, Chartueau CA, Allain P, et al. Formulation and evaluation of bioadhesive pellets containing different carbomers made by extrusion-spheronization. STP Pharm Sci 2002; 12:157–162.

20. Jalal M, Malinowski HJ, Smith WE. Tablet granulations composed of spherical-shaped particles. J Pharm Sci 1972; 61:1466–1468.
21. Clarke GM, Newton JM, Short MB. Comparative gastrointestinal transit of pellet systems of varying density. Int J Pharm 1995; 114:1–11.
22. Devereus JE, Newton JM, Short MB. The influence of density on the gastrointestinal transit of pellets. J Pharm Pharmacol 1990; 42:500–501.
23. Woodruff CW, Nuessle NO. Effect of processing variables on particles obtained by extrusion-spheronization. J Pharm Sci 1972; 61:787–790.
24. Schwartz JP, Nguyen NH, Schnaare RL. Compaction studies on beads: compression and consolidation parameters. Drug Dev Ind Pharm 1994; 20:3105–3129.
25. Millili GP, Schwartz JB. The strength of microcrystalline cellulose pellets: the effect of granulating with water/ethanol mixtures. Drug Dev Ind Pharm 1990; 16:1411–1426.
26. Santos H, Veiga F, Pina ME, et al. Compaction, compression and drug release properties of diclofenac sodium and ibuprofen pellets comprising xanthan gum as a sustained release agent. Int J Pharm 2005; 295:15–27.
27. Malinowski HJ, Smith WE. Effect of spheronization process variables on selected tablet properties. J Pharm Sci 1974; 63:285–288.
28. Malinowski HJ, Smith WE. Use of factorial design to evaluate granulations prepared by spheronization. J Pharm Sci 1975; 64:1688–1692.
29. Erkoboni DF, Fiore SA, Wheatley TA, et al. The effect of various process and formulation variables on the quality of spheres produced by extrusion/spheronization. Poster presentation, AAPS national meeting, 1991.
30. Chariot M, Francès J., Lewis GA, et al. A factorial approach to process variables of extrusion-spheronization of wet powder masses. Drug Dev Ind Pharm 1987; 13:1639–1649.
31. O'Connor RE, Holinez J, Schwartz JB. Spheronization. I. Processing and evaluation of spheres prepared from commercially available excipients. Am J Pharm 1984; 156:80–87.
32. Ojile JE, Macfarlane CB, Selkirk AB. Drug distribution during massing and its effect on dose uniformity in granules. Int J Pharm 1982; 10:99–107.
33. Hellén L, Yliruusi J, Merkku P, et al. Process variables of instant granulator and spheronizer. I. Physical properties of granules, extrudate and pellets. Int J Pharm 1993; 96:197–204.
34. Kleinebudde P, Lindner H. Experiments with a twin screw extruder using a single-step granulation/extrusion process. Int J Pharm 1993; 94:49–58.
35. Schmidt C, Kleinebudde P. Influence of the granulation step on pellets prepared by extrusion/spheronization. Chem Pharm Bull 1999; 47(3):403–412.
36. Lindberg NO, Tufvesson C, Holm P, et al. Extrusion of an effervescent granulation with a twin screw extruder, Baker Perkins MPF 50 D. Influence in intragranular porosity and liquid saturation. Drug Dev Ind Pharm 1988; 14:1791–1798.
37. Harrison PJ, Newton JM, Rowe RC. The characterization of wet powder masses suitable for extrusion/spheronization. J Pharm and Pharmacol 1985; 37:686–691.
38. Landín M, Rowe RC, York P. Characterization of wet powder masses with a mixer torque rheometer. 3. Nonlinear effects of shaft speed and sample weight. J Pharm Sci 1995; 85:557–560.
39. Baert L, Remon JP, Knight P, et al. A comparison between the extrusion forces and sphere quality of a gravity feed extruder and a ram extruder. Int J Pharm 1992; 86:187–192.
40. Baert L, Fanara D, De Baets P, et al. Instrumentation of a gravity feed extruder and the influence of the composition of binary and tertiary mixtures on the extrusion forces. J Pharm Pharmacol 1991; 43:745–749.
41. Ku CC, Joshi YM, Bergum JS, et al. Bead manufacture by extrusion/spheronization—a statistical design for process optimization. Drug Dev Ind Pharm 1993; 19:1505–1519.
42. Rowe RC. Spheronization: a novel pill-making process? Pharm Int 1985; 6:119–123.
43. Harrison PJ, Newton JM, Rowe RC. The application of capillary rheometry to the extrusion of wet masses. J Pharm 1987; 35:235–242.
44. Hicks DC, Freese HL. Extrusion and spheronization equipment. In: Ghebre-Sellassie I, ed. Pharmaceutical Pelletization Technology. New York: Marcel Dekker, 1989:71–100.
45. Harrison PJ, Newton JM, Rowe RC. Flow defects in wet powder asses. J Pharm Pharmacol 1984; 37: 81–83.
46. Harrison PJ, Newton JM, Rowe RC. Convergent flow analysis in the extrusion of wet powder masses. J Pharm Pharmacol 1984; 37:81–83.
47. Pinto JF, Buckton G, Newton JM. The influence of four selected processing and formulation factors on the production of spheres by extrusion and spheronization. Int J Pharm 1992; 83:187–196.
48. Hellén L, Ritala J, Yliruusi P, et al. Process variables of the radial screen extruder. I. Production capacity of the extruder and the properties of the extrudate. J Pharm Tech Int 1992; 4:50–60.

49. Vaervaet C, Baert L, Risha PA, et al. The influence of the extrusion screen on pellet quality using an instrumented basket extruder. Int J Pharm 1994; 107:29–39.
50. Baert L, Remon JP, Elbers JAC, et al. Comparison between a gravity feed extruder and a twin screw extruder. Int J Pharm 1993; 99:7–12.
51. Shah R., Kabadi M, Pope DG, et al. Physico-mechanical characterization of the extrusion/spheronization process. Part I. Instrumentation of the extruder. Pharm Res 1994; 11:355–360.
52. O'Connor RE, Schwartz JB. Extrusion and spheronization technology. In: Ghebre-Sellassie I, ed. Pharmaceutical Pelletization Technology. New York: Marcel Dekker, 1989:187–216.
53. Hasznos L, Langer I, Gyarmathy M. Some factors influencing pellet characteristics made by an extrusion/spheronization process. Part I. Effects on size characteristics and moisture content decrease of pellets. Drug Dev Ind Pharm 1992; 18:409–437.
54. Hileman GA, Goskonda SR, Spalitto AJ, et al. A factorial approach to high dose product development by an extrusion/spheronization process. Drug Dev Ind Pharm 1993; 19:483–491.
55. Baert L, Remon J. Influence of amount of granulating liquid on the drug release rate from pellets made by extrusion spheronization. Int J Pharm 1993; 95:135–141.
56. Wan LSC, Heng PWS, Liew CV. Spheronization conditions on spheroid shape and size. Int J Pharm 1993; 96:59–65.
57. Mehta KA, Kislalioglu MS, Phuapradit W, et al. Effect of formulation and process variables on porosity parameters and release rates from a multi unit erosion matrix of a poorly soluble drug. J Control Rel 2000; 63:201–211.
58. Dyer AM, Khan KA, Aulton ME. Effect of the drying method on the mechanical and drug release properties of pellets prepared by extrusion. Drug Dev Ind Pharm 1994; 20:3045–3068.
59. O'Connor RE, Schwartz JB. Spheronization. II. Drug release from drug-diluent mixtures. Drug Dev Ind Pharm 1985; 11:1837–1857.
60. Mehta KA, Kislalioglu MS, Phuapradit W, et al. Multi-unit controlled release systems of nifedipine and nifedipine: pluronic F-68 solid dispersions: characterization of release mechanisms. Drug Dev Ind Pharm 2002; 28(3):275–285.
61. Zhou F, Vervaet C, Remon JP. Matrix pellets based on the combination of waxes, starches and maltodextrins. Int J Pharm 1996; 133:155–160.
62. Tapia C, Buckton G, Newton JM. Factors influencing the mechanism of release from sustained release matrix pellets, produced by extrusion/spheronization. Int J Pharm 1993; 92:211–218.
63. Kleinebudde P, Jumaa M, El Saleh F. Influence of degree of polymerization on behavior of cellulose during homogenization and extrusion/spheronization. AAPS Pharm Sci 2000; 2(2):21.
64. Millili GP, Wigent RJ, Schwartz JB. Autohesion in pharmaceutical Solids. Drug Dev Ind Pharm 1990; 16:2383–2407.
65. Funck JAB, Schwartz JB, Reilly WJ, et al. Binder effectiveness for beads with high drug levels. Drug Dev. Ind Pharm 1991; 17:1143–1156.
66. Linder H, Kleinebudde P. Use of powdered cellulose for the production of pellets by extrusion/spheronization. J Pharm Pharmacol 1994; 46:2–7.
67. Fielden KE, Newton JM, Rowe RC. The influence of lactose particle size on the spheronization of extrudate processed by a ram extruder. Int J Pharm 1992; 81:205–224.
68. Chien TY, Nuessle NO. Factors influencing migration during Spheronization. Pharm Technol 1985; 4:44–48.
69. Wang C, Zhang G, Shah NH, et al. Compaction properties of spheronized binary granular mixtures. Drug Dev Ind Pharm 1995; 21:753–779.
70. Maganti L, Celik M. Compaction studies on pellets. I. Uncoated pellets. Int J Pharm 1993; 95:29–42.
71. Nicklasson F. Compression mechanics of pharmaceutical aggregates—studies on the tableting of spheronized aggregates with varying composition and porosity. PhD thesis, Uppsala University, Sweden, 2000.
72. Iloañusi NO, Schwartz JB. The effect of wax on compaction of microcrystalline cellulose beads made by extrusion and spheronization. Drug Dev Ind Pharm 1998; 24:37–44.
73. Salako M, Podczeck F, Newton JM. Investigations into the deformability and tensile strength of pellets. Int J Pharm 1998; 168:49–57.
74. Nicklasson F, Alderborn G. Modulation of the tableting behavior of microcrystalline cellulose pellets by the incorporation of polyethylene glycol. Eur J Pharm Sci 1999; 9:57–65.
75. Haslam JL, Forbes AE, Rork GS, et al. Tableting of controlled release multiparticulates, the effect of millisphere size and protective overcoating. Int J Pharm 1998; 173:233–242.
76. Johansson B, Nicklasson F, Alderborn G. Effect of pellet size on degree of deformation and densification during compression and on compactability of microcrystalline cellulose pellets. Int J Pharm 1998; 163:35–48.

13 Continuous Granulation

Chris Vervaet and Jean Paul Remon
Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium

INTRODUCTION: CONTINUOUS PROCESSING OF SOLID DOSAGE FORMS

For decades, the manufacturing of solid dosage forms in the pharmaceutical industry has been synonymous with batch processing, using a series of unit operations to modulate the properties of the material being processed. According to the FDA definition, batch manufacturing uses "a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture" (FDA Part 210 and 211, Current Good Manufacturing Practices for Manufacturing, Packing, or Holding of Drugs). When the predetermined endpoint of the batch process is reached the unit operation is finished and only then product quality is assessed, via off-line analysis in quality control labs using a wide array of (often destructive) analytical tools. During off-line analysis, the processing cycle is stopped and the in-process materials are stored in the manufacturing plant until it is assured that product quality meets the predefined quality parameters. If these quality standards are not met, the entire batch is either rejected or reprocessed.

In contrast, a continuous manufacturing process relies on the "one in, one out" principle, as new materials are continuously added to the process and finished products are continuously removed at the same rate to ensure a constant material volume in the process chamber. The quality is assured by incorporating at-line, on-line, or in-line measurements into the process stream, which allow continuous monitoring of critical process parameters as well as continuous inspection of quality attributes of raw materials, intermediates, and end product. When the monitored parameters remain within the acceptable ranges defined during the development phase, the outcome of the process is guaranteed. Any deviation from the predefined range can be rapidly corrected by real-time adjustment of process parameters via a feedback system. Since continuous processing does not rely on off-line measurement to determine if the material quality is within the predefined specifications, there is no need to interrupt the manufacturing process to make critical decisions about product quality, thus reducing cycle time and space required for material storage.

The pharmaceutical industry has been slow to adopt (or even to consider) the concept of continuous processing (1,2), although its value has already been proven in other industries (polymer, food, dairy, electronics, automobile, and (petrochemical), which have implemented fully continuous production processes for many years. In these industries, the drivers for the shift toward continuous processing were not limited to the reduced costs, the ease of automation and the short response time to growth when a higher output is required, but also the higher yield, extra process knowledge gained, and improved product quality (due the multiple in-process analyzers built into a continuous manufacturing line) were essential features that stimulated the implementation of continuous processing.

Although batch processes are often characterized by limited process control (possibly resulting in batch rejection or reprocessing), high labor costs (due to the multiple manual interventions during processing), high production costs, excessive inventories, and scale-up issues, this mode of processing prevailed within the pharmaceutical industry as it has been hesitant to move from batch processing toward continuous processing for a number of reasons.

Historically, innovation within the pharmaceutical industry has been mainly through the introduction of new drugs and to a lesser extent via novel drug delivery platforms. Because of the high value of the manufactured goods and the associated high profit margins, there was no driver for innovation in conventional pharmaceutical manufacturing processes of solid dosage forms, even when one was aware that the manufacturing process was run suboptimal.

However, faced with greater pressure to reduce costs (e.g., due to the competition from generics or the small drug pipeline) and on the basis of the opportunities offered by continuous processing toward process control (to reduce process variability), the incentives are currently present to introduce continuous processing within the pharmaceutical production plant and companies are actively considering this concept in their strategies.

Another barrier for the introduction of innovative continuous processes has been the stringent regulatory constraints within the pharmaceutical industry, which allowed little room for change and significantly contributed to the aversion to bring new manufacturing technologies to the attention of the regulators (to avoid delaying regulatory approval). However, the current emphasis on quality by design and process analytical technology (PAT) by the regulatory authorities has lowered this hurdle (3). By its very nature, continuous processing with automated and real-time in-process monitoring and control fits perfectly within these concepts. The PAT framework for Innovative Pharmaceutical Manufacturing and Quality Assurance describes a regulatory framework, which stimulates the development and implementation of new efficient tools during pharmaceutical development, manufacturing, and quality assurance, while maintaining or improving the current level of product quality assurance. On the basis of the concept that quality cannot be tested into the product but must be built in by design, the PAT and Quality-by-Design initiatives aim to introduce 21st century technology into the pharmaceutical manufacturing process to better respond to the changing marketplace, and continuous processing is an integral part of this strategy to move toward a risk- and science-based approach for pharmaceutical processing as "facilitating continuous processing to improve efficiency and manage variability, using small-scale equipment" has been identified in the PAT initiative as a way to improve quality, safety, and efficiency. On the basis of these regulatory initiatives pharmaceutical manufacturers should be encouraged to exploit the benefits of continuous processing.

Another regulatory-related issue when introducing continuous processing is that the conventional method to identify a batch is not applicable anymore for continuous processes. However, the FDA batch definition can also accommodate continuous process as "batch" within the definition does not refer to the mode of manufacturing, but to a quantity of material. Hence, material manufactured within a specified time interval of a continuous process can be identified by a unique code (batch number) to allow tracking of the manufactured goods.

The pharmaceutical industry is also dominated by batch processes because of the smaller amounts that must be processed compared with other industries. Batch-processing equipment was the most convenient to use with these operations as often an equivalent continuous unit operation that could accommodate the limited material volume was not available. The small material quantities available during the development stage also dictated the use of a batch process during the design phase of the formulation and manufacturing process, and these batchwise techniques often migrated toward production scale.

On the basis of these considerations, the implementation of continuous processing is still in its infancy in the pharmaceutical industry. However, its importance will certainly increase over the coming years, and it is certain to make an impact on the manufacturing of solid dosage forms as there are many advantages associated with this mode of manufacturing, which are all related to important economic drivers for change (quality, cost, and time):

- Increased quality control, which improves product uniformity, reduces the amount of rejected or reprocessed material, and increases process efficiency and productivity.
- Less scale-up issues: increasing the production capacity does not require larger equipment (with a development, optimization, and validation phase at each scale), but only an extension of process time on the same equipment using the same process settings, providing enormous flexibility, and eliminating material and technology transfer. Given that a continuous process mainly operates under steady-state conditions, product of a given quality can be produced for any length of time.
- More flexibility: time, and not the size of the equipment, determines the total material output, hence the demand for the product can dictate how many hours the system will operate.

- Smaller building volume: smaller equipment, fewer GMP, QC and QA areas (as a result of integrated process monitoring), and reduced warehouse space (due to the elimination of storage of intermediates in between unit operations).
- Lower cost: less labor (less personnel assigned to quality control and quality assurance, fewer manual interventions), less waste (improved product quality and less material rejection), shorter development times (fewer process steps, fewer bioequivalence studies), less utilities and HVAC.
- More efficient use of equipment: equipment is only profitable when in operation and the overall equipment effectiveness (i.e., the percentage of time the equipment is actually making product compared with the maximum) during batch processing within the pharmaceutical industry is too low (typically 30%, with 74% being considered a "good" pharmaceutical process) (4).
- Real-time release based on real-time production records via in-process monitoring (rather than final product testing following batch manufacture).
- Less product at risk, provided that the dimensions of the process are not too large and that accurate and continuous in-process monitoring with feedback systems is in place (hence the importance of PAT to allow adjustment of the variables to maintain the critical quality attributes of the product within the target levels).
- Ease of automation (reducing labor costs, operator interventions and human errors, possibility to run light-off process).
- Enclosed process (no material transfer needed as the different unit operations are directly linked, providing containment for toxic and highly potent drugs).

CONTINUOUS GRANULATION

A shift toward continuous processing in the pharmaceutical industry is not extreme as it may sound as several pharmaceutical unit operations are inherently continuous (e.g., roller compaction, tablet compression, hot melt extrusion, spray drying, packaging, milling). They have a constant flow of material in and out the equipment (i.e., a continuous process). However, they are typically run to process a fixed amount of material (i.e., a batch process), but the capability is present to rapidly change toward the continuous production concept. Continuous tablet manufacturing via direct compression, for example, could be achieved using a ribbon blender to mix the ingredients, with direct feeding of the blend into the hopper of the tablet press. Similarly blending, roller compaction, milling, and tableting could be combined into a continuous manufacturing cycle using dry granulation to agglomerate the powder blend.

However, the challenge for the pharmaceutical industry is to modify the inherently batch processes (e.g., wet granulation, drying, coating) into continuous techniques to fully benefit from the advantages associated with continuous processing in systems that rely on these unit operations. As wet granulation is the most popular method to improve material properties (e.g., flow properties, homogeneity, compressibility) via an agglomeration procedure, the implementation of a continuous granulation step is one of the bottlenecks to introduce a fully continuous production line of solid dosage forms as conventional fluid-bed and high-shear granulators are batch processes.

Although some continuous granulation techniques have been on the market for years, most have found limited application not only because of the reluctance to move toward continuous processing, but also because of equipment-related deficiencies (e.g., only suitable for high material throughputs, which are seldom required for pharmaceutical processing). However, equipment manufacturers have identified the specific needs for continuous granulation within the pharmaceutical industry and as a result a new generation of small and versatile continuous granulators will emerge, also suitable for manufacturing pharmaceuticals at a low production rate (10–50 kg/hr). As these machines could be used during product development, for the production of stability and clinical trial batches, as well as for full-scale commercial manufacturing, the manufacturer is confident that the critical process parameters, design space, and controls identified during development also apply in a manufacturing environment, improving yield and quality, as well as shortening development

Table 1 Overview of the Various Continuous Granulation Techniques Available for Processing of Pharmaceuticals

Mechanical granulation
– High-shear mixer
– Screw extrusion
– Roller compaction
– Extrusion/spheronization
Fluidized-bed granulation
Spray drying
Spray congealing

time. Although the amount of material processed can be increased by prolonging the process run time, this does not entirely eliminate the need of having continuous granulators of different sizes as each continuous granulator has a maximum throughput capacity, and for certain applications this might result in a too long process time to be economically feasible. Faced with this problem, the company can either run the process on two parallel continuous production lines with a limited capacity, or use a single continuous granulation system having larger dimensions. However, as the dynamic range of a continuous granulator is larger compared with a batch granulator, less equipment sizes are required, and in addition, to process the same amount of material, the overall size of a continuous processor is smaller compared with batch granulators.

A critical aspect of a continuous granulation technique is the product homogeneity at start-up and shut-down. Whereas material loss during batch processing only occurs during material transfer between different unit operations, the yield of a continuous process is mainly determined by the time required to reach steady-state conditions within the granulation chamber and by the end-of-batch material holdup in the granulator. As these factors are independent of the amount of material processed, they obviously have less of an impact when larger quantities are processed (i.e., during commercial manufacturing) compared with processing a smaller material volume during the development phase. Following the start-up phase, in-process controls and feedback loops must ensure that the output parameters remain within the predefined intervals to maintain steady-state conditions in response to variations in, for example, raw materials.

Another challenge is to obtain a uniform material residence time in the continuous granulator, that is, to design a process, which is essentially plug flow to minimize the effects of a residence time distribution on product quality. In contrast, all materials processed via a batchwise unit operation have, by the very nature of the process, the same residence time. Whereas plug flow moves the material directly from feed zone toward the discharge zone (resulting in a well-defined residence time for all materials), incoming material is mixed with material already present in the granulation chamber when back mixing occurs (material retention time is less controlled and variable).

The remainder of this chapter focuses on the continuous granulation techniques available for pharmaceutical processing. It describes the working principle of the different techniques (Table 1) and discusses the parameters determining the outcome of the granulation process.

However, compared with batch granulation, scientific reports dealing with continuous granulation techniques are sparse. Although roller compaction, extrusion/spheronization, spray congealing, and spray drying [possibly linked to a continuous fluid bed or with a fluid bed integrated at the bottom of the spray drying chamber to increase granule size and flow properties (4)] can also be used for the continuous production of granules, these applications are not discussed in this chapter as these agglomeration techniques are reviewed in detail in other chapters of this handbook.

CONTINUOUS FLUID-BED GRANULATORS

Conventional batch fluid-bed systems have been adapted for continuous processing, the main modifications being a continuous powder inlet valve and a continuous classifying device to

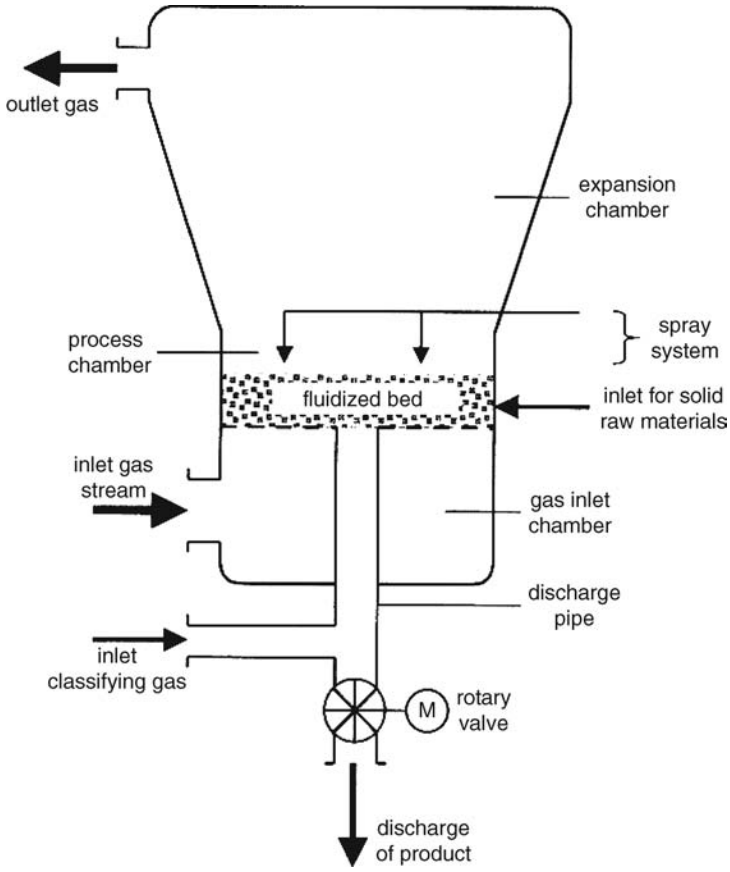


Figure 1 Continuous fluid-bed granulator. Granule particle size is controlled by an upward airflow, which retains undersized particles in the granulation chamber. *Source*: From Ref. 5.

limit the outlet from the granulation chamber to only agglomerated materials. The latter is based on an air separator, which retains undersized particles in the granulation chamber, whereas larger agglomerates are not withheld by the upward airflow and are removed from the granulation process on the basis of their mass (Fig. 1).

The velocity of the upward airflow is controlling the particle size of the granulated material. Material throughput of the AGT series designed by Glatt can be as low as 20 kg/hr, but can be increased to several tons per hour depending on the dimensions of the equipment. As it is essential to maintain steady-state conditions during processing, strict control of the powder feed system is required as a new particle has to be added to the process chamber for every particle removed from the system. If the input and output rates are not matched, material will either accumulate in the granulation chamber or the process will run out of particles, however, even before these extremes occur the powder/liquid ratio will change, thus affecting the agglomerate growth rate and granule characteristics.

This design provides limited control over material residence time as the first-in/first-out principle of material flow in the granulation chamber cannot be guaranteed. Another disadvantage is that all processes (mixing, granulation, drying) take place at the same time inside a single chamber, hence, dry and wet granules can interact with each other.

In contrast, the different phases of a granulation process are spatially separated in a horizontal fluid bed (Fig. 2) as different functional zones (product feed zone, product mixing and preheating zone, spraying zone, drying zone, cooling zone, discharge zone, which are not necessarily mechanically separated from each other) can be identified on the basis of the flow rate, temperature, and relative humidity of the fluidizing/drying air and on the presence of

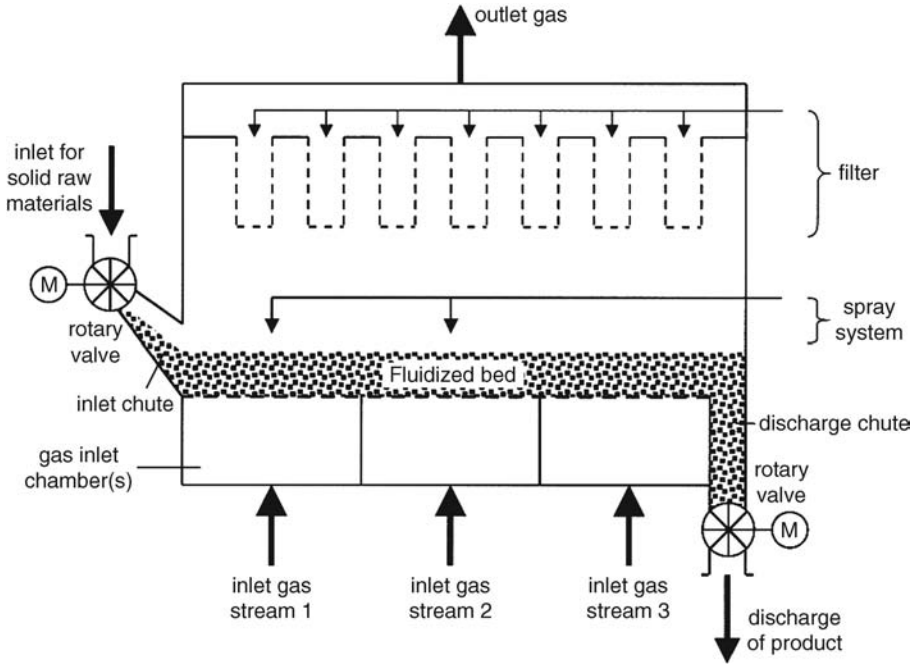


Figure 2 Continuous horizontal fluid bed. *Source*: From Ref. 5.

top- or bottom-spray nozzles. This allows sequential mixing, heating, agglomeration, and drying as the product passes through the longitudinal granulation chamber. For a detailed description of horizontal fluid beds designed by Niro and Glatt, the reader is referred to the manuscript by Gotthardt et al. (6).

Although this technology has proven its value within the food industry and moving bed systems have specifically been designed according to cGMP regulations by, for example, Niro, Glatt, and Heinen, their application within the pharmaceutical industry is not common, the main limitation of this system being their high material throughput rate.

The movement of material from feed zone toward discharge zone of the horizontal fluid bed can be controlled via a specific air distribution plate (gill-shaped openings, Fig. 3), via vibration of the granulation chamber or using a sloped powder bed (as fluidized particles have a liquid-like flow behavior) to guarantee directional transport of the powder, without segregation of the powder particles.

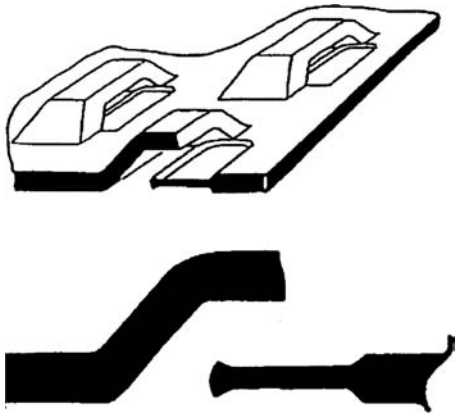


Figure 3 Gill-shaped openings of the air distribution plate of the Contipharm (Niro) horizontal fluid bed. *Source*: From Ref. 6.

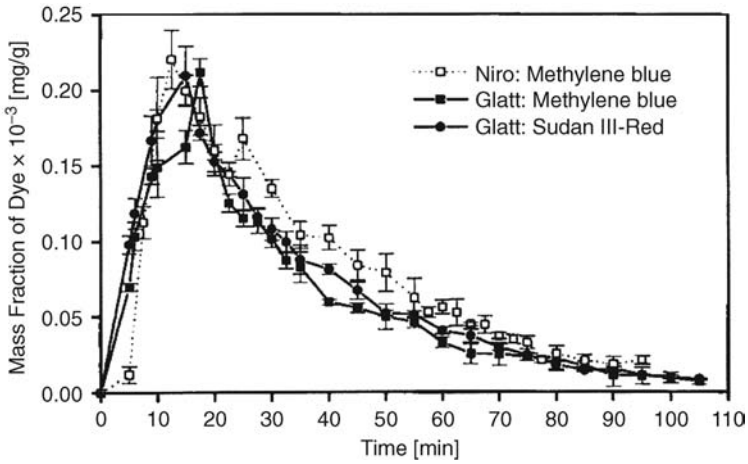


Figure 4 Retention time of material (using methylene blue and Sudan red as colored markers) in horizontal fluid beds. Material throughput rate: 60 kg/hr. *Source*: From Ref. 6.

Gotthardt et al. (6) studied the material movement inside the granulation chambers of two horizontal fluid beds (Niro Contipharm and Glatt Continuous Fluidized-Bed Granulator, both single-cell machines whose granulation chamber is divided into several zones without mechanical separation) using a lactose/maize starch powder mix and a 5% (w/w) aqueous PVP solution as granulation liquid. This study indicated that the gill-plate design of air distribution screen of the Contipharm induced efficient material transport from the inlet toward the outlet. However, when adding dyes (methylene blue or Sudan red) as markers to determine material residence time, the maximum output of methylene blue was detected after 12.5 minutes (using a powder feed rate of 60 kg/hr), afterward the concentration of the marker decreased exponentially but the dye was detected for more than 60 minutes (Fig. 4). The long tail-off of the residence time was not due to the water solubility of the marker as the curves of methylene blue and Sudan red were similar when testing material residence time in the Glatt system. These data indicated that—despite the efficient air-driven material transport—circulation of the powder within the reaction chamber induced random mixing, hence a distribution of the material residence time.

Gotthardt et al. (6) also evaluated the effect of a limited number of process variables on the granule properties: an increase of binder solution spray rate in the Contipharm increased particle size and resulted in a higher moisture content of the granules (when processed at same air temperature and flow rate), while a lower airflow rate in the Glatt horizontal fluid bed induced a higher moisture content because of the reduced drying rate. The effect of these variables was the same as observed during batch fluid-bed processing.

Horizontal fluid beds are unlikely to revolutionize the application of continuous granulation in the pharmaceutical industry as a seamless transition of granulation processes during development, clinical productions, and commercial manufacturing is not possible because of the high throughput rate of these systems and the large amount of material required at start-up, for example, 45 and 50 kg powder was required to obtain a sufficient powder bed at start-up in the Contipharm and Glatt granulator, respectively, as tested by Gotthardt et al. (6). This amount of material is required at start-up as the equipment is filled with raw material similar to batch processing, and only after this material has been granulated, the process switches to the continuous mode by introducing the material via an inlet valve and discharging granules via an outlet valve.

A similar continuous granulation technique based on fluidization of materials is the spouted bed technology (e.g., ProCell, Glatt), which does not introduce the air into the process chamber via a sieve, but via a longitudinal slot. High air speeds at the point of entry ensure that the process can be used for difficult-to-fluidize materials and larger particles, whereas the fast reduction of air speed upon expansion in the process chamber minimizes the loss of small

particles from the process. Material throughput starting from 20 kg/hr is advertized by the manufacturer.

CONTINUOUS MECHANICAL GRANULATORS

Mechanical granulators for continuous wet agglomeration will most likely have the highest impact on the processing of solid dosage forms. Different designs are available (instant granulators, extrusion-based systems, and equipment using a high-shear granulation bowl), several, however, are not optimal for pharmaceutical applications as their minimal throughput is too high to allow their use at all levels (development, clinical trials).

Instant Granulators

Several mechanical mixers have been designed, which use a high mixing intensity inside the granulation unit (e.g., Iverson mixer and Schugi Flexomix system) to ensure instant formation of the granules. A schematic and process description of these systems is presented by Lindberg (7), Appelgren (8), and Vervaet and Remon (4). As the material residence time inside the granulation chamber is very short (in the order of seconds), the start-up phase is short and material holdup is limited as only a small amount of material is processed in the granulation chamber at any given time. Although Lodaya et al. (9) reported that it was possible to prepare high-quality granules of consistent quality during runs from 5 to 30 minutes using powder feed rates of 300 and 600 kg/hr in the Iverson mixer, the high throughput capacity of these systems (e.g., from 50 kg/hr up to several tons per hour when using the Schugi Flexomix) is a major limitation for pharmaceutical applications. In this respect, the Modulomix (Hosokawa), which can be used for continuous mixing as well as agglomeration, could find a wider application range since its working capacity already starts at 10 kg/hr.

Extrusion-Based Continuous Granulators

The core of these simple continuous granulators is a single- or (mainly) twin-screw extrusion system. The modular nature of the screw with different elements allows to accommodate the different process steps (feeding, mixing, granulation, conveying, discharging) within the longitudinal extrusion barrel ("processing in a pipe"), for example, paddles to provide the intense shear required for granulation, whereas screw elements in the feed and discharge zone are used to convey the material.

This technique for granulation of pharmaceuticals was already described by Gamlen and Eardley (10) (for the processing of paracetamol granules) and Lindberg et al. (11) (to manufacture effervescent granules).

The short residence time in the granulation unit ensures that steady-state conditions are quickly reached, and in combination with a minimal product holdup this allows processing at small scale (development, optimization) with limited material loss using the equipment for final manufacturing. On the basis of these properties, this is the most promising technique for continuous wet granulation, and consequently more scientific data are available (compared with the other continuous granulation techniques) on the parameters affecting the process and the quality of granules processed via this technique. Key process variables that must be considered to optimize granule quality are the screw configuration, screw speed, temperature, powder feed rate, liquid feed rate, and die pressure.

Using an intermeshing corotating twin-screw extruder, Keleb et al. (12,13) identified the water content of the wet mass as the main determinant of granule properties, it determined the ability to extrude the formulation and affected yield, fines, and friability. Compared with high-shear granulation, less water was required to efficiently agglomerate a placebo lactose formulation. In these studies, screw speed and total material throughput rate (5.5 to 18.5 kg/hr) had a limited effect on the process yield, particle size distribution, granule compressibility, and tablet properties, provided that both these process variables were adjusted to obtain an acceptable degree of filling in the extrusion chamber. Keleb et al. (13) also demonstrated that particle size, granule characteristics, and tablet properties were constant during an eight-hour granulation run of a lactose/PVP formulation.

Similar to the initial granulation experiments by Gamlen and Eardley (10) and Lindberg et al. (11), Keleb et al. (12) initially produced larger dense granules (porosity: about 6–7%) due

to material densification in the discharge zone of the extruder. However, efficient granulation without extensive densification in the barrel was possible by removing the die block, hence eliminating the need for wet sieving prior to further processing (13).

Keleb et al. (14) showed that continuous granulation via twin-screw extrusion can provide a robust process toward raw material variability as lactose particle size (90–450 mesh) and morphology only had a minor influence on granule and tablet properties, whereas granulation in a high-shear mixer was more affected by these variables. Via extrusion-based granulation formulations with high paracetamol or cimetidine content could be processed, whereas conventional high-shear granulation required an additional binder. In addition, the paracetamol and cimetidine granules prepared by extrusion had a higher process yield and lower friability compared with high-shear processing.

Comparison of twin-screw extruders manufactured by APV and Leistritz showed that granulation of dicalcium phosphate and lactose formulations was possible on both extruders, but—despite their similar screw configuration—transfer of the granulation process between both was not straightforward as the outcome was determined by the extruder type (15), for example, the Leistritz extruder yielded less fines when processing a dicalcium phosphate formulation (Fig. 5), which was also reflected in granule friability, but the granule size was only independent of the material throughput rate in case of the APV extruder (Fig. 6).

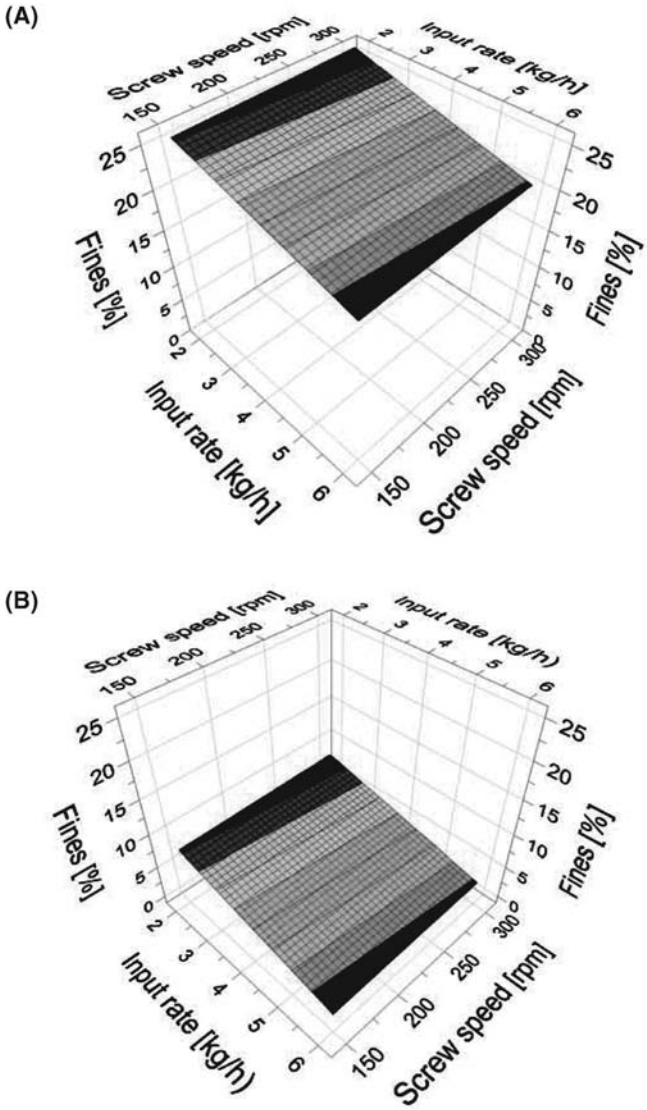


Figure 5 Surface plots of the amount of fines produced in function of screw speed and material throughput rate during wet granulation of dicalcium phosphate using continuous screws extruders: (A) APV extruder and (B) Leistritz extruder. *Source*: From Ref. 15.

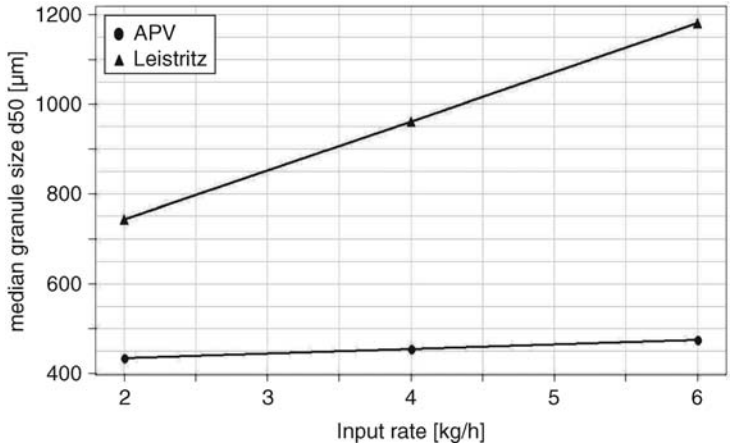


Figure 6 Effect of material throughput rate on the median particle size of dicalcium phosphate granulated using continuous screw extruders manufactured by APV and Leistritz. *Source*: From Ref. 15.

Djuric et al. (16) prepared lactose granules using the Leistritz Micro extruder equipped with different screw configurations (conveying, combing mixer, and kneading elements).

Depending on the design of the extrusion screw, the granule porosity varied between 17.4% and 50.6%, which was correlated with granule friability.

Conveying element yielded the most porous and friable granules, whereas kneading blocks produced the densest material. The effect of the screw elements was also reflected in the tablet characteristics as a higher granule porosity resulted in a higher tablet tensile strength.

This study shows that continuous wet granulation via twin-screw extrusion offers a versatile tool to adjust granule and tablet properties. Similar effects of the screw elements on porosity, friability, and tablet properties were observed when processing mannitol and dicalcium phosphate formulations; at higher throughput rate (6 kg/hr vs. 2 kg/hr), the effect on granules and tablets of screw elements was less pronounced (17).

The degree of dispersive (i.e., reducing the morphological components) and distributive (i.e., dividing and recombining the material without disturbing the individual morphological components) mixing of the different screw elements can be reflected in the distribution and particle size of the material, for example, screw elements with a 15-mm pitch did not properly distribute water in a lactose/theophylline blend compared with elements with a larger pitch, while the dispersivity of kneading blocks reduced the dicalcium phosphate particle size (17).

Continuous melt granulation using a twin-screw extruder is also possible, eliminating the drying step, but requiring a cooling phase of the warm plastic granules before downstream processing. Van Melkebeke et al. (18) developed immediate-release granules of a poorly water-soluble drug via a continuous melt granulation process using PEG 4000 as binder.

A specific type of extruder, which can be used for continuous granulation is the planetary roller extruder. It combines a central spindle (with gears) with spindles, which are positioned around the central spindle and upon rotation of the latter the planetary spindles roll on the central spindle and the internal toothed barrel (Fig. 7). The high contact surface area (about six times larger compared with a conventional twin-screw extruder) provides more intensive interaction with the material.

Material densification at the outlet requires that the material is milled after drying in continuous microwave or contact dryer. A detailed description of this system is provided by Schroeder and Steffens (19). Material throughput rates from 2 to 1000 kg/hr are possible, using a range of only four machine sizes, for example, equipment with a nominal output of 10 kg/hr can realize output of 2 to 20 kg. Because of the excellent blending capacity of this system, preblending of the different components is not required prior to granulation. Schroeder and Steffens (19) showed that a wide array of mixtures formulated with commonly used excipients (lactose, mannitol, starch, cellulose, HPMC, PVP) can be processed via this technique.

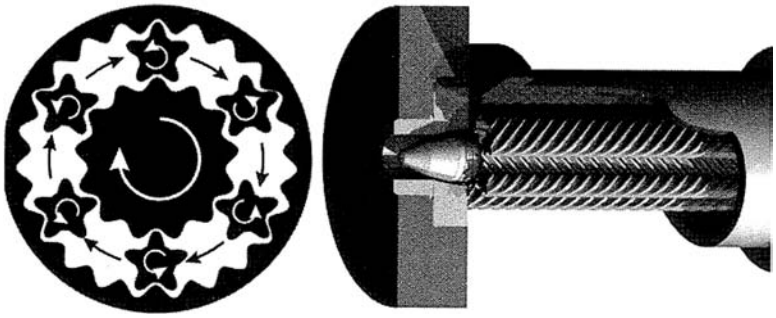


Figure 7 Planetary roller extruder. The arrows indicate the movement during extrusion. *Source*: From Ref. 19.

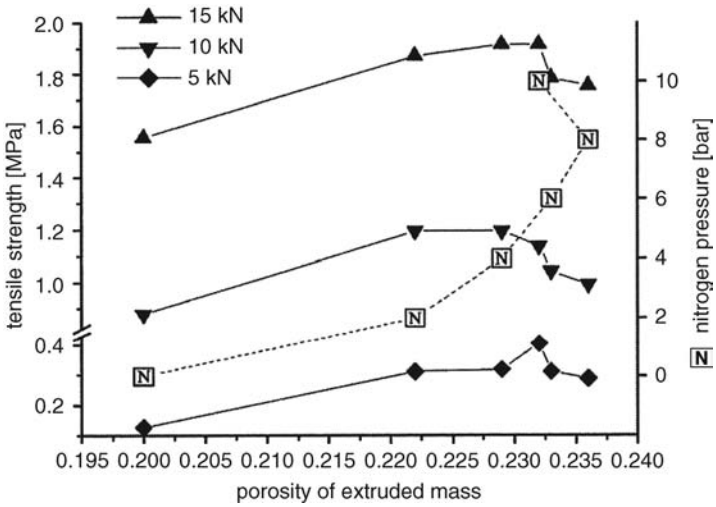


Figure 8 Influence of nitrogen injection on the porosity of lactose/corn starch/povidone granules manufactured using a planetary roller extruder, and on the tensile strength of tablets prepared using these granules. Tablets were manufactured using 5, 10, and 15 kN compression force. *Source*: From Ref. 19.

An intermediate densification step in the extruder allows injecting nitrogen in the formulation upon subsequent reexpansion. This resulted in a higher porosity of lactose/corn starch/povidone granules, which improved their compression properties (Fig. 8). The intensive kneading in the granulation barrel allowed to process formulations with a high content of poorly wetable substances (up to 96% and 92% of ibuprofen and mefenamic acid, respectively) using only a small amount of hydrophilic binder. The resulting granules yielded tablets having a high tensile strength, low friability, fast disintegration, and immediate drug release. In this case, gas injection worsened tablet quality (slower disintegration and prolonged dissolution) because of the displacement of the hydrophilic binder from the surface of the hydrophobic active, resulting in higher contact angles between the granules and water.

MODULAR DESIGNS

GEA recently developed a fully continuous production suite for tablets (via integration of dispensing, blending, granulation, drying, milling, granule blending with external phase [i.e., lubricant and/or disintegrant], and tableting) (Fig. 9).

Since continuous wet granulation is a key component of this process, the Consigma^{TM} granulator/dryer was developed, which integrates three modules: wet granulation module, segmented dryer module, and evaluation module (Fig. 10).

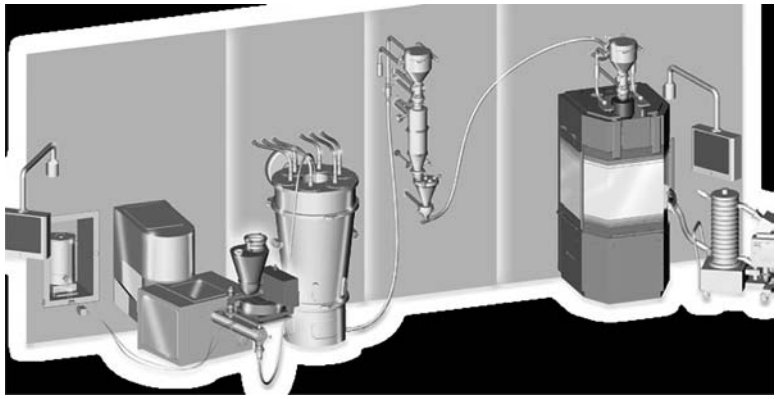


Figure 9 Continuous suite for the production of tablets. *Source*: Courtesy of GEA.

Figure 10 Consigma™ granulator/dryer consisting of a wet granulation module, segmented fluid-bed dryer, and evaluation module. *Source*: Courtesy of GEA.

In this modular design, the following processes can be distinguished:

- Liquid and powder dosing via loss-in-weight feeders: Powder dosing is possible from a container of preblended material (the amount in the container can be used to define batch size), but a more convenient way is to use several feeders to dose each dry ingredient individually and to rely on the mixing capacity of the screw to homogenize the formulation. Obviously, this necessitates accurate dosing devices as weight deviations have a significant impact on the solids/liquid ratio (which determines granule properties) because of the small amount of material inside the granulation unit. In addition, as this agglomeration technique is basically a plug flow process, deviations resulting from poor feeder accuracy will not be eliminated during the process cycle as mixing of materials is limited. Because of the compact design of the unit and as all individual feeders have to feed into a single tube, the number of possible feeders is limited and depends on the barrel length.
- Granulation unit: After the feed zone, the liquid is added and the wetted particles are agglomerated in a short granulation chamber, limiting material residence time in the granulation unit to a few second. The narrow tolerance between the granulation screw and barrel ensure high-shear mixing and efficient agglomeration within a short period of time. Van Melkebeke et al. (20) showed that short extrusion screws were as effective for granulation purposes as the longer screws used during the initial granulation trials via

extrusion (10,12). When dry mixing of the individual powder components is required the length of the screws can be extended prior to the granulation zone to have additional mixing capacity. The narrow tolerance between granulation screw and barrel also minimizes back mixing and ensures plug flow.
– Transfer to dryer: Since no large agglomerates are formed during granulation, wet milling is not required and a continuous flow of wet granules is transported to the dryer via a pneumatic transfer line or via gravity.
– Drying module: Drying is based on conventional fluid-bed technology, but uses a segmented fluid-bed dryer (six separate drying cells) to ensure a first-in/first-out material flow. The continuous flow of granules is split into small packages (1.5 kg in case of a 25 kg/hr throughput unit), each package is dried in a separate drying cell, when the granules in the segment are dry, its content is transferred to the evaluation mode and refilled with a new package of wet granules. Compared with horizontal fluid beds, the segmented fluid-bed dryer can operate with a lower amount of material, hence providing more flexibility for pharmaceutical processing.
– Evaluation module: Milling of the dried granules and evaluation of the granules properties (e.g., particle size, moisture content, content uniformity) using appropriate PAT tools (e.g., NIR spectroscopy). As it takes about 20 minutes for the material to pass through the process line toward the evaluation module, one-third of the one-hour capacity is at risk before adjustments can be made to the process settings, in case major deviations are detected.

Since small scale is key for successful introduction of continuous techniques in the pharmaceutical industry, the Consigma unit can process a small amount of material. Processing of material in a single cell of the segmented dryer is possible (e.g., during formulation development or process optimization) under the same conditions as during full-scale manufacturing (when all drying cells are filled) as the design of the air distribution plate of the segmented fluid bed provides a constant pressure drop (independent of the number of cells in use). In addition, because of the short material residence time in the granulation unit, the response time is fast when process parameters are adjusted, hence only a minimum of material is consumed during development work when multiple settings are evaluated.

The compact design of the Consigma units allows a significant reduction of the room requirements: 22.5 m^3 for a Consigma granulation and drying unit (including bulk containers for powder blend dispensing) versus 490 m^3 for the same production capacity using a batchwise granulation and drying process. Units with a nominal throughput of 25, 50, and 100 kg/hr are available to accommodate for increasing output. As this only requires a change of the screw diameter and larger dimensions of the dryer, the physical size of the equipment does not change anywhere near the magnitude that batch equipment changes with increasing scale. Processing a lactose formulation on Consigma units with a different throughput capacity had no effect of the particle size distribution of the granules (21).

The brand name of this continuous granulator/dryer system, Consigma, refers to the opportunities offered by continuous processing to improve process efficiency, based on the 6σ manufacturing concept with a high yield (99.999,66%) and low cost of quality (1–3%). Efficiency of most pharmaceutical manufacturing processes is currently between 2σ and 3σ (yield: 69.2–93.3%, with cost of quality consuming 20–35% of revenue).

CONTINUOUS GRANULATION USING A HIGH-SHEAR MIXING BOWL

Since high-shear granulation is the most popular method for batch granulation, it is not surprising that continuous granulation techniques have been devised on the basis of high-shear granulation technology.

The Easy Flow® system (Bohle-Conti-Granulator) uses a high-speed blender based on single-pot high-shear mixing technology as wet granulator, combined with a drying system. Continuous processing is possible as an integrated outlet above the impeller enables continuous discharge of the granules (Fig. 11).

A chopper mounted above the impeller conveys the wet granules through a perforated screen (which defines granule size). From the outlet, the wet granules are gravity-fed into a rotating cylindrical dryer (heated from the outside via infrared radiation). Homogeneous

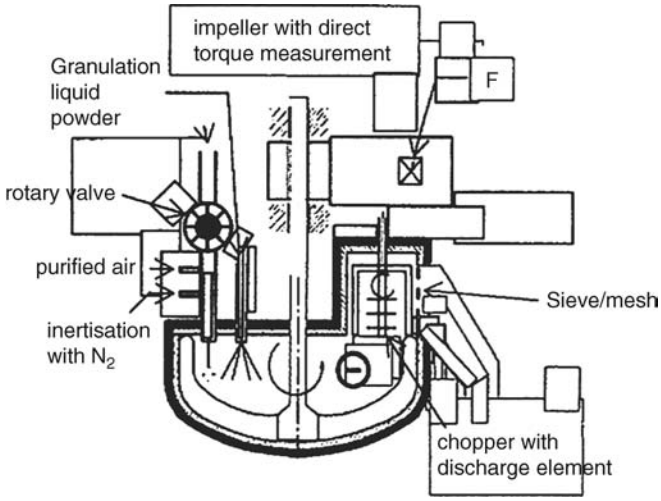


Figure 11 Easy Flow® system for continuous granulation.

drying, material transfer based on the first-in/first-out principle, and complete product removal are guaranteed in this continuous contact dryer by an internal scraper (having a higher peripheral speed compared with peripheral speed of drying pipe). The vacuum within the dryer ensures rapid and gentle product drying. The throughput of the system depends on the capacity of the granulation bowl and on the feed rate of the powder and liquid dosing devices, for the BCG-30 system having a maximum capacity of 30 kg/hr the output rate can typically vary from 8 to 30 kg/hr. Although the compact design of this system and flexible material throughput (allowing its use for lab trials, clinical trials as well as full production) are interesting features for pharmaceutical applications, material residence time is less controlled compared with extrusion-based systems as it does not rely on plug flow. The residence time also varies according to the throughput rate since material transfer from the granulator toward the drying unit is based on an overflow principle.

The Glatt Multicell system uses a conventional high-shear granulator for agglomeration of the powders, but is directly linked to another batchwise unit operation (fluid-bed drying) to design a semicontinuous granulation process (quasicontinuous as defined by the designers of the system). A detailed description of the system is presented in Betz et al. (22) and Werani et al. (23). In short, granulation of a powder blend is performed in a horizontal high-shear mixer. After granulation and wet sieving, the agglomerated powder is pneumatically conveyed to a first fluid bed for the initial drying phase at high inlet air temperature. After a predefined time, these granules are transferred to a second fluid bed for further drying and finally to a third drying cell for cooling and conditioning of the granules for subsequent processing. Hence, a small amount of material is moving sequentially through the processing train and a quasicontinuous system is formed as a second load of powder is metered into the high-shear mixer as soon as the first payload is transferred to the first fluid-bed dryer. Hence, granule output is in discrete packages rather than the gradual output of a true continuous process where product output is proportional to production time.

This semicontinuous approach provides flexibility toward the amount of material processed as this is dictated by number of packages ("subunits") being processed: the lower limit is defined by the subunit size in the high-shear mixer (1–25 kg depending on the size of the equipment) as one could process a single subunit for development purposes or during optimization of the process. However, any number of subunits could be sequentially processed by extending the process run time (typically the interval time between subunits is short, about five minutes). Leuenberger et al. (24) described the successful processing of 600 consecutive 7-kg subunits. Betz et al. (22) demonstrated the consistent material quality of the different subunits produced via this quasicontinuous process, in terms of yield, bulk/tapped volume, and compression properties when processing without interruption up to 100 subunits (8 kg per subunit) of a placebo formulation consisting of lactose, maize starch, and HPMC. When using

this technology, a 23% reduction in floor space was reported compared with a conventional batchwise granulation process, which requires larger units for high-shear granulation and fluid-bed drying.

Another type of mechanical mixer is the Lödige continuous granulation, which consists of a horizontal granulation chamber with a rotating shaft, equipped with different elements to provide different functionalities (preblending, granulation, and shaping of granules). The high rotation speed of the blending/agglomeration elements (shovels) creates a fluid bed–like behavior of the material. The granulation process in this system is highly efficient, however, because of the throughput rate of these systems (smallest capacity 50–100 kg/hr, up to 50 ton/hr), the number of pharmaceutical applications is limited.

REFERENCES

1. Pellek A, Arnum PV. Continuous processing: moving with or against the manufacturing flow. Pharm Technol 2008; 32(9):55–58.
2. Rios M. Continuous processing—finally. Pharm Technol 2007; 31(4):31–34.
3. Bush L. FDA lowers barriers to process improvement. Pharm Technol 2005; 29(10):39–43.
4. Vervaet C, Remon JP. Continuous granulation in the pharmaceutical industry. Chem Eng Sci 2005; 60:3949–3957.
5. Jacob M. Granulation equipment. In: Salman AD, Hounslow MJ, Seville JPK, eds. Granulation. Amsterdam: Elsevier, 2007:417–476.
6. Gotthardt S, Knoch A, Lee G. Continuous wet granulation using fluidized-bed techniques. I. Examination of powder mixing kinetics and preliminary granulation experiments. Eur J Pharm Biopharm 1999; 48:189–197.
7. Lindberg NO. Some experiences of continuous wet granulation. Acta Pharma Suec 1988; 25:239–246.
8. Appelgren C, Eskilson C, Medical L. A novel method for the granulation and coating of pharmacologically active substances. Drug Dev Ind Pharm 1990; 16:2345–2351.
9. Lodaya M, Mollan M, Ghebre-Sellassie I. Twin-screw wet granulation. In: Ghebre-Sellassie I, Martin C, eds. Pharmaceutical Extrusion Technology. New York: Marcel Dekker, 2003:323–343.
10. Gamlen MJ, Eardley C. Continuous extrusion using a baker Perkins MP50 (multipurpose) extruder. Drug Dev Ind Pharm 1986; 12:1701–1713.
11. Lindberg NO, Tufvesson C, Holm P, et al. Extrusion of an effervescent granulation with twin screw extruder, baker Perkins MPF50D. Influence of intragranular porosity and liquid saturation. Drug Dev Ind Pharm 1988; 14:1791–1798.
12. Keleb EI, Vermeire A, Vervaet C, et al. Continuous twin screw extrusion for the wet granulation of lactose. Int J Pharm 2002; 239:69–80.
13. Keleb EI, Vermeire A, Vervaet C, et al. Twin screw granulation as a simple and efficient tool for continuous wet granulation. Int J Pharm 2004; 273:183–194.
14. Keleb EI, Vermeire A, Vervaet C, et al. Extrusion granulation and high shear granulation of different grades of lactose and highly dosed drugs: a comparative study. Drug Dev Ind Pharm 2004; 30: 679–691.
15. Djuric D, Van Melkebeke B, Kleinebudde P, et al. Comparison of two twin-screw extruders for continuous granulation. Eur J Pharm Biopharm 2009; 71:155–160.
16. Djuric D, Kleinebudde P. Impact of screw elements on continuous granulation with a twin-screw extruder. J Pharm Sci 2008; 97:4934–4942.
17. Djuric D. Continuous Granulation with a Twin-Screw Extruder. Düsseldorf: Heinrich-Heine-Universität Düsseldorf, 2008.
18. Van Melkebeke B, Vermeulen B, Vervaet C, et al. Melt granulation using a twin-screw extruder: a case study. Int J Pharm 2006; 326:89–93.
19. Schroeder R, Steffens KJ. Continuous granulation technologies. In: Parikh DM, ed. Handbook of Pharmaceutical Granulation Technology. 2nd ed. New York: Taylor & Francis, 2005:431–457.
20. Van Melkebeke B, Vervaet C, Remon JP. Validation of a continuous granulation process using a twin-screw extruder. Int J Pharm 2008; 356:224–230.
21. Van Melkebeke B. Development and evaluation of a continuous granulation technique using a twin-screw extruder. Ghent University, Ghent, 2009.
22. Betz G, Junker-Burgin P, Leuenberger H. Batch and continuous processing in the production of pharmaceutical granules. Pharm Dev Technol 2003; 8:289–297.
23. Werani J, Grunberg M, Ober C, et al. Semicontinuous granulation—the process of choice for the production of pharmaceutical granules? Powder Technol 2004; 140:163–168.
24. Leuenberger H. New trends in the production of pharmaceutical granules: batch versus continuous processing. Eur J Pharm Biopharm 2001; 52:289–296.

14 Effervescent Granulation

Guia Bertuzzi
IMA SPA ACTIVE Division, Bologna, Italy

INTRODUCTION

Effervescence has proved its utility as an oral delivery system in the pharmaceutical and dietary industries for decades. In Europe, effervescent dosage forms are widespread, and their use is growing in the United States and other countries. Effervescent granulation is an important step of "fizzy" dosage forms production that most of the time cannot be avoided to achieve the desired characteristics of the effervescent tablets. It is very critical also because it can affect stability of the final dosage forms. The first effervescent preparations were described over two centuries ago, in the official compendia; they were in powders to use as cathartic salts. Later, in 1815, a patent describes "a combination of neutral salt or powder which possesses all the properties of the medicinal spring of Seidlitz in Germany, under the name of Seidlitz Powders," which contains sodium potassium tartrate, sodium bicarbonate, and tartaric acid, in the proportions 3:1:1, respectively (1). Effervescent granules and tablets have become more and more popular as dosage forms because they are promptly soluble and easy to take.

To state the growing interest in such forms, in the 1980s, the results of a literature search about effervescent forms were published so as to help scientists working on new development (2).

According to the 6th Edition European Pharmacopoeia, the effervescent forms are defined as "those granules or tablets to be dissolved in water before administration to patients." Effervescent tablets or granules are uncoated and generally contain acidic substances and carbonate or bicarbonate that react rapidly to release carbon dioxide once dissolved in water. Disintegration of the tablets usually occurs within two minutes or even less, because of the evolution of carbon dioxide.

Effervescent forms have many advantages over conventional pharmaceutical forms. They substitute liquid forms when the active ingredient has a little stability in liquid form because they can be administered only by prior dissolving the tablet in water. Active ingredients that are not stable in liquid form are most of the times stabler in effervescent form. This dosage form is easier to administer, particularly helpful to patients, like children, who are not able to swallow capsules or tablets. A pleasant taste, because of carbonation, helps to mask the bad taste of certain drugs. This could help to avoid the gastric side effect of certain drugs. In certain cases, they can shorten drug absorption rate in the body as compared with traditional tablets, with a quicker therapeutic effect (3). They are easy to use and appeal consumers for color and fizzy appearance more than traditional dosage forms.

Effervescent dosage form also helps with patient compliance. For example, chloroquine remains the most widely used medicine for treatment of malaria in endemic countries despite resistance of up to 50% in some areas, because of its affordable price. A study showed that patient compliance increased when the chloroquine phosphate was administered as an effervescent tablet because of the faster response onset than uncoated tablets (4).

Disadvantages of such solid dosage forms are more related to production technology even if processing methods and equipment are the same as the conventional ones. In general, product requirements are similar to conventional granules, namely particle size distribution and shape, uniformity of active distribution, to produce satisfactory free-flowing granules, and capable of tableting using high-speed rotary tablet press. However, it is also necessary to focus attention on some aspects of the process procedure, including compression and packaging because effervescent dosage forms are challenging and consequently difficult to make.

Pharmaceutical industry faces many problems, especially in the preparation of effervescent tablets as it is certainly the application for which the choice of the processing equipment is at least as important as the formulation design.

THE EFFERVESCENT REACTION

Effervescence is the evolution of gas bubbles from a liquid, as a result of a chemical reaction. The most common reaction for pharmaceutical purpose is the acid-base reaction between sodium bicarbonate and citric acid.

$$3NaHCO_3(aq)\,[252g(3\ mol)] + H_3C_6H_5O_7(aq)\,[192g(1\ mol)] \Rightarrow 3H_2O(aq)\,[54g(3\ mol)] + 3CO_2\,[132g(3\ mol)] + 3Na_3C_6H_5O_7(aq)\,[258g(1\ mol)]$$

This reaction starts in presence of water, even with a very small amount, as a catalyzing agent, and because water is one of the reaction products, it will accelerate and will be very difficult to stop. For this reason, the whole manufacturing and storage of effervescent products has to be planned by minimizing the contact with water.

Looking at the stechiometric ratios in the reaction, it is quite easy to understand the reason why effervescent tablets are so large.

Recently, some effervescent systems have been prepared to act as penetration enhancers for drug absorption, not only in oral forms but also in some topical products, such as skin or vaginal applications. In these cases, the reaction takes place directly after administration, in the mouth because of saliva (5), on the wounds because of blood serum (6), or when formulated in a suppository, the effervescence can be provoked by the moisture of the vaginal mucosa to treat vaginal infections or simply adjust the pH.

There are other forms, the effervescence of which is based on a different reaction upon carbon dioxide formation. Effervescence is due to reactants that evolve oxygen or other gasses, which are safe for human consumption even if they are not suitable for oral administration but can be employed in preparations for external use such as antibacterial for dental plate cleaning.

FORMULATION

The criteria to choose the raw materials for effervescent products are similar to those for the conventional tablets, since in either case, good compressibility and compactability are the targets to achieve. The intrinsic characteristics of effervescent forms bring some considerations that will limit the choice of the raw material, including the selection of active ingredient. Moisture content of the raw material is a very significant aspect, because it affects compressibility and stability of the tablets. To avoid premature effervescent reaction during the process or once the tablets are formed, raw materials with very low moisture content have to be used. Since an effervescent tablet is required to dissolve within two minutes or less in a glass of water (about 100 mL), raw materials' solubility and their rate of solubility are other significant aspects. The active ingredient must be either soluble, water dispersible or at least solubilized by salt formation during the dissolution in the glass of water. The rest of the excipients, such as additives like sweeteners, coloring agent, and flavors, also have to be water soluble.

For all these considerations, the list of the excipients for this dosage form has not changed for many years. However, the physical properties of these raw materials have recently improved. Many different grades for each material are now commercially available, including some preformulated grades, which are highly recommended for direct compression. Formulators must choose the excipient grade on the basis of the characteristics of the active ingredient, tablets size, and process technology they have. Therefore, the ultimate use of the effervescent granules or tablets mainly affects the choice of the raw materials.

To design an effervescent formula, it is necessary to consider the stechiometric ratios in the reaction, and the carbon dioxide solubility in water, which is 90 mg/100 mL of water (in STP conditions). The suggested ratio between acid and alkaline components is about 0.6, but sometimes it might be required to increase the acid source to get a pleasant taste. In fact, the alkaline-acid ratio controls both the effervescence capacity and the taste of the solution to administer. When the active ingredients solubility is not pH dependent, the alkaline-acid ratio can be optionally selected. This ratio can also be determined according to the pH that is required for dissolving the active. In fact, when the active solubility increases at the acid side, the pH of the solution is lowered by adding an excess of the acidic agent. Conversely, an excess of alkaline sources must be added when the active ingredient is more soluble at higher pH (7). However, another approach that can be used to increase the active ingredient solubility is to

increase the volume of carbon dioxide to be generated by increasing the alkaline component in the formulation.

As far as other excipients, such as diluents or binders, are concerned, there is a very little space for the formulator to play with, because of the large dimension of the tablet due to the effervescent system. Compressibility cannot be enhanced by additional binders for effervescent dosage form, because of the larger size of the tablet in the first place.

In the latest development in effervescent forms, there are some formulations that have been designed to control the rate of effervescence, so as to obtain a rapid, intermediate or slow rate. The rate control is strictly related to the acid-alkaline components ratio, but the chemical properties of the effervescent excipients or their combinations can have an influence on it, especially when a slow rate of effervescence is required.

RAW MATERIALS

Because of the nature of the effervescence reaction, additional excipients are sparingly used as the alkaline and acid ingredients are also the fillers to get a tablet bulk. They are, indeed, in such a large amount that tablets are much larger than the conventional ones. In case it would be necessary to add a filler, sodium bicarbonate is selected because of its lower cost and because it does not influence final pH of the solution and increases effervescence effect.

Sodium chloride and sodium sulfate are other possible fillers; they are high-density crystalline powders that are very compatible with the other ingredients.

Additives are added in small amounts to make the tablets more attractive for users. Flavors, colors, and sweeteners are used as usual in all the formulations.

Acid Materials

Necessary acidity for effervescence can be provided by three main sources: food acids, acid anhydrides, and acid salts. Food acids, citric acid, tartaric acid, and ascorbic acid are the most commonly used because these have a nice taste, are odorless, not expensive, and easy to handle.

Citric Acid

Citric acid is the more often used acidic ingredient because of its good solubility and pleasant taste. It is mainly commercially available in powder and is either colorless or in white crystals. The particle size grades are: coarse, medium, fine, and powder (only anhydrous). It is very soluble in water and soluble in ethanol (8). It can be used as monohydrate or anhydrate, depending on the selected equipment technology and process conditions. It is very hygroscopic; however, anhydrous form is less hygroscopic than the monohydrate (9). However, caking of the anhydrous ingredient may occur upon prolonged storage at humidity greater than 70%. The monohydrate melts at 100°C, and releases the water of hydration at 75°C. For this reason, it can be used as binder source in hot melt granulation.

Tartaric Acid

It is very soluble in water and very hygroscopic, more than citric acid. In the effervescence reaction with sodium bicarbonate, it behaves like citric acid in producing an evident effervescence. It must be used in a higher amount to get the proper stechiometric proportions, being a diprotic acid, while citric is a triprotic acid. In terms of compressibility, it is also comparable to citric acid (8).

Ascorbic Acid

It is white in crystalline form and light yellow in fine powder. It is not hygroscopic, and this may be helpful in production because it is easier to handle. It is freely soluble in water (1 g in about 3 mL) and absolute ethanol (7). If exposed to light, it gradually gets dark. Its behavior in the effervescent reaction with sodium bicarbonate is comparable to the other acids (citric and tartaric) in terms of release rate of carbon dioxide.

Acid Anhydrides

Anhydrides of food acids are a potential acid source as they are precursors of the corresponding acid by hydrolization in water. The effervescent effect is strong and sustained

by the continuous production of acid in the solution. Water has to be avoided for the whole process when anhydrides are part of a formulation, otherwise they would be hydrolyzed into the corresponding acid before its use (10).

Acid Salts

Sodium dihydrogen phosphate and disodium dihydrogen pyrophosphate are acid salts that have been used in effervescent formulation. They are water soluble, produce acid solution, and react quickly with alkaline sources. They are commercially available in either granular or powder form.

Other Less Frequent Sources of Acid

- Fumaric and nicotinic acids, which are not hygroscopic, but have low water solubility.
- Malic acid has recently been introduced in effervescent formulations because of its smooth and light taste. It is highly hygroscopic and soluble but has less acid strength than the tartaric or citric acids.
- Acetylsalicylic acid, though active ingredient, which is very commonly administered in effervescent preparations, cannot be used as acid source for its low water solubility.
- Adipic acid deserves to be mentioned even if it is useless as acid source because of its low water solubility. It has given good results as lubricant for effervescent calcium carbonate tablets (11).

Sources of Carbon Dioxide

Solid carbonates salts are the most popular source for effervescents; bicarbonate forms are more reactive than carbonates.

Sodium Bicarbonate

It is the major source of carbon dioxide in effervescent forms, able to provide a yield of 52% of carbon dioxide. It is commercially available in five grades according to particle size, from free-flowing uniform granule to fine powder, which are odorless and slightly alkaline in taste. When heated, the bicarbonate is converted into anhydrous sodium carbonate. This reaction is time and temperature dependent. Ninety percent of the conversion is achieved within 75 minutes at 93°C, but starts at 50°C, which must be considered as a critical temperature in processing (7).

Being a nonelastic material it has a very low compressibility but this issue has been improved since it has been produced by spray-drying technique. Direct compressible grades are now available but contain some additives such as polyvinylpirrolidone (PVP) or silicone oil.

Sodium Carbonate

It is commercially available in three different forms, all very soluble in water: anhydrous, monohydrate, and decahydrate (7). It is more resistant to the effervescent reaction, and in some formulations can be used as stabilizing agent in an amount not exceeding 10% of the batch size. It is used as stabilizing agent in certain effervescent formulas because it absorbs moisture preferentially, preventing the effervescent reaction to start. Of course the anhydrous form is preferred for this purpose. Recently, a particular grade of sodium bicarbonate has been produced in round-shaped particles, coated with a carbonate layer to increase bicarbonate stability (12).

Potassium Bicarbonate and Potassium Carbonate

They substitute the sodium salts when sodium ion is not required (13). They are lesser soluble than the corresponding sodium salts and are more expensive.

Calcium Carbonate

Precipitated calcium carbonate occurs as fine, white odorless, and tasteless powder or crystals. Its water solubility is very poor, and is not soluble in ethanol or isopropanol. It is a high-density powder, not suitable for compression. It is normally used as drug in effervescent tablets for patients who suffer from calcium shortage.

It can also be used as alkaline source because it provides stability to the effervescent system (14).

Sodium Glycine Carbonate
Sodium glycine carbonate provides a light effervescence reaction, but rapid disintegration of the tablets, so it has been applied in the preparation of fast dissolving sublingual tablets. It is much more compressible than the other alkaline compounds, and it has been found suitable for direct compression (15).

Binders
The use of a binder in effervescent formulations is limited by the fact that any binder, even if water soluble, will retard the tablet disintegration. Therefore, the amount of binder in a given formula will be a compromise between desired granule strength and desired disintegration time.

As will be described in section "Wet Granulation," water itself is an effective binder for effervescent granules when granulated with all the components together. A small amount of water, finely distributed on the powder bed, acts as a binder by partially dissolving the raw materials and preparing them for agglomeration. Other solvents, for example, ethanol and isopropanol, can be use as granulating liquid to dissolve dry binders.

Binders for dry granulation, such as lactose, mannitol, dextrose, are almost inappropriate, because they would be effective only in larger amount than that allowed by an effervescent formulations. The binder choice in wet granulation is also limited by the method of production and consequently by the amount of granulating liquid.

In case of granulation of both the alkaline and acidic components together with water, it would not make sense to put a binder in the formulation because the small amount of water will never be able to dissolve the binder.

The most popular binder for effervescent tablets is PVP. Types K25 and K30 are preferred for their water solubility and dissolution rate, which are an important issue for the final purpose of effervescent tablets. PVP is effective at low percentage in the formula, starting from 2% and above. It is feasible either for dry or wet granulation. It is soluble in water, alcohols, and hydroalcoholic liquids (7).

Lubricants
Because tableting is a critical step of effervescent production, selecting the lubricant is one of the most important issues. Lubrication of effervescent mixture is quite problematic because of the chemical-physical nature of the lubricants. Most of the lubricants, because of their low water solubility, inhibit the tablet disintegration, which, as already said, must be very rapid in case of effervescent tablets. The effervescent tablets—mainly for marketing reasons—are often required to provide a clear transparent solution, that is, without any insoluble "film" formation on the water surface or any residue left. In selecting a lubricant, proper attention must be given to its solubility in water, along with its compatibility with the active ingredient.

Many different lubricants have been tested for a long time to establish the most appropriate for effervescent tablets (16), including the opportunity to carry out external lubrication of the granules directly in the dies of the tablet press.

Lubricant substances, which are reported in literature as suitable for effervescent manufacturing because they are water soluble, are sodium benzoate, sodium acetate, L-leucine, and carbowax 4000. A very recent application is a combination of calcium and potassium sorbates and micronized polyethylene glycol (PEG) with calcium ascorbate or trisodium citrate (17). Combination of spray dried L-leucine and PEG 6000 has been reported as successful one in literature (18). Other lesser soluble lubricants have been used in formulating effervescent tablets, however, a balance should be found between compression efficiency and water solubility. Magnesium stearate is, however, employed but the most suitable, commercially available type is its combination with sodium lauryl sulfate, a surface-active agent that helps its dispersion (19).

Additives: Sweeteners, Coloring Agents, and Flavors
Coloring agents can include all the dyes soluble and suitable for food such as the FD & C ones and all the natural coloring substances in amounts variable in the range 0.1% to 3.5% of the total weight of the formulation.

Flavors can be selected from synthetic flavors or natural extracts. Lemon, orange, and other fruit essences are particularly suitable to obtain the organoleptic requirement in an amount variable in a range of 0.5% to 3.0% of the total weight of the formulation.

MANUFACTURING OF EFFERVESCENT FORMS

Manufacturing conditions are crucially important even with regard to stability of the products once they have been packed. Almost all the raw materials used for effervescents manufacturing are hygroscopic, so moisture absorption from the air must be prevented to avoid the effervescent reaction to start prior to use the tablets.

The whole production process, as shown in Figure 1 (dosing of the ingredients, mixing or granulating, lubricating, tableting, and packaging), can be carried out in a completely closed and integrated handling system, consisting of intermediate bulk containers (IBCs), tumblers for IBCs, docking and dosing stations.

In this case, only the packaging area will be ventilated with low moisture content of air. Otherwise, traditional open handling systems can be employed but the whole facility has to be conditioned with air at minimum level of moisture content (20). In fact, the suggested conditions throughout the plant are: relative humidity (RH) below 20% and uniform temperature at 21°C, though it is known that 25% of RH at controlled room temperature (25° C) is, however, enough to avoid instability caused by atmospheric moisture (21).

Manufacturing effervescent drugs on a large scale is usually done in a semicontinuous procedure, by paying attention to synchronize all the process steps, to achieve the largest production throughput. A continuous process flow, with continuous feeding of raw materials and collection of granules, can be performed by extrusion of the wet mass and drying in a continuous fluid-bed dryer. Granulation of effervescent mixtures must be, most of the times, executed in batches and is definitely the most critical step of this particular kind of pharmaceutical manufacturing, as it hardly influences the characteristics of the final forms, granules, or tablets, and consequently the following steps of production. Lubrication of the granulation, compression of tablets, and packaging of effervescent tablets should be carefully planned to produce suitable effervescent product.

The critical issues discussed earlier, for the compression of effervescent granules, are related to the low compressibility of the majority of the raw materials, large dimensions of the tablets, poor content of binder in the formulation, and difficulties to lubricate the mixture. For all these reasons, the tableting phase has to be carried out carefully, and even the choice of the tablet press is of great importance. To overcome lubrication difficulties, some suppliers of tablet press have developed equipments that are capable of carrying out an external lubrication of the granules. Antiadherent materials are sprayed directly into the dies of the tablet press, during the pause phase of compression, so as to prevent sticking of granules on dies and punches. External lubrication is not as good a method as using lubricant substances to disperse in the granules. It is not considered the best solution for lubrication because it is considered less compliant to the standard GMP rules. In addition, the assembling and disassembling of the tablet press is more complex. An alternative to achieve better tablets, facilitating the compression, is to tablet the granules while they are still slightly wet, or not dried yet as we are still considering very low moisture content, that is less than 1%. Tablets are then dried and brought to stability by a step in static ventilated oven.

Packaging for both, granules and tablets, must be operated, as already mentioned, in a low humidity environment. The critical aspects about packaging of effervescent drugs are obviously related to stability of the tablets and granules, and the main objective is to protect them, as much as possible, not only during packaging operations, but also once they are packed, so as to preserve them a reasonable shelf-life. The oldest packaging for effervescent preparations consisted of wrapping the acid and alkaline components separately, to avoid the premature effervescent reaction until use. All the effervescent drugs can be packed in individual dose units, in airtight containers made of protective aluminum foil or plastic laminates. Tablets can be packed also by stacking them one by one in plastic or metal tubes, which have almost the same diameter of the tablets so as to minimize the air, which remains in contact with the tablets. The tubes must be resealed every time, after taking out each tablet.

Certain tablets are also wrapped in an aluminum foil before packaging in the tube, and this seems to be the best solution for long-term stability. Patented types of tubes containing silica gel at the internal side of the cap are the most recent invention (22).

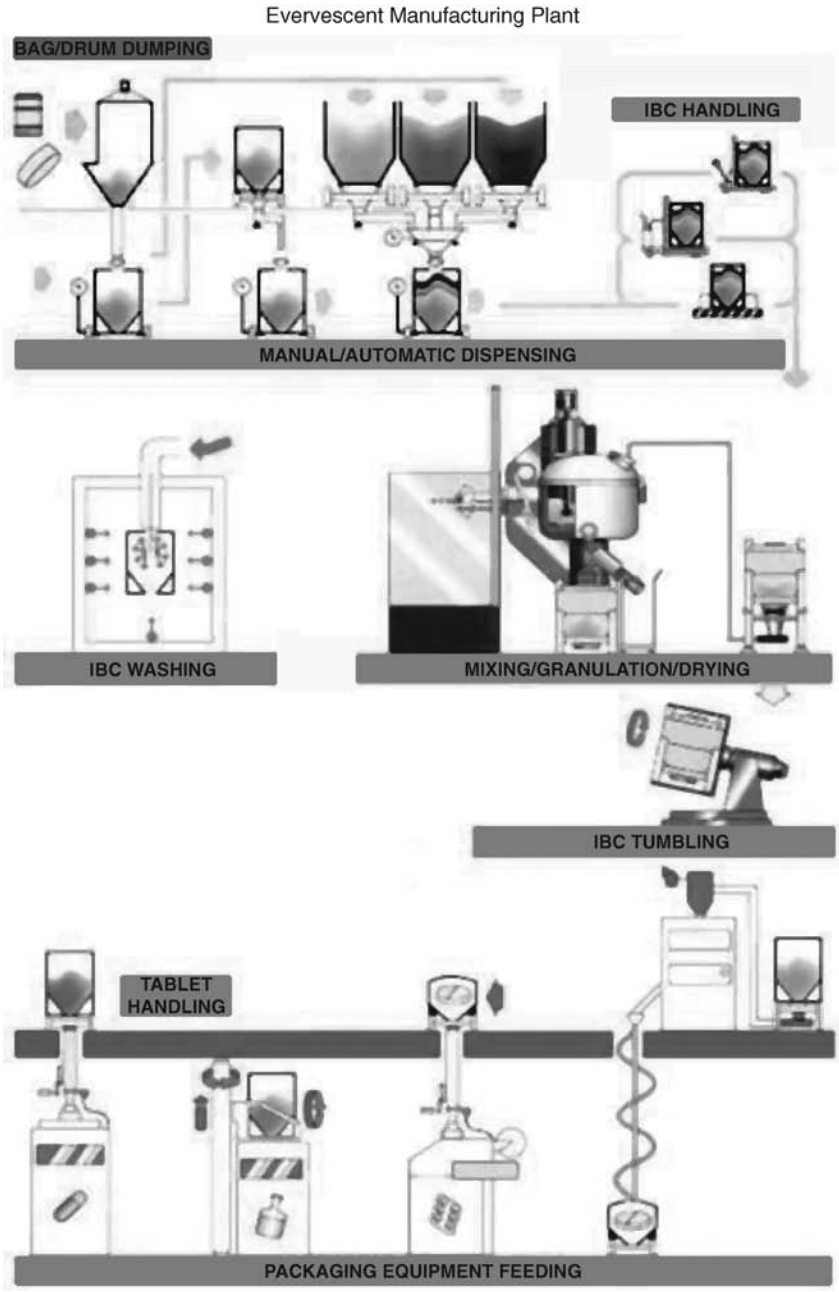


Figure 1 Integrated production plant.

For tablets that are packed in strips, it is essential that the packaging machine must have a fine control on the temperature of the welding unit, so as to obtain an accurate sealing of the strips and avoid overheating phenomenon that could provoke release of residual water from the tablets (21).

Granulation Methods

Two main granulation methods have been known for a long time. The 1911 edition of *British Pharmacopoeia* reported a detailed description of the manufacturing procedure (23).

> "Effervescent granules are made by mixing citric and tartaric acids with the medicament, and the sodium bicarbonate with the sugar when present; and then thoroughly mixing

the one with the other, and granulating the resulting mixture by stirring in a pan heated to between 93° and 104°, passing through sieves of a suitable size, and drying at temperature not exceeding 54°. This method for preparing the granules yields satisfactory results, but the following alternative method has also been suggested: mix the sodium bicarbonate, the sugar, and the medicament, pass the mixture through a number 20 to number 30 stainless steel sieve, subject the mixed acids to the same process, and thoroughly mix the two sifted powders. Place the mixed powders in layers on suitable dish, pan or glass tray, heated to 75° to 85°, if required but not exceeding the higher temperature. When the mass, after being suitably kneaded and compressed, has assumed a uniform plastic condition, suitable for granulation, rub it to a number 5 to number 10 stainless steel sieve, according to the size of granules desired, and dry the granules at a temperature not exceeding 50°."

Only a few aspects have substantially changed in the modern methods.
Two main methods can be executed with various type of granulation equipment:

a. Single-step method: All the components of an effervescent formula are granulated together, handled with care, running the process in a contained manner to maintain the stability of the mixture until the step is completed. This single-step method, normally carried out using dry granulation, hot melt granulation, and certain processes, which are carried out via wet granulation.
b. Multi-step method: The alkaline and the acid components are granulated separately, then mixed together, just before the tableting or packaging step. Usually, these are also typical applications of wet granulation technologies.

Dry Granulation

Dry granulation by roller compactor is definitely the most appropriate method for its simplicity, low costs, and higher product throughput. Number of operations and required space are less and consequently air ventilation is reduced. On the other hand, not all the excipient grades are suitable for such a technology. More sophisticated and thus expensive grades prepared by raw material bulk suppliers are required.

An alternate process to dry granulation is direct compression of the blend of all the raw materials, in an attempt to avoid operating and stability problems. It would be the ideal process for effervescent tablet manufacturing, but its application is limited to a few cases, for example, when the active ingredient cannot be granulated (for instance, when it is already included in a complex like with a cyclodextrine), or contains some water of crystallization.

Wet Granulation

Despite some disadvantages, wet granulation is still the most preferred method for effervescent granulation.

As required for conventional tablets, this method assures homogeneous granules, suitable for compression, able to provide uniform tablets either in terms of weight or active ingredient content.

Since, for this technique it is necessary to use a granulating liquid that might interact with the powders initiating the effervescent reaction, it is essential to handle the process with great care.

A wet granulation process in two separate steps is what is mostly recommended and suitable for conventional equipment like high-shear granulator-dryer and fluid-bed processor. Acidic and alkaline ingredients are granulated separately. The two granules are then mixed together, just before adding the lubricant for tableting. Water, alcohols, or hydroalcoholic solutions can be used indifferently as binding liquid also, because this process is a standard wet granulation process. It is also quite usual to granulate only one of the effervescent sources and add the other one in powder during the final blending. All these possibilities are illustrated in the schematic of Figure 2.

In certain cases, only the acid components of the formulation are granulated and then mixed with the sodium bicarbonate, preferably if it is fine granular grade. Other additives, such as flavors and lubricants, can be then added and mixed later on. This approach increases productivity and reduces costs since one granulation step has been eliminated.

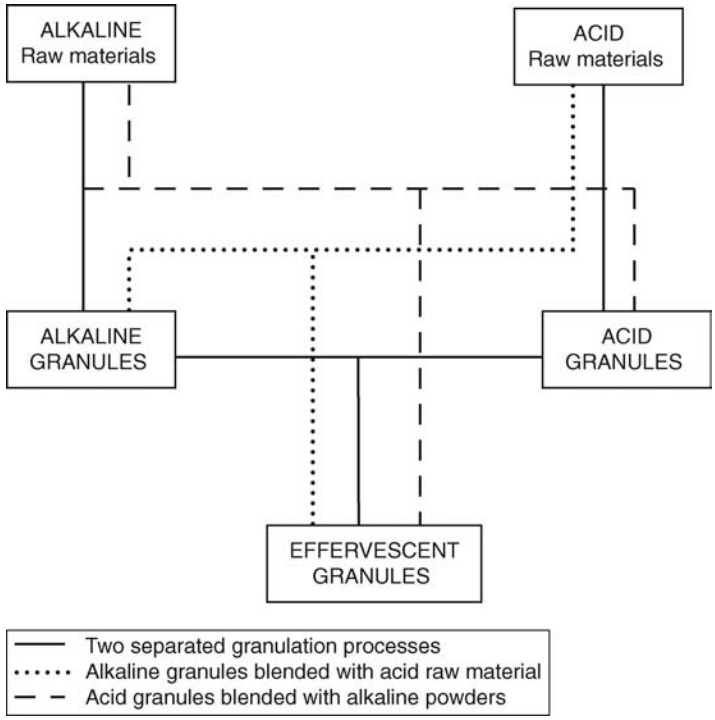


Figure 2 Alternative granulation processes.

The peculiar process that distinguishes effervescent granulation consists a single-step granulation of all the components of the formulation, that can be performed either with nonreactive or reactive liquids with reference to the effervescence reaction.

Single-Step Granulation

Single-step granulation process provides dry effervescent granules directly by granulating the acid and the alkaline materials together. It is possible to use only water as the granulating liquid, thus controlling the effervescent reaction to granulate, or using a nonreactive liquid, like absolute ethanol or isopropanol, but in this case, it is necessary to use a binder to get the agglomeration of the raw materials particles.

Process with water. A very small amount of water, less than 1% of the batch size, can be used to initiate the effervescent reaction. Some carbon dioxide is released, and some water too, which acts as the binding liquid as well. It takes a few minutes (from 5 to10 minutes) to obtain wet granules. The effervescent reaction rate rapidly increases and becomes difficult to stop; it must, however, be terminated very quickly. An immediate start of the drying of the granules will control and stop the effervescent reaction. Single-step technology, such as fluid-bed granulator and high-shear granulator-dryer, are suitable for this purpose.

In high-shear granulator-dryer technology, it is possible to suddenly switch to drying phase by creating vacuum inside the bowl, just after the granulation phase when wet granules are well massed. Vacuum is created in a few seconds, which immediately provokes the decrease of the water boiling point down to about 20°C. At the same time, the bowl is heated up to provide more energy for water evaporation. In a few seconds, the water released on the granules surface will be removed and the effervescent reaction will stop.

The application of microwaves, combined with vacuum inside the bowl of the high-shear granulator (24), can also be used to stop the effervescent reaction and dry the effervescent granules (25).

Thus, drying effervescent granules will, however, be shorter than drying conventional granules granulated with water, because of the very small amount of water involved in the

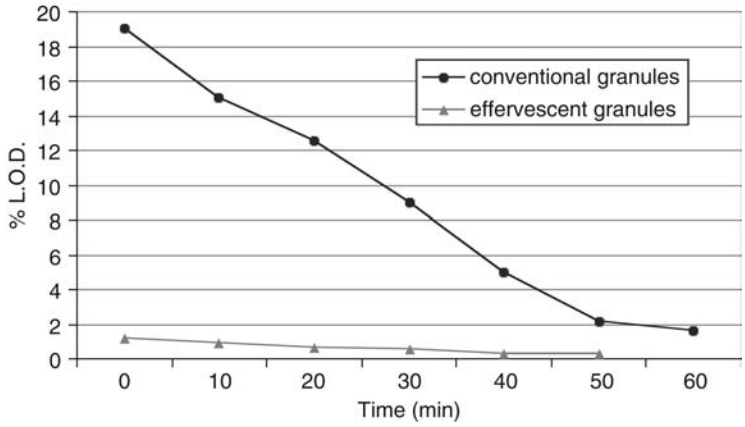


Figure 3 Drying rate of effervescent granules, compared with conventional granules.

process. However, drying still remains a critical step since it is very hard to remove even the smallest quantity of water from hydrophilic or hygroscopic materials. Typical drying time is about 50 minutes for 20 kg batch of effervescent granulation under vacuum. See Figure 3 for comparison of drying of conventional and effervescent granules by vacuum technology.

Drying rate for effervescent granules is lower because moisture content to remove is in a range below 2% of the batch size. Consequently, the drying time, passing from pilot scale to industrial scale, does not increase as much as for conventional granules (Fig. 4).

The great advantage of this method for effervescent preparation consists of the opportunity to install equipment with no explosion-proof requirements.

An example of effervescent aspirin produced in 600-L high-shear granulator-dryer equipped with vacuum and tilting bowl (Fig. 5) (12).

Formulation consists of:

Anhydrous citric acid	116.6 kg
Sodium bicarbonate	154.2 kg
Sodium carbonate	39.2 kg
Acetylsalicylic acid	50 kg

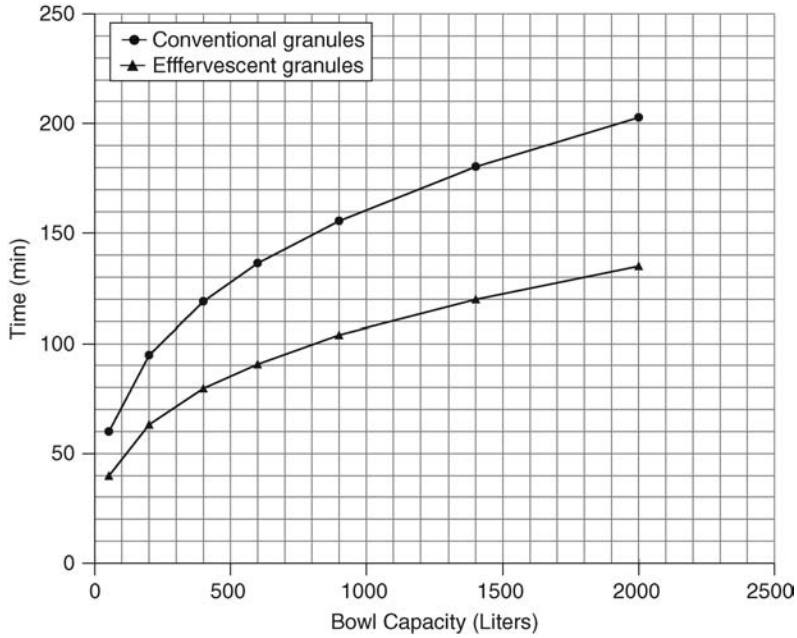


Figure 4 Drying time scale up for high-shear granulator-dryer.

Figure 5 "Rotocube" high-shear granulator-dryer equipped with vacuum and tilting bowl.

The effervescent system is granulated for first, with very small amounts of water (2–4 mL/kg), sprayed in very fine droplets. The acetylsalicylic acid is added later, in the final blending, after granulation is completed.

The results of three batches are reported in Table 1.

The lower yield of the third batch is due to product sticking onto the bowl walls that could not be discharged. The reason why it happened is related to the set parameters during drying phase: in the batch number 3, drying was performed keeping the bowl static, instead of tilting it as in the other batches. The batch size in actual production was then increased to 644 kg in 1400-L equipment.

All the components of an effervescent mixture can be granulated together in a single-step process in a conventional fluid-bed granulator-dryer. Granulation occurs when water is sprayed on the fluidized bed, initiating the effervescent reaction. The reaction is stopped when water is not sprayed anymore and drying phase is carried out with warm dry air. It is quite understandable that this method is difficult to control and reproduce (26). A subsequent patent application (27) describes an improvement of the method reproducibility, which can be achieved by controlling the air humidity (it has to be less than 1 g/m^3), using a hydroalcoholic solution instead of water. Further better results in controlling the effervescent reaction are achieved if spraying and drying phase are combined together.

It is, however, very difficult to reproduce such a process; therefore, an alternative procedure to manufacture effervescent granules has been invented using a rotor fluid-bed spray granulator (28).

Warm air, which is the only device for drying in fluid-bed technology, is not able to stop the reaction all at once as it happens by applying vacuum inside the processing bowl. Therefore, the only way to proceed was to minimize, in some way, the contact between the two

Table 1 Granules Produced with Single-Step Technology in a High-Shear Granulator-Dryer

Batch code	Batch size (kg)	Yield kg	Yield %	Results of samples: Sampling time (min)	Moisture content (≤0.1%)	Acid neutralizing power (≥185 mL 0.1 N acid/tablet)	pH (6.0–6.4)
Batch 1 granulated with 720 mL of water (2 mL/kg)	360	352.2	97.80	30	0.048%		
				60	<0.01%		
				90	<0.01%	244.6	6.1
Batch 2 granulated with 1440 mL of water (4 mL/kg)	360	336.4	93.44	30	<0.01%		
				60	<0.015%		
				After discharge	<0.01%	244.6	6.4
Batch 3 granulated with 1440 mL of water (4 mL/kg). Note: no tilting of the bowl while drying	360	323.5	89.86	60	0.075%	229.8	
				After discharge	<0.01%	245.5	6.25

components of the effervescent system. An intelligent, brilliant hypothesis by Gauthier and Aiache (28) is to alternate the granulation of the acid materials with that one of alkaline materials while still using a single equipment such as rotary fluid-bed system. In literature, a vitamin C formulation is reported to explain this technique but other active ingredients can be used (29).

The process consists of two or three continuous steps to produce effervescent spheres by layering the acid components over alkaline spheres or vice versa. Binding liquid is, however, a hydroalcoholic solution where polyvinylpyrrolidone, the binder must be previously dissolved.

- The first step is the granulation of alkaline components in the rotary fluid bed. In the second step, the granulating solution is sprayed in combination with the acidic powders, which deposit on the alkaline spheres creating an external acid layer separated by a neutral layer of the binder. As agglomeration is completed, drying phase with hot air starts without any interruptions (28).

Process with alcohol or hydroalcoholic solution. As it has been reported in the previous example, it is sometimes preferable to granulate with a hydroalcoholic solution to initiate a lighter effervescence so as to keep the reaction under a better control during the process. Use of alcohols is indispensable in case a binder, like polyvinylpyrrolidone is included in the formulation. In fact, the required water amount to dissolve polyvinylpyrrolidone, so as to obtain the binding action, would be too much, and it would not be possible to keep the effervescent reaction under control.

As always suggested for a conventional granulation process that requires using inflammable liquid, it is convenient to install fully explosion-proof equipment with an accessory solvents recovery utility that will limit the emission of vapors in atmosphere. Solvents recovery will be more advantageous while drying under vacuum than with a fluid bed.

Certain high-shear granulator-dryers are equipped to achieve 99% of solvent recovery by installing a tank to collect the condensate, and by bringing down the possible residual exhaust with a shower of water.

Hot Melt Granulation

Hot melt is an alternative technology to wet granulation (which is discussed in detail in another chapter of this book). Agglomeration of the particles of a powder mixer can be achieved by melting hydrated citric acid, so as to release the hydration water, which acts as the granulating liquid. Once granules are formed, it is necessary to cool them to achieve the proper hardness and mechanical stability. There are two different techniques:

- Surface hot melt granulation (SHMG) consists mixing all the raw materials together in a blender, and then drying the mix in a tray oven at 90°C. Water is then released from citric acid and other ingredients to form granules (30). Unfortunately batch reproducibility of this method is very low.
- Hot melt granulation is normally carried out in high-shear granulator-dryer with the capability to heat up the bowl. In certain cases, the released hydration water of citric acid, starts the effervescent reaction to produce additional water, which acts as the binding liquid. However, this process, for obvious reasons, is difficult to control.

The same process has been applied to fluid-bed spray granulator where low melting point polymers, like PEG or polyoxyethylene glycols can also be used as binders (31).

Hot Melt Extrusion

Hot melt extrusion is a recent patented method to produce effervescent, specially dedicated to produce granules having a controllable rate of effervescence (32). The formulations for this technology must contain a hot melt extrudable binder. Preferred binders are the PEG with molecular weight in the range 1000 to 8000 d, but some other polymers have also been investigated. Binder percentage varies according to the formulation in a range of 20% to 40% of the total weight. There are two main extrusion techniques to carry out in extruders that must be equipped with a solid conveying zone, multiple separate temperature controllable heating zones, and an extrusion die:

a. A blend of all the ingredients, including the active ingredient of the formulation, is hot melt extruded at high temperature, to melt or soften the binder. The extrudate is then ground or chopped to obtain effervescent granules.
b. The acidic agent and the hot melt binder are formulated in the right proportions to obtain a eutectic mixture that has decreased the melting point temperature. This binary mixture is separately melted; the alkaline agent is added as powder in the next step. The melted mixture is then extruded, chopped, or ground as in the previous method.

To control effervescence rate of the final dosage form, it is possible to adjust some parameters like the temperature and rate of extrusion. The temperature range to select can be critical because degradation of the active may occur as well as decomposition of the effervescent components. This range is usually from about 50°C to about 120°C.

The rate of extrusion is related to the time of materials exposure to high temperature, which is usually less than five minutes.

The hot melt extrusion technology, in some cases, can be run as a continuous process, having a higher throughput than batch hot melt granulation process per batch.

All the previous sections provided an overview of all the possible technologies to manufacture effervescent granules but how to choose the most appropriate technique for a certain formulation. An interesting study to figure out the best production method for effervescent tablets was presented by Laugier and Rona (Table 2) (33).

Three technologies were evaluated: dry granulation, hot melt granulation, and wet granulation. The choice of the process technology was strictly related to the physical properties of the raw materials that are particle size, density, flowability, and moisture content. Moisture content is definitely the most significant parameter since the powders mixture has less than 0.2% to 0.3% of moisture content. It would be stable but difficult to tablet and at that point a wet granulation process is required.

Table 2 Manufacturing Process for Effervescent Tablets

	Dry granulation		Granulation by heating		Wet granulation	
Process	Slugging or laminating	Direct compression	Surface hot melt granulation	Hot melt granulation	Granulation + drying (two steps)	Granulation + drying (one step)
Number of steps	6	3	6	5	6	4
Estimated time (hr)	23	10	22	14	15	12
Advantages	Fast process No product transfers No granulation	No product transfers No granulation Short time	No granulating liquid Totally closed	No product transfers No granulating liquid	Batch reproducibility	Batch reproducibility
Disadvantages	Raw materials at low residual moisture	Raw materials for direct compression at low residual moisture (more expensive)	Loss of effervescence	Difficult to carry out	Difficult to clean	Difficult to clean
	Dusty process High manpower required		Long time Dusty process High manpower required	Difficult to clean		
Note		Obsolete	Rarely applied			

The use of high-shear granulator-dryer has been found as the more economic and flexible production method also by others (34). This technology allows using a wider range of excipients grades, avoiding problems related to particle size or moisture content of the raw materials. Even if the granules produced by this technology appear finer, their flow properties are good despite the large fraction of fines. Tableting properties are always in line within the specifications.

REFERENCES

1. Homan P. Pharm J; 267(7179):911–936.Available at: http://www.pharmj.com.
2. Notiziario Chimico Farmaceutico (NCF) December 1984, 19–22; May 1985, 21–23.
3. Moller PL, Norholt SE, Ganry HE, et al., Time to onset of analgesia and analgesic efficacy of effervescent acetaminophen 1000 mg compared to tablet acetaminophen 1000 mg in postoperative dental pain: a single-dose, double-blind, randomized, placebo-controlled study. J Clin Pharmacol 2000; 40(4):370–378.
4. Yanze MF, Duru C, Jacob M, et al. Rapid therapeutic response onset of a new pharmaceutical form of chloroquine phosphate 300mg: effervescent tablets. Trop Med Int Health 2001; 6(3):196.
5. U.S. Patent 6,200,604, 1999.
6. Rapp M. PCT Int Appl 2000.
7. U.S. Patent 6,077,536, 1998.
8. Handbook of Pharmaceutical Excipients, The American Pharmaceutical Association and The Royal Pharmaceutical Society of Great Britain. Washington and London, 1986:6–8, 78–80, 263–265, 234–239.
9. Schmidt PC, Brögmann B. Dtsch Apoth-Ztg 1987; 127:991–997.
10. Repta AJ, Higuchi T. Synthesis, isolation, and some chemistry of citric acid anhydride. J Pharm Sci 1969; 58:1110–1113.
11. IMA Zanchetta R&D Laboratory Archive, IMA SPA ACTIVE Division, Bolgna, Italy.
12. SPI Pharma Group Fall, 2001.
13. Duvall R N., Gold G. Miles Inc., 1990, 6.
14. U.S. Patent 6,242,002, 1999.
15. U.S. Patent 6,284,272, 1999.
16. Strickland WA Jr., Higuchi T, Busse L. J Am Pharm Assoc 1956; 45:51–55.
17. Daher LJ. Bayer Corporation, USA.U.S. Patent, 1999:6.
18. Rotthaeuser B, Kraus G, Schmidt PC. Pharmazeutisches Inst., Eberhard-Karls-Univ., Tuebingen, Germany. Pharm Ind 1998; 60(6).
19. Rudnic EM, Schwatrtz JD. Oral Solid Dosage Forms. 861.
20. Armandou J-P, Mattha AG. Establishment of a geographical and chronological map for relative humidity (R.H.) in an effervescent tablets manufacturing and storage building. Pharm Acta Helv 1982; 57:287–289.
21. Mohrle R. Effervescent tablets. In: Lieberman HA, Lachman L, eds. Pharmaceutical Solid Dosage Forms. Vol 1. New York: Marcel Dekker, Inc., 1980:225–258.
22. http://www.desiccantcity.com/CASE_HISTORIES/History11.htm.
23. The British Pharmaceutical Codex. Published by direction of the Council of the Pharmaceutical Society of Great Britain, 1911. Available at: http://www.scocca.org/herbmed/eclectic/bpc1911/granulae.html.
24. Collette News, Vol 2, Issue 1, May 2001, GEA Powder Technology Division.
25. Aiache JM, Cardot JM. Utilisation des micro-ondes dans la fabrication des formes pharmacutiques. Conference at National Institute for Applied Sciences, Roeuen, France, 1999.
26. J Pharm Sci 1964; 53:1524–1525.
27. U.S. Patent EP 673,644, 2001.
28. Gauthier P, Aiache J-M. Biopharmaceutics department, faculty of pharmacy, clermont-ferrand. Fr. Pharm Technol Eur 2001; 13(10):32, 34, 36–37.
29. U.S. patent 6,210,711, 1999.
30. Yanze FM, Duru C, Jacob M. Laboratoire de pharmacie galenique, pharmacotechnie et de biopharmacie, universite Montpellier I, UFR de sciences pharmaceutiques, Montpellier, Fr. Die pharmazie, December, 2000.
31. Yanze FM, Duru C, Jacob M. Laboratoire de pharmacie galenique, pharmacotechnie et de biopharmacie, universite Montpellier I, UFR de sciences pharmaceutiques, Montpellier, Fr. Drug Dev Ind Pharm 2000; 26(11):1167–1176.
32. U.S. Patent 6,488,961, 1999.
33. Laugier M, Rona R. Pharmaceutical manufacturing and Packing Sourcer (PMPS) 2002:26–28.
34. Pearlswig DM. Simulation modeling applied to the single pot processing of effervescent tablets. Master's Thesis, North Caroline State University, Raleigh, North Carolina.

15 Granulation Approaches in Biotech Industry

Tuo Jin, Weien Yuan, and Hui Li
School of Pharmacy, Shanghai Jiaotong University, Shanghai, P.R. China

INTRODUCTION

Because of the rapid advance in molecular biology, immunology, and microbiology over the past decades, biological therapeutics has become a major category of drugs in clinical applications to date. While biological drugs possess great advantages in terms of therapeutic potency and target specificity, their structural instability has been a long-standing issue in formulating these macromolecules into convenient dosage forms. To avoid denaturing in formulation processes and shelf life, preconverting biotech drugs into solid particles is widely accepted as a useful unit operation. However, the particle-forming processes themselves must not be hazardous to the susceptible structures of biologicals.

The objective to formulate biological agents into solid particles without compromising denaturing has attracted considerable research efforts and alternative approaches in recent years, such as supercritical fluid technology, microcrystallization technology, and protein-protected microencapsulation. To summarize these microparticulate strategies for formulating "biological products" (defined as proteins, peptides, antibodies, and nucleic acids) in this industrial reader-targeted handbook, we would rather extend the meaning of "granulation" from the conventional understanding to an "alternative" extent in this chapter.

Since formulating biological agents to particulate systems will mostly encounter the difficulties associated with these macromolecules' delicate nature and structural susceptibility, a mechanistic discussion regarding the instability issue of biological products will be a great help to discuss granulation approaches in this chapter. Therefore, we will start our story with the physiochemical basis of biomolecules' instability.

THE CHALLENGES IN GRANULATING BIOLOGICAL PRODUCTS

Instability due to Temperature and Moisture

Temperature is a typical formulation parameter used for preparing pharmaceutical dosage forms, and concurrently a susceptible factor to cause biological macromolecules to denature. The biological functions of macromolecules, such as proteins and subunit vaccines, invariably rely on their native conformations, which are maintained by temperature-sensitive hydrogen bonds or other noncovalent interactions between functional groups of the macromolecule. In the process of spray-drying, for example, application of a sufficiently hot gas stream is indispensable to evaporate water of the drug droplets in a short time (few seconds in length). When a protein is exposed to drastically increased temperature over a critical level known as the melting temperature (T_m) or the denaturation temperature (T_d), it undergoes a sharp transition and denatures. For most of proteins, such temperature-induced structural transition is irreversible.

A strategy to avoid temperature-induced denaturing is shortening the time for proteins to be exposed to high temperature during the drying. Temperature exposure is defined by some researchers arbitrarily as the product of temperature and time (1). It has been reported, for example, that exposing tissue plasminogen activator (t-PA) solution at 50°C for 40 sec or at 80°C for 20 sec caused negligible degradation. However, increasing the protein exposure at 80°C for 40 sec resulted in 16% (w/w) degradation (1).

As an associated factor, water content has a great impact on thermal denaturation of proteins being formulated to or stored as powder form. When water content of a protein-loaded powder is increased, the value of T_d and enthalpy of denaturation (ΔH_{hyd}) decrease drastically because of increased protein mobility. For example, human growth hormone (hGH) and bovine growth hormone (bGH) formulated to powder form are stable at 100°C when the moisture is below 1% (w/w), but turn to be highly susceptible under higher moisture (2,3).

It is of interesting to note that dispersing proteins in a hydrophilic glassy matrix may significantly enhance proteins' resistance to temperature and moisture. Breen et al. reported that as long as the glassy state is maintained, proteins dispersed in solid polysaccharide matrix may even gain stability upon absorption of moisture (4).

Instability due to Freeze-Drying Process

Freeze-drying, another well-used method to form powdered pharmaceuticals, consists two unit processes: freezing and drying; both can be hazardous to biological macromolecules. Freezing of an aqueous solution associates with ice formation, which generates shear stress to biomolecules dissolved in the solution from two aspects. First, the sharp ice crystals formed during freezing may pierce or squeeze biological agents; and then, the scattered ice particles formed from a continuous aqueous solution create a large specific surface area (SSA) to adsorb biomolecules dehydrated and phase-separated during freezing (5–8). The two destabilizing mechanisms seem to be complimentary to each other in terms of denaturing proteins. For example, slow freezing increased protein damage prone to phase separation of the original solution (9), whereas high freezing rate is achieved at very low temperatures, generating smaller ice particles and thus enlarging SSA (6). Adsorption of proteins to ice surfaces easily leads to partial unfolding (10). In addition, fast cooling process itself was reported to be damaging to some proteins, such as phosphofructokinase (11), bovine immunoglobulin G (12), catalase (13), and β-galactosidase (13,14).

Dehydration is another protein-denaturing factor involved in a freeze-drying process. Upon dehydration, the water molecules associated with proteins may take off so that the water-soluble protein (most of therapeutic proteins are water soluble) may be exposed to a hydrophobic environment (15).

On the basis of the mechanistic discussion above, a freeze-drying protector for proteins should be able to create hydrophilic environment surrounding the biomolecules thermodynamically upon freezing and dehydration. It is even better that the hydrophilic environment forms a glassy matrix by dehydration to immobilize the macromolecules and prevent them from conformation changes or approaching each other. While application of surfactants and/or raising the concentration of the proteins to be lyophilized (as self-surfactant) was reported to be an effective approach to create hydrophilic microenvironment during freeze-drying, they lack the immobilization effect and may even induce protein aggregation (15).

Hydrophilic-Hydrophobic Interfacial Tension

Most of particle-forming processes rely on hydrophilic-hydrophobic interfacial tension. However, macromolecules possessing higher structures, such as proteins, are highly susceptible to water-oil or water-air interfacial tension. Water-soluble proteins are, in general, folded in such a way that their hydrophobic amino acids are buried inside to form a hydrophobic core and their hydrophilic peptide chain forms the hydrophilic surface. Since protein-folding is maintained by noncovalent interactions between its amino acids, a molecular force in the same magnitude of hydrophobic interactions, proteins (in a mobile form) may easily refold when being exposed to water-oil or water-air interfaces to reduce the system free energy (16). Being driven by the thermodynamic potential for reducing surface tension, the hydrophobic peptide chains of a protein may move up from the core and insert into the hydrophobic phase of the system. In addition, the sticking out hydrophobic chains from adjacent protein molecules may associate with each other due to hydrophobic force and result in irreversible protein aggregation, a major problem for packing proteins of sufficient dosage in microparticles (17–19). Figure 1 describes the mechanisms of protein aggregation and adsorption schematically.

Immunogenicity due to Denatured Proteins

Aggregation and denaturation do not only compromise proteins' bioactivity, but also associate with severe consequences. Denatured or aggregated proteins are often antigenic and sometimes result in severe immunogenicity and serious clinical issues. Neutralizing antibodies resulted from denatured proteins cannot only attenuate the efficacy of the protein drug but also induce significant side effects if the antibodies cross-reacting with patients' endogenous proteins. For example, protein-induced neutralizing antibodies to erythropoietin (EPO) result

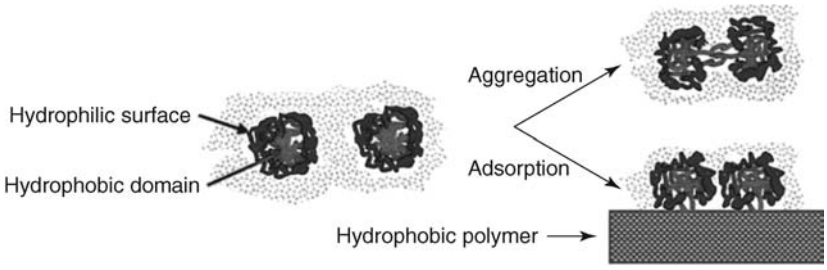


Figure 1 Protein aggregation and adsorption.

in red cell aplasia (20) and induced antifactor VIII (FVIII) antibodies worsen the pathology associated with hemophilia (21). While immunogenicity induced by denatured or aggregated proteins has been a long-standing concern, there has not yet been a regulatory guideline for acceptable levels of such immune responses. In the development of new protein delivery systems, avoiding any increased protein aggregation, as compared with already approved products, is crucial.

Encapsulation Efficiency

Encapsulation efficiency is an important parameter for assessing microencapsulation processes of biological therapeutics such as proteins. For microencapsulation using the so-called "double emulsion" method, proteins in solution state may easily leak to the outer aqueous continuous phase, resulting in unacceptable low encapsulation efficiency (22,23). Replacing the inner protein solution with solidified protein particles may substantially improve encapsulation efficiency, but protein particles still have the chance to contact with the outer aqueous continuous phase, leading to considerable loss of proteins. How to secure higher encapsulation efficiency is another challenge needing to be addressed.

Chemical Basis of Protein Denaturing

There are many mechanisms responsible for the instability of biological therapeutics upon formulating particulate systems from chemical, biological, and physical aspects. Among these mechanisms, irreversible conformation change, including aggregation, is the mechanism lacking in peptides and responsible for the deferred success to commercialize advanced particulate dosage forms of proteins than that of peptides and small molecules. Therefore, we will focus our instability discussion on the noncovalent chemistry.

The energy barrier for protein conformation alteration in solution is in the range of 5 to 20 kcal/mol (24,25), which is much lower than covalent changes (>100 kcal/mol) but similar to those of water-oil interfacial tension and hydrophobic interactions (24). To prevent proteins from denaturing (i.e., irreversible conformation changes), a particulate formulation process should ensure proteins to be maintained with reduced chemical potential (free energy) or to be blocked by an increased the energy barrier for conformation transfer (Fig. 2A, B). For example, loading water-soluble proteins in a solid hydrophilic matrix with abundant hydroxyls may significantly reduce the proteins' free energy and at the same time increase the kinetic energy barrier for their mobility (Fig. 2C). Carpenter et al. reported that while loading proteins in a polyethylene glycol (PEG) solution of low concentration may cause an increase in the protein's ΔG because of the unfavorable PEG environment, the PEG solution prevented proteins from aggregation by resulting in a shrinkage of protein molecules that raised the energy barrier for the protein molecules to extend their hydrophobic domains to each other (26). The same authors also found that increasing PEG concentration, on the contrary, resulted in protein precipitation out of the solution and facilitated protein aggregation. This phenomenon may be explained in that low-concentration PEG only slightly raised the protein's free energy (ΔG) but significantly prohibited the protein-protein contact, while for high PEG concentration, the ΔG increase was substantial for protein molecules to separate out and aggregate (Fig. 2D, E). Phase separation of a protein out of a cosolution with PEG as a function of temperature and PEG concentration was reported by Morita et al (27).

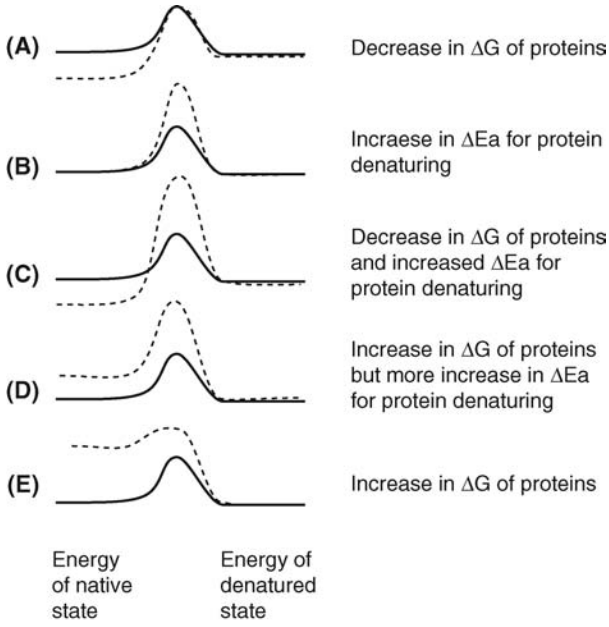


Figure 2 Energy barriers for protein denaturing.

APPROACHES TO PREPARE PARTICULATE FORMULATIONS

Milling

Milling methods include "jet milling" and "media milling." The former is based on direct mechanical impacting and shearing between devices and solid sample, while media milling is "indirect" in that the shear force is applied on the sample through a media fluid. As a conventional method to prepare pharmaceutical particles ranging from 1.00 to 20.00 μm in diameter (28), jet milling requires biological macromolecules such as proteins to be prepared into solid form prior to the milling process, while solidification processes themselves are full of incentives for the macromolecules to denature. It is also difficult to control the size, morphology, and surface properties of these particles as well as the cleaving edge of large chunk particles, that is, the macromolecules make damaged directly by the intensive shear force for milling solid (29,30).

Media milling is relative mild and has been reported for milling protein and peptide drugs to small particles (31). This method uses a fluid as a medium to apply shears to biological solids. Adjei et al. first used media milling (contains non-CFC paddle) to prepare peptide suspension for inhalation for the good heat transfer properties of a medium, which helps to prevent local heating of a solid sample (31). However, non-water (i.e., organic) solvents have to be used in the process to prevent protein dissolution, and proteins have to be presolidified too.

Spray-Drying

Spray-drying method has been intensively studied and widely used for granulating biological products. However, high shear stress at the spray nozzle, huge contact area of water-air interfaces, high temperature for getting rid of moisture in seconds, and difficulty to control particle diameters are all the factors limiting conventional spray-drying methods from its usage in biomacromolecule formulation (32–34).

To detour the difficulties associated with conventional spray-drying, a number of alternative spray-drying processes were proposed. Supercritical carbon dioxide (CO_2) assisted spray is one of the methods in which highly evaporable liquid CO_2 is used as the carrier instead of water to nebulize protein (35). However, water-soluble macromolecules have to be dissolved in water (of reduced amount) and emulsified in a supercritical CO_2 liquid prior to spraying, so that warm nitrogen stream is still needed to evaporate water (36–43).

To avoid high temperature, spray-drying processes associated with a cryo-step were proposed. In these processes, a pharmaceutical fluid loaded with biotherapeutics are sprayed directly into liquid nitrogen (or oxygen or argon), sprayed into air but immediately drop into liquid nitrogen, or sprayed into a precooled CO_2 fluid (44).

Khan et al. and Herberger et al. sprayed protein-loaded polylactide-co-glycolide (PLGA) solution (dissolved in dichloromethane) into liquid nitrogen to form sustained-release PLGA microspheres. In addition to the formulation complexity and irregular particle shape, the process involved adding protein solutions in a PLGA solution prior to spraying, a step known to be hazardous to proteins (45,46). Johnston et al. reported a more reasonable application of the into-nitrogen spray-drying, in which mixed aqueous solutions of proteins and sugars were sprayed into liquid nitrogen to form light particles for inhalation delivery (47). It seems that the particles prepared by the into-nitrogen spray-drying fullfill the criteria of an inhalation dosage form in terms of their porous, light, irregular (in shape), and rapid dissolving nature.

For the process of spray-dropping to liquid nitrogen, a well-known application is the preparation process of Ntropin Depot, a sustained-release PLGA microsphere formulation for hGH (48). During the step that protein-loaded PLGA solution was sprayed out the nozzle and dropping to the liquid nitrogen, the droplets had sufficient time to form spherical particles in the air. The droplets were solidified (dried) after dropping into liquid nitrogen by extracting the organic solvent dissolving PLGA with an ethanol phase placed underneath the liquid nitrogen. For the key issue, loading proteins into PLGA solution without denaturing, the authors preformulated a protein to fine particles by adding divalent metal ions to its aqueous solution (49). While this method seems reasonable technically (50), Nutropin Depot was dropped off from the market because of manufacture complexity and protein burst release. Again, liquid nitrogen may be responsible for formulation difficulties and burst release because of the porous structure of the PLGA matrix formed by immediate solidification at low temperature.

Spraying protein-loaded solutions into precooled compressed CO_2 is another method for preparing bioproducts into particulate forms. In this process, solutions containing bioproducts and protective agents are sprayed into cold supercritical CO_2 to form solid particles immediately (51). While the temperature is mild as compared with that of liquid nitrogen, the method is still limited to preparation of porous or hollow particles' narrow diameter range for inhalation delivery.

Complexation with Divalent Metal Ions

As discussed above, protein particles are better to be formed or preformed under a condition without exposing protein solution to water-oil or water-air interface, a cause of protein denaturation. To achieve this goal, divalent zinc ions were used to precipitate hGH in aqueous solution, in which each zinc ion associated with two hGH molecules, and complex the protein into solid particles (50). Once the solid complex particles are formed, the protein becomes resistant to organic solvent and other hazardous conditions for the reduced protein mobility in the hGH-Zn^{2+} complex.

Yuan and Jin noticed that the hGH-Zn^{2+} complex particles formed as above possess irregular shape and speculated that it was related with the burst release of hGH from PLGA microspheres loaded with the hGH-Zn^{2+} particles (48). They therefore modified the zinc-complexation process by mixing the protein and zinc ions in a PEG solution, and harvested dense, fine, and spherical hGH-Zn^{2+} particles (52). By further microencapsulating the hGH-Zn^{2+} particles into PLGA microspheres, a sustained-release profile with minimal burst was attained (53). However, the authors did not compare two hGH-Zn^{2+} particle-forming processes directly for mechanistic discussion because they prepared the PLGA microspheres without using liquid nitrogen.

Microcrystallization

Crystallization is another approach to prepare native yet stable solid protein particles (54,55). There are plenty of evidences that the native state of proteins can be maintained in their crystalline form in the area of protein structure biology studies. However, crystallizing macromolecular proteins of complex structure, especially to well-controlled sizes, is not an easy

task (56). Even if a milling process may be used to reduce the size of crystallized proteins, the protein instability issues associated with jet milling discussed above will be faced again (57).

Nevertheless, for those proteins that microcrystals can be formed, microcrystallization is a useful approach to formulate protein particulate systems. It has been reported that using PEG as retarding agent, insulin (58) microcrystals, 1 to 2 μm in diameter, were formed at 16°C (58).

For long-term sustained-release applications, the microcrystals may need to be further microencapsulated by degradable polymers. In this case, how to protect proteins dissolved from the bare protein particles dispersed a hydrophobic polymer matrix in the prolonged process of in vivo release may be an issue of study.

Aqueous Phase Separation

Packing delicate proteins into particles of sugars, polysaccharides, or other water-soluble polymers prior to microencapsulation is a well-reported strategy to protect these proteins from denaturing because of organic solvents and hydrophobic polymer matrix (59–64). However, direct freeze-drying proteins with polysaccharide may result in larger, irregular, or fibrous particles that are not suitable for further formulation and other applications.

Using aqueous phase separation is a compelling method to prepare protein-loaded polysaccharide particles for its lack of water-oil interface in the formulation process. In the case of this method, polysaccharide (such as dextran) is separated out as the dispersed phase from its cosolution with PEG (as the continuous phase), and the proteins or peptides are partitioned preferentially in the polysaccharide dispersed phase and solidified (65). The polysaccharide dispersed phase normally fuses to form a block phase when stirring is stopped so that an in situ solidification step is needed. Hennink et al. reported preparation of protein-loaded dextran particles through aqueous two-phase separation, followed by an intraparticle cross-link agent to solidify the dispersed phase (66). However, proteins possessing abundant functional groups have to be exposed to the cross-linking agents.

To avoid cross-linking reactions, Jin et al. reported a nonreactive approach to stabilize and solidify the polysaccharide dispersed phase (loaded with proteins) within PEG continuous phase (67). The inventors added a polyelectrolyte, sodium alginate, into the polysaccharide-PEG aqueous two-phase system to form a "stabilized aqueous-aqueous emulsion." Sodium alginate associates with the dispersed phase and forms a diffuse double layer around the polysaccharide droplets to prevent them from fusion with each other. Proteins or other water-soluble biomolecules can be loaded in the dispersed polysaccharide phase by preferential partition and freeze-dried to form dense glassy particles with the polysaccharide. Once loaded in the polysaccharide glassy particles, proteins have gained sufficient resistance to organic solvents, so that the PEG continuous phase can be removed by suspending the lyophilized powder in an organic solvent able to dissolve PEG.

This stabilized aqueous-aqueous emulsion has an alternative version in which the polysaccharide dispersed phase is stabilized by reducing the operation temperature instead of using the polyelectrolyte (53). Lowered temperature may facilitate aqueous phase separation, reduce mobility of dispersed phase, and avoid interactions of highly delicate proteins with polyelectrolytes.

Another derived method from the aqueous two-phase separation is freezing-induced phase separation (68). In this method, a cosolution containing polysaccharide, PEG, and a protein to be loaded is frozen gradually to allow the system transfer from the single-phase region to the two-phase region of its phase diagram (65). The key issue of this method is to determine the concentration of the cosolution to ensure the polysaccharide dispersed phase is separated out of the continuous solution at a temperature just right-above its freezing point. Therefore, the separated polysaccharide droplets can readily be frozen before fusion to large particles or a block phase (69). Freezing-induced phase separation may also be used to prepare pure protein particles by excluding the polysaccharide in the cosolution subjected to freezing (68).

Sustain-Release Microspheres Loaded with Protected Proteins

A problem to administrate macromolecular biotherapeutics is the needs of frequent injections for months, years, or even lifetime. To reduce injection frequency, sustained-release

microsphere formulations have been successfully used for long-term dosing of many small molecular and peptide drugs. For macromolecular agents such as proteins, however, because of the susceptible higher structure, the system useful for small molecules becomes no longer feasible: there has yet to be a single product in this category commercially available to date despite decades of research efforts. Therefore, we will focus our discussion only on those microsphere systems for which protein stabilizing is taken into account.

There are two strategies reported in the literature for protecting proteins in polymer-based microencapsulation: stabilizing proteins in liquid form using surfactants or hydrophilic polymers and preformulating proteins to solid particles (70,71). For the former, hydrophilic protein stabilizer, such as gelatin, is added in a protein solution to increase its viscosity and reduce protein mobility. Then, the mixed solution is emulsified into an organic solution of a release-control polymer to form a primary emulsion. The primary emulsion is emulsified again into an aqueous continuous phase to form water-insoluble microspheres (70). While the authors claim that bovine serum albumin (BSA) integrity was preserved during the microencapsulation process involving organic continuous phase, this method has not been tested with a bioactive protein.

Preformulating biomolecules such as proteins to solid particles prior to microencapsulation is more reasonable and well-accepted by scientists for microsphere preparation for the proteins' immobility in the polysaccharide matrix and resistance to organic solvents. In these cases, protein particles are preformulated using the methods described above (see sects. "Microcrystallization" and "Aqueous Phase Separation"). To load the protein particles in polymer microspheres, three methods are, in general, reported in the literature, solid-in-oil-in-water (S/O/W), solid-in-oil-in-oil (S/O/O), and solid-in-oil-in-hydrophilic oil (S/O/hO) (53).

For S/O/W method, the particles of biomolecules are first suspended in an organic solution of the polymer (which forms the controlled-release matrix). Then the protein carrying polymer solution is emulsified into a water-based continuous phase to form embryonic microspheres. After removing the organic solvent (by evaporation or extracting) and follow-up freeze-drying the embryonic microspheres, the final product is obtained. The major drawback of S/O/W method is that water may penetrate from the continuous phase into the embryonic microspheres and dissolve the protein-containing particles suspended in the organic phase, so that a water-oil interface may still be formed (72).

To circumambulate the stability concern for S/O/W method, an oily continuous phase was used in the S/O/O method instead of the water-based continuous phase (73). The rationale is that the selected oily continuous phase (such as silicone oil) is immiscible with the organic polymer solution (it does not dissolve the protein particles too), so that the polymer solution may form dispersed droplets in it. The major drawback of this method is that cleaning up the oily continuous phase requires a large volume of volatile organic solvents.

S/O/hO method is a further improvement from the S/O/O method. Instead of real oil, a glycerol-based formulation was used as the continuous phase. In addition to immiscibility with the organic polymer solution, the glycerol-based continuous phase does not dissolve the hydrophilic protein particles but can easily be removed by washing with water after the microencapsulation process. Disadvantages of this method include high viscosity of the glycerol-based continuous phase and its inability to dissolve surfactant molecules. Without surfactants, the protein-carrying particles may accumulate at the interface between the organic polymer droplets and the continuous phase, resulting in loss of proteins and rough microsphere surfaces (53). Adding some water (up to 10%) to the glycerol-based continuous phase may help to dissolve surfactants and concurrently reduce viscosity (53).

A unique yet practically convenient method to prepare uniform microspheres is called Shirasu porous glass (SPG) membrane technology (74). A polymer solution suspended with protein particles, prepared as in sections "Microcrystallization" and "Aqueous Phase separation," is squeezed through a glassy membrane of uniform pore size (called SPG membrane) into a continuous phase (either water or hydrophilic "oil") to form embryonic microspheres (75). The embryonic microspheres are immediately transferred to a cold NaCl solution for extracting organic solvent and hardening. The advantages of SPG membrane technology include uniform microsphere sizes (helping to reduce initial burst release), limited shear stress applied on embryonic microspheres (shear stress is applied before embryonic microspheres are formed), and good reproducibility for scaling up microsphere preparation.

DNA and RNA Particles

DNA and RNA are a new generation of therapeutics highly specific to disease targets. For DNA and RNA to exert their therapeutic efficacy, loading them to particulate delivery systems is needed in terms of preventing enzymatic degradation, intercellular targeting, and endosomal escaping. Since DNA and RNA are multiply charged macromolecules, their particle-forming process may easily be manipulated by using oppositely charged carrier systems. The charged carrier systems may be classified to two categories, cationic polymer and cationic lipids, and particles formed with them are called polyplex and lipoplex, respectively. Some researchers believe that sustained-release systems may help DNA and RNA to achieve controlled long-term and localized expression or silencing, and thus loaded polyplex or lipoplex in polymer-based microspheres (76–80).

A unique way to assemble DNA particles is based on molecular architecture of designed DNA molecules (81). Since the association between DNA chains is sequence-specific, DNAs can be designed in such a way that three or four chains form a "Y" or "X" shape double helix building blocks, respectively. There is an extended single-chain tag at each end of the Y or X shape blocks to exert a screw-nut function to precisely link the blocks to particles.

CONCLUSION

Preparation of particulate carrier systems for biological therapeutics is of great challenging as compared with that for small molecular chemical drugs. While advanced delivery technologies are highly demanded for both newly raised areas (such as siRNA delivery) and those standing near a century (such as invasive delivery of insulin), R&D success and mature technology are limited. This unmet need has offered pharmaceutical industry a great opportunity and encouragement to develop products with market impact.

REFERENCES

1. Mumenthaler M, Hsu CC, Pearlman R. Feasibility study on spray-drying protein pharmaceuticals: recombinant human growth hormone and tissue-type plasminogen activator. Pharm Res 1994; 11: 12–20.
2. Pikal MJ, Dellerman K, Roy ML. Formulation and stability of freeze-dried proteins: effects of moisture and oxygen on the stability of freeze-dried formulations of human growth hormone. Dev Biol Stand 1992; 74:21–37, discussion 8.
3. Hageman M. The role of moisture in protein stability. Drug Dev Ind Pharm 1988; 14:2047–2070.
4. Breen ED, Curley JG, Overcashier DE, et al. Effect of moisture on the stability of a lyophilized humanized monoclonal antibody formulation. Pharm Res 2001; 18:1345–1353.
5. Nail SL, Jiang S, Chongprasert S, et al. Fundamentals of freeze-drying. In: Nail SL, Akers MJ, ed. Development and Manufacture of Protein Pharmaceuticals. New York: Kluwer Academic/Plenum Publishers, 2002:281–360.
6. Tang X, Pikal MJ. Design of freeze-drying processes for pharmaceuticals: practical advice. Pharm Res 2004; 21:191–200.
7. Truong-LeV, Scherer T, inventors; High pressure spray-dry of bioactive materials. Application: WO, 2005.
8. Szkudlarek BA, Anchordoquy TJ, Rodriguez-Hornedo N. pH changes of phosphate buffer solutions during freezing and their influence on the stability of a model protein, lactate dehydrogenase. Book of Abstracts 211th ACS National Meeting, New Orleans, LA, 1996:BIOT-138.
9. Heller MC, Carpenter JF, Randolph TW. Protein formulation and lyophilization cycle design: prevention of damage due to freeze-concentration induced phase separation. Biotechnol Bioeng 1999; 63:166–174.
10. Strambini GB, Gabellieri E. Proteins in frozen solutions: evidence of ice-induced partial unfolding. Biophys J 1996; 70:971–976.
11. Chang BS, Kendrick BS, Carpenter JF. Surface-induced denaturation of proteins during freezing and its inhibition by surfactants. J Pharm Sci 1996; 85:1325–1330.
12. Sarciaux JM, Mansour S, Hageman MJ, et al. Effects of buffer composition and processing conditions on aggregation of bovine IgG during freeze-drying. J Pharm Sci 1999; 88:1354–1361.
13. Jiang S, Nail SL. Effect of process conditions on recovery of protein activity after freezing and freeze-drying. Eur J Pharm Biopharm 1998; 45:249–257.
14. Izutsu K, Yoshioka S, Terao T. Stabilization of β-galactosidase by amphiphilic additives during freeze-drying. Int J Pharm 1993; 90:187–194.

15. Wang W. Lyophilization and development of solid protein pharmaceuticals. Int J Pharm 2000; 203: 1–60.
16. Tzannis ST, Prestrelski SJ. Activity-stability considerations of trypsinogen during spray drying: effects of sucrose. J Pharm Sci 1999; 88:351–359.
17. Carpenter JF, Chang BS, Garzon-Rodriguez W, et al. Rational design of stable lyophilized protein formulations: theory and practice. Pharm Biotechnol 2002; 13:109–133.
18. Katakam M, Bell LN, Banga AK. Effect of surfactants on the physical stability of recombinant human growth hormone. J Pharm Sci 1995; 84:713–716.
19. Tripp B, Magda J, Andrade J. Adsorption of globular proteins at the air/water interface as measured via dynamic surface tension: concentration dependence, mass-transfer considerations, and adsorption kinetics. J Colloid Interface Sci 1995; 173:16–27.
20. Van Regenmortel M, Boven K, Bader F. Immunogenicity of biopharmaceuticals: an example from erythropoietin. Biopharm International 2005; 18:36–52.
21. Purohit VS, Middaugh CR, Balasubramanian SV. Influence of aggregation on immunogenicity of recombinant human Factor VIII in hemophilia A mice. J Pharm Sci 2006; 95:358–371.
22. Li X, Zhang Y, Yan R, et al. Influence of process parameters on the protein stability encapsulated in poly-DL-lactide-poly(ethylene glycol) microspheres. J Control Release 2000; 68:41–52.
23. Sanchez A, Villamayor B, Guo Y, et al. Formulation strategies for the stabilization of tetanus toxoid in poly(lactide-co-glycolide) microspheres. Int J Pharm 1999; 185:255–266.
24. Dill KA. Dominant forces in protein folding. Biochemistry (Mosc) 1990; 29:7133–7155.
25. Volkin D, Klibanov A. Minimizing protein inactivation. In: Creighton TE, ed. Protein Function: A Practical Approach. New York: Oxford University Press, 1989:1–24.
26. Carpenter JF, Crowe JH. The mechanism of cryoprotection of proteins by solutes. Cryobiology 1988; 25:244–255.
27. Morita T, Horikiri Y, Yamahara H, et al. Formation and isolation of spherical fine protein microparticles through lyophilization of protein-poly(ethylene glycol) aqueous mixture. Pharm Res 2000; 17:1367–1373.
28. Hanna M, York P, inventors; Method and apparatus for the formation of particles. EP patent 0706421B1, 1998.
29. Johnson KA. Preparation of peptide and protein powders for inhalation. Adv Drug Deliv Rev 1997; 26:3–15.
30. Snow RH, Kaye BH, Capes CE, et al. Size reduction and size enlargement. In: Perry RH, Green D, eds. Perry's Chemical Engineer's Handbook. New York: McGraw Hill, 1984:1–59.
31. Adjei AL, Johnson ES, Kesterson JW, inventors, LHRH analog formulations. US patent 4897256, 1990.
32. Hallworth GW. The formulation and evaluation of pressurized metered dose inhalers. In: Ganderton D., Jones T, eds. Drug Delivery to the Respiratory Tract. Chistester: Ellis Horwood, 1987:87–118.
33. Labrude P, Rasolomanana M, Vigneron C, et al. Protective effect of sucrose on spray drying of oxyhemoglobin. J Pharm Sci 1989; 78:223–229.
34. Irngartinger M, Camuglia V, Damm M, et al. Pulmonary delivery of therapeutic peptides via dry powder inhalation: effects of micronisation and manufacturing. Eur J Pharm Biopharm 2004; 58:7–14.
35. Pasquali I, Bettini R, Giordano F. Solid-state chemistry and particle engineering with supercritical fluids in pharmaceutics. Eur J Pharm Sci 2006; 27:299–310.
36. Sievers R, Karst U, Milewski P, et al. Formation of aqueous small droplet aerosols assisted by supercritical carbon dioxide. Aerosol Sci Technol 1999; 30:3–15.
37. Sievers R, Karst U, Schaefer J, et al. Supercritical CO2-assisted nebulization for the production and administration of drugs. J Aerosol Sci 1996; 27:497–498.
38. Reverchon E, De Marco I, Della Porta G. Rifampicin microparticles production by supercritical antisolvent precipitation. Int J Pharm 2002; 243:83–91.
39. Sievers R, Miles B, Sellers S, et al. New process for manufacture of 1-micron spherical drug particles by CO_2-assisted nebulization of aqueous solutions. Proceeding of Respiratory Drug Delivery VI, South Carolina, 1998:417–419.
40. Sellers SP, Clark GS, Sievers RE, et al. Dry powders of stable protein formulations from aqueous solutions prepared using supercritical CO_2-assisted aerosolization. J Pharm Sci 2001; 90:785–797.
41. Sievers R, Huang E, Villa J, et al. Rapid gentle drying using dense carbon dioxide to form fine dry powders. Proceedings of Respiratory Drug Delivery VIII, Tucson, Arizona, 2002:675–677.
42. Sievers RE, Huang ETS, Villa JA, et al. Low-temperature manufacturing of fine pharmaceutical powders with supercritical fluid aerosolization in a Bubble Dryer (R). Pure Appl Chem 2001; 73: 1299–1303.
43. Gombotz W, Healy M, Brown L, et al., inventors; Process for producing small particles of biologically active molecules. EP patent 0,432,232, 1994.
44. Willis RC. Crystallize to deliver. Mod Drug Discov 2003; 6(March):12.

45. Khan M, Healy M, Bernstein H. Low temperature fabrication of protein loaded microspheres. Proc Int Symp Control Rel Bioact Mater 1992; 19:518–519.
46. Herberger J, Wu C, Dong N, et al. Characterization of Prolease® human growth hormone PLGA microspheres produced using different solvents. Proc Int Symp Control Rel Bioact Mater 1996; 23: 835–836.
47. Yu ZS, Garcia AS, Johnston KP, et al. Spray freezing into liquid nitrogen for highly stable protein nanostructured microparticles. Eur J Pharm Biopharm 2004; 58:529–537.
48. Johnson OL, Jaworowicz W, Cleland JL, et al. The stabilization and encapsulation of human growth hormone into biodegradable microspheres. Pharm Res 1997; 14:730–735.
49. Costantino HR, Firouzabadian L, Hogeland K, et al. Protein spray-freeze drying. Effect of atomization conditions on particle size and stability. Pharm Res 2000; 17:1374–1383.
50. Cunningham BC, Mulkerrin MG, Wells JA. Dimerization of human growth hormone by zinc. Science 1991; 253:545–548.
51. Tom J, Debenedetti P. Particle formation with supercritical fluids—a review. J Aerosol Sci 1991; 22:555–584.
52. Yuan WE, Wu F, Geng Y, et al. An effective approach to prepare uniform protein-Zn^{2+} nanoparticles under mild conditions. Nanotechnology 2007; 18:145601.
53. Yuan WE, Jin T. Aqueous–aqueous emulsion based sustained protein delivery system and its application in recombinant human growth hormone. Shanghai Jiao Tong University, 2007.
54. Elkordy AA, Forbes RT, Barry BW. Integrity of crystalline lysozyme exceeds that of a spray-dried form. Int J Pharm 2002; 247:79–90.
55. Elkordy AA, Forbes RT, Barry BW. Stability of crystallised and spray-dried lysozyme. Int J Pharm 2004; 278:209–219.
56. Lee MJ, Kwon JH, Shin JS, et al. Microcrystallization of alpha-lactalbumin. J Cryst Growth 2005; 282:434–437.
57. Krycer I, Hersey J. A comparative study of communication in rotatory and vibratory ballmills. Powder Technol 1980; 27:137–141.
58. Kwon JH, Lee BH, Lee JJ, et al. Insulin microcrystal suspension as a long-acting formulation for pulmonary delivery. Eur J Pharm Sci 2004; 22:107–116.
59. Woo BH, Jiang G, Jo YW, et al. Preparation and characterization of a composite PLGA and poly(acryloyl hydroxyethyl starch) microsphere system for protein delivery. Pharm Res 2001; 18:1600–1606.
60. Stenekes RJH, Franssen O, van Bommel EMG, et al. The preparation of dextran microspheres in an all-aqueous system: effect of the formulation parameters on particle characteristics. Pharm Res 1998; 15:557–561.
61. Jin T, Chen L, Zhu H, inventors; Stable polymer aqueous/aqueous emulsion system and uses thereof. US patent 6 805879, 2004.
62. Jin T, Zhu H, Zhu J, inventors; Aquespheres, their preparation and uses thereof. US patent 6 998 393, 2006.
63. Nils OG, Mats R, inventors; Starch microparticles. US patent 6 692 770 B2, 2004.
64. Timo L, Mats R, inventors; Encapsulation method. US patent 6 861 064 B1, 2005.
65. Zaslavsky B, Huddleston J. Aqueous two-phase partitioning: New York: M. Dekker, 1995.
66. Hennink WE, Franssen O, inventors; Microspheres for controlled release and processes to prepare these microspheres. WO98/22093, 1998.
67. Jin T, Zhu H, Zhu J, inventors; Hazard-free microencapsulation for structurally delicate agents, an application of stable aqueous emulsion. PCT WO03/101600A2, 2003.
68. Yuan WE, Wu F, Geng Y, et al. Preparation of dextran glassy particles through freezing-induced phase separation. Int J Pharm 2007; 339:76–83.
69. Jin T, Zhu J, Wu F, et al. Preparing polymer-based sustained-release systems without exposing proteins to water-oil or water-air interfaces and cross-linking reagents. J Control Release 2008; 128: 50–59.
70. Wang N, Wu XS. A novel approach to stabilization of protein drugs in poly(lactic-co-glycolic acid) microspheres using agarose hydrogel. Int J Pharm 1998; 166:1–14.
71. Cleland JL, Jones AJ. Stable formulations of recombinant human growth hormone and interferon-gamma for microencapsulation in biodegradable microspheres. Pharm Res 1996; 13:1464–1475.
72. Geng Y, Yuan W, Wu F, et al. Formulating erythropoietin-loaded sustained-release PLGA microspheres without protein aggregation. J Control Release 2008; 130:259–265.
73. Yuan W, Wu F, Guo M, et al. Development of protein delivery microsphere system by a novel S/O/O/W multi-emulsion. Eur J Pharm Sci 2009; 36:212–218.
74. Nakashima T, Shimizu M, Kukizaki M. Particle control of emulsion by membrane emulsification and its applications. Adv Drug Deliv Rev 2000; 45:47–56.

75. Jin T, Yuan W, Wu F, inventors; Method to prepare composite microspheres of Uniform Size. US provisional patent 61103555, 2008.
76. Howard KA, Li XW, Somavarapu S, et al. Formulation of a microparticle carrier for oral polyplex-based DNA vaccines. Biochim Biophys Acta 2004; 1674:149–157.
77. Zhang XQ, Intra J, Salem AK. Comparative study of poly (lactic-co-glycolic acid)-poly ethyleneimine-plasmid DNA microparticles prepared using double emulsion methods. J Microencapsul 2008; 25: 1–12.
78. Oster CG, Kim N, Grode L, et al. Cationic microparticles consisting of poly(lactide-co-glycolide) and polyethylenimine as carriers systems for parental DNA vaccination. J Control Release 2005; 104: 359–377.
79. Oster CG, Kissel T. Comparative study of DNA encapsulation into PLGA microparticles using modified double emulsion methods and spray drying techniques. J Microencapsul 2005; 22:235–244.
80. Whittlesey KJ, Shea LD. Nerve growth factor expression by PLG-mediated lipofection. Biomaterials 2006; 27:2477–2486.
81. Li Y, Tseng YD, Kwon SY, et al. Controlled assembly of dendrimer-like DNA. Nat Mater 2004; 3:38–42.

16 Granulation of Plant Products and Nutraceuticals

Dilip M. Parikh
DPharma Group Inc., Ellicott City, Maryland, U.S.A.

INTRODUCTION

Nutraceuticals and dietary supplements have been interchangeability used to describe products made from plants, animals, or minerals, which may show therapeutic activity but may not claim the medical benefits in the United States. Most of the world treats dietary supplements like a prescription drugs. In Latin America, Asia, and Europe, dietary supplements must show the efficacy and manufacturers must meet quality standards as the manufacturing of prescription drugs.

Nutraceuticals are the food components made from herbal or botanical raw materials, which are used for preventing or treating different types of acute and chronic maladies. Also known as functional foods and phytochemicals, nutraceuticals are the bioactive chemical and natural compounds that have the medicinal properties to treat and cure number of disorders.

The term "nutraceutical" was coined from "nutrition" and "pharmaceutical" in 1989 by Stephen DeFelice, MD (1). According to DeFelice, nutraceutical can be defined as "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease." However, the term nutraceutical as commonly used in marketing has no regulatory definition (2). The Dietary Supplement Health and Education Act (DSHEA) formally defined "dietary supplement" using several criteria. A dietary supplement (3)

- is a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, a herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients;
- is intended for ingestion in pill, capsule, tablet, or liquid form;
- is not represented for use as a conventional food or as the sole item of a meal or diet;
- is labeled as a dietary supplement;
- includes products such as an approved new drug, certified antibiotic, or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision).

Thus, nutraceuticals (as per the proposed definition) differ from dietary supplements in the following aspects:

- Nutraceuticals must not only supplement the diet but should also aid in the prevention and/or treatment of disease and/or disorder.
- Nutraceuticals are represented for use as a conventional food or as the sole item of meal or diet.

Medicinal preparations derived from natural sources, especially from plants, have been in widespread use since time immemorial. Ancient texts of India and China contain exhaustive depictions of the use of a variety of plant-derived medications.

Most rural populations, especially in the developing world, depend on medicinal herbs as their main source of primary healthcare. The therapeutic potential of herbal drugs depends on its form whether parts of a plant, or simple extracts, or isolated active constituents. Herbal

Table 1 Global Markets for Herbal Medicines

Region	Percentage share of market
European Union	45
Asia	17
Japan	16
North America	11
Others	7
Rest of Europe	4

medicine is now globally accepted as a valid alternative system of therapy in the form of pharmaceuticals, functional foods, etc., a trend recognized and advocated by the World Health Organization (WHO). Various studies around the world, especially in Europe, have been initiated to develop scientific evidence-based rational herbal therapies. Today, about 57% of the top150 brand name drugs contain at least one major active compound that was originally extracted from a plant, and there are at least 119 distinct chemical substances derived from plants that are important drugs currently in use in one or more countries.

The world trade in medicinal plants is estimated to be about US$62 billion. Table 1 shows the major players in this arena (4,5).

According to recently published research report (6), world demand for nutraceutical ingredients will advance 5.8% annually to $15.5 billion in 2010, serving a $197 billion global nutritional product industry. China and India will emerge as the fastest expanding nutraceutical markets as strong economic growth allows them to upgrade and diversify food, beverage, and drug production capabilities. The United States will remain the largest global consumer of nutraceutical ingredients because of the broad, increasing range of nutritional preparations and natural medicines produced domestically. The world nutraceutical demand in 2005 was $11.7 billion, comprising 60% nutrients and mineral, 28% vitamins, and 12% herbal and nonherbal extracts. This number will go up to $15.5 billion by 2010 with a 5.8% annual increase.

Following are the types of nutraceuticals typically manufactured:

1. Nutraceuticals ground, dried, powdered, and pressed from plant materials.
2. Nutraceuticals extracted or purified from plants.
3. Foods that have added active ingredients other than vitamins or minerals and have been scientifically demonstrated to provide health benefits beyond their basic nutritional functions.
4. Nutraceuticals produced, extracted, or purified from marine sources.
5. Nutraceuticals that are produced, extracted, or purified from animals and microorganisms.

To be classified as a dietary supplement, a botanical must meet the following criteria:

1. It is intended to supplement the diet.
2. It contains one or more dietary ingredients (including amino acids, vitamins, minerals, herbs, or other botanicals).
3. It is intended to be taken orally as a pill, capsule, tablet, or liquid.
4. It is labeled as being a dietary supplement.

DOSAGE FORM MANUFACTURING CHALLENGES

Sourcing and Standardization

One of the major constraints in using plants in pharmaceutical discovery is the lack of reproducibility of activity for over 40% of plant extracts. Reproducibility is the major problem, as the activities detected in screens often do not repeat when plants are resampled and re-extracted. This problem is largely because of differences in the biochemical profiles of plants

harvested at different times and locations, differences in variety, and variation in the methods used for extraction and biological activity determination. Furthermore, the activity and efficacy of plant extracts/medicines often result from additive or synergistic interaction effects of the components. Therefore, a strategy should be used to evaluate the qualitative and the quantitative variations in the content of bioactive phytochemicals of plant material. Standardization, optimization, and full control of growing conditions could result in the cost-effective and quality-controlled production of many herbal medicines.

Physicochemical Properties

Herbal drugs are usually mixtures of many constituents. The active principle(s) is (are) in most cases unknown. Selective analytical methods or reference compounds may not be available commercially. Plant materials are chemically and naturally variable.

The source and quality of the raw material are variable. The methods of harvesting, drying, storage, transportation, and processing (e.g., mode of extraction, polarity of the extracting solvent, and instability of constituents) have an effect. Particle shape and size distribution are particular concerns in flow. Botanical powders, particularly barks and roots, are notorious for needle-like fibers. These typically inhibit flow and ultimately cause problems. The best way to minimize the presence of fibers is to mill the powder to a very fine particle size prior to blending. Other issues that pose challenges in flow, particularly with botanicals, are moisture absorption, oiliness, waxy consistency, and static electricity. All of these factors inhibit flow by causing the product to become clumpy, gritty, or sticky. The most common solution is to add a glidant. Glidants have an extremely small particle size (140–400 mesh) and work by coating the surface of larger particles to reduce friction, absorb excess moisture, and enhance flow. Examples of glidants are silicone dioxide, calcium silicate, and talc. Density differences in these ingredients can be addressed by granulating these plant products.

Poor product quality may be due in part to the formidable challenges faced by formulators in developing botanical products. Botanicals may have poor flow, low bulk density, variable particle size distributions, and compression properties significantly different from general-use excipients (7). Also, the doses of botanicals may be very high, and the raw material may be in any form, ranging from crude powdered leaf or root to a finely powdered extract. Foremost among important physical properties are flowability, hygroscopicity, and compression properties. Poor fluidity may result in great difficulty in processing the material, especially on high-speed tableting or encapsulation equipment, leading to problems with fill weight variation and content uniformity. Hygroscopicity may contribute to poor fluidity as well as adversely influence both physical and chemical stabilities.

Minerals in the formulation taste bad. They also tend to react with vitamins and other nutrients, especially in the presence of heat and moisture. There are serious bioavailability, solubility, and tolerability issues to be addressed and sometimes addressing one set of concerns exacerbates another set. A formulator must take all these technical and nutritional factors into account in order to develop the most efficacious product possible.

Some technologies used to overcome some of the challenges posed by mineral fortification include microencapsulation, taste-masking, stabilization with other carriers (hydrolyzed proteins, polysaccharides), chelation, micropulverization, and liposome applications to improve the bioavailability. Mineral chelates are also growing in popularity. The largest issue with trace minerals is homogeneity. If you consider that the recommended use rates for all of these nutrients are measured in micrograms, it becomes a challenge to get that small amount blended across a typical batch so that a label claim can be guaranteed.

Because of the compression difficulties and the low bulk density, herbal products are formulated as capsules. In addition to their challenging physical properties, botanicals are quite complex chemically. There are multiple specific chemical entities classed as phytosterols, including, but not limited, to β-sitosterol, campesterol, and stigmasterol. Typical phytosterol could contain single or mixture of these sterols. Because of its hydrophobic waxy nature, difficult to mill because it clogs the mill, it does not flow after micronization. The low bulk density and waxy nature cause compression problems. As such, granulation of these sticky sterols is mixed with silicon dioxide prior to processing and granulated with PVP in a high shear mixer and fluid-bed drier (8).

Table 2 Definitions of Range of Botanical Materials

Botanical preparation	Definition
Chopped or powdered botanicals	Hand-picked portions of the botanical (e.g., leaves, flowers, roots, and tubers) that are air-dried, and chopped, flaked, sectioned, ground, or pulverized to the consistency of a powder.
Botanical extracts	Extracts are solids or semisolid preparations of a botanical that are prepared by percolation, filtration, and concentration by evaporation of the percolate. The extracting material may by alcoholic, alkaline, acid hydroalcoholic, or aqueous in nature. Typically an extract is 4 to 10 times as strong as the original botanical. The extracts may be semisolids or dry powders termed powdered extracts.
Tinctures	Tinctures are solutions of botanical substances in alcohol obtained by extraction of the powdered, flaked, or sectioned botanical.
Infusions	Infusions are solutions of botanical principles obtained by soaking the powdered botanical in hot or cold water for a specified time and by straining. Typically infusions are 5% in strength.
Decoctions	Decoctions are solutions of botanicals prepared by boiling the material in water for at least 15 minutes and straining. Typically decoctions are 5% in strength.
Fluidextracts	A fluidextract is an alcoholic liquid extract made by percolation of a botanical so that 1 mL of the fluidextract represents 1 g of the botanical.
Botanicals to be treated with boiling water before use[a]	Dried botanicals to which boiling water is added immediately prior to consumption.

[a]USP 29.
Source: From Ref. 9.

Microbiological Issues

The raw materials, pharmaceutical ingredients, and active ingredients used in the manufacture of nutritional and dietary articles may range from chemically synthesized vitamins to plant extracts and animal byproducts. Microbiological process control, control of the bioburden of raw materials, and control of the manufacturing process to minimize cross-contamination are necessary to guarantee acceptable microbial quality in the final dosage forms.

Raw materials, excipients, and active substances as components of nutrition and dietary supplements can be a primary source of microbiological contamination. Specifications should be developed and sampling plans and test procedures should be employed to guarantee the desired microbiological attributes of these materials. From a microbiological perspective, the development of the formulation of nutritional or dietary supplements includes an evaluation of raw materials and their suppliers and the contribution made to the products by each ingredient and the manufacturing processes (Table 2) (9).

Analytical Challenges for Dietary Supplement

Practical examples of some vitamins/minerals formulation challenges are as follows:

- Change of active ingredient source—cyanocobalamin manufacturer, new source with different impurity profile—led to method interference with other vitamins
- Oxidative/reductive interaction of minerals with vitamins like ascorbic acid, vitamin D, and vitamin A
- Use of coated vitamins and minerals to minimize interaction led to poor analyte recovery
- Trace quantities of vitamins or minerals in presence of large quantities of other analytes/matrix—poor recovery/detectability
- Unpredictable manufacturing process impacts

In addition to the analytical challenges of these phytochemicals, several researchers have reported the instability of many of these compounds to heat, light, oxygen, and pH (10—14).

FORMULATION AND PROCESSING

Herbs and plant products for herbal therapies are usually prepared by grinding or steeping the parts of a plant that are believed to contain medicinal properties. The ground plant matter is called the "macerate." The macerate is soaked in a liquid referred to as the "menstruum" in order to extract the active ingredients. Herbal infusions are prepared by treating the herb with water or alcohol (ethanol) or mixtures of the two; coarsely bruised drug boiled in water for a definite period is known as a decoction and tinctures are solutions of the active principles of the drug in alcohol and water. This extraction process leads to the production of the herbal preparations in the form of fresh juice, hot and cold infusions, decoctions, tinctures, pastes, and powders referred to as "pulverata." The resulting therapies come in several forms, including oral tablets, capsules, gel caps, extracts, and infusions. Solid or powdered extracts are prepared by evaporation of the solvents used in the process of extraction of the raw material. Several problems not applicable to synthetic drugs influence the quality of herbal drugs.

To manufacture solid dosage forms from these plant materials or minerals, vitamins, and other nutritional ingredients, different granulation processes can be utilized, which are described in this book. Depending on the quantity of the ingredient a direct compression process can be utilized. Since most of the times, the dietary supplement contains more than one plant or mineral ingredient, direct compression is not feasible. Number of plant extracts are spray-dried and then further processed by using direct compression, dry compaction such as slugging or roller compaction, or wet granulated in high shear mixers. Numbers of these ingredients are hygroscopic and thus require alcohol granulation or are roller-compacted to produce dense enough granules for compression or encapsulation. Following few examples will illustrate how various formulation strategies and process technologies can be used to process dietary supplements and plant-based products.

Successful formulation of chondroitin sulfate and glucosamine HCl tablets depends on conducting preformulation studies of the ingredients.

Ebube et al. studied the different sources of these ingredients and concluded that the preformulation studies help to understand the physicomechanical behavior of chondroitin sulfate and glucosamine HCl and that the application of this knowledge would facilitate development of stable solid dosage forms containing these materials (15).

Spray-Drying

Spray-dried extracts (SDEs) often have a small particle size and consequently poor flow, which may result in variation in weight and poor content uniformity within tablets. Particle size can be enlarged by granulation to increase the flow rate.

Phyllanthus niruri L is a medicinal plant widely distributed and used in folk medicine to treat kidney stone ailments and viral hepatitis. Pharmacological experiments confirm its therapeutic efficacy and safety. SDEs from medicinal plants are often used as active components in solid dosage forms because of their better stability. However, these products generally present deficient rheological properties, inadequate compressibility, and high sensitivity to atmospheric moisture, resulting in difficult direct compression (16).

Direct Compression

Wet granulation of herbal products is not always feasible because of the inherent properties of the ingredients. In one case study the herbal product consisted of spray-dried tengtea powdered extracts at a concentration of 14%. The active ingredient could not be processed by wet granulation because it became very sticky when exposed to water. To avoid a solvent granulation process, a formulation for direct compression was developed with tengtea extract, as well as for ginseng extract using Starch 1500 along with other excipients. Colorcon has listed number of case studies where the formula contained a mixture of 22.5% SDE and 67.5% crude herb powder, which left only 10% of the formulation for excipients. However, by using Starch 1500, the formulation met the criteria for disintegration and hardness (17).

Fluid-Bed Granulation

Herb "Xuchunchongji" consist of 17 kinds of medicinal herbs. It is difficult to dry the thick extract in a usual drier. In this study, Xuchunchongji granule of model drug was directly prepared by spraying the liquid extract as a binder, on the substrate (containing 1:2 ratio of dextrin to sucrose) in a fluid-bed processor (18).

Roller Compaction

1. Roller compaction of a milled botanical (*Baphicacanthus cusia*) with and without a binder, polyvinylpyrrolidone (PVP), was conducted. Larger-sized and less friable granules were obtained with decreasing roller speed. Addition of PVP affected the flowability and binding capacity of the herbal powder blend, which influenced size and friability of the granules. Co-milling of PVP with the herbal powder enhanced the flow of the blends and the effectiveness of the binder, which contributed favorably to the roller-compacted product (19).
2. Aloe gel is the colorless gel contained in the inner parts of the fresh leaves. Chemical analysis has revealed that this clear gel contains amino acids, minerals, vitamins, enzymes, proteins, polysaccharides, and biological stimulators. Fast dissolving tablets of the nutraceutical, freeze-dried *Aloe vera* gel (AVG), were prepared by *dry granulation method*. This study was undertaken to formulate a suitable fast-dissolving nutraceutical tablet of freeze-dried AVG, utilizing factorial design. The results of multiple regression analysis revealed that to obtain a fast dissolving tablet of the AVG, an optimum concentration of mannitol and a higher content of microcrystalline cellulose should be used (20).
3. Because of hygroscopicity of SDE of *Maytenus ilicifolia*, wet granulation could not be carried out. The extract was blended with other ingredients and slugged, milled, and compressed as follows: The SDE from *M. ilicifolia* was blended in a Turbula mixer with other excipients and magnesium stearate. Slugs were produced at a compression force of 22.0 ± 1.0 kN using flat-faced tooling 17 mm in diameter on a single-punch tablet press. The slugs were crushed in a dry granulator to obtain granules with a particle size <2.00 mm. The resulting material was passed through an oscillating granulator using a 1.0-mm sieve. The granulate fraction between 250 and 1000 μm was chosen for tablet optimization (21).
4. Dry granulation parameters influence the granule and tablet properties of SDEs from *M. ilicifolia*, which is widely used in Brazil in the treatment of gastric disorders. The compressional behavior of SDE and granules of SDE was characterized by Heckel plots. The tablet properties of powders, granules, and formulations containing high extract dose were compared (22).

Wet Granulation

1. *Rauwolfia serpentina* powder is soft in nature, poor in die filling, and deforms by initial fragmentation. Patra et al. (23) compared granulating roots of *R. serpentina* with starch paste and compared resultant granulation with a direct compression blend. The compression results from both granulations showed that wet granulated product had better flow property, compressibility, and compactibility compared with direct compression formulations
2. *P. niruri* L SDEs often have a small particle size and consequently poor flow. Because of its water solubility and unknown stability of the major active substance, this extract was granulated with Eudragit E in acetone to make granulation, which provided free flowing granules with lower moisture sorption behavior than original extract. The mechanical properties of the tablets were found to be dependent on the Eudragit E proportion within the granules and the compression force; therefore, a higher proportion of Eudragit E with a smaller compression force resulted in better release of the SDE from the tablets (24).
3. A patent describes similar granulation of a Chinese herb extract, which was granulated with excipients and dried (25).

STORAGE AND STABILITY

Plant products contain variety of biologically active compounds; some of these include isoflavones, flavonoids, carotenoids, bioactive peptides, and vitamins. Proper storage is important from harvesting to final manufacturing of the herbal products. Low-temperature storage is always recommended for phytochemicals. Chang et.al concluded that phenolic stability of hawthorn (*Crataegus pinnatifida* var. *major*) was affected by the storage temperature (26). Dry powders are stored for a long time before being used in the dosage form manufacturing, and the producer needs to understand without testing prior to use that the intended "dose" of the plant product may not be what ends up in the dosage form. For example, ginsenoside in ginseng preparation were found to vary from 0% to a high of 9% (27,28).

Kopleman and Augsburger studied the challenges analyzing the active principle and determine the challenges of processing the popular herbal product St. John's Wort *(Hypericum perforatum*) (29). The authors concluded that storage of the botanical product should be kept at the minimal temperature and care should be taken to avoid not only oxygen and light but humidity as well. They further concluded that the chemical extraction of the crude material as well as further processing may significantly influence the physical and chemical characteristics of the powdered commercial extract. Therefore, it is very important for the supplement manufacturer to perform a complete physicomechanical and chemical characterization when extracts are purchased from multiple suppliers.

GMP AND NUTRACEUTICALS

Adulteration and contamination of herbal medicines appear to be common in countries that are lenient with regard to controls regulating their purity. Adulteration in Asian medicines mostly results from the misidentification of plants. The U.S. FDA and other investigators have also reported the presence of prescription drugs, including glyburide, sildenafil, colchicines, adrenal steroids, and alprazolam, in products claiming to contain only natural ingredients (30).

United States of America

On June 25, 2007, FDA issued the final rules for the nutraceutical/dietary supplement industry—Good Manufacturing Practice (GMPs) for the nutraceutical industry. This is the big change for the industry in the United States where these nutraceutical products were classified up until now under "food" category and were not subject to the same level of current good manufacturing practice (cGMP) requirements, which is now changed. This will require manufacturers to conduct a gap analysis. Whether the issue is cross-contamination or product consistency, the challenge remains the same, to balance procedural and engineering changes to manage risk effectively and cost effectively.

The DSHEA gave the FDA the express responsibility to regulate the manufacturing processes of dietary supplements, and the FDA issued its first proposed rule in 2003 (31). In June 2007, it issued its final rule (32) that requires all dietary supplement manufacturers to ensure by June 2010 that production of dietary supplements complies with cGMPs and be manufactured with "controls that result in a consistent product free of contamination, with accurate labeling"(33). In addition, the industry is now required to report to the FDA "all serious dietary supplement–related adverse events."

Key Requirements of the Final Rule

Scope. The cGMPs apply to all domestic and foreign companies that manufacture, package, label, or hold dietary supplements, including those involved with the activities of testing, quality control, packaging, and labeling, and distributing them in the United States (referred to herein as "companies").

Each company involved in manufacturing, packaging, labeling, or holding dietary supplements is responsible for only those cGMPs that relate to its activities. The final rule is limited to only those involved with dietary supplements—it does not extend to entities that

manufacture, package, label, or hold only dietary ingredients, or to persons engaged only in activities associated with the harvesting, storage, or distribution of raw agricultural commodities that will be incorporated into dietary supplements by other persons. Additionally, the final rule does not apply to retail establishments holding dietary supplements only for purposes of direct retail sale to individual consumers, although this exception does not include a retailer's warehouse or other storage facility, nor does it extend to warehouses or storage facilities that sell directly to individual consumers.

Master manufacturing record. The creation of a master manufacturing record is central to the cGMP scheme, as this record serves as the touchstone for most of the other cGMP requirements to ensure the quality and uniformity of all dietary supplements a company produces. FDA analogizes the master manufacturing record to a recipe, setting forth the ingredients to use, the amounts to use, the tests to perform, and the instructions for preparing the quantity the recipe calls for.

Production and process controls. Production and process controls are the means by which the master manufacturing record is implemented. The final rule requires companies to establish, through written procedures, a specification for any point, step, or stage in the manufacturing, packaging, labeling, and holding process where control is necessary to ensure the quality of the dietary supplement. Companies must provide adequate documentation for why meeting these specifications will help ensure the quality of the dietary supplement, and then adequate documentation that all controls were implemented and specifications met. While not denominated a "hazard analysis and critical control point" requirement, it contains analogous elements.

Identity verification of components. The cGMPs require companies to verify the identity of all components used to manufacture dietary supplements. "Component" is defined as "any substance intended for use in the manufacture of a dietary supplement, including those that may not appear in the finished batch of the dietary supplement. Component includes dietary ingredients (as described in section 201(ff) of the act) and other ingredients."

Because dietary ingredients are the central defining ingredients of a dietary supplement, the final rule requires each manufacturer to perform its own testing or examination to verify the identity of each dietary ingredient prior to use in the manufacturing process. The identity testing requirement applies to manufacturers who purchase dietary ingredients from a dietary ingredient supplier as well as to those who manufacture their own dietary ingredients. For components that are not dietary ingredients, a manufacturer may rely on a certificate of analysis from the supplier if certain criteria are met.

Quality control. In the final rule, FDA clarifies that the cGMPs do not require the creation of an independent quality control unit. Requirements are imposed upon "quality control personnel," defined as "any person, persons, or group, within or outside of your organization, who you designate to be responsible for your quality control operations." Quality control personnel essentially have ultimate oversight authority over cGMP compliance.

Product complaints. The final rule requires that a "qualified person" must review all product complaints to determine whether the product complaint involves a possible failure of a dietary supplement to meet any of its specifications or other cGMP requirements, and if so, to investigate that complaint. Quality control personnel must review and approve decisions about whether to investigate a product complaint and review and approve the findings, and follow-up action of any investigation performed. These reviews and investigations must extend to all relevant batches and records. Product complaints that represent adverse events, covered by the Dietary Supplement and Nonprescription Drug Consumer Protection Act, need to be analyzed, recorded, preserved, and made available for inspection in accordance with the provisions of that act.

Record keeping and records access. The final rule requires companies to keep written records required by the rule for one year past the shelf life date (if used), or two years beyond the date of distribution of the last batch of dietary supplements associated with those records. FDA clarifies that shelf life dating includes "best if used by" dating as well as expiration dating. Records may be kept as original records, true copies, or as electronic records if compliant with 21 C.F.R. Part 11. All records required by the final rule must be "readily available" during the retention period for inspection and copying by FDA "when requested."

Other provisions. The final rule also establishes cGMPs for personnel, physical plant and grounds, equipment and utensils, laboratory operations, manufacturing operations, packaging and labeling operations, holding and distributing, and returned dietary supplements.

Comparison to drug cGMPs. The dietary supplement cGMPs established by the final rule, given their detail and emphasis on controls over every element of production, bear a stronger resemblance to drug cGMPs than they do to the rather general food cGMPs, although the low-acid canned food and acidified food cGMPs are also detailed in the processing aspect of production. Nonetheless, the dietary supplement cGMPs still remain far less onerous than the drug cGMPs. A key difference is that the dietary supplement cGMPs do not require process validation, which is mandated by the drug cGMPs. Rather, the emphasis in the dietary supplement cGMPs is on documentation that relates back to the master batch record in terms of product composition and processing steps. For companies manufacturing both drugs and dietary supplements, if all operations are performed in accordance with the drug cGMPs, then the dietary supplement cGMPs would be satisfied for those products. Following the dietary supplement cGMPs for all operations, however, would not satisfy the cGMP requirements for drugs.

European Union

German market is the biggest for the herbal products. In the late 1970s the Federal Republic of Germany decided to safeguards should be put in place to assure users of the safety and effectiveness of herbal products. By 1978 Commission E was formed with the aim of regulating herbal medicine. The laws are being extended by European commission. The new rules regulate herbal remedies to ensure their safety and effectiveness and prevent insufficient quality control. Potentially harmful substances in some herbs are identified, and possible interactions with other drugs are highlighted.

The Committee on Herbal Medicinal Products (HMPC) was established in September 2004, replacing the Committee for Proprietary Medicinal Products (CPMP) Working Party on Herbal Medicinal Products. The committee was established in accordance with Regulation (EC) No 726/2004 and Directive 2004/24/EC, which introduced a simplified registration procedure for traditional herbal medicinal products in EU Member States.

As part of these objectives, the HMPC provides EU Member States and European institutions its scientific opinion on questions relating to herbal medicinal products. Other core tasks include the establishment of a draft "Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products," as well as the establishment of community herbal monographs.

The Food Supplements Directive (34) requires that supplements be demonstrated to be safe, both in quantity and quality. Some vitamins are essential in small quantities but dangerous in large quantities, notably vitamin A. Consequently, only those supplements that have been proven to be safe may be sold without prescription. A survey conducted in Ireland in 2001, of adults aged 18 to 64 years, suggested that with the possible exception of niacin (flushing) and vitamin B6 (neuropathy), there appears to be little risk of the occurrence of adverse effects because of excessive consumption of vitamins in this population, based on current dietary practices (35).

In 2004, a European directive on the licensing of herbal medicines was introduced following increasing public interest in the use of herbal products and parallel medical concerns regarding the safety of such medicines.

Key Points of the Directive
Following are the key points of the directive:

- The Traditional Herbal Medicinal Products Directive of the EU provides for the first time in the United Kingdom a framework for controlling herbal medicines in a single piece of legislation.
- U.K. legislation aims to control herbal products and herbal practitioners.
- The public tends to regard natural (herbal) products as safe. This is not always the case.
- It is in fact less than 50 years since most medicines used in the United Kingdom were either herbal in origin or based on chemically modified herbal principles.
- Herbal remedies are obtained over the counter and, accordingly, regulation should ensure safety and quality of preparations.
- Efficacy is much harder to ensure as few herbal remedies have undergone definitive clinical trials. The EU directive suggests that 30 years' use, including 15 years in the EU, should be sufficient to attest safety and utility.
- In future, evidence will need to be sought for the efficacy of herbal medicine, but at the same time herbs continue to be an important source of new medicines.

In January 2009 European Medicine Agency (EMA) released draft reflection paper on stability testing of herbal medicinal products and traditional herbal medicinal products.

In June 2009, EMA released draft guideline on selection of test materials for genotoxicity testing for traditional herbal medicinal products/herbal medicinal products. There are number of developments in the European scene and the latest developments can be viewed by the reader on EMA Web site (36).

As a category of food, food supplements cannot be labeled with drug claims in the bloc but can bear health claims and nutrition claims (37). The dietary supplements industry in the United Kingdom, one of the 27 countries in the EU, strongly opposed the directive. In addition, a large number of consumers throughout Europe, including over one million in the United Kingdom, and many doctors and scientists, have signed petitions against what are viewed by the petitioners as unjustified restrictions of consumer choice (38).

The EU proposal for a directive aims to clear up a gray area by requiring that all herbal products that are sold on the EU market be classified as medicinal products. Those which cannot be so classified may be squeezed out.

Russia

Russian legislation, Ministry of Health's order number 117 dated as of 15 April 1997, under the title "Concerning the procedure for the examination and health certification of Biologically Active Dietary Supplements" (BADS), provides the usage of the following terminology:

> As a rule, BADSs are foodstuffs with clinically proven effectiveness. BADSs are recommended not only for prophylactics, but can be included into a complex therapy for the prevention of pharmaceutical therapy's side effects and for the achievement of complete remission.

The development of BADSs and their applications have been very fast moving. They were originally considered as dietary supplements for people who had heightened requirements for some normal dietary components (e.g., sportsmen). Later, they were employed as preventive medicines against chronic diseases.

Canada

Health Directorate of Canada developed a new regulatory framework for natural health products, which came into effect in January 2004.

Among other things, the new regulations call for improved labeling, good manufacturing practices, product and site licensing, and provision of a full range of health claims that will be supported by evidence. However, even in Canada, the only regulatory requirements enforced are that all products intended for medicinal use, including natural health products, are issued

a Drug Identification Number (DIN). These numbers are not required for raw materials such as bulk herbs.

Japan and China

In Japan, health claims and nutrient function claims are also authorized by law. The Japanese have developed the Foods for Specified Health Use (FOSHU) registration process whereas the Chinese have put into place the health food registration process. In Japan, FOSHU health claims are allowed in several categories designated by the government gastrointestinal health, cholesterol moderation, hypertension moderation, lipid metabolism moderation, sugar absorption moderation, mineral absorption, bone health and tooth health. However, new claims and combination of claims are approved on a regular basis (39). The Chinese regulation system defines health foods as foods with specific health functions that are suitable for consumption by specific groups of people and that have the effect of regulating human body functions without treating diseases. Scientific evidence is required as part of the application for nutraceutical registration in both countries, China and Japan.

The scientific data required in both countries are very similar regarding the safety, the efficacy, and the stability profiles. They further require the identification of the active ingredients as well as a statement in regard to their analytical method. In both countries the test method provided by the applicant is validated and then used to test the active ingredient. Where clinical trials are required, the clinical trials must be conducted with either Japanese or Chinese subjects in their respective countries. Most of the application requirements are similar in both countries such as the description of the manufacturing process, the proposed health claims, the dosages, the product packaging and labels, the samples, the applicant and manufacturer details, and the product formula.

A major difference in the processes between Japan and China is the cost of obtaining approval for nutraceuticals registration. In Japan, regular FOSHU approval can cost up to US$1,500,000. In China the health food approval costs range from $17,500 to $34,500 (40). Table 3 gives an overview of approval times for different regions of the world.

Table 3 Approval Timelines for Nutraceutical in Various Countries

Country/ region	Approval time regulatory/Ethics (EC)	Comments
France	60/35	CA was DGS for nutraceutical compound not considered as a drug and is since JUNE 01, 2008, the AFSSAPS (AFSSAPS: Agence Française de sécurité sanitaire des produits de santé)
Belgium	35	Only EC submissions are required if the nutraceutical compound is not considered a drug
U.K.	60	Only EC submissions. Timelines for Ethic approvals are the same as for drugs
Germany	60	Local EC submissions done after central EC approval. Quick timelines would be about 4 wk for central EC and subsequential 4 wk for local EC. For slower local ECs the timeline might be 2 mo sequential to central EC. The local EC submissions can start as soon as central approval is obtained
India	4–8 wk	Only EC approval required if the nutraceutical compound does not fall under the category of drugs
China	2–4 wk	Only EC approval required for nutraceuticals that are no drugs. Timelines are similar to those for drugs
Argentina	4 wk EC/12 wk	Sequential submission: EC (local, 4 wk and central, 2 wk in parallel), then Reg (ANMAT). No specific regulation for clinical trials for nutrients. Therefore, same procedure and timelines for approval as for drugs
Brazil	4 wk Ethics/12 wk	Sequential submission: local EC then Reg (CONEP and ANVISA). No specific regulation for clinical trials for nutrients. Therefore, same procedure and timelines for approval as for drugs

Abbreviations: CA, Competent Authority; DGS, Direction Générale de la Santé; ANMAT, Administración Nacional de Medicantos Alimentos y Technologia Médica; CONEP, Regulatory Conselho Nacional de la Empresa Privada; ANVISA, Agéncia Nacional de Vigiláncia Sanitá.
Source: From Ref. 41.

CONCLUSION

Plant materials are used throughout the developed and developing world as home remedies, in over-the-counter drug products, and as raw material for the pharmaceutical industry, and they represent a substantial proportion of the global drug market. Therefore, it is essential to establish internationally recognized guidelines for assessing their quality.

The possibility of herb-drug interactions is important but "underresearch" is an issue. The World Health Assembly in resolutions WHA31.33 (1978), WHA40.33 (1987), and WHA42.43 (1989) has emphasized the need to ensure the quality of medicinal plant products by using modern control techniques and applying suitable standards (42–44).

The toxicity benchmarks for herbal drugs depend on purity, herbs containing toxic substances, bioavailability, and reported adverse effects. Selection of manufacturing process to produce a solid dosage form requires intimate knowledge of analytical techniques to determine the active moiety and its potency. Granulating plant products and nutraceuticals require the appropriate physicochemical characteristics before embarking on chosen technique. Sometimes the capsule formulation could be forgiving compared with the tablet formulation. The incorporation of various ingredients increases the complexity of formulating and stability of the final dosage forms.

Herbal medicines can act through a variety of mechanism to alter the pharmacokinetic profile of concomitantly administered drugs. Numerous examples exist of drug and herbal interactions. These effects may potentiate or antagonize drug absorption or metabolism, the patient's metabolism, or cause unwanted side reactions.

REFERENCES

1. Brower V. Nutraceuticals: poised for a healthy slice of the healthcare market? Nat Biotechnol 1998; 16:728–731.
2. Zeisel SH. Regulation of nutraceuticals. Science 1999; 285:185–186.
3. FDA/CFSAN resources page. Food and Drug Administration Web site. Dietary Supplement Health and Education Act, 1994.
4. Singh J, Singh AK, Pravesh R. Proceedings of First NIM on Medical Aromatic Plants 2003:50–58.
5. Ved DK, Anjana M, Shankar D. Regulating export of endangered medicinal plant species-need for scientific rigour. Curr Sci 1998; 75:341–344.
6. Freedonia Group Study #2083. Global demand to grow 5.8% yearly through 2010, 2006.
7. Kopelman SH, Augsburger LL. Some physical properties of ginkgo biloba extracts important for tableting and encapsulation. JANA 2000; 3(2):32–37.
8. Phytosterol Nutritional Supplement world patent WO2007038596 A2, 2007.
9. USP <2023> Microbiological attributes of non-sterile nutritional and dietary supplements. Pharm Forum 29(1):296–304.
10. Chatterjee SS, Bhattacharya SK, Wonnemann M, et al. Hyperforin as a possible antidepressant component of hypericum extracts. Life Sci 1998; 63(6):499–510.
11. INA Methods Validation Program. Determination of hypericin and pseudohypericin in St. John's Wort by high-performance liquid chromatography. 107.000. Denver, CO: Institute for Nutraceutical Advancement, 2000:1–4.
12. Orth HCJ, Schmidt PC. Stability and stabilization of hyperforin. Pharm Ind 2000; 62(1):60–63.
13. Fourneron J, Herbette G, Caloprisco E. Pseudohypericin and hypericin in St. John's Wort extracts. Breakdown of pseudohypericin. Comptes Rendes de L'Academie des Sciences Serie II Fascicule C-Chimie 1999; 2(3):127–131.
14. Carr RL. Particle behavior, storage, and flow. Br Chem Eng 1970; 15:1541–1549.
15. Ebube NK, Mark W, Hahm H. Preformulation studies and characterization of proposed chondroprotective agents: glucosamine HCl and chondroitin sulfate. Pharma Dev Technol 2002; 7(4): 457–446.
16. Broadhead J, Rouan SKE, Rhodes CT. The spray-drying of pharmaceuticals. Drug Dev Ind Pharm 1992; 18:1169–1206.
17. From Colorcon Web site. Available at: http://www.Colorcon.com.
18. Cui F, Liu G, Yang M, et al. Studies on direct granulation of compound herbal extracts using fluidized-bed granulator. Proc SCEJ Symp Fluidization 2001; 7:616–622. Available at: http://sciencelinks.jp/j-east/article/200215/000020021502A0153136.php.
19. Heng PW S, Chan LW, Liew CV, et al. Roller compaction of crude plant material: Influence of process variables, polyvinylpyrrolidone, and co-milling. Pharm Dev Technol 2004; 9:135–144.

20. Madan J, Sharma AK, Singh R. Fast dissolving tablets of *aloe vera* gel. Trop J Pharm Res 2009; 8(1):63–70.
21. Soares LA, Ortega GG, Petrovick PR, et al. Optimization of tablets containing a high dose of spray-dried plant extract: a technical note. AAPS PharmSciTech 2005; 6(3):46. Available at: http://www.aapspharmscitech.org.
22. Soares LA, Ortega GG, Petrovick PR, et al. Dry granulation and compression of spray dried plant extracts. AAPS PharmSciTech 2005; 6(3):E359–366.
23. Patra CN, Pandit HK, Singh SP, et al. Applicability and comparative evaluation of wet granulation and direct compression technology to Rauwolfia serpentina root powder: a technical note. AAPS PharmSciTech 2008; 9(1):100–104.
24. Pereira de Souza T, Martínez-Pacheco R, Gómez-Amoza JL, et al. Eudragit E as excipient for production of granules and tablets from phyllanthus niruri L spray-dried extract. AAPS PharmSciTech 2007; 8(2):article 34.
25. USPTO Application No: 20080233215. Excipient and an improved method for manufacturing extracted, evaporated, granulated botanical herb product.
26. Chang Q, Zuo Z, Chow MSS, et al. Effect of storage temperature on phenolics stability in hawthorn (*Crataegus pinnatifida* var. *major*) fruits and a hawthorn drink. Food Chem 2006; 98(3):426–430.
27. Anonymous. Herbal roulette. Consumer Rep 1995; 60(11):698–705.
28. Cui J, Garle M, Eneroth P, et al. What do commercial ginseng preparation contain? Lancet 1994; 344:134.
29. Susan H. Kopleman SH, Larry L. Augsburger. AAPS Pharm Sci 2001; 3(4):article 26. Available at: http://www.pharmsci.org/.
30. Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. J Intern Med 2002; 252:107–113.
31. CFSAN. FDA Issues Dietary Supplements Final Rule. FDA, 2007.
32. FDA. Final Rules: Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements. Federal Register, 2007.
33. U.S. Food and Drug Administration. FDA Issues Dietary Supplements Final Rule. Press release, 2007. Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01657.html. Accessed September 10, 2008.
34. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements.
35. O'Brien MM, Kiely M, Harrington KE, et al. The North/South Ireland Food Consumption Survey: vitamin intakes in 18–64-year-old adults. Public Health Nutr 2001; 4(5A):1069–1079.
36. Human Medicines—Herbal Medicinal Products. Available at: http://www.emea.europa.eu/htms/human/hmpc/hmpcguide.htm.
37. European Commission Web site. Food Safety—Labelling & Nutrition—Health & Nutrition Claims.
38. Controversial EU vitamins ban to go ahead. The Times, July 12, 2005.
39. Bailey R. International Nutraceutical and Functional Food Updates: Japan, Nutraceuticals and Functional Foods Division, 2005:3–4.
40. Patel D, Dufour Y, Domigan N. Functional food and nutraceutical registration process in Japan and China: similarities and differences. J Pharm Pharmaceut Sci 2008; 11(4):1–11. Available at: www.cspsCanada.org.
41. Dehlinger-Kremer M. Nutraceuticals—New Regulation and Clinical Studies Requirements. Paris: CEMO Congress, January 29, 2009.
42. WHO. Basic Tests for Drugs, Pharmaceutical Substances, Medicinal Plant Materials and Dosage Forms. Geneva: World Health Organization, 1998.
43. WHO. Bulletin of the World Health Organization. Regulatory Situation of Herbal Medicines. A Worldwide Review. Geneva: World Health Organization, 1998.
44. WHO. Regulatory Situation of Herbal Medicines: a Worldwide Review. Geneva: World Health Organization, 1998.

ADDITIONAL RESOURCES

1. International Bibliographic Information on Dietary Supplements (IBIDS) Database. Available at: http://ods.od.nih.gov/Health_INformation/IBIDS.aspx.
2. National Center for Complementary and Alternative Medicine (NCCAM). Available at: http://www.aapspharmaceutica.com/inside/Focus_Groups/NutraFocus/index.asp.
3. Natural Ingredient Database. Available at: http://www.vitarichlabs.com/ingredient-database.htm.
4. Hot Herb Directory. Available at: http://www.nutraceuticalsworld.com/articles/2008/07/hot-herb-directory.

5. GRAS Ingredient Directory. Available at: http://www.nutraceuticalsworld.com/articles/2008/06/gras-ingredients-directory.
6. Natural Medicines. Available at: http://www.NaturalDatabase.com.
7. HerbMed. Available at: http://www.herbmed.org.
8. American Botanical Council. Available at: http://www.herbalgram.org.
9. National Center for Complementary and Alternative Medicine. Available at: http://nccam.nih.gov.
10. Phytosterol Nutritional Supplement (world patent WO2007038596 A2).
11. Summary of some of the PATENTS on nutraceuticals:

    a. (WO/2004/047926) Nutraceutical compositions comprising epigallocatechin gallate and raspberry ketone
    Tablet composition for weight reduction: (Direct Compression) Tablets can be prepared by conventional procedures using ingredients specified below: Epigallocatechin gallate (EGCG) 50 mg and raspberry ketone (RK) 50 mg. Other ingredients: microcrystalline cellulose, silicone dioxide (SiO_2), magnesium stearate, and croscarmellose sodium.
    b. Excipient and an improved method for manufacturing extracted, evaporated, and granulated botanical herb product IPC8 Class: AA61K3600FI USPC Class: 424725 USPTO Application No: 20080233215.
    A method for manufacturing extracted, evaporated, and granulated botanical herb products such as concentrated Chinese herbs, comprising: (*i*) providing a Chinese herb raw material; (*ii*) obtaining an extract from the Chinese herb raw material; (*iii*) removing water from the extract, to get a concentrate; and (*iv*) adding an excipient to the concentrate, and then granulating and drying, to get a concentrated Chinese herbal preparation, wherein the excipient contains a capsule protective agent of 1 wt% to 99 wt% with respect to the excipient and a decomposed product of starch of 1 wt% to 99 wt% with respect to the excipient.
    c. US Patent 6495177—Orally dissolvable nutritional supplement.
    Chewable multivitamin supplements are well-known in the nutritional products industry. These vitamin-containing products typically provide a nutritious and bioavailable product, and possess generally good palatability or organoleptic effect. Developers of chewable nutritional supplements continually strive to develop chewable products having improved mouth feel and enhanced taste.
    A chewable prenatal nutritional supplement comprises a prenatally relevant amount of folic acid, a prenatally relevant amount of iron, and an alkyl polysiloxane, wherein the supplement is substantially free of calcium. The invention further relates to a method of making a chewable nutritional supplement. This method comprises mixing a prenatally relevant amount of at least one vitamin or mineral with an alkyl polysiloxane to yield a mixture and incorporating the mixture into a chewable dosage form, such as a tablet. According to this method, one or more other vitamins and minerals can be mixed with the alkyl polysiloxane. In a preferred method, the alkyl polysiloxane is mixed with folic acid, vitamin D3, vitamin A, vitamin B1, vitamin B2, vitamin B6, vitamin B12, vitamin E, vitamin C, an iron compound, and at least one of niacinamide and niacin. One or more active ingredients (e.g., one of an iron compound, vitamin B1, vitamin B2, vitamin B6, vitamin B12, niacin, and niacinamide) can be coated in order to enhance their stability, mask their taste or odor, or both.
    d. Fluidized-bed granulates that have a high proportion of fruit IPC8 Class: AA23L1222FI USPC Class: 426638.
    Manufacture of flavoring granulates, comprising: (A) preparing a solution, emulsion, or suspension comprising: (a) a mixture comprising: (aa) fruit juice and/or fruit juice concentrate; and (bb) a carrier matrix comprising (i) a magnesium salt of one or more solid, edible acids; or (ii) a mixture of: a. magnesium hydroxide, and b. one or more solid, edible acids; and optionally (b) one or more solvents ;

(B) spraying the solution, emulsion, or suspension of (A) into a fluidized-bed granulator to obtain flavoring granulates;

e. The U.S. Patent No. 4,664,920 discloses a powder having a high fruit content that contains a carrier matrix based on magnesium salts with certain acids. The powders are manufactured by means of freeze-drying, spray-drying, or drum-drying. In one example, a powder is manufactured by means of spray-drying that contains 85% by weight of juice solids and 15% by weight of magnesium citrate carrier. Second example describes the manufacture of a powder by means of spray-drying that contains 70% by weight of tomato solids and 30% by weight of magnesium citrate carrier.
f. US Patent 6485741—Granulate with high content of L-carnitine or an alkanoyl L-carnitine. US Patent issued on November 26, 2002.
Granulation carried out in a fluid bed with 92% to 96% active and between 4% and 8% polymer provided granules with capability of compressing it to tablets.
g. (WO/2005/011570) calcium carbonate granulation:
Highly compactable $CaCO_3$ granulation by using high shear granulation and fluid-bed drying.
h. US Patent 2003/0124191A1: Use of an immediate release powder in pharmaceutical and nutraceutical compositions. Various methods such as high shear mixers, one-pot systems, or spray-dryer are used to produce an immediate release powder for buccal drug delivery.

17 Granulation Approaches for Modified Release Products

Neelima Phadnis
Independent Pharma Consultant, Brisbane, California, U.S.A.

Sree Nadkarni
FibroGen Inc., San Francisco, California, U.S.A.

INTRODUCTION

For the purposes of this chapter, "modified release (MR)" is an umbrella term that will be used for describing granulations and/or drug products with a variety of drug-release patterns after administration, for example, sustained-release, controlled-release, pulsatile, and delayed-release products. Examples of some drug-release patterns are shown in Figure 1.

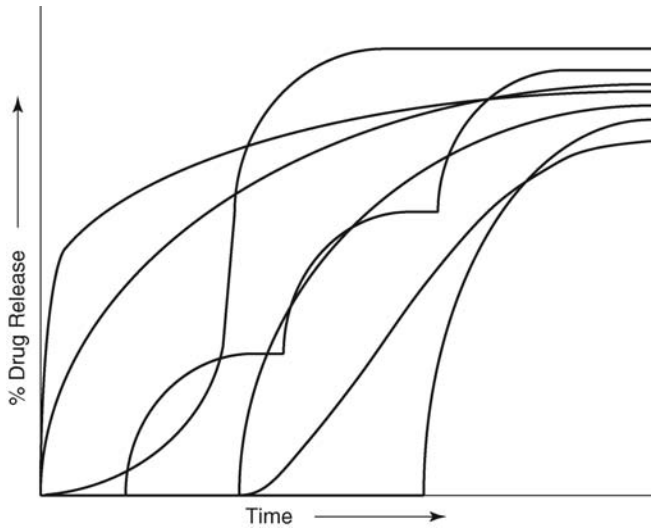


Figure 1 Drug-release patterns as a function of time.

An easily recognizable commercial MR formulation is Ambien CR™, where the benefits of extending the sleep-inducing effects of the active drug are readily apparent. The underlying basis for changing the release pattern of drug from its dosage form (post administration) is to influence the drug's concentration in the biological system and therefore modulate its therapeutic effects in a beneficial manner. Some other benefits of modifying the drug-release pattern through dosage form modification are the following:

- Improvement of patient compliance
- Reduction in the dosing frequency
- Reduction in fluctuations (peaks and troughs) in drug plasma concentrations, to reduce concentration-related side effects or improve effectiveness
- Controlling the site of drug delivery in the gastrointestinal tract

Traditionally, MR dosage forms were introduced to the market after successful commercial launch of a conventional dosage form that demonstrated a safe and efficacious profile within the established therapeutic window. This product lifecycle management strategy was no doubt a combination of an organization's need to capitalize on the intellectual property window of commercial opportunity and deference to the complex technical nature of developing MR products.

More recently, MR is increasingly being considered earlier in the drug development cycle

- as a potential avenue to progress a shrinking pool of viable molecules, rather than going back to the molecular drawing board; and
- to accommodate market drivers that promote a user-friendly dosing regimen.

SCOPE

Dosage forms can be classified in a number of ways:

- Site of administration—oral, intranasal, transdermal, colonic, etc.
- Dosage form appearance, for example, tablets, capsules, patch, and osmotic pump.
- By technology platform, for example, hot melt extrusion, 3D-printing, electrostatic deposition films, and rapid release.

Technically, rapid release granulations/dosage forms require modulation of drug-release profiles to achieve rapid onset of release for quick onset of therapeutic action and may also get categorized as MR preparations. But given the scope of the topic, rapid release formulations are addressed under various related themes in chapters 14, 19, and 20.

Modifying the release pattern of a drug involves leveraging elements that are already used in conventional dosage form development. Accordingly, material and process related aspects (including scale-up and regulations) for designing and manufacturing granulated MR dosage forms have significant overlap with topics covered in other chapters of this book. The subject matter in this chapter will therefore complement information covered elsewhere, offer items for consideration in designing a robust granulated MR product, and highlight applications with select case studies.

The reader is referred to additional literature (1,2) for coverage of nongranulated MR drug delivery systems.

BACKGROUND

To prepare a sound MR dosage form development strategy, it is important to first establish a comprehensive, well-defined target product profile (TPP). The TPP will thus form the basis for material considerations and dosage form performance considerations. These topics are elaborated below.

Establishment of a Target Product Profile

A successful granulated MR (GMR) dosage form development begins with a well-defined TPP. This TPP should include the objective of the exercise and may include one or more of the previously outlined benefits of MR dosing. A well-defined TPP will provide a clear perspective on the clinical and market requirements for a successful drug. It should include aspects such as

- therapeutically effective dose range;
- dosing frequency, that is, twice-a-day versus once-a-day;
- target release profile, that is, constant, zero-order release, or pulsatile release, including minimum and maximum therapeutically effective and safe plasma levels; and
- dosage form considerations, that is, tablet or a capsule, tablet size, shape, etc.

Establishment of a desirable TPP outline could start as early as the physicochemical profiling of the drug substance as material supply and informational database evolves (3). Generating this drug molecule specific TPP helps in managing expectations on whether a granulated MR dosage form is realistic (4) and in the framing of a GMR dosage form development strategy.

Limited drug supply, time, and investment in an interesting molecule may make generation of an MR TPP unrealistic, especially at an exploratory stage of the drug discovery development program. If this situation was to arise and an organization wish to keep its MR options open, a nanoparticle approach may be adopted. As per Chaubal (5), nanoparticles are one unique platform that can bridge the gap between discovery supportive efforts and future MR dosage form development programs.

Material Considerations

Drug Molecule or Active Pharmaceutical Ingredient

Not all drug molecules are amenable to being formulated into a granulated MR dosage form and an MR feasibility assessment is needed at the outset of the program. Once a TPP is established, MR feasibility can be carried out at any stage of development of a compound for which an MR dosage form is being considered. A fairly comprehensive assessment exercise for a drug molecule destined for MR dosage form development is outlined by Thombre (4) and is presented as a flowchart representation in Figure 2.

Taking into account the drug physicochemical, biopharmaceutical, and pharmacokinetic-metabolic properties and available technology, the end product of the assessment is a recommendation for an MR dosage form development strategy (Fig. 2).

In the above assessment, the following two molecular characteristics are important:

- The active pharmaceutical ingredient's (API) Biopharmaceutical Classification System (BCS) categorization—it is useful in defining the bioavailability and route of administration. As illustrated in chapter 23, a drug has to first exist as a dissolved moiety in the fluids at the site of absorption and pass through a biological barrier to reach the site of action. These two steps are governed by two defined characteristics of a molecule—its solubility and permeability. The BCS framework for categorization of drugs (6) was developed a few years ago in recognition of the importance of these characteristics.
- The dose-solubility ratio–is useful in MR technology selection (Fig. 3).

A number of GMR processes are available for supporting the above-identified dosage forms. GMR examples are highlighted in the section covering case studies.

In addition to the intrinsic API characteristics discussed above, a judicious selection of the API solid-state could also become an important exercise in MR dosage form development. An interesting strategy is presented by Chrzanowski (7–9), whereby a salt form that is poorly soluble or practically insoluble in water in the range pH 1.3 to 6.8 or 7.4 is chosen for incorporation into an MR dosage form.

Release Modifying Ingredient(s)

The second most important ingredient in a GMR formulation is the ingredient or a combination of ingredients, which enables modification of the drug-release pattern. The two main classes of release modifiers are polymers and long-chain hydrocarbons.

Polymers. Not surprisingly, many of the polymers used for modulating drug release are high viscosity grades of polymers that are used as binders at low aqueous concentrations and are described in chapter 4. When selecting a polymer for its functional utility, the following characteristics are closely examined (10):

- Reproducibility of physical properties
- Noninterference with the drug's therapeutic action
- Chemical compatibility with the drug

MR polymers can be further classified according to their origin (synthetic, semisynthetic, and natural), pH-solubility profile (pH-independent or pH-dependent), or by their hydrophilic or lipophilic nature. Examples of polymers commonly used in MR formulations are the following: Hydroxypropyl methylcellulose (hypromellose, HPMC), hydroxypropyl cellulose, hydroxyethyl cellulose, HPMC phthalate (HPMCP), poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate, poly(vinyl alcohol), poly(acrylic acid), polyacrylamide, poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polylactides, polyglycolides, poly(lactide-co-glycolides), chitosan, chitin, guar gum, xanthan gum, alginic acid, alginates, and carrageenan.

Incorporation of the polymer or a mixture of polymers into the dosage form is determined by the physicochemical and biopharmaceutical properties of the drug as well as process requirements.

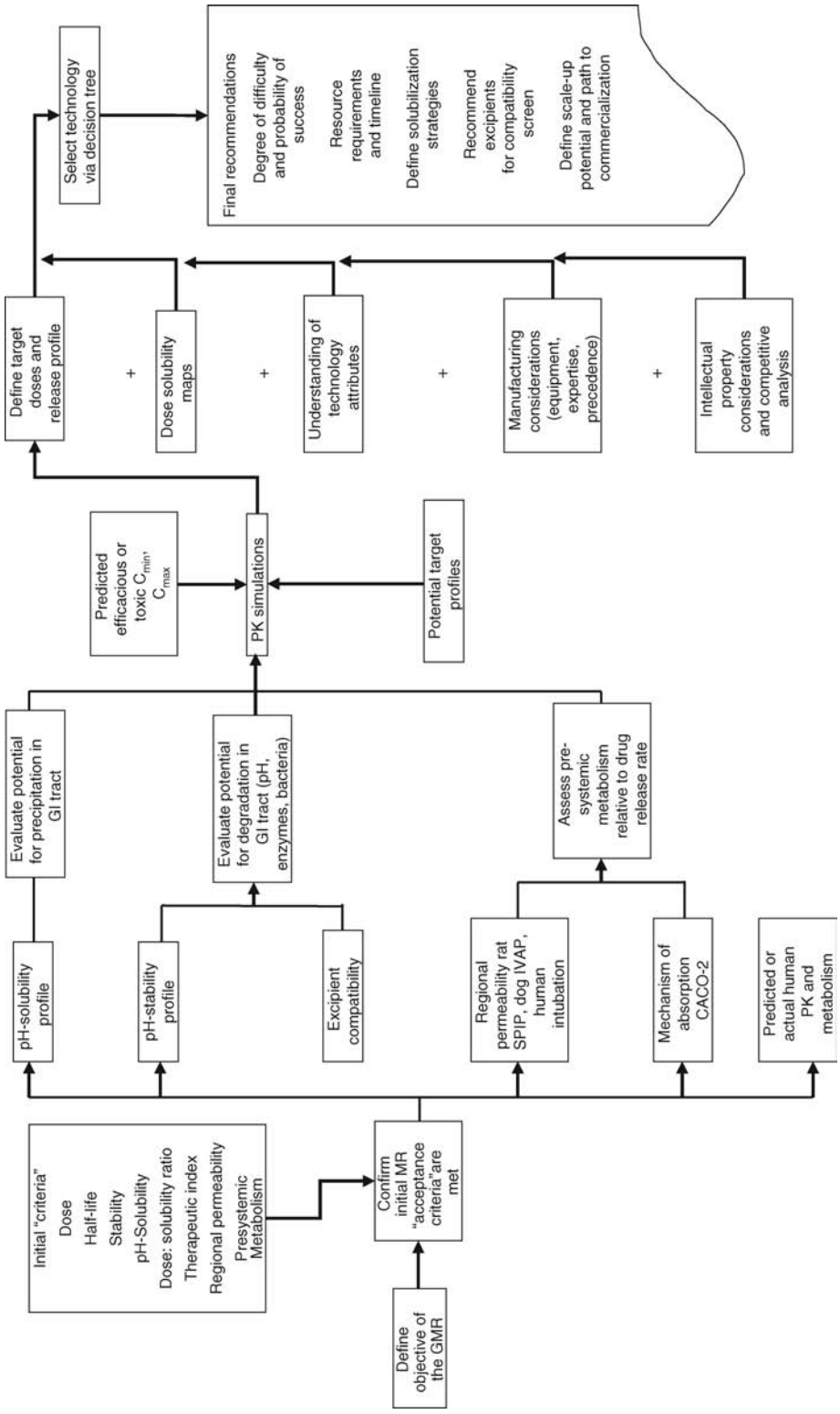


Figure 2 MR feasibility assessment flow chart. *Abbreviations*: MR, modified release; GI, gastrointestinal; IVAP, intestinal vascular access port; PK, pharmacokinetic; SPIP, single pass intestinal perfusion. *Source*: From Ref. 4.

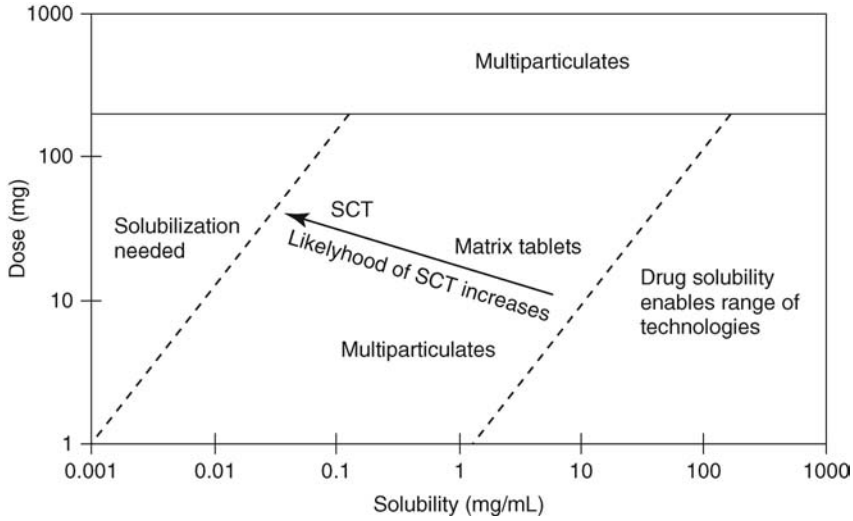


Figure 3 Example of a dose-solubility map to guide controlled-release technology selection. *Abbreviation*: SCT, swellable core technology. *Source*: From Ref. 4.

Long-chain hydrocarbons. Many waxes and fats provide modification of drug release because of their inherent hydrophobic/lipophilic characteristics. Examples included carnauba wax, glyceryl behenate, and glyceryl palmitostearate.

Additional Formulation Ingredients

Other materials for inclusion in the GMR are more specific to the selected granulation platform and are covered in the chapters dealing with specific processes, for example, wet granulation and roller compaction.

Compatibility of all Dosage Form Ingredients

Adequate care must be taken to demonstrate a lack of negative interactions between dosage form components as outlined in chapter 3. This feature of dosage form development is not unique to MR dosage forms and must be executed before launching into a viable GMR dosage form development program (11).

Dosage Form Performance Considerations

By definition, MR dosage forms are differentiated from conventional dosage forms by their distinctive drug-release pattern. Knowledge of the following listed dosage form characteristics is useful in the design and production of MR dosage units with reproducible drug-release patterns.

Drug-Release Mechanism

Manner of drug release from granules (Fig. 4) is typically either by diffusion, swelling, erosion and dissolution, or a combination of the various mechanisms. Mechanistic understanding allows the scientist insights into designing a formulation that can best accommodate the TPP.

This release mechanism is also dictated by the polymer characteristic and the stimulus it experiences in the release medium. Examples of the impact of formulation ingredients or environmental conditions on release modulating properties of hydrogels are provided in Table 1.

Drug-Release Pattern and Predictability

Movement of drug molecules within and out of a dosage form is a mass transport phenomenon. Starting with the simplest diffusive flux equation also known as Fick's first

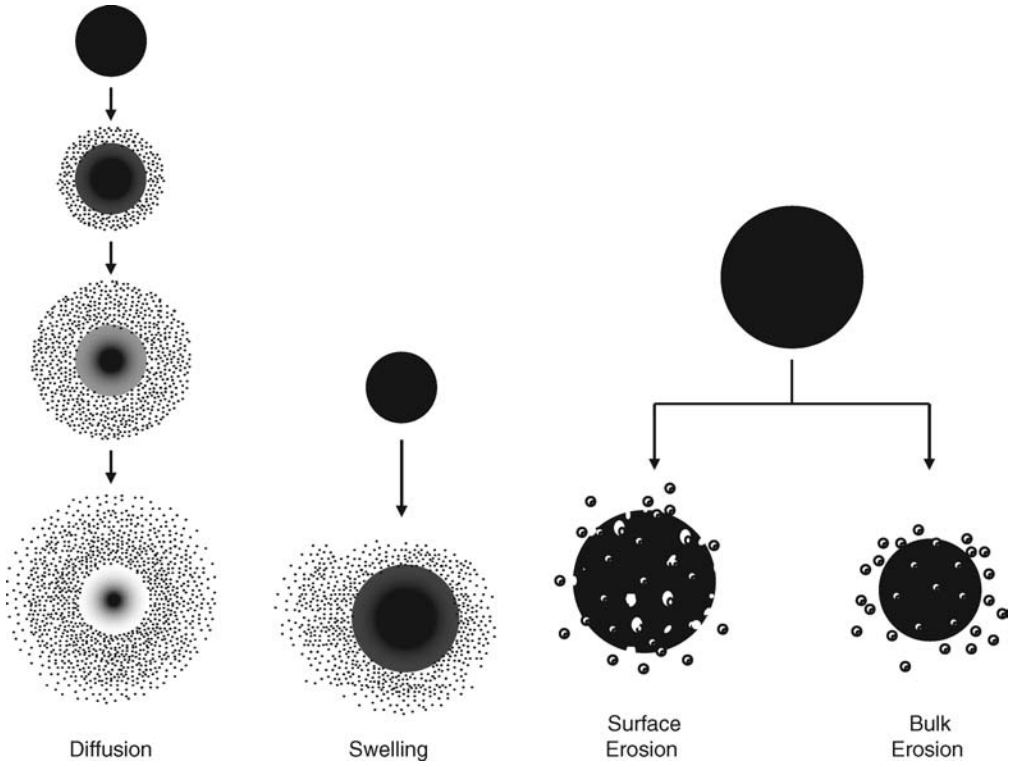


Figure 4 Schematic view of drug-release mechanisms from granules.

Table 1 Formulation Ingredients or Environmental Conditions That Modulate Release of Drug from Hydrogels

Stimulus	Hydrogel forming polymer	Mechanism causing changes in swelling, which in turn leads to release of drug
pH	Acidic or basic	Change in pH
Ionic strength	Ionic	Change in ionic strength—change in concentration of ions
Chemical species	Electron accepting groups	Electron donating compounds—formation of charge transfer complex
Thermal	Thermoresponsive, e.g., poly(*N*-isopropylacrylamide)	Change in temperature—change in polymer-polymer and water- polymer interactions
Electrical	Polyelectrolyte	Applied electric field—membrane charging—electrophoresis of charged drug
Ultrasound irradiation	Ethylene-vinyl alcohol	Ultrasound irradiation—temperature increase

law (12) that relates the amount of material flowing through a unit cross section:

$$J = -D\left(\frac{dC}{dx}\right)$$

where J is the diffusional flux, D is the diffusion coefficient or diffusivity, C is the concentration, and x is the distance of movement.

A number of mathematical equations are reviewed and published in literature (13,14), taking sample geometry and physical phenomena, such as swelling, into account.

Knowledge of the drug-release mechanism and availability of mathematical treatments allows simulations that model and interpret kinetics of the drug-release process from MR dosage forms. An example of the utility of simulating drug release is illustrated in case study 4.

Reproducibility of Drug-Release Pattern

- On a practical level, the drug-release pattern for a dosage form is typically established in vitro via dissolution testing.
- By definition, the drug-release profile is a key characteristic of an MR product.

Accordingly, regulatory agencies have published guidelines for dissolution testing of MR products (15,16). Recognizing that an MR dissolution profile cannot be adequately described by a single point, it is required to define acceptability limits (or set specifications) at multiple time points to demonstrate adequate conformance of a commercial product to that studied in a clinical setting and described in an New Drug Application (NDA) or equivalent document.

Regulatory guidance recommends a minimum of three time points to define the drug-release profile of an MR dosage form and to set specifications. An early time point ensures that no dose dumping is occurring, a middle time point serves as a check for the control of release profile, and a last time point ensures that complete drug release (at least 80%) has taken place.

To establish specifications per regulatory agency guidelines, particular attention needs to be given to the dissolution method developed. An example of how various dissolution test method parameters may affect drug release is briefly covered in case study 4.

Two additional items relating to dissolution testing of MR products are described below.

In vitro–in vivo correlation (IVIVC). When a predictive mathematical model is able to describe a relationship between an in vitro property of a dosage form, for example, drug dissolution profile, and an in vivo response, for example, drug's extent of absorption, an in vitro–in vivo relationship (IVIVR) is said to exist. IVIVR forms the basis for a determination of an IVIVC. The main objective of developing and evaluating an IVIVC is to establish the dissolution test as a surrogate for human bioequivalence studies, which in turn may reduce the number of bioavailability/bioequivalence studies performed during the initial development and approval process as well as with certain scale-up and post-approval changes. An example of an IVIVC for a commercial product is depicted in Figure 6 as part of the discussion in case study 2.

Dose dumping—food effects. As part of the effort to ensure and establish the unique drug-release pattern of an MR product, the relationship between food and alcohol effects on the drug dissolution pattern must also be demonstrated. This topic is of particular concern for drugs with a narrow therapeutic window because the complete dose may be more rapidly released from the dosage form than intended, creating a potential safety risk for the study subjects or the ultimate consumer of the MR product. Utility of in vitro dissolution testing for exploring this issue was recently highlighted (17,18).

TYPES OF MR GRANULATIONS AND CASE STUDIES

Granulated MR dosage forms may be classified as follows:

1. Matrix type
   Depending on the physicochemical properties of the drug and the MR polymer(s), various granulation techniques can be employed, which include the following:
   - Conventional (high shear or fluid bed) wet-granulated tablets with hydrophilic or hydrophobic polymer (barrier coated or uncoated)
   - Specialized granulation techniques, such as rotor granulation, extrusion spheronization, melt granulation (using high shear mixer), and hot melt extrusion.
   - Dry granulated (roller compacted) tablets
2. Multiparticulates
   - Granules in capsules
     - Nonspherical
     - Spherical
   - Barrier coated (spherical) granules

Chapters 5, 6, and 8–10 cover specific process related details for the production of granules classified above. Accordingly, processing effects on drug-release patterns and decision making specific to GMR are highlighted next in the form of case studies.

Case Study 1

In many cases, the move to MR is part of product lifecycle management and a conventional tablet dosage form is available as a starting point for formulation. From a manufacturing perspective, this strategy is advantageous because of the familiarity in handling the materials and known dosage form characteristics.

In this example (19) of how an "immediate release" (IR) wet-granulated caplet formulation can be transformed to a controlled or MR wet-granulated formulation, Dow scientists took a model system containing naproxen sodium as the model drug, and successfully demonstrated the IR to MR transformation using Methocel K4MP as the drug-release retarding polymer (Table 2).

Table 2 Composition of Foamed Binder Formulations

		Immediate release model formulation		Modified release formulation	
	Ingredient	mg	(approx %)	mg	(approx %)
1	Naproxen sodium, USP	220	44.0	100	20.0
2	Methocel K4MP, USP	0	0.0	150	30.0
3	Methocel E5PLV, USP (7% solution)	8.72	2.0	8.81	1.0
4	Microcrystalline cellulose, NF	100	20	75	15
5	Fast Flo lactose-316, NF	152.5	30.5	167.5	33.5
6	Croscarmellose sodium	15	3.0	0	0.0
7	Magnesium stearate, NF	2.5	0.5	2.5	0.5

The change in the drug-release pattern (Fig. 5A, B; IR and MR) is evident for tablets compressed with granulation batches made at the laboratory scale (10 L), pilot scale (150 L), and with commercial scale equipment (600 L).

Another interesting key process improvement covered in this publication is the use of a foamed binder solution that had a consistency of shaving cream (Fig. 5C). Foamed binder solution use eliminates the need for piping, nozzles, and studies for demonstrating the effect of binder addition on granulation characteristics. This is a relatively new technology introduced by Dow in the last few years (20,21) and enables direct addition of the foam to the dry ingredients into the granulator, as shown in Figure 5D.

In conclusion, foam binder technology enables a relatively easy transformation of an IR to MR formulation and reduces the complexity of the scale-up process.

Case Study 2

For some compounds with a short half-life, it is useful to maintain the clinical efficacy of the drug by prolonging the effective plasma level with additional drug release, once the target plasma concentration is achieved with a standard immediate release formulation. Typically, this type of desired drug-release pattern is achieved by a dosage form that is composed of two parts—an immediate release part and an MR part. A specific example is Zolpidem® extended-release or MR, which is a two-layer, biphasic tablet: One layer releases approximately 60% of the dose immediately, and the second layer releases the remainder of the drug content at a slower rate (22). The drug-release pattern and plasma concentration profile for Zolpidem® MR are shown in Figure 6 (23).

In a two-part publication, Ohmori and Makino (24,25) illustrate some of the challenges in developing an MR formulation, using dry granulation as one option to generate an MR matrix in a bilayer tablet. The model drug used was phenylpropanolamine hydrochloride (PPA). A

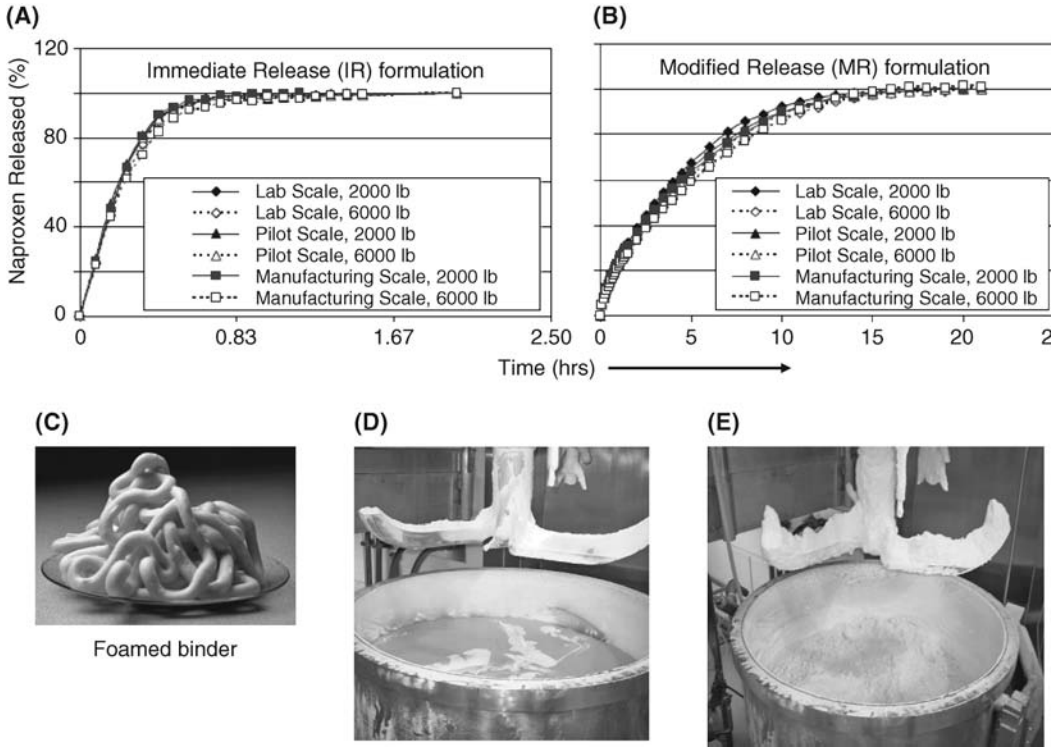


Figure 5 Foamed binder granulation. (**A**) Dissolution of naproxen from IR tablets. (**B**) Dissolution of naproxen from MR tablets. (**C**) Foamed binder. (**D**) 600-L Gral containing 38.3 L of foamed binder on top of 135 kg of MR formulation powders (before wet massing step). (**E**) 600-L Gral after wet massing step during batch process. *Abbreviations*: IR, immediate release; MR, modified release. *Source*: From Ref. 19.

target drug-release profile was initially defined and HPMC (Metolose 2280) was chosen as the release modulating agent. On the basis of preliminary studies, the PPA content in the immediate release layer was pegged at 5 mg, PPA content in the MR layer at 20 mg, and the weight of each caplet layer was finalized at 200 mg.

Since the IR ingredients were wet granulated and the granule median particle size was 214 μm, wet granulation of the MR ingredients was also considered, initially. However, wet-granulated MR granulation was not suited for compression using the bilayer tablet press. To overcome this hurdle and yet have a granulation with a median particle size comparable to that of the IR granules, roller compaction, a dry granulation process was adopted. Median particle size of the roller compacted MR granulation was 225 μm.

Keeping in perspective the number of compression events the drug-release modulating polymer would undergo from blending of ingredients to finished bilayer tablet, the following parameters were studied:

- order of filling granulation into the bilayer tablet press (Fig. 7),
- roller compaction pressure of the MR granules.

Order of filling granulation into the bilayer tablet press was not found to impact the drug-release profile (Fig. 8). This effect was attributed to the ability of HPMC to hydrate rapidly, before the shape factor could additionally influence drug dissolution.

Roller compaction pressure, however, played a role in the production of robust bilayer caplets, and the roller compaction pressure was somewhat co-relatable to the incidence of lamination in bilayer caplets (Fig. 9A).

A follow-up investigation of the laminated bilayer caplets revealed that the lamination did not occur as expected at the interface of the two layers, but within the MR layer. Density

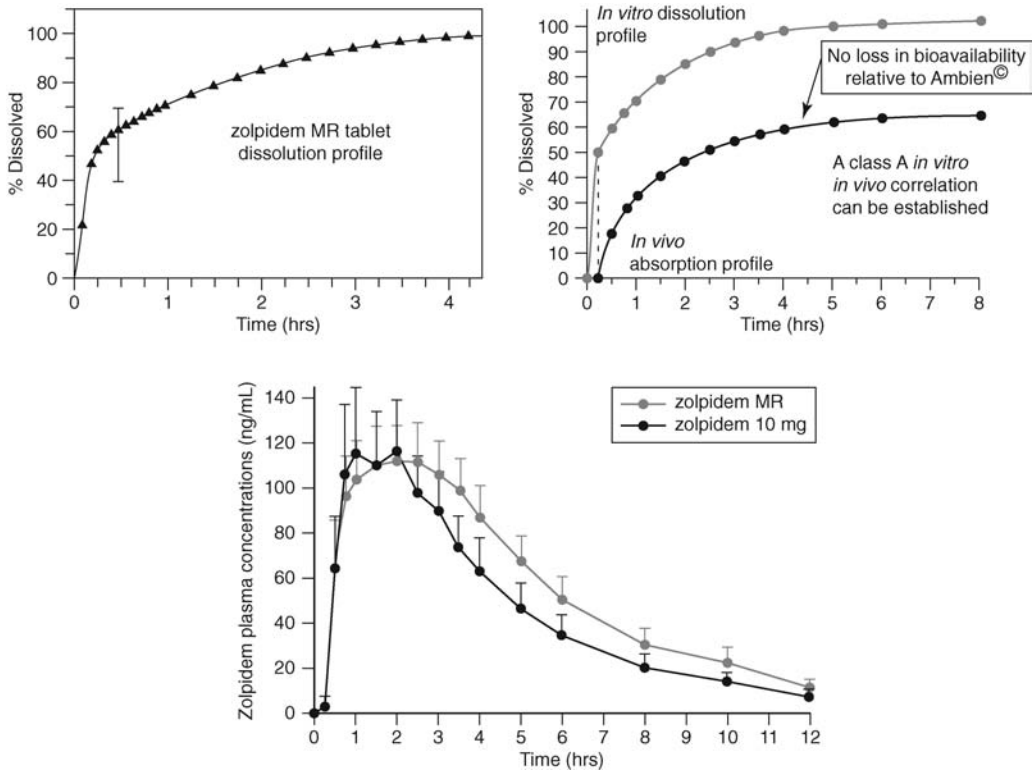


Figure 6 Zolpidem® MR tablets. *Abbreviation*: MR, modified release. *Source*: From Ref. 23.

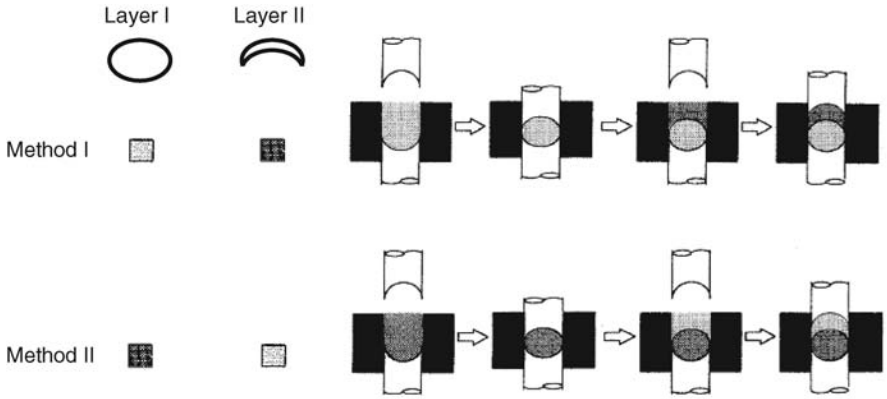


Figure 7 Schematic representation of bilayer compression. ( ) represents immediate release portion and ( ) represents modified release portion. *Source*: From Ref. 24.

distribution studies of the MR layer revealed better uniformity when the MR ingredients were part of the second, convexo-concave layer, as compared to the convexo-convex first layer. Images from one technique (CT scan) used to study the density distribution in tablets by are shown in Figure 9B.

In conclusion, robust bilayer caplets with a target PPA release profile were produced when the wet-granulated IR layer was compressed into the tablet press first, followed by a blend (0 kN roller compaction pressure) of the MR ingredients. While dry granulation was a

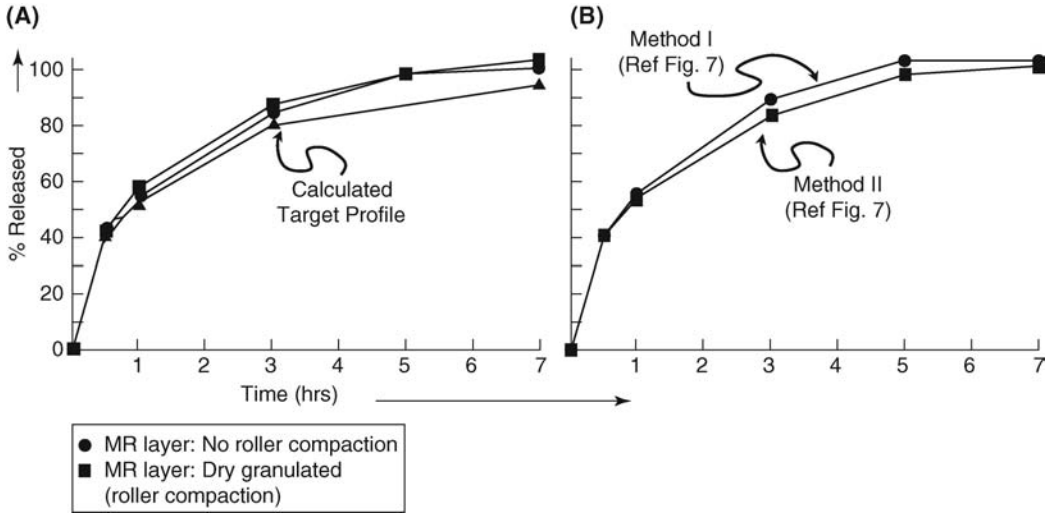


Figure 8 Dissolution of PPA from bilayer tablets. (**A**) Effect of manufacturing method of the modified-release portion ($n = 6$). (**B**) Effect of filling order of the modified-release portion in bilayer compression. *Abbreviation*: PPA, phenylpropanolamine hydrochloride. *Source*: From Ref. 24.

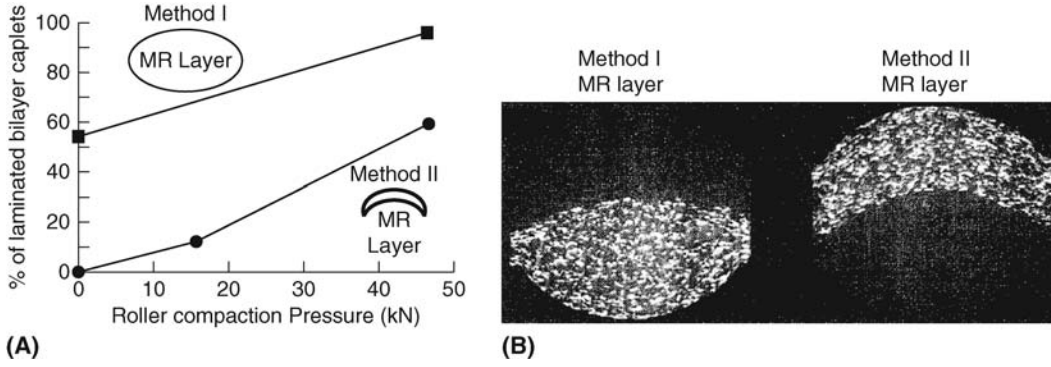


Figure 9 Bilayer caplets (**A**) relationship between manufacturing method and percentage of laminated caplets. (**B**) CT of caplet cross-section in which the calcium from dibasic calcium phosphate present in MR layer is seen as white spots. *Abbreviation*: MR, modified release. *Source*: From Ref. 25.

good alternative to wet granulation, in this instance, granulation of the MR component did not result in a robust end product.

Case Study 3

Spray-drying (chap. 5)—a technique for producing granules by drying of a solution or suspension that is pumped and atomized into a drying chamber under a controlled gas stream, was initially reported for use in improving the dissolution of poorly water-soluble drugs. More recently, it has shown promise in the preparation of MR products. The suitability of a spray-drying process for modifying the release of a model drug from a tablet formulation is illustrated in the following example published by Chen et al. (26,27) as a two-publication set.

Acetaminophen (APAP) was used as the model drug in the formulations studied. Two pH sensitive release modifying polymers, chitosan (CHT) and hydroxypropyl methylcellulose phthalate (HPMCP), were used as the release modulating agents. Interestingly, CHT forms a solution in acid solutions but is insoluble in alkaline solution, whereas HPMCP dissolves in alkaline solutions but is insoluble in acid solutions. To accommodate these types of differing

material properties, adaptation of the spray dryer nozzle configuration from a conventional version to a four-fluid version was attempted. This set of publications illustrated how

- a conventional process is adapted, to accommodate material processing requirements, and
- multiple combinations of polymers with differing properties may be utilized in a meaningful manner for manufacturing an MR product having a drug-release profile of choice.

A diagram of the newer nozzle design is provided in Figure 10A. Solutions containing APAP and each polymer solubilized in suitable aqueous media were pumped separately through the two liquid feed channels of a four-fluid nozzle to obtain composite particles

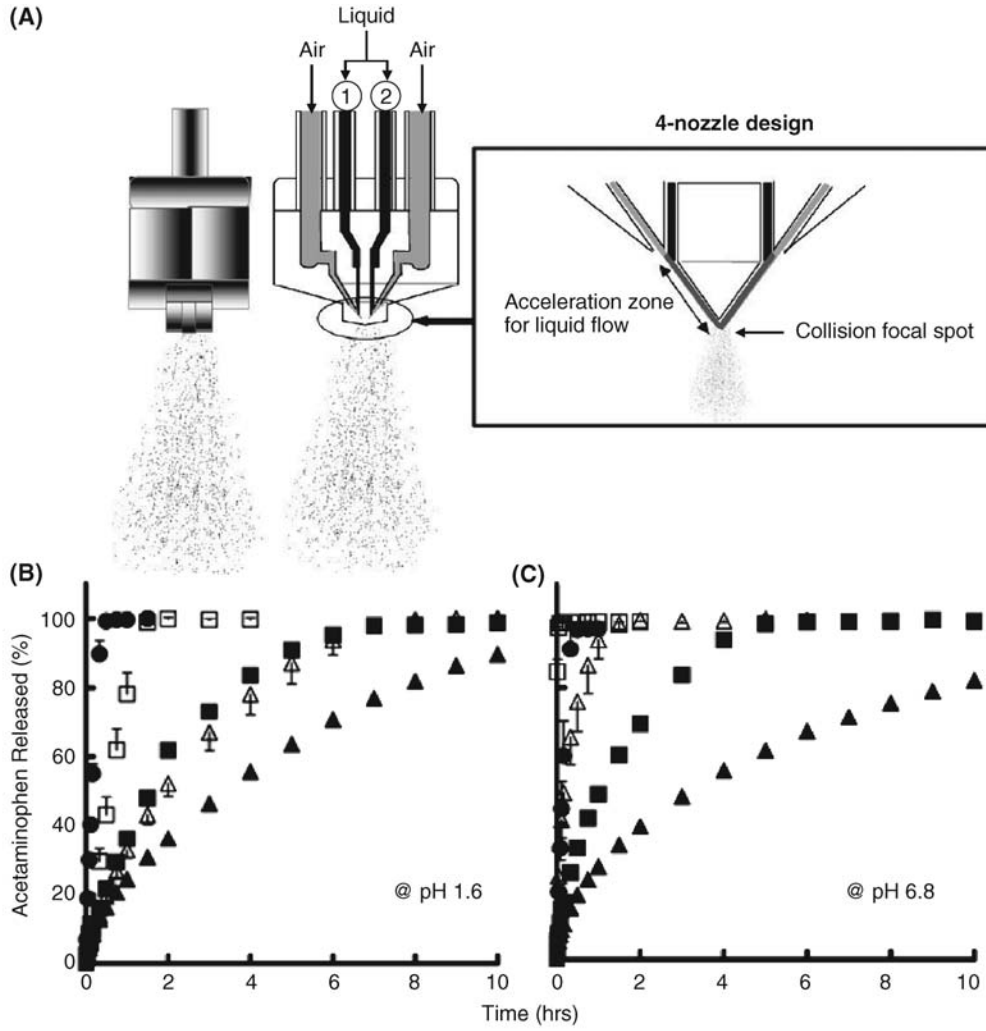


Figure 10 (**A**) Schematic of novel four-nozzle design. (**B**, **C**) Dissolution profiles of APAP-CHT-HPMCP systems. Symbol key: (●) APAP spray dried; (■) APAP:CHT:HPMCP 1:0.5:0.5; physical mixture (▲) APAP:CHT:HPMCP 1:2.5:2.5; physical mixture(□) APAP:CHT:HPMCP 1:0.5:0.5; spray dried (△) APAP:CHT:HPMCP 1:2.5:2.5; spray dried. *Abbreviations*: APAP, acetaminophen; CHT, chitosan; HPMCP, hydroxypropyl methylcellulose phthalate. *Source*: From Refs. 26 and 27.

containing all three materials (APAP:CHT:HPMCP) under a set of predefined drying conditions. Tablets of spray-dried composite particles for each combination of APAP:CHT:HPMCP were obtained using a Carver press type "universal testing machine," and the JP XIV (Japanese Pharmacopeia) paddle method was used to generate APAP release profiles for each tablet preparation. Tablets containing physical mixtures of the three ingredients in the same ratios as that of the spray-dried granulations were also compressed and subjected to dissolution tests.

Figure 10B, C shows the release of APAP as a function of time for tablets manufactured with various spray-dried granulations and physical mixtures of APAP, CHT, and HPMCP, in acid and alkaline media, respectively. From these dissolution profiles, it can be concluded that APAP release is influenced by the presence of pH sensitive polymers. While a physical mixture of the drug and polymers demonstrates some slowing down of the drug-release rate, especially in the acidic dissolution medium, a marked and somewhat pH insensitive product is obtained in the case of spray-dried granules. On the basis of tablet dissolution profiles in the two media, the superiority of the spray-drying technique as an MR granulation process, as compared to the use of a simple physical mixture for tablet production, is readily apparent.

To get a better understanding of how the process affected the processed material at a molecular level, physical characterization of the spray-dried granules and physical mixtures of the three ingredients by DSC, FTIR, and XRD was also undertaken. Studies revealed that APAP existed as a solid dispersion only in spray-dried granules and the carbonyl group in APAP hydrogen bonds with the amino group in CHT.

In conclusion, spray-drying is a viable technique for the production of GMR dosage forms. Spray-drying as a processing method for the production of MR granulations has also been studied for modification of drug delivery to the lung and in dosage forms for antibodies (28,29).

Case Study 4

In a series of five related papers, Fukui et al. (30–34) provide an interesting example on comparing and contrasting the performance of granules obtained from three multiparticulate GMR processing methods. PPA at a 500 mg dose was used as the model drug and ethylcellulose (EC) was chosen as the drug-release retarding agent. Capsules of drug containing matrix-granules prepared by the extrusion process (chap. 12) were compared with those prepared by a layering process in a rotor granulator (Chap. 11) or a fluid-bed rotor granulator (chap. 10).

Starting with a simpler system, an understanding of the drug-release process was first attempted. This exercise served to set the stage for evaluation of the granules obtained by three different granulation methods and identification of one MR granulation process that was most expedient from a commercial manufacturing perspective.

In the first part of the study, two grades of EC (#10 and #100) were used to generate matrix granules by the extrusion process and the release of drug was mathematically modeled. Two equations were deemed necessary for describing the entire drug-release curve, as a function of time:

1. Higuchi's square root equation—for the initial part of the curve $m_t = K_H(t)^{1/2}$, where m_t is the amount of PPA released, K_H is the apparent release rate constant, and t is the release time.
2. The cube root equation—for the later part of the curve $(1–m_t)^{1/3} = K_{App}(t)$, where m_t is the amount of PPA released, K_{App} is the apparent release rate constant, and t is the release time.

Granules containing EC#10 gave a better agreement between the theoretical and experimental data, and thus EC#10 was chosen as the drug-release modulating agent for further studies.

In the second part of the study, effect of EC#10 content and ethanol (EtOH, component of binder solution) content on drug release was studied, in recognition of the fact that the composition of the binder solution influences granule properties. Upon physical examination

of the granules, increasing EtOH and/or EC content in the binder solution facilitated formation of a smoother matrix structure. EtOH concentrations at and above 85% in the binder solution resulted in granules that exhibited a fairly constant value for the transition point at which PPA release changed from the square root profile to the cube root profile.

The dissolution method was challenged next in the third part of the series of experiments. Four parameters were evaluated for their potential influence on in vitro drug release. They were as follows:

- Volume of buffer solution
- pH of the buffer solution
- Paddle rotation speed
- Dosage strength

The data suggested that the analytical method was appropriate for the intended purpose, and except for pH of the buffer solution the other parameters had a lesser impact on the drug-release profile.

The above-described studies now set the stage for comparison of PPA release from three granulations, which differed mainly in the granulation process. The three granulation processes, reported in the fourth and fifth parts of the experimental series are summarized in Figure 11.

While there were slight differences in the dissolution curves (Fig. 12A) for capsules containing granules from the standard wet granulation process (designated capsule A, matrix

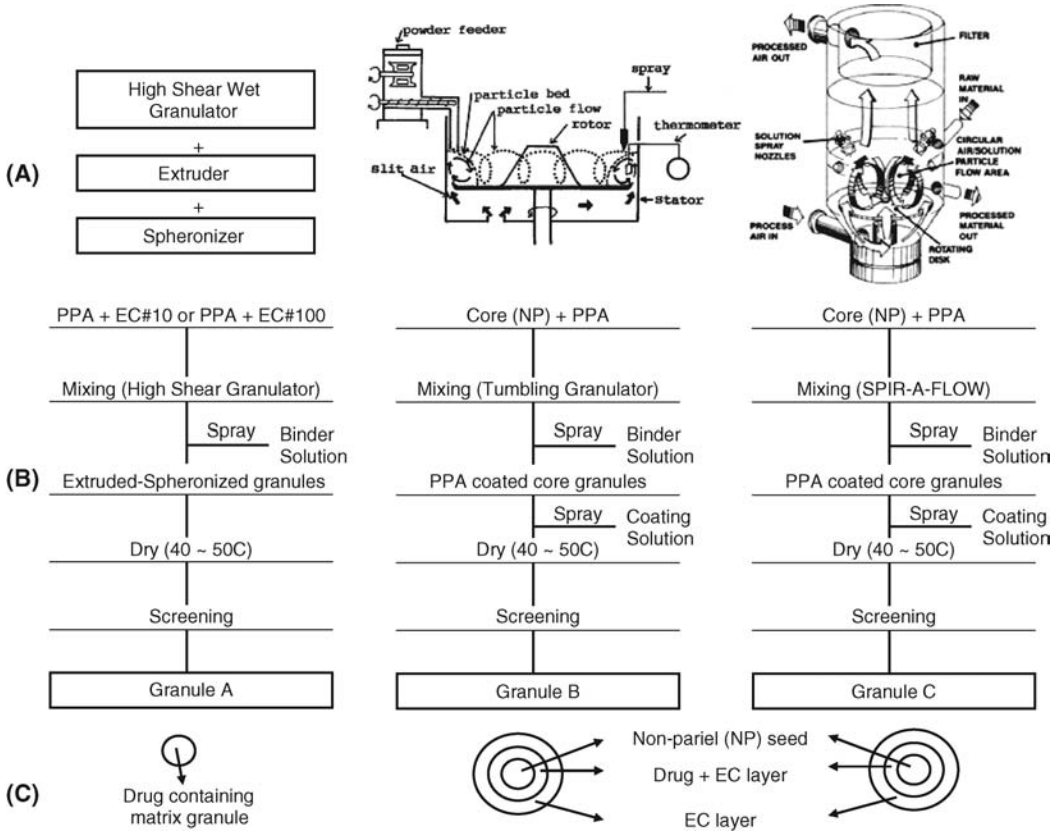


Figure 11 Interpreted summary of the three MR granulation methods used to prepare PPA granules. Schematic representation of (**A**) equipment, (**B**) process, (**C**) granule (drawings not to scale). *Abbreviations*: MR, modified release; PPA, phenylpropanolamine hydrochloride. *Source*: Adapted in part from Refs. 33–36.

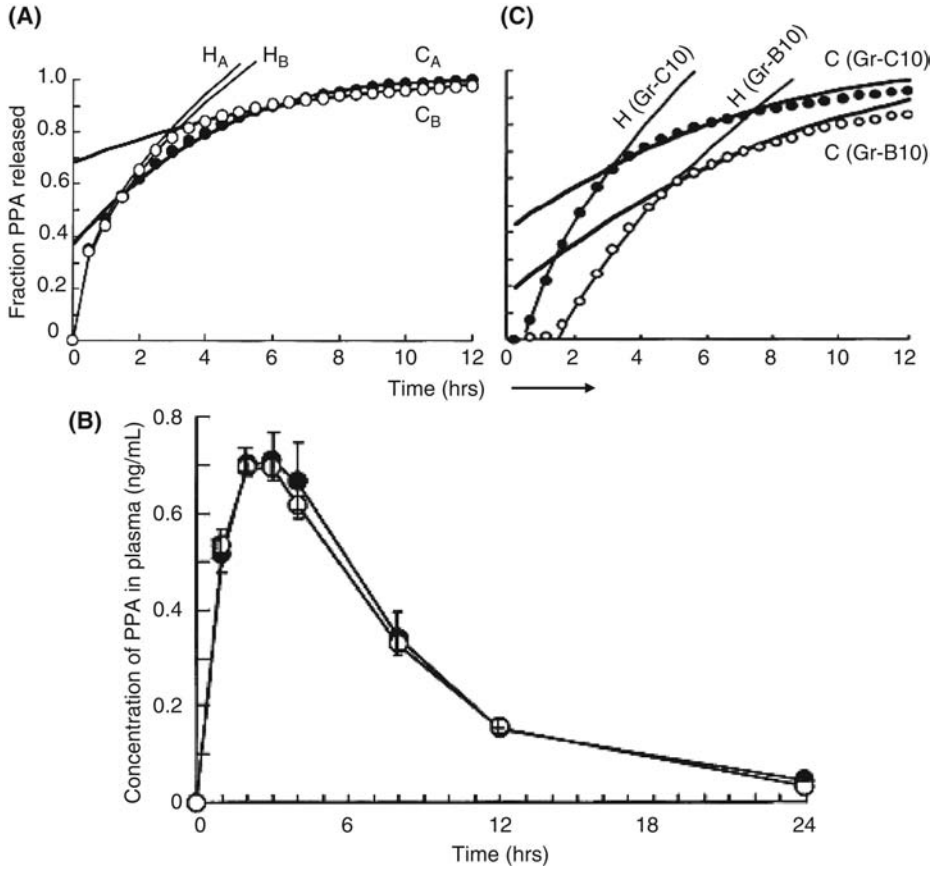


Figure 12 (**A**) Release and simulation curves: (●) capsule A; (○) capsule B. H_A, simulation using the square-root time law equation for capsule A. H_B, Simulation using the square-root time law equation for capsule B. C_A, simulation using the cube-root time law equation for capsule A. C_B, simulation using the square-root time law equation for capsule B. (**B**) Concentration of PPA in the blood of beagle dogs: (●) capsule A; (○) capsule B. (**C**) Release and simulation curves: (○) capsule B*; (●) capsule C. $H_{(Gr\text{-}C10)}$, simulation using the square-root time law equation for capsule C. $H_{(Gr\text{-}B10)}$, simulation using the square-root time law equation for capsule B*. $C_{(Gr\text{-}C10)}$, simulation using the cube-root time law equation for capsule C. $C_{(Gr\text{-}B10)}$, simulation using the square-root time law equation for capsule B*. *Note*: Capsule B and B* granulations only differ in the thickness of EC coat. *Source*: From Refs. 33 and 34.

granules) and the rotor-granulator (designated capsule B, EC layer coated granules), their in vivo plasma concentration curves (Fig. 12B) were comparable.

Capsule A granules showed a higher variability in the correlation curve of in vitro PPA release to in vivo PPA plasma concentration; therefore, authors concluded that capsule B granulation was the more robust formulation.

Since EC layer coated granules performed better in vivo as compared to matrix granules, the fifth part of the experimental series examined the effects of two EC layer coating processes, that is, rotor granulation and fluid bed rotor granulation (Spir-A-Flow) on the release of PPA. The PPA release profiles of EC layered granules varying in EC content between 6% and 10% for both processes were examined.

In contrast to the matrix granules, EC layer coated granules obtained by both processes exhibited a lag time in PPA release (Fig. 12c). The lag time increased with EC content; therefore, this lag time was hypothesized to be an indicator of surface coverage by EC during the layer coating process.

Matching simulation curves generated with previously developed mathematical model(s) to the PPA release profile curves of the newly prepared granules showed excellent agreement.

This match enabled plotting the relationship between the apparent release rate constants (K_H and K_{app}) as a function of EC coating percentage. At the highest EC coating level (10%), K_H and K_{app} values for granules produced by either rotor granulation or fluid bed rotor granulation were similar. Since the fluid bed rotor granulation process did not result in a granulation with superior properties to those produced by simple rotor granulation, a change in process was not deemed necessary.

In conclusion, rotor granulation process was identified as the most convenient GMR process for manufacturing an MR dosage form for the selected model drug.

CONCLUSIONS

Piecing together a granulated MR dosage form is a complex process that may involve several iterative learning cycles in an effort to generate a product having a drug-release pattern of choice. Key material, analytical, and process related considerations are presented in this chapter as tools for a successful dosage form development program that results in a robust and scalable granulation.

REFERENCES

1. Banker GS, Rhodes CR, eds. Modern Pharmaceutics. 4th ed. New York: Marcel Dekker, 2002.
2. Rathbone MJ, Hadgraft J, Roberts MS, eds. Modified-Release Drug Delivery Technology. New York: Marcel Dekker, 2003.
3. Fiese EF. General pharmaceutics—the new physical pharmacy. J Pharm Sci 2003; 92(7):1331–1342.
4. Thombre A. Assessment of the feasibility of oral controlled release in an exploratory development setting. Drug Discov Today 2005; 10(17):1159–1166.
5. Chaubal M. Application of drug delivery technologies in lead candidate selection and optimization. Drug Discov Today 2004; 9(14):603–609.
6. Amidon GL, Lennernas H, Shah VP, et al. A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res 1995; 12:413–420.
7. Chrzanowski F. Preformulation considerations for controlled release dosage forms. Part I. Selecting candidates. AAPS PharmSciTech 2008; 9(2):635–638.
8. Chzranowski F. Preformulation considerations for controlled release dosage forms. Part II. Selected candidate support. AAPS PharmSciTech 2008; 9(2):639–645.
9. Chzranowski F. Preformulation considerations for controlled release dosage forms. Part III. Candidate form selection using numerical weighting and scoring. AAPS PharmSciTech 2008; 9(2):646–650.
10. Rios M. Polymers for controlled release formulation follows function. Pharm Tech 2005; 6(29).
11. Serajuddin ATM, Thakur AB, Ghoshal RN, et al. Selection of solid dosage form composition through drug-excipient compatibility testing. J Pharm Sci 2000; 88(7):696–704.
12. Diffusion and dissolution. In: Martin AN, Bustamante P, Chun AHC, eds. Physical Pharmacy. 4th ed. PA: Lea & Febiger, 1993:325.
13. Kanjickal DG, Lopina ST. Modeling of drug release from polymeric delivery systems—a review. Crit Rev Ther Drug Carrier Syst 2004; 21(5):345–386.
14. Arifin DY, Lee LY, Wang CH. Mathematical modeling and simulation of drug release from microspheres: Implications to drug delivery systems. Adv Drug Deliv Rev 2006; 58(12–13):1274–325.
15. Guidance for Industry. SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, 1997. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070640.pdf.
16. The European Agency for the Evaluation of Medicinal Products. Committee for Propietary Medicinal Products (CPMP). 1999. Available at: http://www.emea.europa.eu/pdfs/human/qwp/060496en.pdf.
17. Chandaroy P, Jiang X, Lee C, et al. *In vitro* alcohol-induced dose-dumping dissolution studies of generic modified-release oral drug products. AAPS J 2008; 10(S2).
18. Fadda HM, Sousa LL, Basit AW. Alcohol induced dose-dumping of modified release budesonide formulations *in vitro*. AAPS J 2008; 10(S2).
19. Foam granulation technology: scale-up of immediate release and controlled release formulations from laboratory scale to manufacturing scale. Available at: http://www.dow.com/PublishedLiterature/dh_0062/0901b803800629e6.pdf. Accessed April 2009.
20. Keary CM, Sheskey PJ. Preliminary report of the discovery of a new pharmaceutical granulation process using foamed aqueous binders. Drug Dev Ind Pharm 2004; 30(8):831–845.

21. Ji J, Nunes CJ, Bindra DS. Selection of binder addition technique in a high-shear wet granulation process: impact of formulation wettability. AAPS J 2008; 10(S2).
22. Doghramji PP. Insomnia: zolpidem extended-release for the treatment of sleep induction and sleep maintenance symptoms. Med Gen Med 2007; 9(1):11.
23. Sanofi-Synthelabo R&D. Available at: http://en.sanofi-aventis.com/binaries/03-06-10_GoldmanSachs_EN_tcm28-19683.pdf. Accessed April 2009.
24. Ohmori S, Makino T. Sustained-release phenylpropanolamine hydrochloride bilayer caplets containing the hydroxypropylmethylcellulose 2208 matrix. I. Formulation and dissolution characteristics. Chem Pharm Bull 2000; 48(5):673–677.
25. Ohmori S, Makino T. Sustained-release phenylpropanolamine hydrochloride bilayer caplets containing the hydroxypropylmethylcellulose 2208 matrix. II. Effects of filling order in bilayer compression and manufacturing method of the prolonged-release layer on compactibility of bilayer caplets. Chem Pharm Bull 2000; 48(5):678–682.
26. Chen R, Okamoto H, Danjo K. Particle design using a 4-fluid-nozzle spray-drying technique for sustained release of acetaminophen. Chem Pharm Bull 2006; 54(7):948–953.
27. Chen R, Takahashi H, Okamoto H, et al. Particle design of three-component system for sustained release using a 4-fluid nozzle spray-drying technique. Chem Pharm Bull 2006; 54(11):1486–1490.
28. Seville PC, Li HY, Learoyd TP. Spray-dried powders for pulmonary drug delivery. Crit Rev Ther Drug Carrier Syst 2007; 24(4):307–360.
29. Kaye RS, Purewal TS, Alpar HO. Simultaneously manufactured nano-in-micro (SIMANIM) particles for dry-powder modified-release delivery of antibodies. J Pharm Sci 2009 February 2 [Epub ahead of print].
30. Fukui A, Fujii R, Yonezawa Y, et al. Analysis of the release process of phenylpropanolamine hydrochloride from ethylcellulose matrix granules. Chem Pharm Bull 2002; 50(11):1439–1442.
31. Fukui A, Fujii R, Yonezawa Y, et al. Analysis of the release process of phenylpropanolamine hydrochloride from ethylcellulose matrix granules II. Effects of the binder solution on the release process. Chem Pharm Bull 2004; 52(3):298–302.
32. Fukui A, Fujii R, Yonezawa Y, et al. Analysis of the release process of phenylpropanolamine hydrochloride from ethylcellulose matrix granules III. Effects of the dissolution condition on the release process. Chem Pharm Bull 2006; 54(8):1091–1096.
33. Fukui A, Fujii R, Yonezawa Y, et al. Analysis of the release process of phenylpropanolamine hydrochloride from ethylcellulose matrix granules IV. Evaluation of the controlled release properties for *in vivo* and *in vitro* release systems. Chem Pharm Bull 2007; 55(11):1569–1573.
34. Fukui A, Fujii R, Yonezawa Y, et al. Analysis of the release process of phenylpropanolamine hydrochloride from ethylcellulose matrix granules V. Release properties of ethylcellulose layered matrix granules. Chem Pharm Bull 2008; 56(4):525–529.
35. Maejima T, Ohsawa T, Kobayashi M, et al. Factors effecting spherical granulation of drugs by tumbling granulation method. Chem Pharm Bull 1992; 40(2):488–492.
36. Freund-Vector technical brochure. Available at http://www.vectorcorporation.com/.

18 Granulation of Poorly Water-Soluble Drugs

Albert W. Brzeczko
Acura Pharmaceuticals, Inc., Baltimore, Maryland, U.S.A.

Firas El Saleh
ISP Global Technologies Deutschland GmbH, Cologne, Germany

Jiao Yang
ISP Pharma Technologies, Inc., Columbia, Maryland, U.S.A.

INTRODUCTION

Over the past two decades, advances in drug discovery techniques have been significant in identifying new and novel therapeutics agents in the pharmaceutical industry. Receptor mapping and molecular modeling coupled with high-throughput screening have revealed plethora drug candidates for numerous disease states. Because of the nature and the location of many of these receptors in a lipophilic membrane, drug candidates having the best molecular configuration and fitting into these receptors may, by design, be poorly water soluble in nature. It is estimated that over 40% of the new chemical entities in drug development are characterized as poorly water soluble (1). Lipitor (atorvastatin calcium), the top selling drug in 2007, and Prevacid (lansoprazole), also in the top 10 in sales in 2007, are examples of drugs with significant therapeutic impact, which are classified as poorly water soluble. It is certain that more will follow. However, poorly water-soluble drugs present a challenge to formulators of pharmaceutical oral solid dosage forms to improve the drug's bioavailability while maintaining product stability, both physically and chemically, and providing a robust commercial process.

From a historical perspective, the classification of drug solubility has been graded according to pharmacopial standards for solubility (2). Ranging from freely water soluble to water insoluble, drug solubility is determined from its equilibrium solubility in water. In addition to categorization based on equilibrium solubility, a bioclassification system (BCS) has been created that not only categorizes a drug based on solubility, but also on its permeability (3). The BSC classes for solubility and permeability are given in Figure 1.

Initially designed as criteria for waiver of bioequivalence testing based on in vitro testing for immediate release, highly soluble, highly permeable drugs (BCS 1) (4), the BCS has been a very valuable tool for determining formulation and processing strategies in the development of oral drug products. Consideration in the BCS solubility criteria is given to drug dose as well as to the pH solubility profile of a drug. Therefore, two drugs may be categorized as sparingly soluble, but drug *A* has a highest therapeutic dose of 1 mg and drug *B* has a highest dose of 100 mg; under the BCS guidance, drug *A* may meet the highly soluble criteria (either class 1 or 3), whereas drug *B* would be considered poorly soluble (class 2 or 4). For the purpose of this chapter, granulation and formulation techniques will be primarily discussed for drugs considered as BCS class 2 and class 4.

As many chapters in this text will reinforce, both wet and dry granulation techniques are important tools to aid in solving oral solid dosage development problems. Improving content uniformity, increasing tablet compressibility, enhancing powder flow, and to some extent, improving dissolution rates and bioavailability are a few examples of the traditional applications of granulation techniques. However, since conventional water-based wet granulation processing such as high-shear, fluid-bed granulation or dry granulation processing, such as roller compaction, does not impart significant change to poorly water-soluble drug particles, conventional granulation practices for poorly water-soluble drugs are limited. It is well documented that the use of surfactants in tablet formulations can improve the dissolution rate of poorly soluble drugs (5). However, as the limits of drug solubility move to

Figure 1 BSC classes for solubility and permeability.

lower solubilities (≤10 μg/mL), traditional granulation techniques and outcomes (i.e., content uniformity, powder flow, compressibility) yield to newer granulation techniques to effect a change to highly lipophilic and highly crystalline drugs to produce drug products with enhanced solubility and bioavailability. Spray drying, which had long been relegated to pharmaceutical excipients production, has more recently emerged as a useful granulation technique in the manufacture of poorly water-soluble drug products (6). In addition to reporting the emerging use of spray drying in pulmonary drug delivery and therapeutic proteins, Parikh notes the growing interest for producing amorphous solid dispersion drug products through solvent-based spray drying. The face of dry-granulation techniques is also changing, wherein conventional roller compaction processing is yielding to thermal dry granulation processing such as hot melt extrusion, and spray congealing (spray freezing). These thermal processes are employed to intimately mix polymers in a molten state [temperature at or above melting temperature (T_m) or glass transition temperate (T_g)] with poorly water-soluble drugs. The resulting solid solutions or solid dispersions from these processes have been reported to improve drug solubility and bioavailability when compared with physical mixtures of drug and polymers (7).

The focus of this chapter will be to highlight the role that granulation technology plays in improving the solubility of poorly water-soluble drugs, particularly around drug particle size reduction and nanoparticle technology, drug complexation, and solid drug dispersion. Increasing drug solubility through particle size reduction has been a mainstay of the pharmaceutical industry. The Noyes-Whitney equation shows a direct relationship between the rate of dissolution and the surface area of the solid (8).

$$\frac{dW}{dt} = \frac{DA(C_s - C)}{L} \qquad \text{[eq. 1]}$$

where $\frac{dW}{dt}$ is the rate of dissolution, A is the surface area of the solid, C is the concentration of the solid in the bulk dissolution medium, C_s is the concentration of the solid in the diffusion layer surrounding the solid, D is the diffusion coefficient, and L is the diffusion layer thickness.

Micronization techniques to decrease particle size and hence impart an increase in specific surface area of the drug include simple comminution processing such as jet milling and ball milling to produce drug particles of size approaching 1 μm. Drugs, such as griseofulvin and spironolactone, have been shown to have improved dissolution and bioavailability when particle size reduction is employed (9,10). However, with the discovery of more highly insoluble drugs, conventional milling techniques have limited results. Newer nanoparticle drug delivery technologies employing specialized milling techniques and supercritical fluids have been very effective to reduce drug particle size approaching 100 nm (11). This significant increase in surface area greatly increases dissolution rate and the potential for enhanced bioavailability. However, as drug particle sizes begin to approach oligomolecular units, the increase in particle

Table 1 Several Commercial Products Using Solubility/ Bioavailability-Enhancing Technology

Technology	Drug	Product
Nanoparticle	Sirolimus	Rapamune®
Nanoparticle	Aprepitant	Emend®
Nanoparticle	Fenofibrate	Tricor®
α cyclodextrin	Limaprost	Opalmon®
α cyclodextrin	Alprostadil	Prostavasin®
Solid dispersion	Itraconazole	Sporanox®
Solid dispersion	Etavirine	Intelence®

surface energy results in spontaneous aggregation through Oswald's ripening, which must be controlled through formulation and/or process. Surface stabilization is typically achieved with the adsorption of a stabilizing agent to the nanocrystal particles.

Increased interest in drug complexation and solid dispersion technologies have emerged recently. Both require the intervention of hydrophilic excipients to increase the solubility of poorly water-soluble drugs. Cyclodextrins (CDs) and their derivatives have been central to this complexation research. CDs are unique cyclic oligosaccharides because the hydrophobic nature of the ring interior surface promotes complexation with hydrophobic drugs. On the basis of the molecular size of the drug, CDs, ranging from six to eight glucose units, are selected to idealize the fit between drug and CD and maximize the complexation. Drug-CD complexes have been shown to be more soluble and bioavailable than the native poorly soluble drug. Soliman et al. (12) reported faster dissolution rates for β- and γ-CD-spironolactone complexes than stable and metastable forms of the drug. It was further shown that hydroxypropyl-β-CD, a CD derivative, showed a 3.6 fold increase in bioavailability when compared with spironolactone alone. Unlike ordered complexes, solid dispersions represent molecular or near-molecular mixtures of drugs and hydrophilic excipients, which can result in a variety of states such as eutectic, solid solution, and glass suspension among others. Because the poorly soluble drug is evenly dispersed in a hydrophilic matrix, enhanced solubility is seen with this technique. Kumar et al. (13) reported improved dissolution rates for terbinafine HCl polyvinylpyrrolidone (PVP), K30 solid dispersions prepared by solvent evaporation with increasing polymer. Overall, granulation techniques used in the formation of stable and bioavailable drug nanoparticles, complexes, and solid dispersions have been established and have been proven commercially. A list of several commercially available drug products for each technology is given in Table 1.

PARTICLE REDUCTION AND NANOPARTICLES

Particle size reduction has been widely used by the pharmaceutical industry to improve the dissolution rate of poorly water-soluble drugs. Conventional methods for reducing drug particle size such as hammer and jet milling are well established and, therefore, present economical, safe, and effective pathways for commercialization of products. However, certain limitations are inherent when conventional size reduction technologies are used. Drugs that are shear and/or temperature sensitive may be susceptible to degradation in comminution processing. Since comminution relies on particle fracture for size reduction, drugs with low melting temperatures or having thermoplastic characteristics may be difficult if not impossible to process by conventional milling. Reduced temperature milling such as cryomilling may be beneficial to aid in the size reduction of low–melting temperature drugs. However, most impactful of conventional milling is its limitation to improve drug dissolution rate as drugs approach water insolubility (<10 μg/mL). Nanoparticles as a drug delivery technique is well established for pharmaceuticals (14) and presents an improvement to conventional milling to enhance dissolution and bioavailability of poorly water-soluble drugs (see chap. 7 on nanotechnology for further reading).

Nanoparticles are materials that are less than or equal to 1 μm in one dimension and more specifically a nanocrystal is single crystalline in nature. In colloidal chemistry, nanoparticles are further limited to 100 nm or less, however, in the pharmaceutical area, nanoparticles can range in size from approximately 10 nm to 100 nm. For nanosized pure

drug particles with both crystalline and amorphous regions or nanosized drug mixtures, the term nanoparticle is appropriately applied. Nanoparticle delivery systems are reported for oral, parenteral, and pulmonary drug delivery. Junghanns (15) reports not only an increase in dissolution rate by surface area enlargement, but also an increase in saturation solubility related to the dissolution pressure increase associated with nanoparticles. Optimal drug nanoparticles with the highest increase in saturation solubility has a 20- to 50-nm particle size and would be amorphous. Stabilization of the nanoparticle amorphous drug is required to confer adequate product shelf life.

Nanoparticles for Poorly Soluble Drugs

Nanoparticles for pharmaceutical applications are produced by two basic methods, comminution or a "top-down" method and precipitation or a "bottom-up" method. Within the comminution method are two primary particle size reduction techniques, bead milling and homogenization. The NanoCrystal® technology for the nanoparticle formation is based on the bead milling process. Bead mills are favorable because they are less expensive, relatively simple to use, available at small R&D scale, and are readily scaleable for commercialization. Milling media (beads), dispersion medium, drugs, and other formulation aids (stabilizers) are charged into the milling chamber. Wet milling is essential to achieve smaller nanoparticle sizes when compared with dry bead milling processing. The dispersion medium would ideally be a nonsolvent for the drug. For poorly soluble drugs, water often serves as the dispersion medium. Surfactants and stabilizers are essential in the production of nanoparticles by nanosuspensions. The choice of surfactant is dependent on the affinity of the surfactant for drug surface and on the physical nature of the interaction (i.e., steric or electrostatic). Generally, steric stabilization on nanoparticles is preferred as it is less susceptible to electrolytes. In some cases, a combination of low- and high-HLB surfactants may be warranted. Milling media are available in a variety of materials but to minimize contamination yttria zirconium, a high strength ceramic, offers metal and contamination free grinding (16). The extent of bead erosion depends on milling material, suspension concentration, drug hardness, and milling time. Impact and shearing forces between the milling media and the suspended drug particles are responsible for particle reduction. Smaller milling media with a higher number of contact points is preferred to produce smaller nanoparticles and as a general rule, the size of the milling media is 1000 times the size of desired nanoparticle size. Plug flow, where particles move at a uniform velocity in the mill, is preferred to achieve a consistent and reproducible grind and residence time. Milling times can be highly variable and is largely dependent on drug hardness, dispersion media, milling energy, surfactant and level used, temperature, and type and size of milling media. The wet suspension from bead mill processing can be dried for oral solid dosage manufacturing or the suspension can be used for delivery as a drug suspension.

In addition to wet bead milling, homogenization presents an additional technique for top-down nanoparticle. Within homogenization techniques, there are two processes reported for nanoparticle formation by disintegration, jet stream and piston gap homogenizations. Jet stream homogenizer produces nanoparticles through a collision of two fluid streams under high pressure, where particle collision and shear and cavitation forces lead to the disintegration of the drug particle. Microfluidizer can generate pressures up to 275 MPa and jet velocities of the colliding streams approaching 500 m/sec. As with wet bead milling, nanoparticle stabilization facilitated by surfactant is required. A disadvantage of jet stream homogenizers as a particle disintegrator is its limitation on the minimum size and the high number of cycles required to achieve a homogeneous size distribution (17). Panagiotou and Fisher compared jet stream homogenizer by disintegration and precipitation processes via microchannel reactors (MCR) and showed that the precipitation process was more efficient at achieving a smaller nanoparticle size for carbamazapine with a narrower particle size distribution (median particle size 304 nm vs. 604 nm by disintegration). The precipitation technique was performed in a single cycle whereas 25 cycles were used for the disintegration technique. A further discussion of jet stream homogenizers in precipitation techniques is given below.

Nanoparticle formation by piston-gap homogenizers was introduced by Müller et al. (18) in the mid 1990s and is used in Dissocubes® Technology. In this technology, a poorly soluble

drug is dispersed in water and by the force of a piston generating pressure up to 4000 bar, is passed through a narrow gap to affect particle reduction. Surfactants are required to facilitate size reduction and stabilize nanoparticles from ripening effects. Gap distances range from 5 to 25 μm and are dependent on the suspension viscosity. High-shear forces and turbulent flow play a role in particle reduction; however, cavitation forces are reported to have the greatest effect (19). From Bernoulli's law, the cross sectional volume flow in a closed system is constant. When the liquid is in the homogenizer gap, a significant increase in dynamic pressure and a decrease in static pressure occur. The liquid starts boiling at room temperature, rapidly forming bubbles. After leaving the homogenizer gap, bubbles rapidly collapse and implode under atmospheric pressure. The cavitation process is the formation and implosion of bubbles, which generates great energy in drug size reduction.

Nanoparticle produced by precipitation or bottom-up processing, as the name suggests, involves a controlled build of the drug particle from a solution. In this technique, drug is dissolved in a solvent and the drug solution is added in a controlled manner to a drug antisolvent under high agitation. The drug precipitates rapidly and controlled in the presence of the antisolvent by generating a large number of nucleation sites and limiting the subsequent growth. Bottom-up processing has an advantage to top-down processing in that particle formation can be done with heterogeneous materials to form cocrystals or coprecipitates, which may further enhance the solubility of the poorly soluble drug compared with the homogeneous drug nanoparticles. Crystal size is controlled by thermodynamic principles, transport phenomena, and reaction kinetics. Key to this process is the presence of homogeneous nanoscale regions throughout the crystallization volume. The process can be as simple as using a static mixer for nanoparticle precipitation; however, results obtained in the R&D lab may not readily scale to larger container where hydrodynamics, vessel volume to surface, and turbulence are not readily reproduced. Recently, a jet-stream homogenization technology using MCR has been reported to replicate the single confined impinging jet reactor scale experience by stacking multiple jet impinging reactor units to achieve the desired production rate (17). In this process, a drug solution is jet impinged into an antisolvent for the drug. Carbamazapine crystals, manufactured by the jet impinging process, were 150 to 300 nm wide and 2 to 5 μm in length, whereas drug particles by conventional mixing were 1 to 2 μm wide and less than 20 μm in length. Zhou et al. (20) showed that danazol nanoparticles made in the MCR process significantly increased specific surface area (14.32 vs. 0.66 m^2/g) and an increase in dissolution rate in five minutes from 35% to 100% when compared with danazol particles "as received" (20).

Supercritical fluid (SCF) technology in pharmaceutical nanoparticles has gained increasing interest over the last two decades (21). Carbon dioxide is the primary supercritical fluid used in this technology because it can be processed in mild operating conditions, both temperature and pressure, is chemically inert and nonflammable and has minimal to low environmental impact compared with organic solvents. Solvent properties of supercritical CO_2 are mostly representative of nonpolar solvents but these properties can vary depending on temperature and pressure conditions of the fluid. When organic solvents are used in processing, the miscibility of CO_2 with most organic solvents typically results in low residual solvent content, avoiding additional downstream processing. Vemavarapu et al. (22) reviewed the various supercritical fluid techniques used in particle formation, of which most use an antisolvent approach because of low drug solubility in supercritical CO_2. Two popular supercritical processes will be discussed, supercritical antisolvent recrystallization (SAS) and rapid expansion of supercritical solutions (RESS). SAS processing requires the drug to be solubilized into a solvent that is sprayed into SCF. The drug should be insoluble in the SCF and the organic solvent, miscible in SCF. As the SCF diffuses into the drug-solvent droplets, the miscible solvent expands with the SCF and precipitation of the drug particles occur. In a batch SAS process, the drug solution is sprayed into a vessel containing the SCF, whereas in a continuous SAS process, the drug solution and SCF are introduced into the vessel concurrently. SAS process has greater flexibility in controlling particle growth through solvent(s) selection and by controlling the solvent extraction conditions of SFC. High residual solvent levels can result in particle agglomeration or crystal growth. Chattopadhyay and Gupta have reported an improvement in the SAS process to obtain smaller nanoparticles with

narrower distribution (23). SAS-EM utilizes an ultrasonic field to enhance mass transfer between the drug solution and SCF and prevents agglomeration due to increased mixing. Griseofulvin nanoparticles of 130 nm were obtained at 180 W energy input.

For supercritical processing, where the drug is soluble in the SCF, RESS processing is favored. These drugs tend to be highly lipophilic with low molecular weight (MW). RESS involves dissolving a drug or a drug-polymer mixture in SCF and spraying the SCF solution into a lower pressure vessel. The rapid expansion by the solution reduces the density of the SCF and supersaturates the drug or drug polymer in the lower-pressure solution, resulting in precipitation of pure drug or drug-polymer particles with reduced size and narrow size distribution. Limitations of the RESS process are that few drugs are soluble in commonly used SFC and process throughput rates for precipitates are slow.

COMPLEXATION

Complexation is well known in organic and inorganic chemistry. Complexes are entities comprising two or more molecules (or ions) that are bound to each other with noncovalent bonds, that is, only with physical forces like hydrogen bonds or van der Waals bonds (24).

Such complexation reactions are an equilibrium between the free components and the complex as in the following equation:

$$mA + nB \Leftrightarrow A_mB_n \qquad \text{[eq. 2]}$$

This reaction has an equilibrium constant that can be calculated as follows:

$$K_{m:n} = [A_mB_n]/A^m \bullet B^n \qquad \text{[eq. 3]}$$

The higher this constant, the more the reaction is inclined to form the complex. Conversely, when it is low, the substances involved in the complexation exist more in the free form than in the complexed form. Some of these complexes are water soluble, and some are not. Also in some cases, complexes are more soluble in water than their initial components and this is what is interesting in the case of poorly water-soluble drugs. Complexation is here interesting when its components are all pharmaceutically acceptable [Active Pharmaceutical Ingredient (API) and excipients]. Known cases of complex formation are of interactions between drugs and hydrophilic polymers, like PVP, HPMC, or HPC. Sanghvi et al. (25) investigated solubility improvement of drugs using *N*-methylpyrrolidone (NMP). They found out that NMP enhances drug solubility by simultaneously acting as a cosolvent and a complexing agent. Since NMP is basically the monomer of polymers like PVP and crospovidone, such behavior is expected from them too. Horn and Ditter (26) found out that such a complexation reaction is dominated by formation of hydrogen bonds, where the drug contains hydrogen-donating groups to PVP. Various phenolic and polyphenolic substances have been studied and their complex stability constants have been calculated. Projecting that on the use of such hydrophilic polymers in forming complexes with drugs, it is beneficial that soluble complexes with a complexation constant that is strong enough are formed. The hydrophilic polymer is soluble in water and by building this complex, it would help solubilize the drug and also prevent recrystallization when available in sufficient quantity in the dissolution medium. This is in fact one of the main mechanisms of the formation of solid dispersions/solutions between drugs and polymers. Such a complex formation, however, is not only beneficial in the use of soluble polymers; Moneghini et al. (27,28) found out that the solubility of carbamazepine and atenolol was not only enhanced when a coprecipitate of the drugs was formed with crospovidone, but simple physical mixtures also increased the solubility of the drugs. The X-ray diffraction peaks of the drug did not disappear as they did in coprecipitates mixed in same ratios with crospovidone, still the solubility of the drugs was increased. This could probably be related to the formation of complexes of the drug and the hydrophilic but water insoluble polymer. This complex is hydrophilizing the drug and making it more prone to interaction with water and thus dissolving better. This is also probably the reason why some drugs in the market contain amounts of crospovidone those are far higher than concentrations used for simple disintegration (29–31). Furthermore, studies have been conducted on the use of crospovidone as a spheronization aid in the production of pellets

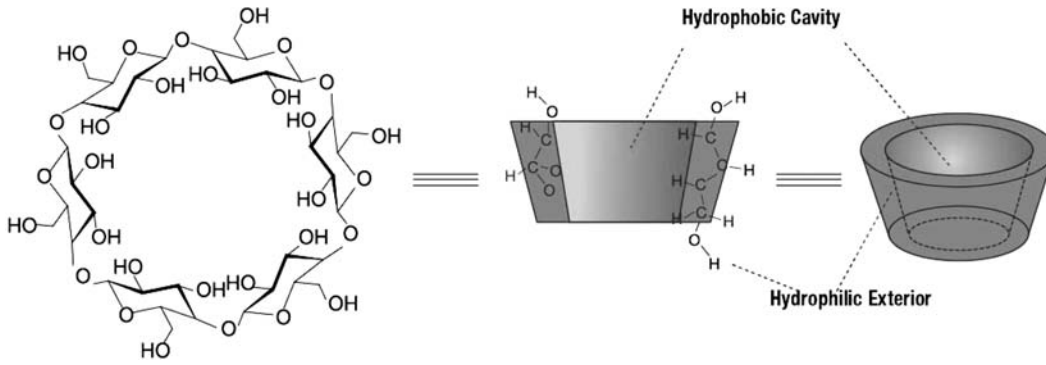


Figure 2 Structure of α-cyclodextrin and its tridimensional toroid shape.

using the extrusion and spheronization processes (32,33). This makes the complexation capability combined with this functionality as an interesting alternative of granulation technique that can be used in the enhancing of the solubility of certain drugs.

Other pharmaceutically relevant substances that have been used in increasing solubility of drugs through the formation of so-called inclusion complexes are CDs. CDs have been first isolated and characterized by Schardinger (34) who identified α- and β-dextrins (34). These two substances are nowadays called α- and β-CDs. γ-CD has been discovered later on by Freudenberg and Jacobi (35). *The Handbook of Pharmaceutical Excipients* defines CDs as follows: "Cyclodextrins are crystalline, nonhygroscopic, cyclic oligosaccharides derived from starch" (36). "Among the most commonly used forms are α-, β-, and γ-cyclodextrin, which have respectively 6, 7, and 8 glucose units. Cyclodextrins are 'bucketlike' or 'conelike' toroid molecules, with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type. The internal surface of the cavity is hydrophobic and the outside of the torus is hydrophilic; this is due to the arrangement of hydroxyl groups within the molecule. This arrangement permits the cyclodextrin to accommodate a guest molecule within the cavity, forming an inclusion complex." Figure 2 shows the structure of α-CD and the toroid shape of the molecule (37).

So-called native CDs, that is, α-, β-, and γ-CDs have solubilities in water of 14.5, 1.85, and 23.2 g/mL, respectively, that are regarded to be low, especially in the case of β-CD (38). This leads to the synthesis of various derivatives that have much higher water solubilities like the methyl, hydroxypropyl, and sulfobutyl ether derivatives.

CDs have different functionalities. They are used in pharmaceuticals mainly in drug stabilization, increasing of drug solubility, preventing drug-drug or drug-excipient interactions and in taste masking. We are interested here in the solubility-increasing features. Since α-, β-, and γ-CDs have internal cavities of increasing diameter and, therefore, volume, each one of them would be more suitable to be a host to a drug molecule than the others depending on the shape and size of the drug molecule and how it fits into the cavity of the CD. Generally, α-CD cavity is most suitable as a host for drugs with straight aliphatic chains, whereas β-CD is more suitable for simple aromatic ring structures and γ-CD is more suitable for larger molecules. Figure 3 shows how prostaglandin-E_1 possibly forms complexes with the different

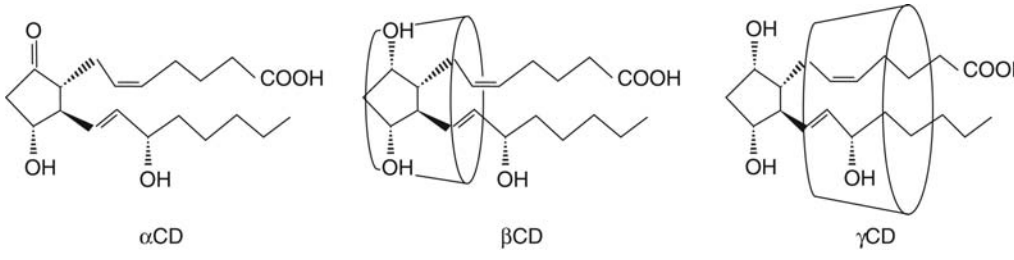


Figure 3 Assumed structures of prostagalndin-E_1-CD complexes. From Ref. 38.

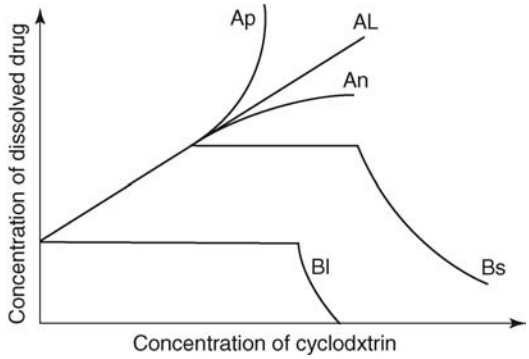


Figure 4 Solubility isotherm types.

types of CD. In this case, the complex of α-CD with the drug has been used in drugs on the market as it increased the stability (of a certain part of the molecule) and solubility of the drug.

Complexes of CDs with drugs could be of a 1:1, 1:2, 2:1 (drug:CD) or even molar ratios. The resulting complexes could have different solubility behaviors as in the solubility isotherms (phase diagrams) shown in Figure 4.

Al, Ap, and An types are very soluble types. Al is usually the type for 1:1 molar complexes, whereas Ap type suggests that more than one drug molecule is interacting with one CD molecule. Bi and Bs types are of limited solubility. In the case of Bs, addition of CD would increase the solubility of the drug till a plateau is reached and further addition would lead to a precipitation of the complex. Bi type is when an insoluble complex is formed. More information on theory and fundamentals of complexation with CD can be found in a review by Brewster and Loftsson (39).

The usual procedure for finding out the CD type with best solubility enhancement of the drug would be by making phase diagrams of solubility of the tested drug in various CDs and then picking the most suitable one for the drug and application. An example is provided by Abdoh et al. (40). They made solubility phase diagrams of α-, β-, γ-, and hydroxypropyl (HP)-β-CD in pH 2.8 and 6.5. They found out that overall complex stabilities were found to follow the decreasing order: γ-CD > HP-β-CD > β-CD > α-CD. 1:1 complexes are formed for all types of CDs and in both pHs I exception of γ-CD at pH 5.8, where the diclofenac sodium formed a 2:1 diclo:γ-CD complex as can be seen in Figure 5.

Once the optimal CD for the investigated drug has been characterized a complex of the drug and this CD can be made using different methods. Most relevant ones in the context of this chapter would be:

Kneading Process

It is very similar to a wet granulation process, only higher amounts of water or solvent-water mixtures are used. The necessary amount of CD is kneaded or mixed with about 15% to 20% its weight of water in a kneader or in a high-shear mixer. The API is then added as a mass of powder or in a predissolved form in an appropriate organic solvent to this kneaded form of CD; the kneading process is continued till the complexation is complete. This can be usually figured out by an increase of power consumption of the motor and by a change in the appearance of the kneaded mass. Hutin et al. investigated such a process and the factors influencing it. Water was added dropwise till the end point of complexation has been detected via torque measurements (41). The kneaded mass, once the complexation is complete, can be dried in a tray dryer or a fluid-bed dryer. The temperature used in drying should be optimized as high temperatures might break the complex. Drying the complexes at a product temperature of 50°C should be suitable for most complexes. Another way of further processing the kneaded mass is by mixing it by extrusion and spheronization aids and then making pellets by extrusion/spheronization. Pellets with relatively high loading of the complex can be obtained this way. Gazzaniga and Sangalli (42) were able to make pellets containing up to around 84% complexes of acetaminophen and ketoprofen and β-CD this way (43). They also found out that even by extruding the physical mixtures of the drugs with β-CD lead to a partial

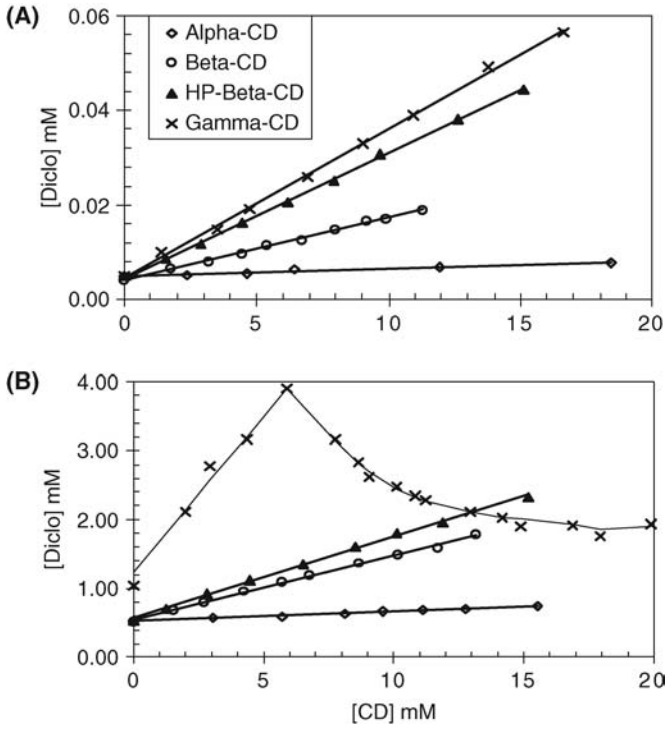


Figure 5 Phase solubility diagrams of diclofenac sodium in aqueous CD solutions of 0.05 M phosphate buffer ($m =$ 0.2 M) at (**A**) pH 2.4 and (**B**) pH 6.5, all at 20°C.

complexation. This would suggest that drugs strongly favoring complex formation with CDs might form complete complexes during the extrusion process and there is no need for kneading the components as a first step. Such pellets can then be dried and further processed like coating with and enteric coating and filling into capsules or mixing with some cushioning excipient and compressing into tablets (44,45).

Solution/Suspension and Then Spray Drying, Freeze Drying, or Layering

Most widely used method of preparing a complex of a drug with CD is in fact in liquid phase. Both CD and drug can be dissolved using organic solvents and/or heat or one or both of them can be suspended. Key factor for the formation of a complex is vigorous mixing for an adequate time to have enough power input to induce complexation. The stirring should be continued for hours and, in some cases, for one to two days. Such suspensions or solutions of complexes can be either freeze or spray dried or can be sprayed in a fluid-bed granulator/coater on a carrier like MCC and some wet binder to form granules that can be compressed, or it can be layered onto nonpareil pellets to build pellets that can be coated or used as is (46). The addition of the hydrocolloid that is used as binder should be avoided during the complexation process as the addition of small amounts of hydrocolloids like HPMC or PVP would enhance the complexation but increasing the concentration further would decrease the complexation stability constant (47).

SOLID DISPERSIONS

Solid dispersion is one of the most important approaches to increase drug solubility and dissolution without chemical modification of drug compounds. Compared with other conventional approaches, solid dispersion can reduce the size of drug particles to a much smaller level, even down to molecular dimension, and stabilize those physically modified compounds from agglomeration, crystallization, and phase separation through the understanding of the interaction between the drug compound and the carrier.

The term solid dispersion refers to the dispersion of one or more active ingredients in a biological inert matrix with a view to enhance oral bioavailability. More specifically solid dispersions were defined as a family of dosage form whereby the drug is dispersed in an inert

matrix carrier at solid state prepared by melting, solvent, or melting-solvent method (48). Depending on drug absorption behavior, the inert carrier can be water-soluble polymers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), polyvinylpyrrolidone/vinyl acetate copolymers (PVP/VA), and hypromellose (HPMC) for poorly water-soluble active, or insoluble polymers such as ethyl cellulose (EC), hydroxypropyl methyl cellulose phthalate (HPMCP), polyacrylates, and polymethacrylates (Eudragit) for modified release. For poor water-soluble compounds, solid dispersions improve drug dissolution rate and solubility through size reduction, improved wettability, and amorphous transformation, and possibly enhance active bioavailability. Marketed products examples containing solid dispersions include Cesamet® marked by Eli Lilly, which was prepared from a dispersion of nabilone in polyvinylpyrrolidone, Intelence™ from Tibotec, which was an amorphous dispersion of etravirine in HPMC, Gris-PEG™ marked by Wander, Accolate® by Astra-Zeneca, Accupril® by Pfizer, and Ceftin® by GSK. With the advent of high-throughput screening of potential therapeutic agents, the number of poorly water soluble compounds has risen sharply and it is expected that the number of drug products using solid dispersion technology will increase dramatically in the next few years.

Structures of Solid Dispersion

It is critically important to have insights on the structures of solid dispersions before to understand their dissolution characteristics. Irrespective of the methodology used to prepare solid dispersions, these can be described in two broad classes on the basis of the magnitude of dispersion, nonmolecular level or molecular level (Fig. 6) (49).

Drug may be present as a separate amorphous phase or as a separate crystalline phase (or in combination of both) for solid dispersion at nonmolecular level. A classical example is eutectic mixtures whereby the molten mix solidifies into a microfine dispersion of the two components under cooling (Fig. 7).

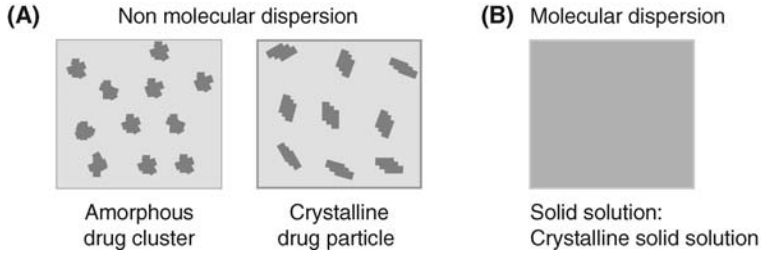


Figure 6 Solid dispersion at nonmolecular basis and molecular dispersion.

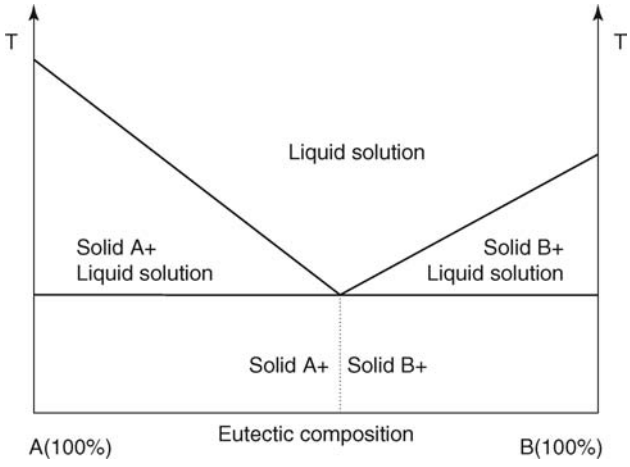


Figure 7 Phase diagram for a eutectic system. *Source*: From Ref. 50.

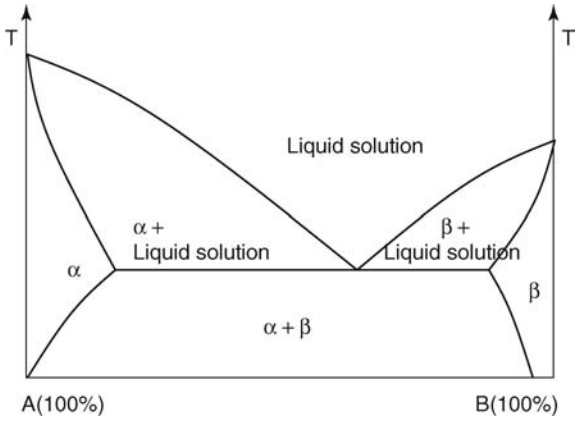


Figure 8 Typical phase diagram of solid solution. *Source*: From Ref. 50.

One must bear in mind that unless the composition is exactly at the eutectic point, the dispersion will contain a mixture of the microfine dispersion and one separated phase of the component in excess of eutectic composition (50). The formation of eutectic system presents a eutectic melting point lower than the melting points of the principle components. Differential scanning calorimetry (DSC) studies are often used to characterize eutectic mixtures in light of melting points. PEG is used for the majority of eutectic formulation for most of heat sensitive compounds because of its relatively low melting point.

Solid solution is another very important family of solid dispersions in which the active ingredient is dispersed at molecular level. The solvate, usually the active ingredients, is solubilized within the inert carrier at solid state and forms a single phase containing components mixed at molecular level. Solid solutions are comparable to liquid solutions as the drug's particle size is reduced to its absolute minimum—the molecular dimension (51). Caution is required in terms of the detection of such a system because the majority of such systems are likely to show only partial miscibility in practice (Fig. 8).

The drug may only be in solution at low concentration, though it is generally believed that solid solution could potentially improve drug dissolution. Because of the limitation of drug solubility in carrier at solid state, the majority of solid solutions are most likely mixtures of solid solution and a second phase of the solvate. Solid solution of poorly water-soluble drugs is of particular interest as a means of improving oral bioavailability. Because the drug is dispersed at molecular level within solid solution, its dissolution rate is determined by the dissolution rate of the inert carrier. By careful selection of a carrier, the dissolution rate of the drug can be improved up to several to hundreds orders of magnitude.

A very important subfamily of solid solution is glass solution, where the active is present as a molecular dispersion in a glassy matrix. Unlike crystalline dispersion, the active is present as amorphous form in glass solution, which further improves drug solubility by removing the lattice energy associated with crystalline structure, according to Yalkowsky general solubility equation.

$$\log S_w = 0.5 - \log K_{ow} - 0.001\,(MP - 25) \qquad \text{[eq. 4]}$$

where S_w is aqueous solubility, K_{ow} is partition coefficient, and MP is the melting point of drug (52). Though DSC and XRD studies are frequently conducted to provide interpretations to the properties of amorphous solid dispersions, the detection of amorphous solid dispersion structure is not as simple as one may imagine. Question still remain as to whether the active is dispersed on a molecular basis to form a glass solution or is present as separated amorphous phase, even though drug crystalline fusion energy is not detected in thermal analysis such as DSC. Great progress has been made by the work of Zografi and coworkers and others in the past decade for a better understanding the basis of amorphous systems (53–56).

Compared with the crystalline counterpart, amorphous drug dispersions are likely to improve the solubility and dissolution rate up to several to hundreds orders of

magnitudes (57). It also provides better compressibility for direct compression. But most of the amorphous solid dispersions are not stable and tend to transform into crystalline state, consequently lose the solubility improvement. Though it is generally believed that amorphous solid dispersion can improve drug solubility, the application of amorphous solid dispersion technology is greatly settled back because of the stability concern. Extensive studies have been done to better understand the factors governing amorphous stability recently; however, little progress has been made on stability prediction. Challenge still presents in front of formulation scientists to understand their amorphous solid dispersion stability. From the aspect of product quality, amorphous drug also has very high hygroscopicity, extra care has to be taken to prevent moisture absorption.

Methods for Preparing Solid Dispersions

Methods preparing solid dispersions include thermal method, for example, hot melt extrusion, spray congealing, and solvent method, for example, spray drying and freeze drying. Regardless of the method used, an important prerequisite to produce microfine dispersions is the miscibility of the drug and the carriers at liquid state.

Hot Melt Method

Hot melt extrusion is a significant step forward for the commercial application of hot melt method. Hot melt extrusion is a very common way of process plastics in polymer industry, but it has not been applied on pharmaceutical purpose until recently. Sekiguchi and Obi (58) first demonstrated hot melt method to prepare solid dispersion. They produced a eutectic mixture consisting of sulfathiazole and a water-soluble inert carrier, urea. The active ingredient and the carrier were mixed together and heated at a temperature above their melting points until melted. The homogenous hot melt was cooled in an ice bath and then milled to reduce the particle size. Though cooling may introduce supersaturation, but because of the fast solidifying rate the dispersed active ingredient was trapped within the carrier matrix without phase separation. A typical hot melt extruder consists of a feeding hopper, barrel, screw, die, screw-driving unit, and a heating/cooling device (Fig. 9).

A blend of the active ingredients, the thermoplastic polymers, and other process agents such as, lubricants and plasticizer, is fed into the barrel through the hopper. The materials are transported through the barrel, which is divided into different zones according to their temperatures by a rotating screw. The blend is simultaneously melted at elevated temperature, homogenized, extruded, and shaped as granules, tablets, sheet, or pellets.

A less commonly used hot melt method is spray congealing. In general sense, spray congealing is quite similar to spray drying and also consists of an atomizer, cooling chamber, cyclone recover, and separation unit (60). A hot molten slurry is formed by melting of active ingredients and the thermoplastic polymer, and then sprayed out of atomizer to form droplets. These droplets are quickly solidified by the heat sink provided by cooled process air flow inside the cooling chamber. The cooled free-flowing particles are collected by cyclone recovery. As with spray drying, spray congealing usually yields particles of similar size and shape. However, properties such as density, moisture, and friability are most often independent of the process because, unlike spray drying, no mass transfer is involved into the solidifying of the droplets. Spray congealing also yields very fine particles and may enhance drug dissolution rate by increasing specific surface area.

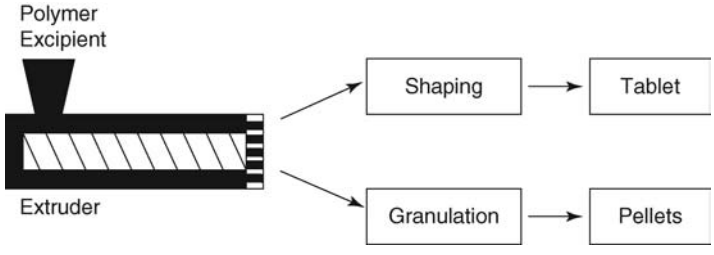


Figure 9 Scheme of a hot melt extruder. *Source*: From Ref. 59.

Solvent Evaporation Method

Solvent evaporation method provides another common way to prepare solid dispersions comprising of the active ingredient(s) and carrier(s). The active ingredient is forced into intimate contact with the carrier by dissolving them together in a common solvent(s). The homogeneous solution is then converted into solid state by removing the solvent quickly. An important prerequisite for the application of solvent evaporation method is that both the active ingredient and the carrier are sufficiently soluble or dispersible in the common solvent. Spray drying technology is the most frequently used process to prepare solid dispersion on a continuous basis, Figure 10 shows the unit operations involved in a common spraying process.

The success of spray drying technology attributes to its ability to not only remove the solvent rapidly, but also control the properties of the powder products: particle size, distribution, shape, uniformity, bulk density, and even particle configuration (61). Coffee, detergent, milk, and excipient industry are excellent examples of spray drying technology industry applications. The capability of rapid solvent removal also makes this technology good fit for the preparation of amorphous solid dispersion. The rapid solidifying process may "freeze" the actives into the glass matrix and prevent the conversion from amorphous state to crystalline state. The spray drying process consists of the following steps: (*i*) formation of a solution containing the active and the carrier; (*ii*) the solution is then atomized into fine droplets; (*iii*) the droplet is exposed to a heated gas media for drying;, and (*iv*) the dry free-flowing powder is collected. However, the particle formation process may not be as simple as one can imagine. Figure 11 presents the mechanism of particle formation in spray drying.

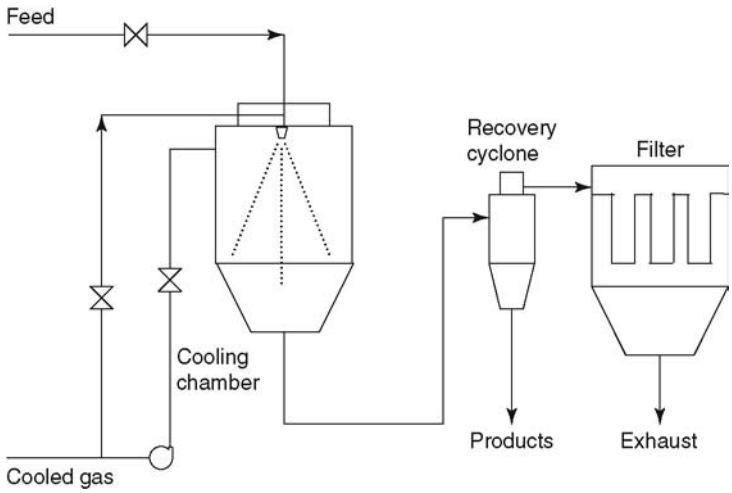


Figure 10 Main components of a typical spray drier. *Source*: From Ref. 61.

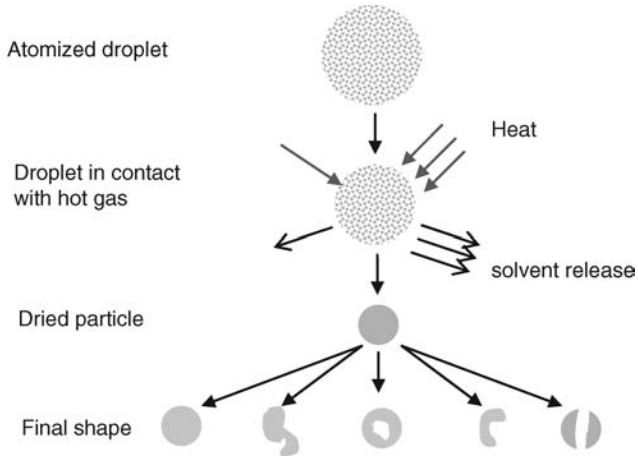


Figure 11 Mechanism of particle formation during spray drying. *Source*: From Ref. 61.

Many aspects of the particle formation process in spray drying are controlled by the relationship between surface recession and diffusion of the solutes. Radial demixing of components may occur during drying process because of different diffusion rates of the components (62,63). For drug/polymer solid dispersion system, a polymer rich outlayer will be structured outside the solid dispersion particles because of the much less diffusion rate of polymer compared with drug molecules, and could result in a delay of the onset of drug release. Although the radial demixing effect is not desired in most situations of solid dispersions, it does lead to the successful design of structured microparticles with functional layers, which can be used to further modify drug release behavior.

Carriers

Polyethylene Glycol

PEGs are polymers of ethylene oxide, with a MW falling in the range of 200 to 300,000. As the MW increases, so does the viscosity. At MW up to 600, PEGs are liquid; in the range of 800 to 1500, they are usually best described as Vaseline-like; from 2000 to 6000, they are waxy; and those with MW of 20,000 and above change to hard, brittle crystals at room temperature. Their solubility in water is generally good, but decreases with increasing MW. The melting point of PEGs is in a range of 37°C to 65°C, and decreases as MW decreases (64). The relatively low melting points are advantageous for the manufacture of solid dispersion using hot melt extrusion method, especially for those heat sensitive compounds. PEGs with MW of 1500 to 20,000 are usually employed in the manufacture of solid dispersion because in this MW range, the water solubility is still relatively high and the melting point is also high enough to produce pharmaceutical acceptable solids.

PEG 8000 was used to form eutectic mixture with fenofibrate (65). The study showed the eutectic composition by generating phase diagram using hot-stage microscope (HSM) and DSC. The in vitro dissolution study proved the improved solubility and dissolution rates of the eutectics solid dispersion compared with the pure drug. The dissolution rates and solubility were also found to increase as the PEG composition increases in the eutectics mixture. PEG is also used to prepare amorphous solid dispersion. A class IV drug, ritonavir, was selected to prepare amorphous solid dispersion with PEG 8000 (66). The in vitro evaluation showed five-fold increases in solubility compared with physical mixture of same formulation. The bioavailability in beagle dogs showed a maximum of 22-fold increase in AUC_{0-24hr} over the physical mixture. The importance of the PEG MW to the performance of the eutectic solid dispersion was illustrated in a study of five poorly water soluble compounds formulated as eutectics with PEG 3350, PEG 8000, and PEG 20000 (67). The study showed that the influence of PEG MW on dissolution performance is dictated by the drug-carrier interactions. Compounds with specific interaction with the carrier will have higher eutectic composition and faster dissolution than with lower MW PEG. Drug/carrier ratio apparently is another main influence on the performance of solid dispersion. If the percentage of the drug is too high, it will exceed the eutectic composition and form separated crystalline region. Law (65,66) showed solid dispersions of fenofibrate in PEG 8000 released drug faster when 15% or 25% fenofibrate loading was used than when 30% or 40% loading was used. These results could be explained on the basis of phase diagram generated by DSC, which indicates that the release profile for solid dispersion with high loading is relatively independent of the dissolution profile of the carrier because of the separated crystalline region of the drug.

In general, PEG is ideal carrier to form eutectics solid dispersion. However, its application in forming amorphous solid dispersion is limited because of the amorphous stability. Compared with other polymer carrier, the chain length the PEG is still very short and incapable of amorphous stabilization, especially at high drug loading. Another limitation of PEG lies in the subsequent formulation into an acceptable solid dosage form. Solid dispersion in low MW PEG is too soft and presents challenges to manufacture a tablet dosage form.

Polyvinylpyrrolidone and Polyvinylpyrrolidone-Polyvinylacetate Copolymer

Polymerization of vinylpyrrolidone leads to PVP of MW ranging from 2500 to 3,000,000. The MW of PVP is specified by the *K* value, which is calculated using Fikentscher's equation (68).

Table 2 *K* values of Polyvinylpyrrolidone and the Corresponding Molecular Weights

K value	Approximate average molecular weight
12	2,500
15	8,000
17	10,000
25	30,000
30	50,000
60	400,000
90	1,000,000
120	3,000,000

Table 2 provides an overview of the *K* value and the corresponding approximate average MW of PVP.

PVP is amorphous polymer with relatively high glass transition temperature, for example, glass transition temperature for PVP K30 has T_g of 163°C (64). For this reason, PVP has limited application for the preparation of solid dispersion using hot melt extrusion. The glass transition temperature also increases as MW. Because of their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersion using solvent method. PVPs are also freely soluble in water and their aqueous solubility decreases as MW. The very good solubility can improve the wettability of the dispersed compound in many cases and offers improved dissolution rates.

The chain length of the PVP has a very significant influence on the dissolution rate of the dispersed compound from the solid dispersion. As the chain length increases, the aqueous solubility of PVP decreases and the viscosity increases at a given concentration. Studies with coevaporates of chloramphenicol and PVP revealed that the dissolution of chloramphenicol was reduced when high MW PVP was used as a carrier (69). Similarly, the slower dissolution of indomethacin from PVP K90 compared with PVP K12 was attributed to the higher viscosity generated by PVP K90 in the diffusion boundary layer adjacent to the dissolving surface of the dispersion (70). The dissolution rates of sulfathiazole and phenytoin were also found reduced as high MW PVPs were used as dispersion agent (71,72).

Drug/PVP ratio is another very important factor governing drug release rate. It is not difficult to understand that the decrease of drug load leads to higher dissolution rate of the dispersed compound because of the improvement of fineness of dispersion, for example, the dissolution rate of albendazole was found to decrease as formulated with less amount of PVP (73). However, this is not always the truth. In the case of piroxicam/PVP solid dispersion system, the release rate increased as the drug/PVP ratio increased from 1:6 up to 1:4, after which the release fell again (74). The X-ray diffraction studies revealed that only the dispersion at 1:4 drug/PVP ratio was amorphous, all other formulations were either crystalline or semicrystalline. The 1:4 ratio proved to be the optimal solid dispersion formula for piroxicam/PVP K30 system.

It is well recognized that PVP facilitates the preparation of amorphous solid dispersion. Amorphous solid dispersion of simvastatin and PVP was prepared by spray drying process (75). Initial characterizations of combined IR, DSC, and XRPD analysis confirmed the presence of amorphous simvastatin dispersed in PVP. The dissolution studies showed that the amorphous solid dispersion presented significant increases in both dissolution rate and saturation solubility over their dry blend. The in vivo evaluation in rats also justified the improvement in therapeutic efficacy of the amorphous solid dispersion over the crystalline counterpart.

The biggest challenge of the amorphous solid dispersions in practice is probably their physical stability. Amorphous drug is not physically stable and tend to transform into crystalline counterpart, which does not have the dissolution and solubility advantages as amorphous drug presents. PVP is not only well known as a solubilizer in solid dispersion, it is

also widely recognized as a very effective amorphous stabilizer. Studies on celecoxib-PVP-meglumine ternary system suggested that PVP functions more as stabilizer and meglumine functions more like solubility enhancer in their amorphous solid dispersion (76). The dissolution rate and saturation solubility of nilvadipine was found substantially decreased compared with the initial dissolution test of amorphous solid dispersion of nilvadipine (77). The amorphous form physical stability of nilvadipine was improved by the use of nilvadipine-PVP/microcrystalline cellulose ternary solid dispersion system. Taylor compared the influence of different polymers on crystallization tendency of molecularly dispersed amorphous felodipine (78). It was concluded that PVP, HPMC, and HPMAS are equally effective at decreasing the nucleation rate of felodipine from amorphous solid dispersion at same given weight percentage of polymer. Indomethacin/PVP has been extensively studied to understand the physical stability from molecular basis (53–55,79). It was revealed that PVP is able to form a miscible binary amorphous phase with indomethacin. The IR spectroscopy studies disclosed the formation of hydrogen bonding between the PVP amide carbonyl and indomethacin carboxylic acid hydroxyl group, which disrupts the self-association of the indomethacin dimers and results in the "solution" nature of the solid dispersion.

Polyvinylpyrrolidone/vinyl acetate (PVP/VA) are vinylpyrrolidone-based copolymers with about 40% vinylpyrrolidone being replaced by vinyl acetate. Compared with PVP, PVP/VA is less water soluble and also has lower glass transition temperature at the same MW. The use of PVP/VA as solid dispersion carrier has been shown to lead to enormous increases in drug releases as well as amorphous stability. Studies with the cytostatic drug HO-221 showed that PVP/VA solid dispersed not only dissolved 25-fold faster than the unprocessed drug powder, but also enhanced the bioavailability in beagles by a factor of 3.5 (80). Zografi compared the physical stabilities of amorphous indomethacin dispersed in PVP and PVP/VA, and found that PVP and PVP/VA are equally effective in crystallization inhibition of indomethacin (55). Poorly water-soluble drugs including indomethacin, lacidipine, nifedepine, and tolbutamide were dispersed into PVP and PVP/VA using hot melt extrusion method (79). The studies showed that the formation of glass solution depends on the temperature of melt extrusion. Physical stability difference was also observed between these solid dispersion systems because of the magnitude to hydrogen bonding between the drug and carrier.

Cellulose Derivatives

Celluloses are naturally occurring polysaccharides that are ubiquitous in the plant kingdom. They consist of high MW unbranched chains, in which the saccharide units are linked by β-1-4-glycoside bonds. By appropriate alkylation, the cellulose can be derivatized to form methyl cellulose (MC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), and many other semisynthetic types of cellulose. A further possibility for derivatization is the esterification of the cellulose to form compounds such as hydroxypropyl methyl cellulose phthalate (HPMCP) and hypromellose acetate succinate.

Both HPC and HPMC exhibit good solubility in a range of solvents including cold water. The average MW of the HPCs ranges from 37,000 to 1,150,000. Studies with flurbiprofen showed that the dissolution rate was improved as low MW HPC was used in the solid dispersion (81). HPMCs have an average MW in a range from 10,000 to 1,500,000 and their glass transition temperatures are as high as 170°C to 180°C. Studies with tacrolimus compared the dissolution profiles of solid dispersions having HPMC, PVP, and PEG as carrier (82). Significant increases in dissolution rates were confirmed for the solid dispersions formulated with all these polymers. However, serve precipitations were observed for PVP- and PEG-based solid dispersions because of supersaturation. Though all the three polymers are equally effective in dissolution rate improvement, their capabilities maintaining supersaturation in solution are significant different, the rank order was HPMC > PVP > PEG. Studies with albendazole, a poor water-soluble compound, showed that the release rate and bioavailability could be improved through preparation of a solid dispersion in HPMC (83). Other drugs that exhibit faster release from solid dispersion in HPMC include poorly soluble weak acids nilvadipine and benidipine (84,85). HPMCPs are cellulose esters, which are often used as enteric coatings. Their average MW ranges from 20,000 to 2,000,000. Depending on their grades, they dissolve at pH 5 (HP50) or pH 5.5 (HP55). Griseofulvin was transformed into

amorphous state by dispersing in HPMCP using coevaporation method (86) and exhibited a significant increase in dissolution rate. Using spray drying technique to form a solid dispersion in HP55, the dissolution rate of the antifungal drug MFB-1041 could be increased by a factor of 12.5 as compared with that of the micronized drug. Furthermore, the oral bioavailability in beagles was almost 17 times better following the administration of the drug in solid dispersion form (87). In the studies of poor water-soluble drug HO-221, it was shown that the dispersion in HPMCP presented equal release of the drug as the dispersion in pH-independent polymers, PVP and PVP/VA, at pH 6.5 buffer solution (79). However, the oral bioavailability study in beagles exhibited 30% to 60% absorption for solid dispersion in PVP/VA, whereas it is completely absorbed for solid dispersion with HPMC. It was concluded that the incomplete absorption is due to the precipitation of the drug following rapid dissolution and formation of a supersaturated solution in the gastric fluid.

Polyacrylates and Polymethacrylates

Polyacrylates and polymethacrylates are glassy materials that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. They are primarily used in oral capsule and tablet formations as film-coating agents and are commonly known by the trade name of Eudragit®. Eudragit E is often used to improve drug release, since it is soluble in gastric fluid below pH 5 and swells at high pH, while Eudragit L and S are water insoluble and used as desired to avoid release in the stomach. Eudragit L is more permeable than Eudragit S grade and films of varying permeability can be obtained by mixing the two types together. Their capability of forming water-insoluble film coat finds most of their pharmaceutical applications in formation of sustained release formulation. Eudragit L has been successfully used to increase the dissolution of griseofulvin and spironolactone at pH value of 6.8 (86).

Surfactants

The release behavior of many poor water-soluble compounds, especially those with very high lipophilicity, can be further improved through the incorporation of surface active agent in the solid dispersion. The most frequently used surfactants include polysorbate, sodium lauryl sulfate (SLS), polyethylene–propylene glycol copolymer (poloximer). Surface active agent improves drug release mainly through increasing drug substance wettability and the solubilization effect. It is generally believed that there are two ways that the surfactant provides solubilization effect to poor water-soluble compound. First, the hydrophobic and hydrophilic blocks of the surfactant tend to form structures well known as micelles in aqueous solution, where drug compounds can be solubilized inside the hydrophobic core of the micelles (88). Second, the surfactant can also interact with the polymer carrier to form a structure known as aggregate, which can solubilize guest molecules inside the hydrophobic core, for instance, PVP was discovered to form aggregate as the presence of sodium lauryl sulfate in the solution (89). Owing to their potential toxicity problems, surfactants are usually used carefully in a very small quantity and they are always used in combination with other carriers. Surfactants may also exert direct influence on drug absorption through alerting drug transport across the membrane (90). Using hot melt extrusion, Tween 80 and SLS were dispersed with API in three different polymers, PVP, PVP/VA, and HPMC. The study showed that significant dissolution rate increases by the surfactant as compared with the solid dispersions without surfactant (91).

REFERENCES

1. Lipinski C. Poor aqueous solubility: an industry wide problem in drug discovery. Am Pharm Rev 2002; 5:82–85.
2. USP28/NF23, 2005, p. 9.
3. Amidon GL, Lennernas H, Shah VP, et al. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 1995; 12:413–420.
4. Draft Guidance for Industry. Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms containing certain active moieties/active ingredients based

on a biopharmaceutic classification system, February 1999, Center for Drug Evaluation and Research (CDER).
5. Heng PWS, Wan LSC, Ang TSH. Role of surfactants on drug release from tablets. Drug Devel Ind Pharm 2007; 16(6):783–789.
6. Parikh D. Advances in spray drying technology: new applications for a proven process. Am Pharm Rev 2008; 11(1):34–41.
7. Zheng X, Yang R, Tang X, et al. Part II: Bioavailability in beagle dogs of nimodipine prepared by hot melt extrusion. Drug Devel Ind Pharm 2007; 33(7):783–789.
8. Wikipedia. Arthur Amos Noyes. Available at: http://en.wikipedia.org/wiki/Arthur_Amos_Noyes.
9. Yamamoto K, Nakano M, Arita T, et al. Dissolution rate and bioavailability of griseofulvin from ground mixture with microcrystalline cellulose. J Pharmakin Pharmadyn 1974; 2(6):487–493.
10. McInnes GT, Ashbury MJ, Ramsay LE, et al. Effect of Micronization on the bioavailability and pharmacologic activity of spironolactone. J Clin Pharmacol 1982; 22(8–9):410–417.
11. Merisko-Liversidge EM, Liversidge GG. Drug nanoparticles: formulating poorly water soluble drugs. Tox Path 2008; 36(1):43–48.
12. Soliman OAE, Kimura K, Hirayama F, et al. Amorphous spironolactone-hydroxypropylated cyclodextrin complexes with superior dissolution and oral bioavailability. Int J Pharm 1997; 149 (1):73–83.
13. Kumar N, Jain A, Singh C, et al. Development, characterization and solubility of solid dispersions of terbinafine hydrochloride by solvent evaporation method. Asian J Pharm 2008; 2(3):154–158.
14. Douglas SJ, Davis SS, Illum L. Nanoparticles in drug delivery. Crit Rev Ther Drug Carrier Syst 1987; 3:233–261.
15. Junghanns JAH, Müller RH. Nanocrystal technology, drug delivery, and clinical applications. Int J Nanomed 2008; 3(3):295–310.
16. PharmTech.com. The challenges of manufacturing nanoparticles through media milling. Available at: http://pharmtech.findpharma.com/pharmtech/Article/The-Challenges-of-Manufacturing-Nanoparticles-thro/ArticleStandard/Article/detail/529752.
17. Panagiotou T, Fisher RJ. Form nanoparticles via controlled crystallization. Chem Engineer Prog 2008; 104(10):33–39.
18. Müller RH, Peters K, Becker R, et al. Nanoparticles – a novel formulation for the IV administration of poorly water soluble drugs. 1st World Meeting of the International Meeting on Pharmaceutics. Biopharmaceutics and Pharmaceutical Technology, 1995.
19. Müller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug in therapy: rationale for development and what we can expect for the future. Adv Drug Deliv Rev 2001; 471:3–19.
20. Zhou H, Wang J, Wang Q, et al. Controlled liquid antisolvent precipitation of hydrophobic pharmaceutical nanoparticles in a microchannel reactor. Ind Eng Chem Res 2007; 46(24):8229–8235.
21. York P. Strategies for particle design using super critical fluid technologies. Pharm Sci Technol Today 1999; 2:430–440.
22. Vemavarapu C, Mollan M, Lodaya M, et al. Design and process aspects of laboratory scale SCF particle formation systems. Int J Pharma 2005; 292:1–16.
23. Chattopadhyay P, Gupta R. Production of griseofulvin using supercritical CO_2 antisolvent with enhanced mass transfer. Int J Pharm 2001; 228(1–2):19–31.
24. Maupas B, Letellier S, Guyon F. Determination of the formation constant for the inclusion complex of methyl-β-cyclodextrin with anticoagulant durgs warfarin and 8-chlorowarfarin in aqueous solution. J. Inclusion Phen. Macrocycl. Chem. 1995; 23(4):259–267.
25. Sanghvi R, Narazaki R, Machatha SG, et al. Solubility improvement of drugs using *N*-methyl pyrrolidone. Pharm Sci Tech 2008; 9(2):366–376.
26. Horn D, Ditter W. Chromatographic study of interactions between polyvinylpyrrolidone and drugs. J Pharm Sci 1982; 71(9):1021–1026.
27. Moneghini M, Voinovich D, Perissutti B, et al. Action of carriers on carbamazepine dissolution. Pharm Dev Technol 2002; 7(3):289–296.
28. Moneghini M, Carcano A, Zingone G, et al. Studies in dissolution enhancement of atenolol. Part I. Int J Pharm 1998; 175(2):177–183.
29. Dietrich R, Ney H. Patent US5997903. Oral-administration forms of a medicament containing pantoprazol. Byk Gulden, 1999.
30. Ganter SM, Wagner RF. Patent WO0197805. Pharmaceutical compositions. Novartis AG, 2001.
31. Blouquin P, Reginault P. Patent WO02056881. Fournier Tablets. 2002.
32. Liew CV, Soh JLP, Chen F, et al. Application of multidimensional scaling to preformulation sciences: a discriminatory tool to group microcrystalline celluloses. Chem Pharm Bull 2005; 35(10):1227–1231.

33. Verheyen P, Steffens KJ, Kleinebudde P. Use of crospovidone as pelletisation aid as alternative to microcrystalline cellulose: effects on pellet properties. 6th World Meeting on Pharmaceutics, Biopharmaceutics Pharmaceutical Technol, Barcelona, 2008:1–2.
34. Schardinger F. Bildung kristallisierter polysaccharide (dextrine) aus stärkekleister durch microben. Zentralbl Bakteriol Parasitenkd Abt 1911, II 29, 188–197.
35. Freudenberg K, Jacobi R. Über schardinger dextrine aus stärke liebigs. Ann Chem 1935; 518:102–108.
36. Rowe RC, Sheskey PJ, Weller P. Handbook of Pharmaceutical Excipients. 4th ed. Pharmaceutical Press and American Pharmacists Association, London and Washington 2004.
37. Cavamax®, Cavasol® and Cavitron® Cyclodextrins Product Guide, International Specialty Products 2007.
38. Frömming KH, Szejtli J. Cyclodextrins in Pharmacy. Dordrecht, Netherlands: Kluwer Academic Publishers, 1993.
39. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev 2007; 59:645–666.
40. Abdoh AA, Zughul MB, Badwan AA. Complexation of diclofenac with neutral and modified cyclodextrins explored through phase solubility, 1H-NMR and molecular modeling studies. J Incl Phen Macrocycl Chem 2007; 57(1–4):503–510.
41. Hutin S, Chamayou A, Avan JL, et al. Analysis of a kneading process to evaluate drug substance-cyclodextrin complexation. Pharm Technol 2004; 28(10):112–124.
42. Gazzaniga A, Sangalli ME, Bruni G, et al. The use of beta-cyclodextrin as a pelletization agent in the extrusion/spheronization process. Drug Dev Ind Pharm 1998; 24(9):869–873.
43. Sangalli ME, Vecchio C, Zema L, et al. Preparation of pellets from beta cyclodextrin/drug mixtures by extrusion/spheronization process. 2nd World Meeting on Pharmaceutics Biopharmaceutics Pharmaceutical Technology, Paris 1998.
44. Lunio R, Sawicki W, Skoczen P, et al. Compressibility of gastroretentive pellets coated with Eudragit NE using a single-stroke and a rotary tablet press. Pharm Dev Technol 2008; 13(4):323–331.
45. Wagner KG, Krumme M, Beckert TE, et al. Development of disintegrating multiple-unit tablets on a high-speed rotary tablet press. Eur J Pharm Biopharm 2000; 50(2):285–291.
46. Gao C, Huang J, Jiao Y, et al. In vitro release and in vivo absorption in beagle dogs of meloxicam from Eudragit FS 30 D-coated pellets. Int J Pharm 2006; 322(1–2):104–112.
47. Loftsson T, Frikdriksdóttir H, Sigurkdardóttir AM, et al. The effect of water-soluble polymers on drug-cyclodextrin complexation. Int J Pharm 1994; 110(2):169–177.
48. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersions. J Pharm Sci 1971; 60:1281–1302.
49. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int J Pharm 2002; 231:131–144.
50. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000; 50:47–60.
51. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drug via solid solutions and eutectic mixtures. I. Theoretic consideration and discussion of the literature. J Pharm Sci 1965; 55:482–487.
52. Yalkowsky S. Aqueous Solubility: Methods of Estimation for Organic Compounds. Marcel Dekker Inc., New York 1991.
53. Hancock BC, Shamblin SL, Zografi G. Molecular mobility of amorphous pharmaceutical solids below their glass transition temperature. Pharm Res 1995; 12:799–806.
54. Taylor L, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm Res 1997; 14:1691–1698.
55. Matsumoto T, Zografi G. Physical properties of solid molecular dispersions of indomethacin with poly(vinylpyrrolidone) and poly(vinylepyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization. Pharm Res 1999; 16:1722–1728.
56. Guo Y, Byrn SR, Zografi G. Effects of lyophilization on the physical characteristics and chemical stability of amorphous quinapril hydrochloride. Pharm Res 2000; 17:930–935.
57. Blagden N, Matas M, Gavan PT, et al. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev 2007; 59:617–630.
58. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. 1. A comparison of the behavior of eutectics mixture of sulphathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull 1961; 9:866–872.
59. Breitenbach J, Grabowski S, Rosenberg J. Extrusion von polymer wirkstoff-gemischen zur herstellung von areneiformen. Spekt d wissenschaft 1995; 11:18–20.
60. Killeen MJ. The process of spray drying and spray congealing. Pharm Eng 1993; 14:57–64.
61. Mujumdar AS, Filkova I. Drying '91. Elsevier Science Publishers, Amsterdam 1991; 55–73.
62. Vehring R, Foss WR, Lechuga-Ballesteros D. Particle formation in spray drying. J Aerosol Sci 2007; 38:728–746.

63. Chow AH, Tong HHY, Chattopadhyay P, et al. Particle engineering for pulmonary drug deliver. Pharm Res 2007; 24:411–437.
64. Rowe RC, Sheskey PJ, Weller PJ. Handbook of Pharmaceutical Excipients. 4th ed. Pharmaceutical Press, London and Chicago 2003.
65. Law D, Wang W, Schmitt EA, et al. Properties of rapidly dissolving eutectic mixtures of poly(ethylene glycol) and fenofibrate: the eutectic microstructure. J Pharm Sci 2002; 92:505–515.
66. Law D, Wang W, Schimitt EA, et al. Ritonavir-PEG 8000 amorphous solid dispersions: in vitro and in vivo evaluation. J Pharm Sci 2003; 93:563–570.
67. Vippagunta SR, Wang Z, Horhung S, et al. Factors affecting the formation of eutectic solid dispersions and their dissolution behavior. J Pharm Sci 2006; 94:294–304.
68. Robinson BV, Sullivan FM, Borzelleca JF, et al. PVP: A Critical Review of the Kinetics and Toxicology of Polyvinylpyrrolidone (Povidone). Lewis Publishers Inc., Boca Raton 1990:11–14.
69. Kassem AA, Zaki SA, Mursi NM, et al. Chloramphenicol solid dispersion system I. Pharm Ind 1979; 41:390–393.
70. Hilton JE, Summers MP. The effect of wetting agents on the dissolution of indomethacin solid dispersion systems. Int J Pharm 1986; 31:157–164.
71. Simonelli AP, Metha SC, Higuchi WI. Dissolution rates of high energy polyvinylpyrrolidone(PVP)-sulfathiazole coprecipitates. J Pharm Sci 1969; 58:538–549.
72. Jachowicz R. Dissolution rates of partially water-soluble drugs from solid dispersion systems. II. Phenytoin. Int J Pharm 1987; 35:7–12.
73. Torrado S, Torrado JJ, Cadorniga R. Preparation, dissolution and characterization of albendazole solid dispersions. Int J Pharm 1996; 140:247–250.
74. Tantishaiyakul V, Kaewnopparat N, Ingkatawornwong S. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone K-30. Int J Pharm 1996; 140:59–66.
75. Ambike AA, Mahadik KR, Paradkar A. Spray-dried amorphous solid dispersions of simvastatin, a low T_g drug: in vitro and in vivo evaluation. Pharm Res 2005; 22:990–998.
76. Gupta P, Bansal AK. Molecular interactions in celecoxib-PVP-meglumine amorphous system. J Pharm Pharmacol 2004; 57:303–310.
77. Hirasawa N, Ishise S, Miyata H, et al. An attempt to stabilize nilvadipine solid dispersion by the use of ternary systems. Drug Dev Ind Pharm 2003; 29:997–1004.
78. Marsac P, Konno H, Taylor LS. A comparison of the physical stability of amorphous felodipine and nifedipine systems. Pharm Res 2006; 23:2306–2316.
79. Foster A, Hempenstall J, Tades T. Characterization of glass solutions of poorly water soluble drugs produced by melt extrusion with hydrophilic amorphous polymers. J Pharm Pharmacol 2000; 53: 303–315.
80. Kondo N, Iwao T, Hirai K, et al. Improved oral absorption of enteric coprecipitates of poorly water soluble drug. J Pharm Sci 1994; 83:566–570.
81. Yuasa H, Ozeki T, Takahashi H, et al. Application of the solid dispersion method to the controlled release of medicine. 6. Release mechanism of a slightly water soluble medicine and interaction between flurbiprofen and hydroxypropyl cellulose in solid dispersion. Chem Pharm Bull 1994; 42:354–358.
82. Yamashita K, Nakate T, Okimoto K, et al. Establishment of new preparation method for solid dispersion formulation of tacrolimus. Int J Pharm 2003; 267:79–91.
83. Kohri N, Yamayoshi Y, Xin H, et al. Improving the oral bioavailability of albendazole in rabbits by the solid dispersion techniques. J Pharm Pharmacol 1999; 51:159–164.
84. Okimoto K, Miyake M, Ibuki R, et al. Dissolution mechanism and rate of solid dispersion particles of nilvadipine with hydroxypropylmethylecellulose. Int J Pharm 1997; 159:85–93.
85. Suzuki M, Miyamoto N, Masada T, et al. Solid dispersions of benidipine hydrochloride. 1. Preparations using different solvent systems and dissolution properties. Chem Pharm Bull 1996; 44:364–371.
86. Hasegawa A, Kawamura R, Nakagawa H, et al. Physical properties of solid dispersions of poorly water soluble drugs with enteric coating agents. Chem Pharm Bull 1985; 33:354–358.
87. Kai T, Akiyama Y, Nomura S, et al. Oral absorption improvement of poorly soluble drug using solid dispersion technique. Chem Pharm Bull 1996; 44:567–571.
88. Nagarajan R. Solubilization of "guest" molecules into polymeric aggregates. Polym Adv Technol 2001; 12:23–43.
89. Lange VH. Wechselwirkung zwischen natriumalkylsulfaten und polyvinylpyrrolidone in wabrigen losungen. Kolloid-Z uZ Polymers 1971; 243:101–109.
90. Malmsten M. Surfactants and Polymers in Drug Delivery. Marcel Dekker, Inc., New York 2002.
91. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: selection of polymer-surfactant combinations using solubility parameters and testing the processability. Int J Pharm 2007; 328:119–129.

19 Granulation Approaches for Orally Disintegrating Formulations

Gopi Venkatesh
Eurand, Inc., Vandalia, Ohio, U.S.A.

INTRODUCTION

The oral route is still the most convenient and appropriate way to dispense or administer most medications as tablets or capsules to patients, young and elderly. The dose strength in most widely used tablets varies widely, that is, from a few micrograms to hundreds of micrograms, while tablets weighing from a few micrograms up to about 1500 mg are commonly manufactured for marketing. Such dosage forms have several disadvantages. For example, it is estimated that 50% of the population have problems swallowing tablets (1,2). It is especially hard for the elderly and children to swallow tablets or capsules, or to medicate patients who are unable or unwilling to swallow tablets or capsules. Moreover, some adults with schizophrenia or bipolar mania may have difficulty in swallowing tablets or, in institutional settings, may hide pills inside their cheek to later spit them out. Furthermore, conventional tablets or capsules usually must be administered with water, which is not always possible or convenient. This leads to poor or even noncompliance with the treatment, which consequently has a negative impact on the efficacy of the treatment such as:

> "Patient nonadherence can limit physician's ability to successfully treat patients and can increase the cost of health care" (3).

There is a strong trend in the pharmaceutical industry toward developing orally disintegrating tablets because they have various benefits for the patient compared with regular tablets. These benefits include quick onset of action, ease of swallowing, and the ability to take the tablets without water. The orally disintegrating tablet (ODT) rapidly dissolves or disintegrates in the buccal cavity, and the resulting slurry or suspension of the drug is more readily swallowed by the patient. In the literature, ODTs are also called orally dissolving, orodisperse, mouth-dissolving, quick-dissolve, fast-melt, and rapid-disintegrating tablets and freeze-dried wafers. The active pharmaceutical ingredient is often coated to impart taste-masking and/or controlled-release (CR) properties and the coating does not completely dissolve or does not permit significant drug diffusion until the drug has been swallowed. Tablets comprising drugs that are particle-coated are more appropriately termed as ODTs because of the delayed release of the active molecule until they are swallowed.

Orally disintegrating dosage forms have grown steadily in popularity as more convenient and potentially safer alternatives to conventional tablets and capsules, as the pharmaceutical industry recognized the issues involving noncompliance/nonadherence to dosing regimens among patients with a concomitant loss of efficacy, increased health care cost. Pleasant tasting, rapidly disintegrating ODT formulations containing bitter, highly water-soluble APIs at high doses (e.g., ODTs containing 500–600 mg of one or more moderately bitter drugs or 150–200 mg of a bitter, highly soluble drug) have been developed.

For pharmaceutical companies, this dosage form offers the following advantages (4,5):

- Life cycle management: Reformulation is a strategy to prolong market exclusivity as it may delay or reduce generic erosion at patent expiry.
- Differentiation in a crowded market.
- Line extension.

On the basis of expanding global market estimations, demand for ODT-adapted drugs is forecasted to increase at 8.9% annually to nearly $3 billion in 2012. There are over hundred

products worldwide presented in this dosage form in therapeutic areas as varied as schizophrenia, migraine, nausea, pain, allergies, gastrointestinal, Parkinson's disease, Alzheimer's disease, diarrheas, cough and cold, etc. Recent market studies indicate that more than half of the patient population prefer ODTs to other dosage forms, and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (greater than 80%).

The ODT is required to rapidly disintegrate on contact with saliva in the oral cavity (or required to meet the disintegration time (DT) specification of less than 30 seconds when tested by U.S. Pharmacopoeia (USP) method <701> disintegration). However, administration of an ODT may not inherently result in a faster therapeutic onset, but it can circumvent problems such as difficulty in swallowing traditional solid oral dosage forms, particularly by pediatric and geriatric patients, or patients with nausea and vomiting.

In this chapter, the term *conventional oral dosage forms* refers to tablets and capsules that must be swallowed with water for dissolution, release, and absorption of the drug in the stomach and distal sites of the GI tract.

Since buccal and mucosal tissues of the oral cavity are highly permeable, orally dispersing tablets, and rapid dissolve films may be used to deliver drugs to the oral cavity for absorption across the oral mucous membranes, thereby avoiding first-pass hepatic metabolism and potentially achieving rapid onset of action and/or increased bioavailability. Physicochemical and organoleptic properties of the active ingredient significantly impact patients' compliance with ODTs designed for mucosal absorption. In addition, some of the drugs that usually degrade rapidly in the stomach may be delivered via ODT tablets and rapid dissolve films for absorption through oral mucosa. The overall preclinical, clinical, and biopharmaceutical development programs necessary to support successful marketing applications [e.g., new drug application (NDA), supplemental new drug application (sNDA), abbreviated new drug application (ANDA), or European Medicines Agency (EMEA)] for ODTs and rapid dissolving films need to address the above-mentioned issues.

In this chapter, various ODT products and technologies are briefly described, physicochemical, organoleptic, and biopharmaceutical attributes of an ideal ODT and challenges likely to be encountered during the development and manufacture of these evolving dosage forms are highlighted.

ORALLY DISINTEGRATING TABLETS

What is an ODT?

Generally, an ODT is a solid dosage form that disintegrates and may dissolve in the mouth (either on or beneath the tongue or in the buccal cavity) without water within 60 seconds or less. ODTs continue to attract attention as an alternative to conventional oral dosage forms. Offering ease of use, the potential for increased patient compliance, and a way to extend the product life cycle of a drug, ODTs continue to make inroads into the market for solid dosage forms since their inception in the 1980s. Lyophilization and direct compression of an ODT formulation are the two mainstream technologies that are being increasingly used to develop ODTs. Rapidly dissolving films (RDFs) or thin film strips form a third category of solid, unit-dose, orally disintegrating products that aim to meet the same objectives of ease of administration, patient convenience, and improved compliance.

Compressed tablet systems are based on conventional tableting technologies mostly using sugar-based excipients, which, having high aqueous solubility and sweetness, impart taste masking and pleasing mouth feel, and vary in their degree of hardness and friability. This variability results in varying disintegration characteristics depending on the type of excipients, preblends, taste-masked or uncoated drug particles, and process used, but typically DTs are higher than for lyophilized ODT formulations (typically 15–60 seconds or higher vs. 3–15 seconds or so for lyophilized ODT products).

Mechanism of Orally Disintegrating Tablet Drugs

Ideally, an ODT is formulated to rapidly disperse in the oral cavity forming a smooth, easy-to-swallow suspension, enabling medication to be swallowed without water, thereby increasing convenience and compliance across a broad range of indications and patient types, including the young, elderly, institutionalized patients and active people (i.e., people "on the move") or

people with migraine. ODTs may release drug in the mouth for absorption through pregastric (e.g., local oromucosal tissues in the oral cavity, pharynx, and esophagus), gastric (i.e., stomach), and postgastric (e.g., small and large intestines) segments of the gastrointestinal tract (GIT). Following swallowing, the drug is absorbed in the same way as conventional solid oral dosage forms. However, orally dispersing tablets or films may also be used to deliver drugs for systemic absorption across the oral mucosa, thereby avoiding first-pass hepatic metabolism and potentially achieving rapid onset of action and/or increased bioavailability. Physicochemical and organoleptic properties of the active ingredient significantly impact mucosal absorption. The ODT formulation may aim to maximize the potential for enhanced bioavailability, to minimize side effects, or to ensure bioequivalence with a perorally absorbed dosage form. ODT dosage forms are also more convenient than other dosage forms, such as effervescent tablets, dry syrups, chewing gums, or chewable tablets, which are commonly used to enhance patient compliance, because of:

(a) ODT tablets do not require water for administration,
(b) it is difficult for elderly patients to chew large pieces of gum or chewable tablets,
(c) patients may experience unpleasant drug taste due to membrane fracture during compression of chewable tablets at high compression forces or mastication, and
(d) ODT tablets meet unmet medical need (e.g., rapid onset of action in migraine patients and to prevent avoiding medication by patients with chronic illness such as depression and schizophrenia due to "cheeking") (6,7).

REGULATORY BACKGROUND

Food and Drug Administration Draft Guidance 2007

After the U.S. Food and Drug Administration (FDA) received and reviewed applications for the initial ODT products, the Center for Drug Evaluation and Research (CDER), Nomenclature Standards Committee defined an ODT as a new dosage form in 1998:

> "A solid dosage form containing medicinal substances which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue" (8).

In April 2007, the FDA issued a draft guidance (Guidance for Industry: Orally Disintegrating Tablets draft guidance) (9) to address issues that have arisen from the growing use of ODT technology based on the drug products that have been approved previously. The FDA specified that the characteristics of initial ODT products included low tablet weight, small size, highly soluble components, and rapid disintegration. "However, as firms started developing additional products using different technology and formulations, many of these later products exhibited wide variation in product characteristics from the initial products," specifies the draft guidance. "Because this shift in product characteristics can affect suitability for particular uses, the Agency developed this guidance."

Although the DTs for ODT products may range from a few seconds to longer than a minute, a large majority of products have in vitro DTs of approximately 30 seconds or less. For this reason, FDA recommends that ODTs "be considered solid oral preparations that disintegrate rapidly in the oral cavity, with an in vitro DT of approximately 30 seconds or less, when based on the U.S. Pharmacopoeia disintegration test method or alternative. "

Although 30 seconds is given as a desired result, FDA says it is not intended to represent an arbitrary distinction between ODT and other tablet forms. "... it is instead representative of a general time period associated with drug products that have been found to have performance characteristics appropriate for a disintegrating tablet meant to be taken without chewing or liquids," specifies the draft guidance. The agency also suggests the weight of the ODT should not exceed 500 mg. If it does, the extent of component solubility, such as tablet residue and needs for liquids, can influence the acceptability of a large tablet being labeled as an ODT.

Industry Response to 2007 Draft Guidance

The industry expressed concern that the specification of not more than (NMT) 30 seconds for disintegrant time (DT) by the USP <701> disintegration test method and especially the weight

restriction (i.e., NMT 500 mg) would severely restrict the use of high-dose medicaments in elderly and institutionalized patients who experience difficulty swallowing large tablets or capsules. Many patients with dysphagia, the elderly and institutionalized, need to consume several medications every day, many of which are high doses, to maintain a healthy life style. These, and the pediatric patients, would be greatly benefited if ODT formulations containing high doses become available; this will also significantly improve compliance/adherence to dosing regimens, hence reduce health care costs. Surprisingly, the FDA decided to restrict the tablet weight to 500 mg and DT to 30 seconds and was silent on the organoleptic properties, which are critical for the patient's acceptance of ODT formulations. For example, more than 92% of children aged 6 to 11 years preferred the strawberry-flavored lansoprazole delayed-release ODT over the peppermint-flavored ranitidine syrup in a taste testing (10). This could result in a compliance issue. The dose or tablet weight and/or DT restrictions should be applicable only in cases containing high fractions of insoluble excipients that may have potential for causing choking especially in children. The industry recommended considering the organoleptic properties of the ODT products while approving the innovators' or generic products. The FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology discussed the issues involved with the innovators as well as generic ODT products at the meeting on July 23, 2008, which was open to the industry representatives.

Food and Drug Administration Guidance 2008 and Its Interpretation

The FDA issued, in December 2008, the draft guidance as the final guidance, "Guidance for Industry: Orally Disintegrating Tablets" (11) that states "ODT products should be developed to match the characteristics such as a DT of NMT 30 seconds when tested by the USP method <701> Disintegration." Since DT is method dependent, it is required to demonstrate correlation with or equivalency to the USP method. Additional parameters for consideration are tablet size and weight, component solubility, and the effect these factors have on the product's intended use. While tablet size or weight is not explicitly included in the definition, the effect large tablets have on patient safety and compliance should be considered. Recommended upper limit is still 500 mg. The Guidance states, "The recommendations are based on the intention of the original definition and on Agency experience with new drug applications and abbreviated new drug applications submitted for this dosage form."

What Does It Mean to the Industry?

The only option open to the ODT product developer is to use less of water-insoluble excipients, especially while developing large dose ODTs with the tablet weight exceeding 500 mg, 1000 mg, or even higher, and ensure that there is no concern for potential choking through questionnaires during organoleptic taste testing of prototypes as well as during pivotal BE studies. The European Pharmacopoeia, however, defines a similar term, *orodispersible tablet*, as a tablet that can be placed in the mouth where it disperses rapidly before swallowing (12). The orodispersible tablets are required to disperse in less than three minutes. In Japan, some ODTs that are typically molded tablets have approved labeling from the Korosho as "easy-to-swallow," but are marketed as ODTs to be administered without water or with a small amount of water (13). Some of the ODT products have been discontinued because of poor performance in the market place, as well as because of poor taste. Thus, there is no consistency between the three regulatory compendia. None of the regulatory agencies is concerned with drug taste, mouth feel, and/or grittiness.

ORALLY DISINTEGRATING TABLET FORMULATION STRATEGIES

Several factors must be considered when selecting the processes for the development of an ODT formulation for a drug candidate that is to be formulated as a bioequivalent product-line extension (PLE) of an existing oral dosage form or as a life cycle management strategy. Under the circumstances, it is assumed that the absorption of the drug molecule from the ODT occurs in the postgastric GIT segments, similar to the conventional oral dosage form. But this scenario may not always be the case. An ODT may have varying degrees of pregastric absorption, and thus, the pharmacokinetic profile (including the maximum plasma concentration, time to achieve maximal plasma concentration, and area under the plasma concentration time curve of

an equal dose of an ODT and a conventional oral dosage form) will vary, especially if the drug is lipophilic and does not require taste masking or the active is extremely bitter and hence require thicker taste-masking coating. Therefore, the ODT will not be bioequivalent to the conventional oral dosage form. Examples are cited in the literature in which the pharmacokinetic profiles and bioavailabilities of the same dose of drug in an ODT are not equivalent to the conventional oral dosage form (1,14–22). For example, ODT formulations of selegiline, apomorphine, and buspirone have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form.

It is possible that these differences may, in part, be attributed to the drug molecule, formulation, or a combination of both. If significantly higher plasma levels and systemic exposure have been observed, pregastric absorption leading to the avoidance of first-pass metabolism may play an important role. This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an ODT. For example, safety profiles may be improved for a drug that produces significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, provided it exhibits substantial absorption in the oral cavity and pregastric segments of the GIT and is not bitter.

Physicochemical Attributes of a Candidate Drug

Before starting formulation development, it is advisable to consider physicochemical attributes of the active pharmaceutical ingredients such as particle size distribution, shape, morphology, aspect ratio, pH-dependent solubility profile, pK_a, known incompatible excipients, organoleptic properties, immediate-release (IR) dosage forms, pharmacokinetic properties (T_{max}, and dose proportionality of C_{max} and AUC, intra- and intersubject variability, food effect, doses and maximum daily doses). The drug substance is characterized in terms of particle size, shape, organoleptic and physicochemical properties, and the doses, dissolution method, and dissolution specifications for the reference-listed drug product are reviewed to determine the appropriate process for taste masking as well as for achieving bioequivalence to reference product. The database is searched for information on similar products previously developed, and strategic development approaches to follow are decided in a brainstorming session.

ORALLY DISINTEGRATING TABLET FORMULATION DEVELOPMENT

An ODT, as a novel dosage form, has several characteristics to distinguish it from the more traditional dosage forms, tablets, or capsules. Because the ODT dosage form disintegrates in the oral cavity of the patient, the disintegrated ODT must be palatable. Taste masking is often of critical importance in the formulation of an acceptable ODT. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups, and chewable tablets simply contain flavors, sugars, and other sweeteners to overwhelm or complement the bitter taste of the drug (23). For example, if one or more of the drugs in the ODT are bitter tasting, the drug-containing particles comprising the ODT must be taste masked, for example, by coating the drug-containing particles with a polymeric membrane to prevent release of the drug in the oral cavity. The more bitter the drug, the thicker the taste-masking coating required and hence, the slower the drug release from the taste-masked drug-containing particles (24). Slower drug release is a particular problem for ODT dosage forms that are intended to be bioequivalent to a reference-listed IR dosage form of the drug. For ODT compositions containing combinations of two or more drugs (e.g., a high-dose/low-dose drug formulation) this problem is particularly acute, because the different drug components of the combination ODT may require different levels of taste masking depending on the degree of bitterness of the drugs (i.e., drugs with low bitterness levels may require little or no taste masking, while highly bitter drugs may require substantial taste masking layers). Adding further complication, taste-masking layers reduce the release rate of poorly soluble drugs more than for more soluble drugs.

In addition to rapidly disintegrating on contact with saliva in the oral cavity, the ODT tablets must provide a smooth, nongritty mouth feel, thereby necessitating the inclusion of rapidly dispersing granules comprising a sugar, sugar alcohol, a saccharide, or a mixture thereof. The final step in the manufacture of ODT tablets is direct compression, that is,

blending of taste-masked drug particles, rapidly dispersing granules in combination with direct compression excipients, minor components such as a flavor, a sweetener, a colorant, etc. to achieve blend uniformity.

Thus, the ODT technology should produce tablets with a hardness/strength sufficiently high and a friability sufficiently low to withstand the rigors of packaging, transportation and distribution, acceptable organoleptic properties (e.g., palatable and smooth (nongritty) mouth feel), and acceptable pharmacokinetic properties (i.e., rapid onset, C_{max}, AUC properties similar to the reference-listed drugs). The most desired attributes of an ODT product are listed in Table 1.

Table 1 Desired Attributes for Orally Disintegrating Tablets

No.	Desired attributes for orally disintegrating tablets
1	Taste-masked drug substance microparticles, irrespective of the solubility, bitterness, particle shape, morphology, or therapeutically effective dose of the drug substance
2	Consist rapidly dispersing granules comprising a water-soluble sugar alcohol, a saccharide or a mixture thereof, and a superdisintegrant
3	Drug particle with an average particle diameter of not more than 400 μm to provide smooth mouth feel
4	Small amount of water-insoluble tableting excipients as compression aid
5	Providing rapid, substantially complete release of the dose from the immediate-release drug particles upon arrival in the stomach
6	Robust formulation with acceptable hardness, friability and bulk, bottle and/or blister packaging suitability for storage, transportation, and commercial distribution

Taste-Masked Particles

Many prescription and over-the-counter pharmaceutical products exert a bitter taste by activating one or more of the bitter taste receptors such as T2R proteins, G protein-coupled receptors (GPCRs) and sensed through ligand-gated ion channel family, TRPM5 present in taste bud cells, the drug dissolved in the saliva interacting with the cells and producing a positive or negative taste sensation (25,26). Physiological and physiochemical approaches have been used to prevent drugs from interacting with taste buds to eliminate and/or reduce negative sensory responses (27).

Taste masking is an essential requirement for orally disintegrating tablets for commercial success. If the active pharmaceutical ingredient has none or a mild taste, it may be granulated with pharmaceutically acceptable diluents such as a sugar alcohol, a saccharide, microcrystalline cellulose or a mixture thereof, a binder (optional), a disintegrant, a flavor, a sweetener, a colorant (optional), etc. preferably in a fluid-bed granulator to produce free-flowing granules with a desired particle size distribution (28). If the drug-containing granules require taste masking, it is essential to ensure that the granules are resistant to attrition during fluid-bed coating or microencapsulation by phase separation. Drug-containing microparticles (e.g., crystals, granules, or drug layered onto inert cores) may be coated with one or more water-insoluble polymers (e.g., ethyl cellulose, neutral acrylate-methacrylate copolymers) by microencapsulation in solvent systems or by fluid-bed coating. Drug dissolution needs to be speeded up, a water-soluble or more preferably a gastrosoluble pore-forming agent (e.g., calcium carbonate or a gastrosoluble polymer) may be incorporated into taste-masking membranes (29,30). Taste-masked drug particles may be evaluated for effectiveness of taste masking in healthy volunteers under a protocol (Table 2). The composition/thickness of the coating is optimized for adequate organoleptic and dissolution properties. It is important to realize inherent subject-to-subject variability in taste evaluation of taste-masked microcapsules or ODTs incorporating these microcapsules. Following taste masking, the microcapsules are subjected to both dissolution testing and evaluation of organoleptic properties, and the coating process/composition is optimized to achieve acceptable taste masking and dissolution.

Controlled-Release Beads

If CR-coated beads are to be incorporated into ODTs, the active is preferably layered onto inert cores (e.g., sugar spheres, cellulose spheres) from a polymeric binder solution or a suspension

Table 2 Oganoleptic Taste-Testing Protocol

Subject's written consent

Medication to be tasted: acetaminophen ODT 250 mg

The test medication, APAP is widely used analgesic and no risk is envisaged because of its intake. However, the subject is advised to spit it out following its oral disintegration in the mouth.

Subject's Written Consent to participate in the study

I have not consumed any drug or alcohol eight hours prior to the study. I have also not consumed any food or coffee during the last two hours. I am fully aware of the procedures to follow and potential risk the medication may cause if swallowed.

I, _____ (name), _____ (address) _____

and tel.: _____, am willingly participating in the study.

Subject's signature _____ Date: _____

I have fully explained to the subject the nature, aim, procedures, and possible risks if swallowed.

Investigator's signature: _____ Date: _____

Case report form—training phase

Subject's case report

I have not consumed any drug or alcohol eight hours prior to the study. I have also not consumed any cigarette, food, or coffee during the last 30 min. I am fully aware of the procedures to follow and potential risk the medication may cause if swallowed.

Sign/date: _____

Medication one

Parameters and test scores [scale 1 (excellent) to 5 (poor)]

1.	DT (seconds):	_____	_____	_____	_____	_____
		10–20	20–30	30–40	40–50	50–60
2.	Taste masking	_____	_____	_____	_____	_____
3.	Grittiness	_____	_____	_____	_____	_____
4.	Mouth feel	_____	_____	_____	_____	_____
5.	Aftertaste	_____	_____	_____	_____	_____

1. Any other observation (too sweet, too much flavor, etc.): _____

Medication two

Parameters and test scores [scale 1 (excellent) to 5 (poor)] for attributes 1–5

1.	DT (seconds):	_____	_____	_____	_____	_____
		10–20	20–30	30–40	40–50	50–60
2.	Taste masking	_____	_____	_____	_____	_____
3.	Grittiness	_____	_____	_____	_____	_____
4.	Mouth feel	_____	_____	_____	_____	_____
5.	Aftertaste	_____	_____	_____	_____	_____

1. Any other observation (too sweet, too much flavor, etc): _____

Case report form—testing phase

Medication one

Parameters and test scores [scale 1 (excellent) to 5 (poor)] for attributes 1–5

1.	DT (seconds):	_____	_____	_____	_____	_____
		10–20	20–30	30–40	40–50	50–60
2.	Taste masking	_____	_____	_____	_____	_____
3.	Grittiness	_____	_____	_____	_____	_____
4.	Mouth feel	_____	_____	_____	_____	_____
5.	Aftertaste	_____	_____	_____	_____	_____

1. Any other observation (too sweet, too much flavor, etc): _____

(*Continued*)

Table 2 Oganoleptic Taste-Testing Protocol (*Continued*)

Medication two

Parameters and test scores [scale 1 (excellent) to 5 (poor)] for attributes 1–5

1.	DT (seconds):	_____ 10–20	_____ 20–30	_____ 30–40	_____ 40–50	_____ 50–60
2.	Taste masking	_____	_____	_____	_____	_____
3.	Grittiness	_____	_____	_____	_____	_____
4.	Mouth feel	_____	_____	_____	_____	_____
5.	Aftertaste	_____	_____	_____	_____	_____

1. Any other observation (too sweet, too much flavor, etc.): _____

in a fluid-bed coater or drug-containing pellets are produced by controlled spheronization (31–35). The IR beads thus produced are coated with one or more functional polymers to produce CR beads exhibiting desired in vitro drug release profiles. Particle size, shape/morphology of taste-masked or CR-coated particles, type of external coating on taste-masked/CR-coated particles (e.g., water-insoluble, enteric cellulosic, or Eudragit polymers) can have significant and often negative impact on physical strength. If compression aids, such as microcrystalline cellulose, do not provide sufficient flexibility, a compressible coating with a hydrophilic polymer may be considered.

Compression Blends

ODTs comprising excipients such as flavors (e.g., strawberry, cherry, vanilla, peppermint, grape, etc. commercially available from flavor manufacturers), citric acid, sodium carbonate, sodium bicarbonate, sweeteners (e.g., aspartame, acesulfame calcium, sucralose, or saccharin sodium), superdisintegrants (e.g., crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose, modified starches, carboxymethyl celluloses), and compression aids (e.g., microcrystalline cellulose such as Avicel, Ceolus, or Prosolv), besides preferably taste-masked particles and/or CR beads containing the active, and main pharmaceutical diluent (e.g., AdvaTab® base granules, or Parteck® M, StarLac®, Ludiflash®, F-Melts, Isomalt (e.g., gelenIQ™ 720 with $D(0.5) = 260$ μm or 721 with $D(0.5) = 220$ μm); Pharmaburst™ or Advantol™ 200) are blended in a V-blender/bin blender for sufficient time to insure meeting USP blend uniformity requirements It is advisable to preblend the minor components of the compression blend in a V-blender of appropriate capacity to achieve a more homogeneous distribution of the minor excipients in the final ODT compression mix and also to establish the rpm (if variable)/time of blending to achieve blend uniformity consistently.

Tableting

Prototype compression blends are compressed for comparative evaluation of organoleptic, tableting and dissolution properties, and formulation optimization. Tool engineers are to be consulted for most appropriate tooling design (shape, round, gelcap, concave, convex, beveled edge, flat radius edge, optimal diameter/thickness ratio, logo, depth of α-numerals) thereby avoiding stress concentrations during tableting. Compression parameters need to be carefully optimized with the most appropriate choice of precompression, main compression, force/gravity feeders, turret speed, and tablet transit through a weight checker/metal detector. External or internal lubrication with a lubricant such as magnesium stearate, stearic acid, sodium stearyl fumerate) may be used. During prototype development, small ODT blends (~0.5–2 kg) may be compressed using a rotary tablet press using partial tooling and gravity or force feeders. However, performing at least one tableting trial using full tooling is recommended before manufacturing pilot or pivotal clinical trial materials. Typically, during formulation development, tablets are compressed at two or more compression forces and wherever possible at two or more turret speeds to establish robustness of the tableting process

and/or establish compression force—friability ranges wherein tablet hardness is maximized and friability minimized without affecting disintegration, dissolution, and organoleptic properties. Organoleptic properties of ODT tablets may be evaluated using a taste-testing panel under a protocol (Table 2).

ORALLY DISINTEGRATING TABLET PRODUCT MANUFACTURING CHALLENGES

Taste-Masking Processes

Depending on the severity and physicochemical properties of the active pharmaceutical ingredients, a number of taste-masking technologies have been established for masking drug taste (27,29,30,36–53). In general, drug particles (e.g., crystals, granules, drug layered onto inert cores, pellets by controlled spheronization) are coated with one or more water-soluble polymers, water-insoluble polymers, gastrosoluble polymers, enterosoluble polymers, low-melting fatty acid esters for sufficient thickness to achieve adequate taste masking. The water-insoluble polymers include ethyl cellulose, cellulose acetate, cellulose acetate butyrate, polyvinyl acetate, and neutral acrylate-methacrylate copolymers (Eudragit RL or RS polymer, NE30D polymer dispersion) for microencapsulation in solvent systems (38) or fluid-bed coating (39). Water-soluble pore formers include methylcellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyethylene glycol. Enterosoluble polymers include cellulose acetate phthalate, hypromellose phthalate, pH sensitive methamethcrylic acid copolymers while gastrosoluble polymers include polyvinylacetal diethylaminoacetate (AEA), aminoalkyl methacrylate copolymer (Eudragit EPO). The ratio of water-insoluble polymer to pore-forming agent can vary widely from 95/5 to 50/50. Alternatively, a water-insoluble polymer and a water-soluble or gastrosoluble or enterosoluble polymers can form separate membrane layers to achieve desired organoleptic and dissolution properties. A gastrosoluble agent such as calcium carbonate, calcium saccharide, calcium succinate, magnesium citrate is incorporated into the taste-masking membrane either by coacervation or by fluid-bed coating (29). The gastrosoluble pore former rapidly dissolves in the acid environment of the stomach creating microchannels for rapid drug release (30). The literature is abundant with examples of bitter tasting drugs being taste masked by coating with water-soluble polymers (e.g., hydroxypropyl, hydroxyethyl cellulose, or hypromellose), water-insoluble polymers (e.g., ethyl cellulose, polyvinyl acetate, cellulose acetate, methacrylate copolymers, Eudragit RL, RS, or NE30D), gastrosoluble polymers or mixtures thereof. The fast-dissolving tablets containing taste-masked granules of pirenzepine HCl or oxybutynin HCl were prepared by coating the drug particles with Eudragit EPO polymer (40). Taste-masked micromatrix particles were formed by spray drying the drug and Eudragit EPO polymer (41,42).

Besides the above-mentioned primary methods of taste masking, aqueous coacervation processes using gelatin, cellulose acetate phthalate, hypromellose phthalate, or mixtures thereof with an alkaline buffer as a coacervating agent for taste making of bitter tasting drugs, such as ibuprofen have been established (44,45). In Prevacid® SoluTab™ by TAP Pharmaceutical, the active, lansoprazole, a basic inorganic salt, and other additives, which were granulated to produce microgranules with an average particle size of less than 400 μm, are first undercoated followed by a delayed-release coating with Eudragit L polymer (46). Monoglycerides having a low melting point, film-forming characteristics are used to microencapsulate macrolide antibiotics and other bitter drugs (47–49). Methods of taste masking using a spray-congealing technique or heat treatment of wax-coated microparticles have been described (50). In MicroMask™ by KV pharmaceutical, drug particles are taste masked by casting or spin congealing melt dispersions or solutions of a drug in a molten blend of fatty acid esters and/or waxy materials with a melting point in the range of 50 to 200°C (51). Cyclodextrins and ion exchange resins are also used for masking unpleasant tasting drugs for incorporating into fast-dissolving tablets (52,53). OptiMask® technology from Physica Pharma consists in creating a matrix between the drug and a masking agent. During the process, the masking agent is finely mixed with the drug. This process ensures a protective environment around the drug, thus avoiding its direct contact with the tongue, without modifying its dissolution profile.

Overcoming the problem of poor taste with extremely bitter drugs makes development of ODT dosage forms particularly challenging. The ability to mask poor drug taste with traditional flavors and sugars is limited, and polymeric microencapsulation of the active ingredient is required to achieve maximum taste-masking effectiveness. However, the very act of taste masking results in slower dissolution resulting in a product not bioequivalent to reference-listed drug. The type and amount of membrane applied depends on the drug's physicochemical properties, especially its solubility at neutral to saliva pHs, its organoleptic properties (i.e., extent of bitterness, and the dosage form application. A major objective these days is to develop patient-friendly ODTs to achieve the desired plasma concentration profiles for the therapeutic agent while maintaining effective taste-masking properties and acceptable mouth feel of the particles so that the ODT is bioequivalent to reference-listed IR drug product.

Biochemical Bitter Blockers

Redpoint Bio (25) and Senomyx (26) have been actively investigating bitter receptors activated by bitter drugs through high-throughput screening assays to create compound libraries for receptor blockers, optimizing potential bitter blockers for potency, physicochemical properties, and product requirements. If successful, this will open up significant opportunities for creating new dosage forms such as ODTs or RDFs containing bitter drugs that have been subjected to first-pass metabolism for rapid absorption through buccal mucosa, thereby providing improved convenience, rapid onset of action, enhanced bioavailability, and better safety profile.

Rapidly Dispersing Granules

Rapidly dispersing granules, direct compression excipient premixes, which comprise one or more functional excipients, such as AdvaTab base granulations, Parteck M, StarLac, Ludiflash, F-Melts, Isomalt, Pharmaburst, are produced by high-shear (HS) granulation, fluid-bed granulation or by spray drying. These excipient premixes need to exhibit desired characteristics such as low hygroscopicity, high solubility to support rapid drug release, high-dilution potential, morphology for free flow, and mixing properties, well-defined particle size distributions (e.g., 100–400 μm), and taste-masking properties. The manufacturing challenges encountered during the development and commercialization of AdvaTab base granulations are briefly described in subsequent sections below.

Case Studies

High-shear granulation. Ohta et al. (54) milled mannitol with an average particle size of 15 μm and crospovidone, both of which were granulated with water in HS granulator, dried in the Glatt fluid-bed dryer, and compressed into ODT tablets at a compression force of 300 kg or higher; stronger tablets (hardness >3.9 kg) were obtained. Furthermore, these ODT tablets disintegrated in 10–15 seconds. ODT tablets comprising lactose granules (average granule size: 300–400 μm) comprising unmilled (average particle size: 80 μm) or milled lactose (average particle size: 15 μm) exhibited tableting properties similar to that of the respective ODT tablets comprising unmilled mannitol (average particle size: 60 μm) or milled mannitol (average particle size: 20 μm). The ODT tablets containing mannitol plus crospovidone granulated with a binder (povidone) solution produced harder tablets at comparable compression forces, irrespective of whether milled or unmilled mannitol was used for granulation. These ODT tablets took longer to disintegrate (more than 100 seconds).

The HS granulation process was evaluated using Vector's GMX 25 HS granulator for granulating and Glatt GPCG 5 for drying the granulated material (55). The sugar alcohol and/or saccharide and disintegrant will typically be present in the rapidly dispersing micro-granules at a ratio of from about 99:1 to about 90:10 (sugar alcohol and/or saccharide: disintegrant). A superdisintegrant such as cross-linked povidone (e.g., Crospovidone XL-10) and a sugar alcohol, a saccharide or a mixture thereof (e.g., D-mannitol or lactose with an average particle size of less than 30 μm) were granulated. Results confirmed that the processing parameters had little or no impact on the performance of the granulation in terms of ODT performance as long as the same amount of water was added during granulation, and the sequence of procedures for wet milling, drying to less than 1% by weight, sieving, milling of oversize material, were followed.

Issues encountered during preliminary HS granulations:

- more friable granules compared with conventional granules containing a binder;
- milling of a high fraction of oversized granules resulted in material with bimodal particle size distributions;
- irregularly shaped granules with a bimodal particle size distribution—particles in three size ranges of (1) more than 300 μm (50 mesh), (2) (350 to 105 μm) and (3) less than 105 μm (140 mesh), resulting in poor material flow during high-speed compression.

The processing conditions were changed (e.g., wet milling and vacuum transfer steps included and the drier load doubled) and optimized for the equipment in use, that is, granulation in the HS granulator, GMX 600, followed by ray drying in a convection oven. Results were acceptable granulation for ODT tableting

Fluid-bed granulation. The fluid-bed granulation process was evaluated using Glatt GPCG 5 equipped with a top spray Wurster insert, as an alternative approach to produce free-flowing granules with higher compressibility, less oversized and undersized (fines) material (55). A superdisintegrant such as cross-linked povidone (e.g., Crospovidone XL-10) and a sugar alcohol, a saccharide or a mixture thereof (e.g., D-mannitol or lactose with an average particle size of less than 30 μm) with or without a binder were granulated. Purified water or a polymeric binder dissolved in SD number 30 alcohol or purified water was sprayed using a nozzle with a port size of 0.8 mm and atomization pressure of 1.5 to 2.5 bar. To avoid the fine powder mixture sticking to the sides of the expansion chamber, the unit was preheated before being charged with the powder mixture. The process was scaled-up to Glatt GPCG 120 with a batch size of 160 kg. A variety of binders (e.g., none, povidone, mannitol, hypromellose, maltodextrin, pregelatinized starch, Starch 1551, hydroxypropyl cellulose) and disintegrants (e.g., crospovidone, Starch 1551, sodium croscarmellose, sodium starch glycolate, low-substituted hydroxypropyl cellulose, or a mixture thereof) were used to produce granulations that were comparable in particle size distribution, compressibility, and tableting properties. The following parameters were varied during these trials: spray rate, atomization pressure, amount of granulating fluid (e.g., purified water or binder solution), product temperature, inlet air volume.

Physical and tableting properties of fluid-bed versus high-shear granulations. The AdvaTab base granulations prepared at different conditions were used to prepare placebo and 160 mg acetaminophen ODT formulations (composition: 27% Microcaps® acetaminophen from production, 1% flavor/sweetener, 5% disintegrant, and AdvaTab base granulation (adjusted to 100%)) and compressed under different compression forces into 13 mm tablets weighing about 620 mg. The minor components of the formulation were preblended in a V-blender prior to blending with required amounts of AdvaTab granules with or without Microcaps acetaminophen, in a V-blender as per the established procedures. ODT tablets were compressed using the Hata tablet press and the Matsui Ex-Lub system at 15 to 25 rpm and at an average magnesium stearate flow of 5.26 g/minute (2.20 volts). Table 3 shows the tableting properties of AdvaTab base granulations, as well as ODT formulations comprising taste-masked acetaminophen drug particles. Extended tableting runs were also carried out to evaluate variations in weight, hardness, and uniformity of dosage forms caused by flow-related issues during high-speed compression. Performance properties of the following typical granulation batches produced under varying conditions in pilot, to commercial-scale HS and fluid-bed granulators are compared in Table 3 and Figures 1 to 3.

The highlights from these trials are the following:

- Semi-commercial/commercial-scale HS granulations are similar to the pilot-scale HS granulations produced in the Powerex VG 5–Glatt WSG 5 system.
- FB granulations produced are more spherical in shape in comparison with the HS granulations (as judged by optical microscopic observations).
- Consequently, the FB granulations, in spite of having significantly higher fractions of fines (i.e., particles <106 μm), flow very well in comparison with the HS granulations.

Table 3 Fluid-Bed and High-Shear AdvaTab Base Granulations and Their Properties

Property	Pilot scale (HS/FB)	Powerx 120/ WSG 120 (2× 40)[a]	GMX 600/ Glatt 200 (2×160)[b]	GMX 600/ Glatt 200 (2×160)[c]	GMX 600/ Glatt 200 (2×160)	Fluid-bed (no binder)[d]	Fluid-bed (PVP binder)[e]
Granules	Sol-2	A-03	PE278-A	PE278-B	PE278-C	1045-167	1045-172
Water addition	20% added	20% sprayed	20% sprayed	Sprayed	Sprayed	Sprayed	Sprayed
Wet milled?	No	No	Yes	Yes	Yes	No	No
Vacuum TT	NA	NA	85 min	85 min	90 min	NA	NA
Drying time	>10 min	<10 min	<10 min	<10 min	<10 min	10 min	5 min
% LOD at 85°C	0.48	0.55	0.05	0.05	0.32	0.75	0.80
Bulk density	0.55 g/mL	NT	0.56 g/mL	0.56 g/mL	0.54 g/mL	0.52 g/mL	0.47 g/mL
Tap density	0.71 g/mL	NT	0.67 g/mL	0.67 g/mL	0.86 g/mL	0.69 g/mL	0.58 g/mL
Compressibility	22.8%	NT	17.3%	17.3%	19.0%	24.1%	18.2%
			Particle size distribution (%)				
>300 μm (50 mesh)	13.5	35.8	28.6	28.6	31.7	12.4	14.7
300 μm to 106 μm	44	43.5	43.8	43.8	51.7	36.1	49
<106 μm (140 mesh)	41	20.7	27.7	27.7	16.8	51.5	36.4
			Tableting properties				
Tableting lot number	1099–135	1089–064	1099–140	1099–145	1099–150	1099–160	1089–165
Compression force	21 kN	21 kN	21 kN	21 kN	21 kN	21 kN	21 kN
Weight (%RSD)	622 (0.6)	621 (0.5)	620 (0.55)	623 (0.88)	623 (0.58)	619 (0.35)	619 (0.48)
Hardness (N)	70 (7.9)	75 (6.8)	77 (5.2)	75 (7.0)	77 (6.3)	67 (7.1)	96 (2.9)
Friability (%)	0.58	0.48	0.46	0.42	0.48	0.53	0.30

[a]High-shear granulation and fluid-bed drying.
[b]Granulation lot (fluid-bed drying process with 2×160 kg GMX 600 batches) not containing milled oversized material.
[c]Same granulation lot containing sieved, milled oversized material after sieving.
[d]Fluid-bed processed granulation lot not containing a binder.
[e]Fluid-bed processed granulation lot containing a binder, povidone.
Abbreviations: HS/FB, high-shear granulation and fluid-bed drying; NA, not available; NT, not tested.

- Acetaminophen ODT tablets prepared using the HS or FB granulations exhibit hardness, friability, and DT comparable to the pilot-scale HS granulations Powerex VG 5–Glatt WSG 5 system.
- The fill weight variations were held tight with a relative standard deviation (RSD) of less than 1%.
- The variations in tablet hardness were held tight with a low RSD of approximately 4% to 7%.
- Except the binder-containing granulation, the acetaminophen ODTs containing the pilot-scale as well as the commercial-scale HS and FB granulations exhibited similar hardness, friability, and DT values (Fig. 1 and Table 3);
- In the compression force range of 18 to 30 kN, the tablet friability values of acetaminophen ODT formulations are not statistically different (Fig. 1 and Table 3);
- In spite of the differences in particle shape and size distribution, no flow-related issues requiring adjustments of the compression parameters were encountered during extended tableting runs.
- However, the binder-containing FB granulations exhibited higher hardness as well as longer DTs at comparable compression forces (e.g., DT: 90 vs. 30 second) and higher friability (e.g., 0.83% vs. 0.48–0.52%).
- In conclusion, no statistically significant differences are apparent in the FB and HS granulations in terms of performance criteria.

Blend Uniformity

A conventional blending process was developed to combine taste-masked active with rapidly dispersing granules and other tablet excipients including a sweetener, one or more flavors, one or more colorants, a disintegrant such as cross-linked povidone, croscarmellose sodium,

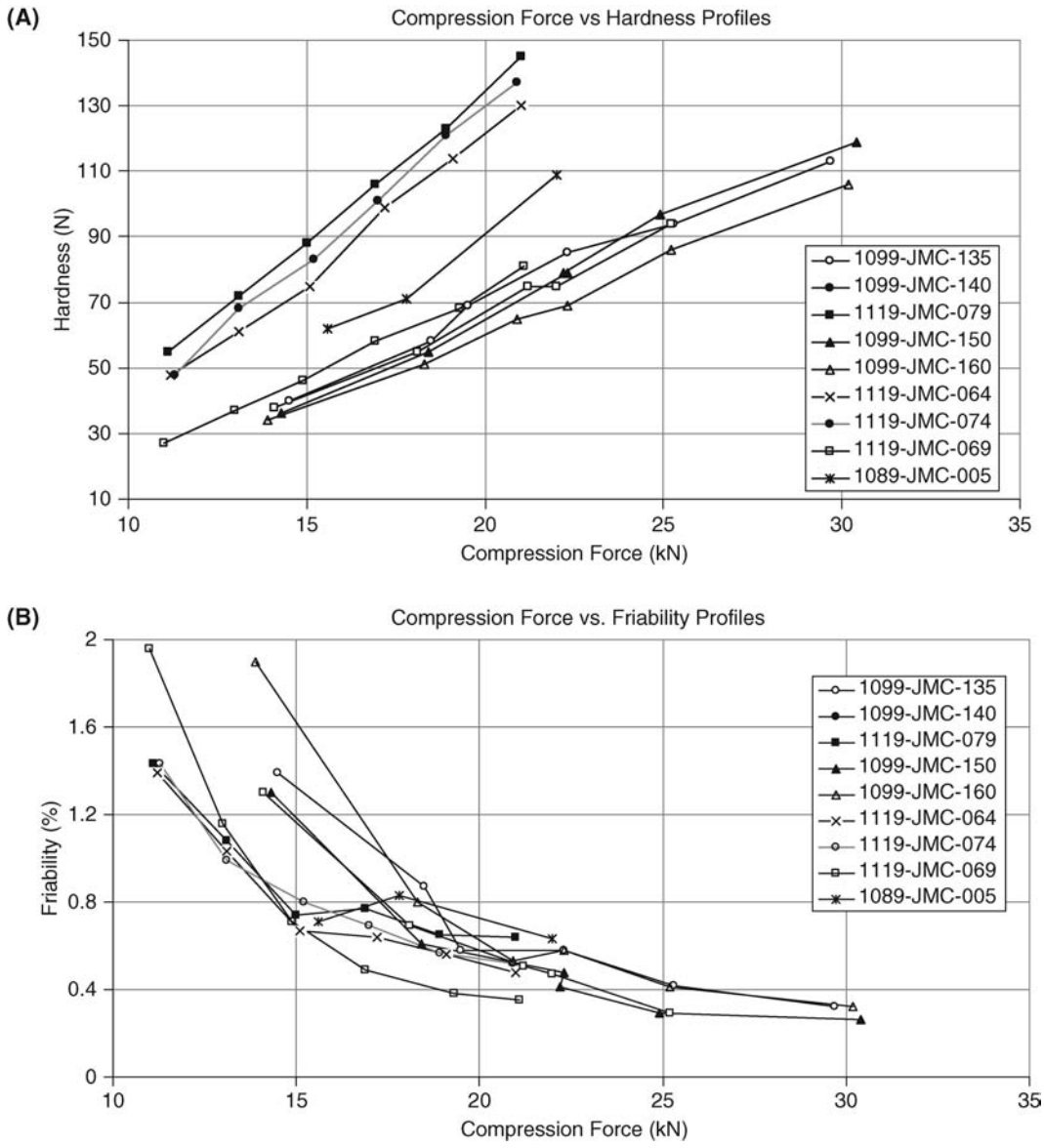


Figure 1 Tableting properties of AdvaTab granules and ODTs. (**A**) Hardness versus compression force and (**B**) friability versus compression force.

sodium starch glycolate, low-substituted hydroxypropoyl cellulose, a mixture thereof, a compression aid such as microcrystalline cellulose (MCC). For example, Eurand has developed an AdvaTab acetaminophen product with a formulation containing approximately 40% Microcaps acetaminophen combined with AdvaTab base granules, a disintegrant, a sweetener, and strawberry flavor. The minor components (e.g., flavor, sweetener, disintegrant, and microcrystalline cellulose) were sieved to deagglomerate and blended in a V-blender to achieve homogeneity. This preblend, taste-masked drug particles, and AdvaTab granules were blended in a 10-cu-ft blender at a batch size of 150 kg for 5, 10, and 15 minutes and samples pulled at each time point were assayed for content uniformity. The results (theoretical assay = 35%) in Table 4 below demonstrate that the percent RSD values determined at different blending times are not statistically different.

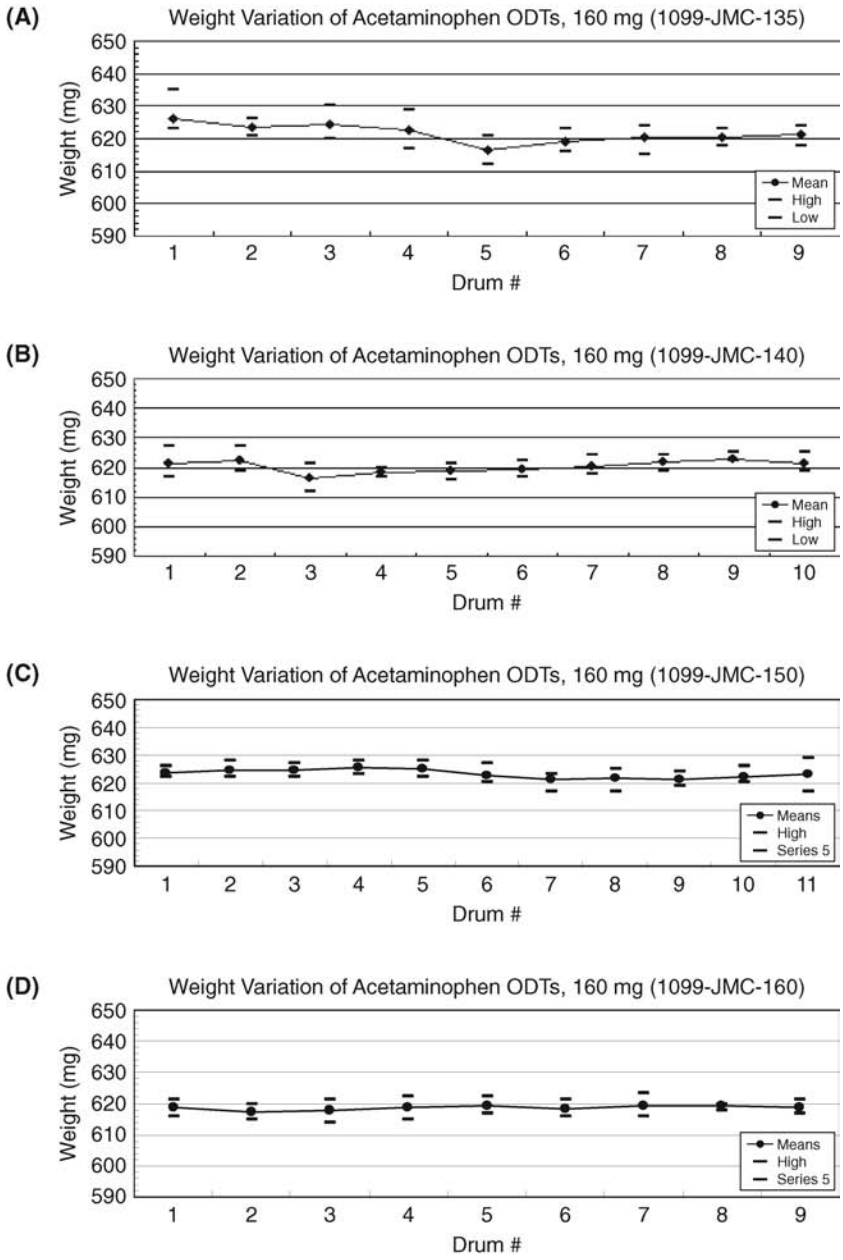


Figure 2 In-process variation of tablet weight.

Compression Process

Tableting trials at any scale during development of ODT are carried out on commercial equipment, which is essentially a rotary tablet press, equipped with an external lubricating system allowing lubrication of punch and die surfaces prior to each compression. A partial set of tooling (at least four pieces) may be used during development and a full set of tooling (32 stations) is used at pivotal and/or commercial-scale compression. During initial tablet

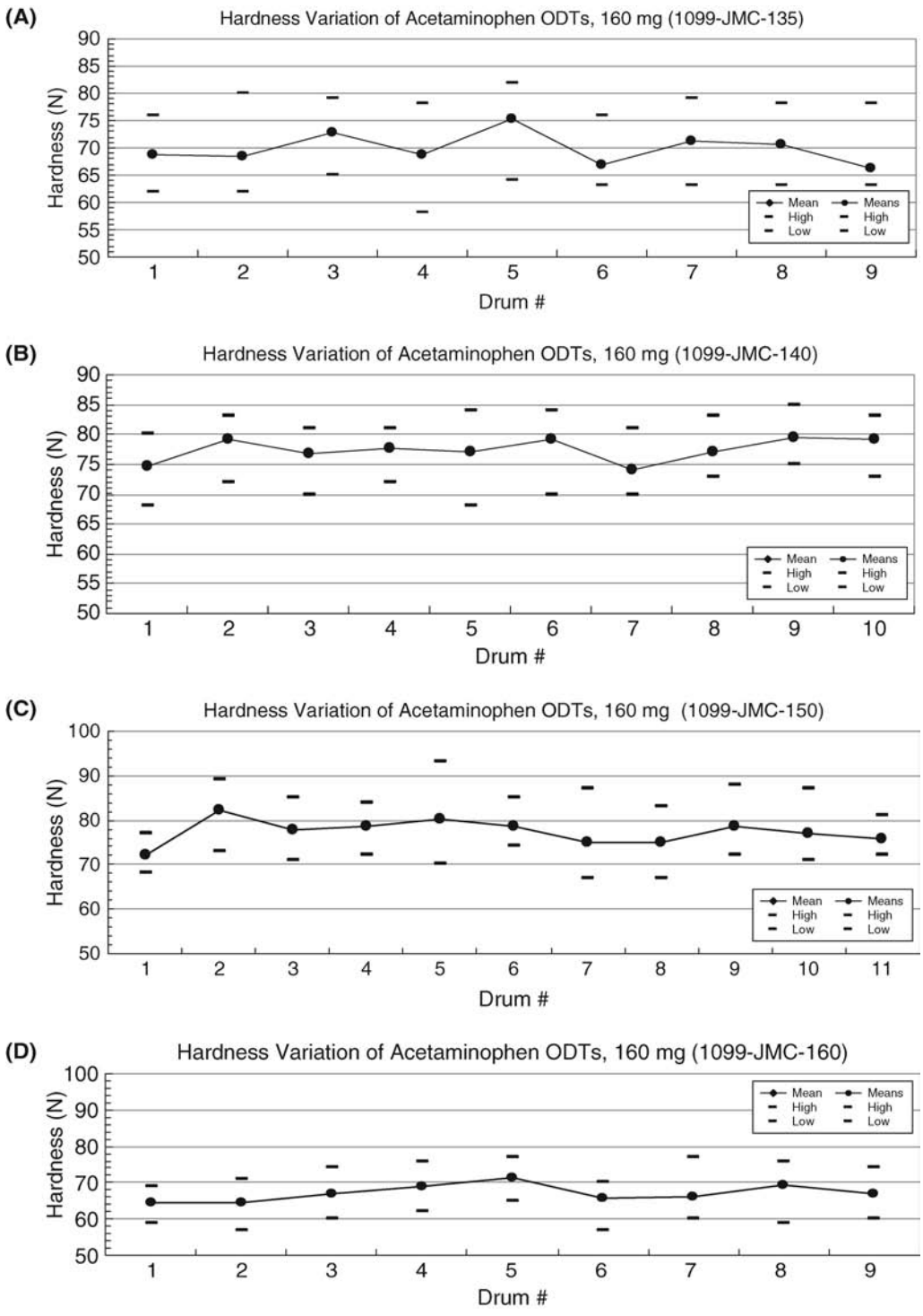


Figure 3 In-process variation of tablet hardness.

press setup trials in the manual mode, the fill depth is adjusted to achieve the target weight set for each specific strength, while the compression force applied is adjusted to achieve the target friability of NMT than 1.0%, preferably less than 0.5% and to determine a suitable hardness range for prototype ODT tablets. Once the adjustments are complete, ODT tablets are compressed in the auto mode until the mix is exhausted. At preset intervals, tablets are collected and tested for weight, thickness, hardness, and friability to ensure quality during tablet production. The tableting process (e.g., composition and tableting parameters) is challenged at least at two tableting conditions (i.e., at low turret speed, low compression force and high turret speed, high compression) for testing of weight, thickness, hardness, friability, uniformity of dosage units, dissolution, organoleptic, properties, and evaluating variations of tablet weight, friability, and hardness during the extended compression runs.

Design of Experiments

To establish blend uniformity and robustness of the ODT formulations containing diphenhydramine HCl, the active drug was layered onto 60 to 80 mesh sugar spheres and taste masked by coating with ethyl cellulose in a 500-gallon coacervation tank was blended with AdvaTab base granules and other pharmaceutically acceptable excipients (e.g., a flavor, a sweetener, a disintegrant, and microcrystalline cellulose—all minor components) to optimize the blending time and the final blending procedure. In a 10-cu-ft V-blender (batch size: 150 kg) operating at 17.5 rpm for a target blend time of 10, 20, 30, and 40 minutes. The results confirmed that in as short as 10 minutes blending time acceptable blend uniformity was achieved. The ODT product was scaled up to the proposed commercial batch size of 600 kg or 1.333 million tablets. Minor changes were made in blender sizes and blending times to accommodate the larger batch size. The following changes were made in the manufacturing processes. For preblending a 10-cu-ft V-blender was used instead of the 2-cu-ft V-blender used for the 10-cu-ft blender batch. The final blend was performed in a 50-cu-ft V-blender. A vacuum transfer system was added to transfer the materials into the 50-cu-ft V-blender. The blending time was increased on the basis of the differences in rpm between the 10-cu-ft and the 50-cu-ft blenders. Uniformity resulted from the blender and drums demonstrate blend uniformity and further supported a 30-minute blend time in the 50-cu-ft blender (batch size: 600 kg) operated at 6±0.5 rpm.

The blend was compressed using a 32 station Hata tablet press equipped with a proprietary external lubrication system to assess/adjust the Hata's gravity feed frame configuration. A vacuum line was used for transferring material from drums to the Hata's material hopper. The first experiment was run at typical settings for compression force and turret speed to establish a baseline (tablet weight: 450 ± 45 mg; hardness range: 18–to 36 N; friability: NMT 0.6%). Tablets were tested at target parameters and all results were acceptable. The second experiment was at the same compression force as experiment 1 with a turret speed of 32 rpm (proposed fastest speed for the batch record). The experiment was executed to demonstrate that the upper speed had no adverse effects on tableting attributes and/or dissolution. The third experiment was designed to evaluate the effect of using the vacuum transfer system to load the Hata's material hopper. The experiment was run at typical compression settings. The experiment was executed to demonstrate the vacuum system used to transport the compression mix from the drum to the hopper had no adverse effects on tableting attributes. The next two experiments were run at slow turret speed/high compression force and high turret speed/low compression force conditions. The compression force was targeted to generate tablets at the upper hardness (~36 N) or lower hardness (~18 N) specification. The results demonstrated tablets run at the upper or lower hardness specification had no adverse effect on tablet attributes and disintegration and dissolution rates. The next experiment was run to verify the Hata's automatic weight control and ejection parameters. These parameters were imputed into the Hata's control system to increase or decrease the tablet fill depth on the basis of tablet compression force. All in-process and content uniformity testing throughout the 1,333,333 tablet batch was acceptable (average hardness: 29 N; maximum hardness: 31 N, and minimum hardness: 24 N; average weight: 451 mg, maximum weight: 457 mg, minimum weight: 445 mg, and average content uniformity: 3.95%).

Table 4 Blend Uniformity Data for ODT Blend Batches

Blend time (min)	Sample location	Sample weight (mg)	% Assay	
			Individual	Mean (% RSD)
		ODT blend batch 1116-CK-093-B		
	A	1138.72	35.6	
	B	948.45	38.4	
	C	1128.23	36.6	
	D	1108.51	36.4	
	E	996.24	38.1	
T-1	F	809.94	37.8	37.0 (2.4)
	G	1049.19	36.3	
	H	979.17	37.3	
	I	914.18	36.8	
	J	1148.61	36.8	
	A	600.27	39.0	
	B	842.65	37.9	
	C	1081.33	36.2	
	D	639.89	37.7	
T-2	E	1028.87	36.8	37.0 (2.6)
	F	1037.73	36.7	
	G	1126.32	36.0	
	H	1157.62	36.8	
	I	1106.3	36.0	
	J	1097.15	36.7	
		ODT blend batch 1116-CK-094-B		
	A	1028.21	36.4	
	B	933.65	36.3	
	C	1100.78	37.2	
	D	993.94	36.1	
15	E	977.9	37.1	36.2 (1.7)
	F	946.86	36.0	
	G	951.53	35.8	
	H	960.33	35.9	
	I	1056.51	35.9	
	J	1036.8	35.1	
	A	996.68	35.1	
	B	1066.68	35.5	
	C	910.65	38.1	
	D	1122.33	36.3	
	E	916.78	36.3	
20	F	822.08	37.8	36.8 (3.3)
	G	1061.15	38.4	
	H	1001.1	35.5	
	I	833.67	37.6	
	J	924.36	37.3	

Scale-Up Issue

Microgranules of lightly bitter EUR-1042 were prepared by charging fluid-bed granulator (e.g., Glatt GPCG 5 at pilot scale and Fluid Air FA0300 at commercial scale) with EUR-1042, mannitol, and crospovidone, and granulating the mixture using purified water as a granulating fluid (55). Batches were made with about 6.3% (w/w), 15.0% (w/w), and 30.0% (w/w) drug concentrations to evaluate the effect of increasing drug concentration on the quality of the resulting granules, as well as the ODT tablets. The fluid air processed microgranules, rapidly dispersing microgranules, and other excipients (sucralose, cherry or

peppermint flavor, Crospovidone XL-10, and microcrystalline cellulose) were blended in a 10-cu-ft V-blender (batch size: 150 kg), and compressed on a Hata tablet press equipped with an Ex-Lub external lubrication system and 11 mm round, flat face, radius edge "trade dress" tooling with an "R" monograph on one side. The turret speed was set at 25 rpm, and the magnesium stearate spray rate was set at a medium spray rate. Severe picking in the island of the "R," scoring along the sides of the tablets, and occasional mottling in the tablet appearance were observed, indicating uneven mixing of the components of the mixture and fines. These problems were not observed during short compression runs of pilot-scale batches. Several conventional remedies such as changes to the processing conditions and ODT formulation, addition of extra disintegrant, varying the turret speed, changing tooling configurations, varying the external lubricant spray rate, adding an internal lubricant to the ODT formulation could not resolve the picking, scoring, and mottling issues. These issues were, however, resolved by the addition of a hydrophilic polymer binder, hydroxypropyl cellulose (HPC), in the granulation fluid.

Bioequivalent Products

ODT formulations containing a high dose of taste-masked acetaminophen (~95% in the particle size range of (425–180 μm) using acetaminophen with more than 80% of the particles in the size range of (425–180 μm) and a low dose of an opioid exhibited rapid dissolution, that is, not less than 85% when tested for dissolution using USP apparatus 2 (paddles at 50 rpm). The results from a randomized, four-way, crossover, pilot bioequivalence study comparing these combination tablets (e.g., two different ratios) with reference-listed IR combination products indicated that the high-dose components of the prototype combination products were not bioequivalent to the corresponding high-dose components of the RLD combination products (56).

Semi-fine grade acetaminophen with more than 85% of the drug particles in the size range of (150–53 μm) were microencapsulated with ethyl cellulose by solvent coacervation in a 500-gallon coacervation tank to produce microcapsules with more than 85% in the size range of (250–73 μm). Acetaminophen ODTs, 250 and 500 mg exhibited rapid dissolutions, that is, not less than 85% in 15 minutes when tested for dissolution using USP apparatus 2 (paddles at 75 rpm in 900 mL of pH 5.8 at 37°C). The compression mixes meeting USP blend homogeneity requirements were compressed into ODTs (appropriate doses at appropriate tablet weights) using the Hata tablet press—Matsui Ex-Lub system. Uniformity of dosage units was established during compression and robustness of ODTs thereof verified by compressing at two tableting conditions (i.e., at low turret speed and low compression force and high turret speed and high compression force) by taking in-process samples at frequent intervals during tablet compression and testing for assay and dissolution. ODTs manufactured at low compression force/low turret speed and high compression force/high turret speed were additionally analyzed for uniformity of dosage and dissolution. The results shown in Table 5 confirmed the ranges for hardness and friability set earlier were suitable to ensure acceptable dissolution performance while at the same time provide sufficient resistance for handling, packaging in blister cards, storage, transport, and commercial distribution. For example, the randomized, three-way, crossover, pivotal bioequivalence study comparing acetaminophen ODT Eurand 500 mg, and Panadol® 500 mg conducted on twenty four healthy volunteers, who received one single dose of each of the following after an overnight fasting—test 1 (one acetaminophen ODT 500 mg to be swallowed with 240 mL of tap water at ~20°C), test 2 (one acetaminophen ODT 500 mg with no water), and test 3 (one Panadol tablet 500 mg to be swallowed with 240 mL of tap water at ~20°C) confirmed that the test product, when administered with and without water, was bioequivalent to the reference product, Dutch Panadol of equal strength, as evident from the plasma concentration - time profiles for test 1, test 2, and Panadol shown in Figure 4.

Packaging and Shipping

A preliminary shipping study is performed on ODT tablets to evaluate the effects of environmental conditions such temperature and relative humidity fluctuations and road conditions during domestic transportation in commercial trailers. It is a good strategy to ship

Table 5 Tableting Properties for EUR-1037 ODT Batches, 250 mg (700 mg × 13 mm) and 500 mg (1400 mg × 17 mm)

Paracetamol ODT batch	ODT strength	Low compression force–low speed	High compression force–high speed	Weight (mg)	Thickness (mm)	Hardness (N)	Tensile strength (N/mm^2)	Tablet friability (%)	Percentage dissolved (in min)			
									5	15	30	45
1116-CK-093-A	250 mg	12 kN at 15 rpm		701	5.16	32	0.303	0.08–0.28	42	88	99	100
			18 kN at 25 rpm	697	4.91	58	0.578	0.03–0.04	42	87	99	100
1116-CK-093-B	500 mg	19 kN at 15 rpm		1396	6.15	46.4	0.283	0.17–0.28	36	83	99	101
			24 kN at 20 rpm	1401	6.05	56.6	0.350	0.08–0.28	41	89	100	102
1116-CK-094-A	250 mg	10 kN at 15 rpm		697	5.20	35	3.31	0.22	52	95	98	98
			18 kN at 25 rpm	697	4.86	75	0.756	0.09	59	95	99	98
1116-CK-094-B	500 mg	18 kN at 15 rpm		1398	6.11	61	0.374	0.16–0.26	52	96	100	100
			28 kN at 20 rpm	1398	5.85	105	0.672	0.09–0.14	57	97	100	100

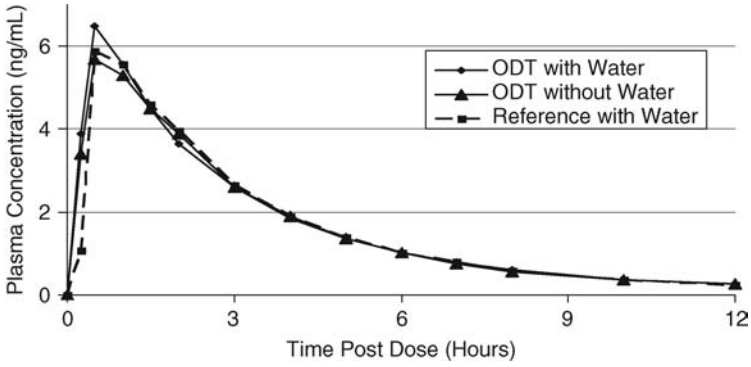


Figure 4 Plasma concentration—time profiles for acetaminophen ODTs versus Panadol®.

tablet lots compressed under two tableting conditions: (*i*) low turret speed and low compression force and (*ii*) high-speed and high-compression force and bulk packaged in 12-gallon fiber drums, each drum containing two individual double-lined four-mil polyethylene bags containing about 10-kg tablets with a desiccant placed between the double layer and outer drum lining. Some drums were cushioned with bubble wrap and while others were not. Environmental conditions (i.e., temperature and relative humidity monitored with data loggers strategically placed inside and outside drums) were monitored during transit and analytical testing was performed on samples taken prior to and after shipment. The product was typically transported to a transfer hub, held for a day and returned to Eurand, Inc. In case of acetaminophen ODTs, weighing 250 and 500 mg and 700 and 1400 mg, the shipment was sent from Eurand at Vandalia, Ohio, U.S.A. to Milan, Italy. A sampling plan in accordance with ANSI/ASQ Z1.4 sampling plan, which is the same as the old MIL-STD 105E (http://www.sqconline.com/mil-std-105.html), was used to test composite ODT samples (e.g., $n = 1250$ tablets each) before and following shipping. The terms are defined as follows:

- critical defect with an AQL level (0.0)—a wrong tablet;
- major defects with an AQL level of 0.65%—atypical size and shape, broken, cracked, split, or capped tablet;
- minor defects with an AQL level of 4.0%—pitted, foreign material, picking sticking, or chipped tablet.

The initial (preshipment) and final (postshipment) test results were compared in Table 6.

The environmental data indicated that the temperature fluctuations within the bulk packaging configuration tested and outside were similar, as to be expected, suggesting temperature sensitive products must be sent under climatically controlled conditions. On the other hand, the relative humidity fluctuations within the drums were significantly less than the external fluctuations. This was further supported by the changes in the moisture content of bulk tablets in fiber drums. The moisture data (Table 7) indicate that the tablets neither lost nor gained any moisture during transit. The quality attributes between the pre- and postshipment samples as well as the cushioned and uncushioned conditions indicate that transport and handling had a minimum effect on physical integrity although there was a marginal increase in the number of tablets that chipped (Table 6 and 8). However, these changes are comparable to

Table 6 Breaks and Chipping of ODTs During Transoceanic Shipping

Tablet lot number	Preshipment	Postshipment
1116-093-A (250 mg at high compression force)	Breaks: 0, chips: 0	Breaks: 0, chips: 0
1116-093-B (250 mg at low compression force)	Breaks: 0, chips: 1	Breaks: 0, chips: 0
1116-094-A (500 mg at high compression force)	Breaks: 0, chips: 0	Breaks: 0, chips: 0
1116-094-B (500 mg at low compression force)	Breaks: 0, chips: 0	Breaks: 0, chips: 0

Table 7 Moisture Changes in ODTs Associated with Transoceanic Shipping

	Moisture level (%)		
Tablet lot number	Preshipment	Postshipment	Difference
1116-093-A (250 mg at high compression force)	1.2	1.3	0.1
1116-093-B (250 mg at low compression force)	1.3	1.3	0.2
1116-094-A (500 mg at high compression force)	1.2	1.4	0.2
1116-094-B (500 mg at low compression force)	1.3	1.4	0.1

Table 8 Defects in ODTs Associated with Transoceanic Shipping

	Critical defects	Major defects	Minor defects
		Specifications	
Tablet lot number	Accept: 0, reject: 1)	Accept: 7, reject: 8	Accept: 21, reject: 22
		Preshipment testing	
1116-093-A (250 mg at high compression force)	0	0	0
1116-093-B (250 mg at low compression force)	0	0	3
1116-094-A (500 mg at high compression force)	0	0	1
1116-094-B (500 mg at low compression force)	0	0	10
		Postshipment testing	
1116-093-A (250 mg at high compression force)	0	0	7
1116-093-B (250 mg at low compression force)	0	0	10
1116-094-A (500 mg at high compression force)	0	0	21
1116-094-B (500 mg at low compression force)	0	0	20

those seen with conventional tablets that are not film coated. In conclusion, the environmental, quality attribute inspection and moisture results indicate that the product is robust and capable of maintaining physical integrity during transportation in tractor-trailers and may be transported uncushioned.

COMMERCIALLY AVAILBLE ODT PRODUCTS AND TECHNOLOGIES

Freeze drying, compression molding, and compaction technologies are described Zydis®, Quicksolv®, and Lyoc® are prepared by freeze drying; FlashDose® is prepared by a molding/cotton candy process; WOWTAB®, FlashTab®, and Frosta® are prepared by granulation followed by compression; OraSolv®, DuraSolv®, OraVescent®, Ziplets®, and AdvaTab are prepared by modified direct compression. Differences between drug delivery systems with regard to their composition (excipients), structure and formulation are extensively reviewed and process development and scale-up challenges are considered elsewhere (6,7,17,57–63). The advantages and the disadvantages of each type of dosage form in terms of dissolution and absorption rate, bioavailability, stability, mechanical strength, taste-masking properties, and patient compliance are highlighted. Most of the fast-dissolving tablet technologies use sugar-based excipients. Sugars are pleasant tasting, and are a good addition to other taste-masking methods. They are also highly water soluble, and dissolve quickly in saliva. Many sugars also impart a pleasant "cool" mouth feel to the final product. Because the amount of sugars in ODTs is lesser as compared with traditional liquid dosage forms, these tablets can be used for children with poor oral hygiene or history of dental caries. Excess handling of tablets of some of the ODT technologies (e.g., notably lyophilized or OraSolv) at the pharmacy and/or by the consumer can introduce enough moisture to initiate dissolution of the tablet matrix and/or moisture or temperature-mediated instability. These techniques are briefly reviewed below for completeness.

Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particle from the disintegrating tablet that is insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. Compressed tablet systems are based on conventional tableting

technology and vary in their degree of hardness and friability, thereby resulting in varying disintegration characteristics depending on the exact materials and process used. DTs (e.g., typically 15–30 seconds) are higher than those for lyophilized ODT formulations. Also, friable products may require specific packaging considerations as in CIMA's OroSolv products. Loosely compressed ODT tablets generally rely on water-soluble excipients and/or super-disintegrants to achieve rapid disintegration. To allow fast-dissolving tablets to disintegrate/disperse in the mouth, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which is difficult to handle, often requiring specialized peel-off blister packaging. Several fast-dissolving dosage forms, especially those based on lyophilization and OraSolv technologies are hygroscopic and cannot maintain physical integrity under normal condition from humidity, which calls for specialized product packaging (1,64). When put on tongue, the lyophilized wafer/tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form (7).

Zydis/Lyoc/QuickSolv Fast-Dissolving Technology

Lyophilization is a pharmaceutical technology that allows drying of heat-sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability. Corveleyn and Remon studied various formulation and process parameters (65,66). Tablets prepared by lyophilization are fragile and possess low mechanical strength, which make them difficult to handle and they also exhibit poor stability on storage under stressed conditions.

Zydis technology from Catalent Pharma Solutions (1,14,67,68) is the most widely used technology for developing/marketing fast-dissolving tablet formulations as freeze-dried, porous wafers containing a drug substance that dissolve in the oral cavity without the need for water. Zydis process involves preparation and dispensing directly into preformed blister packaging of an aqueous drug solution or suspension incorporating two structure-forming agents (also called carriers) with the API, in a ratio optimized for each product, plus any additives specifically required such as flavors, sweeteners, or pH modifying agents. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in commercial-scale freeze-driers, that is, refrigerated cabinets to complete the sublimation process, which removes most of the residual moisture from the tablet. After freeze drying, the aluminum foil backing is applied on a blister-sealing machine. Finally, the blisters are packaged and shipped. The freezing process resulting in a highly porous structure facilitates the rapid dispersion characteristics of the product (typically five seconds or so) when placed in mouth. Several peptide and protein-based drugs use the Zydis ODT technology, including "Grazax," a grass-pollen allergy vaccine by ALK-Abello (Hoersholm, Denmark). Catalent is providing commercial production of Grazax at its facility in Swindon, U.K.

Other patented ODT technologies based on lyophilization include Lyoc (Farmalyoc, now Cephalon, Franzer, PA) and QuickSolv (Janssen Pharmaceutica, Beerse, Belgium). Lyoc is a porous, solid wafer manufactured by lyophilizing an oil-in-water emulsion placed directly in a blister and subsequently sealed (69). The wafer can accommodate high drug dosing and disintegrates rapidly but has poor mechanical strength. QuickSolv tablets or orally disintegrating tablets based on the freeze drying technology from Oregon Freeze Dry, Inc., are made with a similar technology that creates a porous solid matrix by freezing an aqueous dispersion or solution of the matrix formulation (70,71). The process works by removing water using an excess of alcohol (solvent extraction). For all four lyophilized dosage forms, disintegration is extremely rapid.

Commonly used water-soluble carriers in the manufacture of ODTs by freeze drying or lyophilization include lactose, maltodextrins mannitol, and gelatin. The active drug is dissolved or preferably dispersed in an aqueous solution of a carrier. The mixture is dosed by weight and poured into the wells. Ideal candidates for lyophilization technology are chemically stable,

poorly water-soluble drugs with a particle size of preferably less than 50 μm and not requiring taste masking. The major disadvantages of lyophilization technique are that it is expensive and time consuming, fragility makes conventional packaging unsuitable for these products, and has a poor stability under stressed conditions (72). The inability to avoid drug leaching during lengthy lyophilization cycles from taste-masked (e.g., polymer coated) drug particles is another reason for the absence of lyophilized ODT products containing highly bitter drugs.

ELAN/NanoCrystal® Orally Disintegrating Tablet Technology

Elan's NanoCrystal ODT technology (42,73,74) involves combining spray-dried nanocrystals (particle size of 2 μm or less) coated with a surface stabilizer (e.g., a surfactant), with a water-soluble or dispersible excipient (e.g., a sugar, a sugar alcohol, a saccharide, a starch, or a mixture), a disintegrant, a sweetener, a flavor, a effervescence (citric acid and/or sodium carbonate), and a lubricant and compressing into a highly porous ODT. NanoCrystal™ fast-dissolving technology provides for:

- improved pharmacokinetic benefits of orally administered nanoparticles (<2 μm) in the form of a rapidly disintegrating tablet matrix comprising a poorly water-soluble new or marketed drug;
- product differentiation based on a combination of proprietary and patent-protected technology elements.

Compression-Molded Tablets

The preparation of ODT using molding technology employs water-soluble ingredients so that the tablet dissolves completely and rapidly. The manufacturing process consists of pressing into mold plates to form a wetted mass (compression molding) a moistened powder blend with a hydroalcoholic solvent followed by pressing. The solvent is then removed by air drying. Such tablets possess a porous structure that hastens dissolution (75–78). Fast-dissolving tablets containing a drug and saccharides of low and high solubilities (e.g., lactose or mannitol vs. sorbitol or erythritol) were prepared by compression molding of suspensions and removing moisture (46). The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g., mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum (79). The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. Compared with the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture. Masaki (79) uses an agar solution as a binding agent and a blister packaging as well as a mold to prepare an intrabuccally fast disintegrating tablet. A fluid-bed granulation process for producing high-porosity and low–apparent density granules comprising only the acid component of the effervescent couple, sugar alcohols, for incorporation into fast-dissolving tablets was disclosed (80).

OraSolv, DuraSolv, OraVescent Technologies

CIMA Labs, a subsidiary of Cephalon is positioned in ODT technology through its "OraSolv" and "DuraSolv" platforms that are based on compressed tablet technology. OraSolv (61,62,72), an ideal ODT formulation comprising drug particles (uncoated or taste masked) and water-soluble excipients including effervescent couples, disintegrates within 6 to 40 seconds, depending largely on tablet size and compression force. OraSolv tablets are compressed at low compression forces using an integrated, computer-controlled tableting, and packaging system (64,82). DuraSolv, Cima's second-generation fast-dissolving/disintegrating tablet formulation produced in a fashion similar to OraSolv, combines taste-masked active drug particles with a nondirect compression filler (e.g., mannitol powder), an effervescence, an optional direct compression filler, a superdisintegrant, a flavor, and a sweetener (62,83). DuraSolv tablets are prepared by using conventional tabletting equipment and have good mechanical properties (e.g., higher hardness and lower friability, i.e., less than that 2%). DuraSolv is so durable that it can be packaged in either traditional blister packaging, pouches, or bottles.

OraVescent technology is an innovative drug delivery system as exemplified in FENTORA (84,85). OraVescent technology may optimize the delivery of fentanyl across the buccal mucosa. When the FENTORA tablet comes in contact with saliva, carbon dioxide generated/released with transient pH changes accompanying the reaction with the saliva appears to facilitate dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl—a pH "pumping" mechanism.

Elmed-Eisai EMP Technology

EMP technology (4) is used to develop wet-processed ODT tablets. A mixture of a drug, one or more sugars, and a binder is moistened with water or an alcohol–water mixture, the moistened powder mixture is molded under low compression forces, dried producing high strength tablets. These tablets rapidly disintegrate in the oral cavity because of the highly porous structure, and are suitable for bulk packaging.

Astellas WOWTAB Technology

WOWTAB is a successful manufacturing technique based on a combination of modified polysaccharides that have water dissolution characteristics to facilitate fast disintegration (79,86). The technology involves granulating a low moldability sugar (e.g., mannitol erythritol, and/or lactose) and a drug with a solution of a high moldability sugar (e.g., sorbitol, maltitol, maltose). The tablets manufactured at a low compression force are subjected to a controlled high humidity treatment (i.e., at 25°C/60% RH) for up to 24 hours), followed by controlled drying (i.e., to create ODT tablets having highly desired tableting and fast disintegration properties. The technology includes an additional step of significantly improving tablet strength by subjecting ODTs containing a low-melting sugar alcohol such as erythritol to controlled heat treatment at about 140°C for about 5 to 10 minutes (87,88). Because of its significant hardness, the WOWTAB formulation is a bit more stable to the environment than the Zydis or OraSolv. It is suitable for both conventional bottle and blister packaging. The WOWTAB product dissolves quickly in 15 seconds or less. Taste-masked drug particles are often used in some of the commercialized ODT procts. A superior mouth feel due to the patented "smooth melt" action of the proprietary taste-masking technique is also claimed.

Akina's Frosta Technology

The Frosta technology (60,89) utilizes compressing highly plastic granules at low compression pressures to produce ODT tablets using conventional wet granulation processing and rotary tablet machines for cost-effective production of high strength–high porosity, fast disintegrating tablets suitable for packaging in bottles. The one step wet granulation process involves a porous, plastic material, a water penetration enhancer, and a polymeric binder.

Antares Easy Tec® Technology

The technology (90) incorporates a drug, a permeation enhancer, a type C methacrylic acid copolymer used as a disintegrant in combination with a conventional disintegrant in a direct compression tablet formulation. The ODT thus obtained rapidly disintegrates (typically 15–30 seconds, depending on drug load). Easy Tec™ tablets can be manufactured without specialized equipment and because the tablets do not contain an effervescent couple (highly moisture sensitive), their technology represents significant processing/packaging advantages, as well as potential for buccal absorption, over conventional ODT technologies.

Biovail's FlashDose/Shearform Technology

FlashDose (91–93) consists of self-binding shearform matrix termed as "floss." Shearform matrices are prepared by converting sugar alcohols/saccharides such as sucrose, dextrose, lactose, and fructose into amorphous fibers by the simultaneous action of flash-melting and centrifugal force in a heat-processing machine similar to that used to make cotton candy. These fibers are partially recrystallized, which results in a free-flowing floss. The floss is mixed with an active ingredient (often not taste masked) and excipients followed by compression into an ODT tablet that has fast-dissolving characteristics.

Ethypharma's FlashTab Technology

FlashTab (94,95) is an ODT technology developed at Prographarm Laboratories that involves coating a drug (e.g., drug crystals or granules) with a Eudragit polymer (methacrylate copolymer) to provide rapid release of the drug in the stomach, and formulating this microencapsulated drug with an effervescent couple to produce ODTs. FlashTab tablets also consist of coated drug particles with water-insoluble ethylcellulose and/or neutral methacrylic acid copolymers (e.g., NE30D) for masking the drug taste and then combined with a granulated mixture of excipients such as fillers (e.g., direct compression sugar, microcrystalline cellulose) and disintegrants, a flavor, a sweetener, and compressed into better tasting and fast disintegrating tablets.

OraQuick Technology

KV Pharmaceutical's OraQuick, an ODT technology, utilizes a patented taste-masking technology, known as MicroMask, that has superior mouth feel over taste-masking alternatives (51,96). The taste-masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat production than alternative fast-dissolving/disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and antiinfectives.

SoluTab DR Orally Disintegrating Tablet Technology

The technology (33,46) from Takeda Pharmaceutical Company involves producing beads comprising lansoprazole, a proton pump inhibitor, an alkaline stabilizer (e.g., magnesium carbonate), and a polymeric binder and the drug layered beads are coated with an undercoat and further coated with a delayed-release coating (e.g., a combination of enteric and neutral polymers, Eudragit L30D and NE30D). The delayed-release beads, mannitol, lactose, microcrystalline cellulose, crospovidone, a flavor, a sweetener, citric acid, a colorant, and a lubricant are blended in a V-blender and compressed into Pravacid delayed-release ODTs (15 and 30 mg).

Sublingual and Orally Disintegrating Tablet Systems

Orexo AB (97) has developed sublingual tablets (ODTs), drugs (e.g., zolpidem, fantanyl) from which are absorbed through mucous membranes for rapid onset of action. The drug adheres onto water-soluble carrier microparticles (e.g., a mixture of mannitol, crospovidone, and a bioadhesive and/or mucoadhesive promoting agents) in the tablet matrix. The FDA has approved in March 2009 Meda Pharma's Edluar (Sublinox), a sublingual tablet formulation of zolpidem developed by Orexo, for the short-term treatment of insomnia.

SaTab Technology

Sato Pharmaceuticals Company (98) utilizes a proprietary moistening and drying technology to develop and manufacture a number of ODT formulations. A powder mixture comprising a drug, sugar alcohol, and binder is compressed into tablets under low compression pressure, and the tablets pass through specially designed equipment for moistening and drying resulting in highly porous tablets that disintegrate in about 10 seconds on contact with saliva in the buccal cavity.

Sublimation

The key to rapid disintegration for mouth-dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fail to dissolve rapidly because of low porosity of the matrix. Hence, highly volatile ingredients (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid,

camphor, hexamethonium tetramine, naphthalene, phthalic anhydride, urea, and urethane) were compressed along with other excipients into a tablet and the volatile material was then removed by sublimation, leaving behind a porous tablet matrix. Solvents such as cyclohexane were also suggested for the generation of porosity in the matrix (99,100).

Spray Drying

Spray drying is used in pharmaceutical industries to produce highly porous powders (101,102). The processing solvent is evaporated rapidly by spray drying, which renders the product highly porous and thus can be used in manufacturing ODT. In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol, as a bulking agent and sodium starch glycolate or cross carmellose or crospovidone, is used as superdisintegrants. Tablets manufactured from the spray-dried powder showed rapid disintegration and enhanced dissolution.

AdvaTab Technology

Ziplet™ (58,103) utilizes water-insoluble ingredients combined with one or more effective disintegrants to produce ODT with improved mechanical strength and optimal DT at low compression force. This technology handles high drug loading and coated drug particles and does not require special packaging, so they can be packed in push-through blisters or bottles. AdvaTab technology (5,38,54,55,104), a second-generation, modified direct compression process, comprises three complimentary elements—(*i*) AdvaTab granules (also called rapidly dispersing microgranules) produced by a proprietary granulation process (54,55) with or without a drug, (*ii*) taste-masked and/or CR drug particles (Microcaps and/or Diffucaps® technologies), and (*iii*) a patented direct compression tableting system [e.g., a Hata's tablet press—Matsui Ex-Lub system that does not compromise the disintegration characteristics offered by the rapidly dispersing microgranules (105)]. ODT tablets thus produced rapidly disintegrate typically in about 30 to 60 seconds forming a smooth, easy-to-swallow suspension containing taste-masked or CR-coated microparticles. These tablets are suitable for packaging in HDPE bottles or blisters or for transportation in bulk containers.

The proprietary process for the manufacture of rapidly dispersing microgranules [also referred to as AdvaTab base granules, (54,55)], which are used in the manufacture of ODTs, is based on the use of micronized particles of a water-soluble sugar alcohol, a saccharide or a mixture thereof and a superdisintegrant at a ratio of 90/10 to 99/1, and purified water as the granulating fluid. The wet granules are dried in a fluid-bed dryer or in a tray drying oven. The dried granules are sieved and oversized granules are milled and sieved to produce AdvaTab-based granules with desired particle size distributions.

Microcaps Technology

Eurand's Microcaps technology (28,38) utilizes a proprietary coacervation process for microencapsulation. The Microcaps technology efficiently and uniformly coats drug particles with polymeric membranes of varying thickness and porosity. The membranes create an inert barrier between the drug and the taste buds, and a stabilization barrier between the active ingredient and other tablet excipients. These processes result in individual particles of a drug substance being completely enveloped, that is, effectively taste masked. However, the very act of taste masking results in slower dissolution and hence release of the drug for absorption. To circumvent slower dissolutions, modified coating technologies have been developed (29,30). A gastrosoluble agent is incorporated into the taste-masking membrane to take advantage of its insoluble and nonswelling characteristics at saliva pHs, that is, in the oral cavity, thereby achieving better masking of the drug taste. The gastrosoluble pore-forming agent rapidly dissolves in the acid environment of the stomach creating microchannels for dissolved drug to pass through. This permits more rapid release of the active ingredient and enables bioequivalent dosage forms to be formulated even for extremely bitter tasting drugs such as cetirizine that require relatively thick taste-masking polymer layers. Gastrosoluble pore-forming agents include calcium carbonate, calcium saccharide, calcium succinate, magnesium citrate, polyvinylacetal diethylaminoacetate (AEA), aminoalkyl methacrylate copolymer (Eudragit EPO). This modified coating work can be done either by coacervation or by fluid-bed coating

(29,30). Aqueous-based coacervation processes using enteric polymers (e.g., cellulose acetate phthalate, hypromellose phthalate) have also been established.

External Lubrication System

The proprietary direct compression process to produce ODT dosage forms comprising Microcaps-based taste masked or Diffucaps-based CR drug-containing microparticles and AdvaTab microgranules using a commercial rotary tablet press such as a Hata tablet press equipped with an external lubrication device, Matsui's Ex-Lub system (28,34,55,56,104,105) that lubricates punch and die surfaces. This external lubrication system helps lubricating product-contacting punch and die surfaces immediately prior to each compression. For the manufacture of ODT products, typically conventional rotary tablet presses equipped with gravity/force feeders and internal lubrication [i.e., from 0.5% up to 1.5% by weight of a lubricant (e.g., magnesium stearate, stearic acid, sodium stearyl fumarate)] are used. Via a reduction, by approximately 30-fold, of the amount of a hydrophobic lubricant contained in a conventional tablet formulation (the sole function of which is to allow for effective high-speed tableting) water uptake into the ODT tablet core is rapid when the tablet is placed in the mouth. The AdvaTab tablet then can disintegrate quickly in the mouth with a smooth, nongritty mouth feel. In addition, AdvaTab tablets are robust enough to be packaged in either bottles or paper backed peel-off or push-through blisters.

Orally Disintegrating Tablet Formulations Containing Additional Disintegrants

Incorporatation of additional disintegrants into an ODT formulation leads to quick disintegration of tablets and hence improves dissolution. Below critical concentration, tablet DT is inversely proportional to disintegrants concentration. Above the critical concentration level, however, DT remains approximately constant or even increases. Microcrystalline cellulose (MCC), silicified MCC (Prosolv SMCC®), cross-linked carboxymethyl cellulose sodium, cross-linked polyvinyl pyrrolidone and partially substituted HPC, enteric Eudragit polymers, although water insoluble, absorb water and swell because of capillary action and are considered as effective disintegrants in the preparation of first dissolving tablets. Microcrystalline cellulose and low-substituted HPC at a ratio of 8:2 to 9:1 were used in ODT formulations (25,79,90,106–108). Agar powder was also used as a disintegrant since the powder absorbs water and swells considerably without forming a gel at physiological temperatures (107). Ethypharm combines coated drug crystals with microgranules containing a disintegrating agent (e.g., modified cellulose-croscarmellose), which has a high swelling force, and a swelling agent (e.g., starch), which has a low swelling force. Fast disintegration of tablets can also be achieved by incorporating effervescent disintegrating agents, which generates carbon dioxide, and this phenomenon also resulted in partial taste masking of unacceptable taste of the drug (94). Also included is the combination of alginic acid and metal carbonic acid, which on contact with aqueous medium causes swelling of the tablets and carbon dioxide is generated, which leads to rapid disintegration of the tablet (108).

Emerging Technologies

Aprecia is the exclusive pharmaceuticals, nutraceuticals, and cosmetics licensee from the Massachusetts Institute of Technology (MIT) of their 3DP-related patent estate. ZipDose™ is a versatile fast-dispersing dosage form enabling high-dose and/or multidrug products with fast flashing times, unique taste-masking options, and IR/ER combinations (109,110). The process consists of automatically building layer by layer of an active ingredient on a base tablet comprising mannitol, crospovidone, and other excipients (e.g., a flavor, a sweetener, citric acid) from a polymeric binder solution in accordance with a computer-aided 3D design model, and applying a colorant seal coat. The rapidly dispersing tablets exhibit adequate hardness (e.g., tablets weighing about 325 mg having a hardness of 4.8 $\pm$ 0.7 kP) and rapid in vivo dispersion (i.e., typically in about five seconds).

Alpex's ODT based on a patented taste-masking and tableting technology comprising taste-masked drug particles, that allows the administration of drug doses ranging from a few micrograms to about 300 mg and over per dose. Disintegration of tablets occurs in seconds, creating a fresh viscous liquid that can be easily ingested even by people with a limited

swallowing capacity (young or old persons) or compromised ingestion (through Parkinson's, sclerosis, etc.).

Dainippon Sumitomo Pharma received the approval by the FDA for ODT formulations of Amlodipine indicated for the treatment of hypertension/angina pectoris. The product is produced using the company's proprietary formulation technology SUITAB, the ODTs. FastOral® technology from CLL Pharma consists of preparing ODTs comprising one or more drugs dispersed in an excipient mixture (e.g., trehalose, vinyl pyrrolidone–vinyl acetate copolymer (111). Different excipient combinations were evaluated to achieve ODTs with optimal/ideal characteristics (112).

RAPIDLY DISSOLVING FILMS

A more recent breakthrough technology that accelerates market introduction of innovative pharmaceutical products in the form of ODTs is the Oral Thin Film (OTF) or RDF drug delivery technology (113–120) that has emerged as an advanced alternative to the traditional tablets, capsules, and liquids. The first commercial nondrug product to use thin film for cosmetic purposes was the *Listerine* PocketPaks breath strip. Since then, thin film OTC products (e.g., cold, cough, flu, and antisnoring medications) have entered the marketplace. Currently, several RDF products comprising prescription products are in various stages of formulation/clinical development. Thin film strip technology uses a range of water-soluble or solvent-soluble polymers (e.g., natural gums, polyethylene oxide, derivatives of cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, and acrylic-based polymers) and is reported to be able to incorporate water-soluble, insoluble, or taste-masked active pharmaceutical ingredients presented as an API-containing liquid formulation in the form of a solution, emulsion, suspension, or dispersion. Thin elegant films designed for oral administration by placing on or under the tongue or along the inside of the cheek, come in various sizes and shapes like square, rectangle, or disk, and the strips may be flexible or brittle, opaque, or transparent. As the thin film dissolves, the technology enables the drug to be delivered to the blood stream either intragastrically, buccally, sublingually, or gastrointestinally. The optimal properties of film strength and disintegration are obtained with the selection of a particular combination of hydrophilic polymers. Many of the same taste-masking techniques (e.g., flavor–sweetener combinations, encapsulation or particle coating of the API, and complexation with ion exchange resins) used to formulate syrups, soft-chew, or ODT dosage medications can be used in OTFs. It is most desirable to avoid creating taste-masked drug particles larger than 250 μm, as larger particles could potentially present uniformity challenges in the finished dosage form.

Liquid casting is the preferred manufacturing method for RDFs as it avoids exposing APIs to elevated temperatures, and also liquid casting allows for film uniformity and low variability with regard to mass. A typical RSD for uniformity testing of an oral thin film batch prepared by liquid casting is in the order of 1% to 2% RSD (118). These coating techniques include knife-over-roll, reverse roll, slot-die, gravure cylinder, and Meyer rod coating. Drying of the cast bulk liquid is accomplished by passing the coating through an oven or series of ovens to evaporate any solvent(s) used to prepare the liquid. The dried film is wound into a roll and wrapped in foil packaging to ensure environmental protection during handling and storage, before being processed into single, premeasured unit doses. The rolled film can be die-cut into any shape or size or slit into narrower rolls as required for the application. Hot-melt extrusion (HME) is also used to prepare RDFs and involves shaping a polymer into a film via the heating process. A study conducted by Repka and McGinity (121) provided the overview of HME technology and investigated the in vivo bioadhesive properties of HPC films containing seven polymer additives on the epidermis of human subjects. Mishra and Amin (122) evaluated different procedures for taste masking of extremely bitter cetirizine HCl and also mechanical properties of rapid dissolving films incorporating taste-masked drug particles.

For branding purposes and to meet industry regulations, converters may choose to print information directly onto the film unit doses before packaging. Currently, most drug-containing films are packaged by unit in primary packaging. Criteria that may be taken into consideration include the need for unit-dose packaging, barcode labeling, and the content in instructions for use, child-resistant seals, and senior-friendly packaging.

The FDA is likely to approve the change in dosage form for a reference-listed drug product as long as there are no questions about the safety or effectiveness of the product and the uses (or indications); dosage and route of administration of the proposed drug product are the same as the listed drug product. The prescription product development is driven by companies such as Applied Pharma Research (APR), Lavipharm, Labtec, Lohmann Therapy Systems, MonoSolv Rx, Adhesives Research, Lintec Corporation, KyuKyu Pharmaceutical, Givaudan Schweiz, Corium International, etc.

Applied Pharma Research's RapidFilm™ Technology

Applied Pharma Research's RapidFilm technology is a novel, nonmucoadhesive, fast-dissolving oral dosage form. It features a thin film based on a water-soluble polymer. The film disintegrates rapidly within seconds in contact with water or saliva, releases the drug in the mouth and promotes gastrointestinal absorption. The RapidFilm dosage form was especially designed for high patient compliance. "RapidFilm" offers unique potential to deliver a variety of drugs (e.g., hypnotics, anxiolytics, antiemetics, NSAIDs and pain killers, 5-HT_1 agonists for migraine treatment, antiallergics), particularly when a fast onset of action is required. Ondansetron RapidFilm is based on a novel proprietary oral drug delivery technology platform of APR/Labtec (123) and consists of a very thin polymeric film strip incorporating and delivering taste-masked ondansetron. BioAlliance acquired in August 2008 the commercialization rights in Europe to the thin film formulations of ondansetron that is likely to be the first prescription drug product to come to market utilizing the thin film drug delivery technology from APR/Labtec. Donepezil RapidFilm is a new oral formulation of the centrally acting reversible acetyl cholinesterase inhibitor Aricept® (Eisai). Donepezil's main therapeutic use is in the treatment of Alzheimer's disease.

Lavipharm's Quick-Dis™ Technology

Quick-Dis™ is a proprietary patented technology to create flexible, intraoral RDFs in various packaging configurations, ranging from unit-dose pouches to multiple-dose blister packages (118,124). The film when placed on the tongue, rapidly releases the active agent for local and/or systemic absorption. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for Quick-Dis™ film with a thickness of 2 mm. The active ingredient incorporated in a Quick-Dis™ drug delivery system is about 50% released within 30 seconds and 95% within one minute.

Zengen recently launched a chloraseptic relief strip in the United States to deliver benzocaine—a local anesthetic to treat sore throats. Other companies with oral thin film technologies and products include Lohmann Therapy Systems (125), Adhesives Research (126) (Triaminic® Thin Strips™ pediatric cough and cold products, Theraflu® Thin Strips™ cold and flu products, and Gas-X® Thin Strips™ anti-gas relief products), MonoSol Rx (127) with a target date of Qtr-4/2009 for filing an NDA for Ondansetron Thin Films, Lintec Corporation (128), KyuKyu Pharmaceutical Co. Ltd. (129), Givaudan Schweiz (130), and Corium International (131). Lintec's technology provides for rapid dissolve oral film preparations comprising a drug-containing layer and two water-swelling gel-forming layers, which either directly sandwich the drug layer or via intermediate layers.

SUMMARY

ODTs and RDFs have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets with water among pediatric, geriatric, and psychiatric patients with dysphagia. Today, ODTs and RDFs are more widely available as over-the-counter products for the treatment of allergies and cold and bad breath. The target population has expanded to those who want convenient dosing anywhere, anytime, without water. By paying close attention to advances in technologies combined with increasing market acceptance and patient demand, pharmaceutical companies can take advantage of ODTs and RDFs for PLEs or for first-to-market products. Future possibilities for improvements in

ODTs/RDFs and drug delivery are bright. Several drug delivery technologies that can be leveraged on improving drug therapy from ODTs/RDFs have yet to be fully realized.

ACKNOWLEDGEMENTS

The author thank Jin-Wang Lai, Senior Director, R&D Formulations & Analytical Labs for productive discussions and James Clevenger, Craig Kramer, and Philip Stevens for technical assistance.

REFERENCES

1. Seager H. Drug delivery products and Zydis fast dissolving dosage form. J Pharmacol Pharm 1998; 50:375–382.
2. Lindgren S, Janzon L. Dysphagia: prevalence of swallowing complaints and clinical findings. Med Clin North Am 1993; 77:3–5.
3. Harris Interactive (R) Poll, January 2004. Sponsored by Schwarz Pharma—Milwaukee, January 15, 2004. PRNewswire/Results of a first-ever nationwide survey of adults on pill-swallowing difficulties.
4. Orally Disintegrating Tablet and Film Technologies; 5th ed. (Technologies, Market Analysis, & Business Opportunities). Prepared by Technology Catalysts International. Falls Church: Technology Catalysts International, 2008.
5. Harmon TM. Orally disintegrating tablets: a valuable life cycle management strategy. Pharmaceutical commerce, March 2007. Available at: www.pharmaceuticalcommerce.com.
6. Ghosh TK, Sastry SV, Pfister WR. Quick dissolving oral dosage forms: scientific and regulatory considerations from a clinical pharmacology and biopharmaceuticals perspective. In: Ghosh TK, Pfister WR, eds. Drug Delivery to the Oral Cavity: Molecules to Market. New York: CRC Press, 2005; 337–356.
7. Pfister WR, Ghosh TK. Orally disintegrating tablets: products, technologies, and development issues. Pharm Technol 2005; 29(10):136–150.
8. US Food and Drug Administration, CDER Data Standards Manual, 2003. Available at: http://www.fda.gov/cder/index.htm.
9. Guidance for Industry: Orally Disintegrating Tablets, April 2007. Available at: http://www.fda.gov/cder/guidance/index.htm.
10. Tolia V, Han C, North JD, et al. Taste comparisons for lansoprazole strawberry flavored delayed release orally disintegrating and ranitidine peppermint flavored syrup in children. Clin Drug Invest 2005; 25(5):285–292.
11. Guidance for Industry: Orally Disintegrating Tablets, December 2008. Available at: http://www.fda.gov/cder/guidance/index.htm.
12. European Directorate for the Quality of Medicines. Pharmeuropa 1988; 10(4):547. Available at: http://www.pheur.org.
13. Japanese Pharmacopoeia 15th edition 2006. Available at http://www.mhlw.go.jp/topics/bukyoku/iyaku/yakkyoku/index.html (in Japanese); http://www.mhlw.go.jp/english/index.html (in English).
14. Yarwood R. Zydis – a novel fast dissolving dosage form. Man Chem 1990; 61:36–37.
15. Nappi G, Micieli G, Tassorelli C, et al. Effectiveness of a fast-dissolving formulation sublingually administered in the symptomatic treatment of migranine without aura. Headache 1993; 33(6):296–300.
16. Behnke K, Sogaard J, Martin S, et al. Mirtazapine orally disintegrating tablet versus sertraline: aprospective onset of action study. J Clin Psychpharmacol 2003; 23(4):358–364.
17. Pfister WR, Ghosh TK. Intraoral delivery systems: an overview, current status and future trends. In: Ghosh TK, Pfister WR, eds. Drug Delivery to the Oral Cavity: Molecules to Market. New York: CRC Press, 2005:1–40.
18. Mizomoto T, Masuda Y, Takeshi Y, et al. Formulation design of a novel fast disintegrating tablet. Int J Pharm 2005; 306(1–2):83–90.
19. Bradoo R, Shahani S, Deewan B, et al. Fast dissolving drug delivery system. JAMA India 2001; 4(10):27–31.
20. Deepak K. Orally disintegrating tablets. Tablets Capsules 2004; 7:30–35.
21. Ostrander K. Advances in fast-dispersing technologies – Zydis. Presented at the Annual Meeting of the AAPS, Salt Lake City, UT, October 29, 2003.
22. Clarke A, Jankovic J. Selegeline orally disintegrating tablet in the treatment of Parkinson's disease. Therapy 2006; 3(3):349–356.
23. Anon. Flavors and flavoring compounding. Int J Pharm Compounding 1997; 1:90–92.
24. Brown D. Orally disintegrating tablets – taste over speed. Drug Deliv Technol 2001; 3(6):58–61.

25. Salemme FRS. Bitter blocker technology – biochemical bitter blocking for new drug formulations. Drug Deliv Technol 2008; 8:28–33
26. Overview of Senomyx's bitter blocking program for pharmaceutical product. 7/21/2006. Available at: www.senomyx.com.
27. Reo JP, Fredrickson JK. Taste-masking science and technology applied to compacted oral solid dosage, Part 3. Am Pharm Rev 2002; 5(4):8–14.
28. Venkatesh GM, Clevenger JC, Lai J-W, et al. Orally disintegrating tablet compositions of Temazepam. US patent application ser. no. 12/339,908, filed December 19, 2008.
29. Lai J-W, Qian KK, Venkatesh GM. Taste-masked pharmaceutical compositions prepared by coacervation. US patent publication US 20060105038; Lai J-W, Venkatesh GM, Qian KK. Taste-masked pharmaceutical compositions with gastrosoluble pore-formers. US patent publication US 20060105039.
30. Venkatesh GM. Taste-masked pharmaceutical compositions. US patent publication US 20060078614.
31. Venkatesh GM. Diffucaps® technology for controlled-release drug delivery. In: Youan B-BC, ed. Chronopharmaceutics: Science and Technology for Biological Rhythm-Guided Therapy and Prevention of Diseases. New York: John Wiley & Sons, Inc., 2009:125–148.
32. Lehamann K, Petereit HU, Dreher D. Fast disintegrating controlled release tablets from coated particles. Drugs made Germany 1994; 37(2):53–60.
33. Baldi F, Malfertheiner P. Lansoprazole fast disintegrating tablet: a new formulation for an established proton pump inhibitor. Digestion 2003; 67(1–2):1–5.
34. Venkatesh GM, Stevens PJ, Lai J-W. Compositions comprising weakly basic drugs and controlled-release dosage forms. US patent application ser. no. 12/424,201 filed Apr 15, 2009.
35. Sinha VR, Nanda A, Kumria R. Cyclodextrins as sustained-release carriers. Pharm Technol 2002; 26(10):36–46.
36. Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: Recent developments and approaches. Drug Dev Ind Pharm 2004; 30:429–448.
37. Chang RK, Guo X, Burnside BA, et al. Fast dissolving tablets. Pharm Technol 2000; 24(6):52–58.
38. Friend DR, Ng S, et al. Taste-masked microcapsule compositions and methods of manufacture. US patent 6,139,865, 2000.
39. Hamashita T, Matsuzaki M, Ono T, et al. Granulation of core particles suitable for film coating by agitation fluidized bed. II. A proposal of a rapid dissolution test for evaluation of bitter taste of ibuprofen. Chem Pharm Bull 2008; 56(7):882–887.
40. Ishikawa T, Watanabe Y, Utoguchi N, et al. Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter-masked granules by the compression method. Chem Pharm Bull 1999; 47(10):1451–1454.
41. Vilkov Z, Willoughby DJ, Quinn E. Pseudoephedrine combination pharmaceutical compositions. US patent 5,807,579, 1998.
42. Cumming KI, Harris E. Taste-masked formulations. US patent 6,153,220, 2000.
43. Ozer AY, Hincal AA. Studies on the masking of unpleasant taste of beclamide microencapsulation and tabletting. J Microencapsul 1990; 7:327–339.
44. Scarpelli JA. Preparation of high solids, low viscosity carbonless paper gelatin based microcapsules. US patent 5,196,149, 1993.
45. Ghanta SR, Guisinger RE. Procedure for encapsulating ibuprofen. US patent 5,814,332, 1998.
46. Shimizu T, Morimoto S, Tabata T. Orally disintegrable tablets. US patent 6,328,994, 2001.
47. Kayumba P, Hueghebart N, Cordella C, et al. Quinine sulphate pellets for flexible pediatric drug dosing: formulation development and evaluation of taste-masking efficiency using the electronic tongue. Eur J Pharm Biopharm 2007; 66:460–465.
48. Yajima T, Umeki N, Itai S. Optimum heat treatment conditions for masking the bitterness of the clarithromycin wax matrix. Chem Pharm Bull 1999; 47:220–225.
49. Abdelbary G, Prinderre P, Eouani C, et al. The preparation of orally disintegrating tablets using a hydrophilic waxy binder. Int J Pharm 2004; 278(2):423–433.
50. Van Scoik KG. Solid pharmaceutical dosage in tablet triturate form and method of producing same. US patent 5,082,667, 1992.
51. Cuca RC, Harland RS, Riley J, et al. Taste masked pharmaceutical materials. US patent 5,494,681, 1996.
52. Stroppolo F, Ciccarello F, Milani R, et al. Oral pharmaceutical compositions containing cyclodextrin as taste-masking agent. WO patent WO2002/241920.
53. Grother LP, Chandler SG. Use of ion exchange resin for binding bitter tasting drugs formulated in a fast dispersing dosage form Zydis. 2001 AAPS Annual Meeting, Denver, CO (USA).
54. Ohta M, Hayakawa E, Ito K. Intrabuccally rapidly disintegrating tablets and a production method of the tablets, US patent publication US 20030134884.
55. Ohta M, Hayakawa E, Ito K. Intrabuccally rapidly disintegrating tablets and a production method of the tablets, EP 0914818 B1 (unpublished data generated at Eurand, Inc. in accordance with Kyowa Hakko Kogyo's Solblet technology).

56. Venkatesh GM, Gosselin MA, Clevenger JC, et al. Orally disintegrating tablet compositions comprising combinations of high and low-dose Drugs. US patent application ser. no. 61/174,782 filed on May 1, 2009.
57. Habib W, Khankari R, Hontz J. Fast-dissolving drug delivery systems. Crit Rev Ther Drug Carrier Syst 2000; 17(1):61–72.
58. Dobetti L. Fast-melting tablets: developments and technologies. Pharm Technol (Drug Deliv Suppl) 2001; 25(9):44–50.
59. Parakh SR, Gothoskar AV. A review of mouth dissolving tablet technologies. Pharm. Technol 2003; 27(11):92–100.
60. Fu Y, Yang S, Jeong SH, et al. Orally fast disintegrating tablets: development, technologies, taste-masking and clinical studies. Crit Rev Ther Drug Carrier Syst 2004; 21(6):413–475.
61. Sharma K, Pfister WR, Ghosh TK. Quick-dispersing oral drug delivery systems. In: Ghosh TK, Pfister WR, eds. Drug Delivery to the Oral Cavity: Molecules to Market. New York: CRC Press, 2005:261–290.
62. Pather SI, Khankari R, Siebert J. Quick-dissolving intraoral tablets. In: Ghosh TK, Pfister WR, eds. Drug Delivery to the Oral Cavity: Molecules to Market. New York: CRC Press, 2005:291–336.
63. Sastry SV, Nyshasham J. Process development and scale-up of oral fast-dissolving tablets. In: Ghosh TK, Pfister WR, eds. Drug Delivery to the Oral Cavity: Molecules to Market. New York: CRC Press, 2005:311–336.
64. Katzner LD, Jones B, Khattar J, et al. Blister package and packaged tablet. US patent 6,155,423, 2000.
65. Corveleyn S, Remon JP. Formulation and production of rapid disintegrating tablets by lyophilization using hydrochlorthiazide as a model drug. Int J Pharm 1997; 152:215–225.
66. Remon JP, Corveleyn S. Freeze-dried disintegrating tablets. US patent 6,010,719. 2000.
67. Gregory GKE, Ho DSS. Pharmaceutical dosage form packages. US patent 4,305,502, 1981.
68. Yarwood R, Kearnery P, Thompson A. Process for preparing solid pharmaceutical dosage form. US patent 5,738,875, 1998.
69. Lafon L. Galenic form for oral administration and its method of preparation by lyophilization of an oil-in-water emulsion. US patent 4,616,047, 1986.
70. Gole DJ, Levinson RS, Carbone J, et al. Preparation of pharmaceutical and other matrix systems by solid state dissolution. US patent 5,215,756, 1993.
71. Pebley WS, Jager NE, Thompson SJ. Rapidly disintegrating tablet. US patent 5,298,261, 1994.
72. Bogner RH, Wilkosz MF. Fast dissolving tablets: new dosage convenience for patients. US Pharmacist 2002; 27:34–43.
73. Jain RA, Ruddy SB, Cumming KI, et al. Rapidly disintegrating solid oral dosage form. US patent 6,316, 029, 2001.
74. Kaushik D, Dureja H, Saini TR. Orally disintegrating tablets – overview of melt-in-mouth tablet technologies and techniques. Tablets and Capsules 2004; 2(4):30–36.
75. Makino T, Yasuda M, Kikuta J. Fast dissolving tablet and its production. US patent 5,501,861, 1996; US 5,720,974, 1998.
76. Okada M, Ikeda Y, Ono K, et al. Quickly soluble solid preparation. US patent 6,455,053, 2002.
77. Bi Y, Yonezawa Y, Sunada H. Rapidly disintegrating tablets prepared by the wet compression method: mechanism and optimization. J Pharm Sci 1999; 88(10):1004–1010.
78. Shimizu T, Morimoto S, Tabata T. Orally disintegrable tablets. US patent 6,328,994, 2001.
79. Masaki K, Ban K. Intrabuccally disintegrating preparation and production hereof. US patent 5,466,464, 1995.
80. Bonadeo D, Ciccarello F, Pagano A. Process for the preparation of a granulate suitable to the preparation of rapidly disintegrable mouth soluble tablets and compositions obtained thereby. US patent 6,149,938, 2000.
81. Wehling F, Schuehle S, Madamala N. Effervescent dosage forms with microparticles. US patent 5,178,878, 1993.
82. Amborn J, Tiger V. Apparatus for handling and packaging friable tablets. US patent 6,311,462, 2001.
83. Khankari RK, Hontz J, Chastain SJ, et al. Rapidly dissolving robust dosage form. US patent 6,024,981, 2000.
84. Pather SI, Khankari RK, Eichman JD, et al. Sublingual buccal effervescent. US patent 6,200,604, 2001.
85. Pather SI, Siebert JM, Hontz J, et al. Enhanced buccal delivery of fentanyl using the OraVescent drug delivery system. Drug Deliv Technol 2001; 1(10):54–57.
86. Mizumoto T, Masuda Y, Fukui M. Intrabuccally dissolving compressed moldings and production process thereof. US patent 5,576,014, 1996.
87. Liu F, He MM, Nyshadham JR, et al. Water soluble polymer-based rapidly dissolving tablets and production processes thereof. US patent 6,465,009, 2002.

88. Mizumoto T, Masuda Y, Kajiyama A, et al. Tablets quickly disintegrating in the oral cavity and process for producing the same. US patent 6,589,554, 2003.
89. Fu Y, Pai CM, Park SY et al. Highly plastic granules for making fast melting tablets. WO 2004/100857, 2003.
90. Rault I, Pionneir E. Use of an arylic type C polymer as disintegrating agent. US patent 6696,085, 2004.
91. Fuisz RC. Rapidly dissoluble medicinal dosage unit and method of manufacture. US patent No. 4,855,326, 1989.
92. Misra TK, Currington JW, Montwill B, et al. Fast dissolving comestible units formed under high speed/high pressure conditions. US patent 6,048,541, 2000.
93. Fuisz RC, Misra TK, Sanghvi PP. Easily processed tablet compositions. US patent 6,277,406, 2001.
94. Cousin G, Bruna E, Gendrot E. Rapidly disintegratable multiparticular tablet. US patent 5,464,632, 1995.
95. Nouri N, Zuccarelli J-M, Chauveau C, et al. Process for manufacturing coated granules with masked taste and immediate release of the active principle. US patent 6,660,382, 2003.
96. Lagoviyer Y, Levinson RS, Stotler D, et al. Means for creating a mass having structural integrity US patent 6,284,270, 2001; US Patent 6,465,010, 2002.
97. Pettersson A, Nystrom C, Lennernas H, et al. Fentanyl composition for the treatment of acute pain. WO 2000/016751, 1998; Pettersson A, Nystrom C, Hakanssen, Y.; Gastric acid secretion inhibiting composition. WO 2004/035090, 2002.
98. Tatara M, Matsunaga K, Shimizu T. Method and apparatus for manufacturing tablet capable of quick disintegration in oral cavity. US patent 6,316,026,2001.
99. Knitsch K-W, Hagen A, Munz E, et al. Production of porous tablets. US patent. 4,134,943, 1979.
100. Koizumi KI, Watanabe Y, Morita K, et al. New method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material. Int J Pharm 1997; 152:127–131.
101. Allen LV Jr., Wang B. Process for a particulate support matrix for making a rapidly dissolving tablet. US patent 5,587,180, 1996.
102. Allen LV Jr., Wang B, Davies JD. Method for making a rapidly dissolving dosage form. US patent 6,207,199, 2001.
103. Dobetti L. Fast disintegrating tablets. US patent 6,596,311, 2003.
104. Morimoto K, Watanabe Y, Miwa T, et al. Rotary type tableting machine with lubricant spraying means. US patent 5,700,492, 1997.
105. Watanabe Y, Ishikawa T, Mukai B, et al. New compressed tablet rapidly disintegrating in saliva in the mouth using crystalline cellulose and a disintegrant. Biol Pharm Bull 1995; 18(9):1308–1310.
106. Bi Y, Sunada H, Yonezawa Y, et al. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem Pharm Bull 1996; 44(11):2121–2127.
107. Ito A, Sugihara M. Development of oral dosage form for elderly patients. Use of agar as base of rapidly disintegrating oral tablets. Chem Pharm Bull 1996; 44(11):2132–2136.
108. Michaelson I. Rapidly disintegrable tablet composition and method. US patent 4,414,198, 1983.
109. Lee K-J, Kang A, Delfino JJ, et al. Evaluation of critical formulation factors in the development of a rapidly dispersing captopril oral dosage form. Drug Dev Ind Pharm 2003; 29(9):967–979.
110. Yu DG, Shen XX, Han J, et al. Oral fast dissolving 3D fabricated using 3DP, bioinformatics and bioengineering (ICBBE) 2008. The 2nd International Conference 16–18 May 2008:1602–1605.
111. Laruelle C, Zakarian N, Gimet R, et al. Galenic formulations fast disintegrating in the mouth and method for preparing same. EP 1,131,050, 2000.
112. Joshi AA, Lefevre P, Duriez X. Screening and identifying optimal combinations of excipients and super disintegrants in the development of orally disintegrating tablet (ODT) formulations. ODT Excipeint (132) Ko. Available at: www.roquette-pharma.com.
113. Barnhart SD, O'Halloran D, Osborne JI. Quick dissolving films: a novel approach to drug delivery. Drug Del Technol 2003; 3(3):84–90.
114. Barnhart SD, Sloboda MS. Dissolvable films: the future of dissolvable films. Drug Del Technol 2007; 7(8):34–37.
115. Barnhart SD. Thin Film Oral Dosage Forms. Modified Release Drug Delivery Technology. 2nd ed. Vol 1. New York: Informa Healthcare, 2008:209–216.
116. Vondrak B, Barnhart SD. Dissolvable films for flexible product format in drug delivery. Pharm Technol 2008; 32(4): 21–32.
117. Oral thin films. In: Orally Disintegrating Tablet and Film Technologies. 5th ed. Falls Church: Technology Catalysts International, 2008; 18–31.
118. Borsadia SB, O'Halloran D, Osborne JL. Quick-dissolving films—a novel approach to drug delivery. Drug Deliv Technol 2003; 3(3):63–66.

119. Liang AC, Chen Li-Lan H. Fast-dissolving intraoral drug delivery systems. Expert Opin 2001; 11 (6):981–986.
120. Arnum PV. Outsourcing solid dosage manufacturing. Pharm Technol 2006; 30(6):44–52.
121. Repka M, McGinity JW. Bioadhesive properties of hydroxypropylcellulose topical films produced by hot-melt extrusion. J Control Rel 2001; 76(3):341–351.
122. Mishra R, Amin A. Formulation development of taste-masked rapidly dissolving films of cetirizine hydrochloride. Pharm Technol 2009; 48–56.
123. Leichs C, Breitenbach A, Lehrke I, et al. Non-mucoadhesive film dosage forms.WO 2008/040534.
124. Chen L-LH, Pfister WR, Renn DW, et al. Compositions and methods for mucosal delivery. US patent 6,552,024, 2003.
125. Asmussen B, Krumme M. Flat medicinal preparation for transmucosal administration of oxycodon or a comparable active ingredient in the oral cavity for use in pain therapy and in addiction therapy. WO 2001/043728.
126. Zajaczkowski MJ (Adhesive Research, Inc.). Water soluble pressure sensitive adhesive. EP 0681,601 B1, 1994.
127. Fuisz RC, Yang RK, Myers GL. Uniform films for rapid dissolve dosage form incorporating taste-masked compositions. WO 2003/030883.
128. Nogame E (Lintec Corporation). Oral preparations and supports for oral preparations. WO 2002/ 087622.
129. Yasuda Y (KyuKyu Pharmaceutical). Quickly soluble film preparations. EP 1,504765 A1, 2003.
130. Virgalitto MT, Zang J. Edible film. EP 1,443,968, 2002.
131. Cleary GW, Feldstein MM, Kulichikhin VG, et al. Two phase water absorbent bioadhesive composition. US patent 6,803,420, 2004.

20 Melt Granulation

Chris Vervaet and Jean Paul Remon
Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium

INTRODUCTION

Granulation is an important unit operation during the manufacturing of solid dosage forms to improve the processability, fluidity, compactibility, content uniformity, and/or dissolution rate of a formulation. This size enlargement process is commonly done via wet granulation using a solvent (water or organic solvent) to initiate binding between solid particles; however, when the formulation is not suitable for wet processing, dry granulation (chap. 8) or melt granulation can be valuable alternatives.

Melt granulation (also defined as thermoplastic granulation) operates via similar principles as wet granulation, but uses a molten binder as granulation fluid to establish liquid bridges between particles in a heated powder bed. Following particle agglomeration and consolidation, the granules are cooled to room temperature and the solidified binder forms bridges between individual powder particles to yield a solid end product with a granular structure.

This granulation approach has several advantages over conventional wet granulation: (a) the drying step is eliminated since no solvents (water, alcohol, organic solvents) are used during the process, significantly reducing the process time and energy requirements, (b) moisture-sensitive materials can be agglomerated without organic solvents, resulting in an environment friendly process, (c) the amount of liquid added during granulation is carefully controlled (ensuring a consistent granule quality), since uncontrolled solvent evaporation during agglomeration will not occur, and (d) all unit operations of a melt granulation process (mixing, agglomeration, formation of solid bridges) are carried out in the same equipment, offering a safe and simple single-pot process with minimal loss during material transfer. These advantages must be balanced against the risk of thermal degradation of the active ingredient at higher process temperature.

Although often the binder is heated above its melting point in a separate reservoir and added to the powder bed (heated above the melting point of the binder) via the spray-on or pour-on method to induce particle agglomeration (an approach similar to the one used during wet granulation), a solid binder (in powdered form or as flakes) can be mixed at room temperature with the starting material. The latter procedure (melt-in method) even eliminates the liquid addition phase as subsequent heating of the formulation above the melting point of the binder (due to heat developed by friction during mixing or via a heating jacket, hot air, or microwave) initiates granule formation via the liquefied binder.

The binder used during melt granulation is one of the main determinants of granule quality: using hydrophilic binders immediate-release systems are formed as the granules quickly disintegrate or dissolve in aqueous media (1,2). In contrast, a sustained-release dosage form is prepared via melt granulation using lipophilic binders as the water insoluble binder retains its matrix structure in aqueous media (3,4). In general, melt granulation yields denser agglomerates compared with wet granulation since the binder liquid is not removed from the end product. This property can be advantageous for sustained-release formulations, but could hamper water penetration into the granules in case of an immediate-release formulation.

The number of binders (Table 1) used during melt granulation for pharmaceutical applications is limited as—in addition to their safety from a toxicological perspective—the requirements for the formulation during processing, storage, and administration limit the melting range of the binder to a specific temperature interval. Binders with a melting point above 90°C are seldom used to avoid thermal degradation of the active during processing as well as to limit process time and energy consumption. On the other hand, most binders used

Table 1 Overview of Commonly Used Binders During Melt Granulation

Lipophilic binders
Beeswax
Carnauba wax
Microcrystalline wax
Paraffin wax
Cetostearylalcohol
Stearylalcohol
Stearic acid
Palmitic acid
Glyceryl tripalmitate (Dynasan 116)
Glyceryl tristearate (Dynasan 118)
Glyceryl palmito stearate (Precirol ATO)
Glyceryl behenate (Compritol 888 ATO)
Glyceryl monostearate
Hydrogenated soybean oil (Sterotex HM)
Hydrogenated castor oil (Cutina HR)
Hydrophilic binders
Polyethylene glycol 3000–20000
Ethylene oxide/propylene oxide blocks copolymers (poloxamers)
Gelucire 50/13
Gelucire 44/14

for melt granulation purposes have a melting point above 50°C to avoid softening of the dosage form during storage and in case of sustained-release drug delivery systems also to maintain the structural integrity of the matrix at body temperature to avoid excessive drug release (drug-dose dumping) upon oral administration. Although in most cases a specific binder is added to the formulation, the drug itself can act as meltable binder provided that it has the proper melting range and does not degrade upon melting: Dhumal et al. (5) and Crowley et al. (6) used ibuprofen (melting range 74–77°C) and propranolol oleate (melting range 50–56°C), respectively, as meltable substance to agglomerate lactose-based formulation.

As the action of the molten binder is similar to the action of the liquid (water, organic solvent) added during wet granulation, it is not surprising that most melt granulation processes are run using the same equipment as for wet granulation. Mainly, high-shear mixers and fluid-bed granulators have been used for melt granulation, but the viability of rotary fluid-bed granulation, tumbling melt granulation, spray congealing, and hot-melt extrusion for this application has also been established. Although melt granulation has been the topic of fewer research projects in comparison with wet granulation, the formulation and process variables defining the quality attributes of formulations processed via the different melt granulation procedures have been clearly defined. This chapter further describes the different techniques used to manufacture dosage forms via melt granulation and details for each technique some of the formulation and process variables, which determine the properties of the granulated end product.

MELT GRANULATION USING A HIGH-SHEAR MIXER

High-shear mixers have been most frequently used for melt granulation of powders, and the different parameters affecting granule quality have been identified by the extensive work done by Schaefer's group (7–13). These papers and other researchers (14) identified binder content, binder type, binder particle size, binder rheology, powder cohesivity, product temperature, jacket temperature, atomization pressure, mixing time, impeller speed, design of impeller blades, and properties of solid nonmeltable particles as critical variables, and formed the basis to identify the fundamentals of agglomerate formation and growth during melt processing in a high-shear granulator.

Granule formation during melt granulation can occur via two mechanisms: distribution or immersion (Fig. 1) (15).

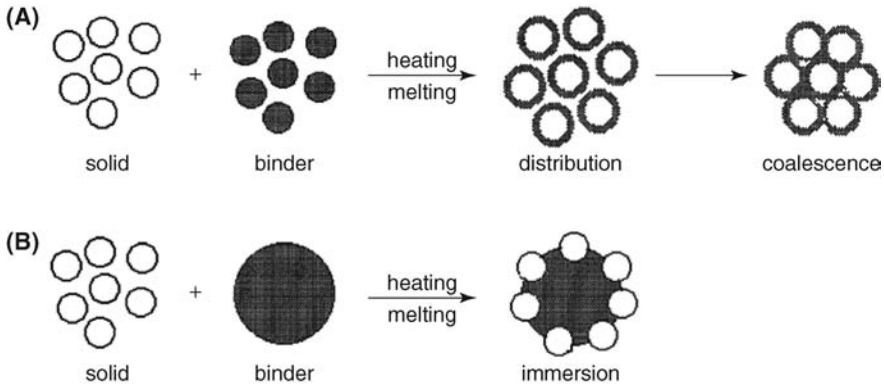


Figure 1 Agglomerate formation mechanism in melt agglomeration. (**A**) Distribution mechanism and (**B**) immersion mechanism. *Source*: From Ref. 15.

In the distribution mechanism, the molten binder liquid is distributed on the surface of the primary particles, and nuclei (held together via liquid bridges) are formed via coalescence of primary particles. Agglomerate growth further occurs via coalescence of nuclei provided that liquid saturation is sufficient. In case of immersion, nuclei are formed when the initial solid particles become immersed in the surface of a molten binder particle/droplet.

During melt granulation, both mechanisms can occur simultaneously, one mechanism, however, will be dominant depending on several formulation and process parameters. The distribution mechanism was promoted when the binder droplet size was smaller than the solid nonmeltable primary particles, while immersion dominates when droplet size exceeds the solid particle size (7,15). This will depend on the atomization conditions in case of spray addition of the binder (spray-on method). In case of the melt-in method, the agglomerate formation mechanism will be controlled by the particle size of the solid binder mixed into the formulation as this determines the initial droplet size after melting of the binder. In case of the pour-on method, droplet size (hence granule formation mechanism) is determined by the extent of shear forces generated by the impeller. Melt granulation in a high-shear mixer often favors the distribution mechanism as binder droplet size during the initial stage of the process can be reduced under the influence of the shear generated by the impeller. The effect of binder addition method on the granule formation mechanism was supported by the data of Scott et al. (16) who indicated that pour-on and melt-in experiments formed granules via the immersion and distribution mechanism, respectively.

A low viscosity binder and/or high high-shear forces (i.e., high impeller speed) promoted the distribution mechanism, whereas a high viscosity and/or low shear forces promoted agglomerate formation via immersion. Hence, running a melt granulation process within or slightly below the melting range of the binder promoted immersion since this increased the viscosity of the binder.

Following nucleation of the primary particles via distribution or immersion, agglomerates grow via coalescence of two granules or layering of small particles on the surface of a granule, depending on the liquid saturation and the deformability of the granules (15). Agglomerate growth continues until a critical size is obtained, after which the size distribution of the agglomerates is controlled via an equilibrium between material consolidation, growth, and breakage. Size reduction via breakage beyond the critical size depends on granule strength and disruptive shear forces, factors being determined by the viscous forces of the liquid bridge, granule densification, primary particle size, and impeller speed.

The cooling rate following melt granulation of a diazepam/lactose formulation with PEG 3000 in a high-shear mixer affected the drug release properties because of changes in the morphology of the agglomerates and crystallinity of the binder; slow cooling agglomerates having a more uniform size and shape and a smoother surface were obtained, whereas flash cooling of the granules using liquid nitrogen reduced the degree of crystallinity of PEG. These factors combined to increase the drug release rate from the flash-cooled agglomerates (17).

MELT GRANULATION USING A FLUIDIZED BED

Initially, a high-shear mixer was most frequently used for melt granulation as the shear forces generated make this technique especially suitable for melt granulation. However, fluidized hot melt granulation is becoming more popular since it offers more accurate temperature control, an essential feature during melt granulation. Whereas the process temperature during high-shear melt granulation is the result of external heating via the jacket of the mixing bowl and frictional heat generated because of agitation of the impeller during processing, the energy input during fluidized hot melt granulation is almost entirely controlled by the temperature of the fluidizing air. The shear forces during fluid-bed processing are too low to affect the process temperature, thus minimizing the risk of uncontrolled particle growth due to poor temperature control. In addition, when the granulation end point is reached the material in a fluidized bed can be rapidly cooled via the fluidizing air, whereas the energy stored in a mass contained in a high-shear mixer must primarily dissipate via the jacket of the mixing bowl, resulting in a longer process time. The less efficient heat transfer during high-shear melt granulation could cause excessive heating due to the frictional heat generated (in function of impeller speed and material load) and/or cause scale-up issues when processing larger batches as the ratio of material mass to bowl surface increases.

Whereas high-shear melt granulation is possible via the spray-on, melt-in and pour-on method, fluidized hot-melt granulation is limited to the spray-on and melt-in method as the dispersive forces in a fluid bed are too low to shear a volume of binder poured into the granulator into droplets of suitable size for controlled agglomeration.

As the use of fluidized hot melt granulation was not as widespread, the fundamentals of its agglomeration mechanism have only been elucidated when the details of granule formation and growth during high-shear melt granulation were already well established. However, several research groups showed that the same mechanisms (distribution and immersion) were involved in both the granulation techniques.

Figure 2 depicts the sequence of events occurring in a fluidized hot-melt granulator using the spray-in method in case of agglomerate formation via the distribution mechanism. After collision of a binder droplet with a solid particle (event 1) in the spray zone the liquid binder distributes on the surface of the nonmeltable particle (event 2). The process temperature

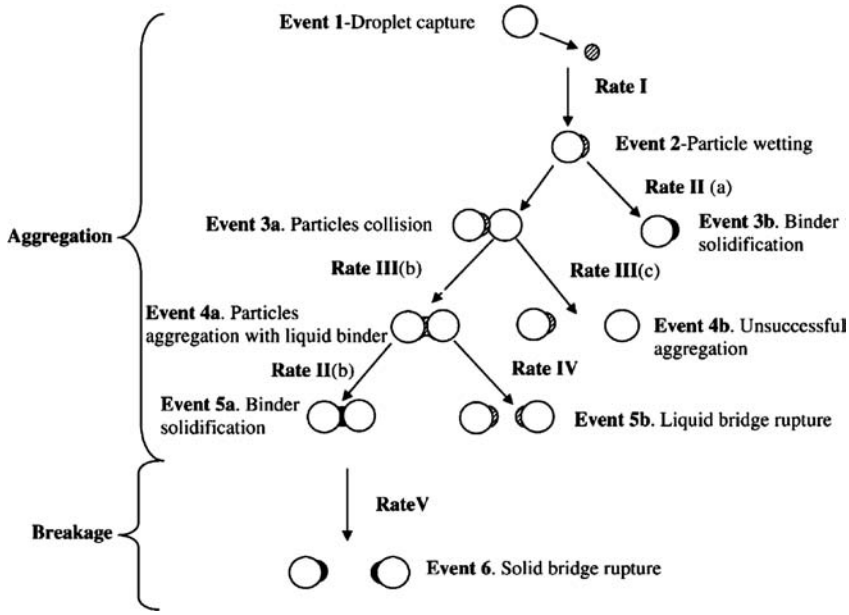


Figure 2 Sequence of events during fluidized bed melt granulation using the spray-on method and following the distribution mechanism of agglomerate formation. *Source*: From Ref. 18.

Table 2 Agglomerate Formation Mechanisms Expected from the Size Ratio Between Binder Droplets and Lactose Particle Size

Lactose particle size	Droplet size		
	30 μm	60 μm	90 μm
164 μm	Distribution	Distribution	Distribution
66 μm	Distribution	Distribution/immersion	Immersion
32 μm	Distribution/immersion	Immersion	Immersion

Source: From Ref. 19.

should be adjusted to avoid binder solidification (event 3b) prior to particle/particle collision (event 3a), and the probability of particle/binder collision can be increased by adjusting the binder addition rate and the powder flux through the spray zone. As a result of particle-particle collision either aggregates are formed (event 4a) or colliding particles rebound if the liquid bridge is not sufficiently strong (event 4b). Afterward, the liquid bridge solidifies to form a granule (event 5a) or ruptures prior to binder solidification (event 5b) because of turbulence during fluidization. Even after solidification of the binder, granules can be destroyed because of attrition and breakage (event 6) because of shear forces (18).

The same relation between droplet/particle size of the binder and particle size of the primary solids was observed during fluidized hot-melt granulation (Table 2) (19,20), the size ratio determining the mechanism of agglomerate formation. However, whereas granule formation during high-shear melt granulation can progress toward distribution because of comminution of droplets during processing, the mechanism during fluidized hot-melt granulation is determined by the atomization conditions (determining binder droplet size) or binder particle size as the shear forces in a fluid bed are too low to change the binder droplet size during processing.

Abberger et al. (19) described that the distribution mechanism results in a more open granular structure and immersion in a denser structure (Fig. 3), hence the risk of uncontrolled agglomerate growth and a less reproducible particle size distribution increases when spraying larger droplets because of the higher degree of liquid saturation of the granules.

In addition to the binder amount (hence liquid saturation), agglomerate growth during fluidized hot melt granulation is also determined by the viscosity of the molten binders (Fig. 4) (20). At high process temperature the low viscosity of the binder allows it to drain from the inside of the agglomerate toward the surface because of the capillary action, allowing further growth by coalescence (as liquid bridges between particles can be formed) once all the primary particles have been captured. In contrast, growth by coalescence is more difficult when a highly viscous binder is incorporated in the nuclei (e.g., because of a lower process temperature) as the binder cannot spread to the surface of the nuclei, hence not all particles are captured, resulting in a mixture of unagglomerated particles and nuclei containing a high binder concentration. Lactose 350 mesh granules (250–2000 μm) agglomerated with PEG 3000 droplets (40 μm) at a process temperature of 50°C contained 62.7% binder, whereas a process temperature of 65°C yielded granules with 32.3% binder content (theoretical binder concentration: 30%).

The research of Walker et al. (21) showed that the growth regimen map initially developed to describe the growth mechanisms in drum or high-shear wet granulation processes (22) could also be used to characterize a fluidized hot melt granulation process using PEG 6000 or Poloxamer® as binders. On the basis of the pore saturation and deformation of the granules, it was identified that the dominant growth mechanism depended on the binder concentration (Fig. 5): at low binder concentration nucleation, followed by steady growth and overwetting.

Tan and et al. (18) developed mathematical models to describe the growth kinetics in a fluidized hot-melt granulator.

While the initial studies on agglomerate formation and growth mechanism in a fluidized hot-melt granulator have been done via off-line analysis of granule structure and size

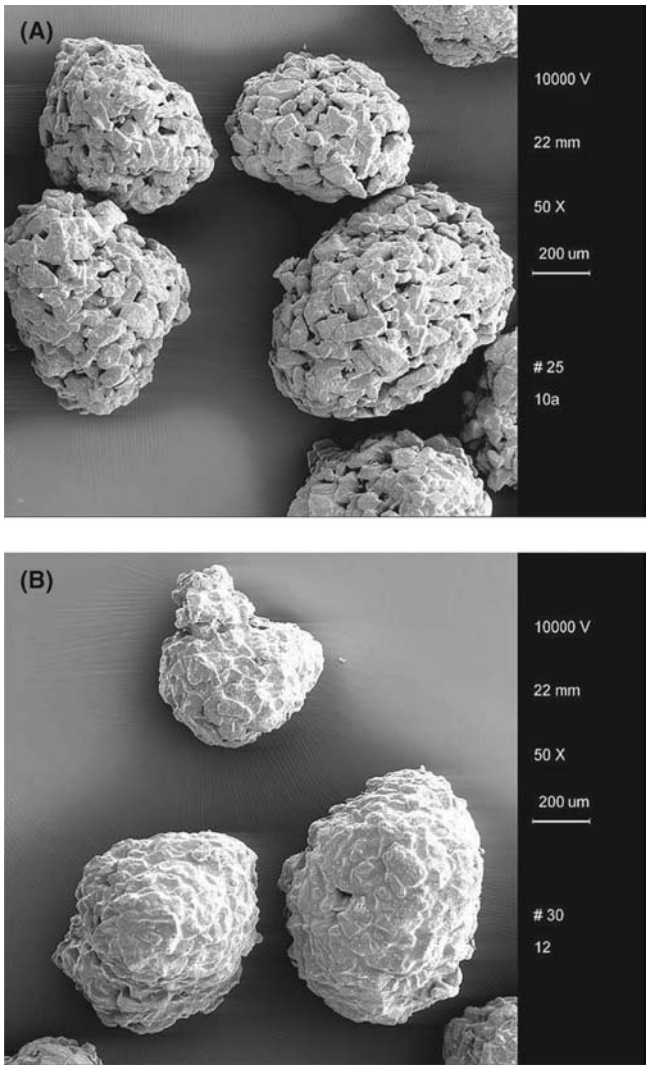


Figure 3 SEM micrographs of agglomerates produced with lactose 125 mesh and 22% PEG 3000. (**A**) A 30-μm binder droplet size yielded porous agglomerates formed via the distribution mechanism, and (**B**) a 90-μm binder droplet size yielded dense agglomerates formed via the distribution mechanism. *Source*: From Ref. 19.

distribution, Walker et al. (23) showed that Raman spectroscopy can be used to gain in-situ information about the structure, density, composition, and nucleation/consolidation of fluidized particles in function of time.

Overall the most important critical variables determining the particle size and granule quality during fluidized hot-melt granulation are concentration, viscosity, spray rate, droplet/particle size of the binder, primary particle size, bed temperature, atomization pressure, air velocity, and atomization pressure (21,24,25). However, fluid-bed melt granulation is less sensitive to the air volume used to fluidize the powder bed compared with wet granulation. During wet granulation, the rate of liquid evaporation is determined by the airflow rate and it is essential that the spray rate is sufficient to exceed the drying rate induced by the airflow to ensure agglomeration and consolidation of the particles during processing. Since no evaporation of the liquid phase occurs during melt processing, the effect of this variable is eliminated.

Kidokoro et al. (26) also identified the crystallization behavior of the binder after fluidized hot-melt granulation as a parameter determining granule quality. The cooling rate affected the crystallization mechanism of PEG 6000, and after rapid cooling, cracks were observed, which reduced sticking of the particles at the surface of the granules and resulted in a significantly higher fraction of fines ($<$150 μm).

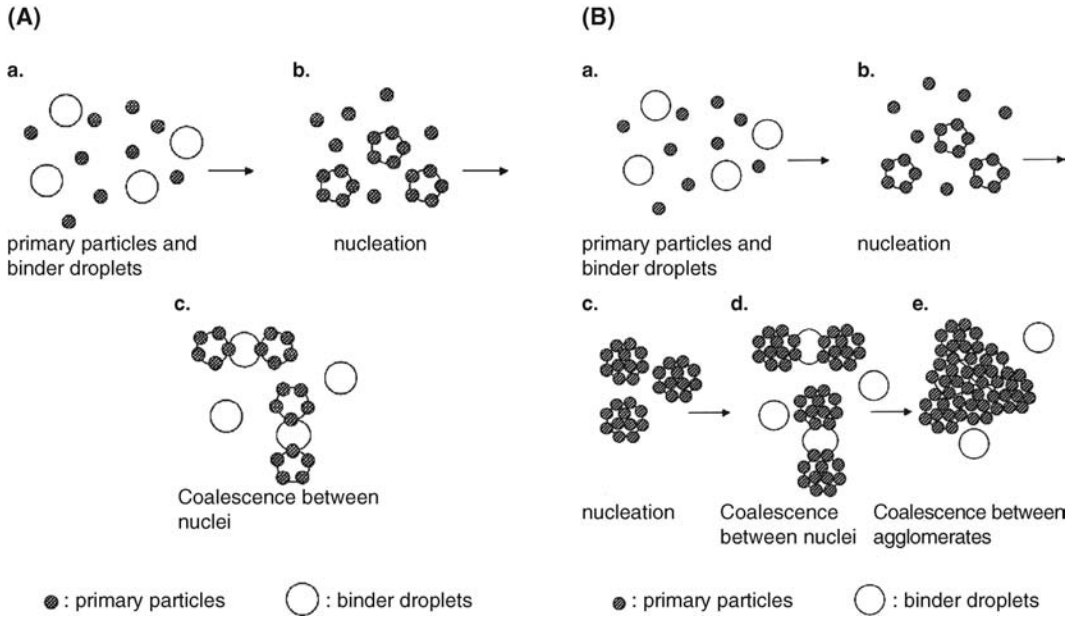


Figure 4 Agglomerates formation and growth mechanisms in fluidized bed melt granulation (**A**) high and (**B**) low viscosity. *Source*: From Ref. 20.

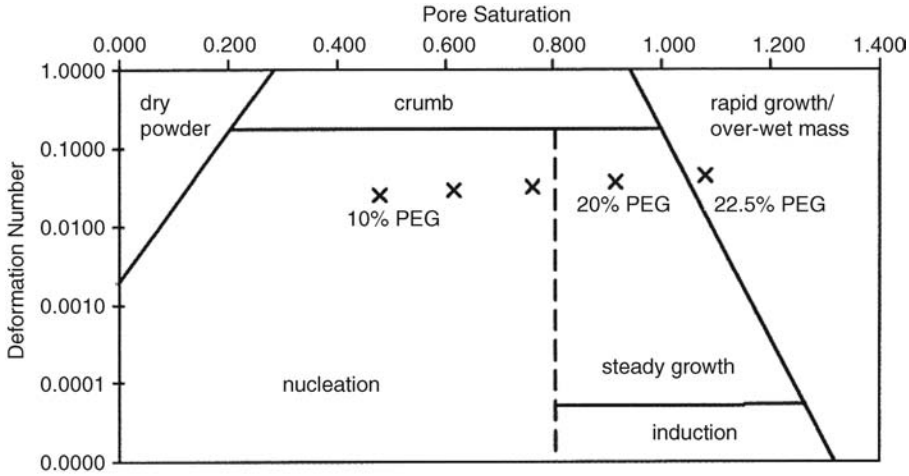


Figure 5 Growth regime map for fluidized bed melt granulation of lactose using PEG 6000 as binder. *Source*: From Ref. 21.

Next to fluidized hot-melt granulation the viability/suitability of a spouted bed for hot-melt agglomeration of a pharmaceutical powder (lactose/paracetamol mixture) was described by Borini et al. (27), the particle size and flowability of the granules being controlled by the binder feed rate (PEG 4000) and atomizing air pressure. Compared with melt granulation in a fluidized bed, the spouted bed offered a shorter processing time.

MELT PELLETIZATION

Within the pharmaceutical industry pellets are defined as spherical granules with a smooth surface and low porosity, having a mean diameter of 0.5 to 2 mm and a narrow particle size distribution. Whereas melt granulation processes in a fluid-bed or high-shear mixer produce

irregular shaped granules having a rough surface and a wide particle size distribution, pellets can also be prepared via melt granulation using specific equipment (e.g., rotary fluid-bed granulators) and/or after strict control of the formulation and process parameters during melt granulation. Pellets manufactured via melt granulation are mainly used for sustained-release applications as matrix pellets can be formed using a water insoluble binder, thus avoiding the additional coating step required to obtain sustained release from pellets manufactured via wet pelletization techniques (e.g., extrusion/spheronization, layering).

Pellets are mainly produced via melt granulation in a rotary fluid bed, which is equipped with a rotating (nonperforated) bottom plate since a conventional fluid bed does not generate sufficient shear forces to densify and deform agglomerates into spherical particles. Fluidization of the powder bed is ensured by air passing through the gap between the rotating plate and the stationary wall of the fluid bed (Fig. 6).

The rotating bottom plate generates centrifugal forces that push the material outward and upward in the fluidization chamber. As a particle reaches the top of the powder bed, it falls inward and downward to create a toroidal movement of the powder bed, which is essential to simultaneously agglomerate, densify, and spheronize for controlled transformation of porous granules into spherical particles having a smooth surface structure and a narrow particle size distribution.

Pelletization using a rotary fluid-bed granulator requires the control of numerous parameters, which determine the outcome of the process: product load, spray rate, nozzle placement (mainly via tangential spray to ensure uniform liquid distribution in the powder bed), surface structure of the rotating bottom plate, atomizing pressure, rotor speed (affecting mixing efficiency, binder distribution and agglomeration), massing time (determining densification and spheronization), airflow rate, fluidizing air temperature, inlet air pressure, gap width and pressure difference (determining material fluidization), binder concentration, binder addition rate, binder particle/droplet size, and binder viscosity. Vilhelmsen et al. (29) identified that pellet size was correlated with binder concentration, massing time, and rotational speed. Agglomerate size and size distribution also depended on the surface structure of the friction plate as higher shear forces induced more agglomeration. A textured bottom plate was essential to generate sufficient shear forces, but this must be balanced with the higher risk of attrition using a textured bottom plate. Binder concentration was the most important variable influencing agglomerate size of a lactose/PEG 3000 mixture. Sufficient binder is required for particle adhesion and to obtain deformable granules, but uncontrolled agglomeration and material adhesion to the wall and friction plate determine the upper limit of binder content. The fundamentals of agglomerate formation and growth mechanism during a melt granulation process of 350 mesh with PEG 3000 in a rotary fluid bed have been characterized by Vilhemsen and Schaefer (30): agglomerate formation and growth occurred

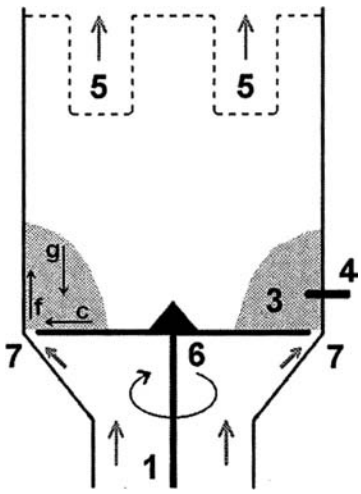


Figure 6 Schematic diagram of a rotary fluid-bed granulator. 1: Inlet air, 3: fluidized product, 4: spray nozzle, 5: exhaust air filter, 6: rotating plate, 7: air gap, c: centrifugal force, f: fluidizing force, g: force of gravity. *Source*: From Ref. 28.

primarily via distribution and coalescence when PEG 3000 particle size was less than 250 μm, while immersion dominated when processing larger PEG 3000 particles via the melt-in procedure. Via the spray-on method, agglomerate formation was a combination of immersion and distribution, while agglomerate growth was via coalescence, independent of PEG mean droplet size. The authors concluded that the mechanism of granule formation and growth in a rotary fluid bed better resembled the mechanism seen in a conventional fluid bed than in a high-shear mixer, despite the higher shear forces in a rotary fluid bed. The authors also claimed that the process was more controllable when adding a solid binder and when immersion was the main agglomerate formation mechanism since a continuous spray promoted rapid growth via coalescence.

A high-shear mixer can be used without modification to manufacture pellets via a melt granulation process as the rotation of the impeller generates sufficient centrifugal force to create the rope-like movement of the powder bed, while the shear forces generated by the impeller are sufficient to densify and deform the granules. However, an optimal formulation is required as the material must have sufficient plasticity to allow spheronization via deformation of the granules. In contrast to wet pelletization, no spheronization aids such as microcrystalline cellulose is added to the formulation to adjust the rheological properties of the formulation and the formulation's plasticity during processing is mainly determined by the molten binder. To obtain pellets via melt granulation a liquid saturation of approximately 100% is required to have sufficient granule deformability. However, this higher liquid saturation increases the risk of uncontrolled pellet growth. In addition, strict control of the process parameters is required to balance densification and plastic deformation to form spherical particles without excessive agglomeration. On the basis of these observations, it is obvious that melt pelletization is more critical as compared with melt granulation.

The higher shear forces in a high-shear granulator compared with a rotary fluid bed can result in a better sphericity, a lower optimal binder concentration (due to enhanced material densification during high-shear processing) and less effect of particle/droplet size on the agglomeration formation and growth behavior. Pellet quality in a high-shear mixer melt granulation process is determined by the interaction of the same variables, which determine granule quality in a conventional melt granulation process using a high-shear mixer: processing/massing time, impeller speed, binder concentration, binder type, jacket temperature, product temperature, particle size of the bulk material, etc. (31–34).

The end point of the melt granulation process in a high-shear mixer can be determined via monitoring the specific energy consumption of the impeller as this parameter is correlated with pellet growth (35) and pellet sphericity (32). This provided a better tool than process time to determine the process end point to control yield and pellet properties.

TUMBLING MELT GRANULATION

The tumbling melt granulation process described by Maejima et al. (36,37) can be defined as a melt-layering process onto seeds using a rotary fluid bed to yield spherical beads. This process combines a mixture of meltable and nonmeltable powders with seeds, and at higher temperature, the powders spontaneously adhere to the seeds on the basis of the binding forces of the molten binder as the bed temperature during processing is at least 5°C above the melting point of the binder (Fig. 7A).

The shape of the resulting pellets is independent of the shape of the seeds as spherical particles are obtained using spherical (nonpareils) as well as nonspherical (cube-shaped sucrose). The quality of the pellets is determined by the binder concentration as sufficient binder must be used to ensure adhesion of the powder to the seeds without inducing agglomeration of the seeds (Fig. 7B) and by the particle size of both the nonmeltable material and the binder. Their size should be less than one-sixth of the seed size as larger nonmeltable particles did not efficiently adhere to the seeds, whereas too large binder particles induced seed agglomeration and coating of the softened binder particles with drug particles without spreading on the seed surface (Fig. 7C). It was shown that this technique was applicable for melt granulation of different combinations of binder (PEG, hydrogenated castor oil, fatty acids) and drug (nicotinamide, diltiazem hydrochloride, theophylline, isoniazide, salicylic acid), and allowed to reproducibly manufacture small (about 400 μm) as well as large (up to 1400 μm)

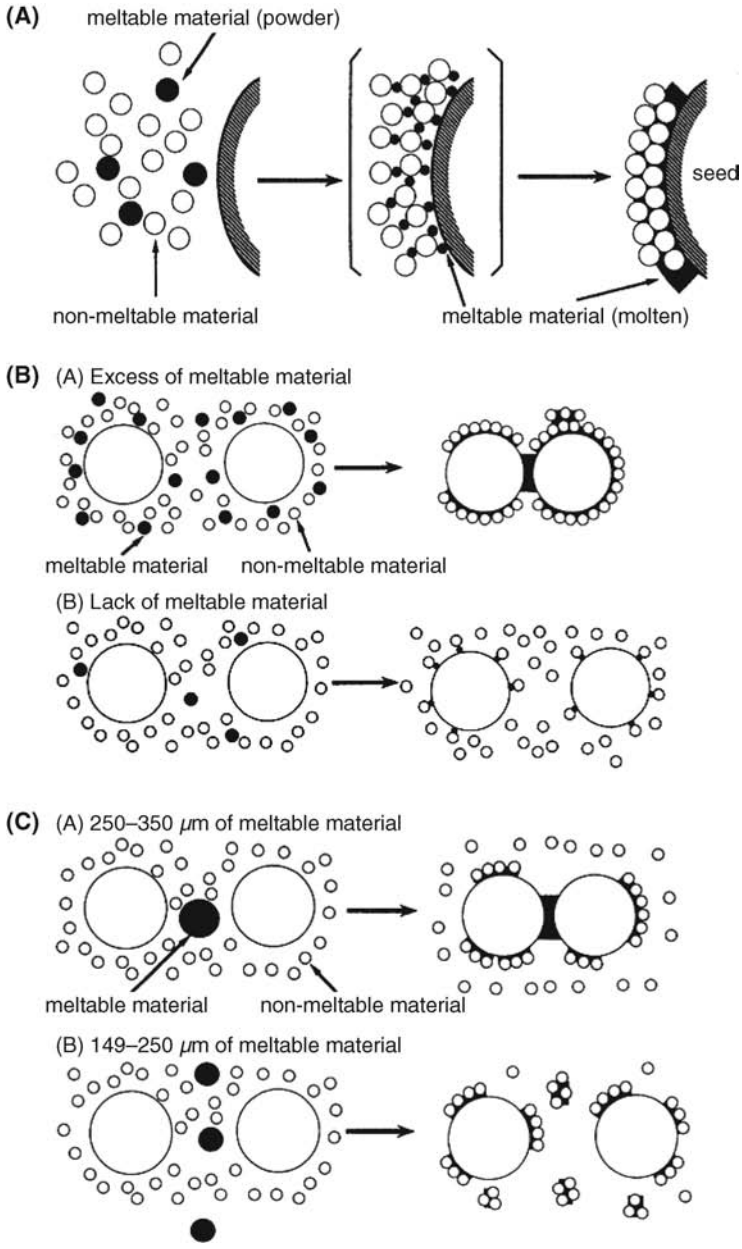


Figure 7 Schematic diagram of (**A**) the tumbling granulation method, (**B**) in function of the binder concentration, (**C**) using a meltable binder with a large particle size. *Source*: From Ref. 37.

pellets with a high process yield. The viscosity of the meltable binder had a negative effect on pellet formation as highly viscous binders induced excessive agglomeration and resulted in granules of low sphericity.

As a direct comparison of different granulation techniques, using the same formulation is seldom performed; it was interesting that Murakami et al. (38) compared the tableting properties of lactose/PEG 6000 granules processed via melt granulation in a high-shear mixer, in a fluid-bed and in a tumbling melt granulator. The compactibility of the granules depended on the agglomeration technique, for this specific formulation the material processed in the high-shear granulator yielded the highest tensile strength of the tablets.

CONTINUOUS MELT GRANULATION

While granulation processes in conventional high-shear mixers and (rotary) fluid beds are batch processes, Van Melkebeke et al. (39) described a continuous melt granulation process using a corotating twin-screw extruder to manufacture free-flowing granules. When the die plate was removed from the exit of the extruder (thus avoiding excessive densification of the material inside the extruder) in combination with a specific screw profile, the main fraction of the granules processed via this technique had a suitable particle size (250–1400 μm) for further processing (e.g., tableting, direct filling into hard gelatin capsules or sachets) without requiring a milling step to remove oversized agglomerates.

Via this process, a poorly water soluble drug (BSC class II, solubility: 1.3 mg/mL) was successfully processed with PEG 4000 (as binder) in combination with PEG 400 and surfactants (as dissolution enhancers) and maltodextrin (as water soluble carrier) to formulate a granular drinking water formulation for veterinary applications. Although no solid dispersion of the drug was formed, drug release of a formulation containing up to 20% active was immediate (>90% within 10 minutes) as the microenvironment created by the hydrophilic additives enhanced drug release.

SPRAY CONGEALING

In addition to the melt pelletization techniques described above, spherical microparticles can also be manufactured via spray congealing. This process, also known as spray chilling or spray cooling, is a melt granulation technique whereby solid particles are dissolved or dispersed in a molten carrier (having a melting point above room temperature). The resulting liquid is atomized in a chamber at a temperature below the melting point of the carrier (i.e., often at ambient temperature) and solid spherical microparticles (Fig. 8) are rapidly formed when the molten carrier in the droplets congeals upon contact with the cooler airflow in the spray-congealing apparatus. On the basis of its operating principle, spray congealing relates to spray drying as conventional melt granulation relates to wet granulation.

Depending on the carrier material, this technique allows (a) to prepare sustained-release particles for oral (41) as well as parenteral (42,43) drug delivery, (b) to enhance the dissolution rate of poorly soluble drugs (even without the formation of solid dispersions) (40,44), (c) to microencapsulate liquids to convert them into solids to improve their handling (45), (d) to stabilize drugs against the environment (43,46), and (e) to mask the taste of a drug (47).

When taking advantage of the numerous potential application of this continuous granulation technique, the risk of thermal degradation of the active pharmaceutical ingredient must certainly be considered since drug exposure to the molten carrier (in the bulk reservoir prior to spray congealing) will be longer in comparison with other melt granulation techniques.

The major limitation of spray congealing, however, is the difficulty to achieve drug loads above 25% as the formulation must be pumped toward the nozzle and atomized in the cooling chamber. At higher drugs loads, the molten formulation is often too viscous to obtain nonaggregated spherical particles having a narrow particle size distribution after atomization through a pneumatic two-fluid, rotary (or centrifugal), or ultrasound-assisted nozzle. A pressure nozzle is less used for spray congealing as the high viscosity of the formulation

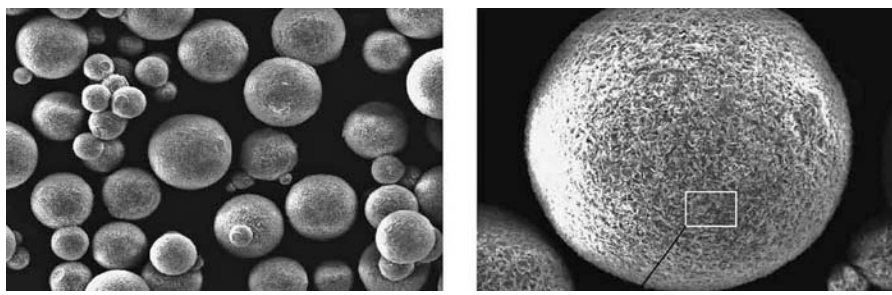


Figure 8 SEM micrographs of spray-congealed particles formulated with praziquantel and poloxamer 188 as meltable binder. *Source*: From Ref. 40.

requires a too high pressure. However, a novel wide-orifice pneumatic nozzle was introduced by Albertini et al. (45) that allowed to efficiently process viscous formulations containing up to 50% solid phase (i.e., propafenone hydrochloride dispersed in carnauba wax, cetostearyl alcohol, or stearyl alcohol) into single spherical microparticles with a narrow particle size distribution.

Although a wide range of particle sizes can be obtained via spray congealing (mean particle sizes from 50 to 3000 μm have been reported), the required size depends on the intended use of the spray-congealed microparticles (e.g., further processing into tablets, parenteral administration, direct filling into hard gelatin capsules), one of the main determinants of particle size is the viscosity of the atomized formulation [e.g., encapsulation of Vitamin E in a PEG 4000 matrix having a viscosity of 200 mPa/sec resulted in about 80% particles larger than 250 μm, whereas a viscosity of 50 mPa/sec using Carnauba wax as matrix yielded about 90% particles smaller than 250 μm (45)]. In addition, those parameters affecting the particle size of spray-dried products also determined the size and quality of spray-congealed formulations: temperature, nozzle type, spray pressure of a two-fluid nozzle, disk speed of a rotary nozzle, etc.

Rapid cooling and solidification of the melt after atomization of the droplets into a spray-congealing chamber can modify the solid state of the carrier and/or drug, altering their physical properties and possibly reducing the stability (42). Emas and Nyqvist (48) identified an unstable form of Carnauba wax after spray congealing, which aged toward a stabler form during storage. This phenomenon could be partly negated via an annealing procedure of the spray-congealed powder at elevated temperature. Similarly, the fast cooling of glyceryl tripalmitate initially yielded unstable α-crystals after spray congealing, which completely transformed to the stabler and denser β form within three days (43).

Although the size (15 to 75 μm) and morphology (spherical, flakes, needles) of the material suspended in a molten pluronic carrier had no influence on the size of the spray-congealed particles (49), nonhomogeneous drug distribution in function of the size of the microparticles has been reported while spray-congealing dispersions due to sedimentation of the drug in the molten carrier before spraying (45,50). Addition of colloidal silicium dioxide as thickening agent in the lipid matrices prevented this (45,50). However, the higher viscosity of the atomized fluid increased the size of the resulting solid lipid microparticles (45).

From a processing point of view, the dimensions of the cooling chamber must be sufficient to ensure a high process yield, hence a large spray-congealing tower may be required when a high production capacity or large particles are required. In addition, the nozzle type used for atomization also determines the dimensions of the cooling chamber depending on the trajectory of the particles: a rotary nozzle requires a wider chamber, whereas a two-fluid nozzle can be combined with a higher but narrower chamber to optimize process yield.

MELT EXTRUSION

Hot-melt extrusion can also be considered a melt granulation technique since a powder formulation is transformed into an agglomerate using a thermoplastic binder. This process uses a single- or twin-screw extruder to transport a powder formulation through a heated extrusion barrel and as the thermoplastic binder melts or softens during this transfer phase the formulation can be pumped through the die to obtain a dense end product having acquired a uniform shape depending on the dimensions of the die. This melt granulation technique is a versatile method to prepare (monolithic and multiparticulate) pharmaceutical drug delivery systems as one can manufacture granules, pellets, tablets, and films for oral, parenteral, transdermal, and transmucosal drug delivery. Via this continuous processing method, solid dispersions of poorly water soluble drugs (to improve their bioavailability) or matrix formulation with sustained drug release can be manufactured. Although hot-melt extrusion is often run at higher temperatures compared with the above-mentioned melt granulation procedures, the risk of thermal degradation of the ingredients is minimized because of the short residence time within the extruder. This process even allows to manufacture dosage forms offering enteric protection of the active pharmaceutical ingredient (51) or complex drug delivery systems via coextrusion to improve patient compliance of polypharmacy patients, to separate incompatible drugs or for line-extension purposes.

However, a detailed overview of this application of melt granulation is outside the scope of this chapter and the readers are referred to the reviews of Repka et al. (52,53) and Crowley et al. (54) for further information on the different pharmaceutical applications of hot-melt extrusion.

REFERENCES

1. Yang D, Kulkarni R, Behme RJ, et al. Effect of the melt granulation technique on the dissolution characteristics of griseofulvin. Int J Pharm 2007; 329:72–80.
2. Newa M, Bhandari KH, Li DX, et al. Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188. Int J Pharm 2007; 343:228–237.
3. Zhang YE, Schwartz JB. Melt granulation and heat treatment for wax matrix-controlled drug release. Drug Dev Ind Pharm 2003; 29:131–138.
4. Grassi M, Voinovich D, Moneghini M, et al. Preparation and evaluation of a melt pelletised paracetamol/stearic acid sustained release delivery system. J Control Release 2003; 88:381–391.
5. Dhumal R, Shimpi SI, Chauhan B, et al. Evaluation of a drug with wax-like properties as a melt binder. Acta Pharma 2006; 56:451–456.
6. Crowley KJ, Forbes RT, York P, et al. Drug-fatty acid salt with wax-like properties employed as binder in melt granulation. Int J Pharm 2000; 211:9–17.
7. Schaefer T, Mathiesen C. Melt pelletization in a high shear mixer. 9. Effects of binder particle size. Int J Pharm 1996; 139:139–148.
8. Schaefer T, Holm P, Kristensen HG. Melt granulation in a laboratory scale high shear mixer. Drug Dev Ind Pharm 1990; 16:1249–1277.
9. Schaefer T, Mathiesen C. Melt pelletization in a high shear mixer. 8. Effects of binder viscosity. Int J Pharm 1996; 139:125–138.
10. Schaefer T, Mathiesen C. Melt pelletization in a high shear mixer. 7. Effects of product temperature. Int J Pharm 1996; 134:105–117.
11. Eliasen H, Schaefer T, Kristensen HG. Effects of binder rheology on melt agglomeration in a high shear mixer. Int J Pharm 1998; 176:73–83.
12. Eliasen H, Kristensen HG, Schaefer T. Growth mechanisms in melt agglomeration with a low viscosity binder. Int J Pharm 1999; 186:149–159.
13. Johansen A, Schaefer T. Effects of physical properties of powder particles on binder liquid requirement and agglomerate growth mechanisms in a high shear mixer. Eur J Pharm Sci 2001; 14:135–147.
14. Voinovich D, Campisi B, Moneghini M, et al. Screening of high shear mixer melt granulation process variables using an asymmetrical factorial design. Int J Pharm 1999; 190:73–81.
15. Schaefer T. Growth mechanisms in melt agglomeration in high shear mixers. Powder Technol 2001; 117:68–82.
16. Scott AC, Hounslow MJ, Instone T. Direct evidence of heterogeneity during high-shear granulation. Powder Technol 2000; 113:205–213.
17. Jorgensen AC, Torstenson AS. Humid storage conditions increase the dissolution rate of diazepam from solid dispersions prepared by melt agglomeration. Pharm Dev Technol 2008; 13:187–195.
18. Tan HS, Salman AD, Hounslow MJ. Kinetics of fluidised bed melt granulation. I. The effect of process variables. Chem Eng Sci 2006; 61:1585–1601.
19. Abberger T, Seo A, Schaefer T. The effect of droplet size and powder particle size on the mechanisms of nucleation and growth in fluid bed melt agglomeration. Int J Pharm 2002; 249:185–197.
20. Seo A, Holm P, Schaefer T. Effects of droplet size and type of binder on the agglomerate growth mechanisms by melt agglomeration in a fluidised bed. Eur J Pharm Sci 2002; 16:95–105.
21. Walker GM, Holland CR, Ahmad MMN, et al. Influence of process parameters on fluidised hot-melt granulation and tablet pressing of pharmaceutical powders. In: 2nd International Workshop on Granulation. Sheffield: Pergamon-Elsevier Science Ltd., 2004:3867–3877.
22. Iveson SM, Litster JD. Growth regime map for liquid-bound granules. Aiche J 1998; 44:1510–1518.
23. Walker GM, Bell SEJ, Greene K, et al. Characterisation of fluidised bed granulation processes using in-situ Raman spectroscopy. Chem Eng Sci 2009; 64:91–98.
24. Walker G, Bell S, Vann M, et al. Pharmaceutically engineering powders using FHMG – the effects of process parameters and formulation variables. Chem Eng Res Des 2007; 85:981–986.
25. Walker GM, Andrews G, Jones D. Effect of process parameters on the melt granulation of pharmaceutical powders. Powder Technol 2006; 165:161–166.
26. Kidokoro M, Sasaki K, Haramiishi Y, et al. Effect of crystallization behavior of polyethylene glycol 6000 on the properties of granules prepared by fluidized hot-melt granulation (FHMG). Chem Pharm Bull 2003; 51:487–493.

27. Borini GB, Andrade TC, Freitas LAP. Hot melt granulation of coarse pharmaceutical powders in a spouted bed. Powder Tech 2009; 189:520–527.
28. Kleinebudde PKK. Direct pelletization of pharmaceutical pellets in fluid-bed processes. Elsevier, 2007.
29. Vilhelmsen T, Kristensen J, Schaefer T. Melt pelletization with polyethylene glycol in a rotary processor. Int J Pharm 2004; 275:141–153.
30. Vilhelmsen T, Schaefer T. Agglomerate formation and growth mechanisms during melt agglomeration in a rotary processor. Int J Pharm 2005; 304:152–164.
31. Voinovich D, Moneghini M, Perissutti B, et al. Preparation in high-shear mixer of sustained-release pellets by melt pelletisation. Int J Pharm 2000; 203:235–244.
32. Heng PWS, Wong TW, Chan LW. Influence of production variables on the sphericity of melt pellets. Chem Pharm Bull 2000; 48:420–424.
33. Thies R, Kleinebudde P. Melt pelletisation of a hygroscopic drug in a high shear mixer Part 1. Influence of process variables. Int J Pharm 1999; 188:131–143.
34. Thies R, Kleinebudde P. Melt pelletization of a hygroscopic drug in a high shear mixer. Part 3. Effects of binder variation. Chem Pharm Bull 2001; 49:140–146.
35. Heng PWS, Wong TW, Shu JJ, et al. A new method for the control of size of pellets in the melt pelletization process with a high shear mixer. Chem Pharm Bull 1999; 47:633–638.
36. Maejima T, Kubo M, Osawa T, et al. Application of tumbling melt granulation (TMG) method to prepare controlled-release fine granules. Chem Pharm Bull 1998; 46:534–536.
37. Maejima T, Osawa T, Nakajima K, et al. Preparation of spherical beads without any use of solvents by a novel tumbling melt granulation (TMG) method. Chem Pharm Bull 1997; 45:518–524.
38. Murakami H, Yoneyama T, Nakajima K, et al. Correlation between loose density and compactibility of granules prepared by various granulation methods. Int J Pharm 2001; 216:159–164.
39. Van Melkebeke B, Vermeulen B, Vervaet C, et al. Melt granulation using a twin-screw extruder: a case study. Int J Pharm 2006; 326:89–93.
40. Passerini N, Albertini B, Perissutti B, et al. Evaluation of melt granulation and ultrasonic spray congealing as techniques to enhance the dissolution of praziquantel. Int J Pharm 2006; 318:92–102.
41. Guo QY, Chan LW, Heng PWS. Investigation of the release of aspirin from spray-congealed micropellets. J Microencapsul 2005; 22:245–251.
42. Li LC, Zhu LH, Song JF, et al. Effect of solid state transition on the physical stability of suspensions containing bupivacaine lipid microparticles. Pharm Dev Technol 2005; 10:309–318.
43. Maschke A, Becker C, Eyrich D, et al. Development of a spray congealing process for the preparation of insulin-loaded lipid microparticles and characterization thereof. Eur J Pharm Biopharm 2007; 65:175–187.
44. Cavallari C, Rodriguez L, Albertini B, et al. Thermal and fractal analysis microparticles obtained by of diclofenac/Gelucire 50/13 ultrasound-assisted atomization. J Pharm Sci 2005; 94:1124–1134.
45. Albertini B, Passerini N, Pattarino F, et al. New spray congealing atomizer for the microencapsulation of highly concentrated solid and liquid substances. Eur J Pharm Biopharm 2008; 69:348–357.
46. Cavallari C, Luppi B, Di Pietra AM, et al. Enhanced release of indomethacin from PVP/stearic acid microcapsules prepared coupling co-freeze-drying and ultrasound assisted spray-congealing process. Pharm Res 2007; 24:521–529.
47. Qi S, Deutsch D, Craig DQM. An investigation into the interaction between taste masking fatty acid microspheres and alkaline buffer using thermal and spectroscopic analysis. J Pharm Sci 2006; 95:1022–1028.
48. Emas M, Nyqvist H. Methods of studying aging and stabilization of spray-congealed solid dispersions with carnauba wax. 1. Microcalorimetric investigation. Int J Pharm 2000; 197:117–127.
49. Mackaplow MB, Zarraga IE, Morris JF. Rotary spray congealing of a suspension: effect of disk speed and dispersed particle properties. J Microencapsul 2006; 23:793–809.
50. Albertini B, Passerini N, Gonzalez-Rodriguez ML, et al. Effect of Aerosil (R) on the properties of lipid controlled release microparticles. J Control Release 2004; 100:233–246.
51. Andrews GP, Jones DS, Abu Diak O, et al. The manufacture and characterisation of hot-melt extruded enteric tablets. Eur J Pharm Biopharm 2008; 69:264–273.
52. Repka MA, Battu SK, Upadhye SB, et al. Pharmaceutical applications of hot-melt extrusion: part II. Drug Dev Ind Pharm 2007; 33:1043–1057.
53. Repka MA, Majumdar S, Battu SK, et al. Applications of hot-melt extrusion for drug delivery. Expert Opin Drug Deliv 2008; 5:1357–1376.
54. Crowley MM, Zhang F, Repka MA, et al. Pharmaceutical applications of hot-melt extrusion. Part I. Drug Dev Ind Pharm 2007; 33:909–926.

21 Sizing of Granulation

Gurvinder Singh Rekhi and Richard Sidwell
Elan Drug Technologies, Gainesville, Georgia, U.S.A.

INTRODUCTION

Tablets are the most frequently administered solid oral dosage forms in contemporary practice. Tablets consist of a mixture of powders or granules that are compacted in the die of a tablet press. Even though the popularity of directly compressible materials has increased, many powders are granulated to overcome the difficulties in obtaining an acceptable tablet dosage form and meeting the product specifications. The most challenging task in a tableting process is to achieve a constant volume of homogenous mixture to flow into the tablet die cavity. Unfortunately, most powder materials do not have inherently good flow properties. This, in turn, demands changing the physical characteristics of the powder or improving the design of the tablet press (1). Therefore, granulation becomes an integral part of a pharmaceutical process that attempts to improve powder-flow characteristics.

The granule properties play a pivotal role in the final performance of a tablet; for example, granule size can affect the flowability, and hence, the average tablet weight and weight variation, and drying rate kinetics of wet granulations. The effect of granule size and size distribution on final blend properties and tablet characteristics is dependent upon formulation ingredients and their concentration as well as the type of granulating equipment and processing conditions employed. Therefore, granulation and sizing of granulation become critical unit operations in the manufacture of oral dosage forms (2,3). To some extent, the same requirements are necessary for capsule manufacture, especially when the drug is bulky or has poor flow properties, or in high-speed capsule-filling machines, where limited compaction occurs.

Few materials used in the manufacture of pharmaceutical dosage forms exist in the optimum size, and most materials must be reduced in size at some stage during production. The advantages of sizing of granules in tablet formulation development are as follows:

1. Mixing and blending of pharmaceutical ingredients are easier and more uniform if the ingredients are of approximately the same size and distribution.
2. Improving color or active ingredient dispersion. Milling may reduce the tendency for mottling, and hence improve the uniformity of color from batch to batch.
3. Wet milling produces uniformly sized wet granules, which promotes uniform and efficient drying.
4. Improving uniformity of dosage units by virtue of uniformity of particle-size distribution and reduction in the segregation of the mix.
5. Enhancing flow properties reduces the weight variation and improves content uniformity.
6. Increasing surface area because of particle-size reduction may enhance the dissolution rate, and thereby, the drug's bioavailability.
7. Reducing dust reduces workers' exposure.

Size reduction alone is not a panacea for all tableting problems. There are some disadvantages to size reduction that may affect the final characteristics of a dosage form, such as degradation of the drug or a change in the polymorphic form as a result of the excessive heat generated, or increase in surface energies leading to agglomeration. Hence, in optimizing the manufacture of pharmaceutical dosage forms, it is important not only to characterize the formulation ingredients, but also to study their effect on the manufacturing process (i.e., whether a granulation should be milled and to what extent based on the final product specifications).

The objective of this discussion is to focus on sizing of granulation after drying in a wet granulation process. However, a process of wet milling for obtaining uniformly sized granules

for uniform drying will also be addressed. A full discussion of the theories of comminution or equipment description is beyond the scope of this chapter. However, the text of this chapter will address the various types of equipment used in the size-reduction process, their merits and demerits, and variables affecting the size-reduction process, scale-up factors, and relevant case studies to be considered in the development and optimization of tablet and capsule manufacture.

THEORY OF COMMINUTION OR SIZE REDUCTION

Comminution, or size reduction, is the mechanical process of reducing the size of particles or aggregates. There is, as yet, only a basic understanding of the mechanism and quantitative aspects of milling (4,5). Reduction of particle-size through fracture requires application of mechanical stress to the material to be crushed or ground. Materials respond to this stress by yielding, with consequent generation of strain. In the case of a brittle substance, complete rebound occurs on release of applied stress at stresses up to the yield point, at which fracture would occur. In contrast, plastic material would neither rebound nor fracture. The vast majority of pharmaceutical solids lie somewhere between these extremes and thus possess both elastic and viscous properties.

The energy expended by comminution ultimately appears as surface energy associated with newly created particle surfaces, internal free energy associated with lattice changes, and heat. For any particle, there is a minimum energy required that will fracture it; however, conditions are so haphazard that many particles receive impacts that are insufficient for fracture, and are eventually fractured by excessively forceful impact. As a result, most efficient mills use <1% to 2% of the energy input to fracture particles and to create new surfaces. The rest of the energy is dissipated in the form of heat from the plastic deformation of the particles that are not fractured, friction, and in imparting kinetic energy to the particles. The greater the rate at which the force is applied, the less effectively the energy is utilized and the higher is the proportion of fine material produced.

A flaw in a particle is any structural weakness that may develop into a crack under strain. The Griffith theory (4) of cracks and flaws assumes that all solids contain flaws and microscopic cracks, which increase as the applied force increases, according to the crack length and focus of the stress at the crack apex. A *granule* is an aggregation of particles that are held together by bonds of finite strength, and the ultimate strength of a wet granule depends on the surface tension of the granulating liquid and capillary forces. After drying, granules develop stronger bonds owing to fusion and recrystallization of particles and curing of adhesives or binding agent. The final strength of a granule depends on the base material, the type and the amount of granulating agent used, and the equipment employed.

A granule or particle may be subjected to one or more of the following four forces during milling:

1. Shear (cutting forces)
2. Compression (crushing force)
3. Impaction (direct, high-velocity collision force)
4. Tension (the force that works to elongate or pull a particle apart)

The mechanism by which sizing of dried granules occurs is similar to that of crystalline materials. Cleavage occurs at the weakest point or points in the granule and it could be at (2):

1. the binder-particle interface,
2. the bridge of binder between the individual ingredient particles being granulated,
3. flaws in the individual ingredient particles within the granules, or
4. a combination of any of these.

Granules held together with lower binding-strength agents such as povidone will require less severe grinding conditions because the fractures take place primarily at the binder bridge or the binder-particle interface.

The milling process can be described mathematically (6–8); however, its theory has not been developed to the point at which the actual performance of a mill can be predicted quantitatively. Three fundamental laws (Kick's Law, Rittinger's Law, and Bond's Law) have been proposed to relate size reduction to a single variable, the energy input to the mill. None of the energy laws apply well in practice (9). Generally, laboratory testing is required to evaluate the performance of a particular piece of equipment; however, a work index and grindability index have been used to evaluate mill performance (5). The efficiency of a milling process is influenced by the nature of the force, as well as by its magnitude. The rate of application of force affects comminution because there is a lag time between the attainment of maximum force and the fracture. Often, materials respond as a brittle material to fast impact and as a plastic material to a slow force.

PROPERTIES OF FEED MATERIALS AFFECTING THE SIZING PROCESS

The milling or sizing process is affected by a variety of factors and has a direct effect on the quality of the final product. The properties of feed material and the finished product specifications determine the choice of equipment to be used for the process of comminution. The properties of feed material include melting point, brittleness, hardness, and moisture content. The desired particle-size, shape, and size distribution must also be considered in the selection of milling equipment.

Materials can be classified as hard, intermediate, soft, or fibrous materials (e.g., glycyrrhiza and rauwolfia) based on Mohs scale. Fibrous materials require cutting or chopping action and usually cannot be reduced in size effectively by pressure or impact techniques. Before selecting and optimizing a size-reduction process, one needs to know the properties of the material and the characteristics of a mill. The important material properties (5,10) are as follows:

1. *Toughness*: Toughness is the material's resistance to the propagation of cracks. Reduction of the particle-size of tough material is difficult, but can sometimes be made easier by cooling the material, thereby diminishing its tendency to exhibit plastic flow and making it more brittle.
2. *Brittleness*: It is opposite of toughness. Size reduction poses no problems except if the amount of fines is to be controlled.
3. *Abrasiveness*: This is an important factor because abrasive materials can wear mill parts and screens; hence, metal contamination may be a problem.
4. *Cohesiveness/Adhesiveness*: Particles sticking together or to machine surfaces are often dependent on moisture content and particle-size. Problems with moisture content can be mitigated by drying the material or avoided by using a wet size-reduction process.
5. *Melting point*: This is critical because considerable heat is generated in size reduction. High temperatures generated can cause melting of the drug, blinding of the screen, or can degrade heat-sensitive materials.
6. *Agglomeration tendency*: This tendency can be counteracted by drying the material, either before or during size reduction. In some cases, mixing with other ingredients during milling might be helpful. Generally, materials having a strong tendency to agglomerate are wetted prior to milling.
7. *Moisture content*: Moisture content above 5% can often lead to agglomeration or even liquefaction of the milled material. Hydrates will often release their water of hydration under high temperatures and may require cooling or low-speed milling.
8. *Flammability and explosiveness*: This is the measure of how readily a material will ignite or explode. Explosive materials must be processed in an inert gas atmosphere.
9. *Toxicity*: This has little influence on the selection of the mill itself; however, it must be considered in determining operator safety, containment, and setup for this type of material.
10. *Reactivity*: The possibility of materials chemically reacting with the materials of construction of the mill (including liners and gaskets) and cleaning solutions must be considered.

CRITERIA FOR SELECTION OF A MILL

The selection of equipment is determined by the characteristics of the material, the initial particle-size, and the desired particle-size of the milled product, that is, coarse, medium, or fine.

The criteria for selection of a mill include the following (4):

1. *Properties of feed material*: Size, shape, moisture content, physical and chemical properties, temperature sensitivity, grindability, and material compatibility.
2. *Product specifications*: Size, particle-size distribution, and shape.
3. *Versatility of operation*: Wet and dry milling, rapid change of speed and screen, and safety features.
4. *Scale-up*: Capacity of the mill and production-rate requirements.
5. *Repeatability*: Ability to meter material to the mill to ensure consistent process.
6. *Product containment*: Loss of costly drugs, health hazards, and contamination.
7. *Sanitation*: Ease of cleaning (clean in place, CIP) and sterilization (sterilization in place, SIP).
8. *Auxiliary equipment*: Cooling system, dust collectors, force feeding, and stage reduction.
9. *Batch or continuous operation.*
10. *Safety*: Electrical classification and inerting (National Electrical Code NFPA 70, or ATEX Directive 94/9/EC).
11. *Economic factors*: Equipment cost, power consumption, space occupied, and labor cost.

After consideration of the foregoing factors for a specific milling problem, it is suggested that a variety of mills should be evaluated for optimum product results such as shape of granules and/or scalability from laboratory to production. In addition to the standard adjustments of the milling process (e.g., screen, speed, rotor design, and feed rate), other techniques of milling may be considered for special materials. Hygroscopic materials can be milled in a closed system supplied with dehumidified air. As the bulk of the energy used in milling is converted into heat, heat-sensitive materials or hard materials that build up in the milling chamber may melt, decompose, or explode. A two- or multistep milling process can be used for harder and difficult-to-grind materials. Materials can be milled using a coarser screen, and the material can then be recycled by screening the discharge and returning the oversized material for a second milling (closed-circuit mill). Alternatively, one may chill the air or gas (carbon dioxide or nitrogen) that transports the product, cool the product prior to processing, or cool the comminuting chamber through which the product passes. A chiller is necessary for all of these options and will add to the cost of processing (11). If this not sufficient to embrittle the material, it may be fed to the mill simultaneously with dry ice. For flammable/explosible dusts, the equipment may be required to meet safety standards such as NEC/NFPA 70 (United States) or ATEX Directive 94/9/EC (Europe) and/or be inerted with nitrogen gas.

CLASSIFICATION OF MILLS

The majority of size-reduction equipment may be classified according to the way in which forces are applied, namely, impact, shear, attrition, and shear compression (Table 1). A given mill may operate successfully in more than one class: a hammer mill may be used to prepare a 16-mesh granulation and to mill a crystalline material to a 120-mesh powder.

The mills used for size reduction of the granules can be divided into two primary categories on the basis of the energy input into the process. Even though there are several high-energy mills available for size reduction, only a few are used in the pharmaceutical industry for the wet or dry sizing process. Milling is an extremely inefficient unit operation with only 1% to 2% of the applied energy being utilized in the actual size reduction. Milling efficiency is dependent on the characteristics of the material used and type of mill employed.

Table 1 General Characteristics of Various Types of Mills

Mechanism of action	Example	Product size	Type of material	Not Used for
Impact	Hammer mill	Moderate to fine	Brittle and dry material	Fibrous, sticky, low-melting substances
Shear	Extruder and hand screen	Coarse	Deagglomeration, wet granulation	Dry material, hard, abrasive materials
Attrition	Oscillating granulator	Coarse to moderate	Dried granulation	Wet granulation, abrasive materials
Shear-compression	Conical-screening mill	Moderate to coarse	Wet, dry granulation	Abrasive materials

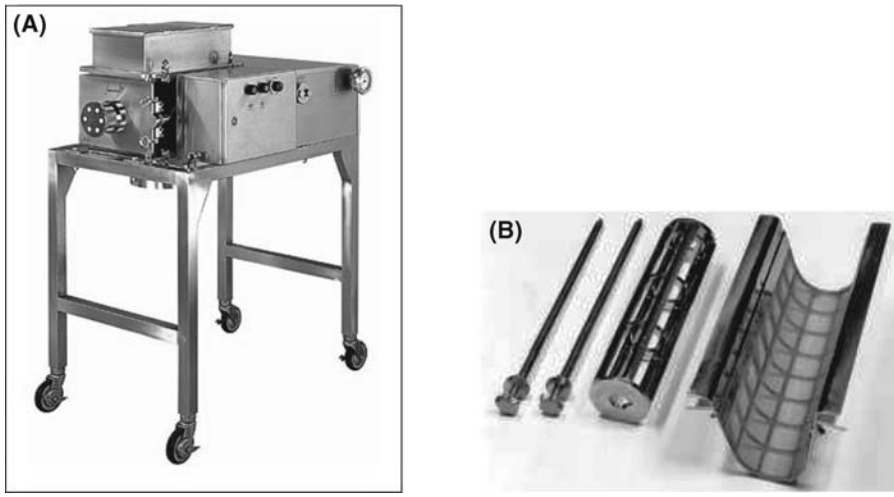


Figure 1 Oscillating granulator: (**A**) Frewitt MF Line and (**B**) rotor, screen, and tensioning spindles.

Low-Energy Mills

Hand Screen

- Size reduction occurs primarily by shear.
- They are made of brass or stainless steel and consist of a woven wire cloth stretched in a circular or rectangular frame.
- They are available in sizes ranging from 4 to 325 mesh; however, for granulation, typically mesh sizes from 4 to 20 are used.
- They are most widely used for sieve analysis or for size reduction of wet and dry granules in the early stages of formulation development.

Oscillating/Rotary Granulator

- They consist of an oscillating bar contacting a woven wire screen, and the material is forced through the screen by the oscillating-rotary motion of the bar (Fig. 1A, B).
- Size reduction is primarily by shear with some attrition.
- Speed, rotary or oscillatory motion, and screen size are important variables to be considered during the sizing process.
- They are used primarily for size reduction of wet and dry granulations, and, to some extent, for milling tablets and compacts that must be reprocessed.
- The narrow size distribution and minimum amount of fines are advantages during the size reduction of dry granulation (2).
- Heat-sensitive and waxy materials can be milled owing to the low heat generated during the sizing process.

- Low throughput rates and possible metal contamination from wearing down or broken screen are some of its limitations.
- Examples include the Frewitt MF line and Fitzmill with bar rotor.

Extruder

- It is primarily used for continuous wet granulation.
- Wet material is forced through a screen and the extruded material is dried in a tray or fluid-bed dryer or can be spheronized to produce granules with a high degree of sphericity and then dried for controlled-release applications.
- Less dust generation and more uniform granules are some of the advantages.
- More information on extrusion may be found in chapter 12.

High-Energy Mills

Hammer Mill

The hammer mill is one of the most versatile and widely used mills in the pharmaceutical industry. The principle of size reduction in the hammer mill is one of high-velocity impacts between rapidly moving hammers mounted on a rotor and the powder particles (Fig. 2A, B).

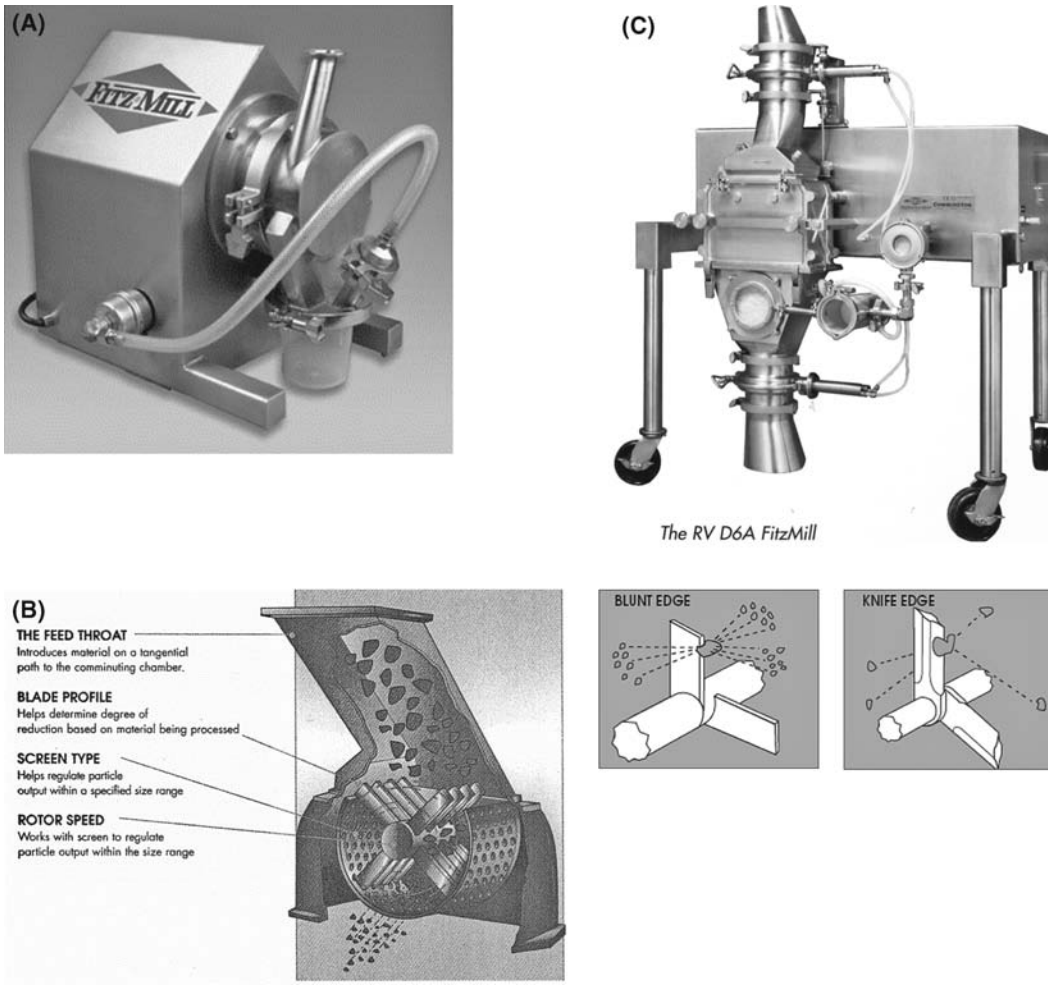


Figure 2 Hammer mill: (**A**) Fitzmill model L1A; (**B**) principle of operation, and (**C**) containment model with nitrogen inerting capability. *Source*: Courtesy of The Fitzpatrick Company.

These mills can produce a wide range of particle-sizes, even down to micrometer size. The particle shape, however, is generally sharper and more irregular than produced by compression methods (5). The force imparted by the hammers and the screen opening size and shape control the degree of particle-size reduction.

- They can be used for size reduction of wet or dry granulations and milling of raw materials.
- There is a wide range of interchangeable feed throats and variable feed-screw systems available to optimize the feed rate (12).
- Hammers can rotate horizontally or vertically, based on the rotor configuration, and at variable speeds.
- Hammers can be fixed or free-swinging.
- Hammers with blunt or impact edges are preferred for pulverizing, and knife or sharp edges are preferred for chopping or sizing of granules (12).
- Screen openings generally vary from 0.3 to 38 mm with round or square perforations, diagonal or straight slots, or with a rasping surface.
- Feed rate and dryness of the granules are important variables relative to the material.
- Type of hammers, rotor speed, screen type, thickness, and opening size are important variables relative to the machine.
- Ease of setup, clean-up, minimum scale-up problems, and ability to handle a wide variety of size and type of feedstock are some advantages.
- Heat build-up, screen wear, and potential clogging of screens are some of the limitations.
- Integrated designs are available for dust containment.
- Examples include the Granumill and Fitzmill.

Conical-Screening Mill

Conical-screening mills are effective for dry (deagglomeration/delumping) and wet milling of soft to medium-hard materials. The comminution chamber consists of an impeller rotating at variable speed imparting a compression or shear force inside a conical screen. The impeller imparts a vortex flow pattern to the feed material, and the centrifugal acceleration forces the particles to the screen surface and up the cone (360°) in a spiraling path (13) (Fig. 3A, B). The dual action of conical-screening mills (size reduction and mixing) makes this equipment more desirable than the use of traditional oscillators (14,15).

- The space between the impeller and the screen can be adjusted.
- The size and shape of the screen holes, screen thickness, impeller configuration, and mill speed are important variables.

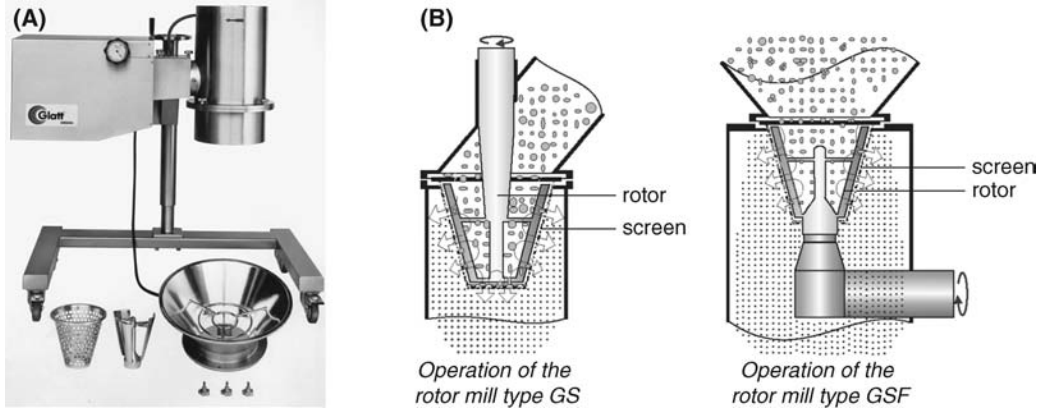


Figure 3 Conical-screening mill: (**A**) Glatt model GSF 180 and (**B**) principle of operation. *Source*: Courtesy of Glatt Air Techniques.

Figure 4 An integrated pharmaceutical manufacturing facility (high-shear granulator–conical-screening mill–fluid-bed drier). *Source*: Courtesy of Niro Inc.

- Used for difficult-to-mill, heat-sensitive material and hard granules.
- Low heat and lower amounts of fines are produced compared with the hammer mill; hence, it produces a narrow particle-size distribution.
- The impeller does not touch the screen; hence, chances of screen breakage and metal contamination are greatly reduced compared with an oscillating granulator.
- Integrated designs available that are attached to a high-shear granulator discharge, which provides a deagglomerated, lump-free product for the dryer (Fig. 4).
- Examples include the Comil, Glatt sieve GS or GSF, and FitzSiv.

Centrifugal-Impact Mills

Centrifugal-impact mills and sieves are useful to minimize the production of fine particles, because their design combines sieving and milling into a single operation. Unlike the conical-screening mills, these consist of a nonrotating bar or stator that is fixed within a rotating sieve basket. This action produces a very low product agitation and impact; hence, no heat is generated. The particles that are smaller than the holes of the sieve can pass through the mill without comminution; however, the larger particles are directed by centrifugal force to impact the stator. Older designs are not preferred because the likelihood of sieve-to-stator contact can result in metal particulates in the product.

The Frewitt SG line (Fig. 5) is an example of this type. Newer designs eliminate metal-to-metal contact and may include an integrated classifier to ensure the desired particle-size distribution for the product (Fitz CM).

WET MILLING

The discussion thus far has been focused on dry milling. These mills can also be used for wet milling or coarse milling. There are several reasons for wet milling; these include the following (16):

1. To increase surface area for more efficient drying
2. To improve size uniformity
3. To improve granule formation
4. To prevent large particles that will shatter to "fines" on dry milling
5. For further mixing or blending of ingredients

Figure 5 Centrifugal-impact mill: Frewitt SG Line. *Source*: Courtesy of Frewitt Ltd.

As discussed in Low-Energy Mills, extruders can be used as a continuous wet granulation method. Wet milling is necessary with low-shear mixers, such as planetary, ribbon, or sigma mixers, but with high-shear mixers, the combination of high impeller speed and built-in choppers produces a product ready for drying. Also, integrated designs are available such that the wet-milling step is no longer a separate operation.

Finally, there are continuous granulators available (M6 NICA granulator) for product applications that do not require extensive kneading treatment and can be used for both batch and continuous operation. The wetted product is discharged in continuous stream through an adjustable opening in the turbine cover. A homogeneous mix is produced in a few minutes and further milling may not be necessary.

VARIABLES AFFECTING THE SIZING PROCESS

Process Variables

As discussed in the Introduction, the granule properties can dictate the properties of the final tablet. Some of the problems faced during the tableting process are flow of granules, maintaining uniform density in the granule bed, and the particle-size distribution. Each of the stages of the granulation can be critical and can affect tableting. In addition to the wet granulation process, the sizing process can be critical for the particle-size distribution that, along with amount of fines, dictates the flow properties. These, in turn, influence the packing and density of the granules. Reproducibility of batches depends not only on the properties of the unmilled dry granules, but also on the mill and milling parameters. Finally, the dry-milling stage is important because of the heat generated that might affect the stability of the final product.

The characteristics of the granules after size reduction depend mainly on the type of mill, impeller type and speed, screen size, and thickness.

Type of Mill

The type of mill chosen can affect the shape of the granules and throughput. The shape of the milled granules can affect the flow properties. An impact mill produces sharp, irregular particles that may not flow readily, whereas an attrition mill produces free-flowing spheroidal particles. An oscillating granulator uses shear and attrition as the main mechanisms for size reduction. The granules produced are more spheroidal because size reduction takes place by

surface erosion. If the same material is subjected to impact by hammers in a hammer mill, the granules will shatter resulting in irregularly shaped particles. If a conical-screening mill is used for the same material for size reduction, it imparts some shear and compression between the rotating impeller and the screen, which may result in a narrower particle-size distribution than other types of mills.

Hammer Mill

There are a number of variables in a hammer mill that can influence comminution (12,17–19). The following section discusses five operating variables in detail:

1. *Rotor shaft configuration*: The hammers may be mounted on a vertical or horizontal shaft (Fig. 6A, B). The vertical shaft mills (Stokes-Tornado mill) have feed inlets at the top and material is fed perpendicular to the swing of the hammers. In the case of horizontal shaft mills (Fitzpatrick-Fitzmill), the material is fed tangentially to the hammer swing. Rotor configuration can influence the particle-size distribution of the granules. In the vertical configuration, the screen is placed 360° around the hammers, and this provides more screen open area and less time for the granules to stay in the milling chamber when compared with the horizontal shaft mills.
2. *Material feed rate*: The feed rate controls the amount of the feed material that enters the comminutor and prevents overfeeding (slugging) or underfeeding (starving) the milling chamber. Although both affect the particle-size distribution, overfeeding is relatively more detrimental. If the rate of feed is relatively slow, the product is discharged readily, and the amount of undersize material, or fines, is minimized. On the other hand, overfed material stays in the milling chamber for a longer time, because its discharge is impeded by the mass of material. This leads to a greater reduction of particle-size, overloads the motor, and the capacity of the mill is reduced. The rule of thumb is to keep the feed rate equal to the rate of discharge. The feed rate can be controlled using variable-feed screws, vibratory feeders, or dischargers controlled by gravity. In addition to controlling the flow, the feed throat must allow the material to enter at a proper angle. There are more than 50 feed-throat designs available that one needs to consider for optimizing the milling process. Most mills used in pharmaceutical operations are designed so that the force of gravity is sufficient to give free discharge, generally from the bottom of the mill.

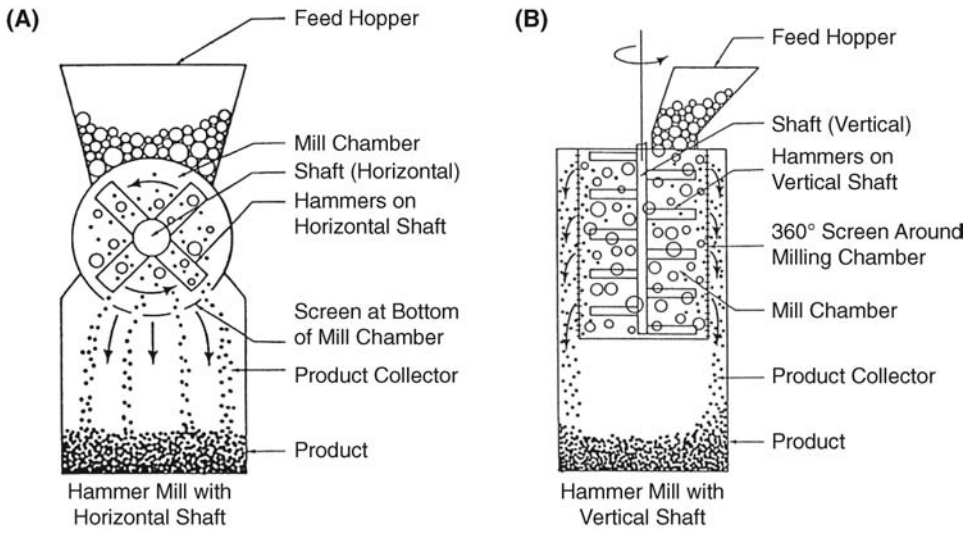


Figure 6 (**A**, **B**) Different types of hammer mills. *Source*: Courtesy of The Fitzpatrick Company.

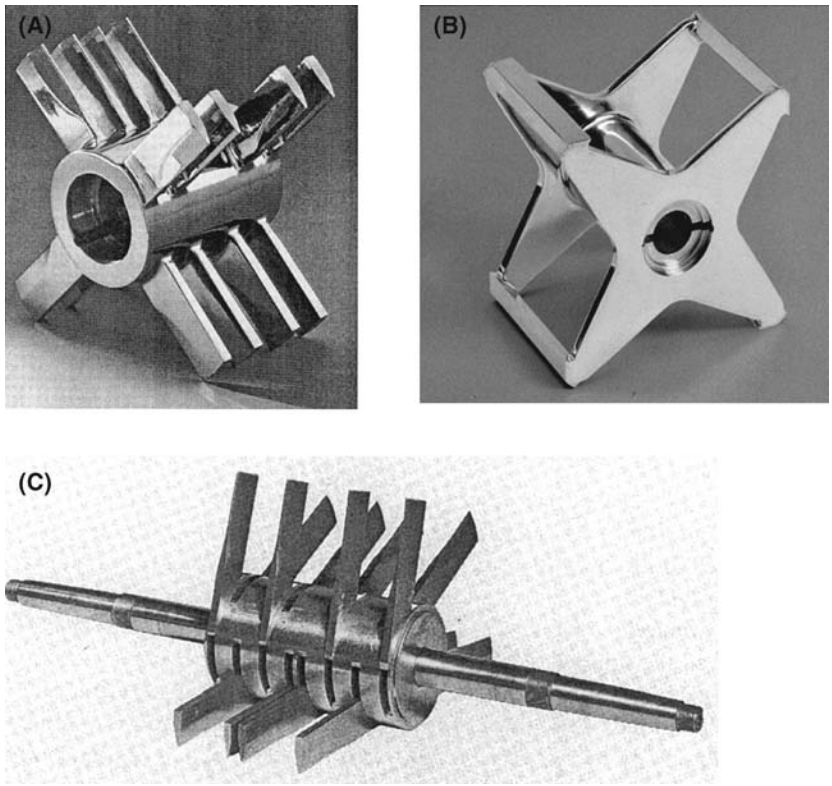


Figure 7 Different types of hammer-mill rotors (Fitzmill): (**A**) cast rotor, (**B**) bar rotor, and (**C**) swing-blade rotor. *Source*: Courtesy of The Fitzpatrick Company.

3. *Blade type*: Comminution is effected by impact of the material with the fast-moving blades and attrition with the screen. Generally, the blades of a hammer mill have a blunt or flat edge on one side and a sharp or knife-edge on the other side. The desired particle-size range determines which blades to use. Many models of hammer mills have a rotor that may be turned 180°, so that the blunt edges can be used for fine grinding or the knife-edge can be used for cutting or granulating. The blunt edge offers impact during milling, generating smaller granules. The knife-edge, because the sharper edge causes cutting of the granules, thereby generates larger granules. Individual blades (blunt, sharp, or reversible) are installed either fixed or swinging (Fig. 7A–C). Fixed blades plough through the material being ground, while swinging blades lie back and depend on the centrifugal force for movement. Fixed blades are preferred over swinging blades because they are easier to clean and work better than swinging blades at low rotor speeds, when grinding fibrous material, or if carefully controlled grinding is needed.

   The material to be ground determines the configuration of the blades on the motor shaft, as well as the blade density. The shape of the blades (straight, stepped, sickle, or other) is largely a matter of designer preference; little empirical evidence exists to establish the superiority of one shape over another. The size of the grinding chamber generally determines the number of blades (e.g., a 6-in. grinding chamber will have 16 blades).
4. *Rotor speed*: The size of a product is markedly affected by the speed of the hammers. As a general rule, and with all other variables remaining constant, the faster the rotor's speed, the finer the grind. Usually, three speed settings are available: slow (1000 rpm), medium (2500 rpm), and fast (4000 rpm). Changes in rotor speed are

accomplished by variable-speed drive or by manually changing the hammer-drive and motor-pulley ratio. Rotor speeds of 2500 to 4000 rpm are typically used with blunt edges in fine grinding applications, whereas speeds of 1000 to 2500 rpm are typically used with knife-edges for coarse grinding. Particle-size distributions are wider at low speed than at medium and high speeds (12). Below the critical rotor speed, material experiences attrition, rather than impact action, which causes more spheroidal granules and may result in overheating of the material.

5. *Screen size and type*: The screen is usually an integral part of the hammer mill and does not act as a sieve. The particle-size of the product depends on the openings in the screen, the thickness of the screen, and the speed of the hammer. The particle-size of the output granules will be much smaller than the size of the screen used, because particles exit at an angle, with high velocity. Screens can be perforated, woven wire type, or with a slot configuration. The screen openings may range in size and open area based on screen configuration. Because of the large forces that the screens are

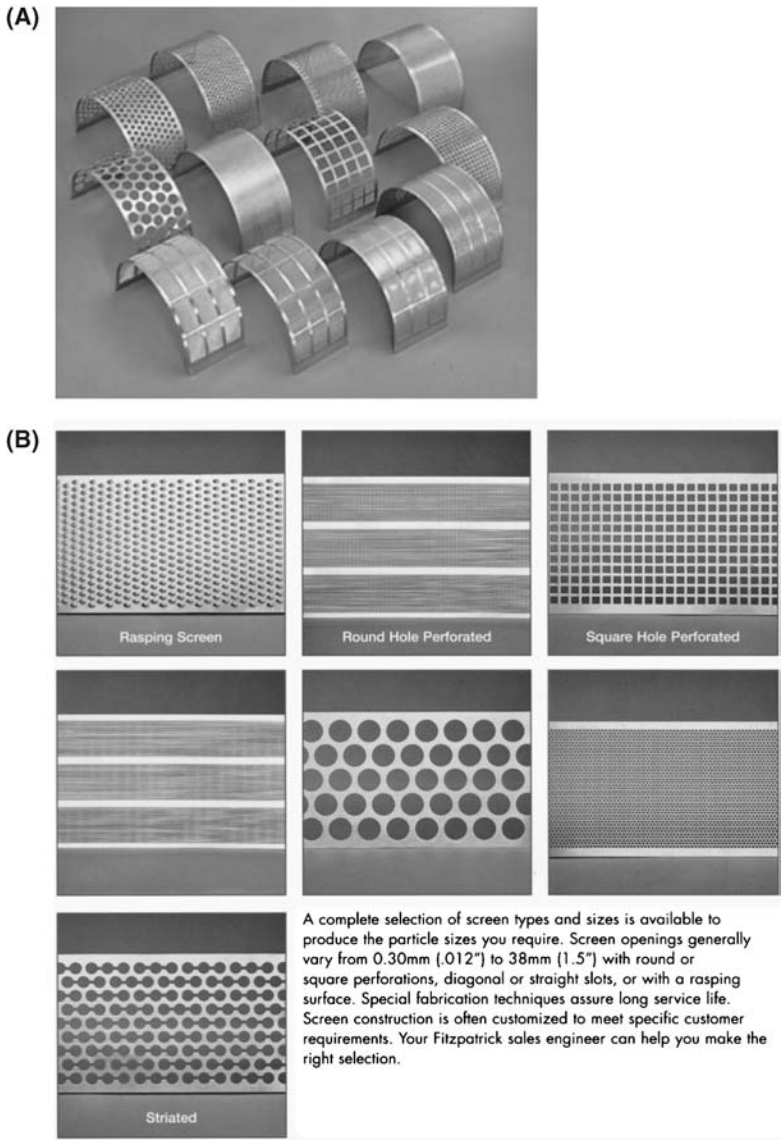


Figure 8 (**A**, **B**) Different types of hammer mill screens. *Source*: Courtesy of The Fitzpatrick Company.

subjected to, the perforated screens are preferred over the woven-type screens. However, if the raw material fuses from the heat generated, or if the material is difficult to mill, woven-type screens are preferred for their increased open area. The herringbone and cross-slot designs are preferred for grinding amorphous and crystalline materials (Fig. 8A, B).

Conical-Screening Mill

Similarly, for conical-screening mills, the operating variables affecting particle-size distribution are type of impeller, impeller speed, and screen size and type:

1. *Material feed rate*: In contrast to hammer mills, conical-screening mills perform with greater efficiency when the comminution chamber is kept relatively full. Underfeeding results in low efficiency and reduced throughput.
2. *Impeller*: There are several types of impellers available (13); however, the four main types used frequently are as follows (Fig. 9A):

   Knife-edge: Its principle mode of operation is shear, and hence, it is used for compression-sensitive, heat-sensitive materials.

   Round-edge: Its principle mode of operation is compression, and it provides high throughput and low retention. It is mainly used for wet or dry deagglomeration/delumping.

   Round-edge with teeth: It is the same as the round-edge impeller except that it has teeth on one side, providing aggressive, high throughput. It reduces fines in milling compacted materials by pre-breaking with teeth and reducing retention time. It is often used for tablet rework.

   Knife-edge low-intensity impeller: It is used where a shear or cut is required; it gives a scissor-like action, for fibrous materials or capsule rework.
3. *Speed*: The speed of the impeller can affect the particle-size of the product. Conical-screening mills available have variable or fixed-speed drives; however, revolutions per minute vary depending on the size of the impeller. It is suggested that one keep the tip speed of the impeller the same on scale-up to achieve the same particle-size distribution.

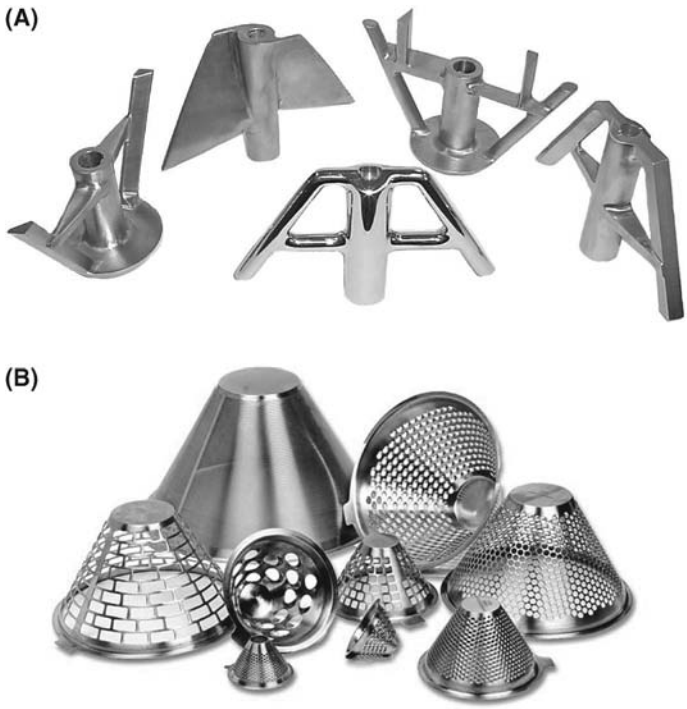


Figure 9 Conical-screening mill (Comil): (**A**) impellers; (**B**) screens. *Source*: Courtesy of Quadro Engineering Corp.

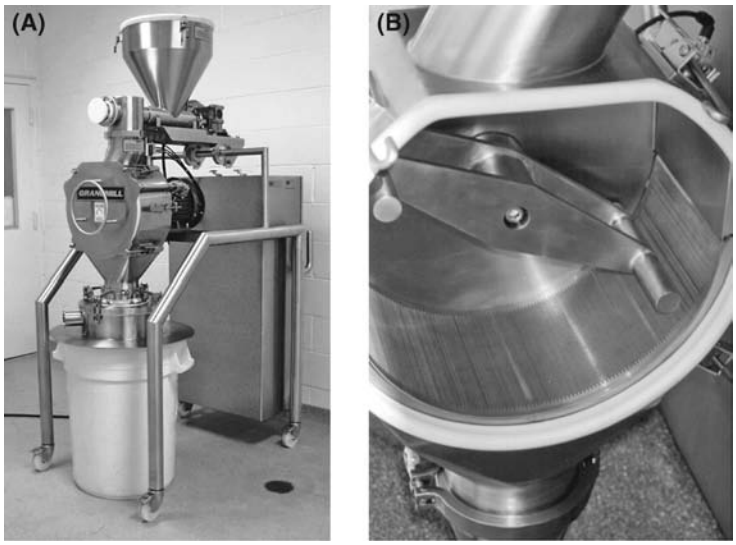


Figure 10 Hybrid design: (**A**) Granumill, and (**B**) detail of Granumill rotor and screen. *Source*: Courtesy of Fluid Air Inc.

4. *Screen size and type*: Screens are available in various sizes (Fig. 9B), based on thickness, open area, and hole configuration such as round, square, slotted, or grater-type openings. Only perforated screens are available.

Various researchers have performed extensive studies of the effects of the foregoing variables on granulation and milling processes (20–22). Motzi et al. (21), on the basis of their observations of significant interaction effects, concluded that effects of mill speed, screen size, and impeller shape on particle-size distribution cannot be evaluated individually but must be evaluated at a level that is a combination of all three.

Hybrid Designs

Hybrid designs, such as the Granumill (Fig. 10A, B), are now available, which utilize a one-piece cantilever rotor with heavy blades mounted parallel to the center shaft. Incorporating a variable-speed drive, these mills operate as screening mills when run at low speed and as impact mills when run at high speed.

Other Variables

There are other variables that can affect the sizing process, such as feed-material properties, granulation process, and drying process. The properties of materials have been discussed in section "Properties of Feed Materials Affecting the Sizing Process." The type of granulation [i.e., dry (roller compaction), planetary, high-shear, or fluid-bed] can determine the strength of the granules, and hence, the sizing process. Furthermore, the drying process, whether tray or fluid-bed, can also be important. Tray-dried granules are usually case-hardened and difficult to mill, whereas the fluid-bed process yields more porous and friable granules. Similarly, granules produced by high-shear granulators are harder, and they are therefore more difficult to mill than those manufactured using low-shear or fluid-bed processes.

SCALE-UP

Hammer Mill

Table 2 shows the scale-up parameters for Fitzmills (12).

In addition to having the same screen size and type used on the lower scale, keeping the rotor tip speed constant is one of the most important considerations in scale-up of a milling

Table 2 Scale-up Parameters for Fitzmill

	Chamber					Rotor			
Model	Capacity[a] factor	Nominal width (in.)	Screen area (in.^{2})	Diameter of rotor (in.)	Rotor configuration	No. of blades	Tip speed factor[b]	Maximum rpm	Maximum horsepower
L1A/MP	0.07×	1.0	8.5	5.4	Horizontal	4	1.42	9000/ 14000	0.5
M5A	0.7×	4.5	76.0	8.0	Horizontal	16	2.09	4600	3.0
D6A/DAS06	1.0×	6.0	109.0	10.5	Horizontal	16	2.75	4600	5.0/15.0

[a]Throughput relative to Model D6 at the same tip speed.
[b]Tip speed = factor × operating speed.
Source: From Ref. 12.

process. Vertical and horizontal rotor configurations may affect throughput and also particle-size distribution.

Conical-Screening Mill

Table 3 shows the scale-up parameters for various Comils (13). In addition to having the same impeller type, screen size, and screen type used on the lower scale, the tip speed of the impeller is one of the key variables in scale-up; thus it should be kept constant.

CASE STUDIES

Comparison of Fitzmill Variables

The variables that can be adjusted or easily changed to provide various different end results are (12) as follows:

- Rotor or tip speed of the blade (Fig. 11A)
- Type of blade used (Fig. 11B)
- Screen size and design (Fig. 11C)
- Feed throat type and design (Fig. 11D)

Comparison of Fitzmill vs. Comil

It is often difficult to predict the results from similar pieces of equipment having the same operating principle at two different scales, let alone using two pieces of equipment having different operating principles. Many times in the development of a pharmaceutical dosage form, the equipment used during formulation development and that used in production are quite different. Apelian et al. (22) studied the effect of particle-size distribution on chlorpheniramine maleate granules using a Fitzmill and a Comil. For the Fitzmill, various screens sizes (1, 2, 3, and so on) at medium speed were evaluated, and for the Comil, impellers (1601 and 1607) at two speeds (1680 and 3420 rpm) using various screen sizes (039, 045, 055, and 055G) were studied. They reported that milling the granulation using a Fitzmill with a screen size of 2, at medium speed, gave a particle-size distribution similar to the granulation milled using a Comil (1601 impeller, 055 screen at 1680 rpm) (Fig. 12). The results of this study suggest that, in making a major change in the milling process, one needs to optimize the critical processing variables to achieve a similar particle-size distribution.

Comparison of Hand Screen vs. Comil

The effect of changing the dry milling from a hand-screen operation to a conical-screening mill is shown in Figure 13. Naproxen granulations (0.5 and 4 kg) were manufactured in a fluid-bed granulator using PVP K-90 as a binder (23). The particle-size distribution of granules (0.5 kg), passed manually through an 18-mesh screen, was much coarser than the granules (4 kg) that were milled using a Comil (Model 197S). A flat-faced impeller (1607) at an impeller speed of 2500 rpm with a spacer setting 0.25 in. and screen number 2A055 (14-mesh) were used for the

Table 3 Scale-up Parameters for Comil

Model	Capacity factor	Impeller diameter (in.)	Screen size (in.) A	B	C	Impeller speed scale-up comparison (rpm)							Motor horsepower	Infeed opening (in.)
197	1×	4.375	5	1.5	3	1200	2400	3600	4800	6000	7200	—	1 or 2	3 round
194	5×	7.625	8	2.5	5	700	1400	2100	2800	3500	4200	5600	5	6 round
196	10×	11.125	12	4	7	450	900	1350	1800	2250	2700	3600	10 or 15	8 round
198	20×	23.250	24	16	7	225	450	675	900	—	—	—	20	11 × 22 rectangular
199	40×	29.469	30	16	12	180	360	540	—	—	—	—	30	12 × 24 rectangular
Tip speed (ft/min)						1400	2800	4200	5600	7000	8400	11200		

A, screen upper diameter; B, screen lower diameter; C, screen height.
Source: From Ref. 13.

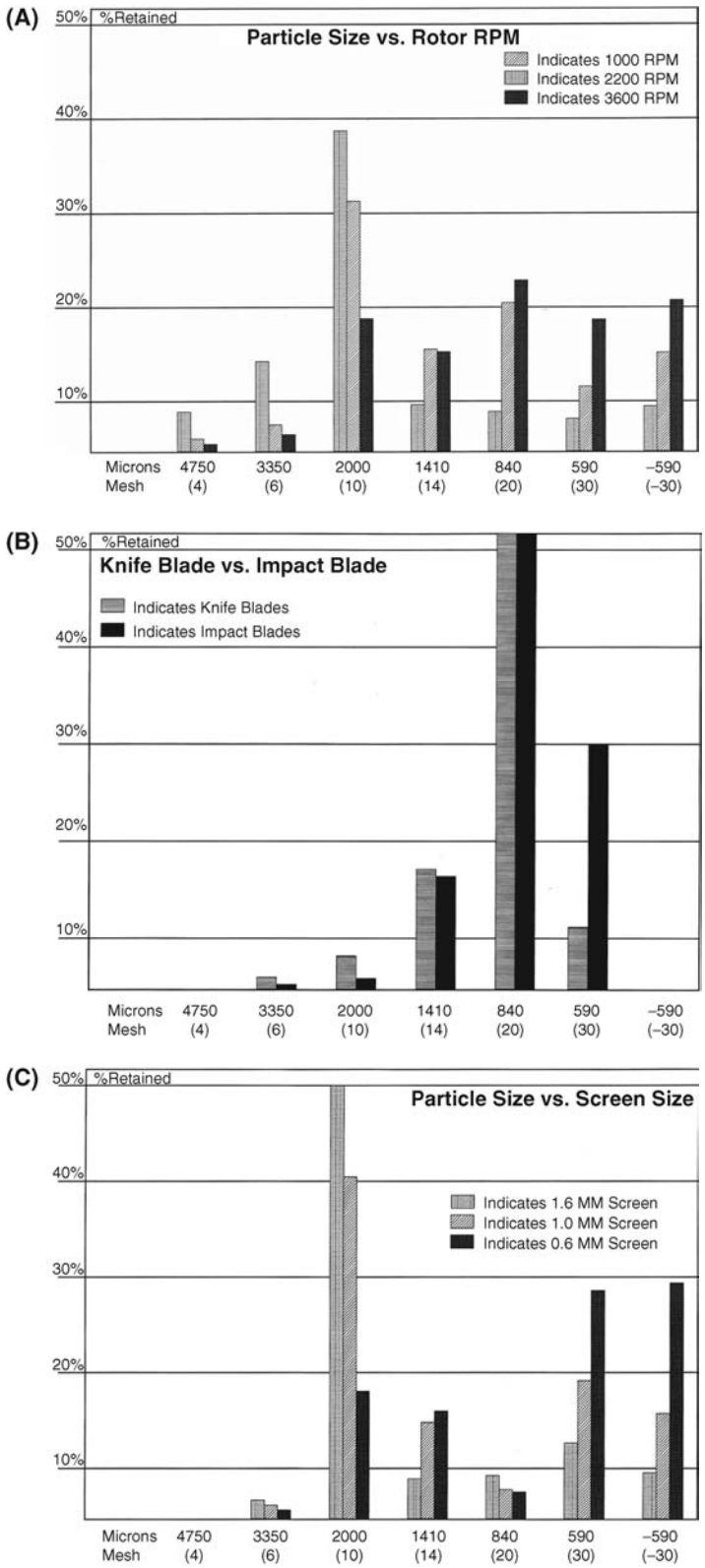


Figure 11 Particle-size distribution milled using a Fitzmill with different (**A**) rotor speeds, (**B**) blades, (**C**) screens, and (**D**) feed throats. *Source*: From Ref. 12.

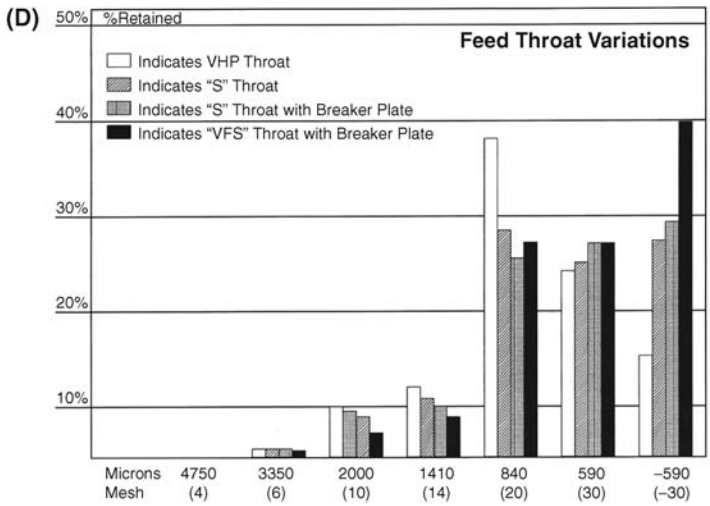


Figure 11 (*Continued*)

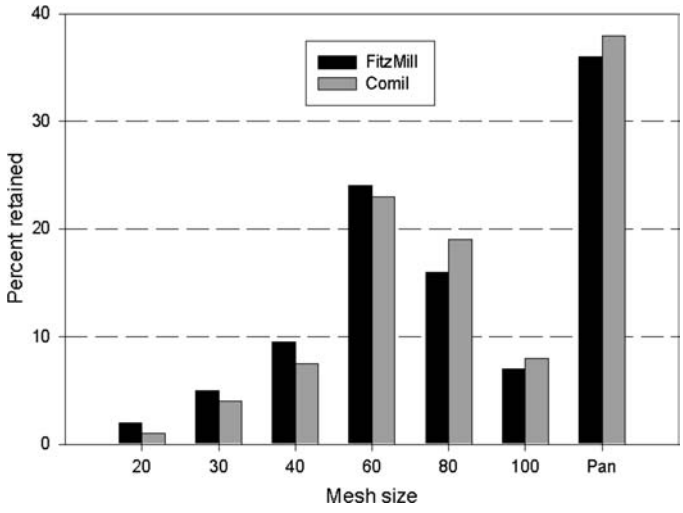


Figure 12 Particle-size distribution of chlorpheniramine maleate granulations milled using FitzMill and Comil. *Source*: From Ref. 22.

milling operation. Even though the granulations were prepared by the same procedure, the milling conditions drastically affected the particle-size distribution. As a general rule, during a switch over from a low-energy milling operation to a high-energy milling operation, the screen size should be coarser in the high-energy mill. The particle velocity is higher and therefore the size of the granule exiting out of the screen is much smaller than the screen opening. As seen from Figure 12, when the screen size was increased to 14-mesh for the conical-screening mill, the amount of fines generated was higher. Hence, during scale-up, optimization of milling conditions may be necessary to achieve the same particle-size distribution.

LIST OF EQUIPMENT SUPPLIERS

1. The Fitzpatrick Company, 832 Industrial Drive, Elmhurst, IL 60126, U.S.A. http://www.fitzmill.com.
2. Fluid Air, Inc. 2550 White Oak Circle Aurora, IL 60502, U.S.A. http://www.fluidairinc.com
3. Frewitt Ltd. P.O. Box 615 CH-1706 Fribourg, Switzerland. http://www.frewitt.com.
4. Glatt Air Techniques Inc., 20 Spear Road, Ramsey, NJ 07446, U.S.A. http://www.glattair.com

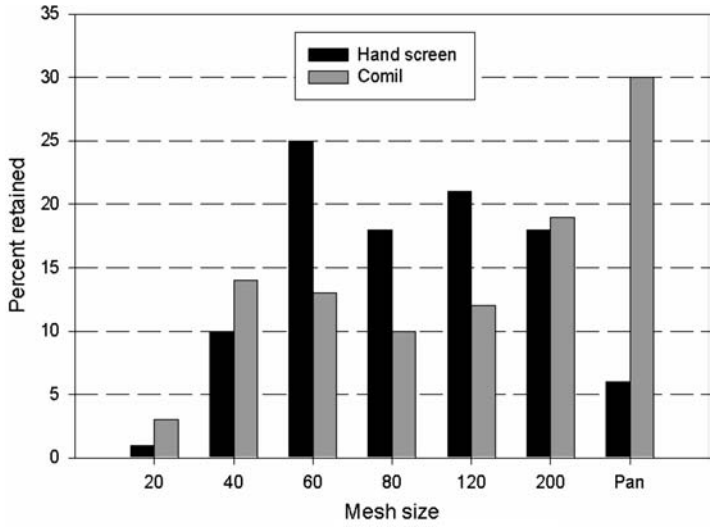


Figure 13 Particle-size distribution of naproxen granulations milled using hand screen and Comil. *Source*: From Ref. 23.

5. Niro, Inc. 9165 Rumsey Road, Columbia, MD 21045, U.S.A. http://www.niro.com.
6. Quadro Engineering Corp., Waterloo, Ontario, Canada N2V1A1. http://www.quadro.com.

ACKNOWLEDGMENTS

The authors would like to thank Dr Murali K. Vuppala of Johnson and Johnson for coauthorship on the first edition of this chapter, Mr Tom Kendrick, Mr Scott Wennestrum, and Mr Leonard Minervini from The Fitzpatrick Company, Mr John Bender from Fluid Air Inc., Quadro Inc., and Glatt Air Techniques Inc. for providing the photographs shown in this chapter.

REFERENCES

1. Prescott JK, Hossfeld RJ. Maintaining product uniformity and uninterrupted flow to direct-compression tableting presses. Pharm Tech 1994; 18:98–114.
2. Lantz RJ Jr. Size reduction. In: Lieberman HA, Lachman L, Schwartz JB, eds. Pharmaceutical Dosage Forms: Tablets. Vol. 2. New York: Marcel Dekker Inc., 1990:107–157.
3. Fonner DE, Anderson NR, Banker GS. Granulation and tablet characteristics. In: Lieberman HA, Lachman L, eds. Pharmaceutical Dosage Forms: Tablets. Vol. 2. New York: Marcel Dekker Inc., 1981:201.
4. Parrot EL. Milling. In: Lachman L, Lieberman HA, Kanig JL, eds. The Theory and Practice of Industrial Pharmacy. Philadelphia: Lea & Febiger, 1986:21–46.
5. O'Conner RE, Rippie ED, Schwartz JB. Powders. In: Gennaro AR, ed. Remington's Pharmaceutical Sciences. Easton: Mack Publishing Company, 1990:1615–1617.
6. Carstensen JT, Puisieux F, Mehta A, et al. Milling kinetics of granules. Int J Pharm 1978; 1:65–70.
7. Steiner G, Patel M, Carstensen JT. Effect of milling on granulation particle-size distribution. J Pharm Sci 1974; 63:1395–1398.
8. Motzi JJ, Anderson NR. The quantitative evaluation of a granulation milling process. III. Prediction of output particle-size. Drug Dev Indust Pharm 1984; 10:915–928.
9. Snow RH, Kaye BH, Capes CE, et al. Size reduction and size enlargement. In: Perry RH, Green D, eds. Perry's Chemical Engineers' Handbook. New York: McGraw-Hill Inc., 1984:8–20.
10. Prior MH, Prem H, Rhodes MJ. Size reduction. In: Rhodes MJ, ed. Principles of Powder Technology. New York: John Wiley & Sons, 1990:237–240.
11. Kukla RJ. Strategies for processing heat-sensitive materials. Powder Bulk Eng 1988; 2:35–43.
12. FitzMill Technical Bulletin. The Fitzpatrick Company, Elmhurst, IL.
13. Comil Product Literature. Quadro Engineering Corp., Millburn, NJ.

14. Poska RP, Hill TR, van Schaik JW. The use of statistical indices to gauge the mixing efficiency of a conical screening mill. Pharm Res 1993; 10:1248–1251.
15. Fourman GL, Cunningham DL, Gerteisen RL, et al. Improved color uniformity in tablets made by the direct compression method: a case study. Pharm Tech 1990; 14:34–44.
16. Schwartz JB. Theory of granulation. In: Kadam KL, ed. Granulation Technology for Bioproducts. Boca Raton: CRC Press, 1990:17.
17. Johnson C. Comminution variables and options. Powder Bulk Eng 1989; 3:40–44.
18. Owens JM. How to correct common hammermill problems. Powder Bulk Eng 1991; 5:38–43.
19. Hajratwala BR. Particle size reduction by a hammer mill I: Effect of output screen size, feed particle-size, mill speed. J Pharm Sci 1982; 71:188–190.
20. Byers JE, Peck GE. The effect of mill variables on a granulation milling process. Drug Dev Indust Pharm 1990; 16:1761–1779.
21. Motzi JJ, Anderson NR. The quantitative evaluation of a granulation milling process. II. Effect of output, screen size, mill speed and impeller shape. Drug Dev Indust Pharm 1984; 10:713–728.
22. Apelian V, Yelvigi M, Zhang GH, et al. Comparison of quadromill and fitzmill used in milling process of granulation. Pharm Res 1994; 11:8–142.
23. University of Maryland at Baltimore (UMAB), School of Pharmacy/Food and Drug Administration (FDA) Collaborative Agreement RFP # 223-91-3401. On Scale-Up and Post-Approval Changes (SUPAC).

22 Granulation Characterization

Cecil W. Propst
SPI Pharma, Grand Haven, Michigan, U.S.A.

INTRODUCTION

The chapter focuses on the following three areas:

1. Definitions
2. Granulation design investigations
3. Performance verification and corrective actions

Physical property characterization techniques such as determination of particle size, surface area, and density are covered in detail in chapter 3 dealing with the characterization of active pharmaceutical ingredients (APIs) and the raw materials for granulating. Rather than repeat the testing detail the information herein adds the characterization of the final granulations and will apply the data to verification of both the granulation design and its performance. Also the discussion of chemical characterization of granulations will be treated in the same way. Concerning performance the evaluation of dissolution, permeation, and in vivo–in vitro correlations will be covered under chapter 23 on properties and bioavailability. In this chapter we will deal with the remaining performance attributes in Table 1.

Several terms will be used throughout the chapter and it is best to define these terms for clarity as they apply to granulations and granulation structure.

DEFINITIONS

A particle, as defined by United States Pharmacopeia (USP) <776>, is the smallest discrete unit of mass (1). Thus, a particle does not need to be a stand-alone individual but must be discretely recognized. A primary particle is that same small discrete unit of mass bound into a granule or an aggregate (or cluster). An aggregate is a loosely bonded set of particles that can be easily broken. A granule is the secondary particle, an agglomerate, made up of primary particles that are firmly bonded together (can survive sieve testing). A film is a semisolid boundary layer either in the granulation matrix or on the surface of the granule. In compressive processing, tableting, units of the primary particle/granules, microunits, are structures that survive the compressive process intact. Voids in a granulation bed represent the volume or space between particles in a granulation bed. As applied to granulation the voids and open pore space within the granules will be considered as bed porosity. Bulk density is the mass of the granules divided by the volume they occupy, which includes the space between the particles (ASTM D5004). Skeletal density considers the mass to the sum of the volumes of the solid material and closed (or blind) pores within the granules (ASTM D3766). True density is mass in the volume that excludes open and closed (or blind) pores.

GRANULATION DESIGN INVESTIGATIONS

Our first goal in characterization of a granulation is confirming the granulation design using a set of characterization tests that correlate to the granulation performance. The focus is to directly link granulation design to performance, if possible. Once the design is confirmed and linked, the design can serve as a model to investigate the granulation performance during corrective action/preventative action investigations. Thus, in design control, the performance will be similar because the design is unchanged.

Table 1 List of Granulation Properties

Physical	Chemical
1. Density	1. Binder distribution
2. Porosity	2. Active form and distribution
3. Surface area	3. Wetability and solubility
4. Size	4. Crystallinity
5. Shape	5. Moisture content
6. Surface free energy	6. Moisture distribution

In this book, a later chapter on "Granulation Properties and Bioavailability" (chap. 23) will add to the characterization, dealing with properties affecting in vivo performance. This chapter will cover the molecular/chemical characterization as it relates to physical performance and stability.

A list of physical granulation performance properties includes the following:

1. Weight uniformity of the final dosage form
2. API physical stability
3. Process repeatability and robustness
4. Mechanical properties of flow and compaction

Important performance considerations are listed in Table 1.

Granulation Design

The design of a granulation is characterized on four levels (2). The levels focus on molecular, granular, surfaces, and bulk properties. The most important level depends greatly on the granulations use. The molecular level is important for content uniformity, stability, consolidation, dissolution, and other issues involving chemical makeup. The granular level is important also for content uniformity, flow, compression, optimizing arrangements, size of primary particles, and transitions issues. Surface studies include both the granular exterior and interior surfaces including transitional surfaces. The bulk properties deal with in-process handling, die filling, flow rate, and bin and hopper designs. All levels of granulations must be accessed as part of the performance of the final dosage form, be it the granules themselves, as part of tablet or a capsule product (3–5).

Focus on Granulation Structure

In the process of forming a granule, primary particles are packed together in a matrix or simply coated or both packed and coated. A transition is formed between contacting surfaces. The composition and thickness of the transition are important to characterize. Salpekar characterized the film transition of an acetaminophen granulation for direct compression as individual coated crystal made using fluid-bed granulator (3). Seager did the same for roll-compacted, fluid-bed, and spray-dried granulations (6). Armstrong characterized the transition in dextrose monohydrate granulations (7).

The primary particle surface alignment types for difference of matrix granules were defined by Newitt and Conway-Jones as pendular, funicular, capillary, and kneaded capillary (8). This structure difference in porosity and binder distribution influences granular performance. A key target for the development of a robust end point of a granulation is to achieve the same packing density. Then granular structure is established each time with granulation porosity and strength controlled by the amount of binding liquid added. Confirmation of the final granulation structure and porosity is therefore important in confirming robustness (8).

Granulation Porosity and Density

Both the characterization of density and porosity require the measurement of volume. Conversion of volume to density is based on knowing the mass in the volume measured. Bulk

density is the mass per volume of a loosely packed bed of granules. The amount of voids in a loosely packed bed varies with particle size, particle size distribution, particle shape, surface cohesiveness, and the method of loading the vessel used for the volume measurement. A monosized set of four spheres of diameter (d) will occupy a cubic container with sides of length $2d$ if arranged in a loosest density arrangement. The void space in the container will be 73.8%. The occupied space of solid is 26.2%.

If we tap the loosely packed granulation, the density of the bed will increase. A tapped density can be found if tapping continues until no further change in volume loss is noted.

The volume occupied by a granule is called the envelope volume. The mass per envelope volume is called the envelope density. If the mass is divided by the space occupied by the granule minus all open pores it is considered the skeletal density. If the volume used removes the space occupied by all open and closed pores it is referred to as the true density of the granule. The minimum volume a mass of granulation occupies under an applied pressure that is considered both above normal process pressure level and at extended dwell time is the minimum compression volume. The maximum compressed density is the mass per the minimum compressed volume.

The ease of packing of a granulation is used as an estimate of granulation flow called the Carr index. The Carr index (9) is calculated as per the following equation:

$$\text{Carr index} = \frac{100 \times (P - A)}{P} \tag{1}$$

where P is the tapped density (after vibration) and A is the bulk density (untapped). The higher the Carr index value, the poorer is the flowability. Values lower than 15 are considered good flow for tableting. Values in the range of 25 to 30 are considered best for capsule filling (4).

Envelope density as a standard test is measurement by solid spherical particle displacement (Micromeritics' GeoPyc Model 1360) to determine the volume and thus density of a sample of granules. The medium displacing void space and enveloping the granules used is a narrow distribution of small, rigid spheres that have a high degree of flowability and achieve a close packing around the object under investigation. The particles are sufficiently small that they conform closely to the surface of the object, yet do not invade the pore spaces. Method must be controlled to get good reproducibility of results. The sample cell in which the dry medium is placed is a precision volume cylinder. A plunger pushes the powder as the cell vibrates; the force of compression is selectable and, therefore, repeatable from test to test. A preliminary compression cycle with only the displacement medium in the cell establishes a zero-volume baseline. The object is then placed in the cylinder with the dry medium and the compression process is repeated. The difference in the distance, h_t, the piston penetrates the cylinder during the test and the distance, h_o, it penetrates during the baseline procedure ($h = h_o - h_t$) is used to calculate the displacement volume or envelope volume (V_{EV}) of the medium, using the formula for the volume of a cylinder of height h:

$$V_{EV} = \pi r^2 h \tag{2}$$

and

$$\rho_{EV} = \frac{m}{V_{EV}} \tag{3}$$

This same technique can be used to access granulation bed densities. In Figure 1, the fines (through 210 μm) of a granulation are completely removed and are used by adding them back as the displacement medium (10). At zero percent fines the tapped density of the coarse is found to be 0.95 gm/cm^3. As the finer particle fraction is added back the voids in the coarse bed are filled. The addition of fines adds mass to each unit of volume by displacing air in the void space. As long as the voids are larger than the fines' particle size the fines can fit into the space. Once all the voids in the larger particle set are filled the tapped density values stop rising. Note as more fines are added, above 30% fines in the plot, the tapped density eventually decreases. An estimate of the void space being filled in the coarse fraction can be made by assuming two particle size fractions are being mixed with a loss of coarse bed void space and replacing it with fines as one rate line and then the addition of fines to the

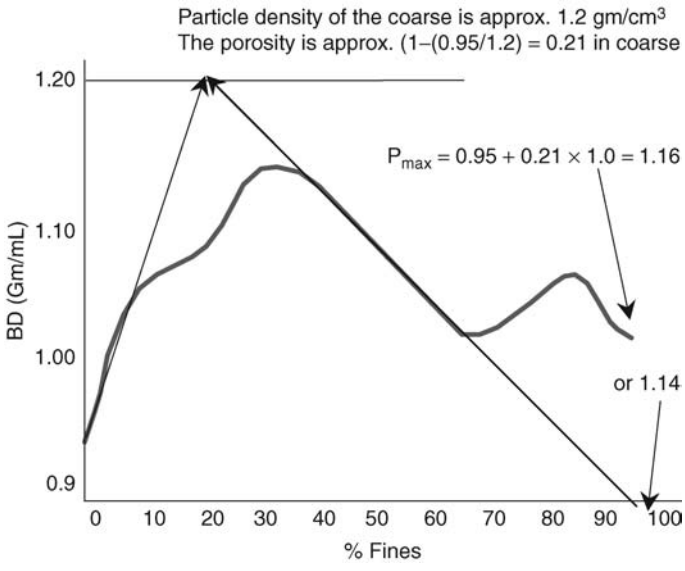


Figure 1 Tapped density profile of calcium carbonate antacid granulation with 200 μm particles removed (fines) and re-added.

bed, having void space of their own, displacing coarse. The tapped density of the fines is 1.16 gm/cm^3 and of the coarse is 0.95 mg/cm^3. The dilution creates two lines: one for increase in tapped density because of adding fines to the voids in the coarse bed and the other due to adding to the voids present in the finer particles into space. The intersection of the two lines is the envelop density of the coarse of 1.2 gm/cm^3.

We can calculate the maximum bed density as:

$$\rho_{max} = \rho_c + \varepsilon_c \cdot \rho_f \tag{4}$$

where ρ_{max} is the maximum bed density, ρ_c is the tapped density of coarse, and ρ_f is the tapped density of fines, or ρ_{max} is 1.16 gm/cm^3.

This effect on bed density is important to control as it has a major influence on fill weight control in both capsule and tablet manufacturing.

The skeletal density of a granule can be determined using a helium pycnometer (AccuPyc 1330, Micromeritics Instrument Inc., Norcross, Georgia, U.S.). This device measures the volume of the space that helium gas can penetrate (11).

Granulation Void Space and Porosity

Total porosity of a granulation bed is found using the following equation:

$$\%\,\text{Bed porosity} = \left[1 - \frac{\rho_{BD}}{\rho_s}\right] \cdot 100 \tag{5}$$

Both the maximum compressed density and true density can also be used for the referenced density versus skeletal density in equation (5). As porosity removal is the process of compression, a reference to maximum compressed density can be useful in roll compaction and tableting (2). Higher starting bed porosity means more air needs to be removed and longer times under pressure required to achieve the same densification. The elimination of bed porosity reduces percolation segregation but can also cause failure to mix when using diffusive mixers such as double cone mixers.

Porosity within a granule helps to define its structure (6). A dried granule relative porosity is calculated by dividing envelope density ρ_{EV} by the skeletal density ρ_s and subtracting from 1:

$$\%\,\text{Granule porosity} = \left[1 - \frac{\rho_{EV}}{\rho_s}\right] \cdot 100 \tag{6}$$

Using either compressed density or true density versus skeletal density will give a better estimate of void space within granule if the pores in the granule are not open. Porosity within a granule is also referred to intragranular porosity.

Paronen and IIkka (11) have suggested that increase in intragranular porosity increases the propensity of the granules to fragment leading to formation of stronger tablets. This allows rapid deformation in high-speed tableting operations. For granulations that are less prone to fragmentation, Johansson et al. (12) showed that increased intragranular porosity increased the degree of deformation, resulting in formation of a closer intragranular pore structure during compression and stronger tablets.

Granule Flowability

A more direct measurement of flow of granules uses a "flow through an orifice" technique (12–14). This test is more of a "use test," because a hopper is charged with the granules and the flow rate during discharge is measured. A variation of this test is achieved by determining the relation between the flow rate and the diameter of the orifice through which it flows. Harwood and Pilpel describe various methods of data analysis for this technique in detail (15).

A method to quantify the cohesiveness of granules, associated flow of particles, and hopper design uses a shear cell. The most popular shear cell was proposed by Jenike (16). The Jenike shear cell features a two-piece split disk cell, which holds a preconditioned sample of granules, a cover is placed on the bed, and then a conditioning weight is placed on the bed to pack it. The conditioning weight is removed and replaced with what is referred to as the normal weight. The bed then has a packing density related to the conditioning weight applied to the cover. A shearing force is applied to move the upper part of the split cell. The upper part is pushed across the lower disk horizontally causing a shear across the sample. The shear force being applied and displacement distance of the upper ring is recorded. Also recorded is the beds' vertical change. If the normal weight is not moved vertically during the shearing of the bed it is a shear force related to the surface cohesion of the bed at that specific conditioning density. A "yield locus" of the shear stress versus the normal nonexpanding or contracting loads is obtained for different conditioning densities. Flow and storage bin design values are calculated from these curves (16).

Granule Strength

Harwood and Pilpel measured granule strength by adding weights to a weighing pan placed over a narrow size cut of granules until the granules were crushed (15). This direct crushing test was modified by both Ganderton and Hunter (17) and by Gold et al. (18). Gold's et al. modification records the force required to crush the granule when a platen is moved at a constant strain rate. Deflections in the load profile are interpreted as break points and the strength is recorded in units of force to cause the breakage. A direct measurement of tensile strength is difficult owing to the lack of understanding of the surface area on which the applied load is acting over.

This method has inherent difficulty in measuring the strength of granules smaller than 40 mesh. Average granule-crushing measurement is more meaningful than individual values.

An attrition method used in determining granule friability uses a Roche friabilator (19,20). In this measurement, a friabilator is charged with a screen cut of granulation to be tested, a set of stainless steel spherical ball are added, and then the friability is tested. The percentage loss of mass is the value that is represented as the granulation friability (21).

High Pressure Characterization

The tableting process compacts a granulation bed in a die cavity forming a tablet using two main processes: compression and consolidation. Compression is the densification, loss in volume, of the granulation bed. Consolidtion is the formation of a solid body. Compaction thus represents the decrease in voids and porosity, the increase in contact surface area (A_{cs}), and the creation of bonds.

Compression requires the movement and/or deformation of particles or portions of the particles. The bed is losing porosity and is densifying. Starting at low pressures the moving units are intact granules displacing air rearranging and packing in the bed. Once set in a fixed position the granule must deform. One mechanism for this is "crushing in place" (22). In a crush in place mode the granule collapses in brittle fracture, losing internal porosity. Another granule deformation mechanism is a "slip into place" where a portion of the granule moves to occupy the open space. Crush in place is more time independent and thus more suited for higher speed tableting processes. Slip in place requires more time to occur.

Semisolid transitions move under pressure and can fill open spaces. Low shear granulations with limited binder distribution commonly form tablets of lower friability and higher harness tablets at lower compression pressures than fluid-bed granulations (23). At higher pressures, however, the fluid-bed granulations make for harder tablets than the low shear formulation because of the more uniform binder distribution contained in a fluid-bed granulation (23).

To measure the compression event requires the measurement of the pressure being applied and the displacement of the compression devise. An instrumented tablet press or a simulator displacement speed of up to 100 mm/sec is one of the standard units used to obtain these measurements. The information of force applied and displacement is used in calculating relative density (equation 7), porosity (equation 8), and degree of volume reduction (equation 9). These values are essential parameters for determining plasticity (Heckel equation) and for packing and deformation pressure and relative densities using the Cooper-Eaten analysis.

$$D = \frac{\rho_a}{\rho_t} \tag{7}$$

$$\varepsilon = 1 - D \tag{8}$$

$$\varepsilon = 1 - \frac{\rho_o}{\rho_o} \tag{9}$$

In each equation, D is the relative density of a powder compact at pressure P, ρ_a is the apparent density of a powder compact at pressure P, ρ_t is the true density of a powder, ε is the porosity, C is the degree of volume reduction (compression) of a powder compact at pressure P, and ρ_o is the bulk density of a powder.

Plastic deformation. The Heckel equation (equation 10) allows for the determination of the yield pressure needed to maintain plastic deformation. It is applied to medium and high pressure situations used in tablet making (22):

$$\ln\left(\frac{1}{1-D}\right) = kP + A \tag{10}$$

where D is the relative density of a powder compact at pressure P. Constant k is a measure of the 1/(yield pressure) of a compressed material. Constant A is related to the die filling and particle rearrangement before deformation and bonding of the discrete particles (23). Thus, a Heckel plot allows for the interpretation of the mechanism of deformation.

Repack and deformation density and pressures. The Cooper-Eaton equation (11) considers that powder compaction occurs in two steps. The first is the filling of the voids in the granulation by rearrangement of granules without any size change. The second proceeds into energies needed for the deformation of the granules pressing them into pores smaller than their size (11).

$$\frac{|1/D_o - 1/D|}{1/D_o - 1} = a_1 \exp\left(-\frac{k_1}{P}\right) + a_2 \exp\left(-\frac{k_2}{P}\right) \tag{11}$$

where D_o is the relative density at zero pressure and D is the relative density at pressure P. Cooper-Eaton constants a_1 and a_2 describe the theoretical maximum densification that could

be achieved by filling voids of the same size (a_1) and of a smaller size (a_2) than the actual particles. The value of $a_1 + a_2$ should equal unity for the equation to apply. The most probable pressures at which the respective densification processes would occur are described by k_1 and k_2 (11).

The bond strength is the breaking force needed to rupture the compact divide by the area of break. In tablets this is determined by compressing a compact diametrically on a tablet hardness tester [Pharmatron tablet tester (model 6D, Dr Schleuniger Pharmatron Inc., Manchester, New Hampshire, U.S.)]. The radial tensile strength of the compacts is calculated from the compact breaking strength and tablet thickness using the equation (equation 12) of Fell and Newton's method (24), in which the radial tensile strength σ_t is given by

$$\sigma_t = \frac{2F}{\pi d t_h} \tag{12}$$

where σ_t is the tensile strength (MPa), F is the force required to cause failure in tension (N), d is the diameter of the compact (mm), and t_h is the thickness of the compact (millimeter).

If the surfaces that are coming in contact are clean and have a bondable surface, bonds will form at these new areas of contacts. The strength of these bond formed is estimated as tensile strength and is the total surface area bonding (A_b) and the bond strength per unit area σ_b (22).

$$\sigma_{TS} = \sigma_b \cdot \frac{A_b}{A} \tag{13}$$

If the total surface area (A_t) is bonding and the compact porosity is zero then the tablet tensile strength is σ_b. σ_b can be estimated from tensile strength, σ_{TS}, measurement if σ_{TS} is determined just prior to the compression failure point for samples of the granulation of the same composition having varying final densities at time prior to failure. Plotting tensile strength versus densities or percent porosity found prior to failure allows extrapolation to the maximum consolidation strength of the granulation prior to rupture. The intercept is σ_b, i.e., the estimate of the surface bonding value for the granulation. This bond formation is part of the process of consolidation, the formation of a solid body.

Focus on Granule Surfaces

Three types of surface interfaces are present in granules: (*i*) the air to solid surfaces; (*ii*) the solid to solid; and (*iii*) solid to semisolid (or liquid) interfaces. Total air to solid surface is the sum of the outer surface of granule and the surface in the granular pores.

Granule Surface Area

The total air to solid surface area of a granulation can be measured by the BET gas adsorption method. Developed by Brunauer, Emmet, and Teller (25), the method features two ranges for the adsorption of gas. A low relative partial pressure range of $0.05 < P/P_0 < 0.35$ of partial pressure of nitrogen (the adsorption gas) to a carrier gas (helium) is used for total surface area. Higher than 0.35 partial pressures is used to measure granule porosity distribution. In the BET equation (equation 16), the slop and intercept are found for a plot of $1/v[(P_0/P)-1]$ on the y-axis and P/P_0 on the x-axis. With known slope and intercept, the value for V_m (the volume of a monolayer of gas adsorbed) is calculated:

$$\frac{P}{V(P_0 - P)} = \frac{1}{V_m C} + \frac{(C-1)P}{V_m C P_0} \tag{14}$$

where V is the volume of gas adsorbed at pressure P, P is partial pressure of adsorbate, C is a constant relating the heats of adsorption and condensation, P_0 is the saturation pressure of adsorbate at experimental temperature, and V_m is the volume of gas adsorbed in monolayer of solid.

A plot of $1/v[(P_0/P)-1]$ on the y-axis and P/P_0 on the x-axis generates a straight line. V_m and C are calculated from both the slope and the intercept of this line. The specific surface area

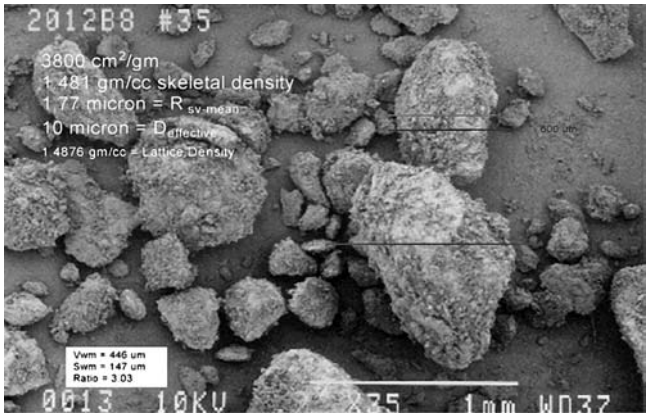


Figure 2 Scanning electron micrographs of mannitol granules. *Source*: Courtesy of SPI Pharma.

(SSA) in units of square meters per gram is calculated using equation (15):

$$\mathrm{SSA} = \frac{(V_{\mathrm{m}} N_0 A_{\mathrm{cs}})}{M} \tag{15}$$

where N_0 is the Avogadro's number, A_{cs} is the cross-sectional area of adsorbate, and M is the mass of solid sample.

With surface area for a material known and also density we now determine the relative volume to surface ratio. An example in Figure 2 is Mannogem® 2080 (SPI Pharma, New Castle, Delaware, U.S.) granulation sample with a surface area, A_{s}, of 3800 $\mathrm{cm}^2/\mathrm{gm}$. It has a true density ρ_{t} of 1.483 $\mathrm{gm}/\mathrm{cm}^3$ by X-ray diffraction. This gives a relative volume to surface ratio, R_{vs}, of 1.77 μm:

$$R_{\mathrm{VS}} = \frac{1/\rho_{\mathrm{t}}}{A_{\mathrm{s}}} \tag{16}$$

If we assume a shape factor of 6 (cubic structure), the relative size of a solid cubical particle with no interior porosity that has an equivalent volume to surface ratio is a 10.6-μm cube. The particle size of the mannitol granulation particle in this example is over 446 μm. Knowing β-mannitol true density by X-ray diffraction is 1.4876 $\mathrm{gm}/\mathrm{cm}^3$, a comparison of the true density to the skeletal density of 1.481 $\mathrm{gm}/\mathrm{cm}^3$ indicates a lack of closed (or blinded) pore space.

Granule Size and Size Distribution

For a spherical particle its diameter is a unique number that describes not only particle size but also surface area, shape, volume, mass (if density is known), and even its sieve diameter. Most of our granulations sizes are quoted relatively to an equivalent spherical particle.

Equivalent Diameters

Equivalent diameters are almost always the diameter equivalent to a sphere. An equivalent diameter can be calculated from a particles' surface area. The equation for that is as follows:

$$d_{\mathrm{s}} = \sqrt{\frac{S}{\pi}} \tag{17}$$

Similarly, an equivalent diameter could be based on particle volume using the following equation:

$$d_{\mathrm{v}} = \sqrt[3]{\frac{6V}{\pi}} \tag{18}$$

For example, result shows the distribution is 11% within the range 150 to 250 μm. That means total volume of all particles in this range is 11% of the total volume of all particles in

whole distribution. The resulting data is for an equivalent sphere of the same volume. Assuming the particles are rods with a diameter of 100 μm and height 300 μm, the volume is 1.18×10^{-6} μm^3:

$$V = \pi(50)^5 150 \tag{19}$$

Convert it into a spherical volume; the diameter is between 100 and 300 μm.

The sphere of equivalent size is 124.8 μm found by the following expression:

$$\sqrt[3]{\frac{6V}{\pi}} = 124.8 \tag{20}$$

On the basis of measurement automation and the ease of value development, there are ratios for number, surface, and volume as weighted mean diameters in wide use:

$$d_{SV} = \sqrt{\frac{\Sigma n_i d_i^3}{\Sigma n_i d_i^2}} \tag{21}$$

This is the surface volume mean diameter. This value is inversely related to the SSA and as such it is very useful in applications that involve surface.

The volume weighted mean diameter has its best uses in mixture studies as the mean gives a relationship of particle size as a mass size mean for comparison:

$$d_{FM} = \sqrt{\frac{\Sigma n_i d_i^4}{\Sigma n_i d_i^3}} \tag{22}$$

For a spherical particle, the volume mean diameter and the surface weighted mean diameter are the same. Thus, their ratio is 1 for spheres:

$$\sim 1 = \frac{d_{SV}}{d_{VM}} \text{for a sphere} \tag{23}$$

In consideration of the mannitol granulation in Figure 2, note the volume weighted mean is 446 μm and its surface weighted mean is 147 μm or a ratio of 3:1.

Particle size can be measured by sieve analysis, laser light scattering, or optical microscopy as described in chapter on API and raw materials for granulating. Light-scattering techniques are also applied to granulations even though granulations do have a larger size. Dry sieve analysis and microscopy are generally the most popular methods for determining size distribution of granules.

Sieve Analysis

Dry sieve analysis is the easiest and most convenient method for measuring granule size (Fig. 3).

A sieve is a screen with normally square apertures (hole). The granulation is placed on top of a stack of five to six sieves, which have successively smaller-sized openings from top of the stack to the bottom. The stack is vibrated, rotated, and/or mallet shocked, or a combination of motions, and the particles collect on top of the sieves. The data is usually represented in terms of percentage retained on the sieve, or percentage that is undersize or oversize versus screen-opening size. It is always important to be sure that enough time is given to the sieving step. Also that the sieve is not blinded and screen holes are plugged. On the basis of screen the smallest screen used in granulation sieving has a 45-μm aperture.

As part of sieve analysis, it is important to assay the sieve cut for content of API, binder, and moisture content. The importance of knowing the chemical distribution versus particle size will be discussed later under uniformity of content.

Laser Particle Size Analysis

Characterization of granule size with laser analyzer is faster measurement technique than sieving and produces a continuous spectrum of particle size data. Even though this technique

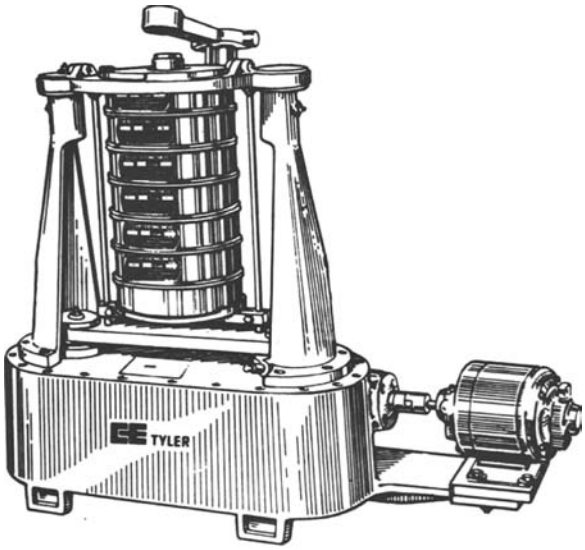


Figure 3 Tyler Rotap sieve unit.

is applied to fine powders it also has benefits when applied to larger granules as well. The data is based on the equivalent spherical volume or spherical surface diameter.

Property estimates provided by laser particle analysis of particles are as follows: (26)

1. Volume weighted mean diameter $d[4,3]$
2. Surface weighted mean diameter $d[3,2]$
3. $d(0.1)$
4. $d(0.5)$ is the mass median diameter (particle size at which 50% by volume of the sample is smaller and 50% by volume is larger)
5. $d(0.9)$

The first two definitions are for the derivative diameters and are calculated as follows:

$$D[m,n] = \left[\frac{\Sigma V_i d_i^m}{\Sigma V_i d_i^n}\right] \sum \frac{d_{\mathrm{SV}}}{d_{\mathrm{VM}}} \tag{24}$$

In the formula V_i is the relative volumes, d_i is the average diameter in a size range, and m and n are integers indicating the type of derivative being generated. The volume weighted average diameter is the $d[4,3]$ derivative and the surface weighted average diameter is $d[3,2]$. If one is looking for the arithmetic average, diameter $d[1,0]$ is used.

Most granulations are larger than the 0.635 μm beam size and thus are not considered to be small for the scattering measurement technique of Fronhofer.

Granulation Shape

Particle shape can be quantified by different methods. One easy way is the relationship of volume weighted mean to surface weighted mean in laser particle size analysis:

$$\Omega_L = \frac{[D[4,3]]}{[D[3,2]]}$$

If the particles are spherical this ratio is equal to 1.

The effect of particle shape on bulk powder properties has been illustrated by Rupp (27). The bulk volume increases as the shape becomes less spherical. The flow rate also drops with loss in spherical shape.

A method that sorts particles by shape is described by Ridgeway and Rupp (28) in which the granulation is fed onto a triangular metal deck and vibrated. Particles of different shape segregate on this deck and are collected for analysis by microscopy or on commercial devices can be weighed for a weight distribution.

Granule Morphology

Getting a look at a granulation under a microscope or doing an SEM (scanning electron microscope) is our first characterization tool. A lot is learned quickly with this technique. Morphology is the visual study of the structure. In essence, in morphology we obtain a quick interpretation of surface appearance, primary particle crystal habits, particle and granule shape, granule size and size distribution, and surface roughness. We can interpret from the image relative concepts of physical behavior and some of the aspects of chemical behavior that relies on structure, such as dissolution. Generally, morphology is assessed visually, and if recorded, the recording is pictures/images of the surfaces taken using cameras mounted to either the optical microscopy or SEM.

The real issues with using image microscopy are two: (*i*) being sure the image is representative as the sample is very small and (*ii*) converting the image into a description or a set of values to allow computer comparisons of the image. Any descriptions should be defined to be understood clearly by others.

A digital microscope can convert the size and area measurements of the particles to digital values. The projected area of the particle is measured often as the cord lengths across the digital image of the granule. The projected area measurement is correlated to the projected area of a sphere whose diameter is reported as (5)

$$d_{\mathrm{p}} = \sqrt{\frac{4A_{\mathrm{p}}}{\pi}}$$

Interior Morphology

Imaging of the interior of a granule is done by dissecting the granule in half and taking either photomicrographs or electron micrographs of the cut surfaces (6,8). It is also beneficial to remove surface or dissect out the core for chemical analysis. Rubinstein and Ridgeway (29) found from less than 2% to as much as 13% PVP on the surface of a magnesium hydroxide granulation based on the temperature of drying of the granulation. A calcium carbonate granulation made from calcium carbonate raw materials containing 4 to 7 μm mean particle diameter with a coarse component of as large as 90 μm created a core granule. The granulation containing sucrose powder, starch, and calcium carbonate granulated to 39% calcium carbonate potency contained a coarse core rich in calcium carbonate. Core was removable for assay (Fig. 4).

Non-core coating was 39% potency. The coarse granulation fraction found on a 590-μm screen, if present at concentration greater than 15%, caused tablet softness and lamination. If less than 5% coarse in the granulation, tablets did not laminate. If a 90 μm and larger outlier particle set was removed from the calcium carbonate raw material by screening prior to granulating, the lamination was also removed. Size of the calcium carbonate was 5 μm volume weighted mean with 90 μm "pinhead" sized particle present.

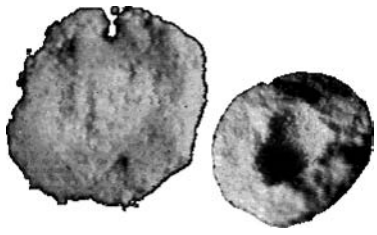


Figure 4 Calcium carbonate granulation core.

Seager et al. (6) went a bit further for acetaminophen granulated by fluid bed, spray-drying, and also roll compaction with gelatin; after making a tablet they cut the tablet in half and dissolved the active out of the granulation using acetone and left the web of gelatin to be observed. The structure of the web was shown to be both uniform in thickness and continuous across from one side of the tablet to the other in fluid-bed processed product. The distribution of gelatin by roll compaction, spray-drying, and fluid-bed processing was imaged in this manner (6).

CHEMICAL CHARACTERIZATION OF GRANULES

Chemical Characterization of Surfaces

The surface on/in a granulation can be microcrystals, primary particles, semisolids, film or crystalline (bridging) materials, and/or, as it is more generally, a combination of these states of matter. The surface chemistry is important to study as cohesiveness, bond formation under pressure, wetability, dissolution, and stability are impacted.

Characterization of Transitions in Granules

Granules are composed of primary particles and some type of transition component, which holds the primary particle together. The transition is most often a crystal or amorphous bridge or a polymer film. In some spray-dried application, the bridge can be a fusion-formed deposition (30). These transitioning materials can be on the surface of the granule and matrixed into the granule structure. Determining the composition and the location of the transition materials leads to an understanding of their roles in the functional properties of the granulation.

Contact Surface Characterization

The surface of the granule can be composed of a transition material, primary particles, or combination of both.

Armstrong et al. (7) studied water addition to both anhydrous dextrose and dextrose monohydrate. Water on dextrose anhydrous has a very complex relationship. As water is added to anhydrous dextrose the surface get tacky as shown by increased tensile strength for tablets made with the granulated powder. This occurs up until 8.6% water addition. Tablet tensile strength achievable increased from 0% water present to 8.6%. Above 9.2% tensile strength achievable falls dramatically as dextrose monohydrate forms and the water is considered in excess. Excess water, above 9.2%, is reported by Armstrong to be a physical barrier that prevents interparticulate bonding. Hydrodynamic resistance to compression is suggested. Greonwold (31) also suggested that excess water in sucrose granulation opposes formation of strong bonds. Lerk et al. (32) also showed that bonding strength in tablets made with glucose monohydrate increased with the level of dehydration temperature used to process the monohydrate. Water soluble carbohydrates are usually dried, "bone dry." Some residual water still remains but always for most mono- and disaccharides less than 1% water remaining is the target for chewable tablets. This low level of moisture is needed to setup in the material stable amorphous transitions. Brittle fracture occurs at these transitions at low pressure, creating clean surfaces to allow at higher-pressure close contact and crystal bond formation creating bonds. In the process of making softer chewable tablets or ODTs (orally disintegrating tablets) where low pressures are applied the presence of the wetted and tacking anhydrous dextrose can cause filming on the tablet punches.

Location of the film transition is important. In the drying step PVP can migrate. Rubinstein and Ridgeway (28) showed PVP concentration on the surface of 12-mm magnesium carbonate granules at the completion of drying varied with the drying temperature. Starting with a 5% PVP in formula and drying at 59.8°C the particle surface content of PVP reached 13%. Dried at 44°C, the surface concentration was closer to 6% PVP and drying at 19.6°C the surface concentration was less than 3%. It is anticipated that the surface concentration of PVP would affect the compactability of the finished granulation.

Amorphous Transitions

Amorphous transition can be present on the surface or sealed in the interior of the matrix of the granule. Spray-dried and fluid-bed made lactose granulation is a typical example.

Differential vapor sorption was used by Habib et al. (33) to quantify based on mass of moisture adsorbed versus the mass not desorbed the amorphous content of marketed lactose granulations. The amount of moisture gained by the sample at relative humidity of 55% or higher was found to be related to the percent amorphous content of the sample. The amorphous contents of four different marketed lactoses [Fast-Flo® (Foremost), Spray Dried® (Foremost), Pharmatose® DCL 11 (Crompton and Knowles), and Super-Tab® (Lactose Company of New Zealand)] together with a crystalline α-lactose monohydrate (Foremost) were determined. The compaction properties of these lactoses were also studied by compressing each excipient to an in-die predetermined porosity of 20% using an Instron at a compression speed of 20 mm/min. The breaking force of these tablets determined and correlated to the amorphous content of the different lactoses with very good correlation. The correlation to the compaction hardness was reported in the following order: Fast-Flo® > Spray Dried® > Super-Tab® > Pharmatose® DCL 11> crystalline α-lactose monohydrate.

Fusion Form Transitions

Mannitol is an example of a material that can be processed with its isomer sorbitol in very low concentration to form a fusion-formed transition (30). The sorbitol is "fused" into the structure of the mannitol particle matrix and does not melt as an independent peak in differential scanning calorimetry (DSC) analysis but melts with the mannitol lowering the heat of fusion per mass of the mannitol expected.

Polymer Transitions

Hydrophilic polymers such as starch paste, polyplasdone (PVP), hypermellose (HPMC), and maltodextrin are examples of film-forming polymers used as granulation transitions. These films hold residual moisture in their interior, and as a result the polymer is plasticized. Thus, changes of the level of moisture present, especially if the polymer is close to its glass transition, will dramatically change the performance of the granulation. On drying, as an example, the PVP will form a hydrated film containing approximately 15% to 20% moisture. If PVP is 5% of the mass of the film and it contains 20% moisture, the granulation will contain 1% moisture in total if only the film possesses moisture.

Hydrophilic colloids are dried to within a narrow range of moisture content. This level leaves the polymer sufficiently wet to plastically deform yet not too wet allowing a strong bond to form.

Moisture Level and Location

When drying is completed larger particles tend to contain more moisture than smaller ones (34). Once drying is completed milling, of course, can liberate moisture and cause issues with condensation and caking.

Approximately one-third of APIs are capable of forming hydrates. Very small amounts of water can form hydrates. This tendency to form hydrates and the characterization of the hydrate should be developed on the API and then applied to the process investigation. A hydrate screening study for nitrofurantoin using acetone/water system was reported by Aaltonen et al. (35)

Characterization of Moisture

Both the level and the location of moisture in a granulation are important for the functionality of the material.

Moisture content of granulations is measured by loss on drying (LOD), Karl Fisher (KF), and/or a water activity method. In an LOD analyzer, the loss in weight is dependent on temperature and length of drying and also dependent on the level to which the moisture is bound into the sample. Also to be observed is the loss of weight because of decomposition, noted as a change in color, during the test. In an LOD analysis, the weight loss is usually determined as an end point but it can also be recorded continuously as the weight is lost in time to create desorption curve (36). This technique is called thermal gravimetric analysis (TGA) and is used to measure moisture energy levels in a granulation (36,37).

KF measures total water. The sample tends to dissolve and any portion of the sample that contained water including the hydrate in dextrose monohydrate will be measured. Some substances such as carbonates interfere with the KF method giving higher results than moisture alone would create.

Water activity is a method that determines the moisture present that is in a free to evaporate state. This measurement is of the water vaporized into the head space of a vacuumed chamber at a controlled temperature, usually at room temperature. Free water holding capacity changes with relative humidity in most solids. In evaluation of granulation it is free water state that is the most often the causing of instability, poor flow, mottling, both softening and hardening of tablets and capsule shells, as well as issues with changes in dissolution and bioavailability.

Chowhan (37) showed that tablets made using low moisture content granulations when exposed to higher humidity increased in hardness and disintegration. Zografi et al. (38) delevoped a very useful predictive equation for calculating the minimum humidity for storage of a granulation or powder to prevent moisture adsorption using the materials tested water vapor sorption energy. Badawy et al. (39) showed in a processing study the moisture content had the largest effect on compressibility of the granulation compared with seven other process parameters. Within the tested levels increasing moisture content increased the granulation compressibility. It should be noted that because of the great diversity of granulation formulation, one has to characterize each of their formulation and process to evaluate the moisture effect on physical and chemical properties.

ACTIVE PRINCIPLE CHARACTERIZATION

API Uniformity

One of benefits to granulating is the ability to generate a uniform dispersion of the API in all granular particles to assure content uniformity. Also the lack of dust is an advantage in controlling cross contamination and employee exposure. In the design to assure mode, it is the granulation consistency that needs to be verified.

In pharmaceutical delivery systems it is the API dose that is being delivered and the target for the design to be assured. The dose (tablet weight times %API) delivered is variable based on the weight of the dosage form and its %API composition. It is important to separate the two, dose form weight from the variation in % composition during investigations and verification of process performance.

Table 2 shows a set of 10 values for the weight of tablets. Also shown is the assay of the individual tablets and a column representing the mg/mg concentration of API in each tablet.

If the dose weight is controlled only by the variability in the tablet weight the mg/mg composition in this example would be a fixed composition and independent of tablet weight.

Table 2 Example of Tablet Weights, Assay Values for Tablets, and mg/mg Concentration Calculation

	Sample weight	Assay mg/sample	Concentration mg/mg (P)	Weight results (Y)	Comb. Est. mg/sample (YP)
1	460.60	245.00	0.5319		
2	463.30	249.00	0.5374		
3	455.50	242.00	0.5313		
4	462.00	247.00	0.5346		
5	464.40	251.00	0.5405		
6	458.20	242.00	0.5280		
7	457.50	245.00	0.5352		
8	476.80	258.00	0.5411		
9	476.50	257.00	0.5393		
10	458.00	243.00	0.5306		
Theoretical	460.00	250	0.5435		
Mean	463.31	247.9	0.5350	459.92	246.062
S	10	10	10	60	
SD	7.342	5.040	0.0045	15.131	8.395%
CV	1.628%	2.356%	0.841%	3.289%	3.395%

Abbreviations: S, count; SD, standard deviation; CV, coefficient of variation.

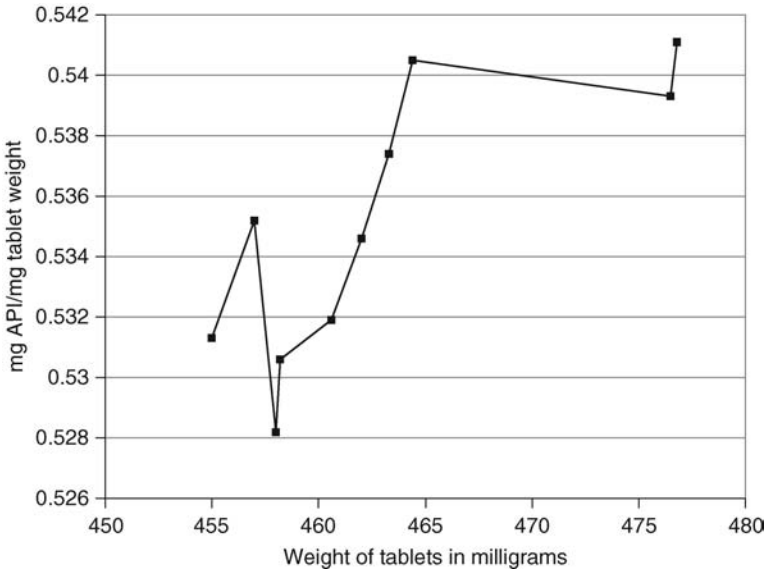


Figure 5 Tablet weight versus assay chart.

As seen in Figure 5 it is not. As the tablet weight increased the mg/mg concentration is increasing showing the heavier tablets are more potent than their weight increase would justify.

An investigation into the composition of the granulation can be made using the sieving approach. Each sieve cut is analyzed for its API and moisture composition. What is expected is a uniform composition of API in each sized fraction. Moisture can be found in higher percentages in larger granules. APIs, if not distributed uniformly, tend to be higher in the finer sized fractions. A nonuniform distribution is acceptable if it is part of a validated system and is consistent in its nonuniformity.

Drugs with high solubility in the granulation solvent have a higher tendency to migrate during drying creating a drug rich surface on the drying particle. Attrition or abrasion during subsequent handling leads to formation of highly drug-concentrated fines relative to the larger particles (10).

Viscosity has a significant effect on drug migration. Drug migration increased from the pendular state being dried to the funicular state being dried. Kapsidou et al. (40) showed drug migration increased with drug solubility and was projected to be a problem above a target range per granulation system. Kiekens et al. (41) showed a minimum liquid viscosity of 100 mPa sec was needed to stop the migration of riboflavin in α-lactose using PVP K-90 as the wet binder.

Crystallinity and Polymorphism

Understanding the effect of granulation on the form of bulk drug has gained increasing attention in the past few years. A detailed description of X-ray diffraction is provided by Suryanarayanan and the references cited therein (42). X-ray diffraction is mostly used to identify the crystalline form of a pure solid substance.

Modulated temperature X-ray powder diffraction (XRPD) is being used increasingly in the pharmaceutical industry at both preformulation and formulation stages. Airaksinen et al. (43) studied polymorphic transitions during drying using two methods: a multichamber microscale fluid-bed dryer or a variable temperature powder X-ray diffractometer. Relative amounts of different polymorphic forms of theophylline remaining in the dried granules were determined by XRPD. The authors concluded that metastable anhydrous theophylline predominated when the granules were dried at 40°C to 50°C. Temperature above 50°C produced mostly anhydrous theophylline, more than 20% of the metastable form remained even at 90°C.

Morris and coworkers (44) reported polymorphic changes when hydroxymethylglutarate coenzyme A reductase inhibitor was wet-granulated with water. The starting material was in the anhydrous form, which then converted to an amorphous form during the wet granulation process. The loss in crystallinity was experimentally determined using XRPD. Exposure of this granulation to an environment of greater than 33% relative humidity caused a form conversion to its crystalline hydrate. This series of experiments demonstrated the usefulness of a sophisticated technique, such as XRPD, in the assessment of the physical stability of APIs during granulation.

Solvates

Räsänen et al. (45) studied the polymorphic conversion of theophylline during wet granulation using NIR. The authors found that at a low level of granulation liquid (0.3 mol of water per mole of anhydrous theophylline), water absorption maxima in the NIR region occurred first at around 1475 and 1970 nm. These absorption maxima were identical to those of theophylline monohydrate. At higher levels of granulation liquid (1.3 $\pm$ 2.7 mol of water per mole of anhydrous theophylline), increasing absorption maxima occurred at 1410 and 1905 nm because of OH vibrations of free water molecules. Aaltonen et al. applied this to in-line NIR and Raman spectroscopy during fluid-bed drying to track the dehydration of theophylline monohydrate (46).

Thermal Analysis

A review of thermal analysis applications to pharmaceutical products is given by Duncan (47). DSC and TGA are both widely used for both active and inactive composition studies. DSC was used in the evaluation of a phase change of chlorpromazine hydrochloride after wet granulation (48). Although the dissolution profiles of both anhydrous forms were equivalent, the two forms had different tableting characteristics. The more stable form I did not exhibit the severe capping problems originally observed for form II. Granulations made with ibuprofen and β-cyclodextrin were evaluated using DSC. Lower ΔH values for oven-dried granulations indicated better complexation and faster dissolution than air-dried granulations (49).

Active Delivery

The solubility and bioavailability of the API are of extreme importance to consider in granulation design and characterization. These properties and means of characterization will be presented in a later chapter.

REFERENCES

1. The United States Pharmacopeia. USP <776>. Rockville MD, 2007.
2. Alderborn G, Wikberg M. Granule properties. In: Alderborn G, Nyström C, eds. Pharmaceutical Powder Compaction Technology. New York, NY: Marcel Dekker Inc., 1996:323–374.
3. Salpekar A, Dent L. Direct tableting acetaminophen compositions. US patent 4661521. 1987.
4. Podczeck F. Powder, granule and pellet properties for filling of two piece capsules. In: Podczeck F, Jones B, eds. Pharmaceutical Capsules. London: Pharmaceutical Press, 2004:101–118.
5. Hoag S, Lim H-P. Particle and powder bed properties. In: Augsburger L, Hoag S, eds. Pharmaceutical Dosage Forms: Tablets. Unit Operations and Mechanical Properties. 3rd ed., Vol. 1. New York: Informa, 2008:17–73.
6. Seager H, Hurt I, Ryder J, et al. Int J Pharm Technol Prod Manuf 1980; 1(2):73.
7. Armstrong N, Patel A, Jones T, et al. The compression properties of dextrose monohydrate and anhydrous dextrose of varying water contents. Drug Dev Ind Pharm 1986; 12:1885–1901.
8. Newitt D, Conway-Jones J. A combination of theory and practice of granulation. Trans Inst Chem Eng 1958; 36:422–442.
9. Carr R. Evaluating the flow properties of solids. Chem Eng 1965; 72:163.
10. Propst C. Tablet Processing, in Problem Solver, FMC Biopolymers 2002. Available at: http:/biopolymers.fmc.com/portals/bio/contents/pharmaceuticals/problem_solver.
11. Paronen P, IIkka J. Porosity-pressure functions. In: Alderborn G, Nyström C, eds. Pharmaceutical Powder Compaction Technology. New York, NY: Marcel Dekker Inc., 1996:55–75.
12. Johansson B, Wikberg M, Ek R, et al. Compression behaviour and compactability of microcrystalline cellulose pellets in relation to their pore structure and mechanical properties. Int J Pharm 1995; 117:57.

13. Gold G, Palermo B. Hopper flow electrostatics of tableting material I. Instrumentation and acetaminophen formulations. J Pharm Sci 1965; 54:310.
14. Pilpel, N. The flow of powders and granular solids. Br Chem Eng 1966; 11:699.
15. Harwood CF, Pilpel N. Granulation of griseofulvin. J Pharm Sci 1968; 57:478.
16. Jenike AW. Gravity Flow of Solids. Bulletin 108. Salt Lake City: Utah Engineering Experimental Station, University of Utah, 1961.
17. Ganderton D, Hunter BM. A comparison of granules prepared by pan granulation and by massing and screening. J Pharm Pharmacol 1971; 23:1S.
18. Gold G, Duvall R, Palermo B, et al. Powder flow studies II: effect of glidants on flow rate and angle of repose. J Pharm Sci 1996; 55:1291.
19. Rumpf H. Aggolmeration. New York: Interscience, 1962:379.
20. Mehta A, Zoglio MA, Carstensen JT. Ball milling as measure of crushing strength of granules. J Pharm Sci 1978; 67:905.
21. Pulverulent Mannitol of moderate friability and process for its preparation. Roquette's US patent 5,573,777, Nov 12, 1996.
22. Amidon G. Physical and mechanical property characterization of powders. In: Brittian H, ed. Physical Characterization of Pharmaceutical Solids. New York: Informa Healthcare, 2007:281.
23. Heckel RW. An analysis of powder compaction phenomena. Trans AIME 1996; 221:1001–1008.
24. Fell J, Newton JM. The tensile strength of lactose tablets. J Pharm Sci 1971; 60:628.
25. Brunauer S, Emmett P, Teller E. Adsorption of gases in multimolecular layers. J Am Chem Soc 1938; 60:309.
26. Allen T. Particle Size Measurement. 4th ed. London: Chapman & Hill, 1990.
27. Rupp R. Flow and other properties of granulate. Boll Chim Farm 1977; 116:251.
28. Ridgeway K, Rupp R. The effect of particle shape on powder properties. J Pharm Pharmacol 1969; 21:30S.
29. Ridgeway K, Rubenstein MH. Solute migration during granule drying. J Pharm Pharmacol 1974; 26 (Dec suppl):24S–29S.
30. Bauer H, Herkert T, Bartels M, et. al. Investigation on polymorphism of mannitol/sorbitol mixtures after spray-drying using differential scanning calorimetry, X-ray diffraction and near-infrared spectroscopy. Pharm Ind 2000; 62:231–235.
31. Greonwold H, Lerk CF, Mulder RJ. Some aspects of the failure of sucrose tablets. J Pharm Pharmacol 1972; 24:352–356.
32. Lerk CF, Zuurman K, Kussendrager K. Effect of dehydration on the binding capacity of particulate hydrates. J Pharm Pharmacol 1984; 36:399.
33. Habib Y, Sprockel OL, Abramowitz R. Evaluation of the amorphous content of currently marketed modified lactoses and its relationship to their compactibility. AAPS meeting in Nashville, TN, 1999.
34. Pitkin C, Carstensen JT. Moisture content of granulations. J Pharm Sci 1973; 62(7):1215.
35. Aaltonen J, Strachan CJ, Pollanen K, et. al. Hydrate screening of nitrofurantoin using hypenated NIR/ Raman Spectroscopy. J Pharm Biomed Anal 2007; 44:477–483.
36. Carstensen JT. Pharmaceutical Principles of Solid Dosage Forms. Lancaster, PA: Technomic Publishing, 1993.
37. Chowhan Z. Moisture, hardness, disintegration and dissolution interrelationships in compressed tablets prepared by wet granulation process. Drug Dev Ind Pharm 1979; 5:41.
38. Zografi G, Grandofi GP, Kontny MJ, et al. Prediction of moisture of moisture transfer in mixtures of solids: transfer via vapor phase. Int J Pharm 1988; 42:77.
39. Badawy S, Menning MM, Gorko MA, et al. Effect of process parameters on compressibility of granulation manufactured in a high-shear mixer. Int J Pharm 2000; 198:51–61.
40. Kapsidou T, Nikolakkis I, Malamataris S. Agglomeration state and migration of drugs in wet granulations during drying. Int J Pharm 2001; 227(1–2):97–112.
41. Kiekens F, Zelko R, Remon JP. Influence of drying temperature and granulation liquid viscosity on the inter- and intragranular drug migration in tray-dried granules and compacts. Pharm Dev Technol 2000; 5:131–137.
42. Suryanarayanan R. X-Ray Powder diffractometry. In: Brittian H, ed. Physical Characterization of Pharmaceutical Solids. New York: Informa Healthcare 1995:187.
43. Airaksinen S, Karjalainen M, Räsänen E, et al. Comparison of the effects of two drying methods on polymorphism of theophylline. Int J Pharm 2004; 276:129.
44. Morris KR, Newman AW, Bugay DE, et al. Characterization of humidity-dependent changes in crystal properties of a new HMG-CoA reductase inhibitor in support of its dosage form development. Int J Pharm 1994; 108:195.
45. Räsänen E, Rantanen J, Jørgensen A, et al. Novel identification of pseudopolymorphic changes of theophylline during wet granulation using near infrared spectroscopy. J Pharm Sci 2001; 90:389–396.

46. Aaltonen J, Kogermann K, Strachan CJ, et al., Dehydration of theophylline monohydrate during fluid bed drying analyzed with in line NIR and Raman spectroscopy. Chem Eng Sci 2007; 62:408–415.
47. Duncan C. The application of thermal analysis to pharmaceutical dosage forms. In: Augsburger L, Hoag S, eds. Pharmaceutical Dosage Forms: Tablets. Unit Operations and Mechanical Properties. 3rd ed., Vol. 1. New York: Informa, 2008:439–464.
48. Wong M, Mitchell A. Physiochemical characterization of a phase change produced during the wet granulation of chlorpromazine hydrochloride and its effects on tableting. Int J Pharm 1992; 88:261.
49. Ghorab M, Adeyeye M. Enhancement of ibuprofen dissolution via wet granulation with beta-cyclodextrin. Pharm Dev Technol 2001; 6:305.
50. Hiestand E. Rational for and measurement of tableting. In: Alderborn G, Nyström C, eds. Pharmaceutical Powder Compaction Technology. New York, NY: Marcel Dekker Inc., 1996:219–244.
51. Chirkot T, Propst C. Low-Shear Granulation. In: Parikh D, ed. Handbook of Granulation. 2nd ed. New York: Informa Healthcare, 2005:229.

23 Bioavailability and Granule Properties

Sunil S. Jambhekar
Department of Pharmaceutical Sciences, Lecom-Bradenton School of Pharmacy, Bradenton, Florida, U.S.A.

INTRODUCTION

The most important property of a dosage form is its ability to deliver the active ingredient to the "site of action" in an amount sufficient to elicit the desired pharmacological response. This property of a dosage form has been variously referred to as its physiological availability, biological availability, or bioavailability.

Bioavailability may be defined more accurately as the rate and extent of absorption of a drug from its dosage form into the systemic circulation. Accordingly, the absorption of a drug following intravenous administration is extremely rapid and complete. However, because of convenience and stability problems, drugs are often administered orally as a tablet or capsule dosage form. Therefore, it is imperative that their rate and extent of absorption in individual be known accurately. Furthermore, equally important is that the factors that influence the rate and extent of absorption of drugs be also known and understood by formulators.

The subject of bioavailability began to receive growing attention as studies showed that the therapeutic effectiveness of a drug from the dosage form depends, to a large extent, on the physiological availability of their active ingredient(s) and is a function of the drug concentration in the patient's blood or plasma. The importance of bioavailability in drug therapy, therefore, stems from the fact that the rate and extent of absorption of a drug from a dosage form can, in fact, affect the patient's response to a drug. In light of these facts, the determination of bioavailability has become one of the ways to assess the in vivo performance of a dosage form following its formulation development. It must, however, be remembered that bioavailability studies, very often, are conducted in normal, fasted, and small number of subjects and, therefore, the results of these studies may not always reflect the true efficacy relationship in patients under treatment conditions.

For many years it was assumed that if a dosage form contained the labeled amount of a drug, its performance could be taken for granted. However, it is now evident for some time that many factors acting individually or in concert may produce the therapeutic failure.

BIOAVAILABILITY PARAMETERS

In assessing the bioavailability of a drug from a dosage form, three parameters are measured following the administration of a drug through a dosage form and obtaining the drug blood concentration–time profile (Fig. 1).

1. Peak concentration $(C_p)_{max}$
2. Peak time (t_{max})
3. The area under the concentration-time curve $(AUC)_0^{\infty}$

The parameters t_{max} and $(C_p)_{max}$ are the measure of the rate of absorption, and $(AUC)_0^{\infty}$ is a measure of the extent of absorption.

Peak time (t_{max})

This parameter represents the length of time required to attain the maximum concentration of drug in the systemic circulation. The parameter describes the onset of the peak level of the biological response and, hence, can be utilized as a measure of the rate of absorption. The faster the rate of absorption, the smaller is the value for the peak time and quicker is

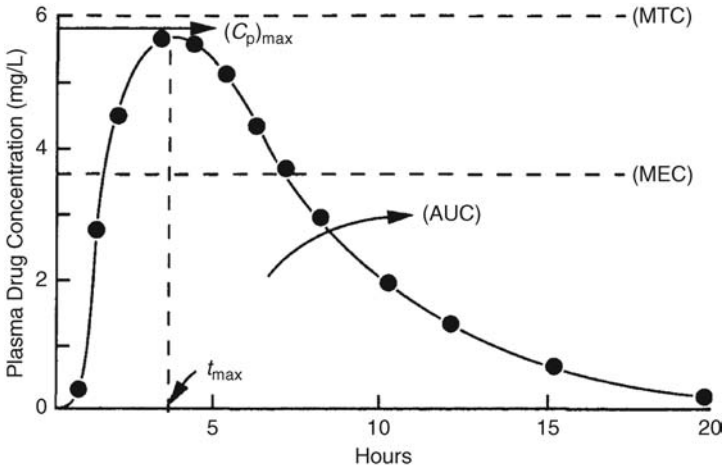


Figure 1 A graphical representation of plasma/serum drug concentration data following the administration of a drug by extravascular route.

the onset of action of the drug. The peak time is determined by using the following equation:

$$t_{max} = \frac{\ln(K_a/K)}{K_a - K} \tag{1}$$

where K_a and K are the first-order absorption and elimination rate constants, respectively.

Equation (1) clearly indicates that larger the value of the absorption rate constant (K_a), the smaller is the value of peak time (t_{max}) and quicker is likely to be the onset of action.

The elimination rate constant (K) is constant for a drug in normal healthy individuals and it changes when organs responsible for the elimination of the drug (i.e., kidney and liver) exhibit abnormalities. The absorption rate constant (K_a), on the other hand, depends on the route of administration, the dosage form, and the formulation of a drug. And, for hydrophobic drugs and/or when the absorption is dissolution rate limited, the faster dissolution is generally reflected in the higher value for the absorption rate constant. Therefore, by changing the formulation of a drug or route of administration, one can alter the peak time and, therefore, the rate of absorption and time for the onset of action.

Peak Plasma Concentration $(C_p)_{max}$

This parameter represents the highest drug concentration in the systemic circulation or the plasma concentration that corresponds to the peak time. Furthermore, this parameter is often associated with the intensity of the pharmacological response of the drug. Therefore, the peak plasma concentration (Fig. 1) of a drug following the administration of a dosage form should be above the minimum effective concentration and below the minimum toxic concentration. The peak plasma concentration can depend upon the absorption rate constant (K_a) and the fraction of the administered dose that eventually reaches the systemic circulation. The higher the absorption rate constant and fraction that reaches the general circulation, the greater is the peak plasma concentration for the administered dose. The route of administration, the dosage form, and the formulation can therefore influence the peak plasma concentration. It is determined by using the following method:

$$(C_p)_{max} = \frac{K_a F (X_a)_0}{V(K_a - K)} (e^{-Kt_{max}} - e^{-K_a t_{max}}) \tag{2}$$

where F is the fraction of the dose that eventually reaches the systemic circulation, $(X_a)_0$ is the administered dose, V is the apparent volume of distribution of a drug, and t_{max} is the peak time.

Since the term $K_aF(X_a)_0/V(K_a - K)$ in equation (2) constitutes the intercept of the plasma concentrations against time profile, equation (2) can be written as

$$(C_p)_{max} = I(e^{-Kt_{max}} - e^{-K_a t_{max}}) \tag{3}$$

where I is the intercept (μg/mL) of the plasma concentrations against time profile.

Area Under the Plasma Concentration–Time Curve (AUC)

This parameter represents the extent of absorption of a drug following the administration of a dosage form. The greater the fraction of the dose that reaches the general circulation, the greater is the extent of the absorption, and hence $(AUC)_0^{\infty}$. The term $(AUC)_0^{\infty}$ expressed as μg/mL·hr, for a drug following its administration by various extravascular routes or various dosage forms that are administered extravascularly, is determined by employing the following equation:

$$(AUC)_0^{\infty} = \frac{K_a F(X_a)_0}{V(K_a - K)}\left[\frac{1}{K} - \frac{1}{K_a}\right] \tag{4}$$

All the terms of the equation (4) have been defined previously.

Equation (4) can further be reduced to

$$(AUC)_0^{\infty} = \text{Intercept}\left[\frac{1}{K} - \frac{1}{K_a}\right] \tag{5}$$

The intercept in equation (5) is the intercept of the plasma concentration–time profile. The extent of absorption can also be determined by using the following equation:

$$(AUC)_0^{\infty} = \frac{F(X_a)_0}{VK} \tag{6}$$

where the term VK is the systemic clearance of the administered drug. This parameter being independent of the route of administration, the formulation, and the extravascularly administered dosage form, it is ostensible that the extent of absorption [i.e., $(AUC)_0^{\infty}$] is controlled by the product of the fraction of the administered dose reaching the general circulation and the administered dose [i.e., $F(X_a)_0$].

FACTORS AFFECTING THE BIOAVAILABILITY

There are number of factors responsible for the variation in bioavailability. Broadly speaking, these factors can be classified as patient related or dosage form related. Patient related factors include age, disease state, abnormal genetic characteristics, and/or gastrointestinal physiology. The detailed discussion on these factors is beyond the scope of the objectives of this chapter.

Dosage form related factors include formulation and manufacturing related variables such as particle size, type, and quantity of excipient used, method of manufacturing, compression pressure, derived properties of the powder, and many other factors.

The fact that the bioavailability of a drug may be significantly affected by its physical state and the dosage forms via which it is administered has been unequivocally demonstrated. And, because drugs are administered through dosage forms, these dosage forms should have adequate stability, complete and consistent bioavailability, and uniform composition.

Following the administration of a drug through a solid dosage form, a sequence of steps is required before the drug reaches the systemic circulation. As shown in Figure 2, an orally administered solid dosage form undergoes disintegration and deaggregation, followed by the dissolution of the drug. The dissolved drug molecules must penetrate the gastrointestinal membrane and picked up by the blood. Each of the steps involved may limit how fast the drug molecules reach the general circulation and, therefore, site of action. The step that offers the maximum resistance is referred to as the rate-limiting step. Which step will be rate limiting, on the other hand, will depend on the physicochemical properties of the dosage form and the physiology of the gastrointestinal tract. However, the focus of the discussion here will be on the physicochemical properties of the dosage form.

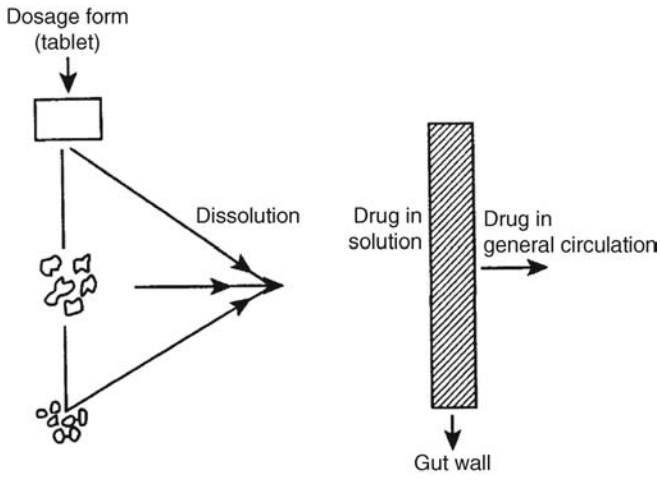


Figure 2 Schematic representation of the process of the drug dissolution and its entry in to the general circulation.

As illustrated in Figure 2, solid dosage form must disintegrate and/or deaggregate before much of the drug is available for absorption. Drug dissolution subsequently occurs from the resulting granules. Therefore, the properties of granules are important in understanding how dissolution is influenced by these properties. Following the ingestion of a solid dosage form, whether or not a drug is deaggregated, it will not be absorbed until it has dissolved into the luminal fluids of the gastrointestinal tract. Because of the effects of disintegration and deaggregation on the dissolution, the remaining discussion will focus on the factors influencing the dissolution of the drug.

DISSOLUTION AND GRANULE PROPERTIES

Among available dosage forms, compressed tablets are the most widely used dosage form. Tablets are generally obtained by using either wet granulation or direct compression process. Wet granulation process consists of mixing a drug with other powdered material and wetting the mixture with an aqueous and/or hydroalcoholic solution of a suitable binder such as gelatin, starch, or polyvinylpyrrolidone. The damp mass is passed through the screens of 8 to 12 mesh and dried to produce cohesive granules. Each granule, in theory, is a blend of an active ingredient and excipients. The granules flow easily through the hopper into the tablet press and are easily compressed.

Many derived properties of the powder greatly influence the granule properties, which, in turn, influence the dissolution of an active ingredient from the dosage form. These derived properties include powder density, porosity, specific surface, particle number, and powder flow. These derived properties are, in essence, determined by the particle size and size distribution. Consequently, particle size and size distribution play a vital role in influencing the bioavailability of drugs, particularly, when dissolution is the rate-limiting step in the absorption process. The important role these properties play in influencing the bioavailability must, therefore, be recognized and taken into consideration during optimization of a dosage form formulation. For example, smaller particle size is desirable, if drug is hydrophobic, to improve the drug dissolution due to increased specific surface; however, too small a particle size may adversely affect the powder flow and content uniformity of a dosage form. Other derived powder properties like true and bulk density and particle size will play an important role in the mixing of powder blends, prior to the granulation and compression. Powder flow is another derived property of importance. Flow of the powder and/or granules can present difficulties in the manufacturing of a tablet dosage form which, in turn, can affect the content uniformity of a drug and the bioavailability.

Many processes used in the tablet manufacturing greatly influence the dissolution rates of active ingredient. The method of manufacture, the size, the moisture content, age and the flow property of the granules, the order of mixing of ingredients during the granulation, as well as the compression force employed in the tableting process, all contribute to the

dissolution characteristics of the final product and, therefore, may be the bioavailability of a drug from the finished product.

Several studies have demonstrated that the granulation process, in general, enhances the dissolution rate of poorly soluble drugs (1). The use of diluents and fillers such as starch (2), anhydrous (3) and spray-dried lactose (4,5), microcrystalline cellulose (6), and compression force, particle size, and lubricants (7) tends to enhance the hydrophilicity of the active ingredients and improves their dissolution characteristics. In this regard, the wet granulation procedure was considered a superior method compared with other methods. However, with newer tableting machines and excipients accompanied by careful formulation and proper mixing sequence will permit preparation of tablets with good dissolution characteristics and not dictated by the method of preparation per se.

Marlow and Shangraw (8) reported that sodium salicylate tablets prepared by direct compression with spray-dried lactose uniformly exhibited more rapid and complete dissolution compared with those prepared by wet granulation. Furthermore, it was reported that the presence of disintegrate in the dry compression was essential for good dissolution. Finholt et al. (9) reported, in a separate comparative study, utilizing phenobarbital tablet that was manufactured by both wet and dry granulation, that both procedures yielded comparable dissolution rates provided a disintegrate was incorporated and mixed with drug before dry granulation. However, the incorporation of disintegrate following the dry granulation of a drug resulted in a slower dissolution rates.

In the manufacturing of tablets by the conventional wet granulation method, there are many independent factors that affect the property of granules and, therefore, the dissolution rate. Although recent advances in granulation technology and the employment of high-shear mixers and fluid-bed granulating equipment have helped to identify critical several in-process variables, the systematic control of variables such as the type and time of mixing of the granules, time and temperature of drying, blending time with lubricant, age of the granules, moisture content of the granules at the time of compression, and the tablet crushing strength are of importance to ensure the consistency in the dissolution, and hence, bioavailability.

In early studies on the physics of tablet compression, Higuchi et al. (10) recognized the influence of compressional forces employed in the tableting process on the apparent density, porosity, hardness, disintegration time, and average particle size of the compressed tablets. Hardness is a measure of resistance of a dosage form to the mechanical deforming. It is a function of high compression forces used in the manufacturing, and it may change with the aging of granules. Higuchi et al. (10) reported a linear relationship between hardness and the logarithm of the compressional force, and the specific surface of the compressed tablets was found to undergo marked changes during the compressional process. The high compression may increase the specific surface and, hence, may enhance the dissolution. On the other hand, the high compression may also inhibit the wettability of a tablet because of the formation of a firmer and more effective sealing layer of the lubricant due to high pressure and temperature that accompany a strong compressional force. Levy et al. (2) reported that salicylic acid tablets, when prepared by double compression, showed an increase in the dissolution with an increase in the precompression pressure due to fracturing of drug particles at higher pressure. The higher compression may also produce slower dissolution, at least in the initial period, because of an increased difficulty of fluid penetration into the compressed tablets. Luzzi et al. (11) and Jalsenjak (12) observed the dissolution rate of sodium phenobarbital to be inversely proportional to the hardness from tablet and microcapsule, respectively.

Another important granule property that influences the dissolution of drug is the moisture content of the granule at the time of compression. Chowhan et al. (13–17) studied the effect of moisture content and crushing strength on ticlopidine hydrochloride tablet friability and dissolution. It was observed (16) that at the moisture content of 1% to 2%, the drug dissolution was inversely related to the tablet crushing strength. However, at the moisture content level of 3% to 4%, there was no clear relationship between the dissolution and the crushing strength.

In later studies by Chowhan et al. (14,17), it was reported that granules prepared by high-speed shear mixer were less porous than those prepared by planetary mixer, and the porosity

of the tablet may improve the dissolution of drug by facilitating solvent penetration provided the entrapment of air in the pores is minimized or avoided.

In yet another important study, Levy et al. (2) studied the effect of the granule size on the dissolution rate of salicylic acid tablets and found that the dissolution rate increased with a decrease in the granule size; the increase in dissolution rate, however, was not proportional to the increase in the apparent surface area of the granules. Furthermore, it was also reported that the dissolution rate decreased significantly with the increase in the age of the granules.

The chemical components of the formulation have also been shown to prolong disintegration time, which subsequently affects the drug dissolution and bioavailability. Inert fillers have been found to potentiate the chemical degradation of active ingredient causing alteration in the disintegration and dissolution time of compressed tablets to change with storage. Alam and Parrott (18) have shown that hydrochlorothiazide tablets, granulated with acacia and stored at temperatures ranging from room temperature to 80°C, increased in hardness with time. This was reflected in increased disintegration and dissolution time. On the other hand, tablets granulated with starch and polyvinylpyrrolidone did not show any change in disintegration and dissolution time.

IN VITRO–IN VIVO CORRELATION

A key goal in pharmaceutical development of dosage forms is a good understanding of the in vitro and in vivo performance of the dosage forms. One of the challenges of biopharmaceutics research is correlating in vitro drug release information of various drug formulations to the in vivo drug profiles (IVIVC, or in vitro–in vivo correlation). Such a tool shortens the drug development period, economizes the resources, and leads to improved quality. This is because the IVIVC includes in vivo relevance to in vitro dissolution specifications. It can also assist in quality control for certain scale-up and postapproval changes. This section of the chapter discusses the Food and Drug Administration (FDA) guidance, various definitions of IVIVC, various levels of correlations and use of such information in oral dosage forms, and biopharmaceutics classification systems (BCS).

The concept and application of the IVIVC for pharmaceutical dosage forms have been a main focus of attention of pharmaceutical industry, academia, and regulatory sectors. Optimization process may require alteration in formulation composition, manufacturing process, equipment, and batch sizes. Implementation of these requirements not only halts the marketing of the new formulation but also increases the cost of the optimization processes. A regulatory guidance for both immediate and modified-release dosage forms has been, therefore, developed by the FDA to minimize the need for bioavailability studies as part of the formulation design and optimization.

IVIVC can be used in the development of new pharmaceuticals to reduce the number of human studies during the formulation development. It is to serve as a surrogate for in vivo bioavailability and to support biowaivers. They could also be employed to establish dissolution specifications and to support and/or validate the use of dissolution methods.

Definitions

Correlation is frequently employed within the pharmaceutical and related sciences to describe the relationship that exists between variables. Mathematically, the term correlation means interdependence between quantitative and qualitative data or relationship between measurable variables and ranks. Two definitions of IVIVC have been proposed by the United States Pharmacopoeia (USP) and by the FDA (19,20).

The USP definition:

> The establishment of a rational relationship between a biological property, or a parameter derived from a biological property produced by a dosage form, and a physiochemical property or characteristic of the same dosage form. (19)

The FDA definition:

> IVIVC is a predictive mathematical model describing the relationship between an in vitro property of a dosage form and a relevant in vivo response. Generally, the in vitro

property is the rate or extent of drug dissolution or release while the in vivo response is the plasma drug concentration or amount of drug absorbed. (20)

Correlation Levels

Five correlation levels have been defined in the IVIVC FDA guidance (20). The concept of correlation level is based on the ability of the correlation to reflect the complete plasma drug level–time profile, which will result from administration of the given dosage form (19).

Level A Correlation

This level of correlation is the highest category of correlation and represents a point-to-point relationship between in vitro dissolution rate and in vivo input rate of the drug from the dosage form (19). Generally, percent of drug absorbed may be calculated by means of model-dependent techniques such as Wagner-Nelson procedure or Loo-Riegelman method or by model-independent numerical deconvolution (19). These techniques represent a major advance over the single-point approach in that these methodologies utilize all of the dissolution and plasma level data available to develop the correlations (19). The purpose of level A correlation is to define a direct relationship between in vivo data such that measurement of in vitro dissolution rate alone is sufficient to determine the biopharmaceutical rate of the dosage form. An in vitro dissolution curve can serve as a surrogate for in vivo performance. Therefore, a change in manufacturing site, method of manufacture, raw material supplies, minor formulation modification, and even product strength using the same formulation can be justified without the need for additional human studies (19). It is an excellent quality control procedure since it is predictive of the dosage form's in vivo performance.

Level B Correlation

A level B IVIVC utilizes the principles of statistical moment analysis. In this level of correlation, the mean in vitro dissolution time (MDT_{vitro}) of the product is compared with either mean in vivo residence time (MRT) or the mean in vivo dissolution time (MDT_{vivo}). MRT, MDT_{vitro}, and MDT_{vivo} will be defined where appropriate. Although a level B correlation uses all of the in vitro and in vivo dates, it is not considered to be a point-to-point correlation, since there are a number of different in vivo curves that will produce similar mean residence time values (20). A level B correlation does not uniquely reflect the actual in vivo plasma level curves. Therefore, one cannot rely upon a level B correlation alone to justify formulation modification, manufacturing site change, excipient source change, etc. In addition, in vitro date from such a correlation could not be used to justify the extremes of quality control standards (19).

Level C Correlation

In this level of correlation, one dissolution time point ($t_{50\%}$, $t_{90\%}$, etc.) is compared with one mean pharmacokinetic parameter such as $(AUC)_0^{\infty}$, t_{max}, or C_{max}. Therefore, it represents a single-point correlation and does not reflect the entire shape of the plasma drug concentration curve, which is a crucial factor that is a good indicative of the performance of modified-release products (19,20). This is the weakest level of correlation as partial relationship between absorption and dissolution is established. The usefulness of this correlation level is subject to the same caveats as a level B correlation in its ability to support product and site changes as well as justification of quality control standard extremes (19). Level C correlations can be useful in the early stages of formulation development when pilot formulations are being selected. While the information may be useful in formulation development, waiver of an in vivo bioequivalence study (biowaivers) is generally not possible (20).

Multiple Level C Correlation

A multiple level C correlation relates one or several pharmacokinetic parameters of interest (C_{max}, AUC, or any other suitable parameters) to the amount of drug dissolved at several time

points of the dissolution profile. A multiple point level C correlation may be used to justify a biowaiver, provided that the correlation has been established over the entire dissolution profile with one or more pharmacokinetic parameters of interest. A relationship should be demonstrated at each time point at the same parameter such that the effect on the in vivo performance of any change in dissolution can be assessed (20).

Level D Correlation

Level D correlation is a rank order and qualitative analysis and is not considered useful for regulatory purposes. It is not a formal correlation but serves as an aid in the development of a formulation or processing procedure (20,21).

Systematic Development of a Correlation

An assumed IVIVR is essentially one that provides the initial guidance and direction for the early formulation development activity. This work sometimes results in revised in vitro targets and reformulation strategy and the same cycle of activity again.

Important Considerations in Developing a Correlation

When the dissolution is not influenced by factors such as pH, surfactants, osmotic pressure, mixing intensity, enzyme, and ionic strength, a set of dissolution data obtained from one formulation is correlated with a deconvoluted plasma concentration–time dataset (20). To demonstrate a correlation, fraction absorbed in vivo should be plotted against the fraction released in vitro. If this relationship becomes linear with a slope of 1, then curves are superimposable, and there is a 1:1 relationship that is defined as point-to-point or level A correlation. The correlation is considered general and could be extrapolated within a reasonable range for that formulation of the active drug entity.

In a linear correlation, the in vitro dissolution and in vivo input curves may be directly superimposable or may be made to be superimposable by the use of appropriate scaling factor (time corrections) (19,20). Time scaling factor should be the same for all formulations and different time scales for each formulation indicate absence of an IVIVC (20). Nonlinear correlation may also be appropriate (19,20).

In cases where the dissolution rate depends on the experimental factors mentioned above, the deconvoluted plasma concentration–time curves constructed following administration of batches of product with different dissolution rates (at least two formulations having significantly different behavior) are correlated with dissolution data obtained under the same dissolution condition. If there is no one-to-one correlation, other levels of correlation could be evaluated (19,20).

The in vitro dissolution methodology should be able to adequately discriminate between the study formulations. Once a system with most suitable discrimination is developed, dissolution conditions should be the same for all formulations tested in the biostudy for development of the correlation (20).

During the early stages of correlation development, dissolution conditions may be altered to attempt to develop a one-to-one correlation between the in vitro dissolution profile and the in vivo dissolution profile (20).

An established correlation is valid only for a specific type of pharmaceutical dosage form (tablets, gelatin capsules, etc.) with a particular release mechanism (matrix, osmotic system, etc.) and particular main excipients and additives. The correlation is true and predictive only if modifications of this dosage form remain within certain limits, consistent with the release mechanism and excipients involved in it (20).

Drugs are often taken just before, with, or after a meal. All these factors may increase variability. A posterior correlation might be established using the patients' data only to increase the knowledge of the drug.

The release rates, as measured by percent dissolved, for each formulation studied, should differ adequately (e.g., by 10%). This should result in vivo profiles that show a comparable difference, for example, a 10% difference in the pharmacokinetic parameters of interest [$(C_p)_{max}$ or AUC] between each formulation (20).

BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The BCS is a drug development tool that allows estimation of the contribution of three fundamental factors including dissolution, solubility, and intestinal permeability, which govern the rate and extent of drug absorption from solid oral dosage forms (22). Permeability is referred to as the ability of the drug molecule to permeate through a membrane into the systemic circulation.

Absorption Number (A_n):

The absorption number (A_n) is the ratio of the mean residence time (T_{res}) to the mean absorption time (T_{abs}) and is calculated by the following equation:

$$A_n = \frac{T_{res}}{T_{abs}} = \left(\frac{(\pi R^2 L/Q)/R}{P_{eff}}\right) \tag{7}$$

Dissolution Number (D_n):

The dissolution number (D_n) is the ratio of mean residence time (T_{res}) to mean dissolution time (T_{diss}) and could be estimated using the following equation:

$$D_n = \frac{T_{res}}{T_{diss}} = \frac{(\pi R^2 L/Q)}{(pr_o^2/3DC_s^{min})} \tag{8}$$

Dose Number (D_o):

$$D_o = \frac{\text{Dose}}{(V_0 \times C_s^{min})} \tag{9}$$

where L is the tube length, R the tube radius, π is 3.14, Q is the fluid flow rate, r_o the initial particle radius, D the particle acceleration, p the particle density, p_{eff} the effective permeability, V_0 the initial gastric volume equal to 250 mL, which is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water at the time of drug administration, and C_s^{min} is the minimum aqueous solubility in the physiological pH range of 1 to 8 (22).

The dose, dose number, solubility, and estimated dissolution number for a number of drugs are reported (22) in the literature. The fraction dose absorbed could be estimated using these three major dimensionless parameters. However, the extent of solubilization and potential particle aggregation in the small intestine are unknown, and therefore the solubility dose and dissolution number of a drug in vivo are difficult to estimate precisely (22). As the drug dissolution and intestinal permeability are the fundamental parameters governing rate and extent of drug absorption, drugs could be categorized into high/low solubility and permeability classes.

Class I compounds such as metoprolol exhibit a high absorption (A_n) and a high dissolution (D_n) number. The rate-limiting step to drug absorption is drug dissolution or gastric emptying rate if dissolution is very rapid (22). This group of drugs is expected to be well absorbed unless they are unstable, form insoluble complexes, are secreted directly from gut wall, or undergo first pass metabolism (23). For immediate release products that release their content very rapidly the absorption rate will be controlled by the gastric emptying rate and no correlation of in vivo data with dissolution rate is expected (22).

When a class I drug is formulated as an extended release product in which the release profile controls the rate of absorption and the solubility and permeability of the drug is site independent, a level A correlation is most likely.

Class II drugs such as phenytoin has a high absorption number (A_n) but a low dissolution number (D_n). In vivo drug dissolution for class II drugs is, therefore, a rate-limiting factor in drug absorption (except at very high dose number, D_o) and consequently absorption is usually slower than class I and takes place over a longer period of time (22). The limitation can be *equilibrium* or *kinetic* in nature. In the case of an *equilibrium* problem enough fluid is not available in the GI tract to dissolve the dose.

Class III drugs, such as cimetidine, are rapidly dissolving and permeability is the rate-controlling step in drug absorption. Rapid dissolution is particularly desirable to maximize the contact time between the dissolved drug and the absorption mucosa.

Class IV drugs are low solubility and low permeability drugs. This class of drugs exhibit significant problems for effective oral delivery. It is anticipated that inappropriate formulation of drugs fall in class IV, as in the case of class II drugs, could have an additional negative influence on both the rate and extent of drug absorption.

SUMMARY

Drug availability following the oral dosing may be thought of as the resultant of the following steps:

1. Getting the drug into solution
2. Moving the drug molecules through the membrane of the gastrointestinal tract
3. Moving the drug away from the site of administration into the general circulation

It is clear from the discussion that the bioavailability of drugs, particularly poorly soluble drugs, mainly depends on the ability of the drug to dissolve at the site of administration. The dissolution, in turn, especially from solid dosage forms such as tablet and capsule, depends on the powder properties, granule properties, and the processing variables used in the manufacture of the dosage forms. The granule properties and other variables, which determine and influence the granule properties, will serve as major topics of discussion in subsequent chapters. Knowledge of these factors and their role in influencing the bioavailability of a drug will allow the formulators to develop an optimum drug dosage form by selecting the process and preparation variables involved in a rational manner.

REFERENCES

1. Solvang S, Finholt P. Effect of tablet processing and formulation factors on dissolution rates of active ingredient in human gastric juice. J Pharm Sci 1970; 59:49–52.
2. Levy G, Antkowiak J, Procknal J, et al. Effect of certain tablet formulation factors on dissolution rate of the active ingredient. II: Granule size, starch concentration, and compression pressure. J Pharm Sci 1963; 52:1047–1051.
3. Batuyios N. Anhydrous lactose in direct tablet compression. J Pharm Sci 1966; 55:727–730.
4. Gunsel W, Lachman L. Comparative evaluation of tablet formulations prepared by conventionally processed and spray dried lactose. J Pharm Sci 1963; 52:178–182.
5. Duvall R, Koshy K, Dashiell R. Comparative evaluation of dextrose and spray dried lactose in direct compression systems. J Pharm Sci 1965; 54:1196–1200.
6. Reier G, Shangraw R. Microcrystalline cellulose in tableting. J Pharm Sci 1966; 55:510–514.
7. Iranloye T, Parrott E. Compression force, particle size, and lubricants on dissolution rates. J Pharm Sci 1978; 67:535—539.
8. Marlow E, Shangraw R. Dissolution of sodium salicylate from tablet matrices prepared by wet granulation and direct compression. J Pharm Sci 1967; 56:498–504.
9. Finholt P, Pedersen R, Solvang S, et al. Effect of different factors on dissolution rate of drugs from powders, granules, and tablets: II Medd Norsk Farm Selsk 1966; 28:238–252.
10. Higuchi T, Rao A, Busse E, et al. The physics of tablet compression. II: The influence of degree of compression on properties of tablets. Am Pharm Assoc Sci Ed 1953; 42:194–200.
11. Luzzi L, Zoglio M, Maulding H. Preparation and evaluation of the prolonged release properties of nylon microcapsules. J Pharm Sci 1970; 59:338–341.
12. Jalsenjak I, Nicolaidou C, Nixon J. Dissolution from tablets prepared using ethycellulose microspheres. J Pharm Pharmacol 1977; 29:169–172.
13. Chowhan ZT, Palagyi L. Hardness increase induced by partial moisture loss in compressed tablets and its effect on in vitro dissolution. J Pharm Sci 1978; 67:1385–1389.
14. Chowhan ZT. Moisture, hardness, disintegration and dissolution interrelationships in compressed tablets prepared by the wet granulation process. Drug Dev Ind Pharm 1979; 5(1):41–62.
15. Chowhan ZT. Role of binders in moisture-induced hardness increase in compressed tablets and its effect on in vitro disintegration and dissolution. J Pharm Sci 1980; 69:1–4.
16. Chowhan Z, Yang I, Amaro A, et al. Effect of moisture and crushing strength on tablet friability and in vitro dissolution. J Pharm Sci 1982; 71:1371–1375.
17. Chowhan Z, Chatterjee B. A method for establishing in process variable controls for optimizing tablet friability and in vitro dissolution. Int J Pharm Technol Prod Mfg 1984; 5(2):6–12.
18. Alam AS, Parrott EL. Effect of aging on some physical properties of hydrochlorothiazide tablets. J Pharm Sci 1971; 60:263–266.

19. United States Pharmacopoeia. In Vitro and In Evaluation of Dosage Forms. 27th ed. Easton, PA: Mack Publishing Company, 2004.
20. Guidance for industry, extended release oral dosage form: development, evaluation, and application of in vitro-in vivo correlations. FDA, CDER, 1997.
21. Sirisuth N, Eddington ND. In vitro-in vivo correlations, systemic methods for the development and validation of an IVIVC metoprolol and naproxen drug examples. Int J Generic Drugs 2002; 3:250–258.
22. Amidon GL, Lennernas H, Shah VP, et al. A theoretical basis for a biopharmaceutics drug classification. The correlation of in vitro drug product classification and in vivo bioavailability. Pharm Res 1995; 12(3):413–419.
23. Dressman JB, Amidon GL, Reppas C, et al. Dissolution testing as a prognostics tool for oral drug absorption: immediate release dosage forms. Pharm Res 1998; 12(3):413–419.

RECOMMENDED READING

Abdou HM. Dissolution, Bioavailability and Bioequivalence. Easton, PA: Mack Publishing Company, 1989.

Blanchard J, Sawchuk R, Brodie B, eds. Principles and Perspectives in Drug Bioavailability. Basel, Switzerland: S. Krager AG, 1979.

Gibaldi M. Biopharmaceutics and Clinical Pharmacokinetics. 4th ed. Philadelphia, PA: Lea and Febiger, 1991.

Jambhekar S. Micromeritics and rheology. In: Ghosh T, Jasti B, eds. A Chapter in Theory and Practice of Contemporary Pharmaceutics. Boca Raton: CRC Press 2005; 137–161.

Leeson LJ, Carstensen J, eds. Dissolution Technology. Washington DC: Academy of Pharmaceutical Sciences, 1974.

Stavchansky SA, McGinity JW. Bioavailability in tablet technology. In: Lieberman HA, Lachman L, Schwartz JB, eds. Pharmaceutical Dosage Forms. Vol. 2, 2nd ed. New York, NY: Marcel Dekker, Inc., 1990.

Emani J. In vitro-in vivo correlations: from theory to applications. J Pharm Pharm Sci 2006; 9(2): 169–189.

Cardot JM, Beyssac E, Alric M. In vitro-in vivo correlation: importance of dissolution in IVIVC. Dissolution Technol 2007; 14(1):15–19.

Galia E, Nicolaides E, Horter D, et al. Evaluation of various dissolution media for predicting in vivo performance of class I and class II drugs. Pharm Res 1998; 15(5):698–705.

Young D, Devane JG, Butler J, eds. In Vitro-In Vivo Correlations. New York: Plenum Press, 1997.

Leeson LJ. In vitro-in vivo correlations. Drug Inf J 1995; 29:903–915.

Jung H, Milan RC, Girard ME, et al. Bioequivalence study of carbamazepine tablets: in vitro-in vivo correlations. Int J Pharm 1997; 152:37–44.

Rekhi GS, Jambhekar S. Bioavailability and In Vitro/In Vivo correlation for propranolol hydrochloride extended release bead products prepared using aqueous polymeric dispersions. J Pharm Pharmacol 1996; 48:1276–1284.

24 Granulation Process Modeling

Ian T. Cameron and Fu Y. Wang
School of Chemical Engineering, The University of Queensland, Queensland, Australia

MODELING OF GRANULATION SYSTEMS

In this section we introduce the background to granulation modeling by asking the questions, "Why model?" and "How can models be used in granulation systems applications?" The following sections seek to answer these questions and demonstrate the benefits that can flow from appropriate granulation process modeling.

Motivation for Modeling

There are many motivations for modeling granulation systems that are common to all process related issues. Process modeling is an area that has grown enormously over the last 50 years. Michaels (1) has pointed out that despite the change of particle technology from an underfunded and widely scattered research enterprise to a thriving globally recognized engineering discipline over the past 30 years, design and analysis of industrial particulate processes often remain rooted in empiricism. Without exception, granulation processes, like many solid-handling operations, continue to be one of the least understood and hence inefficient operations in the process industries. Thus, granulation remained more of "an art than a science" until 15 years ago, as stated by Litster (2). Granulation operations were performed employing popular practice rather than through systematic scientifically based strategies. The ineffectiveness of this approach led researchers into a quest to represent the dynamic or steady state (SS) characteristics of systems through a deeper understanding of the relevant phenomena of the physicochemical mechanisms being studied. Granulation systems have benefited through a growing interest in the building of various models and their deployment to address a range of applications.

Benefits

The benefits from the use of modeling include the following:

- An increased understanding of the governing mechanisms through endeavoring to represent them in the model description.
- An increased understanding of the relative importance of mechanistic contributions to the outputs of the process.
- Capturing of insight and knowledge in a mathematically usable form.
- Documentation of research findings in accessible form for various applications.
- Application of models for improved control performance and process diagnosis.
- Potential reuse of model components for a variety of applications from design through to process diagnosis.
- As a vehicle for new, novel designs of processing equipment.
- As a means to direct further experimentation and process data generation.

Costs

There are several important and not insubstantial costs involved in process modeling, including

- the time to plan, develop, test, and deploy models;
- personnel with the requisite discipline background to generate effective models through insight and modeling skills;

- the effort in laboratory scale or plant scale trials to elucidate process behavior and the cost of doing so;
- the cost of poor modeling practice in terms of inadequate documentation through the modeling phases and loss of corporate memory.

Process Modeling Fundamentals

Process modeling is purpose driven in that a model is developed for a particular application area. These application areas could include the following:

- Improved control performance through the use of process model–based control algorithms.
- Optimal performance of granulation systems through model-based optimization of production parameters such as shortest batch time or optimal product size distribution.
- Improved production scheduling using models to generate improved batch times estimates.
- Plant diagnosis for real-time plant operator guidance systems (OGS).
- Extraction of parameter estimates such as rate constants and granulation kernel parameters.
- Improved design of equipment or development of new designs based on better understanding and use of mechanistic phenomena.

The resultant model must be "fit-for-purpose," and this is achieved by having clearly stated goals for the modeling that are used to help assess the appropriateness of the model form and the model fidelity required for the job. In particular, modeling requires a methodology that is generic in nature.

A Systems Perspective

Models need to be built on a clear systems engineering understanding of the process. A typical system schematic is seen in Figure 1. For the system ($\boldsymbol{S}$) we need to clearly define the inputs ($\mathbf{u}$) and disturbances ($\mathbf{d}$) to our system as well as the outputs ($\mathbf{y}$) and the states of interest ($\mathbf{x}$). The system $\boldsymbol{S}$ converts inputs and disturbances to outputs and is expressed as

$$\mathbf{y} = S[\mathbf{u}, \mathbf{d}] \tag{1}$$

A model $\boldsymbol{M}$ is a representation of the system that transforms inputs to predicted outputs $\mathbf{y^{(M)}}$ in the form

$$\mathbf{y}^{(\mathrm{M})} = M[\mathbf{u}, \mathbf{d}] \tag{2}$$

How close $\mathbf{y}$ and $\mathbf{y^{(M)}}$ are is a key question in model validation.

Approaching modeling from a systems perspective provides a clear framework for developing models and identifying the key issues to be considered. The four principal classes of variables play particular roles in the modeling.

Inputs. The inputs $\mathbf{u}$ are the variables that are manipulated to "drive" the system or maintain its condition in the face of changes from disturbances. Typically we consider such aspects as binder addition rate or mixing intensity as inputs that we can manipulate.

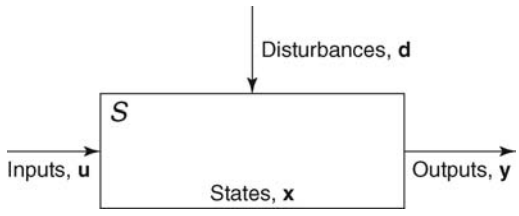


Figure 1 Schematic of a process system.

Disturbances. Disturbances **d** are variables over which we do not have clear control. They arise from raw material properties that might change from batch to batch. They could be environmental factors such as ambient temperature and humidity. They might be fluctuations in input voltage to motors or steam pressure that produce temperature disturbances in heated systems. Principal disturbances in all relevant categories need to be identified.

Outputs. The outputs **y** are the variables of interest for the designer, operator, or manager. They might be quality variables that are related to granule properties such as size distribution, granule moisture, or granule hardness. Other outputs of interest could be related to product temperature, flow rates, and composition. The outputs are necessarily measurable in some way, either directly online such as particle size distribution (PSD) or moisture or via laboratory analysis such as composition.

States. The states **x** of the system represent the internal variables that characterize the system behavior at any point in time.

Finally the system, ***S*** is a major consideration in modeling because of the variety of ways the real system can be represented by the model ***M*** of that system. Numerous forms of the model ***M*** are available. They can have a structure based on capturing fundamental phenomena from the physics and chemistry ("white box" models) to internal structures based on purely empirical approaches known as "black box" models. For black box models, the form is simply a convenient equation that captures the relationships among inputs, disturbances, and outputs.

Modeling Methodology and Workflow

Modeling should not be a haphazard activity. It is essential that a consistent and defensible methodology be adopted. One such methodology is given by Hangos and Cameron (3) and is seen in Figure 2. Each of the seven key steps is a vital part of any modeling activity, emphasizing that modern process modeling is not simply generating a set of equations, it is a much more holistic activity. It is also iterative in nature as seen from Figure 2.

The key aspects can be summarized as the following:

- *Goal-set definition*: making clear the reason for the modeling and the goals to be addressed in the modeling.
- *Model conceptualization*: clarifying the conserved quantities and the governing mechanisms to be included; clearly setting out the assumptions underlying the model.
- *Modeling data*: generating or referencing physical property data or plant data relevant to model building and model validation.
- *Model building and analysis*: putting the model together and then analyzing the model for properties relevant to solution and dynamic properties.
- *Model verification*: the task of ensuring that the coded model in the simulation environment is correctly represented and bug-free.
- *Model solution*: solving the model numerically or in some limited circumstances analytically, which can be challenging.
- *Model calibration and validation*: performing parameter estimation and then validating the model against plant or laboratory data.

The Modeling Goal

The modeling goal plays a vital role in the development of the model. Here we consider the most important general goals and describe briefly what is being achieved. We make reference to the general process system illustrated in Figure 1.

Dynamic simulation problem. Here the model is developed to predict the system behavior in time. We want to predict the outputs **y**, given the inputs **u**, the disturbance pattern **d**, the model structure ***M*** with the model parameters **p**. This is most widely used goal.

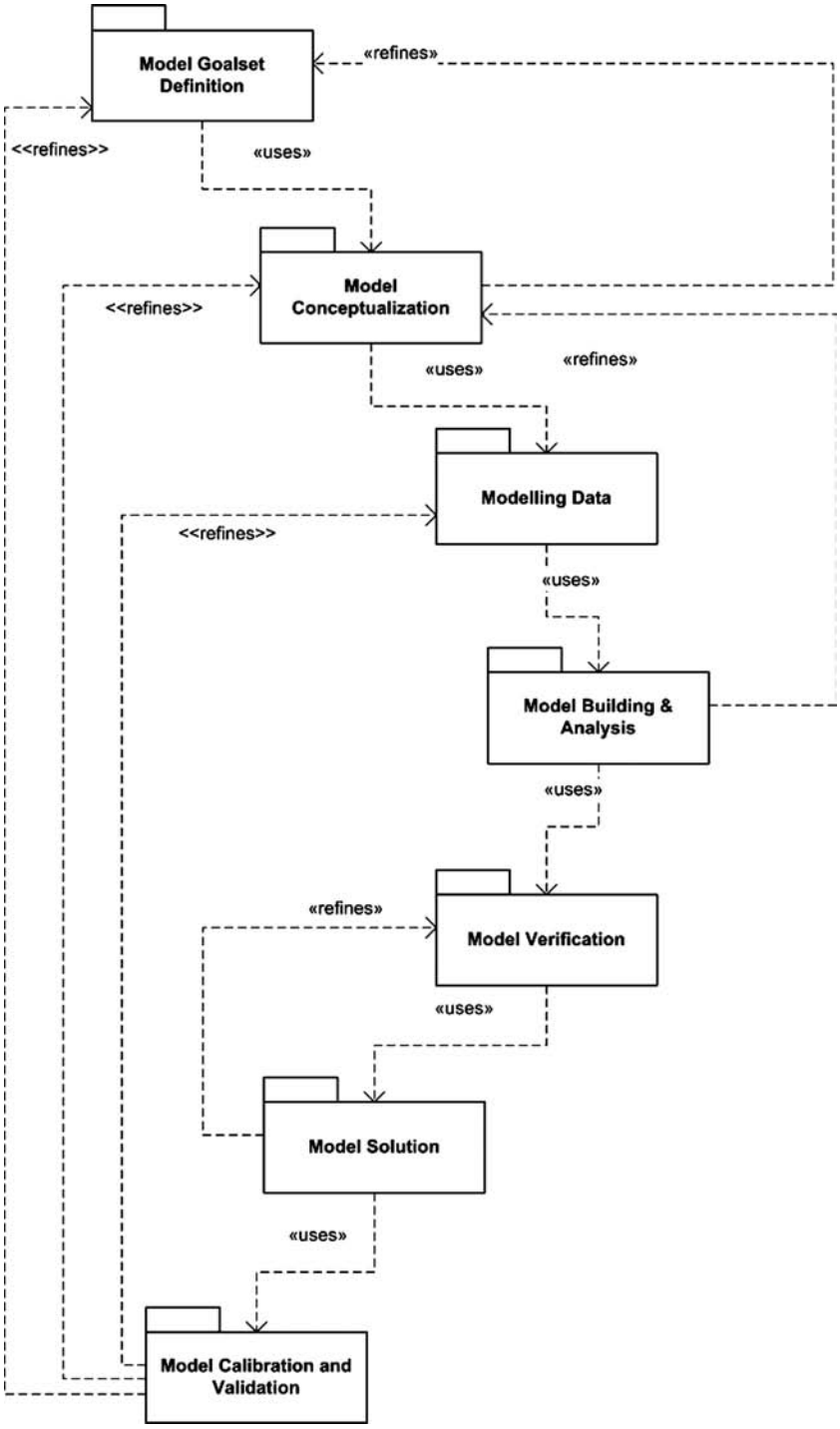


Figure 2 Modeling methodology and workflow.

Design problem. Here we are interested in calculating certain parameters or design variables $\tilde{p}$ from the parameter set given all the other inputs, model form and disturbances, and a set of desired outputs.

Process control.
Regulation and state-driving problems. Here we want to design or compute the inputs **u** for a prescribed response **y** of the system.

System identification problem. Here we want to determine the structure of the model ***M*** and its parameters **p**, using input and output information.

State estimation problem. Here we want to estimate the internal states **x** of a particular model ***M***.

Fault detection and diagnosis problem. Here we find the faulty modes and/or system parameters that correspond to the *measured* input and output data.

These three key areas show the various goals that are often given for modeling of processing systems.

Approaches to Modeling

There are several approaches to modeling process systems. At one extreme is the mechanistic modeling that seeks to incorporate the fundamental physics and chemistry into the model. This is the so-called white box approach. At the other end of the spectrum is the fitting of an arbitrary function to the input-output data—the empirical model. In between we have the so-called gray box models that are normally what is developed. Some relevant comments follow.

Empirical or Black Box Methods

These models are based on actual plant data, typically in the form of time series of input and output data at fixed time intervals. The model is built by selecting a model structure ***M*** and then fitting the model parameters to get the best fit of the model to the data. Model forms such as autoregressive moving average (ARMA) or autoregressive moving average exogenous (ARMAX) types are typically used.

In most cases, techniques are used to vary both the structure and the model parameters to obtain the "best" or simplest model that gives the best fit. Various information criteria like Akaike's or Bayesian measures can be used that essentially get the simplest model for the best fit. It is a form of parsimony in model building. Many packages such as the MATLAB^{TM} identification toolbox help in such modeling.

This approach can be very useful if no significant insight is needed into the model, but a model is needed quickly to be used for a control application. The structural form of the model and the parameter values normally have no physical significance. The application range of such a model is limited to the range of data and hence this can be a significant limitation. Extrapolation is dangerous.

Mechanistic and Gray Box Models

Mechanistic models incorporate the underlying understanding of the physics and chemistry into the models. Typically we can identify two major aspects in mechanistic modeling that cover conservation and constitutive aspects:

- Application of thermodynamic conservation principles for mass, energy, and momentum.
- Application of population balances that track PSDs as various particulate phenomena take place.
- Development of appropriate constitutive relations that define intensive properties, mass, and heat transfer mechanisms as well as particle growth and breakage mechanisms.

The development of mechanistic models is far more complex and time consuming than for empirical models and is only justified when time permits, the model is to be used over a wide operating range, and the relevant insight in establishing the constitutive relations is available.

Inevitably, even the best mechanistic models require some data fitting, leading to the concept of gray box models. This is the normal practice in industrial modeling of such systems. It means that adequate data must be available to carry out the validation studies. This task is particularly difficult for validation of dynamic models.

KEY FACTORS IN GRANULATION MODELING

The modeling of granulation system from a mechanistic perspective inevitably means representing the conservation principles and the constitutive relations that reflect the key factors in granulation. We briefly consider these in turn but refer the reader to the relevant chapters in this handbook for detailed descriptions of the phenomena.

Conservation Principles

The conservation of mass, energy, momentum, and particle number can be important aspects of granulation modeling.

Mass conservation is crucial and is the fundamental concept for any granulation system. Key factors here will be solids or slurry feed rates, any outflows, and the addition of binders and additives to the granulation device. Accompanying the mass balance over the device, there will be the energy balance from which the intensive property of temperature can be estimated.

Of particular importance in granulation systems is the factor of particle populations. The PSD within granulation devices is crucial, and there are a number of mechanisms that simultaneously occur in the device, depending on the powder properties and operating regime. The challenge is in the description of these many mechanisms that are occurring. The following section outlines those mechanisms that require consideration. The section "Representing Granulation Processes Through Population Balances" deals in detail with the development of population balance representations and their variants.

The Principal Constitutive Mechanisms

There are three principal mechanisms that need to be considered.

Nucleation

Nucleation refers to the formation of initial aggregates that are typically a result of interaction between the binder spray droplets and the powder in the device. This mechanism provides the initial stage for further growth through a number of mechanisms. A number of nucleation models have been proposed in the literature.

Growth

Granule growth occurs through two key mechanisms that can be separated for discussion purposes. The topic is discussed more fully in the section on one-dimensional (1D) population balance models.

Layering. Layering refers to the take up of fine particles onto the surface of larger granules. It is often induced by rolling action and is a means of granule growth that creates hard, compact granules. A practical layering model is proposed in section "Optimization and Open-Loop Optimal Control Equations" for solving optimal control of granulation processes.

Agglomeration. Agglomeration or coalescence refers to the successful collision of two particles that result in a composite particle. The success of collisions can be a function of particle size, binder, and powder properties and operational factors such as bed height, powder velocity, and shear for mixer granulators (see sect. "Coalescence Kernels" for more details).

Breakage

Breakage in high shear and drum granulation is a significant issue, being more important in high-shear devices. There are various forms of breakage from cleavage of particles to particle surface attrition where the granule is chipped by collision with other particles, the wall, or impeller. Complexity of breakage models extends from binary breakage models to full particle distributions represented by breakage and selection functions or empirical models (4–6).

The following sections now develop in detail some of the important aspects of granulation process modeling, through the use of population balances and alternative approaches.

REPRESENTING GRANULATION PROCESSES THROUGH POPULATION BALANCES

The particulate nature of solids is characterized by a number of properties, such as size, shape, liquid, and gas content, porosity, composition, and age. These properties are denoted as internal coordinates, whereas the Euclidian coordinates, such as rectangular coordinates (x, y, z), cylindrical coordinates (r, φ, z), and spherical coordinates (r, θ, φ) used to specify the locations of particles are defined as external coordinates.

The most important property for the characterization of particles is particle size. Randolph and Larson (7) have pointed out: "As no two particles will be exactly the same size, the material must be characterized by the distribution of sizes or particle-size distribution (PSD)." If only size is of interest, a single-variable distribution function is sufficient to characterize the particulate system. If additional properties are also important, multivariable distribution functions must be developed. These distribution functions can be predicted through numerical simulations using population balance equations (PBEs).

Ramkrishna (8) provided a brief explanation on the PBE as, "The population balance equation is an equation in the foregoing number density and may be regarded as representing a number balance on particles of a particular state. The equation is often coupled with conservation equation for entities in the particles' environmental (or continuous) phase."

In this chapter, single-variable and multivariable population balances will be described. However, the emphasis will be placed on the single-variable PBEs with size as the only internal coordinate.

General Population Balance Equations

A population balance for particles in some fixed subregion of particle phase space can be conceptually represented in natural words as follows:

$$\begin{aligned}\left\{\begin{array}{c}\text{Density function change}\\ \text{in class, location, and time}\end{array}\right\} = &\left\{\begin{array}{c}\text{disperse in}\\ \text{through boundary}\end{array}\right\} - \left\{\begin{array}{c}\text{disperse out}\\ \text{through boundary}\end{array}\right\}\\ &+ \left\{\begin{array}{c}\text{flow in}\\ \text{through boundary}\end{array}\right\} - \left\{\begin{array}{c}\text{flow out}\\ \text{through boundary}\end{array}\right\}\\ &+ \left\{\begin{array}{c}\text{grow in}\\ \text{from lower classes}\end{array}\right\} - \left\{\begin{array}{c}\text{grow out}\\ \text{from current class}\end{array}\right\}\\ &+ \left\{\begin{array}{c}\text{birth due to}\\ \text{coalescence}\end{array}\right\} - \left\{\begin{array}{c}\text{death due to}\\ \text{coalescence}\end{array}\right\}\\ &+ \left\{\begin{array}{c}\text{breakup in}\\ \text{from upper classes}\end{array}\right\} - \left\{\begin{array}{c}\text{breakup out}\\ \text{from current class}\end{array}\right\}\end{aligned} \tag{3}$$

The superstructure of the general PBE can be represented as follows:

$$\begin{aligned}\frac{\partial}{\partial t} f(\mathbf{x},\mathbf{r},t) = &\nabla_r \cdot \nabla_r [D_r f(\mathbf{x},\mathbf{r},t)] - \nabla_r \cdot \dot{R} f(\mathbf{x},\mathbf{r},t) - \nabla_x \cdot \dot{X} f(\mathbf{x},\mathbf{r},t)\\ &+ B_{\mathrm{c}}(\mathbf{x},\mathbf{r},t) - D_{\mathrm{c}}(\mathbf{x},\mathbf{r},t) + B_{\mathrm{b}}(\mathbf{x},\mathbf{r},t) - D_{\mathrm{b}}(\mathbf{x},\mathbf{r},t)\end{aligned} \tag{4}$$

where f is the multivariant number density as a function of properties and locations, r is the external coordinate vector (also known as spatial coordinate vector) for the determination of particle locations, x is the internal coordinate vector for the identification of particle properties, such as size, moisture content, and age, D_r is the dispersion coefficient, $\dot{\mathbf{R}}$ is the velocity vector in the external coordinate system, $\dot{\mathbf{X}}$ is the rate vector in the internal coordinate system, B_c and D_c are birth and death rates for coalescence, respectively, and B_b and D_b are birth and death rates for breakage, respectively. The first and second terms in the right-hand side of equation (4) represent dispersion and convection particle transport, respectively, whereas the third term quantifies the growths of particles with respect to various properties, such as size and moisture. The birth and death rates for coalescence are given by

$$\begin{aligned} B_c(\mathbf{x},\mathbf{r},t) &= \int_{\Omega_x} dV_{\mathbf{x}'} \int_{\Omega_r} \frac{1}{\delta}\beta(\tilde{\mathbf{x}},\tilde{\mathbf{r}};\mathbf{x}',\mathbf{r}')f(\tilde{\mathbf{x}},\tilde{\mathbf{r}},t)f(\mathbf{x}',\mathbf{r}',t)\frac{\partial(\tilde{\mathbf{x}},\tilde{\mathbf{r}})}{\partial(\mathbf{x},\mathbf{r})}dV_{\mathbf{r}'} \\ D_c(\mathbf{x},\mathbf{r},t) &= f(\mathbf{x},\mathbf{r},t)\int_{\Omega_x} dV_{\mathbf{x}'} \int_{\Omega_r} \beta(\mathbf{x}',\mathbf{r}';\mathbf{x},\mathbf{r})f(\mathbf{x}',\mathbf{r}',t)dV_{\mathbf{r}'} \end{aligned} \tag{5}$$

where β is the coalescence kernel, $\Omega_{\mathbf{x}}$ and $\Omega_{\mathbf{r}}$ are integration boundaries for internal and external coordinates, respectively, δ represents the number of times identical pairs have been considered in the interval of integration so that $1/\delta$ corrects for the redundancy, the term $\partial(\tilde{\mathbf{x}},\tilde{\mathbf{r}})/(\partial\mathbf{x},\mathbf{r})$ accounts for the coordinate transformation such that the colliding pair with original coordinates $[\tilde{\mathbf{x}},\tilde{\mathbf{r}}]$ and $[\mathbf{x}', \mathbf{r}']$, respectively, before collision should be identified by the coordinates $[\mathbf{x}, \mathbf{r}]$ after coalescence. Mathematically, this requires that the density with respect to coordinates $[\tilde{\mathbf{x}}(\mathbf{x},\mathbf{r}|\mathbf{x}'\mathbf{r}'),\tilde{\mathbf{r}}(\mathbf{x},\mathbf{r}|\mathbf{x}'\mathbf{r}')]$ must be transformed into one in terms of $(\mathbf{x}, \mathbf{r})$ by using the appropriate Jacobian of the transformation. Ramkrishna (8) showed that the determinant of the Jacobian of the transformation satisfies the following equation:

$$\frac{\partial(\tilde{\mathbf{x}},\tilde{\mathbf{r}})}{\partial(\mathbf{x},\mathbf{r})} = \begin{vmatrix} \frac{\partial\tilde{x}_1}{\partial x_1} & \cdots & \frac{\partial\tilde{x}_1}{\partial x_n} & \frac{\partial\tilde{x}_1}{\partial r_1} & \frac{\partial\tilde{x}_1}{\partial r_2} & \frac{\partial\tilde{x}_1}{\partial r_3} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \frac{\partial\tilde{x}_n}{\partial x_1} & \cdots & \frac{\partial\tilde{x}_n}{\partial x_n} & \frac{\partial\tilde{x}_n}{\partial r_1} & \frac{\partial\tilde{x}_n}{\partial r_2} & \frac{\partial\tilde{x}_n}{\partial r_3} \\ \frac{\partial\tilde{r}_1}{\partial x_1} & \cdots & \frac{\partial\tilde{r}_1}{\partial x_n} & \frac{\partial\tilde{r}_1}{\partial r_1} & \frac{\partial\tilde{r}_1}{\partial r_2} & \frac{\partial\tilde{r}_1}{\partial r_3} \\ \frac{\partial\tilde{r}_2}{\partial x_1} & \cdots & \frac{\partial\tilde{r}_2}{\partial x_n} & \frac{\partial\tilde{r}_2}{\partial r_1} & \frac{\partial\tilde{r}_2}{\partial r_2} & \frac{\partial\tilde{r}_2}{\partial r_3} \\ \frac{\partial\tilde{r}_3}{\partial x_1} & \cdots & \frac{\partial\tilde{r}_3}{\partial x_n} & \frac{\partial\tilde{r}_3}{\partial r_1} & \frac{\partial\tilde{r}_3}{\partial r_2} & \frac{\partial\tilde{r}_3}{\partial r_3} \end{vmatrix} \tag{6}$$

The birth and death rates for breakage are described as

$$B_b(\mathbf{x},\mathbf{r},t) = \int_{\Omega_r} dV_{\mathbf{r}'} \int_{\Omega_x} b(\mathbf{x}',\mathbf{r}',t)P(\mathbf{x},\mathbf{r}|\mathbf{x}',\mathbf{r}',t)S(\mathbf{x}',\mathbf{r}',t)f(\mathbf{x}',\mathbf{r}',t)\,dV_{\mathbf{x}'} \tag{7}$$

and

$$D_b(\mathbf{x},\mathbf{r},t) = S(\mathbf{x},\mathbf{r},t)f(\mathbf{x},\mathbf{r},t) \tag{8}$$

where $b(\mathbf{x}', \mathbf{r}', t)$ is the average number of particles formed from the breakage of a single particle of state $(\mathbf{x}', \mathbf{r}')$ at time t, $P(\mathbf{x}, \mathbf{r}, |\mathbf{x}', \mathbf{r}', t)$ is the probability density function for particle from the breakage of state $(\mathbf{x}', \mathbf{r}')$ at time t that have state $(\mathbf{x}, \mathbf{r})$, $S(\mathbf{x}, \mathbf{r}, t)$ is the selection function, which represents the fraction of particles of state $(\mathbf{x}, \mathbf{r})$ breaking per unit time.

Equations (5) and (6) involve three different locations: $\tilde{\mathbf{r}}$ and $\mathbf{r}'$ for the colliding pair of particles and $\mathbf{r}$ for the agglomerated particle. Although this treatment is general and mathematically rigorous, it could be unnecessarily complicated for engineering applications.

A common practice is to assume that these three locations are very close to each other during the particle collision and granule formation. That is

$$\tilde{\mathbf{r}} \approx \mathbf{r}' \approx \mathbf{r} \tag{9}$$

This assumption requires that the phenomenon of fast particle jumps in the system is not severe, which is achievable for most industrial granulation processes. If equation (9) holds, equations (5) and (6) can be simplified considerably to obtain

$$\begin{aligned} B_{\mathrm{c}}(\mathbf{x},\mathbf{r},t) &= \frac{1}{2}\int_{\Omega_{\mathrm{x}}} \beta(\tilde{\mathbf{x}},\mathbf{x}',\mathbf{r}) f(\tilde{\mathbf{x}},\mathbf{r},t) f(\mathbf{x},\mathbf{r},t)\frac{\partial(\tilde{\mathbf{x}})}{\partial(\mathbf{x})} dV_{\mathbf{x}'} \\ D_{\mathrm{c}}(\mathbf{x},\mathbf{r},t) &= f(\mathbf{x},\mathbf{r},t)\int_{\Omega_{\mathrm{x}}} \beta(\mathbf{x}',\mathbf{x},\mathbf{r}) f(\mathbf{x}',t) dV_{\mathbf{x}'} \end{aligned} \tag{10}$$

and

$$\frac{\partial(\tilde{\mathbf{x}})}{\partial(\mathbf{x})} = \begin{vmatrix} \dfrac{\partial \tilde{x}_1}{\partial x_1} & \cdots & \dfrac{\partial \tilde{x}_1}{\partial x_n} \\ \vdots & \vdots & \vdots \\ \dfrac{\partial \tilde{x}_n}{\partial x_1} & \cdots & \dfrac{\partial \tilde{x}_n}{\partial x_n} \end{vmatrix} \tag{11}$$

Similarly, equation (7) becomes

$$B_{\mathrm{b}}(\mathbf{x},\mathbf{r},t) = \int_{\Omega_{\mathrm{x}}} b(\mathbf{x}',\mathbf{r},t) P(\mathbf{x}|\mathbf{x}',\mathbf{r},t) S(\mathbf{x}',\mathbf{r},t) f(\mathbf{x}',\mathbf{r},t) dV_{\mathbf{x}'} \tag{12}$$

In the following material, breakage effects have been considered negligible and equation (9) is always assumed to be valid.

One-Dimensional Population Balance Models

One-dimensional (1D) population balance models for both batch and continuous systems are described in this section as special cases of the generalized population balance model stated in the previous section.

Batch Systems

For a well-mixed batch system with only one internal coordinate v (particle size), equation (4) is reduced to

$$\begin{aligned} \frac{\partial}{\partial t} n(v,t) = &-\frac{\partial}{\partial v}[G n(v,t)] \\ &+ \frac{1}{2}\int_0^v \beta(v-v',v') n(v-v',t) n(v',t) dv' - n(v,t)\int_0^\infty \beta(v,v') n(v',t) dv' \end{aligned} \tag{13}$$

where n is the 1D number density, G is known as the growth rate. For notational clarity, we use f and n to denote the multidimensional and 1D number density functions, respectively. Both notations bear the same physical significance. Through a comparison of equation (13) with equations (4), (10), and (11), it is easy to observe the following membership relationships:

$$\begin{aligned} &v \in \mathbf{x}, v' \in \mathbf{x}', \quad (v - v') \in \tilde{\mathbf{x}}, \\ &G = \frac{dv}{dt} \in \dot{\mathbf{X}}, \quad \frac{\partial(\tilde{\mathbf{x}})}{\partial(\mathbf{x})} = \frac{\partial(v-v')}{\partial v} = 1 \end{aligned} \tag{14}$$

Equation (13) is more frequently applied to industrial granulation processes than its generalized format described by equation (4).

Continuous Systems

The PBE for continuous systems with internal and external coordinates each is given by

$$\frac{\partial}{\partial t}n(v,z,t) = \frac{\partial}{\partial z}[\dot{Z}\, n(v,z,t)] - \frac{\partial}{\partial v}[Gn(v,z,t)] + \frac{1}{2}\int_0^v \beta(v-v',v')n(v-v',z,t)n(v',z,t)dv' - n(v,z,t)\int_0^\infty \beta(v,v')n(v',z,t)dv' \tag{15}$$

where the special velocity is defined as

$$\dot{Z} \;=\; \frac{dz}{dt} \;\in\; \dot{\mathbf{R}} \tag{16}$$

Although continuous granulation processes are commonly encountered in the fertilizer and mineral processing industries, most granulation operations in the pharmaceutical industry are performed as batch processes employing either high-shear mixers or batch fluidized-bed granulators. Consequently, most modeling studies on pharmaceutical granulation have focused on batch processes. However, it is important to obtain a complete knowledge in both batch and continuous granulation processes for improved design and operations.

Coalescence Kernels

Conventional coalescence kernels. It is easy to see that a coalescence kernel is affected by two major factors: (*i*) collision probability of the specified pair of particles, and (*ii*) successful coalescence or rebounding after collision. The first factor mainly depends on the particle sizes, granulator configurations, particle flow patterns, and operating conditions. The second issue has been intensively studied by Liu et al. (9) with the identification of the following five most important aspects affecting the success of coalescence: elastic-plastic properties, viscous fluid layer, head of collision, and energy balance. The authors have also observed that there are two types of coalescences distinguished by particle deformations. That is, the type I coalescence is not associated with any particle deformation during the collision, whereas the type II coalescence is accompanied by particle deformations. Liu and Litster (10) further proposed a new physically based coalescence kernel model based on the criteria developed earlier (9). From these fundamental studies, it can be determined qualitatively that the coalescence kernels should depend on particle sizes, energy consumptions, particle deformability, and most importantly, the moisture content (viscous fluid layer). A historical summary of the proposed coalescence kernels is given in Table 1, which is an extension of the table originally presented by Ennis and Litster (11) with the new coalescence kernel developed by Liu and Litster (10) and another kernel from aerosol dynamics (12).

The rate processes of aggregation, consolidation, breakage and nucleation that underlie the granulation process have been well-characterized over the years, as borne out by an exhaustive review by Iveson et al. (19). The various mesoscale processes have been characterized in terms of dimensionless parameters and regime charts have been developed. Although some of the kernels shown in Table 1 are physically based and inspired by the underlying process mechanisms, they are not truly mechanistic.

Mechanistic coalescence kernels. Immanuel & Doyle III (20) and Poon et al. (21) have attempted the derivation of mechanistic kernels for the aggregation and nucleation processes. The mechanistic modeling of the aggregation kernels requires the identification of the net attraction potentials (energies) between the different particle pairs. In the granulation process, the kinetic energy of the particles constitutes the major potential of attraction between the granules ($1/2\ mu_0^2$) (9,19,22). The dissipation of the kinetic energy of the granules is primarily attributed to the viscous forces in the liquid-binder film. Other forces that contribute to the dissipation are the collision energy and the elastic energy of the granules, which come into play only when the particles are involved in an actual collision by overcoming the viscous

Table 1 A Summary of Conventional Coalescence Kernel in the Literature

Kernel	References
$\beta = \beta_0$	Kapur and Fuerstenau (13)
$\beta = \beta_0 \frac{(u+v)^a}{(uv)^b}$	Kapur (14)
$\beta = \beta_0 \frac{\left(u^{2/3}+v^{2/3}\right)}{1/u+1/v}$	Sastry (15)
$\beta = a(u+v)$	Golovin (16)
$\beta = a\frac{(u-v)^2}{(u+v)}$	Golovin (16)
$\beta = \begin{cases} k, & t<t_s \\ a(u+v), & t>t_s \end{cases}$	Adetayo et al. (17)
k: constant, t_s: switching time	
$\beta = \begin{cases} k, w<w* \\ 0, w>w* \end{cases}$ $w = \frac{(u+v)^a}{(uv)^b}$	Adetayo and Ennis (18)
k, *a*, *b*: constants w*: critical granule volume	
$\beta = \beta_0(1/u+1/v)^{1/2}(u^{1/3}+v^{1/3})^2$	Friedlander (12)
$\beta = \beta_0(u^{-1/3}+v^{-1/3})(u^{1/3}+v^{1/3})$	
$\beta\vert_{u,v} = \begin{cases} \beta_1 & \text{Types I and II without permanent deformation} \\ \beta_2 & \text{Type II with permanent deformation} \\ 0 & \text{rebound} \end{cases}$	Liu and Litster (10)

dissipation. Different forces become important in different regimes of particle sizes, binder content, and operating conditions (mixing rates). The capillary repulsive forces between the particles are usually neglected in relation to the stronger viscous forces.

The particles that collide with each other as a result of their kinetic energy will either coalesce or rebound. Coalescence is classified into two types—type I and type II. Type I coalescence occurs when the viscous force is able to overcome the kinetic energy, causing the particles to coalesce before the occurrence of a collision (through the liquid bridge). Type II coalescence occurs when the particles actually collide and lose all the kinetic energy. The elastic energy causes the particles to rebound, being dissipated again in the viscous binder layer. If this dissipation is complete, then coalescence occurs (either with or without complete recovery of the deformation). See Iveson et al. (19) for further mechanistic details.

Net attractive potential for type I coalescence (balancing the kinetic energy with the viscous repulsion) is given by equation (17), where p_1 and p_2 are the two particles, m is the reduced mass of the particles, h is the separation distance between the particles, and u is the varying relative velocity of the particles as they approach each other. The velocity u is also defined in equation (17), wherein h_0 is the depth of the liquid-binder film on the surface, u_0 is the initial approach velocity of the particles (based on the mixing rates in the granulator), and $\mathrm{St_v}$ is the viscous Stokes number.

$$\begin{aligned} \Psi(p_1,p_2,h) &= \frac{1}{2}m[2u(h)]^2 \\ u &= u_0 \text{ for } h > h_0 \\ &= u_0\left[1-\frac{1}{\mathrm{St_v}}\ln\left(\frac{h_0}{h}\right)\right] \text{for } h < h_0 \end{aligned} \tag{17}$$

For type II coalescence, two different sequential processes are involved—the forward and the reverse paths. The process with the higher energetics is the rate-determining process. The net

attractive potential for the two processes are defined in equation (18), where E_c is the energy lost during impact and deformation and u_1 is the velocity at impact. In this equation, u' is the net rebound velocity and δ'' is the permanent plastic deformation in the granules:

$$\Psi_{\text{forward}}(p_1,p_2,h) = \frac{1}{2}m[2u(h)]^2 - E_c$$

$$\Psi_{\text{reverse}}(p_1,p_2,h) = -\frac{1}{2}m[2u'(h)]^2$$

$$E_c = \frac{1}{2}m(2u_1)^2$$

$$u'(h) = u_2 - \frac{3\pi\mu\tilde{D}^2}{16\tilde{m}h^2}\left[(\delta'')^2\left(\frac{h^2}{h_a^2}-1\right) + 2h\delta''\left(\frac{h}{h_a}-1\right) + 2h^2\ln\left(\frac{h}{h_a}\right)\right] \text{ for } 0 < h < h_0$$

$$= u'(h_0) \text{ for } h > h_0$$

$$\delta'' = \left(\frac{8}{3\pi}\right)^{1/2}\text{St}_{\text{def}}^{1/2}\tilde{D}\left[1-\frac{1}{\text{St}_v}\ln\left(\frac{h_0}{h_a}\right)\right]\left[1-7.36\frac{Y_d}{E^*}\text{St}_{\text{def}}^{-1/2}\right]\left[1-\frac{1}{\text{St}_v}\ln\left(\frac{h_0}{h_a}\right)\right]^{-1/2} \tag{18}$$

These SS forces can be incorporated into a dynamic calculation of the aggregation rates and the aggregation kernel, as described in the emulsion polymerization literature (23). This net attractive potential information can be employed in the Smoluchowski formulation as shown in equation (19). The Fuch Stability Ratio W is defined in equation (20) for type I and type II aggregation, respectively. In these equations, r_i is the radius of particle p_i, k is the Boltzmann constant, T is the temperature, and c_1 is an adjustable constant.

$$\beta(p_1,p_2) = c_1\frac{4\pi u_0(r_1+r_2)^2}{W} \tag{19}$$

$$W(p_1,p_2) = (r_1+r_2)\int_{D=r_1+r_2}^{\infty}\frac{e^{\psi(p_1,p_2,D)/kT}}{D^2}dD$$

$$\frac{W(p_1,p_2)}{r_1+r_2} = \max\left(\int_{D=r_1+r_2}^{\infty}\frac{e^{-\psi_{\text{forward}}(p_1,p_2,D-r_1-r_2)/kT}}{D^2}dD, \int_{D=r_1+r_2}^{\infty}\frac{e^{-\psi_{\text{reverse}}(p_1,p_2,D-r_1-r_2)/kT}}{D^2}dD\right) \tag{20}$$

Multidimensional Population Balance Models

Two-Dimensional Population Balance Models

In this section, we study a perfect mixing, batch granulation system with two internal (property) coordinates: particle value v and liquid value v_L. Because of the perfect mixing feature, there is no spatial coordinate in the model. However, the proposed modeling strategy can easily be extended to continuous processes with both internal and external coordinates. The 2D PBE for a batch granulation process is

$$\begin{aligned}\frac{\partial}{\partial t}f(v,v_L,t) = &-\frac{\partial}{\partial v}\left[\frac{dv}{dt}f(v,v_L,t)\right] - \frac{\partial}{\partial v_L}\left[\frac{dv_L}{dt}f(v,v_L,t)\right]\\ &+\frac{1}{2}\int_0^v\int_0^{\min(v_L,v-v')}\beta(v-v',v_L-v_L',v',v_L')f(v-v',v_L-v_L',t)f(v',v_L',t)dv_L'dv'\\ &-f(v,v_L,t)\int_0^{\infty}\int_0^{v_L}\beta(v,v_L,v',v_L')f(v',v_L',t)dv_L'dv'\end{aligned} \tag{21}$$

The relationship between the bivariant number density function f and single-variant number density function n is determined as

$$n(v,t) = \int_0^v f(v, v_L, t)\, dv_L \tag{22}$$

For the aggregation-only processes, the first two terms on the right-hand side of equation (21) representing convective particle transport and particle growth by layering are negligible. Equation (21) is reduced to

$$\begin{aligned}\frac{\partial}{\partial t} f(v, v_L, t) = & \\ & + \frac{1}{2}\int_0^v \int_0^{\min(v_L, v-v')} \beta(v-v', v_L - v_L', v', v_L') f(v-v', v_L - v_L', t) f(v', v_L', t)\, dv_L' dv' \\ & - f(v, v_L, t) \int_0^\infty \int_0^{v_L} \beta(v, v_L, v', v_L') f(v', v_L', t)\, dv_L' dv'\end{aligned} \tag{23}$$

Under certain mathematical assumptions, a 2D PBE can be reduced to two single-dimension PBEs, which will be described in the next section.

Higher-Dimensional Population Balance Models

In consonance with the above study on 2D population balance models, Iveson (24) has suggested recently that a 1D population balance model based on particle size is quite inadequate in accounting for the granulation process. As laid out previously, the three major contributing phenomena that have been identified in recent times in the granulation processes are wetting and nucleation; aggregation, layering, and consolidation; breakage and attrition. Among these the major role played by consolidation is to reduce the porosity of the granules and thereby increase the fractional binder content and the chances of successful aggregation. The rate of aggregation itself is determined by both the size of the granules and its fractional binder content. Thus, at the least, the characterization of the binder content and porosity in addition to the granule size is important in the granulation processes. Iveson (24) also points out the importance of the heterogeneity at the macroscopic level in terms of binder distribution as well as size segregation effects that are required to be accounted for in a rigorous model of the granulation operation. He also points out that several applications also require the explicit characterization of the concentration of the granules.

$$\begin{aligned}\frac{\partial n(m, \varepsilon, w, x, t)}{\partial t} = & B_{coal}(m, \varepsilon, w, x, t) - D_{coal}(m, \varepsilon, w, x, t) \\ & + C(m, \varepsilon, w, x, t) + W(m, \varepsilon, w, x, t)\end{aligned} \tag{24}$$

wherein m is the total mass of the granule particle, ε is the particle porosity, w is the fractional binder content (fraction of binder to solid mass), and x is the composition of the solid (drug vs. excipient). The terms "$B_{coal}\,(m, \varepsilon, w, x, t)$" and "$D_{coal}\,(m, \varepsilon, w, x, t)$" account respectively for the birth and death of particles due to coalescence events. "C" accounts for consolidation and "W" accounts for wetting.

A similar multidimensional population balance model was also proposed by Verkoeijen et al. (25). They extend the Iveson proposal in that they suggest the use of truly mutually independent particle properties as the internal variables. Thus, in a 3D formulation, they propose the use of the volumes of solid, liquid, and gas as the internal coordinates (rather than the particle total volume, binder content, and porosity, which are not mutually independent of each other). This approach results in elegantly separating the underlying mesoscopic processes of aggregation, consolidation, breakage, drying, and layering.

Immanuel and Doyle III (20) propose the following multidimensional formulation of the population balance model for the granulation process, using the individual volumes of solid, liquid, and air as the internal coordinates.

$$\frac{\partial}{\partial t}F(s,l,g,t)+\frac{\partial}{\partial g}\left(F(s,l,g,t)\frac{dg}{dt}\right)+\frac{\partial}{\partial s}\left(F(s,l,g,t)\frac{ds}{dt}\right)+\frac{\partial}{\partial l}\left(F(s,l,g,t)\frac{dl}{dt}\right)$$
$$=\Re_{\text{aggre}}(s,l,g,t)+\Re_{\text{break}}(s,l,g,t)+\Re_{\text{nuc}}(s,l,g,t) \tag{25}$$

where $F(s, l, g, t)$ is the population density function, defined such that $F(s, l, g, t)ds\,dl\,dg$ is the moles of granules of solid volume between s and $s + ds$, liquid volume between l and $l + dl$, and gas volume between g and $g + dg$. $\Re_{\text{nuc}}(s, l, g, t)$ accounts for the rate of nucleation of new granules. $\Re_{\text{aggre}}(s, l, g, t)$ accounts for the gain/loss of granules due to the aggregation process, while $\Re_{\text{break}}(s, l, g, t)$ comprises similar terms due to granule breakage. The partial derivative with respect to g on the left-hand side accounts for the consolidation phenomenon, wherein dg/dt is negative (there is a continuous decrease in the pore volume of the granules as they compact, while the solid and liquid content of each granule is left unaltered). The partial derivative term with respect to s accounts for any simultaneous crystallization and layering of the granule surface with the solid. The term with respect to l accounts for any drying effects. These latter two terms are usually restricted to certain special cases of granulation applications.

Further theoretical and experimental studies on 3D population balance model of granulation have been carried out collaboratively among a number of universities with fruitful outcomes (21,26,27).

Reduced-Order Models

Reduced-Order Models Using the Concept of Lumped Regions in Series

When particle populations are spatial dependent, such as that in a long rotating drum granulator, the population balance model is described by equation (15) with spatial variable z included in the model equation. In many industrial applications, the concept of lumped regions in series is used to reduce the model order. By using this method, a whole granulator is divided into a number of sections with an assumption that perfect mixing can be achieved in each section. The basic idea is schematically depicted in Figure 3.

In Figure 3, Q denotes the number flow rate, the subscripts F and P represent the feed and product streams, respectively, and N_R is the total number of regions used to approximate the granulator. The reduced-order model for equation (15) using the method of lumped regions in series is given by

$$\frac{\partial}{\partial t}n(v,i,t)=-\frac{\partial}{\partial v}[G_i n(v,i,t)]+Q(i-1)\frac{n(v,i-1,t)}{n_t(i-1,t)}-Q(i)\frac{n(v,i,t)}{n_t(i,t)}$$
$$+\frac{1}{2}\int_0^v \beta(v-v',v')n(v-v',i,t)n(v',i,t)\,dv'$$
$$-n(v,i,t)\int_0^\infty \beta(v,v')n(v',i,t)\,dv' \tag{26}$$
$$i=1,2,\ldots,N_R$$

where i represents the ith region, n_t is the total number density, and $Q(0) = Q_F$.

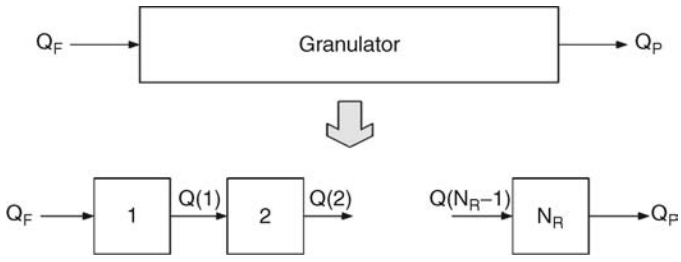


Figure 3 Concept of lumped regions in series.

Model Order Reduction for Multidimensional Population Balances

Biggs et al. (28) have developed a concept of binder size distribution (BSD) to correlate moisture content with particle size. On the basis of BSD, the mass of binder in the size range $(v, v + dv)$ is quantified as $dM = M(v)dv$ and

$$M(t, v) = \rho_L \int_0^v v_L f(v, v_L, t)\, dv_L \tag{27}$$

where ρ_L is the binder density. They showed that given the assumption that at a given size all granules have the same liquid content, the 2D PBE given by equation (23) can be reduced to a set of two 1D equations described as follows:

$$\begin{aligned} \frac{\partial}{\partial t} n(v, t) = & \frac{1}{2} \int_0^v \beta(v - v', v') n(v - v', t) n(v', t)\, dv' \\ & - n(v, t) \int_0^\infty \beta(v, v') n(v', t)\, dv \end{aligned} \tag{28}$$

and

$$\begin{aligned} \frac{\partial}{\partial t} M(v, t) = & \frac{1}{2} \int_0^v \beta(v - v', v') M(v - v', t) n(v', t)\, dv' \\ & - M(v, t) \int_0^\infty \beta(v, v') n(v', t)\, dv \end{aligned} \tag{29}$$

In their experiments, pharmaceutical materials were granulated in a high-shear mixer. Good agreements between experimental and simulation results were achieved enabling the granulation rates to be defined by two parameters: the critical binder volume fraction and the aggregation rate constant.

Reduced-Order Models Using the Method of Moments

The moments are defined as

$$\begin{aligned} M_j &= \int_0^\infty v^j n(v)\, dv \\ \mu_j &= \frac{M_j}{M_0} \\ j &= 0, 1, 2, \ldots \end{aligned} \tag{30}$$

Because of the variety of coalescence kernels, it is impossible to develop a generalized structure for reduced-order models using the method of moments. A special kernel model is assumed in this work. The methodology can be extended to the development of moment models with different kernel structures. The example kernel model is assumed as

$$\beta(v, v') = \beta_0 \frac{v^b + v'^b}{(vv')^a} = \beta_0 \left[\frac{v'^{(b-a)}}{v^a} + \frac{v^{(b-a)}}{v'^a} \right] \tag{31}$$

The discretized format of equation (31) is given by

$$\beta_{i,j} = \beta_0 \left[\frac{v_j^{(b-a)}}{v_i^a} + \frac{v_i^{(b-a)}}{v_j^a} \right] \tag{32}$$

The 1D aggregation-only PBE described by equation (28) with the kernel model given by equation (32) can be reduced to a set of ordinary differential equations as follows:

$$\begin{aligned}
\frac{d}{dt}M_0 &= -\beta_0(\mu_{(b-a)}\mu_{-a})M_0 \\
\frac{d}{dt}M_1 &= 0 \\
\frac{d}{dt}M_r &= \frac{1}{2}\beta_0 \sum_{k=1}^{r-1} \binom{r}{k} [\mu_{(k-a)}\mu_{(r-k+b-a)} + \mu_{(k+b-a)}\mu_{(r-k-a)}]M_0^2, \quad r = 2, 3, \ldots
\end{aligned} \tag{33}$$

where μ is defined in equation (30), for example, by $\mu_{(k-a)} = M_{(k\,-\,a)}/M_0$. Equation (33) involves the determination of fractional and negative moments. If the type of PSD is more or less known, such as log-normal or Γ-distribution, equation (33) is solvable with the incorporation of interpolation and extrapolation techniques. For more general solution techniques, fractional calculus enabling the computation of fractional differentiations and integrations should be used, which exceed the scope of this chapter.

Multi Timescale Analysis

It is often the case that in an interconnected process situation where several processes are being simulated simultaneously those processes operate on distinct timescales. Such is the case when combinations of prereaction units are combined with granulation devices, dryers, and screening in full process flowsheet simulations. It can also be the case within a particular processing unit that incorporates a range of mechanisms.

It can be observed that these processes often operate on different timescales covering the range of microseconds to minutes or even hours. This time separation in scales provides opportunity to make assumptions that can simplify the modeling by separating the phenomena into at least three classes.

- Slow modes (long-time constant behavior)
- Medium modes
- Fast modes (short-time constants)

When we do this analysis, we can often use qualitative methods based on our general understanding of the physics, chemistry, and the rate processes such as heat and mass transfer. As suggested by Robertson and Cameron, the alternative and more complex analytical approach is through the use of eigenvalue and eigenvector analysis that is based on the underlying models of the processes (29). This analysis often allows us to simplify complex models when we model for particular goals by making the following assumptions:

- Slow modes can be treated as being constant over the timeframe of interest.
- Medium modes are modeled in detail.
- Fast modes are regarded as pseudo steady states, being represented by algebraic equations.

This timescale approach can simplify significantly the complexity of the process models depending on the time frame of interest in the simulation and the approach has general application to all forms of models.

A Multiform Modeling Approach

A multiform modeling approach has been proposed by Wang and Cameron (51) in which the granulation process can be represented by a variety of model forms for different end uses. These include (*i*) the distributed parameter population balance model (DP-PBM) described by

equation (15); (*ii*) the lumped parameter population balance model (LP-PBM) represented by equation (26); (*iii*) matrix representation with offline computed matrix elements; (*iv*) linear and local linear models that will be further explained in the section "Application of Population Balance Modeling"; (*v*) input-output, black box models, which will also be described in the same section; (*vi*) a variety of reduced-order models using various techniques, including method of moments and the dimension separation technique stated in the "Reduced-order Models." It can be shown through dynamic simulations that significant computing time reductions can be achieved with properly selected model forms. Since both open-loop optimal control and closed-loop model predictive control (MPC) rely on iterative dynamic optimization, overall computing time reduction makes online applications possible. Furthermore, the development of local linear models allows the applications of well-established linear system theory and techniques to process control, parameter identification, and model order reduction. The demonstrated advantages of the proposed multiform modeling approach imply a big step forward toward the industrial applications of model-based control for granulation processes.

SOLVING POPULATION BALANCES

In this section we look at a number of important solution methods to solve PBEs. This covers conventional, well-established techniques as well as more recent and specialized approaches.

Solution of Population Balance Equations

Conventional Discretization Methods

Hounslow discretization. Hounslow et al. (30) developed a relatively simple discretization method by employing an M-I approach (the mean value theorem on frequency). The PBEs, such as equation (28), are normally developed using particle volume as the internal coordinate. Because of the identified advantages of length-based models, Hounslow et al. (30) performed the coordinate transformation to convert the volume-based model described by equation (28) to a length-based model as follows:

$$\begin{aligned}\frac{d}{dt}n(L,t) = \frac{L^2}{2}\int_0^L \frac{\beta[(L^3-\lambda^3)^{1/3},\lambda]n[(L^3-\lambda^3)^{1/3},t]n(\lambda,t)}{(L^3-\lambda^3)^{2/3}}d\lambda \\ - n(L,t)\int_0^\infty \beta(L,\lambda)n(\lambda,t)d\lambda\end{aligned} \tag{34}$$

in which L and λ denote the characteristic length of particles. The Hounslow method is based on a geometric discretization, with the following ratio between two successive size intervals:

$$\frac{L_{i+1}}{L_i} = \sqrt[3]{2}, \quad \text{or} \quad \frac{v_{i+1}}{v_i} = 2 \tag{35}$$

where L and v represent the characteristic length and volume of particles, respectively, the subscripts $i + 1$ and i denote the size classes. The continuous PBE described by equation (34) is converted into a set of discretized PBEs in various size intervals by using this technique. That is, the change of number density in the ith size interval is given by

$$\begin{aligned}\frac{d}{dt}n_i = n_{i-1}\sum_{j=1}^{i-2}(2^{j-i+1}\beta_{i-1,j}\,n_j) + \frac{i}{2}\beta_{i-1,i-1}n_{i-1}^2 \\ - n_i\sum_{j=1}^{i-1}(2^{j-i}\beta_{i,j}\,n_j) - n_i\sum_{j=1}^{i_{\max}}(\beta_{i,j}\,n_j) \\ i = 1,2,\ldots,i_{\max}\end{aligned} \tag{36}$$

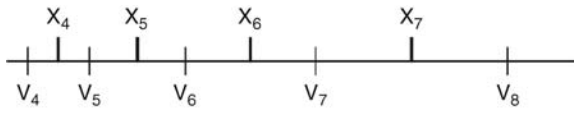


Figure 4 General grid used with Kumar and Ramkrishna numerical technique.

The continuous BSD model described by equation (29) can also be discretized using a similar numerical scheme as follows Biggs et al. (28):

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}M_i = {} & M_{i-1}\sum_{j=1}^{i-2}(2^{j-i+1}\beta_{i-1,j}\,n_j) + n_{i-1}\sum_{j=1}^{i-2}(2^{j-i+1}\beta_{i-1,j}\,n_j) \\ & + n_i\sum_{j=1}^{i-1}[(1-2^{j-i})\beta_{i,j}\,M_j] + \beta_{i-1,i-1}n_{i-1}M_{i-1} \\ & - M_i\sum_{j=1}^{i-1}(2^{j-i}n_j) - M_i\sum_{j=1}^{i_{\max}}(\beta_{i,j}\,n_j) \\ i = {} & 1,2,\ldots,i_{\max}\end{aligned} \tag{37}$$

Kumar and Ramkrishna's discretization technique. Kumar and Ramkrishna (31) developed a discretization method by using a grid with a more general and flexible pattern with fine or coarse discretizations in different size ranges. The size range between two sizes v_i and v_{i+1} is called the ith section, and the particle size in this section is simply denoted by x_i (grid point) such that $v_i < x_i < v_{i+1}$ as seen in Figure 4.

A particle of size v in the size range x_i and x_{i+1} can be represented by two fractions $a(v, x_i)$ and $b(v, x_{i+1})$ associated with the two grid points x_i and x_{i+1}, respectively. For the conservation of two general properties $f_1(v)$ and $f_2(v)$, these fractions satisfy the following equations:

$$\begin{aligned}a(v,x_i)f_1(x_i) + b(v,x_{i+1})f_1(x_{i+1}) &= f_1(v) \\ a(v,x_i)f_2(x_i) + b(v,x_{i+1})f_2(x_{i+1}) &= f_2(v)\end{aligned} \tag{38}$$

By using this composition technique for particle properties, discrete equations for coalescence-only population balance model given be equation (22) have been formulated as follows:

$$\frac{dn_i}{dt} = \sum_{\substack{j,k \\ x_{i-1}\le(x_j+x_k)\le x_{i+1}}}^{j\ge k}\left(1-\frac{1}{2}\delta_{j,k}\right)\eta\beta(j,k)n_j(t)n_k(t) - n_i(t)\sum_{k=1}^{i_{\max}}\beta(i,k)n_k(t) \tag{39}$$

In equation (39), n_i, β, $i_{\max}$ are defined previously, $\delta_{j,k}$ is the Dirac delta function, and η is defined as follows:

$$\begin{aligned}\eta &= \frac{x_{i+1}-v}{x_{i+1}-x_i}, x_i \le v \le x_{i+1} \\ \eta &= \frac{v-x_{i-1}}{x_i-x_{i-1}}, x_{i-1} \le v \le x_i\end{aligned} \tag{40}$$

The first and second terms on the right-hand side of equation (39), respectively, represent the birth rate and death rate of particles in the ith size interval because of coalescence.

Attention should be paid to the selection of the internal coordinates. The original Kumar–Ramkrishna discretization should be applied to volume-based models rather than length-based models. Although both are interconvertible, it is important to check the consistency in numerical computations.

Wavelet-Based Methods

The wavelet-based methods are relatively new numerical schemes for solving PBEs consisting of both differential and integral functions (32). Again, the volume-based PBEs with particle volume as the internal coordinate are used to demonstrate the main characteristics of the wavelet methods. The most important advantage of these methods over other numerical techniques is their ability to effectively deal with steep-moving profiles. In this subsection, we only explain the basic algorithms of the wavelet-collocation method for practical applications using the Daubechies wavelets rather than to provide mathematical insights for general wavelet techniques.

Similar to other collocation methods, the coordinates should be normalized within the interval [0, 1]. For the 1D PBE given by equation (13), this can be done by introducing the linear transformation $x = v/v_{\max}$, where x is the dimensionless particle volume and $v_{\max}$ is the maximum particle size in the system. The original integral intervals [0, v] and [0, ∞] are transformed to [0, x] and [0, 1], respectively. Consequently, equation (13) becomes

$$\begin{aligned}\frac{\partial}{\partial t}n(x,t) = &-\frac{\partial}{\partial x}[G(x)n(x,t)] \\ &+\frac{v_{\max}}{2}\int_0^x \beta(x-x',x')n(x-x',t)n(x',t)\,dx' \\ &-v_{\max}n(x,t)\int_0^1 \beta(x,x')n(x',t)\,dx'\end{aligned} \tag{41}$$

where $G(x)$ is defined as dx/dt rather than dv/dt. For a broad class of engineering problems, the approximate solution of a general function $w(x)$ with J-level resolution can be written in terms of its values in the dyadic points:

$$w_J(x) \approx \sum_m w_J(2^{-J}m)\theta(2^J x - m) \tag{42}$$

where $\theta(x)$ is denoted as the autocorrelation function of scaling function. We first solve the coalescence only PBE with $G(x) = 0$. If J-level wavelet method is used, the matrix representation at the ith dyadic point is given by

$$\frac{\partial n_i}{\partial t} = \frac{v_{\max}}{2}\begin{bmatrix} n_0 & n_1 & \cdots & n_{2^J}\end{bmatrix}\mathbf{M}^{3,i}\begin{bmatrix} n_0 \\ n_1 \\ \vdots \\ n_{2^J}\end{bmatrix} - v_{\max}n_i\mathbf{M}_i^2\begin{bmatrix} n_0 \\ n_1 \\ \vdots \\ n_{2^J}\end{bmatrix} \tag{43}$$

where n_i is the number density at the ith dyadic (collocation) point. The operational matrix $\mathbf{M}^{3,i}$ and vector $\mathbf{M}_i^2$ are constructed as follows. $\mathbf{M}^{3,i}$ are $(2^J + 1) \times (2^J + 1)$ operational matrices at volume points i represented as

$$\mathbf{M}^{3,i} = \begin{bmatrix} M^{3,i}_{0,0} & M^{3,i}_{0,1} & \cdots & M^{3,i}_{0,2^J} \\ M^{3,i}_{1,0} & M^{3,i}_{1,1} & \cdots & M^{3,i}_{1,2^J} \\ \vdots & \vdots & \ddots & \vdots \\ M^{3,i}_{2^J,0} & M^{3,i}_{2^J,1} & \cdots & M^{3,i}_{2^J,2^J}\end{bmatrix} \tag{44}$$

$\mathbf{M}_i^2$ are $1 \times (2^J + 1)$ operational vectors at volume points i described by

$$\mathbf{M}_i^2 = \begin{bmatrix} M^2_{i,0} & M^2_{i,1} & \cdots & M^2_{i,2^J}\end{bmatrix}$$

Elements in the matrix $\mathbf{M}^{3,i}$ are developed as

$$M^{3,i}_{k_1,k_2} = \frac{1}{2^J}\sum_{l=0}^{2^J}\beta(x_i - x_l, x_l) \times \left[\Omega_{l-k_2,i-k_1-k_2}(i-k_2) - \Omega_{l-k_2,i-k_1-k_2}(-k_2)\right] \tag{45}$$

Elements in the operational vectors $\mathbf{M}_i^2$ are given by

$$M_{i,k}^2 = \frac{1}{2^J}\left[\sum_{l=0}^{2^J} \beta(x_i, x_l) H_{k-l}(k)\right] \tag{46}$$

The needed two-term integral of autocorrelation function $H_k(x)$ and three-term integral of autocorrelation function $\Omega_{j,k}(x)$ in equations (45) and (46) are defined as

$$H_k(x) = \int_{-\infty}^{x} \theta(y-k)\theta(y)dy \tag{47}$$

and

$$\Omega_{j,k}(x) = \int_{-\infty}^{x} \theta(y-j)\theta(y-k)\theta(y)dy \tag{48}$$

The autocorrelation function $\theta(k)$ and its derivatives $\theta^{(s)}(k)$ are represented as follows:

$$\begin{aligned} \theta(k) &= \int_{-\infty}^{+\infty} \phi(x)\phi(x-k)dx \\ \theta^{(s)}(k) &= (-1)^s \int_{-\infty}^{+\infty} \phi(x)\phi^{(s)}(x-k)dx \end{aligned} \tag{49}$$

where $\phi(x)$ is the scaling function. $\theta^{(s)}(k)$ can be evaluated by using the following recursive algorithm with $\theta(k) = \theta^{(0)}(k)$:

$$\theta^{(s)}(2^{-J-1}k) = 2^s\theta^{(s)}(2^{-J}k) + 2^{s-1}\sum_{l=1}^{N} a_{2l-1}\left[\theta^{(s)}(2^{-J}k - 2l + 1) + \theta^{(s)}(2^{-J}k - 2l - 1)\right] \tag{50}$$

The differential operators in the PBE can also be evaluated at the collocation points as

$$\begin{aligned} \frac{\partial \mathbf{n}}{\partial x} &= \mathbf{A}(\theta^{(1)})\mathbf{n} \\ \frac{\partial^2 \mathbf{n}}{\partial x^2} &= \mathbf{B}(\theta^{(2)})\mathbf{n} \end{aligned} \tag{51}$$

where $\mathbf{n} = [n_1\ n_2 \cdots n_N]^{\mathrm{T}}$ is a vector, in which n_i is the number density at the ith collocation point, $N = 2^J + 1$ is the number of collocation points, T stands for vector transpose, $\mathbf{A}$ and $\mathbf{B}$ are square matrices computed using the values $\theta^{(1)}(k)$ and $\theta^{(2)}(k)$, respectively. An algorithm for the computation of the matrices $\mathbf{A}$ and $\mathbf{B}$ was described in Liu et al. (33). Consequently, the growth term in equation (41) can be approximated using equation (51).

It should be pointed out that after coordinate normalization, functions of interest are evaluated in the closed intervals [0, 1] rather than $[-\infty, \infty]$ or other intervals. In this case, some modified interpolation functions can be constructed to interpolate the values in dyadic points outside [0, 1] to the desired interval (33,34).

Three PBEs with different kernel models have been successfully solved by using the wavelet-collocation method (32). These kernel models were (*i*) size-independent kernel $\beta = \beta_0 =$ constant, (*ii*) linear size-dependent kernel $\beta(x, x') = \beta_0(x + x')$ and (*iii*) nonlinear size-dependent kernel $Q(x, x') = \beta(x^{1/3} + x'^{1/3})(x^{-1/3} + x'^{-1/3})$. Simulation results have shown that the wavelet-collocation methods are able to achieve fast convergence with high accuracy if adequate resolution levels are selected. The methods are particularly effective for the processes with steep-moving profiles, which are difficult to solve by using other numerical schemes.

In this subsection, the emphasis has been placed on the introduction of basic techniques for the resolution of PBEs using wavelets, which requires to solve $2^J + 1$ ordinary equations for each PBE given by equation (41). Liu and Cameron (35) have recently developed a new wavelet-based adaptive technique, which enables a dramatic reduction of the number of ordinary differential equations to be solved. Furthermore, this adaptive method allows the automatic selection of the minimum wavelet level J with acceptable accuracy. With the

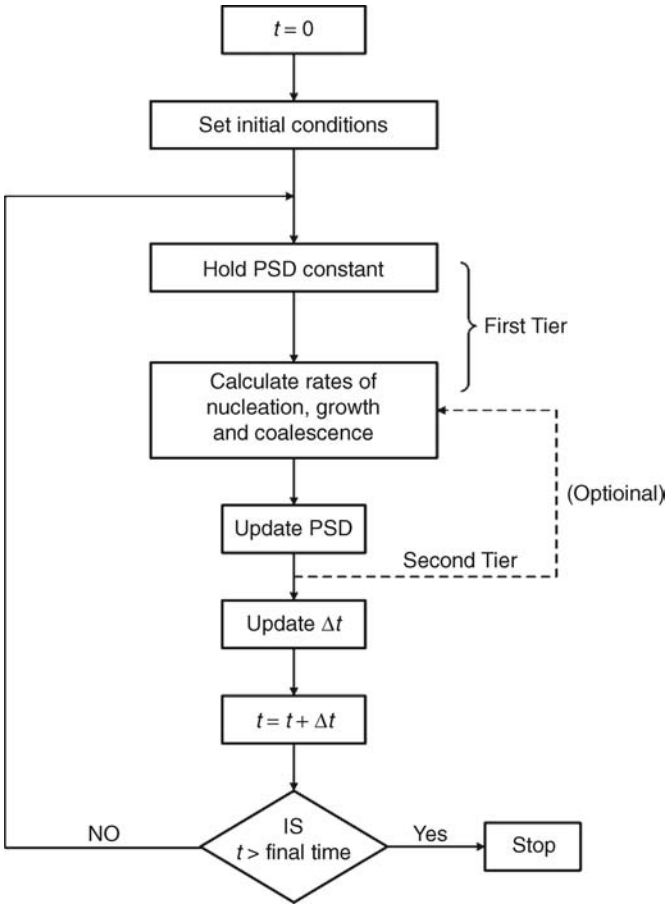


Figure 5 Schematic of a hierarchical two-tier solution strategy for population balance models.

background knowledge described in this chapter, the readers may understand the adaptive technique through studies on the original papers without major difficulties.

The operational matrices $\mathbf{M}^{3,i}$ and $\mathbf{M}_i^2$, matrices **A** and **B**, together with the integral functions H and Ω at various resolution levels are available from the authors.

Hierarchical Two-Tier Technique

A relatively new development in solution techniques has been presented by Immanuel and Doyle III (36). This technique is based on a finite-element discretization of the particle population and tracks the total particles within each of the bins. The equation representing the total particles within each bin is derived from the PBE in a straightforward manner via partial analytical solution. The particle population in each bin is updated employing a hierarchical strategy, as depicted in Figure 5. The individual rates of nucleation, growth, and coalescence in each bin is computed in the first tier of the algorithm (at each time step), and the particle population is updated in the second tier. A simple predictor-corrector technique may be utilized for information exchange between the two tiers.

Employing the two-tier hierarchical solution strategy enables orders of magnitude improvement in the computation times. The improvement in computation times is achieved partly by a reduction of the stiffness of the system equations by a decomposition solution strategy for the nucleation, growth, and coalescence models. In effect, the PBE is reformulated in terms of the individual growth, aggregation, nucleation, and breakage events (as appropriate), thereby accommodating the differences in their timescales. The other major

factor that contributes to this improvement in computation time is the offline analytical solution that is proposed for the aggregation quadratures. This results in casting the complex integrals in terms of simpler terms, major portions of which can be computed just once at the start, thereby leading to a substantial reduction in the computational load. These analytical solutions for the quadratures are derived based on an assumption of a uniform particle density within each element, although this assumption can be easily relaxed to enable larger finite elements. It also involves the assumption that the coalescence kernel for particles between any two bins is a constant [i.e., $\beta(V', V - V')$ in the following equation is constant for all particle coalescences between bins i and j].

$$\Re'_{\text{formation}}(V,t) = \frac{1}{2V_{\text{aq}}}\int_{V=V_{j-1}}^{V_j}\left[\int_{V'=V_{\text{nuc}}}^{V-V_{\text{nuc}}}\beta(V', V-V')F_V(V',t)F_V(V-V',t)dV'\right]dV \tag{52}$$

See Immanuel and Doyle III (36) for the detailed analytical solutions.

Immanuel and Doyle III (20) discuss the extension of the above 1D algorithm to the multidimensional case. The ranges of volumes of solid, liquid, and gas are divided into 3D grids (finite volumes or the bins). In this case, the algorithm models the total particle count within each of these bins, defined such that $F_{i,j,k}$ is the total moles of particles within the (i, j, k)th bin. The layering effect and the drying effect (which account for the continuous change in the solid and liquid contents of the granules) are neglected in this case. Thus, continuous growth is restricted to the gas volume (due to consolidation). In the following equation, g_k is the lower boundary of gas volume in the kth bin along the gas volume, and ΔG_k is the width of the kth bin along the gas volume.

$$\frac{d}{dt}F_{i,j,k} + \left(\frac{F_{i,j,k}}{\Delta G_{i,j,k}}\right)\frac{dg}{dt}\bigg|_k - \left(\frac{F_{i,j,k+1}}{\Delta G_{i,j,k+1}}\right)\frac{dg}{dt}\bigg|_{k+1} = \int_{s_{i-1}}^{s_i}\int_{l_{i-1}}^{l_i}\int_{g_{i-1}}^{g_i}\Re_{\text{aggre}}(s,l,g,t)ds\,dl\,dg \tag{53}$$

Extensions of the analytical solutions for the aggregation integrals to multidimensional cases are straightforward. The aggregation term in the equation above assumes a six-dimensional form in the current 3D case [$\Re_{\text{aggre}}(s, l, g, t)$ itself being a 3D integral]. This six-dimensional integral can be recast as a multiple of three double integrals, each double integral accounting for one internal coordinate. This is possible because the three internal coordinates are mutually independent of each other. The solution to each of the separated double integrals is exactly the same as the ones derived for the 1D case. This simplification is another advantage of representing the population balance in terms of the volumes of solid, liquid, and gas in the granules, rather than in terms of the total particle size, binder content, and porosity.

The effectiveness of the technique has been further demonstrated by Pinto et al. (37) by solving higher-dimensional population balance models with breakage-division phenomena. The same authors (38) have extended the single level discretization strategy to a multilevel discretization based solution of multidimensional population balance models accounting for different fineness of discretization for the different rate processes of nucleation, growth, aggregation, and breakage as warranted by the particular rate process. Consequently, the computational efficiency has been significantly improved.

Solving Differential-Algebraic Equation Systems

Many of the previously mentioned numerical methods lead to large sets of differential equations coupled with sets of nonlinear algebraic equations. These are the so-called differential-algebraic equation (DAE) systems. A number of approaches are available to solve these equation sets, mainly based on implicit or semi-implicit methods such as the backward differentiation formulae (BDF) (39) or variants of Runge–Kutta methods (40,41).

The Mathworks package MATLAB also contains useful DAE solvers that are based primarily on implicit BDF formulae. Solution of these types of problems is generally straightforward. Some issues still remain in obtaining consistent initial conditions for the solution to commence and the solution of high-index problems.

Monte Carlo Methods

There is a long history in studies on the application of Monte Carlo methods to process engineering. The first serious research paper on a Monte Carlo treatment for systems involving population balances could be credited to Spielman and Levenspiel (42). Since then, a significant number of publications have appeared in the literature on the resolution of PBEs using Monte Carlo methods (8). Comprehensive Monte Carlo treatments are described in the literature (8,43). Only selected issues on basic techniques will be addressed in this section.

Classification of Monte Carlo Methods

Monte Carlo methods can be used in two ways for engineering applications:

1. Direct evaluation of difficult functions. For example, the integral given by

$$I = \int_a^b f(x)dx \tag{54}$$

can be evaluated as

$$\begin{aligned} I &= E(Y) = E[(b-a)g(X)] = E[\bar{Y}(n)] \\ \bar{Y}(n) &= \cdots (b-a)\frac{\sum_{i=1}^{n} g(X_i)}{n} \end{aligned} \tag{55}$$

where X_1, X_2, . . ., X_n are random variables defined in the closed interval [a, b], and $E(Y)$ denotes the mathematical estimation of function Y.

2. Artificial realization of the system behavior (8). This method is commonly applied to complex particulate processes, which will be described in some detail in the current section. In the artificial realization, the direct evaluation of integral and differential functions is replaced by the simulation of the stochastic behavior modeled by using a randomness generator to vary the behavior of the system (43). It will be shown later that the important probabilistic functions in the original model equations, such as coalescence kernels for granulation processes, are still essential in Monte Carlo simulations.

Monte Carlo methods for the artificial realization of the system behavior can be divided into time-driven and event-driven Monte Carlo simulations. In the former approach, the time interval Δt is chosen, and the realization of events within this time interval is determined stochastically. In the latter case, the time interval between two events is determined on the basis of rates of processes. In general, the coalescence rates in granulation processes can be extracted from the coalescence kernel models. The event-driven Monte Carlo can be further divided into constant volume methods in which the total volume of particles is conserved and constant number method in which the total number of particles in the simulation remains constant. The main advantage of the constant number method for granulation processes is that the population remains large enough for accurate Monte Carlo simulations (44,45). An additional advantage associated with the constant number methods is its ability to reduce the renumbering effort. Consequently, the constant number method is recommended and will be further explained.

Key Equations for Constant Number Monte Carlo Simulation

Key equations needed in Monte Carlo simulations include the interevent time Δt_q representing the time spent from $q-1$ to q Monte Carlo steps, coalescence kernel K_{ij}, normalized probability p_{ij} for a successful collision between particles i and j, and a number of intermediate variables. The coalescence kernel can be divided into particle property independent part K_c and dependent part $k_{ij}(\mathbf{X}_i, \mathbf{X}_j)$ as follows:

$$\begin{aligned} K_{ij} &= K_c k_{ij}(\mathbf{X}_i, \mathbf{X}_j) \\ i,j &= 1,2,\ldots,N \end{aligned} \tag{56}$$

where **X** denotes the vector of internal coordinates representing particle properties, such as size and moisture content, and N is the total number in the simulation system. It can be seen that equation (56) is similar to the coalescence kernel given by $\beta_{ij} = \beta_0\, k_{ij}(v_i, v_j)$ described in the previous sections for 1D systems. However, it should be pointed out that i and j in equation (56) are used to identify the individual particles, whereas that in β_{ij}, $i, j = 1,2, \ldots, i_{\max}$ are size classes rather than particle identity numbers. In order to avoid confusion, β_{ij} and β_0 are replaced by K_{ij} and K_c, respectively, in Monte Carlo simulations. The normalized probability for successful collision is given by

$$p_{ij} = \frac{k_{ij}}{k_{\max}} \tag{57}$$

where $k_{\max}$ is the maximum value of the coalescence kernel among all particles. The final result of the interevent time is given by

$$\Delta t_q = \frac{2\tau_c}{\langle k_{ij}\rangle}\frac{1}{N}\left(\frac{N}{N-1}\right)^q \tag{58}$$

with

$$\tau_c = \frac{1}{K_c C_0} \tag{59}$$

and

$$\langle k_{ij}\rangle = \frac{\Sigma_{i=1}^{N}\Sigma_{j=1,i\neq j}^{N} k_{ij}}{N(N-1)} \tag{60}$$

In equation (59), C_0 is the total number concentration at $t = 0$ defined by $C_0 = N/V_0$ where V_0 is the volume of particles at the initial time. We have only presented the final results of needed equations here. The interested readers are referred to Smith and Matsoukas (44) for detailed mathematical derivations.

Simulation Procedure

The simulation procedure for the constant number Monte Carlo method applied to coalescence processes consists of the following key steps:

1. Initialization of the simulation system. This includes the determination of sample size (normally 10,000–20,000 particles) followed by assigning the identity number and properties to each particle. The properties must satisfy the initial property distributions, such as particle size and moisture distributions. Set $t_0 = 0$ and $q = 1$.
2. Acceptance or rejection of coalescence. In this step, two particles, i and j, are randomly selected and the coalescence kernel k_{ij} with normalized probability p_{ij} given by equation (57) are computed, followed by the generation of a random probability p_{rq}. If $p_{ij} < p_{rq}$, the coalescence is rejected, and a new pair of particles are selected again to repeat the calculation until $p_{ij} > p_{rq}$, which implies a successful coalescence. When the coalescence is successful, the new agglomerated particle holds the identity number i, and another particle randomly selected from the rest of the system is copied as particle j and go to step 3.
3. Computation of the interevent time. The interevent time for step q is computed using equations (58)–(60). Total operational time is given by

$$t = t_0 + \sum_{m=1}^{q}\Delta t_m \tag{61}$$

   Set $q = q + 1$ and return to step 2.
4. Simulation termination and result validation. As t reaches the prespecified termination time t_f, check the acceptance of simulation results. If acceptable, stop the simulation, otherwise, modify model parameters and start a new simulation process.

It can be seen that the Monte Carlo methods are applicable to both 1D and multidimensional coalescence processes without any theoretical and algorithmic hurdles. However most reported results with good agreement with experimental data are limited to 1D systems, except that reported by Wauters (45). This is mainly due to the lack of reliable multidimensional kernel models rather than the applicability of Monte Carlo methods.

APPLICATION OF POPULATION BALANCE MODELING

Process systems modeling and applications in granulation have been comprehensively reviewed by Cameron et al. (46) and Cameron and Wang (47). In this section we consider the application of population balances to regulatory and optimal control of batch and continuous granulation systems. Models can also be applied to parameter estimation, process and equipment design, state estimation, and fault diagnosis.

Modeling for Closed-Loop Control Purposes

Development of Control Relevant, Linear Models

Since the linear control theory and techniques are better developed and easier to implement than their nonlinear counterparts, it is highly desirable to use linear models for control purposes. In process engineering, the nonlinear models are frequently linearized around certain operating points. The linearization technique is described briefly in this subsection. Let the general nonlinear system is described as

$$\begin{cases} \dfrac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}, \mathbf{u}) \\ \mathbf{y} = \mathbf{h}(\mathbf{x}) \end{cases} \tag{62}$$

where $\mathbf{x} = [x_1\ x_2 \cdots x_p]^T$, $\mathbf{y} = [y_1\ y_2 \cdots y_q]^T$, and $\mathbf{u} = [u_1\ u_2 \cdots u_s]^T$ are vectors of state, output and control variables, respectively, $\mathbf{f} = [f_1\ f_2 \cdots f_p]^T$ and $\mathbf{h} = [h_1\ h_2 \cdots h_q]^T$ are vectors of smooth functions, in which p, q, and s are dimensions of the vectors of state, output and control variables, respectively. In the PBEs given by equations (36), (39), and (53), $x = [n_1\ n_2 \cdots n_p]$, $p = i_{\max}$. In the conventional linearization method is based on the first-order Taylor series expansion around certain operational points. The resulting linear model is given by

$$\begin{aligned} \frac{d\delta\mathbf{x}}{dt} &= \mathbf{A}\delta\mathbf{x} + \mathbf{B}\delta\mathbf{u} \\ \delta\mathbf{y} &= \mathbf{C}\delta\mathbf{x} \\ \mathbf{A} &= \left.\frac{\partial \mathbf{f}(\mathbf{x},\mathbf{u})}{\partial \mathbf{x}^T}\right|_{\substack{\mathbf{x}=\mathbf{x}_o \\ \mathbf{u}=\mathbf{u}_o}}, \ \mathbf{B} = \left.\frac{\partial \mathbf{f}(\mathbf{x},\mathbf{u})}{\partial \mathbf{u}^T}\right|_{\substack{\mathbf{x}=\mathbf{x}_o \\ \mathbf{u}=\mathbf{u}_o}}, \ \mathbf{C} = \left.\frac{\partial \mathbf{h}(\mathbf{x})}{\partial \mathbf{x}^T}\right|_{\substack{\mathbf{x}=\mathbf{x}_o \\ \mathbf{u}=\mathbf{u}_o}} \end{aligned} \tag{63}$$

In the control literature, the symbol δ in front of $\mathbf{x}$, $\mathbf{y}$, and $\mathbf{u}$ is normally omitted for simplicity. The readers should be aware that in the models developed this way, $\mathbf{x}$, $\mathbf{y}$, and $\mathbf{u}$ denote deviations from their respective values at the specified operational point rather than the real values. That is, the linearized model used in control studies is represented as

$$\begin{aligned} \frac{d\mathbf{x}}{dt} &= \mathbf{A}\mathbf{x} + \mathbf{B}\mathbf{u} \\ \mathbf{y} &= \mathbf{C}\mathbf{x} \end{aligned} \tag{64}$$

The discretized PBEs given by equations (36), (39), and (53), and the BSD model described by equation (37) can be linearized to obtain the models with the format given by equation (64). The control variables are normally connected with the coalescence kernels (48).

Instead of directly (numerically) linearizing the plant model, the linear model represented by equation (64) can also be determined by a subspace model identification method, as described by Ljung (49) and applied to MPC of a granulation process by Sanders et al. (50).

It should be pointed out that linear models are only applicable to systems with small deviations from SSs. If the variations of operational conditions exceed acceptable ranges, a piecewise linearization technique should be used, leading to the development of multiple linear models (51). The multiple linear model approach has been applied to advanced control of nonlinear processes by the authors using mini-max optimization techniques, in which a quantitative measure, namely gap metric, is used for the determination of local linear regimes (52).

ARX and ARMAX Models for Linear Model Predictive Control

For MPC purposes, there are two commonly used black box models: ARX model with autoregressive (AR) part and extra (X) input, and ARMAX model with additional moving average (MA) part accounting for disturbances. The method for the development of ARX and ARMAX models is well explained in the book by Ljung (49). The single input, single output ARX is given by

$$y(t) + a_1 y(t-1) + \cdots + a_{n_a} y(t-n_a) = b_1 u(t-1) + \cdots + b_{n_b} u(t-n_b) + e(t) \tag{65}$$

and the ARMAX model is represented as

$$\begin{aligned} &y(t) + a_1 y(t-1) + \cdots + a_{n_a} y(t-n_a) \\ &\quad = b_1 u(t-1) + \cdots + b_{n_b} u(t-n_b) + e(t) + c_1 e(t-1) + \cdots + c_{n_c} e(t-n_c) \end{aligned} \tag{66}$$

In equations (65) and (66), y is the output (controlled) variable, u is the input (manipulative) variable, e is the disturbance; a, b, and c are time-varying coefficients identified online; n_a, n_b, and n_c are defined as prediction, control, and disturbance horizons. The matrix format for multivariable RRX and ARMAX models are described by

$$\mathbf{A}(q)\mathbf{y}(t) = \mathbf{B}(q)\mathbf{u}(t) + \mathbf{e}(t) \quad \text{ARX} \tag{67}$$

and

$$\mathbf{A}(q)\mathbf{y}(t) = \mathbf{B}(q)\mathbf{u}(t) + \mathbf{C}(q)\mathbf{e}(t) \quad \text{ARMAX} \tag{68}$$

In equations (67) and (68), matrices **A**, **B**, and **C** are defined as

$$\begin{aligned} \mathbf{A}(q) &= \mathbf{I}_{n_y} + \mathbf{A}_1 q^{-1} + \cdots + \mathbf{A}_{n_a} q^{-n_a} \\ \mathbf{B}(q) &= \mathbf{B}_0 + \mathbf{B}_1 q^{-1} + \cdots + \mathbf{B}_{n_b} q^{-n_b} \\ \mathbf{C}(q) &= \mathbf{I}_{n_y} + \mathbf{C}_1 q^{-1} + \cdots + \mathbf{C}_{n_c} q^{-n_c} \end{aligned} \tag{69}$$

where q^{-k} is the delay operator representing "delayed by k time intervals", for example,

$$\mathbf{A}(q)\mathbf{y}(t) = \mathbf{y}(t) + \mathbf{A}_1 \mathbf{y}(t-1) + \cdots + \mathbf{A}_{n_a} \mathbf{y}(t-n_a) \tag{70}$$

The compact format of ARX and ARMAX models given by equations (67) and (68) can easily be converted into more intuitive, expanded format exemplified by equation (70). With input (**u** and **e**) and output (**y**) data, the matrices **A**, **B**, and **C** can be readily identified employing the System Identification Toolbox for Use with MATLAB (53). An ARX model for a pan granulation process was developed by Adetayo et al. (54), with a successful application to effective control of the plant.

Linear Model Predictive Control

Linear, control relevant models developed from nonlinear granulation processes are used for MPC. The basic idea of linear MPC is to determine the control actions through the minimization of a cost (objective) function. The objective function normally consists of the deviations between computed and desired outputs, and operational costs. The solution may depend on the weighting functions selected in the objective function to account for the relative importance among various terms. The MATLAB "Model Predictive Control Toolbox 2" (55) can be used to design the MPC. Two successful attempts for control of two different nonlinear

granulation processes using MPC have been reported by Sanders et al. (50) and Glaser et al. (56). Both have shown how linear model predictive controller can be applied on nonlinear granulation processes.

Nonlinear Model Predictive Control Structure

Nonlinear model predictive control (NMPC) schemes consist of simultaneous determinations of manipulative variables and uncertain parameters. In some cases, the open-loop dynamic optimization is carried out for the determination of desired trajectories (set-points). This integrated control strategy was developed by Miller and Rawlings (57) in a study on model identification and control for batch cooling crystallizers, in which the population balance described by partial differential equation was reduced to a low-dimensional model using method of moments. That is, the control objective was average size rather than size distribution in Miller and Rawlings' work. Detailed studies on modeling and MPC of PSD in emulsion copolymerization processes using population balance models have been carried out by Immanuel et al. (58) and Crowley et al. (59). The reported research results have shown that the NMPC schemes using PBEs should also be applicable to pharmaceutical granulation processes due to the similar model structure. The main limitation of the conventional NMPC schemes is the difficulty in the determination of the optimal set-points. In particular, the determination of the set-points under uncertainty remains as an unsolved problem. To fill this knowledge gap, a multilevel NMPC (ML-NMPC) scheme has been proposed by Wang and Cameron (60) and Cameron and Wang (47). The ML-NMPC scheme is shown in Figure 6, which depicts an integration of the modeling strategy originally proposed by Sanders et al. (61) with the model-based control scheme.

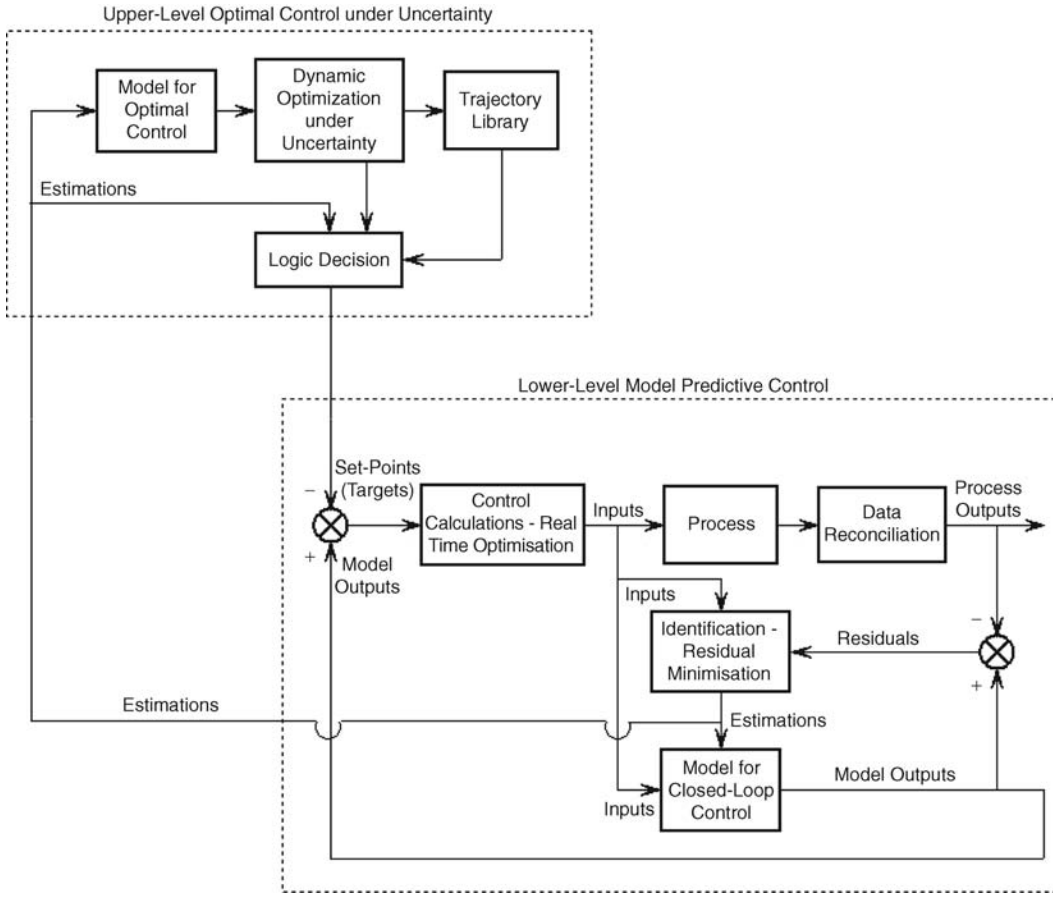


Figure 6 General structure of ML-NMPC using physically based models.

The upper level optimal control employs dynamic optimization algorithm, which will be described in the section "Modeling for Optimal Design, Operation, and Open-Loop Optimal Control." The uncertainty issues can be addressed as follows. On the basis of the operational experience and simulation results, frequently encountered situations can be stored in the optimal control database. When online measurement data are available, the most suitable trajectories can be identified using logic rules. Since both control actions and uncertain parameters can be determined simultaneously using NMPC schemes based on dynamic optimizations, it is envisaged that the combination of upper-level optimal control with NMPC is scientifically justifiable. It can be seen from Figure 6 that two-way interactions between upper and lower control levels can be achieved for effective control of uncertain granulation processes.

A full implementation of ML-NMPC in industrial granulation plants using physically based models has not been reported yet. A simulated study has been carried out by Zhang et al. (48) to control an industrial scale fertilizer plant using a physically based model. The main limitation of the study was that the physically based population balance model was used to generate output data without real online measurements. This implies that if a severe plant-model mismatch occurs, the proposed control strategy may fail. Further work is required to modify the model online, based on the measurement data.

Online Measurement-Based Control Schemes

In addition to model-based control schemes using PBEs, there are a number of practical control schemes in the pharmaceutical industry that do not rely on mathematical models. These include simple feedback control with or without feed-forward compensation, and fuzzy-logic control systems.

Simple feedback control with feed-forward compensation. One of the most important issues for the effective control of granulation processes is the development of fast and reliable measurement techniques for the characterization of particulate systems. Because of the difficulties associated with the direct measurement of particle characteristics, such as particle size distribution, moisture contents and deformability, some indirect monitoring parameters have been adopted as the indicators of particle characteristics. A commonly accepted monitoring parameter in the pharmaceutical industry is the power consumption, which has been successfully used to control the particle size in high-shear mixers at the end-point (62,63). On the basis of a series of investigations carried out by Leuenberger (62), the energy dissipated per unit volume in a high-shear mixer, dW/dV, can be approximately represented as

$$\frac{dW}{dV} = \mu\sigma_c\kappa \propto \frac{1-\varepsilon}{\varepsilon} \tag{71}$$

where W is the power consumption, V is the granulator volume, μ is the apparent coefficient of friction, σ_c is the cohesive stress, κ is the dimensionless shear rate, and ε is the porosity of the powder mass. It is easy to show that the power consumption is related to the saturation level S defined as follows:

$$S = \frac{H(1-\varepsilon)}{\varepsilon}\rho \tag{72}$$

where H is the mass ratio of liquids to solids and ρ is the density of the particle relative to the density of the liquid ($\rho = \rho_S/\rho_L$). Furthermore, Kristensen and Schaefer (64) pointed out that the saturation level defined by equation (72) could be related back to the average granule size. Consequently, the power consumption, the saturation level, and the granule particle size are interrelated, forming a technical basis to use power consumption as a monitoring parameter for the characterization of particles within the high-shear mixer. A detailed description of the control strategy using power consumption as the indicator of particle properties in high-shear mixers is also provided in Leuenberger (62).

Mort et al. pointed out that "with recent development in particle sizing technology, the agglomerate size distribution can be measured in-line at any number of points in the process" (65). The main measurement technique is image-analysis by mounting high-speed

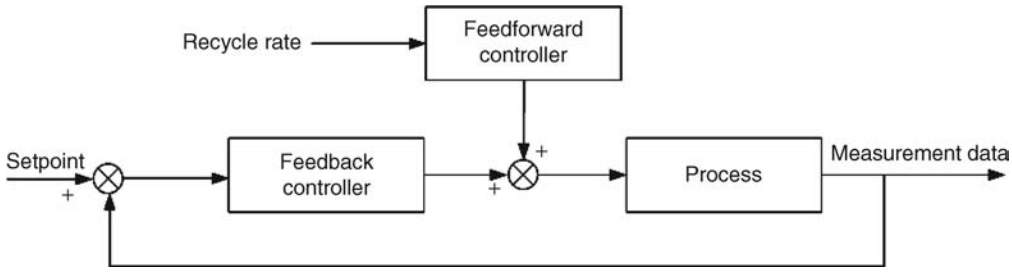


Figure 7 Simple feedback control scheme with feed-forward compensation.

cameras and lighting systems in appropriate locations. Since the direct measurement data of particle sizes are available, the controller design can be based on these data without relying on the indirect indicators under the condition that the rate of binder addition is sufficiently slow to allow for image data to be collected, processed, and fed back. This concept has been used for batch granulation processes in fluidized beds. The same authors also proposed a feed-forward control strategy to compensate the fluctuation of the recycle rate. The simple feedback control with feed-forward compensation scheme is shown in Figure 7.

The measurement data in Figure 7 could be the indirect monitoring parameters (62), or the explicit PSD (65), depending on the relative speed of the measurement system and process dynamics.

Fuzzy-logic control of high-shear granulation. Watano et al. (66,67) have developed a novel system to control granule growth in a high-shear mixer. The system basically consisted of image processing and a fuzzy controller as shown in Figure 8.

In Figure 8, $D(t)$ is the deviation between the desired value (D_d) and measured value (D_m) of granule size, and $\Delta D(t)$ denotes the change rate of measured values, which are mathematically represented as follows:

$$\begin{aligned} D(t) &= D_d - D_m(t) \\ \Delta D(t) &= D_m(t) - D_m(t-1) \end{aligned} \tag{73}$$

Other notations in Figure 8 are explained as follows. $V(t)$ is the result of fuzzy reasoning used to control the output power of the liquid feed pump; K_1 and K_2 represent gains of the input variables.

In the methodology developed by Watano et al. (66,67), four fuzzy variables were used, namely ZR (zero), PS (positive small), PM (positive medium) and PL (positive large). The values of $D(t)$, $\Delta D(t)$, and $V(t)$ were classified into these four categories. Ten rules were proposed to relate measured $D(t)$ and $\Delta D(t)$ with $V(t)$. Consequently, $V(t)$ can be quantified using the if-then statement. An example is given as follows:

If $D(t) = \text{PS}$ and $\Delta D(t) = \text{PL}$, then $V(t) = \text{ZR}$ (rule 2 in Table 2 of Ref. 67).

In such a way, all the combinations of $D(t)$ and $\Delta D(t)$ can be connected with $V(t)$ for the effective control of the process. The technique can be considered as highly successful with the experimental justifications.

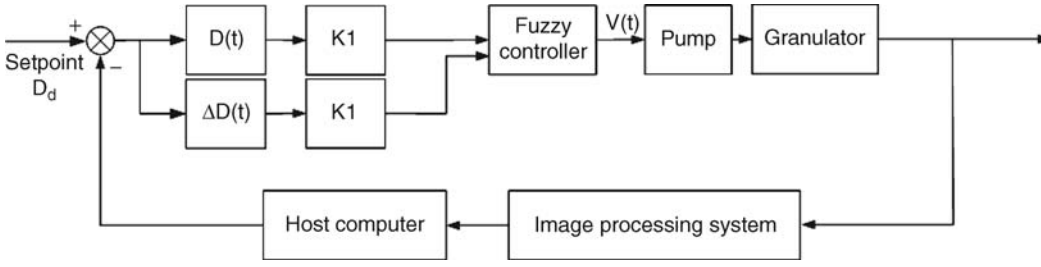


Figure 8 Block diagram of granule size control system. *Source*: From Ref. 66.

Modeling for Optimal Design, Operation, and Open-Loop Optimal Control

Process optimization and open-loop optimal control of batch and continuous drum granulation processes are described in this section as another important application example of population balance modeling. Both SS and dynamic optimization studies are carried out, which consist of (*i*) construction of optimization and control relevant, population balance models through the incorporation of moisture content, drum rotation rate, and bed depth into the coalescence kernels; (*ii*) investigation of optimal operational conditions using constrained optimization techniques; and (*iii*) development of optimal control algorithms based on discretized PBEs. The objective of SS optimization is to minimize the recycle rate with minimum cost for continuous processes. It has been identified that the drum rotation rate, bed depth (material charge), and moisture content of solids are practical decision (design) parameters for system optimization. The objective for the optimal control of batch granulation processes is to maximize the mass of product-sized particles with minimum time and binder consumption. The objective for the optimal control of the continuous process is to drive the process from one SS to another in a minimum time with minimum binder consumption, which is also known as the state-driving problem. It has been known for some time that the binder spray rate is the most effective control (manipulative) variable. Although other process variables, such as feed flow rate and additional powder flow rate can also be used as manipulative variables, only the single input problem with the binder spray rate as the manipulative variable is addressed here to demonstrate the methodology. It can be shown from simulation results that the proposed models are suitable for control and optimization studies, and the optimization algorithms connected with either SS or dynamic models are successful for the determination of optimal operational conditions and dynamic trajectories with good convergence properties.

It should be pointed out that only open-loop optimal control issues for granulation processes without uncertainty are addressed in this section. The integration of open-loop optimal control with closed-loop NMPC for uncertain processes has been reported elsewhere by the authors Wang and Cameron (60).

Statement of Optimization and Open-Loop Optimal Control Problems

A typical batch drum granulation process is schematically shown in Figure 9. There are two operational strategies: (*i*) premix the fine particles with the proper amount of liquid binder followed by the rotating operation until the desired size distribution is achieved; and (*ii*) simultaneous mixing and granulating by spraying liquid binder (and fine powders in some cases) on the moving surface of particles inside the rotating drum. The first strategy involves system optimization without any control action. The optimization problem can be stated as: to determine the optimal moisture content, initial size distribution, rotating rate, and bed depth (drum charge) so that the desired size distribution can be obtained within a minimum time t_f. Optimal control techniques can be applied to the second strategy, which can be stated as follows: for the specified initial conditions, maximize the mass of product-sized particles in minimum time with minimum energy consumption by adjusting the manipulative variables, such as binder spray rate and drum-rotation speed. We will discuss the optimal control problem with the binder spray rate as the single manipulative variable in detail.

A slightly modified continuous drum-granulation process with an additional fine powder stream is shown in Figure 10. As mentioned previously, the additional fine powder stream is used to improve the controllability of the process, which is not seen in the

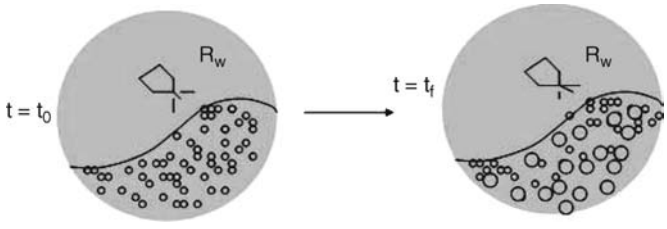


Figure 9 Schematic diagram of batch drum granulation.

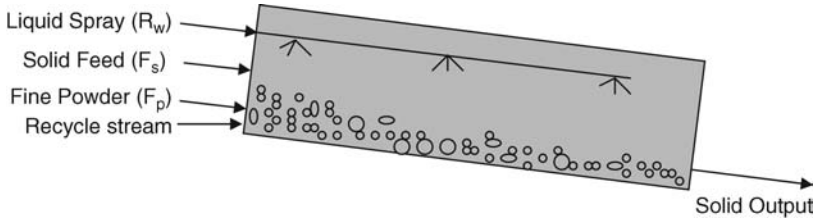


Figure 10 Schematic diagram of continuous drum granulation.

conventional design. Our studies on continuous drum granulation include the SS optimization and optimal state driving from one SS to another. The objective for SS optimization is to achieve minimum recycle rate with minimum cost through the determination of optimal operational conditions, such as rotating rate, binder spray rate, feed flow rate, bed depth, and drum inclination angle. The optimal state driving attempts to drive the system from one SS to another in a minimum time with minimum energy consumption by adjusting the time-dependent manipulative variables, such as binder spray rate, feed flow rate, and optionally additional fine powder flow rate.

Optimization and Open-Loop Optimal Control Equations

The optimization and open-loop optimal control equations consist of model equations and objective functions.

Optimization and control relevant model equations. The discretized PBE for batch system can be described as follows:

$$\frac{d}{dt}n_i = -\frac{\partial}{\partial L}(Gn_i) + B_i - D_i \qquad i = 1, 2, \ldots, i_{\max} \tag{74}$$

where n_i, B_i, and D_i stand for the particle number, birth rate, and death rate in the ith size interval, respectively, $i = 1, 2, \ldots, i_{\max}$, in which $i_{\max}$ is the total number of size intervals. Similarly, continuous processes can also be represented as

$$\frac{d}{dt}n_i = -\frac{\partial}{\partial L}(Gn_i) + B_i - D_i + F^{\text{in}}\frac{n_i^{\text{in}}}{n_t^{\text{in}}} - F^{\text{out}}\frac{n_i}{n_t} \qquad i = 1, 2, \ldots, i_{\max} \tag{75}$$

where F is the number flow rate, the subscript t indicates the total value, and the superscripts identify the inlet and outlet streams. Using Hounslow's discretization methods, the relevant terms in the right-hand sides of equations (74) and (75) are given by

$$B_i = n_{i-1}\sum_{j=1}^{i-2}(2^{j-i+1}\beta_{i-1,j}n_j) + \frac{i}{2}\beta_{i-1,i-1}n_{i-1}^2 \tag{76}$$

$$D_i = n_i\sum_{j=1}^{i-1}(2^{j-i}\beta_{i,j}n_j) - n_i\sum_{j=1}^{i_{\max}}(\beta_{i,j}n_j) \tag{77}$$

and

$$\frac{\partial Gn_i}{\partial L} = -\frac{2G}{(1+r)L_i}\left(\frac{r}{r^2-1}n_{i-1} + n_i - \frac{r}{r^2-1}n_{i+1}\right) \qquad r = \frac{L_{i+1}}{L_i} = \sqrt[3]{2} \tag{78}$$

where $\beta_{i,j}$ is equivalent to the representation $\beta(L_i, L_j)$. Consequently, an original PBE described by a partial differential–integral equation is converted into a set of ordinary differential equations. It is more convenient to convert the number-based PBEs described by equations (74)–(78) to mass-based ones, which are demonstrated by the authors (68).

A control-relevant model was developed by Zhang et al. (48), in which the coalescence kernel is a function of the moisture content. In the newly developed kernel models reported by Balliu (69) and Wang et al. (68), in addition to moisture content, the bed depth and drum speed are also incorporated. Two kernel models, namely size-independent kernel and size-dependent kernel, are used in optimization and control simulations. The size-independent kernel is given by

$$\beta_{i,j} = \beta_0 = a_0 \cdot [(x_m)^{n_1} \mathrm{e}^{-a_1 x_m}] \cdot [(B_\mathrm{d})^{n_2} \mathrm{e}^{-a_2 B_\mathrm{d}}] \cdot (S_\mathrm{d}^{n_3} e^{-a_3 S_\mathrm{d}}) \tag{79}$$

where x_m is the moisture content in particles, B_d is the bed depth, S_d is the drum-rotating rate, a_0–a_3 and n_1–n_3 are constants determined through parameter identification techniques based on the measurement data. The size-dependent kernel is represented as (12)

$$\beta_{i,j} = \beta_0 \frac{(L_i + L_j)^2}{L_i L_j} \tag{80}$$

where β_0 is also defined in equation (79).

Since the main mechanism determining the growth rate G in equations (74) and (75) is layering of the fine powders on the surface of particles, it can be deduced that the growth rate is a strong function of the powder fraction and moisture content. The following correlation is used to calculate the growth rate:

$$G = G_m \cdot \frac{M_\mathrm{powder}}{k \cdot \Sigma M_i + M_\mathrm{powder}} \cdot \exp[-a(x_w - x_{wc})^2] \tag{81}$$

where G_m is the maximum growth rate, M_powder is the mass of fine powder below the lower bound of the particle classes, M_i is the mass of particles in the ith size class, x_{wc} is the critical moisture, and k and a are fitting parameters. Studies on powder mass balance lead to the following equation for batch processes:

$$\frac{dM_\mathrm{powder}}{dt} = F_\mathrm{powder}^\mathrm{in} - 3G\int_0^\infty \frac{M(L)}{L} dL \tag{82}$$

and the following equation for continuous processes:

$$\frac{dM_\mathrm{powder}}{dt} = F_\mathrm{powder}^\mathrm{in} - \frac{M_\mathrm{powder}}{t_R} - 3G\int_0^\infty \frac{M(L)}{L} dL \tag{83}$$

where $F_\mathrm{powder}^\mathrm{in}$ represents the flow rate of additional powder stream in both batch and continuous cases. It can be used as an additional manipulative variable.

The liquid mass balance for batch processes is given by

$$\frac{dx_w}{dt} = \frac{1}{M_\mathrm{t}} R_w \tag{84}$$

where M_t is the total mass of solids in the drum, R_w is the binder spray rate. Similarly, we can develop the liquid mass balance for the continuous process as

$$\frac{dx_w}{dt} = \frac{1}{M_\mathrm{t}} [F_M^\mathrm{in} x_w^\mathrm{in} - F_M x_w + R_w] \tag{85}$$

where F_M^in and F_M are inlet and outlet mass flow rates, respectively, and x_w^in is the moisture content in the feed solids.

In summary, the equations in the control relevant model for batch systems are discretized PBEs given by equation (74), powder dynamics described by equation (82), and liquid dynamics represented by equation (84). The corresponding equations for continuous processes are equations (75), (83) and (85). Both cases share the same kernel models given by equations (79) and (80), and growth-rate model described by equation (81).

Objective functions for system optimization and open-loop optimal control. The objective function for system optimization of batch granulation is

$$\underset{S_d, B_d, x_w}{\text{Minimize}} \left\{ J = \frac{-w_1 M_p(t_f)}{t_f} \right\} \quad \text{Subject to equation (74)} \tag{86}$$

The objective function for batch granulation with the binder spray rate as the only manipulative variable is given by

$$\underset{R_w}{\text{Mimimize}} \left\{ \frac{-w_1 M_p(t_f) + w_2 \int_0^{t_f} R_w \mathrm{d}t}{t_f} \right\} \quad \text{Subject to equations (74), (82), and (84)} \tag{87}$$

In equations (86) and (87), M_p is the mass of product-sized particles, w_1 and w_2 are weighting functions.

The objective function for SS optimization of continuous granulation is

$$\underset{S_d, B_d, F^{in}, R_w}{\text{Minimize}} \{-w_1 F_p + w_2 R_w\} \quad \text{Subject to equations (75), (83), and (85) with left-hand sides replaced by zero} \tag{88}$$

where F_p is the mass flow rate of product-sized particles.

For the state-driving study, we carry out SS optimizations for two different product specifications: the product range for SS1 is 2.0 to 3.2 mm, whereas that for steady state 2 (SS2) is 3.2 to 5.0 mm. The objective function for this optimal state-driving problem is described as

$$\underset{R_w}{\text{Minimize}} \left\{ J = \sum [w_{1,i}(M_i(t_f) - M_i^{SS2})^2] + w_2 \int_0^{t_f} R_w \, \mathrm{d}t + w_3 t_f \right\} \quad \text{Subject to equations (75), (83), and (85)and zero derivatives at final time} \tag{89}$$

where $M_i(t_f)$ and M_i^{SS2} denote the mass of particles in the ith size interval at the final time and for SS2, respectively.

Dynamic Optimization Algorithm

It is not difficult to solve the steady state optimization problems with constraints represented by algebraic equations by using commercial software packages. We mainly explain the dynamic optimization methods used in this work. The basic structure of the algorithm employed in this paper is shown in Figure 11.

In the dynamic optimization algorithm depicted in Figure 11, a control parameterization technique (70) is used to discretize the originally continuous control variables. That is, a control (manipulative) variable $u(t)$ is represented by a set of piecewise constants, u_i, $i = 1, 2, \ldots, q$. These constants are treated as parameters to be determined by using dynamic optimization algorithms.

Since the MATLAB software packages with Optimization Toolbox provide both effective ordinary differential equation (ODE) solvers as well as powerful optimization algorithms, the dynamic simulations reported in this paper are carried out by using the MATLAB Optimization Toolbox (71).

Selected Simulation Results and Discussion

Simulations for both batch and continuous granulation processes are based on a pilot plant drum granulator with the following parameters: length = 2 m, diameter = 0.3 m, nominal hold up = 40 kg, rotation rate = 25 to 40 rpm, retention time range = 6 to 10 minutes. Other process parameters are available in a recent paper by Wang et al. (68).

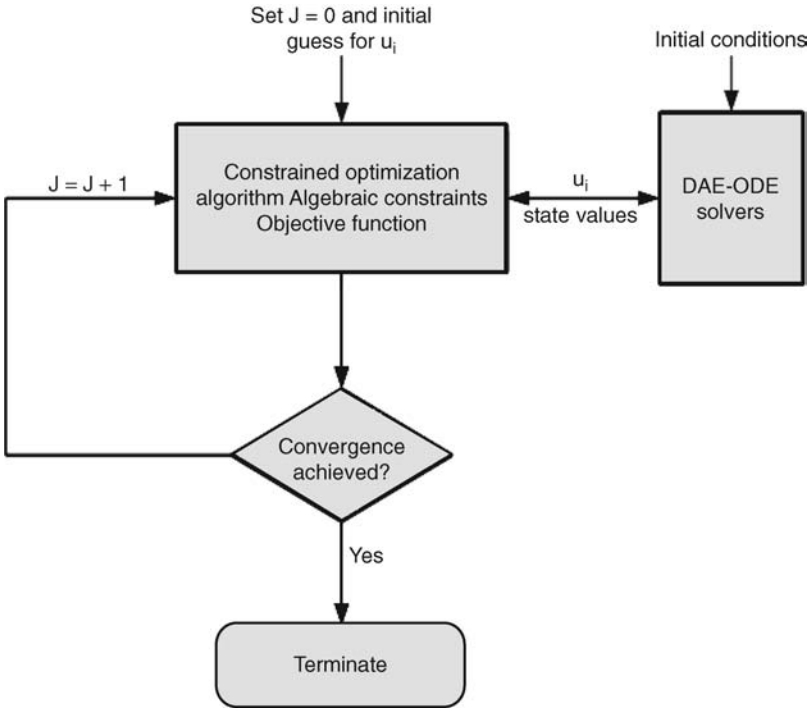


Figure 11 Basic structure of the dynamic optimization algorithm.

The simulated optimal profiles for the batch processes are shown in Figure 12A–C with two data sets with and without constraints on control action. The control constraints restrict lower and upper bounds on the control variables (lower bound = 0 kg/sec, upper bound = 0.015 kg/sec), as well as the gradient of the control actions ($|dR_w/dt| \leq 0.0003$ kg/sec^2). It can be seen from Figure 12D that if the normal constraints on the control variable are replaced by a high upper bound of control variable (0.036 kg/sec) as the only constraint, very high spray rates at the early operating stage with very short spray time leads to the minimum objective function given by equation (87). However, if the normal constraints are activated, the control variable moves smoothly rather than suddenly with the price of a longer operational time. The difference between final times in the two cases is about 104 seconds (283–179 seconds), which is quite significant. The results clearly have implications on equipment design and specifications that could allow the constraints to be moved out thus approaching the best operating policy.

Through SS optimizations using the objective function described by equation (88), optimal binder spray rates for two different specifications on product size ranges are obtained. These are $R_w = 0.050$ kg/sec for 2.0 to 3.2 mm as the product size range, and $R_w = 0.075$ kg/sec for 3.2 to 5.0 mm as the product size range. Figure 13A, B show the profiles using an optimal control policy and a constant spray rate policy. The change of the cumulative mass between initial and final times under optimal control policy is shown in Figure 13C. The control profiles are depicted in Figure 13D. The optimal control policy leads to about 50% reduction on the objective function given by equation (89). The optimal spray policy can be stated as follows: "Gradually increase the spray rate from the first steady state (0.005 kg/sec) to achieve a relatively high spray rate (0.0084 kg/sec) followed by gradual reduction of the spray rate until the spray rate of the second SS value (0.0075 kg/sec) is reached, which will be maintained for the rest of the operational period." From Figure 13, the significance of optimal control studies can be demonstrated by observing the facts that the optimal profiles approach the second SS faster, and the optimal control strategy is easy to implement with smooth movement. It should be pointed out that the

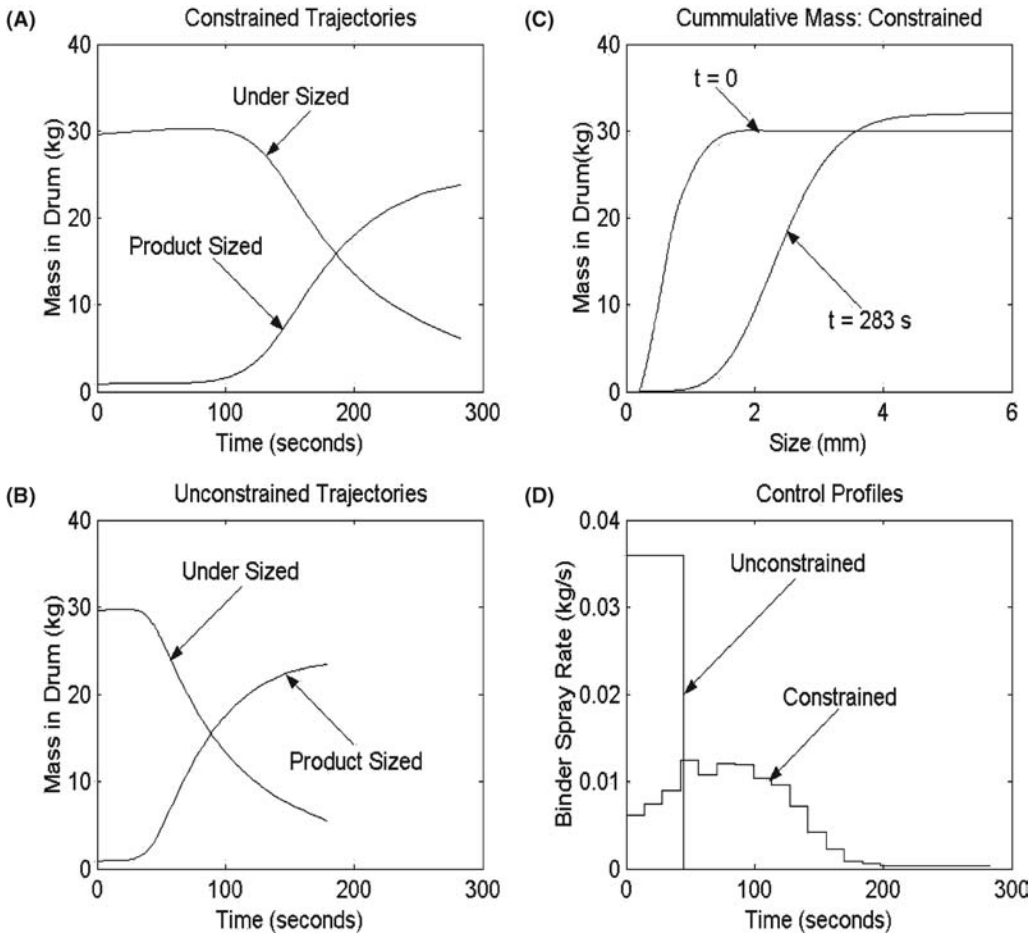


Figure 12 Optimal Control of batch drum granulation.

small difference between two control policies shown in Figure 13 is due to little difference between two product specifications (product ranges from 2.0–3.2 mm to 3.2–5.0). It can be predicted that if the two SSs are far away, profound economic benefit can be achieved. Optimal control strategies are particularly important to plant startup and shutdown operations.

Figure 14 shows the dynamic profiles of optimal state driving from SS1 to SS2 with different levels of constraints. Dynamic changes of product mass, undersized mass, and moisture content are shown in Figure 14A–C, respectively, under two constraint levels. Figure 14D depicts control profiles for these two cases. In addition to the constraints on control actions, the final time constraints ensure the final SS status is imposed on the system. That is, the left-hand sides of equations (75), (83) and (85) should be zero at the final time. However, it is not necessary to achieve zero exactly for the derivatives at the final time. We normally impose the final time constraints as $|dx(t_f)/dt| < \varepsilon$ in which x represents general state variables such as number of particles, mass of powder, and moisture content, and ε is a very small positive number for practical applications with the value depending on the tightness of constraints. The ε values are chosen as 10^{-6} and 10^{-3} for tight and loose constraints indicated in Figure 14, respectively. It can be shown from Figure 14 that the control strategy with loose constraints leads to shorter operational time than that with tight constraints (1827 seconds vs. 1925 seconds). However, the moisture dynamics shows severe offset and oscillation. In optimization simulations, only final time constraints are changed for the two cases. It is interesting to note that the program with tight constraints leads to small and smooth controller movements even though the constraints on the control variable are not altered explicitly. It

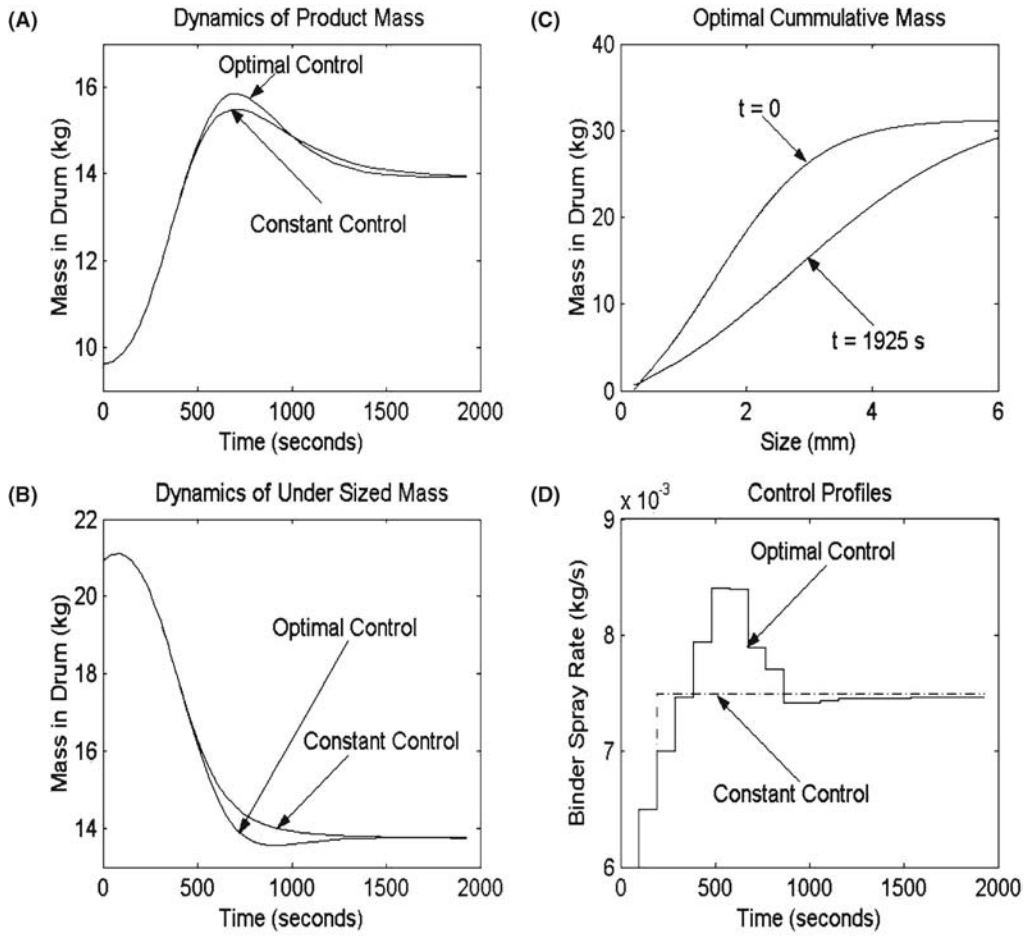


Figure 13 Optimal control of continuous drum granulation.

seems that the loose constraints allow too much manipulative variation that drives the system into a region ($x_w \approx 0.1$) where moisture variations have significant impact on the granulation performance. A marginal benefit identified by 5% time reduction is achievable using loose constraints with a price of process oscillations. Consequently, control strategy with tight final time constraints is superior to that with loose constraints in this particular application.

Through an analysis on the simulation results, the following conclusions can be drawn.

1. Population balance modeling provides an important basis for optimal design and operations for both batch and continuous granulation processes.
2. The effects of liquid content, bed depth and drum rotation rate on the coalescence behavior can be quantified through the development of new kernel models, with the structure described by equations (79) and (80). The simulation results are qualitatively consistent with industrial experience in large-scale fertilizer production.
3. An optimal control strategy and algorithm using commercial optimization software packages connected to reliable DAE/ODE solvers are successful for the determination of optimal trajectories with good convergence properties. This implies that under certain conditions, the more complicated optimal control algorithms, such as that based on the well-known Pontryagin's maximum principle, could be avoided.
4. Since startup and shutdown operations are frequently encountered in granulation plants with huge financial impacts, studies on optimal control strategies can lead to significant economic benefits.

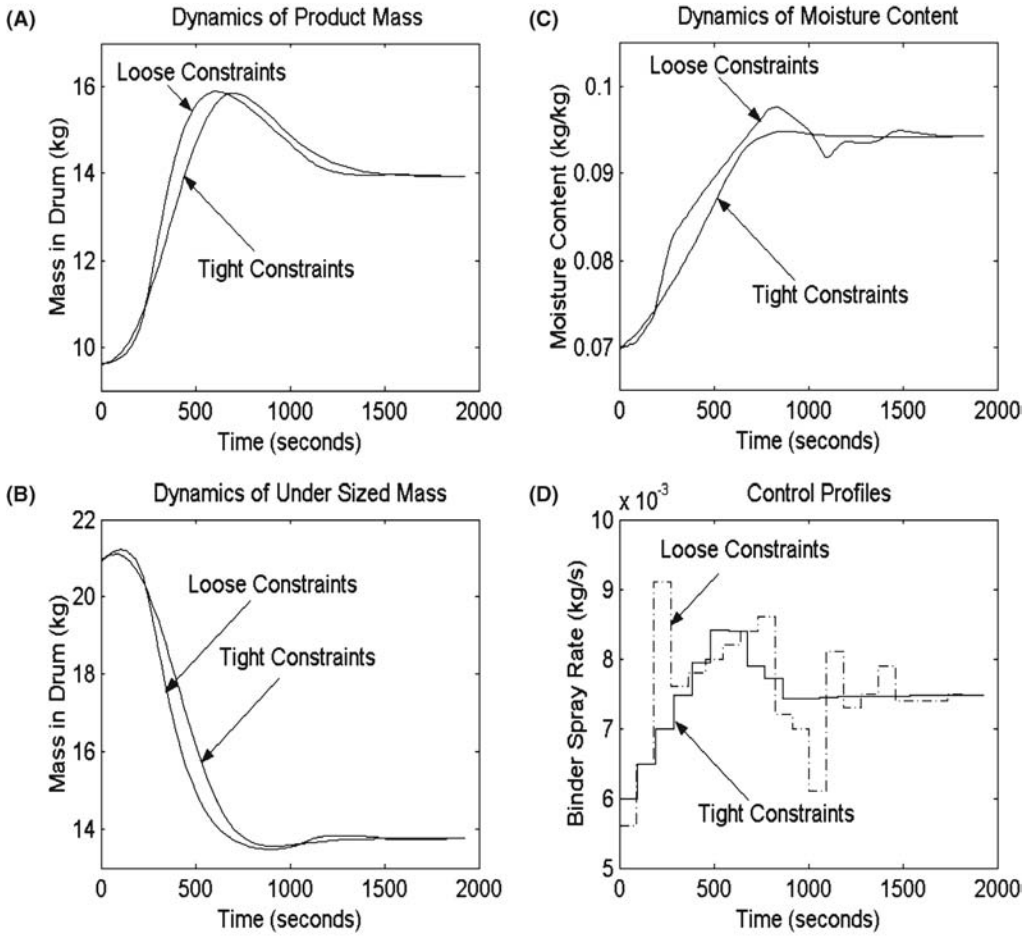


Figure 14 Effects of constraint tightness on optimal control of drum granulation.

SUMMARY

Granulation modeling is an area of growing importance. It is dominated by the population balance approach for developing mechanistic models. However, it requires an improved understanding of the key factors involved in particle nucleation, growth, coalescence, and breakage. It can be witnessed that much has been achieved over the last 10 years through a comparison between the current article and the early review paper published by the authors in 2002 (72). Also, the growing importance of particulate flow patterns is being addressed through approaches such as discrete element methods (DEM), which will hopefully provide a microscale view of particle motions in the granulation device. The challenge is in addressing the multiscale nature of granulation modeling that spans from particle interactions up to the plant level.

The development of empirically based models has provided a simple means of addressing quickly a number of control-related applications. This will continue to be a useful approach for such problems.

Application of models to design, advanced control, and diagnosis will require mechanistic models that continue to incorporate the latest understanding of the underlying mechanisms. A number of mechanistic kernels have been reported in the literature and reviewed in this article. Much work is currently underway in these areas and the incorporation into existing models of new insights will help extend the applicability of process models for granulation.

REFERENCES

1. Michaels JN. Toward rational design of powder processes. Powder Technol 2003; 138:1–6.
2. Litster JD. Scale-up of wet granulation processes: science not art. Powder Technol 2003; 130:5–40.
3. Hangos KM, Cameron IT. Process Modelling and Model Analysis. London: Academic Press, 2001, ISBN 0-12-156931-4.
4. Yekeler M, Ozkan A. Determination of the breakage and wetting parameters of calcite and their correlations. Part Syst Charact 2002; 19:419–425.
5. Salman AD, Fu J, Gorham DA, et al. Impact breakage of fertilizer granules. Powder Technol 2002; 130:359–236.
6. van den Dries K, de Vegt O, Girard V, et al. Granule breakage phenomena in a high shear mixer: influence of process and formulation variables and consequences on granule homogeneity. Powder Technol 2003; 130:228–236.
7. Randolph AD, Larson MA. Theory of Particulate Processes: Analysis and Techniques of Continuous Crystallization. 2nd ed. San Diego: Academic Press, 1988.
8. Ramkrishna D. Population Balances: Theory and Applications to Particulate Systems in Engineering. San Diego: Academic Press, 2000.
9. Liu LX, Litster JD, Iveson SM, et al. Coalescence of deformable granules in wet granulation processes. AIChE J 2000; 46(3):529–539.
10. Liu LX, Litster JD. Population balance modelling of granulation with a physically based coalescence kernel. Chem Eng Sci 2002; 57:2183–2191.
11. Ennis BJ, Litster JD. Size enlargement. In: Perry RH, Green DW, ed. Perry's Chemical Engineering Handbook. 7th ed. New York: McGraw-Hill, 1997.
12. Friedlander SK. Smoke, Dust and Haze. 1st ed. New York: Wiley, 1977; 2nd ed., New York: Oxford University Press, 2000.
13. Kapur PC, Fuerstenau DW. Coalescence model for granulation. Ind Eng Chem Proc Des Dev 1969; 8:56–62.
14. Kapur PC. Kinetics of granulation by non-random coalescence mechanism. Chem Eng Sci 1972; 27:1863–1869.
15. Sastry KVS. Similarity size distribution of agglomerates during their growth by coalescence in granulation or green pelletization. Int J Miner Process 1975; 2:187–203.
16. Golovin AM. The solution of coagulation equation for raindrops, taking condensation into account. Soviet Physics Dokl 1963; 8:191–193.
17. Adetayo AA, Litster JD, Pratsinis SE, et al. Population balance modelling of drum granulation of materials with wide size distribution. Powder Technol 1995; 82:37–49.
18. Adetayo AA, Ennis BJ. A unifying approach to modelling granulation processes coalescence mechanisms. AIChE J 1997; 43(1):927–934.
19. Iveson SM, Litster JD, Hapgood K, et al. Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review. Powder Technol 2001; 117:3–39.
20. Immanuel CD, Doyle III FJ. Solution technique for multi-dimensional population balance model describing granulation processes. Powder Technol 2005; 156:213–225.
21. Poon JM-H, Immanuel CD, Doyle III FJ, et al. A three-dimensional population balance model of granulation with a mechanistic representation of the nucleation and aggregation phenomena. Chem Eng Sci 2008; 63:1315–1329.
22. Ennis BJ, Tardos G, Pfeffer R. A microlevel-based characterization of granulation phenomena. Powder Technol 2001; 65:257–272.
23. Immanuel CD, Cordeiro CF, Sundaram SS, et al. Population balance PSD model for emulsion polymerization with steric stabilizers. AIChE J 2003; 49(6):1392–1404.
24. Iveson SM. Limitations of one-dimensional population balance models of wet granulation processes. Powder Technol 2002; 124:219–229.
25. Verkoeijen D, Pouw GA, Meesters GMH, et al. Population balances for particulate processes—a volume approach. Chem Eng Sci 2002; 57:2287–2303.
26. Poon JM-H, Ramachandran R, Sanders CFW, et al. Experimental validation studies on a multi-dimensional and multi-scale population balance model of batch granulation. Chem Eng Sci 2009; 64:775–786.
27. Ramachandran R, Poon JM-H, Sanders CFW, et al. Experimental studies on distributions of granule size, binder content and porosity in batch drum granulation: inferences on process modeling requirements and process sensitivities. Powder Technol 2008; 188:89–101.
28. Biggs CA, Sanders C, Scott AC, et al. Coupling granule properties and granulation rates in high-shear granulation. Powder Technol 2003; 130:162–168.
29. Robertson GAA, Cameron IT. Analysis of dynamic process models for structural insight and model reduction. Part 1. Structural identification measures. Comput Chem Eng 1997; 21(5):455–473.

30. Hounslow MJ, Ryall RL, Marshall VR. A discrete population balance for nucleation, growth and aggregation. AIChE J 1988; 34(11):1821–1832.
31. Kumar S, Ramkrishna D. On the solution of population balance equations by discretization. I: A fixed pivot technique. Chem Eng Sci 1996; 51(8):1311–1332.
32. Liu Y, Cameron IT. A new wavelet-based method for the solution of the population balance equation. Chem Eng Sci 2001; 56:5283–5294.
33. Bertoluzza S. A wavelet collocation method for the numerical solution of partial differential equations. Appl Comput Harmonic Anal 1996; 3:1–9.
34. Liu Y, Cameron IT, Wang FY. The wavelet collocation method for transient problems with steep gradients. Chem Eng Sci 2000; 55:1729–1734.
35. Liu Y, Cameron IT. A new wavelet-based adaptive method for solving population balance equations. Powder Technol 2003; 130:181–188.
36. Immanuel CD, Doyle III FJ. Computationally-efficient solution of population balance models incorporating nucleation, growth and coagulation. Chem Eng Sci 2003; 58(16):3681–3698.
37. Pinto MA, Immanuel CD, Doyle III FJ. A feasible solution technique for higher-dimensional population balance models. Comput Chem Eng 2007; 31:1242–1256.
38. Pinto MA, Immanuel CD, Doyle III FJ. A two level discretisation algorithm for the effective solution of higher-dimensional population balance models. Chem Eng Sci 2008; 63:1304–1314.
39. Petzold L. A description of DASSL: a differential-algebraic system solver. Proc IMACS World Congress, Montreal, Canada, 1982.
40. Cameron IT. Solution of differential-algebraic systems using diagonally implicit runge-kutta methods. IMA J Numer Anal 1983; 3:273–289.
41. Williams R, Burrage K, Cameron IT, et al. A four-stage index 2 diagonally implicit runge-kutta method. Appl Numer Math 2002; 40:415–432.
42. Spielman LA, Levenspiel O. A Monte Carlo treatment for reaction and coalescing dispersed systems. Chem Eng Sci 1965; 20:247.
43. Kaye BH. Powder Mixing. London: Chapman & Hall, 1997.
44. Smith M, Matsoukas T. Constant number Monte Carlo simulation of population balances. Chem Eng Sci 1998; 53(9):1777–1786.
45. Wauters PAL. Modelling and Mechanisms of Granulation. PhD thesis, The Delft University of Technology, The Netherlands, 2001.
46. Cameron IT, Wang FY, Immanuel CD et al. Process systems modelling and applications in granulation: a review. Chem Eng Sci 2005; 60:3723–3750.
47. Cameron IT, Wang FY. Process systems engineering applied to granulation. In: Agba S, Michael H, Jonathan S, eds. Handbook of Powder Technology. Amsterdam: Elsevier BV, 2006:499–552.
48. Zhang J, Lister JD, Wang FY, et al. Evaluation of control strategies for fertiliser granulation circuits using dynamic simulation. Powder Technol 2000; 108:122–129.
49. Ljung L. System Identification: theory for the user. Upper Saddle River, NJ: Prentice Hall, 1987.
50. Sanders CFW, Hounslow MJ, Doyle III FJ. Identification of models for control of wet granulation. Powder Technol 2009; 188:255–263.
51. Wang FY, Cameron IT. A multi-form modelling approach to the dynamics and control of drum granulation processes. Powder Technol 2007; 179:1–11.
52. Wang FY, Bahri PA, Lee PL, et al. A multiple model, state feedback strategy for robust control of non-linear processes. Comput Chem Eng 2007; 31:410–418.
53. Ljung L. System Identification Toolbox for Use with MATLAB. Natick, MA: The Math Works, 2000.
54. Adetayo AA, Pottman M, Ogunnaike B. Effective control of a continuous granulation process. Proceedings of the Control of Particulate Processes IV, 23–28, Engineering Foundation, New York, 1997.
55. Bemporad A, Morari M, Ricker NL. Model Predictive Control Toolbox 2 User Guide. MATLAB R2007a Version 7.4.0.287 (R2007a), 2007.
56. Glaser T, Sanders CF, Wang FY, et al. Model predictive control of continuous drum granulation. J Process Control 2009; 19:615–622.
57. Miller SM, Rawlings JB. Model identification and control strategies for batch cooling crystallisers. AIChE J 1994; 40(8):1312–1326.
58. Immanuel CD, Doyle III FJ. Hierarchical multiobjective strategy for particle-size distribution control. AIChE J 2003; 49(9):2383–2399.
59. Crowley TJ, Meadows ES, Kostoulas A, et al. Control of particle size distribution described by a population balance model of semi-batch emulsion polymerisation. J Process Control 2000; 10:419–432.
60. Wang FY, Cameron IT. Multi-level optimal control of particulate process with on-line identification. The 7th World Congress of Chemical Engineering (WCCE7), Glasgow, Scotland, July 10–14, 2005.

61. Sanders CFW, Willemse AW, Salman AD, et al. Development of a predictive high-shear granulation model. Powder Technol 2003; 138:18–24.
62. Leuenberger H. Moist agglomeration of pharmaceutical processes. In: Chulia D, Deleuil M, Pourcelot Y, eds. Powder Technology and Pharmaceutical Processes, Handbook of Powder Technology. Vol. 9. Amsterdam: Elsevier, 1994:337–389.
63. Faure A, York P, Rowe RC. Process control and scale-up of pharmaceutical wet granulation processes: a review. Eur J Pharm Biopharm 2001; 52:269–277.
64. Kristensen HG, Schaefer T. Granulation: a review on pharmaceutical wet granulation. Drug Dev Ind Pharm 1987; 13:803–872.
65. Mort PR, Capeci SW, Holder JW. Control of agglomerate attributes in a continuous binder-agglomeration process. Powder Technol 2001; 117:173–176.
66. Watano S, Numa T, Koizumi I, et al. Feedback control in high shear granulation of pharmaceutical powders. Eur J Pharm Biopharm 2001; 52:337–345.
67. Watano S, Numa T, Koizumi I, et al. A fuzzy control system of high shear granulation using image processing. Powder Technol 2001; 115:124–130.
68. Wang FY, Ge X, Balliu N, et al. Optimal control and operation of drum granulation processes. Chem Eng Sci 2006; 61:257–267.
69. Balliu N. An object oriented approach to the modelling and dynamics of granulation circuits [PhD thesis]. Australia: School of Engineering, The University of Queensland, 2004.
70. Teo KL, Goh CJ, Wong KH. A Unified Computational Approach for Optimal Control Problems. New York: Longman Scientific and Technical, 1991.
71. Branch MA, Grace A. MATLAB Optimization Toolbox User's Guide. Natick: The Math Works Inc., 1996.
72. Wang FY, Cameron IT. Review and future directions in the modelling and control of continuous drum granulation. Powder Technol 2002; 124:238–253.

25 Scale-Up Considerations in Granulation

Yinghe He
School of Engineering and Physical Sciences, James Cook University, Queensland, Australia

Lian X. Liu
Particle & Systems Design Centre, School of Chemical Engineering, The University of Queensland, Queensland, Australia

James D. Litster
School of Chemical Engineering and Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, Indiana, U.S.A.

Defne Kayrak-Talay
School of Chemical Engineering, Purdue University, West Lafayette, Indiana, U.S.A.

INTRODUCTION

Scale-up of any engineering process is a great technical and economic challenge. Scale-up of granulation processes in particular is difficult and often problematic because of the inherently heterogeneous nature of the materials used. However, recent improved understanding of the rate processes that control granulation improves our ability to do rational scale-up.

There are two situations where process scale-up is needed:

1. Commercialization of newly developed processes and/or products
2. Expansion of production capacities in response to increased market demand

For pharmaceutical applications, the challenge is almost always associated with new product development. Scale-up in the pharmaceutical industry is unique in that experiments at laboratory and pilot scales are also required to produce product of desired specification for different stages of clinical trials. This gives additional constraints and challenges to engineers and technologists during scale-up.

A change in scale invariably impacts on process conditions and, consequently, on the product quality. For pharmaceutical industries, the Food and Drug Administration (FDA) ranks the impacts on the drug product arising from changes of process conditions including production scales into three levels as shown in Table 1 (1). Level 1 is reserved for changes that are unlikely to have any detectable impact on the formulation quality and performance (2). For all practical purposes, scale-up should aim to achieve an impact equivalent to or less than level 1.

In this chapter, we will first consider general scale-up approaches from a chemical engineering perspective. We will then look specifically at understanding pharmaceutical granulation scale-up through considering granulation as a combination of rate processes. Each rate process is affected by changes in process during scaling, as well as by formulation decisions. Finally, we will present suggestions for scaling of fluid-bed and high-shear mixer granulation that follow from this approach.

GENERAL CONSIDERATIONS IN PROCESS SCALE-UP: DIMENSIONAL ANALYSIS AND THE PRINCIPLE OF SIMILARITY

It is important to recognize that designing a commercial-scale operation via several stages of scale-up is, in one sense, an admission of failure. If we have a strong understanding of our processes, then full-scale design can be performed using appropriate mathematical models,

Table 1 Scale-Up and Post-Approval Changes Level Component or Composition Change Levels

	Percent excipient (w/w of total dosage unit)		
Excipient	Level 1	Level 2	Level 3
Filler	±5	±10	>10
Disintegrant			
Starch	±3	±6	>6
Other	±0.5	±1	>1
Binder	±0.5	±1	>1
Lubricant			
Ca or Mg	±0.25	±0.5	>0.5
Stearate			
Other	±1	±2	>2
Glidant			
Talc	±1	±2	>2
Other	±0.1	±0.2	>0.2
Film coat	±1	±2	>2
Total drug recipient change (%)	5	10	n/a

Source: Adapted from Ref. 2.

given feed formulation properties and clear required product specifications. Mature chemical engineering processes, such as distillation, are designed this way.

However, most solids processing technology do not have this level of maturity yet. In this case, scale-up studies reduce uncertainties in the design and operation of the scaled unit most economically. On this basis, the starting point in scale-up must really be the commercial unit. In theory, once sufficient information for the commercial unit is known, scale-up can be done by applying similarity principles from data collected on a smaller unit. The similarity principle states (3):

> *Two processes can be considered similar if they take place in similar geometric space and all dimensionless groups required to describe the processes have the same numerical values.*

To establish the necessary dimensionless groups, a systematic dimensional analysis needs to be carried out during which Buckingham Π theorem is used to reduce the number of dimensionless groups (4). Assuming that a process can be described by k variables, we can express one variable as a function of the other $k - 1$ variables, that is,

$$x_1 = f(x_2, x_3, \ldots, x_{k-1}) \tag{1}$$

To conform to the dimensional homogeneity, the dimensions of the variable on the left side of the equation must be equal to those on the right side of the equation. With some simple mathematical rearrangements, equation (1) can be transformed into an equation of dimensionless groups (Π terms), that is,

$$\Pi_1 = \phi(\Pi_2, \Pi_3, \ldots, \Pi_{k-r}) \tag{2}$$

Equation (2) is a relationship among $k - r$ independent dimensionless products, where r is the minimum number of reference dimensions required to describe the variables. While the Buckingham Π theorem itself is straightforward, development of a dimensionless expression for a process or a phenomenon requires a systematic dimensional analysis (4). For most engineering problems, variables can be divided into three groups: (*i*) geometric variables, (*ii*) material property variables, and (*iii*) process variables. The reference dimensions are normally the basic dimensions such as mass (M), length (L), and time (T).

It is important to note that a systematic dimensional analysis can only be applied to processes where a clear understanding of the processes is established. Omission of any important variables of the process will lead to an erroneous outcome of the dimensional analysis, inevitably causing major problems in scale-up. Zlokarnik et al. (3) divided the

application of dimensional analysis into five general cases with different level of understanding in each case.

1. The science of the basic phenomenon is unknown—dimensional analysis cannot be applied.
2. Enough is known about the science of the basic phenomenon to compile a tentative draft list—the resulting Π set is unreliable;
3. All the relevant variables for the description of the problems are known—application of dimensional analysis is straight forward.
4. The problem can be described by a mathematical equation—mathematical functions are better than Π relationships, which may help reducing the number of dimensionless groups.
5. A mathematical solution of the problem exists—application of dimensional analysis is unnecessary.

Clearly, the more we understand a process or phenomenon, the better we can scale it up with confidence.

Full application of the similarity principle requires all the relevant Π groups to be measured at the small scale and kept constant during scale-up. Unfortunately, most industrial processes are very complex with many physical and chemical phenomena occurring. This leads to a large set of dimensionless groups required to fully characterize the process. This is particularly the case with processes involving particulate materials such as granulation. Maintaining all the dimensionless groups constant on the two scales is very difficult, if not impossible, because of constraints on the degrees of freedom in variables that can be changed on scale-up. In this case, scale-up can only be done on the basis of *partial similarity*. That is, not all dimensionless numbers can be maintained the same on the two scales.

To scale up on the basis of partial similarity, experiments are carried out on a succession of equipments at different scales and results extrapolated to the final scale. That is, the scale-up ratio is kept low. With conflicting requirements on the dimensionless groups during scale-up, a common approach is to maintain one dimensionless group constant and check the effect of other dimensionless groups on the dependent variable by varying these dimensionless groups during experimentation. Once determined, only the dominant dimensionless number will be kept constant on scale-up. This partial similarity approach is often applied to granulation.

ANALYSIS OF GRANULATION RATE PROCESSES AND IMPLICATIONS FOR SCALE-UP

Many of the required granule product attributes are directly related to the size, size distribution, and density of the granule product. These granule properties develop as a result of three classes of rate process in the granulator (Fig. 1):

1. Wetting and nucleation
2. Growth and consolidation
3. Breakage and attrition

Each of these processes is analyzed in depth by Litster and Ennis (5). In this section, we will summarize each rate process in turn, particularly highlighting the main formulation properties and process variables. Where possible, we will define dimensionless groups that can be used in scale-up.

Wetting and Nucleation

The first step in granulation is the addition of a liquid binder to the powder to form nuclei granules. Within the granulator, the key region for wetting and nucleation is the spray zone where liquid binder droplets contact the moving powder surface. The nucleation process is considered to consist of four stages (Fig. 2).

1. Droplet formation
2. Droplet overlap and coalescence at the bed surface

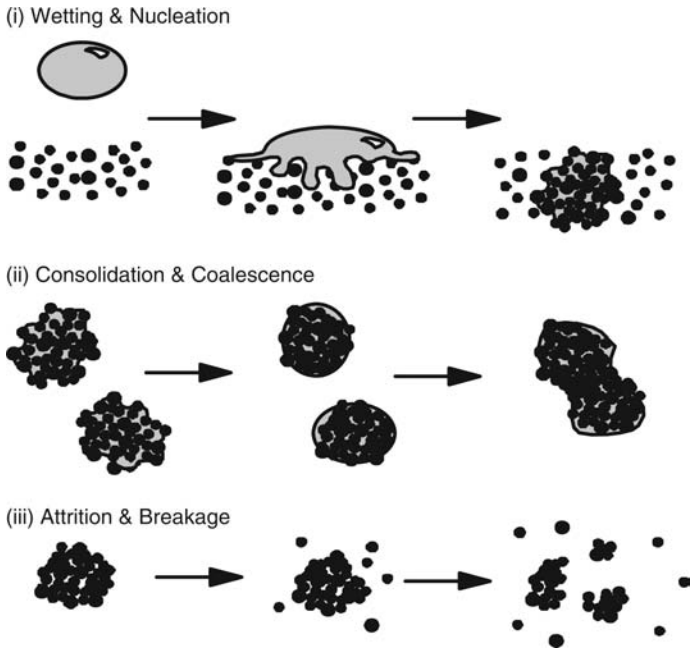


Figure 1 A classification of granulation rate processes. *Source*: From Ref. 5.

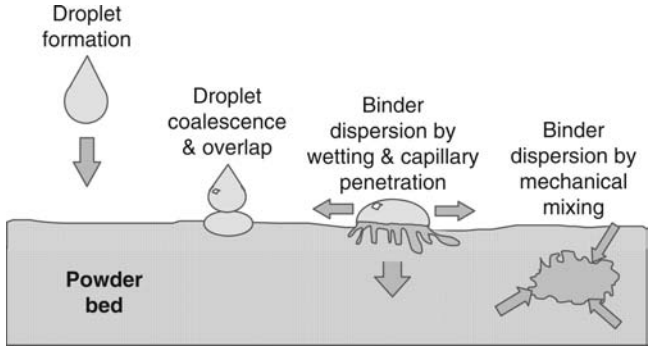


Figure 2 Wetting and nuclei formation in the spray zone of a granulator.

3. Drop penetration into the bed by capillary action
4. Mechanical dispersion of large clumps within the powder bed (only applicable to mixer granulators)

Poor wetting and nucleation lead to broad granule size distributions and poor distribution of the liquid binder, which increase substantially the chances of poor drug distribution. Despite the action of other rate processes, the broad size distributions and poor liquid distribution often persist throughout the granulation.

For ideal nucleation, the granulator should operate in the drop-controlled regime. Here, each drop that hits the powder bed penetrates into the bed to form a single nucleus granule. There is (almost) no drop overlap at the bed surface, and mechanical dispersion of large wet powder clumps is unnecessary.

To predict the required conditions for drop-controlled nucleation, we must understand

1. the thermodynamics and kinetics of drop penetration, largely controlled by *formulation properties*, and
2. the flux of drops onto the bed surface, largely controlled by *process parameters*.

The drop penetration time t_p can be estimated using a model that considers the rate at which liquid flows into the pores in the powder surface under capillary action (6).

$$t_p = 1.35 \frac{V_0^{2/3}}{\varepsilon_{eff}^2 R_{eff}} \frac{\mu}{\gamma_{LV} \cos \theta} \tag{3}$$

where V_0 is the drop volume, μ is the liquid viscosity, and $\gamma_{LV}\cos\theta$ is the adhesive tension between the liquid and the powder. The effective pore size R_{eff} and porosity ε_{eff} of the powder bed are given by

$$R_{eff} = \frac{\phi d_{3,2}}{3} \frac{\varepsilon_{eff}}{(1 - \varepsilon_{eff})} \tag{4}$$

$$\varepsilon_{eff} = \varepsilon_{tap}(1 - \varepsilon + \varepsilon_{tap}) \tag{5}$$

where ϕ is the particle sphericity, $d_{3,2}$ is the specific surface mean particle size, ε is the loose-packed bed porosity, and ε_{tap} is the tapped bed porosity.

For drop-controlled nucleation, the drop penetration time must be small compared with the bed circulation time t_c before that section of powder passes again through the spray zone, that is, the dimensionless penetration time should be small.

$$\tau_p = \frac{t_p}{t_c} < 0.1 \tag{6}$$

To avoid drop overlap on the bed surface and caking of the powder, the dimensionless spray flux ψ must also be kept small. ψ_a is the ratio of the rate of production of drop projected area by the nozzle to the rate at which powder surface area passed through the spray zone and is defined as

$$\Psi_a = \frac{3\dot{V}}{2\dot{A}d_d} \tag{7}$$

Figure 3 shows how the nuclei granule size distribution broadens as the spray flux increases. For drop-controlled nucleation, the dimensionless spray flux should be kept less than 0.2. For $\psi_a > 0.7$, the surface of the powder bed in the spray zone is effectively caked.

We can represent the nucleation behavior in a regime map (Fig. 4). Drop-controlled nucleation is achieved only when *both* ψ_a and τ_p are low. Figure 5 shows an example of full granulation data from a 25-L Fielder mixer granulator on this type of regime map. The granule size distribution is much narrower when nucleation is kept in the drop-controlled regime

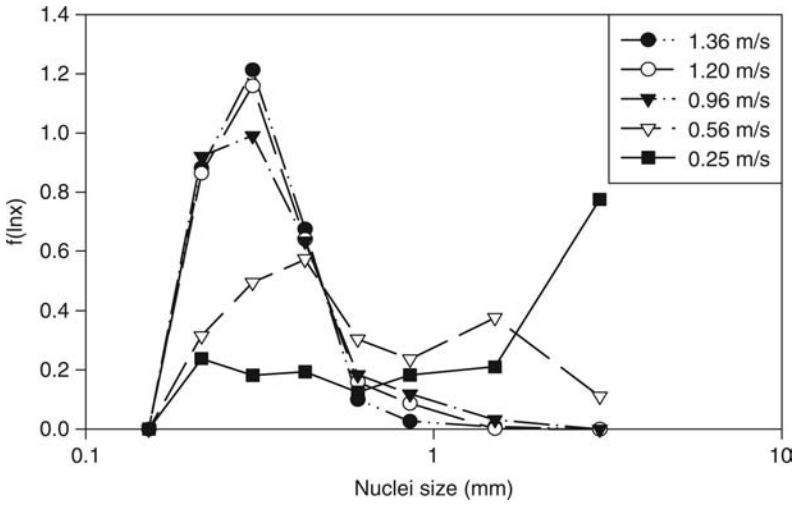


Figure 3 Effect of powder velocity on nuclei size distribution for lactose with water at 310 kPa. *Source*: From Ref. 6.

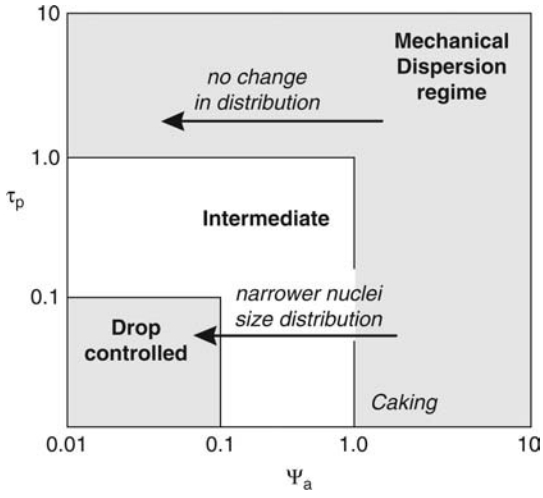


Figure 4 Nucleation regime map. For ideal nucleation in the *drop-controlled regime*, it must have (*i*) low ψ_a and (*ii*) low t_p. In the *mechanical dispersion* regime, one or both of these conditions are not met, and good binder dispersion requires good mechanical mixing.

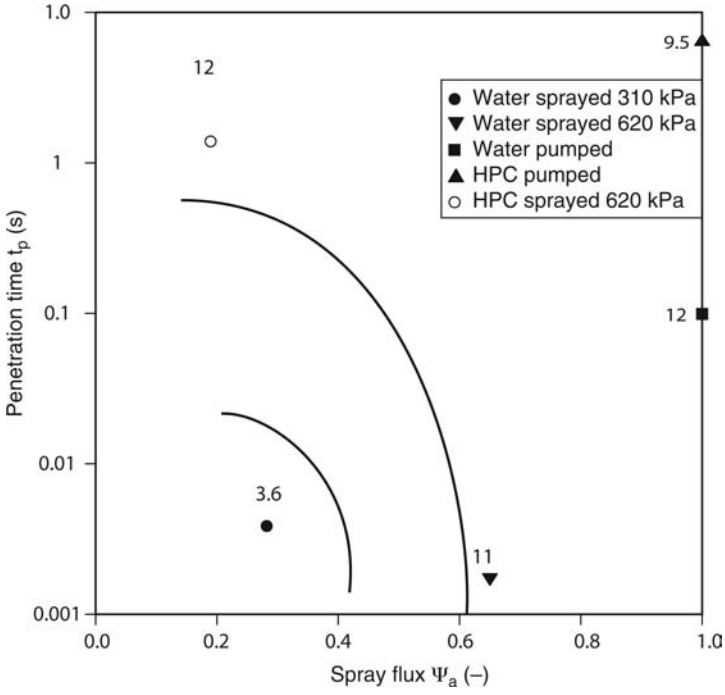


Figure 5 Nucleation regime map in 25-L Fielder mixer at 15% liquid content. Merck lactose with water and hydroxypropyl cellulose (HPC) as liquid binders. *Source*: From Ref. 6.

(lower left-hand corner). This illustrates that poor nucleation usually results in broad final granule size distributions despite the impact of other processes occurring in the granulator.

Growth and Consolidation

Granule growth is very complex. The key question in establishing growth behavior is: will two granules that collide in a granulator stick together (coalesce) or rebound? To answer this question, it is useful to look at two extreme cases that cover most applications.

Deformable porous granules: These granules are typically formed by a nucleation process described above with the drop size of the same order or larger than the powder size.

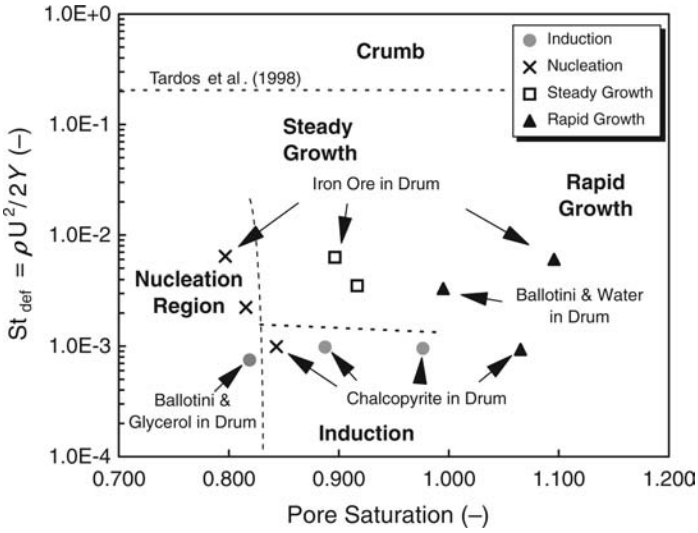


Figure 6 Granule growth regime map. *Source*: From Ref. 7.

Most of the liquid in the granule is contained in the pores between particles in the granule and held there by capillary action. For successful coalescence, this liquid must be made available at the contact point between colliding granules. This model is often suitable for drum mixer granulation.

Near elastic granules: Here the wetted granule is considered as a nearly elastic sphere with a liquid layer on the surface. This is a good model for cases where the drop size is much smaller than the granule size and the granulator has simultaneous drying. This model is often suitable for fluid-bed granulation.

The different growth modes for *deformable porous granules* can be represented on a regime map (Fig. 6). For growth to occur by coalescence, the liquid content needs to be large enough to provide 85% to 105% saturation of the pores in the granule. Granules that are weak, that is, form large contact areas on collision, fall into the *steady growth* regime. When two granules collide, a large contact area is formed and liquid is squeezed to the contact area, allowing successful coalescence. In this regime, granules grow steadily and growth rate is very sensitive to moisture content (Fig. 7A).

Strong granules do not deform much on collision and granules rebound, rather than coalesce. However, as granules consolidate slowly, eventually liquid is squeezed to granule surface and this liquid layer causes successful coalescence. This is the *induction growth* regime (Fig. 7B). At lower moisture contents, nuclei granules form and consolidate. Some growth by layering may occur, but there is insufficient liquid for growth by coalescence. This is the *nucleation* regime. Very weak granules simply fall apart and cannot sustain growth. This is the *crumb* regime.

There are two dimensionless groups that dictate the growth behavior, the Stokes deformation number, $\mathrm{St_{def}}$, and the maximum pore saturation $S_{\max}$, which are defined as follows:

$$\mathrm{St_{def}} = \frac{\rho_g U_c^2}{2Y} \tag{8}$$

$$S_{\max} = \frac{w\rho_s(1-\varepsilon_{min})}{\rho_l \varepsilon_{\min}} \tag{9}$$

where ρ_g, ρ_s, and ρ_l are the granule, particle, and liquid densities; U_c is the effective granule collision velocity; Y is the granule yield strength; w is the liquid content (kg liquid/kg dry powder), and $\varepsilon_{\min}$ is the minimum granule porosity after complete consolidation.

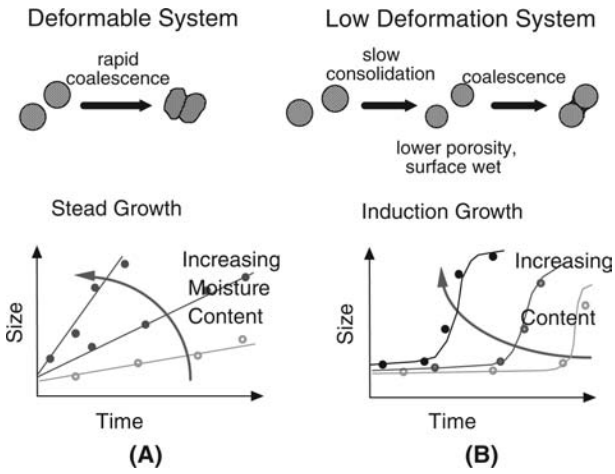


Figure 7 Coalescence growth modes for deformable granules.

Table 2 Estimates of U_c for Different Granulation Processes

Type of granulator	Average U_c	Maximum U_c
Fluidized beds	$\frac{6U_b d_p}{d_b}$	$\frac{6U_b d_p}{d_b \delta^2}$
Tumbling granulators	ωd_p	ωD_{drum}
Mixer granulators	$\omega_i d_p$, $\omega_c d_p$	$\omega_i D$, $\omega_c D_c$

Source: Adapted from Ref. 5.

Understanding where your system sits on the growth regime map is important for troubleshooting and scale-up. Granules that grow in the induction regime are easy to scale with respect to granule size provided that the induction time is not exceeded. However, granule density often changes with scale because consolidation kinetics are important and these kinetics can change with scale. On the other hand, in the steady growth region, it is difficult to control granule size but granule density quickly settles to a minimum value and varies little with process parameters.

To make effective use of the granulation regime map, we need reasonable estimates of the effective collision velocity U_c (controlled by process conditions) and dynamic yield stress Y (a function of formulation properties). Table 2 gives estimates of the average and maximum collision velocities for different process equipments. In high-shear mixers, the difference between the average and maximum collision velocities can be very large.

The dynamic yield stress of the granule matrix is a function of strain rate due to the contribution of viscous dissipation to the granule strength. Therefore, it is dangerous to use static strength measurements to predict performance in the granulator. Iveson et al. (8) show how dynamic yield stress can be estimated from peak flow stress measurements in a high-speed load frame. They were able to correlate data for different formulations and strain rates in a single line when plotted as the dimensionless peak flow stress (Str*) versus the capillary number (Ca) (Fig. 8). This line can be fitted by a simple empirical equation of the form

$$\mathrm{Str}^* = k_1 + k_2 \mathrm{Ca}^z \tag{10}$$

where $\mathrm{Str}^* = \sigma_{pk} d_p / \gamma \cos\theta$ is the dimensionless peak flow stress, $\mathrm{Ca} = \mu \dot{\varepsilon} d_p / \gamma \cos\theta$ is the ratio of viscous to capillary forces, σ_{pk} is peak flow stress, $\dot{\varepsilon}$ is the bulk strain rate, and θ is the solid-liquid contact angle. k_1 gives the static strength of the pellets. k_2 determines the transition between strain rate–independent and strain rate–dependent behavior. z is an exponent that gives the power law dependency of the flow stress on viscosity and strain rate. The best-fit value of z was found to be 0.58 ± 0.04, and the transition between strain rate–independent and strain rate–dependent flow stress occurred at $\mathrm{Ca} \sim 10^{-4}$.

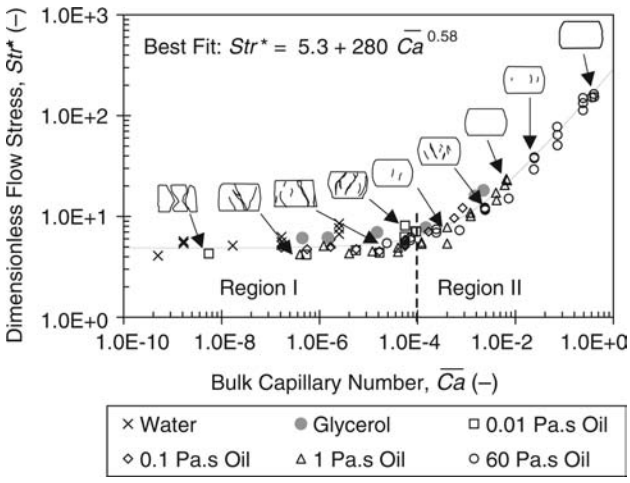


Figure 8 Dimensionless flow stress versus capillary number for widely sized 35-μm glass ballotini with six different binders.

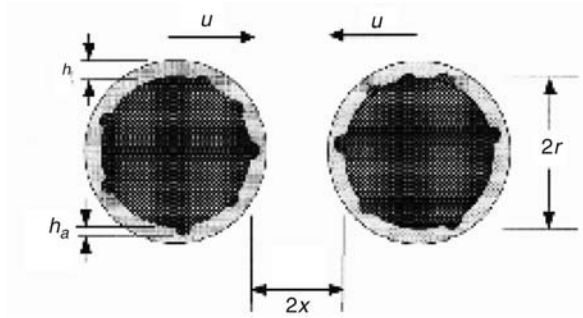


Figure 9 Two near elastic granules colliding—the basis for the coalescence/rebound criteria. *Source*: From Ref. 9.

The rate of consolidation of granules can also be correlated with St_{def}. in the form

$$k_c = \beta_c \exp(a \times St_{def}) \tag{11}$$

where β_c and a are constants and k_c is the consolidation rate constant for a first-order consolidation equation of the form

$$\frac{\varepsilon - \varepsilon_{min}}{\varepsilon_0 - \varepsilon_{min}} = \exp(-k_c t) \tag{12}$$

For *near elastic granules*, the conceptual model originally developed by Ennis et al. (9) considers the collision between two near elastic granules each coated with a layer of liquid (Fig. 9). In this case, the key dimensionless group is the viscous Stokes number St_v.

$$St_v = \frac{4\rho_g U_c d_p}{9\mu} \tag{13}$$

St_v is the ratio of the kinetic energy of the collision to the viscous dissipation in the liquid layer. Successful coalescence will occur if St_v is less than some critical value St* and we can define three growth regimes as follows

1. *Noninertial growth* ($St_{v,max} < St^*$): The viscous Stokes number for all collisions in the granulator is less than the critical Stokes number. All collisions lead to sticking and growth by coalescence. In this regime, changes to process parameters will have little or no effect on the probability of coalescence.
2. *Inertial growth* ($St_{v,av} \gg St^*$): Some collisions cause coalescence, while others lead to rebound. There will be steady granule growth by coalescence. The extent and rate of growth will be sensitive to process parameters, which will determine the proportion

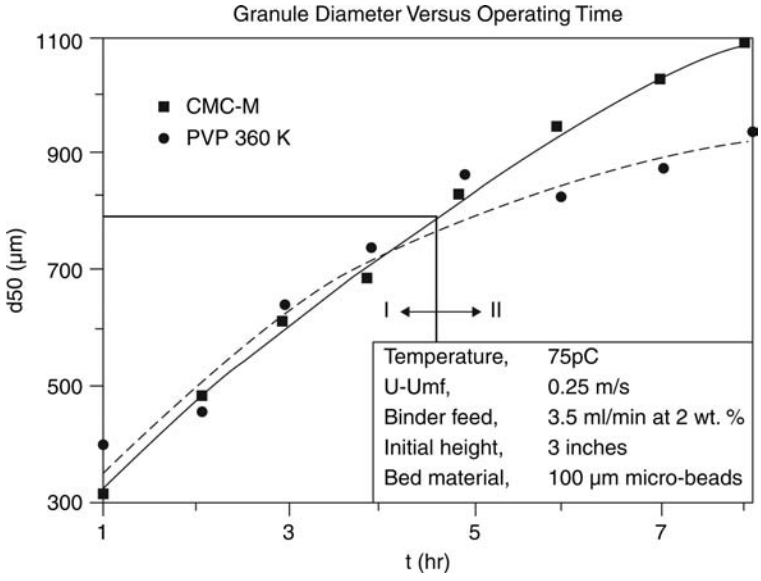


Figure 10 Growth of glass ballotini granules in a fluidized bed with binders of different viscosity. *Source*: From Ref. 9.

of collisions that lead to coalescence. Varying process parameters and formulation properties can push the system into either the noninertial or coating regimes.

3. *Coating regime* ($St_{v,min} > St^*$): The kinetic energy in most or all collisions exceeds viscous dissipation in the liquid layer. There is no coalescence. Granule growth will only occur by the successive layering of new material in the liquid phase (melt, solution, or slurry) onto the granule.

Figure 10 shows an example of granule growth in a fluidized bed where the growth regime changes as the granules grow. Glass ballotini are grown with two liquid binders of different viscosity. Initially, both systems grow steadily at the same rate (noninertial regime). When the granule size reaches approximately 800 μm, the polyvinyl pyrrolidone (PVP) bound granule growth begins to slow, indicating a transition to the inertial growth regime (only some collisions are successful). Finally, the PVP granules level off at a maximum size of approximately 900 μm, showing transition to the coating regime where no granule collisions are successful. In contrast, the more viscous carboxyl methyl cellulose (CMC-M) granules grow steadily throughout the eight-hour experiment, that is, they remain in the noninertial regime for the whole experiment.

Breakage and Attrition

Breakage and attrition really cover two separate phenomena.

1. Breakage of *wet* granules in the granulator
2. Attrition or fracture of *dried* granules in the granulator, drier, or subsequent handling

Breakage of wet granules will influence and may control the final granule size distribution. It is only an important phenomenon for high-shear granulators. Wet granule breakage is much less studied than nucleation and growth. There is very little quantitative theory or modeling available to predict conditions for breakage or the effect of formulation properties on wet granule breakage.

Tardos et al. (10) considered that a granule will break if the applied kinetic energy during an impact exceeds the energy required for breakage. This analysis leads to a Stokes deformation number criteria for breakage.

$$St_{def} > St^*_{def} \tag{14}$$

where St^*_{def} is the critical value of Stokes number that must be exceeded for breakage to occur. However, this model is probably an oversimplification. Figure 8 shows schematics of the failure mode of different formulations in dynamic yield strength measurements. Failure behavior varies widely from semibrittle behavior at low capillary numbers to plastic failure at high capillary numbers. We expect a purely plastic granule to smear rather than break when its yield stress is exceeded. At high impeller speeds, such materials will coat the granulator wall or form a paste. Semibrittle granules will break at high impact velocity, giving a maximum stable granule size or a weak crumb. Nevertheless, equation (14) provides a good starting point for quantifying wet granule breakage.

Liu et al. (11) developed a model to calculate the granule yield strength, which can then be used to calculate St_{def} in equation (8). The model is a modified combination of two models introduced previously in the literature (12,13) for the static and dynamic contributions to granule strength, respectively. The model introduced by Liu et al. (11) takes into account both the effects of capillary force and the viscous force in liquid bridges when calculating the strength of the granule. It also incorporates liquid pore saturation. The model includes a particle shape factor that allows calculating the strength of granules made of nonspherical particles, and is given by the following equation:

$$Y = \mathrm{AR}^{-4.3} S \left[6 \frac{1-\varepsilon_g}{\varepsilon_g} \frac{\gamma_{LV} \cos\theta}{d_{3,2}} + \frac{9}{8} \frac{(1-\varepsilon_g)^2}{\varepsilon_g^2} \frac{9\pi\mu v_p}{16 d_{3,2}} \right] \tag{15}$$

where AR is the aspect ratio of the primary particles, S is the granule pore saturation, ε is the porosity of the granule, $d_{3,2}$ is the specific surface area diameter of the particles, and v_p is the relative velocity of the moving particle inside a granule after impact. Liu et al. (11) performed experiments in a "breakage-only granulator" for a wide range of formulations and determined the St^*_{def} as 0.2. If St_{def} is greater than 0.2, the granules are in the breakage regime. While breakage models remain very basic with simplistic descriptions of granule mechanical properties and many simplifying assumptions, models of the type described in equation (8) with an appropriate calculation of the granule strength [such as Eq. (15)] are immediately useful for scaling and troubleshooting.

Dry granule attrition is important where drying and granulation occur simultaneously (e.g., in fluidized beds) and in subsequent processing and handling of the granular product. We can consider dry granule breakage as a brittle or semibrittle phenomenon. The key granule properties that control the breakage are the granule fracture toughness K_c and the flaw or crack size c in the granule. K_c is set by formulation properties, while c is closely related to granule porosity controlled by the consolidation process in the granulator.

Dry granule breakage usually results in production of fines by wear, erosion, or attrition brought about by diffuse microcracking. Within a fluid bed, there are a large number of low-velocity collisions between particles as they shear past each other. This process is analogous to abrasive wear. For abrasive wear of agglomerates, the volumetric wear rate V is given by Ref. (14):

$$V = \frac{d_i^{1/2}}{A^{1/4} K_c^{3/4} H^{1/2}} P^{5/4} l \tag{16}$$

Where d_i is indentor diameter, P is applied load, H is the hardness of the particles, l is wear displacement of the indentor, and A is apparent area of contact of the indentor with the surface. The number and relative velocity of the collisions depend on the number of bubbles in the bed and hence the excess gas velocity ($u - u_{mf}$). The applied pressure in a fluid bed depends on bed depth. Thus, the attrition rate B_w in a fluidized-bed granulator is

$$B_w = \frac{d_0^{1/2}}{K_c^{3/4} H^{1/2}} L^{5/4} (u - u_{mf}) \tag{17}$$

where d_o is the distributor hole orifice size and L is the fluidized-bed height. Figure 11 shows the attrition rates of several formulations in a fluidized bed with a direct correlation between attrition rate and the material properties grouping in equations (16) and (17).

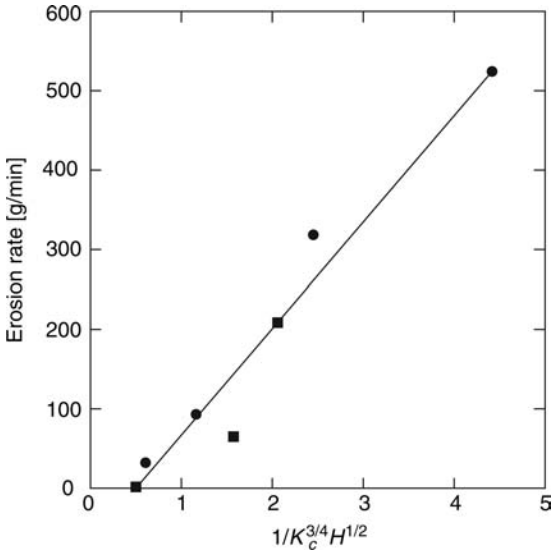


Figure 11 Erosion rates of agglomerate materials during attrition of granules in a fluidized bed. *Source*: From Ref. 15.

Note that equations (16) and (17) only hold for breakage via a wear mechanism. For attrition during impact or compaction, there are different dependencies of the attrition rate on the materials properties (5).

Implications for Scale-Up

Table 3 summarizes the key controlling dimensionless groups for the rate processes described above and the main process parameters and formulation properties that impact on these groups.

In addition to these groups, there are dimensionless groups to describe (1) the geometry of the equipment; and (2) the flow of the powder and granules in the granulator. Both these classes of controlling groups are very equipment dependent.

For scale-up using full-dimensional similarity, *all* these dimensionless groups need to be held constant. This is normally impossible because of the small number of degrees of freedom and large number of constraints. In particular, for regulatory reasons, it is usually not possible to change formulation properties during scale-up except during the very early stages of process development. This leaves only a relatively small number of process parameters as degrees of freedom.

Therefore, a partial similarity approach for scale-up is recommended. The general steps are given below.

1. Maintain similar geometry throughout the scale-up process. For most pharmaceutical granulation equipments, this can be achieved from either 10- or 25-L nominal batch

Table 3 Summary of Controlling Groups for Granulation Rate Processes

Rate process	Controlling groups	Key formulation properties	Key process parameters
Wetting and nucleation	Dimensionless spray flux Ψ Dimensionless penetration time τ_p	t_p, μ, $\gamma \cos\theta$, d_p, ε, ε_{tap}	$\dot{V}$, $\dot{A}$ (influenced by nozzle design and position, number of nozzles, and powder flow patterns)
Growth and consolidation	Stokes deformation number St_{def} Viscous Stokes number St_v Liquid saturation s	Y, ρ_g, μ, $\gamma \cos\theta$, d_p, ε_{tap}	U_c (influenced by powder flow patterns—see Table 2)
Attrition and breakage	Stokes deformation number St_{def}	K_c, H, Y, ρ_g, μ, $\gamma \cos\theta$, d_p, ε_{tap}	U_c, L, $u - u_{mf}$

size to full scale. Be wary, however, in some cases, key geometric parameters do vary with scale in a particular design, for example, relative chopper size, and relative fill height. Manufacturers should be lobbied hard to provide geometrically similar designs at all scales.

2. Set key dimensionless groups to maintain similar powder flow during scale-up. In particular, avoid changes of flow regime during scale-up that make maintaining granule attributes during scale-up impossible.
3. Use your experience and an understanding of your process to decide which product attributes are most important and which granulation rate process is most dominant in controlling these attributes. This is difficult to do a priori, but with good characterization of your formulation and process, the regime map approaches described above are very useful.
4. Use your remaining degrees of freedom in choice of process parameter values to keep the most important one or two rate process dimensionless groups constant.

This approach is most easily demonstrated on particular types of equipments (see sects. "Scale-Up of Fluidized-Bed Granulators" and "Scale-Up of High-Shear Mixer Granulators").

SCALE-DOWN, FORMULATION CHARACTERIZATION, AND FORMULATION DESIGN IN PHARMACEUTICAL GRANULATION

In the development of a new pharmaceutical product, important decisions about the manufacturing process are made with a few grams or tens of grams of formulation. To provide drug product for clinical trials and to provide the final design at a large scale, granulations are often conducted at several laboratory and pilot scales as well. Typical nominal batch sizes are 1, 10, 25, and 65 L scaling to commercial operation at 300 or 600 L.

Small-scale granulations up to 1 L are often done by hand and certainly performed in a equipment that is very different from the equipment that will be used from scales of 10 L and larger. At this level, the general scale-up approach described in section "Implications for Scale-Up" does not hold. How do we *scale down* to make best use of data from granulation of these small amounts?

The key is to consider granulation as a particle design process (Fig. 12). During scaling from 10 L up, formulation properties cannot be varied. Only process parameters can be used to keep key granule attributes in the target range. Therefore, very small-scale experiments should target major *formulation design* decisions, and attempts to mimic completely different geometries at a larger scale should be avoided.

Table 3 summarizes key formulation properties that should be measured. Most of these require relatively small amounts of material and can be measured at this level. By using this data to help estimate key controlling groups for the granulation rate processes in the larger-scale equipment, appropriate changes to the formulation can be made. This avoids major headaches at a later stage. Good communication between the technologists who design the formulations and the process engineers who scale the process and transfer the product to manufacturing is an essential part of this paradigm.

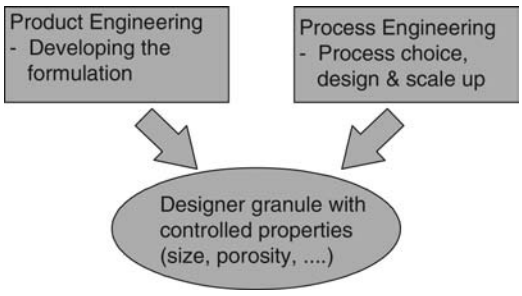


Figure 12 Granulation as an example of particle design. Both formulation properties and process parameters influence granule attributes.

Some of the questions that can be addressed at this stage of formulation development and scale-up include the following:

1. Wetting and nucleation
   a. Contact angle: are the active and all the excipients easily wetted by the liquid binder?
   b. Drop penetration time: is the liquid phase too viscous, or the particle size too small to achieve fast drop penetration?
2. Growth and consolidation
   a. What is the dynamic yield stress of the formulation?
   b. How much liquid binder is required for granule growth?
   c. What is the likely growth regime?
   d. What range of granule density is likely?
3. Attrition and breakage
   a. Will extensive granule breakage occur in the granulator?
   b. What is the dry granule strength (fracture toughness) and porosity?
   c. Are attrition and dust formation during handling likely?
4. Downstream processing issues
   a. Does the formulation compress well for tableting?
   b. Can desired dissolution profiles be met?

Details of how to measure key formulation properties are described in more detail by Litster and Ennis (5).

SCALE-UP OF FLUIDIZED-BED GRANULATORS

There are many different variations of fluidized-bed granulators including bubbling fluidized bed, draft tube fluidized beds, and spouted beds (5). However, in this section, we limit ourselves only to the scale-up of the most commonly used fluidized-bed granulator, that is, bubbling fluidized-bed granulator. In particular, as most fluidized-bed granulators used in the pharmaceutical industry are operated in batch mode, we will concentrate on the scale-up of batch bubbling fluidized-bed granulators.

Bed Hydrodynamics and Scale-Up

Particle growth in a fluidized bed is closely related to the particle mixing and flow pattern in the bed. This dictates that the hydrodynamics of the scaled bed should be the same as the small unit, that is, hydrodynamic similarity. Basic fluidized-bed hydrodynamics are described in chapter 10.

In bubbling fluidized beds, bed expansion, solids mixing, particle entrainment, granule growth, and attrition are intimately related to the motion of bubbles in the bed (Fig. 13). The volume flow rate of bubbles in the bed Q_b, the bubble size d_b, and the bubble rise velocity u_b are the key parameters that characterize the bubbly flow. There are numerous correlations relating these bubble parameters to process conditions (16,17). In general, Q_b is a strong function of the excess gas velocity $u - u_{mf}$. Growing granules are usually Geldart type B powders or perhaps type A powders at the start of the batch. For group B powders, d_b increases with bed height and is a function of excess gas velocity. The bubble rise velocity is directly related to d_b. For the simplest models for group B powders, we can write

$$Q_b = (u - u_{mf})\pi D_F^2 \tag{18}$$

$$u_b = 0.71\sqrt{g d_b} \tag{19}$$

$$d_b \propto (u - u_{mf})^{0.4} L^{0.8} \tag{20}$$

Thus, the excess gas velocity $u - u_{mf}$ and the bed height L are the key process parameters that control bubbling behavior in the bed.

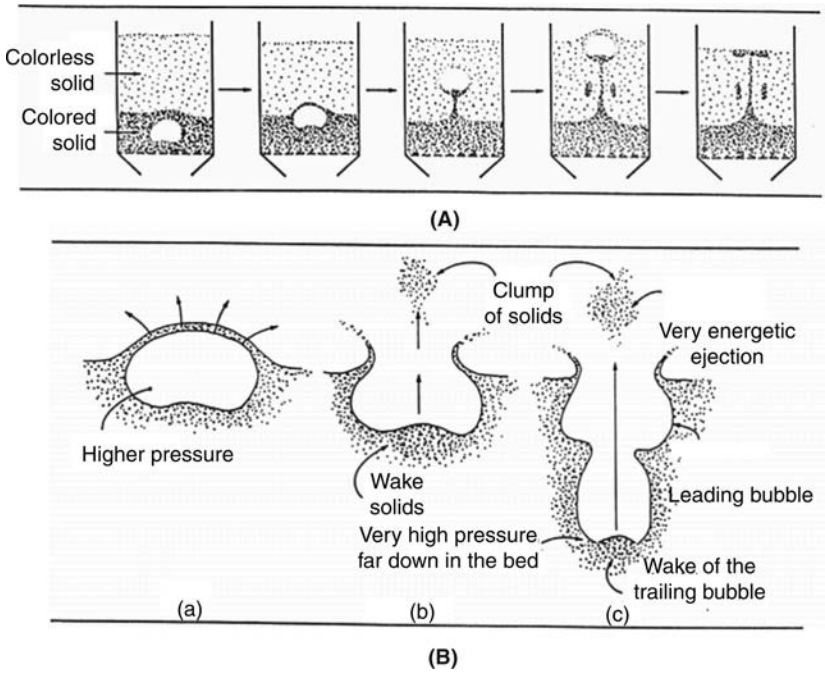


Figure 13 Effect of bubbles on (**A**) solid mixing and (**B**) solid entrainment. *Source*: From Ref. 16.

Several rules exist for scaling up a bubbling fluidized bed under the condition of hydrodynamic similarity. Fitzgerald and Crane (18) proposed that the following dimensionless numbers be kept constant in scale-up.

- Particle Reynolds number based on gas density $d_p u \rho_G / \mu$
- Solid particle to gas density ratio ρ_s / ρ_G
- Particle Froude number $u/(g d_p)^{0.5}$
- Geometric similarity of distributor, bed, and particle L/d_p

where d_p is particle diameter, u is the fluidization velocity (superficial gas velocity), μ is the viscosity of fluidizing gas, ρ_G is the density of fluidizing gas, g is gravitational acceleration, and L is the fluidized-bed height.

In this approach, experiments on the smaller scale are performed with model materials, that is, model gas (different from the larger-scale one) and model solid particles (different particle density, size, and size distribution). For readers interested in following Fitzgerald's scale-up rules, a detailed calculation procedure can be found in Kunii and Levenspiel's book (16), illustrated with an example.

In a series of publication, Glicksman et al. (19–21) divided the scale-up into two regimes, namely, inertia-dominated and viscous-dominated flow regimes. In viscous-dominated flow regime, where particle Reynolds number based on fluid density is equal or less than 4, that is, when $d_p u \rho_G / \mu \leq 4$, the dimensionless numbers that need to be kept constant are

$$\frac{u}{(g d_p)^{0.5}}, \frac{d_p u \rho_s}{\mu}, \frac{L}{d_p}, \frac{D_F}{d_p}, \phi, \text{ particle size distribution, bed geometry} \tag{21}$$

where D_F is the fluidized-bed diameter.

In contrast, in inertia-dominated flow regime, $d_p u \rho_G / \mu \geq 400$, scale-up of the process demands that the following dimensionless numbers are kept constant.

$$\frac{u}{(g d_p)^{0.5}}, \frac{\rho_G}{\rho_s}, \frac{L}{d_p}, \frac{D_F}{d_p}, \phi, \text{particle size distribution, bed geometry} \tag{22}$$

In the intermediate region, where $4 \leq d_p u \rho_G / \mu \leq 400$, both the viscous and inertial forces are important to the fluid dynamics, and all the dimensionless numbers for the two regions above will need to be kept constant during scale-up, that is,

$$\frac{\rho_s \rho_G d_p^3 g}{\mu^2}, \frac{u}{(g d_p)^{0.5}}, \frac{\rho_G}{\rho_s}, \frac{L}{d_p}, \frac{D_F}{d_p}, \phi, \text{ particle size distribution, bed geometry} \tag{23}$$

Experimenting with only ambient air and particles made of the same material but different sizes, Horio et al. (22,23) developed what was later defined as the simplified scaling law. They demonstrated that, with similar bed geometry (ratio of bed height to diameter), using particles of different mean sizes but same distribution characteristics and operating the bed in proportional superficial gas velocities would ensure that the hydrodynamic conditions of the two beds remain similar. Expressed in mathematical terms, it is

$$\begin{aligned} u_2 - u_{mf2} &= \sqrt{m}(u_1 - u_{mf1}) \\ u_{mf2} &= \sqrt{m} u_{mf1} \\ m &= \frac{L_2}{L_1} \\ &\text{bed geometry} \end{aligned} \tag{24}$$

where 1 and 2 refer to the small-scale and large-scale beds, respectively.

Experimental results by Roy and Davidson (24) suggest that, when $d_p u \rho_G / \mu < 30$, the criteria by Horio et al. (22,23) are sufficient to give similarity in behavior. However, when $d_p u \rho_G / \mu > 30$, the more restrictive approach of Fitzgerald and Crane has to be used.

Unfortunately, few of the above scaling rules for bubbling fluidized beds have been strictly followed for the scaling up of fluidized-bed granulators. This is largely because the scaling rules require model materials to be used at the smaller scale, whereas in pharmaceutical granulation, the formulation is unchanged during scale-up. However, the simplified rules presented by Horio, combined with our understanding of granulation rate processes, do provide some guide.

Granulation Rate Processes in Fluidized Beds

Figure 14 shows the rate processes occurring during fluidized granulation. Wetting, nucleation, and layered growth occur in the spray zone of the fluidized bed. Most consolidation and coalescence also occur in or near the spray zone because fluidized-bed granulators are also driers. The drying process "freezes" the granule structure and prevents further growth. Thus, good design of the spray zone is very important, and liquid flow rate is a critical process parameter. Beds should be designed to keep dimensionless spray flux low (drop-controlled regime). If this is not done, the formation of large clumps leads to rapid wet quenching and defluidization with likely loss of the batch. Figure 15 shows how the product granule size distribution is closely related to design of the spray zone. The x-axis variable (spray surface area per mass in granulator) is closely related to our definition of dimensionless spray flux.

Because of the simultaneous drying, our consolidation and growth models for near elastic granules are usually appropriate and the viscous Stokes number is a key controlling group [Eq. (13)]. This model predicts that in batch granulation, granules will grow toward a maximum size corresponding to the critical Stokes number and transition to the coating regimes (e.g., Fig. 10). The average and maximum granule collision velocities are set by the flow of bubbles in the fluid bed and are a function of bubble velocity and size (Table 3).

Fluidized beds produce porous granules because the consolidation time is limited to granule drying time, which is of the order of seconds, rather than minutes. Thus, process changes that reduce drying time (higher bed temperature, lower liquid flow rate, and smaller drop size) will decrease granule density (will increase granule porosity). Increasing the liquid binder viscosity decreases granule voidage by increasing the resistance of the granule to deformation.

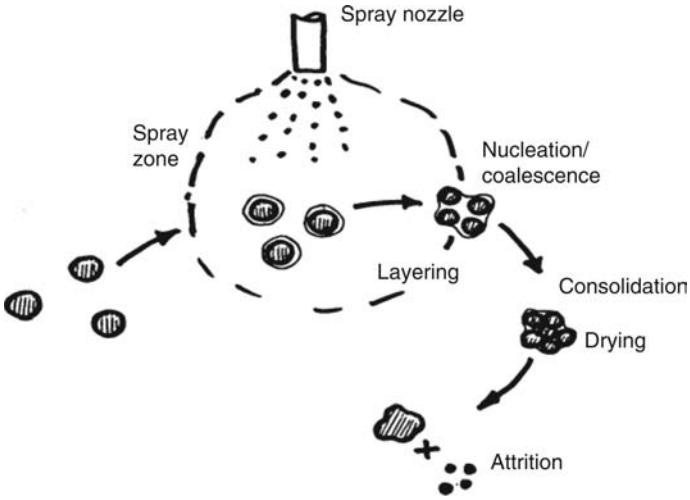
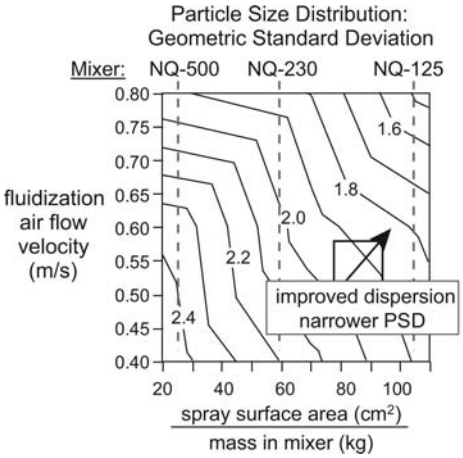


Figure 14 Important granulation processes in the fluidized bed. *Source*: From Ref. 5.



Agglomeration in an Agitated Fluidized Bed

	Mixer Type		
	NQ-125	NQ-230	NQ-500
Powder feed (kg)	0.36	2.23	22.9
Spray area (cm^2)	38.5	132.7	594
Spray area/Feed	107	60	26

Figure 15 Geometric standard deviation of granule size in an agitated fluid-bed granulator as a function of gas fluidization velocity and binder dispersion measured using spray surface area to mass in mixer. *Source*: From Ref. 10.

Dry granule attrition in the fluid bed is an important source of fines. equation (17) quantifies the attrition rate in terms of granule properties and process conditions (Fig. 11). Increasing fluid-bed height increases both consolidation and attrition for two reasons: (*i*) it increases the effective "fluid" pressure on granules in the bed, and (*ii*) it increases the average bubble size in the bed, leading to more vigorous mixing and higher-velocity granule collisions.

Suggested Scaling Rules for Fluid-Bed Granulators

Given this understanding of fluidized-bed hydrodynamics and granulation rate process, we suggest the following guidelines for scaling fluidized-bed granulators.

1. Maintain the fluidized-bed height constant. Granule density and attrition rate increase with the operating bed height.

$$L_2 = L_1 \tag{25}$$

2. If L is kept constant, then batch size scales with the bed cross-sectional area.

$$\frac{M_2}{M_1} = \frac{D_{F2}^2}{D_{F1}^2} \tag{26}$$

3. Maintain superficial gas velocity constant to keep excess gas velocity and therefore bubbling and mixing conditions similar.

$$\frac{Q_2}{Q_1} = \frac{u_2}{u_1} = \frac{D_{F2}^2}{D_{F1}^2} \tag{27}$$

   Note that the scaling rules defined by equation (27) are consistent with Horio's simplified scaling rules [Eq. (24)].
4. Keep dimensionless spray flux constant on scale-up. This is most easily achieved by increasing the area of bed surface under spray (usually by increasing the number of nozzles). By doing this, the liquid flow rate can be increased in proportion to batch size without changing critical spray zone conditions. Thus, batch times at small and large scales should be similar.

$$\dot{V}_2 = \dot{V}_1 \tag{28}$$

$$\frac{A_{\text{spray},2}}{A_{\text{spray},1}} = \frac{D_{F2}^2}{D_{F1}^2} \tag{29}$$

5. Keep viscous Stokes number constant. By adhering to the scaling rules described above, St_v should automatically be similar at small and large scales, leading to similar consolidation and growth behavior.

There are also some cautionary notes relating to the minimum scale for the laboratory-scale studies. Slug flow, a phenomenon where single gas bubbles as large as the bed diameter form in regular patterns in the bed, significantly reduces solid mixing. It occurs in tall and narrow beds. Stewart (25) proposed a criterion for the onset of slugging.

$$\frac{u - u_{mf}}{0.35\sqrt{gD_F}} = 0.2 \tag{30}$$

To ensure that the bed is operating in bubbling mode without risking slugging, the ratio in equation (30) must be kept below 0.2. In addition, both the bed height to bed diameter and particle diameter to bed diameter ratios should be kept low. For pilot fluidized bed, the diameter should be greater than 0.3 m.

To avoid the gas entry effect from the distributor (gas jet), there is also a requirement on minimum fluidized-bed height. The jet length depends on the gas velocity and the size of the opening on the distributor. For the same opening size, jet length increases with gas velocity through the hole; for a given gas velocity through the hole, small holes give shorter jets but are accompanied by a larger pressure drop across the distributor. Even at a superficial gas velocity as low as 0.2 m/sec with a hole size of 9.5 mm in diameter, jet length as long as 0.6 m has been reported (26).

The amount of fluidization gas required to maintain constant fluidization velocity scales linearly with the cross-sectional area of the bed. However, for large fluidized beds, one of the major concerns is the even distribution of the fluidization gas across the whole area of the bed. In addition to the use of a plenum chamber and an even distribution of flow channels across the distributor, the distributor should be designed in such a way that the pressure drop across it is at least 20% of the total.

If these scaling rules are applied, there is a good chance to keep granule properties within the desired range on scaling. If fine-tuning is needed at a large scale, minor adjustments to the liquid spray rate can be used to adjust granule properties, as all the granulation rate processes in fluidized beds are very sensitive to this parameter.

SCALE-UP OF HIGH-SHEAR MIXER GRANULATORS

Effective scale-up of mixer granulators is more difficult than fluidized beds. There are several reasons for this.

- The geometric and mechanical design of mixer granulators varies enormously, as do the powder flow patterns in the mixer. There is no such thing as a generic high-shear mixer, and caution is needed in transferring scaling rules from one design to another.
- Even with the same series from the same manufacturer, geometric similarity is not always maintained between different scales, for example, impeller size in relation to bowl size.
- Powder flow in high-shear mixers is not fluidized, and powder flow patterns are much harder to predict than in a fluidized bed.
- All three rate processes, that is, wetting and nucleation, growth and consolidation, and breakage and attrition take place simultaneously in the mixer granulator of all scales. However, the relative dominance of each of the rate processes can vary significantly on different scales of the same series, let alone in granulators of different series.

In this section, we will focus mainly on vertical shaft mixer, for example, Fielder and Diosna designs. Some of the suggested approaches may be used with caution for other mixer designs.

Geometric Scaling Issues

For a simple vertical mixer design, the key dimensions are the impeller diameter D, which is usually equal to the bowl diameter, the chopper diameter D_c, and the fill height H_m. The dimensionless groups that need to be held constant for geometric similarity are

$$\frac{D_c}{D}, \frac{H_m}{D}$$

In addition, the shape and positioning of the impeller and chopper should be the same on scale-up. Unfortunately, manufacturers do not always adhere to these rules. It is common for the absolute size of the chopper to be invariant, meaning its relative influence is much larger in the small-scale granulator.

Relative fill height is also often varied with scale. This often reflects the small-sized batches required for early-stage clinical trials and the desire to maximize production rate (by maximizing batch size) at full scale. Varying relative fill height is very dangerous, as it can have a major impact on powder flow patterns.

Powder Flow Patterns and Scaling Issues

There are two flow regimes observed in a vertical shaft mixer granulator, namely, bumping and roping regimes (27). At low impeller speeds in the bumping regime, the powder is displaced only vertically as the blade passes underneath, leading to a slow, bumpy powder motion in the tangential direction. There is almost no vertical turnover of the powder bed, as shown in Figure 16A.

At higher impeller speed in the roping regime, material from the bottom of the bed is forced up the vessel wall and tumbles down at an angle of the bed surface toward the center of the bowl. There is both good rotation of the bed and good vertical turnover (Fig. 16B).

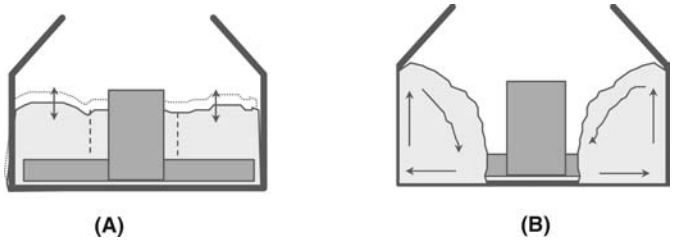


Figure 16 Powder flow regimes in Fielder mixer granulators: (**A**) bumping and (**B**) roping.

The transition from bumping to roping is due to a change in the balance between centrifugal force and gravity. The centrifugal force, which is caused by the rotational movement of the powder from the spinning of the blades, pushes the powder outward toward the wall of the bowl, while gravity keeps the powder tumbling back toward the center of the bowl from the buildup at the wall region. This balance between rotational inertia and gravity is given by the Froude number:

$$\mathrm{Fr} = \frac{DN^2}{g} \tag{31}$$

where N is the impeller speed and g is the gravitational acceleration.

When the Froude number exceeds a critical value, transition from bumping to roping takes place.

$$\mathrm{Fr} > \mathrm{Fr_c} \tag{32}$$

$\mathrm{Fr_c}$ will be a function of relative fill height (H_m/D), impeller design (size and geometry), and powder flow properties.

Roping flow is more difficult to achieve as relative fill height increases because the centrifugal force is only imparted to powder in the impeller region. This region becomes a smaller fraction of the total powder mass as fill height increases. Schaefer (28) also showed that impeller design had a significant effect on both $\mathrm{Fr_c}$ and bed turnover rate.

Cohesive powders transfer to roping at lower values of Fr because momentum from the spinning impeller is more effectively transferred into the powder mass. Note that powder flow properties generally change with the addition of the liquid binder, and therefore, flow patterns will probably change significantly during a batch granulation.

Figure 17 shows dry lactose powder surface velocity data in a 25-L Fielder granulator (27). In the bumping flow regime, the powder surface velocity increases in proportion to the impeller speed. In the roping regime, the surface velocity stabilizes and is less sensitive to impeller speed. In all cases, the surface velocity of the powder is only of the order of 10% of the impeller tip speed. Knight et al. (29) showed that dimensionless torque T is a direct function of Froude number and effective blade height h_{eff}:

$$T = T_0 + k\mathrm{Fr}^{0.5} \text{ where } k = \beta\left(\frac{2h_{\mathrm{eff}}}{D}\right)^b \tag{33}$$

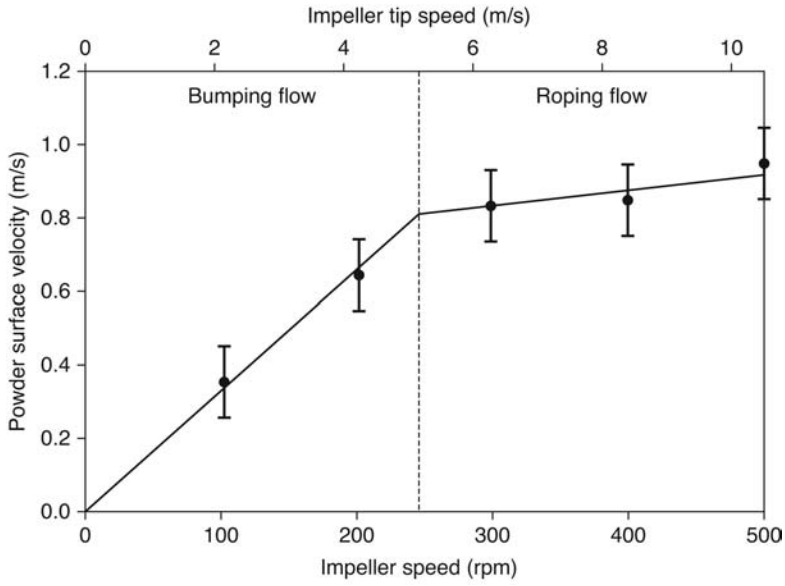


Figure 17 Powder surface velocities as a function of impeller tip speed. *Source*: From Ref. 27.

Thus, to maintain similar powder flow pattern during scale-up, the Froude number should be kept constant, that is,

$$\frac{N_2}{N_1} = \sqrt{\frac{D_1}{D_2}} \tag{34}$$

In addition, the dimensionless bed height should also be kept constant, that is, the same fraction of the bowl is filled at all scales.

$$\frac{H_{m2}}{H_{m1}} = \frac{D_2}{D_1} \tag{35}$$

Historically, mixer granulators have been more commonly scaled up using constant tip speed or constant relative swept volume (28,30). Maintaining constant impeller tip speeds leads to the scaling rule

$$\frac{N_2}{N_1} = \frac{D_1}{D_2} \tag{36}$$

This scale-up rule leads to Fr decreasing as scale increases. Combined with common practice of overfilling full-scale granulators, this approach to scaling can often lead to a change in operating regime from roping to bumping on scale-up.

The constant swept volume approach to scale-up was introduced partly to account for variations in geometry on scale-up. The relative swept volume is defined as

$$\dot{V}_{\mathrm{R}} = \frac{\dot{V}_{\mathrm{imp}}}{V_{\mathrm{mixer}}} \tag{37}$$

where $\dot{V}_{\mathrm{R}}$ is the relative swept volume, $\dot{V}_{\mathrm{imp}}$ is the rate of swept volume of impeller, and V_{mixer} is the mixer volume.

On scale-up,

$$\dot{V}_{\mathrm{R},1} = \dot{V}_{\mathrm{R},2} \tag{38}$$

This approach is useful for comparing granulators where geometry changes with scale. For geometrically similar granulators, equation (38) is equivalent to scale-up with constant tip speed, equation (36).

In addition to constant tip speed, constant Froude number, and constant swept volume approaches, a new approach was introduced for scale-up of high-shear mixer granulators, where shear rate is kept constant across all scales (31). Provided that the bowl and impeller geometries are similar, constant shear stress leads to the scaling rule

$$\frac{N_2}{N_1} = \left(\frac{D_1}{D_2}\right)^{0.8} \tag{39}$$

In summary, in all approaches mentioned above, the main impeller speed (N) is varied according to the following equation.

$$N D^n = \text{constant} \tag{40}$$

where the scaling index "n" equals to 0.5, 0.8, and 1 in constant Fr, constant shear rate, and constant tip speed cases, respectively.

Granulation Rate Processes and Related Scaling Issues

In high-shear mixer granulation, all three classes of rate process can have a significant effect on the granule size distribution. Section "Wetting and Nucleation" describes conditions for good nucleation in the drop-controlled regime and uses examples from mixer granulation. For good nucleation, the granulator should be operated in the roping regime for good bed turnover and the dimensionless spray flux Ψ_{a} should be kept low. This implies careful choice of the liquid flow rate, nozzle design, and positioning in the granulator.

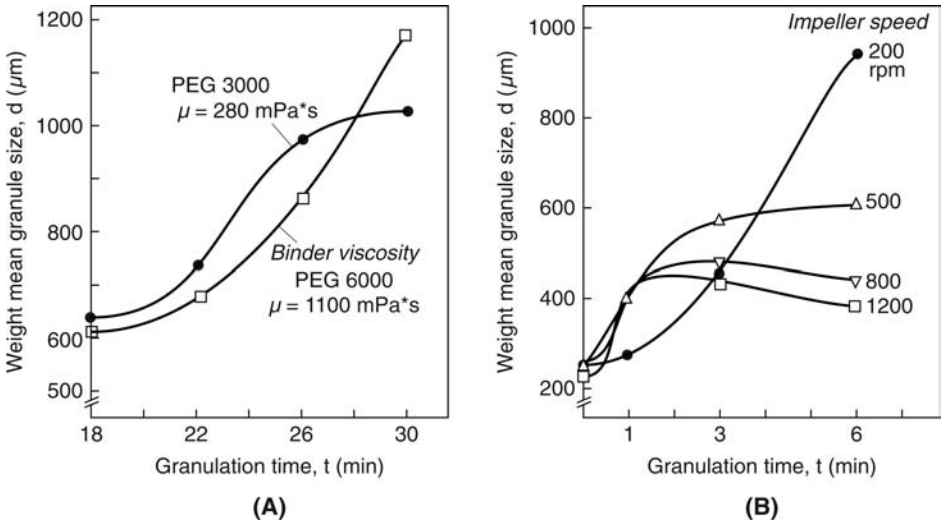


Figure 18 Variations in granule growth rate and extent of growth in a mixer granulator with changes to (**A**) binder viscosity and (**B**) impeller speed. *Source*: From Ref. 30.

To maintain similar nucleation behavior and equivalent liquid distribution, the dimensionless spray flux Ψ_a should be kept constant on scale-up. If spray drop size in the full scale granulator is similar to that in the small scale granulator, this implies

$$\frac{\dot{V}_2}{A_2} = \frac{\dot{V}_1}{A_1} \Rightarrow \frac{\dot{V}_2}{\dot{V}_1} = \frac{A_2}{A_1} \tag{41}$$

A common scale-up approach is to keep the same total spray time and still use a single nozzle at a large scale. Thus, $\dot{V}$ is proportional to D^3. Despite the fact that the powder area flux will increase slightly with scale, this approach generally leads to a substantial increase in dimensionless spray flux. To keep dimensionless spray flux constant, multiple spray nozzles and/or longer spray times should be used at a large scale.

It should be noted that consolidation, growth, and breakage processes are controlled by St_{def}. This can lead to quite complicated growth behavior in mixer granulators. Figure 18 illustrates some of this complex behavior (30). Both decreasing liquid viscosity and increasing impeller speed *increase* the rate of granule growth but *decrease* the final equilibrium granule size. Both these effects increase St_{def}. In the early stage of granulation, this increases the probability of successful coalescence. However, as the granules grow, the critical value of Stokes number for breakage may be exceeded—at least near the impeller blade leading to a balance of breakage and growth and an equilibrium granule size. This example also highlights that most high-shear mixers have a very wide range of collision velocities in different parts of the bed. Granule coalescence will occur in regions of low collision velocity, while breakage and consolidation are more likely near the impeller. To properly quantify and predict this behavior, we need more sophisticated models that divide the granulator into at least two regions and incorporate better understanding of powder flow than we currently have.

Nevertheless, we can make some intelligent comments with regard to scale-up. In a mixer granulator, the maximum collision velocity for a granule will be of the order of the impeller tip speed. To maintain constant St_{def}, the impeller tip speed should be kept constant, that is, equation (36). If a constant Fr rule is used [Eq. (34)],

$$\frac{St_{def,2}}{St_{def,1}} = \frac{U_{c,2}^2}{U_{c,1}^2} = \frac{N_2^2 D_2^2}{N_1^2 D_1^2} = \frac{D_2}{D_1} \tag{42}$$

Thus, St_{def} increases with scale. This will lead to an increase in the maximum achievable granule density and a decrease in the maximum achievable particle size. The actual granule

density and size may depend also on the kinetics of consolidation and growth and are difficult to predict without more sophisticated quantitative modeling. As such, the variation in St_{def} with scale potentially leads to changes in granule attributes that are difficult to predict.

The liquid saturation S [Eq. (9)] should be kept constant on scaling. This implies a similar liquid content on a kg /kg dry powder basis *provided the granule density does not change with scale*. For operation in the steady growth regime, this is a reasonable assumption. However, for operation in the induction growth regime, the change in density with scale is harder to predict.

Recommended Scaling Rules for High-Shear Mixer Granulators and Case Study Examples

The complexity of powder flow and granulation rate processes makes it impossible to recommend a single definitive set of scaling rules. It is important to know which granule attribute is of most importance during scaling and the main granulation rate process that controls this attribute.

Overall, we recommend the following approach:

1. Keep granulators geometrically similar during scale-up where manufacturer's designs allow. In particular, keep dimensionless fill height constant during scale-up [Eq. (35)].
2. To ensure similar powder mixing, keep Froude number constant during scale-up by adjusting the impeller speed according to equation (34). At the very least, make sure $Fr>Fr_c$ at all scales.
3. To achieve good binder distribution, Ψ_a should be kept constant on scale-up. This is likely to mean multiple spray nozzles at a large scale to give sufficient spray zone area [Eq. (41)].
4. To keep St_{def} constant for consolidation, breakage, and growth, keep ND^n constant, where n is in the range of 0.8 to 1.0. This is in conflict with scaling rule 2 above. Therefore, scale up the impeller speed with scaling index (n) in the range of 0.8 to 1.0, provided that at a large scale $Fr>Fr_c$.
5. Spray time during the batch and total batch time scaling rules require a sound understanding of how the kinetics of growth and consolidation vary with scale. We do not know these rules yet, and they are likely to be different for operation in different growth regimes. As a starting point, keeping batch times constant during scaling is probably reasonable provided this does not conflict with other scaling rules (especially rule 3 above). (Note that the second case study presented in this section introduces an alternate approach in determining the spray batch time and total batch time in high-shear granulation.)

Conflicting scale-up goals lead us to consider more sophisticated operating strategies at a large scale including programming impeller speed to change during the batch operation. For example, begin the granulation with high impeller speed (constant Fr) to induce good dry powder turnover. This helps ensure good wetting and nucleation at the beginning of the batch when it is most important. Later reduce the impeller speed to give a similar tip speed to smaller-scale operation to control granule density or size. As the powder mass is now wet, it will be more cohesive and operation above the critical Froude number for rolling flow will be easier to maintain.

Litster and Ennis (5) give a case study for scale-up of a lactose granulation that is useful for illustrating these scaling rules and conflicts. It is represented in the next section.

Case Study 1: Scale-up of a lactose granulation from 25 to 300 L

A lactose-based granulation in a 25-L granulator has given granules with acceptable properties. The operating conditions for the 25-L granulator are summarized as follows (Table 4):

The dimensionless spray flux Ψ_a above was calculated by equation (7)

$$\Psi_a = \frac{3\dot{V}}{2\dot{A}d_d}$$

Table 4 Case Study 1: Operating Conditions for the 25-L Granulator

Parameter	Value
Nominal volume (L)	25
Powder charge (kg)	5
Impeller speed (rpm)	330
Spray time (min)	8
Drop size (μm)	100
ε_{min}	0.3
W	0.15
$\dot{V}$ (m^3/sec)	1.6×10^{-6}
Spray width W (m)	0.13
Powder surface velocity (m/sec)	0.85
Ψ_a	0.22

This granulation is to be scaled to 300 L using the following rules and heuristics:

- Keep Fr constant.
- Keep spray time constant.
- Spray from a single nozzle at a large scale.

How do Ψ_a and St_{def} change on scale-up? What are the implications from granulation rate processes at full scale?

Scaling to 300-L granulation

Assuming geometric similarity,

$$\frac{D_2}{D_1} = 12^{1/3}$$

Keeping Fr constant,

$$N_2 = \left(\frac{D_1}{D_2}\right)^{0.5} N_1 = 218 \text{ rpm}$$

Assume spray width scales with impeller diameter.

$$W_2 = \left(\frac{D_2}{D_1}\right) W_1 = 0.3 \text{ m}$$

Powder surface velocity scales with tip speed.

$$\nu_2 = \left(\frac{D_2 N_2}{D_1 N_1}\right) \nu_1 = 1.28 \text{ m/ sec}$$

Keeping spray time constant with one nozzle,

$$\dot{V}_2 = 12\dot{V}_1$$

Thus, the dimensionless spray flux at 300 L is

$$\psi_{a,2} = \frac{3\dot{V}_2}{2W_2 v_2 d} = \frac{3(12\dot{V}_1)}{2.(12^{1/3}W_1)12^{1/6}v_1 d} = 3.41\psi_{a,1} = 0.75$$

There has been a substantial increase in Ψ_a on scale-up taking the granulation from nearly drop-controlled into the mechanical dispersion regime. This could result in a much broader granule size distribution at a large scale. A similar spray flux could be achieved by using an array of four nozzles spaced at 90° intervals around the granulator (all positioned so that the spray fan is at right angles to the direction of powder flow).

Table 5 Case Study 1: Scale-Up Summary Data

Parameter	25 L	300 L
Nominal volume (L)	25	300
Powder charge (kg)	5	60
Impeller speed (rpm)	330	218
Spray time (min)	8	8
Drop size (μm)	100	100
ε_{min}	0.3	0.3
W	0.15	0.15
$\dot{V}$ (m^3/sec)	1.6×10^{-6}	19.2×10^{-6}
Spray width W (m)	0.13	0.3
Powder surface velocity (m/sec)	0.85	1.28
Ψ_a	0.22	0.75
$St_{def}/St_{def,25L}$	1	2.3

We cannot calculate the value of St_{def} because the dynamic yield stress Y for the lactose/binder system is not given. However, if we neglect changes in Y because of the larger strain rate, then St_{def} will increase as

$$St_{def,2} = \frac{U_{c,2}^2}{U_{c,2}^1} St_{def,1} = \frac{(D_2N_2)^2}{(D_1N_1)^2} St_{def,1} = 2.3St_{def,1}$$

There is a significant increase in St_{def} with scale-up that could impact on the granule density and maximum size. It is not possible to scale with constant St_{def} while simultaneously maintaining constant Fr. A scale-up summary data is tabulated in Table 5.

Case Study 2: Scale-up of a conventional pharmaceutical formulation granulation from 2 to 25 and 300 L

Michaels et al. (32) demonstrated a new approach to high-shear granulation scale-up, which is named as "steady states in granulation." In steady-state approach, the liquid binder is introduced to the powder very slowly to ensure drop-controlled nucleation, and also long time is allowed for wet massing in order to eliminate the effects of both steps on the granule properties. When the wet powder is mixed for a sufficiently long time, simultaneous growth and breakage take the granules to a steady state, where the granule properties do not change anymore. In this approach, during scale-up, the only variable that needs to be adjusted is the impeller speed. The authors applied constant shear stress rule for the impeller speed scale-up, that is, ND^n = constant and $n = 0.8$ [Eq. (39)]. The heuristics and rules applied in this scale-up are as follows:

- Geometric similarity was maintained across all scales.
- Fill ratio was kept constant during scale-up.
- Fluid level was held constant.
- Spray rate and wet mixing time were kept constant during scale-up, however, their durations were much longer compared with the conventional granulation practices (steady-state approach).
- Main impeller speed was varied according to the constant shear stress rule.

The process conditions at each scale are summarized in Table 6 below.

The exact Ψ_a and St_{def} cannot be calculated for this study because of the lack of necessary information, but it can be deduced that both Ψ_a and St_{def} increase during scale-up when the scaling rules mentioned above are used (i.e., single spray, constant spray rate, and constant shear stress rule). However, it should also be noted that the increases in Ψ_a and St_{def} are less in this case compared with constant Fr number case presented in the previous section. Increases in both Ψ_a and St_{def} would cause differences in granule properties in conventional high-shear granulation practices where the wet massing time is limited to few minutes, that is, the rate processes are at transient state. Michaels et al. (32) showed that by applying constant shear rule

Table 6 Case Study 2: Process Conditions at Each Scale

Parameter	2 L	25 L	300 L
Granulator type	Fukae Powtec	Fielder PMA25	Fielder PMA25
Nominal volume (L)	2	25	300
Powder charge (kg)	0.4	5	70
Fluid level (%)	24, 28, 32	24, 28, 32	24, 28, 32
Spray rate (g/min)	8	100	1400
Impeller speed (rpm)	600, 800, 1000	296, 395, 494	146, 194, 242
Chopper speed (rpm)	2000	3000	1000
Wet massing time (min)	30–40	30–40	30–40

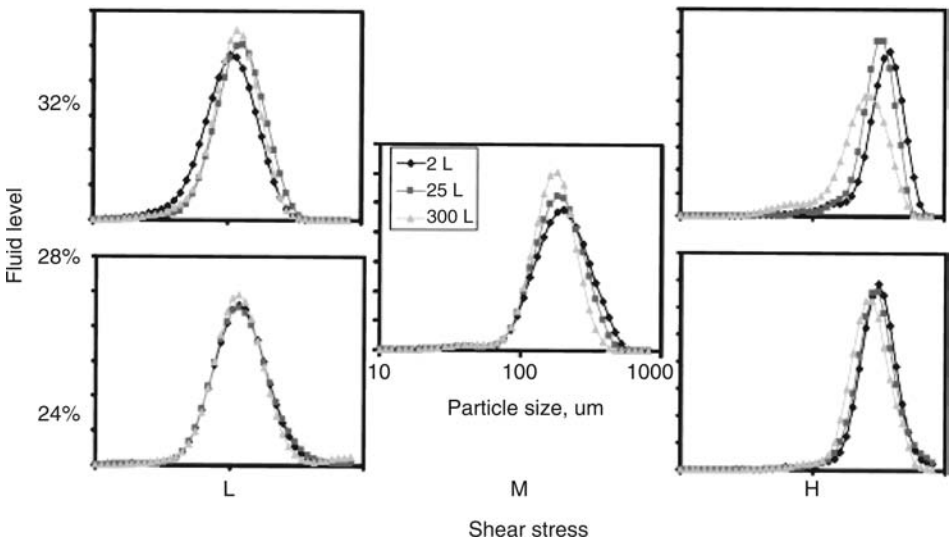


Figure 19 Granule size distribution for steady-state granulation at three scales (2, 25, and 300 L) for three levels of shear stress (low, medium, and high) and three levels of fluid amount (24%, 28%, and 32%). *Source*: From Ref. 32.

and steady-state approach, it is possible to get similar granule properties as you scale-up. Their results showed that at lowest liquid level and lowest shear rate, the granule mean particle sizes for 25 and 300 L deviated only 1% from the mean particle size of the granules produced in 2-L granulator. The worst case was obtained for highest liquid level and highest shear rate combination (31%). At all other conditions, the results were within 18% or better agreement. Figure 19 shows the particle size distribution of the granules from all three scales at different fluid levels and shear stresses. The main concern with steady-state approach might be getting too dense granules that may be a problem in tableting and disintegration. Although, the authors did not perform an extensive study on tablet performance, they showed that the dissolution profiles of tablets made by granules from conventional and steady-state granulation were comparable.

CONCLUDING REMARKS

Scaling of granulators using the traditional chemical engineering dimensional analysis approach of complete similarity is not possible because of the complexity of the process and the constraints on formulation changes during scaling pharmaceutical processes. Nevertheless, scale-up using partial similarity that strives to keep some key dimensionless groups invariant is possible. It is very important to understand the powder flow phenomena in the granulator of choice and to maintain the same flow regime during scaling (bubbling vs. slugging, bumping vs. roping).

The second important requirement is to maintain constant key dimensionless groups that control the important granulation rate process of most interest during scale. This is somewhat easier to do in fluidized beds than in high-shear mixers.

Very small-scale tests, which have no geometric similarity to pilot and full scale, should be used to focus on formulation design and measurement of key formulation properties that influence the granulation rate processes.

Insightful understanding of the granulation processes is essential for the identification of key variables and parameters for the dimensional analysis and scale-up considerations. While development of definitive mathematical models for the granulation processes is incomplete, the scaling approaches recommended in this chapter help reduce uncertainty during new product development and transfer to industrial sites.

NOMENCLATURE

a	constant in equation (11)
A	apparent area of contact of the indentor with the surface
$\dot{A}$	area flux of powder through the spray zone
AR	aspect ratio of particles
b	constant in equation (33)
B_w	attrition rate
Ca	capillary number
d_o	distributor hole orifice size
$d_{3,2}$	specific surface mean particle size
d_b	bubble size
d_d	liquid drop size (diameter)
d_i	indentor diameter
d_p	particle or granule size
D_{drum}	drum granulator diameter
D	impeller diameter of mixer granulators
D_c	chopper diameter of mixer granulators
D_F	fluidized-bed diameter
Fr	Froude number
Fr_c	critical Froude number
g	gravitational acceleration
h_{eff}	effective blade height
H	hardness of granules
H_m	fill height of mixer granulators
l	wear displacement of the indentor
L	characteristic length of a fluidized bed
k	constant in equation (33)
k_1, k_2	constants in equation (10)
k_c	consolidation rate constant
K_c	fracture toughness of granules
M_1, M_2	mass of particles in the fluidized bed
m	scaling ratio
N	impeller speed
n	scaling index
P	load
Q_b	volume flow rate of bubbles in the fluidized bed
S	granule pore saturation
S_{max}	granule pore saturation at ε_{min}
St^*	critical Stokes number
St_{def}	Stokes deformation number
St_v	viscous Stokes number
Str^*	dimensionless peak flow stress
T	dimensionless torque
T_0	extrapolated intercept value of dimensionless torque at an impeller speed of zero
t_p	drop penetration time
u	superficial fluidization velocity
u_1	fluidization velocity on the smaller bed
u_2	fluidization velocity on the larger bed
u_{mf1}	minimum fluidization velocity on the smaller bed
u_{mf2}	minimum fluidization velocity on the scaled bed
u_b	bubble rise velocity
U_c	particle collision velocity
v_p	relative velocity of a particle inside a granule after impact

$\dot{V}_R$	relative swept volume
$\dot{V}_{imp}$	rate of swept volume of impeller
V_{mixer}	mixer volume
$\dot{V}$	volumetric spray rate
w	liquid to solid mass ratio
W	spray zone width
Y	yield stress of granules
z	exponent in equation (10)
β	constant in equation (33)
β_c	constant in equation (11)
γ_{LV}	liquid surface tension
δ	dimensionless bubble space, defined as the ration of bubble space over bubble radius
ε	powder bed porosity
$\dot{\varepsilon}$	bulk strain rate
ε_g	granule porosity
ε_{min}	minimum porosity of granule
ε_{tap}	bed tap density
θ	solid-liquid contact angle
μ	viscosity of binder
ρ_g	granule density
ρ_G	density of fluidizing gas
ρ_s	particle density
ρ_l	binder liquid density
σ_{pk}	peak flow stress
ϕ	particle sphericity
Ψ_a	dimensionless spray flux
ω	drum peripheral speed
ω_i	impeller peripheral speed
ω_c	chopper peripheral speed

REFERENCES

1. Hileman GA. Regulatory issues in granulation processes. In: Parikh DM, ed. Handbook of Pharmaceutical Granulation Technology. New York: Marcel Dekker, Inc., 1997.
2. Skelly JP, Van Buskirk GA, Savello DR, et al. Scaleup of immediate release oral solid dosage forms. Pharm Res 1993; 10:2–29.
3. Zlokarnik M. Dimensional Analysis and Scale-up in Chemical Engineering. Berlin: Spriner-Verlag, 1991.
4. Munson BR, Young DF, Okiishi TH. Fundamentals of Fluid Mechanics. 2nd ed. New York: John Wiley & Sons, Inc., 1994.
5. Litster JD, Ennis B. The Science and Engineering of Granulation Processes. Dordrecht: Kluwer Academic Publishers, 2004.
6. Hapgood KP, Litster JD, Smith R. Nucleation regime map for liquid bound granules. AIChE J 2003; 49 (2):350–361.
7. Iveson SM, Wauters PAL, Forrest S, et al. Growth regime map for liquid-bound granules: further development and experimental validation. Powder Technol 2001; 117(1–2):83–97.
8. Iveson SM, Beathe JA, Page NW. The dynamic strength of partially saturated powder compacts: the effect of liquid properties. Powder Technol 2002; 127:149–161.
9. Ennis BJ, Tardos GI, Pfeffer R. A microlevel-based characterization of granulation phenomena. Powder Technol 1991; 65:257–272.
10. Tardos GI, Irfran-Khan M, Mort PR. Critical parameters and limiting conditions in binder granulation of fine powders. Powder Technol 1997; 94:245–258.
11. Liu LX, Smith R, Litster JD. Wet granule breakage in a breakage only high-shear mixer: Effect of formulation properties on breakage behavior. Powder Technol 2009; 189:158–164.
12. Rumpf H. The strength of granules and agglomerates. In: Kneper WA, ed. AIME Agglomeration. New York: Interscience, 1962:379–418.
13. Van den Dries K, Vromans H. Relationship between inhomogeneity phenomena and granule growth mechanisms in a high-shear mixer. Int J Pharm 2002; 247:167–177.
14. Evans AG, Wilshaw TR. Quasi-static solid particle damage in brittle solids, I. Observations, analysis and implications. Acta Metall 1976; 24:939–956.
15. Ennis BJ, Sunshine G. On wear mechanism of granule attrition. Tribology Int 1993; 26:319–927.
16. Kunii D, Levenspiel O. Fluidization Engineering. 2nd ed. Boston: Butterworth-Heinemann, 1991.

17. Sanderson J, Rhodes M. Hydrodynamic similarity of solids motion and mixing in bubbling fluidized beds. AIChE J 2003; 49:2317–2327.
18. Fitzgerald TJ, Crane SD. Cold fluidized bed modelling. Proc Int Conf Fluidized Bed Combustion, Vol 3, Technical Sessions, 1985:85–92.
19. Glicksman LR. Scaling relationships for fluidized beds. Chem Eng Sci 1984; 39:1373–1379.
20. Glicksman LR. Scaling relationships for fluidized beds. Chem Eng Sci 1987; 43:1419–1421.
21. Glicksman LR, Hyre M, Woloshun K. Simplified scaling relationships for fluidized beds. Powder Technol 1993; 77:177–199.
22. Horio M, Nonaka A, Sawa Y, et al. A new similarity rule for fluidized-bed scale-up. AIChE J 1986; 32:1466–1482.
23. Horio M, Takada M, Ishida M, et al. The similarity rule of fluidization and its application to solid mixing and circulation control. Proc Fluidization V Engineering Foundation, New York, 1986:151–156.
24. Roy R, Davidson JF. Similarity between gas-fluidized beds at elevated temperature and pressure. Proc Fluidization V Engineering Foundation, New York, 1986:293–299.
25. Steward PSB, Davidson JF. Slug flow in fluidised beds. Powder Technol 1967; 1:61–80.
26. Werther J. Influence of the distributor design on bubble characteristics in large diameter gas fluidized beds. In: Davidson JFand Keairns DL, eds. Fluidization. New York: Cambridge University Press, 1978.
27. Litster JD, Hapgood KP, Michaels JN, et al. Scale-up of mixer granulators for effective liquid distribution. Powder Technol 2002; 124:272–280.
28. Schaefer T. PhD thesis, The Royal Danish School of Pharmacy, 1977.
29. Knight PC, Seville JPK, Wellm AB, et al. Prediction of impeller torque in high shear powder mixers. Chem Eng Sci 2001; 56:4457–4471.
30. Kristensen HG, Schaefer T. Granulation: A Review on Pharmaceutical Wet-Granulation. Drug Dev Ind Pharm 1987; 13:803–872.
31. Tardos GI, Hapgood KP, Ipadeola OO, et al. Stress measurements in high-shear granulators using calibrated “test” particles: application to scale-up. Powder Technol 2004; 140:217–227.
32. Michaels JN, Farber L, Wong GS, et al. Steady states in granulation of pharmaceutical powders with application to scale-up. Powder Technol 2009; 189:295–303.

26 Advances in Process Controls and End-Point Determination

Kevin A. Macias and M. Teresa Carvajal
Department of Industrial and Physical Pharmacy, School of Pharmacy and Pharmaceutical Sciences, Purdue University, West Lafayette, Indiana, U.S.A.

GRANULATION: THE ESSENTIAL PROCESS

Process control in one way or another is as old as granulation technology itself. It can be imagined that during pill-rolling, a druggist would evaluate the consistency of the dough for ease in rollability. If pills of insufficient quality were prepared, additional binders or solvents would be added accordingly. Bringing this art of preparing elegant medicaments into industrial pharmacy would have been a natural progression. It is further imagined that this marks the origin of the notable end-point detection method of the squeeze test. This test would be performed during wet massing to assess the quality and indirect binder saturation of the granulation. Through trial and error, the formulator would determine the optimal binder and binder quantity. After gaining more experience with the operation, soon the experienced operator was able to hear when a wet granulation process was nearing completion. This was due to the increased load on the mixing equipment secondary to the adhesive wet mass. In the case of drying granulations in a fluid-bed dryer, one might feel the expansion chamber for increasing temperature to determine the end point of drying. These historical methods take considerable time to "develop" and are reliant solely on empiricism and intuition. Nonbiased techniques to determine process end point have been sought. This necessary transition was to ensure that reproducible products are manufacturing in a reliable way. It is suggested that arising out of being able to "hear" the granulation end point because of the increased load on the mixer are power consumption and torque measurements. More recently, passive acoustic technology has been found to be a successful methodology for determining granulation end point (1).

Arising from the squeeze test was the technology of probe strain (2) and vibration analysis (3,4). For fluid-bed control, moisture content of samples taken during processing has been used to control the process in lieu of feeling the expansion chamber. Success in monitoring moisture and particle size with near-infrared (NIR) spectroscopy has been reported (5).

THE BENEFITS OF PROCESS CONTROL

There is little question for the need to formulate products using a science-based approach. To bring robust products to the market with minimal trial and error, it is important to completely understand the thermodynamics, kinetics, and physics of the concurrent processes occurring during granulation. Fundamental understanding of the processes will allow for the appropriate modeling and monitoring of granulation that is necessary to facilitate control over the process. The knowledge surrounding granulation technology has vastly improved over the last few decades with no signs of losing momentum. Of additional consideration is any type of chemical, solid-state, or functional change that may impact the performance of the pharmaceutical product. Well-known examples exist where polymorphic transformations or hydration have affected oral bioavailability (6,7). The impact of process-induced transformations must be considered during all phases of processing and should be monitored and controlled (8).

Process understanding with emphasis in PAT and QbD has been an initiative of the FDA. This initiative has contributed significantly to the understanding and development of process control. In the following sections, advances in process control and end-point approach will be presented. It is important to remember that the motivation behind controlling pharmaceutical processes has not changed since the first pill was rolled. The main goal is to provide an elegant product to patients while ensuring that every dosage taken will elicit the intended therapeutic

response. It is for the patient that we strive to thoroughly understand our craft in hopes of increasing the quality of life.

END-POINT DETERMINATION—GENERAL REMARKS

The main reasons for completing the granulation process is for enhanced flow and reduced segregation. Granulation is a particle size–enlargement technique and for this reason, end point is often discussed in terms of particle-size distribution. This is an important parameter as it governs the packing arrangement in the filling of tablets and capsules (9,10). Some authors suggest, as a rule of thumb, that the size of the granules should ideally be matched to the size of the tablet dies or capsules (11). This is to minimize weight variation solely based on the probability of the number of granules loaded into the die at any point in time. Particle-size distribution is also important as it contributes to granulation bulk density and flow characteristics. In the determination of bulk density and flow, particle size is only part of the equation. Another factor to consider is the arrangement of primary particles within the granule, collectively known as densification. In addition to the bulk properties of the granulation, granule density influences how the granulation will perform before, during, and after compaction or encapsulation. Maintaining granule structure is of great importance until the final dosage form is prepared. Suggestions for granule density only relate to minimizing the attrition during handling and ensuring coherent tablets can be prepared. Additionally, the porosity of tablets and granules has been established as impacting disintegration and dissolution (12,13). If dense granules are prepared and loaded into capsules, delays in dissolution have been reported. The effect of not meeting the granulation end point is illustrated in Figure 1, the root cause of which was not divulged.

A specific definition of end point is difficult to define for granulation processes. There has been no universal particle-size distribution or optimal granule density identified that once met ensures the desired performance of the formulation and resulting product. It is extremely unlikely that this could ever be identified (14).

With the granulation process fixed for a given product, variation of incoming materials will impact the resulting granulation and product. With formulation and processing conditions held constant and changing starting materials, it is easy to see that there is some process and product variance. Even the most rudimentary methods of assessing these two granule characteristics require some degree of empiricism and can be time consuming. Product development teams have evaluated and implemented various approaches to determine end point during formulation of large-scale production. Excluding purely time-based systems, the techniques currently used by the pharmaceutical industry to obtain wet granulation end points are listed in Table 1.

The approaches listed in Table 1 have minimized "trial and error" tactics, but still possess advantages and disadvantages. The advantages of these techniques are often only due to

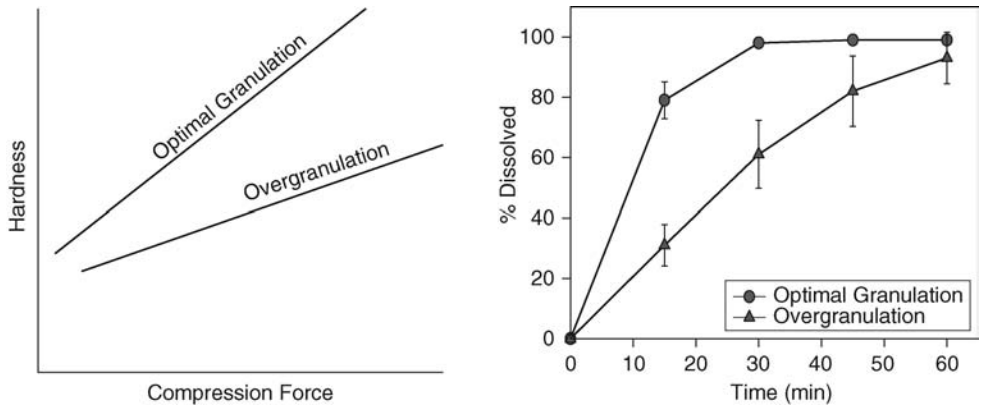


Figure 1 Effect of compaction and dissolution. *Source*: Courtesy of W. Phuapradit, H. Ahmed, and N. Shah, Hoffman LaRoche.

Table 1 Examples of Techniques Used to Measure Critical Properties During Wet Granulation

Technique	Granulation property measured
Boots Diosna probe	Granule density and size
Capacitance	Granule moisture and saturation
Conductivity of the damp mass	Uniformity of liquid distribution, packing density
Impeller torque	End-point determination and scale-up (more sensitive to high-frequency oscillation than power)
Impeller tip speed	Corresponds to shear rate. Some benefit in scale-up for geometrically similar mixers
Power consumption (kW)	Widely used for end-point determination and scale-up
Probe/bowl vibration	Granulation adhesiveness/cohesiveness monitoring and end-point determination
Torque rheometer	Off-line technique for measuring mechanical properties of the granulation

having some measurement technique in place to be able to compare granulations that worked in the past. With abundant historical data, correlations can be made to determine if the granulation process has been successful. The most common disadvantage of these end-point determination methods is low sensitivity. With low sensitivity, it is difficult to pinpoint an exact end point. Methods can be broken down in to the characteristic of interest. These methods reside in tracking particle size or tracking the wet mass strength. The variations measured by power consumption and torque during granulation are attributed to the evolution of the strength of the wet agglomerates and the size of the granules. One issue that must be resolved is that as granules consolidate, the frictional component between the wet granules and the wall changes, which changes the torque necessary to keep the bed in motion. Additionally, as the process of densification proceeds, the bulk density increases, thus reducing the volume of granulation in the process bowl. The reduction in volume also changes the magnitude of the friction between the formulation and the processing equipment. The dynamics of these phenomena change as the scale of granulation changes, therefore a new end-point master curve must be generated at each scale. Conductivity and capacitance describe the relative distribution of binder throughout the granule bed. Although obtaining homogeneity is important, it does not ensure downstream granulation performance. With the availability of so many techniques, it is especially important that each granulation parameter is related to granule properties and downstream granulation performance. As all of the testing is still required during development and scale-up, it is a time-consuming process.

The true goal is to understand the fundamental governing phenomena at work during the process and incorporate this understanding during product development. Doing so will reduce the degree of empiricism that is necessary. Process understanding will also aid in the rational development of mitigation strategies should unforeseen processing issues arise. There has been much interest in developing techniques that will determine the end point of a granulation process such as acoustics, NIR, image analysis, laser diffraction, torque rheometry, power consumption, and capacitance. An ideal end-point determination system would be one that is minimally invasive to the process, has rapid data acquisition, and provides reliable information to the operator. This routine should also supply suggested corrective actions to bring the granulation within prespecified end-point control limits. Using this methodology could lead to the optimization of the granulation process and used for control. Such systems are still under development and ongoing research is being carried out in this field.

Specific cases of granulation end-point determination and control are provided in the following sections. Cases for roller compaction will be followed by fluid-bed granulation. Dense-phase granulation methods have been provided in the final section that summarizes all other methods of wet granulation methods excluding fluid-bed granulation.

ROLLER COMPACTION

An unusual characteristic of roller compaction is that it is operated in batch fashion but the quality of the product (ribbon and granules) can be monitored continuously or at time intervals. For this reason, it is an ideal candidate for a continuous manufacturing process train.

Traditional methods of end-point determination normally involve monitoring the ribbon density and the particle-size distribution after milling the ribbon into granules. Ribbon density has been identified as a critical parameter in determining the operational performance of roller compaction. It has long been held that ribbons of high density will result in long residence times during milling. Excessive milling times could result in the generation of fine particles as the mode of ribbon breakage changes from fracture to attrition. Further, reduced tablet-forming ability is probable for granules prepared with high density. In addition to granule density, compaction efficiency is of importance. If ribbons of low quality are prepared or the native powder escapes the compaction process, a segregating granulation with a poor flow will result. Process efficiency for roller compaction by reducing the percent of fines bypass, optimizing particle size and compression force necessary to manufacture in-spec tablets during roller compaction, has been recently reported by am Ende et al. (15). In the report, topographic representations of the interactions of the processing conditions are provided. One such contour plot describes the increase in percent fines bypass with increasing roll gap and reduction in roll force. By overlaying the graphs, an effective operational space is derived. To further this work and gain control over the process, feedback systems should be considered. As the fundamental relationships between roller compaction settings and product performance are elucidated, monitoring systems can become process control points.

During roller compaction, manual measurements of ribbons occur to assess the quality. Nkansah et al. (16) have proposed a model for deriving the solid fraction of roller-compacted ribbons. This technique defines the volume of ribbons, including volume due to elastic recovery, which should be generated during processing. In measuring the weight of the ribbons actually produced during a steady-state time interval, an estimation of solid fraction can be derived. This model generates an average solid fraction as it does not account for the cross-sectional density variation along the face of the rolls. To further this work, the quantity of bypass and actual gap-pressure should be incorporated.

Neural networks have been applied for the generation of optimal roller-compaction settings (17). A hybrid approach combines neural networks and fuzzy logic to generate neurofuzzy rules (18). This approach has been developed and applied for the prediction of ribbon properties from process variables and powder properties. This methodology seems to be very promising with respect to process optimization and control. Dec et al. (19) concluded in their comparative analysis of roller-compaction modeling methods that computational methods are superior to conventional methods of modeling. Limitations of computational methods lie within the input parameters and in verification of the result.

Real-time NIR monitoring has been implemented to assess the roller-compaction process (20). Prediction of ribbon mechanical properties including relative density, Young's modulus, and tensile strength was possible using this system. Chemical information was also extracted and included API concentration and moisture to predict loss on drying. Because of the large shear involved during roller compaction and tablet compression, polymorphic changes may occur. For this reason, both chemical and physical tests need to be characterized. Raman spectroscopy has been used to assess the form conversion of famotidine under varying compression pressures (21). Incorporating the computational methods with simultaneous monitoring will enable feedback systems and process control during manufacturing.

FLUID-BED GRANULATION

The process of fluid-bed granulation has received considerable research efforts. There is minimal shear during processing, which adds emphasis to the wetting of solids by the binder. Binder-formulation interaction is reliant on the thermodynamics of wetting and the viscosity of the binder solution for the kinetics. Ideally, the spreading coefficient is considered while selecting the binder for a wet granulation process (22). If a poorly wetting binder is chosen, highly friable granules may be produced. Given that the appropriate binder selection has taken place, the size of the droplets and the rate of binder addition must be well controlled. The rate and extent of binder addition must be balanced with the rate of binder evaporation. If not balanced, defluidization, or poor granules may result. For this reason, it is desirable to control the dynamic process of drying and wetting during fluid-bed granulation. Moisture levels need

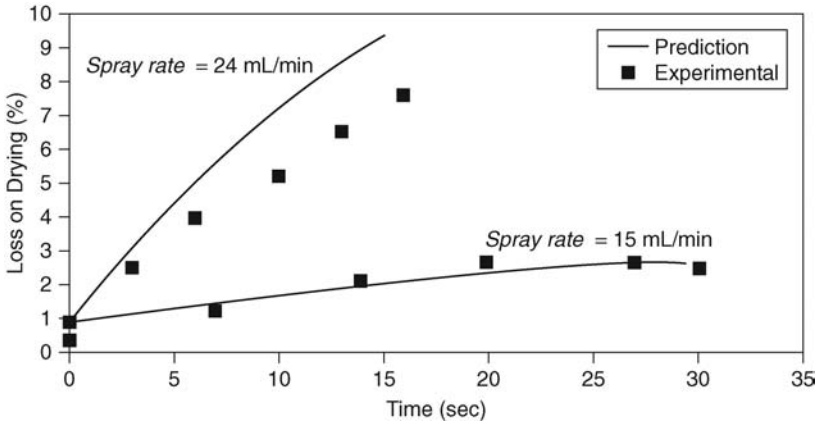


Figure 2 Friability determined for granulations in which the wet mass was characterized in terms of wet mass consistency. *Source*: From Ref. 24.

to be controlled during fluid-bed granulation and subsequent drying. As such, the traditional method of granulation control has been to perform moisture determination tests during processing. After the granulation stage is over, the dry phase ensues. To enable continuous monitoring of the moisture present during processing, NIR spectroscopy has been applied (5). More recently, water content and median particle size have been extracted during processing using NIR methods (23). Hu et al. (24) incorporated thermodynamic models of wetting and evaporation to enable moisture prediction prior to granulation (Fig. 2).

In addition, the authors illustrated modeling control of the impact of changing fluid-bed inlet temperature on the moisture present during granulation. This method of moisture prediction could enable the end point of fluid-bed granulation to be targeted prior to granulation. The ability to predict the moisture present during fluid-bed granulation should facilitate the rapid modeling of new processes and provide rational resolution methods if a process becomes out of specification. This could also prove useful in the development of spectroscopic models while reducing the necessary number of calibration standards.

The moisture content of granules during granulation also determines the probability of successful coalescence and ensuing granule growth. Many modeling aspects account for the probability of coalescence of colliding granules. The most commonly used aspects accounts for the viscous dissipation of granule kinetic energy during granule collision (25). Once the coalescence probability and frequency of granule collisions are determined, a population balance model can be used to describe the change in granule size as the process progresses. To validate these routines, experimentally tracking the change in particle size during granulation is necessary. The focused beam reflectance method (FBRM®) has been successfully used at-line to assess the progression of fluid-bed granulation with respect to the particle growth (26). Techniques such as FBRM and particle vision and measurement (PVM®) microscopy, both allow real-time monitoring without sampling or extracting product. Figure 3 shows the FBRM cutaway view of the probe that tracks the effect of changing critical process conditions and quickly detects undersized and oversized granule distributions. There is a laser source in the field unit that travels down a set of fiber optics into the probe. At the tip of the probe is a set of optics that takes the laser beam and focus it to a very small spot. There is a motor that rotates the optics so that the focused beam scans a circular path at the interface between the window of the probe and the process itself.

Image analysis has successfully monitored the change in granule size during processing (27,28). This should allow for the experimental validation of derived coalescence kernels and population balance models. Watano has demonstrated the ability to control the process of fluid-bed granulation using image analysis and fuzzy logic combined with delay terms to help prevent overgranulation (29).

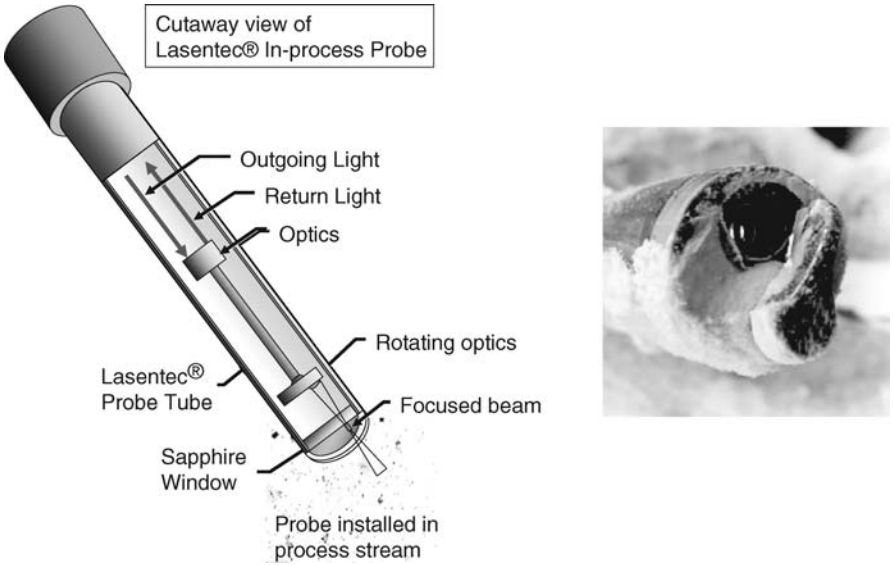
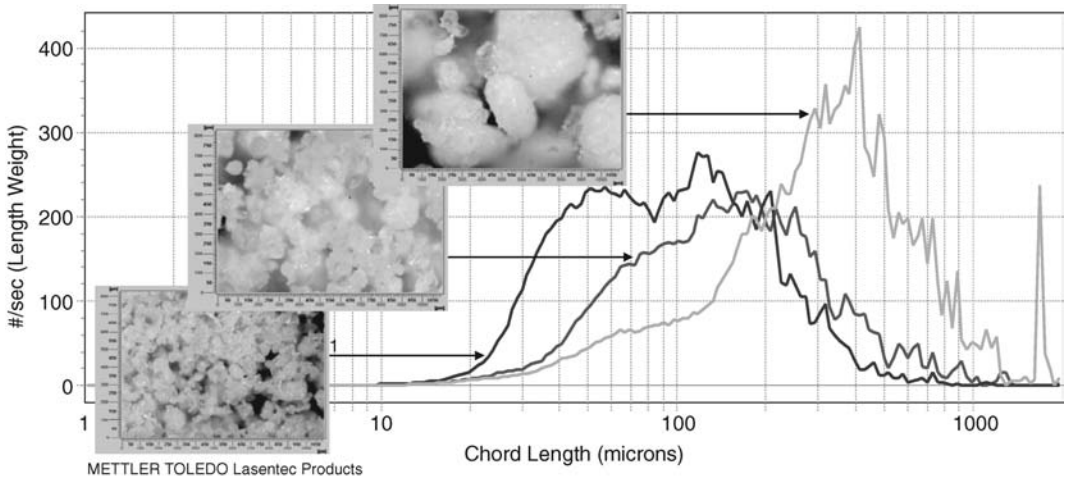


Figure 3 Cutaway view of Lasentec FBRM® probe showing various parts. *Source*: Courtesy of Mettler Toledo Autochem, Inc.

DENSE-PHASE WET GRANULATION SYSTEMS

Traditional methods of end-point detection of dense-phase granulation processes have been related to the degree of saturation of the granules. The physical state of the wet mass during wet granulation has long been a focus for determining end point. The squeeze test, impeller torque rheometry, and power consumption relate to the saturation progression of the granulation. Torque, power consumption, and direct impeller torque have been used simultaneously to test the predictive capability of a low-shear wet granulation to assess the subsequent tablet manufacture (30). To truly characterize the progression of a granulation, the increase in the particle size should be monitored. Difficulty arises when attempting to obtain and characterize a representative sample of the granulation. The idea being that measurements can be obtained in a timely fashion as to provide feedback to adjust the processing conditions to obtain prespecified granule properties. High-shear wet granulation (HSWG) is a dense-phase system and is much harder to monitor and control during processing because of the truncated processing times as compared to other wet granulation techniques. As was the case for fluid-bed granulation, the kinetics of binder distribution must be optimized. The wetting of granulation plays an important part of granulation quality. Hapgood et al. (31) have shown that the rate of water uptake is important in the nucleation of granules. For this reason, the spray flux has been proposed to quantitate the regime of nucleation. Further, fuzzy logic has been implemented to optimize the wetting phase of granulation (32). This is an important step forward as the wetting methodology is the controlling factor as scale increases. Current assessment of particle size is usually completed at-line or off-line after drying has been completed. Attempts have been made to divert the granulation to laser diffraction equipment but are not well documented in the open literature. One of the obstacles in processing in this manner is the blocking of sampling streams due to adhesive properties of the wet mass. This property has also limited the widespread implementation of laser back scattering techniques. One such case is the fouling of Lasentec FBRM during HSWG monitoring. Successful monitoring has been reported for a model formulation developed to minimize probe fouling (33). Figure 4 shows the results of various levels of moisture addition in a high-shear mixer and the resulting particle size increases due to different water addition and different massing time measured by Lasentec FBRM and PVM.



		Water addition (%)	Wet massing time (min)	Impeller speed (RPM)
	1	20	4	542
	2	25	2.5	542
	3	30	4	542

Figure 4 Three levels of moisture addition and massing times with the resultant granule growth measured by Lasentec FBRM® and PVM®. *Source*: Courtesy of Mettler Toledo Autochem, Inc.

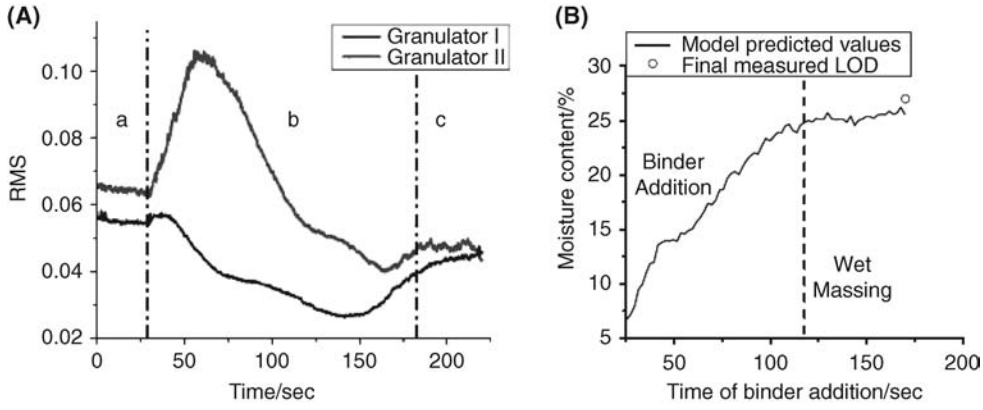


Figure 5 Monitoring the granulation progression through product end-point using sound. (**A**) Typical acoustic RMS profiles obtained from granulations run on both granulators: (a) dry mixing, (b) binder addition, and (c) wet massing. (**B**) Granule moisture content predicted from acoustic emission for a granulation. *Source*: From Ref. 37.

Image analysis has been used, combined with fuzzy logic systems, to control the HSWG process (34). Acoustic monitoring has been reported to successfully identify the end point of HSWG processes (35–38). An example of the success is illustrated in Figure 5 (37).

In addition to particle size, the relative flow of the granulation has been assessed from the wet mass during HSWG shown in Figure 6 (39).

As the Hausner ratio is highly empirical, the relative flow behavior is of comparative interest in the provided example. This clearly indicates that the relative flow can be predicted prior to drying the granules. Once the desired level of flow has been attained, it is important that the granules maintain that level of performance until the end product is manufactured.

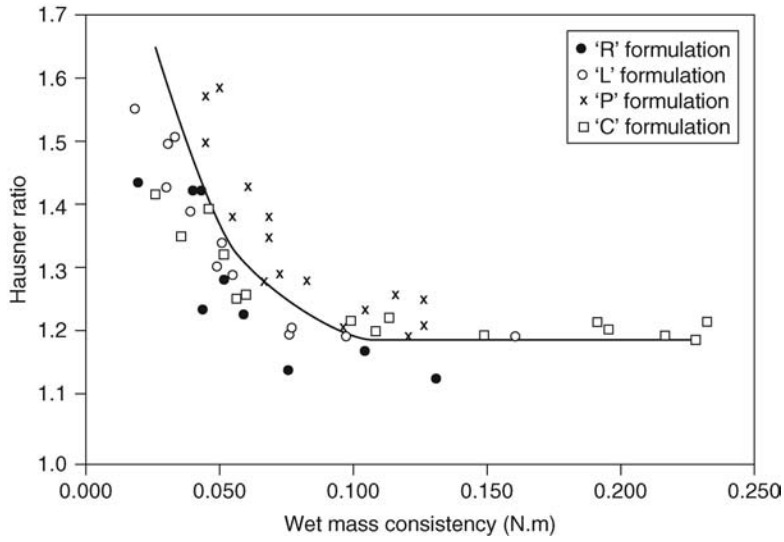


Figure 6 Hausner ratio determined for granulations in which the wet mass was characterized in terms of wet mass consistency. *Source*: From Ref. 39.

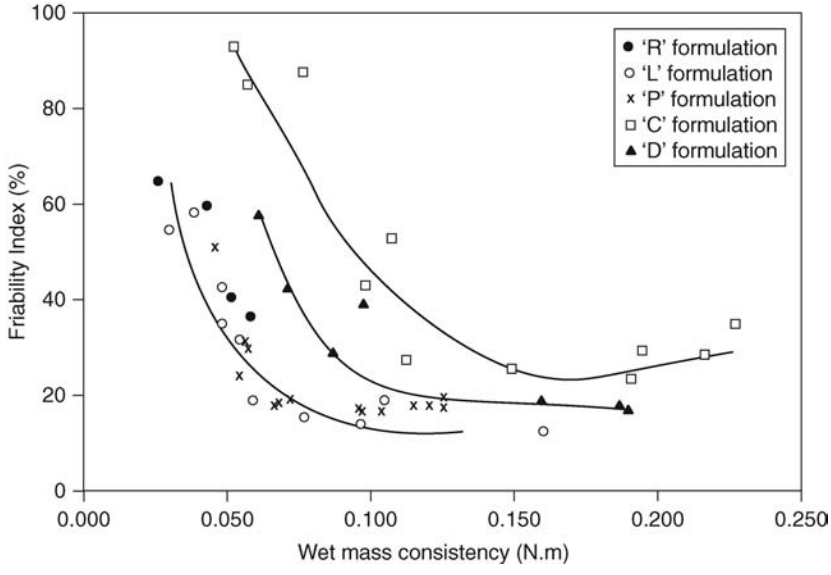


Figure 7 Friability determined for granulations in which the wet mass was characterized in terms of wet mass consistency. *Source*: From Ref. 39.

One mechanism that contributes to the erosion of granulation performance is attrition. Attrition is the generation of fines resulting from granule breakage. To evaluate attrition tendencies, the friability test has been developed. A high friability could lead to complete erosion of the granules generating the original size distribution that went into the granulation process. In Figure 7, the relative friability of granulations is reported for granulations in which the wet mass was characterized prior to drying (39).

Real-time feedback monitoring should be initiated to enable control over the granulation process. This feedback should allow for the adjustments of processing parameters to ensure that the process will prepare agglomerates with desired specifications. Implementation of this

technology during the manufacturing phase may guarantee product quality before stopping the granulation process and proceeding to the drying phase.

The scientific approach to process optimization will allow for decreased time to market newly discovered medication and may reduce the number of failed batches of pharmaceutical granulations.

EMERGING TECHNOLOGY

The mission of the formulator is to decide which approach and efforts will offer an improvement in overall process and product quality. Predictive capabilities of granulation attributes enable ingredient and equipment selections, and optimal manufacturing procedures. This, in turn, will maximize the production rate while reducing risks associated with producing suboptimal granulations. In essence, it will eliminate processing issues and improve granule quality and the resulting end-product quality. Recent advances in technology and modeling capability have allowed for significant advancement in process understanding. A seemingly endless cycle exists between process understanding and the limitation of scientific tools to aid in understanding. The next few years will be contributed to the expansion of our understanding as new technology becomes available. Systems that hold immediate promise include in-line particle size analyzers (40), effusivity (41), and combination techniques (42). Advances in real-time measurements will contribute to our scientific understanding of the granulation process as well as aiding in the detection and mitigation of processing problems.

Complete understanding of the materials and granulation equipment is necessary to design a robust process. The thorough characterization of raw materials to be included in the formulation may be necessary to reduce process variation. After a robust process has been designed, it is necessary to assess the resulting granule characteristics including size and porosity to determine the expected downstream performance. For in-line measurements, NIR has been widely used and it is under constant scrutiny. Table 2 offers a compiled list of advantages and disadvantages observed by various users of this particular equipment at Purdue University. Additionally, this spectrometer offers simple user-friendly software that reduces the learning curve for new operators. In summary, the CDI NIR-256L is an excellent spectrometer with good resolution and a suitable wavelength range for identifying many API's and excipients, and for quantifying mixtures thereof. Real-time data acquisition and probe versatility makes monitoring many types of processes possible, but lack of remote data collection and equipment mounting capabilities limits its usefulness for such activities. Table 3 offers general aspects of the various techniques used for the characterization of granule size.

Table 2 Review of the Control Development Inc. Spectrograph (NIR-256L-1.7T2)

Advantages

- The 1100–2200 nm wavelength range covers a suitable range for identifying many active pharmaceutical ingredients and excipients.
- Spectral resolution of 1 nm is adequate for most applications.
- Rapid integration times, in the order of 10–40 msec, enable rapid acquisition of spectra.
- The NIR-256L is robust, lightweight, and has a small footprint making it very portable between laboratory benches. Its USB interface allows it to be controlled using any IBM compatible computer further enhancing its portability.
- Spec32 software for collecting spectra is easy to use and can export multiple spectra to a single file for analysis in a multivariate programming environment if desired.
- The NIR-256L can be used with a variety of probes and light sources making it very versatile

Disadvantages

- External reference is subject to contamination, abuse, and loss.
- Spectrometer has no remote data acquisition capabilities and cannot be mounted on rotating equipment such as blenders limiting its usefulness for real-time data acquisition from such processes.

Source: Courtesy of David Ely.

Table 3 Review of Various Techniques

Technique	Pros	Cons	Comment
Sieve analysis	Simple technique	Must dry granules	Feasible method to find granulation growth rates
Malvern	Fast	Off-line technique, data is not reliable	Current model is not appropriate
Lasentec FBRM	Online method	Information does not correlate to other techniques. New prototype will be tested	Need further understanding of obtained information
NIR	Online method	Combined particle size and density information	Information is currently not useful for distribution
Optical microscopy	Direct method	Small sample size	Not feasible to measure entire batch
Sympatec	Fast, reliable method	Off-line method	Feasible method to find granulation growth rates

Abbreviation: NIR, near infrared.
Source: Courtesy of David Ely, Carvajal's research group

REFERENCES

1. Rudd D. The use of acoustic monitoring for the control and scale-up of a tablet granulation process. J Process Anal Technol 2004; 1(2)8–11.
2. Kay D, Record PC. Automatic wet granulation end-point control system. Manuf Chem Aerosol News 1978; 49:45.
3. Staniforth JN, Quincey SM. Granulation monitoring in a planetary mixer using a probe vibration analysis technique. Int J Pharm 1986; 32(2–3):177–185.
4. Staniforth JN, Walker S, Flanders P. Granulation monitoring in a high speed mixer/processor using a probe vibration analysis technique. Int J Pharm 1986; 31(3):277–280.
5. Frake P, Greenhalgh D, Grierson SM, et al. Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy. Int J Pharm 1997; 151(1):75.
6. Bauer J, Spanton S, Henry R, et al. Ritonavir: an extraordinary example of conformational polymorphism. Pharm Res 2001; 18(6):859–866.
7. Shefter E, Higuchi T. Dissolution behavior of crystalline solvated and nonsolvated forms of some pharmaceuticals. J Pharm Sci 1963; 52(8):781–791.
8. Morris KR, Griesser UJ, Eckhardt CJ, et al. Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes. Adv Drug Deliv Rev 2001; 48(1): 91–114.
9. Podczeck F, Blackwell S, Gold M, et al. The filling of granules into hard gelatine capsules. Int J Pharm 1999; 188(1):59–69.
10. Podczeck F, Lee-Amies G. The bulk volume changes of powders by granulation and compression with respect to capsule filling. Int J Pharm 1996; 142(1):97–102.
11. Banker GS, Anderson NR. Tablets. In: Lachman L, Lieberman HA, Kanig J, eds. The Theory and Practice of Industrial Pharmacy. 3rd ed. Philadelphia, PA: Lea and Febiger, 1986:313.
12. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963; 52(12):1145–1149.
13. Cruaud O, Duchene D, Puisieux F, et al. Correlation between porosity and dissolution rate constants for disintegrating tablets. J Pharm Sci 1980; 69(5):607–608.
14. Leuenberger H, Puchkov M, Krausbauer E, et al. Manufacturing pharmaceutical granules: is the granulation end-point a myth? Powder Technol 2009; 189(2):141–148.
15. am Ende MT, Moses SK, Carella AJ, et al. Improving the content uniformity of a low-dose tablet formulation through roller compaction optimization. Pharm Dev Technol 2007; 12(4):391–404.
16. Nkansah P, Wu SJ, Sobotka S, et al. A novel method for estimating solid fraction of roller-compacted ribbons. Drug Dev Ind Pharm 2008; 34(2):142–148.
17. Inghelbrecht S, Remon, JP, Fernandes de Augiar P, et al. Instrumentation of a roll compactor and the evaluation of the parameter settings by neural networks. Int J Pharm 1997; 148(1):103–115.
18. Mansa RF, Bridson RH, Greenwood RW, et al. Using intelligent software to predict the effects of formulation and processing parameters on roller compaction. Powder Technol 2008; 181(2):217–225.
19. Dec RT, Zavaliangos A, Cunningham JC. Comparison of various modeling methods for analysis of powder compaction in roller press. Powder Technol 2003; 130(1–3):265–271.

20. Gupta A, Peck GE, Miller RW, et al. Real-time near-infrared monitoring of content uniformity, moisture content, compact density, tensile strength, and Young's modulus of roller compacted powder blends. J Pharm Sci 2005; 94(7):1589–1597.
21. Lin SY, Cheng WT, Wang SL. Thermal micro-Raman spectroscopic study of polymorphic transformation of famotidine under different compression pressures. J Raman Spectrosc 2007; 38(1): 39–43.
22. Zajic L, Buckton G. The use of surface energy values to predict optimum binder selection for granulations. Int J Pharm 1990; 59(2):155.
23. Nieuwmeyer F, Damen M, Gerich A, et al. Granule characterization during fluid bed drying by development of a near-infrared method to determine water content and median granule size. Pharm Res 2007; 24(10):1854–1861.
24. Hu X, Cunningham J, Winstead D. Understanding and predicting bed humidity in fluidized bed granulation. J Pharm Sci 2008; 97(4):1564–1577.
25. Ennis BJ, Tardos G, Pfeffer R. A microlevel-based characterization of granulation phenomena. Powder Technol 1991; 65(1–3):257.
26. Hu X, Cunningham JC, Winstead D. Study growth kinetics in fluidized bed granulation with at-line FBRM. Int J Pharm. 2008; 347(1–2):54–61.
27. Närvänen T, Seppälä K, Antikainen O, et al. A new rapid on-line imaging method to determine particle size distribution of granules. AAPS PharmSciTech 2008; 9(1):282–287.
28. Watano S, Miyanami K. Image processing for on-line monitoring of granule size distribution and shape in fluidized bed granulation. Powder Technol 1995; 83(1):55.
29. Watano S. Direct control of wet granulation processes by image processing system. Powder Technol 2001; 117(1–2):163.
30. Kopcha M, Roland E, Bubb G, et al. Monitoring the granulation process in a high shear mixer/ granulator: an evaluation of three approaches to instrumentation. Drug Dev Ind Pharm 1992; 18(18): 1945–1968.
31. Hapgood KP, Litster J, Smith R. Nucleation regime map for liquid bound granules. AIChE J 2003; 49(2): 350–361.
32. Belohlav Z, Brenkova L, Kalcikova J, et al. Optimization of the high-shear wet granulation wetting process using fuzzy logic modeling. Pharm Dev Technol 2007; 12(4):345–352.
33. Macias K, Carvajal T. An assessment of techniques for determining particle size during high-shear wet granulation. Tablet Capsules 2008; 6(1):32–40.
34. Watano S, Numa T, Koizumi I, et al. Feedback control in high shear granulation of pharmaceutical powders. Eur J Pharm Biopharm 2001; 52(3):337.
35. Briens L, Daniher D, Tallevi A. Monitoring high-shear granulation using sound and vibration measurements. Int J Pharm 2007; 331(1):54–60.
36. Daniher D, Briens L, Tallevi A. End-point detection in high-shear granulation using sound and vibration signal analysis. Powder Technol 2008; 181(2):130–136.
37. Papp M, Pujara C, Pinal R. Monitoring of high-shear granulation using acoustic emission: predicting granule properties. J Pharm Innov 2008; 3(2):113–122.
38. Whitaker M, Baker GR, Westrup J, et al. Application of acoustic emission to the monitoring and end point determination of a high shear granulation process. Int J Pharm 2000; 205(1–2):79.
39. Faure A, Grimsey IM, Rowe RC, et al. Process control in a high shear mixer-granulator using wet mass consistency: the effect of formulation variables. J Pharm Sci 1999; 88(2):191–195.
40. Chan L, Tan L, Heng P. Process analytical technology: application to particle sizing in spray drying. AAPS PharmSciTech 2008; 9(1):259–266.
41. Fariss G, Keintz R, Okoye P. Thermal effusivity and power consumption as PAT tools for monitoring granulation end point. Pharm Technol 2006; 30(6):60.
42. Tok A, Goh X, Ng W, et al. Monitoring granulation rate processes using three PAT tools in a pilot-scale fluidized bed. AAPS PharmSciTech 2008; 9(4):1083–1091.

27 Expert Systems and Their Use in Pharmaceutical Applications

Metin Çelik

Pharmaceutical Technologies International, Inc., Belle Mead, New Jersey, U.S.A. and School of Pharmacy, Near East University, Nicosia, Turkish Republic of Northern Cyprus

Susan C. Wendell

Johnson & Johnson, Raritan, New Jersey, U.S.A.

INTRODUCTION

The pharmaceutical industry has entered the twenty-first century, a new era that will be far more scientific, technologic, and sophisticated than anyone would have imagined just a quarter of a century ago, when it was still a tradition to develop formulation and processes mostly on the basis of trial-and-error method. The future success in all areas of pharmaceutical science will depend entirely on how fast pharmaceutical scientists will adapt to the rapidly changing technology. The regulatory agencies seem to endorse such changes as evidenced by the FDA's recent Process Analytical Technology (PAT) initiative, which requires an understanding and control the manufacturing process to demonstrate that quality was not tested into the product but was built in or by design.

Pharmaceutical scientists will gradually enjoy the availability of the harmonized and fingerprinted (in terms of functionality testing) excipients. Also, the awareness of and the use of artificial intelligence (AI)-based expert systems (ESs) [rule-based systems, fuzzy logic, genetic algorithm (GA), artificial neural networks (ANNs), simulations, etc.] in the areas of preformulation, formulations and process development, regulatory affairs, new drug delivery system development, project management, and all other areas of pharmaceutical science will increase dramatically (1,2).

ESs have been defined in various ways, but all the definitions share a common thread, suggesting that ESs are an artificial means to emulate the way in which human (domain) experts solve problems.

A definition of such systems that may be appropriate for the applications in pharmaceutical science would be "ES is a computer program capable of making recommendations, decisions or predictions based on knowledge gathered from the experts and/or experimental data obtained in the field."

ESs are designed to work in a narrow field of focus such as spray drying and have distinct architecture of components outlined in the following sections. Functional areas of ESs include, but are not limited to, control, design, diagnosis, instruction, interpretation, monitoring, planning, prediction, prescriptions, selection, and simulation. ESs are being used in many disciplines such as agriculture, business, chemistry, communications, computers, education, electronics, engineering, environment, geology, image, information, law, manufacturing, mathematics, medicine, meteorology, military, science, space, and transformations. The literature reported less than 50 ESs in use in 1985; this number increased to more than 12,000 in about seven years (3). However, although problems in the pharmaceutical industry are not necessarily more complicated than some of the problems encountered in the above-listed fields, the number of ESs used in pharmaceutical science is still negligibly low. One of the reasons for the insignificant use of ESs in pharmaceutical applications is the challenge facing ES developers in terms of their verification and validation (V&V) processes, in part because of FDA's interest in the V&V of all types of software. However, the main reason is that pharmaceutical scientists prefer to use well-established concepts. Many in the industry will let somebody else try a new concept first and, if it works, then join the crowd. It is a safe approach to use an established system, but it does not provide us with the immediate benefits of being on the technological

edge. On the other hand, it is always risky to try a new concept, even though the outcome may prove to be rewarding for both the scientist(s) and the company.

The history of ESs has played an integral part in the development of its structure and components. ESs did not begin as a known program with defined components and relationships. Instead, ES was preceded by the general development of AI.

The Dartmouth Summer Research Conference on AI was considered to give birth to the field of AI. The conference occurred in 1956 at Dartmouth College and was formally proposed by McCarthy et al (4). Their proposal stating "We propose that a 2 month, 10 man study of artificial intelligence be carried out during the summer of 1956 at Dartmouth College in Hanover, New Hampshire. The study is to proceed on the basis of the conjecture that every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it" marks the debut of the term "artificial intelligence" (4).

BUILDING AN EXPERT SYSTEM

To build an ES, the full participation of domain expert(s), knowledge engineer(s), and user(s) is essential. A domain expert possesses the knowledge and skill to solve a specific problem in a manner superior to the others. This expert's highly specialized knowledge is stored in the knowledge-based component of an AI-based program by the knowledge engineer. The user can also help define the interface specifications.

Why Build an Expert System

In general, the reasons for the development of an ES can be listed as follows, although every company may have different motivations:

Improved Productivity: The system is expected to be capable of improving the quality of decisions, to reduce the time to reach a decision and/or to provide expertise to locations within the organization where this capability is lacking.
Lower Costs: The system is expected to improve the use of materials during manufacturing and/or to reduce labor costs by allowing a time-consuming task to be completed quickly or acts in place of a highly paid expert.
Improved Quality: The system is expected to improve the quality of the final product or the services supplied by the organization and/or to provide training to personnel that improves their work activities.
Improved Image: The system is expected to improve the organization's image as a leader and innovator.

The above given list also explains the advantages of the ESs over the human experts. The advantages of the ESs are related to knowledge, decisions, safety, and cost. The knowledge of an ES is permanent and easy to transfer, while the human expert's knowledge is perishable and difficult to transfer from one worker to another. The decisions made by human experts can be unpredictable and difficult to document. In contrast, the ES decisions process is consistent and easy to document. In an unsafe or hostile environment, an ES is replaceable, while the human expert is definitely irreplaceable. When cost is an issue, the ES services are often more affordable than those of the human expert.

When compared with human experts, ESs have the following advantages: an ES's knowledge is permanent and can be easily transferrable. The decision process is fast and consistent, therefore predictable, and it is easily documented. Despite these advantages, ESs are not intended to take the place of formulation scientists. They must be considered as vital tools to be used by formulators for the rapid, cost-effective, and scientifically sound development of a dosage form as well as useful for training inexperienced scientists.

However, there are some factors that favor the human expert as opposed to an ES. These factors are much more difficult to quantify but can often be important to a project. A human expert is creative and adaptive and uses sensory experiences. The computer ES is uninspired, needs to be directed, and uses only symbolic input. A human expert has a broad focus and may be able to use knowledge from another field or experience to aid in problem solving,

whereas an ES has a narrow focus constrained to the domain knowledge. Lastly, the human expert has the ability to use common sense knowledge, while the ES can only use technical knowledge.

Phases of an Expert System Development Process

There are many textbooks addressing the strategies and/or tools employed in building ESs in depth (reference books). The following should be considered only a general overview of the phases involved in the development of an ES.

Feasibility Study

A project team assesses whether an ES can or should be developed for a specific problem or project. The team evaluates the motivation for the development of the ES in terms of improving productivity, quality, and image as well as cost reduction. The team also must consider the problem and the people-related feasibility issues very carefully. Some of the important questions that must be answered positively are as follows:

Is the problem solvable?
Are the problem-solving steps definable?
Is the problem stable and well focused and its complexity reasonable?
Is the management supportive of the project, receptive to change, and not skeptical, and does it have reasonable expectations?

If all the answers to these questions are in the affirmative, then the project team should continue to evaluate the other problem—the deployment-related issues concerning the development of the ES for that particular problem or project.

If and when a decision is made in favor of the development of the ES, the project team defines the features and specifications of each component of the ES and develops flow charts for each specific problem.

Acquisition of the Knowledge

The objective of knowledge acquisition is to compile a body of knowledge on the problem of interest that can then be encoded into the ES. There are different types of knowledge and different methods of obtaining them. Some of these types of knowledge are as follows:

1. Procedural (e.g., rules, strategies)
2. Declarative (e.g., facts, objects)
3. Heuristic (rule of thumb)
4. Structural (e.g., rule sets concept relationship)

The major difficulties with the knowledge gathering from the human experts lie in the facts that some domain expert may be unaware of or unable to verbalize the knowledge or may provide irrelevant, incomplete, or inconsistent knowledge.

Design of the Expert System

The knowledge engineer determines which software to use to transform the acquired knowledge into a coded program for the development of the ES. Some of the AI tools (knowledge representation techniques) used alone or in combinations in the development of an ES include decision trees, object-attribute-value (OAV) triplets, rules (*if-then-because* statements) with forward and/or backward chaining, fuzzy logic, GA, case-based reasoning, and ANNs. A successful ES is usually developed by combining more than one AI technique.

Testing the Modules and Development of the Prototype

Case studies with known results are used to test the ability of the rules, databases, and programming to perform properly.

Implementation, Testing, and Troubleshooting of the Final Program
Case studies as well as untested materials and parameters are used to verify the proper operation of the program and to troubleshoot any additional problems identified.

Training of Users
A user acceptance questionnaire is used during the implementation of the program.

Maintenance and Upgrade of the Program
Depending on the availability of the new knowledge and/or the data in the field of a particular ES, an upgrade may be needed to ensure that the ES will evolve continuously to overcome new challenges concerning that specific project or problems.

Critical Issues Concerning the Verification and Validation of an Expert System
Verification of an ES determines whether the system is developed according to its specifications. Validation of an ES determines whether the system meets the purpose for which it was intended. Very critical differences exist between an ES and conventional systems in terms of V&V. An ES is both a piece of software and a domain model, and there may not be a unique, correct answer to a problem given to an ES. An ES can adapt itself by modifying its behavior in relation to changes in its internal representation of the environment.

An ES should be considered correct when it is complete, consistent, and satisfies the requirements that express expert knowledge about how the system should behave. If a system has hundreds of rules, however, it may require thousands of distinct decision paths, and this makes the aspect of correctness hard to establish. This is not, of course, a problem in a conventional programming technique.

These differences between the AI and conventional programming tools provide flexibility and special capabilities to an ES, but these differences also make the use of traditional V&V of an ES difficult. This is one of the problems slowing the development and acceptance of ESs in a regulated industry like pharmaceuticals. Experts do not agree on how to accomplish the V&V of ESs. One of the impediments to a successful V&V effort for ESs is the nature of ESs themselves. They are often used for working with incomplete and uncertain information or ill-structured situations. Because the ES specifications often do not provide precise criteria against which to test, there is a problem in verifying and validating them according to the definitions. This is unavoidable. If there are precise enough specifications for a system, there would not be any need to use an AI tool to develop the system, and a conventional programming language would be sufficient for the development of a piece of software for that system.

In reality, the first part of V&V, that is, verification of an ES, is not so difficult to establish because it is possible, and also highly recommended, to build small modules (sub-ESs) for each problem within a system. This is a significant help to the verification process of the whole system. This is true even if the ES is developed by combining more than one system.

The main problem is the second part of V&V, that is, validation. ESs will make a recommendation on the basis of the domain knowledge. If the domain knowledge is inaccurate, then the recommendation of the ES will naturally be inaccurate. How can someone validate the correctness of knowledge provided by domain expert, or if two domain experts have conflicting views over a problem-solving process, who will decide which is correct?

FDA's requirements for the submission of the software code can also add additional burden to the software validation of an ES. This is a serious obstacle because only a few AI tool providers and ES developers will be willing to share the code. As some of the AI tools may cost more than tens of thousands of dollars, no one could blame the software providers for not wishing to share the code.

Expert System Components

An ES contains three basic components, a knowledge base, a working memory, and an inference engine, as described below. These components can be found in many types of AI programs including decision trees, ANNs, GAs, and fuzzy logic. In addition, many of the

AI tools have an explanation facility providing the reason for the decision or recommendation of the ES.

Knowledge Base
The knowledge base contains the domain knowledge, the information pertinent to the field or problem. The domain knowledge can be acquired from literature and/or experts in the field and is in an electronic form that can be searched and updated easily. The knowledge base is similar to human long-term memory or experience.

One typical way of representing the knowledge in an ES is the rules. In its very basic form, a rule is an *if/then* structure that logically relates information contained in the *if* part to the other information contained in the *then* part. Some derivations of such a structure could also include *else* and/or *because* parts as well.

For example, the following rule represents the knowledge for the selection of a plasticizer to be used with a film-forming polymer:

if
The selected polymer is HPMC only.
and
There is no regulatory restriction for the use of PEG 400 in that country.
then
Recommend PEG 400.
because
PEG 400 is compatible with HPMC and it is efficient in its functionality.

Working Memory
The working memory contains the facts about the problem discovered during the problem-solving session. This component is similar to human short-term memory or current experience. Knowledge in the working memory can be inferred by the system, or it can be obtained by user input. Knowledge inferred by the system is obtained by matching user input with knowledge in the knowledge base to produce new facts.

Inference Engine
The inference engine is the component that models the human reasoning process. It matches facts in the working memory with domain knowledge in the knowledge base and draws a conclusion. It works by searching the database for a match between its contents and the information in the working memory. If a match is found, the conclusion from the match is added to the working memory and the inference engine continues to scan the database for additional matches.

Explanation Facility
A unique feature of an ES is its ability to explain the reasoning used to reach a conclusion. The following part of the example rule given above represents the explanation facility of the ES.

because
PEG 400 is compatible with HPMC, and it is efficient in its functionality.

Because an ES can explain why user input was requested or how a conclusion was reached, the system developer can use this component to uncover errors in the system's knowledge and the user can benefit from the transparency provided into the system's reasoning.

Knowledge Representation

There are a number of techniques that represent the knowledge (3,5–9) including, but not limited to,

OAV triplets,
semantic networks,
frames,

rule-based systems,
fuzzy logic,
ANNS,
GA, and
others: decision trees, hybrid systems (e.g., neurofuzzy systems), case-based reasoning, etc.

These techniques will be briefly described in the following sections. The most successful ES applications integrate more than one technique. For example, the rule-based systems are very good in providing the reasoning for how and why they reach a decision, but they are not best in automated learning (without updating their knowledge base) or recognizing patterns in large amount of data. This gap can be filled by integrating ANNs, which are very powerful in automated learning, although they lack in providing the justification for their predictions. Therefore, combining these two techniques can bring the strength of both approaches while eliminating their weaknesses.

Object-Attribute-Value Triplets

OAV triplets provide a particularly convenient way to represent certain facts within a knowledge base. Each OAV triplet is concerned with some specific (conceptual) entity or (physical) object. For example, our object of interest may be a granule (particle). Associated with every object is a set of attributes. Using the granule as an example (i.e., object), some of the attributes include the following: particle size, particle shape, particle density, particle porosity, surface roughness, moisture content, etc.

For each attribute, there is an associate value, or set of values. For example, in the granule example, the particle size attribute can have the values of large, small, fine, etc. Please note that values could be numerical as well.

Most of OAV triplet systems have also confidence factor associated with each specific triplet. Confidence factors, or certainty factors, refer to a numerical weight given to a fact or a relationship to indicate the confidence one has in that fact or relationship (Fig. 1). There are two kinds of confidence: "expert confidence" (the confidence that an expert feels when suggesting a rule) and "user confidence" (the confidence that a user feels when answering a question).

In a typical ES programming language, there are several ways of handling the uncertain data such as confirmatory (*yes*/*no*) system, numerical range (−1 to 1, 0 to 10, −100 to 100, etc.), systems, increment/decrement system, custom formula systems, and fuzzy logic. In many instances, the user may have to answer a question to determine the confidence factor. In the numerical approach, this is achieved by asking the trueness (definitely false, almost definitely false, probably false, unknown, probably true, almost definitely true, and definitely true) or sureness of a fact or value (Fig. 2). The ES inference engine then converts the answer to a numerical value that computers understand.

Semantic Networks

Semantic networks may be thought of as a network that is composed of multiple OAV triplets in network and characterizes their interrelationships. An advantage of this method is its flexibility to add new objects whenever needed.

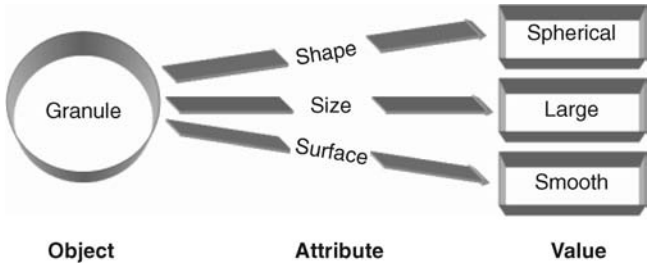


Figure 1 An example for an object-attribute-value triplet fuzzy variables, shape, size, and surface.

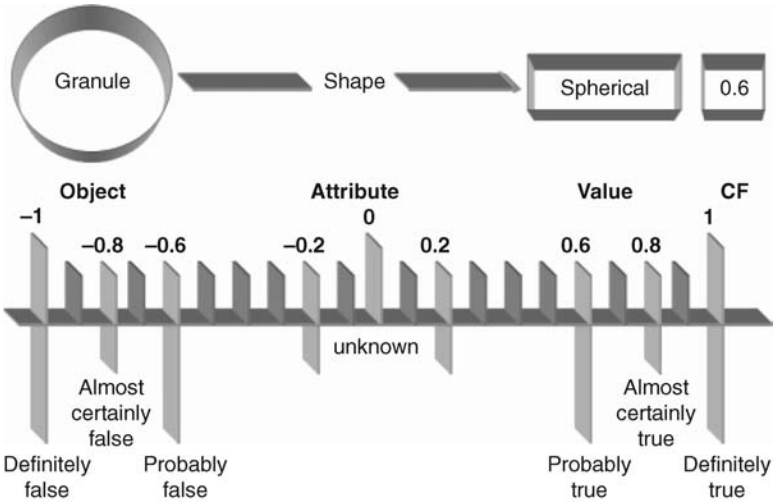


Figure 2 An example for a object-attribute-value triplet with confidence factors.

Table 1 Examples of Fuzzy Variables with Typical Values

Fuzzy variables	Typical values
Size	Fine, small, large, coarse
Shape	Oval, spherical, needle
Temperature	Hot, warm, cold
Tablet strength	Hard, soft
Pressure	High, low

Frames

A frame contains an object plus slots for any and all information related to the object. The contents of slots are typically the attributes, and the attribute values, of a particular object. Therefore, a frame is a natural extension of the semantic networks.

Fuzzy Logic

Fuzzy logic is mainly concerned with quantifying and reasoning about vague or fuzzy terms that appear in our daily lives. In fuzzy logic, these terms are referred to as linguistic variables or fuzzy variables. Some examples of fuzzy variables that are encountered in pharmaceutical applications are given in Table 1.

Fuzzy sets. Classical set theory establishes systematic relation among objects within a set as well as between elements of various sets. A set is a collection of any number of definite, well-distinguished objects, called the elements of the set that share common properties. Thus, an object may either belong to the set or be completely excluded. In other words, if A is a set and x is an element to the set, then x belongs to A, if and only if x satisfies all the membership requirements if A, otherwise, x does not belong to A.

Fuzzy set theory differs from classical set theory in one critical aspect. An element can belong to the fuzzy set, be completely excluded from the fuzzy set, or can belong to the fuzzy set to any intermediate degree between these two extremes. The extent to which an element belongs to a given fuzzy set is called grade of membership or degree of membership. It can be said, therefore, that classical set theory is a special case of fuzzy sets.

Fuzzy sets can be obtained to reflect the general opinion of the scientists or experts in the files, for example, in Figure 3, where fuzzy sets are shown in a piecewise linear form for the issues of three different categories (small, medium, and large) of the size of granule(s). In this

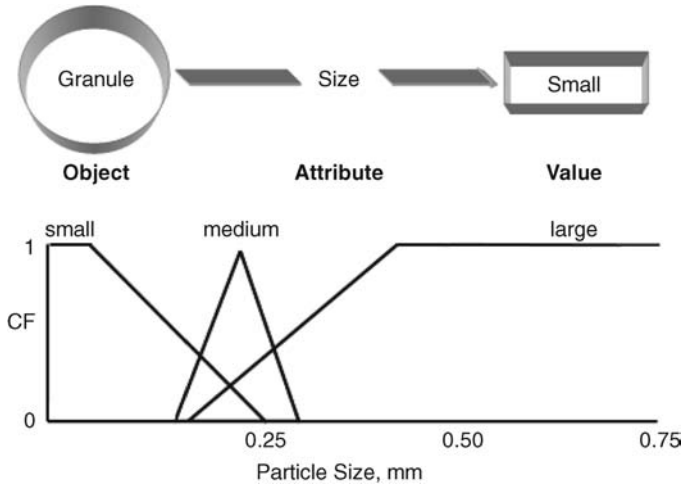


Figure 3 An example for a fuzzy set with confidence factors. Fuzzy variables, particle size; fuzzy values, small, medium, and large.

fuzzy subset, a granule particle with the size of 0.25 mm is a member of medium size with a membership value of about 1, and at the same time a member of small and large sizes with a value of about 0.15 and 0.25, respectively.

Rule-Based Systems

The most common way of representing knowledge is found in rule-based systems, which employ rules to represent the experts' knowledge. Such rules are typically of *if-then* variety. However, in some instances, this is extended to include *if-then-else* or *if-then-else-because* type or rules. In rule-based system, the uncertainty of the knowledge is handled using the method of confidence factors, as described above in the OAV triplets.

In the rule-based ESs, there are different ways of executing the rules. Backward chaining is by far the most common strategy used in the simple rule-based systems, and it is a term used to describe running the rules in a "goal-driven" way. A "goal" is an attribute for which the ES tries to establish a value. In backward chaining, if a piece of information is needed, the program will automatically check all the rules to see if there is a rule that could provide the needed information. The program (inference engine) will then "chain" to this rule before completing the first rule. This new rule may require information that can be found in yet another rule. The program will then again automatically test this new rule. The logic of why the information is needed goes backward through the chain of rules.

Forward chaining is a "data-driven" way to run the rules. In backward chaining, there is always a "goal" to be satisfied and a specific reason why rules are tested. In pure chaining, rules are simply tested in the order they occur on the basis of available data. If information is needed, other rules are *not* invoked. Instead, the user is asked for information. Consequently, forward chaining systems are dependent on the order of the rules. However, since time is not spent determining whether the information can be derived, forward chaining is much faster.

In a control by hybrid backward and forward chaining, the basic approach is data driven, but information needed by rules are derived through backward chaining.

Another technique is to divide an ES to subsets of rules and run some in forward chaining and some in backward chaining.

Artificial Neural Networks

ANNs can be defined as machine-based computational techniques that attempt to simulate some of the neurological processing ability of the human brain. In the human brain, neurons are the information carriers. In the same way, ANNs are composed of interconnected simulated neurons capable of pattern recognition or data analysis. Processing of the data using pattern recognition produces classification of the data, while data analysis produces numerical output. One of the most powerful characteristics of ANNs is the ability to find complex and

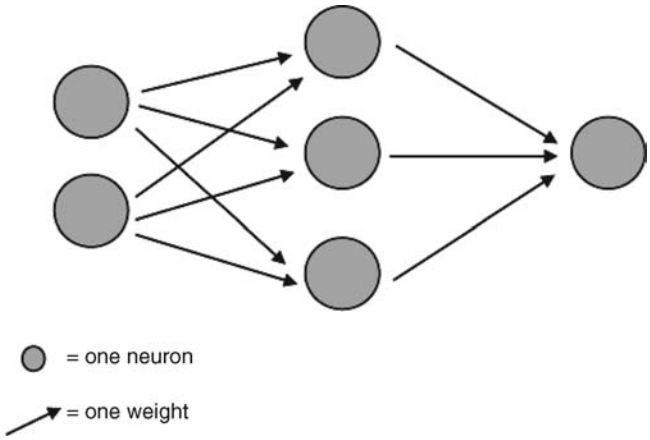


Figure 4 Neuron model.

latent patterns in the information being processed. Unlike most statistical experimental design, analysis of data using ANN does not require a specific number of experiments. Also, neural networks can generate hypotheses that can be tested by other scientific methods, and the outputs of one network can become the inputs to a subsequent network.

Artificial neural network elements. ANNs can be represented by a neuron model like the one found in Figure 4. As seen in this model, an ANN is composed of interconnected processing elements (PE) or neurons. The interconnections represent weights or weighing factors applied to the input values of the neuron as the information is passed forward through the network. These weights are sometimes referred to as synaptic weights since the interconnections are similar to the synapses of the human brain. Output values from each neuron are passed forward to the next layer through its interconnections or used as part of the final output of the network. The architecture of a network is defined by the number of layers in the network, the number of neurons in each layer, the configuration of their interconnections, and the way in which the weights of the interconnections are calculated.

Network types. Generally, there are three basic types of neural networks, feed-forward, feedback, and self-organizing. The network type to be utilized depends on the task to be accomplished. The following paragraphs will describe the network architectures and types of input data suitable for each network type.

Feed-forward networks Feed-forward networks, also called error backpropagation or backprop networks, contain the basic network components described in the neuron model. A feed-forward network is designed by defining its number of layers and the number of neurons in each layer. The number of neurons in the input and output layers is equal to the number of independent and dependent variables, respectively. The input layer serves as a distribution point for the data to the first hidden layer and can only scale the data, not calculate weighting factors. The purpose of scaling the data is to normalize it to a constant numerical range, such as 0 to 1 or -1 to $+1$. Scaling can be performed using linear or nonlinear scaling functions. The number of hidden layers is based on personal preference and rules of thumb. The purpose of the hidden layers is to provide a balance between network accuracy and network generalization. A higher number of hidden layers lead to a narrow, accurate network with a decreased ability to predict outside the boundaries of its original data. Fewer hidden layers will produce a more generalized robust network but may smooth the curve between the data points too much. The balance required between network accuracy and generalization depends on the purpose of the network.

Once the network is designed, it is ready to be trained. Training is the process of tuning the synaptic weights to minimize the difference between the actual output and the network output values. The next step is the error backpropagation step or learning step. Learning in this

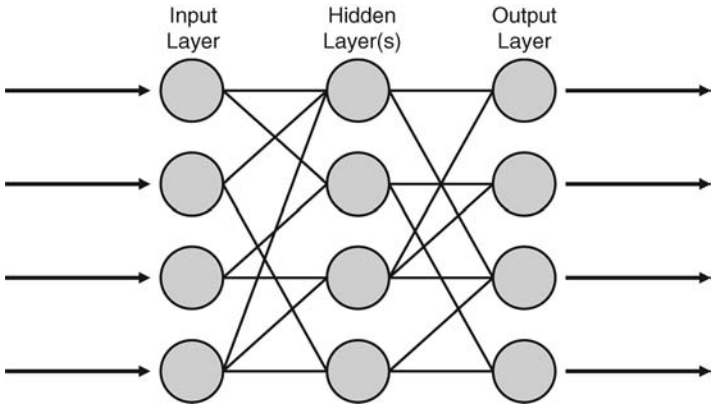


Figure 5 An example for feed-forward networks.

context does not imply the human qualities of understanding, consciousness, or intelligence. Instead, it simply implies the use of data for tuning a set of parameters or, in this case, the tuning of the synaptic weights. Once the network training is complete, the network does not store or refer to the training data. Instead, the trained network is an independent summary of the data. With the weights established by training, the network is capable of producing outputs for input data not originally contained in the training data set. The use of a data set to train a network is called supervised learning and requires that the output data corresponding to the input data be available during training (Fig. 5).

Feedback networks Feedback networks (also called recurrent networks) are similar in structure to the feed-forward networks. The difference between the two types is an additional layer. This layer contains one layer's information from the previous training pass. This extra layer, or context layer, allows the network to see knowledge about previous inputs and is sometimes called the network's long-term memory. The result of this additional layer is that the network responds to the same input differently at different times depending on the previous patterns. The result is that the sequence of the data is as important as the data itself. This use of previous data allows the network to learn time-dependent data such as time series data and financial market data. Recurrent networks are trained the same way as standard feed-forward backpropagation networks except that the patterns must always be presented in the same order.

Classification networks The third kind of network is the classification network or self-organizing network. This network type is able to separate the data into a specified number of categories. It is always unsupervised, which means that the network has the ability to learn without being shown correct outputs in sample patterns. The network architecture contains only two layers, input and output. The number of neurons in the input layer is defined by the data, and output layer has one neuron for each possible output category. During training, the data is presented to the input layer, propagated to the output layer resulting in one neuron providing an active response or being a "winner." The network adjusts the weights for the neurons in a "neighborhood" around the winning neuron on the basis of a two-dimensional feature map whose cells form a rectangular grid. During training, the locations of the responses become ordered as if some meaningful coordinate system for different input features were being created over the network. The neighborhood size is variable. It starts large and decreases with learning until the neighborhood approaches zero and only the winning neuron's weights are changed. The training process is repeated for all patterns for a number of predetermined epochs. At the end of the training, each neighborhood becomes an output classification.

Genetic Algorithms

GAs are mathematical tools that solve optimization problems. This type of problem is usually composed of a number of variables that control a process or outcome, and a formula or algorithm, which combines these variables to fully model the process. The goal of the problem is then to find the values of the variables, which optimize the model in some way, usually by minimizing or maximizing one of the dependent variables. While there are many mathematical methods that can solve optimization problems, these traditional methods tend to break down when the problem is more complex. Examples of complex problems include combinatorial problems or problems where the fitness function is not a smooth, continuous mathematical formula, such as a neural network function.

GAs optimize these complex problems using the methods of evolution, specifically survival of the fittest. Much of the terminology used to describe GAs is partially based on concepts from biology; however, some terms may have different names depending on the author. In this case, "survival of the fittest" means that the GA solves the problem by allowing the less fit individuals in the population to die and selectively breeding the most fit individuals, that is, those who solve the problem best.

The use of GA in combination with neural networks for the optimization of process parameters has been investigated by Cook et al. In this example, a neural network model was developed to predict the effect of several process operating parameters and conditions on the internal bond strength of particleboard. A GA was applied to this neural network model to determine the process parameters that would result in the optimal strength for a given set of operating conditions. This ANN GA system was successful in predicting the process parameters, which allowed the manufacturer to achieve optimal levels of board strength on the basis of the current, variable operating conditions. The ANN portion was used to model the process parameters, while the GA utilized this model to obtain the optimal processing parameters under actual manufacturing conditions.

Other Methods of Knowledge Representation

Decision trees. A decision tree takes as input an object or situation described by a set of properties, and outputs a yes/no decision. Decision trees, therefore, represent Boolean functions. Functions with a larger range of outputs can also be represented. Decision trees are considered to be auxiliary tools in ES development and are usually incorporated with other systems.

Neurofuzzy logic. In the field of AI, neurofuzzy refers to combinations of ANNs and fuzzy logic. Neurofuzzy hybridization results in a hybrid intelligent system that synergizes these two techniques by combining the humanlike reasoning style of fuzzy systems with the learning and connectionist structure of neural networks.

Case-based reasoning. In case-based reasoning, to solve a problem, the inference engine searches and finds a similar problem solved in the past and adapts the old solution to solve the new problem. The system retrieves, reuses, revises, and retains the solutions and provides the basis for almost limitless applications in domain where there are many exceptions to rules and where the problems are not fully understood but there is a database of past examples.

AN EXAMPLE TO EXPERT SYSTEMS: SPRAYEX, A SPRAY-DRYING EXPERT SYSTEM

The example of ES, SPRAYex, was developed by PTI, Inc (10). Briefly, the current version of the system evaluates the spray ability of a given substance alone with no additives involved. This function is implemented using decision trees, rules, and fuzzy logic. Another function of the system is to predict the process conditions to obtain a product with the desired properties in terms of particle size, moisture content, and bulk density by utilizing a number of trained ANNs simultaneously. The system also has a mathematical modeling predicting the interactions between numerous process variables. Finally, the system has a comprehensive database containing material characteristics of six model materials and process conditions for

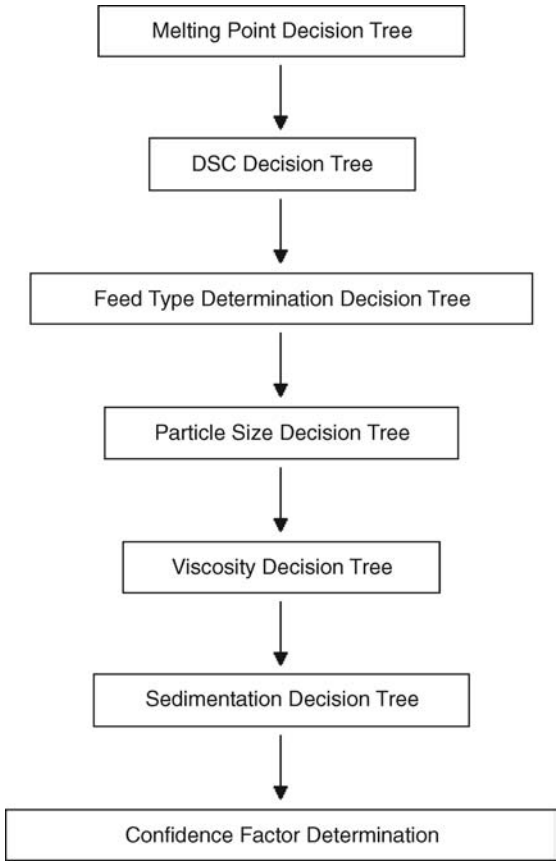


Figure 6 Decision tree sequence.

over 150 spray-drying experiments. The following sections describe the development strategies or functions of the system in more detail.

Spray-Drying Feasibility Decision Trees

The user interface of this system helps the user to input material characteristics and makes a decision by incorporating a number of decision trees to determine the feasibility of a material to be spray dried (11).

The sequence of the execution of the decision trees (Fig. 6) was chosen on the basis of the order required to prepare the feed. First, the material is evaluated on the basis of its melting point. Next, the feed type feasibility is determined on the basis of the DSC scans obtained. Once the feed is determined, it is screened for particle size, viscosity, and sedimentation potential. The analysis of the physical characterization data for the selected model materials using these decision trees resulted in the generation of a confidence factor that represented the ability of the proposed material to be spray dried as a percentage value. These confidence factors were then integrated into a decision-making process. In addition, the generated confidence factors were also stored as part of the database for future reference.

An example of such sequences was based on the melting points (Figs. 7 and 8). Melting point data provide information about the ability of the material to withstand the inlet air temperature of the spray-drying process. If the melting point is low, the material may only be able to be processed in a countercurrent configuration, or it may not be able to be spray dried. It is well known that the minimal acceptable melting point for a material to be processed in a spray dryer is dependent on the spray configuration of the dryer. The melting point decision tree in Figure 7 incorporates a critical melting point to represent this concept. In this tree, materials having a melting point higher than the critical temperature have a confidence level

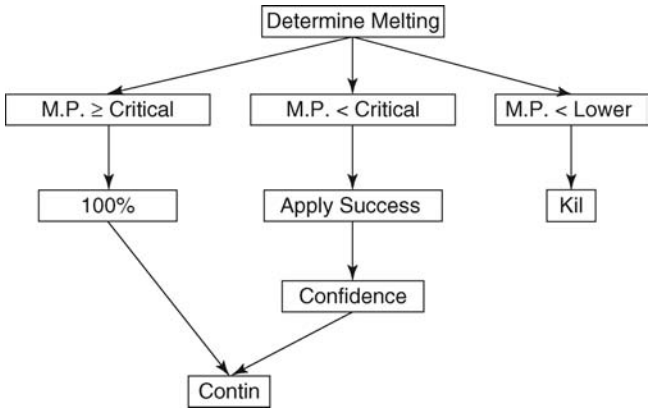


Figure 7 Melting point decision tree.

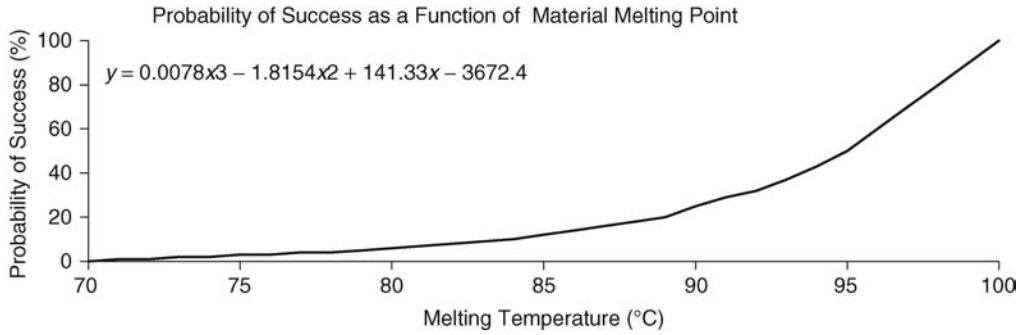


Figure 8 Melting point success function.

of 100% for this variable, which means that the material is 100% feasible for the spray-drying process in terms of melting point. The confidence level for a material with a melting point lower than the critical temperature is determined using an equation representing the probability of success. This equation and a graphical representation of the function are shown in Figure 8. This probability, which increases using a second-order function with increasing melting point, is employed because there is no single melting point above which the material is 100% feasible and below which the material is 100% unfeasible. If the melting point is less than the critical temperature, a confidence factor is determined using this equation.

The critical temperature is designed to be flexible on the basis of dryer configuration. Since the only configuration used during this experimentation was cocurrent product airflow, a single critical temperature was employed. In the cocurrent configuration, the inlet air comes into direct contact with the feed at the point of atomization and flows in the same direction as the feed. If a material that is atomized in the feed melts at a temperature lower than the vaporization temperature of the solvent, then melting may begin to occur in the droplet during evaporation. While this may not always be the case, the general feasibility potential for a material with a melting point under the vaporization temperature is less than 100% for the cocurrent configuration. Since water was the only solvent employed during the experimentation, a critical temperature of 100°C was chosen.

In summary, several critical physical characterization factors of each model raw material were selected for inclusion in the feasibility prediction process. These factors included melting point, solubility, maximum particle size, sedimentation potential, and viscosity. Each of these factors had a direct effect on the ability of the material to be spray dried that could be expressed in a decision tree format.

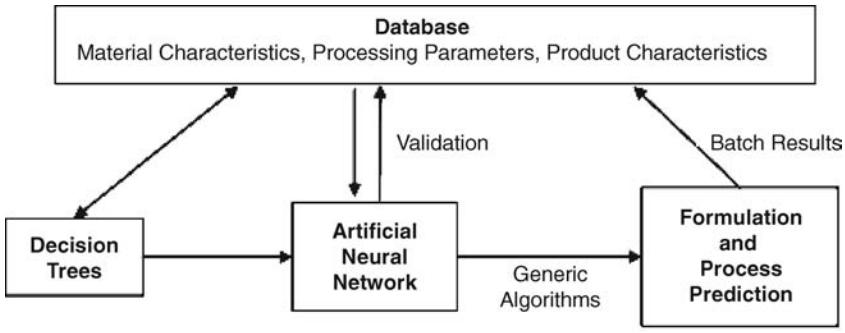


Figure 9 Predictive system diagram.

Prediction of Optimum Spray-Drying Conditions

Using the formulation and process data compiled in this spreadsheet, a number of ANN architectures were evaluated for prediction capability. Evaluation criteria included ability to fit the data, ability to weigh contributing factors, ability to predict outside the model, and tendency toward memorization. Three final networks were constructed for each nozzle configuration. Each network was trained to predict one of the physical characteristics of the spray-dried powder, moisture content, bulk density, and mean particle size. These networks were validated using data previously unseen by the network. These final networks were then converted into predictive functions using GAs and were optimized to values input by the user. This optimization process allowed the prediction of the process parameters required to produce a spray-dried product having user-specified values for moisture content, bulk density, and mean particle size. This optimization also utilizes additional constant parameters such as material characteristics and spray dryer capabilities.

The culmination of this work is a predictive system that is illustrated in Figure 9. This system simultaneously optimizes three neural networks permitting the prediction of formulation and process variables for the spray-drying process (Fig. 10). An example for the trained networks used in the backbone of this system (for the mean particle size prediction of the spray-dried product) is given in Table 2 and Figure 11.

Mathematical Modeling and Database

The example of spray-drying ES also has a mathematical modeling predicting the interactions amongst several processing variables according to classical thermodynamics. This model contains equations based on drying principles that link key attributes from psyschrometric charts to spray drying process variables. While this same task can be achieved without the aid of mathematical modeling, these models provide process settings in a user-friendly format without the tedious calculations required for converting psychrometric terms such as adiabatic saturation temperature, wet bulb temperature, dry bulb temperature, and humidity ratio into practical terms like inlet temperature and feed spray rate. An example display in Figure 12 shows which parameters are being affected if the inlet temperature changes.

Finally, another component of this system is database, which contained information on raw materials (melting points, glass transition temperatures, DSC data, viscosity, and solubility, etc.), equipment (brand name, dimensions, nozzle types, air flow, etc.), and processing conditions (atomization parameters, inlet/outlet air temperatures, feed parameters, pump parameters, nozzle parameters, etc.). Figure 13 is an example of display for a spray-drying experiment (for lactose in this example).

PHARMACEUTICAL APPLICATIONS OF EXPERT SYSTEMS

The applicability of ESs to the pharmaceutical industry has been reviewed by Klinger (12). The review contains definitions and explanations of AI and ESs as well as information about the components and available programming languages. Possible applications for the pharmaceutical industry outlined include pathological evaluation, molecular modeling, biological activity screening, statistical design/analysis/interpretation, manufacturing process/control, automated QA monitoring, drug interaction predictions, production scheduling, and marketing/sales plans.

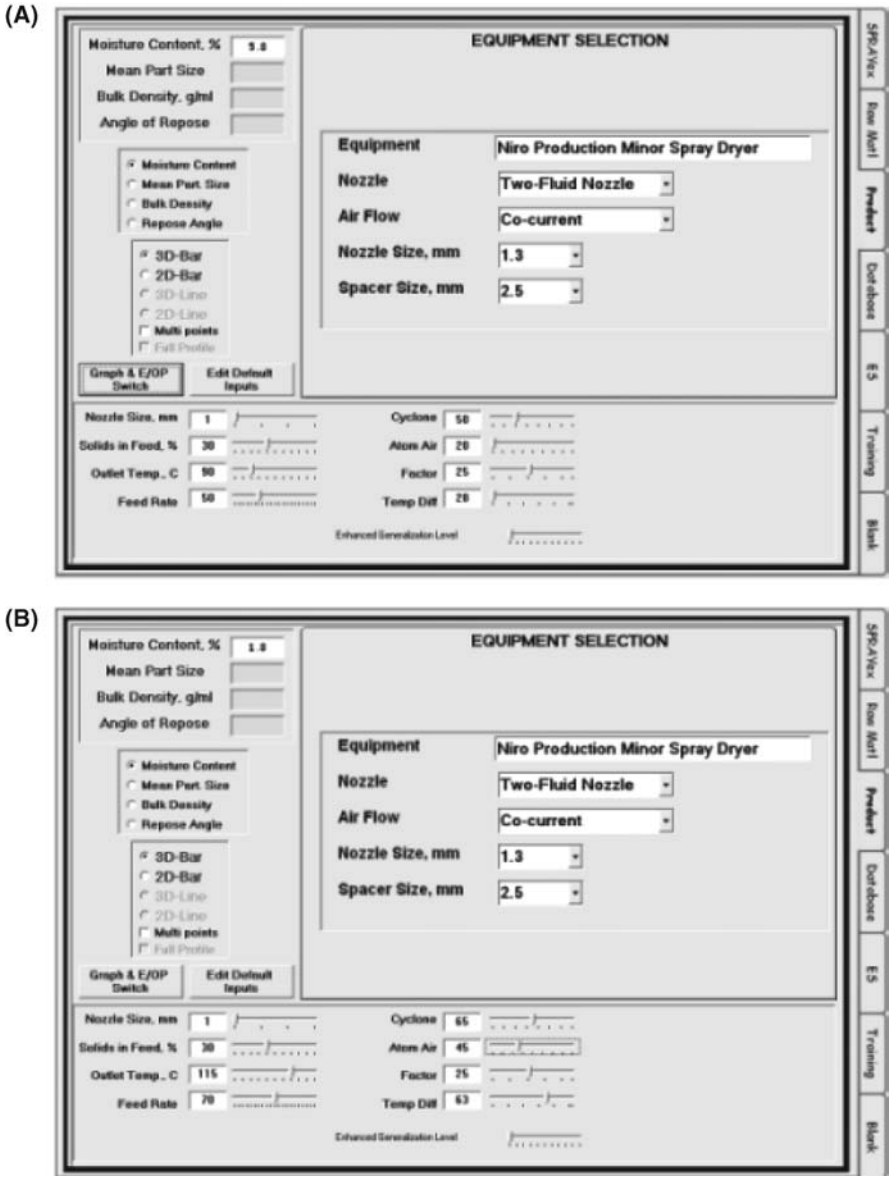


Figure 10 An example for the ANNs-aided prediction of moisture content and optimization of process conditions. Process conditions changing the moisture content of the spray-dried product from (**A**) 5.5% to (**B**) 1.8%.

Table 2 Final Network Statistics for Mean Particle Size Using a Rotary Nozzle

	Training set				Validation set			
	R^2	Corr. Coeff. R	Avg. Abs. Error	Max Abs. Error	R^2	Corr. Coeff. R	Avg. Abs. Err.	Max Abs. Err.
Units	—	—	(μm)	(μm)	—	—	(μm)	(μm)
Final Rotary Mean Particle Size Network	0.9437	0.9715	2.044	19.565	0.1996	0.9645	5.632	11.501

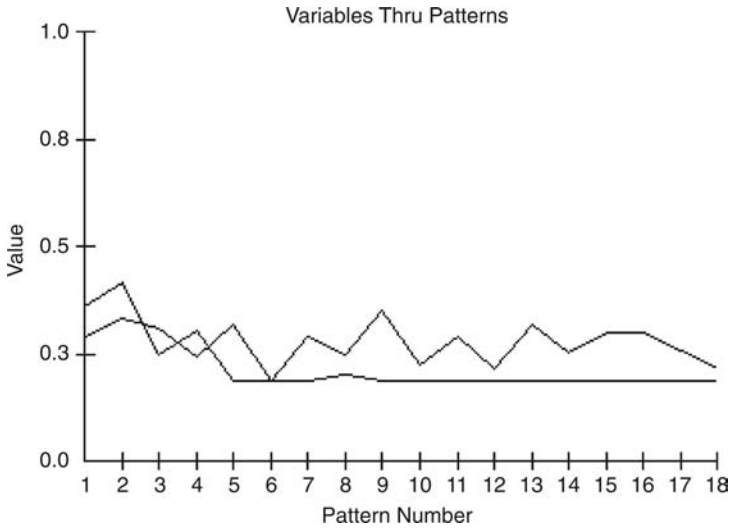


Figure 11 Actual and Predicted Mean Particle Size Values for Validation Data Set Using Rotary Nozzle Configuration.

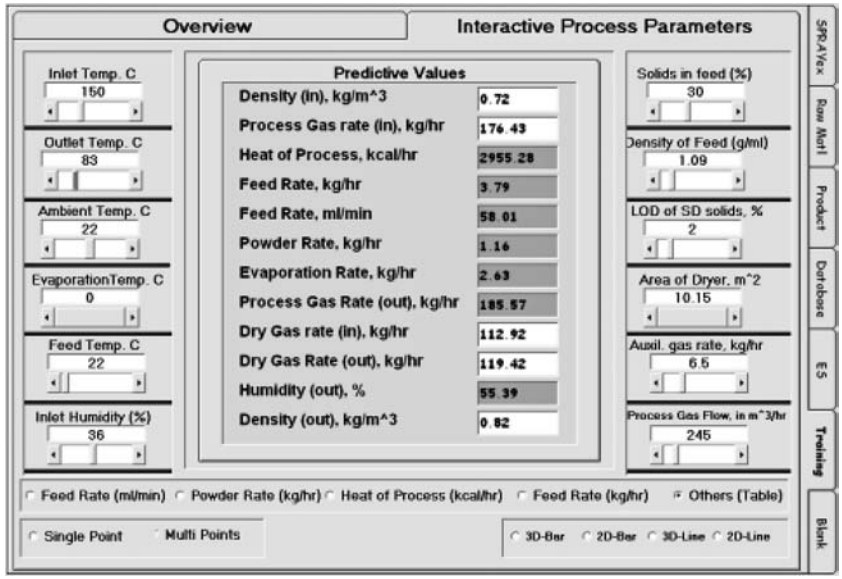


Figure 12 Mathematical modeling showing the processing variables (*dark gray background*) affected by the changes in outlet temperature.

The specific application of ESs to manufacturing process and control was addressed in more detail by Murray (13). The article begins with an outline for choosing processes which manufacturing processes would benefit most from in an ES application. The application described in additional detail is a rule-based ES for the troubleshooting and diagnostics of a high-speed tablet press that was in the process of being developed and some of the experiences resulting from this development.

Another formulation ES was described in the literature by Rowe et. al. (14). This ES was based on a decision tree and was used for the development of parenteral formulations. The decision trees utilized by the system were described in detail. Additional detail about the software used and the advantages for this formulation tool were also included.

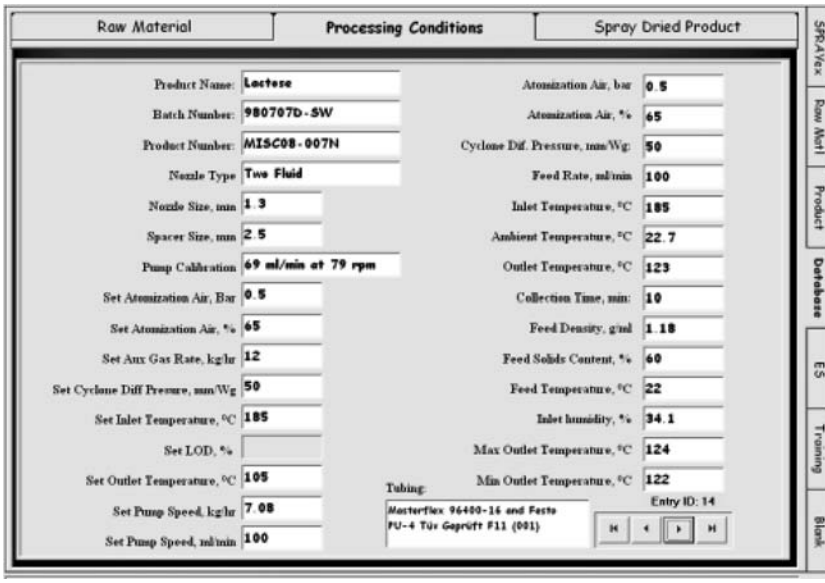


Figure 13 Database component showing the processing conditions for spray drying lactose.

Bateman et. al. (15) described an ES for the development of powder formulations for hard gelatin capsules. A team process incorporating formulators and software engineers was utilized for the acquisition of the information for the knowledge base. From this process, the rules for the knowledge base were discovered and evolved using a process of "iterative refinement." The system also required an excipient database containing excipient physical properties.

A comprehensive review of the commercially available software for use in developing intelligent systems was provided by Rowe (16). Rowe divided the software into five types describing the applications, advantages, and disadvantages of each type as well as diagramming the operation processes. Software tool names and supplier information are also provided.

Within the pharmaceutical literature, ANNs have been applied to several areas. These include clinical pharmacy, drug design (QSAR), product development and optimization, protein drug delivery, biopharmaceutics, and pharmacokinetics.

Hussain et al. describe an ES for the prediction of the in vitro drug release profile from hydrophilic matrix tablets (17). The ES is based on ANN software that is defined as the main component of computer-aided formulation design (CAFD). The purposes outlined for CAFD include the prediction of formulation/process conditions, the simulation of studies, the storage of information for training purposes, and the reduction of time and cost in the product development process. The specific ES described in this work was built using data from the release profiles of eleven active ingredients and three polymer grades of hydroxypropyl cellulose combined at several drug to polymer ratios. The developed system was able to differentiate between the active ingredient salt types, the polymer grades and the drug to polymer ratios and successfully predicted the release profiles of most drugs within the ranges of the training sets. Additional components such as additional formulation variables, process conditions, and performance tests were recommended to make CAFD a useful system.

Neural networks have also been applied to the process of fluidized bed granulation. Watano et al. (18) have specifically applied neural networks to fluid-bed granulation scale-up. A three-layer, backpropagation network was used with the input variables being vessel diameter, moisture content, fluidization air, and agitator rotational speed. The number of neurons in the output layer was also four, and the following outputs were generated: granule mass median diameter, geometric standard deviation, apparent density, and shape factor. Various numbers of middle layer units were tested to determine the optimal number on the basis of the behavior of the error convergence during learning. Evaluation of the final error after 1000 epochs showed the optimal number of middle layer units to be four. The data used

to train the network was obtained from three sizes of laboratory-scale granulators. The trained network was used to predict the granule characteristics of material produced using commercial scale equipment. These granulations were produced, and the actual granule data was compared with the predicted values, and an excellent correlation was observed. Additional networks using the same architecture were also trained by the authors using fewer data points in the training set. From this investigation, it was shown that the training data could be decreased while retaining good accuracy. However, the authors noted that when the number of training sets was less than 13, the accuracy of the predictions decreased.

Murtoniemi et al. have also used ANN to model the fluid-bed granulation process (19). In their work, three input variables, inlet air temperature, atomizing air pressure, and binder solution amount, were varied at three levels. The output variables, mean granule size, and granule friability were measured. This training data was processed using a modified backpropagation algorithm in a basic feed-forward architecture containing one or two hidden layers. The number of neurons in each hidden layer was varied from 3 to 15. In all, 36 networks were trained. Evaluation of the training data revealed that the number of hidden neurons did not greatly affect the average error except when the networks were small and contained only three or four hidden neurons. The data produced by the optimal network was also compared with the data calculated using a regression model. For both outputs, the ANN data was closer to the experimental values than the regression data. In a second article by the same authors, the topology and the training end point of this network were investigated further (20). The purpose of this study was to optimize the ability of the ANN to generalize by varying the number of hidden layer neurons and the training end point. The results again showed that the number of hidden neurons did not affect the ability of the network to generalize. However, the training end point had a significant effect on generalization and on the number of iteration epochs required.

The prediction of in vitro dissolution as a function of formulation variables was also the goal of the work performed by Ebube et al. (21). This study demonstrated the importance of optimizing the number of hidden layers and the number of iterations or epochs. The developed network had two inputs, the level of polymers 1 and 2 and one output, the percentage dissolved in one hour. Optimization of the network resulted in three neurons for the hidden layer and an optimal number of iterations, which varied from 81 to 671 depending on the number of formulations in the training set. The authors also found that the network predicted data outside the training set less accurately than data bounded by the training set. However, the predictive capability of the network was improved using replicate input and output data.

Two reviews of neural network computing are published in the pharmaceutical literature. In a 1993 article, Erb comprehensively describes the backpropagation architecture by citing much of the original neural network literature as well as additional helpful books (22).

CONCLUSION

It is a highly complicated process to develop an ES to the full satisfaction of the users, domain experts, company, FDA, etc. However, none of these obstacles should discourage pharmaceutical scientists. On the contrary, despite all of these problems, the overwhelming advantages of ESs must encourage pharmaceutical scientists to learn more about them. Despite these advantages, ESs are not intended to take the place of formulation scientists. They must be considered as vital tools to be used by formulators for the rapid, cost-effective, and scientifically sound development of a dosage form as well as useful for training inexperienced scientists. In the same way that we cannot do much without computers today, we will not be able to do much without ESs in the future. Sooner or later, all of us will be happily using them. Those who use them sooner will enjoy being the pioneers in their fields. They will also have the personal satisfaction of contributing to pharmaceutical science by catching up with the rest of the world in the application of such useful tools.

REFERENCES

1. Çelik M. Catching up with expert systems. Pharm Technol 2001; 25(7):122–124.
2. Çelik M. The past, present and future of tableting technology. Drug Dev Ind Pharm 1996; 22(1):1–10.

3. Durkin J. Introductions to Expert Systems. Expert Systems Design and Development. Englewood Cliffs: Prentice Hall, 1994:1–25.
4. McCarthy J, Minsky M, Rochester N, et al. A proposal for the Dartmouth summer research project on artificial intelligence. 1955. Available at: http://www-formal.stanford.edu/jmc/history/dartmouth/dartmouth.html.
5. Harmon P, Sawyer B. Creating Expert Systems for Business and Industry. New York: John Wiley & Sons, Inc., 1990.
6. Ignizio JP. Introduction to Expert Systems: the Development and Implementation of Rule-Based Expert Systems: Mc Graw-Hill, Inc., 1991.
7. Schneider M, Kandl A, Langholz G, et al. Fuzzy Expert System Tools. Chichester: John Wiley & Sons, 1996.
8. Swingler K. Applying neural Networks: A Practical Guide. London: Academic Press, 1996.
9. Rowe C, Roberts RJ. Intelligent Software for Product Formulation. London: Taylor & Francis, 1998.
10. SPRAYex. Available at: http://www.pt-int.com/Sprayex.html.
11. Wendel SC. The prediction of spray drying formulations and processes for pharmaceutical powders. PhD Thesis. 2001.
12. Klinger DE. Expert systems in the pharmaceutical industry. Drug Inf J 1988; 22:249–258.
13. Murray FJ. The application of expert systems to pharmaceutical processing equipment. Pharm Technol 1989; 13(3):100–110.
14. Rowe RC, Wakerly MG, Roberts RJ, et al. Expert systems for parenteral development. PDA J Pharm Sci Technol 1995; 49:257–261.
15. Bateman SD, Verlin J, Russo M, et al. The development and validation of a capsule formulation knowledge-based system. Pharm Technol 1996; 20(3):174–184.
16. Rowe RC. Intelligent software systems for pharmaceutical product formulation. Pharm Technol 1997; 21(3):178–188.
17. Hussain AS, Shivanand P, Johnson RD. Application of neural computing in pharmaceutical development: computer aided formulation design. Drug Dev Ind Pharm 1994; 20(10):1739–1752.
18. Watano S, Takashima H, Miyanami K. Scale-up of agitation fluidized bed granulation by neural network. Chem Pharm Bull 1997; 45:1193–1197.
19. Murtoniemi E, Yliruusi J, Kinnunen P, et al. The advantages by the use of NN in modeling the fluidised bed granulation process. Int J Pharm 1994; 108:155–164.
20. Murtoniemi E, Merkku P, Kinnunen P, et al. Effect of NN topology and training end-point in modeling the fluidised bed granulation process. Int J Pharm 1994; 110:101–108.
21. Ebube NK, McCall T, Chen Y, et al. Relating formulation variables to in vitro dissolution using an ANN. Pharm Dev Technol 1997; 2(3):225–232.
22. Erb RJ. Introduction to backpropagation neural network computation. Pharm Res 1993; 10:165–170.

28 Regulatory Issues in Granulation: The Pharmaceutical Quality for the 21st Century—A Risk-Based Approach

Prasad Kanneganti
Genentech Singapore Pte Ltd., Tuas Baylink, Singapore

INTRODUCTION

The pharmaceutical industry is one of the most regulated consumer industries today. Concerned with the safety of its citizens, governments across the world have set up regulations that govern the manufacturing and distribution of finished pharmaceuticals for human consumption. Like the industry, the regulations are also evolving to meet current business needs and emerging technological developments. Current Good Manufacturing Practices (cGMPs) that were initially well established within the pharmaceutical industry in the United States are now widely used across the globe. Globalization of the pharmaceutical industry has taken place rapidly in recent times, fueled by mergers and acquisitions within the industry and also by economic, political, and regulatory drivers. Regulatory harmonization initiatives at the global and regional levels are making steady progress. In recent years, regulatory agencies in the United States and European Union have encouraged use of new technologies for manufacturing. We are seeing the start of a paradigm shift in how pharmaceutical processes are controlled and how product quality is managed.

PHARMACEUTICAL QUALITY MANAGEMENT

Quality management is that aspect of management function that establishes and implements the quality policy formally authorized by senior management. The fundamental elements of quality management are an appropriate infrastructure or quality system and systematic actions known as quality assurance taken to ensure adequate confidence that the product or service will satisfy established requirements for quality. Thus, quality assurance is a management tool covering all matters that individually or collectively influence the quality of a product. It incorporates cGMP as well as other factors such as product design and development. Quality control is a subset of cGMP and concerns mainly sampling, specifications, and testing of raw materials and finished pharmaceutical products. The concepts of quality assurance, cGMP, and quality control are thus interrelated aspects of quality management.

Current Good Manufacturing Practices

cGMP is that part of the quality assurance system that ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization provided by the regulatory agencies. The production of pharmaceutical products involves some risks, for example, cross-contamination, label mix-ups, etc., that cannot be prevented entirely through end product testing, and cGMPs diminish such risks. This quality assurance element is mandated by law around the world for the manufacturing, storage, and distribution of pharmaceuticals. Although the standards set by the U.S. Food and Drug Administration (FDA) (1,2) are well recognized as an industry benchmark, standards from other countries and regions are also well accepted (3,4).

One of the cGMP standards that is gaining worldwide recognition is that set up by the Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Inspection Cooperation Scheme (PIC Scheme) commonly known as PIC/S. The purpose of PIC/S is to facilitate the networking between participating authorities and the maintenance of mutual confidence, the exchange of information and experience in the field of GMP and related areas, and the mutual

training of GMP inspectors (5). PIC/S became operational in November 1995 when the PIC Scheme commenced operating in conjunction with PIC, which had already been operating since 1970. As of January 2009, PIC/S had 36 member countries/regulatory agencies spread over five continents.

In September 2004, the U.S. FDA issued final guidance on a significantly new initiative, Pharmaceutical cGMPs for the 21st Century (6). This initiative was aimed at modernizing FDA regulations to support the early adoption of new technological advances and state-of-the-art science by the pharmaceutical industry. In addition, industry was encouraged to implement an integrated quality system and a risk-based approach for managing production processes and quality assurance.

International Conference on Harmonization

The International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use is a project that brings together the regulatory authorities of Europe, Japan, and the United States and experts from the pharmaceutical industry in these regions to discuss scientific and technical aspects of product registration. With its secretariat in Geneva, Switzerland, ICH aims to achieve greater harmonization in the interpretation and application of technical guidelines and product registration requirements, thus avoiding unnecessary duplication of testing carried out during the R&D phase for new medicines (7).

Guidelines issued by ICH are very useful reference documents for both the industry and regulatory bodies. The topics for these guidelines are divided into four major categories, each with a specific topic code.

- Quality Topics (Q), for example, Stability Testing (Q1), Impurity Testing (Q3)
- Safety Topics (S), for example, Carcinogenicity Testing (S1), Genotoxicity Testing (S2)
- Efficacy Topics (E), for example, Dose Response Studies (E4), Good Clinical Practices (E6)
- Multidisciplinary Topics (M), for example, Medical Terminology (M1), The Common Technical Document (CTD) (M4)

There is no specific ICH guideline for granulation; however, guidelines such as the CTD highlight the requirements for specifications, testing, impurities, stability, and validation in drug product regulatory submissions. In view of the wide international acceptance of these guidelines, it would be prudent to check compliance with requirements specified in them while putting together documentation dossiers to support regulatory filings or technology transfers.

ISO 9000 Standards

The International Organization for Standardization (ISO) is the world's largest developer of standards. ISO's principal activity is the development of technical standards. These are very useful to the industry, regulatory bodies, trade officials, suppliers, and customers of products and services. With its Central Secretariat in Geneva, Switzerland, ISO coordinates a network of the national standard institutes of 161 countries (8). Each country is represented by one member that, unlike in the case of the United Nations, need not be a delegation of the national government.

ISO has gained wide acceptance internationally as a commonly understood baseline for quality, safety, and environment standards. It ensures fair play and facilitates cross-border trade. ISO standards are voluntary, and being a nongovernmental organization, it has no legal authority to enforce their implementation. This is an essential difference with cGMPs that have been legislated into law in several countries.

One of the most popular standards is the ISO 9000 family, which is a generic management system standard that has become an international reference for quality requirements in business-to-business dealings. The latest standard in this series is ISO 9001–2008, which provides a set of standardized requirements for a quality management system regardless of what the user organization does, its size, or whether it is in the private or public sector.

Several excipients used in drug product formulation may be common substances that are also used in the food and cosmetic industries. For manufacturers of such substances, if cGMP is not mandated by law, compliance with ISO 9000 is generally expected by pharmaceutical manufacturers as part of their supplier management program.

MANUFACTURING SCIENCE

The pharmaceutical industry today is facing many challenges. The cost of drug research has increased steeply, and at the same time, R&D productivity is waning. Patent expiry and loss of exclusivity are resulting in decreasing revenues. Manufacturers are thus being forced to improve efficiencies and reduce cost. This is affecting the way manufacturing is carried out, with greater emphasis on the use of science-based tools and quality risk management to improve operational performance and to focus on quality critical elements.

Manufacturing science encompasses knowledge about products and processes, technology used to manufacture and control these processes, and the underlying foundation of a robust quality system at the manufacturing site. This results in the manufacture of medicinal products in a reproducible manner and mitigates risk to the patient.

Regulatory Outlook

Dr Janet Woodcock, who is currently a U.S. FDA Director of Center for Drug Evaluation and Research (CDER), once stated, "Industry must reinvent itself and its relationship with FDA to deal with a future that promises to be very different from today. Archaic regulatory practices that have stifled innovation and made the industry inefficient cannot continue. Part of the problem was that we didn't know what influenced product quality. We treated everything same, every deviation was a threat to product quality but if your processes are under control and well understood, we can do things very differently." This is a clear indication to the industry to strive for process understanding on the basis of science and to unburden the organization on the basis of this understanding.

Another senior FDA official, Dr Mark McClellan, who was the former FDA Commissioner, once remarked, "Pharmaceutical companies must catch up with potato chip and soap flake manufacturers by modernizing operations and applying technology effectively." This remark has often been quoted in the media and at various conferences as a wake-up call to the industry to adopt new technologies and eliminate waste.

The FDA guidance on Pharmaceutical cGMPs for the 21st Century (6) encourages the use of manufacturing science as a basis for innovation and continuous improvement. Following this guidance, there commenced a period of sharing of knowledge between manufacturers and regulators and the application of regulatory processes proportional to the level of risk and applied manufacturing science demonstrated by a manufacturer.

Process Analytical Technology

In September 2004, alongside the guidance on Pharmaceutical cGMPs for the 21st Century, the FDA issued another significant guidance on Process Analytical Technology (PAT). This guidance (9) considers PAT to be a system for designing, analyzing, and controlling manufacturing through real-time measurement of critical quality and performance attributes of raw/in-process materials and processes, with the goal of ensuring final product quality. The goal of PAT is to enhance understanding and control of the manufacturing process.

Most pharmaceutical processes have traditionally been controlled on the basis of time-defined end points, for example, blending for 10 minutes. Such an approach does not always address variation in physical attributes such as particle size and shape for raw materials and differences arising during the process. The PAT toolkit consists of process analyzers, multivariate tools, process control tools, and continuous improvement and knowledge management tools. These tools can be used in combination for a single-unit operation or an entire manufacturing process and its quality assurance to gain a thorough understanding of the process. Process analyzers provide voluminous nondestructive test data gathered at-line, on-line, or in-line. Within the PAT framework, the completion of a process step, for example, granulation end point, is not a fixed time period but the achievement of the desired material attribute.

Process analyzers are well suited for granulation process equipment and can provide real-time data on critical process parameters (CPPs) and critical quality attributes (CQAs). Granulation end point measurements using transducers, motor current, torque, etc., have been standard fixtures on equipment used for pharmaceutical manufacturing for a long time. What has changed now is the data-gathering capability and the availability of statistical data analysis tools such as multivariate analysis that provide a *process signature* in real time.

The FDA's PAT team worked with the American Society for Testing and Materials (ASTM) (10) to establish the Technical Committee E55 on pharmaceutical application of PAT. This committee developed several guidances covering PAT terminology, system management, and system implementation/practice.

A more detailed discussion on PAT can be found in Chapter 29 of this book.

Quality Risk Management

The new paradigm shift in pharmaceutical manufacturing includes use of risk management and risk tools. What is risk? It is a combination of exposure and hazard. This is also sometimes referred to as probability and severity. What is the probability of a certain event such as a product failure due to equipment malfunction occurring, and when does it occur? What is the severity or impact to product quality and patient risk?

The ICH trio consists of pharmaceutical development (Q8) (11), quality risk management (QRM) (Q9) (12), and pharmaceutical quality systems (Q10) (13). Q8 provides guidance on the content of the pharmaceutical development section for the CTD filed for drug products. Manufacturing process development program is expected to identify CPPs that should be monitored or controlled to ensure that the product is of the desired quality. Granulation end point monitoring is provided as an example. Collection of process monitoring data during the development phase enhances process understanding. The design space is a multidimensional combination and interaction of input variables, for example, material attributes and process parameters that have been demonstrated to provide assurance of quality. Figure 1 shows a schematic representation of the design space and compares it with the conventional approach to controlling processes. Working within the design space is not considered as a change, while movement out of the design space is considered to be a change requiring postapproval regulatory filing.

Q9 offers a systematic approach to quality risk management. It is an independent document that complements other ICH quality documents and enables effective and

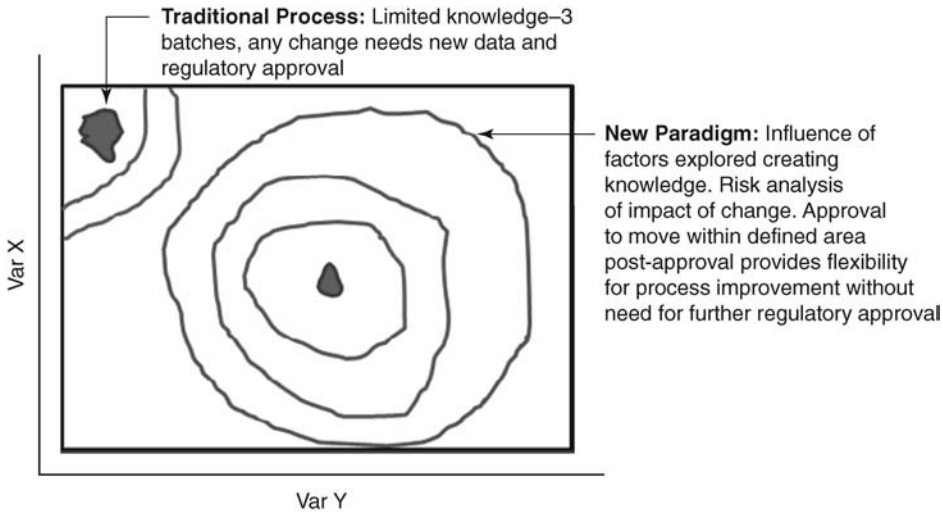


Figure 1 Design space.

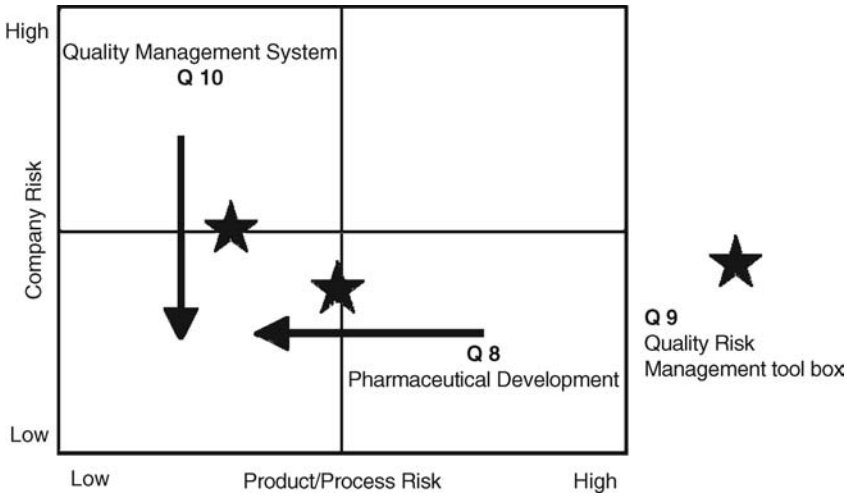


Figure 2 How Q8, Q9, and Q10 contribute to risk reduction.

consistent risk-based decisions by both regulators and industry. It states the following primary principles:

1. The evaluation of the risk to quality should be based on scientific knowledge and ultimately linked to the protection of the patient.
2. The level of effort, formality, and documentation of QRM should be commensurate with the level of risk.

Thus, the element of risk is assessed on the basis of a scientific understanding of the process and quantified where possible. It is important to link the risk to the protection of the patient. Risk assessment documentation is essential; however, this is not just a paper exercise. The effort put in must be in line with the level of risk. Annex I of Q9 provides a list of risk assessment tools.

Q10 describes a comprehensive model for an effective pharmaceutical quality system that is based on ISO quality concepts and cGMPs and complements Q8 and Q9. It can be implemented throughout the different stages of a product life cycle. Figure 2 shows how the ICH trio contributes to risk reduction.

The risk tools described in Q9 can be used to reduce product and process risk during pharmaceutical development, as described in Q8. Similarly, the risk toolkit can be used to reduce the risk to the quality system, as described in Q10. This ultimately benefits the organization as a whole. In June 2009, FDA issued a revised guidance on ICH Q8, adding an annex that clarifies the original document and adds the principle of Quality by Design (QbD) (14). Guidance for industry critical quality attributes, defined in the document as elements that could affect strength, purity, release, and stability, and their impact on development are covered in more detail in the revised guidance. The revised guidance also covers how risk assessment tools can be used to identify and rank parameters, such as process, equipment, and ingredients on the basis of their potential to impact product quality. Other topics covered in the guidance include design space, life cycle management, and quality target product profiles (QTTP).

The product life cycle starts from development through manufacturing and discontinuation (Fig. 3).

During the development phase, QRM is used to identify what to monitor and measure. Risk assessments supported by laboratory scale data generated from design of experiments (DOE) are used to establish what material attributes and granulation process parameters are critical to product quality. The methodology used for monitoring the critical attributes, for example, off-line testing of moisture or use of on-line/in-line NIR devices, is established at the pilot phase. At the manufacturing phase, on-line data generated is

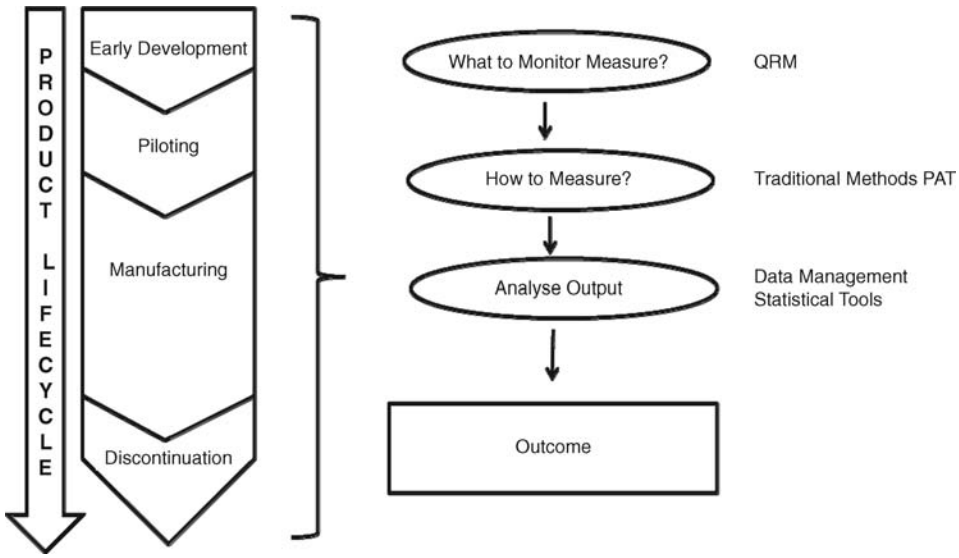


Figure 3 Product/process monitoring.

analyzed in real time using statistical tools. This facilitates timely action to be taken for any adverse trends observed.

III. POSTAPPROVAL CHANGE CONSIDERATIONS

Scale-up of manufacturing is required during transfer of production processes from drug product development laboratories to commercial manufacturing centers or between manufacturing centers. During the manufacture of clinical batches, the amount of active ingredient available is limited and the process equipments available are often scaled-down versions of those used for production of commercial batches. Batch sizes are thus smaller than those used during the manufacture of routine commercial batches. Process scale-up and commercial manufacturing are expedited as the industry attempts to maximize the commercial benefits afforded by patent protection for new drug molecules. Most companies formally record the scientific data that is generated into product development reports. These form the basis for establishing the manufacturing process, specifications, in-process controls, and validation acceptance criteria used during commercial production of the drug product. Product development reports also provide a link between the biobatch/clinical batch and commercial process through development and scale-up. Information from the development phase is used to prepare the chemistry, manufacturing, and controls (CMC) section of an application such as a new drug application (NDA) filed with the FDA (15). Where applicable, reference is also provided to other documents such as drug master files (DMFs) submitted earlier to the FDA by the manufacturer or their vendors (16).

The FDA, with input from the industry, developed guidance for scale-up postapproval changes (SUPAC) for drug products. SUPAC covers components or composition, site of manufacture, scale of manufacture, and manufacturing process/equipment. These guidelines represent the agency's current thinking on the topic and are not binding on the industry or agency with alternative approaches being acceptable. These guidance documents have been well received by the pharmaceutical industry as they enhance its ability to plan and implement change and manage resources efficiently.

The scale-up postapproval changes immediate release (SUPAC-IR) guidance for immediate-release solid oral dosage forms (17) provides recommendations to sponsors of NDAs, abbreviated new drug applications (ANDAs), and abbreviated antibiotic applications (AADAs) who intend, during the postapproval period, to make changes. This guidance was the result of a workshop on the scale-up of immediate-release products conducted by the American Association of Pharmaceutical Scientists (AAPS) in conjunction with the U.S.

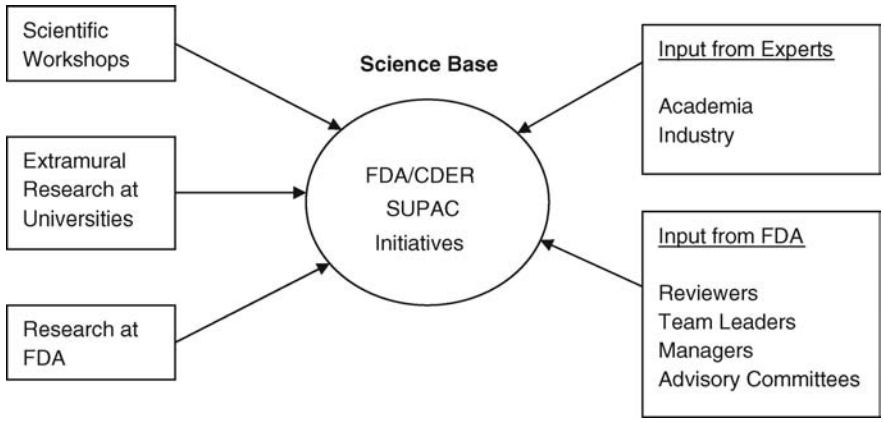


Figure 4 Developments of scale-up postapproval changes guidance documents.

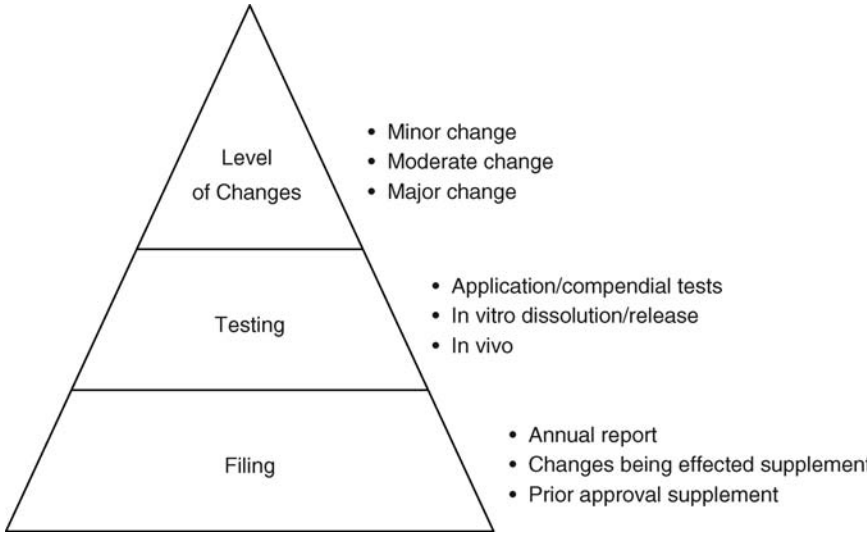


Figure 5 Formats of scale-up postapproval changes guidance documents.

Pharmacopoeial Convention (USP) and the FDA (18). It defines the levels of change, recommended CMC tests for each level of change, in vitro dissolution tests, and/or in vivo bioequivalence tests for each level of change and filing documentation that should support the change (Figs. 4 and 5).

Notification to FDA of postapproval changes to NDAs are made using change documentation known as supplements (19). The regulations describe the type of changes that require prior approval from the FDA before the change can be implemented (preapprovable changes). Under some circumstances, changes can be made before approval from FDA (changes being affected or CBEs) or described in the annual report to the FDA. In the case of CBE supplements, the FDA may, after a review of the information submitted, decide that the changes are not approvable. The SUPAC guidance documents list information that should be provided to the FDA to assure that product quality and the performance characteristics of the drug products are not adversely affected by the changes proposed to be carried out.

Component and Composition Changes

The SUPAC guidance focuses on changes in excipients in the drug product. Changes in the amount of drug substance are not addressed by this guidance. The changes are categorized

Table 1 Scale-Up Postapproval Changes Immediate Release: Component or Composition Change Levels

	Percent excipient (w/w of total dosage unit)		
Excipient	Level 1	Level 2	Level 3
Filler	±5	±10	>10
Disintegrant			
Starch	±3	±6	>6
Other	±1	±2	>2
Binder	±0.5	±1	>1
Lubricant			
Ca or Mg stearate	±0.25	±0.5	>0.5
Other	±1	±2	>2
Glidant			
Talc	±1	±2	>2
Other	±0.1	±0.2	>0.2
Film coat	±1	±2	>2
Total drug excipient change (%)	5	10	n/a

Source: From Ref. 17.

into three levels according to the increasing impact on product quality and performance expected.

Level 1 Changes

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance. Examples of such changes are deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product, changes in the composition of the printing ink to another approved ingredient, etc. Changes in excipients, expressed as percentages (w/w) of total formulation, less than or equal to the percent ranges shown in Table 1, are also level 1 changes. The total additive effect of all excipient changes should not be more than 5%.

The documentations necessary to support this type of change are application/compendial release requirements and stability data for one batch on long-term stability. No in vivo bioequivalence data or additional dissolution data other than that required by the application/compendia is necessary for this submission. The entire documentation package including long-term stability data for the level 1 change is filed with the FDA through the annual report mechanism.

Level 2 Changes

Level 2 changes are those that could have a significant impact on formulation quality and performance. The testing and filing requirements for level 2 changes vary depending on three factors—therapeutic range, solubility, and permeability. Therapeutic ranges are defined as narrow or nonnarrow, and drug solubility and drug permeability are defined as either low or high. A list of narrow therapeutic range drugs is provided in the guidance document. Solubility is calculated on the basis of the minimum concentration of drug, milligram/milliliter (mg/mL), in the largest dosage strength, determined in the physiological pH range (pH 1 to 8) and temperature (37°C ± 0.5°C). Permeability [P_e, centimeter per second (cm/sec)] is defined as the effective human jejunal wall permeability of a drug and includes an apparent resistance to mass transport to the intestinal membrane.

An example of a level 2 change is change in the technical grade of an excipient, for example, Avicel PH102 versus Avicel PH200. Changes in excipients, expressed as percentage (w/w) of total formulation, greater than those listed earlier for level 1 change but less than or equal to a percent range representing a twofold increase over level 1 changes (Table 1), are also deemed as level 2 changes. The total additive effect of all excipient changes should not be more than 10%.

Table 2 Scale-Up Postapproval Changes Immediate Release: Dissolution Testing Categories

Category	Nature of drug	Dissolution medium	Time points (min)	Specification
Case A	High permeability High solubility	0.1N HCl	15	$\geq$85%
Case B	Low permeability High solubility	As stated in application/ compendia	15, 30, 45, 60, 120, or until asymptote is reached	Dissolution profile similar to current formulation
Case C	High permeability Low solubility	Water, 0.1N HCl, USP buffer media at pH 4.5, 6.5, and 7.5 (plus surfactant if justified)	15, 30, 45, 60, 120	90% or asymptote is reached. Profile similar to current product

Source: From Ref. 17.

The documentations necessary to support this type of change are application/ compendial release requirements, batch records, and stability data for one batch with three months' accelerated stability data in supplement and one batch on long-term stability. Dissolution data requirements depend on three scenarios known as cases that cover a high/ low permeability and a high/low drug solubility, as shown in Table 2. No in vivo bioequivalence data is necessary for this submission if the situation falls within one of the cases shown in Table 2. A prior approval supplement that contains all information including accelerated stability data is to be filed. The long-term stability data is filed through the annual report mechanism.

Level 3 Changes

Level 3 changes are those that are likely to have significant impact on formulation quality and performance. Similar to level 2 changes, the testing and filing documentation requirements vary depending on therapeutic range, solubility, and permeability. Examples of level 3 changes are any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges stated for level 1 changes (Table 1) and all drugs not meeting the dissolution criteria listed for level 2 changes (Table 2).

A change in granulating solution volume is not covered under SUPAC-IR as it is a minor change to a normal operating procedure and should be included in the batch record after undergoing validation and manufacturer's site change control procedure. A change in the granulating solvent, for example, from alcohol to water, can be expected to alter the composition of the drug product even though it may be removed during manufacturing, and hence, it is a level 3 change that requires a prior approval supplement.

The documentations required to support level 3 changes are application/compendial release requirements and batch records. If a significant body of information is available, one batch with three months' accelerated stability data is to be included in the supplement and one batch on long-term stability data is to be reported in the annual report. Where a significant body of information is not available, up to three batches with three months' accelerated stability data are to be included in the supplement and one batch on long-term stability data is to be reported in the annual report.

Dissolution data requirements for level 3 changes are as specified for case B in Table 2. In addition, a complete in vivo bioequivalence study is required. This study may be waived if an acceptable in vivo/in vitro correlation has been verified. A prior approval supplement that contains all information including accelerated stability data is to be filed.

Site Changes

Site changes consist of changes in location of the site of manufacture for both company-owned and contract manufacturing facilities. These do not include any scale-up changes, changes in manufacturing process and/or equipment, or changes in components or composition. The new manufacturing locations are expected to have a satisfactory cGMP inspection. Similar to those for component and composition changes, site changes are also categorized into three different

levels that require differing depth of test and filing documentation. Level 1 changes are site changes within a single facility, while level 2 changes are site changes within the same campus. Level 3 changes consist of a change in manufacturing site to a different campus, that is, the facilities are not on the same original contiguous site or in adjacent city blocks. These requirements are summarized in Table 3.

Changes in Batch Size

Postapproval changes in the size of a batch (scale-up/scale-down) from the pivotal/pilot scale biobatch material to a larger or smaller production batch require additional information to be submitted with the change application. Scale-down below 100,000 dosage units is not covered by the SUPAC guidance. All scale-up changes are required to undergo suitable process validation and are to undergo regulatory inspection. There are two levels of batch size changes that cover batch size increases up to and including a factor of 10 times the size of the pilot/biobatch and increases beyond a factor of 10 times, respectively (Table 3).

Manufacturing Equipment/Process Changes

Equipment changes consist of changes from nonautomated or nonmechanical equipment to automated or mechanical equipment or changes to alternative equipment of either the same or different design and operating principle or of a different capacity. Process changes include changes such as mixing time and operating speeds either within or outside application/validation ranges. A change in the process used in the manufacture of the drug product, that is, change from wet granulation to direct compression, is also included. Table 3 provides a summary of the documentation requirements to file changes to manufacturing equipment and process.

Modified-Release Solid Dosage Forms

Modified-release solid dosage forms include both delayed and extended-release drug products. Delayed release is the release of a drug (or drugs) at a time other than immediately following oral administration. Extended-release products, on the other hand, are formulated to make the drug available over an extended period after ingestion so that a reduction in the dosing frequency compared with an immediate-release dosage form is achieved.

Following the successful release of the guidance document for immediate-release solid oral dosage forms (SUPAC-IR), the FDA issued a specific guidance, the scale-up postapproval changes modified release (SUPAC-MR) for scale-up and postapproval changes affecting modified-release solid dosage forms (20,21) in 1997. This guidance covers postapproval changes for modified-release solid oral dosage forms that affect components and composition, scale-up/scale-down, site change, and manufacturing process or equipment changes. It permits less burdensome notice of certain postapproval changes within the meaning of 21 Code of Federal Regulations (CFR) 314.70.

In the case of components and composition, SUPAC-MR covers changes in nonrelease controlling excipients and release controlling excipients separately. The criticality of an excipient to drug release is to be established and appropriate justifications are to be provided if an excipient is claimed as a nonrelease controlling excipient in the formulation of the modified-release solid dosage form. The change level classification, therapeutic range, test and filing documentation for components and composition changes, site changes, changes in batch size (scale-up/scale-down), and manufacturing equipment changes and manufacturing process changes for extended-release solid dosage forms and delayed-release solid dosage forms are summarized in this guidance document.

Changes to Granulation Equipment

The FDA released in January 1999 another guidance document that specifically addressed documentation requirements for filings addressing changes to pharmaceutical manufacturing equipment (22). This is the manufacturing equipment addendum developed with the assistance of the International Society of Pharmaceutical Engineering (ISPE) and is used in conjunction with the SUPAC-IR and SUPAC-MR guidance documents. It includes a

Table 3 Scale-Up Postapproval Changes Immediate Release: Site Equipment and Process Change Requirements by Category

			Documentation			
Type/level	Change permitted	Exclusions	Chemistry	Dissolution	Bioequivalence	Filing
Component/composition						
Level 1	Table 1 total change ≤5%	No change beyond approved target ranges	LTSS commitment	Application/ compendial only	None	Annual report
Level 2	Table 1 total change ≤10%	No narrow therapeutic range drugs	Accelerated stability data plus LTSS commitment	Varies, see Table 2	None	Prior approval supplement
Level 3	Table 1	None	Accelerated stability data plus LTSS commitment	Case B, see Table 2	Full	Prior approval supplement
Site change						
Level 1	Single facility	No scale or process changes	None	Application/ compendial only	None	Annual report
Level 2	Contiguous campus	No scale or process changes	None	Application/ compendial only	None	Changes being effected supplement
Level 3	Different campus	No scale or process changes	Accelerated stability data and LTSS commitment	Case B, see Table 2	None	Change being effected supplement
Scale-up/scale-down						
Level 1	≤10-fold increase in batch size	No change in site, controls, or equipment	LTSS commitment	Application/ compendial only	None	Annual report
Level 2	>10-fold increase in batch size	No change in site, controls, or equipment	Accelerated stability data and LTSS commitment	Case B, see Table 2	None	Change being effected supplement
Manufacturing equipment						
Level 1	Non-automated to automated/non-mechanical to mechanical; new equipment design w/w same capacity	No change in operating principle	LTSS commitment	Application/ compendial only	None	Annual report
Level 2	New design or operating principle	None	Accelerated stability data and LTSS commitment	Case C, see Table 2	None	Prior approval supplement with change justification
Manufacturing process						
Level 1	Operating within validation ranges	None	None	Application/ compendial only	None	Annual report
Level 2	Operating outside validation ranges	None	LTSS commitment	Case B, see Table 2	None	Changes being affected
Level 3	New process (e.g., wet-to-dry granulation)	None	Accelerated stability data and LTSS commitment	Case B, see Table 2	Full	Prior approval supplement with change justification

Abbreviation: LTSS, long-term stability study.
Source: From Ref. 17.

representative list of equipment commonly used in the industry but does not include equipment modified by a manufacturer to meet specific needs. Definitions and classification for broad categories of unit operations such as blending and mixing, drying, particle size reduction/separation, granulation, unit dosage, coating, printing, and soft gelatin encapsulation are provided. For each unit operation, a table categorizing process equipments by class (operating principle) and subclass (design characteristics) along with examples of commercially available equipments is presented.

Granulation is defined as the process of creating granules either by using a liquid that causes particles to bind through capillary forces or by dry compaction forces. Granulation is stated to impact on one or more of the powder properties such as enhanced flow; increased compressibility; densification; alteration of physical appearance to attain more spherical, uniform, or larger particles; and/or enhanced hydrophilic surface properties.

The operating principles listed in the SUPAC manufacturing equipment addendum (22) are as follows:

1. Dry granulation
   Dry powder densification and/or agglomeration by direct physical compaction.
2. Wet high-shear granulation
   Powder densification and/or agglomeration by the incorporation of a granulation fluid into the powder with high power per unit mass through rotating high-shear forces.
3. Wet low-shear granulation
   Powder densification and/or agglomeration by the incorporation of a granulation fluid into the powder with low power per unit mass through rotating low-shear forces.
4. Low-shear tumble granulation
   Powder densification and/or agglomeration by the incorporation of a granulation fluid into the powder with low power per unit mass through rotation of the container vessel and/or intensifier bar.
5. Extrusion granulation
   Plasticization of solids or wetted mass of solids and granulation fluid with linear shear through a sized orifice using a pressure gradient.
6. Rotary granulation
   Spheronization, agglomeration, and/or densification of a wetted or nonwetted powder or extruded material. This is accomplished by centrifugal or rotational forces from a central rotating disk, rotating walls, or both. The process may include the incorporation and/or drying of a granulation fluid.
7. Fluid-bed granulation
   Powder densification and/or agglomeration with little or no shear by direct granulation fluid atomization and impingement on solids while suspended by a controlled gas stream, with simultaneous drying.
8. Spray-dry granulation
   A pumpable granulating liquid containing solids (in solution or suspension) is atomized in a drying chamber and rapidly dried by a controlled gas stream, producing a dry powder.

The classification of granulation equipment in the SUPAC manufacturing equipment addendum (22) is as follows:

1. Dry granulator
   Dry granulator subclasses are primarily distinguished by the densification force application mechanism.
   - Slugging
   - Roller compaction

2. Wet high-shear granulator
   Wet high-shear granulator subclasses are primarily distinguished by the geometric positioning of the primary impellers; impellers can be top, bottom, or side driven.
   - Vertical (top or bottom driven)
   - Horizontal (side driven)
3. Wet low-shear granulator
   Wet low-shear granulator subclass are primarily distinguished by the geometry and design of the shear-inducing components; shear can be induced by rotating impeller, reciprocal kneading action, or convection screw action.
   - Planetary
   - Kneading
   - Screw
4. Low-shear tumble granulator
   Although low-shear tumble granulators may differ from one another in vessel geometry and type of dispersion or intensifier bar, no low-shear tumble granulator subclasses have been identified.
5. Extrusion granulator
   Extrusion granulator subclasses are primarily distinguished by the orientation of extrusion surfaces and driving pressure production mechanism.
   - Radial or basket
   - Axial
   - Ram
   - Roller, gear, or pelletizer
6. Rotary granulator
   Rotary granulator subclasses are primarily distinguished by their structural architecture. They have either open top architecture, such as a vertical centrifugal spheronizer, or closed-top architecture, such as a closed-top fluid-bed dryer.
   - Open
   - Closed
7. Fluid-bed granulator
   Although fluid-bed granulators may differ from one another in geometry, operating pressures, and other conditions, no fluid-bed granulator subclasses have been identified.
8. Spray-dry granulator
   Although spray-dry granulators may differ from one another in geometry, operating pressures, and other conditions, no spray-dry granulator subclasses have been identified.

Table 4 shows a listing of granulation equipment classes and subclasses. Equipment within the same class or subclass would be considered to have the same design and operating principle under SUPAC-IR and SUPAC-MR. As an example, a change from one type of wet high-shear granulator (e.g., vertical type from manufacturer *A*) to another type of wet high-shear granulator (e.g., vertical type from manufacturer *B*) generally would not represent a change in operating principle and would, therefore, be considered to be the same under either SUAPC-IR or SUPAC-MR.

A change from equipment in one class to equipment in a different class would usually be considered a change in design and operating principle. Thus, a change from a wet high-shear granulator to a fluid-bed granulator demonstrates a change in the operating principle from powder densification by wet agglomeration using high shear to powder densification with little or no shear. Such a change would be considered to be different under either SUPAC-IR or SUPAC-MR.

The FDA advises change applicants to carefully consider and evaluate on a case-by-case basis changes in equipment that are in the same class but different subclasses. For example, a

Table 4 Unit Operation: Granulation

Class	Subclass	Examples
Dry granulator	Slugging	Various
	Roller compaction	Alexanderwerk
		Bepex (Hosokawa)
		Fitzpatrick
		Freund
		Vector
Wet high-shear granulator	Horizontal (side driven)	Littleford Day
		Lodige
		Processall
	Vertical (top or bottom driven)	Aeromatic-Fielder (GEA Niro)
		APV
		Baker-Perkins
		L.B. Bohle
		Dierks & Shone
		Diosna (Fluid Air)
		GEI-Collette (GEI International)
		Key International
		Littleford Day
		Lodige
		Powrex (Glatt)
		Processall
		Werner & Pfeiderer
		Zanchetta (Romaco)
Wet low-shear granulator	Planetary	Aaron
		Aeschbach
		AMF
		GEI-Collette (GEI International)
		Hobart
		Jaygo
		Littleford Day
		Ross
		Vrieco
	Kneading	Aaron
		Paul O. Abbe
		Custom Metal Craft
		Dynamic Air
		Jaygo
		Kemutec
		Littleford Day
		Processall
		Ross
		Sigma
		Teledyne Readco
	Screw	Vrieco-Nauta (Hosokawa)
Low-shear tumble granulator	Slant cone or double cone or V-blender	Paul O. Abbe
		Gemco
		Patterson-Kelley
Extrusion granulator	Radial or basket	Alexanderwerk
		GEA Niro
		LCI
		Luwa
		Ross
	Axial	Bepex (Hosokawa)
		Gabler
		LCI
	Ram	LCI
	Roller, gear, or pelletizer	Alexanderwerk
		Bepex (Hosokawa)

Table 4 Unit Operation: Granulation (*Continued*)

Class	Subclass	Examples
Rotary granulator	Open	Freund (Vector) GEA Niro LCI Luwa
	Closed	Aeromatic-Fielder (GEA Niro) Glatt LCI Luwa
Fluid-bed granulator	None identified	Aeromatic-Fielder (GEA Niro) APV BWI Hüttlin (Thomas Engineering) Diosna Fitzpatrick Fluid Air Glatt Heinen Vector
Spray-dry granulator	None identified	Allgaier GEA Niro Glatt Heinen

Source: From Ref. 20.

change from a horizontal (side-driven) wet high-shear granulator to a vertical (top- or bottom-driven) wet high-shear granulator represents a change within a class and between subclasses. This change would not require a preapproval supplement provided the manufacturing process with the new equipment is validated. The data and rationale used to make this determination can be reviewed by the FDA at its discretion. In the event a single piece of equipment is capable of performing multiple discrete unit operations, for example, mixing, granulation, drying, etc., the unit was evaluated solely for its ability to granulate.

International Change Notification

The manufacturing process and equipment change notification outside the United States varies from region to region. A brief description of the manufacturing process is required as part of the filing requirements for marketing a drug product. Some countries require master batch records to be filed, but most others do not require much detail. In addition, a site master file that provides information on the production and control of the manufacturing operations including major process equipment at the site is sometimes required (23).

Regulatory agencies in countries that form the European Community (EC) have adopted a common approach to the procedures for variations to the terms of a marketing authorization. Variations can be by notification such as type IA and type IB that are categorized as minor variations that fulfill the conditions set forth in an annex to the EC regulations (24). A major variation of type II is a variation that cannot be deemed to be a minor variation or an extension of the marketing authorization and requires prior approval. A downscaling of batch size by 10 times or an increase that results in up to 10 times the original batch size approved at the grant of the marketing authorization is a type IA change (25). All other batch size decreases/increases or minor changes in the manufacturing process for the finished product require a type IB filing. A minor change to the manufacture is one where the overall manufacturing principle remains the same and the new process leads to an identical product regarding all aspects of quality, safety, and efficacy.

In Japan, the Pharmaceutical and Food Safety Bureau of the Ministry of Health, Labor and Welfare (MHLW) issued a guideline (26) for describing the manufacturing method in the marketing approval application form. In the manufacturing method description section, it is stated that for process parameters that serve as target values/set values, ranges intended to be

addressed as minor change notification are enclosed in "square brackets" ([]) and those that are addressed in a partial change approval application are to be enclosed in "arrow brackets" (<>). Process descriptions other than target values/set values that are to be addressed in a minor change notification are to be enclosed in "inverted commas" (""), and everything else is to be addressed in a partial change approval application. Critical processes are defined to include process conditions, tests, and other related parameters that need to be controlled within predetermined control values to ensure that the product meets specifications. Examples of critical processes are blending, granulation, particle size reduction, tableting, etc.

VALIDATION OF GRANULATION PROCESSES

Validation is defined by the FDA as establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (27). Process validation is required both in general and specific terms by cGMPs for finished pharmaceuticals—21 CFR Parts 210 and 211. The WHO defines validation as a collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes, including equipment, buildings, personnel, and materials, are capable of achieving the intended results on a consistent and continuous basis (28).

For a manufacturing facility, process knowledge is provided through technology transfer dossiers. Granulation is a critical process step that has a direct impact on the quality of the drug product manufactured and hence requires validation. The overall validation activity at a manufacturing facility is detailed in a document known as the validation master plan (VMP). The validation of the granulation process is described in the VMP. CPPs for granulation such as the rate and amount of granulation fluid added, impeller and chopper speed, and mixing time are identified, and in-process controls such as moisture content and granulation end point measurement are established during the product development phase.

Equipment/Utilities Qualification

The qualification of the manufacturing equipment and control instrumentation is a prerequisite to the qualification of the granulation process. Critical utilities such as purified water, compressed air, gaseous nitrogen, etc., required for granulation are also validated to ensure that they meet the required quality specification at the point of delivery to the granulation equipment.

The qualification of granulation equipment is carried out sequentially beginning with design qualification (DQ), followed by installation qualification (IQ) and operational qualification (OQ), respectively (Fig. 6). The quality of process equipment depends on the effort put into its design, and DQ provides evidence that quality is built into the design of the equipment. Quite often a design rationale instead of a DQ is prepared. This document addresses why a specific piece of equipment was chosen, highlighting its quality and safety considerations and provides evidence of the assessment carried out to judge its suitability for the manufacturing of the drug product.

IQ provides documented evidence that the equipment is installed as designed and specified and correctly interfaced with other systems such as electrical supply and utilities. During this phase of qualification, equipment manuals/drawings, specifications, manufacturers' test records, etc., together with installation documents and "as-built" drawings, are compiled and verified. Calibration of instrumentation and maintenance checks are also established. OQ is a documented demonstration of the fact that the process equipment as installed operates well. At this stage, generally, a manufacturing process simulation is carried out using a placebo formulation instead of the actual drug product recipe. For each qualification phase, a protocol detailing the activity and acceptance criteria is prepared. At the conclusion of the testing activity, a summary report that discusses the results and the readiness to proceed to the next phase of qualification is issued.

Performance Qualification

Performance qualification (PQ) is a documented program that demonstrates that the granulation process when carried out within defined parameters will consistently perform its intended

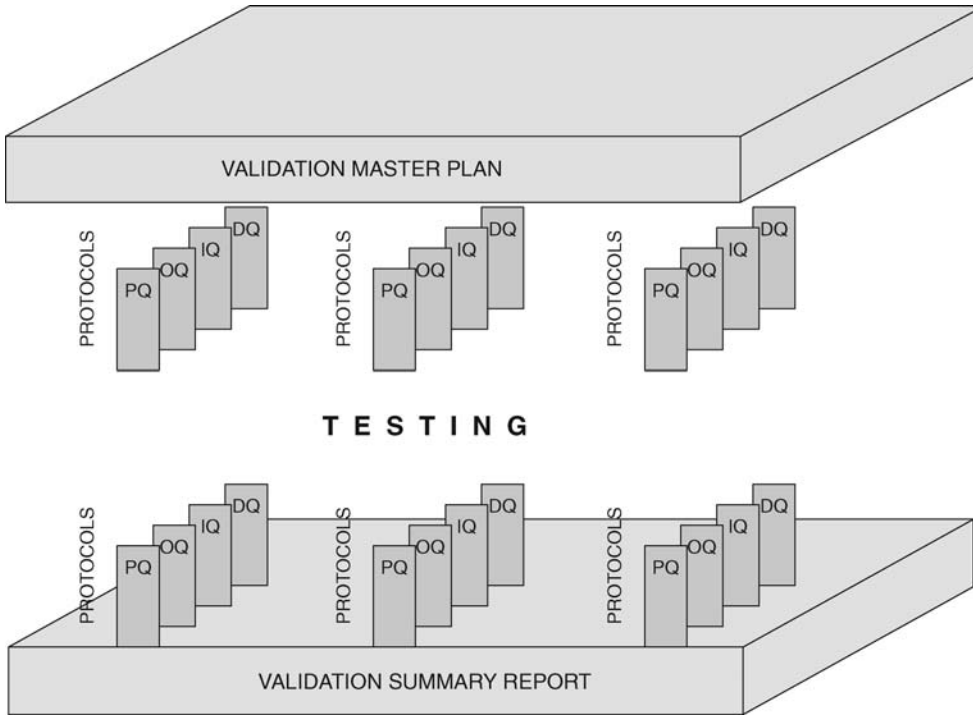


Figure 6 Documentation hierarchies for pharmaceutical process validation.

function to meet its preestablished acceptance criteria. Thus, PQ is dynamic testing that combines the equipment, utilities, and manufacturing process to produce the product under routine operational conditions. Product specifications that become the basis for the acceptance criteria at PQ stage are established during the development of the process with the biobatch or pivotal clinical batch serving as the reference batch. Prospective validation of the granulation process is generally carried out for new products and the data included in regulatory submissions, if necessary. The norm is to manufacture at least three consecutive PQ batches; however, a process capability study can establish the actual number of batches required on the basis of the natural variability of a process (29). Revalidation may be required after changes that significantly impact product quality are made or on a periodic basis at scheduled intervals.

A FDA field inspection guide for validation of oral solid dosage forms lists granulation/mix analysis as a major area for investigation (30). It discusses various types of mixers and granulation equipment and highlights their design features as well as problems associated with their efficiency and validation. Blending validation and content uniformity failures due to poor mixing is of main concern for most conventional mixers (Table 5). This guide also compares dryers and notes that the fluid-bed dryer is superior to the oven dryer as it yields a more uniform granulation with spherical particles.

Computer Validation

Granulation equipment is supported by computer control systems that are getting increasingly sophisticated. Most commercial equipments have programmable logic controllers (PLCs) or embedded microprocessors. International forums with representation from users and the vendors of equipment and software have been set up to address the software life cycle documentation requirements. Good Automated Manufacturing Practice (GAMP) 4 is a globally accepted guidance document developed by ISPE and the GAMP Forum to address computer validation (31). The PIC/S Guide to Good Practices for computerized systems in regulated "GXP" environments developed by international regulatory agencies is also a useful reference document for manufacturers and other users (32).

Table 5 Typical Problems Associated with Mixing Equipment

Mixer type	Design feature	Limitations/problems
Planetary (pony pan)	Open pan/pot Horizontal blending	• Dusty operation. • Cross-contamination problem. • Poor vertical mixing. • Segregation or unmixing of components. • Difficult to validate.
Ribbon blender	Top loading Horizontal and vertical blending Discharge valve Blade clearance	• Moderately dusty operation. • Cross-contamination problem. • "Dead spot/zone" at the discharge valve. • Poor mixing at ends of the center horizontal mixing bar and shell wall. • Cleaning problems with seals/packing. • Risk of overfill leading to poor mixing.
Tumble blender	Twin shell/double cone Mild mixing action	• Mild mixing action. • Powder lumps will not break up. • Low humidity results in static charge build-up. • High humidity leads to lumping.
High shear	High-energy chopper	• Different mixing time compared with conventional mixers. • Drug substance may partially dissolve or recrystallize. • Charring due to heat generation. • Cleaning requires disassembly of chopper.

Source: From Ref. 17.

Electronic records and electronic signatures that have cGMP implications are generally expected by regulatory agencies to be equivalent to paper records and handwritten signatures executed on paper (33). A new guidance that represents FDA's current thinking on electronic records and electronic signatures was released in August 2003 (34). The agency took a narrower interpretation of the requirements stated in 21 CFR Part 11 following feedback from the pharmaceutical industry and vendors that the regulations could stifle technological advances by restricting the use of electronic technology and increasing the cost of compliance. PIC/S also requires the regulated user to validate the system for storage of the information electronically for the required time and to ensure that the data is protected from damage or loss and can be easily retrieved in a legible form (32).

New Guidance for Process Validation

The FDA issued in May 1987 guidance on general principles of process validation. Over the years, this has been a key reference document for manufacturers carrying out process validation (27). Subsequently, a Compliance Policy Guide was released to explain the enforcement policy regarding the timing of the completion of certain process validation activities for drug products and active pharmaceutical ingredients subject to premarket approval (35). Recognizing the role of emerging technologies in the area of process validation, the FDA commenced work on a new guidance for process validation to replace the 1987 guidance. This guidance is currently in draft, and input from industry has been sought (36). This revised guidance conveys FDA's current thinking on process validation and is consistent with basic principles first introduced in the 1987 guidance. It is aligned with Pharmaceutical cGMPs for the 21st Century, use of technological advances in manufacturing and implementation of risk management.

The new guidance defines process validation as the collection and evaluation of data, from the process design state throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products. Process validation activities take place over the life cycle of a product and are carried out in three stages.

- Stage 1: Process design: The commercial process is defined during this stage on the basis of knowledge gained through development and scale-up activities.

- Stage 2: Process qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
- Stage 3: Continued process verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

When finalized, the new guidance on process validation will replace the 1987 guidance.

SUMMARY

The globalization of pharmaceutical manufacturing is proceeding rapidly driven by mergers and acquisitions within the industry and the freeing up of cross-border trade. In addition to known global quality standards such as ISO 9000, harmonization of cGMPs and regulatory filing requirements is making progress driven by ICH and other forums such as PIC/S. Simplification of existing regulations for notification of postapproval changes to regulatory filings has also been achieved through collaboration between regulatory agencies, the pharmaceutical industry, and academia. Regulatory agencies recognize the value of emerging technologies to improve product quality and process capability. cGMP guidances have been revised to encourage the adoption of new technologies, enhance process control, and monitor in real-time CQAs established using risk assessment. Granulation is a critical process step and, hence, requires to be validated as part of overall validation of the manufacturing process. A new regulatory guidance on process validation recommends validation activities to be conducted over the life cycle of a product with continuous quality verification being encouraged. Process engineers and product development researchers today require a sound understanding of regulations governing drug product approval, validation, and change management.

REFERENCES

1. 21 CFR Part 210. Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs, general.
2. 21 CFR Part 211. Current good manufacturing practice for finished pharmaceuticals.
3. Pharmaceutical Inspection Cooperation Scheme (PIC/S). Guide to good manufacturing practice for medicinal products (PE 009-8), January 15, 2009.
4. World Health Organization. WHO expert committee on specifications for pharmaceutical preparations, 37th report, Good manufacturing practices for pharmaceutical products: main principles (Annex 4), Geneva, 2003.
5. Pharmaceutical Inspection Co-operation Scheme. Available at: http://www.picscheme.org.
6. Food and Drug Administration. Guidance on pharmaceutical cGMPs for the 21st century—a risk-based approach, September 2004.
7. International Conference on Harmonization (ICH). Available at: http://www.ich.org.
8. International Organization for Standardization (ISO). Available at: http://www.iso.org.
9. Food and Drug Administration. Guidance for industry on PAT—a framework for innovative pharmaceutical development, manufacturing, and quality assurance, September 2004.
10. American Society for Testing and Materials (ASTM). Available at: http://www.astm.org.
11. International Conference on Harmonization. Guideline on pharmaceutical development Q8 (R1), step 4 version, November 13, 2008.
12. International Conference on Harmonization. Guideline on quality risk management Q9, step 4 version, November 9, 2005.
13. International Conference on Harmonization. Guideline on pharmaceutical quality system Q10, step 4 version, June 4, 2008.
14. International Conference on Harmonization. Guidance for industry Q8 (R1) pharmaceutical development, June 2009.
15. Food and Drug Administration. Guideline for the format and content of the chemistry, manufacturing, and controls section of an application, February 1987.
16. Food and Drug Administration. Guideline for drug master files, September 1989.
17. Food and Drug Administration. Guidance for industry: scale-up and post approval changes for immediate release solid oral dosage forms, November 1995.
18. Skelly JP, Van Buskirk GA, Savello DR, et al. Workshop report: scale up of immediate release oral solid dosage forms. Pharm Res 1993; 10(2):313–316.
19. 21 CFR Part 314.70. Supplements and other changes to an approved application.

20. Food and Drug Administration. Guidance for industry: scale-up and post approval changes for modified release solid oral dosage forms, September 1997.
21. Skelly JP, Van Buskirk GA, Arbit HM, et al., Workshop report: scale up of oral extended-release dosage forms. Pharm Res 1993; 10(12):1800–1805.
22. Food and Drug Administration. Guidance for industry: scale-up and postapproval changes for immediate release and modified release solid oral dosage forms (manufacturing equipment addendum), January 1999.
23. Health Sciences Authority (Singapore). Guidance notes on preparation of a site master file, May 1999.
24. European Commission regulation (EC) No. 1084/2003, June 3, 2003.
25. European Commission. Guideline on dossier requirements for type IA and type IB notifications, July 2003.
26. Japan Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare. Guideline for description of application forms for marketing approval of drugs, etc. under the revised pharmaceutical law—PSSB/ELD Notification No. 0210001, February 10, 2005.
27. Food and Drug Administration. Guideline on general principles of process validation, May 1987.
28. World Health Organization. WHO expert committee on specifications for pharmaceutical preparations, 34th report, Good manufacturing practices: guidelines on validation of manufacturing processes (Annex 6), Geneva, 1996.
29. Kieffer R, Torbeck L. Validation and process capability. Pharm Technol 1998; 22(6):66–76.
30. Food and Drug Administration. Guide to inspections of oral solid dosage forms pre/post approval issues for development and validation, January 1994.
31. International Society of Pharmaceutical Engineering (ISPE). Good automated manufacturing practice guide (GAMP 4), December 2001. Available at: http://www.ispe.org.
32. Pharmaceutical Inspection Cooperation Scheme. Guide to good practices for computerized systems in regulated "GXP" environments (PE 011-1), August 20, 2003.
33. 21 CFR Part 11. Electronic records; electronic signatures.
34. Food and Drug Administration. Guidance for industry on Part 11, electronic records; electronic signatures—scope and application, August 2003.
35. Food and Drug Administration. Compliance policy guide (CPG 7132c.08) on process validation requirements for drug products and active pharmaceutical ingredients subject to pre-market approval, December 2004.
36. Food and Drug Administration. Guidance (draft) on process validation: general principles and practices, November 2008.

29 Quality by Design and Process Analytical Technology in Granulation

Gopi Vudathala
Sanofi-Aventis US LLC, Malvern, Pennsylvania, U.S.A.

Stanley Rodgers
Sanofi-Aventis US LLC, Bridgewater, New Jersey, U.S.A.

John E. Simmons
Simmons FDA Consulting, Chapin, South Carolina, U.S.A.

INTRODUCTION

The introduction of quality by design (QbD) and the implementation of strategically placed process analytical technologies (PAT) provide opportunities for pharmaceutical manufacturers to reduce product end testing and move toward real-time release of finished dosage forms. Firms that choose the PAT path must design their processes in a manner that maximizes and facilitates on-line, in-line, and at-line testing.

FUNDAMENTAL APPROACHES TO QbD AND PAT

International harmonization, illustrated by International Conference on Harmonization (ICH) quality guides Q8, Q9, and Q10, represents recognition that guidance can help to harmonize pharmaceutical regulation and pharmaceutical development on a global basis (1–4).

The concept of design space (Fig. 1) is defined as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of pharmaceutical product quality. Working within the design space paradigm produces acceptable product, and variations within the space are not considered a product or process change. Manufacturing outside of the design space is considered to be a change and would normally initiate a regulatory change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

A pharmaceutical dosage form and associated manufacturing processes can be represented by a series of design spaces that define the manufacturing steps (e.g., granulation) or product so that measurements at critical points can be expressed as ranges or variances, within which the product performs acceptably. The space can be further narrowed to encompass control space, within which the product quality can be controlled by equipment and monitoring technology. QbD is a concept that incorporates some of the following principles:

a. Formulation and process development via experimental design studies.
b. An investigation and understanding of the interactions between inactive ingredients and active ingredient(s) are very important. Interactions between ingredients in a matrix can range from weak (hydrophobic) to strong (covalent bond) and should result in a dosage form that behaves (releases drug and dissolves in the GI tract) in a manner consistent with the patient's needs. The function of each ingredient in the matrix should be understood and controlled in a manner that tolerates variations and ranges that make for a rugged product—one not sensitive to small perturbations in content or process.
c. Dosage forms can be built from a base of knowledge that leverages past experience and builds on discovery during product development and mechanistic-based understanding.
d. A dosage form created using QbD principles should demonstrate a ruggedness or reproducibility factor that tolerates acceptable, understood, and controlled variation so that
    1. all critical sources of variability are identified and explained,

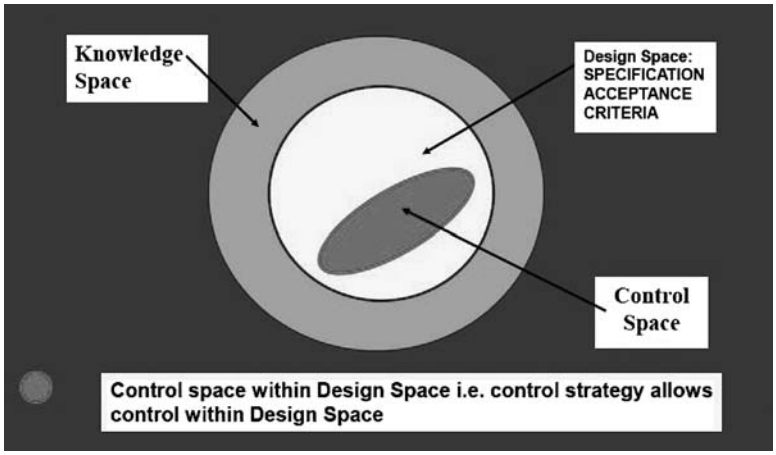


Figure 1 Control space within design space.

2. variability is understood and appropriately managed during the manufacturing process,
3. product quality attributes can be accurately and reliably predicted over the design space, and
4. critical design principles incorporate three actions, evaluate, plan, and measure.

QbD provides a structured framework for documenting and presenting development rationale and experience and knowledge of the formulation and the process, and for ensuring manufacture of products consistently fit for patient use through

i) content uniformity,
ii) potency,
iii) stability,
iv) purity,
v) consistent bioavailability,
vi) a range of potencies,
vii) ready availability for distribution, and
viii) convenience and pharmaceutical elegance.

In the case of solid oral formulations, some of the critical process and control steps revolve around blending, granulation, and drying. These processes are often closely linked and interdependent and control the tablet/capsule properties and release characteristics.

Products and manufacturing processes should be designed to manage variation. QbD principles should be applied through the entirety of the development process, yielding good understanding and control of variation. PAT principles, tools, and practices help enable QbD to achieve the desired state of product control.

QbD and PAT are complimentary and highly interdependent (5,6). As an example, in QbD the selection of equipment operating criteria and critical process control selection is knowledge driven (Fig. 2) and is distinctly different from the approach that emphasizes repetition and optimization and centers on identifying critical process controls coupled with real-time monitoring by PAT technologies.

There is still value to traditional monitoring parameters such as time, temperature, and pressure, etc., because they are convenient to monitor, however, monitoring an analytical end point in real time can be more informative and precise.

Another advantage to this approach is found in the concept of self-assessment in a science-based manner (Fig. 3).

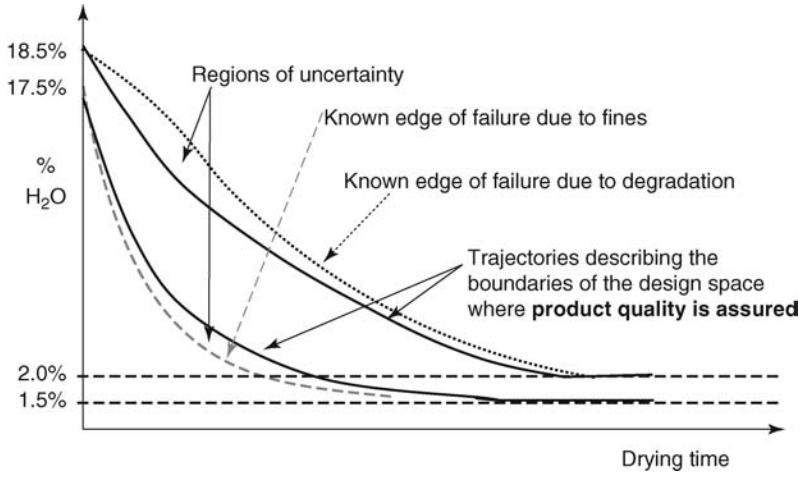


Figure 2 Design space and control space boundaries.

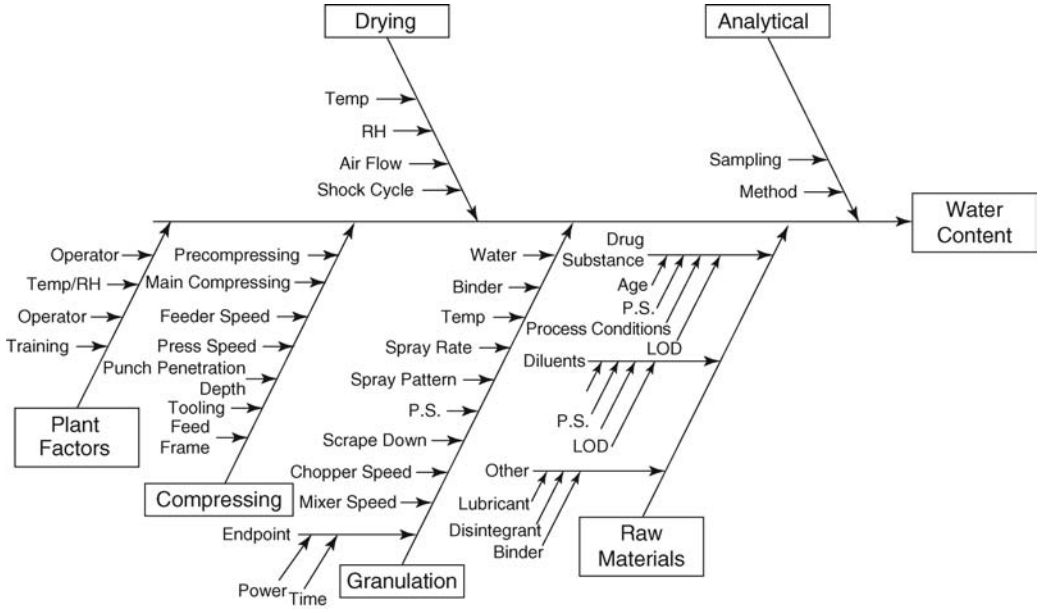


Figure 3 Process fish bone diagram.

The use of PAT speaks to scientific understanding of the product and process and allows for trend monitoring through the collection of thousands of individual measurements. This approach tends to be self-auditing and more comprehensive than the traditional pull-and-analyze approach.

Empiricism is still present; however, with the linking of PAT instrumentation to laboratory or manufacturing data systems, a more statistical process control is reached in real time. It also lends itself to the possibility of reduced end product testing and a more "real-time release"–like environment. Regulators are beginning to understand that repetition and reproduction do not guarantee process and product understanding.

There are still regulatory hurdles to deal with, and most regulatory agencies are in the process of putting policies and regulatory flexibilities into place to facilitate evaluating the QbD approach.

When compared with other industries, the pharmaceutical manufacturing sector tolerates high levels of product defects (on average 5–10%). The semiconductor industry, by contrast, strives for parts per million (ppm) level defects. The semiconductor sector was not always that efficient, but implementation of some of these QbD elements has steadily driven up quality with a reduction in defects.

PROCESS ANALYTICAL TECHNOLOGIES INSTRUMENTATION

PAT comprises of a wide variety of technologies, strategies, and tools capable of shifting the industry's focus from quality control by postmanufacturing testing to quality control during manufacture. PAT can be incorporated into drug substance or drug product control via a number of strategies, which can include qualification of raw materials or components, drug product release testing, and even sophisticated, fully automated, in-line, closed-loop feedback or fed-forward in-process analytical controls (Fig. 4).

PAT can also be beneficially employed in manufacturing process development studies to facilitate increased product knowledge and process understanding that can then be leveraged to optimize commercial processes and potentially target real-time assurance of quality by ensuring consistent product quality while accommodating variation in raw material attributes.

Although PAT is not new, its application in the pharmaceutical industry has increased in recent years because of recognition that it will contribute to continuous improvement efforts and improve return on investment (ROI). Additionally, progress has been aided by rapid developments in optronics, computer technology, and software for extracting data from complex matrices (chemometrics).

PAT is about using knowledge to predict outcomes, fundamentally about creating, confirming, and then applying models. Such models could be statistical and empirical in nature or could be based on mechanistic process understanding. This extensive accumulated modeling knowledge and data will require significantly more powerful tools to ensure integration within and across operations. In addition to instrumentation, tools for multivariate design, data acquisition, and analysis as well as tools for continuous improvement and knowledge management are needed (Fig. 5).

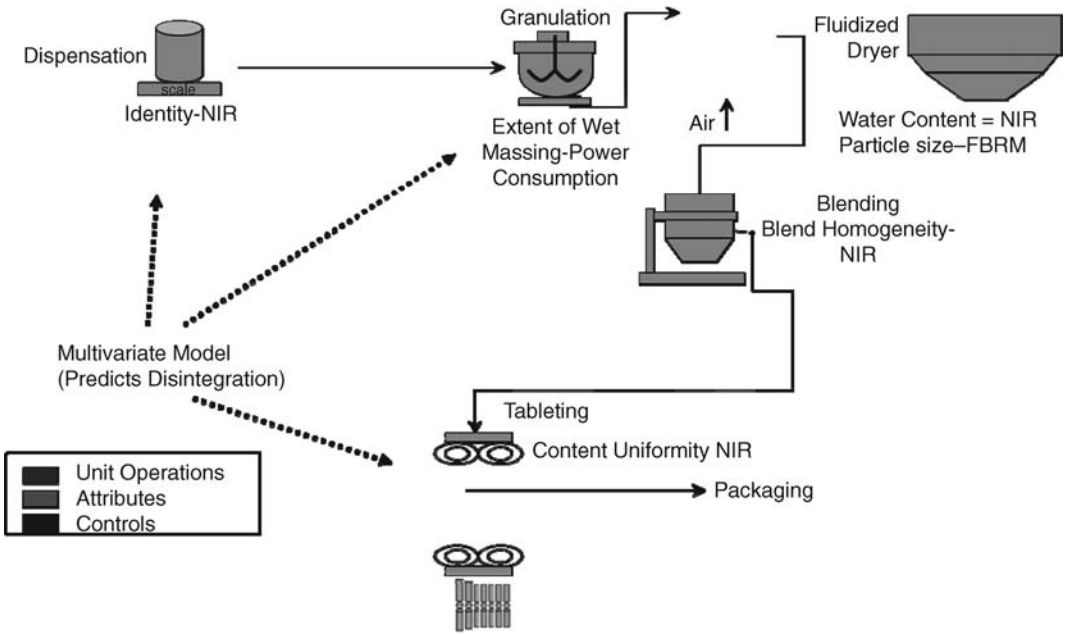


Figure 4 Process analytical technologies and unit operations.

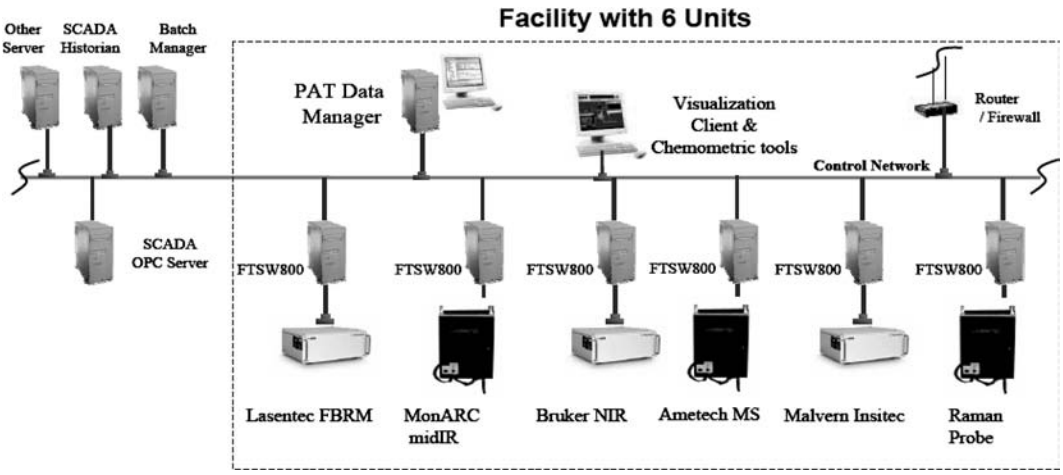


Figure 5 Process analytical technologies and network architecture—six process analyzers.

Furthermore, since most manufacturing facilities are not dedicated to one product or process, one of the fundamental challenges will be to optimize the use of PAT tools while retaining the flexibility of these multipurpose facilities.

Within the context of the above paragraphs, let us look more closely at the PAT instrumentation available and consider its usefulness and limitations.

Near Infared Spectroscopy

Near infrared spectroscopy (NIRS) has become a well-established technique used for several years in the pharmaceutical industry for the identification and assay of raw materials, intermediates, and finished products as well as for in-process control and monitoring. Major advantages of NIRS compared with traditional sampling and testing are its nondestructive nature and its real-time delivery of results; drawbacks include the impact of physical properties on spectra and the current regulatory requirement that it be calibrated against a traditional analytical reference method [although there are examples of scientifically defensible alternative calibration approaches not requiring traditional reference data (7,8)]. Its limitations in sensitivity and selectivity cause its use to require adequate understanding of the principles involved, especially as these principles relate to ensuring that the spectral responses actually correlate with changes in the analyte or property under consideration and are not purely coincidental.

Correlation of the NIRS response to changes in the analyte of interest requires chemometric modeling, using sophisticated software packages (Fig. 6).

This software correlates the spectral responses to latent variables, constrained by calibration reference data. Signal pretreatments are often necessary to eliminate irrelevant information from the spectral responses, such as responses related to density, particle size, or water content when these variables are not of interest.

Near infrared (NIR) has been used to assess granulation particle size, density, and water present on the surface of the granules in situ and in real time (9), tablet assay via NIRS in transmission mode (10), blend and tablet content uniformity, and coating thickness (11) and for tablet assay and hardness testing for real-time release (12–14).

Raman Spectroscopy

Raman scattering emanates from changes in the polarizability of a molecule where the associated vibrational and rotational energy changes result in spectra that resemble those generated by infrared (IR) instruments. It enables accurate quantitative assay in liquids, solids, and multiphase samples. Raman spectroscopy (RS) has been actively used for identification

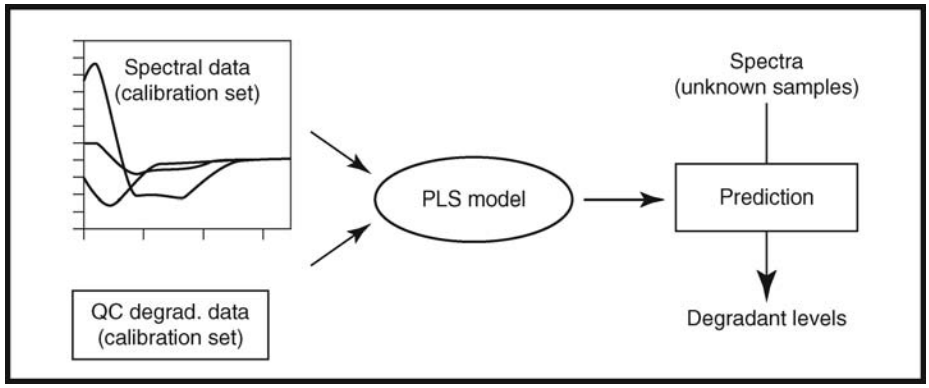


Figure 6 A partial least squares (PLS) regression model is generated on the basis of spectroscopic data and known degradation levels of the calibration set. Subsequently, this model is employed to predict levels of degradation forms on the basis of spectra of unknown samples.

and assay in tablets and capsules, blend uniformity evaluation, and quantification of mixtures of polymorphs (15–17). RS has also been used to monitor active pharmaceutical ingredient (API) hydration state in tablet granulations during fluid-bed drying (18). De Beer (19) used RS as a PAT tool for in-line real-time monitoring of powder blend homogeneity and verified the results by conducting simultaneous NIRS data. Compared with NIRS, RS spectra are more distinct and less overlapped and Raman API spectral responses are typically much stronger, enabling spatial distribution mapping of API in tablets where it comprised <1% of the total tablet weight (20). In addition to being more selective, Raman spectral responses are also generally less sensitive to physical parameters than NIR spectra. RS is more expensive to implement than NIRS and more difficult to use for remote sensing.

X-Ray Powder Diffraction

During wet granulation, size enlargement occurs when a binder is combined with small particles to produce larger, physically stronger agglomerates. A solvent (typically water) is added to the binder and other excipients to wet the mixture. The solvent can facilitate dissolution of the API to cause transformation to other unwanted and potentially less bioavailable polymorphs. X-ray powder diffraction (XRPD) is the method of choice, based on ease of use and suitability of results, for quantifying polymorphs, but it has rarely been used on-line during unit processing. MacCalman (21) used on-line XRPD to quantify polymorphs of an antibiotic API during crystallization. Davis (22) used on-line XRPD to quantify polymorphic transformations during wet granulation, thereby allowing the kinetics to be understood and adequately managed. Future applications could potentially involve closed-loop feedback control of the process to minimize transformation.

Effusivity

Thermal effusivity is a nondestructive technique with recently recognized pharmaceutical applications. It does not require intense data pretreatment or chemometric modeling for method development. Effusivity is a measure of the ability of a material to transfer heat. It is a function of thermal conductivity, heat capacity, and density, as well as particle size, shape, and moisture content.

Mathews (23) observed effusivity relative standard deviation (RSD) to decrease as blending progressed and used it to map powder mixture homogeneity at various V-blender locations and determine blending end point. The components used had different individual effusivity values, enabling this technique to be employed. Roy (24) used effusivity to monitor, optimize, and control fluid-bed drying. This was possible because the much higher effusivity of water compared with blend resulted in a threefold increase in powder effusivity with only a 1% increase in moisture content. Roy (25) also studied thermal effusivity as a technique for determining the end point for magnesium stearate lubrication and theorized that effusivity

increased during lubrication because the magnesium stearate decreased blend porosity and increased density. Ghorab (26) examined thermal effusivity as a PAT tool for monitoring and controlling roller compaction. He observed strong formulation-dependent correlations between effusivity and ribbon physical properties, enabling the conclusion that thermal effusivity could theoretically be employed to monitor these ribbon properties. However, there were some sensor-related issues that complicated on-line effusivity data acquisition. In addition, lot-to-lot variability and the impact of API physical characteristics were not studied. Fariss (27) used a fractional factorial design to evaluate the ability of thermal effusivity and power consumption to predict end point during placebo formulation high-shear wet granulation. Factors were load size, liquid addition rate, and impeller speed; response variables were RSD on thermal effusivity, power consumption, mean granule-specific surface area, and Carr's index. The increase in power consumption during granulation correlated highly with the decrease in thermal effusivity RSD at granulation loadings appropriate to the equipment size employed in the study.

Léonard (28) compared off-line thermal effusivity with tapped density and UV spectroscopy monitoring methods for determining the granulation end point of binary mixtures containing 10, 25, and 50 weight percent acetaminophen in spray-dried lactose. Thermal effusivity during mixing of 1% magnesium stearate with spray-dried lactose was also studied. Calibration curves for all three methods correlated well with as-formulated blend acetaminophen concentration, and values obtained using all three methods exhibited convergence as a function of granulation time, with the exception of thermal effusivity during granulation of the 10% blend, which showed no clear convergence. It was theorized that this lack of convergence occurred because of the relatively small differences in thermal effusivity between acetaminophen and lactose, the low drug loading of the 10% blend, and the relatively high RSD (3–4%) of the thermal effusivity method precision. Thermal effusivity results observed during 1% magnesium stearate blending with lactose exhibited an interesting nonlinearity in that effusivity during mixing increased to values higher than those of either excipient and higher than expected for a linear combination as was observed for the acetaminophen/lactose granulation. While magnesium stearate effusivity is between 200 and 250 $Ws^{1/2}/m^2K$ and that of lactose is 330 to 420 $Ws^{1/2}/m^2K$ (depending on the degree of compaction), blended mixture effusivity ranged from 350 to 470 $Ws^{1/2}/m^2K$ as a function of mixing time. It was theorized that this phenomenon occurs because, upon blending, the much smaller magnesium stearate particles percolate through the pores of the much larger spray-dried lactose particles, decreasing the porosity and increasing the density of the powder bed and therefore amplifying the effusivity increase of the mixture.

Acoustics

Acoustic resonance spectrometry (ARS) is an underutilized technique that could become the method of choice for physical characterization of some analytes. The principle involves applying an acoustic signal to the sample and evaluating the waves reflected. Contact (piezoelectric) and noncontact (air-coupled) methodologies have both been studied. Measurements that can be made by ARS include sample compaction and axial strain, deformation, hydration and drying end point, elasticity, molecular stacking, and homogeneity (29). It requires no sample preparation and is nondestructive. It has successfully been employed to analyze tablets (30), powders (31) and semisolids, and liquids (32,33). ARS can easily be used to quantify API or moisture in tablets because of the high correlation between acoustic resonance spectral features and chemical composition. This chemical/physical relationship can be used to differentiate between different formulations of the same API. Medendorp and Lodder (34) studied the ability of a contact ARS to differentiate between similar-size-and-shape tablets (aspirin, ibuprofen, acetaminophen, vitamin C, and vitamin B_{12}). Successful tablet identification was based on intertablet versus intratablet nonparametric multidimensional standard deviations (MSD). Scan time was 250 milliseconds, ample time to collect an ARS signal from a tablet as it is being compressed on a typical commercial tablet press. The average intertablet MSD was 65.64, while the average intratablet MSD was 1.91. The method was also able to very accurately predict tablet mass, thickness, and density.

Akseli and Cetinkaya (35) used air-coupled ARS to study ibuprofen tablets. Air-coupled transducers could present an advantage over piezoelectric transducers because they obtain a signal without tablet contact. The authors demonstrated the ability of the method to determine such mechanical properties as Young's moduli, Poisson's ratios, core and coating densities, and coating thickness.

GRANULATION TECHNOLOGIES: DESIGN AND CONTROL STRATEGIES: BATCH PROCESSING

Overview

Blending/Mixing

Blending or mixing is the most frequently used operation in oral solid dosage form manufacturing (Fig. 7).

When powders are mixed, several parameters are important for achieving adequate blend content uniformity. If blending is excessive, the particles may segregate or demix because of the differences in particle size distribution and/or shape and/or density. Frequently, content uniformity is assessed by analyzing only the API content, and occasionally, sampling errors can mislead because of the difficulty of sampling blends via a sampling thief. NIRS has been employed to monitor blend homogeneity and predict blending end points. Fourier transform (FT)-Raman spectroscopy mapping techniques have also been applied to characterize the physical and chemical uniformity of low-dose products. On-line NIRS can be used to evaluate the distribution of API and each excipient and monitor compositional variability within the entire blend as it is mixed rather than evaluating blend content uniformity for only API via the traditional one-time approach of sampling representative blender locations at the end of the blending operation. Blending profiles can be obtained for all components, either off-line, at-line, or on-line, allowing insight into the fundamental mechanisms of mixing by facilitating identification of the important process parameters. These data can then be used to create a design space and control strategy for the blending operation that ensures optimum mixing and uniform blends. PAT can be applied for in-process control of initial blending, granulation, and final blending prior to compression or encapsulation.

Granulation

Granulation is a size enlargement process as well as a technique to assure adequate active ingredient distribution. Granulation is required when a formulation cannot be directly compressed. Compared with direct compression, granulation may be necessary to ensure content uniformity when dosage form strength is low compared with its total weight or when

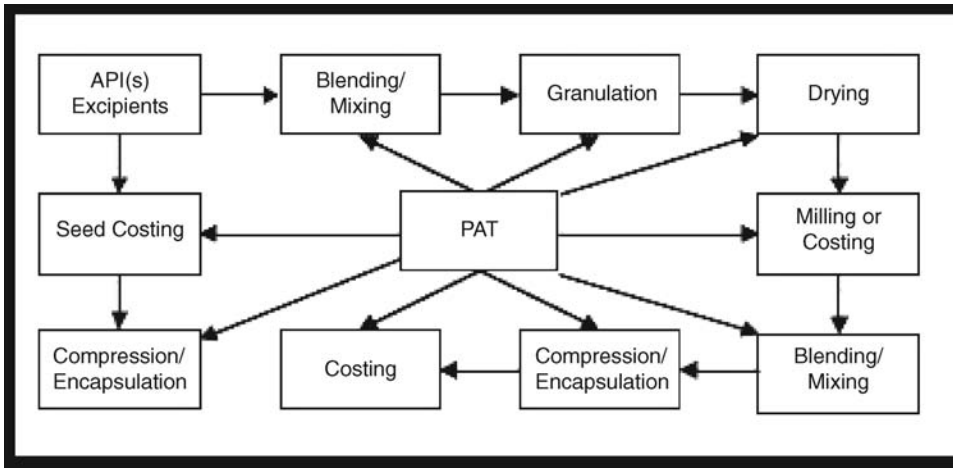


Figure 7 Typical manufacturing processes in oral solid dosage forms.

dosage form strength is high compared with its total weight and the API has poor flowability and/or low bulk density and/or is poorly compressible. Granules are obtained from powder blends by either dry compaction (dry granulation) or adding liquids and mixing (wet granulation). Granule particle size, shape, and mechanical properties are process parameter dependent. Dry granulation unit process methods include slugging (compression of blend into slug-shaped tablets on a tablet press) and roller compaction (also referred to as ribbon blending). Wet granulation technologies include high-shear, low-shear, fluid-bed, extrusion, rotary granulation, etc. In a wet granulation process, important process parameters include granulation end point determination, liquid content, and maintenance of the intended active ingredient solvate and/or polymorph. NIRS has been used to monitor and control dry granulation by roller compaction and to map the process. Roller compaction ribbon monitoring by thermal effusivity has shown a strong relationship between effusivity and physical properties of compacted ribbons. NIRS has also been applied in fluidized-bed or high-shear wet granulation processes to monitor granule particle size and moisture content as well as to determine granulation end point.

Drying

If water or an organic solvent is used in a drug product unit manufacturing operation, the next unit operation typically required is drying to remove the solvent by evaporation. Drying involves transferring heat via conduction, convection, or radiation. Drying time, temperature, dew point, drying end point, and in-process moisture content are potential critical process parameters. NIRS has been widely applied for monitoring the drying process, as NIR is particularly sensitive to water. A compact diode array NIR spectrometer has been proven to be able to determine moisture content in fluid-bed drying operations accurately, on-line and in real time (30).

Granulation drying curves can be generated during development to understand water retention, drying rates, and end point. PAT data can be valuable for optimizing the drying curve and end point as well as for justifying the in-process moisture content acceptance criteria.

Batch Processes: Detailed Discussion

Wet Granulation

Wet granulation using high-shear mixers is one of the most common operations in pharmaceutical drug product manufacture. The process functions to enable intimate mixing of excipients with API, using granulation solvents (typically water). The process involves the generation of liquid bridges between the component powders and liquid by forming electrostatic and/or hydrogen bonds. Liquid dispersion as the powders are wetted causes granule growth, forming agglomerates. As the liquid becomes evenly distributed throughout the granulation mass, the process of granule growth approaches a state of dynamic equilibrium. Once this state is achieved, addition of additional granulation solvent and/or additional mixing will collapse the liquid bridges and result in overgranulation. For this reason, it is important to end granulation in the equilibrium phase to ensure that the desired granulation attributes have been optimized. Granulation end point for commercial manufacture has traditionally been empirically determined using power consumption or impeller torque measurements based on manufacturing experience gained during development, where end point was correlated with ranges of mixing times and speeds. NIRS is increasingly being used in fluidized-bed and high-shear wet granulation processes to monitor granule particle size and moisture content and to determine granulation end point.

Dry Granulation

Dry granulation is typically used when the API/excipient blend is either too fluffy or too susceptible to flowability problems for direct compression to be a viable processing option and/or too susceptible to degradation from heat and/or moisture for wet granulation to be a viable processing option for densification. Without compaction, dry powders may not flow

well enough to feed uniformly into the die cavity of a tablet press or capsules in an encapsulator for processing via direct compression. This lack of uniform flow can result in tablet weight uniformity issues. In addition, differences in the blend components' particle sizes, shapes, and densities can cause segregation and create tablet content uniformity issues. Direct compression may also be impossible because the noncompacted blend does not have sufficient bulk density (is too "fluffy") to fit in the cavities of the tablet press (or in the capsule) at the required mass. Dry granulation can be conducted on a tablet press using slugging, tooling, or via a roller compactor. Dry granulation is sometimes chosen as an alternative to wet granulation when direct compression is not feasible not because wet granulation is not feasible but because the manufacturer is more experienced with dry granulation or to reduce processing time and/or equipment requirements to reduce costs.

Although some roller compactors use gravity feed, typical pharmaceutical roller compactors use auger feeds that accurately and precisely deliver powder to the rollers at a uniform rate in accordance with in-process specifications for precompression force. The compacted granulation is milled and then final-blended with additional excipients, which typically include a lubricant, prior to tablet compression. Properly compacted and final-blended granulation will have sufficiently increased density to allow the target mass to fit in the tablet press or encapsulator as well as uniform consistency and flowability to permit consistent control of tablet or capsule weight and content uniformity.

A roller press consists primarily of a pair of contrarotating rolls equal in diameter, mounted on shafts and turned by an electric motor. The roll gap, or the distance between the two rolls, depends on the pressure applied to the rolls (typically by hydraulic cylinders) and the rate at which the powder is passed between them. Powder is fed into the roll gap via either single- or double-screw augers, where it enters a slip region. In the slip region, particles shift in position and orientation relative to each other and begin to accelerate in speed. The blend is then compacted between the rolls in an area called the nip region. The size of this region depends on the roller diameter and is the region in which the powder's speed begins to match the speed of the roller surface. The compressibility and flow properties of the blend and the production requirements determine the roller diameter, speed, surface type, feeding type, and dwell time needed to produce an adequately densified and uniform granulation ribbon.

Although a long history of roller compactor use exists for pharmaceutical manufacture, formulation for roller compaction and roller compaction process development have traditionally relied on experience, trial and error, and empirical design of experiments. Investigators have begun to model the process (36–39), but no well-established QbD methodology exists to evaluate raw materials for attributes critical to processing by roller compaction. Recognition by health authorities and industry that identification and monitoring via PAT of critical raw and intermediate material attributes during roller compaction could provide a means to better control the process and ensure product quality has prompted studies to investigate the usefulness of NIRS to predict, monitor, and potentially be used in the process control of ribbon critical attributes (40–42). In addition, Soh (43) published a preliminary multivariate model demonstrating the importance of raw material properties. Models with over 20 material attributes were built, and dominant attributes were identified; the data were pooled from different formulations to create generalizations. As a follow-on to this modeling effort, Soh (44) identified the raw material attributes best able to predict ribbon quality (tensile strength of raw material compacts, particle size, span in particle size distribution, tapped density, and angle of fall) through partial least squares regression and showed the usefulness of roll gap and NIR spectral slope as process-critical control parameters for roller compaction.

CONTINUOUS PROCESSING

Continuous processing has been heavily used in food, petrochemical, and electronics processing operations for many years. Although a few pharmaceutical manufacturers have explored it in the past, trends such as more flexible regulatory approaches, cost pressures, increasing needs for controls, and recognition that it would leverage the capability of at- and in-line real-time monitoring and control loops for ensuring quality and minimizing or eliminating release testing are driving factors. In continuous processing-based systems at steady state, the relationship between any process perturbations and corrective control actions

would likely be more discernable than that in batch processes, which tend to be time dependent. This would be particularly true for continuous processing with a small in-process mass. Such a fully integrated processing system, along with complete understanding of each unit operation involved, would be complicated to develop, design, and implement, but compared with a batch operation, it would certainly be smaller and cheaper to operate and maintain, would create less waste, and would facilitate improved quality control (with fewer QC personnel) and thereby provide significantly greater ROI over a product's life cycle. Furthermore, compared with batch processing, it would consolidate processing at one site of manufacture and increase throughput by eliminating the manufacturing interruptions (and storage requirements) common between each of the unit operations in batch processing. It would also significantly reduce manufacturing lead times. While the industry as a whole is interested in this technology and beginning to recognize its potential value, because of the conservative nature of the industry, it will require some compelling reasons to make such a dramatic shift. One particular concern is the need to address the manner in which any off-specification material would be isolated in a manner so as to avoid cross-contamination with compliant material. Another issue is the lack of suitable continuous processing equipment.

CRITICAL QUALITY ATTRIBUTES

The assessment of criticality as it relates to drug product quality is typically determined as a function of risk. Delineating criticality is a function of assessing risk, predicated on understanding the relationship of process variables and material attributes to the quality attributes of the drug product (45). "Critical" may be applied to any feature of material attribute, property, or characteristic of a drug substance, component, excipient, drug product or device, and/or any process parameter, condition, or factor in drug substance or drug product manufacture. Risk assessment is carried out to distinguish noncritical attributes and process parameters from those known or considered to be potentially critical to one or more drug product quality attributes that are known to be critical to safety and/or efficacy. This assessment may incorporate decisions about risk based on prior knowledge or experimental study. The results of this assessment are evaluated to design a risk-based control strategy capable of preventing or mitigating the risk of producing a poor-quality product. A process or material control can reduce criticality by increasing detectability or reducing probability, but it does not change the potential for severity. A process control that reduces criticality is a critical process control parameter, and a material attribute control that reduces criticality is a critical material attribute. Some drug product critical quality attributes (CQA), such as sterility, will always be critical. Many drug product CQA are dosage form specific. Variables or attributes that are considered noncritical are differentiated from potentially critical ones on the basis of understanding how product quality is affected via evaluating the probability and severity of the risk posed to patient safety and/or efficacy. Risk assessment is central to defining criticality. Risk management efforts, as part of continuous improvement, may warrant periodic criticality reassessment. Material attributes or process parameters considered important for business reasons, that is, reducing costs, optimizing yield, etc., are not critical with regard to patient safety and/or efficacy and should not be defined as critical from a regulatory perspective.

Regarding raw material attributes critical to ensuring the quality of solid dosage forms produced by granulation, many material properties are either known to be important or potentially important depending on the dosage form being considered and the proposed formulation and manufacturing unit processes. Although the scientific literature contains many studies linking raw material attributes or properties, process parameters, and product quality attributes, precise knowledge is often lacking regarding the role played by many of the physical properties of pharmaceutical materials as well as the methods employed to quantify these properties (46). Such materials have properties that can vary between lots; these properties can affect behavior during processing as a function of process parameters, including equipment geometry and energy input. Monographs from pharmacopoeias emphasize purity, chemical stability, and assays and are insufficient because they have no specifications for the excipient physical or mechanical properties. Risk-based approaches to solid dosage

formulation and process development as well as modeling efforts (whether empirical or mechanistic) would be enhanced if formulation scientists had comprehensive databases of physical and mechanical properties for commonly used excipients, based on standardized methods. Such databases could then be used to link material attributes to process parameters and final product performance in a much more meaningful manner. Upon identification and confirmation of critical linkages between excipient physical properties and drug product quality attributes, at-line excipient batch acceptance testing by one or more PAT-based methods could be incorporated into the product control strategy to confirm excipient acceptability for use in drug product manufacture.

CRITICAL PROCESS PARAMETERS

Drug product manufacture involves a series of unit operations to produce the intended product. Each unit operation involves physical changes such a mixing, milling, granulation, drying, compaction, and coating. Process parameters for these unit operations include the type of equipment and equipment settings, batch size, and operating conditions, including environmental conditions when relevant (47).

During development, the relationships between material attributes, process parameters, and the quality attributes of outputs (blends, granulations, tablet cores, finished product, etc.) are investigated to determine their relationships and criticality. Critical process parameters have a direct, significant influence on critical drug product quality attributes when they are varied. Analysis of process robustness studies identifies critical process parameters. Ideally, interactions between raw material attributes and critical process parameters should be fully investigated and understood so that critical process parameters can be varied to compensate for changes in critical raw material attributes and therefore produce a drug product with consistent quality. Additonal work may be required at scale-up to confirm results of robustness studies conducted previously at pilot scale, and if the scale-dependancy of any critical process parameters was not established. Since many companies use similar formulations and technologies on a consistent basis, prior knowledge can be leveraged to predict scale dependencies.

IND/NDA DEVELOPMENT VS. LIFE CYCLE MANAGEMENT

The simple question of whether or when to consider, investigate, and implement QbD-PAT has several answers depending on where you are in the product development curve.

The investigational stages of a new product are the most efficient times to examine QbD-PAT. At early stages of development, firms are in their steepest learning curve for the molecule, dosage form, and associated manufacturing. It makes a great deal of sense to couple that learning curve with targeted mechanistic understanding and incorporating things like PAT into process development.

Postponing the decision will likely send the development process work back to earlier stages. The journey through scale-up can be markedly easier if product and process knowledge is the driver.

If a firm is looking at a new formulation of an old drug related to a new route of administration or a reduction in administration frequency, then QbD-PAT principles can be easily incorporated into product development because of the existing level of drug and product knowledge. At this stage, the firm usually possesses a reasonable body of knowledge regarding the molecule, stability, and potential for interaction. The development steps tend to be more truncated and easier to understand scientifically.

If a firm finds itself making postapproval changes to a product or process, for example, new site production, it presents an opportunity and entry point to invest in technologies that may streamline or achieve economies if QbD-PAT can be implemented.

Obviously, production scale manufacturing that involves large numbers of campaigns or lots/batches presents the type of scale that warrants consideration of QbD-PAT strategies. The more frequent the manufacturing cycle, the larger the savings and the more compressed the cycle times.

A commitment to large-scale implementation, however, does present questions as follows:

Do you have capable staff—research, development, and production?
Do you have capable facilities—small-, medium-, and large-scale R&D and production equipment that can be fitted with PAT technology sensors?
Do you have the R&D and capital budgets to make necessary upgrades or changes?
Do you have the capability to validate PAT coupled processes and technologies?
Did you plan appropriately for new technology implementation and inclusion into regulatory filings?
Do you have sufficient IT infrastructure to handle the increased amounts of PAT data (Fig. 5)?

The issue of worldwide development and launch is a desirable goal, however, there is still not global uniformity regarding regulatory bodies' ability to deal with QbD-PAT. Ideally, a firm should strive for one product and one process for global marketing at least in the United States, European Union, and Japan. Many firms develop a product in a staged manner starting with, say, the United States or European Union. In that type of scenario, a firm would likely be able to develop a QbD-PAT manufacturing strategy that would have a high chance of success as FDA and European Medicines Evaluation Agency (EMEA) are probably the most advanced and very comparable in their acceptance, familiarity, and capabilities.

When looking at life cycle management, especially postapproval changes to existing products, do you find yourself in a reactive mode? If you are reacting to out of specification (OOS) problems and filing postapproval changes in a reactive manner, then perhaps consideration of a PAT solution should be an option. Once developed and implemented, it affords better control, real-time trend monitoring, and potential for reduced end product testing. Use of QbD development with definition of a design space could also accommodate variation without the need for frequent postapproval changes.

The following are a short list of real-life scenarios ripe for QbD-PAT implementation:

Scenario 1: Modernizing and updating within an existing facility (essentially same approach and scale)
Scenario 2: Replacement of batch production process with continuous processing
Scenario 3: Specialty or niche products that require small-scale pilot-like facilities
Scenario 4: Scale-up to commercial scale in highly flexible plants with high throughput

There are some distinct advantages to be derived from QbD-PAT-driven product manufacturing, which are as follows:

Improved safety due to minimized operator contact
Few sampling errors/variability and real-time data collection
Reduced cycle time as real-time information eliminates laboratory analysis delays
Improved product uniformity due to real-time measurement and control
Increased ability to identify process problems or artefacts
Shorter development times due to increased understanding of the process
Reduced product release testing and potential for real-time release

As we move toward future steps, firms must start planning appropriate facilities, hire trained technical staff, and develop manufacturing processes that not only employ QbD and PAT but also use the concepts to economic advantage. As an example, equipment design for critical steps such as granulation should encompass blending, granulation, and drying in a single design vessel that employs PAT sensor technology that optimizes process and end point detection.

Such planning is no easy task for firms that are developing products in an environment of cost control and close regulatory monitoring.

CONVINCING MANAGEMENT

Costs and Savings

Just imagine a high-level management meeting where the topic of QbD and PAT has arisen. The VP of R&D says to the VP of Finance, "We need US$500 million to invest in capital expenditure to introduce QbD and PAT into our production and control systems." What would the VP of Finance say? Is it (*i*) "I can put this through the channels for approval next week?" or (*ii*) "What are the benefits of QbD and PAT, and what is the ROI we can expect? How does the company benefit from this?"

You can bet that the VP of Finance's response will be the latter. The same questions are being asked in a number of boardrooms at least in recent history. The pharmaceutical industry needs to be largely convinced that QbD and PAT are good for process understanding as well as for the business of pharmaceutical manufacturing and has an ultimate goal of benefiting the patient. The scope of savings in the pharmaceutical industry is immense. The FDA estimated that potential worldwide savings from efficiency improvement may be as high as US$90 billion. These savings could support (48) the cost of developing 80 to 90 new drugs every year (49). The illustration (Fig. 8) demonstrates the increase in R&D spending, while the number of new drugs and biologics being approved are disproportionally decreasing. How do we evaluate the cost savings and how do we convince management of the need for additional testing and controls, additional equipment, and additional time and resources in our already tight budgets and timelines to establish QbD and PAT, and develop a deeper understanding of our processes and products? These are tough challenges. The pharmaceutical industry will not realize the full potential of QbD and PAT until a good process understanding (which is fundamental to PAT) is achieved, and an improved understanding of design space provides for enhanced product quality, reduced time to market, competitive market advantage, and enhanced patient safety (50).

Should QbD and PAT be introduced in the early stages of pharmaceutical development or in later stages, that is, phase II onward after the commercial dosage form and target product profile are fully established? Should PAT be introduced only for new products or for products that are already marketed?

It is clear that QbD should occur at the early stages of development at which the drug substance and drug product are being characterized, understood, and defined. The boundaries within which any changes in parameters or controls or input do not affect the quality of the drug substance or drug product can be defined as development proceeds. The challenges are, however, to ensure that this additional work does not delay the clinical trials to be conducted for projects in development. The introduction of PAT to a commercial product and process has its benefits in improving the consistent quality of the drug product, reducing/minimizing failures and recalls, but has the challenges of introducing the changes in a manufacturing system that has implications for global registrations and hence may be seen as not a

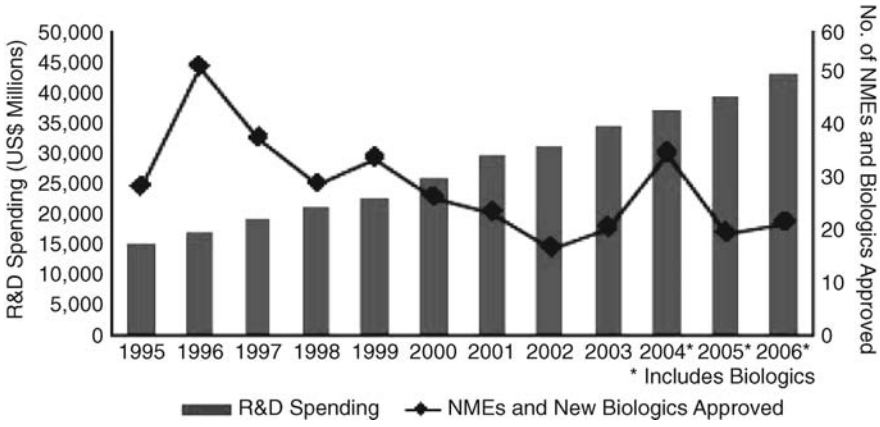


Figure 8 FDA/CDER data, PhRMA data, PricewaterhouseCoopers analysis.

worthwhile change. The cost benefits of lower rates of failure and recalls should be evaluated if the goal is to convince senior management to make these changes.

R&D

The purpose of pharmaceutical development is to design a product and its manufacturing process with consistent quality and performance. Pharmaceutical development covers the drug substance, excipients, drug product, manufacturing process, container closure system, physiochemical attributes, and, where appropriate, microbiological attributes and compatibility of the drug product with reconstitution diluents (51). Consequently, pharmaceutical development focuses on formulations and process to consistently deliver the intended performance of the product using enhanced formulation product and process understanding. This basic tenet is aligned with the FDA's use of product and process understanding as the foundation of its QbD concept, which states that quality cannot be tested into products but should rather be built into products. Hence, this greater product and process understanding may be a path to more flexible regulatory approaches with the FDA.

QbD and PAT should be viewed as investments, not just expenses. The goals should be to minimize total costs and time from discovery through product retirement. PAT and QbD serve as an enabler for operational excellence, combining improvements in manufacturing with improvements in quality and reduction in costs. New technologies offer a competitive advantage. Companies that insist on remaining in their old trajectories may miss the target. A new way of thinking is required to stay ahead. Closing the gap and speeding up drug development with new technologies will be a key strategy in responding to a range of drug development, productivity, and quality concerns.

Manufacturing flexibility can now be directly correlated to the level of scientific knowledge and understanding about the product and the manufacturing process submitted to the Agency. This scientific understanding can be obtained from several sources, including formal experimental designs, PAT, prior knowledge, and/or current knowledge gained from appropriate use of risk management tools. Both product and process understandings are achieved when a product control strategy and specifications can be based on a mechanistic understanding of how formulation and process CQA impact product performance. Product and process understanding is also used for quality risk management and establishment of the design space, specifications, and manufacturing controls. This greater scientific understanding will facilitate risk-based regulatory decisions, improvements in the manufacturing process within the design space without further regulatory review, reduction of postapproval submissions, and, eventually, real-time quality control. Hence, a comprehensive product and process understanding from pharmaceutical development forms the basis for effective product quality science-based risk management (52).

Time and Resource Savings

The FDA's goal of encouraging firms to collect and submit PAT research data is intended to give industry an opportunity to obtain experimental data, analyze it, determine how it relates to product quality, and utilize it in support of product registrations (53). Currently, most pharmaceutical companies have an active PAT effort within product development and/or pharmaceutical manufacturing. A driving force for this effort is to reduce production cycle times through real-time release testing while at the same time maintaining consistent product quality. Although these opportunities are mostly applicable to manufacturing, PAT in product development is advocated as a tool for reducing development/scale-up time. Increasing product and process understanding combined with process monitoring or control can reduce the number of experiments performed during scale-up, resulting in reduced batch failure and faster time to market for new compounds. Another benefit of increased knowledge obtained from pharmaceutical development and manufacturing studies provides the scientific basis to support the creation of the design space, product specifications, manufacturing controls, and overall control strategy. Although the design space is subject to regulatory assessment and approval, it is not considered a process change to work within it (8). However, working outside of the design space is a process change and is considered a regulatory postapproval change. A major pharmaceutical company's application of QbD for a compound in the FDA QbD-PAT pilot

program was successful in delivering savings of hundreds of millions of dollars where, because of a possible out-of-stock situation, QbD enabled rapid change to meet the market demand: the application included a site and scale change and expansion of design space with a Changes Being Effected (CBE-0) supplement. Another example is where the company saved tens of millions of dollars because of major capital avoidance for a continuous process.

QbD is a business strategy and not just a CMC initiative. It is not just a matter of estimating a better ROI or margin or cash flow or a P/E ratio but is about building an enduring strategy (6). Overall, QbD makes you respect scale and provides for risk management. As an integrated approach, it uses predictive tools, provides knowledge management and allows for developing talent with specific skill sets, and delivers the bottom-line through a good ROI.

Corporate management must also weigh the costs of product failure. The enormous expenses and embarrassment involved in a recall of failing batches of product are difficult to factor into the equation. The prospect of a well-controlled quality product resulting in a dependable supply chain can provide benefits that are difficult to quantitate.

SUMMARY

FDA Perspectives

Clearly, the QbD-PAT concepts have captured the attention of the Commissioner and Center Director. As early as 2003, the then Commissioner, Dr Mark McLelland, stated that the pharmaceutical industry needed to improve and had plenty of room for improvement. He also acknowledged FDA's role in inhibiting change. However, the track record of many pharmaceutical companies had been one of high levels of product failures and recalls as well as cycles of compliance followed by noncompliance.

He also noted that many facilities are not state-of-the-art as compared with other industries, and the pharmaceutical industry often struggles with product quality—often at great effort and cost. The industry, in general, puts little emphasis on manufacturing—most efforts are in product development.

Review and Evaluation Perspective

QbD-PAT paradigm infuses more science into the regulatory review and approval process. It represents science-based product design and control and further allows specifications to be based on product performance requirements. This, in turn, affords companies the opportunity to understand and control product variability in a more scientific and precise manner.

Honesty, communication, and data sharing are essential, yet, concerns remain about a common language and the ability to understand one another. It requires cultural change on the part of both industry and agency. Further, it requires a partnership on the basis of trust—not always an easy task for either partner.

Product and process understanding increases when QbD-PAT strategies are employed, and there are fewer surprises for reviewers and investigators.

QbD-PAT does allow for more flexibility in regulatory requirements as well as a more flexible review process. It is being implemented across all FDA-CDER CMC review programs; however, some are at differing stages of development and acceptance. Small molecule review probably leads biotechnology product review largely because of the special considerations needed for implementing QbD-PAT for biotechnology products. Further, a global perspective of world-wide regulatory agencies on the recognition and acceptance of QbD and PAT is necessary for the initiative to be fully successful.

Integrated development and manufacturing should allow for identification of quality surrogates for clinical performance (link critical product attributes to clinical outcomes). Rigorous, mechanistically based, and statistically controlled processes are allowing firms to implement new technologies and promote continuous improvements of their products without involving postapproval review and inspection efforts. It would be unwise not to mention some of the fears such as

1. requiring more detailed, data-laden filings,
2. increased review time,
3. reviewer confusion and misunderstanding,

4. postapproval impact,
5. that dossier quality may not improve, and
6. lack of global harmonization in dossier requirements and reviewer expertise.

There have been and are today pilot programs designed to examine QbD-PAT submissions and develop the required cadre of reviewers. They are and have been beneficial, but it will take time to assess the impact and level of commitment. It will also take time to make necessary adjustments for both the agency and regulated industry—in the meantime, there remain older legacy products, which must be run in parallel and cannot be handled the same way. The FDA and regulated industries continue to discuss the approaches at scientific conferences and workshops—an open dialog has clearly occurred with intense interest on both sides of the issue. The agency continues to produce guidances on this and related topics.

The larger pharmaceutical companies have clearly been able to devote the resources required to develop these approaches, and there is fear that it may result in tiering. Legacy products continue to be a big concern as they are slowest to change and represent a source of waste. Smaller pharmaceutical companies are finding it very difficult to find the capital and technical resources to incorporate QbD-PAT principles in early product development. The regulatory agencies are aware of these problems and have begun to work with the smaller discovery companies to encourage and foster development.

Field/Compliance Perspective

The current good manufacturing practices (cGMP) compliance aspects of QbD-PAT approaches to pharmaceutical manufacturing hold both promise and concern. FDA field-based investigators have been developing a specialized drug investigator cadre for several years now. These selected investigators have been exposed to QbD-PAT facilities and products in both individual and joint (headquarters reviewer) inspections quite successfully. They have also been exposed to the concepts and particulars in centralized field training programs, as have the CDER compliance officers.

QbD-PAT-containing submissions now trigger increased communication between the center scientific reviewers and the field investigators as well as more detailed discussions regarding science-based process, process control, and specifications, etc. Firms should be prepared for higher levels of data sharing and look for the benefits of a more science-based review and inspection.

PAT-mediated manufacturing certainly changes the level and extent of laboratory investigations, and the overwhelming body of data from on-line, at-line, and in-line instrumental monitoring makes audit-based review much easier and more transparent. The investigator's role will evolve into more verification and audit of process, process control, and product testing. Some of the serious concerns revolve around the complexity of manufacturing site computer networks, data processing and integrity, clear indications of any adjustments or corrections, dealing with the sheer size of the data pool, and fraudulent data introduction. It will take time and adjustments to find a balance and comfort level for both industry and the agency regional and district offices.

If one were to look into the future, one might envision the use of remotely transmitted data streams as a prelude to on-site inspections.

Regulated Industry Perspective

> Pharmaceutical companies are changing their business model: R&D is moving from a small pipeline and high costs to a smarter and more efficient organization. Manufacturing is moving from inefficient systems and quality problems to being more efficient with higher responsiveness. The gap between R&D spending and number of new molecular entities and biologics being approved is increasing (Fig. 8).

Unless the pharmaceutical industry demonstrates continuous improvement and adopts new technologies that can bring drugs faster to the market, the pharmaceutical industry will be left behind. QbD and PAT afford us the opportunities to improve our systems, have a deeper understanding of the process and the materials we work with, and deliver drugs to the patient

that are more reliable, consistent in quality, and assure a health benefit for the patient. These are all compelling reasons for the pharmaceutical industry to make the necessary investments into systems and processes whose benefits will far outweigh the initial capital costs. We will be investing for the future.

Regulations should be science based and risk based rather than being based on requirements alone. The applied scientific principles should be tested and reliable. An open partnership between the industry and regulatory bodies based on science will facilitate faster drug development and speed to market and bring the necessary health care benefits to the patient. QbD and PAT offer the possibilities of cooperative regulation based on risk analysis and process understanding to improve manufacturing quality, accelerate drug development, and lower the regulatory burden. Global regulatory agencies/bodies are also key players in this effort and are encouraged to cooperate with the pharmaceutical industry in bringing about the change desired. It is also important that QbD and PAT are part of the manufacturing and development architecture and that the facilities are appropriately equipped with tools to support QbD and PAT principles including, but not limited to, the following: product and process design, data modeling/mining, chemometrics, design of experiments, process analytics and control tools, reporting tools, and continuous improvement and knowledge management tools. Just measuring the quality in the finished product after manufacture is not good enough any more.

> An integrated quality suite can support six sigma and continuous improvement, regulatory process and review through continuous quality verification, management performance, and demand-driven manufacturing and supply. Companies can cope with the changing environment by introducing new production technologies, increasing operating efficiency, reducing product costs, producing individual products to address niche markets, and accelerating the speed to market. There is also a large potential to move to *personalized medicine*, which may require the establishment of a bigger or wider design space to allow for flexibility of manufacturing different dosage forms/strengths with limited experience, continuous optimization, and improvement. QbD and PAT should be viewed as investments, not just expenses. The goals should be to minimize total costs and time from discovery through product retirement.

An improved understanding of the process and design space can lead to a reduction in manufacturing costs due to increased process reliability and resulting quality, lower waste (lost batches due to out-of-specification results), and optimization of materials and resources. Further, global regulatory agencies may need to adapt to new ways of operating under a science- and risk-based paradigm in partnership with the industry, increase the technical expertise within, provide the regulatory flexibility, and reduce reporting burden, to facilitate change. Mechanisms for harmonizing the understanding, requirements, and positions on QbD-PAT should be put in place by ICH and other bodies to progress on these efforts. Furthermore, changes to global health care systems may lead to different pricing and reimbursement policies, which can result in profit pressures for pharmaceutical companies. However, there needs to be a right balance found on the investments made, and improvement in quality and patient benefits, and minimization of losses and regulatory burden, which can then result in an overall effective, multifactorial ROI.

CONCLUSIONS

Change is occurring, and one can see firms taking steps toward the desired state—many have taken a number of steps to move in the "right" direction. QbD, coupled with PAT, is an important element in achieving success. The merging of technologies with a new manufacturing paradigm can offer competitive advantages, however, pharmaceutical companies that insist on remaining in the present state of manufacturing will eventually be left in the rear-view mirror. The future is not a million miles away—much of it is here today. With opportunities, come challenges, and the QbD-PAT trajectory holds tremendous benefits for industry, FDA, and the public. QbD and PAT afford us the opportunities to improve our systems, enable a deeper understanding of the process and the materials we work with, and deliver drugs to the patient that are more reliable and consistent in quality and assure a health

benefit. These are all compelling reasons for the pharmaceutical industry to make the necessary investments into systems and processes whose benefits will far outweigh the initial capital costs. We will be investing for the future!

Author's Note: The views expressed in this chapter are the personal views of the authors and do not necessarily represent the views of the organization at which they are employed.

REFERENCES

1. ICH Q8 Pharmaceutical Development, May 19, 2006.
2. ICH Q8(R1) Pharmaceutical Development Revision 1, draft January 10, 2008.
3. ICH Q9 Quality Risk Management, June 1, 2006.
4. ICH Q10 Pharmaceutical Quality System, April 7, 2009.
5. PAT—a framework for innovative pharmaceutical development, manufacturing, and quality assurance, September 2004.
6. Watts DC, Clark JE. PAT—driving the future of pharmaceutical quality. J Process Anal Technol 2006; 3(6):6–9.
7. Cogdill R, Herkert T, Anderson C, et al. Synthetic calibration for efficient method development: analysis of tablet API concentration by near-infared spectroscopy. J Pharm Innov 2007; 2:93–105.
8. Blanco M, Gautista M, Alcalá M. Preparing calibration sets for use in pharmaceutical analysis by NIR spectroscopy. J Pharm Sci 2008; 97(3):1236–1245.
9. Luukkonen P, Fransson M, Björn I, et al. Real-time assessment of granule and tablet properties using in-line data from a high-shear granulation process. J Pharm Sci 2008; 97(2):950–959.
10. Bodson C, Rozet E, Ziemons E, et al. Validation of manufacturing process of diltiazem HCl tablets by NIR spectrophotometry (NIRS). J Pharm Biomed Anal 2007; 45:356–361.
11. Moes J, Ruijken M, Gout E, et al. Application of process analytical technology in tablet process development using NIR spectroscopy: blend uniformity, content uniformity and coating thickness measurements. Int J Pharm 2008; 357:108–118.
12. Cogdill R, Anderson C, Delgado-Lopez M, et al. Process analytical technology case study part I: feasibility studies for quantitative near-infared method development. AAPS Pharm Sci Tech 2005; 6(2):E262–E272.
13. Cogdill R, Anderson C, Delgado D, et al. Process analytical technology case study part II: development and validation of quantitative near-infared calibrations in support of a process analytical technology application for real-time release. AAPS Pharm Sci Tech 2005; 6(2):E273–E283.
14. Cogdill R, Anderson C, Drennen J. Process analytical technology case study part III: calibration monitoring and transfer. AAPS Pharm Sci Tech 2005; 6(2):E284–E297.
15. Dao N, Jouan M. The Raman laser fiber optics (RLFO) method and its applications. Sens Actuators B 1993; 1-3(11):147–160.
16. Ryder A, Oconner G, Glynn T. Quantitative analysis of cocaine in solid mixtures using Raman spectroscopy and chemometric methods. J Raman Spectrosc 2000; 31:221–227.
17. Clarke F, Jamieson M, Clark D, et al. Chemical image fusion. The synergy of FT-NIR and Raman mapping microscopy to enable a more complete visualization of pharmaceutical formulations. Anal Chem 2001; 73:2213–2220.
18. Hausman D, Cambron R, Sakr A. Application of on-line Raman spectroscopy for characterizing relationships between drug hydration state and tablet physical stability. Int J Pharm 2005; 299:19–33.
19. De Beer T, Bodson C, Dejaegher B, et al. Raman spectroscopy as a process analytical technology (PAT) tool for the in-line monitoring and understanding of a powder blending process. J Pharm Biomed Anal 2008; 48:772–779.
20. Šašić S. Raman mapping of low-content API pharmaceutical formulations. I. Mapping of alprazolam in alprazolam/xanax tablets. Pharm Res 2007; 24(1):58–65.
21. MacCalman M, Roberts K, Kerr C, et al. On-line processing of pharmaceutical materials using in-situ X-ray diffraction. J Appl Crystallogr 1995; 28:620–622.
22. Davis T, Morris K, Huang H, et al. In situ monitoring of wet granulation using online X-ray powder diffraction. Pharm Res 2003; 20(11):1851–1857.
23. Mathews L, Chandler C, Dipali S, et al. Monitoring blend uniformity with effusivity. Pharm Technol 2002; 26:80–84.
24. Roy Y, Closs S, Mathis N, et al. Thermal effusivity as a process analytical technology to optimize, monitor and control fluid-bed drying. Pharm Technol 2004; 28:21–28.
25. Roy Y, Closs S, Mathis N, et al. Online thermal effusivity monitoring: a promising technique for determining when to conclude blending of magnesium stearate. Tablets Capsules 2005; 3:38–47.
26. Ghorab M, Chatlapalli R, Hasan S, et al. Application of thermal effusivity as a process analytical technology tool for monitoring and control of the roller compaction process. AAPS Pharm Sci Tech 2007; 8(1):E1–E7.

27. Fariss G, Keintz R, Okoye P. Thermal effusivity and power consumption as PAT tools for monitoring granulation end point. Pharm Tech 2006; 30(6):60–72.
28. Léonard G, Bertrand F, Chaouki J, et al. An experimental investigation of effusivity as an indicator of powder blend uniformity. Powder Technol 2008; 181:149–159.
29. Lu Z, Hickey C, Sabatier J. Effects of compaction on the acoustic velocity in soils. Soil Sci Am J 2004; 68:7–16.
30. Buice R, Pinkston P, Lodder R. Optimization of acoustic-resonance spectrometry for analysis of intact tablets and prediction of dissolution rate. Appl Spectrosc 1994; 48:517–524.
31. Serris E, Camby-Perier L, Thomas G, et al. Acoustic emission of pharmaceutical powders during compaction. Powder Technol 2002; 128:296–299.
32. Kaatze U, Wehrmann B, Pottel R. Acoustical absorption spectroscopy of liquids between 0.15 and 3000 MHz, I: high resolution ultrasonic resonator method. J Phys E Sci Instrum 1987; 20:1025–1030.
33. Bolotnikov M, Neruchev Y. Speed of sound of hexane plus 1-chlorohexane, hexane plus 1-iodohexane and 1-chlorohexane plus 1-iodohexane at saturation condition. J Chem Eng Data 2003; 48:411–415.
34. Medendorp J, Lodder R. Acoustic-resonance spectrometry as a process analytical technology for rapid and accurate tablet identification. AAPS Pharm Sci Tech 2006; 7(1):E1–E9.
35. Akseli I, Cetinkaya C. Acoustic testing and characterization techniques for pharmaceutical solid dosage forms. J Pharm Innov 2008; 3(4):216–226.
36. Johanson J. A rolling theory for granular solids. J Applied Mech 1965; 32:842–848.
37. Simon O, Guigon P. Correlation between powder-packing properties and roll press compact heterogeneity. Powder Tech 2003; 130:257–264.
38. Turkoglu M, Aydin I, Murray M, et al. Modeling of a roller-compaction process using neural networks and genetic algorithms. Eur J Pharm Biopharm 1999; 48(3):239–245.
39. DecT, Zavaliangos A, Cunningham J. Comparison of various modeling methods for analysis of powder compaction in roller press. Powder Tech 2003; 130(1–3):265–271.
40. Gupta A, Miller R, Morris K. Nondestructive measurements of the compact strength and the particle-size distribution after milling of roller compacted powders by near-infared spectroscopy. J Pharm Sci 2004; 93(4):1047–1053.
41. Gupta A, Miller R, Morris K. Real-time near-infared monitoring of content uniformity, moisture content, compact density, tensile strength and young's modulus of roller compacted powder blends. J Pharm Sci 2005; 94(7):1589–1597.
42. Gupta A, Miller R, Morris K. Influence of ambient moisture on the compaction behavior of microcrystalline cellulose powder undergoing uni-axial compression and roller-compaction: a comparative study using near-infared spectroscopy. J Pharm Sci 2005; 94(10):2301–2313.
43. Soh J, Wang F, Boersen N, et al. Modeling the effects of raw material properties and operating parameters on ribbon and granule properties prepared in roller compaction using multivariate data analysis. Drug Dev Ind Pharm 2008; 34(10):1022–1035.
44. Soh J, Boersen N, Carvajal M, et al. Importance of raw material attributes for modeling ribbon and granule properties in roller compaction: multivariate analysis on roll gap and NIR spectral slope and process critical control parameters. J Pharm Innov 2007; 3-4(2):106–124.
45. Nozal R, Schultz T. PQLI definition of criticality. J Pharm Innov 2008; 2(3):69–78.
46. Hlinak A, Kuriyan K, Morris K, et al. Understanding critical material properties for solid dosage form design. J Pharm Innov 2006; 1(1):12–17.
47. Yu L. Pharmaceutical quality by design: product and process development, understanding and control. Pharm Res 2007; 25(4):781–791.
48. Benson RS, MacCabe DJ. From good manufacturing practice to good manufacturing performance. Pharm Eng 2004; 24:26–34.
49. U.S. FDA. Innovation and continuous improvement in pharmaceutical manufacturing, pharmaceutical cGMPs for the 21st century.
50. Maes I, Liedkerke BV. The need for a broader perspective if process analytical technology implementation is to be successful in the pharmaceutical sector. J Pharm Innov 2006; 1(1):19–21.
51. PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, U.S. Food and Drug Administration. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070305.pdf.
52. Dziki W. PAT in product development and its impact on PAIs, American Pharmaceutical Review.
53. Spavins J. Business benefits of QbD, ISPE 08 annual meeting. October 28 and 29, 2008.

FURTHER READING

Das P, Herrold R, Kinney T, et al. Real time on-line monitoring of fluid bed dryers using NIR spectroscopy. Available at: www.cdipharma.com/downloads/NIR_RealtimeMonitorFluidBed.pdf.

Index

about the book...

Rapid advances in the science of granulation, particle engineering, and process controls, along with regulatory changes, have prompted key opinion leaders and regulatory authorities to develop the ***Third Edition*** of this bestselling reference. Every pharmaceutical scientist should own a copy of this landmark resource:

- **stay up-to-date**—with what's being introduced and implemented in the industry—such as the concept of design space, process optimization and harmonization of regulations by the global health authorities
- **learn from the experts**—more than 45 global experts in manufacturing, engineering, pharmaceutical technology, drug delivery, pharmacy, and other sub-specialty areas share their years of experience to develop a trustworthy, comprehensive reference
- **ensure regulatory compliance**—as regulatory bodies are restructuring and developing a product quality regulatory system which provides a framework for implementing quality by design, continuous improvement, and risk management, it is imperative that scientists continue to adhere to the latest guidelines and protocols
- **save valuable time and money**—by learning how to achieve and manage the most efficient and thus cost effective product development and manufacturing operation in the current competitive environment
- **enhance your research**—new chapters on key topics such as supercritical fluids, nanoparticulate technology, nutraceuticals, biotechnology, controlled release granulation, process control, and expert systems provide in-depth analyses on key drivers in the field

about the editor...

DILIP M. PARIKH is President, DPharma Group Inc., Ellicott City, Maryland, USA. As an industrial pharmacist, he has more than 35 years of experience in product development and manufacturing, process engineering, and operational management of pharmaceutical facilities. He is an invited speaker at various scientific conferences worldwide on solid dosage manufacturing technologies, modified release dosage forms, fluid bed and spray drying technologies, quality by design implementation, and outsourcing pharmaceutical development and manufacturing. He serves on the editorial board of *Contract Pharma Journal.* The author of many scientific journal articles and book chapters, he is also the editor of the first and *Second Edition* of *Handbook of Pharmaceutical Granulation Technology.*

Printed in the United States of America

H100055

ISBN 978-143980789-7

90003

9 781439 807897

informa
healthcare
www.informahealthcarebooks.com

52 Vanderbilt Avenue
New York, NY 10017

Telephone House
69-77 Paul Street
London EC2A 4LQ, UK