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Daniel Bar-Shalom
Klaus Rose *Editors*

Pediatric Formulations

A Roadmap

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Introduction

This is the first book of its kind that specifically addresses pediatric formulations in the context of drug development. Before you read it, we hope that you have asked yourself why such a book was not published 50 or 100 years earlier. When we were asked to edit this book, having asked that question ourselves, we reflected on the existing formulations and found most of them wanting. Now we think that we know where we want to go, and we identified several obstacles. We didn't produce a "how to formulate" textbook for pharmaceutical scientists. The subtitle "a roadmap" indicates that all we can do is to contribute to overcome obstacles we are aware of, help find obstacles we are not aware of, and establish a platform that we hope will help people and institutions to build up the required knowledge.

After you have read the entire book, you will know that you just scratched the surface, but we also hope that you will have found a path to further walk through the jungle of information in print, the internet, related industries, and other sources.

Medicines have a complex background. The good news is that today there are many more effective medicines compared to 100 years ago. There are many players: physicians prescribe medicines, hospital pharmacists procure them at the hospital, and community pharmacists provide them outside the hospital. Companies develop and market new drugs, and after a while, new drugs lose their patent protection and can be produced and sold by other companies as generics. Academic scientists work on the theoretical understanding of diseases, pharmacology, chemistry, and many more aspects. Pediatric pharmacologists have elucidated a lot of what the child's body does to a given drug, and what the drug does to the child's body. All drugs are regulated by authorities to block quack medicines or wrongful claims, to detect side effects, to uncover counterfeits, and many more tasks. Drugs are paid by reimbursement organizations, which may be private, state-owned, or a combination. And of course the patients play a major role as well. And those are just the core players. There are many more, as our society has become more complex, to name a few: law enforcement and the judicial system, the press and other communication channels, the transport systems, and finally, the patients, the parents, the caregivers, patient organizations, and institutions, each with their particular perception of medicines and interests.

All healthcare players will emphasize that the patient's health is the one and only focus of their attention. Depending on your weltanschauung, your professional and personal experience, your cynism, and many more factors, you will accept the statements at face value, or you will put their statements and self-perception into context.

The position of children in our society has changed dramatically during the last century. Entire industries have evolved around them, earning their money by providing toys, clothing, literature, electronic gizmos, education, entertainment, and many more. Among medicinal specialties, pediatrics is a very young discipline. There were many assumptions that took decades to erode. One such assumption was that children need to be protected, so they were protected against clinical trials, but it was clinical trials that have changed the prognosis of most malignancies in children.

The development of age-adjusted drug formulations is not only a technical challenge. Otherwise, you would now be reading the 20th edition of this book. The dynamics behind the development of new medicines and of age-adapted formulations are complex. Background information is given in this volume.

There are two types of drugs on the market: generics (i.e., drugs whose patent protection has expired), and patent protected new ones, developed predominantly by the research-based pharmaceutical industry and, to some degree, by academia. For new drugs, today there are laws, both in the USA and in the EU, that compel the research-based pharmaceutical industry to consider children during drug development. One of the major demands of the authorities is the development of age-appropriate formulations. The other type of drugs, generics, is exempt from mandatory pediatric development, but there are incentives to stimulate it. Ultimately, industry will produce pediatric formulations if there is enough demand.

Let's have a look at which effective medicines existed 100 years ago. There were, for example, powerful cough suppressants containing opioids that were labeled as "suitable for children and adults." They were effective—so effective that you could kill your child with it. We will never know the number of children who didn't survive this treatment.

Source: www.wellcomecollection.org

If you go to a pharmacy museum, you will see that pharmacies sold many, many items 100 years ago. Apart from opioids, there were alcohol, creams and ointments, spices, dried fruits, powder of pulverized mummies, bones and other body parts of convicted criminals, dried fish, and many more. Most of this merchandize is not regarded as medicine today.

You would think that when Alexander Fleming approached British chemical companies in 1940 with the newly discovered penicillin, the companies would jump at the offer to initiate mass production. They all turned him down. The same happened when his successors at his institution flew to the USA in 1941 and approached US chemical companies. Eventually, the Office of Scientific Research and Development helped. It assigned capacities in parallel to its Manhattan project, better known for its key role in the construction of the atomic bombs. In hindsight, the companies that turned Fleming and his successors down were not overly smart, yet in contrast to real-life decisions, it is much easier to say in hindsight what was right and what was wrong. NSAIDS (non-steroidal anti-inflammatory drugs) can help close the arterial duct, but it took decades for clinicians to discover that. Is it reasonable to expect that just by allocating enough resources during drug development, all the potential pediatric uses will be uncovered? Whether it is possible as well as what allocation of resources toward this vision is rational are two additional questions.

Wherever there is a demand, somebody will try to sell something. A hundred years ago, there were many medicines sold against tuberculosis, cancer, infection, aging, and other health challenges. Most had two characteristics in common: First, they provided a good income to manufacturers and pharmacists. Second, they didn't work.

Modern pharmaceutical treatment evolved with the scientific revolution and with modern industry, which was the chemical industry first, the pharmaceutical industry later, and is today the life science or health industry. Powerful drugs were synthesized. It took two major catastrophes—the sulfanilamide elixir in 1936 and the thalidomide in 1961—to open the path to modern drug regulation, where the safety and efficacy of any drug must be proven by clinical and other trials. This signaled the advent of the modern label, a shift from claiming whatever the manufacturer wanted to claim towards a document that reflects what has been proven about the respective medicine for the given condition. This legislation led to new pharmaceutical terms such as "Off-Label," which refers to the use of drugs outside of its label, meaning the use in a therapeutic area or age group for which the drug is not registered. Unlicensed use in pediatrics often involves crushing tablets or opening capsules and suspending the contents to produce a liquid formulation suitable for oral intake. From 1961 on, most drugs in children were prescribed off-label.

Medicine is perceived as something that needs to be taken, not enjoyed, and for most adults, this works: You have a headache, you ingest a tablet. Your senses tell you that shape, surface, hardness, smell, and taste are wrong, but you force the tablet down your throat because you know from experience or because you trust the prescriber that it will help. Children cannot make this informed decision because they do not understand the connection between medicine and disease or because they are unable to override the reactions triggered by their senses. That said, many adults

are unable to swallow adult dosage forms. Therefore, children need oral dosage forms that resemble food they are used to ingest.

Today, many more children diagnosed with cancer survive than in the past. Pediatric oncologists systematically tested adult anticancer drugs in new doses and combinations in children. Most of these treatment schemes were off-label and still are today. These treatments can be life-saving, so off-label use is not bad per se. It can be dangerous if the treating physician or the compounding pharmacist knows too little about the respective drug.

Pediatric legislation was introduced in the USA in 1997 and in the EU in 2006, as a growing gap was perceived by academic scientists and regulatory authorities between the wealth of information available for adult patients and the limited information about drugs in children. The EU legislation is newer and more ambitious and asks for a pediatric investigation plan (PIP) early in development. A standard part of this PIP is often the development of one or even several pediatric formulations. One consequence of the mandatory PIP is that EMA asks for pediatric formulations for all new drugs, resulting in a higher demand for pediatric formulations, in turn felt by companies that have specialized in contract formulation. This applies even for rare and ultra-rare conditions.

We come back to the question about why this book was not published 50 or 100 years earlier. The answer is simple: nobody would have understood the need for such a book, as most of the drugs that today we use routinely did not exist yet. The increased demand for pediatric formulations is triggered by changing regulatory requirements that are discussed in depth in some chapters.

The debate about better medicines for children has in the meantime also reached the global discussion about availability of medicines for all children of this planet. The WHO program “make medicines child size” has special focus on children in developing countries. However, the requirements of medicines in the developed world sometimes contradict those of the developing countries. Technologically advanced formulations should not only be good but also be affordable. We have refrained from addressing this additional dimension.

This book intends to cover the anatomy and physiology of this population group as well as the technical state of the art of formulations where possible, to provide hints about where to find inspiration—such as the food industry—and to give a suitable background on the regulatory framework. Have we covered everything we wanted to cover? Certainly not. However, we tried to provide as accurate an exploration into pediatric formulations as we could, and we hope you enjoy it.

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Part I
The Patient

Chapter 1
Paediatric Development: Anatomy. Age, Weight, Body Surface and Stature, Organ Development

Hannah Batchelor

Abstract Growth and development are two major aspects of childhood not readily apparent in adults. There is extensive data in the literature on anatomical and physiological parameters and growth of humans from all continents and many counties. However, the most comprehensive data are available from European populations or North America.

1.1 Introduction

Reference individuals, for example, mean values used in the calculation of radiological protection, are typically based on data from Western populations and may not be representative of all populations [1]. However, there are data on Asian reference adult values from countries including Bangladesh, China, Japan, India, Vietnam, Pakistan, Philippines and Indonesia [2]. The variability in growth of children may be greater when considering populations in developing countries compared to Western populations as health and diet influence the rate of growth.

In terms of drug delivery, the growth from birth to adulthood is important as dose adjustments are typically in line with overall age, weight or body surface area (BSA) therefore there is a need to measure these values to ensure appropriate therapy. Although there is extensive data on foetal growth, this review only details post-natal development through to adulthood. International Commission on Radiological Protection (ICRP) data on reference individuals is provided for neonates, 1, 5, 10 and 15 years old subjects; therefore these age brackets are used within this review [1].

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1.2 Overall Body Growth

Humans have an extremely long growth period compared to other mammals; with height increasing up to approximately 16 years in females and 18 in males and weight increasing up to 25 years, although the rate of growth in weight is much slower after 18 years [1]. However, growth is known to occur in spurts and not as a single continuous linear phenomenon. The relationship between body mass, height and surface area for Western populations is shown in Fig. 1.1.

The data in Fig. 1.1 show that there is wide variability in the ratio to adult value between weight, height and BSA in the young and these values converge with age.

1.3 Dose Selection for Paediatric Populations

There are many alternative approaches that can be used for initial selection of a drug dose for paediatric patients. In 1940, Dawson [3] reported that doses increased less rapidly than predicted directly from weight based on findings that smaller species are generally more tolerant of drug treatment than larger species. BSA was subsequently proposed in 1950 to be a better algorithm for dose adjustments compared to body weight or age, particularly during infancy and childhood [4]. There are several ways that BSA is calculated from measurements of height and mass (e.g. [5, 6]). More recent models include a scaling factor for drug elimination, typically the allometric 3/4 power model [7] that has been found useful in normalising a large number of physiological and pharmacokinetic variables [8]. It is important to understand the

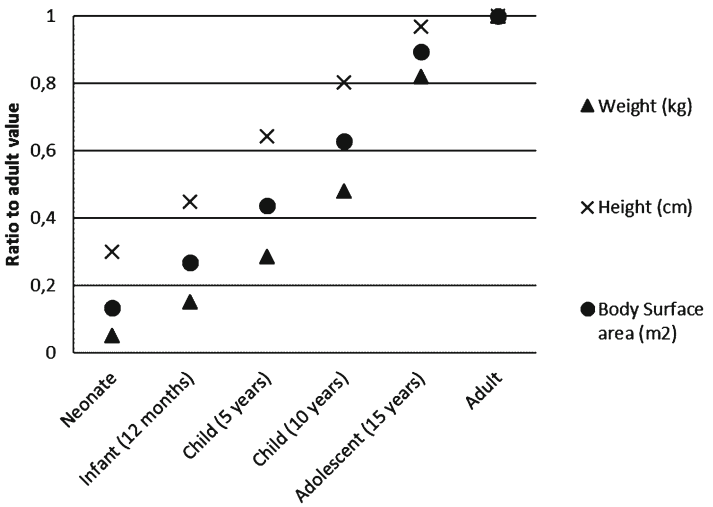

Fig. 1.1 Ratio of weight, height and body surface area to adult values by age (ICRP data [1])

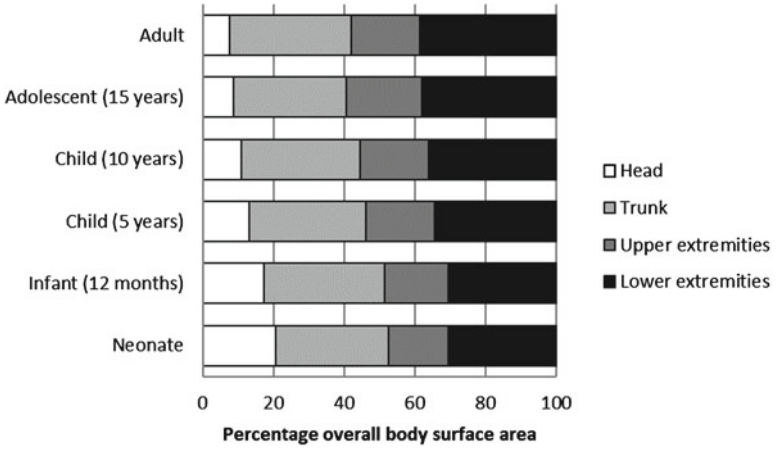

Fig. 1.2 Percentage distribution of body surface area as related to post-natal development

algorithm used in dose adjustment to ensure that the correct dosage adjustment is undertaken for each compound. However, it should be noted that all approaches assume that the child's weight, height and body composition are age appropriate and normal, and that the "reference" normal adult has a BW and BSA of 70 kg and 1.73 m^2, respectively [9]. There are several examples in the literature of instances where child growth is lower than expected with age in developing countries (e.g. [10–12]).

In terms of BSA the relative contributions change with age. During growth the limbs lengthen, thus, especially in the early years of life, the infant is markedly elongating in stature. This is reflected in the relative contributions of the head and lower extremities to BSA that is presented in Fig. 1.2.

At birth the head is a quarter of the total body length, whereas in the adult it is one-seventh [13]. Also the trunk is long with the upper limbs being longer than the lower limbs; from 6 months of age to puberty the extremities grow more rapidly than the head. This is reflected in the postural changes of the infant, from a recumbent one to that of an upright position.

1.4 Anatomical Organ Growth

Organs of interest during paediatric development that impact upon drug delivery include digestive, respiratory and urinary organs. The pattern in growth of these organs is similar to the whole body with a rapid increase in mass in infancy and early childhood followed by a slower growth phase and a second phase of rapid growth at pre-puberty ending in a terminal phase of slow growth in adolescence. The ratio of the mass of these organs compared to adult values is shown in Fig. 1.3.

The plot shows that the organ growth is typically in line with overall body growth for these reference populations which suggests that a child can be considered to be

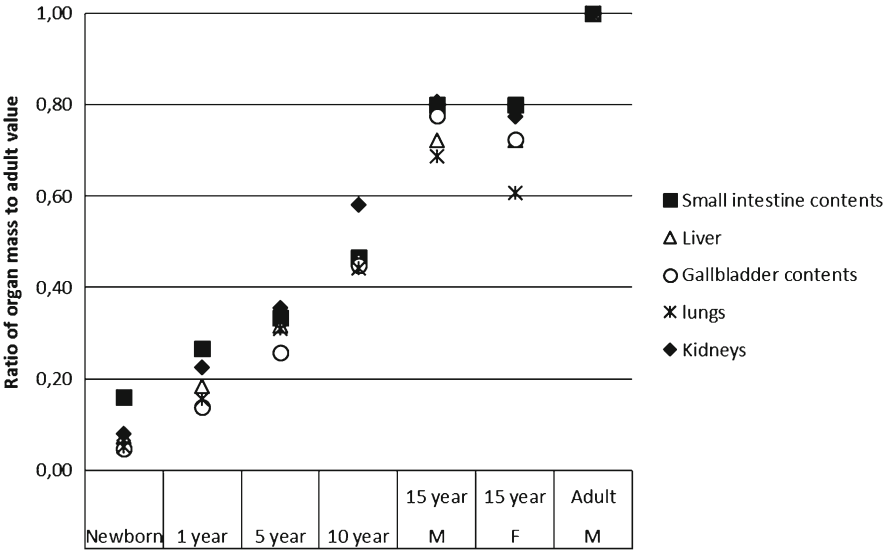

Fig. 1.3 Ratio of organ mass to adult values (by weight) with age [1]

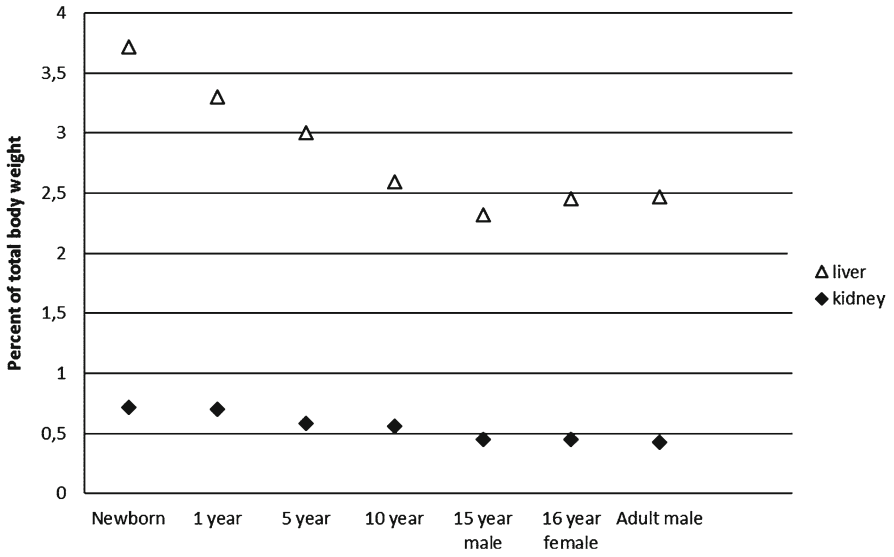

Fig. 1.4 Liver and kidney as percent of total body weight

a small adult. However, the relative size of an organ to the total body weight can provide an alternative view as in Fig. 1.4, where it is obvious that the liver and kidney are relatively much larger in younger children compared to adults.

The growth of a child is complex where not only anatomic growth influences development but also the maturation of many associated physiological processes.

As well as the liver and kidney relative size changing with age there is an associated change in the functionality as elimination pathways mature. Drug elimination clearance, for example, may increase with weight, height, age, BSA, and creatinine clearance [6]. All of these covariates may show a high degree of correlation and they are not mutually exclusive; any one factor may or may not predict between subject differences in clearance.

1.5 Conclusions

Growth results from the interaction of genetics, health and nutrition and is often used as an indicator of well-being. Paediatric development is often measured in terms of physical growth with height and weight measurements being integral to many clinical examinations. As dose adjustments are made on the basis of height and weight there is a need to carefully consider other parameters that may be mature even when height and weight are lower than anticipated for age; for example, liver and kidney function may be greater than anticipated for small age children.

References

1. Basic anatomical and physiological data for use in radiological protection: reference values. A report of age- and gender-related differences in the anatomical and physiological characteristics of reference individuals (2002) ICRP Publication 89. Ann ICRP 32(3–4):5–265
2. Agency IAE (1998) Compilation of anatomical, physiological and metabolic characteristics for a Reference Asian Man. Volume 2: country reports. Results of a co-ordinated research programme 1988–1993
3. Dawson WT (1940) Relations between age and weight and dosage of drugs. Ann Intern Med 13(9):1594–1615
4. Crawford JD, Terry ME, Rourke GM (1950) Simplification of drug dosage calculation by application of the surface area principle. Pediatrics 5(5):783–790
5. Lack JA, StuartTaylor ME (1997) Calculation of drug dosage and body surface area of children. Br J Anaesth 78(5):601–605
6. Anderson BJ, Holford NHG (2008) Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 48(1):303–332
7. Holford NHG (1996) A size standard for pharmacokinetics. Clin Pharmacokinet 30(5):329–332
8. Ritschel WA et al (1992) The allometric approach for interspecies scaling of pharmacokinetic parameters. Comp Biochem Physiol C 103(2):249–253
9. Jones BL, Van Den Anker JN, Kearns GL (2012) Chapter 25—pediatric clinical pharmacology and therapeutics. In: Principles of clinical pharmacology, 3rd edn. Academic, London, pp 417–436
10. Avan BI, Kirkwood B (2010) Role of neighbourhoods in child growth and development: does place matter? Soc Sci Med 71(1):102–109
11. Jones LL et al (2008) A comparison of the socio-economic determinants of growth retardation in South African and Filipino infants. Public Health Nutr 11(12):1220–1228
12. Lee J et al (2012) Socioeconomic disparities and the familial coexistence of child stunting and maternal overweight in guatemala. Econ Hum Biol 10(3):232–241
13. Huelke DF (1998) An overview of anatomical considerations of infants and children in the adult world of automobile safety design. Annu Proc Assoc Adv Automot Med 42:93–113

Chapter 2
Pediatric Development: Physiology. Enzymes, Drug Metabolism, Pharmacokinetics and Pharmacodynamics

Geert 't Jong

Abstract Growth and development consists of a continuum of biologic events that includes somatic growth, neurobehavioral maturation, and eventual reproduction, and has tremendous impact on the pharmacology of drugs in children. This impact is related to changes in body composition, development of organs and organ systems and change in these organs' functions. Ontogeny is the science that studies the origin and development of an organism. Pharmacokinetics of drugs (what the body does to a drug) is summarized in the acronym ADME, which stands for absorption, distribution, metabolism, and elimination.

Abbreviations

ADME	Absorption, distribution, metabolism, elimination
BMI	Body mass index
BSA	Body surface area
CYP	Cytochrome P450
ECW	Extracellular water
FFM	Fat-free mass
FM	Fat mass
GFR	Glomerular filtration rate
HAPMAP	Haplotype map
ICW	Intracellular water
PD	Pharmacodynamics
P-gp	P-glycoprotein

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PGx	Pharmacogenomics
PK	Pharmacokinetics
TBW	Total body weight

2.1 Introduction

Many of the development changes in body composition and organ function influence pharmacokinetics. A better understanding of the various physiologic variables regulating and determining the fate of drugs in the body and their pharmacologic effects has dramatically improved both the safety and the efficacy of drug therapy for neonates, infants, children, and adolescents [17]. During childhood, these changes are dynamic and can be nonlinear and discordant making standardized dosing an inadequate means of effective drug dosing across the span of childhood. The impact of these changes is largely related to function of organs important in metabolism (e.g. the liver) and excretion (e.g. the kidney) and changes in body composition (e.g. body water content, plasma protein concentrations) (see Fig. 2.1).

The first subsection will discuss the anatomical changes in body size and composition. Subsequently, the ontogeny of the developing human and its organs, and the impact on pharmacokinetic of drugs will be discussed.

2.2 Body Size and Composition

Physical growth after birth is a continuum from the extraordinary growth and development that take place in utero. Growth and development is not completed at birth, and maturation is reached much later. Important changes in response to and biodisposition of drugs occur during infancy and childhood. These changes influence the response to drugs and their toxicity and dosing regimens. The first 2–3 years of postnatal life is a period of particularly rapid growth and development. Most of the changes in body composition take place in this period. Puberty is a second period of change, relevant for pharmacokinetic. However, implications for pharmacotherapy are more extensive in the first few years. Figure 2.2a–d shows that both height and weight increase most during these years. Body weight doubles by 5 months and triples by 1 year. Body length increases by 50 % during the first year, and doubles by 4 years. Body surface area (BSA) doubles by the first birthday and triples by 4 years (Fig. 2.3a–d). Growth velocity decreases rapidly from 25 % per month at birth to 4 % at 1 year, and down to 1 % for most of the rest of childhood. Relative body surface is greatest at birth, as compared to body size (Fig. 2.3d). Caloric expenditure increases threefold to fourfold during the first year. Substantial changes in body proportions and composition accompany growth and development, as is shown in the BMI curve (Fig. 2.3e). Major organ systems differentiate, grow, and mature throughout infancy and childhood. Although growth and development are

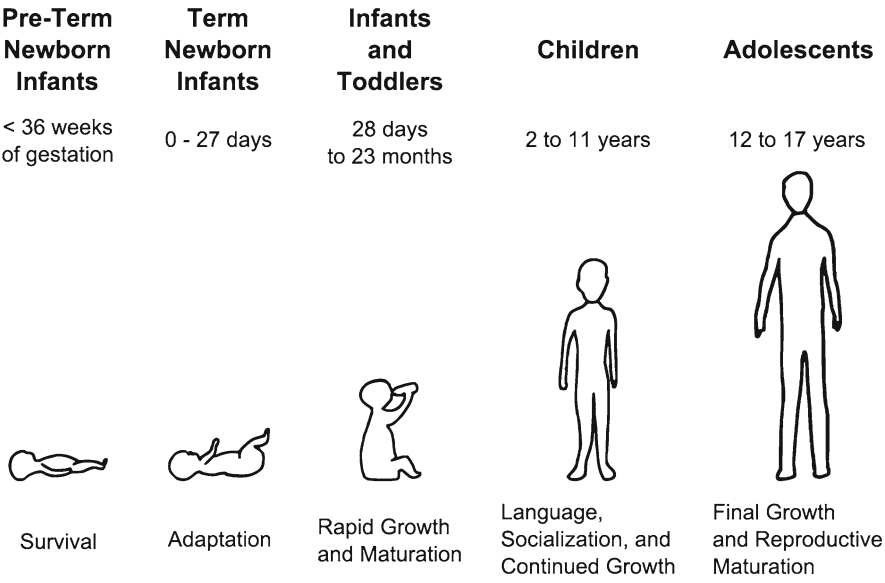

Fig. 2.1 Five stages of development. The pediatric population extends from the preterm and term newborn infant through childhood, and adolescence, or even to young adulthood. Each period of development has its own very specific characteristics, such as period of survival, period of adaptation, period of rapid growth and physiological maturation, period of language, socialization, and continued growth, and period of final growth and reproductive maturation [22]

most rapid during the first several years of life, maturation continues at a slower pace throughout middle and late childhood. This dynamic process of growth, differentiation, and maturation is what sets the infant and child apart from adults, both physically and pharmacologically.

The proportions of body weight contributed by fat, protein, and intracellular water change significantly during infancy and childhood (Fig. 2.4 and Table 2.1) [1, 11, 12]. Total body water (TBW = ICW + ECW) constitutes 85 % of body weight in the preterm neonate and 70–75 % in term neonates. This decreases to approximately 60 % at 4 months and remains relatively constant from this age onwards. Extracellular water decreases all through childhood (Table 2.1). The percentage of body weight contributed by fat is 3 % in a 1.5 kg premature neonate compared with 12 % in a term neonate; this proportion doubles by 4–5 months of age. "Baby fat" is lost when the infant starts walking and protein mass increases from 20 % in the term neonate to 50 % in the adult.

Puberty is an important phase in physical development. The age of onset of puberty varies as a function of ethnicity, health status, genetics, nutrition, and activity level. Generally, puberty begins between 8 and 14 years and occurs almost 2 years earlier in females than males. A pubertal growth spurt is accompanied by remodeling of the body over a relative short period of time with sexual maturation; feminization with more fat content in females and masculinization with more muscular mass in males (Fig. 2.5).

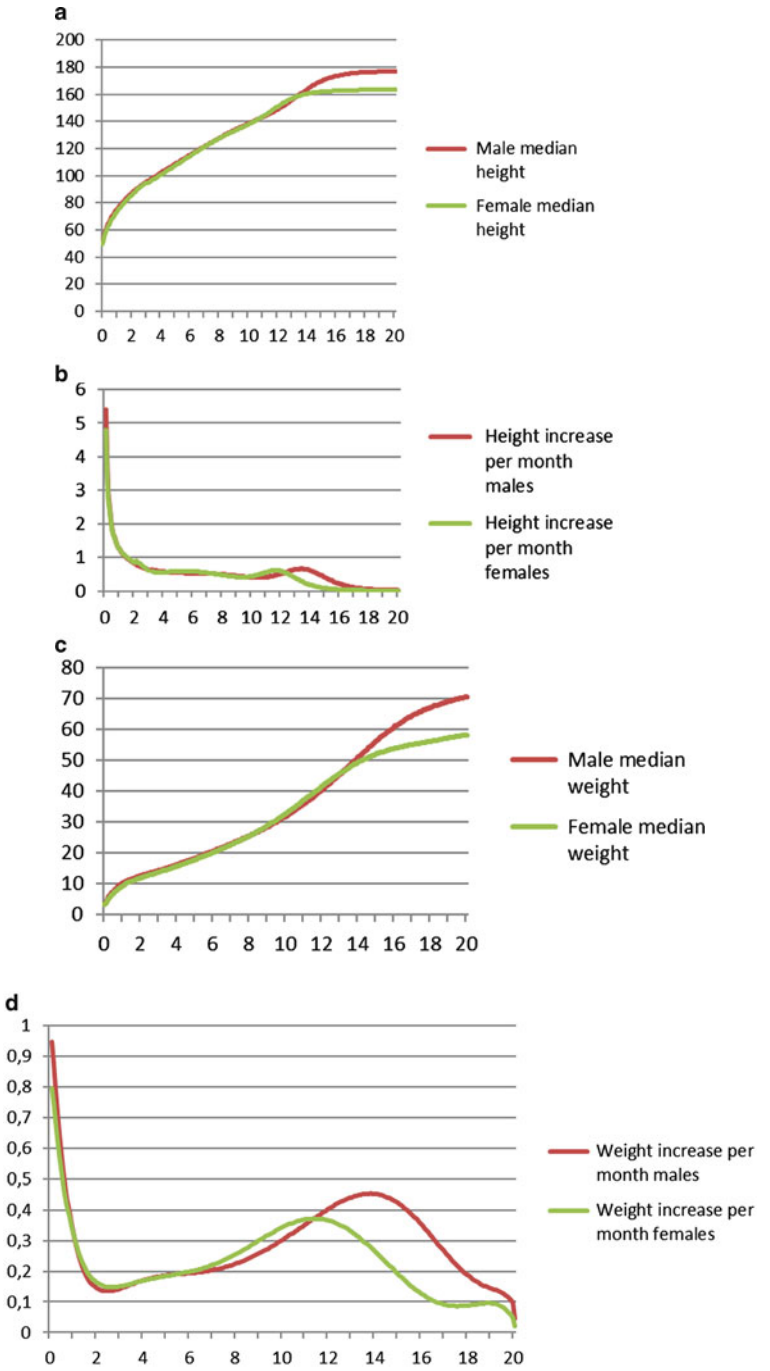

Fig. 2.2 Growth in humans; height and weight [Data: Center for Disease Control and Prevention (CDC) and World Health Organisation (WHO)]. (**a)** Growth chart with median (P50) height in centimeters (cm) in males and females 0–20 years of age. (**b)** Increase in height per month as percentage of height (cm) in males and females 0–20 years of age (calculated for the median height). (**c)** Growth chart with median (P50) weights in kilograms (kg) in males and females 0–20 years of age. (**d)** Increase in weight per month in kilograms in males and females 0–20 years of age (calculated for the median weight)

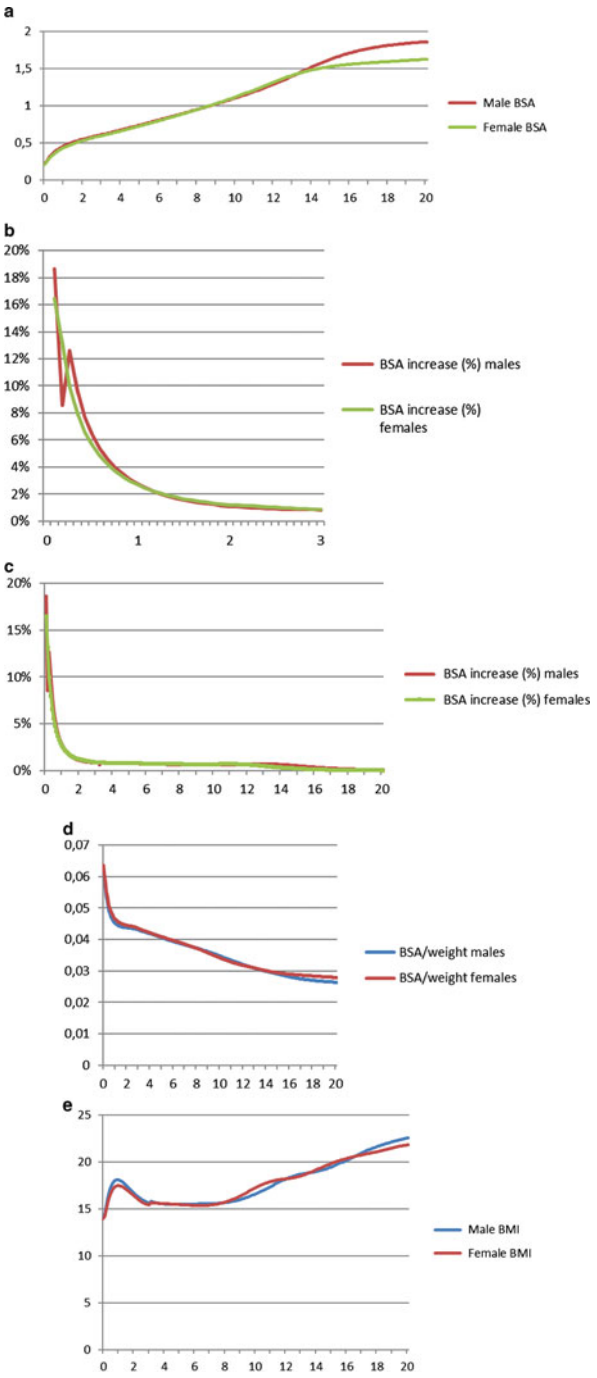

Fig. 2.3 Growth in humans; BSA and body mass index (BMI) [Data: CDC and World Health Organisation (WHO); BMI = weight (kg)/(height (m))^2; BSA calculation based on the Mosteller formula (BSA = $(W \times H/3600)^{1/2}$)]. (**a**) BSA curve for males and females 0–20 years of age. (**b**) BSA increase as percentage of BSA in males and females 0–3 years of age. (**c**) BSA increase as percentage of BSA in males and females 0–20 years of age. (**d**) BSA corrected for total body weight (BSA/TBW (m^2/kg)) curve for males and females 0–20 years of age (indicating relative BSA to be highest when compared to weight in neonates). (**e**) BMI curve for males and females 0–20 years of age

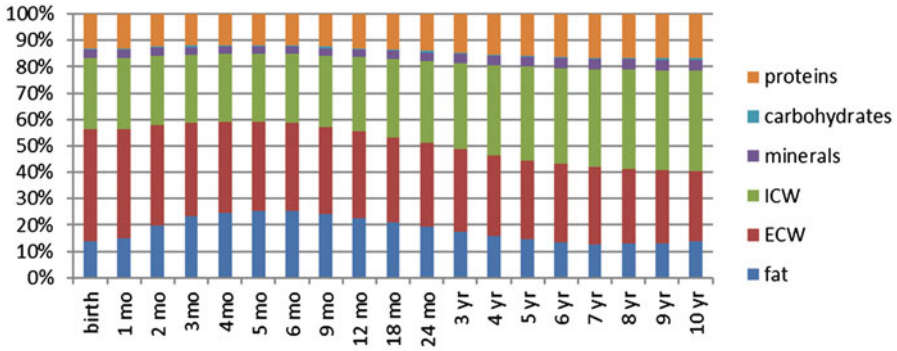

Fig. 2.4 Change in body composition proportions during childhood. *yr* year, *mo* month, *ICW* intracellular water, *ECW* extracellular water

Table 2.1 Body composition

Age	Fat	ECW	ICW	Minerals	Carbohydrates	Proteins
Birth	13.7	42.5	27.0	3.2	0.5	12.9
1 month	15.1	41.1	27.3	3.2	0.5	12.9
2 months	19.9	38.0	26.3	3.0	0.5	12.3
3 months	23.2	35.7	25.8	2.9	0.5	12.0
4 months	24.7	34.5	25.7	2.8	0.4	11.9
5 months	25.3	33.8	25.8	2.8	0.4	11.9
6 months	25.4	33.4	26.0	2.8	0.4	12.0
9 months	24.0	33.0	27.2	2.9	0.5	12.4
12 months	22.5	32.9	28.3	2.9	0.5	12.9
18 months	20.8	32.3	29.9	3.1	0.5	13.5
24 months	19.5	31.9	31.0	3.2	0.5	14.0
3 years	17.5	31.1	32.8	3.4	0.5	14.7
4 years	15.9	30.5	34.2	3.5	0.5	15.3
5 years	14.6	30.0	35.4	3.7	0.5	15.8
6 years	13.5	29.6	36.4	3.8	0.5	16.2
7 years	12.8	29.1	37.1	3.9	0.5	16.5
8 years	13.0	28.3	37.5	4.0	0.5	16.6
9 years	13.2	27.6	37.8	4.1	0.5	16.8
10 years	13.7	26.7	38.0	4.1	0.5	16.8

2.3 Pharmacokinetic

Significant efforts over recent years have been directed at research on pharmacokinetic and pharmacodynamics, but there is still a lack of information about the impact of ontogeny on the activity of drug-metabolizing enzymes, transporters, and other targets [22–24, 26].

Physiological processes that influence pharmacokinetic variables in the infant change significantly in the first years of life, particularly in the first few months.

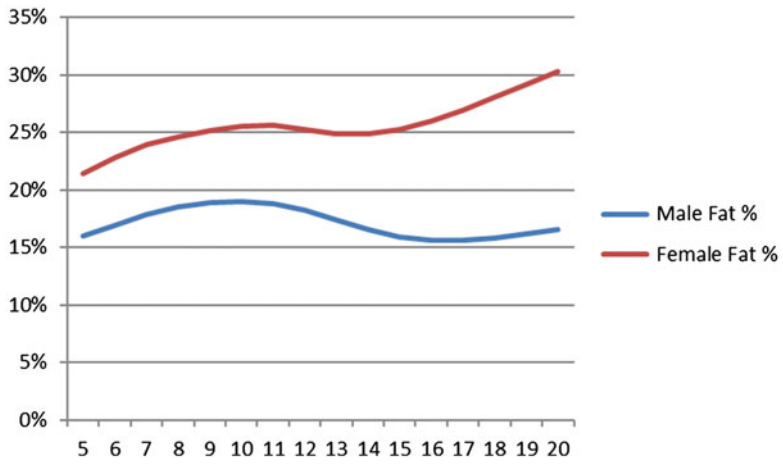

Fig. 2.5 Changes in fat mass (FM) as percentage of total body weight in adolescence (data from [28])

Drug metabolism is divided into absorption, distribution, metabolism, and elimination (ADME), and specific changes to each of these mechanisms will be further discussed. There is a clear distinction in regard to pharmacokinetic between children ≥2 years of age and infants <2 years of (postnatal) age. In children ≥2 years, pharmacokinetic parameters can be predicted from adult data using size differences in pharmacokinetic models. Children are mature and differ from adults only in size—children are small adults, from a pharmacokinetic perspective [15]. Infants <2 years are, of course, even smaller in size than children. When young infants—especially neonates—are being considered, although size is still an important factor, the maturation processes and status are even more important. Age then becomes essential for defining pharmacokinetic in infants compared with children [15] (see Fig. 2.6).

2.3.1 Absorption

Drug absorption in infants and children follows the same general principles as in adults. Drug absorption for therapeutic agents administered by oral, topical, or any other route that involves absorption (intrathecal and intraosseal excluded) depends on both the physicochemical properties of the drug and a variety of patient-related factors (e.g. reduced gastric acidity, reduced emptying time, motility, intestinal immaturity of mucosa leading to increased permeability, high levels of intestinal b-glucuronidase activity, reduced first-pass metabolism, maturation of carrier mechanisms, intestinal colonization, perfusion, reduced bile acid excretion in the case of oral administration). Unique factors that influence drug absorption include blood flow at the site of administration, as determined by the physiologic status of the

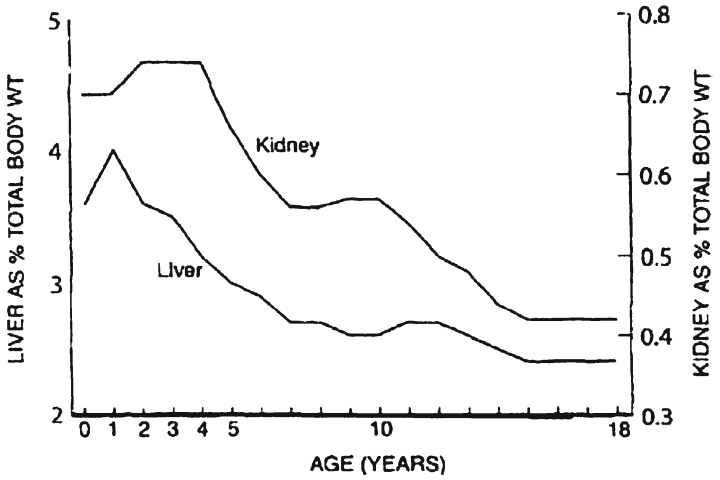

Fig. 2.6 Change in relative liver and kidney mass expressed as percentage of body weight from infancy to young adulthood [26]

infant or child, gastrointestinal function for orally administered drugs, which changes rapidly during the first few days after birth, and skin permeability in topical drugs.

The gut, with its large, folded surface, is our biggest interface to the outside world and is the most common route of administration. Absorption is strongly affected by several changes in physiology that take place during development. As in general growth, the most significant changes take place during infancy and the early years of childhood. In the first hours and days after birth, the intestinal weight and the mucosal mass almost double to accommodate the change from umbilical cord to oral feeding, which is similar to the change from parenteral to oral feeding [9]. Table 2.2 summarizes the age-dependent anatomical and physiological factors that may influence the rate and/or the extent of gastrointestinal absorption [2]. The gastric acid production is lower during infancy than in adults, and results in a higher gastric pH. Significant biochemical and physiologic changes occur in the neonatal gastrointestinal tract shortly after birth. In full-term infants, gastric acid secretion begins soon after birth and increases gradually over several hours. In preterm infants, the secretion of gastric acid occurs more slowly, with the highest concentrations appearing on the fourth day of life. Therefore, drugs that are usually partially or totally inactivated by the low pH of gastric contents should not be administered orally.

Gastric emptying time is prolonged (up to 6 or 8 h) in the first day or so after delivery, and is irregular and erratic in the first year, approaching adult patterns by 6–8 months of age. Therefore, drugs that are absorbed primarily in the stomach may be absorbed more completely than anticipated. In the case of drugs absorbed in the small intestine, therapeutic effect may be delayed. Gut motility is irregular, with a pattern of peristaltic activity different from adults [6], resulting in longer transit times before 6 months of age. Transit times range from 8 to 96 h. Small gut surface area is larger in infants and young children relative to body mass than in adults (as is BSA).

Table 2.2 Age-dependent factors affecting gastrointestinal absorption and the resultant pharmacokinetic outcomes relative to adult levels

	Newborn	Neonate (1 day to 1 month)	Infant (1 month to 2 years)
Physiological factor			
Gastric pH	Neutral → 1	>5	Adult
Gastric emptying	Reduced (variable)	Reduced (variable)	Increased
Intestinal surface area	Reduced	Reduced	Adult
Intestinal transit time	Reduced	Reduced	Increased
Pancreatic and biliary function	Very immature	Immature	Adult
Bacterial flora	Very immature	Immature	Adult
Enzyme/transporter activity	Very immature	Immature	Adult
Pharmacokinetic outcome			
Rate and extension of absorption	Variable	Variable	≥Adult
Gastrointestinal first-pass effect	Very reduced	Reduced	Approaching adult

Ileal active bile salts transport is absent at birth and develops during the first postnatal weeks, and pancreatic exocrine enzymes are less active in newborns and small infants. Human milk has been shown to have a direct impact on the development of the infant's digestive system, which equally impacts the digestion processes of its primary substrate. Intestinal permeability is increased for large molecules, such as proteins and high-molecular-weight drugs. The elimination of drugs through the first-pass effect is decreased due to decreased transporter and enzyme activity in the liver. Because of frequent feeding, and delayed emptying results in nutrients mostly being present in the stomach.

Gastrointestinal enzyme activities tend to be lower in the newborn than in the adult. Activities of α-amylase and other pancreatic enzymes in the duodenum are low in infants up to 4 months of age. Neonates also have low concentrations of bile acids and lipase, which may decrease the absorption of lipid-soluble drugs. Little information regarding the clinical effects of ontogenetic changes of cytochrome P450 enzymes and transporter proteins such as P-glycoprotein (P-gp) in the small bowel is available [16]. Reduced expression of CYP3A and P-pg in newborns and young children can result in increased bioavailability of medicines [10].

Absorption after intramuscular or subcutaneous injection depends mainly, in neonates as in adults, on the rate of blood flow to the muscle or subcutaneous area injected. Physiologic conditions that might reduce blood flow to these areas are cardiovascular shock, vasoconstriction due to sympathomimetic agents, and heart failure. However, sick preterm infants requiring intramuscular injections may have very little muscle mass. This is further complicated by diminished peripheral perfusion to these areas. In such cases, absorption becomes irregular and difficult to predict, because the drug may remain in the muscle and be absorbed more slowly than expected. If perfusion suddenly improves, there can be a sudden and unpredictable increase in the amount of drug entering the circulation, resulting in high and potentially toxic concentrations of drug. Examples of drugs especially hazardous in such situations are cardiac glycosides, aminoglycoside antibiotics, and anticonvulsants.

The skin of the full-term neonate possesses an intact barrier function and is similar to that of an older child or adolescent. However, the ratio of surface area to body weight of the full-term neonate is much higher than that of an adult (Fig. 2.2d). Thus, the infant will be exposed to a relatively greater amount of drug topically than will older infants, children, or adolescents. In contrast, data of human skin from preterm infants indicates an inverse correlation between permeability and gestational age. Permeability rates were 100- to 1,000-fold greater before 30 weeks gestation as compared with full-term neonates, with a three- to fourfold greater permeation rate seen beyond 32 weeks. In vivo studies suggest that this increased dermal permeability in preterm infants is a short-lived phenomenon with the permeability barrier of even the most premature neonates similar to that of full-term neonates by 2 weeks of postnatal life [13]. There are numerous reports in the literature underscoring the importance of skin absorption in neonates primarily showing toxicity after exposure to drugs or chemicals. Therefore, extreme caution needs to be exercised in using topical therapy in neonates and young infants. In contrast, the possibility of turning enhanced skin absorption of drugs to the infant’s advantage was explored by using the percutaneous route to administer theophylline or caffeine for apnea in preterm infants [4].

2.3.2 Distribution

As body composition changes with development, the distribution volumes of drugs also change. The neonate has a higher percentage of its body weight in the form of water (70–75 %) than does the adult (50–60 %). Differences can also be observed between the full-term neonate (70 % of body weight as water) and the small preterm neonate (85 % of body weight as water). Similarly, extracellular water is 40 % of body weight in the neonate, compared with 20 % in the adult (Table 2.1, Fig. 2.4). Since many drugs are distributed throughout the extracellular water space, the size (volume) of the extracellular water compartment may be important in determining the concentration of drug at receptor sites. This is especially important for water-soluble drugs (such as aminoglycosides) [20] and less crucial for lipid-soluble agents. Preterm infants have much less fat than full-term infants [1]. Total body fat in preterm infants is about 1 % of total body weight, compared with 15 % in full-term neonates. Therefore, organs that generally accumulate high concentrations of lipid-soluble drugs in adults and older children may accumulate smaller amounts of these agents in less mature infants. Another major factor determining drug distribution is drug binding to plasma proteins. Albumin is the plasma protein with the greatest binding capacity. In general, protein binding of drugs is reduced in the neonate. This has been seen with local anesthetic drugs, diazepam, phenytoin, ampicillin, and phenobarbital. Therefore, the concentration of free (unbound) drug in plasma is increased initially. Because the free drug exerts the pharmacologic effect, this can result in greater drug effect or toxicity despite a normal or even low plasma concentration of total drug (bound plus unbound). Some drugs compete

with serum bilirubin for binding to albumin. Drugs given to a neonate with jaundice can displace bilirubin from albumin. Because of the greater permeability of the neonatal blood–brain barrier [21], substantial amounts of bilirubin may enter the brain and cause kernicterus [3]. This was in fact observed when sulfonamide antibiotics were given to preterm neonates as prophylaxis against sepsis. Conversely, as the serum bilirubin rises for physiologic reasons or because of a blood group incompatibility, bilirubin can displace a drug from albumin and substantially raise the free drug concentration. This may occur without altering the total drug concentration and would result in greater therapeutic effect or toxicity at normal concentrations.

2.3.3 Metabolism

Upon termination of umbilical blood supply, the liver in the newborn takes on many biosynthetic and detoxification functions essential for adaptation to extrauterine life. These include aerobic metabolism, gluconeogenesis, synthesis of coagulation factors, and bile production and transport. Both liver size and volume relative to total body weight body decrease during childhood (Fig. 2.5) [19]. About 80 % of drugs in clinical use undergo metabolic reactions in the body. Eighty percent of these are metabolized by cytochrome P450s (CYPs). P450 isoforms are expressed in an age-dependent manner [14].

The drug-metabolizing activities of the cytochrome P450-dependent mixed-function oxidases and the conjugating enzymes are substantially lower (50–70 % of adult values) in early neonatal life than later [2, 5]. The point in development at which enzymatic activity is maximal depends upon the specific enzyme system in question. Enzymes most commonly involved in drug metabolism are those of the cytochrome P450 (CYP) family (phase I reactions) and the uridine diphosphate glucuronosyltransferase (UGT), sulfotransferase, glutathione-S-transferase, and *N*-acetyltransferase (NAT) families (phase II reactions). Each of the specific isozymes within a family matures at different rates during the first several years of life. The effect on metabolism of a specific medication depends on the dominant enzymatic pathway(s) responsible for metabolism of the drug [14]. The development of the enzymes involved in human metabolism was classified by Hines [14] in three categories: (1) those expressed during all or part of the fetal period, but silenced or expressed at low levels within 1–2 years after birth; (2) those expressed at relatively constant levels throughout fetal development, but increased to some extent postnatally; and (3) those for which onset of expression can occur in the third trimester, but where a substantial increase is noted in the first 1–2 years after birth. It is for this reason that certain biotransformation pathways, including hydroxylation by the P450 mono-oxygenase system and glucuronidation, demonstrate only limited activity at birth, while other pathways, such as sulfate or glycine conjugation, appear very efficient at birth.

For some genes, such as CYP2D6, longitudinal phenotyping studies in infants and young children have demonstrated that genotype–phenotype concordance is

apparent as early as 2 weeks after birth in term infants [7]. For others, such as CYP2C19, this concordance is mostly absent during infancy, as shown for pantoprazole, and phenotype cannot be predicted from the genotyping in this case [18, 25]. Microbial colonization in newborns also begins at birth, with microbiome composition being affected by mode of delivery, breast vs. formula feeding, hospitalization, antibiotic treatment, and diet [27]. Evidence assimilated from animal studies suggests that factors such as diet also have the potential to modulate the ontogeny of drug biotransformation pathways. Prediction of drug clearance, both on a population basis and at the level of individual patients, is therefore very complex [18].

The process of maturation must be considered when administering drugs to this age group, especially in the case of drugs administered over long periods. Another consideration for the neonate is whether or not the mother was receiving drugs (e.g. phenobarbital) that can induce early maturation of fetal hepatic enzymes. In this case, the ability of the neonate to metabolize certain drugs will be greater than expected, and one may see less therapeutic effect and lower plasma drug concentrations when the usual neonatal dose is given. During toddlerhood (12–36 months), the metabolic rate of many drugs exceeds adult values, often necessitating larger doses per kilogram than later in life. Besides these intrinsic aspects that influence pharmacokinetic during the neonatal period, there are other important events such as inborn or acquired diseases, environment and finally pharmacogenetics and pharmacogenomics.

Pharmacogenetics is the study of the genetically determined variations in an individual’s response to drugs. Pharmacogenomics is defined as the influence of DNA sequence variations on the effect of a drug [18]. The goal of this approach should be to identify which group of patients responds positively, which patients are non-responders, and which experience adverse reactions for the same drug and dose. Interindividual variability in response to any drug is mostly dependent on DNA sequence variations across the human genome, the haplotype map (HAPMAP). This should constitute a powerful tool in understanding genetic variants and drug responses (biomarkers). At present, there is still a significant lag between knowledge in genetics and practical application for modeling of drug profiles (molecule, dose regimen, route of administration) on the genetic/genomic profile of the individual patient. Knowledge about drug-metabolizing enzymes, transporters, and receptors and their ontogeny is limited. To develop truly individualized pharmacotherapy, future clinical trials should consider the complex system formed by genotype, pharmacodynamics, pharmacokinetic, and environmental factors.

2.3.4 Elimination

The most prominent observation is that the mass of kidney relative to age is severalfold greater in preschool-age children than in young adults (Fig. 2.4) [8]. Renal clearance is an important route of drug elimination. While during the neonatal period there is minimal glomerular filtration and active tubular secretion of drugs, there is a

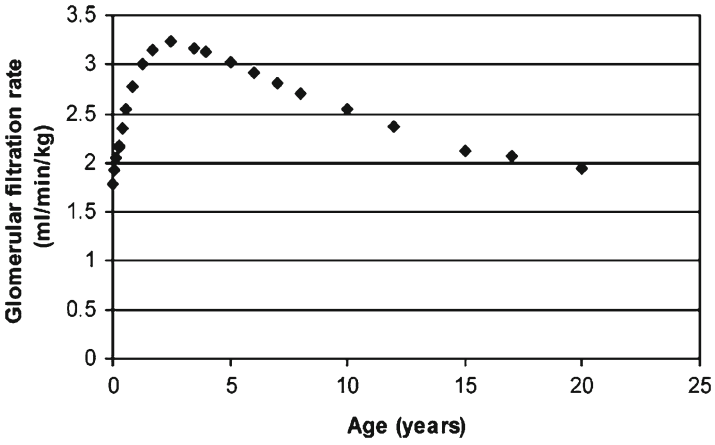

Fig. 2.7 Human GFR vs. age [8]

well-described rapid development in these processes in the post-neonatal period. The glomerular filtration rate (GFR) is much lower in newborns than in older infants, children, or adults, and this limitation persists during the first few days of life. Calculated on the basis of BSA, glomerular filtration in the neonate is only 30–40 % of the adult value. The GFR is even lower in neonates born before 34 weeks of gestation. Function improves substantially during the first week of life. At the end of the first week, the GFR and renal plasma flow have increased 50 % from the first day. By the end of the third week, glomerular filtration is 50–60 % of the adult value; by 6–12 months, it reaches adult values (per unit surface area). Therefore, drugs that depend on renal function for elimination are cleared from the body very slowly in the first weeks of life. A less appreciated fact is that during toddlerhood, there is an "overshoot" of the GFR well above the levels encountered in older children and adults, and there is an early achievement of adult levels in active drug secretion, which stays at a plateau throughout childhood and adulthood. Due to the high GFR in toddlers, dose requirements for renally excreted drugs in this age group are on a per-kilogram basis, much larger than in adults [8]. The need for higher doses of renally cleared drugs during early childhood reflects the enhanced excretory capacity of the kidney in this age group when normalized to body weight. One observes a shorter elimination half-life and faster clearance rate of renally excreted drugs than adult levels (Fig. 2.7). In contrast to animal models, the developmental changes in the human kidney are not linear processes. In particular, GFR in prepubertal children is almost twofold higher compared to adult values, as is the expression and function of the P-glycoprotein transporter. In contrast, no similar "surpass" is seen with organic anionic or cationic transport. Hence, the current adult dosing cannot simply be extrapolated to children. Instead, developmental changes must be taken into account when designing appropriate dosage regimens of renally excreted drugs for

infants and children. In particular, knowledge of the specific drug transporters involved in drug clearance is important to the therapeutic dose adjustment.

Subsequently, during toddlerhood, it exceeds adult values, often necessitating larger doses per kilogram than in adults, as described previously for drug-metabolic rate. Penicillins, for example, are cleared by preterm infants at 17 % of the adult rate based on comparable surface area and 34 % of the adult rate when adjusted for body weight. A decreased rate of renal elimination in the neonate has also been observed with aminoglycoside antibiotics (kanamycin, gentamicin, neomycin, and streptomycin). Since renal function in a sick infant may not improve at the predicted rate during the first weeks and months of life, appropriate adjustments in dosage and dosing schedules may be very difficult. In this situation, adjustments are best made on the basis of plasma drug concentrations determined at intervals throughout the course of therapy. Although great focus is naturally concentrated on the neonate, it is important to remember that toddlers may have shorter elimination half-lives of drugs than older children and adults, due probably to increased renal elimination and metabolism. For example, the dose per kilogram of digoxin is much higher in toddlers than in adults. The mechanisms for these developmental changes are still poorly understood.

References

1. Ahmad I, Nemet D, Eliakim A, Koeppel R, Grochow D, Coussens M, Gallitto S, Rich J, Pontello A, Leu S-Y et al (2010) Body composition and its components in preterm and term newborns: a cross-sectional, multimodal investigation. Am J Hum Biol 22:69–75
2. Alcorn J, McNamara PJ (2003) Pharmacokinetics in the newborn. Adv Drug Deliv Rev 55:667–686
3. Atkinson M, Budge H (2011) Review of the NICE guidance on neonatal jaundice. Arch Dis Child Educ Pract Ed 96:136–140
4. Barrett DA, Rutter N (1994) Transdermal delivery and the premature neonate. Crit Rev Ther Drug Carrier Syst 11:1–30
5. Bartelink IH, Rademaker CMA, Schobben AFAM, van den Anker JN (2006) Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 45:1077–1097
6. Berseth CL (1996) Gastrointestinal motility in the neonate. Clin Perinatol 23:179–190
7. Blake MJ, Gaedigk A, Pearce RE, Bomgaars LR, Christensen ML, Stowe C, James LP, Wilson JT, Kearns GL, Leeder JS (2007) Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. Clin Pharmacol Ther 81:510–516
8. Chen N, Aleksa K, Woodland C, Rieder M, Koren G (2006) Ontogeny of drug elimination by the human kidney. Pediatr Nephrol 21:160–168
9. Commare CE, Tappenden KA (2007) Development of the infant intestine: implications for nutrition support. Nutr Clin Pract 22:159–173
10. De Wildt SN, Kearns GL, Hop WCJ, Murry DJ, Abdel-Rahman SM, van den Anker JN (2002) Pharmacokinetics and metabolism of oral midazolam in preterm infants. Br J Clin Pharmacol 53:390–392
11. Ellis KJ, Shypailo RJ, Abrams SA, Wong WW (2000) The reference child and adolescent models of body composition. A contemporary comparison. Ann N Y Acad Sci 904:374–382
12. Fomon SJ, Nelson SE (2002) Body composition of the male and female reference infants. Annu Rev Nutr 22:1–17

13. Ginsberg G, Hattis D, Sonawane B (2004) Incorporating pharmacokinetic differences between children and adults in assessing children's risks to environmental toxicants. Toxicol Appl Pharmacol 198:164–183
14. Hines RN (2013) Developmental expression of drug metabolizing enzymes: impact on disposition in neonates and young children. Int J Pharm 452(1–2):3–7
15. Holford N (2010) Dosing in children. Clin Pharmacol Ther 87:367–370
16. Johnson TN, Thomson M (2008) Intestinal metabolism and transport of drugs in children: the effects of age and disease. J Pediatr Gastroenterol Nutr 47:3–10
17. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE (2003) Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med 349:1157–1167
18. Leeder JS, Kearns GL, Spielberg SP, van den Anker J (2010) Understanding the relative roles of pharmacogenetics and ontogeny in pediatric drug development and regulatory science. J Clin Pharmacol 50:1377–1387
19. Murry DJ, Crom WR, Reddick WE, Bhargava R, Evans WE (1995) Liver volume as a determinant of drug clearance in children and adolescents. Drug Metab Dispos 23:1110–1116
20. Pacifici GM (2009) Clinical pharmacokinetics of aminoglycosides in the neonate: a review. Eur J Clin Pharmacol 65:419–427
21. Saunders NR, Habgood MD, Dziegielewska KM (1999) Barrier mechanisms in the brain, II. Immature brain. Clin Exp Pharmacol Physiol 26:85–91
22. Seyberth HW, Kauffman RE (2011) Basics and dynamics of neonatal and pediatric pharmacology. Handb Exp Pharmacol 205:3–49
23. Tayman C, Rayyan M, Allegaert K (2011) Neonatal pharmacology: extensive interindividual variability despite limited size. J Pediatr Pharmacol Ther 16:170–184
24. Van den Anker JN, Schwab M, Kearns GL (2011) Developmental pharmacokinetics. Handb Exp Pharmacol 205:51–75
25. Ward RM, Tammara B, Sullivan SE, Stewart DL, Rath N, Meng X, Maguire MK, Comer GM (2010) Single-dose, multiple-dose, and population pharmacokinetics of pantoprazole in neonates and preterm infants with a clinical diagnosis of gastroesophageal reflux disease (GERD). Eur J Clin Pharmacol 66:555–561
26. Yaffe SJ, Aranda JV (2010) Neonatal and pediatric pharmacology. Lippincott Williams & Wilkins, Philadelphia
27. Johnson CL, Versalovic (2012) The human microbiome and its potential importance to pediatrics. Pediatrics 129(5):950–60. doi: 10.1542/peds.2011-2736, Epub 2012 Apr 2
28. Wells A et al (2012) Body-composition reference data for simple and reference techniques and a 4-component model: a new UK reference child. Am J Clin Nutr 96(6):1316–1326

Chapter 3
Developmental Changes in the Processes Governing Oral Drug Absorption

Barbara A.E. de Koning, Miriam Mooij, Trevor N. Johnson, and Saskia N. de Wildt

Abstract Pharmacotherapy in children often consists of oral medication. Effectiveness of oral prescriptions may be influenced by extrinsic (formulation, nutrition, and co-medication) and intrinsic factors (physiological and disease-related variation).

During development the GI characteristics change: swallowing reflexes, excretion of digestive enzymes, intestinal motility, transit time and intestinal transporters and drug metabolizing enzymes. For example, changes in drug efflux transporters result in a decrease or increase in expelling drugs back into the intestinal lumen and thereby in variation in oral bioavailability.

Closing the main information gaps on the ontogeny of GI processes governing oral drug absorption would allow for more accurate prediction of the oral disposition of drugs in children of all ages. Different ex- and in vitro study designs, as drug dissolution/solubility tests, in vitro drug metabolism and transporter studies and in vivo drug-microdosing can be used to elucidate the age-related changes in GI processes to better understand oral drug disposition in children. Using these data in PB-PK models may further guide individualized pediatric drug therapy.

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3.1 Introduction

Pharmacotherapy in children will usually consist of oral medication [1]. Absorption in the gastro-intestinal (GI) tract—and thereby effectiveness of oral medication—may be influenced by drug formulation, food intake, co-medication, and physiological factors. The oral route is characterized by changing environments from the oral cavity with saliva to the GI tract with interplay of digestive enzymes, intestinal motility, transit time and, moreover, intestinal transporters and drug metabolizing enzymes on the cellular level [2]. In children, the interaction between the oral drug and the developmental continuum will influence the systemic exposure to and effectiveness of the medication. Few studies are available on changes in bioavailability and other oral absorption parameters in the pediatric age range, a selection of which is presented in Fig. 3.1.

3.1.1 Swallowing Reflex

Swallowing is a multifactorial mechanism transporting food or liquid from the oral cavity to the esophagus. Swallowing involves coordination of neurologic and aerodigestive systems from the oral cavity to the esophagus.

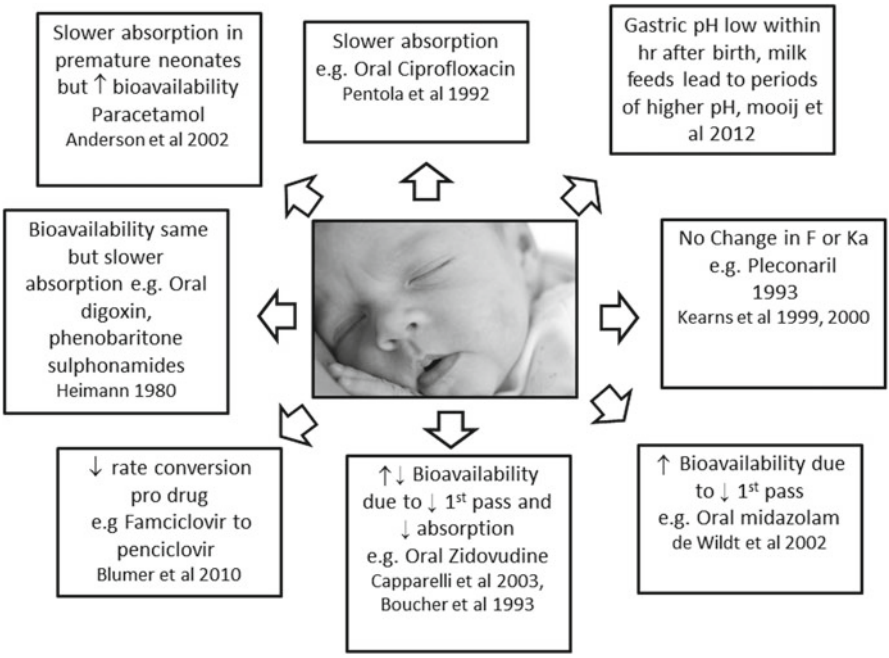

Fig. 3.1 Pediatric drug absorption—evidence from the literature

Quantitative measures such as time at which a (feeding) bolus reaches a specific location and time for a bolus to move from one place to another during a swallow may serve to determine if the process is successful [3]. Besides the voluntary component of swallowing, three different reflexes are also involved in the process; the pharyngeal swallowing reflex, the pharyngo-upper esophageal sphincter contractile reflex, and the pharyngoglottal closure reflex. Reflexive swallowing is crucial to airway protection, as it prevents food or fluid from directly entering the trachea [4], or returning from the esophagus to the trachea. Moreover, all reflexes have a distinct reaction on air and water stimuli [4, 5].

The first swallowing activity appears at around 11 weeks gestation, and further matures over time. Non-nutritive swallowing is well patterned by 34 weeks postmenstrual age. The suction and expression/compression component of sucking in preterm infants can be assessed on a five-point scale [6]. Recently an objective indicator of infants' feeding ability has been developed assessing feeding skills and endurance [7] as an expression of proficiency (number of ml taken during the first 5 min/total ml prescribed × 100) and milk transfer (ml/min).

Overall transfer (percentage of total volume transferred/volume to be taken) and rate of transfer (ml/min) of the feeding bolus is positively correlated with increased gestational age. So, although preterm babies could have developed similar oral motor skills as term babies, term babies can drink faster and more [8].

An important part of oral feeding is pharyngeal and upper esophageal sphincter function but this is not easy to assess. Compared with older neonates who are adapted to feeding, most preterm infants demonstrate poor pharyngeal pressures at the laryngeal inlet coupled with poor coordination of the pharyngeal propulsion with upper esophageal sphincter relaxation [9].

Research does not indicate that growth of the oropharyngeal cavity during childhood may influence swallowing [9], although the position of the feeding bolus in relationship to the laryngeal closure changes from the age of 2 to 48 months [10]. Furthermore, with increasing age or initiation of cup feeding, laryngeal vestibule closure occurs later in the swallowing process.

To our knowledge, salivary content has never been studied in relation to development. Two studies have addressed salivary flow rates in young fasting children and found that the mean salivary flow went up from 28.2 to 39.6 ml/min between 18 and 42 months of age, these changes are not statistically significant [11, 12].

On a more molecular level, recent studies on the salivary transcriptome revealed up-regulation of specific genes involved in the different aspects of oral feeding in newborns. The genes in question are involved in the sensory development, neurodevelopment, cartilage and bone development, cranial nerve development, feeding behavior, and muscular development [13].

Oral medication intake (tablets, capsules, liquids) is also influenced by the maturation state of normal feeding, unless liquid formulations are given via a nasogastric tube. Although liquid formulations overcome the problem of difficulty of swallowing solids, in children who are not fully accustomed to oral feeds, oral suspensions may also present a problem.

Moreover, children's taste sensation can negatively affect liquid ingestion. Sweet tastes are innately preferred by most or all herbivores and omnivores, presumably since sweetness reflects the presence of caloric sugars in plants. Bitter taste signals the presence of potentially toxic compounds and hence substances that are bitter are generally disliked and avoided. Neonates and infants therefore react adversely to bitter taste. A sensitivity to and preference for salty substances also appears to have an innate component, which develops at around 4 months of age. By 2 years of age, children's preferences for salty foods are even greater than those of adults [14]. These preferences in children should be accounted for by masking the taste of drugs, either by formulation or by dissolving the drug in a suitable vehicle. The latter is often challenged by the increased volume of the bottle feeding. However, this problem is not restricted to the (preterm) infant. Also older children and even adolescents (age between 11 and 20 years) often have difficulty swallowing tablets and capsules [15]. In a Danish study 8.5 % of the documented oral medication had been interrupted [16]. This problem might be explained by the smaller dimensions of the puerile pharynx and the developing oropharyngeal musculature [17] and by lack of experience in swallowing drugs. Children can be trained in swallowing oral medication, it was shown that training was successful from 3 years of age [18, 19].

Moreover, adapting formulations from a tablet or capsule to a liquid formulation may negatively influence drug efficacy [1]. Tablets and capsules cannot be divided multiple times without losing dosing accuracy. Regrettably, pediatric formulations for many drugs are lacking, and children often receive unlicensed and off-label drugs of which safety and efficacy are unknown. It is important, therefore, to speed up the licensing of drugs for children. Recently, much research effort was spent on pediatric medicines formulation with a view to facilitating easier oral drug administration. Especially the development of micro-particulate solid dose formulations and mini-tablets seems promising [20, 21] as it may overcome some of the inherent stability issues of oral liquid formulations.

3.1.2 pH

Gastric acid has a main role in food digestion and is an important barrier in gastrointestinal defense. Gastric pH is usually measured by intermittent gastric fluids aspirates or by continuous intragastric pH monitoring (24 h).

In all age ranges gastric pH is strongly acidic. Only in newborn children just seconds after delivery the mean is around 7, but dropping to 2–3 a few hours after birth [22, 23]. This phenomenon is explained by the swallowing of amniotic fluid during birth [22]. Other studies have subsequently shown that the gastric pH remains low at values between 2 and 3 in children of all ages [24–40].

In continuous measurement of gastric pH we usually consider the proportion of time in 24 h that values above 4 occur. In preterm infants this proportion ranged from 46 to 70 % [41, 42]. The age of 2 years seems to be a turning point as this proportion decreased from 51 in children under the age of 2 years to 34 % in older children [43]. This effect is most likely caused by the buffering capacity of the

formula or breast milk with which the younger children are fed, seeing that the older children receive more solids [37, 38, 43]. The influence of the buffering capacity of feeding was also seen in preterm neonates, as the postprandial pH of 7 dropped to 2 within 3 h after feeding [37, 38]. The buffering capacity of milk feeding is often believed to produce a non-acidic gastric environment in neonates. This is true to some extent; however, gastric pH reaches low adult values in between the feeds.

Little is known about the maturation of intestinal pH. One small study using a radio-transmitting pH-sensitive capsule showed an increase from 6.4 to 7.4 from the duodenum to the distal part of the small intestine in children aged between 8 and 14 years. The pH profile was almost identical to that found in healthy adults [44].

Different pH values can induce different absorption profiles to orally given drugs. For example, the antifungal drug ketoconazole is less effectively absorbed in preterm infants, most likely because the gastric fluid is not acidic during drug absorption [45].

3.1.3 pH Changes in GI tract

A drug's chemical nature determines the effect of prolonged periods of elevated gastric pH on its absorption. Weakly basic drugs such as ketoconazole [45] may be absorbed less well, but weakly acidic drugs somewhat better as they are more soluble at higher pH values. In addition, drugs that are unstable at acidic pH may be absorbed better at higher gastric pH values [46].

The effect of changes in gastric pH is probably most evident with drugs from Biopharmaceutical Classification System (BCS) classes II (low solubility, extensive metabolism) and IV (low solubility, low metabolism) [47]. It may be difficult to predict the effect of an age-related change in gastric pH (due to buffering effect of frequent oral feeds in neonates) on oral drug absorption as it is the result of interplay between changing feeding regimens and other developmental changes in oral drug absorption.

3.1.4 Gastric Emptying

The duration of a drug's exposure to a highly acidic environment is determined by the gastric emptying time.

Various techniques are available to establish gastric emptying time, including the gastric emptying breath test, scintigraphic procedure by Technetium-99M liquid gastric emptying scan, and the paracetamol absorption test. The results are expressed in various ways: gastric emptying time, gastric half-emptying time, or residual gastric activity at 1 h.

Gastric emptying time is influenced by stomach content. The L-glycine-1-^{13}C breath test performed in four healthy children (age range 12.1–16.0 years) showed different gastric half-emptying times after fructose or glucose intake (45.5 and 64.3 min, respectively). After ingestion of both sugars the gastric half-emptying time increased significantly to 85.3 min [48].

A meal of solids can increase the gastric half-emptying time even more as shown by a ^{13}C-octanoic acid breath test in nine healthy control patients (mean age 9 years; age range 4–16 years)after eating a meal of bread, ham, juice, and eggs [49]. The mean gastric half-emptying time was 121 min.

The influence of GI reflux on gastric emptying time was evaluated with the ^{13}C-octanoic acid breath test in 22 patients, mean age 13.2 year, with symptoms of gastroesophageal- or duodenogastroesophageal reflux. Surprisingly, gastric emptying time did not significantly differ from that in healthy controls [50]. Celiac disease, which affects the small bowel mucosa villi, was associated with a longer gastric emptying time, but the effect disappeared after initiating a gluten free diet [49]. The authors speculate that mucosal inflammation of the duodenum, with impaired smooth muscle contraction or neurotransmitter release, leads to motor abnormalities in the stomach-duodenal passage and thus longer emptying time. There are no data on gastric emptying in very young children established with breath tests.

Scintigraphic imaging can help establish gastric emptying time, gastric half-emptying time, and residual gastric activity.

This method showed a gastric half-emptying time of 60 min in preterm infants (median gestational age 28.9 weeks; range 26–33) at a median postnatal age of 9 days [51]. They were fed hourly although not using a standard meal size. The residual gastric activity at 1 h was 37.5 % (range 19–100 %) [51].

The influence of GERD (based on pH and/or scintigraphic imaging) on gastric emptying was studied in 477 patients aged 0–18 years [52]. In children without bolus or acidic gastroesophageal reflux, gastric residual activity at 1 h declined with increasing age: 65, 51, and 45 % in the age group up to 3 years, 4–6 years, and over 6 years, respectively. Gastric emptying was significantly delayed only in those children over 6 years suffering from reflux, these results were in line with findings from another study in children suffering from GERD; residual gastric activity was 52 % in 44 infants up to 23 months of age, and 49 % in eight children up to 14 years of age [53]. In yet another study, residual gastric activity in a healthy control group of 11 children with a mean age of 5.6 years was almost similar at 43.3 % [54].

Yahav et al. [55] reported a mean gastric emptying time of 87.8 min in a control group with a mean age 10.4 months. Gastric emptying times in healthy adult controls ranged between 56 (32–85) and 104 (49–126) min, for liquid and solid markers, respectively [56, 57].

In the paracetamol absorption test a pharmacological tracer is applied for measuring the rate of gastric emptying. This technique has been rarely applied in children, therefore age-related changes in outcomes are not known. A small study in 15 critically ill but food-tolerant children (median age 5.3 years) showed a median 1.5 (interquartile range 0.7–2.2) ratio of time to reach paracetamol peak to the maximum paracetamol concentration (T_{max}/C_{max}) [58]. The influence of diet was shown in adolescent participants, as the paracetamol absorption ratio was 1.4 for high-fat meals and 0.5 for low-fat meals [59].

Viewed from a different angle, a population pharmacokinetic study in newly born children showed a low oral paracetamol absorption rate in the first days of life, which then increased and stabilized after 1 week [60]. Gastric emptying time seems to

influence paracetamol absorption as a lag time, which is the time to reach and permeate the absorbing surface of the intestine [2], only occurs after oral paracetamol administration and not after rectal administration. This suggests that gastric emptying time may be the primary determinant of a lag time for oral absorption of paracetamol.

A recent meta-analysis of gastric emptying data from 49 studies covering 1991 healthy subjects ranging from preterm birth to adulthood showed that postnatal and gestational age were not significant covariates for changes in gastric emptying. The only significant influence was meal type; gastric emptying was faster in the order: breast milk > formula milk > semi-solid meal > solid meal [61]. A separate analysis of the data did not reveal a significant relationship between volume of feeds and gastric emptying time.

3.1.5 Antroduodenal Contractions

The rate of gastric emptying is determined by an orchestrated combination of antroduodenal motor activity, fundic contraction, pyloric sphincter relaxation, and intestinal motor activity. Contraction and relaxation of the distal stomach and proximal small intestine can be measured by antroduodenal manometry.

Both in the fasting and intraduodenally fed state, antral motor activity does not differ between preterm and term neonates [62]. Yet, in preterm neonates the proportion of antral clusters upon duodenal activity is much lower than that in term neonates. With increasing gestational age not only the degree of association of antral and duodenal activity [63] rises but also the effectiveness of the contractions on motility [64, 65].

Duodenal cluster activity during fasting lasted shorter in preterm neonates than in term infants but duodenal motor activity in response to feeding increased similarly in both preterm and term infants [62]. Maturation of the duodenal activity is dependent on the timing of the introduction of oral food, as maturation was more pronounced after early (days 3–4) rather than after late (days 10–14) introduction [66]. Moreover, duodenal motor activity response to bolus feeding shows a more immature pattern in preterm infants compared to term infants [67].

In contrast to antral motor activity, proximal intestinal (duodenal) motor activity matures throughout the first weeks of life, with increasing frequency, amplitude, and duration of propagating contractions. No data are available on children beyond the neonatal period.

3.1.6 Intestinal Transit Time

The effectiveness of gastro-intestinal motility is reflected by the orocecal transit time (OCTT), which can be measured with the hydrogen breath test, ^{13}C-ureide breath test, radio-transmitting capsule, red carmine marker test, or scintigraphy. However, each of these techniques has its limitations.

The hydrogen breath test with lactulose as non-absorbable carbohydrate substrate has limited use in the general population, which may include hydrogen-non-responders. Moreover, lactulose may accelerate transit time by its osmotic laxative effect, this was clearly shown in healthy subjects: OCTT after a meal was significantly longer than after lactulose [68]. Studies in the pediatric population using the hydrogen breath test to measure OCTT did not reveal an association with age [68–72]. The transit time differs from 60 to 110 min in children from 1 to 17 years of age, which is the same as in adults [72].

OCTT measured with the lactose-^{13}C-ureide breath test had a mean of 255 min in children from 3 to 17 years of age [69]. In adults the lactose-^{13}C-ureide test was validated against scintigraphy [73]. This test is unsuitable in infants below 6 months because they lack the required enzymatic activity to convert lactose ureide. The significantly longer OCTT with the labeled ureide test than the lactulose-H_2 breath test is thought to be caused by the laxative effect of lactulose [74].

In healthy children aged 4–14 years, intestinal transit times have been established using a radio-transmitting capsule, the mean values were 7.5 and 17.2 h in the small bowel and colon, respectively [44]. From the number of observations it was estimated that the capsule resided in the duodenum for 8 %, in the proximal part for 5 %, the mid part for 12 %, and the distal part for 75 % of the small intestinal passage time. The small intestinal transit time of 7.5 h established with this method is considerably longer than that established by the breath tests. The fact that the capsule, which was larger than 2 mm, moved through the distal part of the terminal ileum for three quarters of the time suggests a longer ileo-cecal transit for large particles.

Lastly, scintigraphy performed in premature neonates (gestational age 29 weeks) showed a mean OCTT of 3.1 h [51].

All techniques show a wide range of intestinal transit times with no clear age-association. Differences in reported transit times seem more or less related to the specific test properties.

Gastric emptying and intestinal transit time are the primary determinants of the rate at which drugs are presented to and dispersed along the mucosal surface of the small intestine. This rate is further influenced by intestinal disease. The time to reach maximal plasma levels of an orally absorbed drug could therefore be prolonged in the very young sick child.

3.1.7 Bile Salts and Pancreatic Enzymes

Bile, secreted from the liver, aids the digestion and absorption of lipids by the intestine.

A study in preterm neonates established intestinal bile concentration in the first few weeks postnatally at 4.55 mmol/l, for small- and appropriate-for-gestational-age neonates alike [75]. Another study showed that type of feeding influenced bile acid concentration, as it was higher in breast-fed infants than in formula-fed infants, but this difference is not statistically significant [76]. Measurements at 2, 7, and 10

days to 7 months postnatally made clear that the total bile acid concentration increases during the first few days to months, reaching comparable adult levels between 10 days and 7 months of age [77]. Digestive enzymes secreted by the exocrine pancreas aid in the digestion of nutrients, his digestive function is measured by the fecal Elastase-1 concentration, which is highly specific for the pancreas and is not degraded during the intestinal passage.

The fecal Elastase-1 concentration was abnormal in all of a group of preterm infants for the first 2 days after birth; while concentrations were normal in 43 % of a group of term infants. This discrepancy may be due to immaturity or insufficiency of the exocrine pancreatic function in premature neonates. Other than this there are no age-related changes in fecal Elastase-1 concentrations [78]. In both preterm and term neonates adult levels of fecal Elastase had been reached after 2 weeks [79].

The body's ability to solubilize and absorb lipophilic drugs is influenced by the effectiveness of the biliary function. Immature conjugation, decreased intestinal–hepatic-loop, and transport defects of bile salts into the intestinal lumen may reduce uptake of fat-soluble vitamins and lipophilic drugs.

3.1.7.1 Drug "First Pass" Metabolism in the Intestine

High levels of drug transporters such as multidrug resistance protein 1 (MDR1/MRP1/P-glycoprotein) in the villus tips on the apical side of small bowel enterocytes, along with CYP3A4 within the cells, form a concerted "first pass" defense mechanism limiting the oral bioavailability of drugs, dietary mycotoxins and other xenobiotics [80].

3.1.8 Development of Intestinal Transporters

Intestinal transporters are quite important to oral drug availability. Drug efflux transporters expelling drugs back into the intestinal lumen may reduce their availability. MDR1 is one of the most important efflux transporters [81]. Found in the brush border of the small intestine, this glycoprotein is genetically controlled by the *ABCB1* gene [82].

MDR1 ontogeny can be described by mRNA expression and protein content (total and glycosylated) and localization in the gut wall can be determined by immunohistochemistry. In duodenal biopsies from children aged from 1 month to 17 years, MDR1 mRNA expression was highly variable and not related to age [83, 84]. This observation was backed up Konieczna et al. [85] who investigated the differential expression of ABC transporters MDR1, MRP1, and BCRP in the intestinal epithelium of developing human embryos. Expression of all three transporters had reached adult levels after 12 weeks of intrauterine development. In contrast, Miki et al. showed an age relationship: mRNA expression was low in fetuses and neonates (14–20 weeks, 1–24 days post delivery) but generally higher in the adult group

(15–38 years) [86]. Van Kalken et al. failed to detect MDR1 expression in the intestine until 28 weeks gestational age [87]. Immunohistochemistry found the MDR1 protein on the apical surface of all enterocytes. In children younger than 3 years, MDR1 was also found on a small upper part of the lateral surface [88].

Variant alleles will often lower the activity of transporters. However, the effect of various alleles for MDR1 on activity of transporters on specific substrates is not always clear cut.

Pediatric post-renal transplant patients (age 0.36–16.3 years) carrying the *ABCB1* c.1236C>T or c.2677G>T variant allele showed higher oral bioavailability and lower pre-hepatic extraction ratios of the MDR1 and CYP3A4 substrate cyclosporine than did over 8-year-old non-carriers [89]. There is some evidence linking genotype of MDR1 with CYP3A4 mRNA expression, suggesting it is a compounded result of altered MDR1 and CYP3A4 activity [90].

Moreover, local or systemic inflammation may influence intestinal transporter activity. MDR1 mRNA expression in non-inflamed duodenal biopsies of children with Crohn's disease was significantly higher than that in normal biopsies [91]. The authors speculate that the discrepancy is due to the systemic inflammation present in Crohn's disease. Other studies, however, have shown down-regulation of drug transporter expression in inflammatory states [92].

Little is known about the postnatal development of the other members of the ATP binding cassette transporters found in the small bowel, such as multidrug resistance protein 2 (MRP2/ABCC2) or breast cancer resistance protein (BCRP/ABCG2) [81, 93–95].

3.1.9 Development of Intestinal Metabolism

Our understanding of the ontogeny of intestinal metabolism is far from complete. The 3A (CYP3A) subfamily of cytochrome P450 is probably most studied. This enzyme subfamily is abundantly expressed in the gut and is involved in the first pass metabolism of numerous orally administered drugs in adults [96].

The ontogeny of CYP3A can be described as changes in mRNA expression, protein expression, or activity level. A striking discrepancy is seen between intestinal CYP3A mRNA and protein expression, which may reflect the influence of a post-transcriptional regulatory mechanism. CYP3A protein expression increases with age [97], whereas CYP3A4 and CYP3A5 mRNA expressions are high in the first year of life and then drop to adult levels [88].

Immunohistochemistry in intestinal biopsies showed that CYP3A protein was present in only half of the enterocytes in children younger than 6 months. In the older children (up to 17 years of age) CYP3A protein was expressed in all enterocytes [88]. This suggests that CYP3A ontogeny is determined by the proportion of enterocytes expressing the enzyme rather than by a gradual turning on of enzyme expression in individual enterocytes. Further study should confirm this assumption as the manner of specimen collection, storage and pre-treatment to immunohistochemistry may have been of influence. Dissociation between protein and mRNA levels during maturation has also been reported for hepatic CYP2D6 [98].

The age-related increase in CYP3A protein levels is mirrored with increasing CYP3A4 activity, which can be measured by the degree of formation of 6beta-hydroxytestosterone from testosterone. This method did not detect CYP3A activity in fetal samples [97] butneonates showed much lower CYP3A activity compared to children older than 5 years [97].

Both mean intestinal CYP3A4 and CYP3A5 mRNA expression did not differ between young (age 0.1–15 years) and adult liver transplant recipients [81]. This finding suggests that intestinal CYP3A mRNA expression does not change beyond childhood. The authors did not study the effect of age within the pediatric cohort. However, these data suggest no age-related changes in CYP3A mRNA expression, although this cannot be excluded [83].

The influence of the CYP3A5 gene polymorphism has been studied in the transplant population. For children and adults alike, *CYP3A5*1* gene carriers express higher levels of intestinal CYP3A5 mRNA levels than do *CYP3A5*3* homozygous patients. In *CYP3A5*1* gene carriers, CYP3A5 mRNA accounted for 20–30 % of all CYP3A mRNA detected [83, 84].

Pediatric clinical trials on the oral bioavailability of CYP3A substrates are rare. Midazolam is a validated probe drug for CYP3A4/5 activity. In agreement with its age-related intestinal expression, the oral bioavailability of Midazolam in preterm infants (28–32 weeks, <10 days of age) is significantly higher than in adults (50 versus 30 %) [99, 100].

Of great clinical interest is evidence that type of feeding (breast milk or formula) seems to impact the developmental pattern of combined intestinal and hepatic CYP3A in neonates. CYP3A4 activity, expressed as the urinary metabolite/dextromethorphan ratio, increased in between two weeks and 6 months of age, but the repeated measurements showed that this increase was faster for formula- versus breast milk-fed children [101].

It is important to reiterate that intestinal MDR1 and CYP3A appear to work in concert to potentially limit oral drug bioavailability [90]. Hence, age-associated variation in intestinal MDR1/CYP3A4 activity may differentially impact substrates depending on their affinity for MDR1 and/or CYP3A4.

Increases in MDR1/P-glycoprotein causes increased efflux and therefore a decrease in substrate uptake. Consequently a lesser amount of intraepithelial drug is presented to the metabolizing enzyme. Decreased efflux can consequently cause greater risk on drug toxicity. However, as the MDR-1 substrate subsequently is presented to the liver the same efflux mechanism can have different consequences.

Increased CYP3A4 expression and activity with age, consequently causes higher oral bioavailability of, e.g. midazolam in premature children compared to adults.

3.1.10 Challenges in Research

To gain more insight in the ontogeny of oral drug absorption we will need to use a study design in which specific factors that are subject to change can be elucidated. After all, oral drug absorption is influenced by the interplay of age, genetic, and disease-related changes and co-medication, in addition to ethnicity and gender.

Nevertheless, the limited number of patients and reluctant willingness of parents and patients to cooperate is a challenge for pediatric studies. Moreover, breath tests are not feasible in all age groups and radioactivity of probe medication in the developing child raises ethical concerns, as does the invasive nature of tissue harvesting.

3.1.11 Research Options

3.1.11.1 GI Tract Model

To gain more insight in physiological influences on oral substrates, different parameters could be tested in an in vitro drug dissolution and solubility model. The Dutch Institute of Innovative Research has developed the TNO Gastro-Intestinal Tract model (TIM), a computer-controlled dynamic system which mimics the physiological human conditions in stomach and intestines [102, 103]. This system allows researchers to measure possible changes in the effective dose of the drug presented to the intestinal mucosa.

3.1.11.2 Modeling and Simulation: PB-PK Models and Population PK

The available data on age-related changes in relevant GI processes can be incorporated into population-based pharmacokinetics (PB-PK) software programs such as Simcyp® or PKsim®. These programs can then simulate the fate of drugs given to children of different ages and provide guidance for age-appropriate dosing. Modeling pediatric drug absorption by this approach still has a long way to go, however, it becomes more feasible as more research data becomes available and will eventually enable the prediction of oral absorption rate and bioavailability in children. However, in the meantime such a modeling approach can be used in terms of "what if" scenarios to investigate the effects of changing parameters on the prediction of absorption parameters.

The usefulness of these programs is limited by the lack of data on changing physiological and biochemical parameters across the pediatric age range. The current data availability is shown in Fig. 3.2, which also indicates areas that require further research including intestinal transporter ontogeny, intestinal fluid dynamics, and characteristics of the intestinal unstirred boundary layer. Moreover, validation of the models is still challenging as pharmacokinetic data on neonates and infants are scarce [104]. Opportunistic sampling and PK analysis in leftover blood drawn for clinical purposes from all patients receiving medication could provide more data. And then, more pediatric population pharmacokinetics (POPPK) studies involving oral drugs are needed, aimed at quantifying drug absorption parameters across the age spectrum rather than using fixed values for oral bioavailability (F) and absorption rate constant (ka).

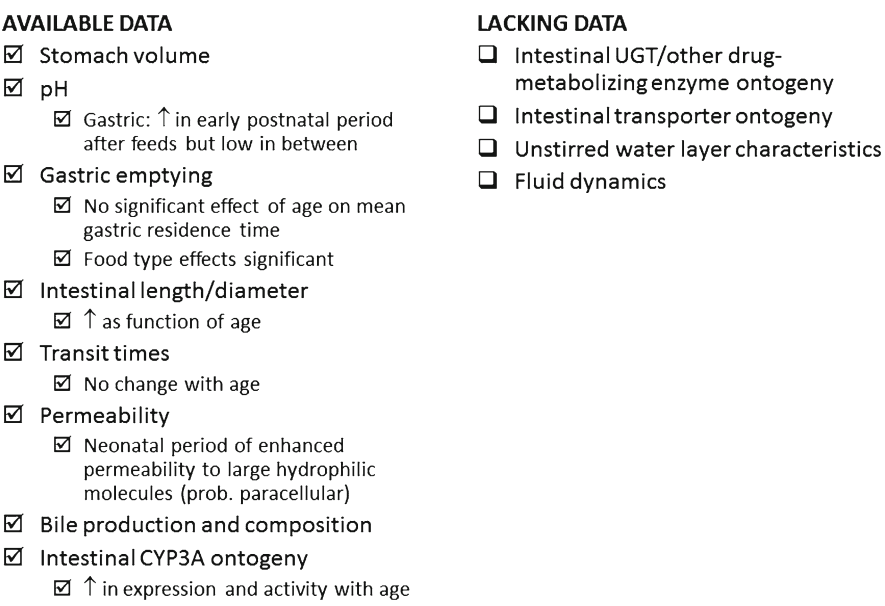

Fig. 3.2 Data availability for pediatric absorption models

3.1.11.3 In Vitro Drug Metabolism and Transporter Studies

The ontogeny of drug metabolizing enzymes and transporters can be studied in intestinal samples from children of all ages. Methods like RT-PCR for drug transporter expression (mRNA) and sensitive LC–MS–MS to measure protein content are used more widespread. The disconnect between drug transporter mRNA and activity should be considered by researchers especially where the solute carriers are involved, e.g. OATP1B1. Leftover tissue from surgical procedures should be collected consistently over a long time to provide enough samples for research purposes.

3.1.11.4 Microdosing

Ontogeny of drug absorption can also be addressed by a mechanism-based approach [105], e.g. studying one specific drug which represents a specific (intestinal) drug metabolizing enzyme. Pharmacokinetic studies in children of all ages may provide valuable information on the ontogeny of that specific pathway. For example, the plasma clearance of midazolam is a validated and widely used method to study variation in CYP3A4/5 activity in both adults and children [106].

Full PK studies to determine oral bioavailability for a probe drug using a multi-day cross-over design are hardly feasible in children for ethical and practical reasons. Children will not benefit from the drug but rather experience the drug effect and run the risk of adverse events.

Alternatively a stable-labeled isotope or a (very weak) radioactive-labeled microdose can be used [107, 108]. Both stable and radioactive approaches make it possible to administer a labeled probe drug in addition to an intravenous therapeutic dose. Parent compound and metabolites can therefore be traced in serum and urine. This enables simultaneous determination of the pharmacokinetics of therapeutic IV and the labeled oral dose. It eliminates the risk of therapeutic effect and toxicity. A prerequisite for the use of microdosing in this context, however, is dose-linearity across the dosing range.

3.1.12 Concluding Remarks

Closing the main information gaps on the ontogeny of GI processes governing oral drug absorption would allow for more accurate prediction of the oral disposition of drugs in children of all ages. Suggested approaches, both in vitro and in vivo, could provide more understanding of oral drug absorption in children. Clinical trials on the influence of age on drug absorption and thereby effectiveness are indispensable to formulate age-dependent drug dosing protocols.

References

1. Schirm E et al (2003) Lack of appropriate formulations of medicines for children in the community. Acta Paediatr 92(12):1486–1489
2. Atkinson AJ et al (2007) Drug absorption and bioavailability, in principles of clinical pharmacology. Academic, Burlington, pp 37–58
3. Kim Y, McCullough GH, Asp CW (2005) Temporal measurements of pharyngeal swallowing in normal populations. Dysphagia 20(4):290–296
4. Dua K et al (2011) Pharyngeal airway protective reflexes are triggered before the maximum volume of fluid that the hypopharynx can safely hold is exceeded. Am J Physiol Gastrointest Liver Physiol 301(2):G197–G202
5. Jadcherla SR et al (2007) Pharyngeal swallowing: defining pharyngeal and upper esophageal sphincter relationships in human neonates. J Pediatr 151(6):597–603
6. Amaizu N et al (2008) Maturation of oral feeding skills in preterm infants. Acta Paediatr 97(1):61–67
7. Lau C, Smith EO (2011) A novel approach to assess oral feeding skills of preterm infants. Neonatology 100(1):64–70
8. Lau C et al (2000) Characterization of the developmental stages of sucking in preterm infants during bottle feeding. Acta Paediatr 89(7):846–852
9. Rommel N et al (2003) Development of the orohypopharyngeal cavity in normal infants and young children. Cleft Palate Craniofac J 40(6):606–611
10. Weckmueller J, Easterling C, Arvedson J (2011) Preliminary temporal measurement analysis of normal oropharyngeal swallowing in infants and young children. Dysphagia 26(2): 135–143
11. Dezan CC et al (2002) Flow rate, amylase activity, and protein and sialic acid concentrations of saliva from children aged 18, 30 and 42 months attending a baby clinic. Arch Oral Biol 47(6):423–427

12. Siqueira WL et al (2007) Salivary parameters in infants aged 12 to 60 months with Down syndrome. Spec Care Dentist 27(5):202–205
13. Maron JL (2012) Insights into neonatal oral feeding through the salivary transcriptome. Int J Pediatr 2012:195153
14. Beauchamp GK, Mennella JA (2011) Flavor perception in human infants: development and functional significance. Digestion 83(Suppl 1):1–6
15. Hansen DL, Tulinius D, Hansen EH (2008) Adolescents' struggles with swallowing tablets: barriers, strategies and learning. Pharm World Sci 30(1):65–69
16. Steffensen GK, Pachai A, Pedersen SE (1998) Peroral medicinsk behandling af born—er der problemer? [Peroral drug administration to children—are there any problems?]. Ugeskr Laeger 160(15):2249–2252
17. Derkay CS, Schechter GL (1998) Anatomy and physiology of pediatric swallowing disorders. Otolaryngol Clin North Am 31(3):397–404
18. Garvie PA, Lensing S, Rai SN (2007) Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. Pediatrics 119(4):e893–e899
19. Czyzewski I et al (2000) Teaching and maintaining pill swallowing in HIV-infected children. AIDS Read 10(2):88–94
20. Spomer N et al (2012) Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. Arch Dis Child 97(3):283–286
21. Zajicek A et al (2013) A report from the pediatric formulations task force: perspectives on the state of child-friendly oral dosage forms. AAPS J 15(4):1072–1081
22. Datta S, Houle GL, Fox GS (1975) Concentration of lidocaine hydrochloride in newborn gastric fluid after elective caesarean section and vaginal delivery with epidural analgesia. Can Anaesth Soc J 22(1):79–83
23. Whetstine LJ et al (1995) Supplemental oxygen and gastric pH in unfed preterm infants. South Med J 88(4):458–461
24. Splinter WM, Schaefer JD (1990) Unlimited clear fluid ingestion two hours before surgery in children does not affect volume or pH of stomach contents. Anaesth Intensive Care 18(4):522–526
25. Splinter WM, Stewart JA, Muir JG (1990) Large volumes of apple juice preoperatively do not affect gastric pH and volume in children. Can J Anaesth 37(1):36–39
26. Nishina K et al (1994) Omeprazole reduces preoperative gastric fluid acidity and volume in children. Can J Anaesth 41(10):925–929
27. Cote CJ et al (1982) Assessment of risk factors related to the acid aspiration syndrome in pediatric patients-gastric ph and residual volume. Anesthesiology 56(1):70–72
28. Oderda G et al (2002) Measurement of postprandial changes in urine acid output to detect changes of gastric acid secretion after proton pump inhibitors in children. Dig Dis Sci 47(8):1843–1849
29. Kraus G et al (1990) Famotidine. Pharmacokinetic properties and suppression of acid secretion in paediatric patients following cardiac surgery. Clin Pharmacokinet 18(1):77–81
30. Jahr JS et al (1991) Effects of famotidine on gastric pH and residual volume in pediatric surgery. Acta Anaesthesiol Scand 35(5):457–460
31. Maekawa N et al (1993) Effects of 2-, 4- and 12-hour fasting intervals on preoperative gastric fluid pH and volume, and plasma glucose and lipid homeostasis in children. Acta Anaesthesiol Scand 37(8):783–787
32. Goresky GV et al (1992) Efficacy, duration, and absorption of a paediatric oral liquid preparation of ranitidine hydrochloride. Can J Anaesth 39(8):791–798
33. Yildiz F et al (1984) Reduction of gastric acid secretion. The efficacy of pre-anaesthetic oral cimetidine in children. Anaesthesia 39(4):314–318
34. Gupta L et al (2011) Long-term follow-up of patients with esophageal replacement by reversed gastric tube. Eur J Pediatr Surg 21(2):88–93
35. Miller BR, Tharp JA, Issacs WB (1990) Gastric residual volume in infants and children following a 3-hour fast. J Clin Anesth 2(5):301–305

36. Rogers IM et al (1975) Plasma gastrin in congenitial hypertrophic pyloric stenosis. A hypothesis disproved. Arch Dis Child 50(6):467–471
37. Smith LJ, Kaminsky S, D'Souza SW (1986) Neonatal fat digestion and lingual lipase. Acta Paediatr Scand 75(6):913–918
38. Omari TI, Davidson GP (2003) Multipoint measurement of intragastric pH in healthy preterm infants. Arch Dis Child Fetal Neonatal Ed 88(6):F517–F520
39. Kelly EJ et al (1993) Gastric acid secretion in preterm infants. Early Hum Dev 35(3): 215–220
40. Kelly EJ et al (1993) The effect of intravenous ranitidine on the intragastric pH of preterm infants receiving dexamethasone. Arch Dis Child 69(1 Spec No):37–39
41. Lopez-Alonso M et al (2006) Twenty-four-hour esophageal impedance-pH monitoring in healthy preterm neonates: rate and characteristics of acid, weakly acidic, and weakly alkaline gastroesophageal reflux. Pediatrics 118(2):e299–e308
42. Omari TI et al (2007) Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. J Pediatr Gastroenterol Nutr 44(1):41–44
43. Demir H et al (2005) Does simultaneous gastric and esophageal pH monitoring increase the diagnosis of gastroesophageal reflux disease? Turk J Pediatr 47(1):14–16
44. Fallingborg J et al (1990) Measurement of gastrointestinal pH and regional transit times in normal children. J Pediatr Gastroenterol Nutr 11(2):211–214
45. van den Anker JN et al (1993) Insufficient ketoconazole concentrations in preterm infants with fungal infections. Eur J Pediatr 152(6):538
46. Budha NR et al (2012) Drug absorption interactions between oral targeted anticancer agents and PPIs: is pH-dependent solubility the Achilles heel of targeted therapy? Clin Pharmacol Ther 92(2):203–213
47. Chen ML et al (2011) The BCS, BDDCS, and regulatory guidances. Pharm Res 28(7): 1774–1778
48. Hoekstra JH et al (1996) Evaluation of $^{13}CO_2$ breath tests for the detection of fructose malabsorption. J Lab Clin Med 127(3):303–309
49. Perri F et al (2000) Gastric emptying of solids is delayed in celiac disease and normalizes after gluten withdrawal. Acta Paediatr 89(8):921–925
50. Hoffman I et al (2007) Duodenogastro-esophageal reflux in children with refractory gastroesophageal reflux disease. J Pediatr 151(3):307–311
51. Bode S, Dreyer M, Greisen G (2004) Gastric emptying and small intestinal transit time in preterm infants: a scintigraphic method. J Pediatr Gastroenterol Nutr 39(4):378–382
52. Di Lorenzo C et al (1987) Gastric emptying with gastro-oesophageal reflux. Arch Dis Child 62(5):449–453
53. Seibert JJ, Byrne WJ, Euler AR (1983) Gastric emptying in children: unusual patterns detected by scintigraphy. AJR Am J Roentgenol 141(1):49–51
54. Miele E et al (2000) Persistence of abnormal gastrointestinal motility after operation for Hirschsprung's disease. Am J Gastroenterol 95(5):1226–1230
55. Yahav J et al (1985) Assessment of intestinal and cardiorespiratory function in children with congenital heart disease on high-caloric formulas. J Pediatr Gastroenterol Nutr 4(5):778–785
56. Graff J, Brinch K, Madsen JL (2000) Simplified scintigraphic methods for measuring gastrointestinal transit times. Clin Physiol 20(4):262–266
57. Bennink R et al (1999) Evaluation of small-bowel transit for solid and liquid test meal in healthy men and women. Eur J Nucl Med 26(12):1560–1566
58. Mayer AP et al (2002) Amylin is associated with delayed gastric emptying in critically ill children. Intensive Care Med 28(3):336–340
59. Lodefalk M, Aman J, Bang P (2008) Effects of fat supplementation on glycaemic response and gastric emptying in adolescents with Type 1 diabetes. Diabet Med 25(9):1030–1035
60. Anderson BJ et al (2002) Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. Anesthesiology 96(6):1336–1345
61. Vijjah P, Bonner J et al (2013) A meta-analysis of the effects of age and meal type on gastric emptying in premature neonates through adults. Abstract presented at the ESDPPP meeting in Sapzburg

62. Berseth CL, Ittmann PI (1992) Antral and duodenal motor responses to duodenal feeding in preterm and term infants. J Pediatr Gastroenterol Nutr 14(2):182–186
63. Ittmann PI, Amarnath R, Berseth CL (1992) Maturation of antroduodenal motor activity in preterm and term infants. Dig Dis Sci 37(1):14–19
64. Morriss FH Jr et al (1986) Ontogenic development of gastrointestinal motility: IV. Duodenal contractions in preterm infants. Pediatrics 78(6):1106–1113
65. Bisset WM et al (1988) Measurement of small-intestinal motor activity in the preterm infant. J Biomed Eng 10(2):155–158
66. Berseth CL et al (1992) Responses of gastrointestinal peptides and motor activity to milk and water feedings in preterm and term infants. Pediatr Res 31(6):587–590
67. al Tawil Y, Berseth CL (1996) Gestational and postnatal maturation of duodenal motor responses to intragastric feeding. J Pediatr 129(3):374–381
68. Vajro P et al (1988) Orocoecal transit time in healthy and constipated children. Acta Paediatr Scand 77(4):583–586
69. Van Den Driessche M et al (2000) Lactose-[^{13}C]ureide breath test: a new, noninvasive technique to determine orocecal transit time in children. J Pediatr Gastroenterol Nutr 31(4): 433–438
70. Khin M et al (1999) Investigation of small-intestinal transit time in normal and malnourished children. J Gastroenterol 34(6):675–679
71. Murphy MS, Nelson R, Eastham EJ (1988) Measurement of small intestinal transit time in children. Acta Paediatr Scand 77(6):802–806
72. Vreugdenhil G, Sinaasappel M, Bouquet J (1986) A comparative study of the mouth to caecum transit time in children and adults using a weight adapted lactulose dose. Acta Paediatr Scand 75(3):483–488
73. Geypens B et al (1999) Validation of the lactose-[^{13}C]ureide breath test for determination of orocecal transit time by scintigraphy. J Nucl Med 40(9):1451–1455
74. Wutzke KD et al (1997) Evaluation of oro-coecal transit time: a comparison of the lactose-[^{13}C, ^{15}N]ureide $^{13}CO_2$- and the lactulose H_2-breath test in humans. Eur J Clin Nutr 51(1):11–19
75. Boehm G et al (1991) Activities of lipase and trypsin in duodenal juice of infants small for gestational age. J Pediatr Gastroenterol Nutr 12(3):324–327
76. Jarvenpaa AL et al (1983) Feeding the low-birth-weight infant. III. Diet influences bile acid metabolism. Pediatrics 72(5):677–683
77. Challacombe DN, Edkins S, Brown GA (1975) Duodenal bile acids in infancy. Arch Dis Child 50(11):837–843
78. Walkowiak J et al (2002) Fecal elastase-1 is superior to fecal chymotrypsin in the assessment of pancreatic involvement in cystic fibrosis. Pediatrics 110(1 Pt 1):e7
79. Nissler K et al (2001) Pancreatic elastase 1 in feces of preterm and term infants. J Pediatr Gastroenterol Nutr 33(1):28–31
80. Zhang Y, Benet LZ (2001) The gut as a barrier to drug absorption: combined role of cytochrome P450 3A and P-glycoprotein. Clin Pharmacokinet 40(3):159–168
81. Dietrich CG, Geier A, Oude Elferink RP (2003) ABC of oral bioavailability: transporters as gatekeepers in the gut. Gut 52(12):1788–1795
82. Cascorbi I (2011) P-glycoprotein: tissue distribution, substrates, and functional consequences of genetic variations. Handb Exp Pharmacol 201:261–283
83. Fukudo M et al (2008) Impact of MDR1 and CYP3A5 on the oral clearance of tacrolimus and tacrolimus-related renal dysfunction in adult living-donor liver transplant patients. Pharmacogenet Genomics 18(5):413–423
84. Fukudo M et al (2006) Population pharmacokinetic and pharmacogenomic analysis of tacrolimus in pediatric living-donor liver transplant recipients. Clin Pharmacol Ther 80(4): 331–345
85. Konieczna A et al (2011) Differential expression of ABC transporters (MDR1, MRP1, BCRP) in developing human embryos. J Mol Histol 42(6):567–574
86. Miki Y et al (2005) Steroid and xenobiotic receptor (SXR), cytochrome P450 3A4 and multidrug resistance gene 1 in human adult and fetal tissues. Mol Cell Endocrinol 231(1–2):75–85

87. van Kalken CK et al (1992) Multidrug resistance gene (P-glycoprotein) expression in the human fetus. Am J Pathol 141(5):1063–1072
88. Fakhoury M et al (2005) Localization and mRNA expression of CYP3A and P-glycoprotein in human duodenum as a function of age. Drug Metab Dispos 33(11):1603–1607
89. Fanta S et al (2008) Pharmacogenetics of cyclosporine in children suggests an age-dependent influence of ABCB1 polymorphisms. Pharmacogenet Genomics 18(2):77–90
90. Lamba J et al (2006) MDR1 genotype is associated with hepatic cytochrome P450 3A4 basal and induction phenotype. Clin Pharmacol Ther 79(4):325–338
91. Fakhoury M et al (2006) Impact of inflammation on the duodenal mRNA expression of CYP3A and P-glycoprotein in children with Crohn's disease. Inflamm Bowel Dis 12(8):745–749
92. Vet NJ et al (2011) The effect of inflammation on drug metabolism: a focus on pediatrics. Drug Discov Today 16(9–10):435–442
93. Zhao W et al (2010) Population pharmacokinetics and pharmacogenetics of mycophenolic acid following administration of mycophenolate mofetil in de novo pediatric renal-transplant patients. J Clin Pharmacol 50(11):1280–1291
94. Ohmann EL et al (2010) Genetic polymorphisms influence mycophenolate mofetil-related adverse events in pediatric heart transplant patients. J Heart Lung Transplant 29(5):509–516
95. Zhao W et al (2009) Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients. Clin Pharmacol Ther 86(6):609–618
96. Hines RN (2008) The ontogeny of drug metabolism enzymes and implications for adverse drug events. Pharmacol Ther 118(2):250–267
97. Johnson TN et al (2001) Enterocytic CYP3A4 in a paediatric population: developmental changes and the effect of coeliac disease and cystic fibrosis. Br J Clin Pharmacol 51(5):451–460
98. Treluyer JM et al (1991) Expression of CYP2D6 in developing human liver. Eur J Biochem 202(2):583–588
99. Paine MF et al (1996) First-pass metabolism of midazolam by the human intestine. Clin Pharmacol Ther 60(1):14–24
100. Mandema JW et al (1992) Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteers. Clin Pharmacol Ther 51(6):715–728
101. Blake MJ et al (2006) Effect of diet on the development of drug metabolism by cytochrome P-450 enzymes in healthy infants. Pediatr Res 60(6):717–723
102. Blanquet S et al (2004) A dynamic artificial gastrointestinal system for studying the behavior of orally administered drug dosage forms under various physiological conditions. Pharm Res 21(4):585–591
103. Brouwers J et al (2011) Food-dependent disintegration of immediate release fosamprenavir tablets: in vitro evaluation using magnetic resonance imaging and a dynamic gastrointestinal system. Eur J Pharm Biopharm 77(2):313–319
104. Johnson TN, Rostami-Hodjegan A, Tucker GT (2006) Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. Clin Pharmacokinet 45(9): 931–956
105. Ince I et al (2009) Tailor-made drug treatment for children: creation of an infrastructure for data-sharing and population PK-PD modeling. Drug Discov Today 14(5–6):316–320
106. de Wildt SN, Ito S, Koren G (2009) Challenges for drug studies in children: CYP3A phenotyping as example. Drug Discov Today 14(1–2):6–15
107. Gorski JC et al (1998) The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. Clin Pharmacol Ther 64(2):133–143
108. Lappin G et al (2011) Comparative pharmacokinetics between a microdose and therapeutic dose for clarithromycin, sumatriptan, propafenone, paracetamol (acetaminophen), and phenobarbital in human volunteers. Eur J Pharm Sci 43(3):141–150

Chapter 4
Paediatric Development: Gastrointestinal

Hannah Batchelor

Abstract Oral administration is the preferred route for delivery of medicines in all populations. However, this route relies on absorption from the gastrointestinal tract. Gastrointestinal development is rapid following birth with significant changes during development, particularly following weaning, which can influence the absorption of drugs. An understanding of anatomical and physiological differences in the gastrointestinal tract in paediatric populations is required to understand drug absorption following oral administration.

4.1 Introduction

4.1.1 The Swallowing Reflex

The act of swallowing is the process whereby matter is conveyed from the mouth to the stomach. The oral phase of the swallow is voluntary and involves moving a bolus to the posterior wall of the pharynx. The second phase is involuntary when the bolus is forced into the pharynx by the tongue at which point inhalation is automatically prevented. The third phase is also involuntary where the bolus transits the oesophagus.

Swallowing is observed in foetuses from 10 to 12 weeks gestation with consistent swallowing by 22–24 weeks' gestation [1]. It has been estimated that the near-term human foetus swallows 500–1,000 mL/day of amniotic fluid [2]. Prior to 4–5 months of age infants are only able to swallow liquids due to the extrusion reflex which prevents any non-liquids from entering the pharynx. With age the infant

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develops the anatomical and physiological capability to swallow solid foods. An adult swallows 17 mL of water with each swallow [3], whereas a child between 1.25 and 3.5 years swallows approximately 4.5 mL per swallow. The frequency of swallowing also varies during development with adults swallowing 585 times in a 24 h period [4] compared to 43 times per hour in a near-term foetus [5]. About one third of swallows accompany eating and drinking whilst the remaining occurs whilst breathing out. Relatively few swallows occur during sleep (<10 %).

4.1.2 Oesophageal Transit

The oesophagus is 25 cm long in adults and serves to move boluses of food and drink from the oral cavity into the stomach. Autopsy measurements on infants and children indicate an oesophageal length of about 8–10 cm at birth, 12 cm at age 1 year, 18 cm at 10 years, and 19 cm at 15 years [6]. The transit time for liquids is approximately 5 seconds in both adults and children as young as 3 months old with no data available for neonates [7].

The normal transit time through the oesophagus is typically less than 10 s. Oesophageal transit ranges from 3.4 ± 1 s for infants to 4.6 ± 1.9 s for patients 8–16 years of age although gastro-oesophageal reflux or oesophagitis is associated with prolonged transit times [8].

It is well recognised that tablets or capsules taken by patients in the supine position may lodge in the oesophagus, causing damage and irritation [9]. If tablets are taken without water, the risk is greatly increased and the units may remain lodged in the lower oesophagus until they disintegrate [10]; the FDA recommends 240 mL of water in adults. Sticking of solid dosage forms in the oesophagus is reported to be more common with gelatine capsules compared to enteric coated tablets in elderly patients [11]. A study that examined the effect of tablet size and shape concluded that size and shape of tablets can affect oesophageal transit time after swallowing while in the standing but not in the supine position; changing the shape of larger tablets from round to oval may aid oesophageal transit [10]. However, other studies have shown that body position does not affect the rate of oesophageal transit in adults [12]. The influence of body position on oesophageal transit in paediatric patients has not been reported although the use of solid formulations in supine patients of any age should be minimised where possible.

4.1.3 Gastric Function and Motility

The structure of the stomach is largely developed by 14 weeks of gestation where the cells that will produce gastrin and pepsin are recognisable [13]. It is generally agreed that gastric pH is neutral at birth although there is debate over the time taken for the pH to reduce following birth with reports of 24–48 h to reach pH 3 [14] with a further rise to neutral after 72 h; or 10 days at neutral followed by a decrease to acidic

values comparable to adults at 2 years [15]. Investigations by Hyman et al. [16] showed hypochlorhydria with gastric pH greater than 4 in 19 % of neonates at 1 week of age, 16 % at 2 weeks of age and 8 % at 3 weeks of age [16]. No infant demonstrated a basal gastric pH greater than 4 after 6 weeks of age. Thereafter, gastric pH falls to a value of 1.5–3.0, which is comparable to adult gastric pH (1.5–2.5). The pH values quoted by Hyman relate to basal acid output which was 12 ± 2 μmol/kg/h at 1 week of age, and increased over the first 4 weeks to 30 ± 5 μmol/kg/h [16]. By the age of 3 years the amount of gastric acid excreted per kilogram of body weight is similar to that excreted in adults. Pepsin secretion is 0.1 mg/kg/h at birth to 3 months increasing to adult values of 1 mg/kg/h at 18 months [17]. The activity of pepsin is reduced in young infants due to the increased pH in these populations.

Gastric juice, produced and secreted by the oxyntic and pyloric glands of the stomach assists in the break-up of solid particles and solubilisation of agents. The daily secretion volume for adults is 1.5–2 L per day (equivalent to 0.9–1.2 mL/kg/h) [18], whereas these are about 1 mL/kg/h in the neonate and increases to 2–3 mL/kg/h by 1–2 years of age [17].

At birth the muscular layers of the stomach are thinner than in the adult and the pylorus is poorly developed and gastric motility is very low [19]. Motor activity within the stomach is limited in the foetus prior to 30 weeks gestation. Amniography has shown movement of markers out of the stomach and along the intestine from 30 weeks gestation [20]. In the first few days of life peristaltic waves are shallow, widely spaced and intermittent. In older infants these waves are prominent and pass from the body of the stomach to the pylorus in rapid succession [21]. In the fasted state the motility pattern in the stomach is regulated by the interdigestive migrating myoelectric complex (IMMC) that follows a three-phase cyclic pattern. In adults those three phases have been designated phase I, 45–60 min of quiescence and essentially no movement of the gastric fluid; phase II, 30–45 min of irregular activity favouring dissolution in the stomach; followed by phase III, 2–10 min of intense contractile activity during which the stomach content is emptied into the small intestine ("housekeeper wave"). A study on term and preterm neonates demonstrated that by term, well-defined fasting motor activity was present with clearly discernible phases I–III.

The majority of information regarding gastric motor activity in infants is gastric emptying of a variety of liquids. In the neonate, delayed gastric emptying has been reported with emptying times of 6–8 h [15] and adult values reached in 6–8 months. However other studies show that feed composition can determine the rate of gastric emptying with gastric half-emptying times for meals of human milk and infant formula of 25.1 ± 11.5 and 51.9 ± 9.8 min, respectively, in preterm infants; the corresponding half-emptying times for term infants were 48 ± 15 and 78 ± 14 min [22].

Gastric half-emptying times were measured in healthy children using Chocolate Technecrispy cake. Children between 5 and 10 years of age gave mean time of 107.2 min [23] although this high value may be a result of the high calorific value of the meal ingested. Another study compared gastric emptying rates in children (mean age 9 years) and adults, using three different test meals: a low caloric pancake (150 kcal), a high caloric pancake (250 kcal) and 210 mL of milk (134 kcal) [24]. No significant difference was found between children and adults in the emptying rate

of the pancake meals although the high caloric meal emptied significantly slower in both groups. The milk test meal, however, was emptied at a faster rate in adults and at slower rate in children compared with the low caloric solid test meal. Moreover, the emptying rate of milk in children was significantly slower than in adults, one theory for this reduced emptying rate is the presence of casein as whey-based milk formulae have shown shorter emptying times [25]. An alternative study reported that gastric emptying times for toddlers, young children and adolescents are generally within the range of values determined for adults [26]. The half-life for gastric emptying in adults has been reported to be 20 min although the exact age at which gastric emptying time approaches adult levels is unclear [14]. Gastric emptying time can dictate the onset of absorption for drugs; this is particularly important for drugs where gastric emptying is the rate-limiting step to absorption. Retention of medicines within the stomach for longer periods also increases the likelihood of acid degradation.

Particle size has been demonstrated to alter gastric emptying times in healthy adults with larger particles taking longer to empty [27]. A meal containing plastic particles of 1–2 mm in diameter showed a statistically similar gastric emptying time to a control meal in adults [28] which suggests that particles of this size are not retained within the stomach. 3D ultrasonography techniques supported this finding where it was demonstrated that material is ground to approximately 2 mm prior to exiting the stomach [29]. Previous reports state that solid particles must be 1 mm or less to pass through the pylorus for children [8]. However, there are also extensive reports of larger particles including coins that are greater than 1 mm passing through the GI tract of children [30]. Limits in dimensions of 6 cm long and 2 cm wide have been suggested in the dimensions that can pass through the pyloric sphincter [31]. The disintegration of tablets into small particles can be a rate-limiting step in drug absorption; this disintegration phase may be slower in children due to the need for smaller particles to pass through the pyloric sphincter.

Enteric coated tablets can show considerable variability in GI transit with multiple-unit enteric coated pellets producing less intra-subject and inter-subject variation compared to single unit tablets [32].The gastric retention time for solid dosage forms, particularly erodible tablets should be considered in children compared to adults due to the passage of particulate material into the small intestine.

4.1.4 Small Intestinal Function and Motility

The small intestine functions to absorb nutrients and is capable of this activity at birth; in terms of drug delivery the small intestine is the major site of absorption of orally administered drugs. At the level of the intestinal mucosa, several surface factors, either non-immunologic (mucin and microvillus membrane) or immunologic (secretory IgA) determine whether and how luminal molecules are absorbed.

The absorptive surface is dependent upon the dimensions of the small intestine. There are contradictory reports as to the length of the intestine during development with Neu [33] reporting a mean length of 275 cm at birth, whereas ICRP [6] reported that the small intestine grew from 45 cm at birth to 260–270 cm in adolescence.

Weaver et al. [34] determined the length of the small intestine from conception to adulthood using data taken from eight published reports of necropsy; they reported that mean length at term 275 cm, at 1 year 380 cm, at 5 years 450 cm, at 10 years 500 cm and at 20 years 575 cm [34]. One explanation for the differences in reported lengths are linked to the differences in anatomical and physiological lengths with anatomical lengths usually recorded at autopsy which are longer than the corresponding physiological lengths.

The diameter of the lumen of the small intestine changes with age and varies with location within the intestine; values in the range 1.2–2.6 cm have been estimated for the small intestine in newborns [6]. For the adult, estimates are in the range 3–6 cm for the first part of the small intestine and decrease to 1.5–2.5 cm for the last part [6].

Contradictory evidence exists relating to the morphology of the small intestine during development, Thompson et al. [35] state that the mean villus surface area in adults and infants (up to 24 months) was similar in both groups, yet mean crypt length was increased by 31 % in infants (270 ± 56 μm) compared with adults (206 ± 29 μm), although mean epithelial cell height was significantly less in infants (27.0 ± 3.0 μm) compared with that in adults (30.9 ± 4.6 μm) [35]. Changes in microvilli were not examined, but the lower enterocyte height in infants compared with that in adults in this study might indicate that enterocyte maturation will develop later in childhood and will include development of microvilli, which are known to amplify the epithelial surface area another 15-fold [35]. However, Walker-Smith [36] stated that at birth, the morphology of the small intestine is characterised by narrow villi and small crypts and during development, villi become wider by 1 month of age, and crypts deepen at weaning [36]. At weaning, luminal mucosal growth is driven by crypt hyperplasia, which results in longer villi and a two-fold increase of the villus surface area [35]. In children the villi of the small intestine tend to be broad leaf-shaped rather than finger-shaped projections (as in adults).

The conclusion from this contradictory literature is that the functional surface area of the small intestine is smaller in neonates. By adulthood, the intestinal surface area is approximately 200 m^2. The increase in surface area during development has significant implications in terms of nutrient absorptive capability [33]. In the absence of literature values of the surface area of the small intestine in paediatric populations it is acceptable to assume that the ratio in length is proportional to the surface area in estimations for paediatric populations, although this is likely to underestimate the overall surface area due to the development pattern of villi.

Using magnetic resonance imaging it has been shown that volume of intestinal fluid in fasted adults is highly variable ranging from 45 to 320 mL [37], yet the intestinal fluid is not homogeneously distributed along the gut but forms fluid pockets. There is no comparative data for paediatric populations, yet it should be assumed that total volumes are lower, likely to be in proportion to the overall volume within the intestinal tract.

Intestinal fluids are comprised of pancreatic juices, bile Brunner's gland secretions and other enterocyte secretions with a total volume of 4 L secreted daily in adults [6]. Pancreatic juice produced in the pancreas and released into the duodenum contains enzymes including α-amylase, chymotrypsin and lipase, the amount of fluids secreted by the exocrine pancreas into the intestine increases with maturation.

Table 4.1 A comparison of the properties of MMCs within the small intestine of children (8 months to 11 years) and adults [48]

	Children ($n=6$) (8 months to 11 years)	Adults ($n=18$)
Duration (min)	5.5 ± 0.6	5.9 ± 0.4
Interval between MMC (min)	99.5 ± 19.4	112.5 ± 11.4
Propagation velocity (cm/min)	29.5 ± 22.9	11.30 ± 0.14

Results show mean ± SEM

Bile produced by the liver, stored and concentrated in the gall bladder and released into the duodenum reduces the surface tension of the GI fluids and can assist in solubilisation of drugs within the GI lumen, adults secrete 0.5–1 L of bile per day [18]. Bile secretion in the first 2–3 weeks of life is poor with luminal concentrations below the critical micelle concentration (2–4 mmol/L), the concentrations increase by four to seven times in the days following birth [38]. Very low birth weight infants have a lower duodenal concentration of bile acids due to lower synthesis and ileal reabsorption of bile. An indirect indication of the bile salt concentration is the surface tension, with bile salts reducing surface tension compared to water. Surface tension values of 33–46 mN/m in the fasted stomach and 28–33.6 mN/m in the upper small intestine have been reported in adults [39, 40]. Although no values are reported in paediatric populations, the evidence suggests that the total bile concentration is likely to be lower in the very young.

The mean pH within the small intestine of adults and children from 8 to 14 years was measured using a pH sensitive radiotelemetry capsule with results showing comparable pH values with pH 6.4 measured in the duodenum rising to 7.4 in the distal part of the small intestine [41, 42]. Measurements on aspirated fluids have also shown comparable pH values in adults and paediatrics ranging from neonates to adolescents [39, 43].

Intestinal transit can be prolonged in neonates due to reduced intestinal motility and peristalsis; however, in older infants this can be reduced due to increased motility [15]. ICRP[6] report paediatric small intestinal transit times of 4 h in neonates and infants rising to 4–9.2 h in children; 4 h in adolescents compared to reports of 2.7–8.5 h in adults [44].

There have been relatively few studies done on pre- and postnatal maturation of intestinal motility [45]. In infants, intestinal motor activity occurs less frequently than in adults, with a different pattern of rhythmic peristaltic activity [46]. In general, intestinal peristalsis in infants is irregular and partially dependent on food intake and feeding habits [45]. Reports on GI motility suggest that the segmental amplitude within the small intestine in adults oscillates between a mean minimum of 9.7 mm and a mean maximum value of 20.5 for the diameter of the small intestine [47]. It is likely that this oscillation is proportionally similar in older children.

Small intestinal motility has been compared between children and adults with Table 4.1 showing the key differences in migrating motor complexes (MMCs) [48]. MMCs were seen as bands of high amplitude rhythmic (11–13 cpm) pressure waves which propagated from the duodenum into the jejunum.

4.1.5 Drug Absorption

Intestinal permeability is reported to be high at birth and decreases progressively during the first week of life [49]. This may be related to the reduced surface area: volume ratio due to the villi being broader and providing a smaller overall surface area; this phenomenon is well documented in rats [50].

Sugar absorption tests are typically used to assess intestinal permeability in premature neonates; following enteral administration of a test solution containing lactulose and mannitol, the excretion of these sugars is measured in urine. The theory behind the sugar absorption test is that in a healthy intestine monosaccharides (e.g. mannitol) are readily absorbed via the transcellular pathway but larger disaccharides (e.g. lactulose) are only absorbed through the paracellular pathway. Therefore the ratio of lactulose:mannitol in the urine is a measure of intestinal integrity. Using sugar absorption tests intestinal permeability is reported to be higher in preterm neonates than in healthy term neonates but only if measured within 2 days of birth suggesting that there is rapid postnatal adaptation of the small intestine [51]. The few bioavailability studies that have examined the absorption of drugs (e.g. phenobarbital, sulfonamides and digoxin) and nutrient macromolecules (e.g. arabinose and xylose) suggest that the processes of both passive and active transport are fully mature in infants by approximately 4 months of age. Generally, the rate at which most drugs are absorbed is slower in neonates and young infants, although the cause of this slower absorption is unknown.

The enteral absorption of drugs was studied in children; D(+)xylose which is absorbed by an active mechanism in the upper small intestine showed no difference in the amount absorbed with age [45]. However, the rate constant, Ka, for enteral absorption of D(+) xylose was nonlinear with age where Ka was less for newborns and young babies (up to 150 days) compared to older children [45]. L(+) arabinose is absorbed by passive diffusion, the pattern for absorption and absorption rate constant showed very similar results to that of D(+) xylose, although the intestinal absorption rate was significantly reduced in neonates. These results were again consistent for sulfonamides with phenobarbitol, digoxin and β-methyldigoxin all showing similar results [45]; these findings suggest that the rate of absorption is slower in neonates and children, yet the amount absorbed is similar (matched by mass). Prolonged gastric emptying time and reduced intestinal motility may be somewhat responsible for the similarity observed in total mass absorbed. A further study was conducted to measure the effects of intestinal motility on absorption using metoclopramide; the results showed an increase in Ka in both young and older infants, yet the ratio of Ka: age remained constant [45]. These results suggest that the reduced Ka observed was not solely due to longer transit times or reduced motility but other factors are also involved.

The lack of high quality pharmacokinetic studies undertaken in the paediatric population limits exhaustive knowledge regarding absorption mechanisms within this population. However, most studies conducted revealed that absorption in neonates and infants is slower than that of children and adults [52].

The membrane fluidity of intestinal cell membranes is age dependent in many species due to increasing cholesterol-to-phospholipids and protein-to-phospholipids ratios and changes in the spectrum of fatty acids [53]. As the changes of phospholipid environment alter the activity of various transporters, the developmental changes of membrane phospholipids become a potential regulator of intestinal transport. However, this hypothesis has not been confirmed conclusively.

In some instances, the lack of xenobiotic metabolising ability observed in infants is not due to absence of certain microflora but rather to immaturity of the bacterial enzyme systems in the gut lumen. For example, the extent of metabolism of several compounds such as digoxin, cholesterol and methane increases with age and this reflects the developmental processing in bacterial enzymes such as b-glucosidase and reductases [54].

Cytochromes P450 3A (CYP3A) and P-glycoprotein (P-gp) are mainly located in enterocytes and hepatocytes. The CYP3A/P-gp system contributes to the first-pass metabolism of many drugs, resulting in limited bioavailability. During the neonatal period, a shift between CYP3A7, the foetal form, and CYP3A4 occurs in the liver, but data on the expression of the CYP3A/P-gp complex in the intestine are very limited. A study to investigate localisation and expression of CYP3A and P-gp were studied in 59 normal duodenal biopsies from Caucasian children aged 1 month to 18 years. The results showed that CYP3A was expressed in all children 6 months and older and in half those up to 6 months. P-gp mRNA expression was found to significantly increase between 6 and 12 months of age [55]. The clinical impact of these results is currently unknown. A study by Johnson et al. [56] investigated expression of CYP 3A with age; an increase in CYP3A expression was observed that was mirrored by a corresponding change in CYP3A4 enzyme activity [56]. Current evidence suggests that P-glycoprotein expression is not at adult levels in the intestine at birth in human; this might lead to differences in absorption of drugs in the very young.

Food is a complicating factor in the absorption of drugs. In babies and infants a wide range of drugs are often mixed with food by the caregivers prior to administration to ensure that the medication is acceptable to the patient [57]. Many medicines are co-administered with food or fruit juice to aid in their acceptability. However, manipulation of medicines with food can have an impact on efficacy and safety for a number of reasons including effects on absorption, bioavailability [58] and metabolisation, and through inaccurate dosing [15]. The impact on bioavailability of mixing of drugs with soft food has been investigated studies in healthy adults [59–64]; no differences in extent of exposure were observed. Food effects in paediatric populations have been investigated in a smaller number of studies (e.g. [65, 66]) where typically there was a decrease in the peak plasma concentration or no significant effect. Other studies have been conducted that measure the degradation of drugs in soft food to predict any ex vivo impact of food manipulation on drug stability (e.g. [67–69]). Previous studies conducted in adults [70–72] have linked physicochemical properties of drugs to the likelihood of a food effect; however, there have been no similar predictions made for paediatric populations.

The lack of a truly fasted state in neonates due to the almost continuous presence of milk in the stomach may affect the absorption of drugs that are (a) lipid soluble due to the lack of lipases or (b) bind to protein present in milk. It is clear that further studies are required to better understand and predict the effect of food on the absorption of drugs within a paediatric population.

References

1. Miller JL, Sonies BC, Macedonia C (2003) Emergence of oropharyngeal, laryngeal and swallowing activity in the developing fetal upper aerodigestive tract: an ultrasound evaluation. Early Hum Dev 71(1):61–87, Epub 2003/03/05
2. Ross MG, Nijland MJ (1998) Development of ingestive behavior. Am J Physiol 274 (4 Pt 2):R879–R893, Epub 1998/05/12
3. Jones DV, Work CE (1961) Volume of a swallow. Am J Dis Child 102:427, Epub 1961/09/01
4. Lear CS, Flanagan JB Jr, Moorrees CF (1965) The frequency of deglutition in man. Arch Oral Biol 10:83–100, Epub 1965/01/01
5. El-Haddad MA, Desai M, Gayle D, Ross MG (2004) In utero development of fetal thirst and appetite: potential for programming. J Soc Gynecol Investig 11(3):123–130
6. ICRP (1979) Report of the task group on reference man. Ann ICRP 3(1–4):iii
7. Guillet J, Wynchank S, Basse CB (1983) Pediatric esophageal scintigraphy. Results of 200 studies. Clin Nucl Med 8(9):427–433
8. Warrington JC, Charron M (2007) Pediatric gastrointestinal nuclear medicine. Semin Nucl Med 37(4):269–285, Epub 2007/06/05
9. Channer KS, Virjee JP (1985) The effect of formulation on oesophageal transit. J Pharm Pharmacol 37(2):126–129, Epub 1985/02/01
10. Channer KS, Virjee J (1982) Effect of posture and drink volume on the swallowing of capsules. Br Med J (Clin Res Ed) 285(6356):1702, Epub 1982/12/11
11. Perkins AC, Wilson CG, Blackshaw PE, Vincent RM, Dansereau RJ, Juhlin KD et al (1994) Impaired oesophageal transit of capsule versus tablet formulations in the elderly. Gut 35(10):1363–1367, Epub 1994/10/01
12. Kasashi K, Tei K, Totsuka Y, Yamada T, Iseki K (2011) The influence of size, specific gravity, and head position on the swallowing of solid preparations. Oral Sci Int 8(2):55–59
13. Dubois PM, Paulin C, Chayvialle JA (1976) Identification of gastrin-secreting cells and cholecystokinin-secreting cells in the gastrointestinal tract of the human fetus and adult man. Cell Tissue Res 175(3):351–356, Epub 1976/12/10
14. Strolin Benedetti M, Whomsley R, Baltes EL (2005) Differences in absorption, distribution, metabolism and excretion of xenobiotics between the paediatric and adult populations. Expert Opin Drug Metabol Toxicol 1(3):447–471, Epub 2006/07/26
15. Bartelink IH, Rademaker CM, Schobben AF, van den Anker JN (2006) Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 45(11):1077–1097, Epub 2006/10/20
16. Hyman PE, Clarke DD, Everett SL, Sonne B, Stewart D, Harada T et al (1985) Gastric acid secretory function in preterm infants. J Pediatr 106(3):467–471, Epub 1985/03/01
17. Agunod M, Yamaguchi N, Lopez R, Luhby AL, Glass GB (1969) Correlative study of hydrochloric acid, pepsin, and intrinsic factor secretion in newborns and infants. Am J Dig Dis 14(6):400–414, Epub 1969/06/01
18. DeSesso JM, Jacobson CF (2001) Anatomical and physiological parameters affecting gastrointestinal absorption in humans and rats. Food Chem Toxicol 39(3):209–228, Epub 2001/03/30
19. Deren JS (1971) Development of structure and function in the fetal and newborn stomach. Am J Clin Nutr 24(1):144–159, Epub 1971/01/01

20. Milla PJ (1996) Intestinal motility during ontogeny and intestinal pseudo-obstruction in children. Pediatr Clin North Am 43(2):511–532
21. Macleod SM, Radde IC (1985) Textbook of pediatric clinical pharmacology. PSG Publishing Co, Littleton
22. Cavell B (1981) Gastric emptying in infants fed human milk or infant formula. Acta Paediatr Scand 70(5):639–641, Epub 1981/09/01
23. Singh SJ, Gibbons NJ, Blackshaw PE, Vincent M, Wakefield J, Perkins AC (2006) Gastric emptying of solids in normal children—a preliminary report. J Pediatr Surg 41(2):413–417, Epub 2006/02/17
24. Maes BD, Ghoos YF, Geypens BJ, Hiele MI, Rutgeerts PJ (1995) Relation between gastric emptying rate and energy intake in children compared with adults. Gut 36(2):183–188, Epub 1995/02/01
25. Fried MD, Khoshoo V, Secker DJ, Gilday DL, Ash JM, Pencharz PB (1992) Decrease in gastric emptying time and episodes of regurgitation in children with spastic quadriplegia fed a whey-based formula. J Pediatr 120(4 Pt 1):569–572, Epub 1992/04/01
26. Human alimentary tract model for radiological protection (2006) ICRP Publication 100. A report of The International Commission on Radiological Protection. Ann ICRP 36(1–2): 25–327, iii. Epub 2006/12/26
27. Olausson EA, Alpsten M, Larsson A, Mattsson H, Andersson H, Attvall S (2008) Small particle size of a solid meal increases gastric emptying and late postprandial glycaemic response in diabetic subjects with gastroparesis. Diabetes Res Clin Pract 80(2):231–237, Epub 2008/02/02
28. McIntyre A, Vincent RM, Perkins AC, Spiller RC (1997) Effect of bran, ispaghula, and inert plastic particles on gastric emptying and small bowel transit in humans: the role of physical factors. Gut 40(2):223–227, Epub 1997/02/01
29. Mundt MW (2007) Assessment of gastric accommodation and gastric emptying using 3D- and Duplex ultrasonography
30. Cheng W, Tam PK (1999) Foreign-body ingestion in children: experience with 1,265 cases. J Pediatr Surg 34(10):1472–1476, Epub 1999/11/05
31. Conners G (2011) Pediatrics, foreign body ingestion. Available from http://www.emedicine.com/emerg/topic379.htm
32. Graffner C, Josefsson K, Stockman O (1986) Intra- and intersubject variation of erythromycin absorption from single-unit and multiple-unit enteric-coated products. Biopharm Drug Dispos 7(2):163–171, Epub 1986/03/01
33. Neu J (2007) Gastrointestinal maturation and implications for infant feeding. Early Hum Dev 83(12):767–775, Epub 2007/10/05
34. Weaver LT, Austin S, Cole TJ (1991) Small intestinal length: a factor essential for gut adaptation. Gut 32(11):1321–1323, Epub 1991/11/01
35. Thompson FM, Catto-Smith AG, Moore D, Davidson G, Cummins AG (1998) Epithelial growth of the small intestine in human infants. J Pediatr Gastroenterol Nutr 26(5):506–512, Epub 1998/05/20
36. Walker-Smith J (1972) Variation of small intestinal morphology with age. Arch Dis Child 47(251):80–83, Epub 1972/02/01
37. Schiller C, Frohlich CP, Giessmann T, Siegmund W, Monnikes H, Hosten N et al (2005) Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. Aliment Pharmacol Therapeut 22(10):971–979, Epub 2005/11/05
38. Navarro J, Schmitz J (1992) Paediatric gastroenterology. Oxford University Press, Oxford
39. Perez de la Cruz Moreno M, Moreno M, Oth M, Deferme S, Lammert F, Tack J, Dressman J et al (2006) Characterization of fasted-state human intestinal fluids collected from duodenum and jejunum. J Pharm Pharmacol 58(8):1079–1089, Epub 2006/07/29
40. Persson EM, Gustafsson AS, Carlsson AS, Nilsson RG, Knutson L, Forsell P et al (2005) The effects of food on the dissolution of poorly soluble drugs in human and in model small intestinal fluids. Pharmaceut Res 22(12):2141–2151, Epub 2005/10/26
41. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD (1988) Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut 29(8):1035–1041, Epub 1988/08/01

42. Fallingborg J, Christensen LA, Ingeman-Nielsen M, Jacobsen BA, Abildgaard K, Rasmussen HH et al (1990) Measurement of gastrointestinal pH and regional transit times in normal children. J Pediatr Gastroenterol Nutr 11(2):211–214
43. Lindahl A, Ungell AL, Knutson L, Lennernas H (1997) Characterization of fluids from the stomach and proximal jejunum in men and women. Pharm Res 14(4):497–502, Epub 1997/04/01
44. Degen LP, Phillips SF (1996) Variability of gastrointestinal transit in healthy women and men. Gut 39(2):299–305, Epub 1996/08/01
45. Heimann G (1980) Enteral absorption and bioavailability in children in relation to age. Eur J Clin Pharmacol 18(1):43–50, Epub 1980/07/01
46. Raddle IC (1985) Mechanisms of drug absorption and their development. In: McLeod SM, Raddle IC (eds) Textbook of pediatric clinical pharmacology. PSG Publishing Co, Littleton, pp 17–43
47. Froehlich JM, Patak MA, von Weymarn C, Juli CF, Zollikofer CL, Wentz KU (2005) Small bowel motility assessment with magnetic resonance imaging. J Magn Reson Imag 21(4):370–375, Epub 2005/03/22
48. Fenton TR, Harries JT, Milla PJ (1983) Disordered small intestinal motility: a rational basis for toddlers' diarrhoea. Gut 24(10):897–903, Epub 1983/10/01
49. van Elburg RM, Fetter WP, Bunkers CM, Heymans HS (2003) Intestinal permeability in relation to birth weight and gestational and postnatal age. Arch Dis Child Fetal Neonatal Ed 88(1):F52–F55, Epub 2002/12/24
50. Zakeri-Milani P, Valizadeh H, Tajerzadeh H, Azarmi Y, Islambolchilar Z, Barzegar S et al (2007) Predicting human intestinal permeability using single-pass intestinal perfusion in rat. J Pharm Pharm Sci 10(3):368–379, Epub 2007/08/31
51. Corpeleijn WE, van Elburg RM, Kema IP, van Goudoever JB (2011) Assessment of intestinal permeability in (premature) neonates by sugar absorption tests. Meth Mol Biol 763:95–104
52. Edington AM, Fokati N (2010) Oral drug absorption in pediatric populations. In: Dressman J, Reppas C (eds) Oral drug absorption: prediction and assessment, 2nd edn. Informa Healthcare, New York, pp 108–126
53. Schwarz SM, Bostwick HE, Danziger MD, Newman LJ, Medow MS (1989) Ontogeny of basolateral membrane lipid composition and fluidity in small intestine. Am J Physiol 257(1 Pt 1):G138–G144, Epub 1989/07/01
54. Ilett KF, Tee LB, Reeves PT, Minchin RF (1990) Metabolism of drugs and other xenobiotics in the gut lumen and wall. Pharmacol Therapeut 46(1):67–93, Epub 1990/01/01
55. Fakhoury M, Litalien C, Medard Y, Cave H, Ezzahir N, Peuchmaur M et al (2005) Localization and mRNA expression of CYP3A and P-glycoprotein in human duodenum as a function of age. Drug Metab Dispos 33(11):1603–1607, Epub 2005/07/29
56. Johnson TN, Tanner MS, Taylor CJ, Tucker GT (2001) Enterocytic CYP3A4 in a paediatric population: developmental changes and the effect of coeliac disease and cystic fibrosis. Br J Clin Pharmacol 51(5):451–460, Epub 2001/06/26
57. Akram G, Mullen AB (2012) Paediatric nurses' knowledge and practice of mixing medication into foodstuff. Int J Pharm Pract 20(3):191–198
58. Winstanley PA, Orme ML (1989) The effects of food on drug bioavailability. Br J Clin Pharmacol 28(6):621–628
59. Chun AHC, Erdman K, Chiu Y-L, Pilmer BL, Achari R, Cavanaugh JH (2002) Bioavailability of lansoprazole granules administered in juice or soft food compared with the intact capsule formulation. Clin Therapeut 24(8):1322–1331
60. Chun AHC, Erdman K, Zhang Y, Achari R, Cavanaugh JH (2000) Effect on bioavailability of admixing the contents of lansoprazole capsules with selected soft foods. Clin Therapeut 22(2):231–236
61. Eliot L, Butler J, Devane J, Loewen G (2002) Pharmacokinetic evaluation of a sprinkle-dose regimen of a once-daily, extended-release morphine formulation. Clin Therapeut 24(2):260–268
62. Pentikis HS, Simmons RD, Benedict MF, Hatch SJ (2002) Methylphenidate bioavailability in adults when an extended-release multiparticulate formulation is administered sprinkled on food or as an intact capsule. J Am Acad Child Adolesc Psychiatr 41(4):443–449

63. Fay MA, Sheth RD, Gidal BE (2005) Oral absorption kinetics of levetiracetam: The effect of mixing with food or enteral nutrition formulas. Clin Therapeut 27(5):594–598
64. Thyssen A, Solanki B, Treem W (2012) Randomized, open-label, single-dose, crossover, relative bioavailability study in healthy adults, comparing the pharmacokinetics of rabeprazole granules administered using soft food or infant formula as dosing vehicle versus suspension. Clin Therapeut 34(7):1636–1645
65. Riccardi R, Balis FM, Ferrara P, Lasorella A, Poplack DG, Mastrangelo R (1986) Influence of food intake on bioavailability of oral 6-mercaptopurine in children with acute lymphoblastic leukemia. Pediatr Hematol Oncol 3(4):319–324
66. Stevens RC, Rodman JH, Yong FH, Carey V, Knupp CA, Frenkel LM (2000) Effect of food and pharmacokinetic variability on didanosine systemic exposure in HIV-infected children. Pediatric AIDS clinical trials group protocol 144 study team. AIDS Res Hum Retrovir 16(5):415–421
67. Shah T, Tse APY, Gill H, Wong ICK, Sutcliffe A, Gringras P et al (2008) Administration of melatonin mixed with soft food and liquids for children with neurodevelopmental difficulties. Dev Med Child Neurol 50(11):845–849
68. Johnson DA, Roach AC, Carlsson AS, Karlsson AA, Behr DE (2003) Stability of esomeprazole capsule contents after in vitro suspension in common soft foods and beverages. Pharmacotherapy 23(6):731–734, Epub 2003/06/25
69. Carrier MN, Garinot O, Vitzling C (2004) Stability and compatibility of tegaserod from crushed tablets mixed in beverages and foods. Am J Health-Syst Pharm 61(11):1135–1142, Epub 2004/07/09
70. Singh BN (2005) A quantitative approach to probe the dependence and correlation of food-effect with aqueous solubility, dose/solubility ratio, and partition coefficient (Log P) for orally active drugs administered as immediate-release formulations. Drug Develop Res 65(2):55–75
71. Gu CH, Li H, Levons J, Lentz K, Gandhi RB, Raghavan K et al (2007) Predicting effect of food on extent of drug absorption based on physicochemical properties. Pharmaceut Res 24(6):1118–1130, Epub 2007/03/27
72. Wu CY, Benet LZ (2005) Predicting drug disposition via application of BCS: Transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharmaceut Res 22(1):11–23

Chapter 5
How to Estimate the Dose to Be Given for the First Time to Pediatric Patients

Gerard Greig

Abstract Current FDA guidance (Food and Drug Administration, Guidance for Industry: General considerations for pediatric pharmacokinetic studies for drugs and biological products. U.S. Department of Health and Human Services, Rockville, MD, November 1998) recommends administration of a fraction of an adult dose to pediatric patients based on mg/kg of bodyweight (BW) or mg/m^2 of body surface area extrapolation of adult doses. However, children are not small adults, and it is recommended to use the systemic exposure [usually the area under the curve (AUC)] to guide the starting dose selection in pediatrics. Systemic exposure is typically the AUC observed at the therapeutic dose in adults. This approach implies the ability to predict the pharmacokinetics in pediatric patients. There are several techniques to predict the pharmacokinetics in children based on knowledge of the pharmacokinetics in adults. The preferred approach is physiologically based pharmacokinetic (PBPK) modeling. PBPK models account for developmental differences between adults and children of differing ages and incorporate known maturation and variability in clearance processes and distribution. However in cases when the PBPK approach is not possible, the recommendation is to use allometry. In the case of larger molecules (for example, with biological products), an mg/kg or allometric scaling approach may be appropriate, unless there is prior information that provides a more drug-specific way to calculate the starting dose. Additional information like the use of a safety factor and other approaches to estimate the starting dose in pediatrics will be described in this chapter.

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5.1 Introduction

In most cases the pediatric clinical development usually begins after phase 2 or 3 has been completed in adults. In this case pediatric development of a drug relies on the following assumptions: (a) the disease etiology is similar between the adult and pediatric population, (b) the exposure–response relationship established in adults can predict that in the pediatric population, and (c) the safety and efficacy established for a recommended adult regimen can be transferred to pediatric populations assuming that comparable drug exposure is achieved [1, 2].

Estimating the dose to be given to pediatric patients is complex since the pediatric population has a much greater diversity than adults. It encompasses the following classes of age: preterm newborn infants, term newborn infants (0–27 days), infants and toddlers (28 days to 23 months), children (2–11 years), and adolescents (12 to 16–18 years) [3]. Not only bodyweight varies from several hundred grams in neonates to eighty kilograms in adolescents but also body composition changes with age affecting distribution of drugs and the eliminating organs/pathways have varying degrees of maturation and hence functionality at different ages. Various examples of drug pharmacokinetics (PK) show that the maturation of hepatic and renal clearance is complete at the end of infancy [4–6]. Lastly PD and safety of drugs in children are different from those in adults. Many drugs administered to neonates show an intensified or even toxic effect; whereas in children the same dosage, based on bodyweight, frequently results in decreased efficacy [7].

This chapter reviews the methods for selecting dosage in pediatrics, i.e. the dose expected to achieve comparable drug effects and comparable levels of safety in children as in adults. Those methods are (a) use of modeling mainly physiologically based pharmacokinetic (PBPK) modeling and (b) normalization of dose to body size, i.e., allometry (normalization by bodyweight and body surface area (BSA) are mentioned because of their historical importance). The last part develops a strategy to estimate the first dose and its escalation/optimization in the pediatric population.

5.2 Dose Estimated by Modeling

PBPK models map the complex drug transport scheme onto a physiologically realistic compartmental structure (Fig. 5.1). PBPK models treat the distribution and clearance of a drug on the basis of the drug's interaction with each organ. The core tissues/fluid/organs include blood (subdivided between the venous and arterial pools), liver, kidney, adipose tissue, muscle, skin, brain, heart, gut, spleen, lung, and rest of the body. Some tissues of special interest can be added depending on the drug's characteristics: (a) other eliminating tissues (lung, intestine), (b) site of administration (skin, subcutaneous tissue, rectum), (c) site of action if a PBPK pharmacodynamic model is developed, (d) tissues/receptors with nonlinear kinetics, (e) relevant tissues when specific toxicities are suspected (reproductive organs, bone marrow). Each tissue is represented by a compartment with a specific volume, blood

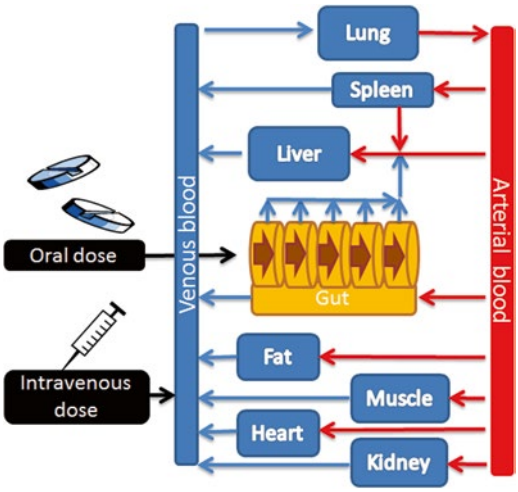

Fig. 5.1 Diagrammatic representation of a PBPK model

perfusion rate, and tissue/plasma partition coefficient (K_p) and fraction unbound in tissue (fu_t). In addition the function of tissue enzymes and transporters can be captured (e.g., by specifying an intrinsic clearance or via kinetic parameters (K_m and V_{max}) and specific protein expression levels). The exchange of substances between the cellular and the interstitial compartment can occur by permeation across the membranes via passive diffusion or by active influx and efflux transport processes. Thus tissues can be defined as either perfusion-limited or permeability-limited.

At each step: absorption, distribution, metabolism and excretion the model takes into account physiology and also drug-specific factors (Table 5.1, Fig. 5.2). PBPK modeling allows (a) integration of in vitro data, (b) a priori prediction of PK, (c) estimation of kinetics in tissue (effect) compartments, (d) extrapolation across species, routes of administration and doses, (e) modeling of subpopulations (e.g., obese patients, elderly) and in our case pediatrics, (f) modeling of variability and uncertainty. At the beginning K_ps, fu_t may be estimated using in silico methods but can be refined by incorporating measured tissue distribution (radioactive labeled compound or LCMS of tissue homogenates) in animal species. Intrinsic metabolic clearance is obtained by in vitro methods [8, 9]. PBPK models are developed by using an iterative learning process which refines the preclinical and clinical experiments and helps to understand the mechanisms of drug ADME and the effect of maturation on all these processes [10, 11].

The first step consists in validating the PBPK model by comparison of the simulated pharmacokinetics to the observed adult data. The second step incorporates adjustments for age dependencies and developmental factors which may be derived from in vitro, preclinical, bibliographic, and in vivo adult data scaled appropriately. This allows making predictions of concentration profiles in different pediatric age groups and deriving PK parameters such as CL, V_{ss}, C_{max}, C_{min}, and AUC [12]. Based on these predictions a pediatric dose can be recommended; this is a dose that allows attaining an expected value of C_{max}, C_{min}, or AUC [8–11, 13–16] (Fig. 5.2).

Table 5.1 Intrinsic and extrinsic factors of a PBPK model

	Physiology	Drug specificity
Absorption	Intestinal fluid volume	Solubility
	Intestinal transit times	Particle size
	Intestinal pH	Charge
	Luminal surface area	Lipophilicity
	Metabolizing enzyme Expression	Formulation
Distribution	Blood flow	Lipophilicity
	Tissue perfusion	Charge
	Tissue volume	Tissue partitioning
	Tissue composition	Plasma protein binding
		Membrane permeability
Elimination	Blood flow	Drug lipophilicity
	Enzyme amounts	Drug charge
		Plasma protein binding
		Membrane permeability
		Enzyme kinetics

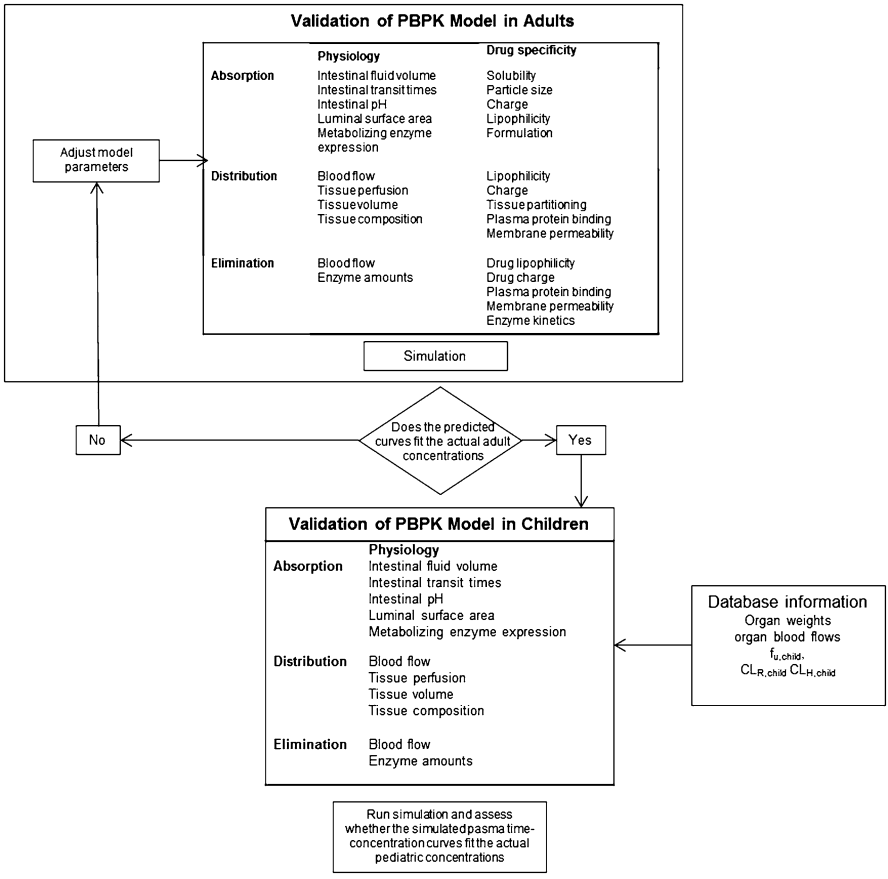

Fig. 5.2 Schematic workflow to establish a pediatric PBPK model

Several examples of estimation of pediatric doses can be found in the literature for the following drugs: paracetamol, theophylline, levofloxacin, alfentanil, morphine [10], ostealmivir [11], and sildenafil [15]. Once the PBPK model is final it is used to run simulations in virtual pediatric populations of various ages, the results of which guide the establishment of an age-specific dosing scheme.

Whereas PBPK modeling is a bottom-up approach the population approach (Pop PK/PD) is a top-down one. Pop PK/PD is adapted to pediatric patients where blood collection is sometimes difficult, since it allows for infrequent sampling, sometimes as few as two to sample samples per subject. Pop PK models are compartmental models that describe the plasma concentration time profiles of a drug by combining a structural PK model with a statistical and random component. The Pop PK/PD models describe quantitative and qualitative relationships between doses, exposure, and PD effects. Pop PK models are a valuable tool for the optimization of pediatric PK studies [17–21]. Several examples can be found where the PK/PD of drugs such as sotalol, carvedilol, or busulfan were characterized in neonates, infants and children as well as the covariates influencing the between-subject variability (BSV). After running trial simulations the authors could propose an age-specific or a weight-specific safe dosing regimen based on BW or age. Nevertheless the doses used in the trials which were analyzed by Pop PK/PD had been established by other ways, and we could not find any example where the pediatric dose was estimated before the start of a trial by using a pop PK/PD approach [18–21].

5.3 Dose Normalized to Body Size

The simplest and oldest approach consists in normalizing the dose to BW bodyweight (BW), since age and bodyweight are obviously correlated.

$$\text{Dose}_{\text{child}} = \text{Dose}_{\text{adult}} \times \left(\frac{\text{BW}_{\text{child}}}{70} \right)$$

where $\text{Dose}_{\text{child}}$ is the dose given to the child of weight BW_{child} and $\text{Dose}_{\text{adult}}$ is the typical dose for an adult weighing 70 kg. In all our formulas general reference will be made to an adult of 70 kg as it is the usual weight of reference.

This formula assumes a linear relationship between age and weight across infancy, childhood, and adolescence, which is not true as one can see from growth charts (Figs. 5.3 and 5.4 [22]). It is widely recognized that there is a nonlinear relationship between weight and drug elimination [23]. Finally this model supposes that all the elimination pathways are at the same stage of maturation across childhood, which is especially wrong regarding infancy [4]. The use of the linear per kilogram model has led to an interpretation that children require or tolerate larger doses expressed as mg/kg than adults because, in children, for many compounds, the drug clearance normalized to BW exceeds that in adults. This would suggest increasing the dosage based on BW in children, although there is a risk of overdosing

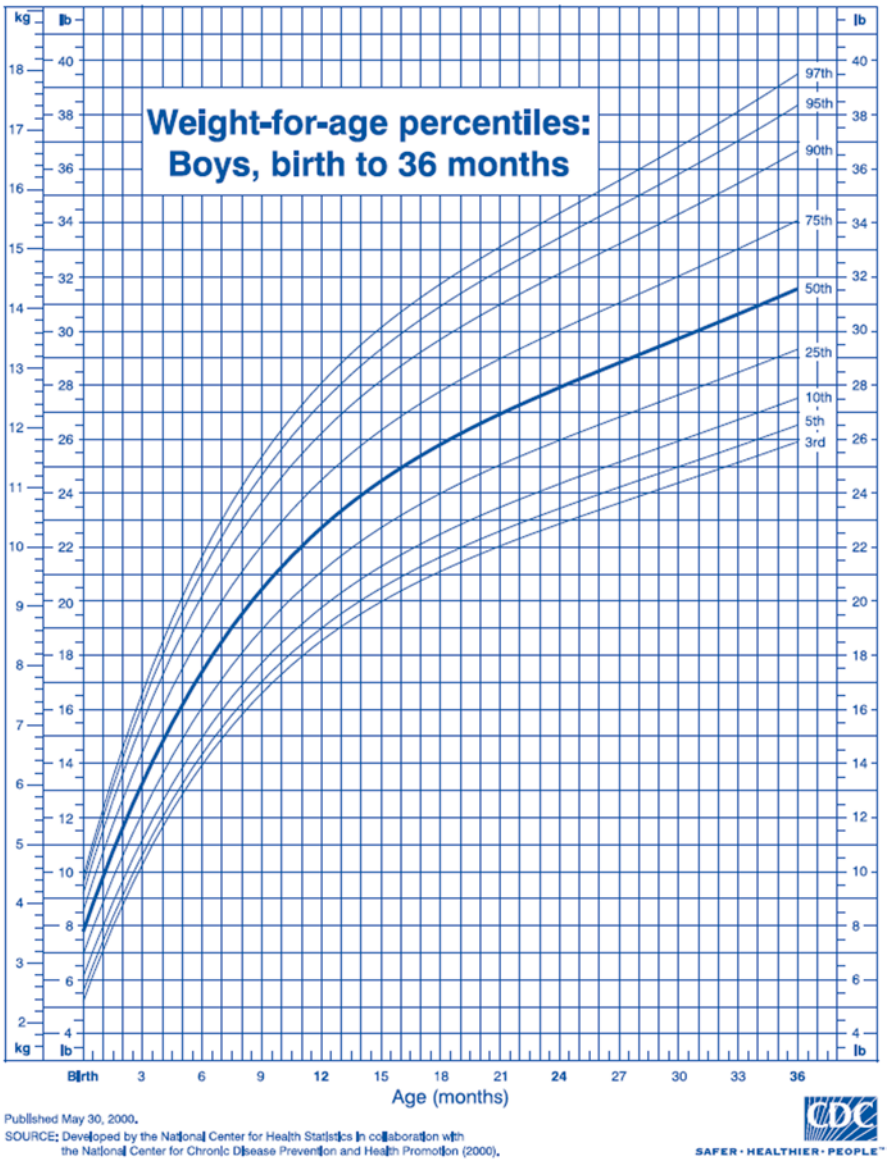

Fig. 5.3 Weight for age percentiles. Boys, birth to 36 months [22]

adolescents or heavy children. On the other hand in neonates clearance normalized to BW is lower than in children and, in this population, estimating the dosage based on BW would result in overdose. Therefore this approach, despite its simplicity, tends to underdose children having a normal BW but to overdose adolescents, obese children, and neonates [7, 24].

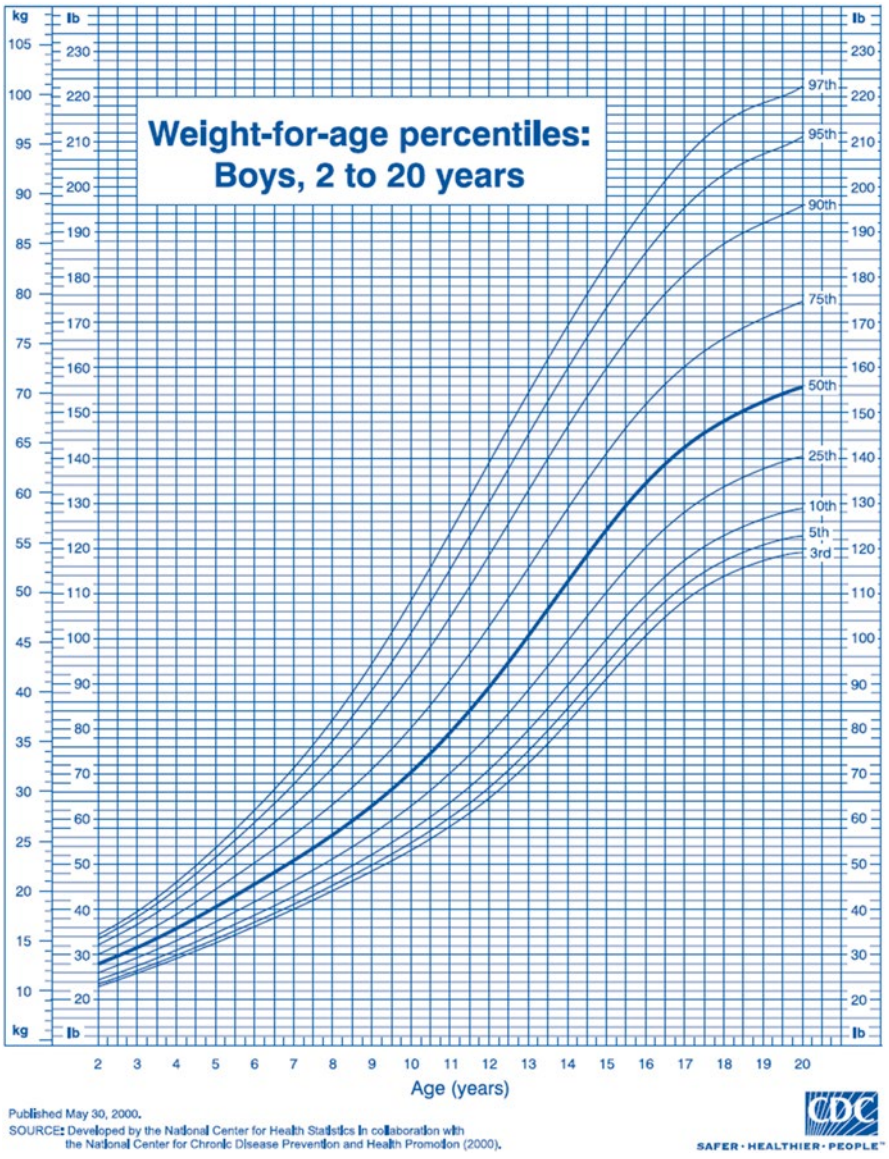

Fig. 5.4 Weight for age percentiles: boys, 2–20 years [22]

Crawford [25] proposed to use BSA to normalize the dose based on the evidence that many mammalian physiological processes are constant when expressed per unit of BSA. Therefore BSA was thought to be a more satisfactory normalizing factor than bodyweight.

Most of the formulas involve height and weight and are of the same functional form:

$$\mathrm{BSA} = a_0 \times \mathrm{Height}^b \times \mathrm{Weight}^c$$

The pediatric dose can be estimated as follows:

$$\mathrm{Dose}_{\mathrm{child}} = \mathrm{Dose}_{\mathrm{adult}} \times \left(\frac{\mathrm{BSA}_{\mathrm{child}}}{1.73} \right)$$

where $\mathrm{Dose}_{\mathrm{child}}$ is the dose given to a child of $\mathrm{BSA}_{\mathrm{child}}$ and $\mathrm{Dose}_{\mathrm{adult}}$ is the typical dose for an adult with a BSA of 1.73 m^2.

The BSA formula assumes that adults and pediatrics are geometrically similar. However this is not true since infants have short legs, relatively big heads and large body trunks. An illustration of this is given by the Lund–Browder chart used to assess the burned BSA in children [26]. Different percentages are used because the ratio of the combined surface area of the head and neck to the surface area of the limbs is typically larger in children than that of an adult. The difference between doses normalized by BSA compared to BW is apparent for pediatric subjects in the younger age range. At the age of 12 the adult reference dose normalized to BSA for a child with a normal condition is 1.2 times the adult reference dose normalized to BW. At the age of 2, the dosage normalized to BSA is 1.7 higher than the dosage normalized to BW. A dosage normalized to BSA avoids the risk of overdosing in older children compared with a dosage normalized to BW. Nevertheless, this dose adjustment by BSA could not prevent neonates and infants from being overdosed with certain drugs such as valganciclovir in neonates [7]. Other disadvantages of using BSA are the complexity of calculation (height, bodyweight and exponents) and the variety of formulas proposed to estimate BSA [7, 27].

5.4 Allometry

Allometric scaling has been used extensively in comparing preclinical pharmacokinetic data across animal species and has also been applied to adjust drug dosages in humans. Many biological characteristics can be predicted by using the following model, where *Y* is the physiological property.

$$\mathrm{Y} = a \times \mathrm{BW}^b$$

In our case *Y* represents clearance since it has been demonstrated that BW to the power of 0.75 allows scaling clearance [23, 24]:

$$\mathrm{CL}_{\mathrm{child}} = \mathrm{CL}_{\mathrm{adult}} \times \left(\frac{\mathrm{BW}_{\mathrm{child}}}{70} \right)^{0.75}$$

where CL_{child} is the clearance of child with weight BW_{child} and CL_{adult} is the typical clearance for an adult weighing 70 kg.

Holford et al. [23, 28, 29] propose to use fat free mass (FFM) instead of BW because fat is a component of the body that contributes little to the metabolic rate and by extrapolation to the clearance of drugs. Mahmood [30] suggests using different exponents for scaling clearance besides 0.75 based on different age ranges, in order to improve this model, which is refuted by others [23] while some others [18, 29] propose the following refinement to the model:

$$CL_{child} = CL_{adult} \times \left(\frac{BW_{child}}{70} \right)^{0.75} \times MF \times OF$$

where MF is the maturation function and OF is an organ function. The maturation function accounts for the age-related increase in clearance apart from the effect of size which is accounted for by the allometric term. MF is an empirical function, modeled with the Hill equation, which takes values between 0 and 1.

$$MF = \frac{PCA^{s}}{PCA_{50}^{s} + PCA^{s}}$$

PCA is the postconceptional age, which allows the specific effect of prematurity on clearance to be accounted for. PCA_{50} is the postconceptional age at which clearance reaches half its maximal value and "*s*" is a sigmoidicity coefficient. PCA_{50} and s depend on the route of elimination of the drug. OF accounts for the pathological variations of clearance. It is equal to 1 in healthy children but can be lower or smaller in diseased patients.

When applied to volume of distribution the exponent is 1 [23, 24]:

$$Vd_{child} = Vd_{adult} \times \frac{BW_{child}}{70}$$

where Vd_{child} is the volume of distribution of a child of weight BW_{child} and Vd_{adult} is the typical volume for an adult weighing 70 kg. This exponent works for several physiological volumes: blood volume, vital capacity. The volume of distribution in the central compartment (V_c), the volume of distribution based on the terminal phase (V_z), and the volume of distribution at steady-state (V_{ss}) show a good correlation when extrapolated from animal to human [24].

From a practical point of view when CL and V_d have been scaled they can be used to estimate the pediatric dose. In most cases the dose to estimate is a maintenance dose. This maintenance dose can be chosen so as to maintain the plasma concentrations above a certain threshold such as a trough value or around an average concentration. In this case the maintenance dose is the product of the target concentration (C_p), the drug clearance (CL_i), and the dosing interval (τ) divided by *F* the bioavailability factor.

$$\text{Dose}_{\text{i}} = \frac{\text{CL}_{\text{child}} \times C_{\text{p}} \times \tau}{F} = \frac{\text{CL}_{\text{adult}} \times \left(\text{BW}_{\text{i}} / 70\right)^{0.75} \times C_{\text{p}} \times \tau}{F}$$

In most cases, F is unknown; but it is assumed to be the same as in adults, which is often not true for infants and very young children [7, 23, 28].

A more simplistic approach consists in scaling from the adult dose [23, 28]:

$$\%\ \text{age of adult dose} = 100 \times \frac{\text{CL}_{\text{child}}}{\text{CL}_{\text{adult}}}$$

In some cases such as epilepsy, a fast effect is sought after and a loading dose is envisioned. This loading dose can be calculated with the following equation after allometrically scaling Vd and assuming a one-compartment model for PK:

$$\text{Dose} = \frac{C_{\max} \times V_{\text{d}}}{F} = \frac{C_{\max} \times \text{Vd}_{\text{adult}} \times \left(\text{BW}_{\text{child}} / 70\right)}{F}$$

5.5 Choice of Approach to Estimate a Dose to Be Given in the Pediatric Population

Our recommendation regarding the choice of the method is based on the FDA "Pediatric Decision Tree" (Fig. 5.5) [2]. According to this decision tree, two questions are important when deciding on a first dose for the pediatric population: "Is it reasonable to assume similar response to intervention?" and "Is it reasonable to assume similar concentration-response in pediatrics and adults?" If the answer is "yes" to the second question it is possible to use a pharmacokinetic parameter such as exposure over a dosing interval (AUC_{τ}) or maximum concentration ($C_{\max}$) to estimate the dose to be given in the pediatric population. A very common approach is to select a $\text{Dose}_{\text{child}}$ that gives the same systemic exposure (usually AUC) as the systemic exposure in adult at the therapeutic approved dose. To relate $\text{Dose}_{\text{child}}$ and this target AUC, we need to predict the PK in children; hence, tools like PBPK or allometric scaling are very important. And our preferred choice is to develop a PBPK model allowing estimation of these parameters in a virtual pediatric population; then to quickly confront the actual concentrations to the predictions. Population PK models can complement the prediction by estimating the actual PK parameters and characterizing the covariates of BSV. If the answer is "no" to the first and second question the situation is that of a First in Man Study. Therefore a very cautious dose escalation is recommended.

We recommend PBPK modeling as the preferred approach for the prediction of pediatric PK and starting doses for pediatric studies since PBPK models account for developmental differences between adults and children of differing ages and incorporate known maturation and variability in the clearance processes.

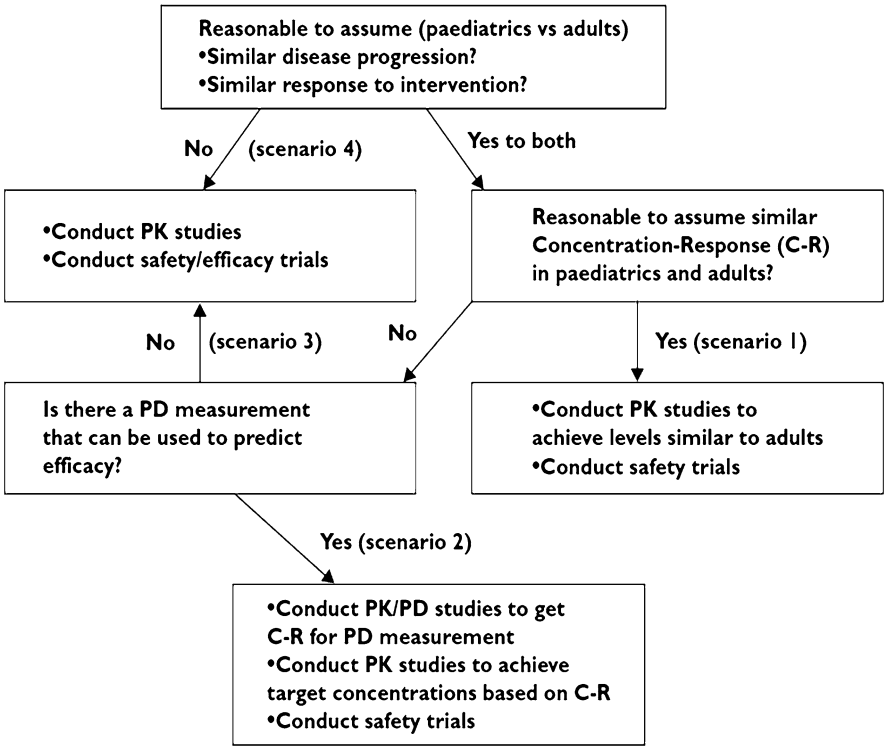

Fig. 5.5 FDA pediatric decision tree [2]

When PBPK modeling is not feasible, normalizing the dose by allometry can be useful in children older than 2 years of age and in adolescents, whose organ function and body composition approximate that of young adults [29, 31, 32]. It is more difficult in infants and children below 2 years, who show massive differences in drug disposition. However Holford et al. advocate that the refinements to allometry which they propose can be applied to this age group. Another alternative to PBPK modeling is the guidelines proposed by Bartelink which integrate pediatric pharmacology and developmental biology with in vivo and in vitro drug PK data [7]. However, this interesting approach has not been widely applied by other authors.

5.6 Practical Considerations for Dose Escalation/ Optimization

When performing the first pediatric study, it is recommended to start with the older children and to subsequently test the drug in the younger ones. We recommend weighting the predicted therapeutic dose with an arbitrary safety factor to accommodate uncertainty about safety in estimating the starting dose in children.

The uncertainty resides in the prediction of safety in the pediatric population from adult human data. It is advisable to study a small cohort (e.g., $n=4-6$) and analyze the safety, PK and/or PD results. If the first dose is safe, then one can proceed to PK- and/or PD-guided dose escalation to reach a predefined target. Once the target is reached, the cohort sample size is increased in order to collect more data (safety, PD and/or efficacy, PK). This approach is intended to decrease the number of patients over- or under-exposed and may even render the starting dose less critical. In general, it is not anticipated that dose finding in children proceeds to a maximum tolerated dose, but that the study protocol stipulates criteria for stopping dose-escalation based on achieving target exposures and/or target levels of PD activity. Rigid protocols do not meet the needs of this vulnerable population. Flexible study designs are required to ensure optimization of dosing regimen in early pediatric studies.

5.7 Conclusion

The dosing recommendation of a drug in the pediatric population is, in most cases, based on the safety, efficacy, and pharmacokinetic data collected in adults. The most common method has been to scale the adult dose to the pediatric patients based on body size. Despite it is easy, this approach does not take into account the effect of ontogeny on the safety, efficacy, and pharmacokinetic of drugs. PBPK models take more time during their development but their great advantage is that they incorporate the effect of ontogeny; they can be updated whenever necessary and can be used to make predictions of the PK in different pediatric age groups, which helps estimate the pediatric doses more safely.

References

1. ICH Topic E 11 (2001) Clinical investigation of medicinal products in the paediatric population. CPMP/ICH/2711/99 (January 2001)
2. Food and Drug Administration (2003) Guidance for industry: exposure-response relationships – study design, data analysis, and regulatory applications. U.S. Department of Health and Human Services, Rockville (April 2003)
3. Food and Drug Administration (1998) Guidance for industry: general considerations for pediatric pharmacokinetic studies for drugs and biological products. U.S. Department of Health and Human Services, Rockville (November 1998)
4. Kearns GL (2003) Developmental pharmacology – drug disposition, action and therapy in infants and children. NEJM 349(12):1157–1167
5. Alcorn J, McNamara PJ (2002) Ontogeny of hepatic and renal systemic clearance pathways in infants. Part I. Clin Pharmacokinet 41(12):959–998
6. Alcorn J, McNamara PJ (2002) Ontogeny of hepatic and renal systemic clearance pathways in infants. Part II. Clin Pharmacokinet 41(13):1077–1094
7. Bartelink IH (2006) Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 45(11):1077–1097
8. Nestorov I (2003) Whole body pharmacokinetic models. Clin Pharmacokinet 42(10):883–908

9. Parrott N, Jones H, Paquereau N, Lave T (2005) Application of full physiological models for pharmaceutical drug candidate selection and extrapolation of pharmacokinetics to man. Basic Clin Pharmacol Toxicol 96:193–199
10. Edginton AN, Schmitt W, Willmann S (2006) Development and evaluation of a generic physiologically based pharmacokinetic model for children. Clin Pharmacokinet 45(10):1013–1034
11. Parrott N, Davies B et al (2011) Development of a physiologically based model for oseltamivir and simulation of pharmacokinetics in neonates and infants. Clin Pharmacokinet 50(9):613–623
12. Johnson TN (2005) Modelling approaches to dose estimation in children. Br J Clin Pharmacol 59(6):663–669
13. Björkman S (2004) Prediction of drug disposition in children by means of physiologically based pharmacokinetic (PBPK) modelling: theophylline and midazolam as model drugs. Br J Clin Pharmacol 59(6):691–704
14. Khalil F, Laër S (2011) Physiologically based pharmacokinetic modeling: methodology, applications, and limitations with a focus on its role in pediatric drug development. J Biomed Biotechnol 2011, 907461, PMID:21716673
15. Hsien L (2010) Identifying paediatric needs in cardiology and the prediction of sildenafil exposure in children with pulmonary arterial hypertension. Inauguraldissertation zur Erlangung des Doktorgrades der Mathematisch-Naturwissenschaftlichen Fakultät der Heinrich-Heine-Universität Düsseldorf (July 2010)
16. Haddad S, Restieri C, Krishnan K (2001) Characterization of age-related changes in body-weight and organ weights from birth to adolescence in humans. J Toxicol Environ Health 64(6):453–464
17. Manolis E, Pons G (2009) Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. Br J Clin Pharmacol 68(4):493–501
18. Tod M, Jullien V, Pons G (2008) Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet 47(4):231–243
19. Läer S et al (2005) Population pharmacodynamics in children with supraventricular tachycardia. JACC 46(7):1322–1330
20. Albers S, Meibohm B, Mir TS, Laër S (2007) Population pharmacokinetics and dose simulation of carvedilol in paediatric patients with congestive heart failure. Br J Clin Pharmacol 65(4):511–522
21. Booth BP (2007) Population pharmacokinetic-based bosing of intravenous busulfan in pediatric patients. J Clin Pharmacol 47:101–111
22. Kuczmarski RJ, Ogden CL, Guo SS et al (2002) 2000 CDC growth charts for the United States: Methods and development. National Center for Health Statistics. Vital Health Stat 11(246):1–190
23. Anderson BJ, Holford NHG (2008) Mechanism-based concepts of size and maturity in pharmacokinetics. Ann Rev Pharmacol Toxicol 48:303–332
24. Anderson BJ, Meakin GH (2002) Scaling for size: some implications for paediatric anaesthesia dosing. Paed Anaesth 12:205–219
25. Crawford J, Terry M, Rourke G (1950) Simplification of drug dosage calculation by application of the surface area principle. Pediatrics 5:783–790
26. Miminas DA (2007) A critical evaluation of the Lund and Browder chart. Wounds UK 3(3): 58–66
27. Bailey BJR, Briars GL (1996) Estimating the surface area of the human body. Stat Med 15: 1325–1332
28. Anderson BJ, Eliis JF (1999) Common errors of drug administration in infants. Causes and avoidance. Paediatr Drugs 1(2):93–107
29. Holford N (2010) Dosing in children. Clin Pharmacol Ther 87(3):367–370
30. Mahmood I (2006) Prediction of drug clearance in children from adults: a comparison of several allometric methods. Br J Clin Pharmacol 61(5):545–587
31. Ginsberg G et al (2002) Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci 66:185–200
32. Scheuplein R, Charnley G, Dourson M (2002) Differential sensitivity of children and adults to chemical toxicity. I. Biological basis. Reg Toxicol Pharmacol 35:429–447

Chapter 6
The Clinical Relevance of Pediatric Formulations

Karel Allegaert, Pieter De Cock, and Johannes N. van den Anker

Abstract Extensive variability in dose and dosing regimens used to treat pediatric patients, based on maturational and non-maturational differences between individuals, is part of the essence of pediatric clinical pharmacology today. Consequently, the pediatric community is in need of drug formulations tailored to the specific needs of neonates, infants, children, and adolescents. This must include valid data on product stability, palatability, and compatibility. Most of the time, children are still treated with medicines that were neither designed, developed nor evaluated specifically for use by children. As a consequence, there is a risk of suboptimal (too low, too high, or too variable) dosing and side effects from potentially toxic ingredients, including excipients.

The topic of excipients will be used to illustrate the clinical relevance and the feasibility of collecting information about formulations for children. This will be followed by a road map reflecting a clinician's view of how the current situation related to child-size formulations can be improved, based on collaborative efforts between manufacturers, agencies, regulatory bodies, caregivers, and academia.

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Abbreviations

ADME	Absorption, distribution, metabolism, and excretion
BW	Birth weight
CL	Clearance
EMA	European medicines agency
ESNEE	European Study for Neonatal Excipient Exposure
EUPFI	European Paediatric Formulation Initiative
FDA	Food and Drug Administration
GRAS	Generally regarded as safe
HIV	Human immunodeficiency virus
IV	Intravenous
PD	Pharmacodynamics
PedCo	Pediatric Committee
PG	Propylene glycol
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PNA	Postnatal age (days)
SPC	Summary of product characteristics
STEP	Safety and Toxicity of Excipients for Paediatrics database
WHO	World Health Organization

6.1 Introduction: The Problem of Extensive Variability in Pediatric Clinical Pharmacology

Extensive variability in doses and compounds administered is the essence of pediatric clinical pharmacology and pharmacy. This mainly relates to maturational changes, although there are also non-maturational contributors to this variability [18]. The impact of developmental changes in drug absorption, distribution, metabolism, and excretion (ADME, pharmacokinetics) is due to variation in body composition (e.g., body water content and protein-binding characteristics), organ weight and organ function (e.g., renal maturation and hepatic maturation) [2, 8, 37]. Since these processes mature neither linearly nor simultaneously, standardized dosing (e.g., mg/kg) is inadequate for children [8, 10, 11, 34, 37]. In addition to the anticipated developmental changes during pediatric life, it is relevant to mention some other, non-maturational contributors [65].

Firstly, the field of pediatric medicine has evolved in a manner similar to the progress made in medical care for adults [14, 37]. This has resulted in further optimization of commonly known pediatric diseases such as asthma, atopy-related diseases, and “minor” surgical diseases. Secondly, more advanced treatment modalities—including drugs—have been introduced to treat diseases in pediatric hemato-oncology, pediatric solid organ transplantation, human immunodeficiency

virus (HIV)/AIDS, and even chronic diseases (e.g., chronic auto-immune deficiencies and diabetes mellitus type 1) [20, 34, 37, 65].

Besides these advances, the variability in weight and clinical characteristics within the pediatric age range has also evolved. Improved knowledge of the developmental physiology before, during and immediately following delivery has resulted in treatment modalities for extreme preterm neonates (<0.5 kg) [15, 19, 28, 31, 35]. As a consequence, there is already a difference of one log value (0.5–5 kg) in weight in neonates admitted to neonatal intensive care units [64]. Combined with the more recent emergence epidemic of pediatric obesity, this results in extensive variability in drug dosing related only to weight or size, irrespective of maturational changes [46]. This variability is further increased by additional disease-related titration in dosing, related to either co-morbidity (e.g., renal failure and hepatic failure) or co-medication (e.g., drug interactions) [37, 43, 48, 51].

For the purpose of translating this extensive range of individual variability, there is a need for drug formulations tailored to the specific needs of neonates, infants, children, and adolescents [45, 52–54, 59]. This must include valid data on product stability, palatability, and compatibility [29]. Children are still commonly treated with medicines that were neither designed nor developed for, nor evaluated in, the relevant pediatric age groups. As a consequence, there is a risk of suboptimal (too low, too high, or too variable) dosing and side effects from potentially toxic ingredients, including excipients [51, 59, 62, 63]. Both professional and non-professional caregivers are still often forced to split and divide adult formulations, and mix them with food or a liquid in order to deliver a dose appropriate for an individual child. For intravenous formulations with “high” concentrations, this might mean that consecutive dilutions are needed. All these manipulations introduce additional dosing inaccuracies. Sometimes, “extemporaneous” formulations will be provided by a pharmacist based on a medical prescription for an individual patient. Although this probably results in a somewhat improved reproducibility, it is still a long way away from having fully tested formulations ready for use. Moreover, practices and guidelines for extemporaneous formulations differ among different pharmacists or regions, introducing the risk of additional uncertainties or errors [8, 21–23, 29, 67, 69–71].

Fortunately, all stakeholders (society, health care providers, the pharmaceutical industry, regulatory agencies, and academia) have become progressively aware of the relevance of this issue [7, 20, 24, 29]. To a certain extent, the formulation science aims to catch up with the legislative environment for formulations and pediatric pharmacological evaluation. The European legislation and similar legal initiatives require manufacturers of innovative drugs to conduct a Paediatric Investigation Plan (PIP) as part of their marketing application approach. As a consequence, these regulations effectively force companies to develop pediatric formulations for new compounds entering the market that could potentially be used for children. Similarly, the regulatory agencies became aware that their guidelines on issues like excipients or subpopulation-specific, preferred formulations had to undergo revision because of newly emerging information, conflicting opinions or unfeasible requests [21–23, 69–71].

Approaches currently being considered include tablets that can be divided into more manageable sizes, "waffles" and minitablets, which are easier for children to take. Alternatives include—but are not limited to—orodispersible tables that dissolve in the oral cavity following contact with saliva, multi-particulate systems in a single capsule to facilitate dose variation and fast-dissolving films with active ingredients.

In this chapter, we aim to illustrate the clinical relevance of these efforts. We will first discuss some issues that arise when excipients are to be administered to children, in order to stress the need to study the "pharmacokinetics and pharmacodynamics" of such compounds in neonates, as well as the feasibility of such studies [1, 3, 25]. This will be followed by an overview of problems encountered in the absence of child-adapted formulations and some suggestions to improve the present suboptimal situation.

6.2 Excipients: The Compounds We Routinely Administer, but Never Prescribe

Besides active substances, formulations of drugs also often contain solvents and additives ("excipients"). These excipients are added to enhance the solubility and stability of the drug over a given shelf-life under variable external conditions, or to improve palatability further [3, 26, 27, 38]. To facilitate the administration and absorption of active compounds, excipients can be used to mix or dissolve the active ingredients. Furthermore, excipients are used to bulk up formulations that contain otherwise highly potent active ingredients, allowing more convenient and accurate dosage. In addition to their use in the single-dosage quantity, excipients can be used in the manufacturing process to aid the handling of active substances. Often, once an active ingredient has been purified it cannot stay in purified form for long. To stabilize the active ingredient, excipients are added to ensure that the active ingredient stays "active" and remains stable long enough to give a shelf-life that makes the product competitive. Finally, excipients can be used to improve palatability. Examples of excipients are lactose, aspartame, ethanol, propylene glycol, benzyl alcohol, sorbitol, poly-ethylene glycol, and mannitol [49].

Although nearly all medicines are formulated with excipients that have been used for many years and are *g*enerally *r*egarded *a*s *s*afe, usually referred to as having "GRAS" status, there are still disease-specific issues (e.g., aspartame in patients with phenylketonuria and lactose in patients with lactase deficiency) and issues related to individual idiosyncratic reactions (e.g., allergic and pseudo-allergic reactions) that need to be considered [47, 68]. Excipients are defined in monographs in the various pharmacopeias, and batches are released on certificates of analysis against monograph specifications, using monograph test methods. However, such monographs usually cover use in adults only, and some excipients are known to be less well tolerated by children, especially young children whose

physiological (elimination) systems are still developing [47, 68]. In addition, the current guidelines proposed by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) on the safe use of excipients in children are limited and conflicting and show wide variation, up to 10–20 folds for some excipients [21–23, 29]. Since excipients may be toxic, carcinogenic, mutagenic, teratogenic or affect reproduction in specific subpopulations of patients, including neonates, focused and detailed research is urgently needed to identify the safe use of excipients in the different age categories (level of exposure) [38].

To illustrate the need for uniform and valid guidelines on the safe use of excipients in neonates and infants, we refer to two historical observations (benzyl alcohol and propylene glycol), both reported in the 1980s, but also a recently reported observation (lopinavir/ritonavir excipient toxicity) to illustrate the continued relevance of this topic [6, 9, 12, 30, 32, 33, 41, 42, 44, 50, 58].

Fatal benzyl alcohol-related poisoning has been described in 10 preterm neonates (<1,500 g) following co-administration of this compound as bacteriostatic with normal saline (1981–1982). Following at least a minimal exposure of 130 mg/kg/day of benzyl alcohol in this cohort, neonates developed metabolic acidosis from the second day of exposure onwards [9, 30, 58]. This was followed by clinical symptoms, including progressive bradycardia, gasping, and clinical seizures (8/10 cases). Further evidence that the clinical syndrome is related to maturational deficiency of benzyl alcohol degradation to benzoic acid was provided [9, 30, 58].

Toxicity to propylene glycol in preterm neonates (<1,500 g) has also been reported, following exposure of up to 3,000 mg/day for at least 5 consecutive days [41, 42]. The high exposures of that time (the 1980s) were due to high concentrations of propylene glycol as co-solvent in parenteral nutrition solutions [41, 42]. The markers of toxicity were either biochemical (e.g., hyperosmolarity, lactic acidosis, elevated plasma creatinine values, and elevated bilirubin concentrations) or clinical (seizures and coma). The same group estimated the elimination half-life to be 10–31 h in neonates, compared to the documented elimination half-life of 2–5 h in adults, but was unable to explain the inter-individual variability within their cohort of preterm neonates. Unfortunately, the potential side effects of excipients still require consideration in contemporary neonatal pharmaceutical care and are not just a thing of the past [1, 6].

In March 2011, the FDA notified health care professionals of serious health problems reported in prematurely born babies. The babies had received Kaletra® (lopinavir/ritonavir), an antiviral medication used in combination with other antiretroviral drugs for the treatment of HIV-1 infection, in oral solution [6, 29]. This solution contained relevant amounts of both ethanol and propylene glycol. Based on the reported side effects, the FDA claimed that prematurely born babies may be at increased risk for health problems, as they have a decreased ability to eliminate propylene glycol. This limited elimination capacity potentially results in adverse events, such as serious cardiac, renal, metabolic, and respiratory problems. Because the consequences of using Kaletra oral solution in neonates immediately after birth

can be severe, and even fatal, the label has been revised to include a new warning. The use of Kaletra oral solution should be avoided in prematurely born babies until 14 days after their due date, and in full-term babies younger than 14 days of postnatal age, unless a health care professional believes that the benefit of using Kaletra oral solution to treat HIV infection immediately after birth outweighs the potential risks. In such cases, the FDA strongly recommends monitoring for increases in serum osmolality, serum creatinine, and other signs of toxicity. As suggested, this warning was based on a case series of observed side effects during Kaletra exposure. Unfortunately, there were no data on propylene glycol or ethanol concentrations in the cases with side effects, so that it was not possible to identify any links between concentrations, interactions, and effects. The clinical covariates suggested (age at birth and postnatal age) were indeed associated with propylene glycol clearance in neonates [17].

At this point, we would like to stress that the excipients described above are compounds to which neonates are fairly regularly exposed in our neonatal intensive care units. To further illustrate this, we refer to the papers of Whittaker et al. [68] and Shehab et al. [58]. These authors quantified the extent of exposure to potentially toxic excipients following administration of oral formulations and thereby documented that 53 % of infants in the eligible target group were exposed to potentially toxic excipients during their in-patient stay. These infants were exposed to over 20 excipients, including ethanol and propylene glycol, chemicals associated with neurotoxicity. Infants with chronic lung disease were exposed to higher concentrations of these excipients. Infants were also exposed to high concentrations of sorbitol, with some infants being exposed to concentrations exceeding the figures given in the recommended guidelines for maximum exposure in adults.

Based on both these historic observations, as well as the more recent reports, it would seem that assessing the safety of excipients should be an essential element of the research and development process and should be considered as part of pediatric investigation plans. In similarity to the clinical pharmacology of mother compounds, excipients display maturational differences in both their pharmacokinetics (concentration–time relationship) and pharmacodynamics (concentration–effect relationship). In addition to the need for improved knowledge of the clinical pharmacology of active compounds, there is a similar need to improve the knowledge of the clinical pharmacology of excipients in neonates [3, 22, 26, 36, 47, 55, 56, 59].

It is relevant here to mention some recently initiated and ongoing collaborative research initiatives that aim to improve both the availability of and the access to information on excipients in neonates (STEP database, i.e. Safety and Toxicity of Excipients for Pediatrics database) already available in the public domain [26, 55], or aim to generate new information (ESNEE research initiative, European Study for Neonatal Excipient Exposure) [25, 61] following analysis of current needs and deficiencies in our knowledge. We will illustrate the feasibility of such studies based on the Leuven propylene glycol research project and discuss some specific problems and the limitations of this research initiative.

6.2.1 The STEP Database

Extensive excipient safety data are publicly available in peer-reviewed scientific journals, government reports and databases, but pediatric data suitable for use in development of pediatric medicines are highly limited. In addition, the available data are distributed over a large number of sources. The available safety data have never been incorporated into a single comprehensive and readily accessible database, while other stakeholders consider their data to be protected, but can be invited to make them public. At present, neither industry nor regulators have a central source of safety data on which to base decisions regarding the need for additional safety studies. Therefore, there is a risk that studies may be conducted unnecessarily, since the data may already exist. Deficiencies should be highlighted to tailor-specific studies that need to be carried out to collect relevant information [26, 55].

A database that provides manufacturers with a basis for screening and selecting excipients for use in pediatric product development, potentially facilitating further product-specific safety and toxicity studies, was urgently needed. Consequently, the European Paediatric Formulation Initiative (EuPFI) took up the task, with the support of the FDA, the EMA and the industry, of collecting all available information on excipients in children and of developing such a database.

In addition to certain manufacturer-related aims, the main aims of this initiative are (1) to conduct a high-level scientific literature review of the pharmacology, toxicology, and safety data of a selected group of excipients in or for pediatric formulations, (2) to help determine the relationship between exposure and evidence of clinically significance toxicity in the pediatric age group or in specific pediatric subpopulations, and (3) to identify knowledge gaps and needed studies or provide the basis for the development of hypothesis-driven safety or toxicity studies.

6.2.2 The ESNEE Research Initiative

The European Study for Neonatal Excipient Exposure (ESNEE) is funded by the ERA-NET PRIOMEDCHILD, a multinational European research initiative with specific focus on developmental clinical pharmacology. As described by the core research group, this study aims to develop a platform for the systematic assessment of excipients in neonates [25, 61].

The first step of this program is to "*set the scene*," i.e. establish which excipients are in use and how much is given to neonates. A pan-European survey is underway, though the preliminary results will be presented with key difficulties. The major challenge has been to access data about excipients in existing medicines. To illustrate the complexity, we refer to Table 6.1, which provides the data on different formulations of phenobarbital as currently marketed throughout Europe, though most likely does not provide the full picture. When converted to an mg propylene

Table 6.1 Different formulations containing phenobarbital as sodium salt for intravenous administration

30 mg/ml	Ethanol 10 %, propylene glycol 75 %
60 mg/ml	Ethanol 10 %, propylene glycol 75 %
65 mg/ml	Ethanol 10 % benzyl alcohol 0.15 %, propylene glycol 67.8 %
130 mg/ml	Ethanol 10 % propylene glycol 67.8 %
200 mg/ml	Ethanol 10 % propylene glycol 70 %

When converted to an exposure ratio (mg propylene glycol/mg phenobarbital), there is a five-fold difference between the different formulations

glycol/mg phenobarbital approach, the different formulations result in relevant differences in propylene glycol co-administration (3.5–25 mg propylene glycol/mg phenobarbital), while some also contain benzyl alcohol.

The second step of the ESNEE program is "*knowledge collection and identifying missing links*," i.e. to determine what is known about the effects of excipients in neonates and juvenile animals. Preliminary results will be presented together with important issues pertaining to trial design and analysis in a systematic review. The third step of the program is to "*generate information on missing links*," i.e. measure systemic concentrations of key excipients in neonates using dry blood spots and plasma samples [25, 61].

The fourth and final step of the ESNEE program is to "*refocus on the clinical relevance*," i.e. to integrate the work from the other steps into a systematic assessment of safety for each excipient. A generic framework for the assessment of excipient safety in neonates will be developed, with the aim of showing how this can be applied by prescribers, pharmacists, manufacturers, and regulators. Propylene glycol will serve as a case study with reference to other excipients [25, 61].

6.2.3 The Propylene Glycol Research Project

Propylene glycol (PG) is a commonly co-administered excipient. PG accumulation potentially results in hyperosmolarity, lactic acidosis, or hepato-renal toxicity in adults, reflecting issues related to both pharmacokinetics (PK) and pharmacodynamics (PD). The clinical relevance has been mentioned earlier [1, 3].

Since newborns display "physiologically" impaired hepatic and renal elimination capacity, description of propylene glycol PK in neonates is warranted. Only when population-specific (side-) effects due to differences in PK have been considered, age-specific PD (e.g., neuro-apoptose long-term effects) can be evaluated [1, 18, 39, 40]. The propylene glycol PD was assessed based on indicators of renal, hepatic, and metabolic (in-)tolerance reported earlier in adults and relating to osmolar changes [1, 72].

Based on the PK and PD data collected in neonates, we suggest that there is a lower limit of propylene glycol tolerance in neonates [17]. These data were collected in neonates who were exposed to propylene glycol as part of their routine clinical needs (propylene glycol co-administered with paracetamol [800 mg PG/1,000 paracetamol/acetaminophen] or phenobarbital [700 mg PG/200 mg phenobarbital]), and observations were limited to intravenous PG only. Median exposure was 34 mg/kg/day, about 3 log values lower than that for the historical cohorts described earlier.

In a first step, median estimates and covariates of propylene glycol clearance (CL) in (pre-)term neonates were quantified [17]. Using a one-compartment model, birth weight (BW, g) and postnatal age (PNA, days) were both identified as covariates for propylene glycol clearance using an allometric function [$CL_i = 0.0849 \times \{(BW/2720)^{1.69} \times (PNA/3)^{0.201}\}$]. This model has already been validated by predicting the propylene glycol concentration-time profiles following a median exposure of 34 mg/kg/day. The developed pharmacokinetic model can also be used to simulate propylene glycol concentrations co-administered with other drug formulations containing propylene glycol [17].

However, such extrapolations beyond the initial observations and dosages have their intrinsic limitations, since a first order elimination has been claimed. We are unsure whether first order elimination still applies when doses of propylene glycol exposure associated with for instance lorazepam are substantially higher than propylene glycol doses associated with paracetamol/acetaminophen or phenobarbital. This assumption of first order kinetics may lead to an underestimation of the exposure to propylene glycol. In addition, other disease characteristics (renal failure, hepatic failure, and perinatal asphyxia) or treatment modalities (formulations containing ethanol and whole body cooling) warrant further study.

Indicators for assessment of pharmacodynamics (toxicity) in neonates related to renal, hepatic, and metabolic tolerance after low-dose propylene glycol exposure in neonates. Neither the renal, nor the hepatic or metabolic homeostasis were affected following median exposure of 34 mg/kg/day for at least 2 days. However, these indicators are based on similar observations on (in-)tolerance in adults and all relate to accumulation and the subsequent osmolar changes [1].

Differences in permeability of the blood–brain barrier due to maturational (age, weight) or disease-related changes (e.g., asphyxia and meningitis), differences in sensitivity to osmolar shifts or synergistic pharmacodynamic effects (e.g., propylene glycol may also result in additional age-specific pharmacodynamics) have not been considered in this study [1]. However, Lau et al. recently provided experimental animal evidence supporting the impact of either propylene glycol alone or propylene glycol combined with phenobarbital on the extent of neuro-apoptosis in a rodent model [39]. Similarly, the Kaletra observation suggests an interaction between propylene glycol and ethanol [1, 6]. Since the aim here is mainly to illustrate the feasibility of such studies, some specific problems and limitations of this propylene glycol research project are provided in Table 6.2.

Table 6.2 Problems encountered in and limitations of the propylene glycol research project

How to retrieve exact amounts of propylene glycol exposure: In our search for sources of intravenous propylene glycol, we noticed that quantities are not routinely mentioned in the SPC (summary of product characteristics). Consequently, we had to contact manufacturers to retrieve this information
How to quantify propylene glycol in biological samples: since the volume available for blood sampling in neonates is limited, a more sensitive quantification method has been developed to enable quantification in low plasma volume samples
How to quantify pharmacokinetics in (*pre-*)*term neonates*: since the number of samples in (pre-) term neonates is also limited, a population pharmacokinetic approach has been applied
How to assess pharmacodynamics in (*pre-*)*term neonates*: based on extrapolation from similar observations in adults, we focused on renal, hepatic, and metabolic (in-)tolerance during and following propylene glycol exposure, also using a formulation controlled approach compares different formulations, containing the same active compound in combination with different excipients
Limitations of the current pharmacokinetic estimates: we have described a one-compartment model, with both birth weight and postnatal age as important covariates. However, we have no data in specific subpopulations (e.g., whole body cooling), no data in neonates co-treated with ethanol (competitive elimination), we cannot assume that a neonate is a "small adult" (renal versus hepatic route of elimination). Finally, the data are limited to a low degree of exposure (median 34 mg/kg/day)
Limitations of the current pharmacodynamics data: we have described propylene glycol tolerance following a median exposure of 34 mg/kg/day, but data are limited to renal, hepatic, and metabolic tolerance (renal tubular effects and central nervous system effects), there are no data on long-term outcome and no data following a higher level of exposure

6.2.4 Perspectives

Just as the knowledge of clinical pharmacology concerning active compounds administered to neonates is increasing, we should aim to increase the knowledge of excipient exposure in neonates and the validity of this knowledge [59–61]. Although formulation itself is in part a *pre*clinical pharmaceutical activity, clinicians should be aware of the relevance of formulation, as well as ongoing initiatives. Ideally, collaboration between researchers, clinical pharmacists, and clinical pharmacologists should result in the definition of valid, lower levels of tolerated and safe exposure to specific excipients for neonates.

This should allow us to shift from eminence-based threshold to evidence-based threshold. For a comparison of this aim with the current situation, we once again refer to the current situation for propylene glycol. The FDA considers a cumulative life-long daily dose of 25 mg/kg/day as the upper limit; the EMA operates with a maximum dose of 400 mg/kg/day in adults and 200 mg/kg/day for children [17]. Using state-of-the-art research techniques—e.g., the high ethical standards, population pharmacokinetic models in study design and analysis, and low blood volume analytical techniques—clinical researchers should be able to improve both the knowledge and the clinical use of these excipients [18, 59, 61].

6.3 Child-Adapted Formulations: A Clinician's Intersubjective Opinion on How to Improve the Current Situation

As mentioned earlier, there is extensive range in individual variability in pediatric drug dosing due to maturational and non-maturational differences, resulting in the clinical need for tailored drug formulations [18]. In a first step, and using an anecdotic approach, we aim to illustrate this clinical need based on case observations as described in literature. We are aware that such an approach is incomplete, but we merely wished to provide observational evidence to support the need for tailored drug formulations. We refer the interested reader to a recently reported systematic review protocol designed to identify the evidence available on drug manipulation [52].

This report [52] aims to describe the challenges of developing a systematic review in an area that potentially involves many drugs and considers outcomes other than effectiveness. In particular, searches required the use of nonspecific terms and the iterative development of a complex search strategy. This research is still ongoing [52]. This must include valid data on product stability, palatability, and compatibility. In a second step, we provide some intersubjective opinions on how to improve the current setting.

6.3.1 Case Observations About the Need for Tailored Pediatric Formulations

Tailoring of pediatric formulations relates either to dose variability or to the excipients used to prepare the formulation. In the absence of appropriate formulations, manipulations of adult dosage forms or extemporaneous preparations are applied. Manipulations may result in additional dosing inaccuracies, irrespective of the route of administration [52, 53, 62].

Most vials for intravenous administration contain relatively high concentrations of the active compound, which are unsuitable for neonates or infants. Some compound-specific illustrations are provided in Table 6.3. Besides the risk related to dosing errors, consecutive dilutions are necessary, and these dilutions introduce an additional risk of dose inaccuracy [62].

We have recently illustrated this for amikacin ("pediatric" vial 50 mg/ml, "adult vial" 260 mg/ml). A population PK approach (NONMEM) was used to investigate clearance (CL) and volume of distribution (V) changes as markers for dose accuracy and variability from time-concentration profiles in 254 preterm neonates given intravenous amikacin. The pediatric vial was used in 56 and the adult vial in 198 neonates. Preterm neonates had an average age of 28 (range 24–30) weeks gestational age and a mean weight of 1,100 (SD 33) g. Separate scale factors were applied to V and CL and their variability for neonates given a dose from the 50 mg/ml vial [2].

Table 6.3 Highly concentrated vials for intravenous administration compared to the regular doses applied in neonates

Midazolam	15 mg/3 ml	0.05–0.1 mg/kg
Paracetamol/acetaminophen	500 mg/50 ml	10 mg/kg
Propofol	200 mg/20 ml	1–3 mg/kg
Phenobarbital	200 mg/1 ml	5 mg/kg
Fentanyl	100 μg/2 ml	1–3 μg/kg
Insulin	300 E/3 ml	0.1–1 E/kg/h
Enoxaparin	40 mg/0.4 ml	1 mg/kg
Ranitidine	50 mg/2 ml	0.5–1 mg/kg

Due to the large differences in concentration, consecutive dilution and associated dosing inaccuracy are more likely

Differences in V and CL parameter estimates and their variability before and after introduction of the 50 mg/ml vial reflect differences in doses administered and bioavailability (dose inaccuracy). In this analysis, it turned out that there were more amikacin plasma concentrations in the target zone with the pediatric vial than with the adult vial (72 and 58 %, respectively). The final model demonstrated an apparent 8 % reduction in the estimate of V and a 29 % reduction in its variability after introduction of the pediatric vial. Clearance was the same in neonates given adult and pediatric vials, but the clearance variability was reduced by 53 %. Based on these observations, we concluded that the introduction of a pediatric vial was associated with a reduction in the observed variability of V and CL, reflecting an improved dosing precision. The 8 % reduction in the estimate of V also suggests that there may be differences in bioavailability between the two types of vials when used in neonates, due to dosing imprecision. There have been recent initiatives (e.g., with caffeine, ibuprofen, and dopamine) to manufacture tailored vials for neonates, but these initiatives are hampered to a certain extent by the associated additional costs for an overall low market volume [16, 52, 53, 62].

Dosing inaccuracy related to inaccurate manipulation is not limited to intravenous formulations. This has recently been shown in an investigation of the impact of crushed versus whole tablets on the pharmacokinetics of lopinavir/ritonavir in children [4]. In essence, administration of crushed 200/50 mg lopinavir/ritonavir tablets to children significantly reduced lopinavir and ritonavir exposure with a decrease in AUC of 45 and 47 %, respectively, as compared to whole tablets [4]. The administration of crushed tablets would require higher doses and therapeutic drug monitoring to ensure adequate lopinavir exposure in patients requiring this practice. At the very least, caregivers should be made aware of the impact of crushed lopinavir/ritonavir tablets on the pharmacokinetics, and subsequent pharmacodynamics [4].

The need to study the impact of formulations on omeprazole pharmacokinetics has also recently been reported for enteric coated granules versus alkali suspension in a non-blinded, two-phase cross-over trial in 10 pediatric patients with severe

neurodevelopmental problems [5]. Omeprazole is often administered through a gastrostomy tube as either (1) a Multiple Unit Pellet System (MUPS®) tablet disintegrated in water (MUPS® formulation), or (2) a suspension in 8.4 % sodium bicarbonate (extemporaneous suspension formulation). This bioavailability study evaluates such practice in tube-fed patients with severe neurodevelopmental problems. In seven of ten patients, bioavailability was higher for the suspension formulation than for the MUPS® formulation. The median (90 % confidence interval) area under the plasma concentration-time curve ratio (MUPS® over suspension) was 0.5 (0.06–2.37). In this population, the omeprazole MUPS® formulation has no apparent advantage over the more easily administered suspension formulation. In our opinion, this is yet another example of the combined maturational and disease-related (e.g., gastric emptying time) impact on the drug absorption processes [5].

Inaccuracy may also relate to inadequate or inappropriate administration devices. It is imperative that pediatric medicines can be administered accurately to ensure that the correct dose is provided and that the administration device is easy to use and acceptable from both the patient's and the carer's perspective. We refer to a recently published reflection paper on currently available pediatric administration devices for oral, inhaled, parenteral, nasal, and ocular administration of pediatric formulations [59, 66].

6.3.2 Setting the Road Map: A Clinician's Opinion

Any relevant road map will require efforts on the part of the various stakeholders (e.g., regulatory agencies, industry, caregivers, academia, and society). To a certain extent, formulation practices are trying to catch up with the legislative environment [59]. Similarly, the agencies have become aware that the initial guidelines on issues like excipients or subpopulation-specific preferred formulations need to be revised because of newly emerging information or changes in opinion. Finally, extemporaneous formulation requires further standardization and evaluation.

In the agencies, dedicated formulation work groups have been set up to encourage manufacturers to develop age-appropriate pediatric formulations, and facilitate this, in an effort to develop relevant, acceptable formulations with convenient and precise dosing characteristics on an industrial scale suitable for marketing. In the EMA, this formulation working group is becoming still more actively involved in the evaluation of pediatric investigation plans (2008 = 54; 2009 = 94; 2010–2011 = 240). Thus, critical points are the route of administration, appropriateness, excipients, taste and palatability, delivery devices, rate of infusion, volume to be administered (e.g., not only fluid load but also size of solid oral formulations), and wastage. In addition, legal initiatives related to information in the Summary of Product Characteristics (SPC) revision should be considered. This is reflected in a recently performed survey on different vials of phenobarbital, as manufactured for intravenous administration by different companies in Europe (Table 6.1).

Most of the data provided in this table (e.g., quantities used) were not fully available in the individual SPC documents, making it impossible for the clinician to calculate the level of exposure of, for instance, ethanol or propylene glycol.

It is our belief that the interactions between these dedicated formulation work groups and manufacturers caused the agencies to revise various reflection papers (e.g., formulation of choice for the pediatric population), concept papers (e.g., future quality guideline), and guidelines (e.g., guideline on pharmaceutical development of medicines for pediatric use and guideline on the investigation of medical products in the term and preterm neonate).

For the industry, the diversity of pediatric pharmaceutical care presents challenges related to dose range, choice of dosage, selection and level of excipients, taste-masking issues, tailored administration devices, and adapted instructions to ensure correct use. However, the principles of the pharmaceutical development of a given product for pediatric patients are not fundamentally different from those for adult patients. Quality by design is based on (1) predefining the objectives, (2) use of a systematic approach, (3) both the pediatric product and its manufacturing process are understood, and (4) decisions being based on quality risk assessment. Since all dosage forms have their advantages and disadvantages, the concept of quality by design makes manufacturers consider these different issues in a systematic, "out-of-the box" approach. For example, if subdivision of tablets is considered to comply with the posology, the efficacy of a break-mark (or break-marks) must be assessed by the manufacturer during product development with respect to the uniformity of dose of the subdivided parts.

Even taking all the initiatives mentioned above into account, it is highly unlikely that extemporaneous formulation or compounding will disappear completely; compounding can be considered as a final, but relevant resort in the absence of other solutions to the problem [7, 13, 36, 38, 57].

Extemporaneous formulation is the manipulation of drugs and chemical ingredients, applying traditional compounding techniques to produce suitable medicines when no commercial form is available. Besides the WHO model list of essential medicines for children, there is also a WHO model formulary for children. However, there are issues related to availability of medicines and ingredients, to information about compounding practices and to potential medication errors. There are also ongoing initiatives to document the variability in compounding practices throughout Europe, with the aim of further improving practices and harmonizing compounding [7, 13, 38, 59].

In conclusion, we endeavored to show the clinical relevance of pediatric formulations. In addition to anecdotic evidence for its clinical relevance, we focused on issues related to excipients. Further focused studies on excipient-specific, age-appropriate thresholds of exposure are feasible and urgently needed. In our opinion, collaborative efforts between manufacturers, regulatory agencies, and caregivers are crucial to improving pediatric product development, availability, and knowledge.

References

1. Allegaert K, Vanhaesebrouck S, Kulo A, Cosaert K, Verbesselt R, Debeer A, de Hoon J (2010) Prospective assessment of short-term propylene glycol tolerance in neonates. Arch Dis Child 95:1054–1058
2. Allegaert K, Verbesselt R, Naulaers G, van den Anker JN, Rayyan M, Debeer A, de Hoon J (2008) Developmental pharmacology: since neonates are not just small adults. Acta Clin Belg 63:522–530
3. American Academy of Pediatrics, Committee on Drugs (1997) "Inactive" ingredients in pharmaceutical products: update (subject review). Pediatrics 99:268–278
4. Best BM, Capparelli EV, Diep H, Rossi SS, Farrell MJ, Williams E, Lee G, van den Anker JN, Rakhmanina N (2011) Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. J Acquir Immune Defic Syndr 58:385–391
5. Boussery K, De Smet J, De Cock P, Vande Velde S, Mehuys E, De Paepe P, Remon JP, Van Bocxlaer JF, Van Winckel M (2011) Pharmacokinetics of two formulations of omeprazole administered through a gastrostomy tube in patients with severe neurodevelopmental problems. Br J Clin Pharmacol 72:990–996
6. Boxwell D, Cao K, Lewis L, Marcus K, Nikhar B (2011) Kaletra oral solution toxicity in Neonates–Lopinavir, ethanol, and/or propylene glycol? In: 18th conference on retroviruses and opportunistic infections, Boston, 27 February–2 March 2011
7. Brion F, Nunn AJ, Rieutord A (2003) Extemporaneous (magistral) preparation of oral medicines for children in European hospitals. Acta Paediatr 92:486–490
8. Broussard L (2010) Small size, big risk: preventing neonatal and pediatric medication errors. Nurs Womens Health 14:405–408
9. Brown WJ, Buist NR, Gipson HT, Huston RK, Kennaway NG (1982) Fatal benzyl alcohol poisoning in a neonatal intensive care unit. Lancet 8283:1250
10. Budnitz DS, Salis S (2011) Preventing medication overdoses in young children: an opportunity for harm elimination. Pediatrics 127:e1597–e1599
11. Caldwell NA, Rackham O (2010) Children's doses should be measurable. Arch Dis Child 95:313
12. Chicella M, Jansen P, Parthiban A, Marlowe KF, Bencsath FA, Krueger KP, Boerth R (2002) Propylene glycol accumulation associated with continuous infusion of lorazepam in pediatric intensive care patients. Crit Care Med 30:2752–2756
13. Conroy S (2003) Extemporaneous (magistral) preparation of oral medicines for children in European hospitals. Acta Paediatr 92:408–410
14. Choonara I (2008) WHO wants safer medicines for children. Arch Dis Child 93:456–457
15. Dabliz R, Levine S (2012) Medication safety in neonates. Am J Perinatol 29:49–56
16. Dart RC, Rumack BH (2012) Intravenous acetaminophen in the United States: iatrogenic dosing errors. Pediatrics 129:349–353
17. De Cock RF, Knibbe CA, Kulo A, de Hoon J, Verbesselt R, Danhof M, Allegaert K (2012) Developmental pharmacokinetics of propylene glycol in preterm and term neonates. Br J Clin Pharmacol. doi:10.1111/j.1365-2125.2012.04312.x
18. De Cock RF, Piana C, Krekels EH, Danhof M, Allegaert K, Knibbe CA (2011) The role of population PK-PD modelling in paediatric clinical research. Eur J Clin Pharmacol 67(Supp 1):5–16
19. Dessi A, Salemi C, Fanos V, Cuzzolin L (2010) Drug treatments in a neonatal setting: focus on the off-label use in the first month of life. Pharm World Sci 32:120–124
20. Donnell C, Nunn T (2011) How to manipulate drugs so they can be given to children. Nurs Child Young People 23:6–7
21. EMA (2005). www.ema.europa.eu/CHMP/PEG/194810/2005. Accessed May 2012
22. EMA (2009). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf. Accessed May 2012
23. EMA (2011). www.ema.europa.eu/CHMP/QWP/180157/2011(draft). Accessed May 2012

24. Ernest T, Craig J, Nunn A, Salunke S, Tuleu C, Breitkreutz J, Alex R, Hempenstall J (2012) Preparation of medicines for children: a hierarchy of classification. Int J Pharm. doi:10.1016/j.ijpharm.2012.05.070
25. ESNEE (2012). http://www.esnee.eu. Accessed May 2012
26. EUPFI (2012). http://www.eupfi.org/gpage11.html. Accessed May 2012
27. Fabiano V, Mameli C, Zuccotti G (2011) Paediatric pharmacology: remember the excipients. Pharmacol Res 63:362–365
28. Fanos V, Yurdakök M (2010) Personalized neonatal medicine. J Matern Fetal Neonatal Med 23(Suppl 3):4–6
29. FDA (2009). http://www.fda.gov/Drugs/DrugsSafety/ucm246002.htm. Accessed May 2012
30. Gershanik J, Boecler B, Ensley H, McCloskey S, George W (1982) The gasping syndrome and benzyl alcohol poisoning. N Engl J Med 307:1384–1388
31. Giacoia GP, Birenbaum DL, Sachs HC, Mattison DR (2006) The newborn drug development initiative. Pediatrics 117(3 Pt 2):S1–S8
32. Glasgow AM, Boeckx RL, Miller MK, MacDonald MG, August GP, Goodman SI (1983) Hyperosmolality in small infants due to propylene glycol. Pediatrics 72:353–355
33. Hall CM, Milligan DW, Berrington J (2004) Probable adverse reaction to a pharmaceutical excipient. Arch Dis Child Fetal Neonatal Ed 89:F184
34. Hoppu K, Anabwani G, Garcia-Bournissen F, Gazarian M, Kearns GL, Nakamura H, Peterson RG, Ranganathan SS, de Wildt SN (2012) The status of paediatric medicines initiatives around the world—what has happened and what has not? Eur J Clin Pharmacol 68:1–10
35. Jacqz-Aigrain E (2011) Drug policy in Europe research and funding in neonates: current challenges, future perspectives, new opportunities. Early Hum Dev 87(Suppl 1):S27–S30
36. Kairuz T, Chhim S, Hasan F, Kumar K, Lal A, Patel R, Singh R, Dogra M, Garg S (2007) Extemporaneous compounding in a sample of New Zealand hospitals: a retrospective survey. N Z Med J 120(1251):U2466
37. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kaufman RE (2003) Developmental pharmacology: drug disposition, action, and therapy in infants and children. N Engl J Med 349:1157–1167
38. Knoppert DC (2009) Pediatric formulations: international issues and potential solutions. Paediatr Drugs 11:55–56
39. Lau K, Swiney BS, Reeves N, Noguchi KK, Farber NB (2012) Propylene glycol produces excessive apoptosis in the developing mouse brain, alone, and in combination with phenobarbital. Pediatr Res 71:54–62
40. Lesko SM, Mitchell AA (1994) Total bilirubin level in relation to excipients in parenteral morphine sulfate administered to seriously ill newborn infants. Paediatr Perinat Epidemiol 8:401–410
41. MacDonald MG, Fletcher AB, Johnson EL, Boeckx RL, Getson PR, Miller MK (1987) The potential toxicity to neonates of multivitamin preparations used in parenteral nutrition. JPEN J Parenter Enteral Nutr 11:169–171
42. MacDonald MG, Getson PR, Glasgow AM, Miller MK, Boeckx RL, Johnson EL (1987) Propylene glycol: increased incidence of seizures in low birth weight infants. Pediatrics 79:622–625
43. Manolis E, Pons G (2009) Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. Br J Clin Pharmacol 68:493–501
44. Masi S, de Cléty SC, Anslot C, Detaille T (2009) Acute amiodarone toxicity due to an administration error: could excipient be responsible? Br J Clin Pharmacol 67:691–693
45. Mehndiratta S (2012) Strategies to reduce medication errors in pediatric ambulatory settings. J Postgrad Med 58:47–53
46. Miller JL, Johnson PN, Harrison DL, Hagemann TM (2010) Evaluation of inpatient admissions and potential antimicrobial and analgesic dosing errors in overweight children. Ann Pharmacother 44:35–42
47. Nahata MC (2009) Safety of "inert" additives or excipients in paediatric medicines. Arch Dis Child Fetal Neonatal Ed 94:F392–F393

48. Nahata MC, Allen LV Jr (2008) Extemporaneous drug formulations. Clin Ther 30:2112–2119
49. No authors listed (2009) What are excipients doing in medicinal products? Drug Ther Bull 47:81–84
50. Orisakwe OE, Nduka JK (2009) Lead and cadmium levels of commonly administered pediatric syrups in Nigeria: a public health concern? Sci Total Environ 407:5993–5996
51. Pandit S, Shah U, Kirby DJ, Nunn T, Tuleu C (2010) Inappropriate oral formulations and information in paediatric trials. Arch Dis Child 95:754–756
52. Rickey RH, Craig JV, Shah UU, Ford JL, Barker CE, Peak M, Nunn AJ, Turner MA (2012) The manipulation of drugs to obtain the required dose: systematic review. J Adv Nurs. doi:10.1111/j.1365-2648.2011.05916.x
53. Rieder M (2010) If children ruled the pharmaceutical industry: the need for pediatric formulations. Drug News Perspect 23:458–464
54. Rosenbluth G, Wilson SD (2010) Pediatric and neonatal patients are particularly vulnerable to epinephrine dosing errors. Ann Emerg Med 56:704–705
55. Salunke S, Gaicoia G, Tuleu C (2012) The STEP (Safety and Toxicity of Excipients for Paediatrics) database. Part 1: A need assessment study. Int J Pharm. doi:10.1016/j.ijpharm.2012.05.004
56. Salunke S, Hempenstall J, Kendall R, Roger B, Mroz C, Nunn T, Tuleu C (2011) European Paediatric Formulation Initiative's (EuPFI) 2nd conference commentary—formulating better medicines for children. Int J Pharm 419:235–239
57. Schell KH (1992) Compliance issues and extemporaneous preparation of medications for pediatric patients. J Pharm Technol 8:158–161
58. Shehab N, Lewis CL, Streetman DD, Donn SM (2009) Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. Pediatr Crit Care Med 10:256–259
59. Tuleu C (2012) Formulating better medicines for children—still paving the road. Int J Pharm. doi:10.1016/j.ijpharm.2012.05.034
60. Turner MA (2011) Neonatal drug development. Early Hum Dev 87:763–768
61. Turner MA, Storme T (2012) European study for neonatal excipient exposure (ESNEE). Eur J Hosp Pharm. doi:10.1136/ejhpharm-2012-000065
62. Uppal N, Yasseen B, Seto W, Parshuram CS (2011) Drug formulations that require less than 0.1 mL of stock solution to prepare doses for infants and children. CMAJ 183:E246–E248
63. van den Anker JN (2005) Managing drugs safely. Semin Fetal Neonatal Med 10:73–81
64. van den Anker JN, Allegaert K (2012) Clinical pharmacology in neonates and young infants: the benefit of a population-tailored approach. Expert Rev Clin Pharmacol 5:5–8
65. van den Anker JN, Schwab M, Kearns GL (2011) Developmental pharmacokinetics. Handb Exp Pharmacol 205:51–75
66. Walsh J, Bickmann D, Breitkreutz J, Chariot-Goulet M (2011) Delivery devices for the administration of paediatric formulations: overview of current practice, challenges and recent developments. Int J Pharm 415(1–2):221–231
67. Werning K, Breitkreutz J (2011) Oral drug delivery in personalized medicine: unmet needs and novel approaches. Int J Pharm 14(404):1–9
68. Whittaker A, Currie AE, Turner MA, Field DJ, Mulla H, Pandya HC (2009) Toxic additives in medication for preterm infants. Arch Dis Child Fetal Neonatal Ed 94:F236–F240
69. WHO (2008). www.who.int/selection_medicines/committees/expert/17/application/paediatric/Dosage_form_reportDEC2008.pdf
70. WHO (2010). www.who.int/selection_medicines/list/WMFc_2010.pdf
71. WHO (2011). www.who.int/medicines/areas/quality_safety/quality_assurance/Provision HealthCareProfessionals QAS11-399Rev1 17082011.pdf
72. Yahwak JA, Riker RR, Fraser GL, Subak-Sharpe S (2008) Determination of a lorazepam dose threshold for using the osmol gap to monitor for propylene glycol toxicity. Pharmacotherapy 28:984–991

Part II
Formulating for Children I, the Oral Route

Chapter 7
General Considerations for Pediatric Oral Drug Formulation

Valentina Shakhnovich and Susan M. Abdel-Rahman

Abstract In pediatrics, the absorption of a perorally administered drug depends on the ability of the formulation to overcome the chemical, physical, mechanical, and biological barriers of the developing gastrointestinal tract. The differences between the pediatric and adult digestive systems are subtle, but physiologically important, and encompass organs from mouth to anus. Although the exact age of GI function maturation remains to be defined, clinically relevant developmental changes that influence drug absorption occur primarily during early childhood. This chapter reviews the developmental changes in gastrointestinal physiology that occur throughout childhood and discusses their relevance to formulation development and drug delivery.

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7.1 Introduction

Although intravenous drug administration is often the most dependable and accurate route of drug delivery, it is not always convenient, feasible, or humane in the pediatric population. Therefore, peroral drug administration is frequently employed, and often preferred, in practice; particularly, in the outpatient, home, daycare, and school settings. For most new drugs, the identification of clinical applications for the pediatric population outpaces formulation development. Consequently, the availability of age-appropriate formulations often serves as the rate-limiting step for the assimilation of drugs into pediatric clinical practice. As the discovery and the development of new chemical entities slows, the demand for pediatric formulations of new and already-existing drugs will rise, reinforcing the need to integrate pediatric formulation development into the early stages of drug development.

In children, the success of any peroral drug formulation will depend on the ability of the formulation to overcome the chemical, physical, mechanical, and biological barriers of the *developing* gastrointestinal (GI) tract. Under normal circumstances, essentially all of the structural components of the mature adult GI system are present in the term infant (Table 7.1) [1, 2]; however, there remain functional differences that are physiologically and clinically relevant to pediatric drug absorption. This chapter will follow the GI tract from mouth to anus and frame the developmental differences in GI physiology in the context of formulation development and drug delivery in children.

Table 7.1 Anatomic and physiologic gastrointestinal development

Age	Hallmarks of development
4 weeks gestation	The tubal structure of the GI tract and its primordial organs (e.g., liver, pancreas, and gallbladder) form
12–14 weeks gestation	Organogenesis of the GI tract is complete
12–14 weeks gestation	Intestinal crypts and villi are established
13–14 weeks	Gastric motor activity becomes apparent
14 weeks gestation	Digestive enzyme activity is detectable, for hydrolases such as sucrase, isomaltase, and glucoamylase, but not lactase
15 weeks gestation	Rudimentary ability to swallow forms
16–18 weeks gestation	Suck reflex observed
24	Machinery for gastric acid production established
30 weeks gestation	Differentiation of the large intestine occurs
34–36 weeks	Coordinated swallowing is demonstrated
Birth	Lactase expression becomes apparent
Postnatal	Intestinal length increases 100-fold throughout gestation and continues postnatally
Postnatal	Gastric pH becomes sustainably more acidic
6–24 months postnatal age	Gastric motility and peristalsis matures

7.2 Oral Cavity

A fundamental, yet frequently overlooked, factor, that influences peroral drug absorption in children, is the ability to get the drug past the oropharynx. The entire deglutition process only lasts 1.5 s yet, during this short time, an oral agent is altered radically in terms of size, shape, volume, pH, temperature, and consistency [3]. Both sensory and mechanical processes work in concert to trigger swallowing, such that when taste, smell, temperature, and texture fail to align, orifice rejection becomes the rule, not the exception [4].

7.2.1 Gustatory and Olfactory Development

Existing data seem to suggest that the ability to detect sweet tastes is present at birth and, in fact, likely develops in utero [5]. The rate of fetal swallowing is demonstrated to increase when sweet tasting solutions are injected into the amniotic sac. Though similar prenatal studies appear to indicate that bitter tastes are also detected in utero, it is generally accepted that an appreciation for bitter, salty, and sour flavors develops during the first 2 years of life [5]. The response to trigeminal stimulation (i.e., temperature, piquancy, and texture) also seems to develop during this time frame. However, olfactory development follows a different trajectory, with the affective response to odor not fully developed until 5–7 years of age [5]. Consequently, formulation strategies that rely on appealing odors, to mask aversive medication tastes, are likely to fail in preschool-aged children. Similarly, formulation strategies that rely on extemporaneous admixture of a gritty or granular drug product, in an otherwise normally accepted food matrix, may be rejected in the young child [4]. Importantly, these challenges extend to special subpopulations of older children. For example, problems with mouth-feel can be difficult to overcome in children with autism spectrum disorder, who are especially resistant to accepting certain peroral textures and flavors [6].

7.2.2 Maturation of Deglutition

Swallowing is a complex process consisting of three coordinated sequential phases (i.e., the oral phase, the pharyngeal phase, the esophageal phase) which together last approximately 1.5 s in the adult [3]. The ability to swallow is innate, and established in rudimentary form as early as 15 weeks of gestational age (GA); however, effective coordinated swallowing is not achieved until 34–36 weeks of GA [7], possibly as early as 29 weeks of GA [8]. Despite the innate ability to swallow at birth, the involuntary extrusion of solids, and some liquids, is still observed; owing to the infant's larger, more anteriorly positioned, tongue and several neurologic reflexes that continue to mature through early infancy [9, 10]. Collectively, these anatomic changes limit peroral drug delivery to liquid-only formulations in young infants.

It remains to be seen whether there exists a role for mucoadhesive, sublingual, and buccal formulations in the infant population.

Though premature infants are able to suckle [8–10], their breathing and swallowing are not always coordinated, making even the administration of liquid drug formulations challenging, unreliable, and potentially dangerous, in this growing pediatric population. Despite immature deglutition, premature infants display a propensity for sucking their fingers, an activity well established in utero by 16–18 weeks of gestation [7, 8]. Though not developed at present, future formulation strategies may attempt to harness this sucking instinct to develop novel drug delivery strategies for this unique pediatric subpopulation.

Assuming that the peroral formulation isn't voluntarily rejected by the child, or involuntarily extruded from the oral cavity, the reflexive pharyngeal phase of swallowing takes place next. This requires pristine coordination of a complex sequence of motions to safely direct an oral bolus into the esophagus, rather than the trachea. Notably, this coordination continues to develop into early childhood, with the impact of utmost significance for the delivery of solid oral formulations. Developers should remain cognizant of the fact that infants and young children are often unable to safely swallow solid dosage forms, without choking or aspirating. Despite the fact that regulatory agencies (e.g., the European Medicines Agency) emphasize this concern [11], the vast majority (70 %) of clinical trials continue to administer tablets or capsules to children younger than 6 years of age, frequently leading to spitting out, vomiting, and redosing of the medications [12].

To circumvent this problem, some formulators are introducing solid mini-tablets that range in diameter from 2 to 3 mm. Studies examining the acceptability of mini-tablets in children (some as young as 6 months of age) demonstrate mixed results [13, 14]. It is likely that the ultimate role of this formulation in young children will depend on the characteristics of the drug being delivered; specifically, whether the drug is of sufficient potency to be contained in a relatively small number of mini-tablets, and whether it is palatable enough to withstand chewing, in children who may reflexively do so before swallowing.

Developmental differences, specific to children, also exist in the third and final phase of swallowing, the esophageal phase, but they appear to have limited bearing on pediatric formulation development. These differences are obvious in the neonate and infant and are directly related to the postnatal size and strength of the esophagus. They do not seem to relate to the primary peristalsis of the esophagus, which is responsible for the transport of materials into the stomach, and is functionally present at birth [15].

7.3 Esophagus

Though the pediatric esophagus (8–14 cm) is comparatively shorter than that of the adult (18–24 cm) [16], age-dependent differences in esophageal transit are unlikely to play a significant role in the delivery of drugs to the stomach. However, this primary anatomic difference in length does make it more likely that a drug will be

successfully expelled from the stomach, back into the mouth, with regurgitation. Normally, the lower esophageal sphincter contracts as the stomach fills, creating an anatomic barrier between gastric contents and the esophagus. However, the integrity of this barrier is not yet fully mature in newborns and infants, increasing their susceptibility to gastroesophageal reflux. In fact, daily regurgitation of stomach contents is reported to occur in up to 65 % of healthy babies [16–18]. Additional features that predispose infants to regurgitation include smaller gastric volumes, frequent liquid feedings, and delayed gastric emptying times, as discussed below.

7.4 Stomach

Not just a reservoir for food, the stomach is a muscular structure responsible for mixing food, and other orally ingested items, with gastric secretions, in preparation for delivery to the intestine. Like the oral cavity and the esophagus, the stomach undergoes a number of physiologic changes, during infancy and early childhood, that can ultimately influence drug absorption [19].

7.4.1 Gastric Volume

At birth, the neonatal stomach is smaller than that of the adult [19], approximating the size of a glass marble on day of life 1, a ping-pong ball on day of life 3, a plum by day of life 10, eventually, reaching adult proportions of a tennis ball or a grapefruit [20]. It logically follows that the functional volume of the human stomach also varies with age, accommodating approximately 5–8 ml of liquid feeds in the first 1–2 days of life, 30–50 ml by the end of the first week of life, 150–180 ml by mid-infancy, and 900–1,000 ml by adulthood [20]. The limited functional volume of the neonatal stomach holds significant implications for peroral drug administration, particularly since the safest and the most commonly used formulations in this age group are liquid. Even 1–2 ml of an oral liquid dosage form, typical of medications like lactulose and zantac, may prove problematic in light of functional gastric volumes approximating 10 ml in the first few days of life (less in preterm neonates). The small functional volume of the stomach, combined with frequent feedings, and the young infant's propensity to reflux, highlights the need for formulators to carefully consider final drug concentrations so that drug dose can be successfully titrated for weight, and still be delivered in a volume that is tolerated by the infant.

7.4.2 Gastric Emptying

Despite the fact that innervation of the stomach is established by 13–14 weeks of gestation, and that gastric motor activity is apparent between 14 and 24 weeks of

gestation, gastric motility and peristalsis are immature at birth, and remain so until 6–24 months of age [1, 21, 22]. Consequently, gastric emptying time appears to be somewhat prolonged in infancy. The impact of age-dependent changes in gastric emptying on drug absorption is nicely illustrated by examining pharmacokinetic data of cisapride. The time to achieve maximum plasma concentrations was highest in preterm infants (5.0 ± 2.6 h), followed by term infants (4.3 ± 3.3 h), and older infants (2.2 ± 1.1 h), as compared with adults (1.8 h) [23].

The extent to which gastric emptying is delayed in the young infant is determined, in large part, by the composition of the fluid being administered [21, 24]. As such, formulators developing oral liquids for young infants should expect that drugs other than those in isosmotic aqueous solutions, delivered without concurrent food, will experience: (1) prolonged exposure to the acidic milieu of the stomach; (2) extended contact time with other gastric contents such as nutrients, enzymes, electrolytes, water, and mucin; and (3) increased time to reach the primary absorptive site (i.e., the small intestine) [25].

It should be noted that the age-dependent differences observed in gastric emptying cannot be solely attributed to the differences in migrating motor complex (MMC) frequency and coordination, observed between preterm newborns, term infants, and adults. MMCs predominate in the fasting state [22], which is of limited relevance in young infants who are fed, on average, every 2 h.

7.4.3 Gastric pH

Although the machinery for acid production is well established by the second trimester of gestation, the overall pH of the newborn stomach is relatively alkaline as compared with older children or adults [19, 26–28]. Exactly how long it takes the neonatal pH to fall, and be maintained below 4, remains an active area of debate, with estimates ranging from hours and days, to weeks and months, after birth [22, 29]. Irrespective of the maturation status of the hydrochloric acid-producing machinery, continual feeding in young infants contributes to a less acidic pH in this population. While the higher pH of the neonatal stomach could, theoretically, impair nutrient assimilation, the gastric phase of protein digestion does not seem to be a critical step in protein breakdown. Furthermore, the lower pepsin and gastric acid production, typical of the infant stomach, appear to be offset by the longer exposure of ingested content to lingual amylase and lipase, which function best at a higher pH [30, 31].

In contrast, the absorption of drugs can be influenced by these developmental pH differences. Drugs that are acid labile, remain relatively protected, putatively resulting in higher circulating drug concentrations. A prototypic example is penicillin, for which maximum plasma concentrations in infants and neonates were 150 and 600 %, respectively, those of children, following the administration of comparable weight-based doses [32]. Drugs with pH-dependent solubility characteristics and formulations that rely on pH-dependent coatings or polymers for taste masking,

sustained drug delivery, etc. may exhibit very different disintegration, dissolution, and drug release characteristics at gastric pH values that are higher than those observed in the prototypic adult population [33, 34].

7.5 Intestines

The vast majority of drug absorption, following oral administration, takes place in the intestines. The small intestine is the primary organ involved in drug absorption, though the colon demonstrates some capacity for absorption as well [30].

7.5.1 Intestinal Mucosa

The absorptive capacity of the small intestine depends, in large part, on the integrity of the intestinal mucosa, which houses the villi and the enterocytes. The anatomic infrastructure for these absorptive elements is established early during gestation, but some alterations continue to occur postnatally. For example, the tight junctions connecting the enterocytes are more permeable during the first few weeks of life, allowing whole macromolecules, including immunoglobulins, to pass through the intestinal epithelium [30, 35].

The intestinal brush-border is also home to digestive enzymes and transporters, most of which demonstrate unique developmental profiles [36–38]. As evidenced by the glucose and sucrose transporters, some proteins demonstrate no appreciable expression until mid-gestation, birth or childhood; while others appear to be over-expressed during fetal life and down regulated at the time of delivery [37]. If ontogeny plays a role in the expression and activity of digestive enzymes and nutrient transporters in the small intestine, then, ostensibly, development must also play a role in the expression of drug-metabolizing enzymes (DMEs) and drug transporters in the small intestine. To date, most of the efforts aimed at defining the age-dependent expression patterns of DMEs and transporters have concentrated on the liver and the kidneys [25, 39]. As such, data from intestinal tissue are lacking; however, limited data support a role for ontogeny in the expression of intestinal proteins, suggesting that the activity of cytochromes P450 3A and 1A1 increase during childhood, the activity of glutathione S-transferase decreases during childhood, and the expression of P-glycoprotein is detected at variable levels during the first few years of life [40–43].

In addition to the enterocytes, other, more sparsely scattered, cells throughout the intestinal mucosa include paneth cells (which are thought to have anti-infectious properties and are known to secrete lysozymes and phospholipases) and tuft cells (which express chemosensory receptors similar to those found in taste buds of the tongue and are thought to play a role in the human affinity for certain types of chemicals in nutrients) [44–46]. Differences in the prevalence of such cells across age groups, and the putative impact on drug absorption, remain to be elucidated.

7.5.2 Intestinal Secretions

The developmental profile of intestinal secretions is well defined (the reader is referred to Wyllie and Hyames, 4th edn, for a comprehensive review). Brunner's glands, found throughout the proximal small intestine, are responsible for the production and secretion of a viscoelastic layer of mucus that lubricates the mucosal lining of the small intestine. The mucus layer consists of mucin, bicarbonate, and a host of other active substances (including epidermal growth factors, surface-active lipids, protease inhibitors, and bactericidal factors), all of which have the potential to interact with ingested drug formulations.

In addition to secretions produced by the intestine, one must also consider the impact of secretions delivered into the intestine from other organs. The biliary system and the pancreas secrete digestive enzymes and bile salts into the small intestine through ducts that enter the duodenum. Though these structures are established early in gestation, and are present at birth, their function is not fully mature. Among the most relevant to drug delivery are the bile acids, which are synthesized from cholesterol in the liver, transported across the biliary canaliculi into the duodenum, and recycled through enterohepatic circulation. The first two processes appear to be age-dependent, with both the synthesis and excretion of bile acids reduced in the young infant [47–49]. Coupled with decreased postprandial pancreatic lipase release [50], fat digestion is impaired over the first few months of life [47]. Consequently, lipophilic drugs, and drugs formulated in lipid-based vehicles, can demonstrate capacity-limited absorption in the neonate and young infant [51, 52].

7.5.3 Intestinal pH

Generally speaking, the pH of the intestine is more alkaline than that of the stomach, gradually increasing along the length of the small intestine [44]. The pH of the distal colon, on the other hand, is more acidic than that of the small intestine, secondary to the activity of the colonic bacteria breaking down undigested carbohydrates [44, 53]. Oral formulations of mesalamine, which are used in the treatment of inflammatory bowel disease (IBD), take advantage of the observed changes in pH to deliver the active medication to specific segments of the intestine. For example, an ethylcellulose-coated formulation of mesalamine releases the drug gradually throughout the GI tract; while a pH-sensitive film-coated tablet, is designed to dissolve only at the higher pH of the terminal ileum and proximal colon [54]. Given that only minor differences in intestinal pH are observed between children and adults [53], these sophisticated formulation strategies can be applied to drug development, irrespective of age.

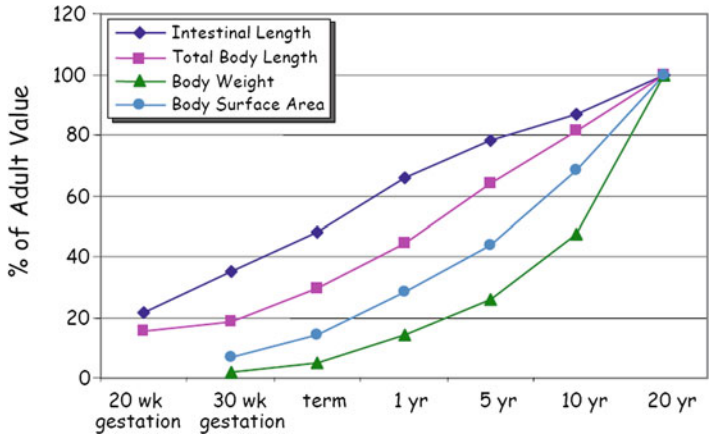

Fig. 7.1 Intestinal length, along with other anthropometric variables, presented as a fraction of adult values

7.5.4 Intestinal Motility

The interstitial cells of Cajal, found in the myenteric plexus of the bowel wall, are now recognized as the pacemakers of intestinal motility [44]. Though their ontogeny remains to be defined, developmental differences have been observed in intestinal motility, particularly in the newborn period. The frequency and amplitude of pulsatile contractions in the intestine are reduced in preterm neonates, resulting in intestinal motility that is erratic, irregular, and prolonged [55]. In the presence of a promotility agent, absorption rates can be enhanced in the newborn, but not to the extent observed in infants greater than 1 month of age [56]. Beyond the neonatal period, the age at which contractility and intestinal transit approximates that of the adult remains unclear; however, in general, formulation considerations, as they relate to motility, can be regarded as independent of age beyond early infancy.

7.5.5 Intestinal Length and Surface Area

There remain differences in the absorption profiles of children and adults that are only partially explained by the anatomic and physiologic changes discussed above [56]. Consequently, numerous references default to an explanation of reduction in absorptive surface area, as the mechanism behind these observable differences. However, the villi and microvilli appear to be fully formed by 12–20 weeks of gestation [36, 57] and intestinal length (relative to adult values) exceeds most other anthropometric measures throughout childhood (Fig. 7.1) [58]. Therefore, it is possible that other factors (e.g., developmental changes in mesenteric blood flow) account for age-dependent differences in absorption [59–61].

7.6 Microbiome

The human intestinal microbiome is a complex microbial community, consisting primarily of bacterial species; although yeast species are now recognized to play an increasing role. The microbiome is comprised of thousands of nonpathologic species of aerobic and anaerobic bacteria, with a composite profile specific to each individual, corresponding to a unique fingerprint of intestinal flora [62]. At birth, the GI tract is sterile; however, colonization occurs within the first few hours to days of life, regardless of gestational age [63]. Initial colonization involves bifidobacteria, enterobacteria, Bacteroides, clostridia, *Staphylococcus aureus* and gram-positive cocci with subsequent changes dependent on gestational and postnatal age, mode of delivery, maternal health, and maternal and neonatal diet [63, 64].

Apart from its roles in digestion and innate enteric immunity, the microbiome also contributes to the deconjugation and (in)activation of several drugs. Mesalamine, for example, is an azo-bonded moiety which remains inert until it is cleaved by colonic bacteria, while digoxin, a cardiac glycoside, is inactivated by colonic bacteria [54, 65]. Interestingly, Linday et al. [65] demonstrate that the frequency with which digoxin reduction products (DRP) are recovered from the urine increases with age and corresponds to an increase in DRP-producing stool cultures. Whether the changes in intestinal microbiota influence the age-dependent disposition of other drug formulations has yet to be established. Similarly, the impact of antibiotics, probiotics, and acid-modifying drugs on the qualitative and quantitative milieu of the dynamic human microbiome cannot be disregarded; particularly, as prescription rates for these medications continue to rise in the pediatric population [66–68].

7.7 Extraphysiologic Considerations

Though the majority of this chapter focuses on appreciable anatomic and physiologic differences that exist between children and adults, there are numerous age-dependent extrinsic factors that influence drug delivery and disposition.

7.7.1 Diet

Both the type and quantity of food administered to children will impact functional gastric volume, gastric emptying, and intestinal transit. Nuclear scintigraphy studies demonstrate nearly log linear gastric emptying kinetics for saline, but these kinetic parameters are significantly slowed by the introduction of nutritive content [21, 22]. Calorically dense or fatty liquids (e.g., nutritionally fortified formulas that contain 22–30 kcal/oz) will empty slower than traditional infant formula or cow's milk, and these liquids empty more slowly than breast milk [69–71]. Thus, the rate of gastric

retention and drug absorption can be expected to vary depending on the type of feeds with which a drug is co-administered.

Feeding frequency can also be expected to impact the absorption of some drugs. Newborns feed on average 8–12 times per day, with meal frequency decreasing to 3–5 times per day by toddlerhood [72]. Apart from a greater propensity for physicochemical drug–nutrient interactions in this setting, young children may also be at greater risk for interactions at the molecular level. Peptide transporter 1 (PEPT1) facilitates the absorption of peptidomimetic drugs, such as ACE inhibitors, amino-beta-lactams, and oseltamivir; however, the normal physiologic substrates for PEPT1 are milk-derived peptides. For infants feeding every 2–4 h, the continual presence of dietary peptides in the intestinal lumen will effectively compete for absorption with co-administered drugs that share the same pathway [73].

Even age-dependent differences in dietary constitution can influence drug delivery in children. Apple juice is ubiquitous in the infant diet, present in countless juices and snacks. In fact, infants in the USA consume 16-times the national average of apple juice [74]. Notably, apple juice can reduce the bioavailability of drugs that serve as substrates for organic anion-transporting polypeptides in the small intestine (e.g., fexofenadine, beta-blockers). As such, drug–diet interactions involving apple juice should be expected to occur with greater frequency in children [75].

7.7.2 Extemporaneous compounding

For drug developers who elect not to pursue a pediatric formulation, the impact of extemporaneous manipulation of the adult formulation on the delivery of the active ingredient should be considered. There exist countless examples of drugs for which bioavailability drops and/or taste becomes unpalatable, when crushed and mixed with commercial excipients or age-appropriate food stuffs [4, 76–78]. As such, it behooves the drug developer to ensure that their compound is compatible with common foods into which the agent will be mixed. They should also ascertain whether the volume of food/liquid required to disperse the drug, and effectively mask any aversive flavor, is age-appropriate for the pediatric population of interest. Finally, the developer should recognize the risk of human error in final product quality and strength, when extemporaneous compounding is required [4].

7.7.3 Concurrent Illness

Many of the developmental principles discussed above are applicable to the otherwise healthy child, with a normally developing GI system, and may not hold true in certain pediatric disease states. There are numerous pathologic conditions that can blunt or destroy the villi, impairing the absorptive capability of the intestine; many of these conditions have their origins in childhood (e.g., IBD, celiac disease).

Other conditions, though not unique to children, are more prevalent in the pediatric population (e.g., *Salmonella* and *Shigella* gastroenteritis in daycares). Importantly, a toddler who is sick with gastroenteritis may barely tolerate small volumes of oral rehydration solution, much less 5–10 ml of a therapeutic agent. In these children, for whom advanced cognitive thought processes have yet to develop, no amount of bargaining may be convincing enough to accept a medication by mouth.

7.8 Conclusion

Many factors influence the absorption of drugs, including properties inherent to the drug (such as pK_a and pH, particle size and charge, solubility and dissolution rate, structure and vehicle matrix) and properties extrinsic to the drug, such as developmental differences in the GI tract. Although the anatomy of the pediatric GI tract is very similar to that of the adult, important physiologic differences remain, providing some explanation for the observed differences in peroral drug absorption in the pediatric vs. the adult population. Innate differences in GI function seem to underlie the somewhat erratic patterns of drug absorption seen in neonates. These differences seem to persist into early infancy and begin to dissipate sometime during toddlerhood and early childhood. In addition, strong preferences for formulation consistency, flavor, and vehicle of delivery, often unique to the young, the ill, or the stubborn child, also help explain the observed differences in peroral drug absorption among neonates, infants, children, and adults.

References

1. Montgomery RK, Grand RJ (2011) Development of the gastrointestinal tract. In: Wyllie R, Hyames JS (eds) Pediatric gastrointestinal and liver disease, 4th edn. Elsevier, Philadelphia
2. Kauffman RE (2005) Drug action and therapy in the infant and child. In: Yaffe SJ, Aranda JV (eds) Neonatal and pediatric pharmacology – therapeutic principles in practice, 3rd edn. Lippincott Williams & Wilkins, Philadelphia
3. Teitelbaum JE (2008) Mouth and esophagus. In: Kleinman RE, Sanderson IR, Goulet O, Sherman PM, Mieli-Vergani G, Shneider BL (eds) Walker's pediatric gastrointestinal disease: physiology, diagnosis, management, vol 1, 5th edn. BC Decker Inc, Hamilton
4. Abdel-Rahman SM, Wells T, Reed M, Kearns GL (2007) Considerations in the rational design and conduct of pediatric clinical pharmacology trials: avoiding the problems and pitfalls. Clin Pharmacol Ther 81:483–494
5. Lawless H (1985) Sensory development in children: research in taste and olfaction. J Am Diet Assoc 85:57–85
6. Ahearn WH, Castine T, Nault K, Green G (2001) An assessment of food acceptance in children with autism or pervasive developmental disorder-not otherwise specified. J Autism Dev Disord 31:505–511
7. Bowie JD, Clair MR (1982) Fetal swallowing and regurgitation: observation of normal abnormal activity. Radiology 144:877–878
8. Grassi R, Farina R, Floriani I, Amodio F, Romano S (2005) Assessment of fetal swallowing with gray-scale and color Doppler sonography. Am J Roentgenol 185:1322–1327

9. Tuchman DN (2008) Disorders of deglutition. In: Kleinman RE, Sanderson IR, Goulet O, Sherman PM, Mieli-Vergani G, Shneider BL (eds) Walker's pediatric gastrointestinal disease: physiology, diagnosis, management, vol 1, 5th edn. BC Decker Inc, Hamilton
10. Delaney AL, Arvedson JC (2008) Development of swallowing and feeding: prenatal through first year of life. Dev Disabil Res Rev 14:105–117
11. Committee for Medicinal Products for Human Use (CHMP) (2005) Reflection paper: formulations of choice for the paediatric population. http://www.emea.europa.eu/pdfs/human/paediatrics/19481005en.pdf. Accessed 18 Aug 2012
12. Pandit S, Shah U, Kirby DJ, Nunn T, Tuleu C (2010) Inappropriate oral formulations and information in paediatric trials. Arch Dis Child 95:754–756
13. Spomer N, Klingmann V, Stoltenberg I, Lerch C, Meissner T, Breitkreutz J (2012) Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. Arch Dis Child 97:283–286
14. Thomson S, Tuleu C, Wong I, Keady S, Pitt K, Sutcliffe A (2009) Minitablets: new modality to deliver medicines to preschool-aged children. Pediatrics 123:e235–e238
15. Cucchiara S, Borrelli O, Di Nardo G (2008) Esophageal motility. In: Kleinman RE, Sanderson IR, Goulet O, Sherman PM, Mieli-Vergani G, Shneider BL (eds) Walker's pediatric gastrointestinal disease: physiology, diagnosis, management, vol 1, 5th edn. BC Decker Inc, Hamilton
16. Rudolph CD, Hassal E (2008) Gastroesophageal reflux. In: Kleinman RE, Sanderson IR, Goulet O, Sherman PM, Mieli-Vergani G, Shneider BL (eds) Walker's pediatric gastrointestinal disease: physiology, diagnosis, management, vol 1, 5th edn. BC Decker Inc, Hamilton
17. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassal E, Liptak G, Mazur L, Sondheimer J et al (2009) Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 49:498–547
18. Henry SM (2004) Discerning differences: gastroesophageal reflux and gastroesophageal reflux disease in infants. Adv Neonatal Care 4:235–247
19. Marciano T, Washil BK (2007) The ontogeny and developmental physiology of gastric acid secretion. Curr Gastroenterol Rep 9:479–481
20. Silverman WA (ed) (1961) Dunham's premature infants, 3rd edn. Hoeber, Inc., Medical Division of Harper and Brothers, New York
21. Saps M, Di Lorenzo C (2011) Gastric motility disorders. In: Wyllie R, Hyames JS (eds) Pediatric gastrointestinal and liver disease, 4th edn. Elsevier, Philadelphia
22. Czinn SJ, Blanchard SS (2011) Developmental anatomy and physiology of the stomach. In: Wyllie R, Hyames JS (eds) Pediatric gastrointestinal and liver disease, 4th edn. Elsevier, Philadelphia
23. Kearns GL, Robinson PK, Wilson JT, Wilson-Costello D, Knight GR, Ward RM, van den Anker JN et al (2003) Cisapride disposition in neonates and infants: in vivo reflection of cytochrome P450 3A4 ontogeny. Clin Pharmacol Ther 74:312–325
24. Gomes H, Hornoy P, Liehn J (2003) Ultrasonography and gastric emptying in children: validation of a sonographic method and determination of physiological and pathological patterns. Pediatr Radiol 33:522–529
25. van den Anker JN, Schwab M, Kearns GL (2011) Developmental pharmacokinetics. In: Seyberth HW et al (eds) Pediatric clinical pharmacology: handbook of experimental pharmacology. Springer, Berlin
26. Agunod M, Yamaguchi N, Lopez R, Luhby AL, Glass GB (1969) Correlative study of hydrochloric acid, pepsin, and intrinsic factor secretion in newborns and infants. Am J Dig Dis 14:400–414
27. Moazam F, Kirby WJ, Rodgers BM, McGuigan JE (1984) Physiology of serum gastrin production in neonates and infants. Ann Surg 199:389–392
28. Rodgers BM, Dix PM, Talbert JL, McGuigan JE (1978) Fasting and postprandial serum gastrin in normal human neonates. J Pediatr Surg 13:13–16

29. Gottrand F (2008) Acid-peptic disease. In: Kleinman RE, Sanderson IR, Goulet O, Sherman PM, Mieli-Vergani G, Shneider BL (eds) Walker's pediatric gastrointestinal disease: physiology, diagnosis, management, vol 1, 5th edn. BC Decker Inc, Hamilton
30. Wahbeh GT, Christie DL (2011) Basic aspects of digestion and absorption. In: Wyllie R, Hyames JS (eds) Pediatric gastrointestinal and liver disease, 4th edn. Elsevier, Philadelphia
31. Garcia-Naveiro R, Udall JN (2011) Maldigestion and malabsorption. In: Wyllie R, Hyames JS (eds) Pediatric gastrointestinal and liver disease, 4th edn. Elsevier, Philadelphia
32. Huang NN, High RH (1953) Comparison of serum levels following the administration of oral and parenteral preparations of penicillin to infants and children of various age groups. J Pediatr 42:657–658
33. Chen R, Okamoto H, Danjo K (2006) Particle design using a 4-fluid-nozzle spray-drying technique for sustained release of acetaminophen. Chem Pharm Bull 54:948–953
34. Patra S, Samantaray R, Pattnaik S, Barik BB (2010) Taste masking of Etoricoxib by using ion-exchange resin. Pharm Dev Technol 15:511–517
35. Jakobsson I, Lindberg T, Lothe L, Axelsson I, Benediktsson B (1986) Human alpha-lactalbumin as a marker of macromolecular absorption. Gut 27:1029–1034
36. Lacroix B, Kedinger M, Simon-Assmann P, Haffen K (1984) Early organogenesis of human small intestine: scanning electron microscopy and brush border enzymology. Gut 25: 925–930
37. Davidson NO, Hausman AM, Ifkovits CA, Buse JB, Gould GW, Burant CF, Bell GI (1992) Human intestinal glucose transporter expression and localization of GLUT5. Am J Physiol 262:C795–C800
38. Boudry G, David ES, Douard V, Monteiro IM, Le Huërou-Luron I, Ferraris RP (2010) Role of intestinal transporters in neonatal nutrition: carbohydrates, proteins, lipids, minerals, and vitamins. J Pediatr Gastroenterol Nutr 51:380–401
39. Gladtke E, Heimann G (1975) The rate of development of elimination functions in kidney and liver of young infants. In: Morselli PL, Garattini S, Sereni F (eds) Basic and therapeutic aspects of perinatal pharmacology, pp. 393–403. New York: Raven Press
40. Johnson TN, Tanner MS, Taylor CJ, Tucker GT (2001) Enterocytic CYP3A4 in a paediatric population: developmental changes and the effect of coeliac disease and cystic fibrosis. Br J Clin Pharmacol 51:451–460
41. Gibbs JP, Liacouras CA, Baldassano RN, Slattery JT (1999) Up-regulation of glutathione S-transferase activity in enterocytes of young children. Drug Metab Dispos 27:1466–1469
42. Fakhoury M, Litalien C, Medard Y, Cavé H, Ezzahir N, Peuchmaur M, Jacqz-Aigrain E (2005) Localization and mRNA expression of CYP3A and P-glycoprotein in human duodenum as a function of age. Drug Metab Dispos 33:1603–1607
43. van Kalken CK, Giaccone G, van der Valk P, Kuiper CM, Hadisaputro MM, Bosma SA, Scheper RJ, Meijer CJ, Pinedo HM (1992) Multidrug resistance gene (P-glycoprotein) expression in the human fetus. Am J Pathol 141:1063–1072
44. Shroyer NF, Kocoshis SA (2011) Anatomy and physiology of the small and large intestines. In: Wyllie R, Hyames JS (eds) Pediatric gastrointestinal and liver disease, 4th edn. Elsevier, Philadelphia
45. Tolhurst G, Reimann F, Gribble FM (2012) Intestinal sensing of nutrients. Handb Exp Pharmacol 209:309–335
46. Sbarbati A, Osculati F (2005) The taste cell-related diffuse chemosensory system. Prog Neurobiol 75:295–307
47. Heubi JE (2011) Bile acid physiology and alterations in the enterohepatic circulation. In: Wyllie R, Hyames JS (eds) Pediatric gastrointestinal and liver disease, 4th edn. Elsevier, Philadelphia
48. Poley JR, Dower JC, Owen CA, Stickler GB (1964) Bile acids in infants and children. J Lab Clin Med 63:838–846
49. Suchy FJ, Balistreri WF, Heubi JE, Searcy JE, Levin RS (1981) Physiologic cholestasis: elevation of the primary serum bile acid concentrations in normal infants. Gastroenterology 80:1037–1041

50. Zoppi G, Andreotti G, Pajno-Ferrara F, Njai DM, Gaburro D (1972) Exocrine pancreas function in premature and full term neonates. Pediatr Res 6:880–886
51. Kearns GL, Bradley JS, Jacobs RF, Capparelli E, James LP, Johnsom KM, Abdel-Rahman SM (2000) Single-dose pharmacokinetics of a pleconaril in neonates. Pediatr Infect Dis J 19:833–839
52. Shankaran S, Kauffman RE (1984) Use of chloramphenicol palmitate in neonates. J Pediatr 105:113–116
53. Kay JL (2011) Review of paediatric gastrointestinal physiology data relevant to oral drug delivery. Int J Clin Pharm 33:20–24
54. Treatment Guidelines (2012) Drugs for inflammatory bowel disease. Treat Guidl Med Lett 10:19–28
55. Berseth CL (1989) Gestational evolution of small intestine motility in preterm and term infants. J Pediatr 115:646–661
56. Heimann G (1980) Enteral absorption and bioavailability in children in relation to age. Eur J Clin Pharmacol 18:43–50
57. Grand RJ, Watkins JB, Torti FM (1976) Development of the human gastrointestinal tract. A review. Gastroenterology 70:790–810
58. Weaver LT, Austin S, Cole TJ (1991) Small intestinal length: a factor essential for gut adaptation. Gut 32:1321–1323
59. Yanowitz TD, Yao AC, Pettigrew KD, Werner JC, Oh W, Stonestreet BS (1999) Postnatal hemodynamic changes in very-low-birthweight infants. J Appl Physiol 87:370–380
60. Martinussen M, Brubakk AM, Vik T, Yao AC (1996) Mesenteric blood flow velocity and its relation to transitional circulatory adaptation in appropriate for gestational age preterm infants. Pediatr Res 39:275–280
61. Martinussen M, Brubakk AM, Linker DT, Vik T, Yao AC (1994) Mesenteric blood flow velocity and its relation to circulatory adaptation during the first week of life in healthy term infants. Pediatr Res 36:334–339
62. Nikkila J, de Vos M (2012) Advanced approaches to characterize the human intestinal microbiota by computational meta-analysis. J Clin Gastroenterol 44(Suppl 1):S2–S5
63. Teitelbaum JE (2011) Indigenous flora. In: Wyllie R, Hyames JS (eds) Pediatric gastrointestinal and liver disease, 4th edn. Elsevier, Philadelphia
64. Morowitz MJ, Denef VJ, Costello EK, Thomas BC, Poroyko V, Relman DA, Banfield JF (2011) Strain-resolved community genomic analysis of gut microbial colonization in a premature infant. Proc Natl Acad Sci USA 108:1128–1133
65. Linday L, Dobkin JF, Wang TC, Butler VP, Saha JR, Lindenbaum J (1987) Digoxin inactivation by the gut flora in infancy and childhood. Pediatrics 79:544–548
66. Plasschaert AIO, Rovers MM, Schilder AGM, Verheij TJM, Hak E (2006) Trends in doctor consultations, antibiotic prescription, and specialist referrals for otitis media in children: 1995–2003. Clin Pediatr 117:1879–1886
67. Cabana MD, Shane AL, Chao C, Oliva-Hemker M (2006) Probiotics in primary care pediatrics. Clin Pediatr 45:405–410
68. Chen IL et al (2012) Proton pump inhibitor use in infants: FDA reviewer experience. J Pediatr Gastroenterol Nutr 54:8–14
69. Ewer AK, Durbin GM, Morgan ME et al (1994) Gastric emptying in preterm infants. Arch Dis Child Fetal Neonatal Ed 71:F24–F27
70. Cavell B (1981) Gastric emptying in infants fed human milk or infant formula. Acta Paediatr Scand 70:639–641
71. Driessche MVD, Peeters K, Marien P et al (1999) Gastric emptying in formula-fed and breast-fed infants measured with the 13C-octanoic acid breath test. J Pediatr Gastroenterol Nutr 29:46–51
72. Stettler N, Bhatia J, Parish A, Stallings V (2011) Feeding healthy infants, children, and adolescents. In: Kliegman RM, Stanton BF, Schor NF, St. Geme JW, Behrman RE (eds) Nelson textbook of pediatrics, 19th edn. Elsevier/Saunders, Philadelphia
73. Ogihara T, Kano T, Wagatsuma T, Wada S, Yabuuchi H, Enomoto S, Morimoto K, Shirasaka Y, Kobayashi S, Tamai I (2009) Oseltamivir (Tamiflu) is a substrate of peptide transporter 1. Drug Metab Dispos 37:1676–1681

74. Murdoch DJ, Krewski D, Wargo J (1992) Cancer risk assessment with intermittent exposure. Risk Anal 12:569–577
75. Abdel-Rahman SM, Johnson FK, Gauthier-Dubois G, Weston IE, Kearns GL (2003) The bioequivalence of nizatidine (Axid ®) in three extemporaneously and commercially prepared oral liquid formulations compared with capsule. J Clin Pharmacol 43:148–153
76. Notterman DA, Nardi M, Saslow JG (1986) Effect of dose formulation on isoniazid absorption in two young children. Pediatrics 77:850–852
77. Nahata MC, Morosco RS, Hipple TF (1994) Effect of preparation method and storage on rifampin concentration in suspensions. Ann Pharmacother 28:182–185
78. Blake MJ, Abdel-Rahman SM, Jacobs RF, Lowery NK, Sterling T, Kearns GL (2006) Pharmacokinetics of rifapentine in children. Pediatr Infect Dis J 25:405–409

Chapter 8
Orosensory Perception

Per Møller

Abstract This chapter provides an introduction to the sensory systems which determine human perception of foods. Since the same sensory systems are stimulated when a patient receives medication via the oral route, properties and effects described in the context of food perception are relevant to the understanding of the perception of pharmacological substances, and these should be taken into account when designing and/or formulating medicines.

The different senses humans are endowed with serve different purposes. Properties of the senses of taste, smell, trigeminality, and touch (mouthfeel) are described as well as the integration of these into flavor perception. It is discussed how memories carried by these senses, which are important for food choice behavior, are distinguished from memory in a "higher" sense such as vision.

Orosensory perception is closely connected to different satiety mechanisms and reward in connection with foods and some aspects of these problems are described. Preference development and acceptance are particularly important in food perception and the mechanisms of these are explained. The same mechanisms are responsible for generation of aversions. Great care should be exercised to avoid these aversions in connection with administration of drugs.

8.1 Introduction

Humans are endowed with many senses which make it possible to obtain information about "what" is "where" in the environment. The senses can be divided into so-called far and near senses [1]. The far senses, vision and audition, are referred to as such because information from objects and events from far away can reach the

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animal via electromagnetic light waves, as is the case for vision, or via pressure waves, as is the case for audition. All other senses, the near senses, require direct physical contact with the materials these senses provide information about. The far senses are also sometimes referred to as the "higher" senses and the near senses as the "lower" senses. Memory, planning, thinking, imagery, and other cognitive processes are intertwined with the senses. The higher senses, vision and audition, lead to more elaborate cognitive processes than the lower senses. Visual and auditory imagery is a case in point, which all people are capable of. Very few people, on the other hand, claim to have olfactory imagery. Some cognitive functions, memory being the best example, pervade all senses, and olfactory, taste, and flavor memory are of crucial importance for food choice behavior [2, 3]. Besides perceptual and cognitive processes, all senses also are capable of generating emotional states and representations. Fear, anger, happiness, etc. are basic emotions, but in the context of foods the most important emotional states relate to evaluation of how well a given stimulus is liked or how disgusting it is. These evaluations, which don't need to be influenced by cognitive processes, are the main drivers for the actions which follow emotional evaluation; whether a stimulus (a food) is accepted or rejected.

Thus, all senses support perceptual, cognitive and emotional processes, but to different degrees. Some senses lend themselves more easily to cognitive processes than other senses do and some more easily represent emotional states [4, 5]. Perceptually, the senses are, of course, phenomenologically different, i.e. smelling a substance is a purely olfactory feat and perceiving a color is brought about by activity in the visual system only. But besides these phenomenological perceptual properties of the senses, certain types of information about the environment can be extracted by more than one sense. Movement of a visible, sound emitting object can be determined by both the visual and the auditory system. The final representation in the brain of the movement of the object is a result of visuo-auditory integration processes. Even if there are only few examples of the same type of information being extracted by different senses, in the far majority of cases, objects and events present themselves to more than one sense. A certain food, e.g., has a smell, texture, and visual appearance. These different types of information all aid in the detection and identification of the food and the perceptual system integrates the different types of information. Besides providing us with a phenomenologically more interesting environment, the many senses also help us obtain more reliable and robust information about objects and events. If, for some reason, the information provided to one sense is too noisy to extract a reliable representation of the environment, information extracted by another sense will help us to reach a reliable representation. Thus, from the perspective of understanding how the sensory systems works, we do not only need to understand each individual system (the olfactory, the gustatory, the visual, etc.), but it is also crucial to understand how the senses act in concert. This is particularly the case for problems regarding food perception and appreciation as will be discussed later in connection with flavor perception.

A fair number of the senses, or sensory modalities, are of crucial importance for perception and affective evaluation of foods and for choice behavior. This has been demonstrated to rely far more on the sensory properties than upon any other parameters.

The senses most important for food perception are, not surprisingly, those which can be activated by stimulation in the mouth: the so-called orosensory senses [6, 7]. Even though stimulation of the orosensory senses determines the sensory experience of a food, visual and auditory information can also play an important role. Vision can raise expectations of the taste and enjoyment that is about to follow, as well as prepares the body for digestion by way of the so-called cephalic reflexes.

Most of what we know about the workings of the senses in humans comes from psychophysical work [6, 7]. Psychophysics is the science which connects the external physical world to our internal psychological states. Psychophysics studies function and functional mechanisms. It describes what the organism is capable of and which (functional) properties it has. For example, that humans can distinguish five basic tastes was originally derived from psychophysical studies. That holds for all other functional properties of the sensory systems. One might say that psychophysics maps out the functional properties of the perceptual (and cognitive and emotional) systems. Only when it has been described what the organism is capable of it is meaningful to search for neural implementations of the functions. Until recently, quite a bit of information about the localization in the brain of the different systems has come from neuropsychological patients, i.e. from patients with various brain lesions. More recently, with the advent of modern neuroimaging methods such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalography (EEG) and magnetoencephalography (MEG), information about localization and timing of processes in the brain can be obtained from normal, healthy people. The different techniques have different virtues and drawbacks. EEG does not have the same exquisite spatial resolution as fMRI has, but it has a temporal resolution which is only limited by the speed of the electronic equipment used in an investigation. In practice, this means that EEG data has a better temporal resolution than 1 ms. Experiments on animals, which for ethical reasons cannot be performed on humans, also contributed to describe some of the underlying neural mechanisms. But, one must always exercise care in using animal data to interpret psychophysical effects as measured in humans.

In the rest of this chapter I will discuss the orosensory senses which are most important for food perception and acceptance: taste, smell, trigeminality, and touch. I will explain what is meant by flavor and discuss some of the problems and effects of flavor. The orosensory senses are closely connected to homeostasis and reward and are crucial in determining acceptance and how (food) preferences are formed. These problems will be discussed at the end of the chapter.

8.2 Taste

The “taste” of a food is an important property, not the least because it accounts for most of the food choices people make. The phrase “taste” is a bit unfortunate because it gives the impression that the sense of taste completely determines the “taste” of a food. As will be made clear in this chapter, this is by no means the case.

Limiting ourselves in this paragraph to the *sense of taste* (gustation), it is customary to talk of five *basic* tastes: sweet, salty, sour, bitter, and umami [6, 7].

The last one, umami, is less well known than the other four. It is often described as the taste of bouillon or glutamate. Umami was discovered by Japanese scientists and the name is meant to indicate "pleasurable taste," and is associated with seaweed, fermented soy, and fish products. The concept of basic tastes comprises the idea that sweet, salty, sour, bitter, and umami tastes are basic, in the sense that none of them can be obtained by any combination of the other four, and that any possible taste sensation can be created by an appropriate mixture of the five basic tastes.

The basic tastes are usually defined in terms of sucrose (sweet), quinine (bitter), sodium chloride (salty), citric acid (sour), and monosodium glutamate (umami). Different types of criticisms have been raised against the concept of basic tastes [8]. But, since the five basic tastes are used worldwide in common language *and* because the scientific literature on taste also uses this categorization, it will take a paradigmatic change to reorganize our knowledge about the sense of taste and at present the concept of basic tastes is very useful.

Specialized taste receptors on the tongue, palate, soft palate, and areas in the upper throat (pharynx and laryngopharynx) are activated when they come in contact with typical tastants such as alkaloids (bitter), many ionic compounds (salty), most acids (sour), sugars (sweet), and amino acids and nucleotides (umami).

Humans have about 7,500 taste buds in the mouth, each of which contains 40–60 taste cells. About two thirds of the taste buds are localized in different kinds of papillae. The rest of the taste cells are distributed in the mouth outside papillae. Taste cells interact with tastants dissolved in liquids in the mouth (water, alcohol, fats) via different receptors. Over the last 10–15 years receptor proteins for bitter, sweet, and umami have been identified. All these receptors are a subclass of the super family of G-protein-coupled receptors (GPCRs) and have been classified as T1R1, T1R2, T1R3, and T2Rs [9, 10].

Receptors for sour and salty tastes are essentially ionic channels, but the identity of the salty receptor is still speculative and controversial. Human taste cells have a lifetime of 5–30 days and are regenerated all through life.

Once a tastant has activated a taste cell, signals are transmitted to the brain for further processing. The first relay is in the nucleus of the solitary tract (NTS) in the medulla. In primates, NTS neurons transmit information to an area in the thalamus, which further connects to areas in the frontal operculum and insula. These two areas are usually referred to as the primary taste cortex [11]. These areas are connected to limbic parts of the brain and to frontal areas, notably the orbitofrontal cortex which also receives input from smell, touch, and visual areas, besides being connected to hypothalamic nuclei which hold information about hunger and satiety.

Despite the fact that we only rarely doubt whether we have added too much salt to a dish or too much tonic in our gin and tonic, or if our coffee is too bitter, the underlying neurophysiological processes that allow us to immediately evaluate these questions are very complicated. We can experience the character of a taste (sweet, salty, sour, etc.), but we can also distinguish different intensities of tastes. Since a taste cell contains receptors for the different basic tastes it can respond to

more than a single basic taste. There is therefore not enough information in the signal from a single taste cell to determine the stimulus. The cell could relay the same signal to the brain when stimulated with a weak sweet solution as when stimulated with a strong bitter solution. Another taste cell with another distribution of receptors will in general respond differently to the weak sweet and strong bitter solutions. There will, on the other hand, be other concentrations of basic tastes which this cell will respond to in the same way. If, however, we consider the distribution of activities in a sufficient number of taste cells, it is possible to determine the character and strength of the taste stimulus. The character and intensity of tastes are thought to be coded by activities in many taste cells. This is referred to as distributed coding.

Outside the laboratory the human gustatory system rarely encounters single basic tastes. Most food stimuli are complex mixtures of chemicals which activate a number of basic tastes simultaneously and there are important interactions between the different tastes in a mixture of tastes [12]. Tastes can suppress or enhance each other. Masking, the nonlinear process in which the addition of compound A decreases the intensity of compound B in a manner that goes beyond linear reductions in intensity, is of great interest to mask bad tastes of pharmacological compounds. This problem is dealt with in Chap. 9 by Charles R. Frey. Mixture interactions at low concentration which generate suppressions in some cases and enhancement in other can be used to modulate the flavor of a food. The effect of salt in breads or in French pancakes is a well-known example. A well-tasting bread or pancake does not taste salty, but following the same recipes for these foods without the salt leads to breads and pancakes which are unpalatable to most people.

The five basic tastes are not sufficient to create all of the thousands of different "tastes" available to us from different foods. Smelling a food gives an impression of its so-called aroma. The sense of smell therefore seems to be important for the perception of foods. Think about how food tastes when you have a common cold, or how wine tastes if you block your nose while drinking it. If smell was not important for the "taste" of food it should be possible to "create" the "taste" of, e.g., an orange, by a particular mixture of the basic tastes—and this is not possible. The sensation of smell produces an almost infinite number of possible "tastes" when combined with the other senses which contribute to the perception of foods. The dimension of the space describing the different possible "tastes" increases enormously from the five dimensions that the sense of taste provides on its own.

8.3 Sense of Smell

Stevenson [13] has identified three major classes of function of human olfaction: in ingestive behaviors (e.g., food detection and evaluation, appetite regulation, breast finding), in avoiding environmental hazards (e.g., fear related, disgust related), and in social communication (e.g., reproductive behaviors and emotional contagion). He also stresses the importance of learning in human olfaction and he points out that

learning and memory in olfaction are distinguished from learning in other sensory modalities by its speed, its resistance to extinction and its often implicit nature. Besides the three classes of function of human olfaction listed by Stevenson, human odor memory supposedly also plays a large role in generating feelings of being at home and of well-being. Furthermore, "Proustian effects," i.e. the ability of odors and odor memory to open up rich recollections and feelings of times and events gone by are important roles of odor memory.

8.4 Structure of the Olfactory System

The receptors for the sense of smell are located in the nose and occupy 4–5 cm^2 in each nostril. It is estimated that humans have about 350 different types of receptor cells. It is noteworthy that this number of different cells is dramatically different from the number of different receptor cells we have in the eye (three types (cones) for day vision and one type (rod) for night vision/vision under low ambient luminance conditions). This difference strongly suggests that coding and processing of visual and olfactory information use different strategies. Most odorants activate many of these 350 different cells, but different smells activate different subsets to different degrees. From the receptor cells in the nose signals are transmitted to neurons in the olfactory bulbs, bulb-formed neural structures located behind the eyes. After signal transformations in the bulbs, olfactory information is relayed via the olfactory tract to the piriform cortex, the so-called primary olfactory cortex, and to amygdaloid areas. The amygdalae (one in each side of the brain) are part of the limbic system, which is strongly implicated in emotional processing. This means that olfactory information reaches emotional brain areas after only two relays. Signals in other senses need to pass more relay stations before reaching the amygdalae and other emotional brain areas. This strongly suggests that the sense of smell has particular salience as a conveyer of emotions. This suggestion has been supported by a number of investigations [14, 15]. From the piriform cortex and amygdaloid areas, signals are relayed to other areas in the brain, both in the midbrain and in the frontal areas of the brain. Various frontal areas have been implicated in olfactory processing, most notably the orbitofrontal cortex. The olfactory brain is ipsilaterally organized, as opposed to the other senses, which are contralaterally organized. Ipsilateral means that signals from the right nostril are transmitted to the same (ipsi) side, i.e. the right side; and signals from the left nostril are transmitted to the left side of the olfactory brain. In a contralateral sense (contra meaning opposite) such as vision, signals from the left visual field are transmitted to the right part of the visual brain and vice versa for signals from the right visual field. Olfaction is also distinguished from the other senses in that olfactory signals do not have to pass through a midbrain relay in the thalamus, as signals in the other senses do, before they are transmitted to limbic areas and to areas in the orbitofrontal cortex. From an anatomical point of view olfaction is wired very differently than the other senses. This, together with the dramatic differences in number of different types of receptor

Table 8.1 Comparison of important properties of the senses of vision, audition, olfaction, gustation, touch, and pain

	Vision	Audition	Olfaction	Gustation	Touch	Pain
Characteristic involved						
Strict intersubjectivity	Yes	Yes	No	No	Yes?	No
Inborn properties	Yes	Yes	No	(Yes)	Yes	Yes
Directional perception	Yes	Yes	No	No	Yes?	Yes temporal
Relative perception	Yes	Yes	No	No	Yes?	Yes
Intensity discrimination	High	High	Poor	Poor	High	High/low
Quality discrimination	High	Very high	Very high	Moderate	High	High
Absolute sensitivity	High	High	High	Moderate	High	High?
Adaptation	Partial	Low	Complete	Partial	Complete	Sensitization
In focus of attention	Mostly	Often	Seldom	Seldom	Sometimes	Mostly

Note how the "higher senses" vision and audition are distinguished from olfaction and gustation. The lower senses olfaction and gustation are seldom in the focus of attention and has very little intersubjectivity, but are more prone to adaptation than vision and audition. Courtesy of E.P. Köster

cells (in, e.g., vision and olfaction), suggests that olfaction has very different properties than, e.g. vision. This anatomically based suggestion is supported by functional comparisons as illustrated in Table 8.1.

8.5 Foods and the Sense of Smell

The sense of smell is crucial for the "taste" of foods. Think about how food "tastes" when your nose is blocked. All foods with other "tastes" than pure sweetness, sourness, saltiness, umami, or bitterness contain aroma substances which are released when the food is chewed and brought to smell receptors in the nose via the nasopharynx which connects the mouth and the nose. Without odor perception our experience of foods would be very limited. People who have lost the sense of smell describe how foods have become boring and how their enjoyment of meals has disappeared. Hedonic value, i.e. whether an odor smells good or bad is by far the most important property of an odor. This holds true both for its role in ingestive behaviors and when it helps us to avoid environmental hazards.

Smell serves us in two ways when we deal with foods. Before we ingest a food we often smell it by sniffing at it. This sniffing behavior allows us to judge if the food is safe to ingest, and we form anticipations of the quality and taste of it. When a smell is estimated or appreciated by sniffing, odorants enter the nose through the nostrils. This type of olfactory perception, called orthonasal perception, also helps to prepare the body for ingestion by means of the so-called cephalic reflexes, such as increasing the flow of saliva in the mouth, increasing the release of insulin in the pancreas and increasing the release of acid in the stomach. The very sight of the food to be eaten also triggers cephalic reflexes [16, 17].

Once we have decided that the food we estimate by smelling is safe and (probably) well-tasting, we ingest it, chew it, and swallow it. During chewing and swallowing,

aroma molecules are released from the food and these reach the olfactory epithelium via the nasopharynx. Olfactory perception via this route is called retronasal olfactory perception. These different functions of olfactory perception seem to be reflected in the neural underpinnings of anticipatory and consummatory food chemosensation. Small and colleagues have found separable and overlapping representations of anticipatory and consummatory chemosensation [18, 19].

There is no strict intersubjectivity in olfaction, see Table 8.1. Olfactory experiments often require at least 20 subjects, whereas 3–5 subjects are usually enough to obtain sufficient statistical power in vision experiments. Olfactory judgment of pleasantness of odors is learned behavior. This is particularly important for the perception and evaluation of foods and explains why very different culinary traditions have developed in different parts of the world based upon what nature has to offer at particular places. We come to like what we have access to.

Olfactory adaptation, i.e. that sensitivity to a stimulus is reduced when we are exposed to it, is very strong and sometimes complete. These effects can be quite quick, rendering an odorant unnoticeable within a few seconds. There are both peripheral (in the nose) adaptation mechanisms and central (in the brain) mechanisms. Furthermore, an odorant does not only adapt the olfactory system's ability to detect the presence of itself (auto-adaptation) but may also affect the system's perception of other odorants (cross-adaptation). These effects strongly affect what we perceive when we engage in continual eating or drinking. If a substance with an unwanted flavor is present in a drink, for example, but is not perceived because it is masked by another flavor component, adaptation to the masker could lead to perception of the unwanted flavor. This might be why the second beer often tastes different from the first you drink.

Smells are seldom in our focus of attention, but this does not mean they do not serve to guide behavior. Recent work has revealed that odors and flavors that are not attended to at all are nevertheless encoded and remembered [20–23]. This type of "incidental" learning builds memories which are less explicit and declarative than memories of a more semantic nature. In our daily dealings with foods we seldom have any intention of encoding what we encounter. The memories we form of such events are of a much more implicit nature and learning is incidental. We nevertheless do remember events and objects even without any intention to do so.

Incidentally learned information about odors and flavors is not based on actual recognition of a certain target, but rather on detection of novelty [24]. That is, when prompted, we detect that a certain stimulus is not identical to the one we encountered previously. When presented with the same stimulus as previously (the target) we are often at chance level at detecting that it is the same stimulus. These effects have also been found in other lower senses than smell [21, 25–27]. Furthermore, in contrast to what is usually found in memory experiments, in the incidental learning experiments on the lower senses referred to above, elderly people remember stimuli as well as young people. These results are relevant to the understanding of eating behavior and choice of foods. They might also help to explain the relative constancy of food preferences over a lifetime despite the rather dramatic changes of the sensory systems with age.

Relying on memory systems with these properties in conjunction with senses which are sensitive to expectation and anticipation effects, that is, senses which will incorporate top-down information into the formation of a percept, might be sufficient to explain the relative constancy of food preferences over life.

Since olfactory stimuli are rather poor in information content compared to, e.g., visual stimuli one might expect that olfaction would be more prone to influences from top-down effects. Such effects have indeed been found in olfaction. Different expectations to an odor dramatically change the activities in the olfactory system [28–30].

8.6 Sense of Trigeminality

Trigeminal stimuli are occasionally referred to as "irritants," since the sensations they give rise to can be unpleasant or even painful. Besides allowing us to perceive hot spices (chili, garlic, mustard, horseradish, ginger, etc.) and CO_2 in fizzy drinks, most chemical substances will also activate the trigeminal system at sufficiently high concentration. This sense is also known as chemesthesis and stimuli which activate the trigeminal system in the mouth are often said to have "oral pungency" [31]. The receptors of the trigeminal system consist of the so-called free nerve endings. These receptors are found in the mouth, the nose, the throat, and around the eyes. When a (food or other) substance scratches in the nose or mouth we experience a trigeminal sensation. It is important to note that trigeminal sensation is not part of the olfactory or gustatory system, but constitutes a separate sense. Trigeminal signals are relayed from the sensory periphery to the brain by the 5th cranial nerve, the trigeminal nerve. Other painful sensations such as cold and heat are also sensed by the trigeminal system as is the physical temperature in the mouth and the cooling effects of menthol and other substances. Many of the functional properties of this system are very different from those of olfaction (smell) and gustation (taste). For example, oral pungency typically has a slow onset but can persist for prolonged periods, minutes to tens of minutes.

This is contrary to the sense of taste, which is most intense for the few seconds the food is in the mouth. Also, trigeminal stimuli might not only adapt (de-sensitize) the system but also induce higher sensitivity to stimuli [32]. These differences in the temporal nature of pungency and taste is of great interest when considering the palatability of foods and the overall satiety they provide. In many cases, the long-term effects of pungency will make foods both more palatable and more satiating.

Without pungency many foods would be bland; imagine horseradish without the heat or garlic with no bite. Clearly, trigeminal sensation plays a crucial role in our evaluation of the palatability of foods.

Trigeminal stimuli also seem to have very interesting effects on metabolism and satiety. It has been reported that trigeminal stimuli can increase fat metabolism [33, 34] and increase satiety [35, 36]. Thereby, by both mechanisms, they potentially provide a contribution to curb the accelerating obesity epidemic.

8.7 Mouthfeel, Sense of Touch

Olfactory, gustatory, and trigeminal sensations are determined by the submicroscopic (molecular) properties of the stimulants. Mouthfeel, on the other hand, is what a food feels like in the mouth. It depends on the macroscopic (and mesoscopic) properties of the food. Properties such as thickness, viscosity, hardness, elasticity, and brittleness are judged by how they feel in the mouth, not by whether they might also have a taste or a smell. These sensations are mostly conveyed by a tactile or touch sensation. Humans have a number of receptors for tactile stimulation with different spatial and temporal sensitivities which relay signals to the somatosensory cortex for further processing of tactile information. In connection with foods it is customary to talk of "texture perception." Not all types of texture perception are, however, only determined by the sense of touch. Therefore, Szczesniak [37] has defined texture as "…the sensory and functional manifestation of the structural, mechanical and surface properties of foods detected through the senses of vision, hearing, touch and kinesthetics."

Thus, it is not only touch which provides the sensation of the texture of a food. Audition and kinesthesis are also contributing to the perception of the texture of a food, as exemplified by the crunchy sounds produced when chewing (fresh) corn flakes.

Human sensitivity to texture under laboratory conditions is very high. Perception of solid particles in a solution is so sensitive that they do not go unnoticed before they are smaller than 3 μm in diameter. This has been exploited commercially in a number of fat replacers and mimetics [38] where spherical microparticulates in the range of 0.1–3 μm are the main functional ingredient. Particles this small are perceived as smooth and may contribute to creaminess.

There is a marked difference between the food that enters the mouth and the wetted bolus which is swallowed later. Different foods follow different pathways during oral handling with respect to degree of structure, degree of lubrication over time, or number of chews.

The texture of a food changes during consumption. The saliva lubricates the food, and enzymes in the saliva affect the viscosity of semisolids and liquids. Problems with saliva production are not uncommon in elderly people and in some neurological diseases. These lubrication problems can cause severe problems with food bolus formation and swallowability of foods.

8.8 Flavor: Integration of Sensory Information

As explained above, many senses contribute to the taste of foods. Even though a number of separate senses contribute to each food sensation, we do not perceive foods as a number of individual sensations, but rather as a coherent (integrated)

whole. Integration of different sensory modalities is commonplace in the sensory system. When you watch a film in a movie theater you perceive the sounds/speech as coming from the actors' mouths, even though the sound is produced by loudspeakers located elsewhere in the movie theater. Information from your visual and auditory systems is integrated centrally in the brain to integrate the different types of sensory information into coherent meaningful wholes.

Much the same happens when we perceive any of the many tastes (flavors) available to us. Flavor is normally defined to be the perception that results from taste, smell (retronasal), trigeminality, and touch (mouthfeel) when a food is eaten [39] and is perhaps the most multimodal of all of our sensory experiences. Visual and auditory information can influence the flavor perceived when eating a food, but these influences are mostly exerted by creating expectations based on prior associations and these types of information are therefore normally not included in the multimodal flavor concept.

The binding of different sensations into coherent wholes takes place within individual senses as well as between different senses. Most food aromas (smells) are mixtures of hundreds of different types of molecules with their own smells. These individual smells are in general completely disguised by the integration into an overall smell of the food. It has been demonstrated that humans are not capable of identifying more than two to three components correctly in mixtures of smells [40]. That is, if a mixture consists of more than three components, we cannot reliably report what these components are. The mixture, of course, still has a characteristic smell. But it is a synthetic perception, which is the result of olfactory integration processes. They abolish perception of the smell of the individual components. These integration processes are of crucial importance for the perception of foods. Nevertheless, a smell which is unpleasant on its own can, when added to a mixture of other odorants, turn this into a more pleasantly smelling mixture. An odorant present in a mixture in such a small concentration that it cannot be detected if it was presented alone can change and improve the overall pleasantness of the mixture. These effects are well known and used in the world of fragrances.

Integration of the different senses into an overall flavor percept has been studied both by psychophysical and by neuroimaging means. Verhagen and Engelen [41] have collected and described many important effects in multimodal food perception. Neuroimaging studies conducted on flavor perception have revealed that a number of brain areas are involved in the integration of signals from the different food-related senses. These include anterior ventral insula, anterior cingulate cortex, amygdala and most notably the orbito-frontal cortex, located in the front of the brain over the orbits of the eyes [39, 42]. This area receives input from smell, taste, touch and vision, and besides being part of a putative flavor circuit in the human brain, the orbito-frontal cortex has also been implicated as the area that computes and represents sensory-specific satiety [43], the well-known phenomenon that liking of a particular food decreases with the amount eaten, without affecting appreciably the liking of other foods.

8.9 Reward and Homeostasis

When we eat and drink we become satiated, and intake normally ends. Much of satiety is controlled by a set of the so-called homeostatic processes, which are negative feedback loop processes that help keep appropriate balances of nutrients in the body.

Hunger is signaled by a number of hormonal substances such as ghrelin in the stomach and NPY, orexin, and AgRP in the hypothalamus. Different nuclei in the hypothalamus are thought to control hunger and satiety and the associated relevant behaviors. Intake of food depresses the hunger signals and leads to an increase in satiety signals such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY), insulin, and leptin. Besides the homeostatic satiety processes, humans also possess the so-called sensory-specific satiety mechanisms as mentioned above. An animal endowed with such mechanisms will tend to eat a varied diet, which in turn will counteract the risk of malnutrition. These mechanisms obviously have much influence in guiding food choices during a meal. These mechanisms are not innate, as demonstrated recently [44]. It was found that sensory-specific satiety in children is coupled strongly to the eaten product, whereas clear transfer effects were found in adults. That is, for adults, eating a food with a certain sensory profile will lead to some transfer of decline in liking to other foods that share one or more characteristic sensory attribute with the food eaten to satiation.

These mechanisms also highlight the importance of reward for food intake. Reward mechanisms are emotional in nature, and these mechanisms might have evolved to guarantee engagement in behaviors important for survival. A varied energy supply is necessary for survival, and eating food in most cases leads to rewarding feelings and pleasure [45, 46]. Dopaminergic pathways in the brain, i.e., neural structures depending on dopamine as neurotransmitter, have long been known to be crucial for reward mechanisms [47]. Recently, however, a new neurology of reward has emerged in which reward is suggested to consist of distinguishable processes in separable neural substrates. In this account liking (emotion or affect) is separated from wanting (or motivation), each having explicit as well as implicit components. Explicit processes can come to awareness, whereas implicit processes exert their influence without being conscious to us [48, 49]. Contrary to previous belief, the pleasure of eating palatable food is not mediated by dopamine but rather by opioid transmission in a neural network including the nucleus accumbens, ventral pallidum, parabrachial nucleus, and nucleus of the solitary tract. Wanting (appetite, incentive motivation), on the other hand, is suggested to rely on a dopaminergic system with projections from the ventral tegmental area to the nucleus accumbens and circuits involving areas in the amygdala and prefrontal cortex [48]. The distinction between liking and wanting was originally based on work on rodents [48], but psychophysical and neuroimaging studies on humans support the distinction [49, 50].

It is reasonable to include learning processes in the set of processes that we need to understand reward. This is particularly important with respect to foods where

almost all liking and wanting are results of learning processes. Since eating is crucial to survival the motivational mechanisms and rewards related to feeding are strong. It might therefore not be very surprising that the biological mechanisms of feeding and addiction overlap throughout evolutionary history. Work in rodents has demonstrated increases in dopamine in the nucleus accumbens induced by food and by amphetamine. The dopamine response to the two types of stimulation is qualitatively identical, although the size of the response is an order of magnitude larger for amphetamine [51]. Similar results have been obtained from neuroimaging studies on humans [52, 53]. Besides dopaminergic systems, several cholinergic systems in the brain have been implicated in both food and drug intake [54]. Berthoud [46] has argued that human food intake control, in the obesogenic environment of affluent societies, is guided by cognitive and emotional processes rather than by homeostatic processes. The hypothalamic system, classically believed to control food intake, has an abundance of connections to other parts of the brain involved in sensory and reward processing, and evidence suggests that these cortico-limbic processes can dominate the homeostatic regulatory circuits in the hypothalamus.

8.10 Preferences and Acceptance

The foods we eat are to a large extent determined by our preferences. Other factors such as price and social context are also important, but within the constraints set by these factors, we eat what we prefer or like.

Research has demonstrated that we are born with very few specific preferences [55]. Newborn babies have a strong preference for sweet and fatty taste and a dislike for bitter taste. From a developmental point of view the preference for sweetness and fat facilitate breastfeeding. The dislike for bitter has been interpreted as an inborn defense against bitter-tasting toxic alkaloids in nature. Most people have to reach adulthood before they have learned to appreciate the bitter taste of beer, coffee, and many vegetables. Besides these few examples, all other preferences are incidentally learned by exposure to the foods of one's culture. This allows man to be omnivorous and able to adapt to whatever eatable materials are found in the environment. There are no fundamental differences between the nervous systems of different human races, but different cultures have nevertheless developed radically different cuisines or food cultures based on what nature provides. This demonstrates very clearly that food preferences are learned and not genetically inherited.

Learning starts in the fetal state [56] and during breastfeeding [57] and continues through childhood and later life. Flavor learning in the fetal state is believed to take place via transfer of flavor substances eaten by the mother to the amniotic fluid and from there to the developing sense organs of the fetus. After birth, and probably all through life, a number of the so-called conditional learning mechanisms act to change food preferences. Conditional learning means that we learn, or change, on the condition that another unconditional stimulus is present together with the stimulus we learn about, the conditional stimulus. In the case of preference learning an

already well-liked stimulus plays the role of the unconditional stimulus, which is a stimulus to which we have an unconditional positive response. The response to the conditional stimulus presented alone is called the conditional response. For a new food, or other substance not resembling anything ever encountered before, the conditional response will most often be a rejection. If, however, the new food is presented together with a stimulus with an already liked taste or positive bodily effect, it turns out that after a few presentations of the conditional and unconditional stimulus together, people will respond differently to the conditional stimulus when it is presented alone. What initially was rejected and not liked will now be accepted and liked. It is as if the properties of the unconditional stimulus have been taken over by the conditional stimulus. If a known liked flavor is paired with a novel flavor, the conditional learning is called flavor–flavor learning. Another type of conditional learning important for changes of preferences for foods is the so-called flavor–nutrient learning. In this type of learning it is the nutrient value/energy in an unconditional stimulus which, when paired with the novel flavor of a conditional stimulus, will increase the liking of the novel flavor.

The so-called mere exposure effect, where a number of exposures to a new flavor changes appreciation of it, is also an important mechanism for preference development [58, 59]. Mere exposure might be a result of conditional learning. In this interpretation, it is the absence of adverse effects, after having been exposed to a novel flavor, which plays the role of the unconditional stimulus [60].

These forms of preference formation mechanisms are believed to be important in forming children's food preferences. They play undoubtedly also a role in the changes of preferences experienced by adults, but for this population it is not as well defined to talk of novel flavors, since a novel flavor might have certain resemblances to other flavors that have been perceived previously. Even though food preferences do change, it is interesting that preferences developed in childhood seem to be quite long-lasting [61]. Whether this is also the case for food or taste aversions is an important question. A food aversion is a strong dislike of a certain taste or flavor. It comes about as a result of conditional learning. If a taste has been experienced in temporal proximity to an adverse effect or illness, an aversion [58] might develop to the taste even though the adverse effect is not causally related to the flavor. Being infected with a stomach infection that eventually causes pain and vomiting will often lead to an aversion of the flavor of the food one consumed while still feeling well, even though the illness is not related to consumption of the food. This type of aversion effect should be considered when administering drugs with known adverse effects. There is a serious risk that the patient will develop aversions to foods eaten in close proximity to the adverse effects. Using flavors to mask "bad taste" of a drug should avoid flavors which are common and important in the patient's food culture. There is a strong need for research into development of food aversions in children who are treated with medicines. Do some flavors in combination with some medicines present less risk of generating aversion than they do with other medicines? It might also be that some food flavors are less amenable to aversion effects than others. Such flavors should be used wherever they are appropriate. If it is not

possible to completely avoid aversion effects, it is important to learn which flavor aversions will have the shortest lifetime and to devise methods to extinguish flavor aversions.

References

1. Köster EP (2002) The specific characteristics of the sense of smell. In: Rouby C, Schaal B, Dubois D, Gervais R, Holley A (eds) Olfaction, taste, and cognition. Cambridge University Press, Cambridge
2. Morin-Audebrand L, Mojet J, Chabanet C, Issanchou S, Møller P, Köster EP, Sulmont-Rossé C (2012) The role of novelty detection in food memory. Acta Psychol 139:233–238
3. Köster EP, Mojet J (2007) Theories of food choice development. In: Frewer L, Van Trijp HCM (eds) Understanding consumers of food products. Woodhead, Cambridge
4. Herz RS (2002) Influences of odors and mood on affective cognition. In: Rouby C, Schaal B, Dubois D, Gervais R, Holley A (eds) Olfaction, taste, and cognition. Cambridge University Press, Cambridge
5. Herz RS (2002) An examination of objective and subjective measures associated to odors, music and paintings. Empirical Stud Arts 16:137–152
6. Doty RL (ed) (2003) Handbook of olfaction and gustation, 2nd edn. Marcel Dekker, New York
7. Firestein S, Beauchamp GK (eds) (2008) The senses: a comprehensive reference, vol 4, Olfaction and taste. Academic/Elsevier, Oxford
8. Delwiche J (1996) Are there 'basic' tastes? Trends Food Sci Technol 7:411–415
9. Chaudhari N, Roper SD (2010) The cell biology of taste. J Cell Biol 190:285–296
10. Dubois GE, Desimone J, Lyall V (2008) Chemistry of gustatory stimuli. In: Firestein S, Beauchamp GK (eds) The senses: a comprehensive reference, vol 4, Olfaction and taste. Academic/Elsevier, Oxford
11. Rolls ET, Scott TR (2003) Central taste anatomy and neurophysiology. In: Doty RL (ed) Handbook of olfaction and gustation, 2nd edn. Marcel Dekker, New York
12. Breslin PAS (1996) Interactions among salty, sour and bitter compounds. Trends Food Sci Technol 7:390–399
13. Stevenson RJ (2010) An initial evaluation of the functions of human olfaction. Chem Senses 35:3–20
14. Herz RC, Cupchik GC (1995) The emotional distinctiveness of odor-evoked memories. Chem Senses 20:517–528
15. Herz RC, Eliassen J, Beland S, Souza T (2004) Neuroimaging evidence for the emotional potency of odor-evoked memory. Neuropsychologia 42:371–378
16. Giduck SA, Threatte K (1987) Cephalic reflexes: their role in digestion and possible roles in absorption and metabolism. J Nutr 117:1191–1196
17. Mattes RD (1997) Physiologic responses to sensory stimulation by food: nutritional implications. J Am Diet Assoc 97:406–413
18. Small DM, Gerber JC, Mak YE, Hummel T (2005) Differential neural responses evoked by orthonasal versus retronasal odorant perception in humans. Neuron 47(4):593–605
19. Small DM, Veldhuizen MG, Felsted J, Mak YE, Mcglone FC (2008) Separable substrates for anticipatory and consummatory food chemosensation. Neuron 57:786–797
20. Møller P, Wulff C, Köster EP (2004) Do age differences in odour memory depend on differences in verbal memory? Neuroreport 15(5):915–917
21. Møller P, Mojet J, Köster EP (2007) Incidental and intentional flavour memory in young and older subjects. Chem Senses 32(6):557–567
22. Sulmont-Rossé C, Møller P, Issanchou S, Köster EP (2008) Effect of age and food novelty on food memory. Chem Percept 1:199–209

23. Köster EP (2005) Does odour memory depend on remembering odours? Chem Senses 30(Suppl 1):i236–i237
24. Møller P, Köster EP, Dijkman N, de Wijk R, Mojet J (2012) Same–different reaction times to odors: some unexpected findings. Chem Percept 5:158–171
25. Mojet J, Köster EP (2005) Sensory memory and food texture. Food Qual Preference 16:251–266
26. Köster MA, Prescott J, Köster EP (2004) Incidental learning and memory for three basic tastes in food. Chem Senses 29:441–453
27. Laureati M, Morin-Audebrand L, Pagliarini E, Sulmont-Rossé C, Köster EP, Mojet J (2008) Food memory and its relation with age and liking: an incidental learning experiment with children, young and elderly people. Appetite 5:273–282
28. de Araujo IE, Rolls ET, Velazco MI, Margot C, Cayeux I (2005) Cognitive modulation of olfactory processing. Neuron 46:671–679
29. Grabenhorst G, Rolls ET, Bilderbeck A (2008) How cognition modulates affective responses to taste and flavour: top-down influences on the orbitofrontal and pregenual cingulated cortices. Cereb Cortex 18:1549–1559
30. Grabenhorst G, Rolls ET (2008) Selective attention to affective value alters how the brain processes taste stimuli. Eur J Neurosci 27:723–729
31. Doty RL, Cometto-Muniz JE (2003) Trigeminal chemosensation. In: Doty RL (ed) Handbook of olfaction and gustation, 2nd edn. Marcel Dekker, New York
32. Green BG (1996) Chemesthesis: pungency as a component of flavor. Trends Food Sci Technol 7:415–423
33. Belza A, Frandsen E, Kondrup J (2007) Body fat loss achieved by stimulation of thermogenesis by a combination of bioactive food ingredients: a placebo controlled, double-blind 8-week intervention in obese subjects. Int J Obes 31(1):121–130
34. Westerterp-Plantenga MS, Diepvens K, Joosen AMCP, Berube-Parent S, Tremblay A (2006) Metabolic effects of spices, teas, and caffeine. Physiol Behav 89(1):85–91
35. Reinbach HC, Smeets A, Martinussen T, Møller P, Westerterp-Plantenga MS (2009) Effects of capsaicin, green tea and CH-19 sweet pepper on appetite and energy intake in humans in negative and positive energy balance. Clin Nutr 28:260–265
36. Westerterp-Plantenga MS, Smeets A, Lejeune MPG (2005) Sensory and gastrointestinal satiety effects of capsaicin on food intake. Int J Obes (Lond) 29(6):682–688
37. Szczesniak AS (2002) Texture is a sensory property. Food Qual Preference 13:215–225
38. Kilcast D, Clegg S (2002) Sensory perception of creaminess and its relationship with food structure. Food Qual Preference 13:609–623
39. Small DM (2012) Flavor is in the brain. Physiol Behav. doi:10.1016/j.physbeh.2012.04.011
40. Jinks A, Laing DG (1999) A limit in the processing of components in odour mixtures. Perception 28:395–404
41. Verhagen JV, Engelen L (2006) The neurocognitive bases of human multimodal food perception: sensory integration. Neurosci Biobehav Rev 30:613–650
42. Rolls ET (1999) The brain and emotion. Oxford University Press, Oxford
43. Kringelbach ML, O'Doherty J, Rolls ET, Andrews C (2003) Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. Cereb Cortex 13:1064–1071
44. Olsen A, Ritz C, Hartvig DL, Møller P (2011) Comparison of sensory specific satiety and sensory specific desires to eat in children and adults. Appetite 57:6–13
45. Berridge KC (1996) Food reward: brain substrates of wanting and liking. Neurosci Biobehav Rev 20:1–25
46. Berthoud H-R (2004) Mind versus metabolism in the control of food intake and energy balance. Physiol Behav 81:781–793
47. Wise RA (2002) Brain reward circuitry: insights from unsensed incentives. Neuron 36:229–240
48. Berridge KC, Robinson TE (2003) Parsing reward. Trends Neurosci 26:507–513

49. Finlayson G, King N, Blundell JE (2007) Liking vs. wanting food: importance for human appetite control and weight regulation. Neurosci Biobehav Rev 31:987–1002
50. Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M (2001) Changes in brain activity related to eating chocolate. Brain 124:1720–1733
51. Bassareo V, Di Chiara G (1999) Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state. Eur J Neurosci 11:4389–4397
52. Volkow ND, Wise RA (2005) How can drug addiction help us understand obesity. Nat Neurosci 8:555–561
53. Wang GJ, Vollow ND, Logan J, Pappas NR, Wong CT, Zhu W et al (2001) Brain dopamine and obesity. Lancet 357:354–357
54. Avena NM, Rada P, Hoebel BG (2008) Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev 32:20–39
55. Birch LL (1999) Development of food preferences. Annu Rev Nutr 19:41–62
56. Schaal B, Marlier L, Soussignan R (2000) Human foetuses learn odours from their pregnant mother's diet. Chem Senses 25:729–737
57. Mennella JA, Jagnow CP, Beauchamp GK (2001) Prenatal and postnatal flavor learning by human infants. Pediatrics 107:1–6
58. Schafe GE, Bernstein IL (2001) Taste aversion learning. In: Capaldi ED (ed) Why we eat what we eat, 3rd edn. American Psychological Association, Washington
59. Hausner H, Olsen A, Møller P (2012) Mere exposure and flavour–flavour learning increase 2–3 year-old children's acceptance of a novel vegetable. Appetite 58:1152–1159
60. Zajonc RB (2001) Mere exposure: a gateway to the subliminal. Curr Dir Psychol Sci 10:224–228
61. Nicklaus S, Boggio V, Chabanet C, Issanchou S (2004) A prospective study of food preferences in childhood. Food Qual Preference 15:805–818

Chapter 9
Flavor Is Not Just Taste: Taste Concealing

Charles R. Frey

Abstract In adults, oral drug delivery can be compromised by patient compliance associated with the bad taste of most drug molecules. In children, the same issue has another dimension: they spit out medicine that tastes bad, and will not listen to reason. Parents may be lucky with medicine that has to be given once, but rarely beyond that if repeated doses are required. So, taste is of critical importance in much of the pediatric age range due to the sensitivity of the pediatric tongue to bad taste and lack of adequate cognitive reasoning to override this sensitivity. Successful delivery systems must inherently overcome this taste concern and many include a means of concealing the drug molecule from taste sensors in addition to a flavor system to taste mask residual free drug. This section focuses on strategies used to conceal drug molecule taste elements from exposure to taste sensors in the oral cavity. Discussed strategies include fluid bed coating, spray drying, coacervation, inclusion complexes, and drug–ion exchange resin complexes.

9.1 Introduction

This section focuses on strategies to minimize exposure of orally delivered solid drug substances to the sensorsoric system responsible for taste perception. The act of minimizing taste in this manner is a common element of a taste masking strategy and it is often referred to broadly as taste masking; however, it will more precisely be referred to as taste concealing in this publication to differentiate it from taste masking elements of flavor addition and control.

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Although oral administration offers a relatively painless and easy means of delivery through a natural consumption pathway into the body, there are several potential obstacles for dosing the pediatric patient including the following:

1. Appearance (It must look "good" to the patient from a certain age on, and to the mother/caregiver.)
2. Swallowing limitations (The patient must have the capacity to swallow it.)
3. Mouth feel (The feel should match the dose form. A "smooth" texture dose form may not allow grittiness, but a "rough" texture may allow some grittiness.)
4. Taste/smell (Dose should be palatable with no adverse odor elements present.)

The degree of cognitive maturation as opposed to more archaic instincts in much of the pediatric age range commonly prevents overcoming these obstacles consistently with a reasoning approach; thus, the dose form must be adjusted to adequately meet the above noted requirements and more reliably achieve adequate patient and parent compliance. Since swallowing an intact tablet or capsule device is not an option for children under 6 years (with quite variable age ranges), dose forms are commonly created in platforms that are chewable, orally dissolve or disintegrate, liquid solution or suspension, or powder/granule (for addition to a food) to allow swallowing with relative ease. Unfortunately, these forms impart significant mouth and taste sensor exposure to the drug during the consumption process. Since many drugs are derived from therapeutically dosed molecules that could be harmful to the body, the infant's aversion to the taste is related in archaic reflex patterns relevant to species survival. Even at therapeutic levels, the taste is often sufficiently bad to prevent compliance; thus, a means of masking drug taste is vital to success of the dosing platform.

Addition of acceptable flavor components to the dose form can effectively mask the taste of some poor tasting drugs; however, a flavor element alone is not adequate in many cases for a variety of reasons including the intensity of the drug taste and a commonly shorter flavor residence time in the mouth and taste receptors. When flavor alone is not adequate, a taste concealing technology becomes necessary. The concealing technology minimizes direct exposure of the drug to taste sensors. Since concealing technologies typically leave residual un-concealed drug or partially concealed drug in the dose form and drug releases over time from dose residuals that are not completely flushed from the mouth, flavor components are typically included to ensure an adequate overall taste mask.

Taste concealing could broadly be extended to any technology that prevents or reduces exposure of drug to taste perception. This could include, but is not limited to, the following areas:

1. Granulations, coating, microencapsulation, or complexing technologies that use a protective layer or structure on or about drug particles to minimize exposure of drug to taste sensation.
2. Chemical modifications that provide a drug or pro-drug form that has better taste characteristics.
3. Technologies that work in association with mouth taste sensors to prevent a drug molecule interaction with the sensor (this might more appropriately be termed taste sensor masking).

Areas 2 and 3 are outside the scope of this section. Area 2 involves generation of new chemical entities with reduced or eliminated bad taste. Area 3 is an area of active current research involving sensor masking. There are elements of taste sensor masking in flavor systems or excipients used in coating formulations, which may be the result of serendipitous use of formulation excipients or a generally recognized or identified complimentary nature of flavor system taste profiles.

Area 1 will be the focus of the discussion in this section with a primary emphasis on the use of fluid bed coating technology for microencapsulation of drug containing particles. This is arguably the most versatile technique for taste concealing. Granulation, spray drying, coacervation (phase separation), cyclodextrin inclusion complexation, and drug–ion resin complexes will be mentioned or discussed in less detail.

Taste masking and taste concealing have been subjects of concern and study for many years and there is a large amount of literature available on the subject. This section does not attempt to summarize reference literature on taste concealing, but rather focuses on theoretical aspects, some history on the approaches, and the critical elements of successful application.

9.2 Taste Concealing Goals

The general goals and considerations for taste concealing and taste concealed particles are as follows:

1. Conceal the drug from taste sensors until it is cleared from the mouth. Any release in the mouth will contribute to bad taste.
2. Conceal the drug adequately for up to several minutes or more in the mouth to minimize latent adverse taste from residual particles that could get trapped around teeth, gums, or taste buds. After swallowing the bulk of the dose, drug particles can remain trapped long enough between the teeth, around the gums, or in other places of the oral cavity to impart a latent offensive taste. The closer a latent taste onset is to the dosing event, the greater the potential for the bad taste to be associated with the drug dose.
3. Maintain integrity through final dosage form processes such as compression forces associated with tableting a chewable product or water exposure in final solid dosage form processing. Any fracture of taste concealed particles may compromise the taste. Taste concealing is typically a delayed release application and the delay time in a solid dosage form product is often related to exposure to mouth fluids. Any exposure of taste concealed particles to water prior to ingestion will start the release process and potentially contribute to bad taste.
4. Optimize particle size for the dosage form, mouth feel requirements, and mouth clearance. If particles are too large, they may fracture easily or contribute to a gritty mouth feel. If they are too small, they may more easily be trapped in the mouth cavity or in and around taste sensors. Optimal size is somewhat dependent on the dosage form; a smooth texture may require finer particles, a coarse texture

will likely tolerate larger particles. In general, taste concealed particle sizes range between the extremes of near 1,400 μm to less than 50 μm depending on the technology used and requirements of the dose form.
5. Use only oral pharmaceutically approved excipients within the dosing limits of the patient group. Some approved excipients used in taste concealing have patient dose limits that may limit the amount that can be incorporated in a formulation.
6. Use excipients that impart acceptable taste, no taste, or have a taste that can be masked.
7. Release the drug appropriately once it is past the mouth or to the delivery location in the gut to make it biologically available. Taste concealing is a transient need of the delivery process.
8. The process used to make taste concealed particles must meet economic concerns of the application.

The above points underlie a significant portion of the discussion in the following sections.

9.3 Fluid Bed Coating

A commonly used and versatile microencapsulation technology for taste concealing is fluid bed coating. Fluid bed coating includes the classic equipment designs of bottom spray (Wurster), top spray, and tangential spray (Fig. 9.1). Other variations of these designs may be available in the equipment market, but these will not be elaborated on here.

Each of these systems involves use of a two-fluid nozzle to spray a coat formulation into a fluidized bed of particles. As particles move through the spray region, coat

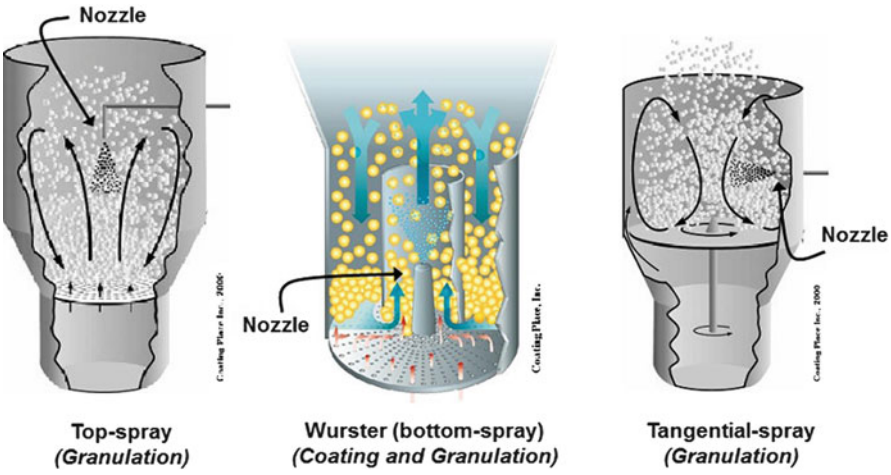

Fig. 9.1 Fluid bed coaters

solution or suspension spray droplets contact the particles as solvent in the coat formulation is evaporated. Solvent vapors are carried away with the fluidizing air leaving a residue of the non-volatile coating ingredients on particle surfaces. The deposited residue is the filmcoat and the process is continued until the desired level of filmcoat has been applied. It is also possible to spray a molten material such as a wax directly as a coating without a water or organic solvent vehicle. This is commonly referred to as a "hot melt" process and it requires appropriate nozzle, pump, and liquid line heating to maintain coating material in a liquid state until it passes the nozzle. Hot melt applications can be very economical as ~100 % of the sprayed material is non-volatile; thus, the need for solvent vehicle evaporation is eliminated. Process temperature is adjusted to appropriately congeal a hot melt coating on particle surfaces.

Due to the nature of particle movement associated with their configurations, top and tangential spray systems are primarily used for granulating. Granulation alone can offer adequate taste concealing properties for mildly bad tasting material. Granules formed from these systems must be sufficiently robust to maintain particle integrity through tablet compression processes; if granules break significantly during compression, taste can be compromised.

Wurster fluid bed coating technology can be used for granulating, but it is also a well-established technology for coating individual small particles. The process was patented at the University of Wisconsin by Dr. Dale E. Wurster in the 1960s [2–6]. His initial goals involved tablet coating but the process evolved to its forte of small particle coating. The process is generally capable of coating relatively narrow particle size distributions ranging from near 50 μm to several centimeters in size but its unique niche is from near 50 μm to 2 or 3 mm. This range encompasses the preferred taste concealed particle size range; thus, it is a good fit for this application.

The Wurster process is characterized by a differential process air stream that fluidizes and cycles particles upward through a central spray region of the coating unit. The nozzle is located in the center of the spray region and directed upward (concurrently with particle flow). As particles accelerate through the spray region, spray droplets contact the surfaces and solvent vehicle evaporates to build the film coat. Coat formulations can be water, organic solvent, or hot melt-based. Following movement upward through the spray region, particles decelerate in the expansion chamber region of the coater and fall back into the outer region of the coat chamber to feed back into the spray region. Particles complete a cycle once every ~6 to 10 s in a properly run system. Each batch stays in the process until the required coat level has been applied. Under ideal conditions each particle receives a uniform coating of the deposited film coat.

9.3.1 Filmcoat Parameters

In addition to the ability to uniformly coat particles to a controlled filmcoat thickness with the Wurster process, filmcoat formulations can be developed with the balance of concealing and drug release properties required for taste concealing

Table 9.1 Generalized coat requirements

Drug solubility	Taste	Coat thickness	Coat properties
Low	Mildly bad	Thin	High porosity or complete dissolution
Low	Very bad	Thick	High porosity or complete dissolution
High	Mildly bad	Thin	Low porosity
High	Very bad	Thick	Low porosity

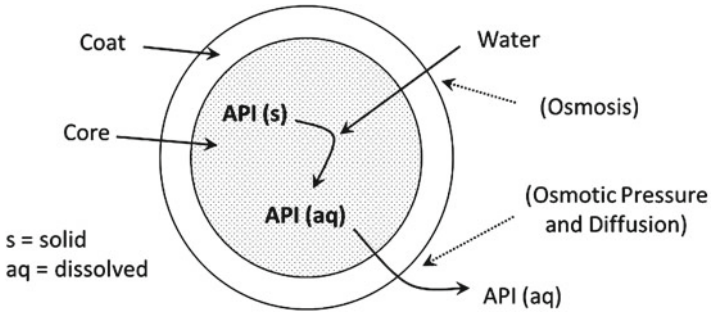

Fig. 9.2 Release processes in a taste concealed particle

applications. Film coat requirements vary with contributing factors such as drug solubility, intensity of bad taste, drug chemical structure, drug release requirements (immediate, sustained, enteric, etc.), and particle size. Table 9.1 contains generalized information on critical taste concealing factors with regard to the taste and solubility properties of the drug.

Drug solubility significantly influences release rate from a taste concealed particle, which subsequently influences filmcoat requirements. Taste concealing filmcoats are formulated with required levels of solubility and porosity. If a completely dissolving filmcoat adequately conceals taste, a drug will release as the filmcoat dissolves in the digestive tract. When completely dissolving filmcoats do not adequately conceal, filmcoats with lower solubility and controlled porosity may be required. Figure 9.2 illustrates the simplified processes occurring around a particle taste concealed in an insoluble filmcoat. All filmcoats have some level of permeability. As moisture diffuses through the coat layer, drug will dissolve inside the particle and dissolved drug will diffuse out through the coat layer. In addition to these diffusion processes, osmotic forces can develop within the particle depending on the osmolality of the contents. A soluble drug or core formula component will quickly dissolve and develop significant osmotic pressure within the particle. This pressure effectively pumps dissolved drug from the particle. Osmotic pressures can be sufficient to fracture the filmcoat and rapidly release the contents; thus, film strength and modulus can be important considerations.

A soluble drug may completely release through an insoluble taste conceal membrane, but a low solubility drug might not. A low solubility drug dissolves less

readily; thus, osmotic concerns are reduced and the film coat requirements may shift. If diffusion and osmotic pressure are not adequate to release the drug within bioavailability time constraints, a higher permeability filmcoat or completely dissolving filmcoat may be needed. Often water soluble "pore formers" are added to an insoluble filmcoat formula to modify porosity and promote drug release. It is also possible to incorporate other water soluble excipients in the core to impart control of osmotic forces.

Thin and thick coats generalized in Fig. 9.1 are roughly 5 and 15 μm, respectively; however, higher levels may be required for a poorly run process or a less than optimal filmcoat formulation. Although coat thickness is a key factor in this approach to taste concealing, the actual thickness need is difficult to establish. In actual practice, the coating process is relatively dynamic with some levels of agglomeration, accretion of fine particles on larger particles, and fracturing (attrition) of particles into smaller fragments. The extent of these phenomena is dependent on core particle integrity, filmcoat strength, process parameters, and the physical forces of fluidization and nozzle atomization air on the particles. The result is commonly significantly less than the ideal of each particle being coated to an identical thickness. The coating on each individual particle is typically uniform; however, any particle attrition that occurs during processing exposes drug and increases the surface area, both of which increase the need for more coating to conceal. Agglomeration and accretion reduce surface area and may reduce the overall coating need. The ability to consistently control agglomeration, accretion, and attrition is vital to a successful Wurster fluid bed taste conceal application.

The 5–15 μm coat thickness estimate creates a practical limit for the fluid bed filmcoat process. Table 9.2 indicates the theoretical coat level requirements for 5 and 15 μm coat thickness on various particle sizes at varying core and filmcoat densities. As particle size decreases, bulk surface area increases; thus, smaller particles require higher coat levels than larger particles to achieve a comparable coat thickness. Note that 50 μm particles theoretically require over 80 % coat level to achieve a 15 μm film thickness at one density combination. Many drug products or platforms cannot bear the higher cost associated with applying high taste concealing coat levels.

These filmcoat requirements influence the payload within the taste concealed particles. A material with 20 wt% coat level would have an 80 wt% payload if it is a pure drug core, while a 40 wt% coat level would only be 60 wt% payload. The amount of taste concealed particles required to reach the drug dose must fit within the constraints of the final size of the finished product. For example, a 50 mg dose from an 80 % payload product would require 62.5 mg of taste concealed particles per dose, while the same 50 mg dose from a 60 % payload would require 83 mg.

Also note the particle size associated with the added coat layer. The higher coat levels that may be needed to achieve adequate taste concealing contribute to particle growth. This growth can potentially exceed particle size limits associated with either downstream processing or the dosage form.

In actual practice, there are significantly increasing challenges to coating as particle size decreases below 200 μm. Depending on coat formulation properties,

Table 9.2 Theoretical coating assessment

Core size (μm)	Coat thickness (μm)	Coat level (wt%)	Coat level (vol.%)	Core density (g/cm^3)	Coat density (g/cm^3)	Final size (μm)	Final density (g/cm^3)
50	5.0	36.4 %	42.1 %	1.4	1.1	60	1.27
50	15.0	70.9 %	75.6 %	1.4	1.1	80	1.17
50	5.0	50.5 %	42.1 %	1.0	1.4	60	1.17
50	15.0	81.3 %	75.6 %	1.0	1.4	80	1.30
100	5.0	20.6 %	24.9 %	1.4	1.1	110	1.33
100	15.0	48.5 %	54.5 %	1.4	1.1	130	1.24
100	5.0	31.7 %	24.9 %	1.0	1.4	110	1.10
100	15.0	62.6 %	54.5 %	1.0	1.4	130	1.22
200	5.0	11.0 %	13.6 %	1.4	1.1	210	1.36
200	15.0	29.0 %	34.2 %	1.4	1.1	230	1.30
200	5.0	18.1 %	13.6 %	1.0	1.4	210	1.05
200	15.0	42.2 %	34.2 %	1.0	1.4	230	1.14
500	5.0	4.6 %	5.8 %	1.4	1.1	510	1.38
500	15.0	13.0 %	16.0 %	1.4	1.1	530	1.35
500	5.0	7.9 %	5.8 %	1.0	1.4	510	1.02
500	15.0	21.1 %	16.0 %	1.0	1.4	530	1.06
1,000	5.0	2.3 %	2.9 %	1.4	1.1	1,010	1.39
1,000	15.0	6.8 %	8.5 %	1.4	1.1	1,030	1.37
1,000	5.0	4.1 %	2.9 %	1.0	1.4	1,010	1.01
1,000	15.0	11.5 %	8.5 %	1.0	1.4	1,030	1.03

equipment design, and process parameters, a significant amount of accretion of fine particles on the surface of larger particles and particle agglomeration are likely. This has a potentially positive effect on reducing the coating need since bulk surface area will decrease with accretion and agglomeration. Depending on the final particle size goals, this aspect of particle growth can significantly reduce yields if an oversize cut is removed.

9.3.2 Filmcoat Formulations

It becomes apparent with these size, coat thickness, and processing considerations that film coat composition is a key to a successful taste concealing application. Taste concealing formulations involve a balance of filmcoat physical and chemical properties, filmcoat thickness, taste concealing efficacy, and drug release. A taste concealing filmcoat that works effectively for one drug may not perform as well on another drug for a variety of reasons related to any of these formulation balance parameters.

Any material approved for oral pharmaceutical use could potentially be used as a taste concealing excipient; however, there is typically an underlying strategy to accomplish the goal. An inherent requirement of a taste concealing excipient is that the excipient itself has no taste, an acceptable taste, or a taste that can acceptably masked

Table 9.3 Water insoluble coat materials

Chemical	Example	Comments
Ethyl cellulose	Dow Wolff ethyl cellulose	Various viscosity grades available
	Ashland ethyl cellulose	Various viscosity grades available
	Surelease dispersion	25 % aqueous dispersion
	Aquacoat ECD dispersion	30 % aqueous dispersion
Cellulose esters	Eastman cellulose acetate	Various grades/substitution levels available
	Eastman cellulose acetate butyrate	Various grades/substitution levels available
Low substituted hydroxypropyl cellulose	Shin-Etsu L-HPC	–
Acrylic neutral ester polymers	Evonic eudragit NE 30D dispersion	30 % aqueous dispersion
Acrylic sustained release polymers	Evonic eudragit RS	100 % polymer or aqueous dispersions
	Evonic eudragit RL	100 % polymer or aqueous dispersions
Polyvinyl acetate	BASF kollicoat SR 30D	30 % aqueous dispersion
Shellac	Emerson Marcoat 125	Water-based shellac dispersion
Zein	Freeman industries	Corn protein
Waxes	Hydrogenated oils	–
	Carnauba	–

Table 9.4 Water soluble coat materials

Chemical	Example
Hydroxypropyl methyl cellulose	Dow Wolff Methocel E series
	Shin-Etsu pharmacoat
Hydroxypropyl cellulose	Ashland Klucel
	Nisso-HPC
Hydroxyethyl cellulose	Ashland natrosol
Povidone	ISP plasdone
	BASF Kollidon
Vinylpyrrolidone—vinyl acetate copolymers	BASF Kollidon VA 64
Polyvinyl alcohol—polyethylene glycol graft copolymer	BASF Kollicoat IR
Polyvinyl alcohol—polyethylene glycol graft copolymer and polyvinyl alcohol	BASF protect
Modified Pea starch	Roquette Lycoat and ReadiLycoat
Polyethylene glycol	Dow carbowax

by flavor ingredients. Tables 9.3, 9.4, and 9.5 contain limited lists of formulation materials that could be used in taste concealing applications. Formulators should refer the United States Pharmacopeia, National Formulary, or other applicable regulatory resources for lists of allowed taste concealing formulation excipients. This search should include not only the allowed use in an oral dosage form but also any ingestion

Table 9.5 pH dependent water soluble materials

Chemical	Example	Comments
Acrylic enteric polymers	Evonic eudragit L	–
	Evonic eudragit S	Colonic delivery
	Evonic eudragit L100-55	–
	Evonic eudragit L30 D55	–
	Evonic eudragit FS 30D	Colonic delivery
	BASF kollicoat MAE	100 % polymer or aqueous dispersion
Cellulose acetate phthalate (Enteric)	Eastman CAP cellulose ester	–
	FMC aquacoat CPD dispersion	30 % aqueous dispersion
Hydroxypropyl methyl cellulose phthalate (Enteric)	Shin-Etsu HPMCP	–
Hydroxypropyl methyl cellulose acetate succinate (Enteric)	Shin-Etsu aqoat	–
Acrylic acid-soluble polymers (Reverse enteric)	Eudragit E	–
	Kollicoat smartseal 30D	–

limits that may apply. Some acrylic materials have ingestion limits that can potentially be exceeded at coat levels and dosing requirements of some taste concealing formulation strategies. Limits are commonly set as mg of excipient per kg of body weight. Body weight in the pediatric age range can be relatively low; thus, an ingestion limit can easily be reached.

Tables 9.3, 9.4, and 9.5 are categorized by solubility properties: Table 9.3 contains examples of water insoluble materials, Table 9.4 a list of water soluble materials, and Table 9.5 a list of materials with solubility in specific pH ranges. These lists are not comprehensive but help convey the strategies used to create a formulation. Taste concealing formulations are commonly created from one or more coating materials. A basic strategy was touched on in the previous section. If a water insoluble material masks well but does not release the drug adequately, it could potentially be applied at a lower coat level to promote release. Nevertheless, if proper release is only realized at a coat level that is too thin to adequately taste conceal, a compatible pore forming ingredient from the water soluble list or limited pH solubility list could be added to the coating. The pore former provides variable concealing properties, but will dissolve from the coat as it is exposed to fluids in the mouth and/or gastrointestinal tract and leaves a porous layer of water insoluble components. The amount of porosity is related to the amount of pore former. Coat level and pore former content can be optimized for the taste concealing and release. In the extreme, it is possible to achieve adequate taste concealing with a water soluble polymer alone if the drug taste is only mildly offensive.

The pH soluble materials in Table 9.5 offer selective solubility for more targeted delivery. Enteric polymers are used to prevent drug release through the mouth and stomach, but release in the intestinal tract. Dissolution onset begins in the pH range of ~5.5 to ~7.0 depending on the enteric material and dissolution rate accelerates as

pH increases beyond the onset point. Enteric polymers are weak acid materials with pK_a values in the ~4.5 to ~6.0 range; these polymers dissolve as acid groups are more fully deprotonated at pH values above the pK_a. As a result of a short duration in the mouth at relatively neutral pH, effective taste masking can be realized either with enteric polymer alone as the principle concealing and release component or as a pore former. A potential benefit of its use as a pore former is the ability to tailor sustained release mechanism in the intestinal region through control of coat porosity. Use of enteric polymer alone as the primary film forming ingredient may be necessary to ensure adequate release of a poorly soluble drug since complete removal of the coating occurs in the dissolution process.

The acid soluble polymers in Table 9.5 are weak bases that dissolve when protonated at lower pH levels. These materials are sometimes referred to as "reverse enteric" polymers. They offer useful taste concealing properties by remaining insoluble at relatively neutral conditions of the mouth, but dissolving at more acidic pH levels in the stomach. Since pH conditions of the stomach can vary significantly from fasted to fed state and transit time through the stomach can vary, dose timing in relation to patient activity can be critical to achieving required drug release with a reverse enteric taste concealing formulation.

Use of enteric and reverse enteric materials should take into consideration the acid or base properties of the drug. A basic drug encapsulated with an enteric coating can promote dissolution of the coating at the inside surface of the coating. An acidic drug can do the same to a reverse enteric coating. This process can result in poor concealing properties and shelf instability. Interface coating layers can be applied to minimize the drug/coat interactions.

In addition to filmcoat release properties, the solvent vehicle used for the coat solution/suspension can be a critical factor. Solvent can influence filmcoat morphology by its effect on molecular conformation or arrangement. A solvent vehicle that is also a good solvent for the drug can promote "bleed" of the drug into the developing filmcoat as filmcoat is deposited on the core. This bleed could translate to a higher coat level requirement to achieve adequate taste concealing. Solvent selection can also influence the wetting properties of the coat solution spray droplets as they contact the particle surface during application, which could influence filmcoat quality. Highly volatile solvents may contribute to premature drying near the nozzle tip resulting in poor film integrity or spray drying (low coating efficiency).

Additional excipients that could be beneficial in a taste concealing application include plasticizer, glidants, pH modifiers, or process aids. Plasticizers are required by many polymers to reduce brittleness or optimize film forming properties. Taste concealing performance can be significantly different for a hydrophobic plasticizer than a hydrophilic one. Glidants such as talc, magnesium stearate, or glycerol mono-stearate help mitigate agglomeration of particles during or after coating in formulations that are prone to particle accretion. pH modifiers such as bicarbonates, carbonates or citric acid or its salts can be used to preserve a localized pH condition that might perhaps help conceal taste, minimize drug solubility, or stabilize a product. Charge transfer agents such as silicon dioxide or clays can be used to improve particle flow during processing by minimizing electrostatic concerns inherent in many applications.

9.3.3 Other Considerations

Upon application of fluid bed technology for taste concealing, some less obvious concerns are realized. Some of this has been touched on in the above discussion. Notable concerns include the following:

1. Although granulating processes offer a means to taste conceal mildly bad tasting material, a significant limitation is the structure of formed agglomerates. Agglomerate structures can have many nooks, crannies, and surfaces internal to the agglomerated particles that are not exposed to spray droplets from the nozzle; thus, those surfaces do not receive additional coating once formed in the process. This same concern will be realized with any agglomerates that form in a process intended to individually coat particles. If sufficient coating is applied to bridge the open gaps between particles within the formed agglomerate particles, an adequate taste conceal may be realized.
2. Core particle engineering prior to application of a taste concealing coat can be critical to the success of a taste conceal application. Fluidization and coat solution/suspension atomization impart significant physical forces on particles during processing. This can create a very dynamic coating environment in which particles can be fracturing, agglomerating, and abrading throughout the process. This can result in a continuous presence of exposed drug surface and prevent adequate taste concealing regardless of the amount coating applied. An adequate balance of mild physical process conditions, particle strength, and coating or binder strength may be critical to achieving adequate taste concealing.
3. Residual uncoated or poorly coated drug can be accepted as an immediate release element in applications such as enteric or sustained release; however, any such residual in a taste concealed product can easily compromise the taste. Care taken to minimize the presence of such residuals during discharge of taste concealed product from the coating process can be critical to the taste profile.

Drug particles that are taste concealed with a fluid bed process are generally used in chewable, orally dissolving, film strip, and point of use mix/blend formulations. They are not typically used in commercial liquid formulations due to filmcoat limitations including shelf stability concerns related to the migration of solvent and dissolved drug through an applied coat layer.

9.4 Spray Drying or Spray Congealing

Spray drying, spray congealing, and related processes offer some potential for taste concealing mildly bad tasting materials. These processes generally involve creation of matrix particles near 30 μm and below. Spray drying involves use of a solvent vehicle to carry coating and dissolved or suspended drug through an atomizing nozzle followed by evaporative removal of the solvent to create these matrix particles.

Spray congealing involves suspension or dissolution of drug in a molten material matrix such as a wax followed by spray through an atomizing nozzle and congealing of the molten material. Both processes yield matrix particles with drug dispersed or dissolved in the matrix. Critical concerns of these processes for taste concealing include the following:

1. A small percentage of residual drug remains exposed at or near the outer surface of the particles. This may compromise taste unless a subsequent taste concealing coat or flavor system is applied.
2. Spray dry matrices are commonly composed of hydrophilic materials such as starches or gums that provide minimal taste concealing properties.
3. Spray congealed matrices are hydrophobic materials that delay or extend release of the drug.

As a result of these concerns, there is limited taste concealing capacity and limited control of drug release.

9.5 Coacervation

Coacervation has found limited use for taste concealing, but it is potentially applicable depending on the release profile needs and drug properties. The basics of coacervation were realized with the development of carbonless paper copying technology by Barrett K. Green in the 1940s and 1950s. The process is characterized by formation of a coating on particles or liquid droplets while they are dispersed in a liquid phase. The encapsulated particles are commonly referred to as a coacervate and they can be isolated from the liquid phase by centrifugation or filtration processes followed by a drying process or a spray drying process. Details on the process and its history can be found on the internet [1].

Coacervation is based on colloid chemistry. Following formation of a colloid, changes related to the nature of the colloid material can be introduced to precipitate or deposit the colloid material. Changes can include temperature changes, addition of a non-solvent, pH changes, or addition of suitable crosslinking ion or ion pairing material of opposite charge depending on the chemistry of the system. If an insoluble particulate material such as an insoluble drug is included prior to precipitation, a three phase system can be created. This system consists of the solid particles individually encapsulated in the gel-like colloid material all suspended in the liquid phase. When precipitation is induced, the colloid material forms a solid shell around each particle to produce the coacervate.

Use of coacervation for taste concealing or other oral delivery purposes is limited by drug solubility and coacervate chemistries. Although it offers a viable means of taste concealing, there is the challenge to identify systems that properly release the drug. There is less flexibility to tailor systems for specific taste and drug release targets compared to that available with fluid bed film coating technology. For soluble drugs dosed for sustained delivery, it offers a potential means of sustain delivery and taste concealing.

Table 9.6 Materials for potential use in coacervation and oral delivery platforms

Material	Solvent system
Gum arabic	Aqueous
Carrageenan	Aqueous
Citric acid or salts	Aqueous
Dextrin	Aqueous
Ethyl cellulose	Organic solvent
Starches	Aqueous
Guar gum	Aqueous
Hydroxypropyl cellulose	Aqueous
Methyl cellulose	Aqueous
Hydroxypropyl methyl cellulose	Aqueous
Polyethylene glycols	Aqueous
Polyvinyl pyrrolidone	Aqueous or organic solvent
Potassium or sodium alginate	Aqueous
Shellac	Organic solvent
Xanthan gum	Aqueous

The coacervation chemistry employed must be based on materials approved for use in oral pharmaceutical products. A list of materials potentially applicable to coacervate chemistry and oral delivery platforms is provided in Table 9.6. The reader is referred to applicable regulations such as the United States Pharmacopoeia or National Formulary for assessment of material approval for use in oral pharmaceutical applications.

9.6 Inclusion Complexes

Inclusion complexes offer a potential means to taste conceal mildly bad tasting drugs or drugs with low dose requirements. Inclusion of a drug or portion of a drug within a cavity or structure may conceal the bad tasting portion of the drug from availability to taste sensors. Depending on stability and structure of the complex, taste concealing may be adequate for liquid or solid formulations.

The most common inclusion complexes involve cyclodextrins as the host molecule. Many drugs or drug functions have a suitable size to fit in cyclodextrin cavities. If the taste center is adequately concealed from exposure to taste sensors, taste concealing properties may be realized. In general, cyclodextrins have a limited taste concealing capacity, but can be effective if the drug fits appropriately in the cyclodextrin cavity. Enzymatic degradation of the cyclodextrin molecule in the gut assures release of the drug from the complex.

Cyclodextrin history and their application are discussed in Sect. 10.3 of this book. That section contains more detail on cyclodextrins and preparation of cyclodextrin complexes.

In addition to the concealing feature, cyclodextrins have a mildly sweet taste that may contribute to better overall taste.

9.7 Ion Resin Technology

Ion exchange resins provide a charged surface where oppositely charged ions or polar molecules can ionically bind. Most drug molecules have basic or acidic functionalities that ionize under suitable conditions or are relatively polar; thus, they can be bound to an appropriately charged resin surface to form an ion resin complex. Once bound and in the absence of significant competing ions, the drug is effectively immobilized on the resin surface and not readily available to taste receptors. This provides a potential means of concealing taste without use of a coating. Once the complex is past the mouth and reaches the gut, higher concentrations of competing ions displace the drug to make it bioavailable. As bioavailable drug uptake occurs, the equilibrium naturally shifts toward complete drug bioavailability.

Resin materials, the principles that govern ion exchange, and drug loading processes used to prepare taste concealed ion resin complexes are the same as those described in Sect. 10.2 of this book. Nevertheless, when applying resins for taste concealing, residual, free drug removal at the end of the drug loading process may be critical to performance. Washing steps used to remove this free drug may be necessary. A strategy for drug–ion resin taste concealing is shown in Fig. 9.3.

When using ion resin technology for taste concealing, it is critical that the ionic strength of the gut is adequate to displace the drug from the resin to meet bioavailability requirements. High affinity drugs may not completely be displaced or the equilibrium could extend throughout gastrointestinal transit and yield a sustained release bioavailability pattern. Dissolution test strategy should take released drug uptake into consideration since this will likely affect drug release rate.

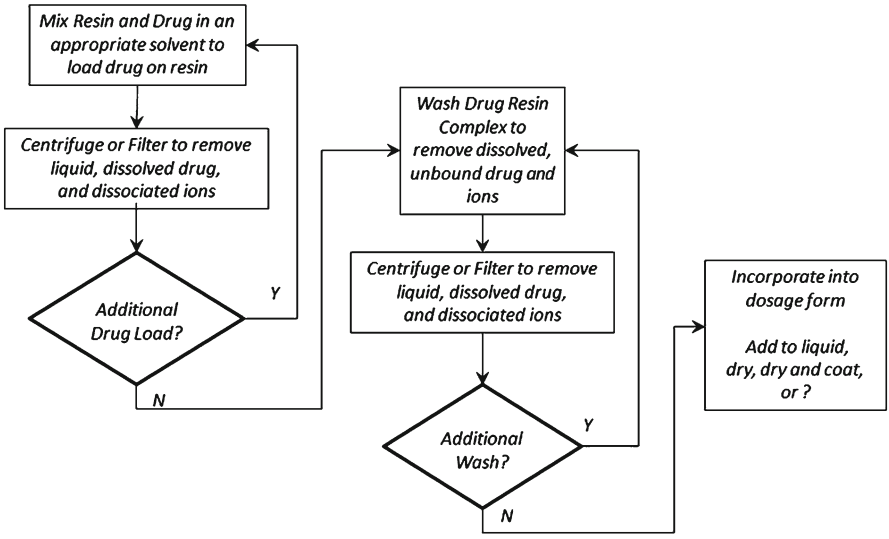

Fig. 9.3 Drug–ion resin taste concealing strategy

Ion resin complexes can be incorporated into liquid or solid dosage forms. Formulation should contain minimal amounts of ionized components to avoid compromising taste by prematurely displacing bound drug from the resin.

9.8 Taste Conceal Performance Specifications

The taste specification for any taste concealed product is difficult to establish. The human tongue, electronic tongue, and dissolution testing each offer a potential means of assessing taste performance. The human tongue is perhaps the most ideal option since this is the discriminating sense that brings about the taste concealing requirement; however, there are several significant obstacles to application of the human tongue:

1. Use of the human tongue requires potential exposure of drug to the tongue. Depending on the drug properties, this may not be acceptable or allowed due to safety considerations for the individual.
2. The human tongue has varying sensitivity depending on the individual and the recent taste history of the individual. In addition, taste sensitivity of an individual can change with drug exposure history. These concerns compromise the consistency of the tongue.
3. Even if the human tongue option were allowed, the human pediatric tongue would ultimately be the discriminating system and reliable feedback may not be achievable.

Electronic tongues use electronic taste sensing technology to measure the intensity of a taste. They can potentially be calibrated to detect and measure the bad taste associated with drug molecules. This offers a potentially unbiased means of assessing the taste performance of a taste concealed product. Use of these devices requires a proper means of calibrating instrument sensitivity for the sample matrix and correlation of electronic tongue results with final dose form taste performance. The many variables associated with device and taste performance create significant challenges to establishing a reliable specification.

Dissolution testing under conditions similar to the mouth can provide a release profile for the drug. Release in the early portion of the profile can provide an indication of taste performance; however, this early release must be correlated with final dose form performance. Since most taste conceal systems employ flavor ingredients to overcome early release and latent release from retained particles in the mouth, it is difficult to establish reliable acceptance criteria.

Perhaps the best means of assuring consistent, acceptable performance of a taste concealed product is to properly design the process and set appropriate specifications for critical parameters. For example, particle size distribution in a fluid bed coating process influences the amount of surface area in the bulk material. Particle size distribution before coating, during coating, and at the end of coating will

influence a taste conceal layer thickness and taste performance. Correlation of particle size distribution at critical points in the process with taste performance can provide a means of quality assurance.

References

1. RT Dodge Website (2012) Articles on coacervation and its history. http://www.rtdodge.com/dodge_coacer.html and http://www.coacervation.net/
2. Wurster DE (1963) Granulating and coating process for uniform granules. US Patent No. 3089824 to University of Wisconsin
3. Wurster DE (1964) Apparatus for coating particles in a fluidized bed. US Patent No. 3117027 to University of Wisconsin
4. Wurster DE (1965) Apparatus for the encapsulation of discrete particles. US Patent No. 3196827 to University of Wisconsin
5. Wurster DE (1965) Process for preparing agglomerates. US Patent No. 3207824 to University of Wisconsin
6. Wurster DE (1966) Particle coating apparatus. US Patent No. 3241520 to University of Wisconsin

Chapter 10
Liquid Formulations

Charles R. Frey and J. Scott Madsen

Abstract Liquid formulations are a preferred or required oral dosage form for many in the pediatric age group. They require a stable, dissolved, or suspended form of the drug that meets release, bioavailability, and taste requirements. Both immediate and sustained release liquid products are possible. Liquid formulation strategies include direct incorporation of drug in a dissolved or suspended state, incorporation of drug in the form of a suspended drug:ion exchange resin complex, and incorporation of drug in the form of a dissolved or suspended drug:cyclodextrin inclusion complex. This chapter briefly discusses pertinent history and application of these technologies in relation to oral liquid formulations for pediatric patients.

10.1 Immediate Release

Many liquid formulations are inherently immediate release products. Placing a native drug directly in a liquid solution for delivery eliminates the hydration and disintegration processes that are required to release drug from a solid dosage form. Extending release for a liquid product may be a significant challenge.

An aqueous solution of a water soluble drug can potentially be incorporated into an immediate release liquid product. Poorly soluble drugs can be incorporated as a suspension; however, the poor solubility may prevent achievement of immediate release. Regardless of the dissolved or suspended state, the drug must be stable with respect to oxidation and hydrolysis. Depending on drug properties it may need to retain a consistent active form or morphology during the product shelf life. Also, the formulation itself must taste acceptably to the patient at the dosing concentration.

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Stability and solubility concerns alone prevent application of many drugs directly into a liquid formulation. The bad taste of most drugs limit successful direct incorporation into a liquid dose form depending on the extent of bad taste and dose/concentration requirement. Due to these constraints, there is a narrow range of drugs that are directly incorporated into a shelf stable liquid product.

Successful formulations generally are appropriately pH buffered and flavored, and contain any other required stabilizers, suspending agents, and preservatives to meet the stability and delivery goals.

10.2 Ion Resin Complexes

10.2.1 Introduction

Ion resin complexes can potentially be used for immediate release formulations depending on drug affinity for the ion exchange resin; however, they are particularly useful for extended release liquid formulations. The stability afforded with the bond to the ion exchange resin coupled with the ability to control drug release from the resin offers a platform for extended release from an oral liquid product. Successful use of this technology was first disclosed in a 1980 patent [4].

The key challenges encountered when formulating shelf stable oral liquid dosage forms include the following:

1. Overcoming the bad taste of the drug.
2. Achieving a desired release profile.
3. Maintaining drug stability.

Ion resin suspension technology offers a potential means of addressing all these concerns. Most drug molecules have basic or acidic functionalities that ionize readily or they are relatively polar; thus, they can potentially be bound to an appropriately charged ion exchange resin surface to form an ion resin complex. Once bound and in the absence of significant competing ions, the drug is effectively immobilized and in some cases stabilized with respect to some degradation processes. The bad taste of a drug may be reduced significantly by the ionic binding, which reduces drug availability to taste receptors; thus, it can provide an effective means of taste concealing. The ion resin complex produced by binding a drug to the insoluble polymeric matrix of an ion exchange resin may exhibit taste and odor properties of the ion exchange resin itself, not of the drug.

Ion resin complexes can be incorporated into a variety of shelf stable solid oral dosage forms in addition to liquids. Upon ingestion, the high ionic strength of the gut displaces drug from the resin to make it bioavailable. This release from the resin is governed by ion exchange equilibria and as released drug is taken in by the body, the equilibrium shifts toward complete drug bioavailability. Undigested resin passes through the gastrointestinal tract.

Drug release profiles with this technology can be manipulated through a number of variables, including drug affinity factors, particle size, drug:resin ratio, and the application of controlled release coatings on the drug resin complexes. Drug molecules with low affinity for the resin typically maintain an immediate release profile as they are easily displaced from the resin in the gut. Drug molecules with high affinity for the resin are more difficult to displace from the resin and may naturally exhibit an extended release profile. Particle size distribution can significantly affect drug release as well. Typically, smaller particles offer more surface area and therefore faster drug release than larger particles. The ratio of drug:resin used in the preparation of an ion resin complex can also affect the rate of drug release. While drug release can be controlled to a minor extent for both low and high affinity materials through resin selection, particle size, drug:resin ratio, and liquid formulation parameters, the addition of a coating is often needed to achieve a target extended release pattern. Drug release in these systems is regulated primarily by the diffusion rate of competing ions through the applied membrane, which is controlled by the membranes thickness and porosity. Release rates of up to 12 and 24 h from a liquid suspension format can be achieved with this technology.

10.2.2 Ion Exchange Resins

Ion exchange equilibria are governed by the relative affinity and concentrations of competing ions for available exchange sites. A high affinity ion will easily displace a low affinity ion. A low affinity ion at relatively high concentration can effectively displace a high affinity ion. The same principle is used in ion exchange water softening systems where high affinity divalent ions such as calcium are trapped on a cation exchange resin as they easily displace low affinity sodium ions. When the resin is exhausted and primarily in the calcium form, it is regenerated by passing a saturated solution of sodium chloride over it; the high population of sodium ions effectively displaces the higher affinity calcium ions to return the resin to the sodium form. The exchange process for a cationic drug loading is illustrated in Fig. 10.1.

Ion exchange resins approved for use in oral pharmaceutical products are listed in Table 10.1. A strong cation exchange resin (sulfonate-based Amberlite IRP69), weak cation exchange resins (carboxylate-based Amberlite IRP64 and Amberlite IRP88), and a strong anion exchange resin (quaternary ammonium-based Duolite AP143) are available. Approval is also anticipated for a weak anion exchange resin based on a tertiary amine function. Resin selection is based on several factors including the anionic or cationic character of the drug and its affinity for the resin. Ion affinity can be controlled somewhat on the weak acid resins through pH adjustments while affinity for the strong acid resin is relatively fixed by drug ionic properties. Additional resins under the trade names Indion, Tulsion, Purolite, and Kyron are used in some regulatory markets.

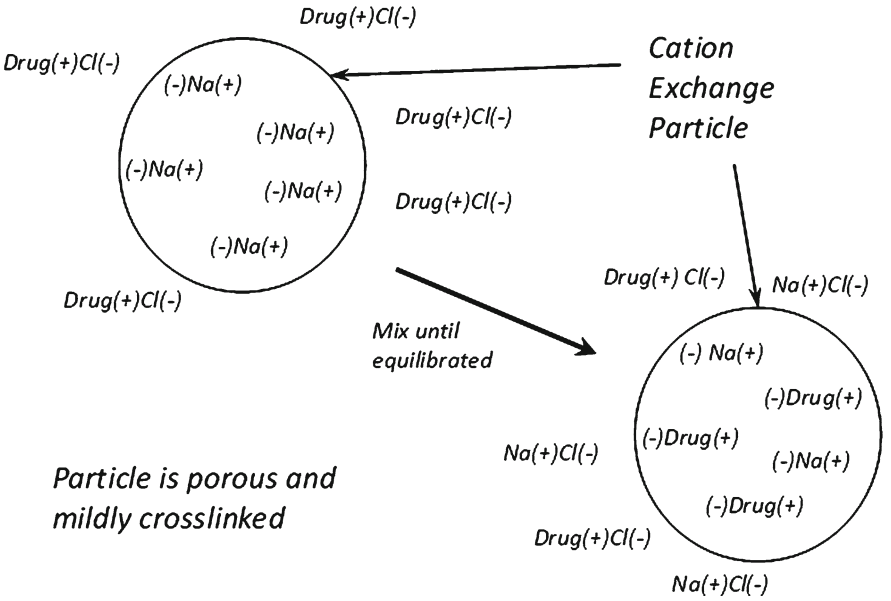

Fig. 10.1 Cation exchange process illustration

Table 10.1 Commercial ion exchange resins

Name	Polymer	Functionality	Ionic form
Amberlite IRP64	Methacrylic acid–divinylbenzene polymer	$-COO^-$	H^+
Amberlite IRP88	Methacrylic acid–divinylbenzene polymer	$-COO^-$	K^+
Amberlite IRP69	Styrene–divinylbenzene	$-SO_3^-$	Na^+
Duolite AP143	Styrene–divinylbenzene	$-NR_3^+$	Cl^-

10.2.3 Drug Loading

Drug loading on the resin can potentially be done in a flow through column or bed of the resin; however, it is more commonly done in a batch process by mixing drug and resin together in an appropriate solvent media. The solvent is commonly water, but other polar solvent systems such as ethanol may be applicable if needed. As drug dissolves, the drug ions exchange with the counterion of the resin. Loading efficiency is dependent primarily on the equilibrium of the exchange. For maximum loading, the drug:resin ratio is maximized to force the equilibrium to more complete loading. In addition, multiple loading steps can potentially be used to force additional load. For less than maximum loading a lower drug to resin ratio can be applied.

Temperature, pH, and choice of solvent for the drug loading process can also be manipulated to maximize drug loading. This process works even for low solubility drugs because uptake of the drug by the ion exchange resin allows more drug to dissolve until equilibrium is achieved.

To reduce free drug and competing ion content, the drug resin complex slurry is typically filtered or centrifuged to remove the liquid portion, which contains the displaced counterions of both the drug and resin and remaining free, dissolved drug. The amount of drug lost to meet high loading requirements can be significant; thus, optimization of this loading and washing process can be a critical economic consideration. Additional washing processes can then be used to remove residual free salt ions and residual free drug. The resulting wet cake is then processed as required by the dosage form. This processing could include direct incorporation into a liquid suspension, drying for incorporation into a solid dosage form, or drying and coating for incorporation into a solid or liquid dosage form. If coated particles are incorporated into a liquid suspension product, it is critical that any swelling associated with rehydration has been adequately addressed in the formulation to minimize or eliminate film coat fracturing. Dried drug resin complexes containing up to ~40 % drug load can be achieved depending on the exchange capacity, loading process, drug structure, and coating requirements.

Note that the ionic form of the cation exchangers varies. In general, the counterions are weak affinity ions that are relatively easy to displace with an ionized drug. Although counterion affinities are all relatively low, the affinity of cations for the cation exchange materials is ranked from potassium with the highest affinity, to sodium, to hydrogen with the lowest affinity. The potential ramifications of counterion choice may be of minimal importance, but the following factors should be considered:

1. Resins are highly porous structures with exchange sites throughout the particles and they shrink or swell in relation to the ionic form. The shrink and swell is related to ion size with the following size order: drug > K^+ > Na^+ > H^+. Hydration level and degree of crosslinking within the resin will also influence the amount of swell.
2. Drug ions are larger than the original resin counterions; thus, resins will typically swell with drug load.
3. Drug will not typically load to the full exchange capacity of the resin due to the exchange equilibrium and steric constraints associated with drug ion size. Typical loadings for Amberlite IRP69 cation exchange resin and Duolite AP143 anion exchange resin are between 5 and 75 % and 5 and 50 % of the exchange capacity, respectively, according to manufacturer product data sheets.
4. As drug loads, resin and drug counterions remain in the liquid phase. The hydrogen form of the resin will yield an acidic liquid phase.
5. If coating of the drug resin complex is required, the shrink and swell inherent in the resin can have a catastrophic effect on the film coat. The amount of shrink or swell and the steps taken to allow for it are vital to the success of the coating process.

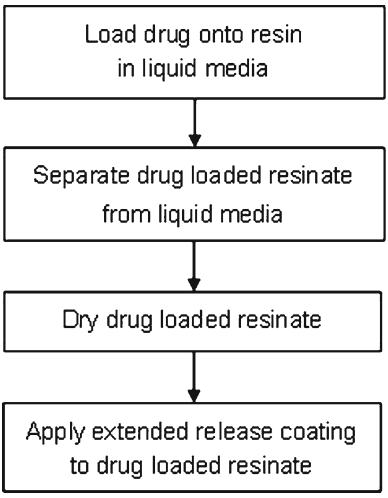

Fig. 10.2 Drug loading strategy for an ion resin complex liquid product

10.2.4 Coating Drug Resin Complexes

Coating of the drug resin complex is typically done with the Wurster (bottom spray) fluid bed coating process using a semipermeable coating polymer such as ethylcellulose. The Wurster process is described in the Taste Concealing section of this book. Unless another means of adequately overcoming the resin shrink and swell factors is employed, the coating is often applied from a solvent vehicle to take advantage of the added film coat strength associated with film coat morphology and higher polymer molecular weight compared to aqueous latex or pseudo latex systems. High modulus films may also be used to stretch as the resin swells.

A shelf stable ion-resin suspension is composed of drug loaded resin with a coating (if coating is required) along with flavor, viscosity, suspension, and non-ionic preservative agents. These suspensions shift to an equilibrium after preparation as ion exchange processes continuously occur on the suspended drug resin complex even if a controlled release membrane has been applied. Although the coating may slow the rate of equilibration, it will eventually reach an equilibrium point. The complexity of this equilibration can be significant if multiple drug resin complexes are incorporated into a single product as residual high affinity drug will easily displace low affinity drug. The exchange of drugs between the two drug resin complexes and varying film coat requirement for the two drugs can significantly shift the release profiles.

10.2.5 Process Overview

A general flowchart of the preparation of a coated drug loaded resin is shown in Fig. 10.2.

Table 10.2 Drugs loaded successfully on an ion exchange resin

Basic drugs	pK_a	Acidic drugs	pK_a
Acycloguanosine	1.86	Nicotinic acid	2.17
Tinidazole	2.34	Mefanamic acid	3.69
Deferiprone	3.04	Indomethacin	4.17
Cimetidine	6.73	Diclofenac	4.18
Oxycodone	7.53	Repaglinide	4.19
Remacemide	7.76	Ketoprofen	4.23
Nicotine	8	Ibuprofen	4.41
Morphine	8.14	Valproic acid	4.82
Hydrocodone	8.48	Lansoprazole	8.48
Rivastigmine	8.62	Ambroxol	8.69
Dextromethorphan	9.1	Omeprazole	9.08
Propranolol	9.14	Acetaminophen	9.86
Betaxolol	9.17	Topiramate	12.37
4-Aminopyridine	9.25	Carbemazepine	13.94
Chlorpheniramine	9.33		
Paroxetine	10.32		

Table 10.3 Example commercial products

Product	Active ingredient	Application
Delsym	Dextromethorphan	Sustained release antitussive
Tussionex	Hydrocodone and chlorpheniramine	Sustained release antitussive/antihistamine

10.2.6 Applications

Table 10.2 contains a list of drugs reported to have been successfully applied to an ion resin [5]. Although many of these may not fall in the pediatric focus of this book, this gives a sense of the potential scope of application. In general, basic drugs will load successfully under suitable conditions on a cation exchange (acidic) resin; acidic drugs on an anion exchange (basic) resin.

Table 10.3 contains examples of commercial drug:resin suspension products.

10.3 Cyclodextrins

Inclusion complexes are structures composed of a guest molecule within a host cavity. The most widely used host structures are cyclodextrins. These cyclic oligosaccharides favor inclusion of non-hydrophilic substances within their toroidal structures. A good overview of cyclodextrin history and application can be found in several review articles [1–3, 6]. The first observation of cyclodextrins was recorded in 1891, the microorganisms that naturally produce them were first isolated in ~1906, and the first cyclodextrin structure elucidations were reported in 1936 and 1948–1950. A 1953 German patent

has been noted to describe many of the potential benefits of cyclodextrin inclusion complexes for drug formulation [6]. There is a significant amount of published literature on cyclodextrins and their uses and much of it is somewhat redundant. One of the challenges to a formulator is to assimilate it all in order to extract what may be relevant to a particular application. A condensed overview of cyclodextrin use in relation to oral pharmaceutical formulations is attempted in this section.

Cyclodextrins are composed of (α-1,4)-linked α-D-glucopyranose units. Sizes commonly used in pharmaceutical products contain six (α-cyclodextrin or α-CD), seven (β-cyclodextrin or β-CD), and eight units (γ-cyclodextrin or γ-CD). Chemical structures are shown in Fig. 10.3 and properties are summarized in Table 10.4.

Several derivatives of these natural cyclodextrins have been synthesized or developed to optimize their utility in various ways. Goals of derivatization generally include:

- Improved solubility of the cyclodextrin and its guest–host complex
- An improved fit for the guest molecule
- Addition of functional sites (catalytic or otherwise) on the cyclodextrin surface

Derivatives generally substitute an R group for the H atom of one or more hydroxyl functions in the cyclodextrin and/or create a polymeric structure. Properties of several derivatives for pharmaceutical application are summarized in Table 10.5. Methyl- and hydroxypropyl derivatives have been successfully commercialized.

β-Cyclodextrin and its derivatives have received the most attention in oral pharmaceuticals since it is most suitably sized for many drug molecules. USP/NF monographs exist for β-cyclodextrin (Betadex), γ-cyclodextrin (Cyclodextrin, Gamma), and Hydroxypropyl-β-cyclodextrin (Hydroxypropyl Betadex). The regulatory status of cyclodextrins continues to evolve. Cyclodextrins are sold under several trade names including Cavamax, Cavasol, Cavitron, Kleptose, and Trappsol,

The full scope of potential advantages of cyclodextrin inclusion complexes in oral pharmaceutical formulations includes the following:

- Stabilization of unstable compounds
- Reduced volatility of volatile compounds
- Prevent irritation from poorly soluble crystalline materials
- Transform liquids to a solid crystalline form
- Increase drug dissolution rate and solubility
- Increased bioavailability
- Taste concealing
- Protection of drug to oxidation or polymerization
- Reduce reactivity of incompatible compounds

Cyclodextrins provide a means to solubilize poorly soluble drugs and stabilize reactive drugs for successful incorporation into solution or suspension liquid dosage forms.

Cyclodextrin complexes are often 1:1 pairings of a guest molecule within a cyclodextrin ring; however, complexes of 1 guest with two or more cyclodextrin ring caps can occur. In addition, association of guest molecules with the outer surface of the cyclodextrin can occur.

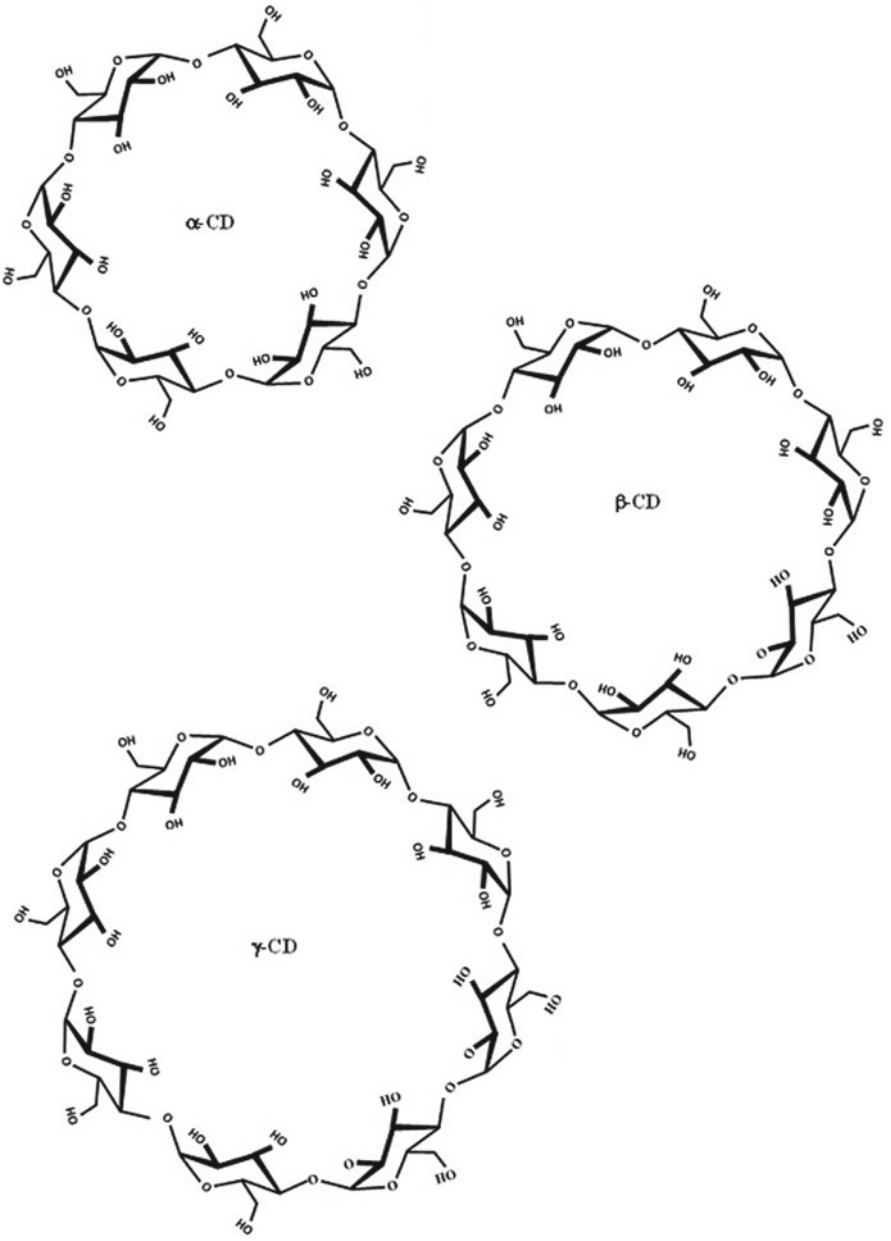

Fig. 10.3 Cyclodextrin structures

Cyclodextrin complexes are typically formed in a liquid environment. Depending on the physical characteristics and needs of the formulation, a variety of methods including solution, co-precipitation, neutralization, slurry, kneading, and grinding processes have been employed. In general, water is relatively loosely contained in the

Table 10.4 Properties of natural cyclodextrins

Material	Glucose units	Molecular weight	Cavity diameter (Å)	Cavity depth (Å)	Solubility (g/100 mL)
α-Cyclodextrin	6	973	5–6	7–8	14.5
β-Cyclodextrin	7	1135	7–8	7–8	1.85
γ-Cyclodextrin	8	1297	9–10	7–8	23.2

Table 10.5 Properties of selected cyclodextrin derivatives

Material	R group	Glucose units	Molecular weight	Solubility (g/100 mL)
2-Hydroxypropyl-β-cyclodextrin	$-CH_2CHOHCH_3$	7	Dependent on extent of substitution	>60
Methyl-β-cyclodextrin	$-CH_3$	7	Dependent on extent of substitution	>50
Sulfobutyl sodium-β-cyclodextrin	$-(CH_2)_4SO_3^-Na^+$	7	Dependent on extent of substitution	>50
2-Hydroxypropyl-γ-cyclodextrin	$-CH_2CHOHCH_3$	8	Dependent on extent of substitution	>50
Branched-β-cyclodextrin	Glucosal or maltosal	7	Dependent on structure and substitution	–

cyclodextrin cavity due to the relatively hydrophobic internal surface of the cavity and an unfavorable orientation of the water molecules. Less hydrophilic materials of appropriate size displace the water with relative ease to form a more stable complex. Complexes can be isolated by filtration or centrifugation to yield a clear solution of the soluble complex. Spray drying or lyophilization can be used to create a dry complex.

Potential concerns of cyclodextrin:drug inclusion complex application include the possibility of inducing drug polymorphism or co-crystal formation depending on drug properties and the presence of other formulation components.

Drug release from a complex is generally achieved by displacement with large amounts of water or the presence of competing molecules. Contents of the gut provide water and competing molecules. Drug release is also realized with enzymatic degradation of the cyclodextrin structure in the gut.

References

1. Del Valle EMM (2003) Cyclodextrins and their uses: a review. Proc BioChem. doi:10.1016/S0032-9592(03)00258-9
2. Loftsson T, Jarho P, Masson M, Jarvinen T (2005) Cyclodextrins in drug delivery. Expert Opin Drug Deliv 2:335–351
3. Magnusdottir A, Masson M, Loftsson T (2002) Cyclodextrins. J Incl Phenom Macroc Chem 44:213–218

4. Raghunathan Y (1980) Prolonged release pharmaceutical preparations. US Pat No 4,221,778 to Pennwalt Corporation
5. Rohm and Haas Website (2012). http://www.rohmhaas.com/ionexchange/pharmaceuticals/formulations_Faq.htm. Accessed 3 Sept 2012
6. Szejtli J (2004) Past, present, and future of cyclodextrin research. Pure Appl Chem 76:1825–1845

Chapter 11
Paediatric Solid Formulations

Sejal R. Ranmal, Susan A. Barker, and Catherine Tuleu

11.1 Introduction

Oral drug delivery remains the most widely accepted and preferred route of administration in paediatric and adult populations alike, both from a manufacturing and end-user perspective [1, 2]. The lack of appropriate formulations available for children is a well-acknowledged problem [3–6], as is the paucity of evidence to support formulation selection and design [7]. While liquid medicines have historically been considered the "gold-standard" in paediatrics, the emergence of innovative drug delivery technologies has led to a paradigm shift towards research and development into solid oral dosage forms for use across this heterogeneous population.

Provision of a suitable dosage form is an important factor which governs the age-appropriateness of paediatric formulations; it should enable both safe and accurate dose administration for all intended indications and settings. Aside from the physico-chemical characteristics of the API and other pre-formulation factors, formulators also need to give due consideration to the unique needs of the paediatric patients during the pharmaceutical design of medicines. Formulations need to be well accepted by both children and their caregivers, to support patient adherence

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Table 11.1 Desirable characteristics of oral paediatric formulations, adapted from [8–10]

Formulation	– Achieve adequate bioavailability
	– Dose uniformity and dose appropriate/adjustable to intended age
	– Minimal, non-toxic excipients
	– Stable (while in storage, in use and across variable global climates)
	– Palatable (preferably with a neutral taste)
	– Enable safe, accurate and reliable dose administration
End-user needs	– Easy and convenient to administer (preferably ready-to-use, otherwise requiring minimal handling)
	– Minimal impact on lifestyle, including minimum dose frequency and transportable
	– Acceptable among end-users (patients, caregivers and healthcare professionals) across socio-cultural settings
	– Suits patient capabilities (e.g. ability to swallow, co-ordination to administer)
Resource dependences	– Readily supplied with a suitable administration device (where needed) and clear information for use
	– Consistently available and accessible to patients
	– Affordable (including cost to manufacture and procure/supply)
	– Commercially viable

and consequently benefit therapeutic outcomes. Further desirable characteristics of oral medicines, related to the formulation, end-user needs and resource dependences are highlighted in Table 11.1 and reflect the needs of a global community.

Given the extensive physiological and development differences across this group (ranging from neonates to adolescents) it is unlikely that one single formulation could fulfil all requisites and be deemed appropriate for all intended ages. Rather than a "one-size-fits-all" approach, investigators aim to tailor each formulation to cover the widest age range, ensuring pharmaceutical development strategies are effective and economical whilst providing authorised products for each target subset. The rationale for choice, including advantages and disadvantages of the administration route and proposed dosage form design, needs to be discussed and justified within the paediatric investigation plan (PIP) [8]. A structured framework employing a benefit-risk approach towards formulation selection has been proposed; this involves a rigorous and systematic evaluation of each potential dosage form against factors associated with three criteria, namely efficacy, safety and patient access [11]. A positive benefit-risk balance needs to be demonstrated [8]; however, a pragmatic compromise between industry potentials and regulatory ideals is also needed, to ensure pharmaceutical development, and consequently patients' access to medicines, is not hindered.

11.2 The Rationale for Solid Formulations

Considering the diversity in dosage form type and delivery system design, solid oral formulations are one of the most common modalities for drug delivery. Tablets and capsules have been a robust and widespread means of delivery since the nineteenth

century and remain popular from a manufacturing and commercial point of view. Their use may be somewhat limited in the paediatric population, due to inability of very young children to swallow monolithic dosage forms intact, as well as the lack of evidence to demonstrate how geometric attributes such as size and shape need to be addressed, to render their design appropriate for children. Evidently, conventionally sized dosage forms for adults are not always appropriate for children of different ages, leading to the need for pharmaceutical compounding and drug manipulations [12–14]. It is well acknowledged that patients, caregivers and indeed healthcare professionals often need to physically alter currently available dosage forms, for ease of administration, to obtain the appropriate paediatric dose, or both. The dangers of physical modification of dosage forms, from both a safety and efficacy perspective, are well recognised and as such, this practice should be surpassed by the development and authorisation of rationally designed paediatric formulations.

More contemporary solid formulations include multiparticulate, (oro-)dispersible and chewable forms. These negate the need to swallow large units intact and can potentially provide a flexible and individualised approach to drug delivery, with prime application in paediatrics. Ease of ingestion and dose flexibility are the primary advantages of liquid medicines which have traditionally led to their precedence over solid formulations for children. In comparison with solid dosage forms however, liquid formulations are notoriously more challenging and expensive to formulate, and generally have a more limited shelf-life.

Solid dosage forms also offer other key advantages related to the desirable characteristics highlighted in Table 11.1. From a manufacturing perspective these relate to stability, excipients use, palatability and functionality. Many drugs show poor stability in aqueous solutions and the necessity of added excipients such as preservatives, stabilisers, suspending agents and solubility enhancers (both in quantity and type) is complicated by the fact that there is limited evidence of their safety and toxicity in children of different ages [15–17]. The development of palatable formulations is another important challenge; many drugs exhibit an unpleasant taste and this is one of the fundamental formulation attributes affecting overall patient acceptance [18, 19]. Monolithic dosage forms offer superior taste-masking strategies, such as encapsulation or application of polymer coatings, although the development of chewable and (oro-)dispersible formulations may encompass the same taste-masking challenges that are encountered with liquids. Another key advantage for solid dosage forms is the opportunity for the development of functionalised formulations (such as modified, prolonged and delayed-release systems), which is technically more challenging with liquids. This not only gives the potential for targeted drug delivery but can also benefit patients by reducing dose frequency and minimising burden on lifestyle (e.g. the need to administer medicines at nursery or school).

Another important advantage to patients and caregivers includes the provision of easy, safe and convenient dose delivery with solid formulations. In the case of both age extremities of the population, small volumes can be difficult and inaccurate to measure, while larger dose volumes for older children would be inappropriate. Target dose volumes of $\leq$5 mL for children under 5 years and $\leq$10 mL for those of 5 years and over have previously been proposed, and in most cases, this would necessitate the provision of multiple dosage form strengths [20].

There is also limited control to ensure complete dose intake, particularly for very young children who may spit the medicine out. Liquid medicines also require delivery devices (e.g. spoons, cups or oral syringes) which have previously been linked to medication administration errors [21–23]. Dose accuracy can also be compromised by use of inappropriate measuring devices (e.g. teaspoons) and limited health literacy among caregivers [24].

Conversely, solid formulations offer complete and accurate dose delivery, facilitated by individual, uniform dose units or packages (e.g. sachets or capsules for multiparticulates), which are easy to administer. Dose adaptation with solid unit dosage forms for ingestion intact is limited and numerous strengths may need to be developed when flexibility is required. However, pharmaceutical development and product design strategies require a careful balance of risks and benefits associated with this. An appropriate number of formulations of different strengths should be available to cover the needs of the target age groups; however, a disproportionate number may be a risk factor for medication errors in practice. Attributes of solid formulations, such as size, shape and colour, can be adapted to provide aesthetic final products that can be more easily differentiated to reduce these risks. In spite of this, care must be taken to ensure they are not too attractive or bear a strong resemblance to confectionery [8, 25].

Development of appropriate formulations is a global health challenge, and as such, the distinct requirements in resource-limited settings must also be considered [26, 27]. The World Health Organization (WHO) has recommended prioritising the development of formulations which would also be suitable for use in developing countries, namely flexible solid dosage forms, which can be administered in more than one manner (e.g. dispersed or taken orally as a whole) [1]. One such example is tablets that are orodispersible or alternatively could be used to prepare oral liquids suitable for younger children, e.g. dispersible and soluble tablets. An important basis for this rationale is cost; oral liquid medicines are generally more expensive than solid formulations [28], while it is feasible to manufacture (oro-)dispersible tablets in settings with conventional tableting facilities [29]. Though, proprietary technologies, special attention towards packaging to overcome moisture uptake, and the need for specific excipients may all bear some cost limitations.

Also in relation to resource-limited settings, solid formulations have the added advantage of superior stability and having low bulk and weight, thus being easy to transport and store. In addition to aiding the logistics of procurement and distribution, the added advantage of being less conspicuous minimises problems with confidentiality and social stigma. These practical advantages in transportation and conspicuousness have reportedly led to caregivers preferring tablets over syrups in such settings and the effect of social factors on overall formulation acceptance should not be overlooked [30]. Other studies have shown that better acceptability of tablets over syrups has facilitated both adherence and in some cases clinical outcomes, for malaria [31] and HIV [32] treatments among children in sub-Saharan Africa. Formulations intended for reconstitution to a liquid form (e.g. reconstituted antibiotics) may be inappropriate in light of availability and access (or lack thereof) to clean drinking water and refrigerators in many areas of the world. Nevertheless,

some evidence suggests that parents and caregivers invest in clean water (e.g. by purchasing bottled water) when administering medicines to children [33]; the most economical use of this would be for use when swallowing medicines intact or dispersing medicines in a small volume (e.g. dispersible or soluble tablets).

11.3 Types of Solid Dosage Forms and Their Application in Paediatrics

11.3.1 Dispersible, Soluble and Effervescent Preparations

Dispersible, soluble and effervescent preparations are presented as solid formulations that are intended to be dispersed or dissolved in water prior to administration. Dispersible and soluble tablets should disintegrate within three minutes in a small amount of water, to yield a homogenous dispersion or solution. These forms would be further advantageous for APIs and excipients compatible and suitably palatable when dispersed in breast milk, as they could be suitable for use with children younger than 6 months old [1]. Effervescent powders, granules or tablets are also added to water to produce a draught, but large volumes are usually required. This may be problematic if children are unable or unwilling to drink the whole volume, as dosing errors may occur. Moreover, as these preparations exist as liquids prior to administration, ensuring acceptable palatability is also essential.

While these formulations require minimal preparation prior to use, health literacy of caregivers may be an important factor to consider in their use. Clear instructions should detail appropriate diluents and volumes to dissolve or disperse in, and caregivers should be instructed not to administer the solution before effervescence has subsided, to minimise the ingestion of hydrogen carbonate. Further in relation to their global use, access to clean water and stability issues in humid climates during manufacturing and storage need to be considered. Although the application of these preparations as flexible solid dosage forms is advocated, in cases where these formulations are not suitable for swallowing intact, the potential risks associated with administration prior to dispersion or dissolution need to be assessed [8].

Nevertheless, use of these dosage forms in paediatrics is highlighted by the success of Coartem® Dispersible tablets (Novartis Pharma AG, Basel, Switzerland), an artemisinin-based combination therapy (ACT) which has been a life-saving medicine for millions of infants and children worldwide. Early development studies assessed palatability as well as bioavailability [34], and clear instructions for use on packaging, as illustrated in Fig. 11.1, have facilitated its use [35]. The EMA guideline encourages companies to consider the use of novel packaging like this, to support children's acceptance and adherence, as well as being convenient for caregivers and reducing the risk of errors [8]. Future trends also include the development of a fixed dose combination (FDC) anti-retroviral tablet, which is scored to enable division into eight dose-specific subunits, as well as being fast disintegrating [36].

Fig. 11.1 The Coartem® Dispersible packaging, illustrating how to make up the formulation and administer it to infants to provide a 3-day treatment course

11.3.2 Orodispersible Formulations

Orodisperible formulations can include tablets (ODTs) as well as oral lyophilisates and thin oral dispersible films (ODFs). They are intended to be placed directly in the mouth, where they rapidly disintegrate in saliva, usually within seconds, thus surpassing the need to swallow and the need for water. These formulations are well suited for APIs with high aqueous solubility; however, their application may be restricted by limited drug loading. ODTs can function as flexible forms if, in addition to disintegration in the mouth, they could also be administered in a small amount of liquid prior to administration or they could be swallowed intact. Enabling flexibility with regard to dose is limited, although some ODTs have functional scorelines, and in the case of ODFs, this could potentially be achieved if films could be cut or in other ways divided (however, no ODFs with this capability are currently available).

During pharmaceutical development, particular attention has to be paid to ensure organoleptic properties including texture (or mouthfeel) and palatability are acceptable. Taste-masking may be further challenging due to the limited quantity of flavouring agents and sweeteners which can be incorporated into the dosage forms, particularly ODFs [20]. Formulations may be moisture sensitive, while the low compression force needed to produce ODTs may lead them to be friable and thus difficult to handle and package. In theory, orodispersible preparations may be applicable for use across the paediatric population including infants and young

children; however, evidence of their use and acceptability in these subsets is lacking. Rapid disintegration or adherence to mucosa may facilitate their use in younger children, since this makes them unlikely to be spat out. However any risks associated with their unintended use must also be considered (e.g. if they are chewed or swallowed whole), particularly for very young children who may lack the cognitive capacity to understand the instructions for their correct use. The rapid absorption, improved bioavailability and rapid action achieved using these dosage forms can be advantageous, but the risks of higher drug absorption leading to poisoning in children have also been reported [37].

11.3.3 Chewable Preparations

These formulations are intended to be chewed before being swallowed and pharmaceutical development measures will include ensuring acceptable organoleptic properties and palatability, as well as ensuring dosage forms are easily crushed following mastication. In addition to chewable tablets, medicated chewing gums are another innovative drug delivery system [38]. Many over-the-counter vitamin preparations for children are available as "gummy" chewable dosage forms, although their close resemblance to confectionery may limit potential development and safe use [39].

Children's deciduous (or "milk") teeth usually start erupting around 6 months of age and the complete set of 20 are usually present between 2 and two-and-a-half years. Many chewable preparations for children are licensed from the age of 2 years, and these formulations have been found to be safe, well tolerated and advantageous in children from this age [40]. In fact, mastication before swallowing is an innate default mechanism for articles which enter the mouth [2], thus these formulations may be preferable in children of this age, who might not fully understand the instruction to swallow or retain other dosage forms. The natural tendency for children, particularly around 2–3 years of age, to chew even mini-tablets has been shown [41, 42]. Conversely, as with (oro-)dispersible preparations, the consequences of swallowing chewable tablets intact should be investigated; it may even be preferable for these tablets to be formulated such that both methods of administration are possible [1].

11.3.4 Tablets and Capsules

Tablets and capsules designed for ingestion intact are the most commonly prescribed dosage forms considering their relatively cheap cost to manufacture and convenience for patients. However an unresolved research need in this field involves demonstrating the age from which these dosage forms can be developed and safely prescribed for paediatric patients. In addition to capability, children's willingness to take medicines in this form also needs to be evaluated. The EMA initially published

Table 11.2 Proposal for acceptable tablet dimensions (width or length whichever is longest) in the initial draft EMA guideline on pharmaceutical development of medicines for paediatric use [45]

Age subset	Acceptable tablet dimensions
6 months to <2 years	None; multiparticulates acceptable
2–5 years	3–5 mm (small tablets)
6–11 years	5–10 mm (medium tablets)
12–18 years	10–15 mm (large tablets)

a comprehensive reflection paper which, whilst recognising the inherent variability amongst children and the influence of individual patient and disease-related factors, proposed an average age of 6 years old from which children could swallow solid oral dosage forms [20]. However this recommendation lacked sound scientific rationale, instead being based on anecdotal feedback and supported by few studies reporting behavioural training outcomes [43] and analysing prescribing patterns [5, 44].

The impending EMA guideline initially expanded recommendations by providing stringent guidance on the appraisal of acceptable tablet sizes as a function of age, as shown in Table 11.2, whereas undefined "small" capsules were similarly deemed acceptable for children from the age of 6 years [45]. This prescriptive guidance was removed from the subsequent revision, again for lacking a strong evidence-based rationale; however, justification for the design characteristics of these dosage forms is still a regulatory requirement for investigators [8]. Adapting geometric dosage form attributes could enable monolithic dosage forms to be tailored to the requirements and capabilities of specific age subsets; however, evidence to guide this dosage form design is lacking.

Where appropriate, functional scoring may add some level of flexibility by enabling the dose to be adapted [46]; however, these should be appropriately labelled to be distinct from scorelines intended to aid administration only. It is a well-acknowledged practice that patients and caregivers often modify formulations to enable medicines to be successfully administered; however, for numerous safety and quality reasons, the need for this should be minimised. Interventions such as behavioural training or use of swallowing aids may enhance acceptability of these dosage forms further [43, 47, 48]. Nevertheless, the investigation and use of these interventions has usually been in specific therapeutics populations, and a lack of evidence supporting their time, resource and cost effectiveness may limit wider use in practice.

11.3.5 Multiparticulate Technologies

Multiparticulate systems are versatile platform technologies with considerable promise for application in paediatric pharmaceutical development. These dosage forms consist of multiple, small discrete units, including powders, pellets, beads and granules, which can be presented as dosage forms in themselves (e.g. "sprinkles") or

further processed to produce other solid formulations (including tablets, capsules, (oro-)dispersible and chewable preparations). This thus gives these technologies potential to cater for the various doses and patient capabilities through infancy, childhood and adolescence. It should be noted that currently, regulatory guidance only uses harmonised compendial terminology for dosage forms and routes of administration, thus pellets or mini-tablets are not referred to as specific examples [8].

Powders and granules can be administered in sachets/stick-packs or hard capsules, which allow the contents to be taken directly or after being sprinkled onto food or drink. Provision of different sizes and strengths of the final product allows accurate and reliable dosing in the individualised manner that is often required across the paediatric population. Multiparticulates which are labelled for administration via sprinkling should have a target size of 2.5 mm with no more than 10 % variation over this size to a maximum size of 2.8 mm, as recommended by the FDA [49]. This is to ensure adequate mouthfeel and reduce the risk of inadvertent chewing.

Anatomically, infants can start swallowing thick, semi-solid foods from 6 months, and this could include administration of powders and multiparticulates in these foods [50, 51]. Indeed, appropriate compatibility studies will be required to assure that the API and formulation do not lead to adverse physical or chemical interactions with the foods or drinks that they can be mixed with. Patients and caregivers should also be provided with other important information for use, including the type and quantity of foods or drinks which can be utilised, ensuring that volumes are appropriate to assure complete ingestion of the intended dose. As with (oro-) dispersible formulations, when formulations are mixed with food and drink vehicles, acceptability and palatability needs to be demonstrated to avoid potential risks of aversion, particularly in the case of breast milk.

The application of coatings can allow multiparticulates to be specifically functionalised and subsequently processing them into other solid formulations is feasible, though it may be challenging. Other challenges may be faced when taste-masking multiparticulates, such as ensuring uniform thickness of barrier coatings. Further, the detrimental effect of chewing to the coating and dosage form may be problematic in younger children. These platform technologies also have the potential to produce fixed dose combinations (FDCs), which combine multiple drugs into a single dosage form for convenient and reliable administration. These are especially advocated in resource-limited countries for conditions requiring multi-drug treatment (such as tuberculosis and HIV) and have reportedly benefited patient therapies [32, 52, 53].

11.4 The Evolution of Mini-tablets

Mini-tablets are a unique dosage form which afford the advantages of multiparticulates, with regard to ease of administration and dose flexibility, coupled with the established and cost-effective manufacturing techniques of tableting. As such, research into the application of this dosage form for the paediatric population has recently shown much progress, in terms of both pharmaceutical development and

potential use in clinical practice. Further, as mini-tablets could potentially overcome swallowing difficulties, they may also be applicable for other populations, such as geriatric patients with dysphagia.

11.4.1 Technical Aspects of Pharmaceutical Development

The use of mini-tablets has mainly been described in the literature as sustained release multiparticulates, often involving encapsulation or compaction of mini-tablets with different release matrices or coatings, to obtain modulated release profiles. Furthermore, the potential for muco-adhesive or floating mini-tablets within the stomach to aid the control of drug release has also been investigated, as well as sustained release mini-tablets for ocular use. Presently, the aspects to consider in the pharmaceutical development of mainly immediate release, or even orodispersible mini-tablets [54] are discussed.

An important factor to consider when designing mini-tablets is the drug release profile. It is expected that smaller compacts will show a faster release rate due to the higher specific surface area compared to larger tablets. The dimensions of the compact may be varied to modify the release kinetics from matrix mini-tablets [55, 56]. However the size of individual non-disintegrating multiparticulates may influence the gastric emptying, gastrointestinal transit and all the various developmental aspects of the gastrointestinal physiology relevant to bioavailability. Thus, caution should be exercised as such information in children, especially younger ones, is currently sparse or simply not known [57, 58]. Moreover gastric emptying times may differ between formulations, such as oral liquids, tablet and mini-tablets. As a consequence drug absorption may vary and it might not always be straightforward to obtain bioequivalence. In a recent study however, rapidly dissolving levetiracetam mini-tablets were shown to be bioequivalent with the originator tablets [59], and such alternative medicinal products make it easier and more convenient to individualise treatment.

Various definitions of the size of mini-tablets can be found, probably due to historical technological limitations. Mini-tablets can be manufactured with a conventional high-speed rotary tablet press, adapted with multi-tip punches. Therefore, pharmaceutical mini-tablets can now be as small as 1 mm in diameter [60], while the WHO defines them as no bigger than 4 mm in diameter [1]. Those above this size would simply be small tablets and many are already on the market [61]. High loading can be achieved depending on the tabletability of the drug itself. However, from a patient perspective, mini-tablets may be tricky to handle due to their small size, unless specific packaging (e.g. a stick-pack or capsule) or devices (e.g. a counting or measuring device) are used. Presentation of the final medicinal product in individually dosed stick-packs or capsules can facilitate dose control, and as with multiparticulates, administration can be direct or following sprinkling onto appropriate foods.

Miniaturisation of the tablets can have the potential to impact on many of the compaction events. One of the key factors for these changes is the shift (increase) in the ratio of outer surface particles to core particles as depicted in Fig. 11.2. Moreover considering biconvex mini-tablets, they would be almost spherical.

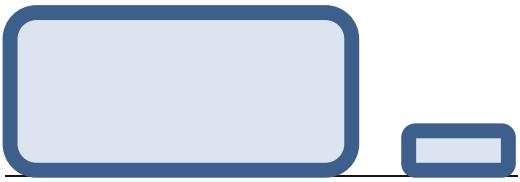

Fig. 11.2 Diagrammatic representation of a 10 and 3 mm compact, with the 3 mm compact showing a higher proportion of surface (*dark blue*) to core (*pale blue*) particles

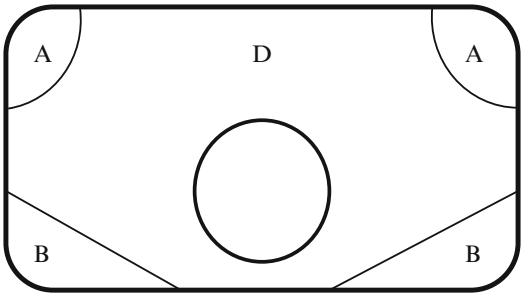

Fig. 11.3 Diagram of the density distributions within flat faced tablets after uni-axial compression area *A* = high density, *B* = low density, *C* = high density and *D* = low density (adapted from Train [62])

As particles in contact with the die walls are more distorted and bonded compared to particles within the core of compacts, particles in contact with the punches are also bonded more strongly than core particles, but the degree of bonding is not as strong as the bonding at the die walls [62]. This can lead to a high-density region on the outside edge, which can be thought of as a "skin" or "shell". In the instance of mini-tablets, the "shell", which is of increased density and hence strength, accounts for a relatively higher proportion of the compact as represented in Fig. 11.2. This could increase the tensile strength or eliminate lamination [63].

During compaction, significant uneven particle movement between the central and peripheral regions occurs, as the outer particles may undergo increased localised friction in connection with shear stress. In turn this could lead to density distributions within the compact as exemplified in Fig. 11.3 with flat faced tablets [64]. High-density regions (Fig. 11.3, regions A and C) are associated with increased tensile strength and can be beneficial to prevent breakages [65]. Capping and lamination can initiate from regions of low density (Fig. 11.2, regions B and D). It is not known, while extrapolating knowledge from larger tablets to mini-tablets, if the typical pattern of density as shown in Fig. 11.3 will remain, or if the regions will overlap to the extent that less or no density distributions are observed, or if the "shell" accounts for all or the majority of the compact. Nevertheless these changes are likely to cause differences in tableting behaviour.

Differences in the tabletability, compressibility and compactability behaviour may also be observed due to mini-tableting altering powder movement on compression, force transmission, ejection stresses, radial die wall stresses, the load relief

during compression and the relaxation during decompression [66]. The narrow diameter of the die used in mini-tableting requires excellent flow to obtain tablets within the uniform desired weight range. However, care must be taken to avoid flooding the die table with powder, particularly when running at slow speeds or with few punches. Therefore on top of direct compression some papers describe the use of granules [60]. The maximum particle size becomes increasingly important with small tablet diameters. A ratio of die diameter to maximum particle size of 3 or more was recommended [67], with the depth of the die being similarly considered [68]. Particles which are too large may lead to high tablet variability as only a few compose each 2 mm tablet. However, the minimum particle size is also important as particles which are too small risk falling in the void between the die and the punch, hence a narrower particle size range is required for mini-tablets than larger ones.

Direct compression also requires excipients to present good flow and compactability properties and is dependent on morphological coherence between components. The potential for expansion in the die during compression of the excipients and powder mix, in addition to the pure drug, should also be considered during formulation development. Mini-tablet punches are delicate components and the maximum compression force that a punch can withstand is not linear with diameter. Whereas 7 mm punches can cope with a wide range of forces, such that certain formulation issues can be overcome by increasing the compression force, for 2 mm tablet punches, this is limited to ~2 kN which may be critical when devising formulation strategies.

For manufacturing considerations, the suitability of standard tablet tests also has to be considered. For example, the large volumes of dissolution media used in dissolution testing (typically 900 mL) would be even less applicable for dosage forms intended for children, though this is a wider general issue for all paediatric formulations and not just mini-tablets. The standard mesh aperture for pharmacopeial disintegration equipment is ~2 mm which would let mini-tablets pass through, while the effects on the disintegration of reducing the mesh aperture are not known. Likewise, the friability test is designed for standard sized compacts; the dramatic diameter and weight reduction of the mini-tablets, without altering the drum diameter is likely to affect results. The Pharmacopeial friability tests require for tablets with a unit weight of more than 650 mg to take a sample of 10 whole tablets. However for an individual unit mass of 650 mg or less, a sample as near as possible to 6.5 g which would correspond to approximately 325 mini-tablets weighing 20 mg [69]. Some authors have suggested the use of small glass beads to overcome the loss of the stress inside the friabilator [70]. This might be a vital consideration when mini-tablets are envisaged to be coated.

The hardness (resistance to crushing) of mini-tablets is difficult to measure; the usual Schleuniger-type hardness testers are not able to register the small breaking force, often leading to non-Pharmacopoieal methods being employed instead. Further, the allowable weight variation in the British Pharmacopoeia (BP) is greater for smaller tablets (with the smallest size range quoted <80 mg in weight), which may have a secondary effect of variability in dose between mini-tablets. Assuming perfectly uniform distribution of the drug substance in the powder mix, a ±10 % variability in weight may lead to a similar variability in dose, which may pose more significance in a paediatric population than in adults.

11.4.2 Emerging Evidence of Suitability

In addition to developments in the pharmaceutical manufacture of mini-tablets, studies have also been undertaken to assess their acceptability and suitability for use in the paediatric population. A principal study demonstrated that pre-school children aged 2–6 years old were able to swallow a 3 mm uncoated mini-tablet, with acceptance increasing with age (46 % of the children aged 2 years swallowed the mini-tablet versus 87 % of 5 years olds) [41]. A subsequent study reduced both the size of mini-tablets used to 2 mm and the age of participants to as young as 6 months of age. Acceptance of the uncoated mini-tablets was at least equal to, or in some cases better than, that of a sweet-tasting syrup, and even infants and toddlers as young as 6–12 months of age were able to swallow a single tablet [42]. Although, chewing prior to swallowing the mini-tablet was also observed, particularly among children aged 2–4 years. A recent randomised controlled trial also assessed larger mini-tablets (4 mm uncoated tablets) in comparison with 3 other dosage forms (a powder, suspension and syrup) among children aged 1–4 years, and found that tablets were significantly better accepted [71].

Nevertheless, further research is required to demonstrate the application of mini-tablets in clinical practice. The exploratory studies mentioned involved administration of a single mini-tablet, demonstrating the proof of content of their suitability (or swallowability) among young infants and toddlers. However, considering the limited dose loading per individual mini-tablet, it is envisaged that in therapeutic cases, multiple mini-tablets will be required to provide the appropriate dose. Commercial mini-tablets include Lamisil® Oral Granules (terbinafine, Novartis) which are licensed from the age of 4 years and presented as 2 mm mini-tablets in a stick-pack for sprinkling onto soft food. For mini-tablets which are administered directly into the mouth (without sprinkling onto food first), end-user acceptability and the appropriate quantity, in relation to patient-related factors such as age, is yet to be evaluated. Administration of multiple mini-tablets will change organoleptic properties such as mouthfeel, and whether young children will successfully swallow each unit needs to be investigated.

Further from a methodological perspective, those participating in, or consenting for their child to participate in, such studies inherently have a positive attitude the dosage forms being investigated. The recruitment rates of the aforementioned studies varied from 45 to 56 %. It is also important to understand perceptions of such novel dosage forms overall, both positive and negative, and in larger sample sizes, as this may aid in identifying potential barriers to acceptability in the larger population. Although the pharmaceutical manufacturing ability of mini-tablets has been well demonstrated, further evidence of end-user acceptability is still needed.

11.5 Conclusions

While development of novel solid formulation technologies has widened the scope of potential paediatric drug delivery systems, there is a recognised lack of evidence-based knowledge of their suitability and acceptability across the population.

Generally, there has been a lack of formulation information published in paediatric studies and clinical trials [72, 73] and few studies addressing patient-related outcomes including formulation acceptance in relation to adherence [74]. The EMA paediatric guideline requires end-user acceptability of paediatric medicinal products to be assessed as an integral part of pharmaceutical development studies [8]. Assessing both children's ability and willingness to take these formulations, as well as considering the needs and preferences of caregivers, is needed.

Furthermore, education about solid formulations, and wider exposure of their use, may be essential to support their acceptance among patients, caregivers and healthcare professionals in different cultural settings. This is exemplified in the low uptake of dispersible paediatric formulations as FDC anti-retroviral therapies in some regions [75]. Although the modest use here may be influenced by a variety of factors, particularly the lack of specific healthcare initiatives, lack of historical use and familiarity among all stakeholders has also been suggested as a contributing factor. Until recently, liquid medicines have generally had precedence in paediatrics, and although the rationale for solid formulations is strong, exploring and supporting their appropriate use in clinical practice is still needed.

References

1. World Health Organization (WHO) (2012) Annex 5 Development of paediatric medicines: points to consider in formulation. Forty-sixth Rep. WHO Expert Comm. Specif. Pharm. Prep. World Health Organization, Geneva, p 235
2. Mrsny RJ (2012) Oral drug delivery research in Europe. J Control Release 161:247–253. doi:10.1016/j.jconrel.2012.01.017
3. Nahata MC (1999) Lack of pediatric drug formulations. Pediatrics 104:607–609
4. Standing JF, Tuleu C (2005) Paediatric formulations—getting to the heart of the problem. Int J Pharm 300:56–66. doi:10.1016/j.ijpharm.2005.05.006
5. Schirm E, Tobi H, de Vries T et al (2003) Lack of appropriate formulations of medicines for children in the community. Acta Paediatr 92:1486–1489. doi:10.1111/j.1651-2227.2003.tb00837.x
6. Van Riet-Nales DA, de Jager K, Schobben AFAM et al (2011) The availability and age-appropriateness of medicines authorized for children in the Netherlands. Br J Clin Pharmacol 72:465–473. doi:10.1111/j.1365-2125.2011.03982.x
7. Ranmal S, Tuleu C (2013) Demonstrating evidence of acceptability: The "Catch-22" of pediatric formulation development. Clin Pharmacol Ther 94:582–584. doi:10.1038/clpt.2013.154
8. European Medicines Agency (EMA) (2013) Guideline on pharmaceutical development of medicines for paediatric use (Draft) (EMA/CHMP/QWP/805880/2012 Rev. 1). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137023.pdf. Accessed 1 June 2013
9. Krause J, Breitkreutz J (2008) Improving drug delivery in paediatric medicine. Pharm Med 22:41–50, doi:10.1007/BF03256681
10. Kristensen HG (2012) WHO guideline development of paediatric medicines: points to consider in pharmaceutical development. Int J Pharm 435:134–135. doi:10.1016/j.ijpharm.2012.05.054
11. Sam T, Ernest TB, Walsh J et al (2012) A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms – an application for paediatric dosage form selection. Int J Pharm 435:115–123. doi:10.1016/j.ijpharm.2012.05.024
12. Ernest TB, Craig J, Nunn A et al (2012) Preparation of medicines for children – a hierarchy of classification. Int J Pharm 435:124–130. doi:10.1016/j.ijpharm.2012.05.070

13. Richey RH, Craig JV, Shah UU et al (2012) The manipulation of drugs to obtain the required dose: systematic review. J Adv Nurs 68:2103–2112. doi:10.1111/j.1365-2648.2011.05916.x
14. Skwierczynski C, Conroy S (2008) How long does it take to administer oral medicines to children? Paediatr Perinat Drug Ther 8:145–149. doi:10.1185/146300908X254206
15. Ernest TB, Elder DP, Martini LG et al (2007) Developing paediatric medicines: identifying the needs and recognizing the challenges. J Pharm Pharmacol 59:1043–1055. doi:10.1211/jpp.59.8.0001
16. Fabiano V, Mameli C, Zuccotti GV (2011) Paediatric pharmacology: remember the excipients. Pharmacol Res 63:362–365. doi:10.1016/j.phrs.2011.01.006
17. Salunke S, Giacoia G, Tuleu C (2012) The STEP (Safety and Toxicity of Excipients for Paediatrics) database. Part 1—A need assessment study. Int J Pharm 435:101–111. doi:10.1016/j.ijpharm.2012.05.004
18. Cram A, Breitkreutz J, Desset-Brèthes S et al (2009) Challenges of developing palatable oral paediatric formulations. Int J Pharm 365:1–3. doi:10.1016/j.ijpharm.2008.09.015
19. Baguley D, Lim E, Bevan A et al (2012) Prescribing for children – taste and palatability affect adherence to antibiotics: a review. Arch Dis Child 97:293–297. doi:10.1136/archdischild-2011-300909
20. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) (2006) Reflection paper: Formulations of choice for the paediatric population. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf. Accessed 1 June 2013
21. Yin HS, Wolf MS, Dreyer BP et al (2010) Evaluation of consistency in dosing directions and measuring devices for pediatric nonprescription liquid medications. JAMA 304:2595–2602. doi:10.1001/jama.2010.1797
22. Walsh J, Bickmann D, Breitkreutz J et al (2011) Delivery devices for the administration of paediatric formulations: overview of current practice, challenges and recent developments. Int J Pharm 415:221–231. doi:10.1016/j.ijpharm.2011.05.048
23. Ryu GS, Lee YJ (2012) Analysis of liquid medication dose errors made by patients and caregivers using alternative measuring devices. J Manag Care Pharm 18:439–445
24. Yin HS, Mendelsohn AL, Wolf MS et al (2010) Parents' medication administration errors: role of dosing instruments and health literacy. Arch Pediatr Adolesc Med 164:181–186. doi:10.1001/archpediatrics.2009.269
25. Food and Drug Administration Center for Drug Evaluation and Research (CDER) (2012) Guidance for industry: Safety considerations for product design to minimize medication errors (Draft Guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf. Accessed 1 June 2013
26. Craig SR, Adams LV, Spielberg SP, Campbell B (2009) Pediatric therapeutics and medicine administration in resource-poor settings: a review of barriers and an agenda for interdisciplinary approaches to improving outcomes. Soc Sci Med 69:1681–1690. doi:10.1016/j.socscimed.2009.08.024
27. Sosnik A, Seremeta KP, Imperiale JC, Chiappetta DA (2012) Novel formulation and drug delivery strategies for the treatment of pediatric poverty-related diseases. Expert Opin Drug Deliv 9:303–323. doi:10.1517/17425247.2012.655268
28. Hill SR (2012) Putting the priorities first: medicines for maternal and child health. Bull World Health Organ 90:236–238. doi:10.2471/BLT.11.088658
29. Nunn T, Williams J (2005) Formulation of medicines for children. Br J Clin Pharmacol 59:674–676. doi:10.1111/j.1365-2125.2005.02410.x
30. Nahirya-Ntege P, Cook A, Vhembo T et al (2012) Young HIV-infected children and their adult caregivers prefer tablets to syrup antiretroviral medications in Africa. PLoS ONE 7:e36186. doi:10.1371/journal.pone.0036186
31. Ansah EK, Gyapong JO, Agyepong IA, Evans DB (2001) Improving adherence to malaria treatment for children: the use of pre-packed chloroquine tablets vs. chloroquine syrup. Trop Med Int Heal 6:496–504. doi:10.1046/j.1365-3156.2001.00740.x
32. Bagenda A, Barlow-Mosha L, Bagenda D et al (2011) Adherence to tablet and liquid formulations of antiretroviral medication for paediatric HIV treatment at an urban clinic in Uganda. Ann Trop Paediatr 31:235–245. doi:10.1179/1465328111Y.0000000025

33. Adams LV, Craig SR, Mmbaga EJ et al (2013) Children's medicines in Tanzania: a national survey of administration practices and preferences. PLoS ONE 8:e58303. doi:10.1371/journal.pone.0058303
34. Abdulla S, Amuri B, Kabanywanyi AM et al (2010) Early clinical development of artemether-lumefantrine dispersible tablet: palatability of three flavours and bioavailability in healthy subjects. Malar J 9:253. doi:10.1186/1475-2875-9-253
35. Hamed K, Grueninger H (2012) Coartem(®): a decade of patient-centric malaria management. Expert Rev Anti Infect Ther 10:645–659. doi:10.1586/eri.12.51
36. Kayitare E, Vervaet C, Ntawukulilyayo JD et al (2009) Development of fixed dose combination tablets containing zidovudine and lamivudine for paediatric applications. Int J Pharm 370:41–46. doi:10.1016/j.ijpharm.2008.11.005
37. Ceschi A, Hofer KE, Rauber-Lüthy C, Kupferschmidt H (2011) Paracetamol orodispersible tablets: a risk for severe poisoning in children? Eur J Clin Pharmacol 67:97–99. doi:10.1007/s00228-010-0943-x
38. Chaudhary SA, Shahiwala AF (2010) Medicated chewing gum—a potential drug delivery system. Expert Opin Drug Deliv 7:871–885. doi:10.1517/17425247.2010.493554
39. Lam HS, Chow CM, Poon WT et al (2006) Risk of vitamin A toxicity from candy-like chewable vitamin supplements for children. Pediatrics 118:820–824. doi:10.1542/peds.2006-0167
40. Michele TM, Knorr B, Vadas EB, Reiss TF (2002) Safety of chewable tablets for children. J Asthma 39:391–403. doi:10.1081/JAS-120004032
41. Thomson SA, Tuleu C, Wong ICK et al (2009) Minitablets: new modality to deliver medicines to preschool-aged children. Pediatrics 123:e235–e238. doi:10.1542/peds.2008-2059
42. Spomer N, Klingmann V, Stoltenberg I et al (2012) Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. Arch Dis Child 97:283–286. doi:10.1136/archdischild-2011-300958
43. Meltzer EO, Welch MJ, Ostrom NK (2006) Pill swallowing ability and training in children 6 to 11 years of age. Clin Pediatr (Phila) 45:725–733. doi:10.1177/0009922806292786
44. Yeung VW, Wong ICK (2005) When do children convert from liquid antiretroviral to solid formulations? Pharm World Sci 27:399–402. doi:10.1007/s11096-005-7911-z
45. European Medicines Agency (EMA) (2011) Guideline on pharmaceutical development of medicines for paediatric use (Draft) (EMA/CHMP/QWP/180157/2011). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/06/WC500107908.pdf. Accessed 1 June 2013
46. Food and Drug Administration Center for Drug Evaluation and Research (CDER) (2013) Guidance for industry: tablet scoring: nomenclature, labeling, and data for evaluation. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269921.pdf. Accessed 1 June 2013
47. Ghuman JK, Cataldo MD, Beck MH, Slifer KJ (2004) Behavioral training for pill-swallowing difficulties in young children with autistic disorder. J Child Adolesc Psychopharmacol 14:601–611. doi:10.1089/cap.2004.14.601
48. Garvie PA, Lensing S, Rai SN (2007) Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. Pediatrics 119:e893–e899. doi:10.1542/peds.2006-1488
49. Food and Drug Administration Center for Drug Evaluation and Research (CDER) (2012) Guidance for industry: size of beads in drug products labeled for sprinkle. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240243.pdf. Accessed 1 June 2013
50. Van de Vijver E, Desager K, Mulberg AE et al (2011) Treatment of infants and toddlers with cystic fibrosis-related pancreatic insufficiency and fat malabsorption with pancrelipase MT. J Pediatr Gastroenterol Nutr 53:61–64. doi:10.1097/MPG.0b013e31820e208e
51. De-Regil LM, Suchdev PS, Vist GE et al (2011) Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age. Cochrane Database Syst Rev. doi:10.1002/14651858.CD008959.pub2

52. Haberer JE, Cook A, Walker AS et al (2011) Excellent adherence to antiretrovirals in HIV+ Zambian children is compromised by disrupted routine, HIV nondisclosure, and paradoxical income effects. PLoS ONE 6:e18505. doi:10.1371/journal.pone.0018505
53. O'Brien DP, Sauvageot D, Zachariah R, Humblet P (2006) In resource-limited settings good early outcomes can be achieved in children using adult fixed-dose combination antiretroviral therapy. AIDS 20:1955–1960. doi:10.1097/01.aids.0000247117.66585.ce
54. Stoltenberg I, Breitkreutz J (2011) Orally disintegrating mini-tablets (ODMTs) – a novel solid oral dosage form for paediatric use. Eur J Pharm Biopharm 78:462–469. doi:10.1016/j.ejpb.2011.02.005
55. Lopes CM, Sousa Lobo JM, Costa P, Pinto JF (2006) Directly compressed mini matrix tablets containing ibuprofen: preparation and evaluation of sustained release. Drug Dev Ind Pharm 32:95–106. doi:10.1080/03639040500388482
56. Roberts M, Vellucci D, Mostafa S et al (2012) Development and evaluation of sustained-release Compritol® 888 ATO matrix mini-tablets. Drug Dev Ind Pharm 38:1068–1076. doi:10.3109/03639045.2011.638302
57. Bowles A, Keane J, Ernest T et al (2010) Specific aspects of gastro-intestinal transit in children for drug delivery design. Int J Pharm 395:37–43. doi:10.1016/j.ijpharm.2010.04.048
58. Batchelor H, Kendall R, Desset-Brethes S et al (2013) Application of in vitro biopharmaceutical methods in development of immediate release oral dosage forms intended for paediatric patients. Eur J Pharm Biopharm. doi:10.1016/j.ejpb.2013.04.015
59. De Mey C, Dimitrova V, Lennartz P, Wangemann M (2012) Bioequivalence of a novel minitablet formulation of levetiracetam. Arzneimittelforschung 62:94–98. doi:10.1055/s-0031-1297965
60. Tissen C, Woertz K, Breitkreutz J, Kleinebudde P (2011) Development of mini-tablets with 1 mm and 2 mm diameter. Int J Pharm 416:164–170. doi:10.1016/j.ijpharm.2011.06.027
61. United States National Library of Medicines, National Institute of Health Pillbox (Beta Version). http://pillbox.nlm.nih.gov/. Accessed 1 June 2013
62. Train D (1956) An investigation into the compaction of powders. J Pharm Pharmacol 8:745–761
63. Lennartz P, Mielck JB (1998) Minitabletting: improving the compactability of paracetamol powder mixtures. Int J Pharm 173:75–85. doi:10.1016/S0378-5173(98)00206-3
64. Eiliazadeh B, Pitt K, Briscoe B (2004) Effects of punch geometry on powder movement during pharmaceutical tabletting processes. Int J Solids Struct 41:5967–5977. doi:10.1016/j.ijsolstr.2004.05.055
65. Sinka IC, Burch SF, Tweed JH, Cunningham JC (2004) Measurement of density variations in tablets using X-ray computed tomography. Int J Pharm 271:215–224. doi:10.1016/j.ijpharm.2003.11.022
66. Kachrimanis K, Malamataris S (2005) Compact size and mechanical strength of pharmaceutical diluents. Eur J Pharm Sci 24:169–177. doi:10.1016/j.ejps.2004.10.007
67. Flemming J, Mielck JB (1995) Requirements for the production of microtablets: suitability of direct-compression excipients estimated from powder characteristics and flow rates. Drug Dev Ind Pharm 21:2239–2251. doi:10.3109/03639049509065904
68. Kachrimanis K, Petrides M, Malamataris S (2005) Flow rate of some pharmaceutical diluents through die-orifices relevant to mini-tableting. Int J Pharm 303:72–80. doi:10.1016/j.ijpharm.2005.07.003
69. Thomson SA (2009) An investigation in to the compaction and clinical potential of mini-tablets for paediatric drug delivery. Ph.D. Thesis. University of London, London, p 282
70. De Brabander C, Vervaet C, Fiermans L, Remon JP (2000) Matrix mini-tablets based on starch/microcrystalline wax mixtures. Int J Pharm 199:195–203. doi:10.1016/S0378-5173(00)00383-5
71. Van Riet-Nales DA, de Neef BJ, Schobben AFAM et al (2013) Acceptability of different oral formulations in infants and preschool children. Arch Dis Child 98(9):725–731. doi:10.1136/archdischild-2012-303303
72. Standing JF, Khaki ZF, Wong ICK (2005) Poor formulation information in published pediatric drug trials. Pediatrics 116:e559–e562. doi:10.1542/peds.2005-0327

73. Pandit S, Shah U, Kirby DJ et al (2010) Inappropriate oral formulations and information in paediatric trials. Arch Dis Child 95:754–756. doi:10.1136/adc.2009.175661
74. Van Riet-Nales DA, Schobben A, Egberts TCG, Rademaker CMA (2010) Effects of the pharmaceutical technologic aspects of oral pediatric drugs on patient-related outcomes: a systematic literature review. Clin Ther 32:924–938. doi:10.1016/j.clinthera.2010.05.005
75. Waning B, Diedrichsen E, Jambert E et al (2010) The global pediatric antiretroviral market: analyses of product availability and utilization reveal challenges for development of pediatric formulations and HIV/AIDS treatment in children. BMC Pediatr 10:74. doi:10.1186/1471-2431-10-74

Chapter 12
Semi-solid Formulations

Irwin C. Jacobs

Abstract Oral dosage forms generally consist of solids (tablets, capsules, powders, or granules), liquids (solutions, solids in suspension, and emulsions), or possibly semi-solids such as pastes or gels. When one might think of a semi-solid dosage form, delivery systems other than oral forms could also come to mind such as topical gels, buccal delivery gels (delivery to the oral mucosa), or possibly vaginal, eye, or nasal. This review does not include soft chewable gelatin capsules but will concern itself only with oral delivery systems that are semi-solid in form.

12.1 Introduction

As oral semi-solids, there are three systems that have recently appeared in the marketplace or proposed in the literature. These include: (1) gummies which are a very stiff, almost a hard chewable gel form; (2) soft chewable gels or squeezable gels much like a dessert type gelatins or the new energy gel supplements; and (3) pudding type semi-solids.

Gummy type oral dosage forms are based on confectionery technology. This technology, derived from early pectin and starch formulations, was first developed in Germany in the early 1900s by Hans Riegel. He began the Haribo Company, which made the first gummy bears in the 1920s. While gummy candy has been manufactured since this time, it had limited worldwide distribution until the early 1980s.

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It was then when Haribo began manufacturing gummy bears in the United States. Gummy dosage forms are generally composed of gelatin, sweeteners, flavorings, and colorings. Because of its nature, a gummy can be molded into literally thousands of shapes.

The word "gel" may be derived from "gelatin" or from "jelly" and may come from the Latin word "gelu" meaning frost. This is essentially a liquid setting to a semi-solid that does not flow readily. The gel could also be further defined as constrained within a 3-D polymeric matrix. Gels may contain organic or inorganic colloids as a dispersed phase intimately associated with a continuous phase which in the cases described here are aqueous and generally termed hydrogels.

Puddings have been used as delivery systems for sprinkle type formulations. In Western countries a pudding generally consists of a milk-based dessert thickened by cooking with starch or possibly gelatin or carrageenan. Children are often given pureed cereals, vegetables, and meats in a thickened form for easy swallowing. This becomes the reason behind sprinkling a nutritional supplement or pharmaceutical onto a food type product such as pudding or apple sauce for better compliance. More recently, a gellan gum formulation has been disclosed in the literature describing a thickened liquid in a similar form as a pudding [1].

12.2 Advantages of These Systems

Patient compliance and safety are generally at the top of the list for healthcare practitioners when recommending pharmaceutical dosage forms. Convenience is also often high on the list when choosing dosage forms by a consumer. With these thoughts being considered, the use of gummies, gels, or puddings could assist in improving compliance in children or in improving convenience since water is not needed for any of these forms and they do not have spill issues associated with liquid dosage forms.

Dysphagia which is a dysfunction of normal swallowing, is now common in general populations but certainly more common in elderly patients and in long-term care facilities as well as being associated with certain illnesses [2]. These patients require appropriate dosage forms rather than the inappropriate drug administration of crushing or cutting sustained release or enteric coated tablets with the associated consequences such as overdosing or degradation of the active in the stomach. Alternately, these patients may not comply with timely dosage schedules because of the difficulty in swallowing especially large dosage forms. There may even be adverse events such as choking, irritation in the oral cavity, or upper airway obstruction. The use of thickened liquids, gels, or pudding textures can provide fairly large dosage forms that can be administered and swallowed quite easily without the risks as described for large solid oral dosage forms.

These larger dosage forms can allow high drug loading without the difficulty in swallowing and can provide convenience and improved patient compliance especially for traveling and busy adults. Salivation can be stimulated through enhancement of taste and smell and/or texture which can further facilitate swallowing.

12.3 Difficulties with These Dosage Forms

The harder gummy dosage form has to be sized appropriately so as not to cause a choking hazard and have a good preservative system because of the moderate water content. The gels also have to be sized appropriately or considerations given in formulation as to ease of breakage of the gel if it becomes lodged in the trachea or esophagus. There are a number of concerns with the gummy dosage form including overdosing since the form may be seen as candy by children who might take more than they should. There is also the problem of sticking of the dosage form to the teeth. The dosage form also needs to be sized carefully for the targeted consumer so as not to be a choking hazard.

The pudding formulation needs to hydrate properly and in a short period of time while it includes the active ingredient for reduction of any spillage potential. The gel formulations have to contain an effective preservation system to prevent microbial contamination. Any gel formulation must remain uniformly gelled in extended storage to prevent any loss in dose uniformity.

12.4 Gummies

Gummies are generally gelatin-based dosage forms and can be considered as lozenges or troches. One has to only go to the local pharmacy or discount store to find numerous types of gummy bear supplements containing a wide range of active ingredients including vitamins, minerals, omega-3 oils, fibers, Echinacea, and other dietary supplement actives. The dosage form has become exceedingly popular. The forms generally contain gelatin, natural or artificial sweeteners, natural or artificial colors, citric acid as an acidulent, flavors, and materials such as coconut oil, beeswax, or starch to prevent sticking. Starch or other gums such as acacia or gellan gum [3] has been used to improve texture or temperature stability. The use of citric acid or other acidulants not only enhances flavor but provides the lowered pH necessary to prevent microbial contamination.

Manufacturing generally uses a molding form with either starch or vegetable oil systems to facilitate removal from the form or sticking during storage in the product container.

12.5 Gels/Jellies

A recent publication described the results from tasting of soft chewy placebo prototypes in children and adults [4]. The data indicated that soft and chewy dosage forms generate high appeal by both parents and children although they may differ in what they perceive as appropriate and acceptable. The conclusion was that softer, textured medication would be an improvement in pediatric medications.

There appears to be a need for alternative, novel oral dosage forms such as gels or jellies to deliver active ingredients. These forms would be easy to swallow without discomfort yet not have great potential for choking or suffocation. Gels or jellies are made using substances that undergo a degree of cross-linked or association when hydrated or dissolved in an aqueous medium. Jellies are transparent or translucent depending on whether the polymers are present as dissolved or as colloidal suspensions. Two phased gels can be formed by several inorganic clays such as magnesium aluminum silicate.

Hydrocolloids are often classified as either thickening agents or gelling agents. When developing the gel or jelly dosage form, one would prefer to develop a formulation that forms a physically stable molded shape that once formed, will not change its shape in a defined shelf storage time. Some further gel descriptors include:

- Hard/soft—How much force does it take to rupture a gel?
- Brittle/elastic—In other words, does the gel break suddenly or does it simply deform?
- Cohesive—Does the gel break up in the mouth or on handle much like a soft dessert gel?
- Gummy—Is the gel hard and cohesive, or somewhat rubbery?
- Adhesive—Does the gel adhere to the teeth or palate?
- Thermally reversible/irreversible—Thermally reversible gels melt on heating to a sufficiently high temperature with the exception of methyl cellulose which sets on heating and melts when cooled. Irreversible gels will not melt when heated which include high acyl gellan gum and gelatins cross-linked with the enzyme hemicellulase or alginates when complexed with divalent metal ions. These thermal reversing or irreversible systems are further described in Swarbrick [5].
- Syneresis—This occurs on shrinkage of a gel allowing the liquid to weep or exude out of the gel over time. This shrinking is caused by molecular interactions of the gelling agents and can be observed in custards or yogurts. Agar can exhibit this syneresis when a force is applied to the gel.

Targeted patient groups for this type of formulation would not only include those suffering from dysphagia but also children with varying compliance issues because of taste, smell, or need for swallowing large dosages. Because of the ease in swallowing of this dosage form in a larger mass, the gel can deliver dosages of well over one gram. For example, due to their ease in handling, the compositions of this type of dosage form may be consumed as “on-the-go” by consumers while performing other activities. The visual and textural properties of the gel dosage form may also make the compositions very appealing to consumers, and particularly to children. For example, the gels can be molded into a variety of shapes and/or a variety of colors that would be appealing to children.

The formulation development of an oral gel dosage form should take in a number of considerations to cover aesthetic and performance characteristics which would include mouth feel, taste, physical appearance, stability both in the context of gel

strength, lack of syneresis as well as free of microbial contamination. Each of the following formulation parameters needs to be considered:

- Active ingredient: A wide variety of actives including over the counter actives, and prescriptive medications as well as dietary supplements can be considered. Prerequisites include stability in the slightly acidic aqueous environment, particle size as not to be gritty, taste that would not be so strong as to overwhelm the flavor in the gel and lack of interaction with whatever gelling system is used and at the concentrations of the requisite dose strength.
- Viscosity agents: A number of polymers have been described in the literature including gellans, carrageenans, hydroxypropyl methyl cellulose, gelatin, modified starches, carboxymethyl cellulose, silk fibroin, agar, pectin, xanthan gum, and pullulan.
- Solvents: Purified water should be used with the addition of propylene glycol or glycerin with the latter being used to aid in facilitating dissolution of the gums by first forming a dispersion of the gums in the glycol or glycerin.
- Preservatives: Suitable preservatives are documented in the literature including methyl and propyl and butyl parabens, benzoic acid or its sodium salt, and sorbic acid or its potassium salt.
- Emulsifiers: These may be necessary for the emulsification of oils such as omega-3 oils. Examples include sorbitan mono-oleate and polyoxyethylene sorbitan monooleate.
- Sweeteners: These can include sugar alcohols such as sorbitol, mannitol or xylitol, sucrose, maltose, fructose, or artificial sweeteners such as aspartame, acesulfame-K, or sucralose.
- Flavors: These can be used alone or in combination and need to be chosen wisely based on target populations, national preferences, and masking capabilities required by the active ingredient(s).
- Smell and color: These are important considerations to complement the flavor but also aid in the taste masking performance based on total sensory perceptions.
- pH: The pH of the final formulation can affect the taste profile but can also affect the performance of the preservative system.

Gel properties can most properly be demonstrated through the use of a texture analyzer such as the Texture Technologies TA.XT Plus analyzer. The instrument is capable of differentiating various formulations by measurement of the gel strength, the point of rupture of the gel and what is termed gel extensibility. The gel strength is the value of the maximum stress just before breakage. The rupture point can be defined as the maximum stress divided by the strain value just before breakage. Lastly, an important property in the development of a gel dosage form is its extensibility; that is, the maximum strain value before breakage. These points are demonstrated in the stress/strain curve shown in Fig. 12.1. The ratio of shear stress to strain is known as the shear modulus and is a measure of the gel's ability to resist deformation. That value in the model gels shown in Fig. 12.1 is approximately 100 Pa.

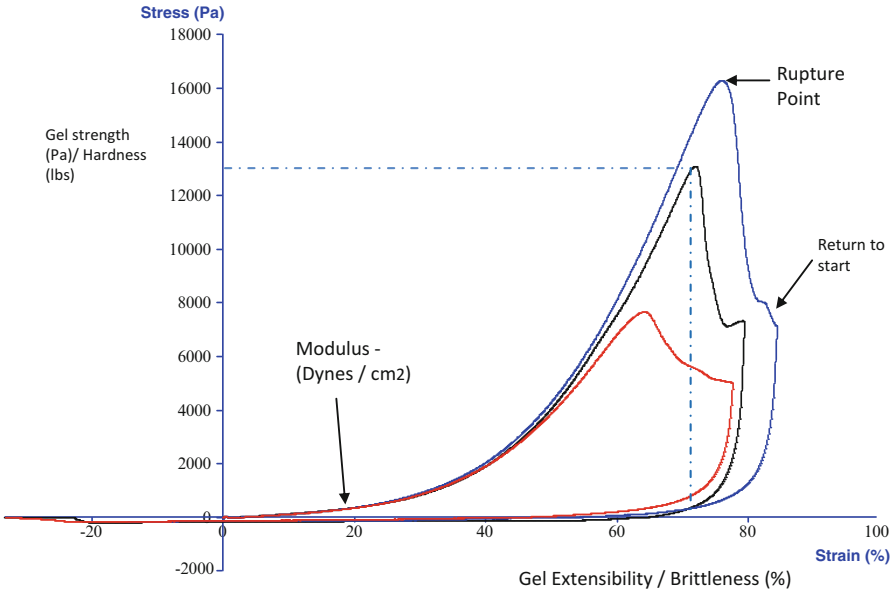

Fig. 12.1 Sample texture analysis graph of gel dosage form stress–strain curve for three different gel samples. *Red*: sample A; *black*: sample B; *blue*: sample C. Modulus: The slope of the linear section at the very beginning of the stress–strain curve

One issue that should be addressed with this type of dosage form is the possibility of lodging in the esophagus. Duncan Craig has addressed this issue for gelatin dosage forms which were designed to enrobe a particularly large solid oral dosage form. This was accomplished with the use of a synthetic cellulose derivative present in the gel to improve the gel's lubricating effect [6]. This invention record also describes an apparatus for measuring the resistance of a composition to shear comprising a probe that can be moved downwards at a constant speed for a determined distance through a tube and measuring the resistance to shear over the distance.

Alternately, to simulate movement through the esophagus, a gel form can be placed in a tube of similar diameter and the tube held either at an angle or vertically to measure the transit time. This will assist in development by differentiating various gel formulations as suitable for further study (Fig. 12.2) (S. Gee, Particle dynamics, Int., St. Louis, personal communication).

A number of gel systems have been reported in the open literature and the patent literature. These include the following:

1. A gellable composition comprising a mixture of 1, gellan, 2, xanthan gum, and 3, a galctomannan and/or glucomannan gum capable of producing a gel wherein the ratio of gums is (1): [(2)+(3)] is 1: greater than or equal to 2 [7]. This was developed as for fruit desserts.
2. A konjac mannan containing thermally reversible gel comprising konjak mannan and xanthan gum and free of any alkali agent for solidifying konjak mannan and a process for producing the reversible gel [8].

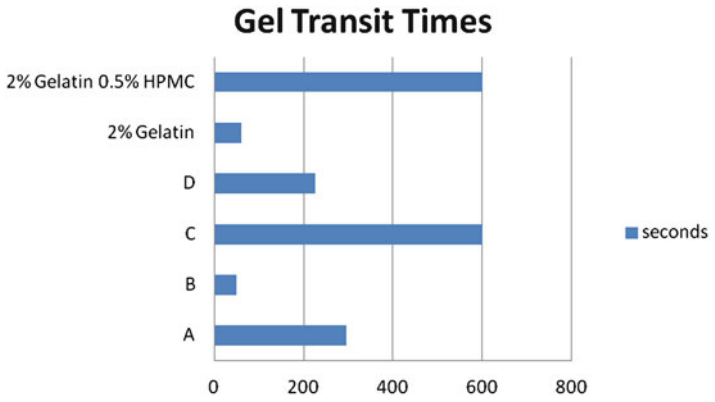

Fig. 12.2 Conditions of test: gel transit times through an 8″ long 3/4″ inner diameter acrylic tube

3. A new oral dosage form for elderly patients by preparation with silk fibroin gel [2]
4. This paper discusses gels formed by gelatin, agar, gellan gum, pectin, and xyloglucan and assesses them for gel strength and in vitro and in vivo release characteristics [9]. The results indicate that gellan at 1.5 % (w/v) and xyloglucan at 1.5 % (w/v) had acceptable gel strengths for ease of swallowing and retaining their integrity in a rat stomach to sustain the release of paracetamol over 6 h.
5. A gel formulation was developed as a possible formulation for compliance of dysphagic and geriatric patients which uses a mixture of methyl cellulose (1–2 %) and pectin (0.5–2.0 %). The gels were assessed for gel strength and in vitro and in vivo release of paracetamol in rat models [10].
6. Thermally reversible gels were formed following oral administration of solutions of xyloglucan to rabbits using theophylline as a model. This provided sustained release properties [11].
7. A gel formulation in a flexible packet is described that can be squeezed from a container having an outlet which defines a flow channel [12]. This channel closure device is designed to open or close the flow channel. The gel may have a viscosity of 7,500–40,000 cps.
8. Another squeezable gel system is described in a patent whereby a mixture of cellulose derivatives and a carboxyvinyl polymer is used to form the gel [13].
9. A patent from Elan describes a gelatin dosage form which contains particles of active ingredient which has been milled to under 2 μm and includes surface stabilizers on the milled particles.
10. A patent describes a process for the formation of a spreadable or pourable gel. This “fluid gel” is obtained by subjecting a solution of components such as xanthan and konjac gums, to shear while cooling the solution from above its gelation temperature [14].

Recently, a new gelling agent-based oral dosage form suitable for administering a variety of active ingredients was developed at Particle Dynamics, International.

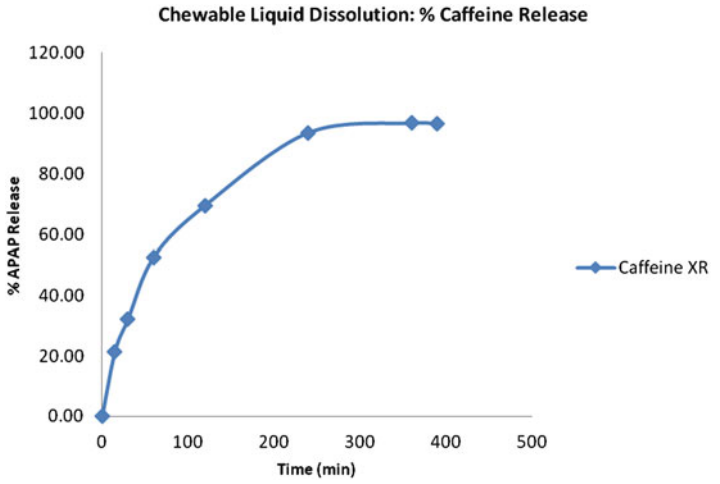

Fig. 12.3 Percent release of caffeine from 5 g dosage form in USP Apparatus II dissolution bath—75 rpm, pH 6.8 phosphate buffer

The overarching goal of the new dosage form development effort was ease of administration especially for large amounts of active ingredient. In fact, the dosage forms of this new oral dosage form may be consumed entirely by passing through the oral cavity and then swallowing by the subject with very little effort, much like one would swallow an oyster or small block of dessert gel. However, typically most consumers may exert at least some effort by chewing the dosage form. This new dosage form typically contains a significant fraction of water. For example, in various embodiments, the dosage forms include an active ingredient(s) in a proportion of at least about 0.1 g active ingredient per g composition, or at least about 0.2 g active ingredient per g composition with dosage forms of over 5 g quite easily swallowed.

Another advantage of the gelling agent-based dosage forms of the present invention is relatively low formation of free water, described earlier as syneresis. Low syneresis allows for ease in handling the gelling agent-based dosage form as well as dose uniformity during extended storage. Additionally, and alternatively in combination with the low syneresis, the gels of this formulation exhibit suitable structural integrity (e.g., gel strength) to provide stability, but do not exhibit such a rigid texture that makes the gels unbreakable during consumption or pose a choking hazard. For example, the present compositions generally exhibit higher melting points than gelatin-based compositions and, thus, are more stable during storage and are more stable during use under conditions where the temperature of the composition may be raised (e.g., during transport or storage or use by a consumer).

One example of a slight modification of this gel dosage form was the ability to create an extended release dosage form. This is illustrated in Fig. 12.3.

Fig. 12.4 Packaged prototype gel oral dosage form

This oral dosage form can be packaged using standard blister packaging with foil sealing. Examples of colors, shapes, sizes are shown below in Fig. 12.4.

References

1. Bar-Shalom D et al (2012) U.S. Application 20120039969
2. Hanawa T et al (1995) Chem Pharm Bull (Tokyo) 43(2):284–288
3. Yu N, Fang Q, Hu Y, Majuru S, Hariharan M, Banner Pharmacaps Research and Development
4. Wiet S, Bunick F (2010) Third annual conference of the EUPFI, Berlin
5. Ofner CM, Klech-Gelotte CM (2007) Gels and jellies. In: Swarbrick J (ed) Encyclopedia of pharmaceutical technology, vol 3, 3rd edn. Informa Healthcare, New York
6. Craig D et al (2011) U.S. Patent Application 20110111108
7. Prest C, Buckley K, US Patent 4,746,528
8. Toba S, Yoshida H, Tokita T, US Patent 4,676,976
9. Miyazaki S et al (2009) Drug Dev Ind Pharm 35(7):780–787
10. Itoh K, Hatakeyama T, Shimoyama T, Miyazaki S, E'Emanuele A, Attwood D (2011) Drug Dev Ind Pharm 37(7):790–797
11. Miyazaki S, Kawasaki N, Endo K, Attwood D (2001) J Pharm Pharmacol 53(9):1185–1191
12. Ross MSF, US Patent 6,102,254
13. Mehta R, Moros D, US Patent 6,656,482
14. Williams P, US Patent 7,208,480

Chapter 13
The Challenge of Automated Compounding

Daniel Bar-Shalom

Abstract In an ideal world, doses of medicines would be tailored for the specific patient with the specific condition. If combinations are indicated, preferably, all drugs would be administered in one oral dosage form once or twice daily and the taste of the drugs would be concealed. The dosage form would resemble something children are used to intake. We are not there, but we might get there some day.

For now, microencapsulation seems to be one path to conceal the taste of drugs, to prevent drug–drug and drug–excipient chemical incompatibilities and, if possible, for modified release. Fast-hydrating dry granulates which swell into pudding-like vehicles have been developed as carriers for the microencapsulated drugs. Robots can accurately dispense the prescribed drugs into appropriate packages, but US and EU registration procedures so far could not handle drug registration within the framework of automated compounding. This might be the challenge of coming years and decades.

The technical challenges in producing the components are examined, analysis procedures evaluated and the regulatory aspects are tentatively discussed.

13.1 Introduction[1]

Children constitute a very special, heterogeneous population group; they are rather picky about the taste, smell, and texture of food and medicine [1]. Many, if not most, hospitalized children require multiple drug therapies [2, 3]. Many drugs are not

[1] Please refer to the chapter "The Compounding Pharmacist: Training, Sources, Creativity in Compounding" by Linda F. McElhiney in this book.

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available in pediatric-specific formulations, the result being that the children get "magisterial" or "compounded" reformulations of adult drug-products.

Maybe the time is ripe for a new approach, comparable to the switch from paper-based literature towards e-books, e-mails, and e-reading. This would be the replacement of ready-to-use pills, liquids, or other pharmaceutical forms by a personalized, customer-adapted general formulation based on microencapsulation which is then compounded automatically, and at the end of the physical formulation pathway administered to the patient. This may appear as a technical challenge at first glance. It is not, most of the components are available. Properly approached, this path to a solution would include the regulatory aspects of drug development and hence the entire drug development process. But it would in the far or not so far future replace today's rigid regulatory requirements by an easy technical solution. So it's worth to consider.

13.2 The Situation

As a rule, each drug must be formulated separately as a liquid or semi-solid formulation, unless the compatibility information is available, because chemical reactions between different drugs are unpredictable and cannot be assumed not to happen. Furthermore and because of time constrains, most magisterial formulations cannot be fully optimized for taste, the result being that the children get sub-optimal formulations one after the other leading to increasing reluctance to accept the next one. In addition, it is very difficult to ensure that the dose is uniform from day to day as sedimentation and stability issues are common for liquid preparations. Finally, the whole process is extremely expensive as it requires inordinate amounts of pharmacist time (for reformulation) and nurse time (for administration) and the dosage is, at its best, erratic in terms of uniformity.

While 35 % of the commercially available drugs in Europe are authorized for use in children, 80 % of prescriptions for children at hospitals are unlicensed or off-label. The oral pediatric market is characterized by consisting of a few large therapeutic areas. An informal review of magisterial formulations in one of the two Dutch hospitals specializing in pediatrics showed that approximately 15 drugs appear in more than 90 % of the dispensed oral preparations. This number seems to apply in other countries too (personal communications). In a survey of the oral compounding at hospitals in New Zealand, revealed a comparable situation [4]. A study of the European situation reveals many problems and pitfalls in the present situation [5] and a review explores the intricacy of pediatric compounding [6].

13.3 Dosage Form Components

13.3.1 Microencapsulation

Masking the taste of a drug by adding sweeteners and flavors is difficult. Masking the taste of a number of drugs in combination amplifies the problem. It is therefore suggested to microencapsulate each drug separately and use the microencapsulated drug as the standard "active ingredient" in the compounding. The microencapsulation for *taste concealing* is addressed in the chapter "Flavor is not Just Taste: Taste Concealing" by Charles Frey in this book. However, it must be mentioned that poorly soluble drugs pose a special problem in that they display a tendency to remain in the microencapsulate after exposure to water and therefore creativity must be invested to solve this particular problem [7, 8].

To address the danger of chemical interactions between the individual Active Pharmaceutical Ingredients (APIs), the possibility of exploiting microencapsulation has been studied and it seems to be possible to combine taste concealing with prevention of chemical interactions. In this study, Aspirin and Ranitidine—both white powders—were found to react when place, dry, in the same vial to form a nasty-dark green substance in days. The microencapsulated drugs, under the same conditions did not react or the reaction was delayed considerably [9].

Finally, there is the option of using the microencapsulation also to achieve controlled release with drugs requiring frequent administration.

The particle size of the microencapsulate should, on the one hand, be so large that the particles cannot lodge themselves between the papilla on the tongue (over 50 μm?). This is speculation because, as usual, there is a dearth of information about children. On the other hand, large particles would result in a gritty pudding reducing acceptance (less than 200 μm? [9]). The "acceptable" size varies with the texture of the vehicle and the characteristics of the particles [10]. Caveat: The information is mainly derived from adult studies but a study by Segovia et al. showed that: children had higher papillae and taste pore densities, smaller papillae, smaller pore diameters, and the papillae had a more consistent rounder shape than those of adults. The higher papillae and pore densities may account for the greater sensitivity of children in small regions of the anterior tongue to sucrose. And further that: the taste system of children does not appear to be able to fully integrate this greater local sensitivity as indicated by adults having higher whole-mouth sensitivity. These latter data suggest that the innervation of fungiform papillae and taste buds is in a state of incomplete organization and that central neural pathways are not developed fully in mid-childhood [11]. To further complicate all this, it must be remembered that the tongue is covered with mucus and that the tongue may be fissured—Plicated Tongue—the incidence of this being reported in children to be between 0.5 and 29.2 % in different population groups [12]. Food might be trapped in fissures (and so may particles too) [13].

13.3.2 Pudding Granulate: "Dry Pudding"

Note: The word "pudding" is used here to indicate a semi-solid vehicle. You may substitute with your favorite; yoghurt, porridge, puree, and so on. "Dry Pudding" is used to denote the components of the vehicle before hydration. The appearance, consistency, texture, taste, and so on can be adjusted.

One way of addressing those problems can be the development of simple but very fast-hydrating formulations. It is possible to produce a combination of Gellan, sugar and flavor that swells into a pudding-like gel in 4–20 s after exposure to water [14], the shorter the better and it is assumed that less than 30 s from the moment the water is added until the pudding is ready is acceptable. More work is needed here.

Work at the School of Pharmaceutical Sciences, University of Copenhagen has shown that other agents, including Xanthan, Guar and Locust Gums, Cellulosis and Carrageenan can be used too in formulating mixtures and/or granulates capable of hydrating in less than 40–60 s. The basic composition investigated was Polymer-Sugar-Flavor. There are many possible combinations such as Hydroxy-Propyl MethylCellulose (HPMC)-Maltitol-Vanillin or Carboxy-Methylcellulose (CMC)-Sucrose-Vanillin or Xanthan Gum-Maltitol-Vanillin and so on. For flavor, Vanillin was the first choice as it is a stable, single molecule flavoring agent and usually well accepted by children [15], it also enhances the perception of sweetness [16]. The choice of sugar is not trivial. Different sugars, in combination with a given polymer at the same ratio, result in "puddings" with different viscosities, stickiness, mouthfeel, and so on. Some sugars are sweeter than others, some have a "cooling" effect, some are cariogenic, some indigestible by humans, some can be used by colonic bacteria, some are contraindicated in diabetes, some have laxative properties, and so on [17].

It was contemplated that, in some cases, it would be desirable to adjust the pH of the pudding so that eventual enteric coatings would not dissolve in the vehicle, even before reaching the stomach. HPMC and Xanthan Gum are examples of non-ionic polymers that could be used together with acidifiers such as citric or malic acid while CMC-based puddings lost viscosity at low pH. In this cases, it seemed more appropriate to use Berry or Citrus flavoring rather than Vanillin because the formers are associated with "acid" while the latter is with "sweet" and it is important to harmonize all the organoleptic parameters as described in the chapter by Per Møller in this book. Conceivably, it is possible to adjust the particle sizes of all components of the dry pudding and ensure a satisfactory uniformity of content when dosed but it is probably best to granulate the components to a particle size similar to that of the microencapsulated drug.

Evaluation of the pudding is challenging because small children cannot report and older ones might report what they feel the questioning person wants to hear [18]. That said, a pudding without drug can be regarded as just a (food) pudding and thus tested in children as food rather than medicine. The food industry has developed tools for evaluating food in children [11]. The Gellan pudding mentioned in [1], has been tested (for acceptance), without drugs, in kindergarten children in Denmark by Teknologisk Institut [19]. Such an approach is helpful in determining

the preferences of a given group of children; as an example, in that test, children preferred the strawberry-flavored pudding over the others but preferred the *red* pudding over the "off white" (not colored, which they found "strange") but both were identically strawberry-flavored.

Once the pudding parameters have been addressed, tools to ensure quality must be found. Rheometers and in particular Texture Analyzers were found to be very informative but more work is needed here in particular when evaluating puddings with particles [20–23].

13.3.3 Putting It Together and Testing the Administered Product

The granulate is mixed with the microencapsulated drug(s) and packed (see below). The care-giver adds a measured amount of water and the granulate swells within seconds into an (hopefully) appealing pudding where the microencapsulate is more or less homogeneously dispersed. The microencapsulate is supposed to release the drug(s) upon reaching the stomach or the duodenum, for enteric coated particles, the duodenum onwards. From a quality assurance point of view, two challenges arise: (1) Rheometers and Texture Analyzers results are affected by suspended particles and (2) the patency of the taste concealing should be examined.

The interval from the moment the care-giver adds the water until the pudding passes the oral cavity and throat may vary, the child or the care-giver may be distracted and the actual ingestion delayed. If the particles release drug(s) too early, the taste concealing is defeated. This can be the subject of a consumer test but that is time consuming. In the work described here, the assumption is that the taste concealing should keep the drug concealed for 5–10 min. Instrumental testing of the release in the pudding (prior to ingestion) was challenging in that conventional methods either require extraction and separation steps which might result in false positives (HPLC) or where the gel interferes with the transparence (Spectrophotometry). An emerging technique, the UV Imaging, could directly visualize the release (or the lack of release) from individual particles in the gel. The instrument used was ActiPix SDI300 (Paraytec Ltd, York, UK) [24, 25] and it proved possible to follow the release of the drug and even quantify it [26]. Figures 13.1–13.4 illustrate the release of drug from the particles.

13.3.4 Packaging

The combination of microencapsulate and granulate (Dry Pudding) has to be packed in a container to ensure its stability and to facilitate its handling. A number of solutions are possible: a sachet or a capsule to be emptied onto a measured amount of water (a cup or a spoon, for example) or the Dry Pudding might be packed in the

Fig. 13.1 Particles in pudding after 10 s

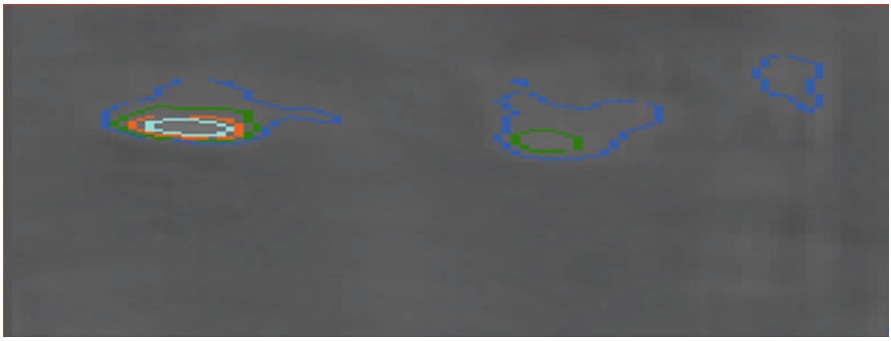

Fig. 13.2 After 60 s

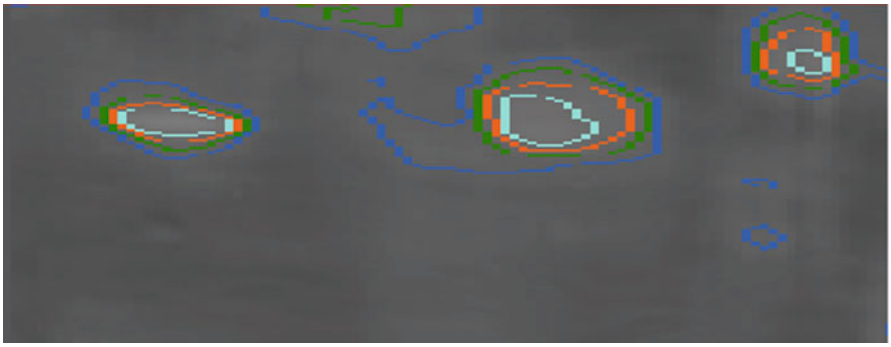

Fig. 13.3 After 10 min

final container such as a disposable cup or spoon or, for younger patients, a syringe for oral dispensing. The packaging should also make the dispensing reliable and uncomplicated. Here, as in the development of the granulate, inspiration can be abundantly found in the food industry.

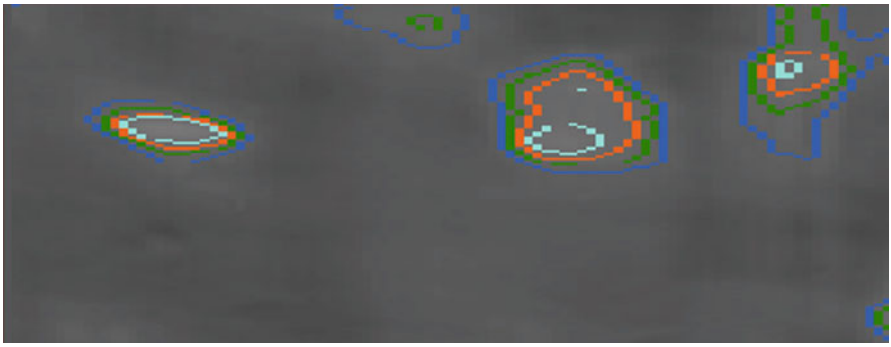

Fig. 13.4 After 30 min

13.4 Dispensing

13.4.1 The Robot

The vision is to have a robot able to accurately dispense the microencapsulated particles and the granulate into the packaging containers. Such instruments exist and are, in fact, routinely used in pharmaceutical and other industries. They are able to dispense powders, liquids, particles, and semi-solids (Fig. 13.5).

The machines are modular and can be mass produced reducing their price. An example of the vision is to use an automatic dispensing machine (robot) with a number of receptacles for containers each carrying one microencapsulated drug and one reserved for the granulate. The receptacles are designed to accept only the proper container with the appropriate drug in a lock-and-key fashion.

One aspect that needs to be addressed (but has not been deal with at the time of this writing) is the mechanical robustness of the microencapsulated drugs when dispensed by the robot.

13.4.2 The Software

Using a computer to control the robot opens for interesting additional features: after the prescription is keyed into the computer (or electronically sent by the prescriber), it is checked for apparent inconsistencies (e.g. against the age or mass of the child) and for pharmacological drug-to-drug incompatibilities. The results of the analysis are presented to the pharmacist whom ultimately decides “go/no go” thus assuming the responsibility.

Fig. 13.5 Robot dispensing a powder. The "holder" is an analytical balance. Picture courtesy of Chemspeed Technologies AG

13.4.3 Finishing the Product

The pharmacist approves the prescription. The robot doses the needed microencapsulated drugs in the proper amounts into the individual packaging followed by the proper amount of granulate and seals the packaging. The individually packed doses are labeled stating the patient's identity and the time of dosage (eventually electronically labeled with barcode or similar to further safeguard against errors and enable "App-control" in recording the actual time of administration) and filled into a secondary packaging.

13.5 Regulation

The concept of automated dispensing is not, in itself, new. Automated dispensing of chemotherapeutic agents has been around for some time and is credited with prevention of errors. Conceptually the concept presented here does not differ from the chemotherapy case. Eventually the regulatory agencies might have to be consulted, or not, depending on the legal pathway interested hospitals, machine producers, software developers, etc. It is a way to re-empower the pharmacist and it is a path towards individualized/personalized/customized oral therapy.

13.5.1 Validation in Polypharmacy

As pointed above, having two drugs in the same vessel, even in the dry state, is not without dangers. There is a comprehensive literature on API–excipient incompatibilities [27, 28] but little about API–API incompatibilities (while logic says that APIs are more "reactive" than excipients and therefore the chances of chemical interactions increased) and therefore all microencapsulated drugs must be tested against each other, against the dry pudding and in all possible combinations. The expectation being that the proper encapsulation will prevent the interactions through the proper choice of excipients and techniques.

13.6 Cost

One of the main obstacles the pharmaceutical industry sees in formulating for children is that the target population usually is a marginal part of the total population, the exception being, of course, products specifically developed for pediatric conditions. This is aggravated by the fact that children are an heterogeneous lot, often requiring dose-tuning. If a pharmaceutical company could clinically test a drug in the microencapsulated way outline above, validate it for use in this context, register it in this way, and then market it in this way, this particular obstacle would be removed.

Having to test just one product for the whole age range (and for that matter, including adults unable to swallow tablets and capsules) and marketing it as an ingredient for compounding, should result in significant savings compared with multiple dosage forms or strengths and with having to have primary and secondary packaging and leaflet and so on.

13.7 Conclusions and Perspectives

A concept as described above is a just proposal. It might prove valuable in preclinical and clinical development and in marketing of drugs for children and for adults with swallowing difficulties. It might serve as a basis for modifications, expansions or elements of it might inspire other. It can, potentially, alleviate the problems of polypharmacy and it might lead to the reduction in incidence of errors. The main message remains, children are a new "species" as long as oral formulations are concerned and therefore we must learn all we can about them, research where information is not available and use our creativity. It cannot be emphasized enough how much the food industry can help us in achieving the goal of developing adequate oral medicines for our children.

References

1. Bar-Shalom D (2011) Am Pharm Rev (September 1)
2. Feudtner C, Dai D, Hexem KR, Luan X, Metjian TA (2012) Prevalence of polypharmacy exposure among hospitalized children in the United States. Arch Pediatr Adolesc Med 166(1):9. doi:10.1001/archpediatrics.2011.161
3. Morden NE, Goodman D (2012) Pediatric polypharmacy: time to lock the medicine cabinet? Arch Pediatr Adolesc Med 166(1):91–92. doi:10.1001/archpediatrics.2011.162
4. Kairuz T et al (2007) Extemporaneous compounding in a sample of New Zealand hospitals: a retrospective survey. N Z Med J 120(1251):U2466. http://journal.nzma.org.nz/journal/120-1251/2485/content.pdf
5. Brion F et al (2003) Extemporaneous (magistral) preparation of oral medicines for children in European hospitals. Acta Paediatr 92(4):486–490
6. Ernest TB et al (2012) Preparation of medicines for children: a hierarchy of classification. Int J Pharm 435(2):124–130
7. Manal A, Sema O (2012) Formulation of microencapsulated active pharmaceutical ingredients for oral administration in a semi-solid formulation for UNICEF-children. Master Thesis, University of Copenhagen (September)
8. Lucka B. Master's Thesis, University of Ljubljana, Slovenia (in preparation)
9. Hounsgaard AM (2011) Formulation of microencapsulated particles for taste masking and hindering of drug incompatibility for geriatric and pediatric combination products. Master's Thesis, School of Pharmaceutical Sciences, University of Copenhagen
10. Lawless HT, Heymann H (2010) Sensory evaluation of food: principles and practices. Springer, Berlin
11. Segovia C et al (2002) A quantitative study of fungiform papillae and taste pore density in adults and children. Brain Res Dev Brain Res 138(2):135–146
12. Vörös-Balog T et al (2003) Prevalence of tongue lesions in Hungarian children. Oral Dis 9(2):84–87
13. Byrd JA et al (2003) Glossitis and other tongue disorders. Dermatol Clin 21(1):123–134
14. Bar-Shalom D et al (2012) US Application 20120039969
15. Rowe RC, Sheskey PJ, Siân CO (2006) Handbook of pharmaceutical excipients, fifth edition. Pharmaceutical press 798–799
16. Labbe D et al (2007) Subthreshold olfactory stimulation can enhance sweetness. Chem Senses 32:205–214
17. Bornet FR (1994) Undigestible sugars in food products. Am J Clin Nutr 59(3 Suppl): 763S–769S
18. Matsui D (2007) Assessing the palatability of medications in children. Paediatr Perinat Drug Therapy 8(2):55–60
19. Data on file, Egalet a/s, Værløse, Denmark
20. Canan A, Manmeet KS (2011) Design of vehicles for oral medication of heterogeneous groups, based on mass medication scenarios and inspired by food science. Master's Thesis, School of Pharmaceutical Sciences, University of Copenhagen
21. Bjørnsholt P, Seric S (2013) Development and characterization of a fast hydrating semi-solid formulation for oral pediatric use based on cellulosics. School of Pharmaceutical Sciences, University of Copenhagen
22. Wren S, Lenke J (2011) Am Lab (February)
23. Coban C, Bircan G (2013) Investigation of non-ionic cellulosics for development and characterization of semi-solid dosage forms for pediatric patients. Master's Thesis, School of Pharmaceutical Sciences, University of Copenhagen
24. Wren S, Lenke J (2011) Pharmaceutical dissolution and UV imaging. J Am Lab 43:33–36
25. Ye F, Yaghmur A, Jensen H, Larsen SW, Larsen C, Østergaard J (2011) Real-time UV imaging of drug diffusion and release from Pluronic F127 hydrogels. Eur J Pharm Sci 43(4):236–243

26. Bar-Shalom D et al (2013) New applications of UV imaging in stability testing: release of drug from coated particles in pediatric semi-solid dosage forms, controlled release annual meeting
27. Bharate SS et al (2010) Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients. J Excipients Food Chem 1(3):3–26
28. Wu Y et al (2011) Reactive impurities in excipients: profiling, identification and mitigation of drug–excipient incompatibility. AAPS PharmSciTech 12(4):1248–1263

Chapter 14
Pediatric Formulations in Clinical Testing and the Challenge of Final Market Formulation

Norbert Pöllinger

Abstract Age-appropriate medicines are required to allow compliance with treatment and safe delivery of a pediatric drug product. As drug products for adults are often not suitable for use in children, new pediatric formulations must be specifically developed.

14.1 Introduction

Pediatric clinical studies are usually initiated both for exploratory dose-finding study and for pivotal efficacy and safety confirmatory studies. Ideally, the pediatric formulation intended to be commercialized should be used for the complete development program. Similar to clinical programs with adults, a change of the formulation during clinical testing should be avoided wherever possible.

The taste of oral dosage forms must be acceptable—palatability has become an integral part of pediatric formulation development to ensure the acceptance of medicines by children. As palatability is an important feature of PIP, simple enabling test formulations not solving the taste issue may not be useful for relevant clinical studies.

For pediatric drug products the micropellet concept is considered to be of particular interest as it provides a number of child-friendly forms including taste masking.

With micropellets many different formulation variations and dosage strengths are made available: oral suspensions, sachets and stickpacks, dispersible tablets and orally dispersible tablets (ODTs), MUPS tablets, and capsules. Fixed dose combinations and the application of micropellets with devices such as drinking straw or

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dose sipping syringe are additional options. Micropellets can be applied in a liquid form such as a suspension even to neonates which is not possible with larger sized solids dosage forms such as microtablets.

Depending on the pediatric age groups, adult formulations may not be suitable for use in children, and new pediatric formulations must be specifically developed for the pediatric studies, and for the market [1]. The physical, metabolic, and psychological processes inherent to growth from birth to adulthood reveal that children cannot be regarded as small adults nor can they be regarded as a homogenous group in themselves. As a consequence, clinical trials in adults are not necessarily predictive for children. Thus, in many cases clinical trials will be needed in children of different ages in order to demonstrate that a pediatric medicine is safe and effective in all of the target age groups for which the medicine is being developed [2].

The EU pediatric regulation mandates a pediatric investigation plan (PIP) for any new medicine at the end of human pharmacokinetic studies or after proof of concept. The European Medicines Agency (EMA) will not validate a submission without an approved PIP which must address the potential future use of the drug for all pediatric groups from preterm newborns to adolescents. US FDA would review the pediatric plan (PP), but pediatric discussions will not impede adult registration [3].

In this chapter potential formulation approaches for oral solid pediatric dosage forms are considered. With the example of taste-masked micropellets a formulation development scenario is demonstrated.

14.2 Pediatric Clinical Development and Pediatric Formulation Development

Pediatric clinical studies are usually initiated when data have been collected in adult patients, which provide the opportunity to learn from knowledge in adults. Ideally, both safety and efficacy have already been established in adult patients in the same indication (Fig. 14.1).

A two-step pediatric clinical development approach could be applied.

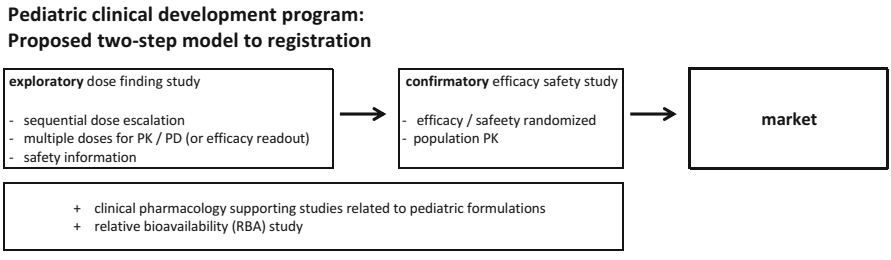

Fig. 14.1 Pediatric clinical development programs

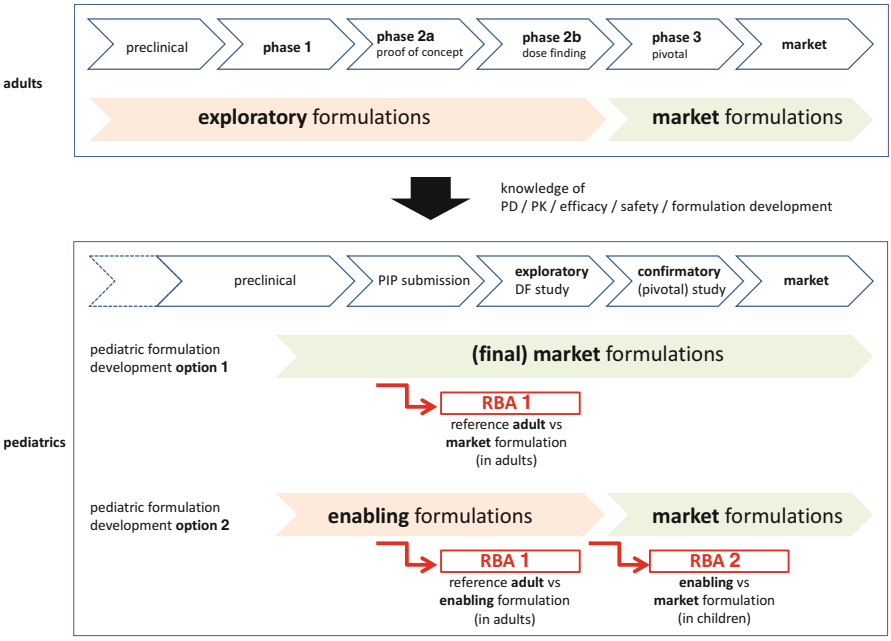

Fig. 14.2 Clinical and formulation concept for pediatrics

In order to keep the extent of changes in PK and PD (safety, efficacy) as little as possible between the exploratory and confirmatory phases, the *exploratory* dose-finding study should ideally from clinical pharmacology point of view be conducted with the final pediatric formulation (market formulation). If a preliminary enabling formulation were to be used in the exploratory study, changes should be carefully assessed in terms of possible impact on PK and PD of the drug.

The *confirmatory* study is the pivotal efficacy and safety study. The confirmatory trials should always be conducted with the final to be marketed pediatric formulation.

Similar to adult clinical programs, a change of the formulations used in the confirmatory study and in the market triggers the need for a pivotal BE study—a scenario which should be avoided wherever possible due to consequences of failure to establish bioequivalence (BE) [1].

Preliminary "enabling" formulations could be an option for early clinical pediatric trials. Applying this concept, supporting clinical studies such as relative bioavailability (RBA) must be taken into account to establish the bridge from adult and/or enabling formulation to the final pediatric market formulation [1].

In view of the need for a relative bioavailability study (RBA) required to compare an enabling and a market formulation, the resources and cost needed for the pediatric formulation development of both an enabling and a market formulation should be compared and assessed (Fig. 14.2).

Simple formulation concepts may not be applicable if taste masking or modified/controlled release must be achieved. Powder mixes or granules available from adult formulation development do not easily cover the requirements of taste masking or drug release as required for a pediatric medicine. The development and use of taste-masked and controlled release pediatric market formulations for early pediatric clinical studies could be justified even if longer lead times and resources may be required.

14.3 Oral Pediatric Formulations: General Considerations

The oral administration is the preferred route of administration. Oral dosage forms are well accepted in all age groups if administered in a suitable form allowing accurate and flexible dosing. When the taste is acceptable, oral liquids are favored by children. Ideally, medicines should be available in both liquid and solid oral dosage forms. Palatability has become an integral part of formulation development to ensure acceptability of medicines by children (quality part of PIP). While adults can overcome the innate reluctance to swallow a bitter pill, small children cannot make that educated decision. In particular bitter taste lingers longer than other tastes and cannot be simply overcome by adding other taste like a flavor. As a consequence, a bad taste must be encapsulated to render the taste imperceptible (Fig. 14.3).

	neutral tasting API	inconvenient tasting API	very bad tasting API
taste masking required ?	-	+	+++
Oral solid dosage forms			
granules	√	√	-
powders	√	√	-
minitablets *	√	√	√
micropellets			√
Oral liquid dosage forms			
solutions	√	√	-
suspensions	√	√	suspension with micropellets**
Taste masking approaches			
flavors	-	√	-
sweeteners	-	√	-
complexation	-	√	-
salt formation	-	√	-
cyclodextrins	-	√	-
coating	-	(-) (√)	√

* minitablets: applicable from age > 6 months

** suspensions: applicable from birth
suspension to be prepared with coated micropellets from sachet / stickpacks / dispersible tablets / capsules (single dose formulations) or as oral liquid (multi-dose suspension)

Fig. 14.3 Pediatric formulation concepts considering the taste of API

When oral pediatric drug products shall be developed a number of important aspects such as the dosage form, the topic of fixed or individualized doses, the potential combination of APIs, the excipients to be used, and the taste must be considered in depth. In addition, the specific age of the pediatric patients, the specific conditions to be treated, and the specific cultural and treatment settings must be taken into account. Dosage forms which facilitate the administration of a range of doses and that are acceptable to children of different ages are helpful for meeting a broad range of children's needs. It is the objective of the Pediatric Regulation to develop formulations and preparations which will be industrially manufactured and controlled [2].

Pediatric oral dosage forms must be age-appropriate. Industry considers flexibility in choice of excipients and dosage forms essential. In each case a justification on the basis of science and risk/benefit must be provided.

Liquid oral dosage forms such as syrups, solutions, or suspensions are applicable to neonates (0–28 days), infants (1 month to 2 years), young pre-school children (2–5 years), children (6–11 years), and adolescents (12–18 years). On the other hand, powders, granules, pellets, tablets, and capsules applied as such are barely acceptable or unacceptable for the very young patients [4].

Normal-size tablets or capsules are not applicable to children. Breaking tablets is often not precise and not applicable to coated tablets as functional coatings providing, e.g., taste masking would be destroyed. Minitablets with a diameter of 2 mm are applicable to children from 6 months [5].

For pediatric drug products the spectrum of pharmaceutical excipients is limited. To make a choice for an excipient not only the technological characteristics and properties are to be considered, but safety, the duration of treatment, potential side effects like allergies and sensitization must also be taken into account. Well-known excipients should be preferred but novel excipients cannot be excluded completely (e.g., coating polymers). In pediatric formulations, the concentration of excipients should be limited as much as possible. Providing modern and high quality medicines for children without having the full excipient spectrum available can be a challenge.

14.4 Micropellets: A Technology Platform for Pediatric Medicines

Powders and granules may be a convenient option to prepare pediatric medicines when the taste of a drug is not bad and palatability is good with simple taste "adjusting" applications such as adding flavors and sweeteners.

When a bad tasting API must be formulated to a pediatric medicine, the micropellet concept is a potential option as it provides a complete encapsulation of the bad tasting drug. Micropellets can be applied in liquid forms such as suspensions even to neonates which is not possible with microtablets.

Micropellets are spherical particles with a particle size <500 μm.

Micropellet formulations can be processed using accepted excipients and established cost-effective industrial processes.

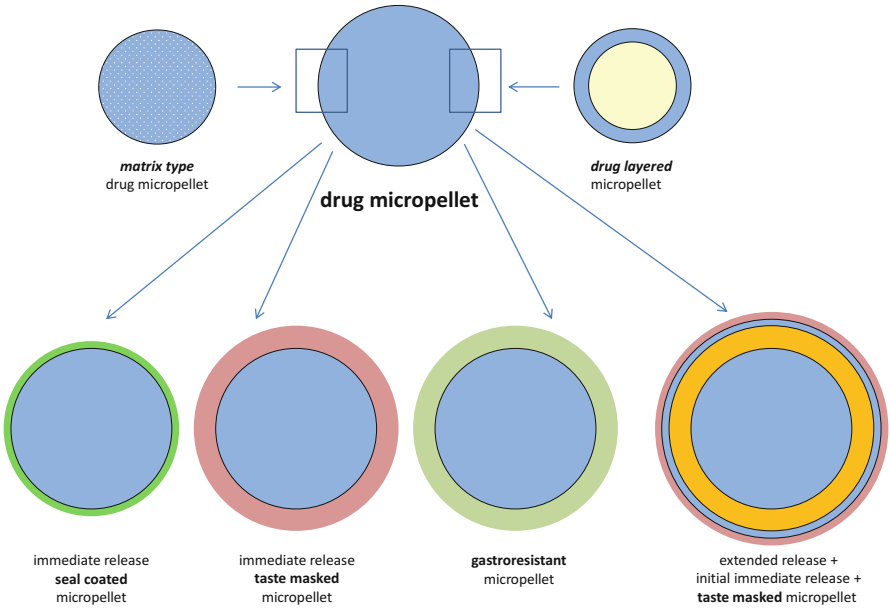

Fig. 14.4 Different micropellet formulation a

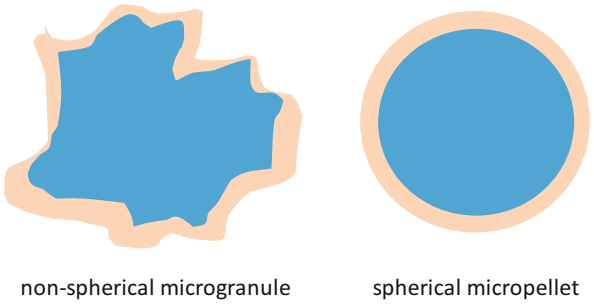

Fig. 14.5 Coated microgranules and micropellets

Micropellets are considered to be a promising pediatric formulation approach allowing many different formulation variations and dosage strengths with one single multiparticulate formulation (Fig. 14.4).

Spherical micropellets of said size are an ideal substrate for Wurster fluid bed coating applications of any kind. Due to their spherical shape and smooth surface and thereby not too big surface area, less coating material is required than for the coating of powders or irregular-shaped granules. As for pediatric medicines as less as possible excipients should be used, this can be considered as an advantage for pediatric formulations (Fig. 14.5).

A broad spectrum of micropellet types are available.

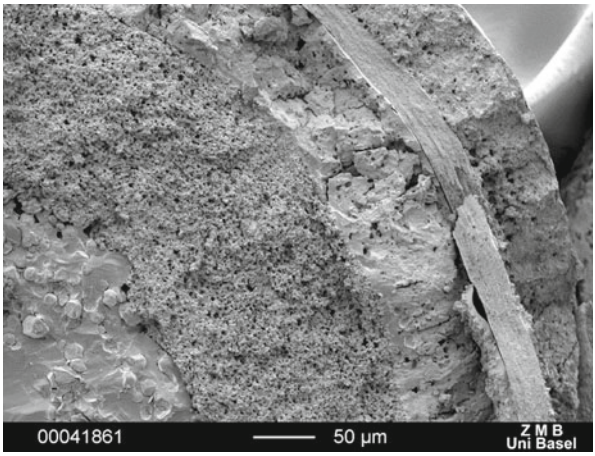

Fig. 14.6 SEM picture of complex micropellets

The manufacturing processes for micropellet processing are established industrial manufacturing processes available from lab to commercial scale. Industrial scale up of micropelletization and micropellet coating processes is a state of the process (Fig. 14.6).

Micropellets allow access to a broad variety of formulation options for pediatric medicines:

- Oral suspensions (ready to use/to be prepared from a dry suspension with aqueous or non-aqueous liquids; multiple dose preparation)
- Sachets and stickpacks
- Dispersible tablets
- Orally dispersible tablets (ODTs)
- MUPS tablets
- Fixed dose combinations
- Capsules (capsules to be swallowed or to be used as package of a single dose)
- Application of micropellets with devices (e.g., drinking straw, dose sipping syringe)

14.5 Pediatric Oral Dosage Form Development for Clinical Testing and Market

The goal is to develop relevant and acceptable pediatric formulations with convenient and precise dosing characteristics on an industrial scale suitable for marketing at affordable cost. The procedure is demonstrated using the micropellet formulation approach (Fig. 14.7).

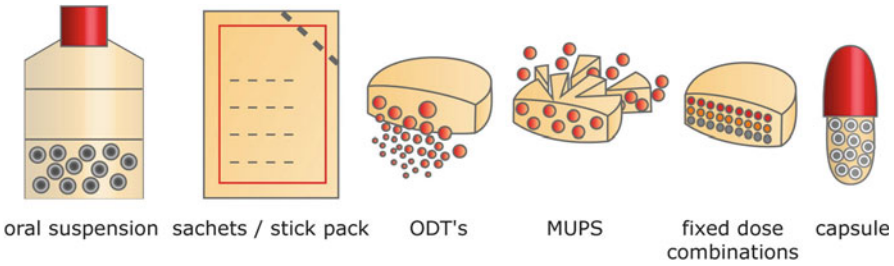

Fig. 14.7 Pediatric drug products with micropellets

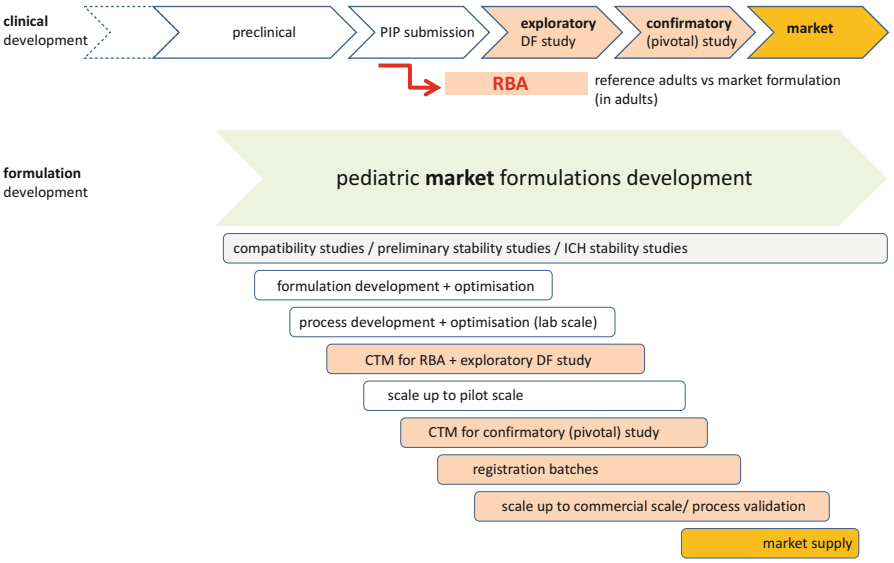

Fig. 14.8 Pediatric formulation development: final market formulation for clinical development

When a pediatric market formulation is to be developed for an RBA study (comparison of pediatric formulation with adults reference formulation in adults) and early exploratory as well as pivotal confirmatory pediatric clinical studies, the basic drug product formulation concept must inherently allow for sufficient flexibility with respect to different dosage strengths and different ages. For the different pediatric groups different dosage strengths must be made available ideally with one basic formulation (Fig. 14.8).

With the micropellet technology platform a high flexibility in the pediatric field is achieved:

- Different dosage strengths with one micropellet quality
- Fixed and individualized doses possible
- Enhancement of solubility and bioavailability (coprecipitates, adsorbates, solubilisates)

- Broad variability of drug release profiles achievable (immediate release/gastro-resistant/modified release micropellets including taste masking)
- Taste-masked micropellets allow for different application forms such as oral liquids, sachets, stickpacks, dispersible tablets, ODTs, MUPS, minitablets, capsules
- Micropellets to be sprinkled on semi-solid food or applied with devices like straws and sipping syringes
- API combinations combining micropellets with different APIs

As palatability is a standard feature in PIP, the taste-masking requirement must be fulfilled in clinical development from the beginning. Simple taste-masking concepts are not applicable for very bad tasting drugs. From that point of view, an efficient taste-masking technology must be used.

The knowledge from adult formulation development should be used as far as possible for pediatric formulation development in order to achieve optimal results with reasonable resources.

Excipients compatibility studies and basic stability data should be available early and can be planned in an overall adults/pediatric formulations development concept.

14.6 Taste-Masked Antibiotic Micropellets: A Case Study

Taste-masked micropellets containing a high-dosed extremely bitter antibiotic drug were developed. A 250/500 mg dose should be presented in an oral liquid (Fig. 14.9). The particle size of the high drug loaded micropellets was specified to be smaller than 500 µm (Fig. 14.10). The taste masking of the micropellets should be stable for 14 days in an aqueous suspension. Nevertheless, a fast dissolution of the antibiotic at neutral pH was requested (Fig. 14.11).

The basic formulation concept is based on two main processing steps:

- Matrix micropellets manufactured out of the crystalline API; particle size of the spherical and smooth matrix micropellets: ~200–400 µm; yield: ~95 %;
- Application of a seal coat and a taste-masking coat on top of the matrix micropellets resulting in a particle size of <500 µm; yield: >95 %;

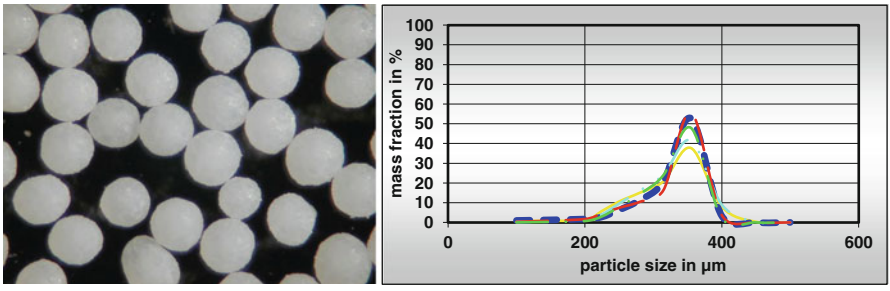

Fig 14.9 Matrix type antibiotic micropellets made with MicroPx technology

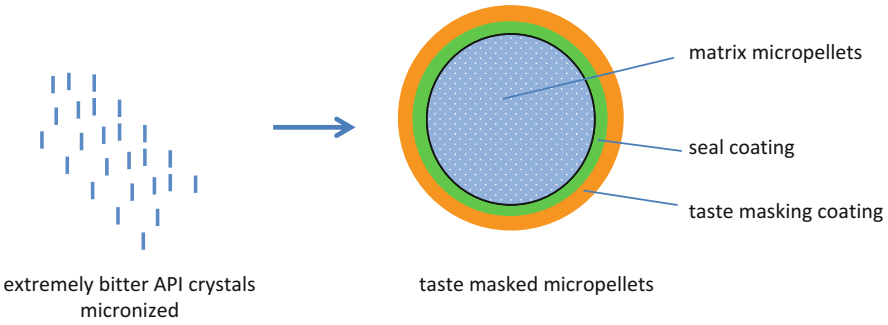

Fig. 14.10 Formulation concept of taste-masked micropellets

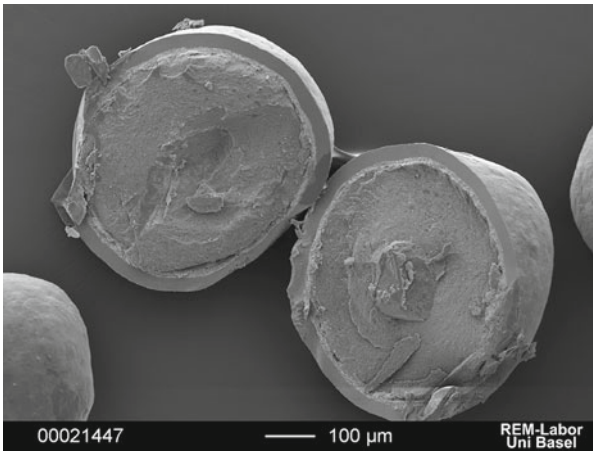

Fig. 14.11 Taste-masked antibiotic micropellets

14.7 Conclusion

Different formulation concepts and scenarios up to registration and commercialization are considered. Pediatric formulation usually starts when an API has been evaluated in adults up to the proof of concept phase. At this time, basic results concerning pharmacokinetics, pharmacodynamics, and safety have been established. In view of the knowhow which can be transferred from adult studies, pediatric clinical development studies may preferably be performed with the final market formulation rather than with preliminary enabling formulations. As palatability is an important feature of PIP, simple test formulations not solving the taste problem are not useful for relevant clinical studies.

By this means it is quite likely that registration may be achieved with one relative bioavailability study only. On the other hand, when pharmaceutical drug product

development starts with a preliminary enabling formulation and later switches to the final market formulation, a second RBA must be performed. This assumption should be considered as an integral part of drug product development.

Micropellets are considered to be a flexible pediatric technology platform allowing a broad variety of oral drug products for children. Palatability is adequately covered with taste-masked micropellets. Said relevant and acceptable pediatric micropellet formulations can be manufactured with established technologies and produced in any industrial scale for commercialization at affordable cost.

References

1. Ricci B (2012) Bridging studies in support of pediatric formulation development. In: EuPFI 4th conference, Prague
2. Guideline on pharmaceutical development of medicines for pediatric use; EMA/CHMP/QWP805880/2012, p 4/24
3. Rose K (2012) A paediatric investigation plan case study. Pharm Med 26(5):287–295
4. Sam T (2011) Exploring a risk management: approach towards developing the optimal paediatric formulation – applying quality by design and multi-criteria decision making. In: EuPFI 3rd conference, Strasbourg
5. Klingmann V, Spomer N, Stoltenberg I, Lerch C, Meissner T, Breitkreutz J (2011) Acceptance of drug-free minitablets in young children. In: EuPFI 3rd conference, Strasbourg

Chapter 15
Buccal/Sublingual Drug Delivery for the Paediatric Population

Viralkumar F. Patel, Darragh Murnane, and Marc B. Brown

Abstract Oral mucosal drug delivery has emerged as a potential route of drug administration which represents a strategy of maximising the availability of the oral route for easy administration without the need to swallow a dosage form whilst offering the possibility of local delivery and direct access to the systemic circulation thus avoiding first pass metabolism. However, changes in anatomical, physiological and biochemical functions that occur from birth to adolescence are required to be considered when designing such formulations. Currently marketed formulations include liquids, semi-solids and solid dosage forms; however, there is significant research in developing alternative dosage forms for oral mucosal delivery such as nanotablets, films, microparticles and mouth sprays which is partly due to problems (e.g., posology or excipients present in formulation) associated with using currently marketed products in children. Despite the development of novel technologies including NanoTabs and mucosal sprays, there still remains relatively few products approved for use in the paediatric population. This is likely explained by the fact that alongside the normal problems that need to be overcome during product development, additional issues including compliance, palatability, paediatric safety, the needs and capabilities of carers and the implications of global paediatric regulatory guidance need to be considered.

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15.1 Introduction

Recent legislation in the European Union (EU) and the United States (US) has led pharmaceutical companies to have to consider the paediatric population during the early stages of product development including the potential routes of administration of medicines appropriate for children [1–3]. Oral administration is the drug delivery route of choice in children with the exception of neonates where the parenteral route of administration is preferred [4]. However, there is increasing evidence of limitations associated with such enteric oral delivery in children including gastric intolerance, enzymatic degradation and first pass metabolism. A particular barrier to enteric oral delivery is the presentation of some age related disease conditions that affect swallowing (e.g., dysphagia). Thus, oral mucosal drug delivery represents a strategy of maximising the availability of the oral route for administration without the need to swallow a dosage form whilst offering the possibility of local delivery and direct access to the systemic circulation thus avoiding first pass metabolism [5]. However, there are many changes in the anatomical, physiological and biochemical functions of the oral mucosa that occur from the birth to adolescence that influence the pharmacokinetics and pharmacodynamics of a drug that need to be considered when designing such formulations for the paediatric population [6].

15.2 The Physiology of the Oral Mucosa and Its Implications for Paediatric Drug Delivery

The physiological development of the buccal/sublingual mucosa in children is difficult to predict and extrapolation of safety and efficacy data derived from an adult trial may not be appropriate for children of different age groups. The permeability of the buccal/sublingual mucosa of children is often greater than that of an adult mucosa for certain drugs due to the differences in physiology as well as factors such as salivary flow, enzymatic environment and the thickness of the mucosa [7]. In a study by Sonesson et al. [8] the rate of buccal salivary secretion in young children of 3 years of age was found to be lower than in adults as a result of underdeveloped salivary glands. This suggests that mucoadhesive formulations may be retained for a longer period of time at the site of application resulting in an increased concentration of drug being absorbed across the mucosa and subsequently a higher drug plasma concentration. In another study [7], the buccal administration of lidocaine patches in children of 2–7 years old produced a four to five times higher maximum plasma drug concentration (C_{max}) in blood compared to an adult population at 9 min. In addition the time to attain maximum plasma concentration after patch application was comparable in children and adults despite the patch application time being shorter in the former (5 min) compared to the latter (15 min). Obviously the relatively lower body mass and blood volume in children is thought to be one of the reasons for the higher C_{max} observed compared to adults. However, other investigators have

reported a trend towards decreased permeability to water with age especially in the sublingual mucosa of females [9]. The slight thinning of the epithelium with a concomitant flattening of the epithelial–connective tissue interface resulting in a more compact structure of the mucosa may be the reason behind this phenomenon [10]. Such differences need to be considered when evaluating the potential for efficacy and toxicity of a buccally/sublingually applied medicine in children.

15.3 A Review of the Currently Marketed Oral Mucosal Products for Drug Delivery in Paediatrics

The availability of approved products for paediatric use via the buccal/sublingual mucosa varies depending on the regulatory market area. Despite several products being marketed in the United States for buccal/sublingual mucosal delivery in adults, none are approved for a paediatric indication [11]. However, some products have been approved for paediatric indications in the United Kingdom and are summarised in Table 15.1. Such approved products span a range of dosage forms that are used for the treatment of systemic conditions as well as in the topical therapy of localised oral diseases. The marketed dosage form options include liquids, semi-solids and solid dosage forms, although currently there is significant research in developing alternative dosage forms for oral mucosal delivery such as nanotablets, films, microparticles and mouth sprays [5]. Liquid formulations including solutions, suspensions and emulsions are easy to administer and the dosage can be easily measured out. However, such dosage forms can present some issues with regard to short term stability and are generally bulky in nature, both of which can adversely influence the supply chain and increase cost, thus limiting their wider acceptability by both healthcare professionals and the pharmaceutical industry. Additionally liquid formulations typically require the use of preservatives and antioxidants to avoid microbial growth or spoilage for products intended for multiple dosing. However, the use of certain preservatives (e.g., Thiomersal) is not always desirable for paediatric therapies as they have reported toxicity in this lower age group population [12]. Other disadvantages can include that the residence time of the formulation in the oral cavity can be low [13] and the administered dose is often either swallowed or expectorated both of which can lead to poor drug delivery at or to the mucosal membrane.

Semi-solid dosage forms such as gels, pastes and ointments are an alternative to solutions especially where buccal residence of the drug is required for a prolonged period of time. Currently, gels are only the semi-solid formulation approved to be used in paediatrics via buccal/sublingual route (Table 15.1) and are intended typically for topical oral treatment (e.g., teething and anti-fungal gels). Solid dosage forms such as lozenges, tablets, capsules and films/wafers appear to be the obvious choice for development because of the improved drug stability, ease of manufacture and their less bulky nature all of which increases paediatric patient compliance and

Table 15.1 Summary of oral mucosally applied products available in the United Kingdom for paediatric populations

Name of the drug	Brand name	Name of company	Approved use	Approved age range	Comments	References
Buprenorphine hydrochloride	Temgesic sublingual tablets 200, 400 μg	Reckitt Benckiser Pharmaceutical Ltd	Treatment of moderate to severe pain	6 years or more	According to the SmPC, the dose for the children under 12 years of age is based on weight and is 1/2 tablet for children weighing from 16 to 25 kg, 1/2 to 1 tablet for 25–37.5 kg and 1 to 1 ½ tablets for 37.5–50 kg and should be given every 6–8 h. Hence the patient needs the dosages in fractions of tablets. As per the product description provided within the SmPC and patient information leaflet (PIL), Temgesic tablets are "round white tablets, marked with an L on one side and a sword on the other". It means that dividing the tablets into two halves may not be accurate as the formulation lacks the break line and thus could increase the chance of dosing error. This can impact the effectiveness of treatment. The physical and chemical stability of the formulation upon adaptation needs to be considered.	[14]
	Tephine sublingual tablets 200, 400 μg	Sandoz Limited	Treatment of severe pain following surgery or injury, myocardial infarction and severe pain associated with cancer	2 years or more or children weighing more than 16 kg	The recommended dose for Tephine sublingual tablet in a patient weighing 16–35 kg is 100 μg but according to the SmPC [15] the Tephine is not divisible hence it is of limited use in patients weighing more than 16 kg.	[15]
Midazolam hydrochloride	Buccolam oromucosal solution	ViroPharma Ltd	Treatment of prolonged, acute, convulsive seizures	3 months to <18 years	To be used by parents/carers in patients with confirmed epilepsy. Administration in infants must be carried out in a hospital setting where therapeutic monitoring is possible. The advantage of this formulation is that it is colour coded and pre-filled according to the strength of the formulation to reduce chances of under- or over-dosing.	[16]

Miconazole	Daktarin oral gel, Daktarin sugar free 2 % oral gel	Janseen-Cilag Ltd McNeil products Ltd	Oral treatment and prevention of fungal infections of the oropharynx and of superinfections due to Gram-positive bacteria	4 months or more	Despite being approved for the same indication, the products have a different posology and method of administration and hence there is an increased chance of error on switching the patient from a normal oral gel to the sugar-free formulation. For example, in the case of Daktarin oral gel, it is recommended to use one spoonful (5 ml) four times a day in children from the age of 6 years and over, one spoonful two times a day in children from the age of 2 to 6 years and half a spoonful (2.5 ml) should be used in children from the age of 4 months to 2 years [16]. In the case of Daktarin sugar free 2 % oral gel, it is recommended to apply a small amount of gel directly to the affected area with a clean finger four times a day in children from the age of 6 years and twice a day in children from the age of 4 months to 6 months with no indication of the quantity of the gel to be used despite such a huge difference in the child's age.	[17, 18]
Lidocaine hydrochloride, chlorocresol and cetylpyridinium chloride	Anbesol teething gel	Alliance Pharmaceutical	Temporary relief of pain caused by recurrent mouth ulcers, denture irritation and teething	No age restriction	Anbesol teething gel contains 66.605 % ethanol (alcohol), i.e. up to 0.754 ml per dose, which is equivalent to 15.1 ml beer or 6.3 ml wine per dose which may be harmful to children who may not have yet developed tolerance for alcohol or in children suffering from liver disease or epilepsy.	[19]
Dextromethorphan	Boot dry cough relief lozenges	The Boots Company PLC	Cough suppressant for the relief of acute non-productive (dry, tickly) cough associated with respiratory tract infection	6 years or more	Each lozenge contains 1.4 g of sucrose and 1.1 g of glucose. According to the normal dosing schedule, the patient is likely to take 9.8 g of sucrose (37.93 calories) and 7.7 g of glucose (30.8 calories) every day which may restrict use in patients suffering from type II diabetes or those with poor glucose control.	[20]

decreases the cost of goods. As such lozenges and tablets are the most commonly approved products for the buccal/sublingual route in paediatric patients (Table 15.1). However, where prolonged contact with the mucosa is required semi-solid formulations may offer greater paediatric acceptability than solid dosage forms as the former can be spread evenly and thinly over the mucosa rather than having to be deliberately retained and thus obstructing swallowing, eating and drinking.

15.4 Specific Difficulties with Using Marketed Oral Mucosal Products in Paediatric Therapy

Despite there being several marketed products demonstrating the applicability of oral mucosal delivery, several complications adversely influence the use of such commercialised medicines in many child treatment groups. For example, issues surround the posology, dose and excipients of such formulations making them difficult for use in children (Table 15.1). For example, Temgesic sublingual tablets need to be split in order to administer the required dose for children [14] yet there is an absence of a break line which would make dosage division easier and more accurate (Table 15.1). Tephine sublingual tablets are not available in a strength suitable (or even manually divisible) for children weighing 16–35 kg [15]. Another example is the case of Daktarin sugar-free gel where it is recommended to apply a small but undefined amount of gel directly to the affected area four times a day in children above 6 years of age and twice a day in children between 4 months and 6 years [18]. Also the presence of a high quantity of alcohol and sugar in Anbesol teething gel and Boot's dry cough relief lozenges, respectively, may restrict their use in certain paediatric populations such as those children who are either intolerant to alcohol or suffering from liver disease or epilepsy, or who are suffering with diabetes, respectively [19, 20].

Glyceryl trinitrate (GTN) provides an excellent example of an active pharmaceutical ingredient benefitting from the avoidance of first pass metabolism when administered via the sublingual route and was, in fact, one of the first drugs successfully developed to be delivered via the buccal/sublingual mucosa in adults. Currently, an injectable formulation is available for use in children to control hypertension as well as in heart failure [21]. However although conventional and sustained release buccal tablets and spray formulations have been developed for adults none are approved for use in children. In addition, although fentanyl has been formulated in lozenges, buccal tablets and recently in a thin film to avoid the extensive first pass metabolism when administered for oral enteric delivery, none are available for children less than 12 [22]. This is despite the same drug being used in injectable form and as transdermal patches for pre-operative analgesia and severe chronic pain, respectively, in children [23]. However, a study by Camacho Parreño et al. [24] reported off-label use of an oral transmucosal fentanyl citrate lozenge formulation for analgesia for bone fracture alignment in children. The author emphasised that transmucosal fentanyl could be used as an alternative to other pain medications but that more studies would

be required to establish effective and safe use of fentanyl in children. The obvious problem being whether such transmucosal medications can be manipulated to get the reduced dose required for paediatrics.

15.5 Current Research Trends in Oral Mucosal Drug Delivery

Previous research into the improvement of drug delivery via the buccal/sublingual mucosa has resulted in the development of several novel dosage forms like solutions, lyophilised and bioadhesive tablets and lozenges, chewing gum, solution sprays, laminated systems, patches, hydrogels, adhesive films, hollow fibres and microspheres [5]. Formulators have used creative approaches that incorporate a combination of strategies to create a balance between patient convenience and clinical benefits [5] but not all of these may be appropriate for use in the paediatric population. For example, bioadhesive formulations need to be kept within the mouth for longer period of time compared to conventional formulations to achieve the desired therapeutic outcome but children may not be compliant for such extended periods.

Palatability including texture, flavour and taste plays a major role in the compliance and concordance of children to treatment. Individuals differ in their experiences when tasting the same product as genetics plays a significant role in perception of palatability [25]. Taste in children is an even bigger problem because the sense of taste develops as the child grows [26]. It is reported that children have a stronger liking for sweet [27] and salty tastes [28] compared to adults, but yet they seem to be more sensitive to a bitter taste [29, 30] and although adults may think that the worse a medication tastes the better it works, this perception does not work in children. Several approaches have been explored to mask the taste of drugs such as the addition of chemicals (flavours, sweeteners, pH modifier), encapsulation of the drug (coating or matrix formation using polymer, or complexation with cyclodextrins) and the development of a novel formulation (liposomes, double emulsion) [31]. However, such approaches have very limited application in formulations designed to be delivered via the buccal/sublingual mucosa because any such alteration may impact drug release at the site of absorption. It is also essential to consider that the excipients included to increase palatability may not be approved for use in children [32]. Hence more research is needed to address the issue of taste masking without compromising formulation performance.

The size and shape of the formulation should also be considered carefully for oral transmucosal administration for each target age group depending on the stage of childhood development. However, in a study by Spomer et al., it was found that the overall acceptance of 2-mm uncoated mini-tablets was at least equal to or even better than that of sweet tasting syrup, even for children aged 2 years or less. Almost 40 % of the children aged 1–2 years refused the liquid formulation, but only 10 % refused the mini-tablet [33].

While traditionally employed for enteric delivery, multi-particulate delivery systems have also been explored for buccal/sublingual administration [34]. The benefit of these drug delivery systems is the flexibility provided to adapt the dose when required for a posology determined by bodyweight or age [35]. The other benefits from a formulation perspective are the potential for enhanced retention at site of administration via mucoadhesion and tailoring drug release. Striant® (Testosterone) and Onsolis® (Fentanyl citrate) are currently approved products for use in adults utilising mucoadhesion strategies to prolong the residence time of the formulation with the oral mucosa [36, 37]. These formulations have used polycarbophil, hypromellose and carbopol 934P, carboxymethyl cellulose and hydroxyethyl cellulose as mucoadhesive polymers [36, 37] and this strategy can be extended to develop suitable paediatric mucoadhesive formulations. The multi-particulate dosage form is usually placed directly in a patient's cheek or under the tongue and can be supplied in a bottle (with appropriate dosing scoop) or a pre-packed sachet or capsule which allows for more accurate dosing.

Thin film dosage forms and lyophilised wafers fall under the category of orodisperisble dosage forms which usually melt or disperse/dissolve within a matter of seconds when placed under the tongue or beneath the cheek. Thin films hold great potential for the paediatric population as they are easy to administer, are difficult to spit out due to rapid dispersion and can provide a range of dosages appropriate for use in children [38]. These formulations are usually compact (the size of postage stamp), and hence do not require bulk packaging and can be packed in a sachet to provide a unit dose. The films can be easily manipulated without altering the quality of formulation by cutting into the desired size, if required, for children of different ages. However, taste is a challenge for such formulations as they have very limited capacity to hold flavourings to mask the taste of the drug or film-forming agents without them crystallising upon film-drying. Potentially this could be overcome by incorporating a drug coated with polymer using particle coating technology [39].

Oral mucosal sprays have been extensively explored in adults as a mean of directly delivering the drug in a liquid formulation to the oral mucosa [40]. Such an approach has potential for use in children but issues including the smaller size of the oral cavity available for spray application and local irritation at the site of application along with difficulty in modifying the dose must be considered. Nevertheless advantages such as rapid application to the desired site, negligible chances of spitting out the formulation, mucoadhesion, dose manipulation and accurate and controlled dosing may outweigh these concerns.

AceIRX Pharmaceutical Inc. has filed a patent (US 20090010992) in the US for "Drug formulations for oral transmucosal drug delivery to paediatric patients" [41]. The invention describes the development and evaluation of small volume bioadhesive dosage forms called "NanoTabs" containing the opioid sufentanil, for the oral transmucosal delivery route with the help of a dosing applicator or device. The NanoTabs formulation which is administered with an applicator, offers a practical solution where: (1) intravenous (IV) access is not available; (2) initiation of IV access requires sedation; (3) the patient cannot or will not swallow pills; (4) pre-procedural

sedation or a relatively rapid onset of action is required which cannot be achieved by oral GI administration and (5) for paediatric patients who are not able to use the other non-invasive routes of administration effectively [41]. The NanoTab ranges between 8 and 15 mg in weight, with an active ingredient in the range of 0.001–10 mg per NanoTab. The formulation is currently under phase III trial evaluation for use in post-operative patient controlled analgesia and is reportedly likely to overcome the programming and delivering errors associated with traditional intravenous patient controlled analgesia which has led to patient deaths [42].

Although not approved for use in children as yet, Schechter et al. [43] have evaluated the potential of fentanyl citrate-based lozenges applied for oral transmucosal delivery for use in painful procedures such as bone marrow aspiration or lumbar puncture in 48 children whose ages ranged from 3 to 18 years. The study concluded that such delivery resulted in the children suffering less procedural pain when compared to children who were on placebo. However significant incidence of nausea and vomiting may ultimately limit their paediatric use.

Recently, Gerrard et al. proposed a new concept "nipple shield delivery system (NSDS)" to deliver an anti-HIV drug to prevent mother-to-baby transmission of the disease. The approach to deliver the drug to infants incorporates a drug-loaded insert into a NSDS. The drug is released directly into milk during breastfeeding [44]. Though the goal of this research is to deliver the drug orally through the breast feeding mechanism it can be extended to target the oral mucosa by incorporating mucoadhesive properties in the formulation [45]. LMA international, a device manufacturing company developed the LMA MADdy™ paediatric laryngo-tracheal mucosal atomisation device which consists of a small atomising tip at the end of a flexible applicator that is partially concealed by a colourful, child-friendly blowfish and used for dispensing topical medications to the nose, mouth, throat, hypopharynx, larynx and trachea in a fine, gentle mist. It is not a pre-filled device and hence gives flexibility to adapt the dose [46].

15.6 Conclusions

Oral mucosal drug delivery is a suitable alternative to enteric drug delivery for paediatric patients and offers the potential avoidance of first pass metabolism along with an easy and accessible site to deliver the drug for local or systematic administration. Nevertheless despite these advantages and the development of novel technologies including NanoTabs and mucosal sprays, there still remain relatively few products approved for use in the paediatric population. This is likely explained by the fact that alongside the normal problems that need to be overcome during product development, additional issues including compliance, palatability, paediatric safety, the needs and capabilities of carers and the implications of global paediatric regulatory guidance [47, 48] need to be considered, when developing or applying such adult formulations for use in children.

References

1. Breitkreutz J (2008) European perspectives on pediatric formulations. Clin Ther 30:2146–2154
2. Dunne J (2007) The European regulations on medicines for paediatric use. Paediatr Respir Rev 8:177–183
3. Rodriguez W, Selen A, Avant D et al (2008) Improving pediatric dosing through pediatric initiatives: what we have learned. Pediatrics 121:530–539
4. Committee for Medicinal Products for Human Use (CHMP) Reflection paper: formulations of choice for the paediatric population. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf. Accessed 2 Dec 2011
5. Patel VF, Lui F, Brown MB (2011) Advances in oral transmucosal drug delivery. J Control Release 153:106–116
6. Costello I (2007) Paediatric pharmacokinetics and pharmacodynamics. In: Florence AT, Moffat AC (eds) Paediatric drug handling, 1st edn. Pharm Press, London
7. Leopold A, Wilson S, Weaver JS, Moursi AM (2002) Pharmacokinetics of lidocaine delivered from a transmucosal patch in children. Anesth Prog 49:82–87
8. Sonesson M, Eliasson L, Matsson L (2003) Minor salivary gland secretion in children and adults. Arch Oral Biol 48:535–539
9. Williams DM, Cruchley AT (1994) Structural aspects of aging in the oral mucosa. In: Squier CA, Hill MW (eds) The effect of aging in oral mucosa and skin. CRC, Boca Raton, pp 65–74
10. Squier CA, Wertz PW, Williams DM, Cruchley AT (1994) Permeability of oral mucosa and skin with age. In: Squier CA, Hill MW (eds) The effect of aging in oral mucosa and skin. CRC, Boca Raton, pp 91–98
11. http://www.medilexicon.com/drugs-list/pediatrics.php. Accessed 15 July 2012
12. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM096228. Accessed 14 Feb 2013
13. Kaye JL (2011) Review of paediatric gastrointestinal physiology data relevant to oral drug delivery. Int J Clin Pharm 33:20–24
14. Temgesic. www.medicines.org.uk. Accessed 14 June 2012
15. Tephine. www.medicines.org.uk. Accessed 14 June 2012
16. Buccolam. www.medicines.org.uk. Accessed 14 June 2012
17. Daktarin oral gel. www.medicines.org.uk. Accessed 22 June 2012
18. Daktarin Sugar free 2% oral gel. www.medicines.org.uk. Accessed 22 June 2012
19. Anbesol Teething gel. www.medicines.org.uk. Accessed 14 June 2012
20. Boots Dry Cough Relief Lozenges. www.medicines.org.uk. Accessed 14 June 2012
21. Glyceryl Trinitrate, Paediatric Formulary Committee. BNF for Children (online). BMJ Group, Pharmaceutical Press, and RCPCH Publications, London. http://www.medicinescomplete.com. Accessed 18 Oct 2012
22. Actiq. www.medicines.org.uk. Accessed 14 June 2012
23. Fentanyl, Paediatric Formulary Committee. BNF for Children (online). BMJ Group, Pharmaceutical Press, and RCPCH Publications, London. http://www.medicinescomplete.com. Accessed 18 Oct 2012
24. Camacho Parreño S, Prieto MF, Santana VM, Sanchez MTS (2012) Off-label oral transmucosal fentanyl citrate analgesia for bone fracture alignment in children. Eur J Hosp Pharm 19:103
25. Bartoshuk LM (2000) Comparing sensory experiences across individuals: recent psychophysical advances illuminate genetic variation in taste perception. Chem Senses 25:447–460
26. Birch LL, Fisher JO (1998) Development of eating behaviors among children and adolescents. Pediatrics 1(Suppl 2):539–549
27. Beauchamp GK, Cowart BJ (1987) Development of sweet taste. In: Dobblng J (ed) Sweetness. Springer, New York
28. Beauchamp GK, Moran M (1984) Acceptance of sweet and salty tastes in 2-year-old children. Appetite 5:291–305

29. KaJulra H, Cowart BJ, Beauchamp GK (1992) Early developmental change in bitter taste responses in human infants. Dev Psychobiol 25:375–386
30. Mennella JA, Peplno MY, Reed DR (2005) Genetic and environmental determinants of bitter perception and sweet preferences. Pediatrics 115:e216–e222
31. Bar-Shalom D (2011) Pediatric formulations – are we living in the past? Am Pharm Rev. http://www.americanpharmaceuticalreview.com. Accessed 27 Sept 2012
32. Shojaei AH (1998) Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci 1:15–30
33. Spomer N, Klingmann V, Stoltenberg I, Lerch C, Meissner T, Breitkreutz J (2012) Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. Arch Dis Child 97:283–286
34. Limbachiya S, Nagar H, Dodiya H, Mehta D (2013) Development and characterization of fast dissolving mucoadhesive microsphere of nebivolol hydrochloride using modified methacrylate polymer. Int J Pharm Sci 3:136–141
35. De Matas M, Okwelogu C, York P (2009) Paediatric dosage forms: proposal of a versatile platform technology. Chim Oggi Chem 27:20–24
36. Onsolis. http://www.onsolis.com/pdf/onsolis_pi.pdf. Accessed 18 Feb 2013
37. Striant. http://www.actientpharma.com/filebin/pdf/products/58816-10_Striant_full_PI_4pager.pdf. Accessed 18 Feb 2013
38. Dixit RP, Puthli SP (2009) Oral strip technology: overview and future potential. J Control Release 139:94–107
39. http://www.catalent.com/index.php/news-events/news/Catalent-Licenses-Technology-with-NJIT. Accessed 4 March 2013
40. Novamist Technology. http://www.novadel.com/technology/index.htm. Accessed 18 Oct 2012
41. Palmer P, Schreck T, Tzennis S, Hamel L, Poutiatine AI (2009) Drug formulations for oral transmucosal administration in pediatric patients. US 20090010992. www.uspto.gov. Accessed 24 July 2012
42. ARX-01 Sufentanil NanoTab PCA System. http://www.acelrx.com/pipeline/index.html. Accessed 24 July 2012
43. Schechter NL, Weisman SJ, Rosenblum M, Bernstein B, Conard PL (1995) The use of oral transmucosal fentanyl citrate for painful procedures in children. Pediatrics 95:335–339
44. Gerrard SE, Baniecki ML, Sokal DC, Morris MK, Urdaneta-Hartmann S, Krebs FC, Wigdahl B, Abrams BF, Hanson CV, Slater NK, Edwards AD (2012) A nipple shield delivery system for oral drug delivery to breastfeeding infants: microbicide delivery to inactivate HIV. Int J Pharm 434:224–234
45. http://justmilk.org/index.html. Accessed 5 Oct 2012
46. http://www.lmana.com/pwpcontrol.php?pwpID=6358. Accessed 5 Aug 2012
47. European Medicine Agency (2011) Draft guideline on pharmaceutical development of medicines for paediatric use. Committee for Medicinal Products for Human Use (CHMP). http://www.ema.europa.eu. Accessed 19 July 2012
48. World Health Organization (2008) Report of the informal expert meeting on dosage forms of medicines for children. December 2008. http://www.who.int/selection_medicines/committees/expert/17/application/paediatric/Dosage_form_reportDEC2008.pdf. Accessed 5 Aug 2012

Part III
Formulating for Children II, Non-oral Routes

Chapter 16
Topical and Transdermal

William J. McAuley, Matthew Traynor, and Marc B. Brown

Abstract Formulations designed to be applied to the skin, in particular for the treatment of skin diseases are commonly used for children. There are a number of important issues with regards to the use of these types medicines in the pediatric population in comparison to adults; for example children have a greater risk of experiencing systemic side effects as a result of treatment. This chapter discusses the roles of the different formulations used for topical and transdermal treatment, their design and considerations specifically relevant for the development of these medicines for children.

16.1 Introduction

This can in many cases provide suitable therapeutic treatment and also reduce systemic exposure to the drug in comparison to other routes of delivery, thereby minimising side effects and toxicity. Transdermal formulations for children are less common than topical treatment. However for suitable drug candidates they offer, in particular, the advantage of providing controlled, prolonged release of a drug. This minimises dosing frequency, improving patient compliance and thus therapeutic treatment for all patient groups including children.

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16.2 Skin Conditions in Children

The topical route of administration is of particular importance in the paediatric population, as skin diseases are common in children worldwide, with the prevalence of conditions reported as being between 23 and 95 % [1–7] with most of these being treated topically. As a population group children have considerably different incidences of particular skin diseases to the adult population. Some conditions such as seborrheic dermatitis and Mongolian spots are quite common in neonates but may not require any treatment, however, others such as atopic dermatitis can have a significant impact on an individual's quality of life and are becoming more prevalent in young children [8]. The actual incidence of atopic dermatitis in children is reported to vary between 3 and 28 % depending upon the age and background of the population being studied [9–13], with 85 % of cases initially occurring before 5 years of age [14] and 50 % of cases being resolved by adolescence [15]. Of the adult population affected only 17 % have onset of the disease after adolescence [16, 17].

Other conditions such as acne, impetigo and skin infestations such as head lice are typically much more prevalent in the paediatric (and adolescent) population groups. Acne is a particularly common, typically prevalent in 81–95 % of adolescent boys and 79–82 % of adolescent girls [18–20] but individual studies have reported point prevalence of up to 92–95 % in adolescents aged between 12 and 20 years old [7]. In contrast, the prevalence of clinical adult acne has been reported as being as low as 3 % in men and 12 % in women [21].

Some conditions such as napkin/diaper dermatitis (nappy rash) are predominantly thought of as affecting paediatric populations when in fact they also affect a large number of the adult population. The prevalence in infants has been estimated to be between 7 and 35 % [22] although a study in the UK demonstrated a prevalence of 25 % in the first 4 weeks of life alone [23]. However it is sometimes overlooked that this disorder can affect persons of any age who wear napkins or incontinence pads [24] and although the exact incidence of napkin/diaper dermatitis in adults is unknown, it is likely to be quite high, given that 13 million American adults suffer from urinary incontinence, and adult napkin sales exceeded $1.5 billion in 1996 [25, 26].

In contrast to the above conditions, psoriasis is relatively rare in babies and small children and only a third of those who will develop the condition will do so by the age of 16. Among children aged 0–18 years old the median onset of psoriasis was found to be between 7 and 10 years of age [27–30]. A UK study showed a prevalence of psoriasis of approximately 0.6 % in children aged 0–9 years and 1.4 % in children aged 10–19 years [31]. A further study showed that the prevalence of psoriasis showed a constant increase throughout the years 0–18 so that by the age of 18, ten times more individuals are affected with psoriasis than at age 1 [32]. The figures reported at ages 9 (0.56 %) and 18 (1.24 %) are comparable with those of earlier studies [34]. Adult prevalence of psoriasis has been reported in various studies to be between 0.6 and 4.8 % [31, 33–48] with the variance explained by differences in the definition of prevalence, the method of definition (e.g. self-reported vs physician diagnosis) and the population groups studied [31].

The skin conditions encountered in paediatric populations worldwide vary considerably by country. In developing countries such as India, infections and infestations are more common while in more developed countries atopic dermatitis has a higher prevalence which is thought to be influenced by socioeconomic and environmental factors such as excessive cleaning, carpets and central heating [2, 49]. For example, a study in India reported a point prevalence of atopic dermatitis of 6.5 % [2] as compared to studies in Western countries that report point provenances between 11 and 22 % [50, 51].

16.3 Topical Products Used for Children

A large array of topical products and formulation types are available for children, including, for example, emollients, anti-inflammatories, anti-infectives, local anaesthetics, and acne and psoriasis treatments. Common formulation types include semisolids such as creams ointments and gels, more fluid formulations such as shampoos and lotions with other formulation types such as sprays and powders also being available. This wide range of products is perhaps unsurprising given the considerable burden of skin disease and the desirability of treating these conditions topically if possible. Additionally the use of certain other products is particularly common in children, such as the use of local anaesthetics prior to minor skin procedures, including venepuncture or venous cannulation. However few topical products are marketed exclusively for children with some products available for adults not being licensed for paediatric use. The ages of children for which different products are licensed vary considerably, in some cases no age range is specified, whilst in others a minimum age is quoted, with ages of 1, 2 and 12 being relatively common.

16.4 Skin Structure

In designing topical/transdermal formulations it is important to have an awareness of skin anatomy and physiology, as this is useful for consideration of the site of drug action, skin condition, the delivery of a drug and the overall formulation development process. The skin presents a considerable barrier to the absorption of drugs and it has been estimated that typically only a few percent of a topically applied dose is bioavailable [52]. However a variety of different factors affect the skin's permeability to drugs and again appreciation of these can help inform the topical/transdermal formulation development process.

Figure 16.1 is a schematic cross section of the skin showing the three macroscopic layers: the subcutaneous tissue, the dermis and the epidermis.

The subcutaneous tissue contains the main blood vessels to the skin and has thermal and mechanical support and energy storage functions. It consists of fat cells arranged in lobules connected with elastin and collagen. This layer also contains the

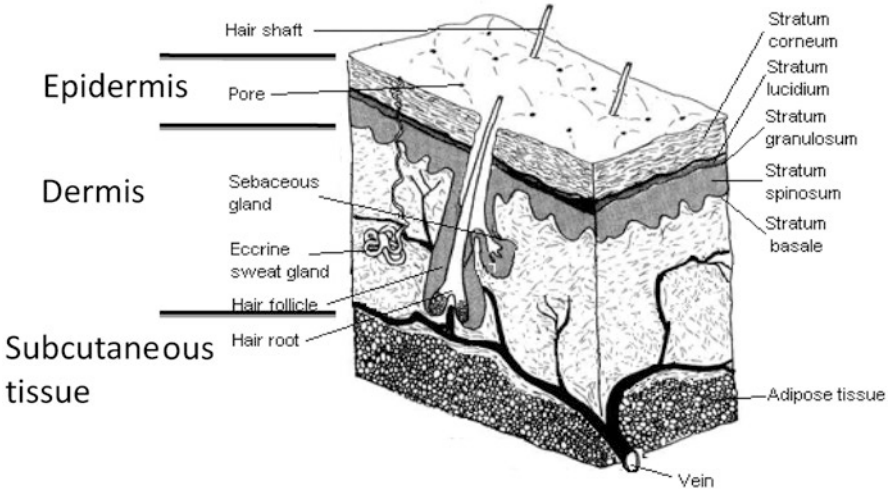

Fig. 16.1 Schematic cross section showing the anatomy of the skin (adapted from Brown et al. [53])

main blood and lymphatic vessels and nerve fibres which link to the skin tissue. The next layer, the dermis makes up the majority of the actual skin thickness and is approximately 2–5 mm thick. It contains connective tissue that provides elasticity and flexibility to the skin, with cells being sparsely distributed throughout. It also contains an extensive vasculature, which supplies the skin with required nutrients and removes waste products and nerves and lymphatic vessels are also present. The blood vessels in the dermis have an additional important role in heat regulation and are the site of access of drugs applied to the skin into the systemic circulation. Skin appendages including hair follicles with associated sebaceous glands and eccrine and apocrine sweat glands originate in the dermis. The sebaceous gland secretes sebum, a waxy/oily substance on which forms a thin discontinuous layer over the skin surface and predominately consists of a mixture of triglycerides, fatty acids, wax esters, squalene and cholesterol. Eccrine glands, present over most of the body secrete sweat, a dilute salt solution and primarily are involved in temperature regulation. In contrast apocrine sweat glands develop during puberty and are mainly localised to the axilla and anogenital regions. They produce a secretion that largely consists of proteins, lipoproteins and lipids. It is the secretion from the apocrine sweat glands that is associated with body odour, produced by the action of bacteria on the secretion.

The outermost of the three macroscopic layers is the epidermis. This layer is much thinner that the dermis and although the actual thickness depends on body region it is typically 80 μm thick. The layer lacks blood vessels and consists primarily of keratinocytes though other cells including melanocytes, which produce melanin and protect the body from UV radiation and Langerhan's cells, part of the immune system are also present. The epidermis is continually being renewed, with cells

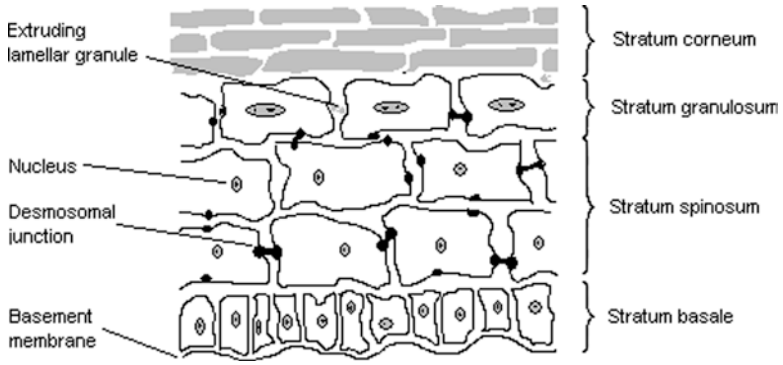

Fig. 16.2 Schematic representation of various strata of epidermis

undergoing a complex differentiation process so that cells which are sloughed off from the surface in a process known as desquamation are replaced by cells from below. Histological examination allows subdivision of the epidermis into four further layers, which represent stages in the differentiation of keratinocytes. A magnified schematic illustration showing these layers can be seen in Fig. 16.2 above.

The keratinocytes of the basal layer (stratum basale) are viable cells connected to the basement membrane and able to undergo cell division, with the newly produced cells moving further into the epidermis and towards the surface of the skin. As the cells migrate through the epidermis they differentiate; the next histological layer is known as the stratum spinosum and is comprised from two to six layers of keratinocytes. The cells change from being columnar in shape to polygonal and have a spiny appearance which is a result of connections appearing between the cells known as desmosomes. These desmosomes connect the cells providing structural integrity to the epidermis. The cells also start to produce keratin filaments. With further differentiation granules become visible in the cytoplasm of the next layer, the stratum granulosum. These granules contain precursors of the (intercellular) lipids, which exist between the cells in the outermost layer, the stratum corneum. Within the stratum granulosum the keratinocytes continue to produce keratin, their organelles break down and the cells begin to flatten. The final layer, the stratum corneum, is an example of a stratified squamous epithelium. By the time that the keratinocytes have reached this layer, all of the cell organelles have degraded and the keratinocytes consist primarily of keratin, held within a proteinaceous envelope. As they are fully keratinised or cornified at this stage, the cells are commonly known as corneocytes. The cells are flattened, for example, they may be 1–2 μm deep but 50 μm wide, although their dimensions depend to some extent on body region. The cells are imbedded in a structured intercellular lipid matrix, which was produced in the stratum granulosum and extruded into the intercellular spaces. The stratum corneum is relatively thin, typically 10–20 μm thick, though again this varies according to body region. A common analogy used to describe the stratum corneum is the "bricks and mortar" model, with the corneocytes being represented by bricks and the intercellular lipid by the mortar.

The stratum corneum acts as the main barrier to the loss of water from the body and to the prevention of ingress of foreign substances. Thus the layer is also generally the main barrier to the absorption of drugs into and across skin, and is important for understanding drug administration by this route. Additionally correct functioning of the stratum corneum, maintaining correct skin barrier properties has been recognised as important in the management of several skin diseases, in particular for inflammatory dermatoses such as atopic dermatitis and psoriasis. For example, a predisposing factor for atopic dermatitis is the loss of function gene variants for filaggrin, a protein which is important for formation of the stratum corneum [54]. Moreover the proteolytic degradation products of filaggrin, present in the stratum corneum are a significant contributor to natural moisturising factor. Natural moisturising factor assists in keeping the stratum corneum hydrated and flexible and decreased levels are typically found in patients with atopic dermatitis. Additionally changes in the stratum corneum intercellular lipid composition and packing, which are believed to be linked to the increased transepidermal water loss (TEWL) in the condition have been observed in patients with atopic dermatitis [55].

16.5 Skin in the Paediatric Population

Development of the stratum corneum and skin barrier formation in the foetus starts at approximately 20 weeks gestation. The development initially occurs at specific sites, typically around hair follicles which then increase in size to eventually cover the entire body [56]. The skin barrier function gradually improves with time with full maturation occurring a few weeks before birth (around week 34). The skin barrier function from around weeks 30 to 32 has been shown to be equivalent to that of an adult using TEWL measurements, i.e. the determination of the amount of water evaporating across the skin [57]. The reduced skin barrier function of preterm infants has been exploited to deliver theophylline transdermally to preterm infants [58], but the fully developed skin barrier function of normal full term babies suggests that special considerations for the absorption of drugs by the skin in paediatric patients are not necessary. However this does not mean that a paediatric patient is necessarily the same as an adult when considering topical treatment. This is primarily because the surface area to body mass ratio of a child is considerably larger than that of the adult meaning that the systemic exposure of a child to a topically applied treatment can be considerably greater than that of an adult, potentially leading to systemic side effects. Systemic side effects in children from topically applied medicines have been observed with particular treatments. Examples include with adrenal suppression in children who have been treated with topical corticosteroids and neurotoxicity following the topical treatment of scabies [59, 60]. In practical terms to manage this risk with treatments such as topical corticosteroids, treatment is often advised to be limited to relatively short time periods with continuous therapy being avoided where possible. Additionally it should be considered in the design of any topical/transdermal drug delivery system that skin of children may have an increased irritant response in comparison to adults [61].

16.6 Skin Factors Affecting Topical Absorption

As discussed above, with the exception of premature babies, the barrier function of skin in the paediatric population is believed to be the same as that for adults. However there is considerable variation in skin drug absorption across skin from different regions of the body. For example, higher drug absorption occurs from the face, neck or genitals greater in comparison to the trunk, legs or arms [62]. The presence of hair follicles can have a significant effect, particularly at body sites where they are at high density such the scalp. Their presence may increase absorption though the effect may vary with the particular type of drug characteristics and be larger for hydrophilic drugs [63]. Regional variation in skin permeability has been exploited with testosterone containing transdermal patches having been designed for application to the scrotum and scopolamine containing patches being applied behind the ear, both of these body sites showing relatively high drug absorption [62]. Typically increased drug absorption is expected across diseased skin, examples include nappy rash as well as lesions in eczema or psoriasis [64]. This may be beneficial enabling improved delivery of a particular drug and thus therapeutic treatment. However care must also taken, particularly with conditions such as nappy rash that can involve a relatively large area. The increased absorption because of the damaged skin barrier and the inherently lower skin barrier function of the region may lead to systemic side effects [65]. Potentially the increased drug absorption across diseased skin may make it possible to deliver drug molecules that are ordinarily very difficult to get across skin, for particular skin conditions [66]. The decreased barrier function of diseased skin also has implications for treatment as the skin's barrier function will recover with improvement in the condition, reducing drug absorption.

16.7 Drug Absorption Across the Skin

There are three main routes that drugs can traverse the stratum corneum, the main barrier to skin absorption. These can be visualised with reference to Figs. 16.1 and 16.2. The transappendageal route involves drugs being absorbed through hair follicles and other appendages, effectively bypassing the stratum corneum. Overall drug absorption via this route is believed to be low with the available surface area having been estimated to be approximately 0.1 % of the total available surface area. Nonetheless it is important when delivering drugs to the appendages, e.g. for acne treatment and as mentioned previously may be important for hydrophilic drugs and at particular body regions, such as the scalp. In contrast the transcellular route which involves drug diffusing into the stratum corneum's corneocytes, across the intercellular lipid spaces and back into deeper corneocytes continually until it reaches the stratum granulosum, has the largest available surface area and a relatively short diffusional pathlength. Although this suggests that this route would be the most likely for drug permeation the multiple partitioning steps from cells to the intercellular

lipid spaces and back into the corneocytes are thought to be unfavourable. Instead it is the intercellular pathway, where the drug diffuses through the intercellular "mortar" that is thought to be the most likely route for drug transport across the stratum corneum. This route only offers approximately 1 % of the available surface area, and in contrast to the transcellular route is much more tortuous; the increased diffusional pathlength contributing to the skin's barrier function.

16.8 Formulation Factors Affecting Drug Transport Across the Skin

Although the skin is an effective barrier to the absorption of many chemicals, the characteristics of individual permeants affect this with particular drug molecules showing a much greater propensity to cross it than others. Drugs that have a low molecular weight, that are lipophilic but also have some hydrophilic character, enabling absorption both into the relatively lipophilic stratum corneum as well as the deeper, hydrophilic skin layers, penetrate the skin best [67, 68]. Diffusion of drug molecules across skin can successfully be described through application of Fick's laws of diffusion. The simplest case is that where there is a constant concentration gradient of drug across the skin, such as occurs when an infinite dose is applied to the membrane and sink conditions existing on the other side. A common form of Fick's first law can be then be applied (Eq. 16.1).

$$\mathrm{J} = \mathrm{KDC}_{\mathrm{app}} / \mathrm{h} \tag{16.1}$$

where J is the rate of drug transport across the skin (flux), D is the diffusion coefficient of the drug in the skin, K is the partition coefficient of the drug from the formulation to the superficial layer of the stratum corneum, C_{app} is the applied concentration and h is the diffusional pathlength. The description of Fick's law in terms of concentration works well when a single vehicle is used, for example, in the case of a simple aqueous drug solution, as the concentration of the drug is increased, a proportional increase in drug flux is expected. In this case the concentration of the drug in the vehicle is representative of its thermodynamic activity. A modified form of Eq. (16.1) incorporating thermodynamic activity is given below (Eq. 16.2) where α is the thermodynamic activity of the drug in the formulation and γ is the thermodynamic activity of the drug in the stratum corneum.

$$J = \frac{\alpha D}{\gamma h} \tag{16.2}$$

Equation (16.2) indicates that drug flux across the skin does not necessarily correlate with the concentration of the drug in the formulation and instead it is the thermodynamic activity of the drug that is important. To envisage this it is perhaps easiest to consider the saturation of the drug in the formulation instead of its concentration.

The solubility limit of the drug in a particular formulation is the concentration at which the formulation is fully saturated with drug. The drug concentration at which this occurs varies depending on the particular formulation, however, regardless of the actual concentration, at the solubility limit the drug is at its maximum (stable) thermodynamic activity which has a value of 1. Changes in formulation may alter the drug's solubility in the vehicle, thus the thermodynamic activity of the drug may be altered and thus delivery into the skin even though the drug may be at the same concentration in the two different formulations [69]. This is an established issue, for example, one study in the 1980s found that there was often no correlation between the drug concentration in particular topical corticosteroid preparations and skin absorption [70]. Currently there is a proprietary 0.1 % hydrocortisone cream available in the UK which is clinically equivalent to 1 % hydrocortisone cream BP [71] again providing evidence that that skin penetration does not always correlate with drug concentration and that formulation is critical with regard to delivery of drug across the skin. However formulation factors other than the thermodynamic activity of the drug in the formulation are also important.

Formulations for application to the skin may include excipients that will improve drug absorption, known as penetration enhancers. A large number of different excipients can have this effect and common examples of such molecules include ethanol, propylene glycol and isopropyl myristate. For example, the propylene glycol content of a formulation has been linked with the formulation's capability to transport aciclovir across the skin [72]. Ethanol has been shown to increase the concentrations of terbinafine in the stratum corneum [73] and is used in a terbinafine containing product designed to treat athletes foot with a single application. Other examples of excipients that can increase drug absorption include fatty acid derivatives such as isopropyl myristate, surfactants, fatty acids, terpenes and dimethylsulphoxide [74]. When more than one penetration enhancing excipient is used in a formulation, synergy can occur between them further increasing drug absorption [75, 76]. Penetration enhancing excipients may be included in the formulations for reasons other than improving drug absorption; for example, they may be solubilisers, enabling the target drug concentration to be incorporated in the formulation, or surfactants that are being used to stabilise an emulsion. Nonetheless their presence may increase drug absorption. Selection of penetration enhancers to include in a formulation depends upon the formulation type and the nature of the drug, however, as with all other excipients consideration also needs to be given to the effect of the enhancer on the formulation's cosmetic acceptability, compatibility with other formulation ingredients as well as its potential to cause irritancy or toxicity.

Formulations that are occlusive may also increase skin drug absorption [77]. Through slowing the evaporation of water across the skin (reducing TEWL), occlusive formulations cause the stratum corneum to hydrate and swell increasing drug permeability [78]. Ointment bases typically are occlusive and, for example, topical corticosteroid ointments are often more potent than the corresponding cream formulation [79, 80]. Additionally in infants, the nappy may act as an occlusive dressing, and increase drug absorption in the treatment of nappy rash.

16.9 Formulation Type

A wide range of formulation types are available for application to the skin. Most commonly semisolid and liquid formulations are used for topical applications with transdermal patches being the most common formulation when a systemic effect is required. The three most commonly encountered semisolid topical formulations are ointments, creams and gels with a range of liquids also being available. Vehicle aesthetics are particularly important when the product is to be applied frequently over long periods of time, as poor aesthetic properties are believed to be linked to poor patient compliance and treatment outcomes. To a large extent these aesthetics will relate not only to patient preference but also to the condition and the specific site. For example, greasier formulations such as ointments may be preferred for dry scaly lesions with liquids or foams being preferred for hairy areas such as the scalp as they are much easier to apply. It has been estimated that patient adherence to topical treatment regimes may be as low between 32 and 61 % for a variety of skin conditions [81]. Commonly reported reasons for poor patient compliance include, perceived lack of efficacy, staining of clothes, time required for application, interference with daily activities and fear of side effects as well as patient preference for a particular product type [82]. Formulations typically go through significant physical changes once they are applied to the surface of the skin affecting their aesthetic properties. For example, rubbing a thixotropic formulation will reduce its viscosity, affecting its "feel" and may also affect drug release from the formulation and skin absorption. Evaporation of any volatile solvent present will alter the nature of what resides on the skin surface and may reduce the solubility of the drug and result in drug precipitation, or potentially induce supersaturation, where the thermodynamic activity of the drug in increased above that of a saturated drug solution, improving drug delivery. However the residue left on the skin surface may seem quite different to what was applied thus affecting patient acceptability.

Ointments principally consist of a mixture of wax/fat and oil into which a drug is incorporated. They can be very simple dosage forms, for example, consisting of just the drug in a wax phase and are often preferred for chronic dermatological disorders where dry, scaly skin presents such as in atopic dermatitis and psoriasis. This is because they are occlusive which is beneficial for the treatment of the dry skin and may also improve the delivery of the drug. Commonly hydrocarbons such as white soft paraffin or liquid paraffin are used to form the ointment base, though triglyceride derivatives and more recently silicones may also be used. Through altering the proportions of wax and oil the consistency of the product can be modified with an increased oil content making it looser and a higher wax content making it more viscous. This approach may be used to try to improve the aesthetic properties and ease with which the product can be applied. However, ointments are usually considered tacky and greasy upon application regardless of how they are formulated. This may reduce cosmetic acceptability, reducing their use by patients and ultimately any therapeutic benefit. Although ointments may be desirable as a formulation type for a range of conditions given their emollient properties, development of an ointment formulation may be difficult given the poor solubility of many drugs in

ointment bases. For such situations drug solubility can be improved by including suitable solvents in which the drug has a good solubility and are miscible with the base. Examples that are used include isopropyl myristate and propylene glycol. Additionally surfactants have occasionally been added to ointments; this helps improve their water miscibility making them easier to wash off. Whilst the vast majority of ointments are hydrophobic, hydrophilic ointment bases are also available which are formed from polyethylene glycols (PEGs). These are not occlusive but are useful for application to wounds, hydrophobic ointments tending not to be suitable for this task.

Creams are semisolid emulsions consisting of either of an oil dispersed in water (known as an o/w emulsion) or water dispersed water in oil (known as a w/o emulsion). Similar materials used for an ointment base can be utilised for the oil phase in the cream. Emulsions are thermodynamically unstable and require emulsifying agents to ensure that product remains in a suitable physical form over its shelf life. Emulsifying agents are usually anionic or non-ionic surfactants or a mixture of surfactants, although polymeric emulsifiers may also be used, and they are the main determinant affecting the type of emulsion formed (o/w or w/o). The eventual use for the product is an important consideration when deciding on an emulsion type for a particular product. From a cosmetic acceptability point of view, o/w emulsions are generally considered less "greasy" and thus have greater acceptability. However, w/o creams may be deemed preferable for drier skin conditions. In general o/w emulsions are much more common compared to w/o, which may be related to the greater availability of suitable emulsifying agents stabilising o/w emulsions in comparison to w/o emulsions as much as the improved aesthetic properties of such formulations. Similar to ointments, creams which may contain a high proportion of lipid provide an emollient effect hydrating the skin through restricting TEWL content and are often used for dry and inflammatory skin conditions such as in patients with dermatitis, psoriasis and eczema. Indeed emollient products commonly used in the management of dry skin conditions are sometimes simply cream or ointment bases with the base of some proprietary topical corticosteroids also being commercially available as emollients.

Gels consist of a liquid phase to which a thickening (gelling) agent, usually a polysaccharide or acrylate polymer is added. The liquid phase is usually an aqueous- or an alcohol-based cosolvent system and the consistency of the overall product is modified through choice of the particular gelling agent and the concentration used. They are generally considered aesthetically pleasing and are often translucent or transparent. Humectants such as glycerol or propylene glycol may be included in the formulation to ensure that the polymer residue formed following application when the gel dries retains water and exists as a thin flexible film rather than as solid lumps of polymer. These humectants may also improve drug solubility in the vehicle and additional solvents such as ethanol, isopropyl alcohol and PEG may also be included in the gel for this reason. Gels typically lack the occlusive capabilities of ointments and creams and are usually used for the treatments where this effect is not advantageous. They are also suitable for application to wounds. Emulsified gels are essentially biphasic systems containing an aqueous gel dispersed with a lipid phase

and may be similar to creams. These are more occlusive than conventional gels and the lipid phase facilitates the incorporation of hydrophobic drugs.

In addition to semisolid topical formulations there are also a number of liquid formulations. These may be solutions, suspensions, emulsions or liquids thickened with a gelling agent. They are, however, all characterised by a decreased viscosity, which allows them to flow freely. Much of the discussion above for topical semisolids also applies to liquids. The main advantage of their use is their ease of application to large areas of skin and to the scalp where the presence of hair makes application of semisolids difficult. Another relatively recent formulation type which is used particularly for application to the scalp is medicated foam. Foams are essentially a dispersion of air in a liquid and are commonly generated by using a pressurised aerosol which contains a liquid with air dissolved in it. Upon actuation, when the pressure is removed the air dissolved in the liquid comes out of solution and the foam is formed. Foaming agents, commonly surfactants are needed to ensure the foam forms [83]. Foams typically leave a low quantity of residue on the skin following application and have been shown to increase drug bioavailability and patient acceptability over conventional formulations [84].

In addition to the drug and the main ingredients used to produce a particular formulation type, a number of other excipients may also be included in a formulation to perform a variety of functional roles. These roles may include, improvement of drug solubility in the formulation to allow incorporation of the drug at a particular concentration, improvement of product aesthetics to increase patient compliance, improvement of drug and/or formulation stability and prevention of microbial growth and contamination. For many formulations such as o/w emulsions and aqueous gels, water is the main drug solvent and various water miscible solvents such as PEG, propylene glycol and alcohols (e.g. ethanol) can be included to improve drug solubility. Drugs in aqueous solutions may be susceptible to oxidative degradation and therefore such products may require the addition of an antioxidant. The stability of drugs and the behaviour of certain excipients can be affected by pH requiring the addition of buffers to the formulation. For example, the stability of betamethasone valerate is pH dependent, and formulation at an inappropriate pH can cause loss of efficacy. Additionally, the control of pH may be important for particular excipients; carbomers which are common gelling agents have a particular pH range in which they can function effectively. Antimicrobial preservatives are usually included in formulations containing water to prevent contamination by micro-organisms and spoilage of the product. In contrast, for non-aqueous systems such as ointments preservatives are rarely required. The selected preservative(s) need to exhibit activity against a wide spectrum of micro-organisms and in addition for multiphase formulations such as emulsions, care must be taken to ensure that there is a suitable concentration of the preservative in the appropriate phase. This is because the preservative will partition between the oil and the aqueous phases of the emulsion. Bacterial contamination typically occurs in the aqueous phase and at the oil/water interface. Thus appropriate preservative concentrations need to be present in these regions. Other considerations that influence the actual concentration of preservative required include the presence of other excipients within the formulation that have

antimicrobial activity. For example, ethanol which may be included in a formulation as a penetration enhancer is also a preservative. Examples of some preservatives commonly used in topical dosage forms include hydroxybenzoates, benzyl alcohol and phenoxyethanol.

16.10 Transdermal Systems

Transdermal treatments which provide a systemic effect are used much less frequently in the paediatric age group than topical treatments. Only a few transdermal products are licensed for children but examples include fentanyl and methylphenidate patches with fentanyl being licensed for the treatment of pain for children 2 years and over and methylphenidate for the treatment of attention deficit hyperactivity disorder from 6 years. Although other forms of transdermal formulations are available, such as ointments that are applied and secured in place with surgical tape, adhesive transdermal patches which are clearly defined single unit systems are the most commonly used. The transdermal route offers particular advantages for the systemic administration of drugs. In particular these include providing controlled, prolonged release of the drug so that the dosing frequency can be reduced. This is often associated with improved patient compliance and is particularly useful for children when, for example, they attend school. As a route of administration it is easily accessible and is generally considered to have good patient acceptability. Moreover for drugs such as fentanyl the avoidance of first pass metabolism is useful therapeutically. The ability to control the release rate of a medication, prolonging the dosing interval is a particular advantage for transdermal patches in children, as generally to achieve this with oral medications either a relatively large tablet formulation or controlled release granules which are sprinkled on soft food such as yoghurt or apple sauce or in a liquid such as water are used. Large tablets are typically difficult for children to swallow and the controlled release granules must not be chewed before ingestion, something that may be difficult to ensure during administration. A study that compared parent preferences for different methylphenidate formulations found that approximately one third of parents would prefer a transdermal patch over oral treatments [85]. Similarly parents and clinicians are often satisfied with the performance and use of transdermal fentanyl patches [86]. However for small children the ease of accessibility of transdermal patches can be problematic as they may be able to remove them and they may be recommended to be applied to the upper back to prevent this. The ability of children to remove transdermal patches is a wider issue than simply the loss of therapeutic effect that would be expected with patch removal. As a result of the skin's very good barrier to drug permeation, drug absorption across the skin is slow and patches often contain much more drug than they actually deliver. Should a child remove a patch and then ingest or suck the patch they may then be exposed to a toxic concentration of the drug. Infant fatalities following ingestion of discarded, used fentanyl patches have been reported [87].

There are two main transdermal patch designs, matrix and reservoir systems. Matrix systems can be further divided into two categories, the simplest drug in adhesive design consisting of a backing membrane, an adhesive layer into which the drug is incorporated and a release liner. To apply the patch the release liner is removed and the patch pressed on to the skin. The development of such matrix patches is not trivial, however, as the adhesive layer needs to perform two functions appropriately; attach the patch to the skin surface and deliver the drug into the body and it may take a significant amount of development time to ensure that the adhesive formulation performs these two functions appropriately. However once the formulation has been developed manufacturing of these types of transdermal patches is relatively straightforward and inexpensive. A more complex matrix patch design consists of two separate drug in adhesive layers separated by a rate limiting membrane. In contrast reservoir patches have the drug in a liquid or semisolid reservoir separated from the adhesive by a semi-permeable membrane which controls the rate of drug delivery. This typically makes development of the particular formulation more straightforward in the first instance, but increases the complexity of the manufacturing process, increasing costs. Additionally the compartmentalisation of the drug increases the risk of problems occurring with the product, for example, if the semi-permeable membrane separating the drug containing reservoir from the adhesive fails, too much drug may be released from the patch causing toxicity.

There are some notable differences in the excipients used for transdermal patches in comparison to semisolid preparations, the main one being the pressure sensitive adhesive which maintains the patch in contact with the skin. The main adhesives used are acrylic copolymers, silicone polymers or rubber. Acrylic co-polymers have the advantage of being relatively inexpensive and that the properties of the adhesive can be easily customised by selection of the monomers used in the polymer and the degree of cross linking of the polymer chains and that they tend to have good compatibility with drugs and other excipients. However a level of residual monomer may remain in the adhesive, which may cause skin irritation. Silicone adhesives in contrast have low irritancy potential and the ability to deliver a relatively large proportion of the incorporated drug, however, they are expensive and many drugs and excipients have a low solubility in them which may make formulation development more difficult. Rubber adhesives can be made from either synthetic or natural rubber with synthetic derivatives being more common given the potential for natural rubber to cause allergic reactions. They are relatively inexpensive, however, similar to silicone adhesives they tend to have a low capability to dissolve drugs which can increase the required time for formulation development. In addition to the adhesive and drug, adhesive modifiers may be needed to adjust the properties of the adhesive such that it performs suitably. For example, ingredients such as insoluble polymers or metal oxides may be used to make the adhesive more viscous. Other excipients may be used to act as penetration enhancers to increase drug permeation across the skin as discussed for topical treatments previously or to form the reservoir for reservoir patches, ethanol being a commonly used example.

Other important constituent parts of the transdermal patch include the backing film and release liner and may affect product performance. For example, Daytrana,

the methylphenidate patch has had problems with the adhesive sticking to the release liner affecting patient use [88]. Backing films can affect drug delivery depending on the level of occlusion it provides with those that are too occlusive potentially causing skin maceration and irritation.

16.11 Skin Irritation

An important consideration is the design of a topical or transdermal dosage form is the potential for the drug and in particular, formulation excipients to produce skin irritation. This is perhaps of even greater importance when formulating for children as there is some evidence that they are at greater risk of suffering irritation [61]. A wide number of different types of molecule may induce irritation, which can occur when the irritant traverses the stratum corneum and interacts with keratinocytes. This can induce the keratinocytes to release inflammatory cytokines inducing the infiltration of inflammatory cells and keratinocyte proliferation. Keratinocytes also play a pivotal role in allergic contact dermatitis by responding to allergens producing a range of pro-inflammatory cytokines which eventually induce the specific immune response. One common source of irritants in topical formulations is the surfactants used to stabilise emulsions. In particular ionic surfactants are capable of causing irritation [89]. Aqueous Cream BP, an emollient commonly available in the UK was found to induce irritation in 56 % of children with atopic dermatitis [90] and negative issues associated with the use of this cream have been ascribed to the sodium lauryl sulphate (an anionic surfactant) content of the formulation [91]. As a result of the irritancy potential of such surfactants, many formulations are now developed with non-ionic surfactants which have lower irritation potential and polymeric emulsifiers such as carbomers, celluloses and polyacrylates are also being used to stabilise emulsions. In particular the large molecular weight of polymeric emulsifiers restricts their ability to be absorbed across the stratum corneum, thus reducing their potential to cause irritation. However surfactants are not the only excipients that can cause irritation and many other excipients including penetration enhancers, preservatives and adhesives also have the potential to do so.

16.12 Conclusions

Topical treatments for localised skin conditions are commonly used in the paediatric group. They offer the advantage of providing high, localised skin concentrations which can optimise therapeutic treatment and minimise systemic side effects. Though the skin barrier to the absorption of chemicals in full term infants is similar to that of adults, because of differences in the surface area to body mass ratio children are at a greater risk of systemic toxicity than adults. Transdermal products are less commonly used in children but a few products are licensed for use. They offer controlled

drug delivery and some parents seem to prefer them over oral treatments. Overall selection of topical or transdermal formulations depends on the specific indication the suitability of a particular formulation for a particular condition and its overall aesthetic properties. With the considerable skin barrier properties much effort has been investigated in trying to maximise skin absorption but this must be balanced against considerations such as the avoidance of skin irritation to ensure optimal patient treatment.

References

1. Bechelli LM, Haddad N, Pimenta WP, Pagnano PMG, Melchior E, Fregnan RC, Zanin LC, Arenas A (1981) Epidemiological survey of skin diseases in school-children living in the Purus valley (Acre state, Amazonia, Brazil). Dermatologica 163(1):78–93
2. Dogra S, Kumar B (2003) Epidemiology of skin diseases in school children: a study from northern India. Pediatr Dermatol 20(6):470–473
3. Fergusson DM, Dimond ME, Shannon FT (1984) Morbidity during the preschool years. Aust Paediatr J 20(4):281–287
4. Kottenhahn RK, Heck JE (1994) Prevalence of pediatric skin diseases in rural Honduras. Trop Doct 24(2):87–88
5. Mahe A, Prual A, Konate M, Bobin P (1995) Skin diseases of children in Mali – a public-health problem. Trans R Soc Trop Med Hyg 89(5):467–470
6. Popescu R, Popescu CM, Williams HC, Forsea D (1999) The prevalence of skin conditions in Romanian school children. Br J Dermatol 140(5):891–896
7. Ghodsi SZ, Orawa H, Zouboulis CC (2009) Prevalence, severity, and severity risk factors of acne in high school pupils: a community-based study. J Invest Dermatol 129(9):2136–2141
8. Foley P, Zuo YQ, Plunkett A, Marks R (2001) The frequency of common skin conditions in preschool-age children in Australia – atopic dermatitis. Arch Dermatol 137(3):293–300
9. Mar A, Marks R (1999) The descriptive epidemiology of atopic dermatitis in the community. Australas J Dermatol 40(2):73–78
10. Peat JK, Vandenberg RH, Green WF, Mellis CM, Leeder SR, Woolcock AJ (1994) Changing prevalence of asthma in Australian children. Br Med J 308(6944):1591–1596
11. Schultz Larsen F (1993) The epidemiology of atopic dermatitis. In: Burr ML (ed) Epidemiology of clinical allergy. Monographs in allergy. S. Karger AG, Basel, 9–28
12. Walker RB, Warin RP (1956) The incidence of eczema in early childhood. Br J Dermatol 68(5):182–183
13. Williams HC (1992) Is the prevalence of atopic-dermatitis increasing. Clin Exp Dermatol 17(6):385–391
14. Kay J, Gawkrodger DJ, Mortimer MJ, Jaron AG (1994) The prevalence of childhood atopic eczema in a general-population. J Am Acad Dermatol 30(1):35–39
15. Correale CE, Walker C, Murphy L, Craig TJ (1999) Atopic dermatitis: a review of diagnosis and treatment. Am Fam Physician 60(4):1191–1198
16. Ozkaya E (2005) Adult-onset atopic dermatitis. J Am Acad Dermatol 52(4):579–582
17. Williams HC, Strachan DP (1998) The natural history of childhood eczema: observations from the British 1958 birth cohort study. Br J Dermatol 139(5):834–839
18. Lello J, Pearl A, Arroll B, Yallop J, Birchall NM (1995) Prevalence of acne-vulgaris in Auckland senior high-school-students. N Z Med J 108(1004):287–289
19. Lucky AW, Biro FM, Huster GA, Morrison JA, Elder N (1991) Acne-vulgaris in early adolescent boys – correlations with pubertal maturation and age. Arch Dermatol 127(2):210–216
20. Rademaker M, Garioch JJ, Simpson NB (1989) Acne in schoolchildren no longer a concern for dermatologists. Br Med J 298(6682):1218–1219

21. Goulden V, Stables GI, Cunliffe WJ (1999) Prevalence of facial acne in adults. J Am Acad Dermatol 41(4):577–580
22. Jordan WE, Lawson KD, Berg RW, Franxman JJ, Marrer AM (1986) Diaper dermatitis: frequency and severity among a general infant population. Pediatr Dermatol 3(3):198–207
23. Philipp R, Hughes A, Golding J (1997) Getting to the bottom of nappy rash. Br J Gen Pract 47(421):493–497
24. Virgili A, Corazza M, Califano A (1998) Diaper dermatitis in an adult – a case of erythema papuloerosive of Sevestre and Jacquet. J Reprod Med 43(11):949–951
25. Fantl J, Newman D, Colling J et al (1996) Urinary incontinence in adults: acute and chronic management: clinical practice guideline number 2, 1996 update (Report No. 96-0682). Agency for Health Care Policy and Research (AHCPR), Rockville
26. Ward DB, Fleischer AB, Feldman SR, Krowchuk DP (2000) Characterization of diaper dermatitis in the United States. Arch Pediatr Adolesc Med 154(9):943–946
27. Fan X, Xiao FL, Yang S, Liu JB, Yan KL, Liang YH, Sun LD, Du WH, Jin YT, Zhang XJ (2007) Childhood psoriasis: a study of 277 patients from China. J Eur Acad Dermatol Venereol 21(6):762–765
28. Kumar B, Jain R, Sandhu K, Kaur I, Handa S (2004) Epidemiology of childhood psoriasis: a study of 419 patients from northern India. Int J Dermatol 43(9):654–658
29. Nanda A, Kaur S, Kaur I, Kumar B (1990) Childhood psoriasis – an epidemiologic survey of 112 patients. Pediatr Dermatol 7(1):19–21
30. Seyhan M, Coskun BK, Saglam H, Ozcan H, Karincaoglu Y (2006) Psoriasis in childhood and adolescence: evaluation of demographic and clinical features. Pediatr Int 48(6):525–530
31. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis D (2005) Prevalence and treatment of psoriasis in the United Kingdom – a population-based study. Arch Dermatol 141(12):1537–1541
32. Augustin M, Glaeske G, Radtke MA, Christophers E, Reich K, Schaefer I (2010) Epidemiology and comorbidity of psoriasis in children. Br J Dermatol 162(3):633–636
33. Barisic-Drusko V, Paljan D, Kansky A, Vujasinovic S (1989) Prevalence of psoriasis in Croatia. Acta Derm Venereol Suppl 146:178–179
34. Braathen LR, Botten G, Bjerkedal T (1989) Psoriatics in Norway – a questionnaire study on health-status, contact with paramedical professions, and alcohol and tobacco consumption. Acta Derm Venereol Suppl (Stockh) 142:9–12
35. Brandrup F, Green A (1981) The prevalence of psoriasis in Denmark. Acta Derm Venereol 61(4):344–346
36. Falk ES, Vandbakk O (1993) Prevalence of psoriasis in a Norwegian Lapp population. Acta Derm Venereol Suppl (Stockh) 182:6–9
37. Gelfand JM, Stern RS, Nijsten T, Feldman SR, Thomas J, Kist J, Rolstad T, Margolis DJ (2005) The prevalence of psoriasis in African Americans: results from a population-based study. J Am Acad Dermatol 52(1):23–26
38. Kavli G, Forde OH, Arnesen E, Stenvold SE (1985) Psoriasis – familial predisposition and environmental-factors. Br Med J 291(6501):999–1000
39. Kavli G, Stenvold SE, Vandbakk O (1985) Low prevalence of psoriasis in Norwegian Lapps. Acta Derm Venereol 65(3):262–263
40. Koo J (1996) Population-based epidemiologic study of psoriasis with emphasis on quality of life assessment. Dermatol Clin 14(3):485–496
41. Lindegard B (1986) Diseases associated with psoriasis in a general-population of 159,200 middle-aged, urban, native Swedes. Dermatologica 172(6):298–304
42. Lomholt G (1964) Prevalence of skin diseases in a population; a census study from the Faroe Islands. Dan Med Bull 11:1–7
43. Naldi L, Colombo P, Placchesi EB, Piccitto R, Chatenoud L, La Vecchia C (2004) Study design and preliminary results from the pilot phase of the PraKtis study: self-reported diagnoses of selected skin diseases in a representative sample of the Italian population. Dermatology 208(1):38–42
44. Nevitt GJ, Hutchinson PE (1996) Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. Br J Dermatol 135(4):533–537

45. Quirk CJ (1979) Skin-disease in the Busselton population survey. Med J Aust 1(12):569–570
46. Rea JN, Newhouse ML, Halil T (1976) Skin-disease in Lambeth – community study of prevalence and use of medical-care. Br J Prev Soc Med 30(2):107–114
47. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T (2004) Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc 9(2):136–139
48. Yip SY (1984) The prevalence of psoriasis in the mongoloid race. J Am Acad Dermatol 10(6):965–968
49. Williams H (1998) Epidemiology of skin diseases. In: Champion R, Burton J, Burns D, Breathnach S (eds) Textbook of dermatology. Blackwell Science, Oxford, pp 139–158
50. Beasley R, Keil U, von Mutius E, Pearce N, Ait-Khaled N, Anabwani G, Anderson HR, Asher MI, Bjorkstein B, Burr ML, Clayton TO, Crane J, Ellwood P, Lai CKW, Mallol J, Martinez FD, Mitchell EA, Montefort S, Robertson CF, Shah JR, Sibbald B, Stewart AW, Strachan DP, Weiland SK, Williams HC (1998) Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: Isaac. Lancet 351(9111):1225–1232
51. Laughter D, Istvan JA, Tofte SJ, Hanifin JM (2000) The prevalence of atopic dermatitis in Oregon schoolchildren. J Am Acad Dermatol 43(4):649–655
52. Wiedersberg S, Naik A, Leopold CS, Guy RH (2009) Pharmacodynamics and dermatopharmacokinetics of betamethasone 17-valerate: assessment of topical bioavailability. Br J Dermatol 160(3):676–686
53. Brown MB, Traynor MJ, Martin GP, Akomeah FK (2008) Transdermal drug delivery systems: skin perturbation devices. In: Jain K (ed) Methods in molecular biology. Humana Press, New Jersey
54. O'Regan GM, Sandilands A, McLean WHI, Irvine AD (2009) Filaggrin in atopic dermatitis. J Allergy Clin Immunol 124(3):R2–R6
55. Janssens M, van Smeden J, Gooris GS, Bras W, Portale G, Caspers PJ, Vreeken RJ, Hankemeier T, Kezic S, Wolterbeek R, Lavrijsen AP, Bouwstra JA (2012) Increase in short-chain ceramides correlates with an altered lipid organization and decreased barrier function in atopic eczema patients. J Lipid Res 53(12):2755–2766
56. Hardman M, Byrne C (2006) Skin structural development. In: Elias P, Feingold K (eds) Skin barrier. Taylor & Francis, New York
57. Kalia YN, Nonato LB, Lund CH, Guy RH (1998) Development of skin barrier function in premature infants. J Invest Dermatol 111(2):320–326
58. Cartwright RG, Cartlidge PHT, Rutter N, Melia CD, Davis SS (1990) Transdermal delivery of theophylline to premature-infants using a hydrogel disk system. Br J Clin Pharmacol 29(5):533–539
59. Coureau B, Bussieres J-F, Tremblay S (2008) Cushing's syndrome induced by misuse of moderate- to high-potency topical corticosteroids. Ann Pharmacother 42(12):1903–1907
60. Singal A, Thami GP (2006) Lindane neurotoxicity in childhood. Am J Ther 13(3):277–280
61. Zhai HB, Meier-Davis SR, Cayme B, Shudo J, Maibach H (2012) Irritant contact dermatitis: effect of age. Cutan Ocul Toxicol 31(2):138–143
62. Wester R, Maibach H (2005) Regional variation in percutaneous absorption: principles and applications to human risk assessment. In: Bronaugh RL, Maibach HI (eds) Percutaneous absorption drugs – cosmetics – mechanisms – methodology, 4th edn. Taylor & Francis Group, Boca Raton, pp 85–93
63. Ogiso T, Shiraki T, Okajima K, Tanino T, Iwaki M, Wada T (2002) Transfollicular drug delivery: penetration of drugs through human scalp skin and comparison of penetration between scalp and abdominal skins in vitro. J Drug Target 10(5):369–378
64. Ortiz PG, Hansen SH, Shah VP, Menne T, Benfeldt E (2009) Impact of adult atopic dermatitis on topical drug penetration: assessment by cutaneous microdialysis and tape stripping. Acta Derm Venereol 89(1):33–38
65. Ozon A, Cetinkaya S, Alikasifoglu A, Gonc EN, Sen Y, Kandemir N (2007) Inappropriate use of potent topical glucocorticoids in infants. J Pediatr Endocrinol Metab 20(2):219–225

66. Gould AR, Sharp PJ, Smith DR, Stegink AJ, Chase CJ, Kovacs JC, Penglis S, Chatterton BE, Bunn CL (2003) Increased permeability of psoriatic skin to the protein, plasminogen activator inhibitor 2. Arch Dermatol Res 295(6):249–254
67. Singh P, Roberts MS (1994) Skin permeability and local tissue concentrations of nonsteroidal antiinflammatory drugs after topical application. J Pharmacol Exp Ther 268(1):144–151
68. Magnusson BM, Pugh WJ, Roberts MS (2004) Simple rules defining the potential of compounds for transdermal delivery or toxicity. Pharm Res 21(6):1047–1054
69. Reid ML, Jones SA, Brown MB (2009) Transient drug supersaturation kinetics of beclomethasone dipropionate in rapidly drying films. Int J Pharm 371(1–2):114–119
70. Stoughton RB, Wullich K (1989) The same glucocorticoid in brand-name products – does increasing the concentration result in greater topical biologic activity. Arch Dermatol 125(11):1509–1511
71. British National Formulary 65 (2013) British Medical Association and the Royal Pharmaceutical Society of Great Britain, London
72. Trottet L, Owen H, Holme P, Heylings J, Collin IP, Breen AP, Siyad MN, Nandra RS, Davis AF (2005) Are all aciclovir cream formulations bioequivalent? Int J Pharm 304(1–2):63–71
73. Alberti I, Kalia YN, Naik A, Bonny JD, Guy RH (2001) Effect of ethanol and isopropyl myristate on the availability of topical terbinafine in human stratum corneum, in vivo. Int J Pharm 219(1–2):11–19
74. Williams AC, Barry BW (2004) Penetration enhancers. Adv Drug Deliv Rev 56(5):603–618
75. Lee PJ, Ahmad N, Langer R, Mitragotri S, Shastri VP (2006) Evaluation of chemical enhancers in the transdermal delivery of lidocaine. Int J Pharm 308(1–2):33–39
76. Sato K, Sugibayashi K, Morimoto Y (1988) Effect and mode of action of aliphatic esters on the in vitro skin permeation of nicorandil. Int J Pharm 43(1–2):31–40
77. Hollingsbee DA, Fairbrother JE, Martin GP, Marriott C, Monger L (1991) The effect of a hydrocolloid dermatological patch (actiderm) in potentiating the skin blanching activity of triamcinolone acetonide. Int J Pharm 77(2–3):199–209
78. Pershing LK, Silver BS, Krueger GG, Shah VP, Skelley JP (1992) Feasibility of measuring the bioavailability of topical betamethasone dipropionate in commercial formulations using drug content in skin and a skin blanching bioassay. Pharm Res 9(1):45–51
79. Curdy C, Naik A, Kalia YN, Alberti I, Guy RH (2004) Non-invasive assessment of the effect of formulation excipients on stratum corneum barrier function in vivo. Int J Pharm 271(1–2):251–256
80. National Psoriasis Foundation (2009) Topical treatments for psoriasis, including steroids. http://www.psoriasis.org/document.doc?id=164
81. Gupta G, Mallefet P, Kress DW, Sergeant A (2009) Adherence to topical dermatological therapy: lessons from oral drug treatment. Br J Dermatol 161(2):221–227
82. Ellis RM, Koch LH, McGuire E, Williams JV (2011) Potential barriers to adherence in pediatric dermatology. Pediatr Dermatol 28(3):242–244
83. Arzhavitina A, Steckel H (2010) Foams for pharmaceutical and cosmetic application. Int J Pharm 394(1–2):1–17
84. Andreassi L, Giannetti A, Milani M (2003) Efficacy of betamethasone valerate mousse in comparison with standard therapies on scalp psoriasis: an open, multicentre, randomized, controlled, cross-over study on 241 patients. Br J Dermatol 148(1):134–138
85. Lloyd A, Hodgkins P, Dewilde S, Sasane R, Falconer S, Barke ES (2011) Methylphenidate delivery mechanisms for the treatment of children with attention deficit hyperactivity disorder: heterogeneity in parent preferences. Int J Technol Assess Health Care 27(3):215–223
86. Zernikow B, Michel E, Anderson B (2007) Transdermal fentanyl in childhood and adolescence: a comprehensive literature review. J Pain 8(3):187–207
87. Teske J, Weller J-P, Larsch K, Troeger HD, Karst M (2007) Fatal outcome in a child after ingestion of a transdermal fentanyl patch. Int J Leg Med 121(2):147–151
88. Wokovich AM, Shen M, Doub WH, Machado SG, Buhse LF (2011) Evaluating elevated release liner adhesion of a transdermal drug delivery system (TDDS): a study of Daytrana methylphenidate transdermal system. Drug Dev Ind Pharm 37(10):1217–1224

89. Effendy I, Maibach HI (1996) Detergent and skin irritation. Clin Dermatol 14(1):15–21
90. Cork M, Timmins J, Holden C, Carr J, Berry V, Tazi-Ahnini R, Ward S (2003) An audit of adverse drug reactions to aqueous cream in children with atopic eczema. Pharm J 271:747–748
91. Tsang M, Guy RH (2010) Effect of aqueous cream BP on human stratum corneum in vivo. Br J Dermatol 163(5):954–958

Chapter 17
Parenteral Liquids for Intravenous and Transdermal Use

Utpal U. Shah and Matthew Roberts

Abstract Parenteral administration, specifically the intravenous route, is the most widely used method of drug administration in very ill preterm and term neonates and children and during unconsciousness. In other circumstances, some drugs need to be given parenterally due to instability and enzymatic degradation in the gut, variable oral absorption, the need for rapid onset of action, high or sustained levels not achievable by other routes or to avoid first-pass metabolism and gastrointestinal side effects. Consequently, intravenous, intramuscular and subcutaneous injections are commonly used administration routes.

17.1 Introduction

Whilst it is accepted that for the above reasons parenteral drug delivery may be necessary, the challenges associated with these routes for the paediatric population should be borne in mind and addressed during product development.

The difficulties with injections are that they usually have to be administered by professionally trained staff, can cause pain and the anxiety associated with needle phobia in the paediatric population can be significant. There are also psychological and social conflicts experienced by children in integrating chronic parenteral medication regimes into their daily routines, which also have effects on parents and carers. Furthermore, in consideration of the development of a parenteral product for paediatric use, the effect of the choice of the route, formulation, presentation and

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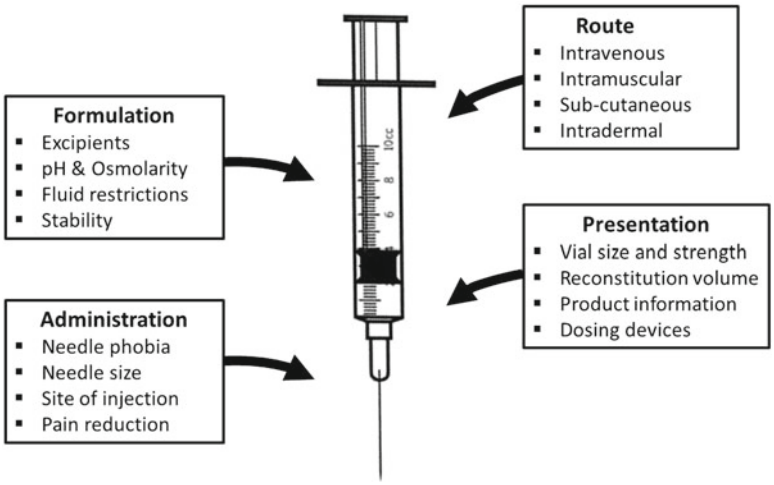

Fig. 17.1 Summary of considerations in developing paediatric parenteral formulations

administration on several clinical and practice parameters must also be considered. These are summarised in Fig. 17.1 and discussed within this chapter.

17.2 Route

When selecting a parenteral route it is important to consider the physiological development of the child, access to the route, pharmacokinetics (absorption, distribution, metabolism, excretion) and toxicity characteristics of the drug and formulation. The acceptability and pain felt by the patient, especially for chronic diseases where co-operation and adherence may become problematic should also be taken into account.

Depending on the clinical condition of the patients, the target population may already have venous access for drug administration via an indwelling peripheral or central venous cannula. This also serves to reduce the pain and fear associated with multiple injections. Thus the intravenous route is more common than the intramuscular or subcutaneous route in hospitalised patients. Other routes, e.g. intra-osseous may be used in emergency situations where venous access cannot be established. Depending on the therapeutic category and indication of the drug in question, the suitability of the use of such routes should be determined and information provided in the summary of product characteristics.

17.2.1 Intravenous (IV)

Venous access is gained by insertion of small cannulae into peripheral veins, or by larger catheters into central veins or by semi-permanent central venous catheters with subcutaneous reservoirs.

Administration via a peripheral vein cannula is simpler, less invasive and easier to manage compared to a central vein but blockages are more common, it is used for a short period, only a single lumen is available and drugs which exhibit a pharmacological effect on the veins are not suitable for this method of administration. The slower blood flow in peripheral veins means formulation characteristics such as hyperosmolarity, extremes of pH, and irritant drugs and excipients can lead to phlebitis and extravasation, which may lead to loss of the vein for therapy and tissue damage. Conversely, insertion and maintenance of a line and catheter into a central vein requires skilled staff, general anaesthesia, has associated morbidity, has a higher infection risk and is expensive to insert. However, a central line can be kept in place on a long-term basis and the faster blood flow allows for the administration of hyperosmolar and irritant formulations (e.g. cytotoxics) as they are rapidly diluted. This route is also valuable for fluid restricted patients where irritant formulations that are usually further diluted for peripheral vein delivery can be given in low volumes as a more concentrated solution. Catheters with multiple lumens allow for the simultaneous administration of more than one drug where compatibilities permit.

Such simultaneous administration is common in neonates since intravenous access is limited. However, flow-rate variability at low infusion rates (0.1 to ~5 ml h^{-1}) is a constant problem in IV therapy for newborns where sudden changes in the volume delivered may have serious consequences. Other contributing factors include vertical displacement distance of syringe pumps relative to the patient, volume of administration sets, presence or absence of anti-siphon valves and inline filters [1]. Infusion flow-rate variability can be minimised by using the highest feasible pre-programmed flow-rate in combination with small syringes and low resistance valves amongst other measures [1].

The IV route usually involves frequent infusions requiring preparation under sterile conditions, which is resource intensive and can delay treatment. The infection risk is also higher with the IV route compared to other routes.

In relation to paediatrics, intravenous access in young children may be challenging. For example, peripheral venous access can be very difficult due to smaller veins in children. It can lead to tissue damage or extravasation and repeated cannulations for regular, repeated treatments can be a major challenge to the child, their family and healthcare professionals. Neonates and infants may be especially prone to tissue necrosis related to extravasation because of their inability to communicate pain and because of the limited extravascular tissue space on the scalp and the dorsum of the hand and foot [2].

17.2.2 Intramuscular (IM)

There may be inter-individual and age-related differences in drug absorption in the paediatric population following intramuscular delivery due to a higher variation in muscle mass, depth of muscle and fat layers and muscle blood flow. The limited muscle mass in preterm and term neonates limits the use of IM injections [3].

Intramuscular injections are painful. The volume administered will affect the pain felt and is usually restricted to 2–3 mL. Adverse effects of the IM route commonly include persistent pain which may affect mobility, erythema and haematoma, and rarely include muscle contracture, nerve damage, abscess formation, bleeding, tissue necrosis, cellulitis and gangrene [4, 5] and thus this route is avoided in children wherever possible. The complications of muscle contracture and nerve damage are also influenced by the appropriateness of the injection site, needle size and angle of injection for the age and size of the child and the nature of the preparation.

17.2.3 Subcutaneous (SC)

The SC route is limited to formulations that are non-irritating to the tissue and do not cause necrosis and sloughing at the injection site. The volume administered needs to be small to avoid pain. Whilst the volume in adults should be ≤2 mL [6], for children it is usually restricted to ≤1 mL.

17.2.4 Intradermal (ID)

The intradermal route is usually used to elicit an immune response, for example, to test for previous tuberculosis infection through ID injection of Tuberculin Purified Protein Derivative. Depot corticosteroid preparations are sometimes given by this route. The distinctive immunological properties of the skin make the epidermis and dermis attractive sites for prophylactic vaccination and ID vaccines have been considered safe, immunogenic and feasible alternatives to IM and SC routes that warrant further investigation [7].

There has also been a renewed interest in dose sparing strategies to mitigate future vaccine shortages following the recent H1N1 influenza virus pandemic and previous shortages. The ID route may offer similar or better immunogenicity compared to SC and IM routes thus enabling the use of reduced doses. In terms of safety, sparse influenza vaccine studies in children have reported that the ID route resulted in a higher incidence of febrile reactions compared to the SC route and a greater frequency of local reactions (erythema) compared to the IM route. Nevertheless, ID vaccination might be more immunogenic in children than in adults and recent developments of new injections devices mean that the future of ID vaccination is promising [7]. Accurate ID injection in terms of depth and volume injected using conventional needles is particularly challenging and painful in neonates, infants and toddlers and the recent advances in delivery devices that alleviate these issues should be utilised if considering this route.

17.2.5 Intraspinal

Intraspinal injections of local anaesthetics via lumbar puncture are used effectively in neonates through to adolescents to provide anaesthesia, analgesia and sympathetic and motor block mainly for surgery to the lower part of the body and also for cardiac surgery due to the effectiveness of this route in suppressing cardiovascular and stress responses to surgery. The flexibility of the spine, short distance between skin and spinal space and a wide lumbar spinal canal make dural puncture easier in children than adults [8]. However, for babies weighing <5 kg epidural administration via an indwelling catheter is preferred. The advantages over general anaesthesia are that respiratory support is not usually required unless the patient is sedated, spinal block can be given on a fed stomach and there is a lower incidence of emesis. It is also a useful route in resource limited settings as it is safe, simple and relatively inexpensive compared to general anaesthesia. The drawback of single-injection spinal anaesthesia is the short duration of action and related inter-individual variability limiting its use to procedures no longer than 75 min. When an extended action is required, adjuvant drugs are combined with spinal anaesthetics to modify the onset, intensity and duration of spinal block. Adverse effects of using this route are similar to those in adults and include a position-dependent headache that worsens in the upright position and improves on lying down and transient neurological symptoms such as pain in the gluteal region and tingling in the feet [8]. In contrast to adults, cardiovascular complications are uncommon in children even at higher doses [8].

17.3 Formulation

17.3.1 Excipients

Some excipients used in parenteral formulations may be unsuitable for younger children as metabolic pathways are still developing, particularly in neonates and infants. The safety profile of excipients in target paediatric populations should be considered during formulation development and selection, recognising that in clinical practice off-label use is prevalent in children and that a formulation strategy that moves towards minimising risks in unlicensed age groups as well is preferred by the clinical community. The lowest feasible quantities of excipients should be used. There is a general lack of paediatric safety data for excipients since such testing is usually conducted in adults and therefore the maximum safe exposure levels in younger children for many excipients still need to be determined. The daily intake of some excipients may exceed the accepted safe limits per kilogram of body weight in adults. Consideration should be given to the daily and cumulative exposure and accumulation. Juvenile animal studies can be useful to identify mechanisms and adverse outcomes that can be monitored in clinical studies and post-marketing surveillance. It may be feasible to assess the acute toxicity of excipients currently in

paediatric use through marketed products (licensed and unlicensed uses), by monitoring effects on biochemical parameters from existing exposures.

Examples that highlight differences in paediatric handling of excipients include benzyl alcohol, used as preservative in injections, which is detoxified by a saturable conjugation pathway in the liver. The detoxification pathway is immature in neonates and can lead to the potentially fatal accumulation of benzoic acid. Current recommendations are to exclude benzyl alcohol in products for neonates and to avoid its use in children up to 3 years of age unless carefully evaluated. Benzyl alcohol may also cause pain on injection and hypersensitivity. Benzoic acid, sodium benzoate and potassium benzoate when used in parenteral dosage forms may increase the risk of jaundice in neonates [9].

Propylene glycol (PG) is used in injectable products of poorly water soluble drugs and multivitamin concentrates. Children below 4 years have a lower alcohol dehydrogenase activity to metabolise PG leading to accumulation, with a half-life of 16.9 h in neonates compared to 5 h in adults. Therefore high levels of PG should not be administered to children below 4 years of age. Adverse effects include central nervous system depression, seizures, lactic acidosis, hyperosmolality (causing laxative effects), renal, hepatic and ototoxicity and cardiovascular effects. Recent work has shown that a median exposure of 34 mg/kg/day for 48 h does not affect maturational changes in renal, hepatic and metabolic function in preterm neonates [10]. The antioxidant sodium metabisulphite contributes to the formation of neurotoxic cysteine in neonates and can have hypersensitivity reactions such as broncospasm and anaphylaxis.

Polysorbate 80, used as an emulsifier, was linked to toxicities and deaths in premature infants administered an intravenous Vitamin E preparation in the United States in 1984 [11, 12]. A Polysorbate 80 dose > 72 mg/kg/day was associated with adverse effects in these patients.

Preterm neonates and children with renal failure are at the highest risk of aluminium toxicity affecting neurological development and bone mineralisation because of their reduced urinary aluminium elimination. Parenteral nutrition and medications contain aluminium and the FDA has set an exposure limit of <5mcg/kg/day. Containers, infusion bags, administration sets and syringes are also contaminated with aluminium to some extent which may be leached during use. Commercial parenteral nutrition products are the main source of aluminium exposure, however, levels can be increased by 40 % during dose manipulation and leaching from containers and administration sets [13], potentially reaching toxic levels depending on amount of intake, duration of exposure and specific patient factors. Infusion solutions containing calcium and phosphate salts tend to be the most contaminated. Excipients such as citrate, phosphate and disodium edetate are all able to bind with aluminium and promote its extraction from containers. Hence manufacturers should be aware that handling and product preparation, especially in neonatal care where dilutions and manipulations are often required, may significantly increase aluminium exposures. The development of excipient-free parenteral formulations and use of plastic containers in preference to glass help to minimise aluminium contamination and inadvertent exposure [13].

The suitability of excipients for the different parenteral routes in terms of irritancy and local tissue damage must be assessed. For the IM route, mixed cosolvent systems containing propylene glycol and ethanol have an additive effect whilst those containing polyethylene glycol 400 may have a protective effect on the myotoxicity generated by IM injections [14]. Liposomes prepared from phospholipids are highly biocompatible with skeletal muscle and are able to reduce the interaction between the encapsulated drug and the surrounding tissue, thus reducing the degree of myotoxicity following IM injection [15]. The choice of diluent may reduce both short-term and long-term discomfort associated with IM injection and the use of lidocaine instead of sterile water as a diluent may be of benefit [16]. Furthermore, buffering to a higher pH (approximately 7.4) increases the amount of pharmacologically active lidocaine and may result in more effective anaesthesia [17].

For the intraspinal route, the close proximity of subarachnoidally injected drugs with neural tissue requires consideration of the potential neurotoxicity of drugs and formulations to be injected into the cerebrospinal fluid. Formulations should not contain antioxidants and preservatives that have a potential for neurotoxicity.

17.3.2 pH and Osmolarity

Irritant intravenous formulations can cause phlebitis, constriction and occlusion of smaller fragile peripheral veins especially in neonates and infants. The resultant high back pressure can lead to extravasation (infiltration) of the medication into the subcutaneous tissue and leakage at the point of cannula insertion into the vein. Extremes of pH and non-iso-osmolar formulations contribute to irritancy, may cause more tissue damage on extravasation and cause pain on injection for most parenteral routes. Therefore iso-osmolar formulations at physiological pH are preferred where stability allows.

Buffer characteristics and pH also influence muscle damage. In vitro studies have indicated that myotoxicity of buffers containing carboxylic acid groups (acetate, succinate and citrate) is directly affected by the pH of the solution and can be minimised by formulating at low buffer capacity and near physiological pH [18]. Furthermore, a significant reduction in pain upon IM administration of MMR vaccines has been associated with moving from an acidic to more physiological pH (7.2–7.6) of the formulation [16].

For SC injections, citrate buffers are associated with local pain [19] and it has been shown that when non-physiological pH must be used for stability reasons, the lowest possible buffer concentration should be used to minimise pain and may enable more rapid normalisation of the pH at the site of injection [20].

Hyperosmolar formulations are those with an osmolarity higher than that of plasma (>290 mosmol/L), which leads to a reversible dehydration and crenation of blood cells. Hypo-osmolar injections can cause blood cells to swell and burst and this haemolysis can be dangerous if a large number of cells are affected. Therefore, excipient concentrations are important. Sodium chloride and glucose are appropriate

Table 17.1 Fluid requirements per 24 h [21]

Body weight < 3 kg	150 mL/kg (start at 40–60 mL/kg if newborn)
3–10 kg	100 mL/kg
For each kg between 10 and 20 kg	Add 50 mL/kg
For each kg over 20 kg	Add 20 mL/kg to maximum of 2,000 mL in adult female and 2,500 mL in adult male
Sodium requirement	3 mmol/kg
Potassium requirement	2 mmol/kg
Glucose requirement	2.4–4.8 g/kg

tonicity adjusting agents that can be used to attain an iso-osmolar formulation. Alternatively, dilution should be carried out prior to administration, but fluid restrictions need to be considered. Hyperosmolar injections may be suitable for administration without further dilution via a faster flowing central vein as previously mentioned. Infusions should be of neutral pH and iso-osmolar unless intended to be co-infused with other solutions. Clear warnings must be given about the need for dilution or co-infusion.

17.3.3 Fluid Restrictions

Intravenous drug therapy has a major impact on the daily fluid allowance in children, which depends on the child's age and weight. For example, neonates are usually restricted to 150 mL/day (including nutritional intake). The need for numerous medications that require large dilution volumes and flushing into the circulation can significantly deplete the daily fluid and electrolyte allowance such that both drug and nutritional therapy is compromised. Approximate daily fluid and electrolyte requirements for paediatric patients based on body weight can be calculated from Table 17.1.

Hence manufacturers should take the above factors into account during development of intravenous injections and recommendations for dilution and flushing of intravenous drugs should be aimed towards the lowest manageable volumes whilst addressing issues of osmolarity, pH and chemical irritancy. Residual volumes in giving sets and intravenous lines may be significant for neonates, and thus special low volume medical devices should be considered for this age group. The flexibility to be able to administer more concentrated preparations provides significant advantages and can be clinically crucial when fluid intake is restricted.

17.3.4 Stability

For products used in adults, additional in-use chemical and physical stability data of reconstituted and/or further diluted products to be used in paediatric settings should be generated since preparation and administration may differ. For example, preferred

dilution fluids may differ and for products aimed at neonates, the environmental conditions within the neonatal unit that affect drug stability should be considered, e.g. temperature, humidity and UV light [22]. Compatibility of i/v formulations with typical diluents, syringes, tubing and infusion bags also needs to be considered. The preferred infusion fluids for paediatric patients are glucose 5 and 10 %, sodium chloride 0.45 and 0.9 % and combinations of glucose and saline.

17.4 Presentation

Where parenteral products are marketed in inappropriate strengths or dose volumes for use in children, the requirement for dose calculation, measurement of very small volumes, part-usage of vials and multiple dilutions increase the risk of medication errors [23]. Incorrect rate of intravenous administration, incorrect dose and incorrect administration technique have all been reported with parenteral delivery to paediatric patients [24]. It is important to balance the need for dilution for osmolarity and dilution for dose measurement with daily fluid allowances. Simple, unambiguous instructions on dose preparation and administration are required to reduce risk of errors [25].

17.4.1 Reconstitution and Displacement Volumes

Injectable drugs presented as lyophilised powders need to be reconstituted with an appropriate diluent. Whilst for adults displacement volumes are usually regarded as negligible, they need to be taken in account in paediatric patients. Thus the displacement volume should be clearly stated and the volume of diluent to be added should result in a final drug concentration that allows simple calculation of proportional doses where some patients will require a dose volume less than the total volume after reconstitution.

Marketing a range of vial sizes (volumes) and concentrations to cater for the different age and weight ranges to be treated alleviates the issues of dose measurability, dose errors and wastage. The need to perform serial dilutions to obtain a measurable dose volume should be avoided. However, it may not be economically viable to produce several variations of a drug product and it may in fact contribute to an increased risk of medication error through confusion during prescribing and selection of the wrong strength during dispensing or administration. Hence a rational limited number of vial sizes and concentrations should be made available. In certain circumstances where a small volume vial is made available for neonates or infants, the use of multiple vials to draw a dose for single injection for elder age groups may be deemed acceptable.

Where small volumes do need to measured, the size of the syringe that allows accurate measurement should be specified. Volumes below 0.1 mL are difficult to

measure, may increase the risk of error [26] and should be avoided. In these instances, a paediatric cartridge rather than a traditional vial could be considered for use with automatic dosing devices similar to insulin injector pens to deliver accurate low doses (see Sect. 17.5).

Compatible infusion fluids should be stated. Paediatric specific administration information should be given about dilutions volumes and rates of infusion or injection.

17.5 Administration

Anecdotal evidence suggests that infants as young as 5 months will react to the sight of an injection if they have had one before. Negative early experiences may lead to persistent challenges of engagement with healthcare. If children struggle, there is a risk of injury to themselves and/or their carers. In addition, the impact of hidden parental distress should be taken into consideration as needle procedures are stressful events for parents during their child's treatment. In severe cases of non-compliance there may be a need for play specialists or restraints. Other safety concerns include the risk of needle-stick injuries during preparation, cross-contamination and safe disposal of sharps.

The appropriateness of the chosen needle dimensions for the intended route of administration should be assessed based on paediatric physiology as they are a factor in the incidence of pain and local reactions. Increasing the needle length for IM injections may reduce pain and adverse effects since the needle is more likely to penetrate the muscle mass [16].

A better immune response for IM compared to SC has been seen with several vaccines and both the injection technique and the needle length are crucial for ensuring the proper IM delivery and thus are directly related to vaccine safety and immunogenicity [27]. It is generally agreed that that anterior thigh (vastus lateralis) should be used for intramuscular immunisation injections until the age of 18–36 months due to the relatively large muscle mass and lack of vital structures, followed by the upper arm (deltoid) area for older children [16].

To reduce the risk of postdural puncture headache following intraspinal injection, a small diameter atraumatic needle with a stylet should be used. Twenty-seven-gauge spinal needles with lengths of 25–38 mm for infants, 50 mm for small children and adult length spinal needles for school-aged children have been used [8]. Post-puncture complications can be difficult to assess in younger children due to the inability of infants to verbally communicate their complaints, leading to misinterpretation of physical and behavioural changes by clinicians.

Several pharmacological and non-pharmacological techniques have been proposed for the reduction of pain associated with IM injections in children, including topical anaesthetic creams and patches, vapocoolant spray, oral sucrose solutions, oral tactile stimulation and parental holding.

The use of paediatric syringe pumps and microbore tubing allows the delivery of precise and regulated infusion rates of medications that can be prepared in 1–60 mL syringes and removes the need for multiple injections. However, this hinders patient mobility and drug adsorption to syringes and tubes should be determined which may require administration sets to be primed before use [25].

Various indwelling catheters have been developed to aid compliance in patient groups that have needle phobia or experience painful injections. They are placed subcutaneously and remain in place for an average of 3–5 days. Such systems have been used for administering doses as low as 0.5 U of insulin via syringes or pen devices [28]. Where spinal anaesthetic delivery is difficult in neonates <5 kg body weight, epidural delivery via an indwelling catheter technique allows the titration of the optimal dose, and can be used for postoperative pain management in this vulnerable group [8].

Compared to the vial and syringe method of drug delivery, pen devices such as those used for insulin therapy, have improved patient acceptability and adherence to chronic injection regimes. Although more expensive, these devices have also reduced the pain felt and allow more accurate dosing, especially of low volume doses. Whilst advances in pen design and function have been made recently, the choice of pens targeted at children is still limited and further development is required [29].

Needle-free liquid and powder jet injectors have been developed to address needle phobia and pain. They also remove the hazards associated with handling and disposing of needles. These devices operate by using compressed gas or a spring mechanism which is used to eject a jet of liquid or powder under pressure from the device onto the skin, the formulation then penetrates to the subcutaneous or muscle layer.

However, liquid jet technology has shown variable adverse reactions (soreness, redness and swelling) and patient acceptability, which may be due to the limited flexibility in their settings [30]. Recently, pulsed microjets that limit the penetration depth of the liquid jets into skin and thus potentially minimise these effects have shown effective delivery of insulin to rats [31] and development of such devices may improve acceptability for children. Liquid jet injectors have been used to deliver a range of vaccines, proteins such as insulin, growth hormone, erythropoietin and interferon, ampicillin, lidocaine, midazolam, steroids and bleomycin. These jet injectors are claimed to be amenable to parenteral formulations intended for needle-based injection. However, efficacy and safety criteria need to be met. Factors affecting drug penetration that require further investigation are mechanical properties of the skin, injection volume and the distance between the injector orifice and skin when the device is actuated (stand-off distance). Determination of the size and shape of the jet induced hole in skin, development of predictive models that require an understanding of fluid dynamics of the skin, skin failure mechanisms and fluid dispersion into tissue is also needed. Importantly, these factors need to be investigated in relation to age. The stability of drugs in jets needs to be established as shear forces are higher compared to needle-based injections. A clear understanding of the pain caused by this administration method and local reactions is needed and whether they are drug, formulation or device specific [32].

Powder jet injectors provide the advantage of ease of storage and improved stability compared to liquid formulations. These injectors deliver drugs in dry powder form into the superficial layers of skin. As some particles are retained in the stratum corneum, impact velocity, particle size and particle density become important design parameters in determining the depth of penetration into the skin layers [30, 33]. In addition, increasing relative humidity and temperature have been shown to increase penetration depth [34]. However, the final particle location can be affected by inter-individual differences in skin layer thickness [33]. Reports have suggested that pain-free delivery can be achieved, but mild erythema, hyper-pigmentation, flaking and discolouration at the injection site following administration of dry powder DNA vaccines to adults have been recorded, although most reactions resolved within 1 month [30]. It is unknown whether repeated administration would result in persistent formulation or device-related adverse effects. If injection site reactions are related to the excipients within a liquid formulation and not the drug itself, they may be reduced through reformulating to a powder for jet injection. The authors are not aware of any products currently in advanced development using this technology. The disadvantages associated with the development of jet injectors are the cost of the technology and the noise on activation of the devices. Furthermore, strict specifications for the gas pressure and nozzle geometry of the device and for the particle size, shape, morphology and density may pose technical challenges.

17.6 Conclusions

Parenteral product development for children requires a matrix of overlapping considerations involving the rationalisation of choice of route, use of non-toxic excipients, appropriate formulation and presentation coupled to the practicalities and challenges associated with drug administration in paediatric practice. Administration devices and methods therefore play a significant role in the acceptability of parenteral products. The development strategy also needs to take into consideration the global locations of the target population, often rural, resource limited settings in developing countries. These present issues such as lack of cold storage, shortage of sterile diluents and administration equipment and increased risk of infections.

References

1. Van der Eijk AC, van Rens RMFPT, Dankelman J, Smit BJ (2013) A literature review on flow-rate variability in neonatal IV therapy. Pediatr Anesth 23:9–21
2. Phelps SJ, Helms RA (1987) Risk factors affecting infiltration of peripheral venous lines in infants. J Pediatr 111:384–389
3. World Health Organization (2010) Development of paediatric medicines – points to consider in pharmaceutical development. http://www.who.int/medicines/services/expertcommittees/pharmprep/Rev2- PaediatricMedicinesDevelopmentQAS08-257Rev1 8102010.pdf

4. Bergeson PS, Singer SA, Kaplan AM (1982) Intramuscular injections in children. Pediatrics 70:944–948
5. Dewit SC (2001) Fundamental concepts and skills for nursing. W.B Saunders Company, Philadelphia
6. Ansel HC, Allen LV, Popovich NG (2004) Pharmaceutical dosage forms and drug delivery systems, 8th edn. Lea and Febiger, Philadelphia
7. Vankerckhoven V, Van Damme P (2010) Clinical studies assessing immunogenicity and safety of intradermally administered influenza vaccines. Expert Opin Drug Deliv 7:1109–1125
8. Kokki H (2012) Spinal blocks. Pediatr Anesth 22:56–64
9. European Medicines Agency (2006) Committee for Medicinal Products for Human Use (CHMP). Reflection paper: formulations of choice for the paediatric population. http://www.emea.europa.eu/pdfs/human/paediatrics/19481005en.pdf
10. Allegaert K, Vanhaesebrouck S, Kulo A, Cosaert K, Verbesselt R, Debeer A, de Hoon J (2010) Prospective assessment of short-term propylene glycol tolerance in neonates. Arch Dis Child 95:1054–1058
11. Alade SL, Brown RE, Paquet A Jr (1986) Polysorbate 80 and E-Ferol toxicity. Pediatrics 77:593–597
12. Martone WJ, Williams WW, Mortensen ML, Gaynes RP, White JW, Lorch V, Murphy MD, Sinha SN, Frank DJ, Kosmetatos N (1986) Illness with fatalities in premature infants: association with an intravenous vitamin E preparation, E-Ferol. Pediatrics 78:591–600
13. De Oliveira SR, Bohrer D, Garcia SC, do Nascimento PC, Noremberg S (2010) Aluminum content in intravenous solutions for administration to neonates: role of product preparation and administration methods. J Parenter Enteral Nutr 34:322–328
14. Brazeau GA, Fung HL (1989) Use of an in vitro model for the assessment of muscle damage from intramuscular injections: in vitro–in vivo correlation and predictability with mixed solvent systems. Pharm Res 6:766–771
15. Lima EM, Oliveira AG (2002) Tissue tolerance of diclofenac sodium encapsulated in liposomes after intramuscular administration. Drug Dev Ind Pharm 28:673–680
16. Schechter NL, Zempsky WT, Cohen LL, McGrath PL, McMurty CM, Bright NS (2007) Pain reduction during paediatric immunizations: evidence-based review and recommendations. Pediatrics 119:1184–1198
17. Hayward CJ, Nafziger AN, Kohlhepp SJ, Bertino JS (1996) Investigation of bioequivalence and tolerability of intramuscular ceftriaxone injections by using 1 % lidocaine, buffered lidocaine, and sterile water diluents. Antimicrob Agents Chemother 40:485–487
18. Napaporn J, Thomas M, Svetic KA, Shahrokh Z, Brazeau GA (2000) Assessment of the myotoxicity of pharmaceutical buffers using an in vitro muscle model: effect of pH, capacity, tonicity, and buffer type. Pharm Dev Technol 5:123–130
19. Frenken LA, van Lier HJ, Jordans JG, Leunissen KM, van Leusen R, Verstappen VM, Koene RA (1993) Identification of the component part in an epoetin alfa preparation that causes pain after subcutaneous injection. Am J Kidney Dis 22:553–556
20. Fransson J, Espander-Jansson A (1996) Local tolerance of subcutaneous injections. J Pharm Pharmacol 48:1012–1015
21. Intravenous fluid therapy (2003) In: Medicines for children, Royal college of paediatrics and child health, London, p G54
22. European Medicines Agency (2007) Guideline on the investigation of medicinal products in the term and preterm neonate. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003754.pdf
23. Beaney AM (2010) Preparation of parenteral medicines in clinical areas: how can the risks be managed? A UK perspective. J Clin Nurs 19:1569–1577
24. Ghaleb MA, Barber N, Franklin BD, Wong IC (2010) The incidence and nature of prescribing and medication administration errors in paediatric inpatients. Arch Dis Child 95:113–118
25. Walsh J, Bickmann D, Breitkreutz J, Chariot-Goulet M (2011) Delivery devices for the administration of paediatric formulations: overview of current practice, challenges and recent developments. Int J Pharm 415:221–231

26. Uppal N, Yasseen B, Seto W, Parshuram CS (2011) Drug formulations that require less than 0.1 mL of stock solution to prepare doses for infants and children. CMAJ 183:246–248
27. Groswasser J, Kahn A, Bouche B, Hanquinet S, Perlmuter N, Hessel L (1997) Needle length and injection technique for efficient intramuscular vaccine delivery in infants and children evaluated through ultrasonographic determination of subcutaneous and muscle layer thickness. Pediatrics 100:400–403
28. Hanas R (2004) Reducing injection pain in children and adolescents with diabetes: a review of indwelling catheters. Pediatr Diabetes 5:102–111
29. Hanas R, de Beaufort C, Hoey H, Anderson B (2011) Insulin delivery by injection in children and adolescents with diabetes. Pediatr Diabetes 12:518–526
30. Arora A, Prausnitz MR, Mitragotri S (2008) Micro-scale devices for transdermal drug delivery. Int J Pharm 364:227–236
31. Arora A, Hakim I, Baxter J, Rathnasingham R, Srinivasan R, Fletcher DA, Mitragotri S (2007) Needle-free delivery of macromolecules across the skin by nanoliter-volume pulsed microjets. Proc Natl Acad Sci U S A 104:4255–4260
32. Shah UU, Roberts M, Gul MO, Tuleu C, Beresford MW (2011) Needle-free and microneedle drug delivery in children: a case for disease-modifying antirheumatic drugs (DMARDs). Int J Pharm 416:1–11
33. Kendall M, Mitchell T, Wrighton-Smith P (2004) Intradermal ballistic delivery of micro-particles into excised human skin for pharmaceutical applications. J Biomech 37:1733–1741
34. Kendall M, Rishworth S, Carter F, Mitchell T (2004) Effects of relative humidity and ambient temperature on the ballistic delivery of micro-particles to excised porcine skin. J Invest Dermatol 122:739–746

Chapter 18
The Challenges of Paediatric Pulmonary Drug Delivery

Darragh Murnane and Marc B. Brown

Abstract The lungs offer a (relatively) easy access route by inhalation for drug delivery, both in terms of topical therapy of lung conditions as well as for systemically acting therapies. In paediatric therapy, it is the former which has been most exploited for the delivery of agents such as bronchodilators, corticosteroids and antibiotics where localized drug delivery can minimize systemic exposure and resultant side-effects.

18.1 Introduction

The widespread use of gaseous anaesthetics reveals also the potential of the large lung surface area, thin epithelial barrier (typically <1 μm) and extensive vascularization of the lungs for systemic delivery of compounds, including peptides and proteins. Pulmonary drug delivery is achieved effectively through the inhalation of pharmaceutical aerosols. However, the lung has evolved anatomical and physiological mechanisms to exclude potentially harmful aerosols. Investigation of these barriers in pulmonary drug delivery has resulted in the development of devices and aerosol formulations to achieve effective pharmacological therapy.

Most inhalation products have been developed with the adult patient in mind and translated to paediatric populations. Children have special needs both in terms of pulmonary physiology and anatomy but also cognitive and physical ability which means that adult therapies are not always well translated into paediatric care. In this chapter the potential uses of aerosol therapy in childhood diseases will be

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highlighted and the particular issues pertaining to aerosol therapy of the developing respiratory tract will be addressed. Rather than justifying pharmacological therapy of specific diseases or populations, the emphasis of the chapter will be on physicochemical properties of aerosol that influence effective drug delivery as well as the formulation strategies that are employed for their delivery. It is the aim of this chapter to provide the reader with the necessary knowledge to judge the appropriateness of inhaled therapy in clinical situations.

18.2 Cognitive, Anatomical and Respiratory Development During Childhood

In order to achieve effective therapeutic outcomes, adherence and concordance with therapy is of paramount importance. The dramatic changes in cognitive, social and emotional skills provide barriers to effective use of therapies. However the anatomical and physiological development during childhood also provides barriers to achieving effective aerosol delivery in paediatric patients. Ultimately children must be *able* to use their medicine accordingly, whether they are reliant on a parent for their care or not. Often children are not able to adopt the correct inhalation manoeuvre for their inhaler [1], particularly when they are below school-going age. Conversely, cognitive barriers may represent a barrier to the use of a device in children who can control their inhalation, and many children commit errors when using their inhaler [2].

The ultimate goal of therapy is to achieve deposition of an aerosol in the lung, however, deposition depends on the anatomy of the airways as well as the inhalation process. Children's airways are smaller than adults and the ventilation and anatomy change substantially during childhood [3]. Infants tend to breathe diaphragmatically at high frequency, and low flow rates through the nose [4]. The lung volume increases by alveolar enlargement (thereby increasing the surface area) and breathing becomes mixed nasal–oral between 2 and 5 years of age. Between 5 and 11 years, parallel to skeletal growth, airways increase in calibre, thereby lowering resistance and breathing becomes slower or deeper. By this age, many children are also able to control their oral breathing suitable for inhalation of aerosol therapy. Infants breathe mainly through the nose with irregular patterns of high flow rate, and spend longer in exhalation or crying, leading to reduced lung penetration of aerosols [5]. Thus the success of lung dosing depends critically on the control of the process of inhalation, which many children are unable to achieve.

18.3 Can Inhaled Medicines Be Delivered for More Than Lung Therapy in Infancy and Childhood?

The majority of inhaled therapies are intended to treat respiratory diseases such as infectious diseases or chronic lung disease such as asthma. The discussion of inhaled therapies which follows in this chapter will focus on topical therapy or respiratory diseases.

However, the high surface area, thin epithelial barrier and absence of mucociliary clearance make the terminal bronchioles and alveolar regions of the lung a particularly effective deposition site for drug absorption. Even in adults the challenges of achieving distal lung delivery of aerosols is daunting. However, the substantial increases in bioavailability which are possible for proteins ultimately culminated in the marketing (and subsequent withdrawal) of inhaled insulin as Exubera® (Nektar/Pfizer) [6]. There have also been reports of development of inhaled therapies of fentanyl and other opioids for pain treatment [7] or dyspnoea [8]. With the exception of the development of inhaled growth hormone [9] systemic therapies have not been developed with children in mind, and inhaled insulin was not licensed for paediatric use. Systemic inhaled therapy is certainly worth consideration in adolescent populations where an adult product is available. In younger children, however, the ability to achieve reproducible deep lung deposition is less assured with conventional inhalers. Rather provided a suitable solution can be formulated, nebulized drug delivery may provide a drug delivery stratagem.

18.4 Aerosol Deposition in the Lungs

Deposition is the term applied to the processes by which the particles within an aerosol cloud leave the inhaled airstream and accumulate on airway epithelium. Accepting that childhood is a period of immense change in pulmonary anatomy and physiology, it is necessary to consider the processes which occur when an aerosol is inhaled into an "ideal" lung to provide the scientific framework for analysing the problems posed by the requirement to access the pulmonary route for drug delivery in children. The upper airways condition inhaled air and extend from the nasal cavity and the mouth to the larynx. Nasal breathing is rather effective at filtering particles from the air, however, the high velocity of airflow in the upper airways imposes turbulence which leads to particle deposition in the oropharynx even during mouth breathing (Fig. 18.1). The airways branch 23 times with a decrease in calibre but increase in number [12]. Thus through the conducting and pulmonary airways the surface area of the lungs increases until the air reaches the alveolar epithelium. The changes in airflow direction at each bifurcation lead to inertial impaction of particles. Additionally, the airflow velocity becomes laminar-to-stagnant by the bronchiolar–alveolar region such that aerosol particle deposition can occur by sedimentation and diffusion [13] (Fig. 18.2).

18.4.1 Aerosol Properties Affecting Pulmonary Deposition

Achieving deposition of particles within the lung for therapeutic effect is not trivial. The strongest evidence (albeit in the case of adults) is that for lung deposition to occur aerosol particles must possess a particle diameter below 10 μm [17]. Particles with a size of 1–10 μm deposit by a combination of impaction and sedimentation,

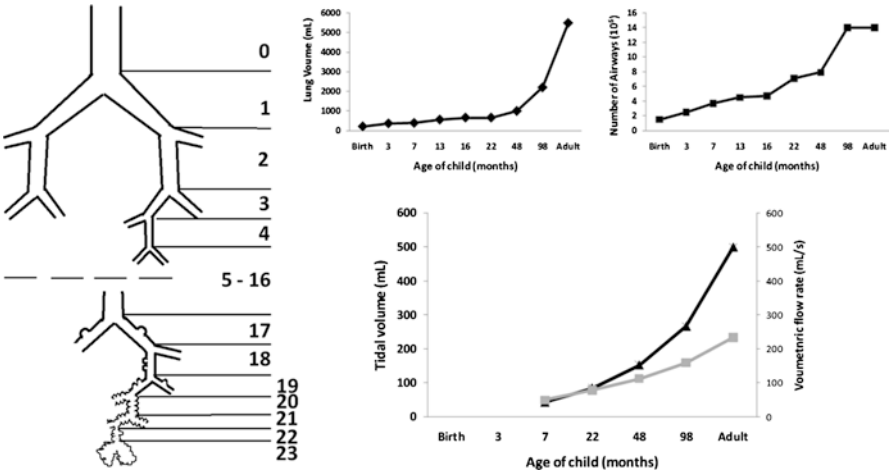


Fig. 18.1 Schematic of the pulmonary anatomy according to the Weibel model of the adult lung. The number of airways increases with each branch point but the airflow and diameter of the airways decrease. As the child ages from infancy there is an increase in lung volume (*top left graph*) and the number of airways (*top right graph*) to adult levels as shown by Dunnill [10]. Of relevance to paediatric drug delivery, the inhalation flow rate and tidal volume under sedentary conditions increase with age to adulthood (*bottom graph*). In infancy the flow rate is determined by the tidal volume [11]

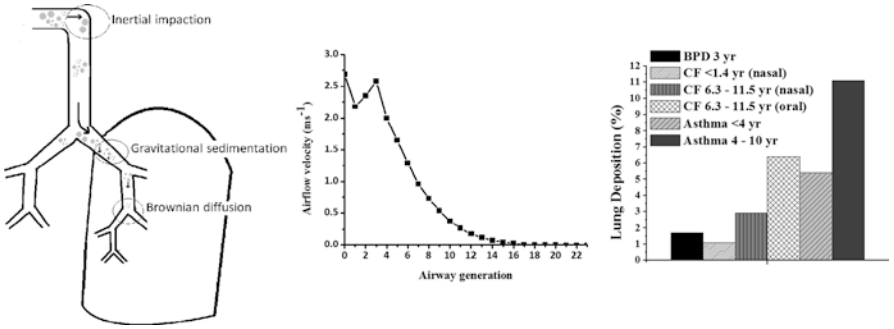


Fig. 18.2 Schematic of the deposition mechanisms for aerosols inhaled into the respiratory tract (*left*). Inertial impaction occurs for the largest particles in airstreams with high velocity. Sedimentation and diffusive deposition occur for particles with small sizes in stagnant air. A simulation showing airflow in the pulmonary airways decreasing to stagnant conditions due to the dichotomous branching of the airways (*Centre*), simulated after [13] with morphometric scaling after [14]. Representation of lung deposition fractions in children of different ages suffering from lung diseases. *BPD* bronchopulmonary dysplasia, *CF* cystic fibrosis. Data taken from [4, 15, 16]

and there is an overlap between deposition by sedimentation and diffusion for particles with a size 0.1–1.0 μm. However, particles <0.1 μm deposit solely by diffusion [18, 19]. Inertial impaction dominates in the conducting airways where airflow is of high velocity and turbulence. Diffusion and sedimentation which occur in laminar

airflow are time-dependent processes, hence deposition fractions increase with a long aerosol residence time in the lung and a close proximity of particles to the airway wall.

The deposition of particles by impaction and sedimentation depends on the aerodynamic diameter, d_{ae}, of the aerosol, which is defined as the diameter of a unit density sphere that possesses the same settling velocity as the particle being considered:

$$d_{ae} = d_g \sqrt{\frac{\rho}{\chi}}$$

where d_g is the geometric diameter, ρ is the particle density (g cm^{-3}) and χ is the dynamic shape correction factor.

Specifically, a d_{ae} of 2–6 μm is required for deposition in the conducting and tracheobronchiolar airways, whilst a size of 1–3 μm is preferable for targeting deposition to the peripheral (smaller) airways and for systemic delivery. From the above equation, it can be seen that the effective size of the particles depends on the density and shape of the particle. Hence a large particle may penetrate the deep lung if it is either needle-shaped or possesses low density.

18.4.2 Physiological and Pathophysiological Factors Affecting Pulmonary Deposition

The major physiological factors to be considered in connection with particle deposition relate to the airflow and geometry of the airways. The interaction of a particle with the airway walls is of higher probability in smaller calibre airways. In this context it is important to consider also the pathological situation, when airways are obstructed (e.g. by accumulation of secretions, narrowing of the airway or alteration of bifurcation angles). For example, due to central and peripheral airway obstruction in asthma, there is a marked decrease in the peripheral deposition of smaller particles which should deposit in peripheral airways [20]. The lung ventilation characteristics (both tidal volume and frequency) are equally as important as the airways anatomy in influencing drug deposition. High ventilation rates with shallow volume decrease the residence time of the aerosol in the lung and consequentially, sedimentation and diffusional deposition are decreased [17]. This leads to the routine clinical advice for inhalation the aerosol with a deep breath followed by a period of breath-holding. High inhalation flow rates (e.g. panting) favour inertial impaction in accordance with:

$$S = B\,m\,v$$

where B is the mobility of the particle (i.e. the velocity per unit of force), m is the particle mass (i.e. size) and v is velocity with which the particle is travelling.

Thus particles which are large or travelling with high velocity will fail to progress beyond a sharp directional change. With the exception of nebulizer use, patients inhale medicines with a pronounced inspiratory peak rather than sinus breathing [21]. Thus there is a high oropharyngeal deposition in those who inhale from aerosol products such as metered dose or dry powder inhalers (DPIs). With an increased inhalation rate the deposition profiles of aerosols are shifted toward the central and upper airways because of enhanced inertial impaction as well as increased turbulence in generations 0–10 [22]. It is also possible to alter the deposition profiles of inhaled aerosols by controlling the ventilation profile of the patient [23].

18.4.3 Deposition in the Paediatric Drug Delivery

The same principles governing respiratory tract particle deposition apply to children as adults; however, the ventilation characteristics and anatomy dictate diverse outcomes for aerosol with similar physicochemical properties. Because younger children (<4 years) breathe nasally, the impact of nasal deposition when children use facemasks must be considered for children. It may therefore be necessary to design an aerosol with different physicochemical properties for children in order to mitigate the enhanced extra-thoracic airway deposition patterns. In particular, it is necessary to avoid nasal/oropharyngeal deposition that leads to side-effects and possible systemic absorption. Because of the low inhaled volumes, longer relative exhalation period and the high turbulence during irregular breathing, the relative central/peripheral airway deposition ratios may change in children with the reduced time for small particle deposition in the deep lung.

Young children who inhale their aerosol through a mouthpiece rather than a facemask receive lower total doses because of the contribution of their concomitant nasal breathing [24]. However, when a facemask is used extra-thoracic (i.e. nasal) deposition is very high leading to lower relative lung dosing [25]. Thus children should be encouraged to use mouthpieces as soon as possible to maximize pulmonary deposition.

Unlike adults, the evidence regarding sites and extent of deposition for aerosols in children as a function of physicochemical properties is inconclusive [14]. The ideal particle size for deposition is suggested to be smaller than 3.6 μm for infants [26]. Particles <2.1 μm are relatively insensitive to ventilation changes in comparison to larger particles. However, unfortunately, the marketed formulations may not always be suitable. Larger particles are mainly affected by inertial impaction and nasal and upper airway deposition is enhanced for particles in the range 3–5 μm. However, equally particles in the range 0.5–3 μm which deposit by sedimentation require breath-holding for effective deposition. Thus it is difficult to accurately assign the ideal particle size for inhalation therapy. Studies have shown that effective deposition fractions in younger children can be achieved with extra-fine aerosol (<2 μm) [26, 27]. However the clinical consequences of enhanced deposition of extra-fine aerosols in children [28] must be balanced with the risks of increased systemic exposure and potential toxicity.

18.5 Aerosol Generation Systems for Pulmonary Therapy

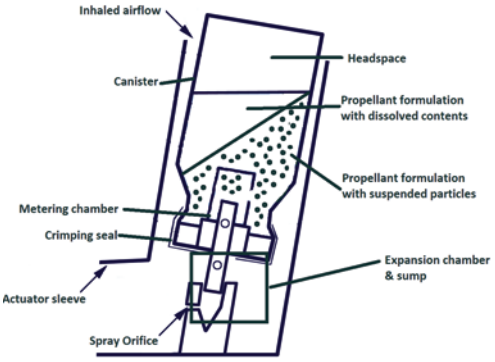
The main platforms for production of aerosols on demand are techniques which produce droplets from bulk solutions or suspension (i.e. nebulization), techniques which release dry powder particle clouds (i.e. DPIs), or techniques which release condensation vapours (e.g. cigarettes). With the exception of solution-based inhalation formulations, the majority of orally inhaled medicinal products contain aerosolizable drug in particulate form. The latter particles must be produced in the low micron size range for formulation into drug delivery products. Particles are typically produced by crystallization and subsequent particle size reduction (micronization). It will become obvious that the dosage manufacture is highly specialized for inhalation. Manufacture often requires expensive equipment or complex processes which are incompatible with extemporaneous product manipulation or small batch operations (e.g. pressurized systems cannot readily be manipulated, nor dry powder blends readily diluted without altering the inhaled drug dose). However the final of the three dosage forms, nebulization, may offer some scope for extemporaneous production in-house for treatment of children in the absence of other suitable dosage forms.

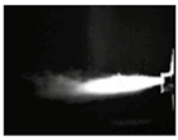
18.6 Pressurized Metered Dose Inhalers

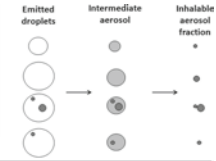
The pressurized metered dose inhaler (pMDI) is a cheap, convenient and portable dosage form that contains multiple doses. All pMDI products have a roughly similar design consisting of one or more active pharmaceutical ingredients (in solution or suspension), a liquefied propellant with excipients, all filled into a canister and sealed with a metering valve. A metering valve that limits the volume dispensed upon actuation controls the dose available for the patient to inhale. The formulation is a liquid under pressure in the canister; however, upon actuation of the valve, the high vapour pressure of the propellant causes a two-phase fluid (liquid–vapour) to exit the device at high velocity through an atomization (spray) orifice which is a component of a plastic actuator. pMDIs are the most used inhalation device worldwide (Fig. 18.3).

18.6.1 Formulation Components and Aerosol Formation

The propellant constitutes greater than 80 % of a formulation and the toxicology, vapour pressure, solvency power, flammability and density are all important properties. The currently employed propellants are hydrofluoroalkanes (HFA) with high vapour pressures, low boiling points and low densities. The low density leads to the rapid sedimentation of denser suspended drug microcrystals resulting in unstable suspensions and dose variability unless the pMDI is shaken appropriately. HFA propellants show comparatively higher water and drug substance solubility in







Device	Age range	Effectiveness	
pMDI + Antistatic spacer[1]	< 4 yr	5.4 % lung deposition	
	4 – 10 yr	9.6 % lung deposition	
pMDI + electrostatic spacer[2]	7 – 12 yr	Plasma concentration 1.9 ng/mL	
pMDI + non-electrostatic spacer[2]	7 – 12 yr	Plasma concentration 4.3 ng/mL	
		Facemask	mouthpiece
pMDI + spacer[3]	1 – 2 month	3 % respirable	-
	2 - 3 yr	21 % respirable	-
	4 – 6 yr	35 % respirable	22 % respirable
	10 – 15 yr	-	40 % respirable

Fig. 18.3 The components and principles of operation of a pressurized metered dose inhaler (pMDI, *left*). Upon actuation a high velocity aerosol cloud of polydisperse droplets is emitted (photograph). The propellant in large emitted aerosol droplets evaporates to form intermediate droplets (which may contain suspended drug microparticles of polydisperse size distribution) and finally residual respirable particles. Volatile solution formulations result in particles of smaller diameter than suspension formulations. Spacer devices are often employed to improve the specificity of lung deposition, however, lung deposition is age-dependent, and is affected by electrostatic charge on the spacer, as well as the choice of facemask or mouthpiece. [1]Wildhaber et al. [16]; [2]Anhoj et al. [29]; [3]Dubus and Anhoj [24]

comparison to other propellants such as chlorofluorocarbons. Ingress of water can cause solvency changes and dissolved drug can precipitate or Ostwald ripening of suspensions can occur. One of the greatest problems is the low solubility of many surfactants in HFAs, leading to difficulties stabilizing suspension formulations. Thus it is important for patients to shake their inhalers effectively to disperse drug particle sediments.

Upon actuation of a pMDI, the opening of the metering chamber to the atmospheric pressure across the spray orifice promotes evaporation of the propellant. A gas–liquid mixture is thus propelled through the spray orifice resulting in the formation of an atomized aerosol cloud. The vapour pressure and viscosity of the formulation determine the fluid flow and hence the aerosol properties. To produce small droplets a combination of a high vapour pressure formulation and small spray orifice diameter is necessary [30]. The primary aerosol is typically comprised of large droplets which may contain some or no drug or excipients. The droplets evaporate resulting aerosol particles which may be of a size suitable for inhalation. For solution pMDI formulations (e.g. QVAR™ or Modulite™), the inhaled particle size distribution is determined entirely by the size of the initial droplets and the evaporation rate, and can be carefully tuned to produce droplets of the required diameter for inhalation. The smallest possible particle size for a suspension formulation is that of the original micronized particles (or their aggregates) following evaporation of the propellant. To maximize lung delivery, it is thus important to formulate a stable suspension with minimal particle aggregation [31].

18.6.2 Patient Use of Metered Dose Inhalers

The pMDI generates an aerosol cloud under the atomizing force of the propellant independent of a patient's respiratory effort. However, the aerosol produced is polydisperse in size and contains large droplets when inhaled directly from the actuator, typically in the order of tens of micrometres. The large droplets are also emitted at high velocity, decreasing from approximately 58 to 5 ms^{-1} depending on the distance from the spray orifice. The consequences of the large particle size and the high velocity are the ballistic impaction of a large fraction of the aerosol cloud in the oropharynx [32]. Throat deposition is high in those patients who do not breathe at the same time as pMDI actuation (i.e. poor actuation coordination). This is one of the most common causes of cognitive error in pMDI use, however, even patients with good technique show lung deposition of less than 1/3 of the emitted dose [33]. Although smaller particles from solution pMDIs are advocated to maximize lung deposition in children, high oropharyngeal deposition is still observed in children using breath-actuated inhalers that were designed to overcome need for coordination [28]. Thus the pMDI including breath-actuated pMDIs may not be the best device for use in children unless combined with an auxiliary device.

18.6.3 Metered Dose Inhalers and Spacer Devices: The Paediatric Option

Valved holding chambers (VHCs) are a spacer device that can reduce oropharyngeal deposition of pMDIs by temporally separating the actuation and inhalation events. Modern VHCs include face masks and encouragement aids designed to appeal to children. VHCs are perceived to reduce extra-thoracic deposition while not altering fine particle lung deposition. However some pMDI–VHC combinations have demonstrated substantial oropharyngeal deposition [34]. Early studies showed dose retention in the VHCs of 50–80 % for salbutamol [35]. Dose deposition in the VHC can occur by impaction in smaller devices; however, evaporation of the aerosol cloud in the VHC promotes formation of a small particle aerosol. The residence time in the VHC dictates the period available for not only evaporation of the aerosol cloud but also sedimentation of the particles. The residence time is a function of the inhaled volume, inhalation frequency and flow rate of the patient and paediatric patients will require multiple inhalations to inhale the dose. Upper airway deposition is physiologically enhanced in children, but the sedimentation occurring during long residence times can result in lower lung deposition in younger children due to VHC retention [36].

The problem of electrostatic interactions between the (typically) plastic VHC devices and the charged pMDI aerosol cloud is a well-known phenomenon, leading to VHC-particle retention. This is particularly the case for paediatric patients who require long inhalation times when sufficient time is provided for electrostatic

deposition to occur. The consequences are that following multiple actuations dose retention in the spacer decreases [37]. Hence bioavailability will alter during the use of the VHC and the electrostatic effect would become important each time the device is washed with water. Washing with a surfactant solution coats the plastic with an antistatic layer, thus avoiding the problem. However, it is more usual that modern VHCs are constructed using conducting plastics or with antistatic linings in order to remove the requirement for parent/patient co-operation with washing and appropriate drying techniques. Antistatic spacers are unaffected by washing and have been reported to improve drug dose delivery for a fluticasone propionate pMDI compared to conventional VHC [38].

18.7 Dry Powder Inhalers

DPIs are also portable but do not require coordination of inspiration and actuation of the dose. DPIs are also suitable for the administration of doses as high as mg quantities, unlike pMDIs. DPIs are either single dose devices, where the formulation is typically contained in a capsule or multiple single unit dose devices where the formulation is contained in a series of unit dose blisters on a strip. Multidose devices are also manufactured, where the formulation is contained in a reservoir and metered by the patient prior to inhalation. The majority of marketed DPIs require a patient's inhalation manoeuvre to aerosolize the drug particles from the formulation and are termed passive devices. In recent years several active devices have also been developed, which use external energy (e.g. compressed air) to achieve aerosolization. When considering DPIs, therefore, it is important to consider the properties of the inhalable particles, the formulation containing those particles and the interactions that occur when the patient inhales through the device.

18.7.1 Formulation Components and Aerosolization of Powder Inhalers

Particles in this respirable size range (<10 μm) exhibit high cohesivity and adhesivity, leading to the particles forming powder agglomerates which are difficult to efficiently aerosolize. The micronized particles for use in DPIs naturally tend to adhere to the device or cohere as large agglomerates. In order to achieve an aerosol suitable for lung deposition (i.e. small particle size), the agglomerated particles must be effectively dispersed. It is difficult to achieve uniform filling of capsules and devices with particles of this size due to poor flow properties, and hence micronized particles are not particularly suitable for high dose formulations. Rather a host of particle design techniques have been developed including to improve powder flow and dispersibility, including spray drying. Such products have now reached the market and include Tobramycin Inhalation Powder™ [39]. In the case of low dose therapies

(<1 mg), it is necessary to blend micronized particles with a diluent such as lactose monohydrate particles (with a size in the range 50–100 μm) to form an ordered mixture known as a carrier-based formulations. The Turbuhaler® products from Astra Zeneca employ a granulation approach where the micronized API particles are granulated with an appropriate wetting liquid with/or without the addition of a bulking agent to aid uniform dose metering.

During aerosolization, the forces of adhesion between the particles in the granules or in the carrier-based blends must be overcome. Not every inhaled drug particle posses the correct balance of cohesive and adhesive forces in the lactose blend for aerosolization to be effective. Strong adhesive bonds to the carrier result in poor aerosolization upon inhalation. However, although high cohesive forces lead to good re-dispersal, uniformity of dose content can be difficult to achieve. It is possible to employ so-called ternary agents in form of micronized lactose [40] or low surface free energy materials (e.g. leucine or magnesium stearate) that modify the cohesive/adhesive force balance with the carrier [41]. For DPIs the product performance has been shown to depend on the properties and history of the micronized particles in the formulations, the physicochemical properties of the carrier, the blending process employed of drug and carrier and the force of the airflow which produces aerosolization. The important properties of the carrier have been extensively reviewed [42]. For example, the lactose crystal size and shape are extremely important properties to consider as is the ratio of the drug particles to the carrier component. The micronization process used for the drug particles results in solid state damage particularly on particle surfaces [43]. Such regions of disorder are susceptible to adsorption of water vapour leading to increased adhesion forces to the carrier. For this reason, DPIs must be protected from exposure to excessive environmental relative humidity.

18.7.2 Patient Use of DPIs

When a patient inhales through a DPI the powder is fluidized, entrained and ultimately de-agglomerated under aerodynamic shear to form the aerosol. Impaction of entrained powder on device walls is also important, while vibrational or centrifugal forces upon spinning of the capsule in capsule-based products (e.g. Cyclohaler™ or Handihaler™) also contributes to aerosolization. In order to achieve effective de-agglomeration into a respirable aerosol a fast, forceful inhalation is required [44]. Otherwise a large particle size aerosol or where the drug particles adhere to the carrier is produced, leading to high throat deposition. Devices are classified as low, medium or high resistance devices and the resistance dictates the airflow which a patient can achieve through the device to achieve aerosolization. For example, many patients with respiratory disease are unable to inhale effectively through medium to high resistance devices [45]. As patients exhibit variability in their inhalation strength, there is also high degree of inter-patient variability in lung deposition from traditional DPIs (range: 5–28 %) [32]. The suitability of a device for a

particular patient can be assessed using devices such as the In-Check Dial produced by Clement Clarke International. The tenet being, that if a patient cannot produce a suitable peak inspiratory flow rate (PIFR) through the device, then aerosolization will not be effective for that device. It is clear that many patients with the cognitive abilities to use their DPI may simply not be able to inhale through their device with sufficient strength to achieve deagglomeration of the formulation suitable for pulmonary deposition.

18.7.3 The Role of DPIs in Paediatric Therapy

DPIs require manual dexterity, correct sequencing of dose priming, and the use of an appropriate inhalation manoeuvre, and therefore appear on the face of it, to be the least suitable option for paediatric therapy. The evidence for the place of DPIs in therapy is conflicting because of the high rate of errors when children use DPIs [46]. Older children (>8 years) show greater competence and detailed training can be used effectively, thus there appears to be an age-dependence in the suitability of DPI use. Given a choice older children and adolescents favour DPIs over pMDI + VHC combinations, due to convenience and portability.

Not all children have the appropriate degree of control of lung function to use DPIs correctly. It is important to inhale with a high flow rate and volume through the device, and this is a particular problem with high resistance devices such as the HandiHaler™ and Turbuhaler™ for children with low lung capacity. In children as much as adults, a prescribing tool such as the In-Check™ Dial is useful in judging suitability of DPI use, but such tools may also be used as training aids for children [47]. Children as young as 6 years [48, 49] or even 3 years of age [50] are able to generate a suitable inspiratory flow with low-medium resistance DPIs (Fig. 18.4). However the evidence for high resistance devices is more ambiguous and low-to-medium resistance devices appear to offer greater consistency in aerosolization performance in younger children. Clinical efficacy has, however, been shown for children using high, medium and low resistance devices. Therefore it is crucial to assess the respiratory capacity and the dexterity of the paediatric patient, when judging the suitability of DPIs for paediatric inhalation therapy.

18.8 Nebulized Drug Delivery

Nebulizers are systems that use an external source of energy to create aerosol droplets of drug solutions or suspensions which the patient inhales as a cloud. The most typical external source of energy is a jet of compressed air; however, nebulizers also use ultrasonic vibrations to achieve aerosol formation. Nebulizers have an important place in acute care where respiratory function is compromised and to treat infants

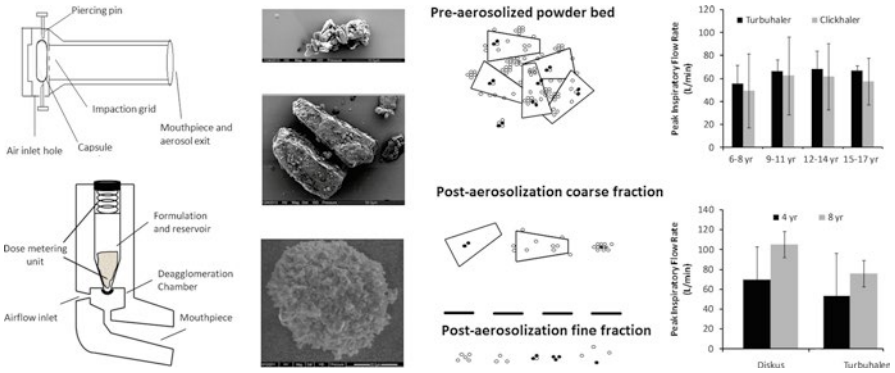


Fig. 18.4 Example designs of a single-dose capsule-based (*top left*) and reservoir multiple-dose (based on Teva's Airmax® device) dry powder inhalers (DPI). Powders in the respirable size range (e.g. salmeterol xinafoate in the *top micrograph*) agglomerate into non-respirable fractions. Micronized particles are typically blended with a large particle size diluents (e.g. lactose monohydrate, *centre micrograph*) or granulated (*bottom micrograph*). The powder blend disperses under the force of inhalation by a patient generating a non-respirable coarse fraction of carrier, carrier-adhered drug and large agglomerates, or a fine fraction of respirable particles or small agglomerates. The magnitude and variability of the inspiratory force generated by children varies according to the device design and age of the child data are mean ± RSD, from [49, 51, 52]

and children when control of lung function is not optimal for using portable devices. Nebulizers are relatively expensive, but offer the benefit of delivery of high doses of drug under conditions of normal tidal breathing.

18.8.1 Principles of Nebulizer Operations

Droplets formed during nebulization are spherical in shape and typically released as fine mist. The properties of these droplets depend on the combination of the feed formulation, the device geometry and mechanical energy applied. Air-jet nebulizers operate on the Bernouilli principle and require a compressed air supply. Ultrasonic nebulizers supply mechanical energy produced by vibrations of a piezoelectric crystal or by vibration of a membrane. Nebulizers produce slow-moving aerosol clouds, that are compatible with many ventilation systems used in respiratory support (e.g. in pre-term neonatal care). In jet nebulization compressed air is passed through a small orifice entraining the formulation liquid from one or more adjacent capillaries, leading to droplet dispersal. Jet nebulizers are suitable for the administration of suspensions and high concentration solutions [53]. The droplet size distribution of the aerosol is determined by the jet-capillary configuration, the airflow rate and the formulation (e.g. viscosity and surface tension). Vibrations in ultrasonic nebulizers generate capillary waves in the fill liquid leading to droplet generation at the surface of the fill liquid. To produce small droplet diameters a high airflow is

required for jet nebulizers. In ultrasonic nebulization the droplet formation is determined by the frequency of vibration.

The droplets formed from nebulizers are polydisperse and baffles must be used to retain large droplets in the chamber. The formed droplets evaporate and/or coalesce before inhalation, and this depends on the adequacy of the diluting carrier airflow. Ultrasonic nebulization may be unsuitable for thermolabile substances including biopharmaceuticals because the fill volume tends to increase in temperature. They are also not suitable for nebulization of suspension formulations [54]. Jet nebulizers are suitable for use with suspensions, but require fill volumes of at least 2–3 mL and long nebulization times. The drug output rate for both depends on the drug concentration in the formulation, and an optimum formulation exists, thus dilution is not advisable unless the dose emission characteristics can be confirmed [55].

18.8.2 Aerosol Formulation Considerations

The majority of formulations are aqueous solutions using water-soluble salt of the drug for its high solubility (e.g. salbutamol sulphate) and to prevent precipitation upon storage. In suspension formulations, it is necessary to include surfactants (e.g. polysorbate 80) to prevent particle aggregation which would increase the eventual particle size of the aerosol. Aqueous formulations should be adjusted to isotonicity to avoid bronchoconstriction upon inhalation. Cosolvents may be required including ethanol and glycerol, to solubilize poorly soluble compounds (e.g. Ventavis™ iloprost trometamol). Other typical excipients included in formulations include antimicrobial preservatives (e.g. benzalkonium chloride), chelating agents (e.g. disodium edetate) and protein peptide formulations often require additional stabilizing agents [56]. It is important to note that the aerosol cloud properties are determined by the properties and components of the formulations (e.g. volatility due to cosolvent use or concentration of non-volatiles, surface tension or viscosity). Hence the practice of mixing formulations or dilution of nebulization liquids is best avoided in order to achieve consistency of product performance, especially given the fact that such a degree of variability exists from nebulizer-to-nebulizer.

18.8.3 Improved Nebulizer Designs

Vented nebulizers overcome the problem with traditional jet nebulizers where the airflow is not usually sufficient for tidal breathing. By providing extra make-up air droplet coalescence nebulization time is reduced. Breath-assisted vented nebulizers restrict aerosol output to the inspiratory phase of the inhalation cycle, thus improving the specificity of lung deposition and improving output rates [57]. Similar technologies have been developed to control lung site deposition by controlling the timing of aerosol release/generation during the breathing cycle [58]. The latter technologies

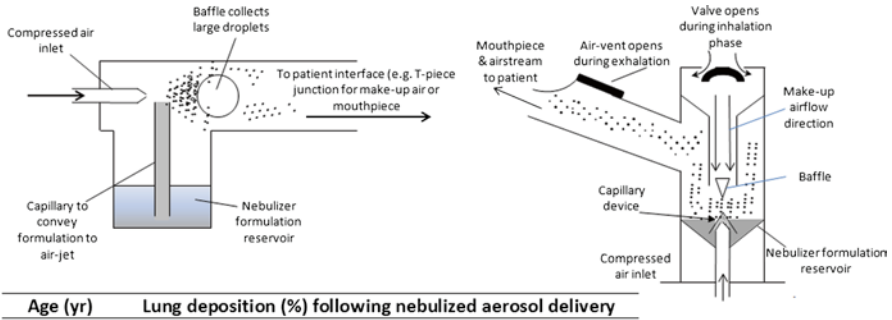
are usually termed adaptive aerosol delivery systems and require microcomputer monitoring of the inhalation process for a patient.

Vibrating mesh nebulizers represent the latest development of nebulization technology offering high portability and low power requirements (AA batteries). By controlling the diameter of the mesh aperture, the droplet size can be controlled in the size range 1–6 μm, and no baffles are required since the majority of the primary aerosol is inhalable. In active devices the vibration of the membrane achieves aerosolization, but in passive devices the vibration is achieved with an ultrasonic horn in contact with the fill liquid. Mesh nebulizers are suitable for delivery of viscous, high concentration and suspension formulations [59]. However, excessive viscosity and surface tension impedes aerosolization rates. Many mesh devices are also suitable for use with low fill volumes [60] and produce slow-moving aerosol clouds, the generation of which can be coordinated with patient inhalation. Thus mesh nebulizers offer a potential solution as a portable drug delivery device for patients who cannot use pMDIs or DPIs correctly.

18.8.4 Nebulizers–Patient Interactions in the Paediatric Setting

For infants and younger children, nebulization offers an excellent drug delivery options since the aerosol is created without requiring any specialized breathing manoeuvres. Marketed nebulizers differ substantially in their delivery performance for a formulation, hence regulators recommend specific nebulizers to be used with licensed formulations. With traditional jet nebulizers, airflow of 6–8 L min^{-1} is required for effective aerosol delivery [53]. However, this can be above the tidal breathing of infants leading to waste to the environment rather than inhalation. The dose emission from jet nebulizers is also continuous regardless of the breathing cycle, leading to further waste and potential for facial deposition. For children from about 6 months to 1 year upwards inspiratory flow rates approximately match nebulizer outputs. When using vented nebulizers that provide for make-up air, older children with higher lung volumes dilute the nebulized aerosol when compared to a younger child. Therefore the overall inhaled dose is lower in older children [61].

Nasal inhalation results in reduced lung deposition fractions in comparison to oral inhalation regardless of delivery device. When sealed masks are used with infants and children facial deposition can occur leading to side-effects or irritation [62]. However, when the facemask is held at a distance (even as small as 2 cm) from the child, the dose available for lung deposition decreases to less than half that with a tightly fitting mask [63]. Vibrating mesh nebulizers may be more suitable than jet nebulizers for use with younger children because the small droplets produced are more likely to escape nasal and oropharyngeal deposition when using facemasks. Vibrating meshes are also useful for speeding up administration times without compromising bioavailability in children [64]. Adaptive aerosol delivery systems have also been shown to be acceptable for children under 4 years when using a face mask [65] (Fig. 18.5).



Age (yr)	Lung deposition (%) following nebulized aerosol delivery			
	Facemask			Mouthpiece
	Not crying	Crying	Poorly fitting	
<0.5	0.8 [1]			
0.5-1.4	1.3 [1]			
2-3	8.0 [2]	1.0 [2]	0.1 [2]	
<4	5.4 [3]	1.3 [3]		
6-8	2.9 [1]			6.0 [1]

[1]Chua et al. (1994), [2] Keller et al. (2004), [3] Wildhaber et al. (1999)

Fig. 18.5 Schematic of a traditional air-jet nebulizer (*left*) and a more modern breath-enhanced nebulizer (*right*). Upon inhalation, additional make-up air is inhaled through a one-way valve thus entraining the aerosol for inhalation. Upon exhalation, the inlet valve closes and an exhalation vent opens, thereby reducing aerosol emission during the exhalation period. Because the make-up is drawn the nebulizer, breath-enhanced systems are less sensitive to changes in environmental humidity. The data demonstrate the low specific lung deposition during crying periods as well as achieved in young children using face masks compared to a mouthpiece. [1]Chua et al. [15]; [2]Keller et al. [66]; [3]Wildhaber et al. [16]

18.9 Concluding Remarks

The field of pulmonary drug delivery is one which is fraught with many uncertainties for the paediatric specialist. The benefits of local therapy of airway diseases are clear and desirable and systemic drug delivery offers real potential for improvements in therapy, even in children. However, a relatively simple analysis demonstrates that there is a high incidence of side-effects following inhaled therapy means the proposed benefits may not always be met. Unlike other delivery routes, the basic anatomy and physiology that constitute the barrier to drug delivery changes vastly from pre-term infant up to the adolescent. Thus the patient population are far from small adults, and very heterogeneous. Infants and young children, in particular, represent a difficult patient group to treat. However, even with an appropriately chosen aerosol (i.e. small particle size) and device (i.e. nebulizer of pMDI with a VHC) drug delivery to these children is possible. It is clear that the earlier a switch to oral inhalation using a mouthpiece can be achieved the better pulmonary drug deposition will be. However the choice of drug delivery platform in such competent children is less equivocal owing to the heterogeneity of the patient popularity. Every child should be assessed individually for his/her cognitive and physical capacity to use a range of inhalation devices and parents and children should be trained and routinely

counselled on correct use. It is important, however, to consider that the worst device is the one a child will not use. Ultimately the decision to use inhaled therapy requires not only prescribing of a device the child can use, but will use because concordance and adherence to therapy achieve best outcomes for children.

References

1. Kamin W, Kreplin A (2007) Teaching the inhalation manoeuvre to asthmatic children by means of visual feedback. Pneumologie 61(3):150–156 (Article in German)
2. Lavorini F, Magnan A, Dubus JC, Voshaar T, Corbetta L, Broeders M, Dekhuijzen R, Sanchis J, Viejo JL, Barnes P, Corrigan C, Levy M, Crompton GK (2008) Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. Respir Med 102(4):593–604
3. Couriel JM, Child F (2004) Applied physiology: lung function testing in children. Curr Paediatr 14(5):444–451
4. Amirav I, Newhouse MT (2012) Deposition of small particles in the developing lung. Paediatr Respir Rev 13(2):73–78
5. Iles R, Lister P, Edmunds AT (1999) Crying significantly reduces absorption of aerosolised drug in infants. Arch Dis Child 81(2):163–165
6. Mastrandrea LD, Quattrin T (2006) Clinical evaluation of inhaled insulin. Adv Drug Deliv Rev 58(9–10):1061–1075
7. Farr SJ, Otulana BA (2006) Pulmonary delivery of opioids as pain therapeutics. Adv Drug Deliv Rev 58(9–10):1076–1088
8. Dudgeon DJ, Lertzman M (1998) Dyspnea in the advanced cancer patient. J Pain Symptom Manage 16(4):212–219
9. Walvoord EC, de la Pena A, Park S, Silverman B, Cuttler L, Rose SR, Cutler G, Drop S, Chipman J (2009) Inhaled growth hormone (GH) compared with subcutaneous GH in children with GH deficiency: pharmacokinetics, pharmacodynamics, and safety. J Clin Endocrinol Metab 94(6):2052–2059
10. Dunnill MS (1962) Postnatal growth of the lung. Thorax 17:329–333
11. Musante CJ, Martonen TB (2000) Computer simulations of particle deposition in the developing human lung. J Air Waste Manage Assoc 50(8):1426–1432
12. Weibel ER (1963) Morphometry of the human lung. Springer, Berlin
13. Martonen TB (1993) Mathematical-model for the selective deposition of inhaled pharmaceuticals. J Pharm Sci 82(12):1191–1199
14. Isaacs KK, Martonen TB (2005) Particle deposition in children's lungs: theory and experiment. J Aerosol Med (Deposition Clearance and Effects in the Lung) 18(3):337–353
15. Chua HL, Collis GG, Newbury AM, Chan K, Bower GD, Sly PD, Lesouef PN (1994) The influence of age on aerosol deposition in children with cystic-fibrosis. Eur Respir J 7(12):2185–2191
16. Wildhaber JH, Dore ND, Wilson JM, Devadason SG, LeSouef PN (1999) Inhalation therapy in asthma: nebulizer or pressurized metered-dose inhaler with holding chamber? In vivo comparison of lung deposition in children. J Pediatr 135(1):28–33
17. Heyder J (2004) Deposition of inhaled particles in the human respiratory tract and consequences for regional targeting in respiratory drug delivery. Proc Am Thorac Soc 1(4):315–320
18. Carvalho TC, Peters JI, Williams RO (2011) Influence of particle size on regional lung deposition: what evidence is there? Int J Pharm 406(1–2):1–10
19. Rostami AA (2009) Computational modeling of Aerosol deposition in respiratory tract: a review. Inhal Toxicol 21(4):262–290

20. Sbirlea-Apiou G, Lemaire M, Katz I, Conway J, Fleming J, Martonen T (2004) Simulation of the regional manifestation of asthma. J Pharm Sci 93(5):1205–1216
21. Broeders MEAC, Molema J, Hop WCJ, Folgering HTM (2003) Inhalation profiles in asthmatics and COPD patients: reproducibility and effect of instruction. J Aerosol Med 16(2):131–141
22. Martonen TB, Katz IM (1993) Deposition patterns of aerosolized drugs within human lungs: effects of ventilatory parameters. Pharm Res 10(6):871–878
23. Brand P, Friemel I, Meyer T, Schulz H, Heyder J, Haubetainger K (2000) Total deposition of therapeutic particles during spontaneous and controlled inhalations. J Pharm Sci 89(6):724–731
24. Dubus JC, Anhoj J (2004) Inhaled steroid delivery from small-volume holding chambers depends on age, holding chamber, and interface in children. J Aerosol Med (Deposition Clearance and Effects in the Lung) 17(3):225–230
25. Le Souef PN, Devadason SG (2002) Lung dose of inhaled drugs in children with acute asthma. J Aerosol Med (Deposition Clearance and Effects in the Lung) 15(3):347–349
26. Mallol J, Rattray S, Walker G, Cook D, Robertson CF (1996) Aerosol deposition in infants with cystic fibrosis. Pediatr Pulmonol 21(5):276–281
27. Schuepp KG, Devadason S, Roller C, Wildhaber FH (2004) A complementary combination of delivery device and drug formulation for inhalation therapy in preschool children. Swiss Med Wkly 134(13–14):198–200
28. Devadason SG, Huang T, Walker S, Troedson R, Le Souef PN (2003) Distribution of technetium-99m-labelled QVAR™ delivered using an Autohaler™ device in children. Eur Respir J 21(6):1007–1011
29. Anhoj J, Bisgaard H, Lipworth BJ (1999) Effect of electrostatic charge in plastic spacers on the lung delivery of HFA-salbutamol in children. Br J Clin Pharmacol 47(3):333–336
30. Brambilla G, Ganderton D, Garzia R, Lewis D, Meakin B, Ventura P (1999) Modulation of aerosol clouds produced by pressurised inhalation aerosols. Int J Pharm 186(1):53–61
31. Murnane D, Martin GP, Marriott C (2008) Investigations into the formulation of metered dose inhalers of salmeterol xinafoate and fluticasone propionate microcrystals. Pharm Res 25(10):2283–2291
32. Pauwels R, Newman S, Borgstrom L (1997) Airway deposition and airway effects of anti-asthma drugs delivered from metered-dose inhalers. Eur Respir J 10(9):2127–2138
33. Newman SP, Brown J, Steed KP, Reader SJ, Kladders H (1998) Lung deposition of fenoterol and flunisolide delivered using a novel device for inhaled medicines – comparison of RESPIMAT with conventional metered-dose inhalers with and without spacer devices. Chest 113(4):957–963
34. Hirst PH, Bacon RE, Pitcairn GR, Silvasti M, Newman SP (2001) A comparison of the lung deposition of budesonide from Easyhaler®, Turbuhaler® and pMDI plus spacer in asthmatic patients. Respir Med 95(9):720–727
35. Dubus JC, Dolovich M (2000) Emitted doses of salbutamol pressurized metered-dose inhaler from five different plastic spacer devices. Fundam Clin Pharmacol 14(3):219–224
36. Barry PW, O'Callaghan C (1999) A comparative analysis of the particle size output of beclomethasone di propionate, salmeterol xinafoate and fluticasone propionate metered dose inhalers used with the Babyhaler, Volumatic and Aerochamber spacer devices. Br J Clin Pharmacol 47(4):357–360
37. Clark DJ, Lipworth BJ (1996) Effect of multiple actuations, delayed inhalation and antistatic treatment on the lung bioavailability of salbutamol via a spacer device. Thorax 51(10):981–984
38. Louca E, Leung K, Coates AL, Mitchell JP, Nagel MW (2006) Comparison of three valved holding chambers for the delivery of fluticasone propionate-HFA to an infant face model. J Aerosol Med (Deposition Clearance and Effects in the Lung) 19(2):160–167
39. Geller DE, Weers J, Heuerding S (2011) Development of an inhaled dry-powder formulation of tobramycin using PulmoSphere™ technology. J Aerosol Med Pulm Drug Deliv 24(4):175–182
40. Adi H, Larson I, Chiou H, Young P, Traini D, Stewart P (2006) Agglomerate strength and dispersion of salmeterol xinafoate from powder mixtures for inhalation. Pharm Res 23(11):2556–2565

41. Begat P, Price R, Harris H, Morton DAV, Staniforth JN (2005) The influence of force control agents on the cohesive-adhesive balance in dry powder inhaler formulations. "KONA" Powder Sci and Technol Jpn 23:109
42. Kou X, Chan LW, Steckel H, Heng PWS (2012) Physico-chemical aspects of lactose for inhalation. Adv Drug Deliv Rev 64(3):220–232
43. Buckton G (1997) Characterisation of small changes in the physical properties of powders of significance for dry powder inhaler formulations. Adv Drug Deliv Rev 26(1):17–27
44. Srichana T, Martin GP, Marriott C (1998) Dry powder inhalers: the influence of device resistance and powder formulation on drug and lactose deposition in vitro. Eur J Pharm Sci 7(1):73–80
45. Cegla UHU (2004) Pressure and inspiratory flow characteristics of dry powder inhalers. Respir Med 98(Suppl 1):S22–S28
46. Kamps AWA, van Ewijk B, Roorda RJ, Brand PLP (2000) Poor inhalation technique, even after inhalation instructions, in children with asthma. Pediatr Pulmonol 29(1):39–42
47. Desager KN, Geldhof J, Claes R, De Backer W (2006) Measurement of inspiratory flow through three different dry powder inhalation devices using In-Check™ in children with asthma. Pediatr Asthma Allergy Immunol 19(1):6–13
48. Bronsky EA, Grossman J, Henis MJ, Gallo PP, Yegen U, Della Cioppa G, Kottakis J, Mehra S (2004) Inspiratory flow rates and volumes with the Aerolizer dry powder inhaler in asthmatic children and adults. Curr Med Res Opin 20(2):131–137
49. Parry-Billings M, Birrell C, Oldham L, O'Callaghan C (2003) Inspiratory flow rate through a dry powder inhaler (Clickhaler®) in children with asthma. Pediatr Pulmonol 35(3):220–226
50. Nielsen KG, Skov M, Klug B, Ifversen M, Bisgaard H (1997) Flow-dependent effect of formoterol dry-powder inhaled from the Aerolizer®. Eur Respir J 10(9):2105–2109
51. Bisgaard H, Klug B, Sumby BS, Burnell PKP (1998) Fine particle mass from the Diskus inhaler and Turbuhaler inhaler in children with asthma. Eur Respir J 11(5):1111–1115
52. Wildhaber JH, Devadason SG, Wilson JM, Roller C, Lagana T, Borgstrom L, LeSouef PN (1998) Lung deposition of budesonide from Turbuhaler in asthmatic children. Eur J Pediatr 157(12):1017–1022
53. Hess DR (2008) Aerosol delivery devices in the treatment of asthma. Respir Care 53(6):699–723
54. Nikander K, Turpeinen M, Wollmer P (1999) The conventional ultrasonic nebulizer proved inefficient in nebulizing a suspension. J Aerosol Med (Deposition Clearance and Effects in the Lung) 12(2):47–53
55. Le Brun PPH, de Boer AH, Heijerman HGM, Frijlink HW (2000) A review of the technical aspects of drug nebulization. Pharm World Sci 22(3):75–81
56. Gonda I (1996) Inhalation therapy with recombinant human deoxyribonuclease I. Adv Drug Deliv Rev 19(1):37–46
57. Le Brun PPH, de Boer AH, Gjaltema D, Hagedoorn P, Heijerman HGM, Frijlink HW (1999) Inhalation of tobramycin in cystic fibrosis – Part 1: the choice of a nebulizer. Int J Pharm 189(2):205–214
58. Bennett WD, Brown JS, Zeman KL, Hu SC, Scheuch G, Sommerer K (2002) Targeting delivery of aerosols to different lung regions. J Aerosol Med 15(2):179–188
59. Dhand R, Sohal H (2008) Pulmonary drug delivery system for inhalation therapy in mechanically ventilated patients. Expert Rev Med Devices 5(1):9–18
60. Newman S, Gee-Turner A (2005) The Omron MicroAir vibrating mesh technology nebuliser, a 21st century approach to inhalation therapy. J Ther Res 5(4):29–33
61. Collis GG, Cole CH, Lesouef PN (1990) Dilution of nebulized aerosols by air entrainment in children. Lancet 336(8711):341–343
62. Brodie T, Adalat S (2006) Unilateral fixed dilated pupil in a well child. Arch Dis Child 91(12):961
63. Everard ML, Clark AR, Milner AD (1992) Drug delivery from jet nebulizers. Arch Dis Child 67(5):586–591

64. Coates AL, Denk O, Leung K, Ribeiro N, Chan J, Green M, Martin S, Charron M, Edwardes M, Keller M (2011) Higher tobramycin concentration and vibrating mesh technology can shorten antibiotic treatment time in cystic fibrosis. Pediatr Pulmonol 46(4):401–408
65. Nikander K, Arheden L, Denyer J, Cobos N (2003) Parents' adherence with nebulizer treatment of their children when using an adaptive aerosol delivery (AAD™) system. J Aerosol Med (Deposition Clearance and Effects in the Lung) 16(3):273–281
66. Keller M, Jauernig J, Schueepp K, Stangl R, Ohl S, Roller C, Devadason S, Wildhaber J (2004) Using infant deposition models to improve inhaler system design. Respiratory Drug Delivery IX, Palm Desert

Chapter 19
Nasal, Ocular and Otic Drug Delivery

Hannah Batchelor

Abstract Non-invasive routes of administration of drugs are attractive in paediatric populations. The nose, eye and ear offer opportunities for drug delivery for localised (and systemic) treatment. This chapter considers anatomical and physiological differences in children compared to adults such that delivery of medicines at these sites is safe and efficacious. In addition the benefits and limitations of formulations used at these sites are discussed with particular relevance for the paediatric population.

19.1 Nasal Drug Delivery

19.1.1 Introduction

Nasal preparations are typically used to treat local diseases including nasal allergy, rhinitis, bacterial sinusitis or nasal polyps in children. However, there has also been interest in delivery via the nasal cavity for systemic therapeutics, particularly where a rapid onset of action is required.

Nasal administrations of drugs have several significant advantages over current practices. The nose has a very rich vascular supply, it facilitates direct absorption to the systemic blood supply and increases bioavailability of the drug, compared to oral administration [1]. The highly vascularised nasal mucosa and the olfactory tissue in direct contact with the central nervous system allow nasally administered drugs to be rapidly transported into the bloodstream and brain, with onsets of action approaching that of intravenous therapy.

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Intranasal drug administration is fast with onsets of action approaching that of intravenous therapy [2], following administration of the medicine the child can sit or stand up due to the rapid absorption. In addition there is no requirement for the medicine to be sterile.

19.1.2 Structure of the Nose

In adult humans the nasal cavity volume is 15–20 mL, the surface area is 150–180 cm^2 and it is covered by a 2–4 mm thick mucosa, of which 5–10 cm^2 is olfactory, and the remaining 145–170 cm^2 respiratory [3, 4]. Although the surface area of the olfactory epithelium is relatively small it can enable direct access to the central nervous system by bypassing the blood–brain barrier [5]. The absorptive surface includes cells that are ciliated; these ciliated cells have approximately 100 cilia on their apical surface which are used to transport mucus towards the nasopharynx [6]. Other cells within the nasal cavity are covered with microvilli which also act to enlarge the overall surface area.

Mucociliary clearance involves the combined actions of the mucus layer and the cilia, and is an important factor in the physiological defence of the respiratory tract against inhaled hazardous particles. It is assumed that the speed of mucociliary clearance in healthy human adults is about 5 mm/min [7], although this is affected by pharmaceutical excipients [8] and diseases (including cystic fibrosis and diabetes) [9]. These differences in mucociliary clearance can affect exposure to intranasally administered drugs.

Nasal mucus which is secreted mostly from submucosal glands is composed of water (95 %), glycoproteins (2 %), other proteins (1 %), inorganic salts (1 %) and lipids (<1 %) [10]. The mucus layer is made up of two components: a lower low viscosity layer of 5–10 μm and an upper more viscous layer of 0.5–5 μm [11, 12]. Hydrophilic drugs are highly soluble in mucus which makes them susceptible to mucociliary clearance. Medicines deposited on the nasal surface are cleared via mucociliary clearance mechanisms; inhaled particles are eliminated within 15–30 min [11, 13].

Intranasal baseline pH is approximately 6.3 in adults [14]; this will affect the solubility of drugs whose pK_a is around this value.

Drugs are absorbed across the nasal epithelium according to the drug's intrinsic physicochemical properties. For passive diffusion the concentration gradient drives absorption, therefore a highly concentrated solution within the nasal cavity will drive absorption.

To ensure adequate coverage of the nasal epithelium the maximum volume to be administered in each nostril is 150 μL in adults to avoid run off into the pharynx [15]. The unit volume administered is also important because it appears that the administration of a single volume of 100 μL leads to deposition over a greater surface area than that obtained with the administration of two 50 μL volumes [16, 17].

19.1.3 Age Related Differences in the Nose

Porter et al. (1997) [18] demonstrated that nasal volume was shown to correlate with age, height and weight in children. Xi et al. (2011) [19] reported that the nasal airway volume and surface area of the 5-year-old child is 40.3 and 65.7 % that of an adult, respectively. Dose adjustments made based on weight and height should match the overall surface area such that the applied dose is similar in adults and children and absorption will be matched.

There are no reports on the differences in nasal mucus, nasal pH or mucociliary clearance in paediatric patients compared to adults. Therefore it is assumed that these properties remain the same in children as in adults.

Balbani et al. [20] reported that in Brazil between 1996 and 2000 there were 233 cases of toxicity in children caused by topical nasal medicines, the main causes of toxicity were accidental intake and error in administration.

19.1.4 Impact of Differences in Paediatric Nose Structure and Physiology on Drug Performance

There are no reported differences in toxicity or clinical efficacy resulting from nasal drug delivery when comparing paediatric to adult patients. The dose adjustment is typically undertaken by instillation of fewer nasal drops or fewer nasal sprays to ensure that the relevant dose is administered.

19.1.5 Local Delivery

Localised delivery to the nose is often measured in terms of administered dose, droplet or particle size distribution, spray pattern and plume geometry. Spray pattern and plume geometry define the shape of the expanding aerosol cloud, while droplet size determines the likelihood of deposition within the nasal cavity by inertial impaction [21]. The distribution within the naval cavity determines the efficacy of the treatment. When formulations are compared it is the aspects of the dispersion that are used to document bioavailability and bioequivalence [21].

19.1.6 Systemic Delivery

Systemic delivery of drugs via the nasal cavity is attractive due to the low barrier to permeation and the rich vascular nature. Examples of marketed nasal product include drugs for treatment of migraine, e.g. zolmatriptan (Zomig®), sumatriptan

(Imitrex®) and butorphanol tartrate (Stadol NS); treatment of severe pain, e.g. fentanyl (PecFent®; Instanyl®); for smoking cessation (Nicorette®) and for treatment of menopausal symptoms (Aerodiol®). Systemic delivery of the following drugs has been examined in children: midazolam for acute seizure [22]; fentanyl for pain relief [23]; diamorphine for pain relief [24]; ketamine for sedation [25]; sumatriptan for migraine relief [26]. More recent research has examined the use of nasal absorption enhancers to increase the bioavailability of drugs delivered via the nasal cavity [1].

19.1.7 Nasal Vaccines

Within the possibilities for mucosal vaccination, the nasal cavity is one of the most promising sites due to (1) its reduced enzymatic activity compared to other possible administration routes (e.g. oral route), (2) its moderately permeable epithelium and (3) the high availability of immuno-reactive sites [27]. Typically particulate formulations are used for nasal vaccination.

Fluenz™ influenza nasal vaccine (AstraZeneca) has recently been approved and is expected to be available in European markets for the 2012–2013 influenza season. Fluenz™ has been tested to demonstrate that is it appropriate for use in children over 2 years of age [28, 29].

19.1.8 Nasal Formulations

Intranasal medications can be delivered in several methods. Drops can be applied from a syringe, the drug can be nebulised or given through pressurised aerosol. All have been demonstrated to be effective [9]. Recently, an atomiser, delivering the drug in a pushed atomised spray was developed. While it is believed that metered-dose systems provide the greatest dose accuracy and reproducibility, the device ease of use vary significantly.

19.1.8.1 Nasal Liquids (Drops and Sprays)

Many different vehicles can be used for delivery intranasally; polymers and gels can be used to increase the viscosity and thereby increase the residence time within the nasal cavity [30]; bioadhesive microspheres may also increase residence time [31]. The viscosity of the solution can affect the deposition area, with solutions of higher viscosity having a reduced deposition area [17].

An atomised nasal spray results in distribution of the nasal formulation over a larger surface area compared to nasal drops; this leads to less drug loss to the pharynx and improved clinical effectiveness [32]. The spray administration and plume angles are key determinants of optimal nasal drug delivery. The combination of an

administration angle of 30° and a plume angle of 30° led to deposition primarily in the anterior region of the nose, with a deposition efficiency close to 90 % [33].

Nasal solutions use drug in a high concentration within the formulation as only a small volume can be administered (approximately 150 μL). Suspensions for nasal administration typically contain micronised drug to ensure rapid dissolution in situ [34].

Nasal liquid systems drain from the nose to the gastro intestinal tract, upon passage these can result in an unpleasant or bitter taste. Although there has been no reports of flavoured commercial formulations there are patents that detail the use of taste-masking or flavouring agents within nasal liquid formulations [35, 36]. The use of flavours may well enhance acceptability within the paediatric population.

19.1.8.2 Nasal Powders

Nasal powders are inhaled by patients. The supply of a powder will increase the stability of the drug compared to a liquid formulation, in addition it is less likely to require taste masking. It is believed that the powder forms a viscous gel within the nasal mucus which may assist in retention within the nasal cavity.

19.1.8.3 Nasal Particulate Delivery Systems

Particulate drug carrier systems may be used to aid in systemic uptake from nasal administration where the carrier may protect the drug from enzymatic degradation, increase the drug dissolution rate, intensify the contact of the formulation with the mucosa, enhance the uptake by the epithelium and act as a controlled release system resulting in prolonged blood concentrations [37].

Nanocarriers can effectively increase the amount of antigen that reaches the immune system, for a full review, see Csaba et al. (2009) [27].

19.1.8.4 Nasal Ointments and Emulsions

Emulsion formulations provide prolonged residence time within the nasal cavity to enhance the duration of action of the drug. Emulsions that are ionic can also form electrostatic interactions with the mucus present within the nasal cavity to further enhance retention. The presence of oil within these formulations can lead to improved absorption although the disadvantages of ointments and emulsions are associated within lack of dose accuracy and poor patient acceptability.

19.1.8.5 Nasal Gels

Gels can be localised within the nasal cavity to promote retention and/or absorption. They can incorporate agents to reduce the irritation that is often associated with

liquids or powders. The disadvantage of gels is their distribution where viscous gels can be localised and not homogenously distributed. Specialist devices are often used to dispense gels due to their higher viscosity.

19.1.9 Discussion/Conclusions

Nasal drug formulations are used within paediatric populations routinely. There are no reported paediatric specific formulations that differ to adult products. However, the similarities in anatomy and physiology ensure that products are likely to perform in the same way in adults compared to children with few reported adverse effects following nasal drug delivery.

19.2 Ocular Drug Delivery

19.2.1 Introduction

Many ocular medications are used in children to treat common bacterial and viral infections, inflammation and allergy, uveitis and glaucoma, as well as other conditions including myopia, amblyopia and strabismus. Eye conditions are prevalent in paediatric populations; within the United Kingdom more than 5 % of children have had at least one eye condition by the age of three [38].

The ocular tissues can be reached either by local or systemic drug administration. The route of administration can be broadly divided into those targeting the anterior or posterior sections of the eye. The absorption, distribution and elimination of drugs may be altered in children compared to adults; the effects of this on ocular drug delivery are detailed.

19.2.2 Structure of the Eye (Fig. 19.1)

The anterior segment of the eye consists of external cornea, conjunctiva, aqueous humour, iris-ciliary body and lens. The cornea and lens obtain most of their necessary nutrients from aqueous humour; with tear fluid providing additional nutrients to the cornea. The iris-ciliary body and conjunctiva are highly vascular tissues. The aqueous humour is a dynamic watery fluid that is continuously secreted by the ciliary body and drained via the canal of schlemm.

The posterior segment of the eye consists of outer sclera, choroid, retina and vitreous humour. The sclera is an avascular tissue that acts as a protective layer. Beneath the sclera is the highly vascular choroid that supplies nutrients to the outer sclera and inner retina. The retina is primarily responsible for image formation and

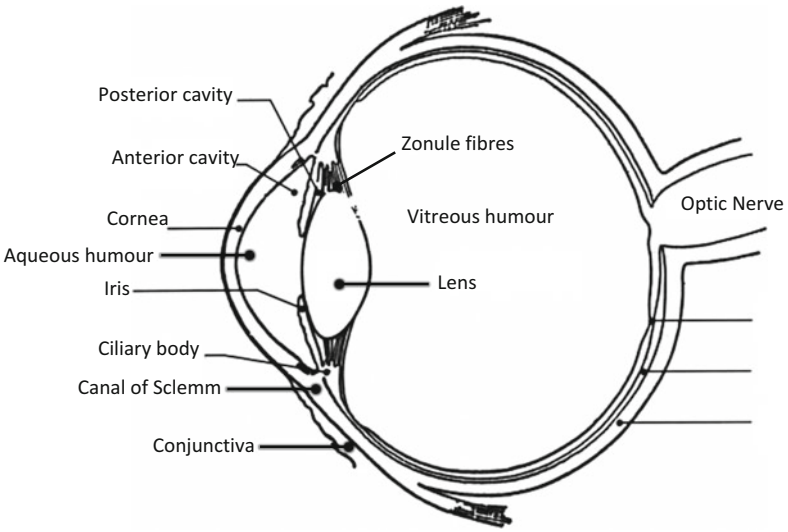

Fig. 19.1 The human eye

therefore vision. The blood–retinal barrier (BRB) is comprised of retinal pigment epithelium and the endothelium of retinal blood vessels. Unlike the aqueous humour the vitreous humour is a clear watery viscous fluid that is replaced at a slow rate.

19.2.3 Age Related Differences in the Eye

The eye of the newborn is roughly two thirds of its adult size at birth, it reaches adult size around ages 3–4 years [39]. In the eye, membranes are thin in neonates and infants, absorption and corneal permeation may be more rapid in infants and neonates [40, 41]. The cornea of the neonate has 70 % of the absorptive surface of the adult cornea, but the total intraocular volume is barely one third of the adult eye [42]. The area of contact between the posterior conjunctiva and the eye globe has been approximated to 4 cm^2 in adults [43]; this surface area would be reduced in children. The ratio of surface area to internal volume could lead to drugs becoming somewhat concentrated within the eye of paediatric patients.

19.2.3.1 Tear Volume

Basal tear volume increases with age; typical volumes reported are 0.5 μL (range 0.6–2 μL) for neonates, 2.5 μL (range 1.4–7.75 μL) for infants (mean age 7 weeks) at an older age, and 6 μL (range 2.73–12.75 μL) in adults [44]. This age related reduction in tear volume can lead to topically applied medications becoming concentrated in younger patients.

Adult pharmacokinetic studies have shown that a 20 μL eye drop achieves the maximum tear film concentration as the low capacity of the precorneal area limits the overall retained volume [45]. The average size of a conventional ophthalmic eye drop is 42.6 μL (ranging from 33.3 to 59.0 μL) [46].

There is no literature data regarding the capacity of the precorneal area in paediatric patients. However, Lawrenson et al. reported that the dimensions of the palpebral aperture change with age; with a rapid increase in width and length occurs from birth to 1 year [47]. These changes in palpebral aperture size have an effect on the exposed ocular surface area with a 50 % increase in mean surface observed from 0–17 to 36–53 weeks [47].

Therefore it could be assumed that the precorneal area in children is reduced compared to adult values with the greatest rate of change being in the first year of life.

The bulk of the tear volume drains through the nasolacrimal system, however, a significant proportion of tears are lost to evaporation. Tears drained via the nasolacrimal system enter the gastrointestinal tract where any drug contained within the tear fluid is subject to gastrointestinal absorption processes.

19.2.3.2 Tear Composition

Tear fluid is a complex aqueous solution containing proteins, metabolites, electrolytes and lipids. The normal pH range of tears in adults was reported as 6.5–7.6 with a mean value of 7.0 by Abelson et al. [48]. Carney and Hill [49] reported that tear pH in adults ranged from 5.2 to 8.6 with a mean value of 7.45 and a reduction to 7.25 was observed in the closed eye. Tear pH was measured in 173 newborn infants and a mean pH value of 6.74 ± 0.26 was recorded [50]. The lower pH value observed in newborn infants may be a result of the fact that they have their eyes closed for longer periods than adult subjects. Slight changes in pH can affect the solubility of drugs; ciprofloxacin has a minimum solubility at pH 7; therefore small change in pH around pH 7 can greatly affect its solubility [51].

The composition of tear fluid in adults has been shown to be affected by eye closure; immediately upon waking higher levels of IgA as well as reactive complement components and activated polymorphonuclear leukocytes have been reported [52]. The equivalent studies have not been carried out in neonates. However, since neonates spend a large proportion of their time sleeping, coupled with a low turnover of tears, a tear composition closer to the adult closed eye is likely. Yet IgA levels may not be as high as anticipated as the ocular secretory immune system may not be fully mature at birth [53–55]. Any potential deficiency in IgA may be offset by the presence of lysozyme, whose levels in full-term neonates appear to be equivalent to those found in adults [53, 56]. Pre-term babies may show reduced levels of antimicrobial proteins [56], and as a result may therefore more vulnerable to infection. The levels of proteins within tear fluid can affect binding of drugs with drug bound to protein being unable to permeate the cornea; therefore reduced protein levels in younger patients may lead to higher free drug concentration within the tear

fluid and consequently greater absorption and effects. In ocular delivery the use of competitive inhibition has been investigated as a means of increasing the free fraction of certain drugs delivered to the eye [57].

19.2.3.3 Blinking Rate

Upon instillation of an eye drop the tear film will increase until a blink occurs. Thus, the volume instilled in excess is diminished rapidly by reflex blinking causing overflow to the cheek and by the extended drainage capacity through the nasolacrimal system.

From a developmental perspective, blink rate increases with age and reaches adult levels by age 20 years. The blink reflex was assessed following glabellar tap in 164 infants and children from ages 2 days to 18 years and in 18 adults aged 18–50 years [58]. The results showed that the mean number of glabellar taps required to induce a blink increased from 2.7 at 0–2 months of age to a peak of 13.3 at age 3–4, remained at more than 10 until age 6, after which a rapid decline occurred, reaching the adult level of two to five taps at age 12 years [58]. Spontaneous blink rates were measured in 269 children and 179 adults; with blink rate increasing with age as shown in the table below [58].

Age	Mean spontaneous blink rate (per minute) [58]
0–2 months	0.7
1–4 years	3.4
5–10 years	6.1
11–15 years	10.3
15–20 years	11.3
>20 years	16.0

The rate of blinking will affect the clearance of the excess solution from the eye with more rapid clearance expected in adults compared to paediatric patients.

19.2.4 Impact of Differences in Paediatric Eye Structure and Physiology on Drug Performance

Topical application of ocular drugs may cause serious adverse ocular or systemic side effects. Children are at greater risk of systemic side effects because ocular dosing is not weight-adjusted, and infants are especially vulnerable particularly in cases where drug metabolism is reduced in the young and/or an immature blood–brain barrier [59].

There are examples where topical administration of ophthalmic medicines in children has led to elevated systemic drug concentrations or systemic side effects; examples include:

- Elevated plasma levels of brimonidine 1,459 and 700 pg/mL following instillation by eye (compared to reported adult studies that show a maximum concentration of 60 pg/mL) leading to somnolence or coma [59, 60].

- Blood levels of timolol in five small children ranged from 3.5 to 34 ng/mL, in contrast to 2.45 ng/mL in adults following topical ocular administration [61].
- Systemic exposure of latanoprost ophthalmic solution 0.005 % once daily was higher in a <3-year age group (166 pg/mL) versus other groups (49, 16 and 26 pg/mL for the 3 to <12-year, 12 to <18-year and ≥18-year age groups, respectively [62]).

The increased systemic exposure observed in paediatric patients has been attributed to absorption of eye drops into the systemic circulation where the reduced size of the patient results in higher plasma levels of circulating drug.

Calculating dosages for paediatric patients is complex; body weight, surface area, development, metabolism, other medications taken and physiologic function can all affect the dosage. Pharmacokinetic models that adjust dosage based on aqueous humour volume ration have previously been proposed for pilocarpine, a drug delivered topically [63]. It is estimated that a newborn requires only one half of the adult dosage of eye drops to obtain an equivalent ocular concentration, two thirds of the adult dosage is required at age 3, and 90 % of this dosage at age 6 [42].

19.2.5 Systemic Ocular Drug Delivery

Systemic delivery of therapeutic agents to the eye is poor. Systemic delivery to the eye requires permeation of the blood–aqueous barrier to reach the anterior chamber or the blood–retina barrier to reach the posterior section of the eye. The blood–aqueous barrier, composed of the uveal capillary endothelia and ciliary epithelia, limits the access of compounds from the systemic circulation to the anterior chamber, whereas the blood–retina barrier limits the drug diffusion from the systemic blood to the retina and vice versa.

Access to the aqueous humour of the anterior and posterior chambers is restricted by the blood–aqueous barrier. Compounds administered systemically can penetrate the vessels of the ciliary body and diffuse through the iris into aqueous humour in the posterior chamber. Movement into the posterior chamber from the anterior chamber is restricted by the diaphragm like action of the iris on the lens. The permeability of the blood–aqueous barrier is reported to be unaffected by age between 13 and 72 years [64].

Numerous studies have investigated the retinal and vitreous penetration of systemically administered antibiotics and antivirals. Fluconazole, ciprofloxacin, meropenem, ofloxacin and rifampin all showed good aqueous humour and vitreous humour concentrations after systemic administration [65–70].

19.2.6 Local Targeting of the Anterior Segment

Local delivery of therapeutic agents ensures that the drug is present at higher concentrations than may be achieved following systemic administration with reduced incidence of side effects.

Drug absorption following topical delivery can occur by two routes: the corneal and non-corneal (conjunctival/scleral) pathways. In the precorneal space, solution drainage, lacrimation and tear dilution, tear turnover, conjunctival absorption and the corneal epithelium limit transcorneal penetration. The low fraction of applied drug reaching the anterior chamber further undergoes rapid elimination from the intraocular tissues and fluids by distribution into non-target tissues and as a consequence of aqueous humour flow.

Corneal permeability has been shown to decrease with age in a rabbit model; where the permeability of pilocarpine was higher in the younger cornea (representing a neonate) compared to that representing a 3-year-old child [41]. Additional studies [71–73] support this data and indicate that corneal permeability is well correlated with epithelial maturation. The permeability differences due to age may be attributed to structural variations, for example, the overall corneal thickness or may in fact reflect more subtle differences in one or more of the corneal layers [41].

The non-corneal or conjunctival/scleral route of absorption involves penetration across the conjunctiva and sclera and then into the intraocular tissues. This mechanism of absorption was once thought to be non-productive. However, many studies have shown that the conjunctival/scleral route is significant for compounds with poor corneal permeability such as inulin, timolol maleate, gentamicin, bimatoprost and prostaglandin PGF2-ALPHA [74–77]. Indeed rabbit conjunctival tissue is relatively more permeable than corneal tissue in terms of paracellular permeability [71].

Typically the anterior segment of the eye (cornea, conjunctiva, sclera, anterior uvea) is treated using formulations including solutions, suspensions, ointments and gels which contain excipients to increase the contact time of the formulation with the eye to maximise the bioavailability of the drug from the formulation. Eye drops are the most commonly used formulation yet they are rapidly drained from the ocular surface and, therefore, the time for drug absorption is only a few minutes and bioavailability is very low, typically less than 5 % [78]. The high rate of clearance of formulations from the eye is rapid due to tear turnover, although the differences in tear production and blinking rate may lead to slower clearance in neonates compared to adults.

19.2.7 Targeting the Posterior Segment

The anatomic and physiologic barriers of the eye render drug delivery to the posterior segment (vitreous humour, retinal pigmented epithelium, retina and choroid) tissues a major challenge. A fundamental mechanistic understanding of the absorption, distribution and elimination pathways for delivery of drugs to the posterior segment is required for rational treatment paradigms.

19.2.7.1 Via Systemic Routes

Penetration of drugs into the posterior segment of the eye from the systemic circulation is restricted by the BRB. For a drug to cross the BRB, it should exhibit either

optimum membrane partition characteristics or should target one of the membrane transporters present on the retinal pigmented epithelial (RPE) cells [79].

The blood–aqueous barrier (formed by the nonpigmented layer of the epithelium of the ciliary body and the endothelium of the blood vessels of the iris) is dual facing as it is exposed to both the anterior and posterior eye; typically hydrophilic substances penetrate the anterior chamber whereas lipophilic substances (e.g. chloramphenicol and tetracycline) penetrate the posterior segment of the eye [79].

Following drug diffusion into the posterior segment of the eye the drug is often localised at the site of appearance rather than distributed homogenously throughout the vitreous humour and negligible drug concentrations are present at the centre of the vitreous body [80]. For a drug to have high concentration in the posterior segment following systemic administration the drug must be able to traverse the RPE, have some depot effect and have a prolonged concentration gradient to drive the diffusion process.

Most of the drugs used in the treatment of posterior segment diseases are not able to penetrate the membranes to reach the desired site of action. Therefore, in practice large doses of intravenously administered drugs (e.g. steroids, antibiotics, antivirals) are required to create the necessary concentration gradients to drive transport into the vitreous humour. Typically drugs are delivered via intravitreal and periocular routes to target the posterior segment of the eye. However, there are very few paediatric medicines licensed that target the posterior segment of the eye.

19.2.7.2 Via Topical Routes

Penetration and distribution of a drug into the posterior tissues of the eye after topical administration is rare. However, memantine HCl and brimonidine tartrate have been show to reach the vitreous and retina after topical ocular delivery [79].

To maximise penetration of topically administered eye drops to the posterior segment the patient should be supine to allow the formulation to flood the conjunctival cul de sac and the diffusion into the posterior sclera is maximised [81]. Lipophilic drugs are more likely to be able to traverse the membranes and target the posterior segment following topical application.

19.2.7.3 Via Intraocular Injections

Direct intraocular administration circumvents the many barriers that prevent drugs penetrating the eye when delivered either topically or systemically. However, this route has low patient acceptability and requires a health professional to administer the medicine. More recent research has looked at solid metal microneedles measuring 500–750 μm in length as a means of delivering drugs into the eye via intrascleral and intracorneal routes in a minimally invasive manner. This theory was assessed by Jiang et al. [82] who demonstrated that microneedles were mechanically strong

enough to penetrate into human cadaveric sclera and that the drug coating rapidly dissolved off the needles within the scleral tissue within 30 s after insertion. This delivery method has yet to be tested in a clinical setting.

19.2.8 Ocular Formulations

19.2.8.1 Solutions

The precorneal residence of an ophthalmic solution can be increased by the inclusion of viscosity enhancing or bioadhesive polymers as excipients. Various polymers have been used including carbopol gels, cellulose derivatives, dextran, gelatin glycerin, polyethylene glycol, poloxamer 407, polysorbate 80, propylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone to prolong the ocular residence time. The use of such excipients, however, remains applicable to only hydrophilic drugs and the advantage of increasing the viscosity must be balanced against the potential disadvantage of inducing ocular disturbances due to the blurring of vision as a result of a change in the refractive index on the ocular surface.

Certain polymers have additional properties to increase the residence time including those able to interact with the mucous layer covering the corneal and scleral surface [83–85]. Furthermore polymers that undergo a phase transition from a solution to a gel within the eye can have benefits (e.g. pH [86], temperature or mono/divalent ion concentration [87]). For a full report on polymers and their function in ocular drug delivery the reader is referred to [88]. The use of microspheres and liposomes in targeting the anterior segment of the eye has largely focussed on improving corneal adhesion and permeation by incorporating various bioadhesive and penetration enhancing polymers within the outer surface of the microparticles [89].

A significant issue with solutions is the volume of liquid dispensed from each drop is difficult to control which leads to wastage. Using an appropriate drop volume would reduce wastage of product and may assist in reducing systemic side effects in younger children [90]. Reducing drop size cannot be achieved by just changing the size and opening of the tip of the dropper. Formulations vary in their surface tension which results in different size drops when the volume of fluid is the same. Investigations have focussed on altering surface tension by changing the inactive ingredients, alternatively a spray system may offer benefits in terms of smaller droplet size [91].

Due to the mechanism by which eye drop solutions are cleared, taste of the formulation may need to be considered in certain cases. An unpleasant bitter taste following eye drops has been reported for many drug products (e.g. in adults using topical therapy for lowering intraocular pressure [92]). There are currently no flavoured eye drops available for paediatric patients that may improve acceptability of the formulation although there are several patents in this area including orange and lemon flavoured Opcon-A® eye drops [93]. The regulatory burden associated with inclusion of a flavouring agent within an ocular solution is significant as full ocular toxicity testing is likely to be required for any flavouring agent.

19.2.8.2 Suspensions

The use of suspensions in ophthalmology is limited as suspensions present problems with regard to physical stability and method of sterilisation, having to be prepared aseptically due to the unsuitability of other techniques. Sieg and Robinson [94] claimed that for a suspension formulation to show any advantage over a saturated solution in terms of ocular bioavailability, the dissolution rate of the particles must be equal to or greater than their rate of clearance from the precorneal area. As described previously tear fluid may be retained for longer in very young children therefore there may be greater drug concentrations within the tear fluid as more may be dissolved. This may lead to a greater effect of a drug administered as a solution to the very young compared to an adult patient.

19.2.8.3 Ointments

Ophthalmic ointments typically have greater retention in the precorneal region compared to aqueous formulations [95] meaning that the frequency of application can be reduced. However, their major limitation is the associated blurring of vision caused by administration of the ointment; this factor is less of an issue for night time use and may be less problematic in younger children. Ointments are administered following instructions such as; "Apply 1.5 cm of ointment every 3 hours"; this type of instruction allows for dosage adjustments to be made to account for younger patients if required. This is an advantage compared to solutions and suspensions where the drop size is determined by the formulation and dropper supplied.

19.2.8.4 Gels

Eye gels are used as a means to deliver longer acting agents with the most used example being timolol maleate. The product can be formulated to be applied as a solution that gels upon contact with the ocular surface [96]. The systemic absorption can also be reduced by use of a gel as the drug is retained at the ocular surface rather than cleared via the nasolacrimal route. There are no particular differences with this formulation for use in children as compared to adults.

19.2.8.5 Inserts

Ocular inserts are solid or semi-solid devices, usually made of polymeric materials that are placed in the conjunctival sac to deliver drugs to the ocular surface. Biodegradable silicone-based ocular implants have been developed to continuously release cyclosporine A for several years. These devices have higher bioavailability for deep ocular tissues compared to topical delivery [97, 98]. Insertion and replacement of these CyA implants require surgery and thus these appear to be more suitable for severe ocular diseases that need long-term treatment.

The potential advantages offered by inserts include accurate dosing for adults, increased ocular residence time, reduction in systemic side effects, improved patient compliance due to reduced frequency of administration and potential to control the release of drugs over time as well as increased shelf-life. Despite the advantages of ocular inserts, their main disadvantage is the foreign body sensation accompanied with their initial administration. However, this disadvantage did not prevent the adoption of this technology in several successfully marketed ocular inserts (Ocusert®, Ocufit® SR and Minidisc®) [99]. The accuracy of dose, although measured for adults is not adapted for paediatric patients therefore these may only be suitable for older children.

19.2.8.6 Punctal Plugs with Active Ingredient

Occlusion of puncta through punctal plugs is common non-medical treatment of dry eyes as punctual plugs block the flow of the tears through the canaliculi which connects eyes to the nose. Insertion of punctal plugs has been reported to improve tear film stability and tear osmolarity and also to improve vision for dry eye patients [100]. Commercial punctal plugs range in length from 1.1 to 2 mm and in diameter from 0.4 to 1.1 mm. Typical drug eluding punctal plugs consist of cylindrical cores coated with an impermeable shell where the drug essentially diffuses out from the circular cross-section in contact with the tears [101–103]. The rate of drug diffusion can be controlled to ensure delivery of therapeutic doses over a prolonged period, as demonstrated by Gupta and Chauhan [104] using cyclosporine A as an example drug.

Although dry eye severe enough to warrant treatment is rare in children the use of punctual plugs in children with a mean age of 7 years was reported by Mataftsi et al. [105], however, there are no reports of punctual plugs incorporating active ingredients in children.

19.2.8.7 Contact Lens

Ophthalmic drug delivery through contact lenses significantly increases drug residence time and bioavailability compared to drug delivery via eye drops [106].

Nanoparticle-laden lenses for extended delivery of several drugs including cyclosporine A have been developed [107, 108]. Additionally biomimetic and "imprinted" contact lenses to increase the drug-loading and release durations have been developed with most work undertaken on timolol [109–111]. Also, recently, Ciolino et al. [112] developed a lens containing a layer of drug-loaded PLGA (poly[lactic-*co*-glycolic acid]) film sandwiched between layers of pHEMA (poly[hydroxyethyl methacrylate]) for extended delivery of ciprofloxacin.

To date there are no commercially available drug releasing contact lenses although Vistakon Pharmaceuticals has completed a clinical trial of a contact lens that would release ketotifen-4 to treat allergic conjunctivitis; the eligibility for this study was from aged 8 years so there is potential for this device to be used in older paediatric patients [113].

Visulex® Noninvasive Iontophoretic Ocular Drug Delivery Device

The Visulex® (Aciont Inc., Salt Lake City, UT) is a non-invasive, iontophoretic ocular drug delivery scleral-lens shaped application device which maintains a drug reservoir on the same location on the eye's conjunctival surface to minimise solution leakage, exposure of the drug to the cornea and surface clearance effects. Iontophoresis is a method of drug delivery that utilise electric current to deliver ionised molecules to intraocular tissues where the ionised molecules are driven by specially designed ocular surface electrodes. Iontophoresis offers benefits of targeting of drugs to specific regions within the eye. There is no literature evidence that details the use of iontophoresis in paediatric populations.

19.2.8.8 Subconjunctival Injection

Subconjunctival injections are routinely used for the administration of anti-infective drugs, mydriatics or corticosteroids for conditions not responding to topical therapy. Following injection the drug will diffuse through the sclera to reach the anterior and posterior sections and the vitreous humour avoiding the cornea which has low permeability compared to the sclera. As the subconjunctival space is limited this type of formulation is only suitable for drugs that are readily soluble. In addition, to avoid frequent administration of subconjunctival injections a slow release formulation is preferred [114]. Typically a concentration of 1 μg/mL may be achieved in the vitreous following this type of administration [114].

19.2.8.9 Intravitreal Injection

Direct intravitreal injection of drugs into the vitreous cavity is employed to achieve higher drug concentrations in the vitreous and the retina. However, repeated injections are needed to maintain drug concentrations at an effective therapeutic level over a certain period of time since the half-life of drugs in the vitreous is relatively short. Repeated intravitreal injections result in extreme patient discomfort and may lead to complications such as vitreous haemorrhage, infection and lens or retinal injury. Formulation strategies focus on improving the retention site at the site of injection or the use of drugs with a long half-life to avoid frequent administration of intravitreal injections.

19.2.8.10 Microparticles for Sustained Release Injection Formulations

Drugs can be formulated to be encapsulated within microparticles, for example, microspheres or liposomes which can be the basis of an intravitreal injection to provide sustained release of a drug. Microspheres of biodegradable polymers such as poly(lactic acid) (PLA) or PLGA have shown to effectively deliver drugs to the vitreous and retina and can be tolerated by the ocular tissues [115].

19.2.8.11 Intravitreal Inserts

Solid biocompatible implantable devices for sustained or controlled intravitreal drug delivery to the posterior segment of the eye have been developed employing diverse approaches and includes the use of implantable devices such as osmotic mini-pumps, nonbioerodible and bioerodible drug-loaded pellets, configured capillary fibres, biodegradable scleral plugs, scleral discs, polymeric matrices and scaffolds of various geometries providing unique mechanisms of drug release for the delivery of drugs to the posterior segment of the eye [116].

Nonbioerodible devices are able to offer the advantages of sustained release and reduced host response. However, bioerodible intravitreal drug delivery devices have gained much popularity over nonbioerodible devices due to the fact that they are eventually absorbed or excreted by the body eliminating the need for surgical removal of the device after the drug-load has been depleted thereby increasing patient acceptance and compliance [116].

The rate of polymer erosion from bioerodible ocular inserts can be affected by numerous factors including pH or temperature which may cause a transient increase or decrease in the erosion rate of the device. The rate of erosion may differ in paediatric patients if the pH within the eye is different; currently this is unknown although as stated previously the pH of tears in neonates is lower than in adults. The surface area of the drug delivery device also plays a significant role in its erosion geometrical shapes with surface areas that do not drastically change as a function of time are typically used. During erosion the dimensions of the device compared to the overall eye shape may influence the rate of surface area decrease and again this may be different in paediatric patients compared to adults. Most implantable devices have fixed dimensions that control the dose administered therefore these are of limited use in very young patients.

OphthaCoil®

Pijls et al. [117] developed an intraocular drug delivery device called “OphthaCoil” this device consists of a drug-loaded mucoadhesive hydrogel on a thin coiled metallic wire. On contact with tear fluid the hydrogel coating swells and drug is released into the tear film. A disadvantage of the OphthaCoil device is the fact that removal of the device is required after the drug-load is depleted.

Vitrasert®

Vitrasert (Chiron Vision Inc., Irvine, CA) is a nonbiorerodible device that requires a 4–5 mm sclerotomy at the pars plana for implantation. It was indicated for the local treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). Safety and effectiveness in paediatric patients below 12 years of age was not established [118]. This product was withdrawn in Europe at the request of the marketing authorisation holder in 2002 [119].

Retisert® and Medidur® Devices

Retisert (Bausch & Lomb, Rochester, NY) is a nonbioerodible device that was designed to release 0.59 μg/day of fluocinolone acetonide into the vitreous cavity to treat diabetic macular oedema [120]. Safety and effectiveness in paediatric patients below 12 years of age has not been established [121].

Medidur® device (Alimera Sciences Inc., Atlanta, GA and pSivida Inc., Watertown, MA) also contains fluocinolone, but it is a much smaller device and the insertion procedure is similar to an intravitreal injection. This device is authorised as Iluvien® within the UK to treat diabetic macular oedema. The EMA granted a waiver for the use of fluocinolone in paediatric patients as diabetic macular oedema does not occur in paediatric patients under the age of 12 and that the medicinal product does not represent a significant therapeutic benefit in children aged 12–18 as clinical studies are not feasible [122].

I-vation®

The I-vation® technology [SurModics (Pty) Ltd., Eden Prairie, MN] consists of a helical coil with an eluting polymer containing triamcinolone. The device is self-anchoring within the sclera. This product is not currently available clinically. The EMA granted a waiver for triamcinolone for paediatric populations on the groups that clinical studies cannot fulfil a therapeutic need of the paediatric population [123].

19.2.9 Discussion/Conclusions

Ocular drug delivery systems are prescribed for use in paediatric populations despite there being limited information about their rational use. Anatomical and physiological differences in the eye of neonates and infants leave them vulnerable to systemic effects of topically administered ocular drugs. Further studies are required to understand how formulations behave in a paediatric population. In addition, there may be a need for a paediatric delivery device to provide a smaller dose of topically applied medicines.

19.3 Otic Drug Delivery

Many inner ear disorders cannot be adequately treated by systemic drug delivery. A blood–cochlear barrier exists, similar physiologically to the blood–brain barrier, which limits the concentration and size of molecules able to leave the circulation and gain access to the cells of the inner ear.

19.3.1 Introduction

Drugs that act on the ear in paediatric populations include therapies for otitis externa, otitis media and the removal of ear wax. These medicines are most frequently applied as ear drops and sprays. A small volume is generally used as excess will be lost out of the ear passage.

19.3.2 Structure of the Ear

The ear can be divided into three parts: external ear, middle ear and inner ear. The external auditory canal (EAC) is a tube that leads from the external to the middle ear. Salvinelli et al. [124] measured the length of the EAC in adult cadavers and reported the length as 23.5 ± 2.5 mm and the greatest and least diameters to be 9.3 ± 0.9 and 4.8 ± 0.5 mm, respectively.

The tympanic membrane separates the external ear from the middle ear; within the middle ear is the tympanic cavity which is a small epithelial lined cavity hollowed out of the temporal bone that contains three auditory ossicles. The distal part of the middle ear is continuous with numerous mastoid air spaces in the temporal bone. The middle ear is the site at which infections can spread, for example, head colds can lead to mastoid infections.

The inner ear (also called the labyrinth due to its complex structure), which contains both the organ of hearing, the cochlea, and the organ of balance, the vestibular system, is embedded deep within the skull near the brainstem in the petrous bone. The extreme inaccessibility of the cochlea, coupled with its very small size, renders cochlear drug delivery difficult. The complexity of the cochlear structures and their extreme sensitivity to the changes in fluid volume also must be considered in the design of formulations and delivery systems as the sensory cells of the cochlea must be protected from noise and surgical trauma.

The pH of the EAC varies between 5.0 and 5.7 and is therefore slightly acidic, these conditions inhibit bacterial growth [125].

19.3.3 Age Related Differences in the Ear

The outer ear in humans is not completely mature at birth, and various anatomical and physiological changes occur with age. The EAC of an infant is straighter, narrower and much shorter than the adult's EAC.

Previous techniques used to estimate ear canal length include optical and acoustic measurements (e.g. [126, 127]). Measurements of ear canal volume use alternative techniques which are less invasive. Noh and Lee [128] measured EAC volume in 194 children with a mean age of 58 months reporting a mean value of 0.56 mL.

Previously the volume was reported to increase from 0.42 to 0.97 mL from 2.8 to 5.8 years of age [129]. The EAC volume in adults is reported to be approximately 0.696–0.979 mL [130].

Dosing devices allow smaller doses to be administered in paediatric patients and as there is no significant systemic uptake from medicines administered aurally there are little anticipated differences in treatments in paediatric patients compared to adults.

19.3.4 Topical Otic Delivery

Topical formulations are used to provide high drug concentrations at the disease site, for example, anti-inflammatory drugs are used to treat acute otitis externa.

Formulations applied to the ear are administered directly into the ear canal, this structure should be manipulated to ensure that the medicine enters into the ear rather than being lost externally. Typically a fixed number of drops are used or the ear canal can be filled with solution. The ear can be plugged post-administration using cotton wool.

19.3.5 Inner Ear Drug Delivery

Inner ear drug delivery methods can be divided into two main categories based on the location of entry of the drug. Intratympanic delivery involves depositing the therapeutic agent in the middle ear, relying primarily on diffusion through the round window membrane (RWM) for access to the scala tympani. The second method, intracochlear, depends on a cochleostomy with direct delivery into the inner ear space, completely bypasses the middle ear.

Intratympanic drug delivery relies on high drug concentrations driving diffusion into the scala tympani from the middle ear. However, the RWM is known to be variable in terms of permeability which limits dosing accuracy [131]. In addition drug delivered to the middle ear can be lost into the pharynx via the Eustachian tube. Typical formulations used include biodegradable polymers, hydrogel-based systems, nanoparticles, microcatheters and osmotic pumps [132]. Typically delivery systems used in intratympanic drug delivery use local triggers to stimulate drug release including temperature or pH [119].

The thickness of RWM has been reported to decrease in ageing mice [133] which is likely to increase permeability across this membrane although similar studies in humans showed no change in the mean thickness with ageing [134]. Typically membranes are also thinner in the very young therefore there may be greater permeability in the youngest patients compared to adult populations although there is currently no data to support this theory.

19.3.6 Intracochlear Drug Delivery

Direct intracochlear drug delivery involves placement of drugs within cochlear perilymphatic spaces. Molecules perfused into a perilymph compartment (ideally the scala tympani) have direct access to the cells of the inner ear [132]. Methods of delivery include direct perfusion using micropumps and osmotic pumps. Research is being conducted on modifying the electrodes of cochlear prostheses to integrate drug delivery components, while yet others are developing novel implantable delivery devices [135].

Direct injections and infusions delivered via syringe have been administered both in research and in a clinical setting; however, these do not allow for prolonged delivery [119]. Numerous other devices which can be used for sustained release or multi-dose delivery to the inner ear have been developed in attempts to overcome the shortcomings of direct transtympanic injection. These include the Silverstein MicroWick (Micromedics, Eaton, MN), the Round Window Microcatheter or μCath™ (Durect Corp. Cupertino, CA) in conjunction with an electronically controlled pump, the Alzet osmotic pump (Durect Corp. Cupertino, CA) and other devices still in earlier stages of development.

19.3.7 Formulations

19.3.7.1 Otic Solutions

The pH of otic solutions can be low as the reduced pH can inhibit bacterial growth. Historically otic formulations may have been sterile and isotonic; this was mainly due to ocular formulations being used within the ear, rather than a clinical requirement. There is no need for otic formulations to be either isotonic or sterile.

Typically otic solutions are simple solutions of drugs in water or other solvents (e.g. glycerol, propylene glycol, alcohol/water, mineral oil). The choice of vehicles is determined by the solubility of the drug within the product as the concentration needs to be high to account for the low volume typically administered. Excipients to increase the viscosity may be included to assist with administration or retention within the ear canal. Otic solutions are usually administered as drops, sprays or washes.

Lipophilic vehicles are used in treatments designed to assist in the removal of ear wax; as their oily nature assists in solubilisation to remove the wax.

19.3.7.2 Otic Gel

The use of gels as drug delivery systems to prolong trans-tympanic delivery to the middle ear has been described by Khoo et al. [136]. Previously this route of

administration was limited by the impermeability of the intact tympanic membrane to small hydrophilic drugs; however, research demonstrated that incorporation of chemical permeation enhancers into the formulation provided enhanced permeability. This formulation is yet to be commercialised by offers promise in the treatment of acute otitis media in paediatric patients.

19.3.7.3 Otic Foam

Otic Pharma developed a foam formulation technology (FoamOtic™) that aims to overcome the disadvantages of eardrops including: ineffective delivery to the infection site within the ear canal; retention of the drug within the ear; the administration of the product to the patient and the need for the patient to lie down following administration. A foam formulation A ciprofloxacin foam has been developed that was shown to be as efficacious as the solutions treatment for acute otitis externa [137].

19.3.7.4 Microwick Technology

The Silverstein MicroWick™ consists of an absorbent wick that is passed through a vent hole in the tympanic membrane and inserted to contact the round window within the middle ear. The wick absorbs medication that is administered in the external ear and transports it to the RWM for diffusion into the inner ear [138].

19.3.7.5 Osmotic Pump

Osmotic pumps have been employed to test the effectiveness of steroid treatment to prevent hearing loss from noise trauma. The small volume pump is subcutaneously implanted and a cannula is routed to the round window niche or directly into the cochlea. Various models allow for reservoir volumes of 0.1–2 mL and flow rates from 0.1 to 10 μL/h, and the pumps provide continuous infusion for 1 day to 6 weeks [139]. The pump operates by osmotic pressure in the outer section of the pump forcing drug in an inner, impermeable chamber out through the cannula. Delivery cannot be started or stopped nor can the flow rate be changed in situ. The benefits of osmotic pumps are that they offer a controlled delivery profile and proven surgical technique.

19.3.7.6 Cochlear Implants

Cochlear implants stimulate the auditory neurons in the cochlea through an electrode inserted into the scala tympani. Med-El and Cochlear Ltd. are examples of companies investigating the combination of drug delivery with an implant. Combining a

drug delivery platform with the implant electrode, drugs such as neurotrophic factors may prevent further auditory degradation and maintain the number of surviving nerve fibres, thus improving the effectiveness of cochlear implants for long-term use [140].

19.3.8 Discussion/Conclusions

Otic drug formulations are used within paediatric populations routinely. There are no reported paediatric specific formulations that differ to adult products. However, the similarities in anatomy and physiology ensure that products are likely to perform in the same way in adults compared to children with few reported adverse effects following otic drug delivery. There is a need for some caution in drug delivery to the inner ear as the membranes may be more permeable in the youngest within the paediatric population which may lead to increased drug absorption and a greater likelihood of adverse events.

References

1. Illum L (2012) Nasal drug delivery—recent developments and future prospects. J Control Release 161(2):254–263
2. Borland M, Jacobs I, King B, O'Brien D (2007) A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. Ann Emerg Med 49(3):335–340
3. Sarkar MA (1992) Drug metabolism in the nasal mucosa. Pharm Res 9(1):1–9
4. Pontiroli AE, Calderara A, Pozza G (1989) Intranasal drug delivery – potential advantages and limitations from a clinical pharmacokinetic perspective. Clin Pharmacokinet 17(5):299–307
5. Illum L (2004) Is nose-to-brain transport of drugs in man a reality? J Pharm Pharmacol 56(1):3–17
6. Petruson B, Hansson HA, Karlsson G (1984) Structural and functional aspects of cells in the nasal mucociliary system. Arch Otolaryngol 110(9):576–581 (Chicago, Ill: 1960)
7. Proctor DF, Lundqvist G (1973) Clearance of inhaled particles from the human nose. Arch Intern Med 131(1):132–139
8. Morgan K, Patterson D, Gross E (1968) Responses of the nasal mucociliary apparatus to airborne irritants. In: Barrow C (ed) Toxicology of the nasal passages. Hemisphere Publishing Corporation, London, pp 123–133
9. Grassin-Delyle S, Buenestado A, Naline E, Faisy C, Blouquit-Laye S, Couderc L-J et al (2012) Intranasal drug delivery: an efficient and non-invasive route for systemic administration: focus on opioids. Pharmacol Ther 134(3):366–379
10. Kaliner M, Marom Z, Patow C, Shelhamer J (1984) Human respiratory mucus. J Allergy Clin Immunol 73(3):318–323
11. Marttin E, Schipper NGM, Verhoef JC, Merkus FWHM (1998) Nasal mucociliary clearance as a factor in nasal drug delivery. Adv Drug Deliv Rev 29(1–2):13–38, Available from http://www.sciencedirect.com/science?_ob=GatewayURL&_origin=ScienceSearch&_method=citationSearch&_piikey=S0169409X97000598&_version=1&_returnURL=http%3A%2F%2Fwww.scirus.com%2Fsrsapp%2F&md5=048655bbe65c873a9cd96d837edd818d

12. Sanderson MJ, Sleigh MA (1981) Ciliary activity of cultured rabbit tracheal epithelium: beat pattern and metachrony. J Cell Sci 47:331–347
13. Illum L (2003) Nasal drug delivery – possibilities, problems and solutions. J Control Release 87(1–3):187–198
14. Washington N, Steele RJC, Jackson SJ, Bush D, Mason J, Gill DA et al (2000) Determination of baseline human nasal pH and the effect of intranasally administered buffers. Int J Pharm 198(2):139–146
15. Dale O, Hjortkjær R, Kharasch ED (2002) Nasal administration of opioids for pain management in adults. Acta Anaesthesiol Scand 46(7):759–770
16. Newman SP, Steed KP, Hardy JG, Wilding IR, Hooper G, Sparrow RA (1994) The distribution of an intranasal insulin formulation in healthy volunteers: effect of different administration techniques. J Pharm Pharmacol 46(8):657–660
17. Kundoor V, Dalby RN (2011) Effect of formulation- and administration-related variables on deposition pattern of nasal spray pumps evaluated using a nasal cast. Pharm Res 28(8):1895–1904
18. Porter MJ, Maw AR, Kerridge DH, Williamson IM (1997) Manometric rhinometry: a new method of measuring the volume of the air in the nasal cavity. Acta Otolaryngol 117(2):298–301
19. Xi J, Si X, Kim JW, Berlinski A (2011) Simulation of airflow and aerosol deposition in the nasal cavity of a 5-year-old child. J Aerosol Sci 42:156–173
20. Balbani APS, Duarte JG, Montovani JC (2004) Retrospective analysis of toxicity of eardrops, topical nasal and oropharyngeal medicines, documented in São Paulo, Brazil. Rev Assoc Med Bras 50(4):433–438
21. Newman SP, Pitcairn GR, Dalby RN (2004) Drug delivery to the nasal cavity: in vitro and in vivo assessment. Crit Rev Ther Drug Carrier Syst 21(1):21–66
22. Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M (2000) Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study. BMJ 321(7253):83–86
23. Borland M, Jacobs I, Geelhoed G (2002) Intranasal fentanyl reduces acute pain in children in the emergency department: a safety and efficacy study. Emerg Med 14:275–280
24. Wilson J, Kendall J, Cornelius P (1997) Intranasal diamorphine for paediatric analgesia: assessment of safety and efficacy. J Accid Emerg Med 14(2):70–72
25. Malinovsky J, Servin F, Cozian A, Lepage J, Pinaud M (1996) Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth 77(2):203–207
26. Fuseau E, Petricoul O, Moore KH, Barrow A, Ibbotson T (2002) Clinical pharmacokinetics of intranasal sumatriptan. Clin Pharmacokinet 41(11):801–811
27. Csaba N, Garcia-Fuentes M, Alonso MJ (2009) Nanoparticles for nasal vaccination. Adv Drug Deliv Rev 61(2):140–157
28. Carter NJ, Curran MP (2011) Live attenuated influenza vaccine (FluMist®; Fluenz™): a review of its use in the prevention of seasonal influenza in children and adults. Drugs 71(12):1591–1622
29. Scott LJ, Carter NJ, Curran MP (2012) Live attenuated influenza vaccine (Fluenz™): a guide to its use in the prevention of seasonal influenza in children in the EU. Paediatr Drugs 14(4):271–279
30. Pennington AK, Ratcliffe JH, Wilson CG, Hardy JG (1988) The influence of solution viscosity on nasal spray deposition and clearance. Int J Pharm 43(3):221–224
31. Illum L, Jorgensen H, Bisgaard H, Krogsgaard O, Rossing N (1987) Bioadhesive microspheres as a potential nasal drug delivery system. Int J Pharm 39(3):189–199
32. Primosch RE, Guelmann M (2005) Comparison of drops versus spray administration of intranasal midazolam in two- and three-year-old children for dental sedation. Pediatr Dent 27(5):401–408
33. Foo MY, Cheng YS, Su WC, Donovan MD (2007) The influence of spray properties on intranasal deposition. J Aerosol Med 20(4):495–508

34. Chaturvedi M, Kumar M, Pathak K (2011) A review on mucoadhesive polymer used in nasal drug delivery system. J Adv Pharm Technol Res 2(4):215–222
35. Roy SB, Swain K, Patel SA, Magar L (2011) Aqueous pharmaceutical compositions of fluticasone and olopatadine. International Patent number: WO2011141929 (A3), 17 November 2011
36. Keller M, Corbainie E (2009) Macrolide compositions having improved taste and stability International Patent number: WO/2009/109390, 11 September 2009
37. Jain AK, Khar RK, Ahmed FJ, Diwan PV (2008) Effective insulin delivery using starch nanoparticles as a potential trans-nasal mucoadhesive carrier. Eur J Pharm Biopharm 69(2):426–435
38. Cumberland PM, Pathai S, Rahi JS, Millennium Cohort Study Child Health Group (2010) Prevalence of eye disease in early childhood and associated factors: findings from the millennium cohort study. Ophthalmology 117(11):2184–2190, e1–3
39. Isenberg SJ, Apt L, McCarty J, Cooper LL, Lim L, Del Signore M (1998) Development of tearing in preterm and term neonates. Arch Ophthalmol 116(6):773–776
40. Friedman TS, Patton TF (1976) Differences in ocular penetration of pilocarpine in rabbits of different ages. J Pharm Sci 65(7):1095–1096
41. Francoeur M, Ahmed I, Sitek S, Patton TF (1983) Age-related differences in ophthalmic drug disposition III. Corneal permeability of pilocarpine in rabbits. Int J Pharm 16(2):203–213
42. Patton TF, Robinson JR (1976) Pediatric dosing considerations in ophthalmology. J Pediatr Ophthalmol 13(3):171–178
43. Macdonald EA, Maurice DM (1991) Loss of fluorescein across the conjunctiva. Exp Eye Res 53:427–430
44. Esmaeelpour M, Watts PO, Boulton ME, Cai J, Murphy PJ (2011) Tear film volume and protein analysis in full-term newborn infants. Cornea 30(4):400–404
45. Nagataki S, Mishima S (1980) Pharmacokinetics of instilled drugs in the human eye. Int Ophthalmol Clin 20(3):33–49
46. Apt L, Gaffney WL (2009) Adverse effects of topical eye medication in infants and children. In: Tasman W, Jaeger EA (eds) Duane's ophthalmology, 2009th edn. Lippincott Williams & Wilkins, Philadelphia
47. Lawrenson JG, Murphy PJ, Esmaeelpour M (2003) The neonatal tear film. Cont Lens Anterior Eye 26(4):197–202
48. Abelson MB, Udell IJ, Weston JH (1981) Normal human tear pH by direct measurement. Arch Ophthalmol 99(2):301
49. Carney LG, Hill RM (1976) Human tear pH. Diurnal variations. Arch Ophthalmol 94(5):821–824
50. Dahl H, Dahl C (1985) Hydrogen ion concentration of tear fluid in newborn infants. Acta Ophthalmol 63(6):692–694
51. Ross DL, Riley CM (1990) Aqueous solubilities of some variously substituted quinolone antimicrobials. Int J Pharm 63(3):237–250
52. Sack RA, Beaton A, Sathe S, Morris C, Willcox M, Bogart B (2000) Towards a closed eye model of the pre-ocular tear layer. Prog Retin Eye Res 19(6):649–668
53. Patrick R (1974) Lacrimal secretion in full-term and premature babies. Trans Ophtalmol Soc UK 94:283–289
54. Watson RR, McMurray DN, Martin P, Reyes MA (1985) Effect of age, malnutrition, and renutrition on free secretory component and IgA in secretions. Am J Clin Nutr 42(2):281–288
55. Sullivan DA, Allansmith MR (1988) The effect of aging on the secretory immune system of the eye. Immunology 63(3):403–410
56. Etches PC, Leahy F, Harris D, Baum JD (1979) Lysozyme in the tears of newborn babies. Arch Dis Child 54(3):218–221
57. Shell JW (1982) Pharmacokinetics of topically applied ophthalmic drugs. Surv Ophthalmol 26(4):207–218
58. Zametkin AJ, Stevens JR, Pittman R (1979) Ontogeny of spontaneous blinking and of habituation of the blink reflex. Ann Neurol 5(5):453–457
59. Levy Y, Zadok D (2004) Systemic side effects of ophthalmic drops. Clin Pediatr 43(1):99–101

60. Berlin RJ, Lee UT, Samples JR, Rich LF, Tang-Liu DDS, Sing KA et al (2001) Ophthalmic drops causing coma in an infant. J Pediatr 138(3):441–443
61. Passo MS, Palmer EA, Van Buskirk EM (1984) Plasma timolol in glaucoma patients. Ophthalmology 91(11):1361–1363
62. Raber S, Courtney R, Maeda-Chubachi T, Simons BD, Freedman SF, Wirostko B (2011) Latanoprost systemic exposure in pediatric and adult patients with glaucoma: a phase 1, open-label study. Ophthalmology 118(10):2022–2027
63. Patton TF (1977) Pediatric dosing considerations in ophthalmology–dosage adjustments based on aqueous humor volume ratio. J Pediatr Ophthalmol 14(4):254–256
64. van Best JA, Kappelhof JP, Laterveer L, Oosterhuis JA (1987) Blood aqueous barrier permeability versus age by fluorophotometry. Curr Eye Res 6(7):855–863
65. Çekiç O, Batman C, Yaşar U, Başci NE, Bozkurt A, Kayaalp SO (1999) Human aqueous and vitreous humour levels of ciprofloxacin following oral and topical administration. Eye 13(4):555–558
66. Lesk MR, Ammann H, Marcil G, Vinet B, Lamer L, Sebag M (1993) The penetration of oral ciprofloxacin into the aqueous humor, vitreous, and subretinal fluid of humans. Am J Ophthalmol 115(5):623–628
67. Mian UK, Mayers M, Garg Y, Liu QF, Newcomer G, Madu C et al (1998) Comparison of fluconazole pharmacokinetics in serum, aqueous humor, vitreous humor, and cerebrospinal fluid following a single dose and at steady state. J Ocul Pharmacol Ther 14(5):459–471
68. Schauersberger J, Amon M, Wedrich A, Nepp J, El Menyawi I, Derbolav A et al (1999) Penetration and decay of meropenem into the human aqueous humor and vitreous. J Ocul Pharmacol Ther 15(5):439–445
69. Wong KW, D'Amico DJ, Oum BS, Baker PA, Kenyon KR (1990) Intraocular penetration of rifampin after oral administration. Graefes Arch Clin Exp Ophthalmol 228(1):40–43
70. Cekic O, Batman C, Yasar U, Basci NE, Bozkurt A, Kayaalp SO (1998) Penetration of ofloxacin in human aqueous and vitreous humors following oral and topical administration. Retina 18(6):521–525
71. Huang AJ, Tseng SC, Kenyon KR (1989) Paracellular permeability of corneal and conjunctival epithelia. Invest Ophthalmol Vis Sci 30(4):684–689
72. Mishima S, Hedbys B (1967) The permeability of the corneal epithelium and endothelium to water. Exp Eye Res 6:10
73. Klyce S, Crosson C (1985) Transport processes across the rabbit corneal epithelium: a review. Curr Eye Res 4:323
74. Schoenwald RD, Deshpande GS, Rethwisch DG, Barfknecht CF (1997) Penetration into the anterior chamber via the conjunctival/scleral pathway. J Ocul Pharmacol Ther 13(1):41–59
75. Bito LZ, Baroody RA (1981) The penetration of exogenous prostaglandin and arachidonic acid into, and their distribution within, the mammalian eye. Curr Eye Res 1(11):659–669
76. Ahmed I, Patton TF (1985) Importance of the noncorneal absorption route in topical ophthalmic drug delivery. Invest Ophthalmol Vis Sci 26(4):584–587
77. Bloomfield SE, Miyata T, Dunn MW (1978) Soluble gentamicin ophthalmic inserts as a drug delivery system. Arch Ophthalmol 96(5):885–887
78. Maurice DM, Mishima S (1984) Ocular pharmacokinetics. In: Sears ML (ed) Pharmacology of the eye. Springer, Berlin
79. Hughes PM, Olejnik O, Chang-Lin J-E, Wilson CG (2005) Topical and systemic drug delivery to the posterior segments. Adv Drug Deliv Rev 57(14):2010–2032
80. Palestine AG, Brubaker RF (1981) Pharmacokinetics of fluorescein in the vitreous. Invest Ophthalmol Vis Sci 21(4):542–549
81. Maurice DM (2002) Drug delivery to the posterior segment from drops. Surv Ophthalmol 47(Suppl 1):S41–S52
82. Jiang J, Gill HS, Ghate D, McCarey BE, Patel SR, Edelhauser HF et al (2007) Coated microneedles for drug delivery to the eye. Invest Ophthalmol Vis Sci 48(9):4038–4043
83. Davies NM, Fair SJ, Hadgraft J, Kellaway IW (1991) Evaluation of mucoadhesive polymers in ocular drug delivery. I. Viscous solutions. Pharm Res 8(8):1039–1043

84. Gurny R, Ibrahim H, Aebi A, Buri P, Wilson CG, Washington N et al (1987) Design and evaluation of controlled release systems for the eye. J Control Release 6(1):367–373
85. InSite Vision DuraSite® (18-07-2012) http://www.insitevision.com/durasite
86. Ibrahim H, Bindschaedler C, Doelker E, Buri P, Gurny R (1991) Concept and development of ophthalmic pseudo-latexes triggered by pH. Int J Pharm 77(2–3):211–219
87. Greaves JL, Wilson CG, Rozier A, Grove J, Plazonnet B (1990) Scintigraphic assessment of an ophthalmic gelling vehicle in man and rabbit. Curr Eye Res 9(5):415–420
88. Kuno N, Fujii S (2011) Recent advances in ocular drug delivery systems. Polymers 3:193–221
89. Mishra GP, Bagui M, Tamboli V, Mitra AK (2011) Recent applications of liposomes in ophthalmic drug delivery. J Drug Deliv 2011:1–14
90. Kumar S, Karki R, Meena M, Prakash T, Rajeswari T, Goli D (2011) Reduction in drop size of ophthalmic topical drop preparations and the impact of treatment. J Adv Pharm Technol Res 2(3):192–194
91. Van Santvliet L, Ludwig A (2004) Determinants of eye drop size. Surv Ophthalmol 49(2):197–213, Available from http://www.sciencedirect.com/science?_ob=GatewayURL&_origin=ScienceSearch&_method=citationSearch&_piikey=S0039625703001838&_version=1&_returnURL=http%3A%2F%2Fwww.scirus.com%2Fsrsapp%2F&md5=c923097d5f32374eeeee75aa1dcb3f4e
92. Jampel HD, Schwartz GF, Robin AL, Abrams DA, Johnson E, Miller RB (2003) Patient preferences for eye drop characteristics: a willingness-to-pay analysis. Arch Ophthalmol 121(4):540–546
93. Salamone JC, Xia E (2006) Ophthalmic solution with a flavoring agent. US patent 2006/0292188, 14th December 2006
94. Sieg JW, Robinson JR (1975) Vehicle effects on ocular drug bioavailability I: evaluation of fluorometholone. J Pharm Sci 64(6):931–936
95. Takaoka M, Yokoi N, Ishibashi T, Kinoshita S (2004) Assessment of retention and drug-release of ophthalmic ointment on the ocular surface. Nihon Ganka Gakkai zasshi 108(5):307–311
96. Nagarwal RC, Kumar R, Dhanawat M, Pandit JK (2011) Modified PLA nano in situ gel: a potential ophthalmic drug delivery system. Colloids Surf B Biointerfaces 86(1):28–34
97. Robinson MR, Lee SS, Rubin BI, Wayne AS, Pavletic SZ, Bishop MR et al (2004) Topical corticosteroid therapy for cicatricial conjunctivitis associated with chronic graft-versus-host disease. Bone Marrow Transplant 33(10):1031–1035
98. BenEzra D, Maftzir G (1990) Ocular penetration of cyclosporine A in the rat eye. Arch Ophthalmol 108(4):584–587
99. Deshpande PB, Dandagi P, Udupa N, Gopal SV, Jain SS, Vasanth SG (2010) Controlled release polymeric ocular delivery of acyclovir. Pharm Dev Technol 15(4):369–378
100. Burgess PI, Koay P, Clark P (2008) SmartPlug versus silicone punctal plug therapy for dry eye: a prospective randomized trial. Cornea 27(4):391–394
101. Beeley NRF, Coldren BA (2011) Punctal plugs for controlled release of therapeutic agents. US Patent number 20110251568 A1, 13 October 2011
102. Cohan BE, Diamond H (2000) Ophthalmic insert and method for sustained release of medication to the eye. International Patent number: WO2000062760 A1, 26 October 2000
103. Freilich D (2008) Ophthalmic insert US Patent number US20080086101 A1, 10 April 2008
104. Gupta C, Chauhan A (2011) Ophthalmic delivery of cyclosporine A by punctal plugs. J Control Release 150(1):70–76
105. Mataftsi A, Subbu RG, Jones S, Nischal KK (2012) The use of punctal plugs in children. Br J Ophthalmol 96(1):90–92
106. Li CC, Chauhan A (2006) Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 45(10):3718–3734
107. Kapoor Y, Chauhan A (2008) Drug and surfactant transport in cyclosporine A and Brij 98 laden p-HEMA hydrogels. J Colloid Interface Sci 322(2):624–633
108. Kapoor Y, Chauhan A (2008) Ophthalmic delivery of cyclosporine A from Brij-97 microemulsion and surfactant-laden p-HEMA hydrogels. Int J Pharm 361(1–2):222–229

109. Ali M, Horikawa S, Venkatesh S, Saha J, Hong JW, Byrne ME (2007) Zero-order therapeutic release from imprinted hydrogel contact lenses within in vitro physiological ocular tear flow. J Control Release 124(3):154–162
110. Venkatesh S, Sizemore SP, Byrne ME (2007) Biomimetic hydrogels for enhanced loading and extended release of ocular therapeutics. Biomaterials 28(4):717–724
111. Hiratani H, Fujiwara A, Tamiya Y, Mizutani Y, Alvarez-Lorenzo C (2005) Ocular release of timolol from molecularly imprinted soft contact lenses. Biomaterials 26(11):1293–1298
112. Ciolino JB, Hoare TR, Iwata NG, Behlau I, Dohlman CH, Langer R et al (2009) A drug-eluting contact lens. Invest Ophthalmol Vis Sci 50(7):3346–3352
113. Vistakon Pharmaceuticals (2012) A single-center, randomised, double-masked, placebo-controlled, parallel-group study evaluating the safety of a novel contact lens in healthy normal volunteers. http://clinicaltrials.gov/ct2/show/NCT00889252
114. Lee TW-Y, Robinson JR (2009) Drug delivery to the posterior segment of the eye IV: theoretical formulation of a drug delivery system for subconjunctival injection. J Ocul Pharmacol Ther 25(1):29–37
115. Kimura H, Ogura Y, Hashizoe M, Nishiwaki H, Honda Y, Ikada Y (1994) A new vitreal drug-delivery system using an implantable biodegradable polymeric device. Invest Ophthalmol Vis Sci 35(6):2815–2819
116. Choonara YE, Pillay V, Danckwerts MP, Carmichael TR, du Toit LC (2010) A review of implantable intravitreal drug delivery technologies for the treatment of posterior segment eye diseases. J Pharm Sci 99(5):2219–2239
117. Pijls RT, Sonderkamp T, Daube GW, Krebber R, Hanssen HHL, Nuijts RMMA et al (2005) Studies on a new device for drug delivery to the eye. Eur J Pharm Biopharm 59(2):283–288
118. Bausch, Lomb (2013) Vitrasert: FDA package insert http://www.drugs.com/pro/vitrasert.html. Accessed 9 Nov 2013
119. EMEA (2002) Vitrasert implant: withdrawal of the marketing authorisation in the European Union. Information available at http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/12/WC500018350.pdf. Accessed 9 Dec 2013
120. Driot JY, Novack GD, Rittenhouse KD, Milazzo C, Pearson PA (2004) Ocular pharmacokinetics of fluocinolone acetonide after Retisert™ intravitreal implantation in rabbits over a 1-year period. J Ocul Pharmacol Ther 20(3):269–275
121. Bausch, Lomb (2009) Retisert. Patient information leaflet. Available from http://www.drugs.com/retisert.html. Accessed 9 Dec 2013
122. Agency EM (2010) European Medicines Agency decision. P/91/2010. In the granting of a product specific waiver for fluocinolone acetonide (EMEA-000801-PIP01-09) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council
123. Agency EM (2009) European medicines agency decision of 15 June 2009 on the granting of a product specific waiver for triamcinolone acetonide (EMEA-000465-PIP01-08) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended
124. Salvinelli F, Maurizi M, Calamita S, D'Alatri L, Capelli A, Carbone A (1991) The external ear and the tympanic membrane. Scand Audiol 20(4):253–256
125. Neher A, Nagl M, Scholtz AW (2008) Otitis externa: etiology, diagnostic and therapy. HNO 56(10):1067–1079
126. Zebian M, Hensel J, Fedtke T (2012) How the cross-sectional discontinuity between ear canal and probe affects the ear canal length estimation. J Acoust Soc Am 132(1):8–14
127. Zemplenyi J, Gilman S, Dirks D (1985) Optical method for measurement of ear canal length. J Acoust Soc Am 78(6):2146–2148
128. Noh H, Lee D-H (2012) Direct measurement of ear canal volume in a pediatric population: can we explain its individual variation in terms of age and body weight? Int J Pediatr Otorhinolaryngol 76(5):658–662
129. Margolis RH, Heller JW (1987) Screening tympanometry: criteria for medical referral. Audiology 26(4):197–208

130. Shanks JE, Lilly DJ (1981) An evaluation of tympanometric estimates of ear canal volume. J Speech Hear Res 24(4):557–566
131. Banerjee A, Parnes LS (2004) The biology of intratympanic drug administration and pharmacodynamics of round window drug absorption. Otolaryngol Clin North Am 37(5):1035–1051
132. Swan EEL, Mescher MJ, Sewell WF, Tao SL, Borenstein JT (2008) Inner ear drug delivery for auditory applications. Adv Drug Deliv Rev 60(15):1583–1599
133. Kitamura Y, Teranishi M-a, Sone M, Nakashima T (2002) Round window membrane in young and aged C57BL/6 mice. Hear Res 174(1–2):142–148
134. Sahni RS, Paparella MM, Schachern PA, Goycoolea MV, Le CT (1987) Thickness of the human round window membrane in different forms of otitis media. Arch Otolaryngol Head Neck Surg 113(6):630–634
135. Swan EEL (2009) A fully implantable intracochlear drug delivery device: development and characterization. Available at http://hdl.handle.net/1721.1/55258. Accessed 9 Dec 2013
136. Khoo X, Simons EJ, Chiang HH, Hickey JM, Sabharwal V, Pelton SI et al (2013) Formulations for trans-tympanic antibiotic delivery. Biomaterials 34(4):1281–1288
137. Marom T, Yelin R, Goldfarb A, Rakover Y, Shlizerman L, Eilat E et al (2010) Comparison of safety and efficacy of foam-based versus solution-based ciprofloxacin for acute otitis externa. Otolaryngol Head Neck Surg 143(4):492–499
138. Silverstein H (1999) Use of a new device, the MicroWick™, to deliver medication to the inner ear. Ear Nose Throat J 78(8):595–600
139. Pararas EEL, Borkholder DA, Borenstein JT (2012) Microsystems technologies for drug delivery to the inner ear. Adv Drug Deliv Rev 64(14):1650–1660
140. Duan ML, Ulfendahl M, Laurell G, Counter AS, Pyykkö I, Borg E et al (2002) Protection and treatment of sensorineural hearing disorders caused by exogenous factors: experimental findings and potential clinical application. Hear Res 169(1–2):169–178

Chapter 20
Rectal Drug Delivery

Hannah Batchelor

Abstract The rectal route of administration is particularly useful for infants and children who have difficulty in swallowing oral medicine. This route is also used in cases of nausea and vomiting, or where upper intestinal disorders present may affect the absorption of a drug. There is no need for taste masking of drugs delivered rectally.

20.1 Introduction

Rectal preparations are used to treat both local and systemic disorders in children. Medicines are typically delivered as creams, ointments, suppositories, foams, sprays and enemas.

Important drawbacks of the rectal route of drug administration include the patient and carer's lack of acceptance (cultural reluctance in some countries) and the interruption of drug absorption (removal of the delivery system) by defecation.

20.2 Structure of the Rectum

The rectum is the terminal portion of the large intestine. In adults the rectum varies from 10 to 15 cm in length, while the circumference varies from 15 cm at the rectosigmoid junction to 35 cm or more at its widest portion [1]. The resultant surface area in adults is 200–400 cm^2 [1]. The surface of the rectum is epithelial mucosa that

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does not have villi at the surface thus the surface area calculation can be made based on the dimensions of a cylinder. When empty the rectum contains approximately 3 mL of mucus in a layer approximately 100 μm thick. The pH within the rectal cavity in adults is between 7.2 and 7.4 although rectal fluids have little buffering capacity [2].

The blood supply to the rectum changes with distance from the anus; the inferior rectal vein closest to the anus and the superior rectal artery further inside the rectal cavity. Drug absorbed at the inferior portion enters the rectal veins which drain to the internal pundendal veins and bypasses the liver. However, drug absorbed further inside the rectum enter the superior haemorrhoidal veins which connect to the portal vein where drugs are transported to the liver. This difference is important for systemic absorption of drugs which are extensively metabolised as the plasma levels reached will depend upon where absorption occurred. The main mechanism of absorption from the rectum is via passive diffusion across the mucous membrane.

Typically, the volume of formulation that can be retained within the adult rectum is 10–25 mL [3].

20.3 Age Related Differences in the Rectum and Their Impact on Medicines Performance

The diameter, length and volume of the rectum changes during development, with the adult dimension being reached at about 10 years of age [4]. The rectal length increases with age from 4 cm as a neonate; 6 cm at 1 year; 7 cm at 5 years; 9 cm at 10 years; 10 cm at 15 years and 10.5 cm as an adult [5]. The diameter of the rectum in children age 7 was approximated as 21 mm by Joensson et al. [6]. The surface area of the rectum in children, as expected, is smaller than in adults. Assuming that the adult rectum mean surface area is 300 cm^2 [1] and that the surface area is linearly related to rectum length then the surface area for age categories can be calculated. This calculation is shown in Table 20.1.

Dose adjustments in paediatric patients are typically made based on weight, height or body surface area. In terms of rectal drug delivery for systemic effects the rectal absorptive surface area is an important factor to consider. The relationship between rectal surface area, body weight and body surface area is also shown in Fig. 20.1.

Table 20.1 Approximated rectal surface area based on rectal length by age

Age	Rectal surface area (cm^2)
Neonate	114
1 year	171
5 years	200
10 years	257
15 years	286
Adult	300

Rectal length data sourced from Valentin [5]

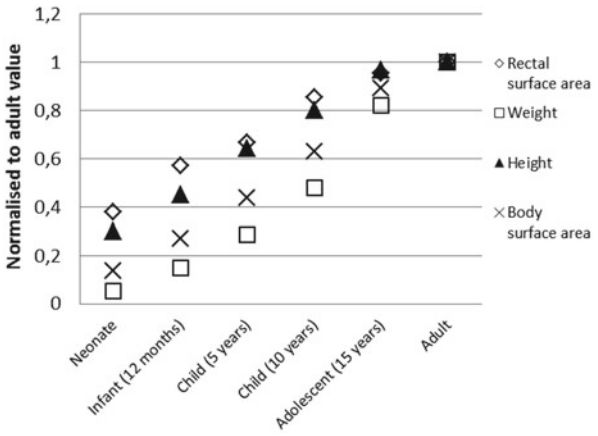

Fig. 20.1 Comparison of rectal surface area to typical dose adjustment parameters (weight, height and body surface area) by age of paediatric patient

The data in Fig. 20.1 show that a paediatric patient's height most closely correlates to their rectal surface area compared to other typically used measures. Although dose adjustments are relatively simple for solutions and suspensions, the use of suppositories restricts simple dose adjustment in many cases. Using paracetamol as an example drug the rectal dosages recommended within the British National Formulary (BNF) for children are quoted as mg/kg, therefore using on weight to adjust the dose required [7]. Other drugs may be dosed based on age of patient with no reference to weight or height (e.g. diazepam recommended dose by rectum is 1.25–2.5 mg in neonates and 5 mg for 1 month to 2 year old infants) [7].

Rectal delivery of paracetamol in preterm infants was investigated by van Lingen et al. [8], the results showed that there was rapid absorption with higher concentrations attained in patients from 28 to 32 weeks compared to those over 32 weeks although the dose administered was calculated on a mg/kg basis. The greater absorption in the youngest patients may be a factor of both reduced thickness of the rectal wall akin to reduced thickness of external skin observed in preterm infants as well as the developmental immaturity of hepatic metabolism [9].

The mean pH within the rectal cavity of children has been reported to be 9.6 (range 7.2–12.1); the pH value was not affected by age and gender [10]. This elevated pH compared to adult values is of importance in drugs which are ionised and whose pK_a is significant at this value (e.g. codeine base has a pK_a of 8.1). In a previous study, rectal absorption of morphine was increased with increased pH of the delivery vehicle [11]. Mixing of drug with the rectal fluids may elevate the pH and therefore have an impact of exposure. This pH difference may account for some of the variability noted in rectal drug absorption in paediatric patients [12].

20.4 Local Delivery

Agents used locally within the rectum include therapies for haemorrhoids, local anaesthetics and soothing agents. Agents acting locally are formulated such that a thin coating of drug containing formulation is retained within the rectum. Typically suppositories, ointments, creams and enemas are used.

20.5 Systemic Delivery

The rectum is used as a site of administration for a range of systemically acting agents. In children these are today limited to agents for pain relief (e.g. paracetamol, diclofenac sodium, morphine); antibacterials (e.g. metronidazole); seizures (e.g. paraldehyde, sodium valproate); sedatives (e.g. midazolam) and for nausea and vertigo (e.g. phenothiazines). Systemic agents need to be absorbed from the rectum and the formulation selected can determine the rate of absorption.

Historically oral liquid preparations or injectable solutions have been administered rectally when oral administration was not appropriate. The rectal delivery of oral liquid preparations of antiepileptic agents was investigated by Graves and Kriel [13]; they found that most were well tolerated and demonstrated clinical efficacy. Administration of solution formulations provides a rapid onset of action as the drug is readily available at the site of absorption whereas drug within solid or semi-solid formulations needs to diffuse and dissolve prior to presentation at the absorptive surface. In children, as in adults, the rapid onset of action provided by a solution formulation is desirable in certain therapeutic areas. A diazepam rectal solution provided rapid systemic concentrations and improved clinical action compared to a diazepam suppository in children [14].

20.6 Rectal Formulations

Solutions and suppositories are most commonly used for rectal dosing. Suppositories are usually formulated with a quick-melting base. Studies of both suppositories and solutions have shown migration of administered drug, but this appears to be limited to the rectum area [15]. Migration of enemas with as little volume as 80–100 mL may result in drug found in the colon and even in the ileum [16].

20.6.1 Enemas

Enema formulations are delivered as rectal injections and are typically non-viscous solutions or suspensions. The vehicles can be aqueous or oily and in some cases the

vehicle can be the therapeutic agent, for example bowel evacuation resulting from arachis oil retention enema.

Rectal solutions typically have a neutral pH and are near isotonic to minimise irritation to the local tissue. However, phosphate enemas have a lower pH (5–5.8) and are highly concentrated to promote fluid movement from the intestines into the intestinal tract and resulting in peristalsis to aid in colonic evacuation.

In adults enema volume can vary from 1 to 20 mL for a micro-enema to volumes greater than 50 mL for a macro-enema (also known as a retention enema) [17]. Evacuation enemas can have significantly greater volumes (>500 mL). In paediatric patients examples of micro-enemas include sodium citrate (5–10 mL) for children aged 3–18 years. Based on a phosphate enema formula, typical volumes of enemas for children are 45–64 mL for children aged 3–7 years; 65–100 mL for children aged 7–10 years and 100–128 mL for children from 12 to 18 years [7].

Enema formulations can be used across a range of ages as dose adjustments can be made by alteration of the volume administered. The excipients used in adult formulations are appropriate for use in children.

20.6.2 Suppositories

Suppositories can be manufactured in a range of shapes and sizes although a torpedo shape is most commonly used. The typical dimensions of suppositories are listed in the table below.

	Dimensions	
Nominal size	Length (mm)	Diameter (mm)
1 g	20–25	8–10
2 g	22–28	8–15
4 g	30–35	10–20

Following administration of a suppository melting or liquification of the base has to occur and this process will determine the spreading of the drug over the rectal surface. Following liquification the drug must diffuse through the rectal mucus layer prior to absorption through the membrane.

Suppositories are usually solid suspensions or emulsions. Gelatin capsules that contain liquids can also be used as rectal suppository formulations (e.g. artesunate rectal capsules).

Paediatric suppositories are typically manufactured at an appropriate size for children (1 g nominal size). In certain cases portions of adult suppositories may be used in paediatric patients as it is assumed that there is a uniform distribution of the active substance in the suppository matrix. However, there is unlikely to be any accuracy or stability data for such a practice and the resulting shape may not be optimal for rectal insertion.

20.6.3 Gels

A rectal gel may offer the potential to increase retention time within the rectal cavity. A two-compartment, muco-adhesive gel formulation of artesunate was developed for use in children; this formulation was prepared as a solid for reconstitution to provide the required stability for use in tropical climates [18]. Although gels may offer advantages in dose flexibility they require administration which may be messy without appropriate applicator devices.

20.6.4 Rectal Foam

A foam is a dispersion of gas within a liquid. Rectal foams combine a drug formulation with gas that is administered rectally via an applicator extension to an aerosol. The rectal foam expands within the rectal cavity and the drug formulation makes contact with the rectal mucosa enabling even application. The advantages of a foam include the use of an applicator to administer the formulation avoids contact with hands and the greasiness of an ointment for example; in addition, the retention of the drug within the rectal cavity is increased via use of a foam as the reduced density of the product reduces the risk of seepage. Examples of rectal foams include Proctofoam HC®, Colifoam® and Salofalk® which are all listed within the BNF for use in children aged 12–18 years. Although there are no existing products recommended for use in younger children the technology does not preclude this formulation strategy from future use in younger children.

20.6.5 Rectal Spray

A rectal spray is a solution formulation that is dispensed from a spray pump to ensure even distribution within the rectal cavity. A spray minimises the excessive volume that may be used with a simple solution as the dispenser ensures that the product makes contact with the mucosal surface. This results in less drug wastage and is also preferred by patients as there is less seepage of the drug. An example used in children is Perianal® corticosteroid formulation.

20.6.6 Creams and Ointments

Rectal creams and ointments are readily available for paediatric use. These have dosage flexibility advantages yet some products require manual application which can be messy and awkward for self-administration, coupled with concerns from

carers regarding discomfort for administration to children. Administration devices used in conjunction with creams and ointments can reduce these barriers to the use of rectal creams and ointments.

20.7 Conclusions

The formulation of paediatric dosage forms for rectal administration follows the same principles as for adult products. Dosage adjustments in paediatric populations need to be considered carefully for systemically absorbed rectal products. The dimensions of paediatric suppositories should be considered to maximise patient and carer acceptability.

References

1. De Boer AG, Moolenaar F, De Leede LGJ, Breimer DD (1982) Rectal drug administration: clinical pharmacokinetic considerations. Clin Pharmacokinet 7(4):285–311
2. Lukhvidova ZhM, Persits BP, Novoselets SA, Matofanova LF (1974) Determination of ph of the rectal mucosa with the aid of a new recorder (Opredelenie ph slizistoi obolochki priamoi kishki pri pomoshchi novogo datchika). Eksp Khir Anesteziol (3):38–39 (Epub 1974/05/01)
3. Mackay M, Phillips J, Hastewell J (1997) Peptide drug delivery: colonic and rectal absorption. Adv Drug Deliv Rev 28(2):253–273
4. Woody RC, Golladay ES, Fiedorek SC (1989) Rectal anticonvulsants in seizure patients undergoing gastrointestinal surgery. J Pediatr Surg 24(5):474–477
5. Valentin J (2002) Basic anatomical and physiological data for use in radiological protection: reference values: ICRP Publication 89. Ann ICRP 32(3–4):1–277
6. Joensson IM, Siggaard C, Rittig S, Hagstroem S, Djurhuus JC (2008) Transabdominal ultrasound of rectum as a diagnostic tool in childhood constipation. J Urol 179(5):1997–2002 (Epub 2008/03/22)
7. Paediatric Formulary Committee (2013) BNF for children (online). BMJ Group, Pharmaceutical Press, London, and RCPCH Publications. http://www.medicinescomplete.com. Accessed on 9 Aug 2013
8. van Lingen RA, Deinum JT, Quak JME, Kuizenga AJ, van Dam JG, Anand KJS, Tibboel D, Okken A (1999) Pharmacokinetics and metabolism of rectally administered paracetamol in preterm neonates: presented in part at the annual meeting of the European Society for Pediatric Research, Rotterdam, The Netherlands, July 3–6, 1994. Arch Dis Child Fetal Neonatal Ed 80:F59–F63
9. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE (2003) Developmental pharmacology — drug disposition, action, and therapy in infants and children. N Engl J Med 349(12):1157–1167
10. Jantzen JP, Tzanova I, Witton PK, Klein AM (1989) Rectal pH in children. Can J Anaesth (Journal canadien d'anesthesie) 36(6):665–667 (Epub 1989/11/01)
11. Moolenaar F, Yska JP, Visser J, Meijer DK (1985) Drastic improvement in the rectal absorption profile of morphine in man. Eur J Clin Pharmacol 29(1):119–121
12. Jantzen JP, Erdmann K, Witton PK, Klein AM (1986) The effect of rectal pH values on the absorption of methohexital. Anaesthesist 35(8):496–499
13. Graves NM, Kriel RL (1987) Rectal administration of antiepileptic drugs in children. Pediatr Neurol 3:321–326

14. Dhillon S, Ngwane E, Richens A (1982) Rectal absorption of diazepam in epileptic children. Arch Dis Child 57(4):264–267
15. Jay M, Beihn RM, Digenis GA (1985) Disposition of radiolabelled suppositories in humans. J Pharm Pharmacol 37(4):266–268
16. Van Hoogdalem EJ, De Boer AG, Breimer DD (1991) Pharmacokinetics of rectal drug administration, Part II. Clinical applications of peripherally acting drugs, and conclusions. Clin Pharmacokinet 21(2):110–128
17. Washington N, Washington C, Wilson C (2001) Drug delivery to the large intestine and rectum, physiological pharmaceutics: barriers to drug absorption, 2nd edn. Taylor and Francis, London, pp 143–180
18. Gaudin K, Barbaud A, Boyer C, Langlois M-H, Lagueny A-M, Dubost J-P et al (2008) In vitro release and stability of an artesunate rectal gel suitable for pediatric use. Int J Pharm 353(1–2):1–7

Chapter 21
Intraosseous Infusions in Infants and Neonates

Jose Ramet, Maria A.L.J. Slaats, and Catharina J. Elsing

Abstract Intraosseous (IO) infusion is mainly used as an alternative for the vascular access when obtaining an intravenous (IV) access is difficult. Since recently, IO access is also useful as the initial access in cardiac arrest. Obtaining emergent IV access can be difficult, unacceptably time consuming and may be almost impossible in case of vascular collapse. Vascular collapse may occur in critically ill children in emergency situations such as hypovolemic shock or cardiac arrest. Therefore IO infusion is an important technique in the guidelines of pediatric cardiopulmonary resuscitation (CPR).

21.1 Introduction

Several guidelines and protocols state the importance of IO infusion. For example, the guidelines of pediatric resuscitation by the American Heart Association (AHA) recommend the use of IO infusion in the pediatric advanced life support (PALS) since 1988 [1, 2]. The PALS contains a set of lifesaving protocols and is used for emergency care of critically ill infants. The first step of this protocol is to secure the airway and provide adequate ventilation. The next priority is assessing the circulation. Return of spontaneous circulation (ROSC) can be established with chest compressions and ventilation alone (basic life support) but in some cases a vascular access is necessary for resuscitation with fluids or medication. This is where IO infusion can play an important role [2–4] (Fig. 21.1).

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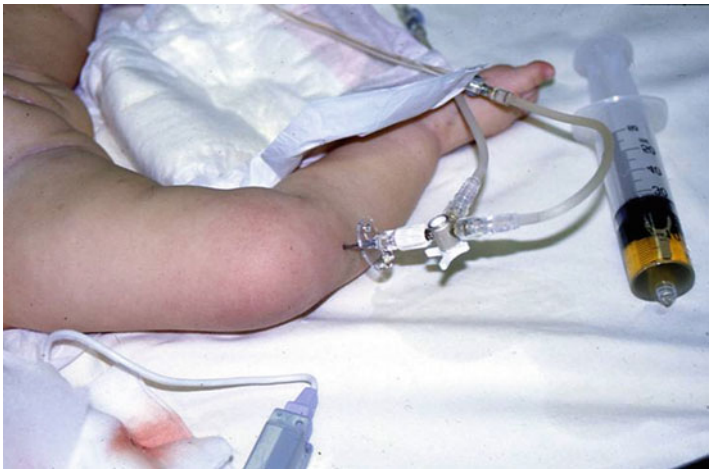


Fig. 21.1 Intraosseous infusion

21.2 Historical Background of the IO Infusion

The suitability of the IO route for vascular access was first described in 1922. Initially it was placed in the sternum of adults [5, 6]. The first experience with the use of the IO access on the sternum of pediatric patients was in 1940 [7]. But after complications such as mediastinal abscess forming, a review was published regarding bone marrow in the sternum, tibia, and femur [8]. Conclusion was that the marrow space in the sternum of children less than 3 years of age should not be used because of the small size and irregular distribution of the marrow deposits. The review suggested the lower end of the femur and the upper end of the tibia for infusion of fluids in infants up to 4 or 5 years of age [9, 10]. Through the years several studies described the IO access on children of all ages and recommended it as a great advantage [11]. In 1947, Heinald et al. [12] described a success rate of more than 95 % in nearly 1,000 IO infusions in children from 2 days to 4 years of age. During the 1950s and 1960s, the use of IO access decreased because of advantages in IV catheters (butterfly needles, plastic catheters, and improved techniques for insertion). From 1980 onwards more clinical reports about the IO access for resuscitation in children were published which increased recognition of the importance of this technique [11, 13]. Since the 1980s the IO infusion is included in the PALS course for children younger than 6 years of age, but only when IV access fails [1]. The 1992 JAMA guidelines recommended the use of IO access in children younger than 6 years of age, yet with a certain condition regarding time. The IO access should be utilized if reliable venous access cannot be achieved within three attempts or 90 s [14]. The 2000 guidelines recommended rescuers to increase attention to immediate use of the IO access in any patient with cardiac arrest, also in children

over 6 years of age [15]. There are no real changes in the guidelines of 2005 or 2010 but they rather emphasize that the rescuer should decide how quickly the IO access should be performed. The 2005 guidelines recommend the intravascular (IV and IO) route of drug administration instead of the endotracheal route. The 2010 guidelines state that when unsuccessfully establishing IV access for 1 min, the IO needle can be inserted instead and IO infusion is useful as the initial vascular access in cases of cardiac arrest [2, 16, 17]. The European Pediatric Immediate Life Support (EPILS) course was launched in 1992. Basic life support, bag-mask ventilation, chest compressions, choking, and IO access are included. With this course, the technique of obtaining IO access can easily be learned by nurses, EMS (emergency medical services) personnel, and doctors [2, 18, 19].

21.3 Anatomy and Physiology

IO infusion provides access to the systemic venous circulation through the bone marrow or medullary cavity of long bones. The cortex overlying the metaphysis of long bones is relatively thin and easy to penetrate. The administered substance enters the medullary cavity of long bones, which is composed of a network of venous sinusoids that are drained by a single central venous canal. This framework provides an entry point into the central venous circulation, which will not collapse in circumstances of hypovolemia, shock, or other critical illnesses. The central venous canal empties via the intramedullary or emissary vessels directly into the venous circulation [20].

The major vessels into which the veins drain depend upon the insertion site of the IO access:

- Proximal tibia: popliteal vein
- Femur: branches of the femoral vein
- Distal tibia: great saphenous vein
- Proximal humerus: axillary vein
- Manubrium sternum: internal mammary and azygos vein

The anterior inferior iliac spine, clavicle, and radial styloid have also been used successfully for IO vascular access, as have bones without medullary cavities.

Because the intramedullary vessel of the marrow space empties directly into the central venous system, the onset times of medications administered IO are comparable to those administered IV.

The proximal tibia is the preferred site in children because the bone is relatively flat and identification of underlying bony landmarks is less likely to be obscured by large amounts of soft tissue. Also, this location is remote from the head and the upper body, where several interventions may be ongoing in an emergency situation. It is generally agreed on that this site can be used in children up to 6–8 years old. The insertion site is at the flat surface of the tibia and can be identified approximately 1–2 cm below and slightly medial (up to 1 cm) to the tibial tuberosity [20, 21].

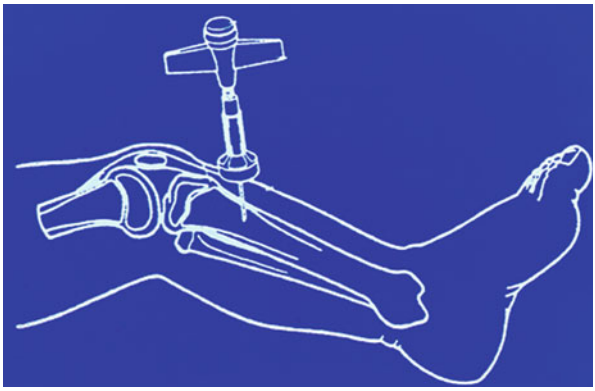


Fig. 21.2 Proximal tibia site

The distal tibia has easily palpable landmarks and less cortical thickening than the proximal tibia and is therefore the preferred site in older children. The insertion site spans the flat portion of the tibia, approximately 1–2 cm proximal to the superior margin of the malleoli in the midline [21].

The distal femur can be used when tibial and humeral sites are not indicated. It is more challenging for obtaining IO infusion, because overlying soft tissue and muscle often make identification of bony landmarks more difficult [21].

Tibial IO access was found to have the highest first-attempt success for vascular access and the most rapid time to vascular access during out-of-hospital cardiac arrest compared with peripheral IV and humeral IO access [22] (Fig. 21.2).

21.4 Indications

IO infusion is indicated as an alternative in life-threatening conditions in all ages when peripheral or central IV route cannot be established or failed. Establishing peripheral venous access is quicker, easier to perform, and safer than central venous cannulation. Although a central venous catheter can provide more secure long-term access, the placement requires training and experience and the procedure can be time consuming. Therefore central venous access is not recommended as the initial route of vascular access during an emergency. IO infusion is a safe, rapid, and effective procedure because the vascular marrow space remains stable.

Life-threatening conditions include cardiopulmonary arrest, shock, sepsis, major traumatic injuries, severely dehydrated children, extensive burns or edema, and status epilepticus. In cardiac arrest IO access can be the initial route, allowing the administration of resuscitation medication and fluids.

Thus, IO access should not be the definitive access but it provides an easier obtaining of definitive therapy by peripheral or central IV access [2, 4, 23, 24].

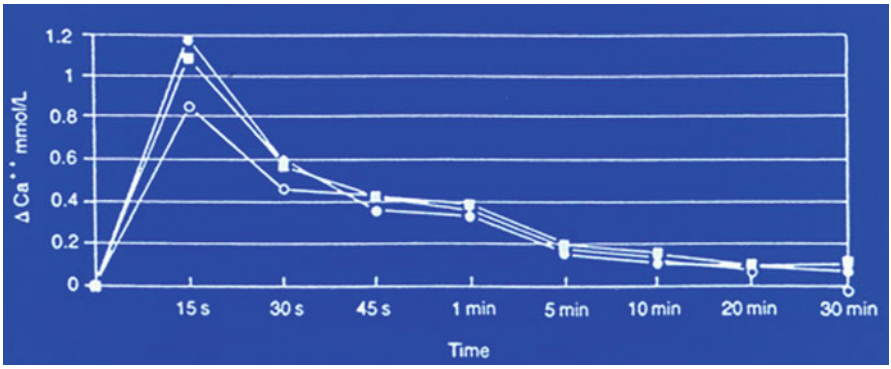


Fig. 21.3 Change in ionized calcium concentration (CA^{++}) over time, comparing the central intravenous (*solid circles*), intraosseous (*open circles*), and peripheral intravenous (*solid squares*) administration of 10 mg/kg of calcium chloride. No statistically significant difference was noted between the three routes

21.4.1 The Setting

IO infusions are used in the prehospital setting, emergency department, and hospital setting such as intraoperative or patients on the intensive care. Reports exist about the use of IO access in the operating room in nonemergent situations, after unsuccessful attempts of peripheral IV placement. IO infusion is not the first line management intraoperative but some reviews suggest it should be part of the algorithm in anesthesia when attempts at peripheral or central access are unsuccessful [20, 25–28].

21.4.2 Fluid and Drug Administration and Analysis of Blood Samples

When the IO infusion has been established, fluids, blood products, and all IV medications can be administered including epinephrine, adenosine, antibiotics, heparin, insulin, anesthetic agents, catecholamines, and resuscitation medications such as sodium bicarbonate, atropine, calcium chloride, 50 % dextrose, vasopressin, and lidocaine. Onset of action and drug levels for most drugs are comparable to venous administration. Only atropine has shown a prolonged duration of action with IO administration; in this case the marrow cavity might act as a depot [2, 19, 29].

Analysis of the bone marrow blood samples should include: type and cross match for blood type/group, chemistries, hemoglobin, blood cultures, and blood gas measurement during CPR but acid–base analysis is inaccurate after sodium bicarbonate administration. Flushing with a bolus of saline is needed after each drug to get a better dispersal in the bone marrow and promote entry into the central circulation [2, 16, 17] (Fig. 21.3).

21.4.3 IO Lines in Neonates

IO lines can be used in the treatment of preterm, low-birth-weight infants and neonates, with the smallest child reported in literature weighing 800 g. This procedure should be quick, safe, and effective in emergency situations [30–35].

In 2001 a review suggested IO access should be established if umbilical venous access cannot be established [35]. The guidelines of 2010 recommend temporary IO access for providing fluids and medications in case of resuscitation of critically ill neonates. This may be indicated following unsuccessful attempts to establish IV vascular access or when caregivers are more skilled at securing IO access [36]. Some new studies suggest that IO access should be considered first instead of umbilical venous (UV) access when rapid IV access is required in the neonate, especially by professionals who do not routinely place UV catheters. A study comparing UV and IO access in 2011 concluded that IO access can be performed more quickly and is easier to learn than UV catheter placement [37, 38].

21.5 Contraindications

Situations in which IO infusion should absolutely be avoided:

- In case of a fracture, a previously penetrating IO needle in the target bone (within 24 h) or vascular injury in the target bone, because of the chance of extravasation and the risk of compartment syndrome.
- In patients with fragile bones, for example, osteogenesis imperfecta or osteopetrosis. Obtaining IO access may cause a fracture after puncture of the fragile bone.
- In the inability to locate the landmarks of the puncture place in situations such as burns or cellulitis.
- In previous placement or attempted placement in the same leg or site, because of consequent extravasation into soft tissue compartments through the previous puncture site.
- Obvious overlying infection at the proposed puncture site, because of the risk of seeding infection.
- In patients with right-to-left cardiac shunts such as tetralogy of Fallot, persistent foramen ovale and pulmonary atresia because of the higher risk for a cerebral fat or bone marrow emboli [11, 20, 24, 26, 39, 40].

21.6 Procedure

When IO access is indicated, first of all it is important to obtain informed consent and provide sufficient explanation about the procedure to patient and caretakers. When no caretaker is available, there is broad agreement in the emergency medical

care community that this urgent lifesaving procedure can also be performed without informed consent, but the emergency situation should be carefully documented and later explained to patient and caretaker(s).

In the following section the choice of device and technical procedure of obtaining IO access will be discussed [21].

21.6.1 Choice of Device

1. Manual needles: manual needles designed specifically for IO access are available for use in children of all ages. These needles have specific features making them appropriate for obtaining IO access. If an IO needle is not available, large-bore spinal-, bone marrow- and butterfly needles may be used [21, 30, 41]. Examples of manual needles: Jamshidi® (Cardinal Health, McGaw Park, IL, USA), Dieckmann Modification® (Cook Critical Care, Bloomington, IN, USA) [20].

2. Spring-loaded device: this impact-driven device allows the single deployment of a needle to a preset depth of insertion, calculated on the basis of the patient's age.

Example: B.I.G.® (WaisMed Ltd, Houston, TX, USA), FAST1® (Pyng Medical Corporation, Vancouver, BC, Canada) [20].

The B.I.G.® introduced in 2000 was the first automatic IO device. The device is available in sizes that allow use from neonate to adult. For term newborns up to children of 12 years of age, the pediatric red-colored B.I.G.® with 18 gauge needle and adjustable insertion depth of 0.5–1.5 cm is used. For patients over 12 years of age, the adult blue-colored B.I.G.® with 15 gauge needle and insertion depth of 2.5 cm is used. It is indicated for use in the proximal tibia or proximal humerus [20, 42].

The FAST1® is an impact-driven device specifically designed for sternal use in adults. But it has also been approved in adolescents down to 12 years of age. Placement takes place at a depth of 6 mm into the manubrium through the use of manual pressure. A pediatric device is in its developmental phase [20].

3. Drill-assisted device: this battery-powered device is shaped and operates such as a small drill. It allows placement of needles of various lengths suitable for children and adults. The needle is 15 gauge and the appropriate needle length is selected based on the patient's weight:

- 15 mm (pink): for patients 3–39 kg
- 25 mm (blue): for patients ≥40 kg with normal subcutaneous tissue
- 45 mm (yellow): for patients ≥40 kg with significant tissue or edema overlying the bone

Example: EZ-IO® (VidaCare Corporation, Shavano Park, TX, USA) [20, 22, 43].

Evidence to guide the choice of device is limited to observational studies and small trials that do not allow direct comparisons among all devices available.

In general, to raise the chance of success of obtaining IO access, adequate training of the clinician is an essential feature.

21.6.2 Preparation

The patient should be placed in a manner that makes the site of insertion easily accessible. In the case of the proximal tibia or distal femoral site, a rolled towel can be placed under the popliteal fossa, it may help to maintain stability of the leg.

Equipment for preparation:

- Antiseptic solution to clean the insertion site
- A surgical mask and eye covering for the person performing the procedure, including sterile gloves
- 10 ml syringe and a syringe with saline flush

If the patient is awake local anesthesia (lidocaine 1 %) prior to obtaining IO access should be administered [21, 42–44].

21.6.3 Placement and Obtaining IO Access

1. Manual placement (*assuming the use of the proximal tibial location*) [21, 45]

- The nondominant hand can be used to stabilize the limb distal and lateral to the insertion site. This allows for counter pressure against the IO placement and to prevent distal leg movement during the procedure. To decrease the risk of needle stick injury, the hand should not be placed behind the insertion side.
- The safety cap should be removed from the needle and the needle should be placed perpendicular against the skin overlying the flat surface of the tibia insertion site. Or in skeletally immature children, at a slight angle (10–15°) from vertical (caudad for the proximal tibia, cephalad for the distal tibia or femur).
- The needle will puncture the skin and continue through the soft tissue. By using firm, steady pressure and a rotating or coring motion the bony cortex will be penetrated. Once the medullary cavity is reached, a sudden "give" with loss of resistance is noted. At this point, continued pressure should be avoided because this could push the needle through the opposite side of the bone.
- The needle cap and stylet should be removed. If the device has a supporting flange, it can be screwed down to the skin surface while stabilizing the needle.

2a. Spring-loaded technique: *B.I.G.*® [21, 42]

- Identify the placement site
- It is important to choose the appropriate size bone injection gun according to the patient's age (infant to 12 years of age: pediatric, over 12 years of age: adult). In children, set the insertion depth using the marker located on the device as follows:
  - 0–3 years: 0.5–1 cm
  - 3–6 years: 1–1.5 cm
  - 6–12 years: 1.5 cm

2b Spring-loaded technique: *FAST1®* (*for IO catheter placement in the sternum*) [21, 44]

– Identify the sternal notch and place a finger perpendicular to the notch. Apply the patch notches against the finger while maintaining alignment of the patch with the sternal notch (remove the bottom half of the backing and secure the patch to the patient's sternum and chest.)
– Ensure that the clear "target zone" is centered over the manubrium (remove the sharp plug and introducer from the package. Remove the clear sharps cap from the introducer.)
– Confirm alignment of the target patch and then, while firmly holding the introducer perpendicular to the manubrium, place the bone probe needles into the circular target zone.

3. Drill-assisted technique [21, 43]

– In the drill-assisted technique it is important to select the appropriate needle size on the basis of the patient's weight and amount of subcutaneous tissue over the selected insertion site.
– By placing the needle against the skin at a 90-degree angle and applying steady pressure, the needle will penetrate the soft tissue and bone. Once resistance decreases or the appropriate depth as indicated in the needle is reached, the trigger may be released. By holding the needle, the drill can be pulled backward and off the needle to disconnect.

21.6.4 Confirmation of Correct Catheter Placement

It is important to confirm the correct placement of the catheter. Several methods can be used:

1. The needle should stand on its own, because of lateral support provided by the bony cortex.
2. Bone marrow can be obtained with aspiration of the needle or catheter. It is important to note that this may not always occur even with a properly placed needle or catheter.
3. Flushing of the needle or catheter occurs without local swelling at the insertion site. Because the bone marrow cavity is not distensible, it is normal to sense resistance during manual flushing into the IO cannula.
4. Ultrasonography by using a bedside Doppler ultrasound can also be used to confirm placement [21, 44, 46].

After the correct placement, if desired a sample for laboratory analysis can be obtained.

If the patient is awake, slowly administer 0.5 mg/kg lidocaine (2 % [20 mg/nl] preservative-free formulation, maximum dose 40 mg) through the IO catheter prior to flushing.

Once placement is confirmed, flush the needle with normal or heparinized saline to prevent complications (see Sect. 21.7) and connect it to the conventional IV tubing. Secure the bone marrow needle with tape and a dressing, but avoid the use of dressings that will prevent you from monitoring the site for infiltration, infection or limb swelling. In case of the utilization of the FAST1®, secure the protector dome directly over the target patch [21, 42, 44].

21.6.5 Removal of the Catheter

The IO catheter provides rapid temporary vascular access, but it should be removed as soon as more definitive access is obtained (preferably within 24 h but the optimal duration of IO access is still the subject of controversy) [21].

Removal of the needle occurs by grasping of the shaft and pulling up with a slightly rotary motion.

Removal after use of a battery-powered device or B.I.G® consists of attachment of a Luer lock syringe or safely latch to the catheter hub. While stabilizing the extremity, pulling straight back with a slight rotary motion. When removing the FAST1® it is important to remove the infusion tube including the metal tip.

After removal of any kind of catheter, apply pressure to the IO site and dress the site using aseptic technique [21, 42–44].

21.7 Complications

Like every invasive procedure, the use of IO access brings the risk of complications along. But the complication rate is low and serious complications are rare due to education about the correct technique of placing [11, 20, 21].

The inability to insert an IO needle can be due to technical difficulties or using the wrong technique:

- Infrequent flushing of the needle or continuous infusion can give clogging of the needle with marrow, clot, or bone spicules.
- Incorrect identification of landmarks, for example, by burns.
- Bending of the needle.
- Fragile bones, for example, osteogenesis imperfecta.
- Failure to aspirate marrow can occur in patients with abnormally dense bone or with a small marrow cavity [11, 31].

However the complication rate is low, the following complications can occur after tibia/femur IO infusion:

- *Local hematoma*
- *Pain*

- *Subcutaneous or subperiosteal infiltration*
  A review of the literature in 2007 concluded that subcutaneous or subperiosteal infiltration is the most common complication. It is caused by incomplete placement of needle or by a dislodged needle [25, 47].
- *Compartment syndrome*
  To minimize the risk of complications the limb should be monitored carefully for any signs for compartment syndrome. Every 10–15 min a check-up should be done for distal pulses, capillary refill, the diameter of the limb, the turgor and symptoms such as weakness, pain on passive stretch of muscles, and hypoesthesia (see Sect. 21.6.4).

  When this syndrome is suspected after IO infusion, surgical decompression is needed. Diagnostic testing, for example, by arteriography is not necessary in this case because it may delay surgical decompression [21, 48–51].
- *Osteomyelitis*
  In a review of the literature in 1985 the incidence of osteomyelitis was 0.6 % in 4,270 cases. The incidence of osteomyelitis has decreased over the years. The risk of osteomyelitis is increased when IO needles remain too long in place because the risk of infection increases. In practice, the needle is usually removed as soon as another means of vascular access (either peripheral or central) is available, ideally within 6–12 h and preferably within 24 h [10, 11, 20, 21].
- *Skin necrosis*, *cellulitis*, *septicemia*, *bacteremia, and subcutaneous abscess*
  Infections are associated with extravasation of fluid, inadequate skin disinfection, and prolonged placing of the needle. Infections can be treated with antibiotics and local skin care. Together with osteomyelitis, skin necrosis was described in the earliest report of IO infusion complications [10, 20, 21].
- *Fat or bone embolism*
  Concerns have been raised about fat embolism with IO infusions through animal studies. But there are no documented cases of either fat or cortical bone emboli after IO infusions in infants and children. A probable reason is the relatively fat-free bone marrow in children [20].
- *Fracture of the bone and damage to the growth plate*
  There is no need for concern about growth plate injuries and bone deformity because there are no effects reported on the growth plate in long-term follow-up studies [52].

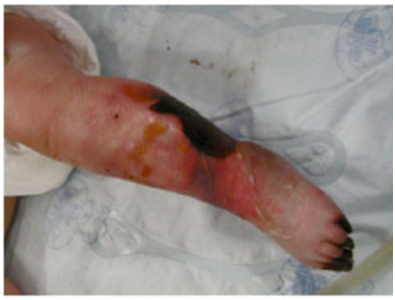
  Fractures caused by excessive force or by fragile bones (such as osteogenesis imperfect, osteopenia, osteopetrosis, or osteoporosis), allow leakage, extravasation, and potential compartment syndrome to occur. Follow-up radiographs should be obtained for all children in whom IO access has been attempted [53].

Uncommon complications in case reports:

- *Amputation and IO access in infants* (see Fig. 21.4): causes of amputation are prolonged resuscitation, compartment syndrome, infusion of potentially irritating solutions (inotropes, sodium bicarbonate, and calcium), and patients who were transported with needles in situ [54].

Case report: Amputation and IO access in infants

A 5-month-old girl was resuscitated at a local hospital for pulseless cardiac arrest caused by unrecognized congenital diaphragmatic hernia. Emergent bilateral proximal tibial IO access was achieved with a power driven system. Resuscitation included 1:10 000 adrenaline solution, 200 mL normal saline, 15 mmol sodium bicarbonate, 10 µg/kg dopamine infusion, and whole blood. In total over 400 mL of solution was infused, predominantly through the left leg. She was transferred for laparotomy, and subsequent ventilatory and inotropic support in the pediatric intensive care unit. Both distal lower limbs were pale but not tense on admission; by day seven, the right limb was perfused but her left leg had become demarcated with notable mottling to mid-calf level. Bilateral posterior tibial fractures were noted at the level of IO access. The patient was taken to theatre on day 12; all lower limb compartments were explored but were non-viable and an amputation was performed below the knee. She had no further sequelae and was discharged at one month. At six months, her right lower limb had no deficit and extension at the left knee was maintained [54].



Lesson: Place IO needles carefully, limit fluid infusion and length of infusion to avoid limb ischemia in children

Fig. 21.4 Case report [54]

Case report: Successful intraosseous infusion

A five-month-old infant was brought to the emergency department in profound hypovolemia requiring immediate tracheal intubation. A peripheral venous access was established and 35 ml of colloid were rapidly infused. Unfortunately, fluid extravasated and the intravenous line had to be removed. As further attempts to gain intravenous access were unsuccessful, an intraosseous needle was inserted into the left tibia 1 cm below the tibial tuberosity, and colloid and human albumin solution were infused rapidly, followed by 1.4% sodium bicarbonate. After ninety minutes of intraosseous rehydration, 2 peripheral venous lines were inserted, and the intraosseous needle was removed. Bacteriological and viral cultures were negative. Four days after admission, the child was discharged in good condition [57].

Fig. 21.5 Case report [57]

- *Cerebral arterial air embolism in a child after IO infusion*: in a right to left shunt [55].
- *Iatrogenic tibial fracture*: follow-up radiographs should be obtained for all children in whom IO access has been attempted [53, 56].
- *Gangrene of toes* associated with a thrombophlebitis [10] (Fig. 21.5).

21.8 Summary and Recommendations

- IO infusion is as a safe, rapid, and effective procedure of vascular access in critically ill children of all ages.
- The anterior tibia is the preferred site in children because the bone is relatively flat and identification of underlying bony landmarks are less likely to be obscured by large amounts of soft tissue.
- IO infusion is indicated as an alternative in life-threatening conditions in all ages when peripheral or central IV route cannot be established or failed.
- IO infusions are used in the prehospital setting, the emergency department and hospital setting such as intraoperative or on the intensive care.

- When IO infusion has been established, fluids, blood products, and all IV medications can be administered.
- IO lines can be used in the treatment of preterm, low-birth-weight infants, and neonates, with the smallest child reported in literature weighing 800 g.
- IO infusion is contraindicated in the case of fractured bones, fragile bones, the inability to locate landmarks of the site of punction, previous placement in the same leg, infection, and right-to-left cardiac shunts.
- Types of devices are manual needles, spring-loaded devices, and drill-assisted devices. Placement should occur in the correct way according to the specific type of device. It is important to confirm the correct position of the catheter, to remove the IO catheter as soon as more definitive access is obtained (preferably within 24 h) and to obtain the proper education and training to prevent complications.
- Complications are rare, but the most serious complications are extravasation, infection, compartment syndrome, and osteomyelitis.

References

1. Leon Chameides (1988): Vascular Access. In : Leon Chameides (Author), Textbook of pediatric advanced life support. American Heart Association/American Academy of Pediatrics, Dalles/Elk Grove Village, 1988. ISBN 10: 0874936098 / ISBN 13: 9780874936094, pp. 37-47
2. Kleinman ME, Chameides L, Schexnayder SM et al (2010) Part 14: pediatric advanced life support: 2010 American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 122:S876–S908
3. Smith R, Davis N, Bouamra O, Lecky F (2005) The utilisation of intraosseous infusion in the resuscitation of paediatric major trauma patients. Injury 36:1034–1038
4. Banerjee S, Singhi SC, Singh S et al (1994) The intraosseous route is a suitable alternative to intravenous route for fluid resuscitation in severely dehydrated children. Indian Pediatr 31(12):1511–1520
5. Drinker CK, Drinker KR, Lund CC (1922) The circulation in the mammalian bone marrow. Am J Physiol 62:1–92
6. Josefson A (1934) A new method of treatment – intraosseous injection. Acta Med Scand 81:550–554
7. Tocantins LM, O'neill JF (1940) Infusion of blood and other fluids into the circulation via the bone marrow. Proc Soc Exp Biol Med 45:782–783
8. Ravitch MM (1943) Suppurative anterior mediastinitis in an infant following intrasternal injection. Arch Surg 47:250–257
9. Tocantins LM, O'neill JF (1941) Infusions of blood and other fluids via bone marrow: application in paediatrics. JAMA 117:1229
10. Tocantins L, O'Neill J (1945) Complications of intra-osseous therapy. Ann Surg 122(2):266–277
11. Rosetti V, Thompson B, Miller J, Mateer J, Aprahamian C (1985) Intraosseous infusion: an alternative route of pediatric intravascular access. Ann Emerg Med 14:885–888
12. Heinild S, Sondergaard T, Tudvad F (1947) Bone marrow infusion in childhood: experiences from a thousand infusions. J Pediatr 30:400
13. Glaeser P, Losek J (1986) Emergency intraosseous infusions in children. Am J Emerg Med 4:34–36
14. Emergency Cardiac Care Committee and Subcommittees, American Heart Association (1992) Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Part VI. Pediatric advanced life support. JAMA 268(16):2262–2275

15. American Heart Association in collaboration with International Liaison Committee on Resuscitation (2000) Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care: international consensus on science, part 10: pediatric advanced life support. Circulation 102(Suppl I):I-291–I-342
16. American Heart Association (2005) Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 12: paediatric advanced life support. Circulation 112:164–167
17. Biarent D, Bingham R, Richmond S, Maconochie I, Wyllie J, Simpson S, Rodriguez Nunez A, Zideman D (2005) European resuscitation council guidelines for resuscitation 2005, section 6. Paediatric life support. Resuscitation 67(Suppl 1):S97–S133
18. Phillips B, Mackway-Jones K, Jewkes F (2000) The European Resuscitation Council's Paediatric Life Support Course 'Advanced Paediatric Life Support'. Resuscitation 47:329–334
19. Fiorito BA, Mirza F, Doran TM et al (2005) Intraosseous access in the setting of pediatric critical care transport. Pediatr Crit Care Med 6(1):50–53
20. Tobias J, Ross A (2010) Intraosseous infusions: a review for the anesthesiologist with a forus on pediatric use. Anesth Analg 110:391–401
21. Nagler J, Krauss B (2011) Intraosseous catheter placement in children. N Engl J Med 364(8):e14
22. Reades R, Studnek JR, Vandeventer S, Garrett J (2011) Intraosseous versus intravenous vascular access during out-of-hospital cardiac arrest: a randomized controlled trial. Ann Emerg Med 58(6):509–516
23. Haas NA (2004) Clinical review: vascular access for fluid infusion in children. Crit Care 8:478–484
24. Evans RJ, Jewkes F, Owen G, McCabe M, Palmer D (1995) Intraosseous infusion – a technique available for intravascular administration of drugs and fluids in the child with burns. Burns 21:552–553
25. Glaeser PW, Hellmich TR, Losek JD, Smith DS (1993) Five-year experience in prehospital intraosseous infusions in children and adults. Ann Emerg Med 22:1119–1124
26. Stewart F, Kain Z (1992) Intraosseous infusion: elective use in pediatric anesthesia. Anesth Analg 75:626–629
27. Harte F, Chalmers P, Walsh R, Danker P, Sheikh F (1987) Intraosseous fluid administration: a parenteral alternative in pediatric resuscitation. Anesth Analg 66:687–689
28. Neuhaus D, Weiss M, Engelhardt T, Henze G, Giest J, Strauss J, Eich C (2010) Semi-elective intraosseous infusion after failed intravenous access in pediatric anesthesia. Paediatr Anaesth 20:168–171
29. Prete MR, Hannan CJ, Burkle FM (1987) Plasma atropine concentrations via intravenous, endotracheal, and intraosseous administration. Am J Emerg Med 5(2):101–104
30. Ellemunter H, Simma B, Trawoger R et al (1999) Intraosseous lines in preterm and full term neonates. Arch Dis Child Fetal Neonatal Ed 80(1):F74–F75
31. Ramet J, Clybouw C, Benatar A, Hachimi-Idrissi S, Corne L (1998) Successful use of an intraosseous infusion in an 800 grams preterm infant. Eur J Emerg Med 5(3):327–328
32. Kelsall A (1993) Resuscitation with intraosseous lines in neonatal units. Arch Dis Child 68:324–325
33. Heyder-Musolf J, Giest J, Straub J (2011) Intraosseous access on a 1300 g septical premature infant. Anasthesiol Intensivmed Notfallmed Schmerzther 46:654–657
34. Engle W (2006) Intraosseous access for administration of medications in neonates. Clin Perinatol 33:161–168
35. Atkins DL, Chameides L, Fallat ME et al (2001) American Heart Association. International Liaison Committee on Resuscitation. Resuscitation Science of Pediatrics. Ann Emerg Med 37(Suppl 4):S41–S48
36. Wyllie J, Perlman JM, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, Guinsburg R, Hazinski MF (2010) Part 11: Neonatal resuscitation 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation 81(Suppl):e260–e287

37. Rajani AK, Chitkara R, Oehlert J, Halamek LP (2011) Comparison of umbilical venous and intraosseous access during simulated neonatal resuscitation. Pediatrics 128:e954–e958
38. Abe KK, Blum GT, Yamamoto LG (2000) Intraosseous is faster and easier than umbilical venous catheterization in newborn emergency vascular access models. Am J Emerg Med 18(2):126–129
39. Orlowski JP, Julius CJ, Petras RE et al (1989) The safety of intraosseous infusions: risks of fat and bone marrow emboli to the lungs. Ann Emerg Med 18:1062
40. Orlowski JP (1994) Emergency alternatives to intravenous access. Intraosseous, intratracheal, sublingual and other-site drug administration. Pediatr Clin North Am 41:1183
41. Lake W, Emmerson A (2003) Use of butterfly as an intraosseous needle in an oedemaous preterm infant. Arch Dis Child Fetal Neonatal Ed 88:F409
42. Bone injection gun training movie (2012) http://www.waismed.com/BIGmovie.html. Accessed 16 August 2012
43. Needle sets – Directions for use. Vidacare, Shavano Park, Texas, USA. http://www.vidacare.com/admin/files/VIDO5-8016-REVH_02-26_HIRES.pdf
44. Trainer's manual. FAST1 intraosseous infusion system. May 2011. http://www.pyng.com/wp/wp-content/uploads/PM-002j%20FAST1%20Trainer's%20Manual.pdf
45. Ruddy RM (2006) Illustrated techniques of pediatric emergency procedures. In: Fleisher GR, Ludwig S, Henretig FM (eds) Textbook of pediatric emergency medicine, 5th edn. Lippincott Williams & Wilkins, Philadelphia, p 1880
46. Tsung JW, Blaivas M, Stone MB (2009) Feasibility of point-of-colour Doppler ultrasound confirmation of intraosseous needle placement during resuscitation. Resuscitation 80(6):665–668
47. Buck ML, Barbara SW, Jefferson MS (2007) Intraosseous drug administration in children and adults during cardiopulmonary resuscitation. Ann Pharmacother 41:1679–1686
48. Vidal R, Kissoon N, Gayle M (1993) Compartment syndrome following intraosseous infusion. Pediatrics 91:1201–1202
49. Atanda A, Statter MB (2008) Compartment syndrome of the leg after intraosseous infusion: guidelines for prevention, early detection and treatment. Am J Orthop 37:198–200
50. Launay F, Paut O, Katchburian M, Bourelle S, Jouve JL, Bollini G (2003) Leg amputation after intraosseous infusion in a 7-month-old infant: a case report. J Trauma 55(4):788–790
51. Burke T, Kehl D (1993) Intraosseous infusion in infants: case report of a complication. J Bone Joint Surg Am 75(3):428–429
52. Claudet I, Baunin C, Laporte-Turpin E et al (2003) Long-term effects on tibial growth after intraosseous infusion: a prospective radiographic analysis. Pediatr Emerg Care 19:397–401
53. La Fleche FR, Slepin MJ, Vargas J, Milzman DP, Virginia N (1989) Iatrogenic bilateral tibial fracture after intraosseous infusion attempts in a 3 month old infant. Ann Emerg Med 18:1099–1101
54. Taylor CC, Clarke NMP (2011) Amputation and intraosseous access in infants. BMJ 342:1308–1309
55. Van Rijn RR, Knoester H, Maes A, van der Wal AC, Kubat B (2008) Cerebral arterial air embolism in a child after intraosseous infusion. Emerg Radiol 15:259–262
56. Bowley DMG, Loveland J, Pitcher GJ (2003) Tibial fracture as a complication of intraosseous infusion during pediatric resuscitation. J Trauma 55:786–787
57. Carbajal R, Paupe A, Lenclen R, Blanc P, Olivier-Martin M, Simon N (1995) Intraosseous infusion in children. Arch Pediatr 2(4):339–342

Part IV
Compounding

Chapter 22
Compounding for Children: The Compounding Pharmacist

Linda F. McElhiney

Abstract There is a need for pharmacists who specialize in compounding. Since pharmacy schools focus on clinical practice, pharmacists must be trained in compounding through special training programs. A compounding pharmacist must have access to good, quality compounding resources, use his or her professional knowledge to develop new formulas and dosage forms to meet the specific needs of patients. With the proper training, education, expertise, and resources, a compounding pharmacist can provide a valuable service in treating pediatric patients.

22.1 Introduction

Prior to World War II, all pharmacists were trained compounding pharmacists. Most medications were not mass-produced by drug manufacturers and pharmacists were responsible for preparing medication for patients based on physician orders or prescriptions. In the 1930s, about 75 % of all prescriptions in the United States were compounded. The art and science of compounding was taught in all pharmacy schools as part of the required pharmacy curriculum. The Industrial Revolution and emerging drug manufacturers significantly changed the practice of pharmacy and the need for compounded medications. By the 1970s, less than 1 % of prescriptions were actually compounded. The focus for pharmacists became dispensing and patient counseling.

By the 1980s and 1990s, the number of compounded preparations started to increase due to the emergence of homecare services, hospice, and total parenteral nutrition. Drug manufacturers started to produce less dosage form options for their

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products to decrease expenses and increase profit margins. Most drugs in the United States are not FDA-approved for use in children, so the drug manufacturers do not develop pediatric dosage forms. Today, many drugs used to treat children are prescribed "off-label" based on published clinical evidence and must be compounded into dosage forms that meet the needs of pediatric patients. Now there is a need again for pharmacists who are specifically trained in compounding.

22.1.1 Training and Education

The Doctor of Pharmacy (Pharm. D.) curriculum is the entry-level degree now offered by pharmacy schools in the United States. The curriculum focuses on clinical practice, medication management, and being part of the healthcare team to provide quality patient care. Routine dispensing functions are now delegated to pharmacy technicians. Several pharmacy curriculum programs have eliminated required compounding courses and only offer elective compounding courses or do not offer them at all. Where can a pharmacist get the specialized training and education necessary to provide compounding services?

Several chemical wholesalers and professional organizations all over the world do recognize the lack of compounding training in the pharmacy schools and offer a variety of different compounding courses for pharmacists and technicians:

- General non-sterile compounding
- Sterile compounding
- Compounding for hospice patients
- Compounding for Bio-Identical Hormone Replacement Therapy (BHRT)
- Compounding for pain management

New specialty compounding courses and seminars are constantly being developed and offered by the wholesalers and organizations. The information about these courses and seminars are usually posted on their websites with online registration available.

Any pharmacist that wants to specialize in compounding, especially for pediatrics patients, should take a general non-sterile compounding and a sterile compounding course. These courses will cover most of the dosage forms used in pediatrics: oral liquids, topicals, suppositories, capsules, troches, medicated lollipops and gummies, ophthalmics, inhalations, otic preparations, nasal preparations, and parenterals. They also offer hands-on experience in using the latest compounding equipment and technologies.

To obtain more education and increase knowledge and expertise specifically focused on pediatric compounding, subscribe to professional pharmacy and compounding journals. They often contain information on new drugs, pediatric case reports, clinical studies, and formulations. Another way to keep current on the newest drug treatments and dosage forms is to join local, national, and international professional compounding organizations. They have regularly scheduled meetings

and seminars that offer continuing education classes and it is an opportunity to network with other compounding pharmacists that may also do pediatric compounding. Some professional pharmacy organizations have specialty groups, such as pediatric or compounding groups, within the organizations and allow members to join the specialty group(s) of choice.

22.1.2 Compounding Resources

Proper training and education is not enough to become a good compounding pharmacist and an expert in treating pediatric patients. Compounding pharmacists need good investigative skills in order to develop new drug formulations or dosage forms to treat children. There is no single resource available that can provide all of the information needed to develop pediatric drug formulations. Several references need to be searched and the different pieces of information need to be put together like a puzzle.

In the early 1990s, there were very little compounding references available. Old editions of *Remington's* and the *United State Pharmacopeia* (*USP*) were available that contained compounding information and formulations; however, the information was not comprehensive, outdated, or not very useful. The American Society of Hospital Pharmacists, now known as the American Society of Health-System Pharmacists (ASHP), published a small compounding reference titled *Extemporaneous Formulations* and Lois Reynolds authored a publication titled *Extemporaneous Ophthalmic Preparations*, which, in the 1980s and the early 1990s, were the newest references available. Now there are dozens of reliable compounding resources available to help all pharmacists prepare compounded formulations to meet the needs of their patients.

22.1.2.1 Technical Support

In addition to courses and seminars, most of the chemical wholesalers and compounding suppliers offer compounding technical support at no additional cost, for a nominal fee, or with a paid membership. The technical support staff usually consists of pharmacists and technicians, whose responses are obtained within 24 h or less by the inquirers. Questions may be submitted through online requests posted on the companies' websites, via e-mail, or called directly by phone. Pharmacists can also obtain copies of stability studies for compounded formulations and published compounding articles through these services.

22.1.2.2 Journals

Peer-reviewed journals often publish stability studies for compounded formulations or pediatric case reports on the use of new medications. These journals are

usually provided as part of the pharmacist's membership in a professional pharmacy organization.

The most comprehensive journal with compounding information is the *International Journal of Pharmaceutical Compounding* (*IJPC*). It contains information articles on compounded treatments and case reports, formulations, peer-reviewed stability studies, and basic compounding information to improve and enhance pharmacists' and technicians' compounding skills and knowledge. Subscribers can choose to obtain a monthly hard copy of *IJPC*, as well as an electronic version. Subscribers can also join a compounders' list serve which allows them to share information with other compounders from all over the world. It can be a valuable resource when trying to find compounding information.

22.1.2.3 Texts

Several published text references are available in the United States and Europe that provide reliable compounding information. Some of them are published and sold through professional pharmacy organizations, while others are sold through independent publishers. Select textbooks that would aid the pharmacy staff in finding information for pediatrics and build a good compounding resource library.

The *USP* is a "living" textbook because it is continuously updated by appointed Committees of Experts. It is used and recognized internationally as a compounding resource that provides information on good compounding practices, quality assurance, and assigning beyond-use dating. More drug monographs are being developed and added to the *USP* so that patients will receive consistent compounded medications throughout the world. It is available as a hardback text or there is an abbreviated online version.

The *British Pharmacopeia*, *a private non-government organization*, offers similar information as the *USP* and more commonly used in Europe. The Pharmaceutical Press, located in London, publishes the *British National Formulary* (*BNF*) and the *BNF for Children* (*BNFC*) that provides formula and treatment information for drugs available in the United Kingdom. Individual European country governments, such as Spain, Germany, France, Italy, The Netherlands, and the United Kingdom, also publish national formularies and provide legal guidance regarding compounding. Not all of these government-provided formulations are up-to-date. The Spanish formulary hasn't been updated in years and contains less than 25 formulas. The pharmacists in Spain rely on currently published information, such as the *United States Pharmacopeia* (*USP*) and the *International Journal of Pharmaceutical Compounding*. The compounding pharmacist must choose the references that are most applicable for the pharmacy's location and include them in the pharmacy's compounding reference library. Compounding pharmacy practice is popular in other countries, such as Australia, Brazil, and Canada and professional pharmacy organizations in these countries also publish and sell references that may be useful for pediatric compounding.

Other good text references published in the United States that are recommended for a compounding library include the following:

- *Trissel's™ Stability of Compounded Formulations* (Trissel LA)
- *Extemporaneous Formulations for Pediatric, Geriatric, and Special Needs Patients* (Jew RK, Soo-Hoo W, Erush SC)
- *Pediatric Drug Formulations* (Nahata MC, Pai VB)
- *Suppositories* (Allen LV, Jr.)
- *The Art, Science, and Technology of Pharmaceutical Compounding* (Allen LV, Jr.)
- *Compounding Guide for Ophthalmic Preparations* (McElhiney LF)

22.1.2.4 Online Resources

Physicians often need help with dosing and treatment options for their pediatric patients. It is very useful for a compounding pharmacist that specializes in pediatrics to have access to medical libraries online. This is a great resource to find clinical evidence to support an unlabeled use for medications, compounded formulations, and compounding stability information from other medical journals. Medical libraries provide good, reliable search engines, such as Medline and OVID. If an article is not available in the library, the librarian staff can often "borrow" or obtain the article from another medical library upon request. Pharmacists can subscribe to drug databases, such as Lexi-Comp Online or MicroMedex online. Lexi-Comp contains extemporaneous preparation information, usually under the pediatric section, that is based on a published stability article. MicroMedex provides information on unlabeled uses for medications based on published studies. This information can be used to obtain articles from the medical library. These databases will also provide general information about the drugs, monitoring parameters, and dosing guidelines for both adult and pediatric patients.

The best comprehensive compounding resource available online through a subscription is CompoundingToday.com. It contains numerous databases, tools, formulas, standard operating procedures, a sterile products database, and up-to-date compounding information. It saves a lot of labor time in researching compounding information because it is literally "one-stop shopping" for compounding information. Pharmacists can use this online resource to help them develop compounded formulas for their patients, even when there may not be any other published information available because the physicochemical characteristics of drugs can be obtained. CompoundingToday.com is owned by the same company as the *International Journal of Pharmaceutical Compounding*.

22.2 Creativity in Compounding

The solutions to pediatric medical problems may not always be taught in the classroom, found in a textbook, or searched online. A compounding pharmacist may need to be creative in developing a formulation to treat a pediatric patient. For example, a

10-month-old baby with thrush does not have the comprehension or coordination to use a compounded antifungal mouthwash. It is not possible to teach a baby to "swish and swallow" or "swish and spit." The parent or caregiver may even have a difficult time administering an oral dose of the antifungal medication because the baby has a sore mouth and throat and may not want to swallow anything, especially a funny-tasting liquid. In this situation the compounding pharmacist can prepare a nystatin popsicle. The cold popsicle will help relieve the soreness in the mouth and throat, make the medication taste better, and the parent or caregiver can easily hold the baby while he licks and sucks on the small popsicle.

Some mentally challenged children are resistant to taking oral medication and suppositories are also not an option. How can a selective serotonin reuptake inhibitor (SSRI) be administered to these patients? The SSRI can be compounded into a pluronic lecithin organogel (PLO) and the medication can be administered by rubbing on the inner wrist where it is easily absorbed and provides therapeutic results. It is non-invasive and the parent or caregiver does not have to struggle with the patient.

There children and adults who are unable to swallow anything must receive all of their medication and nutrition through a feeding tube or a nasogastric tube. Since most medications have no official pediatric indications, they are often not available in suitable dosage forms such as oral suspensions or solutions. Proton pump inhibitors, such as lansoprazole, have been studied in children with gastrointestinal problems; however, initially it was difficult to administer them. Prevacid® (lansoprazole) is only available in capsules containing coated beads or an oral powder that also contains smaller coated beads. The beads do not dissolve in water or acidic beverages, so when the reconstituted oral powder was administered via a tube, the tube would clog and had to be replaced. The pharmacist must compound a lansoprazole suspension that has a basic pH to dissolve the coated beads in order to provide a suitable dosage form for tube administration.

The pharmaceutical manufacturers often do not produce these types of dosage forms because they are often not chemically stable for extended periods of time to make it feasible for mass, commercial production. Since the drugs are usually not studied in pediatric patients, governing bodies, such as the Food and Drug Administration (FDA) in the United States, do not approve indications for use in pediatric patients and the manufacturers do not develop oral liquids. Although there is a need for these dosage forms, the patient population is relatively small and it is simply not feasible economically for pharmaceutical manufacturers to produce them.

The compounding pharmacist needs to really assess the individual needs of each pediatric patient to develop a dosage form that will effectively treat the patient. Pediatric patients are not mini-versions of adults and it is up to the compounding pharmacist to find a way to administer the medication that is needed. With the proper training, education, expertise, and resources, a compounding pharmacist can provide a valuable service in treating pediatric patients who cannot be treated with commercial drug products.

Part V
Materials

Chapter 23
Food Ingredients

Parnali Chatterjee and Marie Ojiambo

Abstract Food products for newborns, infants, and children contain functional ingredients that are critical for optimal growth and health outcome later in adult life. Infant formulations are the only source of nutrition for newborns and infants, who are unable to meet all their nutritional requirements from human milk. Hence, formulations for infants and children of all ages are supplemented with various macro- and micronutrients to simulate human milk. Some functional ingredients have undergone randomized clinical trials (RCT) in healthy children and have proven to be moderately beneficial when compared to human milk. On the other hand, there are many functional ingredients, including cholesterol, lysozyme, and lactoferrin, that are present in higher concentration in the human milk, but have not been fortified in infant formulations due to the lack of appropriate clinical trials to evaluate their nutritional value in infants. Therefore, this chapter will focus on various macro- and micronutrients commonly found in infant formulations and nutritional supplements for children of all ages with respect to their allowable quantities, nutritional value, and observable health benefits.

Abbreviations

FDA	US Food and Drug Administration
FDC	Food Drugs and Chemicals
GRAS	Generally recognized as safe
RCT	Randomized clinical trials

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23.1 Food Ingredients

Food products for newborns, infants, and children contain ingredients that are critical for optimal growth and health outcome later in adult life. It is a well-known concept that poor nutrition during early stages of life can contribute to chronic adulthood diseases, such as obesity, diabetes, and cardiovascular diseases [1]. Infant formulas are the only source of nutrition for newborns and infants, who are unable to meet all their nutritional requirements from human milk. Hence, formulations for infants and children of all ages are fortified with various macro- and micronutrients to simulate human milk [31, 32]. In order to ensure that infant formulations provide necessary nutritional benefits to all term infants, manufacturers of formulations are closely monitored by FDA's Center for Food Safety and Applied Nutrition (CFSAN) for quality and levels of functional ingredients that are safe for consumption (Federal Food, Drug, Cosmetic Act, Title 21, Section 412). Therefore, food ingredients incorporated in infant formulations are generally recognized as safe (GRAS) for consumption and adhere to FDA's regulations on food additives (Federal Food, Drug, Cosmetic Act, Title 21, Section 409). Some of the functional ingredients have undergone randomized clinical trials (RCT) in healthy children and have proven to be moderately beneficial when compared to human milk. On the other hand, there are other functional ingredients, including cholesterol, lysozyme, and lactoferrin, that are present in higher concentration in human milk, but have not been supplemented in infant formulations due to the lack of appropriate clinical trials to evaluate their nutritional value in infants. Therefore, the objective of this section is to highlight various macro- and micronutrients commonly found in infant formulations and nutritional supplements for children of all ages with respect to their allowable quantities, nutritional value, and observable health benefits.

23.1.1 Types of Food Ingredients

Macronutrients constitute the bulk of functional ingredients in infant formulation and nutritional supplements [2]. These include carbohydrates and lipids that function as the energy providers and proteins as the nitrogen source for growth and body composition. Macronutrients are added in infant formulations to provide approximately 20 kcal/ounce energy to infants, but higher energy formulations are also available that provide an equivalent of 24 kcal/ounce energy by way of higher content of macronutrients, with micronutrient concentration remaining constant in all formulations [2]. The maximum allowable quantity of macronutrients in infant formulas is currently under serious consideration due to alarming reports of childhood obesity and diabetes [3].

Micronutrients are ingredients that are recommended by the FDA to be included in food products in specified quantities for children of all ages [2]. These include probiotics, prebiotics, minerals, antioxidants, low molecular weight compounds (nucleotides, etc.), and vitamins, among others. Among the micronutrients that are

required by the FDA to be included in all infant formulas, zinc, iron, and selenium deserve special attention. These micronutrients are added to the formulations either premixed or as individual ingredients.

Macro- and micronutrients are mixed together by dry blend manufacturing process or they can be incorporated by spray drying during the wet blend process. Micronutrients are added later in the wet blend process as these are heat and moisture sensitive ingredients. According to the FDA [33], the manufacturer must assure that the formula will provide sufficient nutrition for growth and development of infants, that the manufacturer will produce the formula under good manufacturing practices, and that every batch of the formula will meet the necessary nutrient criteria as specified under the FDA's CFSAN and regulations in 21 CFR [2]. Hence, impurities, microbiological content, and nutritional value of infant formulations have to be closely monitored as they are intended for term infants and children with a developing immune system. The allowable quantities, nutritional value, and observable health benefits of food ingredients that constitute the macro- and micronutrients in formulations intended for infants and children are summarized below.

23.1.2 Properties of Macronutrients

23.1.2.1 Carbohydrates

Caloric requirement of a term infant (<6 months) or a child (1 year) is between 90 and 120 kcal/kg/day. Carbohydrates provide 40–45 % of total daily calories required by a developing infant and hence called as essential macronutrients [2]. Most infant formulas have a higher carbohydrate (9–13 g/100 kcal), protein, and mineral content with low fat content as compared to the human milk [4]. Lactose is the major source of carbohydrate in human milk and standard milk-based formulations. It has been shown to confer innate immunity in newborns and infants by inducing antimicrobial peptides in the gastrointestinal epithelia that protect against pathogens [5].

Lactose is absorbed from the gastrointestinal tract once it is hydrolyzed by enzyme "lactase" into glucose and galactose. Hence, children deficient in "lactase" (due to congenital defect or lack of the enzyme) are unable to absorb lactose and develop flatulence, diarrhea, and gastrointestinal bloating following ingestion of milk due to the build-up of lactic acid, hydrogen, and carbon dioxide [6]. Adverse effects due to lactose intolerance can develop in infants and children with ingestion of less than 3 g of lactose. Therefore, in pediatric formulations, lactose can be substituted with corn syrup, corn syrup solids, maltodextrin, starch, erythritol, and powdered cellulose.

Other than lactose, infant formulations also include soy-based products that are lactose-free and provide approximately 20 kcal/ounce energy as lactose-based products [7]. These lactose-free products contain corn syrup solids as carbohydrate source, soy protein isolate as protein source, and vegetable oils as the fat content, with vitamins and minerals. They are indicated in infants who suffer from

galactosemia (hereditary lactase deficiency) and those with documented IgE-mediated allergic reaction to casein (protein in cow's milk, [8]). The lactose-free formulations prevent flatulence, diarrhea, and gastrointestinal bloating following ingestion of lactose in infants and children. Clinical studies conducted to test lactose-free infant formulations have found that formulations containing carbohydrates other than lactose in infant formulas do not affect normal growth and development of term infants [9, 10].

23.1.2.2 Proteins

Protein supplements provide 9 % (1.8–4.5 g/100 kcal of formula) of total daily calories required for a developing infant (90–120 kcal/kg/day) from a formulation. Human milk is low in protein content but has higher concentration of essential amino acids than infant formulas. Casein (acid insoluble) is the major protein (80 %) in infant formulas, while whey protein (acid soluble) is the predominant protein (80 %) in human milk [11]. Components of whey protein include α-lactalbumin, β-lactoglobulin, cysteine, and tryptophan among other amino acids. Human milk contains higher proportion of α-lactalbumin than whey-based infant formulas. Whey protein induces protein synthesis, enhances the immune system, and has antioxidant effect on the body. In addition, whey protein is easily digestible as compared to casein [12]. For infants with documented IgE-mediated and atopic allergic reaction to casein, hypoallergenic products are available that have extensively hydrolyzed proteins such as whey proteins and soy-based protein isolates [30]. Moreover, in an attempt to closely simulate human milk, casein is increasingly being substituted with whey proteins in many infant formulations. Despite the substitution, infant formulations are still not similar to human milk since the composition of proteins and amino acids is different in the two products.

23.1.2.3 Lipids

Lipids contribute 30–54 % (3.3–6.0 g/100 kcal of formula) of total daily calories required for a developing infant (90–120 kcal/kg/day) from a formulation. Human milk is composed of triacylglycerols (98–99 %), phospholipids (0.8 %), free fatty acids (<1 %), and cholesterol (0.9 %), in addition to other minor components [13]. Long chain polyunsaturated fatty acids (LC-PUFA) such as arachidonic acid (AA, C20:4n6) and docosahexanoic acid (DHA, C22:6n3) are two animal fats that are present in human milk. Their levels in infant formula are usually lower than that in human milk. Arachidonic and docosahexanoic acid are found in brain cells that are precursors of prostaglandins, prostacyclins, thromboxanes, and leukotrienes. Several large RCT studies have reported significantly enhanced cognitive, visual, immune, and motor functions in infants and children on human milk than on infant formula without LC-PUFA. Supplementation of infant formulations with combination of AA and DHA LC-PUFA in the ratio of 1.5 has been shown to improve cognitive and visual functions comparable to that observed in preterm and term

infants on human milk. More recently, a study conducted by Willatts et al. [14], found that children on LC-PUFAs containing formula were faster at processing information compared with children who received no supplementation of LC-PUFAs in their formula.

23.1.3 Properties of Micronutrients

Probiotics are dietary products and supplements that are included in infant formula and milk-based nutritional products as viable microorganisms that alter the microflora of the gastrointestinal tract with the intention of enhancing innate and adaptive immunity of infants and children [15, 16]. Probiotics include microorganisms of the genera *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* that have the ability to predominate over pathogenic bacteria in the gastrointestinal tract. These probiotic microorganisms produce small metabolic byproducts such as short-chain fatty acids including butyrates. These metabolic byproducts usually function as immune modulators, especially in newborns with developing immune system, and in infants and children with compromised immune system. Numerous RCT have highlighted the benefits of including probiotics in milk-based products for treating infectious diarrhea and for lowering the risk of atopic dermatitis in infants and children among others [16, 17].

Prebiotics are non-digestible food products consisting of fructo- and galacto-oligosaccharides (fructose chains with glucose at the terminus) that are added as supplements to infant formulas in order to enhance the proliferation of "beneficial" colonic probiotics such as *Bifidobacterium.* Inclusion of prebiotic supplements has been shown to lessen gastrointestinal and respiratory infections in infants and children. Combination of 10 % inulin with 90 % 5–60 monomers of fructose and 2–7 monomers of galacto-oligosaccharide called as GOS at 0.8 g/dL was found to be safe in infant formula by European Commission in 2001 and is available as a prebiotic in infant formulations [18]. Supplementation of infant formulas with inulin and GOS has shown to lower febrile incidences and improve immune response in infants and toddlers [17, 19]. Since, inulin and oligofructose are bifidogenic, they help in lowering the count of pathogens such as *Clostridia* in infants and toddlers and enhance the count of probiotics such as *Bifidobacterium* and *Lactobacilli* and are comparable to that observed in infants on human milk [18].

23.1.3.1 Nucleotides and Nucleosides

Nucleotides and nucleosides are low molecular weight, nitrogenous compounds that aid in de novo protein synthesis, act as growth factors and building blocks, and have immuno-modulating effects. Human milk has a higher proportion of nucleotides than infant formula. In a controlled, randomized, and blinded clinical trial, it was found that fortification of infant formula with nucleotides enhanced the

antibody responses of infants to immunization as compared to human milk [20]. Another RCT with nucleotide fortified infant formula (<5 mg/L nucleotides) concluded that nucleotide supplementation can lead to increased body weight and brain weight in infants [21]. Despite positive ramifications of nucleotide fortified infant formula, the authors concluded the need for further long-term studies evaluating the effect of nucleotides on cognitive development in infants.Hence, infant formulas can be fortified with nucleotides and nucleosides up to 16 mg/100 kcal. Infant formulas fortified with dietary nucleotides are available in Japan since 1965 and in Europe for the past two decades. However, infant formulas are not supplemented with nucleotides in the US due to the lack of large RCT that can validate the benefits of including nucleotides in infant formulas in healthy infants.

23.1.3.2 Minerals

According to Section 412(i) of the Federal Food, Drug, and Cosmetic Act (the FD Act), infant formulations must contain 29 functional ingredients, of which the minimum and maximum levels of nine minerals are specifically mentioned. Minerals that are required by the FDA to be included in infant formulations include calcium (Ca), phosphorus (Ph), magnesium (Mg), iron (Fe), zinc (Zn), manganese (Mn), copper (Cu), iodine (I), sodium (Na), potassium (K), chloride (Cl), and selenium (Se).

Iron

Iron is an important trace element. It is stored in the body as hemoglobin in the erythrocytes and bound to several enzymes including cytochrome P450 in the liver and other organs. Iron serves as a carrier of oxygen to the tissues from the lungs and as an electron carrier within the cells, especially mitochondria [22]. A newborn or an infant has no iron reserves in the body and has to rely on dietary iron to meet its iron requirements (0.9–1.3 mg/kg/body weight). Therefore, deficiency of iron can lead to anemia in a newborn or infant. Since iron is necessary for brain development, deficiency of iron can cause poor neurodevelopment [23]. The concentration of iron in human milk is 0.2–0.4 mg/L, which is much lower than that in infant formula (4.0–12.0 mg/L). Lactoferrin is an iron-binding glycoprotein which is present in human milk that enhances the bioavailability of elements including iron, zinc, manganese, copper, and selenium from the gastrointestinal tract [34]. This is due to the presence of an intestinal receptor for lactoferrin which facilitates the uptake of iron and manganese in the systemic circulation. Therefore, the competition between iron and other divalent cations such as zinc and copper is significantly reduced, leading to higher bioavailability of iron from human milk [24, 25]. Since infant formula is not fortified with lactoferrin, a much higher concentration of iron is required (4.0–12.0 mg/L) to meet the nutritional requirements of a growing infant [26]. Fortification of infant formula with iron as ferrous sulfate can cause reduced bioavailability of other divalent cations such as zinc, copper, and manganese from infant formula [24, 25]. Attempts at introducing lactoferrin in infant formula, so as

to lower the concentration of the elements in infant formula has not met with success as more research is warranted on the type of lactoferrin that can be supplemented in infant formulas and RCT evaluating the efficacy of such a product.

Selenium

During the enactment of Section 412(i) of Federal Food, Drug, and Cosmetic Act (the FDC Act), selenium was not considered as an essential ingredient in infant formulations. In the past decade, numerous reports have emerged that highlight the antioxidant properties of including selenium in diet, especially in infant formulations. Hence, selenium has been recognized as an essential nutrient to be included in infant formulations. Selenium is an essential trace element found in humans that plays a vital role in a vast number of biological functions, important among them include, regulation of thyroid hormones and as an antioxidant. Selenium can be derived from plant sources, meats, seafood, and nuts. Deficiency of selenium can cause a form of cardiomyopathy (Keshan disease) which occurs exclusively in children [27] while excessive consumption of selenium from diet can lead to chronic selenium toxicity (selenosis). Chronic selenium toxicity is characterized by nail and hair brittleness, skin rash, irritability, abnormalities of the nervous system, and gastrointestinal upsets. Hence, levels of selenium have to be regulated, especially in infants [27]. The Food and Nutrition Board of National Research Council proposed a recommended dietary allowance (RDA) of 10 μg/day of selenium in infants (<6 months) or 2.0–7.0 g selenium/100 kcal of formula. Currently, infant formulations available in the US contain 1.8–3.0 g selenium/100 kcal of formula.

Zinc

Zinc is another trace element that is critical for growth and development. Zinc deficiency can lead to anorexia, growth impairment, and compromised immune system. Infants and children with atopic dermatitis are found to have low serum and erythrocyte zinc content [28]. Human milk contains 2 μg/mL of zinc, while the content of zinc in infant formulas is much higher at 3–5 μg/mL. Due to the presence of lactoferrin in human milk, bioavailability of zinc from human milk is much higher (~60 %) than from infant formula (~25–40 %; 29]. Moreover, lower concentration of zinc in human milk prevents competition between zinc and other divalent cations such as iron, copper, and manganese, leading to higher bioavailability of zinc from human milk than from infant formula.

23.1.4 Conclusion

Food ingredients and supplements in nutritional products for newborns and infants serve as a substitute for human milk. Hence, food ingredients undergo extensive

clinical evaluation as excipients in infant formulations by the FDA before being introduced in the market. In order to simulate human milk, infant formulations have been fortified with food ingredients that are generally recognized as safe. But, there are many more ingredients in human milk for which there are no safety studies to determine the interplay between the ingredients. Unlike excipients, for which relatively few RCT have been conducted in pediatric population, food ingredients have been subjected to rigorous clinical trials, since infant formulations may be the only source of nutrition for infants and children in certain situations.

References

1. Barker DJ (1998) In utero programming of chronic diseases. Clin Sci (Lond) 95(2):115–128
2. Current Manufacturing Regulations and Guidelines, FDA, Title 21, Part 107, Infant Formula, Subpart D, Nutrient Requirements, Code of Federal Regulation
3. Martorell R, Stein AD, Schroeder DG (2001) Early nutrition and later adiposity. J Nutr 131:874S–880S
4. Nevin-Folino N, Miller M (1999) Enteral nutrition. In: Samour PQ, Helm KK, Lang CE (eds) Handbook of pediatric nutrition, 2nd edn. Aspen Publishers, Inc., Gaithersburg, pp 513–549
5. Cederlund A, Kai-Larsen Y, Printz G, Yoshio H, Alvelius G, Lagercrantz H, Strömberg R, Jörnvall H, Gudmundsson GH, Agerberth B (2013) Lactose in human breast milk an inducer of innate immunity with implications for a role in intestinal homeostasis. PLoS One 8(1):1–12
6. Rings EH, Grand RJ, Büller HA (1994) Lactose intolerance and lactase deficiency in children. Curr Opin Pediatr 6(5):562–567
7. American Academy of Pediatrics. Committee on Nutrition (1998) Soy protein-based formulas: recommendations for use in infant feeding. Pediatrics 101(1 Pt 1):148–153
8. Oldaeus G, Björkstén B, Jenmalm MC, Kjellman NI (1999) Cow's milk IgE and IgG antibody response to cow's milk formulas. Allergy 54(4):352–357
9. Lasekan JB, Jacobs J, Reisinger KS, Montalto MB, Frantz MP, Blatter MM (2011) Lactose-free milk protein-based infant formula: impact on growth and gastrointestinal tolerance in infants. Clin Pediatr (Phila) 50(4):330–337
10. Mimouni F, Campaigne B, Neylan M, Tsang RC (1993) Bone mineralization in the first year of life in infants fed human milk, cow-milk formula, or soy-based formula. J Pediatr 122(3):348–354
11. Lien EL (2003) Infant formulas with increased concentrations of α-lactalbumin1. Am J Clin Nutr 77(Suppl):1555S–1558S
12. Kinsella JE (1984) Milk proteins: physicochemical and functional properties. Crit Rev Food Sci Nutr 21(3):197–262
13. Jensen RG, Hagerty MM, McMohan KE (1978) Lipids of human milk and infant formulas: a review. Am J Clin Nutr 31(6):990–1016
14. Willatts P, Forsyth S, Agostoni C, Casaer P, Riva E, Boehm G (2013) Effects of long-chain PUFA supplementation in infant formula on cognitive function in later childhood. Am J Clin Nutr 98(2):536S–542S
15. Thomas DW, Greer FR, Committee on Nutrition (2010) Probiotics and prebiotics in pediatrics. Pediatrics 126:1217–1231
16. van der Aa LB, Heymans HS, van Aalderen WM, Sprikkelman AB (2010) Probiotics and prebiotics in atopic dermatitis: review of the theoretical background and clinical evidence. Pediatr Allergy Immunol 21(2 pt 2):e355–e367
17. Kukkonen K, Savilahti E, Haahtela T (2007) Probiotics and prebiotic galactooligosaccharides in the prevention of allergic diseases: a randomized, doubleblind, placebo-controlled trial. J Allergy Clin Immunol 119(1):192–198

18. Veereman G (2007) Pediatric applications of inulin and oligofructose. J Nutr 137:2585S–2589S
19. Arslanoglu S, Moro GE, Boehm G (2007) Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. J Nutr 137(11):2420–2424
20. Pickering LK, Granoff DM, Erickson JR, Masor ML, Cordle CT, Schaller JP, Winship TR, Paule CL, Hilty MD (1998) Modulation of the immune system by human milk and infant formula containing nucleotides. Pediatrics 101(2):242–249
21. Singhal A, Kennedy K, Lanigan J, Clough H, Jenkins W, Elias-Jones A, Stephenson T, Dudek P, Lucas A (2010) Dietary nucleotides and early growth in formula-fed infants: a randomized controlled trial. Pediatrics 126:e946–e953
22. Mascotti DP, Rup D, Thach RE (1995) Regulation of iron metabolism: translational effects mediated by iron, heme and cytokines. Annu Rev Nutr 15:239–261
23. Domellöf M (2011) Iron requirements in infancy. Ann Nutr Metab 59(1):59–63
24. Lonnerdal B (1985) Dietary factors affecting trace element bioavailability from human milk, cow's milk and infant formulas. Prog Food Nutr Sci 9(1–2):35–62
25. Lönnerdal B (1989) Trace element absorption in infants as a foundation to setting upper limits for trace elements in infant formulas. J Nutr 119(12 Suppl):1839–1844
26. Blecker U, Sothern MS, Suskind RM (1999) Iron-fortified infant formulas. Pediatr Rev 20(10):359
27. Diplock AT (1981) Metabolic and functional defects in selenium deficiency. Philos Trans R Soc Lond B Biol Sci 1294(1071):105–117
28. Toyran M, Kaymak M, Vezir E, Harmanci K, Kaya A, Giniş T, Köse G, Kocabaş CN (2012) Trace element levels in children with atopic dermatitis. J Investig Allergol Clin Immunol 22(5):341–344
29. Johnson PE, Evans GW (1978) Relative zinc availability in human breast milk, infant formulas, and cow's milk. Am J Clin Nutr 31(3):416–421
30. Chung CS, Yamini S, Trumbo PR (2012) FDA's health claim review: whey-protein partially hydrolyzed infant formula and atopic dermatitis. Pediatrics 130(2):e408–e414
31. Davis A, Baker S (1996) The use of modular nutrients in pediatrics. J Parenter Enteral Nutr 20(3):228–236
32. Greer FR (1995) Formulas for the healthy term infant. Pediatr Rev 16(3):107–113
33. Guidance for Industry: Infant Formula Guidance Documents and Regulatory Information (2006) http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/default.htm
34. Hertrampf E (1986) Bioavailability of iron in soy-based formula and its effect on iron nutriture in infancy. Pediatrics 78(4):640–645

Chapter 24
Excipients and Active Pharmaceutical Ingredients

Parnali Chatterjee and Mohammed M. Alvi

Abstract Raw materials in pediatric formulations such as excipients, food ingredients, and active pharmaceutical ingredients (APIs) have received significant attention from regulatory agencies worldwide in recent times due to safety concerns. Not all excipients and food ingredients are "inert" and have been shown to interfere with the growth and development process in pediatric population. Though raw materials incorporated in drug products require extensive safety testing prior to their inclusion in the formulations, there are very few excipients that have undergone randomized clinical trial (RCT) in the pediatric subpopulation. Therefore, this chapter will provide an overview of selected excipients and APIs that are routinely included in pediatric products with reference to their chemical structure, chemical reactivity, and allowable daily intake for pediatric use.

Abbreviations

API	Active pharmaceutical ingredient
ADME	Absorption, distribution, metabolism, and excretion
FDA	US Food and Drug Administration
FDC	Food Drugs and Chemicals
GRAS	Generally recognized as safe
RCT	Randomized clinical trials

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24.1 Introduction

Excipients, ingredients in food products, and active pharmaceutical ingredients (APIs) in pediatric formulations have received significant attention from regulatory agencies worldwide due to safety concerns. Not all excipients are pharmacologically inactive and have been implicated in interfering with the growth and development process in pediatric population. Though raw materials incorporated in drug products require extensive safety testing according to the Federal Food, Drug and Cosmetic Act of 1938 prior to their inclusion in the formulations, there are very few excipients that have undergone randomized clinical trial (RCT) in pediatric subpopulation. Moreover due to the growth and developmental changes, there is huge variability in absorption, distribution, metabolism, and excretion (ADME) profile among the pediatric subpopulation, such that newborns and infants may be more sensitive to an excipient than a toddler. Hence, there are few excipients that can be considered "safe for consumption" within the pediatric subpopulation. This chapter will provide an overview of selected excipients and APIs that are routinely included in pediatric products with reference to their chemical structure, chemical reactivity, and allowable daily intake for pediatric use.

24.2 Excipients

Pharmaceutical excipients intended for incorporation into dosage forms are approved ingredients that are considered "inactive" and generally recognized as safe (GRAS) for human consumption. Excipients make up the bulk of any drug product and are included to impart stability, ensure accuracy and precision, homogenous blending, mask bitter taste, improve flowability, add bulk density, and control the release of API thereby improving patient compliance, bioavailability, efficacy, and reduce toxicity of the API [1, 2]. Though excipients are considered "inactive" and can be exempted from listing on certain drug products, they are required by the FDC Act to be listed on ophthalmic, topical, and parenteral products. Hence, excipients are subjected to exhaustive short-term and long-term toxicological studies prior to their inclusion in drug products for adult population but are not tested in pediatric subpopulation. Studies in pediatric population are a challenge from an ethical stand-point and are limited by blood sample availability and physiological changes that occur early in life and up to adulthood [3]. Moreover, information from clinical studies establishing efficacy and dosage regimen for adult population cannot be extrapolated to the pediatric population due to the rapid growth and developmental changes occurring in children. Currently, pediatric medications are available as drops, elixirs, syrups, suspensions, sprinkles, capsules, orally disintegrating tablets, chewable tablets, injectables, etc. [4]. Many excipients such as lactose and sorbitol when included in pediatric formulations can induce diarrhea in children, benzyl alcohol can cause toxicity in neonates, while aspartame-based sweeteners can induce seizures and headaches in children,

adverse effects that are not commonly observed in formulations for adult population. Therefore, the objective of this section is to highlight the excipients commonly found in pediatric products, chemical reactivity of the functional groups present in the molecules, impurities present in the excipients, and concentrations at which excipients exert their toxicity in pediatric population.

24.2.1 Classification of Excipients

Excipients can be classified depending on the (1) origin of source such as plant, animal, mineral, and synthetic-based, (2) functional role they play in the formulation such as binders, diluents, disintegrants, fillers or bulking agents, glidants, lubricants, coloring agents, preservatives, sweeteners, surfactants, solvents, coating agents [5], and (3) chemical substituents present in the excipients such as alcohols, acids, esters, carbohydrates, glycerides, halogenated derivatives, mercury salts, sulfites, etc. Notable examples of excipients found in pediatric formulations are included in Table 24.1.

Table 24.1 Classification of pharmaceutical excipients

1. Classification of pharmaceutical excipients based on function
Binders
Example: PVP, HPMC
Coloring agents
Example: E number colorants
Coating agents
Example: Phthalates
Diluents
Example: Lactose, microcrystalline cellulose
Disintegrants
Example: Sodium starch glycolate, croscarmellose sodium
Fillers/bulking agents
Example: Lactose
Glidants
Example: Colloidal SiO_2
Lubricants
Example: Magnesium stearate, sodium stearyl fumarate, sodium behenate
Preservatives
Example: Sodium benzoate, thiomerosal
Sweeteners
Example: Sorbitol, mannitol, dextrose, aspartame, saccharin, sucralose
Surfactants
Example: Tweens, spans, polysorbates, poloxamers, lecithins
Solvents
Example: Ethyl alcohol, benzyl alcohol, propylene glycol, sorbitol, PEGs

(continued)

Table 24.1 (continued)

2. Classification of pharmaceutical excipients based on origin of source
Animal source
Example: Lactose, gelatin, stearic acid
Mineral origin
Example: Silica, calcium phosphate
Plant source
Example: Alginates, starches, sugars, cellulose
Synthetic excipients
Example: Polyethylene glycol, polysorbates, polyvinylpyrrolidone
3. Classification of pharmaceutical excipients based on chemical substituents
Alcohols
Example: Ethyl alcohol, benzyl alcohol, propylene glycol
Carboxylic acids
Example: Benzoic acid
Carbohydrates
Example: Mono-, di- and polysaccharides, sucrose, lactose, mannitol
Dyes
Example: Tartrazine, amaranth
Esters/ethers
Example: Fatty acid esters or ethers
Glycerides and waxes
Example: Peanut oil, bees wax
Halogenated hydrocarbon derivatives
Example: Freons, chlorbutol, halothane
Organic mercurial salts
Example: Thiomerosal
Phenolic compounds
Example: BHA, BHT
Proteins
Example: Albumin, gelatin
Polymers
Example: HPMC, Eudragits

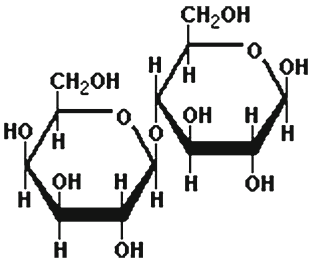
24.2.2 Properties of Selected Excipients

No excipient is inert and above a certain concentration can produce adverse reactions in the pediatric population. Based on the FDA Guidance document of 2005, excipients for pediatric formulations should be chosen such that the ADME profile of the target population, length of the therapy, and dosing interval is taken into consideration. In addition, substitutions to the commonly used excipients in pediatric formulations can be made that include reducing the amount or elimination of preservatives such as thimerosal, benzyl alcohol, and propylene glycol from vaccines and other drug products that are administered to children below the age of 6 years. In a number of vaccines and formulations, thimerosal, benzyl alcohol, or propylene glycol has been replaced by benzalkonium chloride, methyl and propylparaben (0.1–0.3 %), bronopol

(2-bromo-2-nitropropane-1,3-diol), sodium azide, or 2-phenoxyethanol. Salient properties of excipients commonly found in pediatric formulations are described in the following section and allowable daily intake is given in Table 24.2.

24.2.2.1 Fillers/Binders

Lactose



Synonyms: Lactin; Lactose; D-Lactose; Galactinum; Aletobiose; Osmolactan; Lactobiose; Milk sugar
General appearance: White powder, either in crystalline or amorphous state
Molecular formula: $C_{12}H_{22}O_{11}$
Formula weight: 342.3 g/mole
Water solubility: Very soluble in water (5–10 g/100 mL)

Lactose is a reducing disaccharide of glucose and galactose. It can occur in two anomeric forms, α-lactose (monohydrate) and β-lactose (anhydrous). The two forms can be used as a diluent and filler for direct compression and wet granulation in tablets and capsules, and a bulking agent for powders in 20 % of all formulations in the market. In crystalline form it is less reactive, while the carbonyl group in amorphous lactose can react readily with primary and secondary amines in the API via Maillard reaction to give a Schiff's product, which can undergo Amadori rearrangement and form Glycosamine [6]. Maillard reaction is known to occur in infants due to carbohydrate-derived carbonyl groups present in milk-based infant formulas and protein amino groups [7]. The by-products of Maillard reaction can function as electrophiles and cause adverse reactions in newborns and infants. Such reaction products have been shown to cause histological changes in the proximal tubules of kidneys in rats and increased levels of microprotein in human urine [8, 9].

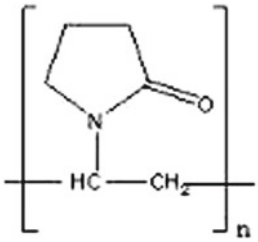
Lactose is absorbed from the gastrointestinal tract (git) once it is hydrolyzed by the enzyme "lactase" into glucose and galactose. Hence, children deficient in "lactase," are unable to absorb lactose (due to congenital defect or lack of the enzyme) and develop flatulence, diarrhea, gastrointestinal bloating following ingestion of milk due to the build-up of lactic acid, hydrogen, and carbon dioxide. Lactose intolerance in infants and children can lead to prolonged episodes of bloating, diarrhea, dehydration, and metabolic acidosis [9]. Adverse effects due to lactose intolerance can develop in infants and children with ingestion of less than 3 g of lactose.

Table 24.2 Allowable daily intake (ADI) in children, no observable adverse event level (NOAEL), adverse effects of pharmaceutical excipients in the formulations [23, 24]

Excipient	Allowable daily intake (ADI)	Adverse effects
Diluent		
Microcrystalline cellulose	Not specified	Intestinal absorption, long-term effect not known, should not be used in children <2 years
Dyes		
"E number" additives: Sunset yellow (E110), Quinoline yellow (E104), Carmoisine (E122), Allura red (E129), Tartrazine (E102), and Ponceau 4R (E124)	2.5 mg/kg (Sunset yellow)	Negative effect on children's behavior and ADHD
Solvents/co-solvents		
Benzyl alcohol (BA)	Not specified	Toxic syndrome observed in neonates (attributed to the practice of "flushing out" umbilical catheters with solutions containing BA); severe respiratory complications and even death in neonates caused by dilution of nebulization solutions with BA-preserved saline
Ethyl alcohol	Max 10 % (12 years) Max 5 % (6–12 years) Max 0.5 % (<6 years)	Due to high blood–brain barrier permeability; CNS effects at 0.01 g/L; intoxication, lethargy, stupor, coma, respiratory depression, cardiovascular collapse
Peanut oil	Not specified	Use in infant formula and topical preparations can lead to later episodes of hypersensitivity
Propylene glycol	25 mg/kg	No known toxic dose; but potentially life-threatening complications such as cardiovascular, hepatic, respiratory, and CNS adverse reactions especially in neonates where the biological half-life is prolonged to 17 h compared with adults, 5 h
Sweeteners		
Aspartame	40 mg/kg/day	Source of phenylalanine, can cause phenylketonuria; hyperactivity in children but unproven
Lactose	Not specified	Diarrhea, gaseousness or cramping; intestinal disorders
Saccharin	5 mg/kg/day	Hypersensitivity reactions (mainly dermatologic); pediatrics with allergy to sulfonamides should avoid saccharin; carcinogenic potential (banned in Canada)
Sorbitol	0.3 g/kg	Diarrhea, gastrointestinal disorder
Sucralose	5 mg/kg/day	Not specified
Surfactant		
Polysorbate 80	10 mg/kg/day	E-Ferol syndrome (Thrombocytopenia, renal dysfunction, hepatomegaly, chlestasis, ascites, hypotension and metabolic acidosis) in low birthweight infants
Polyvinylpyrrolidone	0–50 mg/kg	Not specified
Preservatives		
Benzoic acid, Potassium benzoate, Sodium benzoate	up to 5 mg/kg (sum of all)	Caffeine and sodium benzoate should be injected simultaneously; elicits non-immunological contact reactions including urticaria and atopic dermatitis in neonates
Thimerosal	Not specified	Possible links with toxicity in pediatric vaccines and childhood autism; though unproven

Therefore, in pediatric formulations, lactose can be substituted with starch, calcium hydrogen phosphate dehydrate, erythritol, and powdered cellulose. These powders have flow properties similar to lactose (calcium hydrogen phosphate dehydrate has a smaller angle of repose than lactose), and produce tablets that can disintegrate in shorter time than lactose.

Polyvinylpyrrolidone



Synonyms: PVP, polyvidone povidone, poly [1-(2-oxo-1-pyrrolidinyl)ethylen] 1-ethenyl-2-pyrrolidon homopolymer 1-vinyl-2-pyrrolidinon-polymer copovidone
General appearance: White powder
Molecular formula: $(C_6H_9NO)n$
Formula weight: Average MW 360,000 g/mole
Water solubility: Readily soluble

PVP can be used as a binder, clarifying agent, stabilizer, bodying agent, tableting adjunct, dispersing agent, and for masking taste in formulations. Polyvinylpyrrolidone-based excipients including Povidone and Crospovidone may contain peroxides, formates, and aldehydes as by-products that can be generated as a result of the manufacturing processes or due to oxidative instability of the excipients over time and are more reactive than hydrogen peroxide [10]. Recently, PVP has been shown to cause immediate or contact dermatitis reaction in children [11].

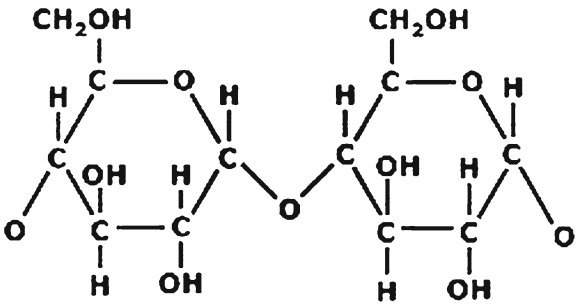
Hydroxypropylmethylcellulose

Synonyms: Modified cellulose; propylene glycol ether of methyl cellulose
General appearance: White or slightly beige powder or granule
Molecular formula: C_3H_7O
Molecular weight: 59.09 g/mole
Water solubility: Soluble

Hydroxypropylmethylcellulose (HPMC) is used as a thickener for aqueous and non-aqueous systems that can produce clear films with grease resistance, can function as binders, lubricants, steric stabilizer and aids in water retention. Inclusion of

HPMC and HPMCAS (hydroxypropylmethylcellulose acetate succinate) as a coating agent in oral formulations can lead to the formation of minor quantities of glyoxal or dialdehyde (phthalamide and succinamide impurities) impurities with certain APIs such as duloxetine hydrochloride [12] and cause toxicity. Formation of the impurities is hastened in the presence of moisture and high temperature. Since duloxetine is prescribed to the pediatric population for treating anxiety disorders, levels of the impurities are closely monitored during formulation development.

Starch

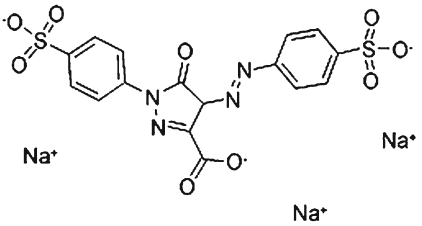


Synonyms: Alpha-starch, (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(hydroxymethyl)-6-[(2*R*,3*S*,4*R*,5*R*,6*S*)-4,5,6-trihydroxy-2-(hydroxymethyl)oxan-3-yl]oxy-oxane-3,4,5-triol
General appearance: Fine, white, odorless powder.
Molecular formula: $(C_6H_{10}O_5)n$
Molecular weight: Variable hydrophilic polymer
Water solubility: Very soluble

Starch can be used as a binder for wet granulation, disintegrating agent, diluent in capsules, and powder formulations. Lignin, maltose, and hemicellulose are known impurities in starch. Maltose and acetyl formoin, impurities found in starch, have been implicated in the formation of Amadori rearrangement degradation products with APIs containing primary and secondary amines such as antiallergic medication, desloratadine [13]. Since starch is an excipient that is routinely found in most solid dosage forms, studies involving interactions between starch and APIs are especially warranted before inclusion in pediatric formulations.

24.2.2.2 Coloring Agents

Tartrazine

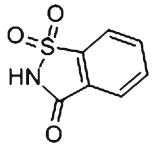


Synonyms: CI NO 19140; CI acid yellow 23; CI 19140; E102; Lake tartrazine; Kiton Yellow T; Hydrazine yellow; Food yellow No. 4
General appearance: Deep yellow powder
Molecular formula: $C_{16}H_9N_4Na_3O_9S_2$
Molecular weight: 534.36 g/mole
Water solubility: Very soluble

Azo dyes such as tartrazine, amaranth, Erythrocine B, ponceau, indigo carmine improve aesthetics of a product by imparting color to the formulation but are known to produce adverse effects such as contact dermatitis, gastrointestinal intolerance, brochospasm, eosinophilia, angioedema, and urticaria in children. These side effects observed with azo dyes are similar to those observed with aspirin. Moreover, clinical trials have implicated azo dyes to hyperactivity in children, but recent controlled and RCT with azo dyes have refuted the claim [14]. Such dyes can be substituted with vegetable dyes such as annatto, malt beta-carotene, and turmeric or not used at all in pediatric formulations.

24.2.2.3 Sweeteners

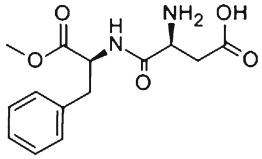
Saccharin



Synonyms: Saccharin; Saccharin 550X; Syncal®, *o*-benzoic acid sulfimide
General appearance: White crystals, odorless or faintly aromatic odor, sweet in taste.
Molecular formula: $C_7H_5NO_3S$
Molecular weight: 183.18 g/mole

Saccharin is considered a low calorie-artificial or non-nutritive sweetener according to the Academy of Nutrition and Dietetics [15]. Non-nutritive sweeteners such as saccharin have no carbohydrate value and hence produce minimal or no energy. Daily intake of saccharin has been found to be 0.2–0.9 mg/kg in adult population, while that number is 3-times in diabetics. In children, amount of saccharin that is ingested through chewable acetaminophen or aspirin tablets has been found to be similar to that found in diet soda cans and considered to be "excessive" by an FDA/NCI sponsored epidemiology study. Saccharin is an *o*-toluene sulfonamide that causes "sulfa" type of hypersensitivity reaction in children including wheezing, urticaria, pruritis, nausea, vomiting, diarrhea, tachycardia, headache, diuresis and sensory neuropathy [14]. Infant formula sweetened with saccharin has been found to induce insomnia, irritability, and hypertonia. Therefore, American Medical Association recommends limited intake of saccharin in infants and pregnant woman.

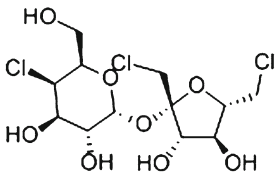
Aspartame



Synonyms: L-aspartyl-L-phenylalaninemethyl ester; L-asp-phemethylester; *H*-asp-pheome; Equal; Aspartame
General appearance: White powder or tablets
Molecular formula: $C_{14}H_{18}N_2O_5$
Molecular weight: 294.3 g/mole

Similar to saccharin, aspartame is a non-nutritive sweetener with minimal or no carbohydrate value and regarded as safe by the FDA [15]. It is an aspartic acid and phenylalanine derivative that is increasingly used in sugar-free and chewable formulations. Serum levels of phenylalanine can significantly increase on ingestion of high amounts of aspartame. Hence, content of phenylalanine should be clearly indicated in the drug product label. Consumption of aspartame should be closely monitored, especially in children with autosomal recessive phenylketonuria, since levels of phenylalanine could significantly rise on ingestion of aspartame. Daily intake of aspartame in children can be between 5 and 10 mg/kg, for those without any dietary restrictions. A number of adverse effects such as headaches, panic disorders, mood changes, and seizures have been reported as a result of high dose (>30 mg/kg/day) and long-term ingestion of aspartame, but none of adverse effects could be proven by a single-dose randomized double-blind clinical trial [16]. Aspartame can be replaced by stevia, date sugar, maple sugar, maple syrup molasses, and agave nectar in pediatric formulations.

Sucralose

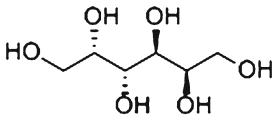


Synonyms: 1,6-dichloro-1,6-dideoxy-beta-D-fructofuranosyl 4-chloro-4-deoxy-alpha-d-gala; 4,1′,6′-trichloro-4,1′,6′-trideoxy-galacto-sucrose
General appearance: Off-white amorphous solid
Molecular formula: $C_{12}H_{19}C_{l3}O_8$
Molecular weight: 397.63 g/mole
Water Solubility: Soluble

Sucralose is a non-nutritive sweetener that is regarded as safe by the FDA. It is a chlorine derivative of sucrose and is 600 times as sweet as sucrose. It finds its

application in the pediatric formulations, food and beverages [17]. Sucralose is slowly absorbed from the gastrointestinal tract and has a greater impact on the gut bacteria. Recent data suggest a link between increased intake of saccharin and sucralose to the prevalence of irritable bowel syndrome in children and in adult population [18].

Sorbitol

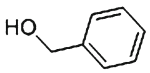


Synonyms: Cholaxine; Diakarmon; D-Sobit; D-Sorbite
General appearance: White crystalline powder, odorless colorless solid, sinks and mixes with water
Molecular formula: $C_6H_{14}O_6$
Molecular weight: 182.17 g/mole
Water solubility: Soluble

Sorbitol is a hexahydric polyol and a nutritive sweetener which produces sweetness with less energy intake (2.6 vs 4 kcal/g of energy for sucrose). Polyols are labeled as "sugar-free" by the Academy of Nutrition and Dietetics [15]. Ingestion of sorbitol at doses of 0.5 g/kg body weight has been shown to cause gastrointestinal distress, bloating, diarrhea, and abdominal pain in children depending on the age due to the metabolism of sorbitol to pyruvic acid and lactic acid by the liver. At higher doses (10–20 mg/kg body weight), sorbitol can produce a laxative effect in the intestine, shortens the transit time, thereby decreases energy value. Since newborns and infants have immatured and developing epithelial barriers and drug metabolizing enzymes, absorption of sorbitol is limited, but enhanced in the presence of glucose and fatty acids. Accumulation of sorbitol in the body of newborns and infants has been implicated in diabetic-like symptoms in the body such as retinopathy. Therefore, pediatric formulations containing sorbitol have labeling requirements that state the content of sorbitol in the drug product.

24.2.2.4 Alcohols

Benzyl Alcohol

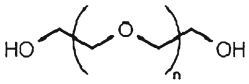


Synonyms: (Hydroxymethyl) benzene; Bentalol; Benzalalcohol; Benzalcohol; Benzenemethanol;
General appearance: A clear colorless liquid with a pleasant odor, slightly denser than water, flash point 194 °F, boiling point 401 °F, contact may irritate skin, eyes, and mucous membranes.

Molecular formula: C_7H_8O
Molecular weight: 108.14 g/mole
Water solubility: Very soluble

Benzyl alcohol is used as a solubilizing agent and a preservative in many injectables and solutions for pediatric consumption. Ingestion of drug products containing large volumes of benzyl alcohol (32–105 mg/kg/day) has been implicated in respiratory and metabolic complications and death in neonates [19]. Benzyl alcohol is present in bacteriostatic water and saline for injection, hence, these products contain labels stating "Not for use in Newborns." Nausea, vomiting, fatigue, rash, fever, or angioedema can occur in children due to parenteral products containing benzyl alcohol as a preservative.

Polyethylene Glycol

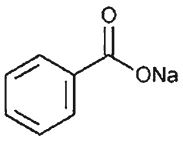


Synonyms: 1,2-ethanediol, Carbowax, Polyglycol, Polyethylene glycol 200, 300, 400, 600, 1000, 1450, 3350, 4000, 6000, 8000, and 20,000
General appearance: Clear colorless viscous liquid.
Molecular formula: $HOCH_2–(CH_2–O–CH_2)n–CH_2OH$
Molecular weight: 200–9,500 g/mole

Polyethylene glycol (PEG) is used as a solubilizing agent in many topical, oral, and injectables for pediatric consumption. PEG at a dose of 0.7 g/kg/body weight can effectively be used for treating constipation in infants and children. Reactive hydroperoxides, formaldehyde (2–165 ppm), and acetaldehyde (2.7–12.5 ppm) are impurities that have been detected in aqueous solutions of PEG due to the oxidation and breakdown of polymeric chains of PEG in formulations [20]. These impurities can form adducts with the API and cross-link with formulation gelatin capsule shell to form insoluble protein, causing slow dissolution and incomplete drug release. Since children are twice as susceptible to the effects of hydroperoxides and aldehydes due to immatured or over-expression of drug metabolizing enzymes, levels and nature of impurities should be closely monitored before inclusion in pediatric formulations.

24.2.2.5 Preservatives

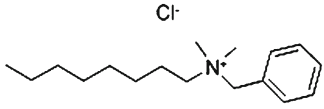
Sodium Benzoate



Synonyms: Benzotron(r); benzoic acid sodium salt; Fema 3025
Molecular formula: $C_7H_5NaO_2$
Molecular weight: 144.1 g/mole
Water solubility: Soluble

Sodium benzoate is used as a preservative in pediatric formulations containing amoxicillin-clavulanic acid and other antibiotics. It is regarded as safe by the FDA. In some cases, sodium benzoate has been implicated in cutaneous urticaria in children through non-immunologic pathways [21].

Benzalkonium Chloride

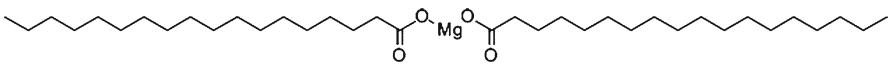


Synonyms: Benzyldimethylalkylammonium chloride; BKC; alkyl (C 14–16) dimethylbenzyl-ammoniuchlorides; benzyldimethyl (mixedalkyl) ammoniumchloride
General appearance: Colorless or yellowish powder or gummy amber solid, aromatic odor, very bitter taste
Molecular formula: $C_{17}H_{30}ClN$
Molecular weight: 283.88 g/mole
Water solubility: Soluble

Benzalkonium chloride is used as a preservative, biocide, surfactant, emulsifying agent, and as a pigment dispersant. Children are exposed to benzalkonium chloride through nasal sprays containing corticosteroids, decongestants, and saline solution [19]. Benzalkonium chloride produces bronchoconstriction, cough, pruritis, facial flushing, and burning sensation in a dose-dependent manner. Since the concentration of benzalkonium chloride in nasal products for children from a multi-dose bronchodilator (50 μg/0.5 mL) is low, children are mostly likely not susceptible to the adverse effects of the preservative. In addition, single-dose vials of bronchodilators can be recommended for children without the need for preservation using benzalkonium chloride.

24.2.2.6 Lubricants

Magnesium Stearate



Synonyms: dibasic magnesium stearate; Dolomol; magnesium di-stearate; Magnesium stearate medicinal; stearate de magnesium: magnesium octadecanoate
General appearance: White powder

Molecular formula: $C_{36}H_{70}MgO_4$
Molecular weight: 591.24 g/mole
Water solubility: Insoluble

Magnesium stearate is used as a diluent and an anti-adherent agent in formulations. It is a mixture of magnesium salt of fatty acids, palmitic acid and stearic acid. Magnesium stearate and stearate salts can interact with APIs, especially drugs that are prone to hydrolysis via ion-catalyzed mechanism such as aspirin, leading to degradation products such as salicylic acid, salicyl salicylic acid, and acetyl salicyl salicylic acid [12]. A casual link between aspirin related drugs and Reye's syndrome, which is characterized by hypoglycemia, hypoketonemia, elevated ammonia, and organic aciduria in pediatric population, has long been established in formulations containing magnesium stearate and aspirin [22]. Fatty acids in magnesium stearate are susceptible to contact dermatitis, though rare cases of allergies have been noted in children. Despite numerous reports of incompatibilities magnesium stearate continues to be a widely used lubricant in oral dosage forms.

24.3 Conclusions

Excipients serve many functions in a formulation by improving product delivery, as an absorption enhancer and improve flow properties of an API during manufacturing process. Therefore, there are very few drug products that can be manufactured without an excipient. Excipients incorporated in pediatric formulations require safety evaluation in specific subset of the pediatric population due to the variability in ADME profile among the subpopulation. RCT to evaluate the safety of excipients in pediatric population are not only limited by availability of pediatric patients but by blood samples and difficulty in extrapolating the results to the pediatric subpopulation. It is highly unlikely that all excipients would be subjected to RCT in pediatric population such that the recommended daily intake could be determined, nor will there be a list of "selected excipients" that could be exclusively used in pediatric population. It would therefore be in the best interest of the scientific community to evaluate the safety profile of the excipients included in the drug products during the course of the drug development process in the pediatric population.

References

1. Fabiano V, Mameli C, Zuccotti GV (2011) Paediatric pharmacology: Remember the excipients Pharmacol Res 63(5):362–365
2. Pifferia G, Restani P (2003) The safety of pharmaceutical excipients. Farmaco 58:541–550
3. Whittaker A, Currie AE, Turner MA, Field DJ, Mulla H, Pandya HC (2009) Toxic additives in medication for preterm infants. Arch Dis Child Fetal Neonatal Ed 94(4):F236–F240
4. Pawar S, Kumar A (2002) Issues in the formulation of drugs for oral use in children. Paediatr Drugs 4(6):371–379

5. Smolinske SC (1992) Handbook of food, drug, and cosmetic excipients. CRC Press LLC, Boca Raton, Florida
6. Ahlneck C, Zografi G (1990) The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. Int J Pharm 62:87–95
7. Aidrian J (1982) The Maillard reaction. In: Rechcigl M (ed) Handbook of nutritive values of processed food, vol 1. CRC Press, Boca Raton, Florida, pp 529–608
8. Langhendries JP, Hurrell RF, Furniss DE, Hischenhuber C, Finot PA, Bernard A, Battisti O, Bertrand JM, Senterre J (1992) Maillard reaction products and lysinoalanine: urinary excretion and the effects on kidney function of preterm infants fed heat-processed milk formula. J Pediatr Gastroenterol Nutr 14(1):62–70
9. Tsukahara H, Ohta N, Sato S, Hiraoka M, Shukunami K, Uchiyama M, Kawakami H, Sekine K, Mayumi M (2004) Concentrations of pentosidine, an advanced glycation end-product, in umbilical cord blood. Free Radic Res 38(7):691–695
10. Pedrosa C, Costa H, Oliveira G, Romariz J, Praça F (2005) Anaphylaxis to Povidone in a child. Pediatr Allergy Immunol 16(4):361–362
11. Yoshida K, Sakurai Y, Kawahara S, Takeda T, Ishikawa T, Murakami T, Yoshioka A (2008) Anaphylaxis to polyvinylpyrrolidone in Povidone-iodine for impetigo contagiosum in a boy with atopic dermatitis. Int Arch Allergy Immunol 146(2):169–173
12. Wu Y, Levons J, Narang AS, Raghavan K, Rao VM (2011) Reactive impurities in excipients: profiling, identification and mitigation of drug-excipient incompatibility. AAPS PharmSciTech 12(4):1248–1263
13. Yu X, Buevich AV, Li M, Wang X, Rustum AM (2012) A compatibility study of a secondary amine active pharmaceutical ingredient with starch: identification of a novel degradant formed between desloratadine and a starch impurity using LC-MS(n) and NMR spectroscopy. J Pharm Sci 102(2):717–731
14. Boris M, Mandel FS (1994) Foods and additives are common causes of the attention deficit hyperactive disorder in children. Ann Allergy 72(5):462–468
15. Fitch C, Keim KS (2012) Position of the Academy of Nutrition and Dietetics: use of nutritive and nonnutritive sweeteners. J Acad Nutr Diet 112(5):739–758
16. Connolly A, Hearty A, Nugent A, McKevitt A, Boylan E, Flynn A, Gibney MJ (2010) Pattern of intake of food additives associated with hyperactivity in Irish children and teenagers. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 27(4):447–456
17. Crowley PJ, Martini LG (2011) Excipients in pharmaceutical products. Encyclopedia of Pharmaceutical Technology. Marcel Dekker Inc., New York
18. Qin X (2012) Etiology of inflammatory bowel disease: a unified hypothesis. World J Gastroenterol 18(15):1708–1722
19. American Academy of Pediatrics, Committee on Drugs (1997) Pediatrics (2):268–278
20. Waterman KC, Adami RC, Hong J (2003) Impurities in drug products. In: Ahuja S, Alsante KM (eds) Handbook of isolation and characterization of impurities in pharmaceuticals. Academic/Elsevier Science, San Diego, pp 75–88
21. Mori F, Barni S, Pucci N, Rossi ME, de Martino M, Novembre E (2012) Cutaneous adverse reactions to amoxicillin-clavulanic acid suspension in children: the role of sodium benzoate. Curr Drug Saf 7(2):87–91
22. Gosalakkal JA, Kamoji V (2008) Reye syndrome and reye-like syndrome. Pediatr Neurol 39(3):198–200
23. Combined Compendium of Food Additive Specifications evaluated by JECFA (The Joint FAO/WHO Expert Committee on Food Additives)
24. FDA, Food Additives permitted for direct addition to food for human consumption, 21 CFR, Part 172

Part VI
Clinical Development and Regulatory Aspects

Chapter 25
Clinical Testing in Children

Klaus Rose

Abstract Clinical trials systematically compare safety and efficacy of different therapeutic interventions. Since the 1960s proof of efficacy and safety through appropriate clinical trials are a legal requirement for the registration of drugs, and that made the advent of drug labels in the modern sense of the word. Regulatory clinical trials have become one cornerstone of the drug development process. Pivotal trials are decisive for registration: a drug may show promising results in early trials; if it fails in the pivotal trials, it is abandoned—or developed for another indication. In parallel to industry-sponsored clinical trials with regulatory purposes, academic trials continued. They aim at improving interventions without regulatory concerns. When modern labels were introduced, children were largely excluded from regulatory clinical trials. With increasing understanding of the child's developing body and how it interacts with drugs, i.e., with the evolvement of pediatric clinical pharmacology, dosing based on mechanical formulas was understood to be insufficient. Pediatricians used the increasing number of available, highly effective, adult drugs off-label also in children, but a gap was perceived between the attention given to adults as compared to children. The child version of the British National Formulary (BNF) was a pragmatic attempt for reconciliation. Pediatric oncologists developed new off-label treatment schemes for adult anticancer drugs—also a pragmatic approach. Since 1997, US pediatric legislation encourages pharmaceutical companies to generate additional pediatric data. The 2006 EU pediatric legislation aims at investigating the potential pediatric use of new drugs already during early drug development and at their registration in children. In short, we have at least four developments: (1) a better understanding of the child's developing body and how it impacts drug treatment; (2) the expansion of the framework and the science of human clinical trials into addressing child-specific aspects; (3) facilitation of

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generating additional pediatric data by US legislation; (4) EU's wish to use pharmaceutical industry's financial and research potential for the benefit of children. Both US and EU legislation request age-adapted pediatric formulations.

25.1 Clinical Trials in Man

Clinical trials assess *and compare healthcare interventions, mostly drugs, diagnostics, vaccines, and medical* devices. Historically, treatment of patients was based on empiricism and anecdotal reports on the efficacy of interventions. Ancient surgeons learned from individual masters, and improvement was by trial and error. However, in the long term anecdotal reports alone are insufficient. Clinical trials minimize as much as possible the variables that could be confounders and apply the intervention of interest side by side to another intervention (or lack thereof) that serves as control. One of the most important features of a clinical trial is the identification a priori of endpoints. The endpoints are the desirable outcomes of the interventions at play [1].

In a study described in 1753 by James Lind in his book, "A Treatise of the Scurvy," he divided 12 scorbutic sailors into 6 groups of 2. All received the standard diet but, in addition, group one was given a quart of cider daily, group two received 25 drops of vitriol (sulfuric acid), group three received six spoonfuls of vinegar, group four received a pint of seawater, group five received two oranges and one lemon (citrus fruit), and the last group received a spicy paste plus a drink of barley water. The citrus fruit treatment stopped early when they ran out of fruit, but by that time one sailor was fit for duty and the other had almost recovered. Apart from citrus fruits, only cider showed some treatment effect. By today's standards, the trial had several serious flaws, including non-adherence to the protocol due to logistical deficiencies. The basic approach, however, i.e., the systematic and open-minded comparison of different treatments, was in line with modern testing. For various reasons, the findings from this trial did not translate immediately into action in the royal navy [2–4].

Systematic testing was and is part of the scientific and technical revolution. Testing in man has become more frequent with the availability of standardized drugs, devices, diagnostics, and scientific publications. During and after World War II, medical research expanded at an extraordinary rate [5]. After 1945 the world was outraged by the murders conducted in humans in general and specifically in children by Nazi physicians such as Josef Mengele and by Japanese physicians in occupied China [6, 7]. The judges in the trial against Nazi medical doctors in Nuremberg, Germany, published in 1947 a list of principles that became the "Nuremberg Code." This code promulgated key issues of human experimentation [8]. The outrage after World War II did not lead to the application of the newly pronounced Nuremberg Code to experimentation in man in the USA [9].

In 1964, the Declaration of Helsinki (DoH) was adopted by the World Medical Association (WMA) as a set of ethical principles for the medical community regarding clinical research in man; children are not mentioned in any version of the DOH, but are part of the mentioned research subjects that are "legally incompetent" [10].

In 1966 the US American Harvard anesthesiologist Henry K. Beecher summarized 22 selected academic research projects that had been published in academic research journals that were unethical by contemporary ethical standards. One example was infection of mentally retarded children with hepatitis [5]. These were academic trials. Beecher's explanation of the reason for the massive increase of clinical research was the increased availability of government funds. Since then the funds available for clinical research have continued to grow, and so the basic challenge has continued to exist: hidden interests of the sponsor vs. the interests of the study participant. In the beginning of large-scale clinical trials in post-World War II North America were often performed in young male adult prisoners, and included the testing of toothpaste, deodorants, shampoo, skin creams, detergents, liquid diets, eye drops, foot powders, and hair dye [6, 11].

Two major types of clinical trials are still frequently differentiated: academic ("investigator-initiated") clinical trials that compare different interventions or a new concept with standard treatment; the major aim of these trials is the creation of scientific publications that are the key factor in career progress of academics. The other trial type is in the framework of the development of drugs, diagnostics, vaccines, or medical devices. The key difference is that the latter aims at the registration of a product, so the study design must either have the pre-trial imprimatur of the regulatory authority or must follow official regulatory guidance [12]. There is still broad conviction that research initiated by academia is noble by character while research organized with the aim of commercialization is less noble. This belief is much stronger in Europe than in North America.

For both types of clinical research the same ethical and legal framework developed in the last century to balance society's interest to learn and the need to protect study participants. The key features are the study subject's voluntary participation, his right to terminate study participation whenever he wants, the need to fully inform the patient about potential benefits and risks, and the requirement to document this informed consent in writing, and an acceptable benefit-risk-ratio. All these features are codified in the rules of good clinical practice (GCP) [1].

25.2 Modern Drug Labels, Pediatric Disclaimers, and Pediatric Clinical Pharmacology

With the industrial revolution began the chemical production of drugs on a large scale in the nineteenth and twentieth century [13]. Modern medicines have a potential dual effect: their therapeutic potential is often enormous, see the immediate lifesaving effects of antibiotics, and often they also have the potential for harm. In 1936, a liquid formulation of sulfanilamide, an antibiotic, was brought to the market in the USA. The used solvent had not passed any safety testing—this was not required in 1936. Within days after introduction deaths were reported to the FDA. FDA seized the entire production lot. More than 100 patients died in this catastrophe. The public outcry lead to a serious revision of the FDA legislation,

mandating for the first time safety experiments in animals before a drug could be brought to the market [14]. In 1961/1962 a second major global catastrophe occurred when it became apparent that the sleeping pill thalidomide caused deformation in unborn babies when taken by pregnant women. Thousands of children were born with shortened and deformed arms and legs. With a few exceptions, these children were born outside of the USA, as thalidomide had not been licensed there. "Only" a few children were born with defects in the USA due to the generous and not controlled distribution of thalidomide tablets by medical doctors within so-called clinical trials that lacked even minimal documentation [13, 15]. Today, GCP requires a precise documentation of each single tablet and an emergency call-back of medication in case a safety issue is identified. The thalidomide catastrophe led to the US Kefauver-Harris amendments in 1962 that mandated drug manufacturers to perform adequate clinical trials to proof safety and efficacy of drug covering the claims of the respective drug in the drug label [16].

With the increased role of regulatory authorities their influence on drug development has increased considerably. Most clinical trials organized for commercial purposes are regulatory trials, i.e., trials that intend to back a marketing authorization application (MAA) in the EU or a submission in North America, Japan, or the rest of the world. Often the development budget of medium or large drug company exceeds by far the research budget of an academic institution or network. The costs of drug development have increased considerably. The development costs of a new drug today are estimated to be around US$1 billion. Within these costs, research, preclinical safety, and formulation development are comparatively low compared to the enormous costs of large phase 3 clinical trials.

Until the 1990s most pharmaceutical companies performed their clinical trials in-house. Since then, they are increasingly outsourced to clinical research organizations (CROs) that offer services from strategic development advice to protocol design and execution of the respective study including selection of adequate trial centers, organizing investigator meetings, coordinate patient recruitment, and offer support for electronic data capturing. The execution of clinical trials has become a business in its own right and looking at the enormous costs of clinical trial, it can also be described as a whole industry of its own [17, 18].

Regulation on drug development and modern labels initiated as national processes. For example, the Kefauver-Harris amendments were a national USA legal initiative [16], which was then followed by legal action by most other industrialized states. Today this had led to an international framework for drug development, the "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)". It was founded in 1990 to respond to the increasingly global face of drug development and to the need of international harmonization [19]. The title itself shows how difficult it is to get very different partners on one table and to agree at least on a common name. These partners are the trade unions of pharmaceutical industry in the USA (PhRMA) [20], Europe (EFPIA) [21], Japan (JPMA) [22], worldwide (IFPMA) [23] and the regulatory authorities of USA (FDA) [24], EU (EMA) [25], and Japan (MHLW) [26], with other regulatory authorities as observers. Both sides use academic specialists for specific issues.

The specific framework for clinical trials is documented in the ICH guideline ICH E6 on "GCP" [1]. Finalized in 1996, it summarizes the rules how clinical trials should be performed to meet the requirements so that the generated data are usable for registration purposes. It lists the responsibilities of the institutional review board (IRB)/ethics committee that must approve any trial, the responsibilities of the clinical investigator and his institution, the responsibilities of the sponsor of the trial including the logistics of the trial, the requirements for the study protocol, the investigator's brochure, and for other essential documents for the clinical trial. Of course, these principles must also be adhered to in clinical trials in children.

25.3 Pediatric Medicine and Clinical Trials in Children

Pediatrics is a rather young academic discipline compared to the history of other medical sub-specialties [27]. Looking through the development of pediatric medicine over the past century we see that the focus of attention shifted continuously with the mainstream of innovation and advances in learning. "Safe Milk Campaigns" to pasteurize milk, or the application of silver nitrate in newborns eyes to prevent blindness are today almost forgotten, as are the pediatric wards full of iron lungs, keeping children with polio alive during the 1950s. Children in modern society enjoy the best medical care that has ever been available in history, and children have certainly fully participated from medical progress over the past century, see, e.g., the advances in vaccination, in surgery of inborn heart failures, in child transplant medicine, and many more fields. Nevertheless, we observe today a new focus on improvement of drug treatment of children, which reflects further advances not only in pediatrics but also in the methodology of clinical research, and of a number of related scientific fields.

In reaction to the Kefauver-Harris amendments pharmaceutical manufacturers introduced pediatric disclaimers to document that the respective drug had not been tested in children. They did that to prevent being sued in case of adverse events. This left the medical doctor in the dilemma of either prescribing a drug he assumed to be effective and not prescribing the drug and withhold a potentially effective treatment. The potential legal liability shifted to the prescribing doctor and away from the manufacturer [28, 29].

In parallel to the increasing availability of modern drugs clinical pharmacology evolved as a new discipline, investigating absorption, distribution, metabolism, and excretion (ADME) of drugs [30]. As a sub-specialty pediatric clinical pharmacology evolved, initially as an academic movement [31]. The child's body is in many aspects not just a small adult body. In younger children the organs are not yet mature, and the liver, kidney, and other organs work differently from adults. Key learnings were summarized by the publication of Kearns 2003 [32]. The key message of pediatric clinical pharmacology is that due to the different organ systems dosing in children cannot be deduced mechanistically from the weight or body surface of children, specifically the very young. The consequence of this difference is that

by using mechanistic formulas and tables only (almost each EU country had a different pediatric formula) there is always a risk of over- or under-dosing, i.e., a given a dose has no clinical effect, or is toxic to the child. While in adolescents usually the adult dose is OK, systematic testing is specifically important in young and very young children.

There are also occasional observations made by clinicians that drugs approved for a given indication in adults can work in a completely different disease in children. Famous examples are indomethacin and ibuprofen, non-steroidal antiinflammatory drugs that show efficacy in closing the arterial duct, a vessel that in the unborn child connects the pulmonary artery with the aorta. Normally this vessel closes at birth. If it remains open, it can lead to pulmonary hypertension and impair the child's development [33].

The ICH guideline E11 "Clinical Investigation of Medicinal Products in the Pediatric Population" was finalized and adopted by FDA, EMA, and MHLW in 2000. In contrast to the rather technical title the objective is much broader: "The guidance provides an outline of critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population" (1.1, Objectives of the Guideline). It addresses pediatric formulations, time of pediatric development, types of drugs (for lifesaving in children only; lifesaving both in adults and children; all other drugs), age classification of children, and ethical issues in pediatric clinical research, and a number of technical issues such as withdrawal of blood. ICH E11 is a high level key document that everybody who wants to work in pediatric drug development should be familiar with [34].

25.4 US and EU Pediatric Pharmaceutical Legislation

Pediatricians, pediatric clinical pharmacologists, and regulatory authorities worked together in the US to address the problem of pediatric disclaimers and the fact that many modern medicines were not registered in children [35].

In 1997 BPCA (best pharmaceuticals for children act) [36] within FDAMA (FDA modernization act) offered for the first time a voluntary reward to pharmaceutical industry of a 6-month market exclusivity extension for the generation of pediatric data. The technical term for this patent extension is "pediatric exclusivity." BPCA was later complemented by the pediatric research equity act (PREA) [37], which gave the FDA the authority to mandate clinical trials and other measures to better consider children's treatment in the overall drug development. Both BPCA and PREA were re-authorized several times and became permanent law in 2012 [38].

The EU pediatric legislation came into force in 2007 [39]. It parallels the US legislation, but is much more ambitious. MAAs for new drugs must be submitted with a Paediatric Investigation Plan (PIP) approved by the European Medicines Agency (EMA) Paediatric Committee (PDCO), unless the EMA confirms in writing the applicability of a class waiver. Generic drugs are exempt, orphan drugs are not. Although it is the EMA CHMP (Committee for Medicinal Products for Human Use) that decides the approval of new drugs, the PDCO can block a submission. EMA will

not validate a submission without an approved PIP. The PDCO is composed of 33 members plus another 33 alternates. Each member state is represented by two: one member and one alternate; additional members represent CHMP, pediatric healthcare professionals, and patient advocacy groups. The PDCO decides about PIPs, waivers (no development in children), partial waiver (no development in specific age groups), and deferrals (later performing of studies).

The PIP must cover all age groups as defined by ICH E11: preterm newborns (<36 weeks gestational age), newborns (0–27 days), infants and toddlers (28 days to 23 months), children (2–11 years), and adolescents (12–17 years) [9]. The applicant should submit it at the end of human pharmacokinetics (PK), which EMA sees as the end of phase 1, i.e., before proof of concept. The PIP includes chapters on preclinical testing, including juvenile animal studies; formulation(s), e.g., intravenous for preterm newborns, liquids for infants and young children; clinical pharmacology for dosing; and clinical trials. To what degree it makes sense to ask for a detailed pediatric investigation plan at a development stage where more than half of the drug candidates will never reach phase 3 is a discussion beyond the scope of this book. Reference is made to other publications [40–42]. For developers of pediatric formulations the key message is that legislation in both the USA and Europe is increasing the demand for the development of more age-adjusted formulations.

25.5 Barriers Against Clinical Trials in Children

Why were there less clinical trials in children in the past? Well, there were many pediatric clinical trials in the past. Many of the 22 studies listed 1966 by Beecher were performed in children. The discussion today about inclusion of children into the pharmaceutical progress is predominantly aimed at the commercial drug development that on one side has without doubt been quite successful, on the other side has successfully managed to give the pharmaceutical industry a public image comparable to that of the tobacco industry.

There is a broad area of therapeutic indications where extensive pediatric research has been done in the past without additional pediatric legislation. For many decades, vaccine studies have been mostly performed in children. The same holds true for antibiotics, although the registration of an antibiotic for pediatric use is per se not always in the interest of children—many cases of otitis media are treated with antibiotics, but most of these treatments are unnecessary [43, 44]. Growth hormone was developed before the EU pediatric drug legislation. Where children represent a market on their own, they attract business. We see this with special shops for children's clothes, children's toys, children's push chairs, children's education, and so on [45]. Parents are prepared to spend a lot of money for their children. With drugs it is slightly different as usually parents do not pay directly but through a reimbursement institution. These institutions have many other clients to take care of as well. In consequence, they will go for the best price. There is no other population group that is that often treated with generic medication.

In the public opinion, participation of children in clinical trials has been perceived in the past in an ambivalent way. There is general agreement that children should not be abused as "guinea pigs" in clinical research. On the other side, probably nobody on this planet would object against treating children with cancer in the best way known to the medical community. Virtually all children with cancer in the developed world are treated routinely in the framework of clinical trials. The advances of pediatric cancer therapy resulted, e.g., in about 90 % of children with acute lymphatic leukemia to survive, a survival rate adult oncology could only dream about. Child oncology started in the last century with the systematic experimental use of cytostatic agents that had been developed for adult cancer treatment in the 1950s and 1960s. While initially mostly homeopathic, i.e., very low doses were prescribed, increased experience lead to treatment protocols that increased survival by about 10 % with the year of diagnosis since the 1970s. This was achieved by higher dosing and new combination of different drugs and treatment modalities. However, there is at present little progress to be expected from further increasing toxicity in pediatric drug treatment [46]. Instead, the pediatric oncology community is hoping for the development of new compounds better suited to treat childhood cancer [47]. Where the child's life is at stake and no well-established treatment is available, few parents hesitate to have their child treated within a clinical trial. Interestingly, most drugs used on a daily base in pediatric cancer treatment are not licensed for this treatment, as most used drugs are in clinical use since decades and are no longer patent protected. They were developed and licensed for adult cancer types and in most cases there is no incentive to register them for pediatric indications.

The present EU and US legislation ensure that new drugs will have an earlier age-appropriate formulation. This is specifically important for the very young. Most children under 7 years of age cannot swallow tablets, and for preterm newborns often special intravenous formulations are required.

This leaves three large areas open.

Firstly, as long as drugs are developed mainly for marketing reasons, the developers will aim at diseases where they have a chance to retrieve their original investments. At present, these are predominantly adult diseases. Some adult diseases exist in rare cases also in children, e.g., some types of cancer, or neurodegenerative diseases that can show first signs already in the second decade of life.

Secondly, there are many rare diseases in children that so far could not be treated successfully. Here modern technology carries some hope. First enzyme deficiency diseases can today successfully be treated with enzyme replacement therapy. In the last years, rare diseases have been discovered by research-based pharmaceutical industry as a new hot spot for drug development, predominantly as the old mass marketing model is increasingly abandoned. For many frequent diseases there are already enough generic medications available so the development of, e.g., yet another antihypertensive family of drug is more difficult to justify towards the reimbursement institutions than it used to be decades ago.

Thirdly, there are many old medications that are no longer patent protected. There are many additional therapeutic indications where they could be used in

children or could better be used in children. But with the existing generic drugs on the market most companies will not take the risk to develop a new formulation as the development costs will probably not be retrieved from the market. The EU pediatric legislation tried a special incentive, the "pediatric use marketing authorisation (PUMA)" in the hope of attracting more development of special pediatric formulations for off-patent drugs. Unfortunately, this model was developed without input from people experienced in business. The consequence was that the number of successful PUMA projects is extremely limited.

25.6 Ethical Challenges of Clinical Trials with Children

In legal terms, the key difference between a child and an adult is that the child is not yet a legal subject in its own right: it cannot act on its own, but only through the parents [34, 48, 49]. In former times, children per se had no rights at all; today the world is full of well-intended international declarations of the rights of children, and many universities offer own postgraduate study programs on the rights of children.

In the past the prevailing opinion was that it was unethical to abuse children as guinea pigs. Today's view has shifted towards a position that it is equally unethical to expose children to untested drugs.

The legitimacy of clinical research with children is today much less disputed than decades ago. Children cannot give informed consent, as they are not yet full legal subjects in the sense of the law. It is the parents who must give informed consent. The debate about e.g., if one or both parents need to give this consent, to what degree this is practical, and what to do in special cases such as when the mother of the child is a minor herself fill entire libraries [50–52]. It is expected today that children in clinical trials today should be asked to give their assent, and this should be documented in written form [10]. This requires age-appropriate explanation of the potential benefits and risks of the study participation. Usually one more elaborate versions are used for adolescent patients, and a simpler one for children from about 7 to 11 years of age. For an in-depth reading of ethical challenges of pediatric clinical trials we refer to the broad literature [53].

25.7 Operational Challenges of Clinical Trials with Children

With the increasing awareness of the need of clinical trials in children there is now more experienced personnel available than used to be the case decades ago. Key issues of operationally dealing with children in clinical trials derive from the key differences between children and adults.

Children cannot survive alone. They are mostly part of a family, and so a clinical trial must take into consideration the entire family. No mother will adhere to a rigid visit scheme that does not allow flexibility if brother or sister of the patient is ill.

No mother will return to a shabby hospital with unfriendly nurses that chase away the playing brother or sister.

The most visible physiological difference is the size of children. A 10 kg child has less blood than an adult, and a 500 g preterm newborn has even less blood to spare for routine laboratory and hematology investigations. The normal laboratory values in children are often different. The maturity of the organs is different, with different drug–drug interactions for different drugs. Depending on the organ system and the way of administration, there is a myriad of aspects to be taken into consideration. The skin of preterm newborns is much thinner and more permeable than adult skin. Measuring of blood pressure with adult devices is an adventure, at best. We refer to good textbooks of pediatric physiology. Also the issue of blood withdrawal is discussed broadly in the literature [54].

Children's attention span is also different from adults. A child will not listen for an hour to the explanation of a clinical trial. The physician has maybe 5 min. So he has to prioritize his messages.

A child's world differs from the adult world in many more aspects. The emotions are stronger, the understanding of institutions is less systemic, and the understanding of time and geographic dimensions is different.

Both the investigation site and the visiting study monitor should be aware of all these special traits. They should have special training.

25.8 Conclusions

Planning and performing clinical trials with children requires a solid fundament of the basics of GCP in general and additional special knowledge and training. The changed regulatory environment is at present pushing the demand for better age-adapted formulations of children.

References

1. ICH Guidelines (1996) Good clinical practice E6. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf
2. Lind J (1772) A treatise on the scurvy, 3rd edn. S Crowder et al, London
3. Dunn PM (1997) James Lind (1716–94) of Edinburgh and the treatment of scurvy. Arch Dis Child 76:F64–F65
4. Bartholomew M (2002) James Lind's treatise of the scurvy (1753). Postgrad Med J 78:695–696, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1742547/pdf/v078p00695.pdf
5. Beecher H (1966) Ethics and clinical research. N Engl J Med 274(24):1354–1360
6. Weyers W (2003) The abuse of man. An illustrated history of dubious medical experimentation. Ardor Scribendi, New York, pp 161–235
7. Mozes-Kor E (1992) The Mengele twins and human experimentation. In: Annas G, Grodin M (eds) The Nazi doctors and the Nuremberg Code. Oxford University Press, New York
8. Weindling P (2001) The origins of informed consent: the International Scientific Commission on medical war crimes, and the Nuremberg Code. Bull Hist Med 75(1):37–71

9. Childress JF et al (eds) (2005) Belmont revisited. Georgetown University Press, Washington
10. WMA Declaration of Helsinki (2008) Original version 1964. In: Williams JR (ed) The declaration of Helsinki and public health. Bull World Health Organ 86(8):650–652. http://www.who.int/bulletin/volumes/86/8/08-050955.pdf. WMA Declaration of Helsinki (2013) Ethical principles for medical research involving human subjects. 64th WMA General Assembly, Fortaleza, Brazil. http://www.wma.net/en/30publications/10policies/b3/index.html.pdf
11. Hornblum AM (1998) Acres of skin. Routledge, New York
12. Meinert CL, Tonascia S (1986) Clinical trials: design, conduct, and analysis. Oxford University Press, New York. ISBN 978-0-19-503568-1
13. Hilts PJ (2003) Protecting America's health. Alfred A. Knopf, New York. ISBN 0-375-40466-X
14. Wax P (1995) Elixirs, diluents, and the passage of the 1938 federal food, drug and cosmetic act. Ann Intern Med 122:456–461
15. Taussig HB (1962) A study of the German outbreak of phocomelia. JAMA 180:1106–1114
16. Meadows M (2006) Promoting safe and effective drugs for 100 years. FDA Consumer Magazine, The Centennial Edition/January–February 2006. http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/default.htm
17. Association of Clinical Research Organisations ACRO. http://www.acrohealth.org/
18. European CRO Federation. http://www.eucrof.eu/
19. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). www.ich.org
20. Pharmaceutical Research and Manufacturers of America (PhRMA). www.phrma.org
21. European Federation of Pharmaceutical Industries and Associations (EFPIA). www.efpia.eu
22. Japan Pharmaceutical Manufacturers Association (JPMA). www.mhlw.go.jp
23. International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). www.ifpma.org
24. US Food and Drug Administration. www.fda.gov
25. European Medicines Agency. www.emea.europa.eu
26. Japan Ministry of Health, Labor and Welfare. www.mhlw.go.jp
27. Colon AR (1999) Nurturing children: a history of pediatrics. Greenwood Pub Group, Westport, ISBN-10: 0313310807, ISBN-13: 978-0313310805
28. Shirkey H (1968) Therapeutic orphans. Pediatrics 72:119–120
29. Wilson JT (1999) An update on the therapeutic orphan. Pediatrics 104(Suppl 3):585–590, http://pediatrics.aappublications.org/cgi/content/full/104/3/S1/585
30. Orme M (2010) Clinical pharmacology in research, teaching and health care. Considerations by IUPHAR, the International Union of Basic and Clinical Pharmacology. Basic Clin Pharmacol Toxicol 107:531–559. http://onlinelibrary.wiley.com/doi/10.1111/j.1742-7843.2010.00602.x/pdf
31. Seyberth HW, Rane A, Schwab M (eds) (2011) Pediatric clinical pharmacology, Handbook of experimental pharmacology 205. Springer, Berlin
32. Kearns GL et al (2003) Developmental pharmacology – drug disposition, action, and therapy in infants and children. N Engl J Med 349:1157–1167
33. Van Overmeire B et al (2000) A comparison of ibuprofen and indomethacin for closure of patent Ductus Arteriosus. N Engl J Med 343:674–681, http://www.neonatologie.ugent.be/ibu-indo.pdf
34. ICH Guideline (2000) Clinical investigation of medicinal products in the pediatric population E11. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf
35. Rose K (2008) Ethical, regulatory and scientific challenges in paediatric drug development. Pharm Med 22(4):221–234
36. Best Pharmaceuticals for Children Act (BPCA), Pub. L. No. 107–109, 115 Stat. 1408. http://history.nih.gov/research/downloads/PL107-109.pdf. Accessed 29 June 2012
37. Pediatric Research Equity Act of 2003. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077853.pdf

38. FDA Fact Sheet: Pediatric Provisions in the Food and Drug Administration Safety and Innovation Act (FDASIA). http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm311038.htm
39. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF
40. Fiebig D (2012) Preparing the Paediatric Investigation Plan application. Med Writing 21(2):108–113
41. Tomasi P (2012) Writing applications for Paediatric Investigation Plans and waivers. Med Writing 21(2):1–4
42. Rose K (2012) Challenges of paediatric drug development and impact of paediatric legislation. Med Writing 21(2):99–103
43. Del Mar C, Glasziou P, Hayem M (1997) Are antibiotics indicated as initial treatment for children with acute otitis media? A metaanalysis. BMJ 314:1526–1529
44. Sanders S, Glasziou PP, Del Mar CB, Rovers MM (2004) Antibiotics for acute otitis media in children. Cochrane Database Syst Rev 2004(1). Art. No. CD000219. doi:10.1002/14651858.CD000219.pub2
45. Cook DT (2004) The commodification of childhood: the children's clothing industry and the rise of the child consumer. Duke University Press, Durham, ISBN-10: 082233268X, ISBN-13: 978-0822332688
46. Stiller CA, Kroll ME, Pritchard-Jones K (2012) Population survival from childhood cancer in Britain during 1978–2005 by eras of entry to clinical trials. Ann Oncol 23:2464–2469
47. Innovative Treatment for Children with Cancer (ITCC). European Consortium. www.itcc-consortium.org
48. Nelson RM (2009) Additional protections for children enrolled in clinical investigations. In: Mulberg AE, Silber S, Van Den Anker JN (eds) Pediatric drug development – concepts and applications. Wiley-Blackwell, Hoboken. ISBN 978-0-470-16929-2
49. Neubauer D, Laitinen-Parkkonen P, Matthys D (2007) Ethical challenges of clinical research in children. In: Rose K, Van Den Anker J (eds) Guide to paediatric clinical research. Karger Publishers, Basel
50. Grodin MA, Glanth LH (eds) (1994) Children as research subjects. Oxford University Press, New York
51. Ross LF (2006) Children in medical research: access versus protection. Oxford University Press, New York
52. Westra A (2011) The moral limits of medical research with children. Off Page Publishers, Amsterdam. ISBN 978-94-90371-80-7
53. Lamprill J, Fowler PA (2007) Consent and assent in paediatric clinical trials. In: Rose K, Van Den Anker J (eds) Guide to paediatric clinical research. Karger Publishers, Basel
54. Hawcutt DB et al (2010) Points to consider when planning the collection of blood or tissue samples in clinical trials of investigational medicinal products in children, infants and neonates. In: Rose K, Van Den Anker JN (eds) Guide to paediatric drug development and clinical research. Karger Publishers, Basel

Chapter 26
Pediatric Formulations and Dosage Forms and Future Opportunities: Impact of Regulations in the USA and Implementation of Quality by Design

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Abstract The advances in pharmaceutical sciences and technology have been so significant that Peter Drucker's quote that "the future has already happened" applies readily for medicines developed for adults. For pediatric patients, the future is about to happen. The continuation of focused partnerships and knowledge sharing and leveraging are critical to ensure that pediatric patients have timely access to high quality drug products that were developed with pediatric patients in mind. An overview of regulatory efforts, regulations and legislation to address the challenges for pediatric drug development are discussed. The implementation of regulatory incentives, the Pediatric Rule, Best Pharmaceuticals for Children Act, and Pediatric Research Equity Act, is having an impact and has led to incorporation of information for dosing of approximately 500 drug products since 1998 starting with implementation of the Pediatric Rule. There are significant accomplishments and a lot more work ahead for the pediatric community. The labeling information is usually for older pediatric patients and the need for information for safe and effective dosing of patients of 6 years old or younger remains. Some of the study outcomes are inconclusive with respect to safety and efficacy, and support the hypotheses that better understanding of drug delivery to pediatric patients is needed for determining and delivering the right dose to the pediatric patients. The 2012 Food and Drug Administration Safety and Innovation Act and implementation of Quality by Design paradigm focusing on drug product design and manufacturing process are expected to have a synergistic effect for continuing to advance development of pediatric dosage forms and formulations for the benefit of the pediatric patients.

Disclaimer: The findings and conclusions in this chapter are the views of the author and have not been formally disseminated by the US Food and Drug Administration and should not be construed to represent any Agency determination or policy. No official endorsement by the FDA is intended or should be inferred.

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26.1 Introduction

Significant advances are taking place for ensuring access of the pediatric patient populations to critical medicines. The concerted efforts and commitment of the global pediatric community are raising awareness and building support for development of dosage forms and formulations suitable for pediatric patients.

In the 1980s approximately 20 % of the drug products had information for use in pediatric patients and the remainder lacked information and dosing recommendation for their safe and efficacious use. At that time, ethical principles for conducting pediatric studies were not as developed and established as today. It was accepted that most drugs would be used off-label by the health-care practitioners and only very few drug products contained labeling information for pediatric patients [1–3]. Off-label prescribing included dosing recommendations that were not studied in pediatric patients for safety and efficacy. In addition, it was routinely expected that the commercially available drug product would be manipulated (e.g., crushing tablets and mixing into soft foods) so that the dosage form would be rendered age-appropriate. Generally, pediatric dose was determined by adjusting the adult dose according to body-weight or body-surface area of the pediatric patients [4]. The disease progression and response to treatment were considered to be similar in pediatric and adult patients and a body-weight scaling was used for determining the pediatric dose. As published extensively, this approach does not take into account the impact of growth and maturation for the heterogeneous pediatric patient population ranging from the neonates to young adults.

The turning point for studying and labeling drug products for pediatric patients has been the increasing awareness and commitment that pediatric dosing needs to be determined in pediatric studies conducted with the level of scientific and clinical rigor as expected in the studies conducted for the adult patients. The 1977 report of the American Academy of Pediatrics expressed the concerns that physicians were forced to use therapeutic agents “in an uncontrolled experimental situation” when they were prescribing for pediatric patients and that it is imperative that drugs for use in pediatric patients are studied in pediatric patients under “controlled circumstances” [3]. In 1979, Food and Drug Administration (FDA) published labeling requirements for pediatric patients in the Federal Register [5]. Around that time, there were many publications highlighting the lack of information for safe and efficacious use of drugs in pediatric patients, also referred to as the therapeutic orphans [6–14]. The impact of absence of pediatric data for decision-making was summarized as “resulting in outcomes ranging from beneficial to ineffective or harmful due to the off-label treatment of pediatric patients” [15–17].

The increased awareness of the need for pediatric dosage forms and formulations identified several key barriers in 1980s and 1990s, including the following [18–21].

- Conducting pediatric studies were considered unethical and not feasible due to lack of trained personnel and suitable facilities
- Technology for age-appropriate dosage forms covering the broad dosing range of pediatric patients from newborn to adults was lacking or not fully developed

- Developing pediatric dosage forms and formulations required additional drug development efforts, particularly, after the adult formulation was developed
- Investment of resources was challenged
  - The treatments for pediatric patients were mostly for acute conditions or for short term therapy
  - Pediatric patients represented a small (10 % or less) segment of the pharmaceutical market
  - Prioritization of company resources usually favored the major adult disease marketplace and was heavily influenced by the first-to-market paradigm
- Most of the medicines used in pediatric patients were off-patent and there were no financial incentives for generic companies to further study off-patent drugs for their use in pediatric patients
- For many years, off-label use was considered acceptable practice for treating pediatric patients

In order to overcome the concerns in these areas, it was evident that there was a greater need for partnerships and leadership to harness and expand the expertise and the resources for generating knowledge for pediatric studies, dosing information, and development of pediatric dosage forms and formulations. Thus, the financial incentives provided by the regulatory agencies were considered a necessary and reliable mechanism for moving forward pediatric drug development.

In this chapter, an overview of the impact of regulations on development of pediatric dosage forms and formulations, the expected impact of implementation of Quality by Design (QbD) paradigm on pediatric drug development, and future expectations will be discussed. The scientific and technical considerations for developing pediatric dosage form and formulations are discussed in many of the chapters of this book.

26.2 The Impact of Regulations

The efforts of the pediatric community with the leadership of many individuals, academia, pharmaceutical and health-care organizations, and regulatory agencies led to a step-wise process for conducting controlled pediatric studies for generating knowledge critical for development of safe and effective pediatric medicines. Following the 1977 report of the Committee on Drugs, the labeling requirement was introduced in 1979 [5]. This was followed in 1994 by the Final Rule which introduced extrapolation of efficacy, when applicable, from adults to pediatric patients for labeling [22, 23]. It was determined that if the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients, FDA may conclude that pediatric efficacy can be extrapolated from adequate and well-controlled studies conducted in adults. This information would be supplemented with safety studies in the indicated patient population with other information obtained in

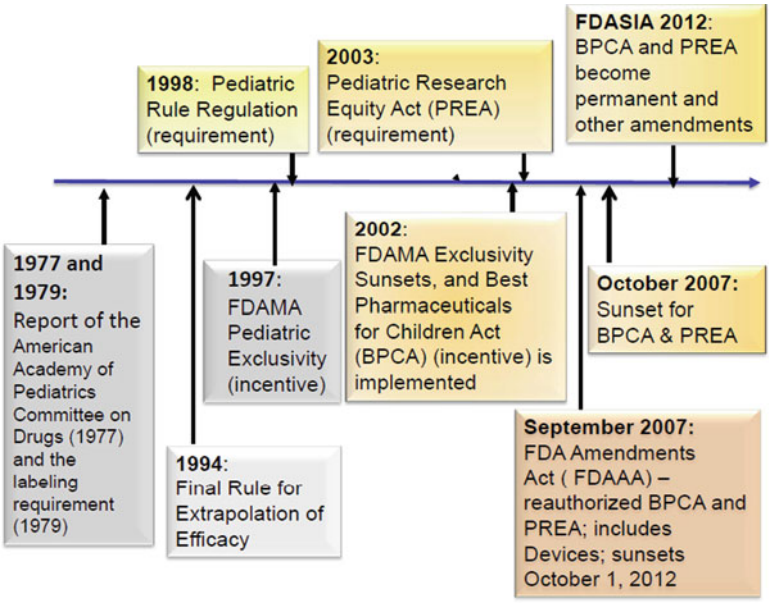


Fig. 26.1 Chronology of pediatric efforts, regulations, and legislation in the USA

pediatric patients, such as pharmacokinetic studies. If efficacy data from one pediatric age group can be extrapolated to another pediatric age group, a study may not be needed in each pediatric age group. This approach enabled sequential study of pediatric age groups from the older age groups to the youngest. These efforts led to FDAMA in 1997 and establishment of the Pediatric Rule in 1998 [24, 25]. The chronology of these efforts starting in 1977 with the report of the American Academy of Pediatrics and leading to the subsequent pediatric regulations in the USA are depicted in Fig. 26.1: A chronology of key pediatric efforts and regulations in the USA.

Exclusivity opportunities are described in the FDA guidance document following implementation of the FDA Modernization Act in 1997 and the 1998 Final Rule which made pediatric studies a requirement [26]. The Best Pharmaceuticals for Children Act (BPCA) in 2002 authorized a 6-month marketing exclusivity as an incentive program for manufacturers who would conduct pediatric clinical trials in response to an FDA Written Request letter [27].

In 2003, the Pediatric Research Equity Act (PREA) codified the authority of the US FDA to require pediatric studies of certain drugs and biological agents and also expanded the role of NIH, particularly, related to studies for off-patent drugs used as pediatric medicines [28]. The next landmark legislations are the 2007 Food and Drug Administration Amendments Act (FDAAA) and the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) [29, 30].

As part of PREA and BPCA and their reauthorization in 2007, the Sponsors and the Applicants were asked for information related to pediatric dosage forms and formulation, however, according to the 2012 FDASIA, drug sponsors are required

to provide information and documentation related to development of pediatric formulation efforts. This is a much needed change with respect to understanding and interpreting available data as well as for collecting data for future studies. For reproducing study results and/or interpreting study outcomes and understanding why some studies are inconclusive, dosing information is critical. Drug delivery information including bioavailability and stability are needed to ensure that indeed the intended dose was delivered according to the intended delivery profile. A remarkable portion of the pediatric study publications does not include information on the dosage form, how it was rendered age-appropriate and how bioavailability and stability assessments were made [21, 31–33]. Given the limitations with the available age-appropriate dosage forms and formulations, some products, particularly, those that are off-patent, are administered as extemporaneous preparations. For using extemporaneous preparations, clear preparation and use instructions are needed for the drug product labeling. The preparation instructions should include the suitable vehicle (such as apple sauce, yogurt and pudding, and/or suitable liquids) for mixing, the preparation steps, and the use conditions based on stability assessments. The related considerations are discussed in detail elsewhere [34, 35]. A primary concern with extemporaneous preparations is the potential for medication errors. Dosing errors including due to serial dilution of concentrated liquid dosage forms have been reported [36–39].

In addition, difficulties identified in conducting pediatric studies that can also lead to inconclusive results and/or need for additional data, include small sample sizes for a given indication for assessing safety and efficacy, complexity of the clinical trials, and lack of suitable dosage forms and formulations [40–44]. Some of the variability in the data may also be attributed to the dosage form and/or the formulations. Full characterization of the study populations, and the dosage form and formulations used in the clinical trials may assist in data analyses and interpretation. Considering the relatively small sample sizes of the pediatric studies, particularly, those with rare diseases, novel study designs with appropriate study end points, and data collection and analyses techniques may be needed.

A summary of key features of FDAAA 2007 and FDASIA 2012 is provided in Table 26.1. The key drivers for the 2012 FDASIA are the need to elevate the scientific and clinical rigor in pediatric studies similar to those conducted for adult patients, and the timely generation of labeling information including discussion of pediatric study plans at the End of Phase II (EOP 2) meetings.

The FDASIA 2012 makes BPCA and PREA permanent and advances implementation of BPCA such that a financial incentive (6-month pediatric exclusivity) is provided to Applicants/Sponsors for conducting the identified pediatric studies while PREA requires Applicants/Sponsors to assess safety and effectiveness of new drugs/biologics in pediatric patients for use in the conditions which parallel the conditions studied in the adult populations. A Sponsor/Applicant can request for a drug product studied under PREA to be studied under BPCA as well for pediatric exclusivity [28].

Another significant impact of FDASIA 2012 is that it shifts discussion of pediatric drug development to an earlier time, to the End of Phase 2 (EOP2) meeting.

Table 26.1 Some key features of FDAAA 2007 and FDASIA 2012 with respect to pediatric drug development

FDAAA 2007	FDASIA 2012
• BPCA and PREA were reauthorized • New labeling: results of pediatric studies under BPCA or PREA should be included in label, regardless of outcome (positive, negative, or inconclusive) • Pediatric focused post-marketing safety reporting for all products studied under BPCA or PREA • WR letters may include approved and unapproved uses and preclinical studies • New transparency: posting complete reviews • Posting of annual progress if studies are deferred • Development of age-appropriate formulation required • New pediatric medical device provisions • Expanded role of NIH	• Both BPCA and PREA become permanent • Sponsors are required to submit study plans at the end of Phase 2 • Process related to PREA deferral or waivers is detailed • New provision to allow extension for deferred studies under PREA • All age groups, including neonates, must be considered and included as appropriate in the WR letters (if neonates are not included justification must be provided) • Public meetings/discussions will be scheduled to encourage and accelerate development of new therapies for pediatric rare diseases • Within 180 days of the meeting, the FDA must issue a report including a strategic plan for the development of these therapeutics

Generally, pediatric drug development would start after development of the drug products for adult patients. This approach would extend development time and may necessitate an entirely different dosage form and/or formulation for the pediatric patients. It would be years before the pediatric patients may have access to the benefits of the drug product. Anecdotally, pediatric drug development has been likened to five drug development programs and this may be attributed to the sequential development approach. However, if the drug product may have a potentially acceptable therapeutic benefit for the pediatric patients, and the adults, early discussions at the EOP2 meetings could help to develop "age-friendly" and/or "flexible" dosage forms that are both flexible and available for use by a more diverse patient population including pediatrics and adults. This would lead to an integrated program instead of a sequential drug development program.

The impact of these laws is significant in obtaining pediatric information for drug labeling [45–47]. A summary of the labeling changes made as the result of implementation of BPCA and PREA included: Expanded age, New or Enhanced Safety Information, Safety and Efficacy Not Established, Box Warning with Pediatric Information, Specific Dosing Change/Adjustment, New Molecular Entity, Pediatric Formulation, Extemporaneous Formulation, and PK differences between pediatrics and adults. The results obtained from September 1998 to September 2008 (total labeling changes for 398 drug products) and September 1998 to March 2013 (total labeling changes for 483 drug products) are illustrated in Fig. 26.2 [46, 47]. The labeling changes for each category is represented as a percentages of the total number of labeling changes made during the indicated period, 561 and 669, respectively, for the periods ending September 1998 and March 2013.

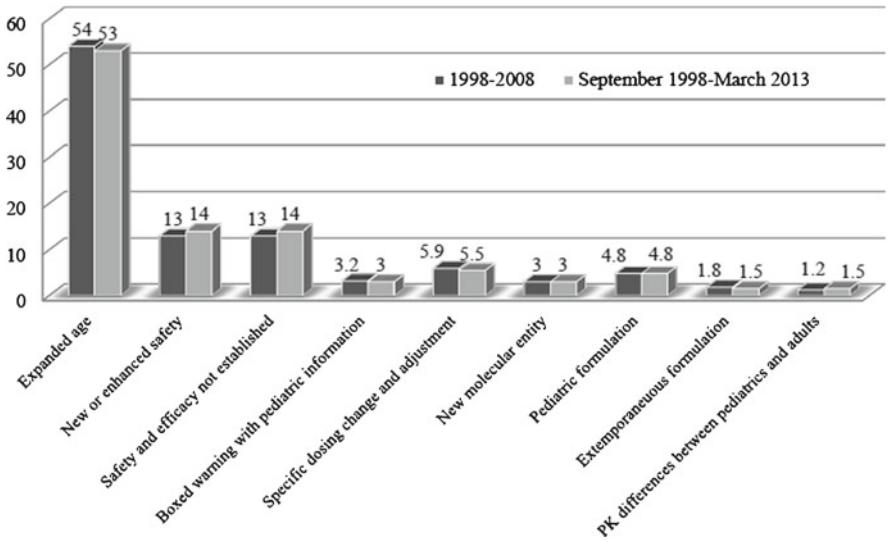


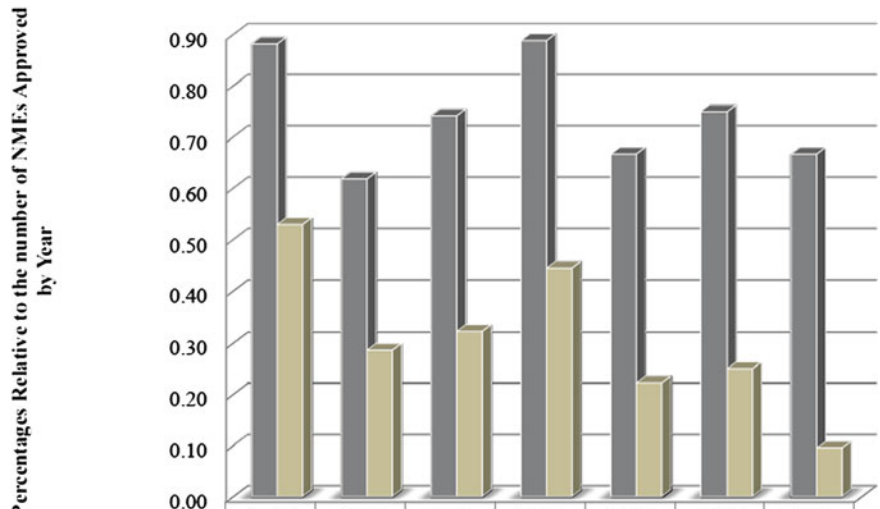
Fig. 26.2 Impact of regulations on pediatric drug labeling. The impact of implementation of the Pediatric Rule, BPCA and PREA: labeling changes as a percentage of total number of labeling changes made during September 1998 to September 2008 ($n=561$) and September 1998 to March 2013 ($n=669$)

As shown in Fig. 26.2, during the last 15 years, the labeling information tracked for drug products that may be used in pediatrics, shows that the expansion of the age groups represent approximately 53 % of the total number of labeling changes. In both periods, ending September 2008 or March 2013, the results are also similar for the percentage of labeling changes with respect to new or enhanced safety information (14 %) and the labeling changes indicating that safety and efficacy was not established (14 %). One interpretation of these results may be that there is some difficulty in getting efficacy and safety information from the studies conducted in pediatric patients and that there is a need for additional data for further evaluation. This may be due to multiple reasons including study designs and study end points, and age-appropriateness of the dosage form and formulations used in these studies. This observation is somewhat strengthened by the congruency in the labeling information related to specific dosing change and adjustments (6 %), and pediatric formulations (5 %) during both periods. Age-appropriate dosage forms and formulations with known bioavailability and desired delivery pattern are needed to evaluate safety and efficacy of medicines and determine the right pediatric doses. The next cluster of labeling changes represent a small fraction (2–3 %) of the total number of changes and are related to new molecular entity, boxed warning with pediatric information, extemporaneous formulations, and the pharmacokinetic differences observed between pediatric and adult patients. These changes relate to the

changes made for 398 and 483 drug products during the periods of September 1998 to September 2008 and September 1998 to March 2013, respectively. Overall, multiple factors are expected to contribute to these observations and to the differences in the magnitude of the clusters of information. Novel study designs, age-appropriate study end points, and "flexible" and/or "age-appropriate" dosage forms and formulations may be needed for further understanding of the contributing factors and for optimizing development of drug products for pediatric patients.

In order to determine the impact of the pediatric regulations and legislation on pediatric information in drug labeling, ePDR was reviewed [48] according to the approach reported by Wilson in 1977 and 1999. Information in the 2009 ePDR was reviewed for pediatric labeling with additional verification against the pediatric database. The pediatric labeling information was categorized as (a) adequate: the drug was approved for pediatric use, had been studied, or had safety, efficacy, or dosing information for all appropriate pediatric populations; (b) inadequate: labeling lacked data on dosing, safety, or efficacy in at least one pediatric subpopulation; and (c) partially labeled (a subgroup of inadequately labeled): adequate labeling for at least one but not all appropriate pediatric subpopulations. This analysis showed that of the 260 drug products (identified according to Wilson's criteria), 41 % were adequately and 5 % were partially labeled for pediatric use. A total of 46 % of the relevant drug products had some information on pediatric use in labeling compared to the 20 % of drug products having some pediatric information in the labeling in the 1980s.

Similarly, pediatric information in drug product labels for New Molecular Entities (NMEs) has increased from 20 % in 1999 to 41 % of the total number of NMEs ($n = 142$) over the period of 2002–2008 [48]. The information with respect to potential pediatric use, pediatric labeling, and the number of NMEs approved for each year from 2002 to 2008 is illustrated in Fig. 26.3. As expected, not all approved NMEs would have potential pediatric use. For example, conduct of pediatric studies are waived for conditions that would not apply to pediatric patients such as age-related macular degeneration, Alzheimer's disease, benign prostatic hypertrophy, infertility, osteoarthritis, Parkinson's disease, and various cancers including breast, pancreatic, prostate, and uterine. In addition, the clinical trials may be waived or deferred, as appropriate, when conduct of such studies would be impossible or highly impractical [29]. Inspection of potential pediatric use, pediatric labeling, and the total number of NME approvals by year show that pediatric labeling is less than that determined as the potential use of the NMEs in the pediatric population. The potential for use of NMEs in pediatric patients by year, ranged from 62 % (of the total NMEs approved in 2003) to 89 % (of the total NMEs approved in 2005). While these numbers are encouraging, a small fraction of the NMEs had pediatric labeling. The pediatric labeling as a percentage of the number of NMEs approved by year, was lowest (10 % of the total number of NMEs approved) in 2008 and highest (53 % of the total number of NMEs approved) in 2002. Considering the multitude of factors that may be influencing these results, this comparison is intended as an exploratory trends analyses and not a numerical direct comparison. It appears that



	2002	2003	2004	2005	2006	2007	2008
Potential Pediatric Use	0.88	0.62	0.74	0.89	0.67	0.75	0.67
Pediatric Labeling	0.53	0.29	0.32	0.44	0.22	0.25	0.10

Fig. 26.3 Pediatric labeling and potential pediatric use as a percentage of approved NMEs by year (2002 to 2008). Note: the number of NMEs approved yearly from 2002 to 2008 is obtained from e-PDR

there may be opportunities to explore and enrich the information gained in pediatric studies and ultimately, the knowledge base for pediatric labeling.

Another consideration to keep in mind is that these data were collected before the impact of FDAAA could be detected, and the future results may be significantly different. It is anticipated that the gap in pediatric labeling and potential use in pediatrics will be reduced significantly with the impact of the recent legislations (FDAAA 2007 and FDASIA 2012), leveraging of knowledge gained and continuation of dedicated and targeted efforts of the global pediatric community.

Similar to the legislation passed in the USA, the EU has also created incentives to stimulate the testing of drugs in this special population [49]. Although both laws require pediatric formulations in the development process of new drugs, there are still a large number of off-patent drug products that are being used in pediatric patients. There are many joint efforts between international organizations including FDA, EMA, WHO, and other stakeholders for successful implementation of ICH E-11 (Clinical Investigation of Medicinal Products in the Paediatric Population). These efforts discussed in many publications focus on (a) development of dosage forms and formulations for enabling optimal delivery of the drug substance to the pediatric patients, (b) improvement of study designs including study end points appropriate for assessment of efficacy, and (c) safety studies and safety assessment based on long term follow-up for determining impact of chronic therapy on growth and maturation of pediatric patients [50–60].

Another outcome of these collaborations is expected to be on the use of extemporaneous formulations. Currently, while extemporaneous preparations may be the only available option for some products, it is the author's belief that significant advances in drug development, targeted research, and dedicated efforts will also change the landscape of use of extemporaneous preparations.

26.3 The Impact of Implementation of QbD Paradigm

The QbD efforts, initiated almost a decade ago for ensuring product quality and outlined in numerous ICH guidance documents, is also getting established as a broader approach in drug development. The definition of QbD in ICH Q8 R2 is "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" [61].

As outlined above, QbD is a systems thinking approach that requires greater knowledge and understanding of the components of the system functioning individually and collectively so the system can be optimized as a whole. A natural outcome of implementation of the QbD paradigm is reported as efficiency in drug development leading to better decision-making and streamlining of the efforts [62]. It has been estimated that implementation of QbD can reduce drug development time by approximately up to one-third by understanding critical quality attributes early in drug development programs [63]. Furthermore, a significant synergy is anticipated between the implementation of QbD in drug development and the pediatric advances as an outcome of FDASIA. This approach will facilitate and possibly, also change the adult dosage forms such that flexible dosage forms, suitable for a greater patient population and a broad dosing range (as with administration of multiple units, such as mini-tablets), will be developed. The pediatrics dosage forms and formulations will not be a modification of the already developed adult dosage form but developed as a "flexible" dosage form suitable for use by a broad range of patients.

Another outcome of implementation of QbD is that it will emphasize novel approaches and study designs so that it can also facilitate learning that can be leveraged and used for life-cycle management as well as for development of subsequent similar drug products. The framework created by implementation of QbD in pharmaceutical development and also, in the related areas, is expected to facilitate further knowledge generation and knowledge sharing for the benefit of the pediatric patients.

26.4 Opportunities

Many challenges have been recognized as well as opportunities for development of pediatric medicines. The opportunities for development of pediatric dosage forms and formulations are considered to be of greater and of sustained impact, and will

be discussed in reference to two key related areas: the impact on the patient benefit and on the drug products.

26.4.1 Greater Patient Benefit

The last decades have witnessed a significant expansion of knowledge related to greater understanding of growth and maturation of the pediatric patients, the disease progression, clinical end points, and drug pharmacokinetics and pharmacodynamics and efforts for development of age-appropriate dosage forms [50, 51, 60, 64–70]. While many groups have independently worked in these areas, collaborations and availability of research funding and leadership from many organizations have created a significant momentum. The better understanding of patient characteristics and response to therapy can lead to high quality drug products. The drug products will then be designed, developed, and manufactured in such a way that reliable and intended in vivo drug product performance is ensured. Targeted efforts are needed for optimizing study designs and for developing dosage forms and formulations that can reproducibly deliver the intended dose in the desired manner to pediatric patients.

An earlier concern was the lack of adequate training and facilities for conducting controlled pediatric clinical trials. Development of training and research programs that were funded by many groups, including the development and funding of the Pediatric Pharmacology Research Units (PPRU) by NIH in 1994 has been successful and has led to many research programs for pediatric patients. The PPRU network that sunsetted in 2010 provided information for labeling of numerous drug products for pediatric patients. Subsequently, the Pediatric Clinical Trials Network was established by NICHD in 2010, and it has been building on the knowledge and experience gained from the PPRU efforts. In parallel, NICHD has also formed expert groups for addressing and generating relevant knowledge in specific topics encompassing biopharmaceutics, clinical pharmacology, and pediatric formulations [68–70].

Other ongoing efforts have been related to establishing ethics principles and developing guidelines for conduct of pediatric studies for collecting data in clinical trials in a manner that protects and ensures welfare of the pediatric patients [71].

Integration of biopharmaceutics and QbD was considered a viable approach for integrating patient needs with the drug product quality considerations. The 2009 FDA co-sponsored workshop on integration of QbD and biopharmaceutics explored opportunities for their effective integration [72, 73]. The goal was identifying the critical areas/enablers for ensuring that the drug product performed as intended for the patient benefit. This effort starts with delineation of patient needs which drive the development program so that the product design, development, and manufacturing process are linked with the desired in vivo performance of the drug product. Overall, implementation of the QbD paradigm is expected to enhance patient benefit through greater understanding of the factors contributing to drug product performance and introduce and advance methodology facilitating science- and risk-based assessments.

26.4.2 Greater Understanding of Drug Product

Greater understanding of the drug product can be achieved with greater understanding of the drug substance, the manufacturing process and its targeted design and development so that it meets the patient needs. Opportunities leading to greater learning and understanding of the drug product are going to also advance the necessary methods and tools that will in turn support its development. Typically, for pediatric drug products, we expect the dosage form to be age-appropriate and/or "adaptable" or "flexible" so that it can deliver the right dose in the intended manner to the targeted patient population. Furthermore, as a safety and efficacy consideration, the dosage form should be of acceptable size, shape, and palatability for the pediatric patients. Taste and palatability considerations, may be considered as challenges, however, are leading to many opportunities for development of pediatric dosage forms. Efforts gained in this area may lead to development of standardized taste-masking approaches and manufacturing methods that may render the dosage form(s) suitable across patient populations. Emphasis on learning and confirming approaches can lead to greater understanding of in vitro and in vivo performance of a drug product and yield opportunities beyond the original target of a pediatric dosage form and formulation. Robust and reliable in vitro and in vivo methods for characterizing and optimizing the drug product performance can generate knowledge which can be leveraged for its use in a diverse/larger patient population and for supporting development of similar drug products.

Implementation of the QbD paradigm on pediatric drug development is expected to create a synergy, particularly, with implementation of FDASIA. The following key areas of impact were highlighted as the synergistic effect of QbD on development of pediatric formulations at the 2011 mini-symposium on Application of QbD to Development of Pediatric Formulations and Dosage Forms at the 38th Annual CRS Meeting (63).

- Reducing development time and availability of more choices: Considering the possibility that the drug substance may also be used in pediatric patients, and selecting accordingly the drug product design and manufacturing processes that may lead to a drug product that can be used by both pediatric and adult patients, may reduce the number of formulations for testing, and can reduce development time and avoid late stage development efforts.
- Benefits of a systems approach: Integration of QbD and biopharmaceutics, enable transparent risk- and benefit assessments with respect to in vivo drug product performance, determination of critical factors for optimal product performance and development of tools and enablers to facilitate better decision-making. This approach is also likely to lead to innovative methods and tools.
- Transparency leading to broader and greater patient benefit: By sharing and leveraging information and knowledge on critical considerations, tools and enablers for supporting development of the old and new drugs (including those that are off-patent), a strong platform can be developed for sharing of lessons learned at a larger scale within the pediatrics community.

The second key note, delivered by Dr. Dianne Murphy (Pediatric Product Development: The Path to the Present) at the same workshop highlighted the accomplishments of the pediatric community to date and the future direction of pediatric efforts [74]. Understanding the response to therapy in pediatric patients, development of suitable study end points and access to pediatric dosage forms and formulations and integrating all of the key considerations in a multi-dimensional and multi-disciplinary manner will harness the impact of implementation of QbD for ensuring product quality.

26.5 Summary

The focused and dedicated efforts of many groups and partnerships for advancing development of pediatric medicines are successful and like any great beginning, require continuation of support from the pediatric community.

Implementation of the FDA Acts FDAAA and FDASIA and the QbD paradigm as described in the guidance documents can facilitate early integration of pediatric drug delivery considerations into the drug development programs. The conduct of pediatric studies of high scientific and clinical rigor, advancements in drug delivery science cognizant of the needs of pediatric patients, and knowledge sharing and leveraging can lead to timely development of safe and efficacious medicines for pediatric patients.

The challenges are interpreted here as opportunities requiring novel approaches for meeting the unique needs of the pediatric patients. Innovative approaches can only be strengthened by the continued commitment of the pediatric community including members who are care-givers, scientists, pharmaceutical and health-care organizations, academic institutions, governments, and research foundations.

26.6 Future Ahead

Advances in pediatric initiatives continue to highlight the need for commercially available pediatric formulations. It is imperative that the dosage form and formulation should deliver the intended dose, in the intended manner, and meet the needs of the targeted pediatric patient population.

In addition to meeting today's needs, it is important that the strategy of research and drug development programs include meeting future needs of the pediatric patients on a global scale.

The current research topics include drug delivery, improving bioavailability, selection of the excipients for pediatric dosage forms and formulations, daily limits for the excipients, the potential for interactions between excipients, flavoring agents, and the sweeteners. Research in these areas is steering the development of pediatric and possibly, adult dosage forms and formulations. It is possible that the innovative

methods and concepts will lead to novel methodology likely to be used in development of dosage forms and formulations for a larger group of patients including pediatric and adult patients.

> One extension of Takeru Higuchi's quote "Drugs should be designed with delivery in mind" [75] may be "Drugs should be designed with delivery and drug products should be developed with pediatric patients in mind".

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References

1. Shirkey H (1968) Therapeutic orphans. J Pediatr 72:119–120, reprinted in 1999 in Pediatrics 104:583–584
2. Wilson JT (1975) Pragmatic assessment of medicines available for young children and pregnant or breast-feeding women. In: Morselli PL, Garattini S, Sereni F (eds) Basic and therapeutic aspects of perinatal pharmacology. Raven, New York, pp 411–421
3. American Academy of Pediatrics, Committee on Drugs (1977) Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics 60:91–101
4. Munzenberger PJ, McKercher P (1980) Pediatric dosing: the pharmacist dilemma. Contemp Pharm Pract 3:11–14
5. US Food and Drug Administration (1979) Labeling and prescription drug advertising: content and format for labeling for human prescription drugs. Fed Regist 44:37434–37467
6. Wilson JT, Kearns GL, Murphy D, Yafee SJ (1994) Pediatric labeling requirements. Implications for pharmacokinetic studies. Clin Pharmacokinet 26:308–325
7. American Academy of Pediatrics, Committee on Drugs (1995) Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics 95:286–295
8. Wilson JT (1999) An update on the therapeutic orphan. Pediatrics 104:585–590
9. Coté CJ, Kauffman RE, Troendle GJ, Lambert GH (1996) Is the "Therapeutic Orphan" about to be adopted? Pediatrics 98:118–123
10. American Academy of Pediatrics, Committee on Drugs (1996) Unapproved uses of approved drugs: the physician, the package insert and the Food and Drug Administration: subject review. Pediatrics 98:143–145
11. Blumer JL (1999) Off-label uses of drugs in children. Pediatrics 104:598–602
12. Kauffman RE (1991) Fentanyl, fads, and folly: who will adopt the therapeutic orphans? J Pediatr 119:588–589
13. Wilson JT (1999) Questions and answers on labeling of drugs for children. Drug Inf J 33:375–383
14. Schirm E, Tobi H, de Vries TW, Choonara I, De Jong-van den Berg LTW (2003) Lack of appropriate formulations of medicines for children in the community. Acta Paediatr 92:1486–1489
15. Rodriguez W, Roberts R, Murphy D (2001) Adverse drug events in children: the US Food and Drug Administration perspective. Curr Ther Res 62:711–723
16. Roberts R, Rodriguez W, Murphy D, Crescenzi T (2003) Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. JAMA 290:905–911
17. Nunn T, Williams J (2005) Formulation of medicines for children. Br J Clin Pharmacol 59:674–676

18. Milne CP (2002) Exploring the frontiers of law and science: FDAMA's pediatric studies incentive. Food Drug Law J 57:491–517
19. Milne CP, Bruss JB (2008) The economics of pediatric formulation development for off-patent drugs. Clin Ther 30:2133–2145
20. Breitkreutz J (2008) European perspectives on pediatric formulations. Clin Ther 30:2146–2154
21. Mennella JA, Beauchamp GK (2008) Optimizing oral medications for children. Clin Ther 30:2120–2132
22. US Food and Drug Administration (1994) Specific requirements on content and format of labeling of human prescription drugs: revision of "pediatric use" subsection in the labeling, Final Rule. Fed Regist 59(238):64240–64250
23. US Food and Drug Administration (1996) Guidance for industry, the content and format for pediatric use supplements
24. Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act (1997) Content and format of pediatric use supplements. Food and Drug Administration. Modernization Act of 1997. Public Law No. 105–115
25. US Food and Drug Administration (1998) Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients; final rule. Fed Regist 63:66631–66672
26. US Food and Drug Administration (1999) Guidance for industry: qualifying for pediatric exclusivity under section 505A of the Federal Food, Drug, and Cosmetic Act. Revised September 1999
27. Best Pharmaceuticals for Children Act (2002) Public Law No. 107–109
28. Pediatric Research Equity Act (2003) Public Law No. 108–155
29. US Food and Drug Administration Amendments Act (FDAAA) of 2007 (September 27, 2007) Public Law No. 110–85 (Best Pharmaceuticals for Children Act, 2007 and Pediatric Research Equity Act of 2007)
30. US Food and Drug Administration Safety and Innovation Act (FDASIA) (2012) Title V, July 9, 2012 (112th Congress) Public Law 112–144
31. Standing JF, Khaki ZF, Wong ICK (2005) Poor formulation information in published pediatric drug trials. Pediatrics 116:e559–e562
32. Pandit S, Shah U, Kirby DJ, Nunn T, Tuleu C (2010) Inappropriate oral formulations and information in paediatric trials. Arch Dis Child 95:754–756
33. Standing JF, Tuleu C (2005) Paediatric formulations-getting to the heart of the problem. Int J Pharm 300:56–66
34. Allen LV Jr (2008) Dosage form design and development. Clin Ther 30:2102–2111
35. Nahata MC, Allen LV Jr (2008) Extemporaneous drug formulations. Clin Ther 30:2112–2119
36. Koren G, Barzilay Z, Greenwald M (1986) Ten-fold errors in administration of drug doses: a neglected iatrogenic disease in pediatrics. Pediatrics 77:848–849
37. Ross LM, Wallace J, Paton JY (2000) Medication errors in a paediatric teaching hospital in the UK: five years operational experience. Arch Dis Child 83:492–497
38. Yin HS, Mendelsohn AL, Wolf MS, Parker RM, Fierman A, van Schaick L, Bazan IS, Kline MD, Dreyer BP (2010) Parents' medication administration errors role of dosing instruments and health literacy. Arch Pediatr Adolesc Med 164:181–186
39. Doherty C, Mc Donnell C (2012) Tenfold medication errors: 5 years' experience at a university-affiliated pediatric hospital. Pediatrics 129:916–924
40. Abdel-Rahman SM, Reed MD, Wells TG, Kearns GL (2007) Considerations in the rational design and conduct of phase I/II pediatric clinical trials: avoiding the problems and pitfalls. Clin Pharmacol Ther 81:483–494
41. Knellwolf AL, Bauzon S, Della Casa Alberighi O, Lutsar I, Bácsy E, Alfarez D, Panei P (2011) Framework conditions facilitating paediatric clinical research. Ital J Pediatr 37:12
42. Ernest TB, Elder DP, Martini LG, Roberts M, Ford JL (2007) Developing paediatric medicines: identifying the needs and recognizing the challenges. J Pharm Pharmacol 59:1043–1055

43. Tuleu C, Breitkreutz J (2013) Educational paper: formulation-related issues in pediatric clinical pharmacology. Eur J Pediatr 172:717–720
44. Mandel D, Littner Y, Mimouni FB, Lubetzky R (2006) Conclusiveness of the cochrane neonatal reviews: a systematic analysis acta. Paediatrica 95:1209–1212
45. Benjamin DK Jr, Smith PB, Murphy MD, Roberts R, Mathis L, Avant D, Califf RA, Li JS (2006) Peer-reviewed publication of clinical trials completed for pediatric exclusivity. JAMA 296:1266–1273
46. Temeck J (2010) Pediatric product development in the U.S. FDA Seminar, Copenhagen. http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM262309.pdf
47. FDA Pediatrics Page (2013) Labeling database as of March 2013. http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase
48. Sachs AN, Avant D, Lee CS, Rodriguez W, Murphy DM (2012) Pediatric information in drug product labeling. JAMA 307:1914–1915
49. Regulation No. EC 1901/2006 (2006) European parliament and the council, European Commission (Brussels), December 12, 2006
50. Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMEA) (2006) Reflection paper: formulations of choice for the paediatric population
51. International Conference on Harmonization (ICH) Topic E-11 (2001) Clinical investigation of medicinal products in the pediatric population. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf
52. Sixtieth World Health Assembly, Better Medicines for Children (May 2007) WHA60.20
53. World Health Organization (2011) Essential medicines for children. http://www.who.int/childmedicines/en/
54. Beggs SA, Cranswick NE, Reed MD (2005) Improving drug use for children in the developing world. Arch Dis Child 90:1091–1093
55. Permala J, Hassali MA, Awaisu A, Shafie AA (2010) Dosing information in a standard drug reference: are pediatrics still therapeutically neglected? Pediatr Int 52:290–295
56. McNally GP, Railkar AM (2009) In: Mulberg AE, van den Anker JN, Silber SA (eds) Formulation of pediatric dosage forms in pediatric drug development, concepts and applications. Wiley, New York, pp 553–566
57. Krause J, Breitkreutz J (2008) Improving drug delivery in paediatric medicine. Pharmaceut Med 22:41–50
58. Breitkreuz J, Tuleu C, Solomonidou D (2007) Paediatric formulations. In: Rose K, van den Anker JN (eds) Guide to paediatric clinical research. Karger AG, Basel
59. Smyth RL, Edwards AD (2006) A major new initiative to improve treatment for children. Arch Dis Child 91:212–213
60. Walsh J, Bickmann D, Breitkreutz J, Chariot-Goulet M, on behalf of the European Pediatric Formulation Initiative (EUPFI) (2011) Delivery devices for the administration of pediatric formulations: overview of current practices, challenges and recent developments. Int J Pharmaceut 415:221–231
61. Guidance for Industry (2009) ICH Q8(R2) Pharmaceutical Development, Revision 2. http://www.fda.gov/downloads/Drugs/…/Guidances/ucm073507.pdf
62. Potter C (2009) PQLI application of science- and risk-based approaches (ICH Q8, Q9, and Q10) to existing products. J Pharm Innov 4:4–23. doi:10.1007/s12247-009-9051-9
63. Winkle H (2011) Key note "QbD and Pediatric Drug Development" application of QbD to development of pediatric formulations and dosage forms. In: Mini-symposium, CRS 38th annual meeting & exposition of the controlled release society, Gaylord National Hotel & Convention Center, National Harbor, MD
64. Becker ML, Leeder SJ (2010) Identifying genomic and developmental causes of adverse drug reactions in children. Pharmacogenomics 11:1591–1602. doi:10.2217/pgs.10.146
65. Bartelink IH, Rademaker CMA, Schobben AFAM, van den Anker JN (2006) Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 45:1077–1097

66. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE (2003) Drug therapy: developmental pharmacology: drug disposition, action, and therapy in infants and children. N Engl J Med 349:1157–1167
67. Rodriguez W, Selen A, Avant D, Chaurasia C, Crescenzi T, Gieser G, Di Giacinto J, Huang SM, Lee P, Mathis L, Murphy D, Murphy S, Roberts R, Sachs HC, Suarez S, Tandon V, Uppoor RS (2008) Improving pediatric dosing through pediatric initiatives: what we have learned. Pediatrics 121:530–539
68. Abdel-Rahman SM, Amidon GL, Kaul A, Lukacova V, Vinks AA, Knipp GT, and Members of the BCS Task Force (2012) Summary of the national institute of child health and human development-best pharmaceuticals for children act pediatric formulation initiatives workshop—pediatric biopharmaceutics classification system working group. Clin Ther 34:S11–S24
69. Giacoia GP, Taylor-Zapata P, Mattison D (2008) Eunice Kennedy Shriver national institute of child health and human development pediatric formulations initiative: selected reports from working groups. Clin Ther 30:2097–2101
70. Giacoia GP, Taylor-Zapata P, Zajicek A (2012) Eunice Kennedy Shriver national institute of child health and human development pediatrics formulation initiative: proceedings from the second workshop on pediatric formulations. Clin Ther 34:S1–S10
71. Shaddy RE, Denne SC, the Committee on Drugs and Committee on Pediatric Research (2010) Clinical report—guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics 125:850–860
72. Gray VA (2009) Meeting report: University of Wisconsin/AAPS/FDA workshop applied biopharmaceutics and quality by design for dissolution/release specification setting: product quality for patient benefit. Dissolution Technol 16:35–39
73. Selen A, Cruañes MT, Müllertz A, Dickinson PA, Cook JA, Polli JE, Kesisoglou F, Crison J, Johnson KC, Muirhead GT, Schofield T, Tsong Y (2010) Meeting report: applied biopharmaceutics and Quality by Design for dissolution/release specification setting: product quality for patient benefit. AAPSJ 12:465–472
74. Murphy D (2011) Key note (pediatric product development: the path to the present) application of QbD to development of pediatric formulations and dosage forms. In: CRS 38th annual meeting & exposition of the controlled release society, Gaylord National Hotel & Convention Center, National Harbor, MD
75. Stella VJ (2001) My mentors. J Pharm Sci 90:969–978

Chapter 27
Paediatric Pharmaceutical Legislation and Its Impact on Adult and Paediatric Drug Development: The EU Regulatory View

Siri Wang and Karl-Heinz Huemer

Abstract The Paediatric Regulation in the European Union sets up a framework governing mandatory requirements and incentives for industry in development of new medicinal products as well as a series of accompanying measures to facilitate approaches to gain access and improve exchange of relevant information on medicinal products in paediatric use. This chapter first presents an overview of this regulatory framework and the requirements that have to be met by industry. It describes the role of the Paediatric Committee (PDCO) at the European Medicines Agency (EMA) and the main points to consider in discussing Paediatric Investigation Plans (PIP). The second part focuses on the specific implications of this regulatory framework on the development of drug formulations for paediatric populations. Essential elements to ensure suitably adapted formulations are reviewed, focusing on dosing appropriateness, acceptability and safety for all relevant age groups.

27.1 Historical Background

Following similar initiatives in the USA that led to the FDAMA (FDA Modernization Act) in 1997, the discussion in Europe to specifically address requirements for drug use in the paediatric population dates back at least to the 1990s, mainly initiated by academic and scientific societies like the European Society of Developmental

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Perinatal and Pediatric Pharmacology (ESDP) [1]. The basic idea that there is a need to establish a legislative framework with regard to paediatric medicines was one of the outcomes of an expert round table, organized by the European Commission at the European Medicines Agency (EMA) in 1997 [2].

The European Commission also initiated discussions on the performance of clinical trials in children, mainly in collaboration with the International Conference on Harmonization (ICH) finally resulting in the ICH guideline "Note for guidance on clinical investigation of medicinal products in the paediatric population" (ICH Topic E11) which entered into force in 2002 [3].

In parallel, at the EMA the Committee for Proprietary Medicinal Products (CPMP) founded an ad hoc Paediatric Expert Group (PEG). With implementation of Regulation EC no.726/2004, when CPMP was reorganized to the Committee for Medicinal Products for Human Use (CHMP), the PEG was transformed into one of its temporary working parties comprising experts of different areas and also establishing links to other CHMP working parties and the Committee for Orphan Medicinal Products (COMP). Mandate of the PEG was coordinating activities at the EMA and advising its scientific bodies.

The Council of Health Ministers adopted a resolution addressed to the European Commission in 2000 raising the desire for a legislative proposal on the topic of paediatric medicines with high public health priority. After an extended impact assessment (comprising also economic and social consequences) of such a prospected legislation outlining started with a first draft proposal in 2004. After amendments agreement was reached in Dec 2005. The Regulation was adopted by the European Parliament in June 2006, published in December 2006 and entered into force on 26 Jan 2007. It comprises Regulation No. 1901/2006 and amending Regulation No. 1902/2006.

27.2 The Main Points in the Regulation

The Paediatric Regulation sets up a framework governing mandatory requirements and incentives for industry in development of new medicinal products as well as a series of accompanying measures to facilitate approaches to gain access and improve exchange of relevant information on medicinal products in paediatric use. By such means it aims to facilitate the development and accessibility of medicinal products for use in the paediatric population and to ensure that medicinal products used in children are subject to ethical research of high standards and are appropriately authorized. In addition the information available on the use of medicinal products in the various paediatric populations should be improved.

It is also stated that this should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorization of medicinal products for older age groups; to the latter aim, measures in children can be deferred, which means that studies in children can be initiated and/or completed

after the application for marketing authorization in adults is submitted. Clearly, to avoid delays compliance with the required early submission of PIP/waiver applications is critical (see below).

One of the cornerstones of the Regulation is establishing a Paediatric Committee (PDCO) within the EMA composed of one member and one alternate member from each Member State of the EU (plus Norway and Iceland); for five countries, these two members should also be the representatives in the CHMP. In addition, the European Commission appoints three members + alternates to represent health professionals and three members + alternates to represent patient associations. The Member states should coordinate their nominations, to ensure that scientific areas relevant to paediatric medicinal product development are well represented.

The PDCO has several roles as defined in the Paediatric Regulation, among those are:

- It has to assess and to agree on the content of paediatric investigation plans (PIP) for medicinal products as proposed by industry including agreement on proposed modifications of such PIPs.
- It can also waive the need for a paediatric development or can agree to defer specific developmental steps for specific medicinal products where deemed appropriate.
- At request assessing compliance of an applicant with the agreed PIP.
- At request of assessing bodies (CHMP or National Competent Authorities) it can be involved in assessing data generated in accordance with an agreed PIP and can formulate opinions on the quality, safety or efficacy for the use of such products in the paediatric population.
- It should advice and assist scientifically in elaboration of any documents related to fulfil this regulation.
- It should establish and keep updated a specific inventory of paediatric medicinal product needs.
- It should advise the EMA and the European Commission on conducting research into medicinal products for paediatric use.
- It should advise and support EMA in establishing a European Network of existing national and European networks, investigators and centres with expertise in performing studies in the paediatric population.

The regulation has put into force the requirement for an agreed opinion with the PDCO prior to an application for marketing authorization (MAA) for any unauthorized medicinal product for human use (Art. 7). In principle, all paediatric subsets/age ranges have to be covered in a PIP. Such PDCO opinions can include agreements on generating data in trials and/or collecting information in compliance with an agreed paediatric investigation plan (with or without deferrals). For all agreed measures a compliance check prior to MAA submission has to be performed by the PDCO (or by a National Competent Authority [NCA] for non-centralized route applications). A positive outcome is required for a valid MAA. On the other hand, a PDCO opinion can also contain a product-specific waiver or a class waiver, limiting the obligation to conduct certain paediatric studies.

The need for agreement on a PIP is also given in case of already authorized medicinal products which are protected either by a supplementary protection certificate (SPC) or by a patent qualifying for such SPC (Art. 8). For these products a PIP is needed if a MAA for a new indication, a new pharmaceutical form or a new route of administration is planned. Several products are exempted from the need for a PIP, including those submitted via the route of a generic, homeopathic, herbal or well-established use application.

Opinions on agreed PIPs have to contain measures to assess the quality, safety and efficacy of a medicinal product in all concerned paediatric subsets. They also need to include timelines and measures to adapt the formulation of the medicinal product to make its use more acceptable, easier, safer or more effective for relevant subsets of the paediatric population.

Waivers can be granted for part or all of the paediatric population. This has to be based on evidence either that a product is ineffective or unsafe, or that a condition for which the product is intended does not occur, or that the specific product would not represent a significant therapeutic benefit over existing treatments.

This clearly implies that lack of such evidence would not be a reason for waiving a development. Therefore such waivers can be very specifically limited to one or more paediatric population subsets and/or condition. The reason why a waiver is granted is part of the opinion and this information is also published.

One of the challenges of this regulation in the EU is the early point in time when such a proposal should be submitted. Unless duly justified this should be not later than upon availability of the human pharmacokinetic data in adults. This should not be misinterpreted as a need to start the paediatric development so early, but should rather ensure that there is sufficient time to integrate the paediatric plan appropriately into the integral development of a product. The actual timing of paediatric trials to be performed would then be agreed by also granting deferrals for the planned measures if a delayed initiation or completion for collecting some data seems appropriate. Such early discussion can, depending on the development planned, for example, safeguard sufficient time in elaborating on age-appropriate formulation efforts without generating delays.

Deferrals can be agreed for initiation or completion of any measures that are included in a paediatric development plan, if scientifically or technically justifiable on grounds related to public health. In practice this very often will imply that adult data are available prior to initiating paediatric trials. However, also other reasons could be valid justifications for deferring measures, e.g. longer recruitment time. Linking deferral timelines to regulatory milestones rather than scientific reasons (e.g. approved marketing authorization in adults) would not be considered an appropriate justification.

The Paediatric Regulation also foresees a specific voluntary procedure for products not covered by Art. 7 or 8. For already marketed off-patent products a paediatric indication can be claimed by submitting a dossier including documents establishing quality, safety and efficacy in the paediatric population, including an age-appropriate formulation. Such a Paediatric Use Marketing Authorisation (PUMA, Art. 30) would qualify for a 10-year (market and) data protection if performed in compliance with a prior agreed PIP.

27.3 Implications

What does this mean in practical terms? A company that has the intention to develop a new drug product, or plans new pharmaceutical forms/routes or new indications for an approved medicinal product still under patent protection, will have to consider whether this product can fulfil a paediatric need, including all subsets/age ranges up to 18 years. And it will be required to submit this plan to the EMA PDCO to discuss the planned development or argumentation for waiving or deferring measures in this development plan.

The paediatric needs that exist in the planned condition will have to be considered. Such unmet medical needs are determined based on occurrence of a condition and lack of or limitations in current therapeutic options. It should be kept in mind that this regulation was introduced to counteract the fact that industry only rarely proceeded in this direction voluntarily.

In practice drug developers still tend to delay PIP submissions, not having decided yet how this development will look like or still looking for arguments to support a desired waiver. For example, companies are unsure about the appropriate design of the paediatric study (e.g. what endpoint could be feasible or how many children could be recruited). Furthermore, the need to develop a formulation in smaller children might depend on the fact whether this drug later will be used in a specific (lower) age range. But again: actually it would facilitate planning to have at least a cursory overview of possible later requirements if they are discussed as early as possible. Should later development generate evidence that paediatric needs or agreed PIP measures are no longer applicable, there is the option to propose changes via a procedure for modification of an agreed PIP, at any time and as often as needed.

The risks of delayed submission have become evident in many instances, most notably delays of the planned marketing authorization date due to not having agreed a PIP in time. This is partly due to insufficient understanding of the implications of the Paediatric Regulation, especially in drug developers from outside the EU. Often it also relates to misunderstandings how paediatric needs are related to a planned condition, which often is artificially narrowed to focus on the population with the highest marketing potential. Such narrowing would not be supported by the Paediatric Regulation, as very often there are differences in conditions in the paediatric population as compared to adults. Hence this would compromise the rationale behind the Regulation, the main aim of which is to increase knowledge and availability of drugs in children based on generated evidence.

Other difficulties often encountered in late submissions are that data already generated (outside an agreed PIP) are insufficient or that opportunities to cover some points are missed. This can result in seemingly redundant requests, which would be against the intention to prevent unnecessary trials. However, a trial with design flaws (e.g. non-valid endpoint, sample size, etc.) cannot be considered as sufficient evidence that would justify not repeating a more or less similar one with appropriate design. Here the first trial might be considered unethical, as being insufficiently planned. Often companies are hesitant to include, e.g. adolescents in a Phase 2 or 3

development. This could result in a request to include them in a separate trial, which can cause delays before proceeding to younger age groups. Therefore such decisions should be discussed well in advance to prevent such situations.

It should also be kept in mind that extrapolation of generated data can be used in some cases to supplement the paediatric development. This can, dependent on the medical setting, affect any data from preclinical, efficacy, safety to dosing and pharmacokinetics. It should also be considered that often in paediatric settings fully powered comparative trials might not be feasible. But there are many innovative options for other approaches, which in such cases should be proposed and discussed to find a satisfactory agreement.

In conclusion, while not being an effort that industry often will deliver voluntarily, early involvement of the regulatory bodies will facilitate further planning and, in case new generated evidence would make necessary changes in such a program, this is not hampered by such an approach.

27.4 Paediatric Formulations

The Paediatric Regulation highlights in its preamble the problems resulting from the absence of suitably adapted medicinal products, and specifically mentions the non-availability of suitable formulations and routes of administration, as well as the use of magistral or officinal formulations of potentially poor quality. These challenges are best known by the paediatric patients themselves, their parents, and the healthcare professionals in their daily struggle to adapt and modify the existing medicinal products in an attempt to benefit from the therapeutic advantage of the product. Crushing, splitting, diluting or dissolving may significantly affect factors like dosing accuracy, PK profile or acceptability, and medication errors may occur when doses are prepared or calculated.

Consequently, the regulation clearly states that the PIP must include a thorough description of any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.

There are basically three major factors that decide whether a formulation is suitable for the target age group: the formulation must be acceptable for the patient, ensure the right dose, and it must be safe. These three factors should be considered and fulfilled for all relevant age groups for which the product is developed. It is therefore expected that the PIP application includes a thorough discussion on the proposed formulations and their suitability for the target age groups, covering aspects of acceptability, dosing accuracy and safety.

Acceptability implies that a formulation can be easily administered to the relevant age groups and is crucial for optimal adherence and intended effect. It covers a range of aspects like taste, size, volume, complexity of manipulation, local tolerance and pain. One of the major hurdles for children taking oral medicines is the tablet and capsule size, large sizes being maybe appropriate for adults but definitely

less suitable for children. Interestingly, information about size of existing products is often lacking in the initial PIP applications, which could indicate insufficient awareness of this aspect. Size is particularly important if the tablet or capsule is developed to be swallowed whole, due to, e.g. film coating for taste masking or modified release design for optimal absorption profile. For such products crushing and scoring may significantly affect taste, bioavailability or PK, and therefore size is crucial for overall usefulness of the product. Generally, increased attention towards potentially more child friendly oral solid formulations like "mini-tablets" and dispersible and orodispersible tablets is highly needed and welcomed, but is to date not a frequent approach seen in the PIP applications.

Bad taste of oral liquids is a well known factor that affects medication adherence in children, and could be caused by both active substance and excipients. Companies are encouraged to explore avenues to avoid poor patient acceptability by optimizing taste masking. This could include standard approached like adding sweeteners or flavours, or more sophisticated methods like microencapsulation. Careful consideration is needed to balance any taste issue with the strength and volume required.

Although significant clinical experience indicates that many children face major challenges in swallowing tablets and oral liquids, more precise knowledge is still limited about taste preferences and which tablet/capsule sizes being appropriate for which age groups. Consequently, to ensure that children in the relevant age group are actually able to take the medicine as intended, data to support and confirm acceptability and palatability of the product is requested in the PIPs, e.g. as a part of the paediatric clinical studies that will be performed. However, it should be emphasized that early focus on the appropriateness of the formulation is important as a poorly acceptable formulation might indeed affect the outcome of the paediatric trial performed.

In all cases where a more suitable formulation is not feasible and there is doubt about whether the formulation (and in particular its size) would be appropriate for the patient age group, it is important that alternative approaches are explored and outlined. Recommendations regarding opening capsules, dissolving, dispersing or crushing tablets, or mixing with food can be very useful for patients, parents or healthcare professionals, but would require sufficient considerations of the potential impact on the performance of the drug.

The strength of any liquid form will decide the volume to be withdrawn from a container and given to the patient. Dosing small children using strengths suitable for adult for will often imply too small volumes to accurately administer the dose to the child. Dilution steps to solve the problem with small volumes have shown to significantly increase the risk of calculation and administration errors and should be avoided if possible. Again suitable devices to enable accurate dosing are essential.

Osmolality of the administered drug should be appropriate for the target age group. Depending on the route of administration high osmolality drugs will have to be diluted to reduce the risk of pain, irritation, necrosis and necrotizing enterocolitis, elements that can be age dependent. However, whenever dilution is necessary careful consideration must be put on its impact on stability of the product, on proper instructions for dilution and on the volume load.

Although excipients are traditionally thought to be inert and safe, several cases have shown that this is not always true, particularly for very young children where a continuously developing organism may give rise to different excipient safety profiles compared to adults. Significant discussions have been ongoing for solvents like ethanol and propylene glycol, preservatives like thiomersal, benzyl alcohol and parabens, and for solubilizers and colourants. The Paediatric Regulation's call for adapted formulations implies that products intended for use in children must have an acceptable safety profile also in terms of excipients. The PIP should therefore have a thorough presentation of the safety data available for the proposed excipients, justifying the excipient exposure taking into account the target age group, route of administration and duration of treatment. There is, however, sparse data available specifically relevant to children and in particular to neonates, and it is generally recommended to avoid excipients with potential safety concerns when developing paediatric formulations. Additional safety data, e.g. through juvenile animal studies or additional safety monitoring might be requested by regulators whenever the excipient safety profile is not fully reassuring.

27.5 Specific Considerations on Formulations for Neonates

Neonates, and even more so preterm newborns, are the patient groups where medicinal products are most often used off label [4]. The need for PK, efficacy and safety data in this population frequently implies separate clinical trials with careful consideration of sampling scheme, appropriate endpoints and disease characteristics. Particular attention should, however, also be put on whether the formulation is suitable for this patient group, ensuring accurate dosing and safe administration.

In many cases, intravenous administration may be the only feasible route of administration to neonates. Appropriate strength will be vital for on one side the sufficient dosing accuracy, often depending on suitable administration and dosing devices such as pumps, and on the other side the limitation in volumes acceptable for neonates with fluid restrictions. In clinical practice, data on compatibility with other commonly administered parenteral drugs will often be needed for treatment to be feasible within the available time and volumes. Therefore, where relevant, such data should be included in the development plan. Ten times dosing error is more often seen in neonatal units due to the fact that the doses are very small compared to the total dose in the vial or bag [5]. Consequently, a separate presentation would often be considered needed.

Intravenous administration may not always be possible or physicochemically feasible, e.g. due to solubility or stability issues, therefore in some settings oral administration is considered needed and appropriate also for neonates. In such cases administration through feeding tubes may be necessary and sometimes the only possible way to administer the drug product. Consequently, factors like adherence to tube material, particle sizes, viscosity and rinsing volumes are essential for safe and accurate dosing, and the PIP would have to include data on dose recovery and

feasibility of administration through the relevant tubes. Indeed, such elements may also be relevant for older children whenever tube feeding is likely in the target patient group.

In summary, any adult presentation will rarely be entirely suitable for smaller children and especially neonates, and a specific formulation or presentation will often be needed to ensure correct dosing and safe use in these lowest age groups.

27.6 Collaboration on Paediatric Formulations

European and worldwide initiatives have been taken during the last years, also related to formulations. WHO's campaign "Make medicines child size" and the European Initiative for Paediatric Formulation (EuPFI) [6] are two important examples. PDCO and EMA have regular contact with FDA and with WHO when relevant, and collaboration is established with EuPFI, where EMA has observer status.

As part of its focus on paediatric formulations, PDCO has established a subgroup (PDCO's Formulation Working Group, FWG). Attention is put on combined quality, safety and clinical aspects of formulations. The group consists of PDCO members, national quality experts, clinical pharmacy experts, clinicians and academic experts, and collaborates closely with EuPFI and FDA. A systematic approach to PIP quality aspects aims at a broader and more consistent "cross product assessment".

27.7 Conclusions

The Paediatric Regulation aims at better medicines, including more suitable formulations, for children in Europe. Still in its early phase, the focus on medicines properly adapted for the paediatric population will continue.

The importance of early submission of the PIP is valid also for formulation aspects. The final agreed age groups for which the product is intended will inevitably affect the decision whether the formulation strategy is optimal, and early agreement on lower age cut-off will be important for a rational formulation development. However, at this point of product development it is most often not clear whether dose will be critical in terms of dose–response and whether the need for dose titration is foreseen for other reasons and such aspects could most likely also influence the choice of formulation. It should be emphasized that for proper dose finding in the paediatric population a certain degree of flexibility in dosing is normally needed, and wide dose banding (often due to existing adult formulation that to a limited degree would allow dosing flexibility) could compromise the results of the paediatric clinical trials. Therefore, depending on the lower age cut-off for the development plan and/or the properties of the active substance, a preliminary formulation for use in clinical trials that allows dosing flexibility might be needed. Obviously, in addition to dosing accuracy, both acceptability and safety of such formulations should also

be carefully considered. The modification of the preliminary formulation into the product intended to be marketed might necessitate bridging studies depending on the active substance and the formulations proposed.

It is important that the pharmaceutical forms developed have a certain degree of robustness in terms of practical handling and ease of administration to make them useful and safe in both in-hospital and homecare settings if applicable. This is particularly relevant for medicines for children, since several different caregivers are often involved in addition to the child itself. Dosing device, presentation and proper instructions are vital factors to increase adherence and to reduce the risk of medication errors and should be adapted to the target patient group.

Companies are indeed encouraged to consider new technology and innovative approaches to meet the need for paediatric specific formulations. In this context it is also important to remind drug developers that the need for flexible dosage forms, both in terms of dosing adjustment and flexibility of mode of administration, is significant also in other patients populations, for example, geriatric patients, patients with feeding tubes and intensive care patients. Some of the apparently paediatric specific factors will be valid also for these settings and paediatric formulation development should therefore be an early and integrated part of the overall drug development program.

References

1. European Society for Developmental Perinatal & Pediatric Pharmacology. www.esdppp.org. Accessed 17 Dec 2013
2. The European paediatric initiative: history of the paediatric regulation (2007) (EMEA/17967/04 Rev 1). http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/09/WC500003693.pdf
3. European Medicines Agency (2001) Note for guidance on clinical investigation of medicinal products in the paediatric population (ICH Topic E11) (CPMP/ICH/2711/99). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf
4. European Medicines Agency (2010) Report on the survey of all paediatric uses of medicinal products in Europe (EMA/794083/2009). http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101006.pdf
5. Simpson JH, Lynch R, Grant J, Alroomi L (2004) Reducing medication errors in the neonatal intensive care unit. Arch Dis Child Fetal Neonatal Ed 89(6):F480–F482
6. European Paediatric Formulation Initiative. http://www.eupfi.org/. Accessed 17 Dec 2013

Chapter 28
Pediatric Pharmaceutical Legislation in the USA and EU and Their Impact on Adult and Pediatric Drug Development

Klaus Rose

Abstract Drug development is a complex undertaking, not an academic exercise. The key players, mainly pharmaceutical industry, regulatory authorities and academia, have different logics and interests. Industry consists of large, medium, and small companies who compete (or cooperate), win or fail. For some decades large companies seemed to set the tone in drug development, but that paradigm may be changing. Pediatric legislation has imposed the logic of public health over this already complex process. The intention is certainly laudable. The key question is if it works, and to what degree the US and EU legislation are comparable. The breakthrough improvements in pediatric oncology in the last decades happened without direct contribution from regulatory authorities. The successful treatment schemes for children with cancer are off-label and will remain so. Breakthrough innovations in rare pediatric diseases such as cystic fibrosis or enzyme deficiencies were not triggered by pediatric legislation. The number of label changes, of submitted pediatric investigation plans (PIPs), or of clinical trials that companies must commit to have in themselves limited significance. Do all label changes improve child treatment? Do trials in rare diseases make sense if there are not enough patients on this planet? Does the interference of the European Medicines Agency (EMA) and its pediatric committee (PDCO) in worldwide research in rare pediatric diseases promote child health, or does it harm? At the end, the reader will have to answer these questions for himself. A framework is offered for guidance through the maze of dimensions that need to be taken into consideration.

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28.1 Introduction

Drug development is a complex and highly regulated process. The main players are regulatory authorities, practicing clinicians, academic clinicians, patients, reimbursement organizations, tax payers, research-based innovative pharmaceutical industry, generic industry, and more. The involved players are different in their interests, their internal dynamics, and their views about their counterparts. Pediatric pharmaceutical legislation is an intervention into this process with the intention to use it for the benefit of children [1].

For the first years of the US pediatric legislation the only financial mechanism was a reward of 6 months patent extension for pharmaceutical companies, which in turn delayed introduction generic copies of the respective medicine by 6 months [2]. Of course generic companies lobbied against this legislation. As there is almost no generic competition in Japan, this type of incentive cannot work there. This is the main reason that so far no successful pediatric legislation has been introduced in Japan [3].

The US legislation was 10 years in place before the EU introduced its own pediatric legislation. The EU pediatric regulation is a follow-up to the US legislation, however, with some key differences [4,5]. It relies much more on mandatory development. There is a reward, but it plays a much lesser role, as companies are "motivated" to submit pediatric investigation plan (PIP) by the threat to have their registration of new medicines blocked without an agreed PIP. The European legislation is also more ambitious than the US one. Drugs for orphan diseases, biologics, and vaccines were excluded from the US legislation, while the EU pediatric regulation includes them all. Furthermore, the PIP must be submitted at the end of phase 1, i.e. well before any efficacy data of the drug have been generated at all.

28.1.1 Dimensions How to Assess the Impact of the Pediatric Legislation

28.1.1.1 Awareness About the Need for Research with Children and Removal of Barriers

Without the pediatric pharmaceutical legislation, this book would certainly not have been published at this time. While in the US pediatric requirements will not block registration of new drugs in adults, in the EU companies can no longer register new drugs without an approved PIP. The development of adequate age-appropriate formulations is part of the PIP requirements. Under the threat of non-registration, awareness of pediatric drug development has diffused very fast into the pharmaceutical industry.

Criminal experiments performed during the Second World War by German and Japanese doctors had a considerable influence on public perception of experiments

with human beings. It took decades in adult medicine to develop a framework to balance the wish to learn from systematic experimentation against the need to protect the patient. Within this balance, the mainstream attitude towards children was that they needed protection against clinical research. It took decades to make people accept that experiments with children with cancer could save lives [22].

Cytotoxic and other agents had been developed for adult malignancies. In the beginning they were administered to children in homeopathic doses only, as it was assumed that the children would die anyway. "What is quite remarkable is that all of the drugs used to treat most childhood cancers were developed and approved in the 1950s, 1960s, and 1970s. Even though we had everything in hand by the 1970s, improvements did not happen overnight, but instead over the course of 30 years" [23]. Most treatment schemes for children with cancer are still off-label and will never be registered. The medications used in these schemes are mostly old and no longer patent-protected. The driving force behind the revolution in pediatric cancer treatment was the clinical pediatric oncologists that systematically tested medicines in children with cancer in international clinical trials [6–10]. The regulatory authorities did not play a major role in the revolution of pediatric oncology.

Pediatric clinical research networks were established in the USA from the 1990s on and are spreading across Europe today. Most ethics committees are aware of the need to research in children, although the degree of their preparation varies considerably. The readiness of parents to allow their child to participate in a clinical trial depends on the severity of the disease. If the child's life is at stake, most do not hesitate. If the condition is less threatening, consent is often more difficult to get. Awareness of the nature of clinical trials and specifically pediatric clinical trials is still less than would be desirable in the training scheme of medical doctors as well as in the general public. Nevertheless, the awareness of the need to remove barriers against clinical research in children has increased. Some barriers remain, some have been removed. The trend is obvious. The US and EU pediatric legislation have contributed to this movement.

28.1.1.2 Administrative Measures by the Regulatory Authorities

Before pediatric legislation, there was a large degree of uncertainty in pediatric pharmaceutical treatment. Specialized centers of pediatric oncology had a pretty good knowledge of the drugs prescribed and administered even though most of the drugs were used off-label. It was different in the field of general medicine. Which dose would a general practitioner prescribe in treating a child? And which dose would a pediatrician prescribe? Pediatricians were trained for off-label use, but what about drugs that had been introduced after they had finished their training? The inclusion of pediatric information into the prescription information is an endeavor that will go on for decades in both the US and EU. Drastic improvements in pharmaceutical child care cannot be expected, but a gradual improvement and availability of key information to all medical practitioners is a definite plus.

Regulatory authorities measure the success of their pediatric activities in several algorithms. One of these algorithms is the number of label changes, i.e. additional pediatric information introduced into the drug labels, be it more dosing information, information about efficacy in children, or contraindications.

Both FDA and European Medicines Agency (EMA) have a large number on these label changes on their respective websites.

The FDA has on its website separate links with detailed information about the following issues:

- New Pediatric Labeling Information Database
- Safety Reporting Updates
- Pediatric Study Characteristics Database
- List of Exclusivity Determinations (PDF—179 KB)
- Medical, Statistical, and Pharmacology Reviews 7/9/2012 to present
- Medical, Statistical, and Pharmacology Reviews 9/2007 to 7/2012
- Medical, Statistical, and Pharmacology Review Summaries 1/2002 to 9/2007

(http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm)

One example: clicking on the first bullet point shows that so far for 470 drugs pediatric information has been added into the information sheet. It is followed by a description of each single drug and the information that has been changed. For specific drugs it will be necessary to go into the FDA website and search for information.

Figure 28.1 is taken from the EMA report 2012 to the EU commission [11] which gives a good overview over the achievements of the legislation in the view of the EMA.

In short: so far, over 1,000 PIPs have been submitted, and from Fig. 28.1 we see that in 2011 476 PIPs had been approved. The number of pediatric clinical trials has increased, many new medications have been registered with a pediatric indication, and a few companies have received a reward in the form of an SPC, which for the non-patent-lawyer can be translated into 6 months patent extension. As the report is online, more details can be retrieved from it without major efforts. Similar conclusions can be found in a paper by Olski et al. [12], where they present a retrospective analysis of all PIPs submitted to the EMA between 2007 and 2009. The authors' conclusions: "The key objective of the Paediatric Regulation, namely, the availability of medicines with age-appropriate information, is going to be achieved." [12]

28.1.1.3 Number of Clinical, Non-clinical and Pediatric Formulation Studies

The US pediatric legislation exposed for the first time the industry to a large scale work on pediatric clinical trials. Where there had been a market, regulatory clinical trials had been performed before this legislation, e.g. for vaccines, for human growth hormone, or for antibiotics. With the incentives offered by FDAMA the

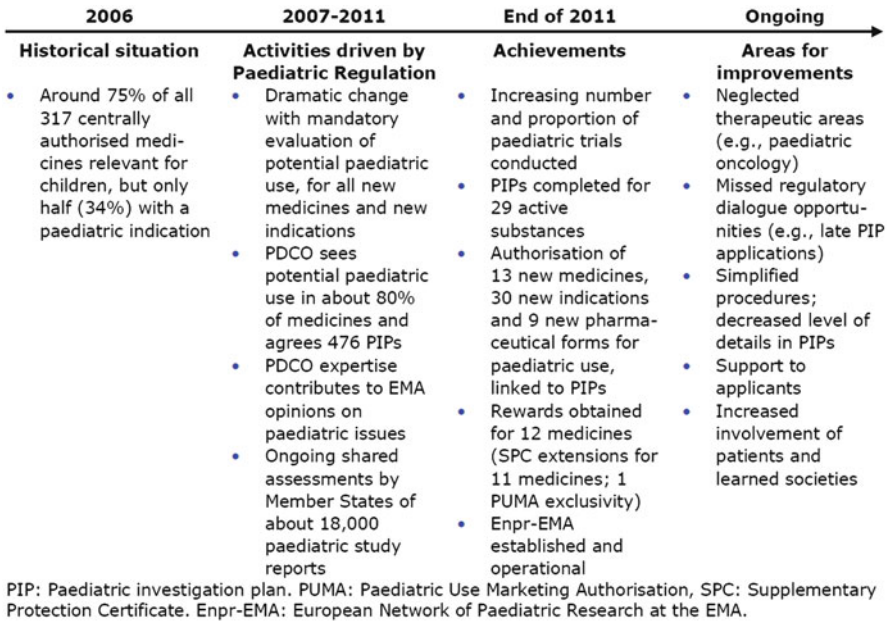

Fig. 28.1 Highlights of the impact of Paediatric Regulation after 5 years

number of clinical trials in children increased. There are many data on this on the FDA website.

The EU-triggered PIP is more demanding. Companies must commit to "measures" which can include preclinical studies in young animals, development of age-adapted technical formulations, modeling and simulation studies, clinical studies, long-term pharmacovigilance measures, and more. All these measures can be executed by the respective company itself, or can be outsourced to a specialized service provider. The tendency in the pharmaceutical industry is to outsource more and more of these services. The traditional service providers have increased in size over the last decades, and the number of specialized companies has increased as well. This includes clinical research organizations (CROs) for research in adults and children, CROs for research in juvenile animal studies, and development of pediatric formulations. The latter is usually a relatively small part of the entire pediatric developing program—but it is the focus of this book.

A semi-formal group has been formed in Europe that serves as a platform between pharmaceutical companies and university. The regulatory authorities participate as observers. This consortium's name is European Paediatric Formulation Initiative (EuPFI), its website www.eupfi.org.

The number of pediatric clinical studies, juvenile animal studies, and formulation development studies is gradually increasing. CROs of all specialties listed above are increasingly confronted with requests for pediatric research.

28.1.1.4 Impact of the Legislation on Children's Health

In its report to the congress 2001 the FDA gave a few tentative parameters how better medicines for children might have measurable health outcomes: "Superior drug treatment information is expected to permit quicker recoveries from childhood illnesses, with fewer attendant hospital stays, physician visits and parental work days lost." [24] So far no convincing reports have been brought forward that would elucidate the impact of the US or EU pediatric legislation in this dimension.

When the US legislation was introduced, there was palpable enthusiasm among pediatricians, regulatory authorities, and patient organizations. A fast improvement of pediatric pharmaceutical treatment was expected. These hopes have made place to a more conservative assessment. With a long-term view, it will eventually benefit children that more information on side effects, adequate dosing, contraindications, and more are available. But these improvements are very gradual. A similar enthusiasm could be observed in Europe, with the ambition to do more for the health of children than the US. With the EU legislation in its seventh year, also in Europe this initial enthusiasm is making place to a more conservative assessment. There is overall agreement that it will eventually and gradually serve child health to have more information screened and authorized by the authorities. On the other side, the revolution in pediatric oncology took place without licensing the used drugs, drug combinations, and other treatments specifically in children.

28.1.1.5 Impact of the Legislation on Public Expenses

At the EMA, roughly 30 positions were created to overlook the PIP procedure. In the larger EU countries one or several employees of the national regulatory authorities work exclusively in the support of the respective national PDCO representative. The main central costs of the PDCO members (2×33) are monthly flights to London, three or more nights hotel accommodation, and usual travel expenses. The majority of PDCO members are employed by national regulatory agencies, so the PDCO members' salaries are covered by the national regulatory authorities or other institutions that employ them; after regulatory authorities, the most frequent employers are hospitals.

28.1.1.6 Administrative and Financial Burden of the Pediatric Legislation for Industry

The administrative burden of a PIP negotiation is considerable. The PIP procedure between company and PDCO is about 1 year. It is not flexible, and absorbs considerable resources. PIPs are designed as plans that, once negotiated, cover the entire pediatric development, which can take years. With very limited clinical data and without any efficacy data little of what is planned will later be executed as planned. The negotiation procedure is exhausting for both sides, and at the end of the procedure, the PIP contains commitments that often represent too enthusiastic assumptions about recruitability of patients.

The EMA itself estimates in its 2012 report to the EU commission that per PIP 3–5 modifications of the original PIP will have to be negotiated [11]. This does not include those PIPs that are withdrawn after 1 year of negotiation because the PDCO comes up with new ideas in the last moment and the company disagrees. In this case, a company can withdraw the PIP to avoid a negative opinion that would be published on the EMA website.

A regulatory consultancy will charge 200–300 h for a PIP consultancy. However, this sum can be multiplied by 3 or 5 if additional clinical input is required. For most PIPs the service of at least one experienced clinician is highly recommended. So far, these costs have covered only the planning phase of the pediatric clinical and other trials. The costs of the execution of the trials can be measured as adult trials. Usually, pediatric clinical trials cost 2–5 times more per patient as adult trials, simply because everything is more complex.

Large companies have in the meantime their internal pediatric drug development matrix organization. Over the years considerable experience builds up within each individual company. This is replenished by new hires that have had some PIP experience with their previous company.

It is different for small and medium sized companies. The PDCO expects each company to be completely up-to-date in pediatric epidemiology, medicine, and diagnostics. Only in rare cases will this information be available in-house. So a new type service provider has evolved: PIP consultants. You find them in regulatory consultancies and/or in specialized companies. CROs offer complete packages for both the regulatory consultancy, including PIP negotiations and later the execution of all studies the company has committed to.

Do these negotiations contribute to child health? EMA and companies will here have different opinions. But in the meantime critical positions have been published, e.g. by representatives of pediatric oncology research. Detailed in-depth development plans for individual drugs focus on aspects that later will not reflect the therapeutic use of the respective medication at the bedside. Instead of focusing on the disease, as do pediatric oncologists, the focus remains on the individual drug. Furthermore, it is now the PDCO that decides about priorities in pediatric clinical oncology research, and not the clinical pediatric oncology community [7–10].

There is no doubt that the EMA has established a well-functioning pediatric machinery. In contrast to the US, where the main negotiation about pediatric development remains with the respective FDA division and the central pediatric structures participate in an advisory role, the PDCO has its own structure that negotiates pediatric development. The decisive question is to what degree this machinerie contributes to child health.

28.1.1.7 Worldwide Impact on Patient Recruitment

Already for clinical studies triggered by the US pediatric legislation, an increasing number of studies were performed outside of the US. While initially most companies performed their trials in-house, the execution of clinical trial has been increasing

outsourced to CROs. A number of CROs claim to have specific experience in pediatric clinical research.

With the EU legislation requiring a PIP early in development, and not excluding rare and orphan diseases, companies have to commit to clinical studies, which they perform where patients can be recruited. In frequent diseases this is less a problem, but in rare diseases it has the consequence that increasingly with rare diseases are recruited worldwide for EU-PIP triggered clinical trials.

28.1.2 Strengths and Limitations of Pediatric Legislation

28.1.2.1 Off-Label and On-Label Use of Medicines

The revolution in the treatment of child cancer has not made the horror of child cancer disappear, but it has changed fundamentally the dynamics. Fifty years ago most diagnoses in child malignancies were a death sentence. Today there is hope, as many patients survive. Each child diagnosed with a malignant disease faces potential death. Each diagnosis starts a period of horror to the patient himself, his parents, and the entire family. The main treatment components of child cancer are drug treatment, surgery, and radiation. Most of the drugs used in this treatment are comparatively old. They were developed in the 1940s, 1950s, and 1960s to treat adult malignancies. They were then step by step experimentally used in children, beginning with homeopathic doses as the physicians were convinced that the children would die anyway, to efficient treatment schemes involving high dose cytotoxic treatment.

Most of these treatment schemes are not licensed by the regulatory authorities. They are licensed for adult cancer treatment. In the hands of well-trained specialists off-label use of drugs is OK for first class medical care. Pediatric oncologists supported both the US and EU pediatric legislation in the hope that new medicines could be used in children earlier and not decades after their introduction. Reflection papers on pediatric oncology show that the reality is a bit more difficult.

Child malignancies are different from adult cancer. Most of them are rare or very rare. It was an *assumption* that inclusion of children into the drug development process for adult drugs would result in a major progress in the treatment of pediatric malignancies.

As outlined above, it is in general desirable to have use of medication in children documented in the labels. But child treatment is not improved automatically because a regulatory authority gives its blessings to a specific treatment. In the hands of well-trained specialists, new combination of cytotoxic agents is used safely.

28.1.2.2 Limitations of the Pediatric Pharmaceutical Legislation

In our market-driven society, only products are developed that eventually will be sold, be it drugs, cars, fashion, nourishment, laptops, or toys for children and adults. Drug development has become so complex that academic institutions cannot handle

the entire process. Penicillin was developed in academia. But because the way to produce it had already been published, there was no patent on the first penicillin, and pharmaceutical industry was reluctant to produce it. Eventually Fleming successors succeeded in the US after lengthy negotiations [13].

There are also philanthropic projects where considerable resources are assigned, e.g. the drugs for neglected diseases initiative (www.dndi.org). And there are publicly funded development programs both in the US and in the EU. Public funding in the US is higher. In Europe, the EU-funded pediatric drug development research is a drop into the ocean compared to the subsidies handed out to agriculture. Besides that, there are national grant mechanisms in each EU member state. Both research funding and non-for-profit philanthropic projects are complex own worlds.

Pediatric legislation addresses only industry-driven pharmaceutical development. Pediatric legislation cannot change the aims of drug research. Regulatory authorities cannot order pharmaceutical companies in which area they are allowed to develop drugs, and where not. It enforces pediatric consideration of drugs still predominantly developed for adults. But even diseases that carry the same name in adults and children can be very different. The more enthusiastic an authority is, the more it pushes companies to investigate the pediatric counterparts of an adult disease, even if that pediatric disease is rare or ultra-rare.

Profit-oriented drug development continues to be driven by those areas where the easiest profit can be made. This is mostly adults. Pediatric legislation enforces that for these drugs additional pediatric considerations are made. The ways they do it are different between the US and EU. The US system relies more on voluntary incentives and has gradually introduced mandatory requirements, but not in a way that they would block adult development. The EU legislation threatens with non-validation of registration at the EMA. Drugs targeting orphan diseases are excluded from pediatric obligations in the US. The EU is more enthusiastic and requires a PDCO approval even in ultra-rare conditions.

28.1.2.3 Meaningfulness of Impact Measures

The number of submitted PIPs or label changes shows that the authorities have triggered a lot of activity and keep industry busy. Do they translate into better healthcare for children? On this, the existing data are very limited. Furthermore, the answers will be different from different perspectives.

More pediatric information in the labels is desirable in principle. They are essential where they avoid over- or under dosing or serious side effects. The majority of drugs used in pediatric medicine are old and off-patent and will not get a more precise pediatric labeling neither through the US nor the EU pediatric legislation. Pediatricians have prescribed them for decades. Newly developed drugs must consider children. It depends very much of the specific disease to which degree additional pediatric data lead to better therapeutic outcomes.

At an FDA hearing in 2012, the majority of external clinicians agreed that no separate dosing recommendations are required in adolescents (12–17 years).

Additional clinical studies in adolescents have limited value in many therapeutic areas where it is safe to use adult doses. Blind enforcement of separate adolescent clinical studies will not help one single patient. Thus, just the number of trials triggered by legislation is in itself of limited value.

The early US-driven pediatric trials had in hindsight limited value. Producers of cytotoxic agents administered their compound to a number of children with different malignant diseases. The overall efficacy was negative, the compound did not get a registration in children, but the producers got their patent extension. But these were experiences from an early phase of the US pediatric legislation. Most of the data published on the FDA website are quite impressive.

The EU pediatric committee is enthusiastic in the wish to investigate the potential use of drugs in children. In areas where a given disease is rare or extremely rare in children, drug developers and the PDCO make different assumptions. For a company that has started PIP considerations late and is now under time pressure, the only strategy to get the PIP fast will be to accept PDCO assumptions regarding numbers of recruitable patients. After years of opening study centers, training personnel, organizing investigator meetings, and paying the involved CRO, the company can then go back to EMA, report that instead of 50 patients just 3 could be recruited, and will submit a request for modification. The PDCO will consider this. But time and resources from clinicians, industry and CROs have been wasted.

By their nature, EMA and PDCO will insist that 100 % of negotiated studies and every single request for modification are beneficial for child health in the long term. A company that had to invest considerably into a trial that at the end has to be terminated because there were no patients will have a different opinion.

28.1.2.4 Discretion and Balance of Regulatory Authorities

The pediatric legislation is an intervention into a complex process. In adult drug development the regulatory authorities decide if the submitted data are sufficient for a registration or not. With the pediatric legislation, the authorities have some discretion about the direction of drug development. In the US, there are two laws. With the mandatory law "pediatric research equity act" (PREA), FDA can mandate studies in children. With the voluntary law, FDA can reward the company with 6 months pediatric exclusivity [14]. Of course not all companies will be happy with the number of mandatory trials they have been ordered. In the EU, the EMA differentiates between "indication" and "condition" [11]. Indication is the specific indication for which a first drug approval has been requested. Condition, however, is a broader term. Postmenopausal osteoporosis is an indication within the broader condition of osteoporosis. Osteoporosis in children can be triggered by use of steroids. If a drug can potentially also be used in steroid-induced osteoporosis, EMA will insist on a PIP [25]. Although the regulatory authorities cannot order a company to develop drugs for specific disease areas, the discretion to which the EMA can define a condition and ask for pediatric studies is rather broad [15,16].

28.1.2.5 Workload for PIP Requests for Modifications (RfM)

In its 2012 report the EMA estimates that for each PIP three to five modifications are required. Each modifications goes through a 60 days negotiation procedure, preceded by a letter of intent 2 months ahead of submission and a period of 30 days during which the submission of the request for modification (RfM) must be validated. Including internal preparation, this procedure takes about half year. As the PIP is in principle a single document that must cover all measures, i.e. preclinical, clinical, and technical development steps for pediatric development, it is a very detailed plan that must be prepared by the submitting company and is then vigorously negotiated with the PDCO. Then this plan is modified three to five times on average. For the involved companies this is a major operational effort, as it is for the PDCO, that in the meantime spends half of its time with negotiating RfMs. The question is to what degree the design of elaborated and detailed development plans at an early phase makes sense, if later this has to be revised several times, again with a lot of details.

28.1.3 Tentative Assessment

Research-based pharmaceutical industry is not driven by pediatric healthcare. It is driven by developing medications that eventually somebody will pay. As long as this worked well with the development of yet another beta-blocker against hypertension, pharmaceutical R&D in hypertension was an Eldorado. All the pediatric legislation in both the US and EU could do and can do it to try to enforce at least some consideration of children in the adult drug development process. Since 1997 a lot has been learned about pediatric hypertension. The key reason is that there are some many adult antihypertensive drugs that negotiated pediatric development first with FDA and then with EMA. Not because pediatric hypertension is a major health threat in children.

Pharmaceutical industry stands between several sensitive social areas. Most companies are owned by shareholders. If a company fails to be profitable for a while, the value of its shares will fall and a new CEO will come, or it will have to merge with another company.

The products developed by pharmaceutical industry save lives and/or improve quality of life. Millions of people in modern society live only due to the availability of modern drugs, e.g. diabetes, HIV, asthma, cancer, rare diseases. Many more diseases do no longer spread terror and devastation because they are prevented by vaccination. There is a link between the totally business-oriented management of drug development and the bedside care by nurses, medical doctors and other healthcare professionals.

The reputation of pharmaceutical industry could be better [26, 27]. Some of the most investigated diseases in the focus of drug development in the past included myocardial infarction and stroke. Underlying causes are hypertension, dyslipidemia, obesity, suboptimal nutrition, and “modern lifestyle” (smoking, TV, booze,

lack of physical activities). Not everybody with such a lifestyle is guaranteed to get a stroke or myocardial infarction. To prevent stroke or myocardial infarction in one person many individuals must take daily pills. A paradise for marketeers. As long as the reimbursement institutions paid for yet another beta-blocker, they were developed. The debate how many beta-blockers we need is today becoming less relevant. We have already five generations of antihypertensive drugs. Of course there are companies that dream of a sixth or seventh generation. But good medications exist already, and the original products are gradually replaced by generics. Now companies must look for other areas where the probability of a return of investment is sufficient to invest. One such area is rare diseases [17].

Pharmaceutical companies' research can result in lives saved and quality of life restored. Companies want to use this for their image. Looking at the cover pages of annual reports of major pharmaceutical companies you could think that they all are in the philanthropic business, caring for babies and poor sick people. The team entrusted with designing the annual report is usually part of a communication agency. This team will simply test which type of photographs produce a high emotional positive feeling, and will use these. In consequence, the glossy self-presenting prints and websites of big pharmaceutical companies contain some degree of cynicism. Another aspect is very simple: pharmaceutical industry is economically successful and well connected to the academic world [18]; that makes it an easy target for sensationalist media.

For decades regulatory authorities had to register drugs that focused on those areas where a profit could be made. These were not the areas where a public health view would desire the highest focus of research. Furthermore, the development of a drug today costs more than a billion $ [19]. Once registered, the production costs are relatively low. This is another aspect that makes it easy to attack pharmaceutical industry.

There are other business areas with a high disparity between end price and costs of production, e.g. the world of fashion. Fashion does not result in life-saving drugs but just in better feeling for those who buy. Parents spend a fortune today to buy age-adapted cloths for their little ones. It is not always the rich parents who buy the ultimate designer clothes for their children. Child fashion is relatively new in history. A 100 years ago, children were dressed as little adults. But no politician has so far requested children's cloths to be affordable or to intervene in the market of children's cloths.

The consideration of children in the drug development process is a requirement originating from a public health point of view, imposed over the market-driven process of drug development. The creation of regulatory authorities and the introduction of modern labels were comparable in this regard. They ended the era of complete "freedom," where a manufacturer could claim whatever he wanted about his product. The 1963 the US Kefauver–Harris amendments introduced the obligation to prove safety and efficacy of new drugs by adequate clinical and other trials. The pharmaceutical industry (which then was still called chemical industry) protested, as did the American Medical Association, because this threatened to reduce

the position of medical experts in assessing the value of a given drug [28]. Since then, drug development has progressed, pharmaceutical industry has grown, and the medical system is more complex. Our society has become more complex, and many people who would have died of a banal bacterial infection or of child cancer in the past survive today.

It was the progress in medical care, the everyday availability of powerful drugs on one side and the image of pharmaceutical industry on the other side, and the desire of academic clinical pharmacologists, academic pediatricians, and regulatory authorities to let children participate "more" from pharmaceutical progress that culminated in the US pediatric legislation in 1997, and then in the EU pediatric legislation in 2006.

Today, companies have to submit a PIP at the end of phase 1 to the EMA [16], and pediatric study plans (PSP) to the FDA at the end of phase 2 [14]. The mandatory PIP requirement results in the EMA being the first regulatory agency with which pediatric development is discussed. EMA and FDA have some degree of collaboration on pediatric development, including a confidentiality agreement and monthly teleconferences. The early PIP requirement and the threat of blocking adult registration have put the EMA in the driver seat for pediatric negotiation. As outlined above, this does not mean that the EMA drives pediatric development.

Research-based pharmaceutical industry is focusing increasingly on rare diseases [17]. Many rare diseases begin in childhood. It is each company's economic decision to invest into a rare disease. Or into a subgroup of patients within a rare disease. Cystic fibrosis (CF) is caused by a defective cystic fibrosis transmembrane conductance regulator (CFTCR), which regulates fluid flow within cells and affects the components of sweat, digestive fluids, and mucus. In 4–5 % of CF patients the CFTCR defect is caused by the G551D mutation. Ivacaftor (Kalydeco) helps to restore the CFTCR function, resulting in a massive improvement of the patients' quality of life. The development of such new drugs is NOT a result of pediatric pharmaceutical legislation. In the US, drugs for orphan diseases are exempt from mandatory pediatric development. CF is such an orphan disease. In Europe, the first ivacaftor PIP was submitted in 2008. As of December 2013, the most recent PIP decision published on the EMA website is from December 2013, representing the outcome of the 8 ensuing RfM procedures [11]. Ivacaftor is registered since 2012 in both the US and EU in children above 6 years. Ivacaftor was developed by a pharmaceutical company in conjunction with the Cystic Fibrosis Foundation.

There is no doubt about the good intentions of the pediatric pharmaceutical legislation. History shows that good intentions are no guarantee for a good outcome. We have a somewhat balanced approach originating in the US, and a new enthusiastic and ambitious approach in the EU that gives the EMA an enormous power in enforcing pediatric consideration in drug development. The number of label changes, the number of submitted PIPs and the number studies triggered by agreed PIPs are in themselves no guarantee that these steps and changes will improve children's health.

Drug development without considering children is no longer possible. And we have now a first textbook on age-appropriate pediatric formulations.

References

1. Rose K, Della Pasqua O (2011) Development of paediatric medicines: concepts and principles. Handb Exp Pharmacol 205:111–124
2. Rodriguez W, Maldonado S (2010) United States paediatric legislation impact on paediatric drug studies. In: Rose K, van den Anker JN (eds) Guide to paediatric drug development & clinical research. Karger, Basel
3. Nakamura H, Ozaki M (2010) Facilitation of paediatric research in Japan. In: Rose K, van den Anker JN (eds) Guide to paediatric drug development & clinical research. Karger, Basel
4. Ramet J, Lehman B, Rose K (2010) Europe and the path to better medicines for children. In: Rose K, van den Anker JN (eds) Guide to paediatric drug development & clinical research. Karger, Basel
5. Wright EA, Rose K (2010) European Union paediatric regulation theory and practice. In: Rose K, van den Anker JN (eds) Guide to paediatric drug development & clinical research. Karger, Basel
6. Boklan J (2006) Little patients, losing patience: pediatric cancer drug. Mol Cancer Ther 5:1905–1908, http://mct.aacrjournals.org/content/5/8/1905.full.pdf
7. Magrath I, Steliarova-Foucher E, Epelman S et al (2013) Improving cancer care for children and young people 2—paediatric cancer in low-income and middle-income countries. Lancet Oncol 14(3):e104–e116, http://press.thelancet.com/childhoodcancer2.pdf
8. Pritchard-Jones K, Pieters R, Reaman GH et al (2013) Improving cancer care for children and young people 1—sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries. Lancet Oncol 14(3):e95–e103, http://press.thelancet.com/childhoodcancer1.pdf
9. Sullivan R, Kowalczyk JR, Agarwal B et al (2013) Improving cancer care for children and young people 4—new policies to address the global burden of childhood cancers. Lancet Oncol 14(3):e125–e135, http://press.thelancet.com/childhoodcancer4.pdf
10. Vassal G, Zwaan CM, Ashley D (2013) Improving cancer care for children and young people 3—new drugs for children and adolescents with cancer: the need for novel development pathways. Lancet Oncol 14(3):e117–e124, http://press.thelancet.com/childhoodcancer3.pdf
11. EMA 2012-1 (2012) 5-Year report to the European commission. General report on the experience acquired as a result of the application of the paediatric regulation. 8 July, EMA/428172/2012. http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf
12. Olski TM, Lampus SF, Gherarducci G, Saint-Raymond A (2011) Three years of paediatric regulation in the European union. Eur J Clin Pharmacol 67:245–252
13. Drews J (2000) Drug discovery: a historical perspective. Science 287:1960–1964
14. Tassiari M (2012) Pediatric regulations: permanent laws and new provisions under FDASIA. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM332078.pdf
15. EMA 2012-2 (2012) Medicines agency (EMA): policy on the determination of the condition(s) for a paediatric investigation plan/waiver (scope of the PIP/waiver). http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/09/WC500133065.pdf
16. Tomasi P (2012) Writing applications for paediatric investigation plans and waivers. Med Writ 21(2):1–4
17. Thorat C et al (2012) What the orphan drug act has done lately for children with rare diseases: a 10-year analysis. Pediatrics 129:516–521, http://pediatrics.aappublications.org/content/129/3/516.long
18. Bodenheimer T (2000) Uneasy alliance. Clinical investigators and the pharmaceutical industry. NEJM 342(20):1539–1544
19. DiMasi JA, Hansen RW, Grabowski HG (2003) The price of innovation: new estimates of drug development costs. J Health Econ 22:151–185

20. Rose K (2008) Ethical, regulatory and scientific challenges in paediatric drug development. Pharm Med 22(4):221–234
21. Adamson P (2013) Developing drugs for pediatric malignancies. Clinical Advances in Hematology & Oncology 11(4):227–229
22. FDA (2001) The pediatric exclusivity provision - January 2001. Status Report to Congress. http://www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm049915.pdf. Accessed 17 Dec 2013
23. Rose K (2012) A paediatric investigation plan case study. Pharm Med 26(5):287–295
24. Heinemann L (2008) Are all clinical studies sponsored by industry not valid? J Diabetes Sci Technol 2(6):1161–1163
25. Brezis M (2008) Big pharma and health care: unsolvable conflict of interests between private enterprise and public health. Isr J Psychiatry Relat Sci 45(2):83–94
26. Hilts PJ (2003) Protecting America's Heath. In Alfred A. Knopf, New York, ISBN 0-375-40466-X
27. EMA PIP deicision EMEA-000335-PIP01-08-M08 of 30 October 2013. http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500154705.pdf. Accessed 16 Dec 2013

Chapter 29
Checks and Balances in the EU: The Role of the European Ombudsman, with a Focus on the Paediatric Regulation

Rosita Agnew

Abstract The European Ombudsman is an independent and impartial body that holds the EU administration to account. The Ombudsman deals with complaints lodged against the European Medicines Agency, most of which concern lack of transparency. In dealing with these complaints, the Ombudsman has underlined the importance of ensuring that European citizens trust the Agency and have confidence in the important work it carries out on their behalf.

During the course of 2012, the European Ombudsman issued a draft recommendation to the Agency in relation to the latter's application of the EU's Paediatric Regulation. Specifically, the case concerned the Agency's procedures for deciding whether pharmaceutical companies should be obliged to carry out studies to investigate whether a pharmaceutical product could be used to treat children. The case is a useful illustration of the Ombudsman's essential role in holding the European Medicines Agency to account. More generally, it helps demonstrate that the Union has inbuilt checks and balances that seek to ensure that its institutions act legally, in full respect of fundamental rights, and in accordance with principles of good administration.

29.1 Introduction

The European Ombudsman is an independent and impartial body that holds the EU administration to account. The Maastricht Treaty established the office of European Ombudsman as part of the citizenship of the European Union. Article 20 of the

The points made, and any possible errors, in this chapter are solely attributable to the author. The views expressed are not necessarily supported by the Ombudsman.

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Treaty on the Functioning of the European Union (TFEU) provides for the right to complain to the European Ombudsman as one of the rights of citizenship of the Union. The Charter of Fundamental Rights of the EU (Article 43) also includes this right. Possible instances of maladministration come to the Ombudsman's attention mainly through complaints, although he also conducts inquiries on his own initiative.

Article 228 TFEU, which governs the Ombudsman's work, empowers him to receive complaints concerning instances of maladministration in the activities of Union institutions, bodies, offices, and agencies, with the exception of the Court of Justice of the European Union acting in its judicial role. In response to a call from the European Parliament for a clear definition of maladministration, the Ombudsman offered the following, which the Parliament welcomed in a resolution: "Maladministration occurs when a public body fails to act in accordance with a rule or principle which is binding upon it."

The European Ombudsman has always taken the view that to avoid maladministration an institution needs to respect (1) legal rules and principles, (2) principles of good administration, and (3) human or fundamental rights. At the time this formulation was developed, the Charter of Fundamental Rights of the European Union was not legally binding. Now that it is legally binding, there is a higher degree of overlap between the three categories, but there also continue to be important differences between them, especially in situations where the law leaves an institution a degree of choice as to how to act.

29.2 The Remedy of the European Ombudsman Compared to Actions Before the Courts

The basic function of an ombudsman is to investigate and report on complaints. Unlike courts, most ombudsmen have no power to make legally binding decisions. Where the rule of law and democracy are strong, public authorities have an incentive voluntarily to accept an ombudsman's findings and recommendations. That incentive is public opinion, which recognises the ombudsman as an independent and impartial figure, whose authority should not be flouted even if there is no illegality involved in doing so.

The non-binding nature of decisions is, paradoxically, a strength rather than a weakness, as it allows an ombudsman to be more accessible and to have more flexible procedures than a court. The European Ombudsman can sometimes provide an avenue of redress in cases where no effective judicial remedy would be available against an EU institution. In terms of accessibility, any citizen of the Union or any natural or legal person residing or having its registered office in a Member State may lodge a complaint with the Ombudsman. The time limit to complain is *2 years* from the date on which the complainant had knowledge of the facts. Moreover, it is not necessary for the complainant to be individually affected by the maladministration, or even to be affected at all, because the Ombudsman can also deal with *actio popularis* complaints. It is also possible to have recourse to the Ombudsman in

order to challenge acts or omissions that do not have any effects on the legal situation of the persons concerned. That is not possible in judicial proceedings before the EU Courts for annulment, or for failure to act. Complaints to the Ombudsman can therefore be made in many situations where an action before the Court would fail on technical grounds. Finally, the Ombudsman's investigations involve more than questions of strict legality. For the courts, this is the sole criterion of assessment of the institutions' actions. As mentioned above, the competence *ratione materiae* of the European Ombudsman is the broader concept of maladministration.

29.3 Complaints Concerning the European Medicines Agency

The European Medicines Agency (hereinafter "the Agency") plays an important role in the approval and the monitoring of medicines placed on the market in the EU. Its work has a direct impact on the health of European citizens. It is vitally important, therefore, that citizens should trust EMA and have confidence in its work.

The Ombudsman deals with complaints lodged against the Agency, most of which concern lack of transparency. By way of example, the Ombudsman received a complaint from a citizen who had asked the Agency for access to documents containing details of all suspected serious adverse reactions relating to an anti-acne medicine. The Agency refused to grant the request, arguing that Regulation 1049/2001 on public access to documents[1] did not apply to reports concerning suspected serious adverse reactions to medicines. After investigating the complaint, the Ombudsman concluded that the EU rules on access to documents indeed apply to all documents held by the Agency.[2] He recommended that the Agency review its refusal to grant access to the adverse reaction reports. The Ombudsman also recommended that, as part of its information policy, the Agency could provide additional clarifications to make it easier for people to understand such data and their significance. The Agency accepted the Ombudsman's recommendation by announcing the release of the reports.

In dealing with this, and other, complaints, the Ombudsman has underlined the importance of ensuring that European citizens trust the Agency and have confidence in the important work it carries out on their behalf. The Agency's work has a direct impact on the health of European citizens. It is, therefore, crucial that the Agency give the widest possible access to documents and pursue a proactive information

[1] Regulation (EC) No. 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents, OJ 2001 L 145 p. 43.

[2] See Article 73 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ 2004 L 136, p. 1.

policy for the benefit of citizens. The Agency has demonstrated its commitment to a proactive approach, notably by publishing a new access to documents policy aimed at giving the public much broader access to documents in its possession.[3] The Ombudsman applauded the Agency's constructive approach to improving its transparency policy. By taking this important policy step, the Agency gave wider effect to recommendations the Ombudsman made in connection with two important cases concerning access to documents.[4]

29.4 Complaint in Relation to the Paediatric Regulation

During the course of 2012, the European Ombudsman issued a draft recommendation to the Agency in relation to the latter's application of the Paediatric Regulation.[5] Specifically, the case concerned the Agency's procedures for deciding whether pharmaceutical companies should be obliged to carry out studies to investigate whether a pharmaceutical product could be used to treat children.

The inquiry that gave rise to the draft recommendation was based on a complaint from two pharmaceutical companies. The case arose against the following backdrop:

In 2006, the EU adopted a Paediatric Regulation better to protect the health of children in Europe. By that date, more than 50 % of the medicinal products administered to children had not been authorised for use in children and had not been subjected to appropriate trials. Among the problems associated with this statistic are increased risks of adverse reactions to medicinal products, including death, and ineffective treatment through under-dosage.

The Paediatric Regulation aims to improve the availability of medicinal products tested for paediatric use by obliging pharmaceutical companies to carry out studies in accordance with an agreed paediatric investigation plan (hereinafter, a "PIP"). At the same time, the Regulation also seeks to avoid unnecessary trials in children. To ensure that research is only conducted to meet the therapeutic needs of the paediatric population, the Paediatric Regulation provides for the Agency to waive the obligation to carry out studies in children in certain cases.

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[3] European Medicines Agency policy on access to documents concerning medicines for human and veterinary use (ref EMA/110196/2006), adopted on 30 November 2010, effective as from 1 December 2010.

[4] See in particular the Ombudsman's decisions in case 2560/2007/BEH, available at: http://www.ombudsman.europa.eu/en/cases/decision.faces/en/5459/html.bookmark and in case 2493/2008/FOR, available at: http://www.ombudsman.europa.eu/en/cases/decision.faces/en/11360/html.bookmark. This latter case is the example provided above.

[5] Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004, OJ 2006 L 378, p. 1.

The complaint that gave rise to the draft recommendation was submitted by two pharmaceutical companies. They argued that the Agency was wrong to reject their application for a waiver with respect to the requirement to carry out studies on the use of their drug (candesartan) in the treatment of heart failure in children. Invoking the fact that the Agency granted a waiver to the two other products in the same product class (losartan and valsartan, which are, like candesartan, angiotensin II type 1 receptor blockers or "ARBs"), the complainants alleged that the refusal to grant them a waiver infringed the principle of equal treatment, was not based on an objective and fair assessment, and was not reasoned.

The Ombudsman's examination of this case led him to conclude that the Agency's decision to deny a waiver to candesartan was one that it was entitled to reach in substance. After a careful review of the non-public versions of the losartan, valsartan, and candesartan decisions, the Ombudsman was able to verify that the Agency's Paediatric Committee considered: (1) that the size of the relevant paediatric population justified testing only one of the two products which could be the subject of a PIP for the indication heart failure (namely, valsartan and candesartan) and (2) that, of the two, candesartan was the more appropriate candidate product.

However, the Ombudsman considered that the Agency (1) failed to ensure adequate transparency of the process through which it reached its decisions and as a result (2) failed to provide adequate reasons for those decisions.

The Ombudsman's view was that systemic changes are needed to avoid similar maladministration in the future. He, therefore, made a draft recommendation as follows[6]:

> The Agency should, in future, document fully its assessment of all waiver applications, with a view to ensuring consistent and complete reasoning in its decisions.
>
> The Agency should commit to drafting guidelines aimed at assisting its Paediatric Committee to follow a coherent structure of analysis in future cases.
>
> The Agency should provide the complainants with an adequate statement of reasons concerning the decision not to grant a waiver to candesartan. Such a statement would confirm to the complainants that its Paediatric Committee carried out a comparative assessment in the context of its examination of the valsartan waiver application, which was consistent with the comparative assessment it carried out in the context of its examination of the candesartan waiver application.
>
> The Agency should, (a) in accordance with its existing commitments regarding a proactive transparency policy, (b) with a view to assisting interested parties fully to understand its decisions, and (c) taking due account of the need to protect legitimate public and private interests, disclose decisions and their annexes resulting from the application of the Paediatric Regulation, including those related to the losartan, valsartan, and candesartan waiver applications.

In making this draft recommendation, the Ombudsman underlined that it is vital, for paediatric patients, parents, and practitioners, that the European Medicines Agency always correctly apply the Paediatric Regulation. More generally, given the major societal implications of the Agency's work, it is vital that its stakeholders and

[6] The draft recommendation is available at: http://www.ombudsman.europa.eu/en/cases/draftrecommendation.faces/en/11553/html.bookmark.

European citizens trust the Agency and have confidence in its work. The Ombudsman, therefore, expressed his hope that the Agency would respond positively to his draft recommendation.

In its detailed opinion on the draft recommendation sent to the Ombudsman on 28 September 2012, the Agency outlined the measures it had taken, or planned to take, to increase transparency in paediatric medicines procedure. These include (1) publication of the complete opinion of the Paediatric Committee; (2) publication of the justification for accepting or refusing PIP, waiver, and deferral applications; and (3) guidance for the Paediatric Committee on the justification for accepting or refusing PIP, waiver, and deferral applications. In their observations on this opinion, the complainants agreed that the "proposed new EMA initiatives will pave the way for greater transparency in the decision-making process". The Ombudsman's decision in this case will be issued in the course of 2013.

29.5 Conclusion

This case is a useful illustration of the Ombudsman's essential role in holding the European Medicines Agency to account. More generally, it helps demonstrate that the Union has inbuilt checks and balances that seek to ensure that its institutions act legally, in full respect of fundamental rights, and in accordance with principles of good administration.

Any citizen or resident of the EU, or business, association, or other body with a registered office in the EU, can lodge a complaint with the Ombudsman in any of the 23 official EU languages. A complaint can be made by writing a letter to the Ombudsman or by using the electronic complaint form that is available on the Ombudsman's website: http://www.ombudsman.europa.eu.

Part VII
Concluding Remarks: The Future of Pediatric Formulations

Chapter 30
The Dangerous Business of Predicting the Future

Daniel Bar-Shalom, Hannah Batchelor, Linda F. McElhiney, and Klaus Rose

Abstract Pharmaceuticals do not fall from the sky. Before they are available, they must be developed. This historical framework has three aspects—the past without which we cannot understand the present, and the present which we have tried to make more understandable in all this book's chapters. And the future? Our crystal ball is a bit opaque. We can extrapolate some of today's technical developments into the near future, such as the technique of microencapsulation. Other dimensions are more difficult to predict, such as the future of US and EU pediatric legislation, which role patient advocacy groups will play in 10 or 20 years, towards which priorities the public opinion will swing during the next decades, and how politicians will channel it. And then there are the truly unknown unknowns, those surprises in science, social environment and any other aspect of life that most of us did not and do not expect (apart from the true prophets, which we are not).

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30.1 Predicting the Future is a Dangerous Business

On a purely technical level, it is relatively safe to predict which innovations will be relevant for the development of oral pediatric formulations in the near future. Microencapsulation seems to be one path where a lot of research will be invested in the near future, seeing the promising results of research performed so far.

Another question is the challenges and opportunities of automatic compounding. To integrate automatic, personalized compounding into the drug development process might result in no longer registering, e.g., tablets or prepacked liquid formulations. It would allow medication to be compounded in a personalized way in the hospital and maybe even in specialized community pharmacies and then given to the individual patient. This would require a rather radical re-thinking about the relationship of drugs during clinical trials and in later medical use, both on the side of regulatory authorities and developing companies.

On a political level, a review of the EU regulation is scheduled for 2018. In 2013 there is still broad support for the EU pediatric legislation and the pediatric committee (PDCO) of the European Medicines Agency (EMA) by most health care professionals; however, first critical voices have been published [1, 2]. And more countries and/or regions might introduce additional legislation.

We do not know how the world economy will evolve over the next decades, how much private money will be invested into drug development, and to what degree the present, relatively small, public funding for drug development in children will stay, shrink, or grow.

The recipients of pediatric medicines are also changing. Preterm newborns that survive today with or without long lasting health problems did not survive half a century ago. The extent to which neonatology might further evolve is also unknown. Will neonatals become a separate field, distinct from pediatrics?

How will the innovation landscape evolve? Will start-up companies replace the rather ineffective discovery and development machineries of the large pharmaceutical companies? Will the entrepreneurial spirit become stronger among younger academic researchers? As things look right now, public funding might become less, but who predicts the future with precision?

To what degree will innovative and breakthrough medicines be facilitated and reimbursed, even if they are expensive? When drugs for rare diseases were rare, the money for a few patients with very high daily treatment costs could usually be found somewhere. Now we have a growing pipeline of orphan drugs. Which priorities will be decided in the USA, Europe, and in emerging countries?

Will the principle of a standard dose remain as the routine way of registration, or will individualized and/or personalized doses become part of the registration process?

To what degree will medicines be paired with diagnostic kits towards a personalized and individualized treatment?

Which role will smartphones and similar devices play in pediatric drug treatment in the next years and decades? Will companies continue to print patient information, even if nobody reads anymore these prints?

Which new pediatric excipients will be developed? Which food ingredients will be used as pharmaceutical, pediatric excipients? Will novel taste masking/taste concealing/taste suppressant strategies emerge?

Which role will further development of in vitro and in vivo tools to speed up general drug development play in the development of medicines for children?

Which routes of administration will be regarded are underexploited or overexploited in a few years?

Specifically in serious conditions, polypharmacy will play an even stronger role. How will pharmaceutical and medical training keep pace with this?

With the recent compounding tragedies that have happened in the USA [1–3], there is more attention about standardizing and regulating compounding. Private organizations such as the United States Pharmacopeia are evaluating their compendial standards for compounding to possibly provide global standards for compounding so that the same compound may be prepared in the same manner, whether it is in Europe, Asia, or the Americas. It is very possible that compounding organizations may unite all over the world to develop global standards for compounding in order to provide high quality care to patients. The need for compounding will always exist as long as there are children or adults who need specialized dosage forms that are not commercially available. The key issue will always be how do pharmacists develop and prepare these dosage forms to provide high quality care for the patients.

We have listed those unknowns that we are aware of. There might evolve other issues that today are not known or regarded as secondary. But we do not know them today.

We hope you enjoyed the book.

References

1. CDC (2012) Multistate fungal meningitis outbreak investigation. http://www.cdc.gov/HAI/outbreaks/meningitis.html and http://www.cdc.gov/hai/outbreaks/currentsituation/
2. ISMP (2012) Sterile compounding tragedy is a symptom of a broken system on many levels. ISMP Newsletters October 2012. http://www.ismp.org/newsletters/acutecare/showarticle.asp?id=34
3. Kastango ES (2013) Lessons learned from compounding tragedies. Can J Hosp Pharm 66(3):152–153. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3694934/

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