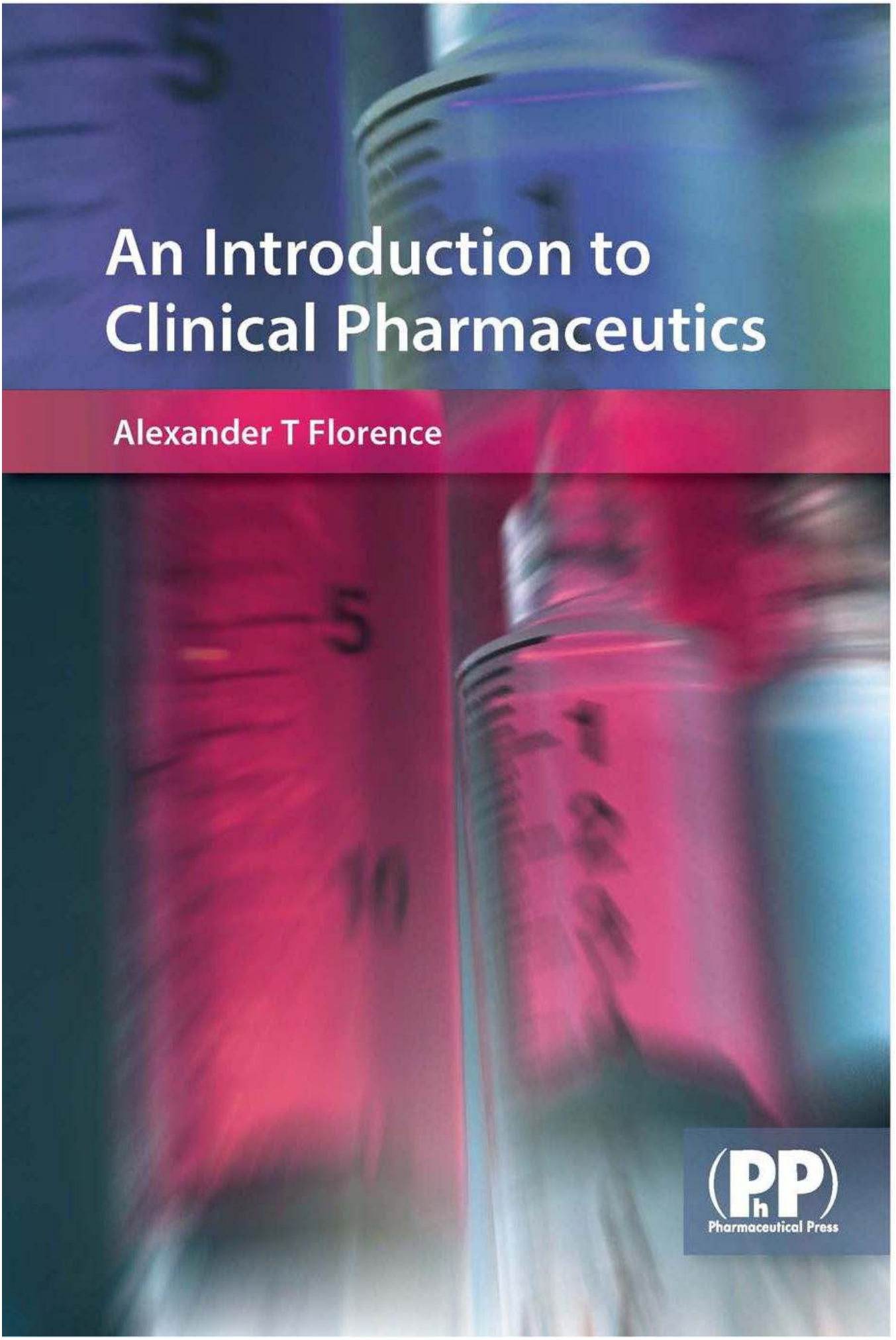
An Introduction to Clinical Pharmaceutics
Alexander T Florence
Pharmaceutical Press

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Preface

This book has had a long period of gestation. I made a proposal for a book such as this in 1982 to Robert Campbell of Blackwell Scientific Publications Ltd. He encouraged me to write it, provided it was 'reasonably short and inexpensive.' Over the intervening years in collaboration with David Attwood, four editions of *Physicochemical Principles of Pharmacy* appeared, the latest in 2006 and the concise version, *FASTtrack: Physical Pharmacy*, in 2008. We also co-wrote *Surfactant Systems* published in 1983. These and other activities took over and the present book obviously did not materialise. But it has always remained an ambition to complete it, especially as the pharmacy scene has been changing and some subjects are now under pressure of one kind and another, in spite of the four-year degree programme. A few subjects such as pharmaceutics and pharmaceutical chemistry appear to not a few students to be too far away from real practice. Well it depends on how we define practice and what practice will look like in the future.

The main premise of the book is that the subject matter of pharmaceutics is relevant far beyond the confines of the laboratory and pharmaceutical industry. Undergraduate and postgraduate lectures that I have given over the years incorporated many of the concepts espoused in this book. It was not until retirement from the Deanship of the School of Pharmacy, University of London in 2006 that there was some more time to write this book. It is not meant to be a compendium, nor is it for advanced practitioners, but more a primer that I hope will encourage readers to think about the principles of applying basic scientific facts to solving problems in medication. If it provides a single insight to any student or practitioner that enables the solution of one medication conundrum, it will have been worth it. A warning: it is not written in that linear style that has been the bane of many subjects, as it takes too long from the very first principle to get to the application or the problem. The basics are covered in AT Florence and D Attwood, *Pharmaceutical Principles of Pharmacy*, 4th edition, 2006 or D Attwood and AT Florence, *Physical Pharmacy* 2007, both published by the Pharmaceutical Press.

I thank Louise McIndoe and Charles Fry of Pharmaceutical Press for their encouragement and patience, and my wife Florence for her critiques and support.

Alexander T. Florence
Edzell Angus, UK and Nice, France
2009

Introduction

This book is designed to be an introductory text to aid the understanding of the role of basic pharmaceutics in determining or modifying clinical outcomes. Pharmaceutics is often considered by pharmacy students at least early in their academic career to be relevant only to the design and production of dosage forms. This is one of the keystones of pharmacy, of course. While it goes without saying that dosage forms are vital for the delivery of medication to the body, they are not always inactive vectors. Not only that, not all dosage forms are produced in industry, so there are clinical needs for special formulations, for example those for neonates, that call pharmaceutics knowledge to the fore. However, this is neither a formulation textbook nor a pharmaceutics textbook. What it attempts to do is to connect the concepts that are part of most pharmaceutics curricula, not only issues of formulation but also the underlying phenomena such as surface tension, rheology, solubility, crystallisation, aggregation and adsorption among others, to a wider clinical and practice base. At the same time we discuss here the ways in which formulations, dosage forms and devices as well as excipients can influence the outcome of therapy, not least their infrequent but important ability sometimes to cause adverse events.

Cases and examples from the literature are important learning aids in the book. The cases discussed are not necessarily new: there is much to learn from the lessons and mistakes of the past. The skill of the professional is not to know everything but to recognise when and where to access information and to apply it to new practice situations.

The book is aimed at undergraduate pharmacy students, those on taught Masters courses of clinical and hospital pharmacy, and new practitioners who require an updating on the relevance of the phenomena that are virtually unique to pharmacy. Examples and implications of each phenomenon are discussed with a brief reminder of the underlying pharmaceutics.

A pharmacist's deep knowledge of medicines as physical products helps the patient, the physician and the nurse tackle the increasingly complex world that is medicine today. The Princess Royal, on a visit to the School of Pharmacy as Chancellor of the University of London, when one clinical tutor

suggested that we aimed to convert scientists into practitioners said perceptively 'surely it should be the other way round!' It is important for a profession such as pharmacy to have sets of knowledge different from those of other health care professionals. It must also generate its own body of knowledge if it is to remain relevant.

For one reason or another, there has developed a disjunction between the scientific basis of pharmacy, or what were the traditional divisions of the pharmaceutical sciences, and practice. Industrial pharmacy has been the most direct beneficiary of the traditional sciences taught in the traditional manner. Yet only a minority, albeit a vital minority, of graduates practise in industry, and not all do so in formulation research and development. Few schools of pharmacy now have traditional subject divisions. Nevertheless it is sometimes considered, even by those expert in pharmacy education and some students too, that subjects such as pharmaceutical chemistry and pharmaceutical technology have little place in the day-to-day practice of pharmacy. The emphasis on the patient has sometimes obscured the emphasis on the product. Clinical pharmacy as a discipline may major on therapeutics, but we must offer more, else no one will claim more than passing knowledge of the products that are central to pharmacy. Our input must be founded on the basics honed and challenged in the clinical environment of primary and secondary care. The more pharmacists know about the products they handle, the more patients will benefit: if applied to its full there emerges a discipline of clinical pharmaceutics, whence the title of this book, the application of the unique knowledge base in the subject to patients and to clinical situations. Biopharmaceutics has been a surrogate for this practical application. It is of course vital. What we try to tease out here are topics that fall between subject divisions. If we do not retain these skills and apply them more obviously – applying our knowledge of the both the nature of the materials used in formulation and their biological effects or influence – patients lose out.

This small book, then, attempts to place some of the basics of pharmaceutics into the context of clinical practice in its broadest sense: the application of pharmaceutics and some pharmaceutical chemistry to patient care. One must not repeat the mistake of working in subject silos. The administration of a medicine to a patient is the direct application of pharmaceutics, but the issue goes much deeper. We cannot utilise and apply only the knowledge that the physician or the nurse has and act only as watchdogs. Clinical pharmaceutics is not promoted here simply to maintain its academic input, but because it is centrally important, as I hope the examples in the book will demonstrate. It is easy to jettison skills that exist now because of their temporary or apparent disuse: the future of medicine is changing so rapidly that many skills will be required to successfully handle the complexities of modern therapies, not least in some specialist environments, even in the extemporaneous preparation of specialised dosage forms. Possibly the best way to

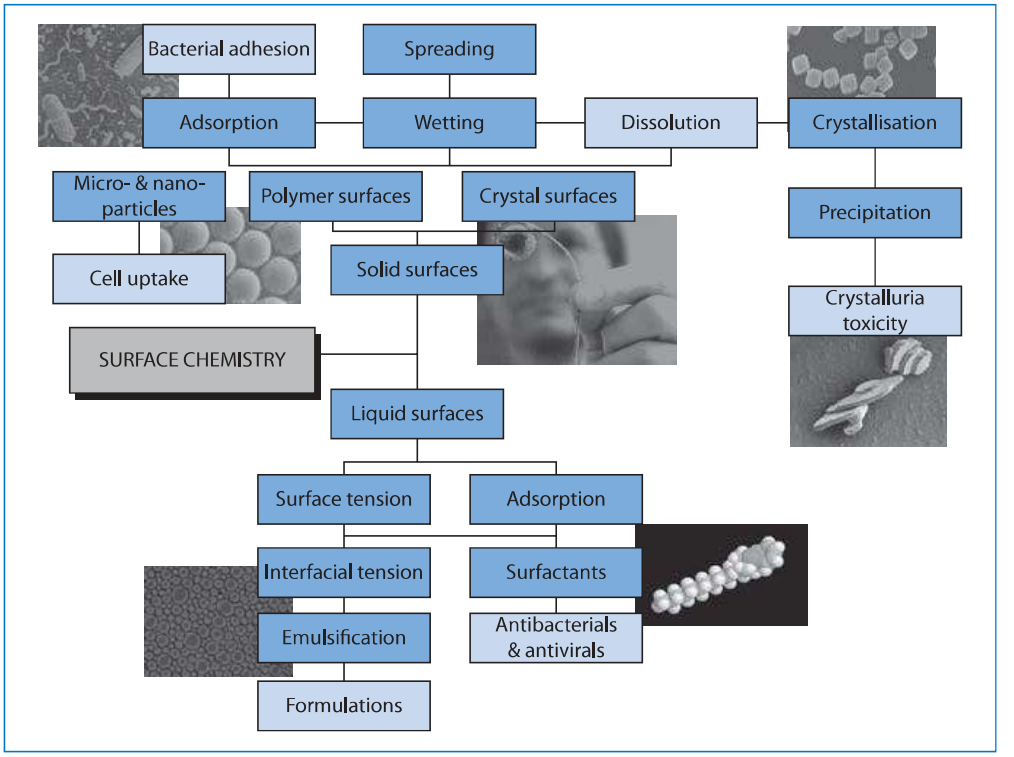


Figure I.1 The ubiquitous importance of one of the basic subjects – surface chemistry – taught in pharmaceutics and physical pharmacy. The areas involved include formulations, cell uptake, antibacterials and antivirals, bacterial adhesion, dissolution and precipitation *in vivo*. Some of these connections are explored in Chapter 1.

illustrate just some of the connections between pharmaceutics and 'real life' is given in the Figure I.1. It refers only to surface chemistry, but we could construct other such diagrams for the other basic areas too.

It is not easy to prepare for a future that is largely unknown. To learn from the experience of the past is beneficial. Whether the approach used in this book is successful remains to be seen. I would be happy to hear from readers of errors in interpretation and new and better examples to illustrate the themes.

Alexander T. Florence
Edzell Angus, UK and Nice, France
2009

Book outline

The first chapter addresses the question 'what is clinical pharmaceutics' using as many examples as possible. Chapter 2 follows with a discussion of excipients, not infrequently inadvertently bioactive substances. Chapter 3 reasserts the view that chemistry is important in the discipline, while Chapter 4 is entitled 'Looking at formulations'. This encourages us to view products in the round, as dose forms to aid in the delivery of reproducible doses but also as agents for irreproducibility on odd occasions and causes of adverse events in a minority. Chapter 5 considers adverse events caused by the dosage form or by excipients, or by the nature of the formulation and the way in which it can influence outcomes. Chapter 6 addresses some issues of medicines for the young and for the old.

Generic medicines are rightly used widely in practice after the expiry of patents on innovator products, although to varying degrees in Europe. Chapter 7 points out the differences in the evaluation of generic medicines when the drug substance is a small molecule and when it is a large biological agent. The latter are forming a larger percentage of the therapeutic arena. Here, for example, we explore the concept of biosimilarity rather than identicality.

Chapter 8 speculates about the future form of medicines and raises the question of the role of pharmaceutics in personalised medicines.

About the author

Alexander T. Florence is Emeritus Professor at The School of Pharmacy, University of London from which he retired as Dean in 2006. Previously he was JP Todd professor of Pharmacy at the University of Strathclyde. His research interests have been in physical pharmacy, pharmaceutics, surfactants and pharmaceutical nanotechnology. He continues to lecture and to write on these subjects and for a long time has sought to better integrate the basic, applied and clinical sciences in pharmacy. He is the co-author with David Attwood of *Physicochemical Principles of Pharmacy* (4th edition 2006) and *FASTtrack: Physical Pharmacy* (1st edition 2008) both published by the Pharmaceutical Press.

1

What is clinical pharmaceutics?

This chapter promotes the view that the fundamentals of pharmaceutics have a wider significance than is sometimes recognised. These fundamentals include among other things concepts of surface tension, adsorption, rheology, crystallisation and solubility. The chapter also underlines that fact that the chemical composition, physical nature and properties of dosage forms have an influence not only on bioavailability but on the quality of action of many drugs. Adverse reactions to medicines, which are a serious problem, are most often and rightly attributed to the drug substance, but they can also be caused or influenced by excipients, including dyes, flavouring agents, stabilisers, electrolytes or solvents. Even the physical form of the dose may be a factor in adverse events, as in the case of non-disintegrating slow-release tablets, which can become trapped in diverticula in the gut, or injections that precipitate on administration. Most of the topics in this introductory chapter, aimed at introducing the field in a general way, will be discussed in more detail later in the book.

Introduction

It is essential that pharmacists know more about the nature of medicines than the public and patients or indeed other health care professionals. It is clear to most practitioners that pharmacology and therapeutics are vital to practice; nonetheless, there has been a tendency to think of pharmaceutics as a subject that is necessary in the undergraduate curriculum but that has little significance to those graduates who will not work in industry or who are not involved in manufacturing in hospitals. It is not claimed here that pharmaceutics is more important than other subjects, but there are at least three aspects of pharmaceutics that should be relevant to practice, perhaps in an unexpected order:

- First, how concepts such as surface tension, crystallinity, precipitation, viscosity, adsorption and solubility are relevant in a range of clinical situations.

- Second, an understanding of the nature of the dosage form and its properties and how these can influence outcomes or modulate or even cause adverse events.
- Third, knowing intimately the nature and properties of the ingredients other than the active substance.

These examples are often important in idiosyncratic reactions to medicines, and more generally in the behaviour of many drugs *in vivo*.

Physical concepts

The last two points listed above are possibly more obvious than the first, so we begin with the topics outlined in the first point to demonstrate some instances where knowledge of these physical parameters can provide insight into medication outcomes and biological behaviour. The phenomenon of crystallisation is a good example.

Crystallisation

Figure 1.1 summarises some of the situations in which the solid state is important. Highlighted are crystalluria, gout, the precipitation of drugs before or after injection, inhalation therapy and understanding the potential toxic effects of particulates.

A case of crystalluria reported recently[1] illustrates one of the propositions put forward in this book. The case concerned a 60-year-old man infected with HIV whose medications included efavirenz, emtricitabine,

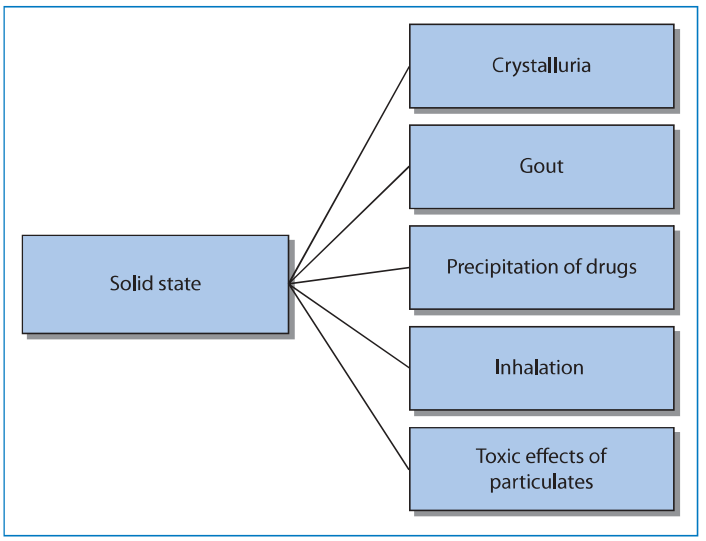


Figure 1.1 Schematic of situations in which the solid state is important.

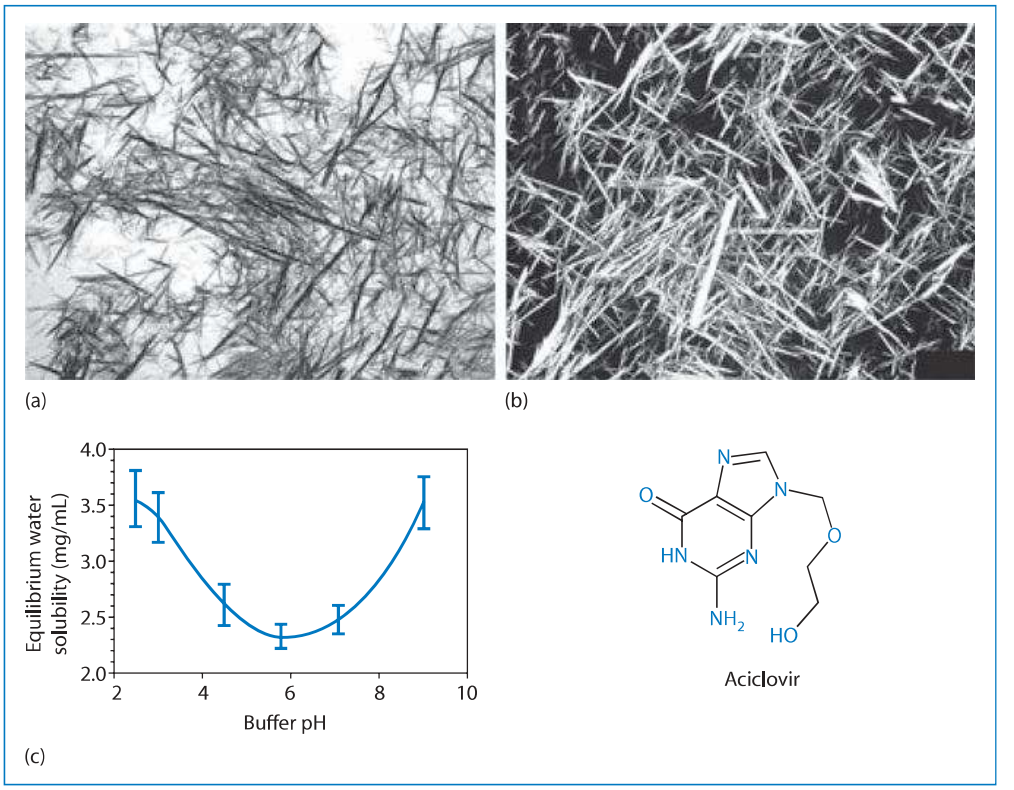


Figure 1.2 (a, b) Photomicrographs of aciclovir crystals harvested from the urine of the patient in question (a) and a pure sample (b). (From reference 1.) (c) The solubility–pH relationship for aciclovir is shown along with its chemical structure. (From reference 2.)

tenofovir and pravastatin sodium: a heady cocktail. Two hours after he had received aciclovir, his urine became cloudy and white in the proximal part of a Foley catheter. Microscopic analysis showed birefringent needle-like crystals 'consistent with the precipitation of acyclovir [aciclovir]' as shown in Figure 1.2. Additional treatment with intravenous aciclovir did not result in urinary crystallisation of the drug. Aciclovir (pK_a values: 2.27 and 9.25) has a solubility in water at 25°C of >100 mg/mL. At physiological pH, aciclovir sodium is un-ionised and has a minimum solubility in water (at 37°C) of 2.5 mg/mL (Figure 1.2b).[2] The concentration of aciclovir in human urine after *oral* administration of 200 mg reaches 7.5 µg/mL,[3] clearly not exceeding its aqueous solubility. As urine is concentrated as it passes along nephrons, urine drug concentrations increase. Determination of saturation solubilities of drugs in urine is more predictive of problems.

While crystallisation of drugs *in vivo* will be discussed later, this case illustrates that a knowledge of the solution properties of drugs and the pH at which drugs might precipitate or become saturated in body fluids and compartments is essential if we are to make contributions to patient care

using our unique knowledge. Knowledge of the solution properties of drugs is of course applied directly in the formulation and delivery of intravenous mixtures of drugs or when drugs are added to infusion fluids.

Some time ago an editorial in the *Lancet*[4] discussed the topic of crystals in joints. It pointed out that it is not only in gout that crystals (of monosodium urate monohydrate, or of calcium pyrophosphate in pseudogout) appear but that calcium hydroxyapatite deposits cause apatite deposition disease. The discussion indicated that synovial fluid may contain pieces of cartilage, strands of fibrin, cholesterol crystals and, in some patients, steroid crystals remaining after intra-articular injection. Biological systems are of course complex. Urine and blood are more complex than water, so simple theories of solution properties cannot be applied directly, especially when we introduce formulations into already multicomponent environments. Nevertheless, theory and equations give clues as to what might be happening *in vivo*. Without them we only guess.

Rheology

Rheology, which deals with the flow properties or the viscosity of liquids and semi-solids, has many implications in the function and role of natural substances, such as mucus and synovial fluids. Figure 1.3 lists some of these connections.

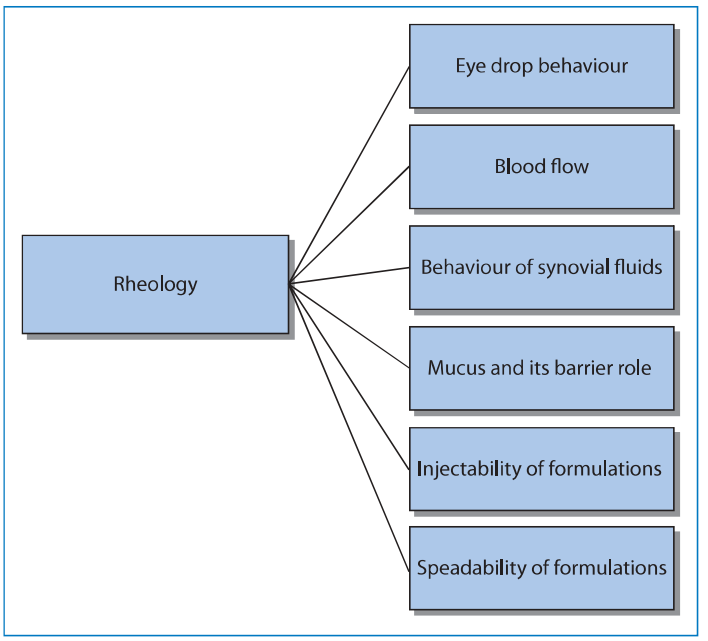


Figure 1.3 Areas in which rheology is important: the spreading and elimination of eye drops; blood flow; synovial fluid performance; mucus as a viscous protectant in the gastrointestinal tract; the injectability of formulations; and the 'spreadability' of formulations, say, on the skin.

The rheology of liquid medications can be important in determining their ease of handling. The viscosities of oily vehicles as depots for long-acting neuroleptics and steroids range from 3.9 cP to 283 cP and can determine their dispersion in muscle. Viscous liquids are retained at sites of administration.

The rheology of creams and ointments can affect patient acceptance and, of course, spreadability: very viscous systems may spread unevenly. The viscosity of ophthalmic preparations has clear implications for comfort and spreading. If the viscosity is too high then the spreading of the drops on the corneal surface is impaired; patients might experience discomfort as eyelids may adhere to the corneal surface.

Viscous solutions of sodium hyaluronate have been used to enhance the nasal absorption of vasopressin.[5] Solutions of hyaluronic acid (HA) with molecular weights greater than 3×10^5 Da have been found to be effective, while HA with a molecular weight of 5.5×10^4 Da was not as effective. The viscosity of hyaluronate solutions and many other materials can be selected according to the mean molecular weight. Viscosity increases with increasing molecular weight, larger macromolecule fractions having higher viscosities. Macromolecule concentration and added salt concentrations also affect the flow of these systems, the latter through changing the net surface charge on the molecules. Increasing concentrations of polymer increase viscosity. Increasing electrolyte concentrations can increase or decrease viscosity depending on whether the polymer is charged or not. There are biological implications of macromolecular viscosity as discussed below.

Synovial fluid acts as a lubricant between adjacent joints. The properties of synovial fluid that contribute to this biological function include its viscoelasticity (see Box 1.1). In osteoarthritis, hyaluronan in the form of sodium hyaluronate, with a molecular weight of some 10^6 Da, is injected into the synovial joint space. The product supplements the natural lubricant fluids. The molecule is highly folded in the absence of shear, but with increasing shear the molecule unfolds and has the characteristics of a pseudoplastic material (see Box 1.1). Products such as Fermathron comprise a clear solution of 1% hyaluronate in phosphate-buffered saline.

Intra-articular hyaluronic acid

Synovial fluid is rheopexic, which, as stated in Box 1.1, means that stress increases with time in steady shear. This is thought to be due to protein aggregation with time and the influence of stress. It is suggested that there is a connection between the observed rheopexy and the remarkable lubrication properties of synovial fluid;[6] one can envisage that the fluid that exists between two bony surfaces becomes more effective in 'cushioning' the contacts as its viscosity increases with the forces placed on it.

Products such as Hyalgan, Artzal, Synvisc, Suplasyn, Hyalart and Orthovisc have been developed for administration into the synovial space

Box 1.1 Rheological terms and descriptors

- **Newtonian** and **non-Newtonian** liquids:
  Viscosity η = shear stress (τ)/rate of shear (γ).
  Shear-thinning systems are termed **pseudoplastic** while shear-thickening systems are known as **dilatant**.
- **Thixotropic** systems show a decrease in apparent viscosity when stirred at a constant rate over a period of time. In **rheopexic** systems viscosity builds up with time on stirring at a constant shear.
- **Viscoelasticity** is the property of materials that exhibit both *viscous* and *elastic* characteristics when undergoing *deformation*. Viscous materials, like honey, resist *shear flow* and *strain* linearly with time when a stress is applied. Elastic materials strain instantaneously when stretched and quickly return to their original state once the stress is removed. Viscoelastic materials have elements of both these properties.

of joints to enhance the activity of the natural synovial fluid. The perception that higher-molecular-weight HA is superior to lower-molecular-weight (MW) species is based on the suggestion that high-molecular-weight HA normalises synovial fluid and results in effective joint lubrication. However, it is claimed[7] that there is little evidence from a meta-analysis of clinical trials to support these ideas. Higher-molecular-weight HA are chemically cross-linked forms and are claimed to have a greater residence time in the joints.[8] *In vivo*, HA with a higher viscosity has been found to be more effective in lubricating joints.[9] There is some controversy about modes of action. It has also been suggested that viscoelasticity does not in fact form the foundation of the beneficial properties of these injections.[10] This point is added because explanations of the behaviour of complex systems are fraught with confounding factors. One must, however, speculate from a reasoned base when necessary. It is highly reasonable to conclude that one of the important properties of hyaluronan and hyaluronan solutions is their pseudoplastic behaviour. These then serve as lubricants when joint movements are slow and as shock absorbers when movements are fast.[11] In *ex vivo* experiments, HA with higher viscosity was more effective in lubricating joints.

Viscous solutions and disorders of the eye

Sodium hyaluronate, chondroitin sulfate and methylcellulose have been compared for maintaining the form of the anterior chamber of the eye.[12] The rheological characteristics of the polymers used in the anterior chamber are

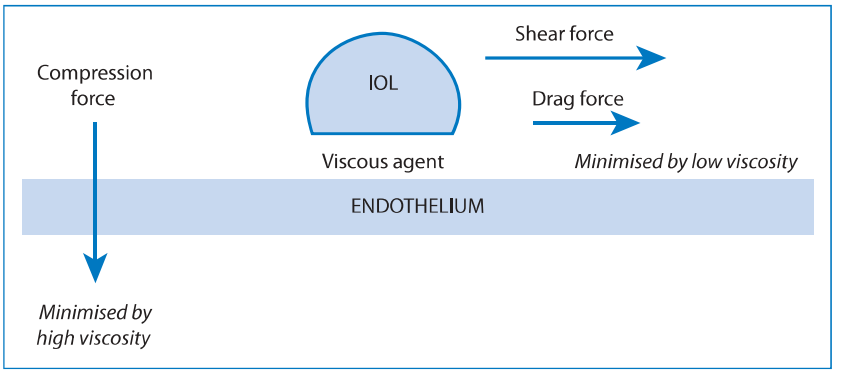


Figure 1.4 A schematic diagram of the forces on an intraocular lens (IOL). The applied force on the IOL is represented by two vectors: the compression force and the shear forces. High viscosity transmits more of the shear force to the endothelial surface. The compression force is minimised by a high viscosity (note the similarity to synovial fluid) and the drag force is minimised by low viscosity.

key. Pseudoplastic fluids are ideal for maintaining the chamber since they are more viscous at rest. Sodium hyaluronate and methylcellulose are pseudoplastic, while chondroitin sulfate displays Newtonian flow properties.

High viscosity is critical when the agent is applied in a thick layer to prevent mechanical damage to the corneal epithelium when an intraocular lens is drawn across the endothelium. Compression and shear are responsible for the damage:[12] thin layers of highly viscous HA convey the shear forces to the endothelium, whereas thick layers provide a physical barrier to compression, as can be seen in Fig. 1.4. Clearly there are analogies to synovial fluid here.

Optiflex is an ophthalmic product containing sodium hyaluronate with a molecular weight of 4×10^6 Da in a sterile isotonic vehicle. When injected through a cannula it becomes less viscous, but it regains its viscosity in the anterior chamber of the eye. It is used for lubrication and protection of cells and tissue during surgical procedures.

In the extreme, viscosity also affects drop size (though surface tension is the primary determinant of size, as we will see later). The ideal viscosity of ophthalmic solutions has been suggested to be between 15 and 30 mPa s, as this does not affect drop formation or delivery but offers better retention in the eye. More viscous systems blur vision as they can inhibit blinking. In general, solutions that possess pseudoplastic behaviour offer less resistance to the movement of the eyelids and are more comfortable than Newtonian liquids.[13]

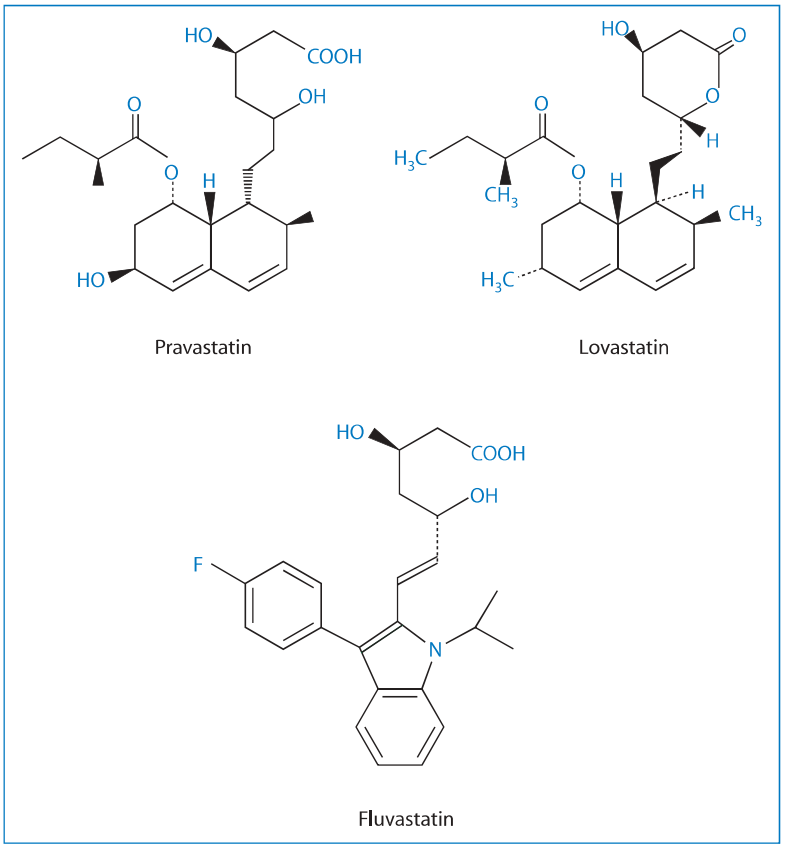
Effect of drug lipophilicity on blood rheology

High dose intravenous (IV) immunoglobulin therapy increases blood viscosity to an extent that can impair blood flow.[14] Blood rheology is complex, affected by patient age, exercise and various pathologies. The binding of drugs to fibrinogen can increase blood viscosity. The effects of pravastatin and

simvastatin on blood rheology have been studied in patients with type II hyperlipoproteinaemia.[15] This work[15] concludes that:

> administration of pravastatin sodium, but not simvastatin, reduced the plasma fibrinogen levels and blood viscosities to normal levels in type II hyperlipoproteinemic patients while both drugs reduced total cholesterol levels. The hydrophilicity of pravastatin sodium and its small binding capacity to plasma protein may be responsible in part for the beneficial hemorheologic effects observed.

Here hydrophilicity is correlated with low plasma protein binding. Lovastatin, simvastatin, atorvastatin, fluvastatin and cerivastatin are hydrophobic statins. At physiological pH (7–7.4) the relative lipophilicity of various statins currently in clinical use follows the order simvastatin ≈ cerivastatin > lovastatin ≈ fluvastatin ≈ atorvastatin >> pravastatin. Pravastatin is 70–300 times more hydrophilic than the other statins.[16]



The relative hydrophobicities of drug molecules cannot always be determined visually from their structures, as there are other determinants of solubility such as hydrogen bonding and the cohesion of the crystals. Lovastatin's methyl substituent instead of a pravastatin's hydroxyl is one clue; the structure of fluvastatin is quite different but contains the very hydrophobic fluorine

substituent. Lipophilic and non-lipophilic statins have different metabolic pathways, the former using the CYP3A4 pathway, while the latter do not utilise the CYP pathway.

Surface tension, wetting and de-wetting

Surfaces and interfaces are ubiquitous. They may be solid, such as the surface of workbenches, or be flexible or hard plastics like catheters and giving sets. The cell membrane is an also interface. The corneal epithelium is a surface. Wherever there are surfaces, surface active molecules and many lipids will adsorb to them. Many formulations such as emulsions, suspensions and creams depend on surfactants for their formation and stability. There are surface-active drugs (including the phenothiazines, some local anaesthetics) that interact with membranes because of their amphipathic structure. Bacteriostatic and bactericidal excipients like benzalkonium chloride and similar molecules are also surface active. In eye drops these molecules not only perform their primary function but can also adsorb onto hydrogel contact lenses and at the tear film–corneal interface. Adsorption onto hydrogel contact lens polymers can lead to the slow release of these molecules and to eye damage.

Figure 1.5 summarises the ubiquity of surface tension and surface chemical effects, from formulation, surface-active drugs and excipients, through lung

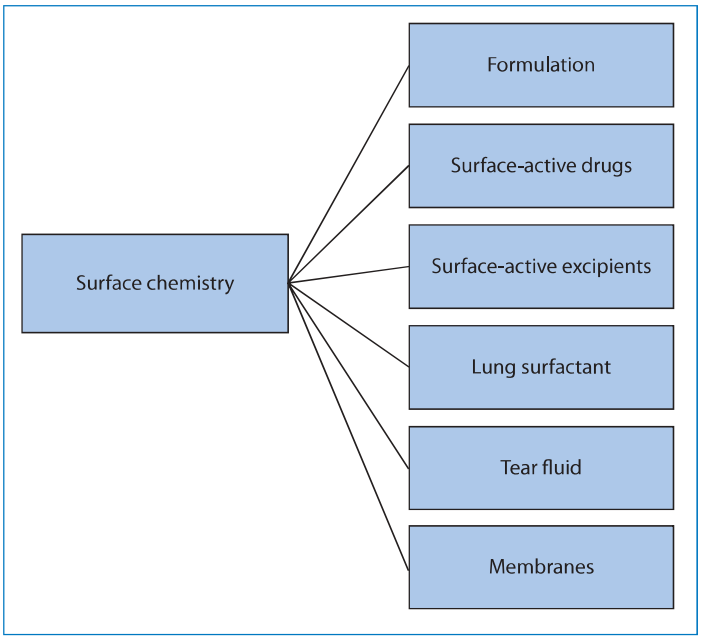


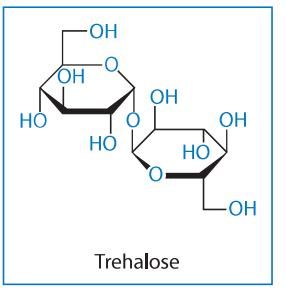
Figure 1.5 A simplified version of the diagram shown in the Introduction (p. xiii). Surface chemistry is important directly in formulation, in understanding surfactants and surface-active drugs and excipients, natural surfactants as in the lung and in tears, and the manner in which drugs and excipients interact with membranes.

surfactant and tear fluids. The next section discusses tears and tear films, the behaviour of which involves several surface effects, especially in the presence of materials such as benzalkonium chloride, mentioned above.

Tear fluid

Tears are released from the Meibomian glands in the eye. Tears are important for lubrication of the eye. When we blink the tear film is replenished and re-spread, thus compensating for evaporation of the aqueous film and preventing the drying that would otherwise occur. In some patients, the supply of tear fluid, comprising a largely aqueous solution containing protein, lipids and enzymes, is impaired. Tears spread over the surface of the cornea, which is hydrophobic. The tears contain phospholipids, which act as a surfactant, lowering the surface tension of the fluid and allowing spreading. The thin lipid layer on the surface of the tear film (like most lipid monolayers) also prevents or slows down evaporation of the aqueous medium beneath. Dry eye[17] (xerophthalmia; Sjögren's syndrome) is caused when the tear film thins to such an extent that it ruptures, exposing the corneal surface to the air. Drying out of patches on the corneal surface follows. This can be painful and must be avoided. Evaporation over 5–10 minutes can actually eliminate the tear film completely.[18]

Artificial tear fluids may replace the natural tear fluid with varying degrees of similitude. Most aim for formulations that have an appropriate viscosity, but not necessarily identical rheological properties. Hydroxypropylmethylcellulose (HPMC) is a component of many commercial replacement or 'artificial' tear products, as are the water-soluble macromolecules carboxymethylcellulose (CMC), polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP). Trehalose[19] has also been studied as an agent for amelioration of the symptoms of dry eye. Trehalose is one of those molecules which, because of its hydrophilicity, increases the surface tension of water, but at 0.8 mol/L it has a viscosity of only ~2 cP at 30°C. The aim is usually to reproduce the wetting and rheological properties of tear fluids, but in this case wetting is not enhanced. Increased concentrations, however, will have higher viscosities.



Trehalose

The formation and rupture of tear films was explained over 30 years ago by Holly.[18] Eye drops can disrupt the natural tear film, either by the physical

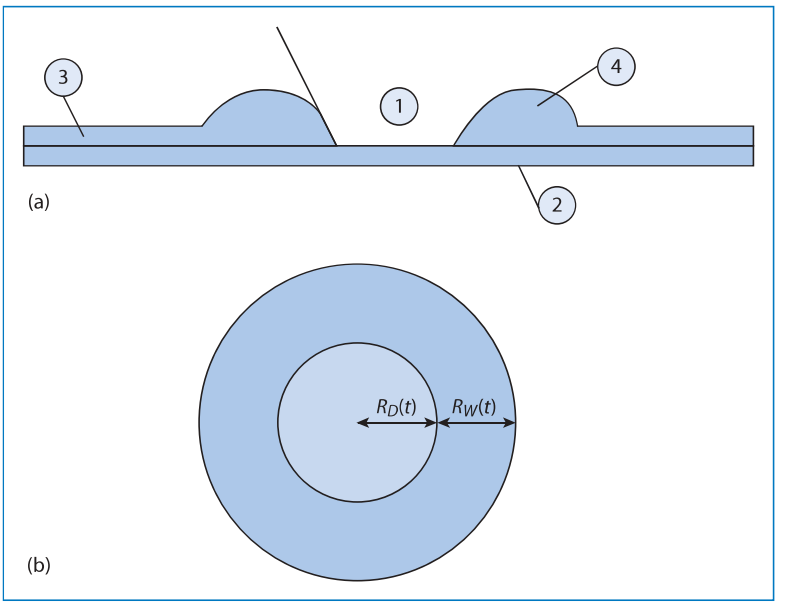


Figure 1.6 (a) Simplified diagram showing a thin liquid film (3) on a surface such as the cornea (2). When the film reaches a critical thickness, instability causes the film to rupture and surface forces pull the film away from that point, leaving an exposed surface (1). The liquid in the film is gathered in a rim (4). The contact angle between the broken film and the corneal surface will be reduced on addition of an agent that lowers surface tension. On the other hand, the adsorption of, say, benzalkonium chloride on the surface, with the onium group towards the negative cells, will render the surface in (1) more hydrophobic, exacerbating the situation. (b) Schematic diagram used to calculate the radial velocity of de-wetting. (Diagram from reference 20.)

action of the drugs they contain or through additives such as benzalkonium chloride. The latter is a component of eye drops but it can be toxic as it is a cationic surfactant (see Chapter 3), and can adsorb onto the corneal surface in dry eye syndrome, rendering the surface even more hydrophobic. The film can then de-wet the surface, thereby exposing the corneal epithelial cells to the air. The process may start at a given point on the corneal surface. A critical thickness for stability is breached and the film breaks, as shown in Figure 1.6.[20]

Dry eye encompasses a number of ophthalmological complaints shown in Figure 1.7.

Tear film formation may be compromised but not necessarily cause clinical problems unless the eyes are challenged with smoke or dust or certain drugs. Contact lenses may also of course affect tear film formation and stability.

Neonates have normal tear fluid but low rates of blinking.[21] This incomplete blinking[22] allows time for the film to evaporate, as discussed above, and to cause the dry spots that lead to exposed corneal epithelium. A low rate of tear fluid turnover is believed also to be the cause of reduced barriers to potential pathogens. The tear film in effect has a 'washing function' reducing

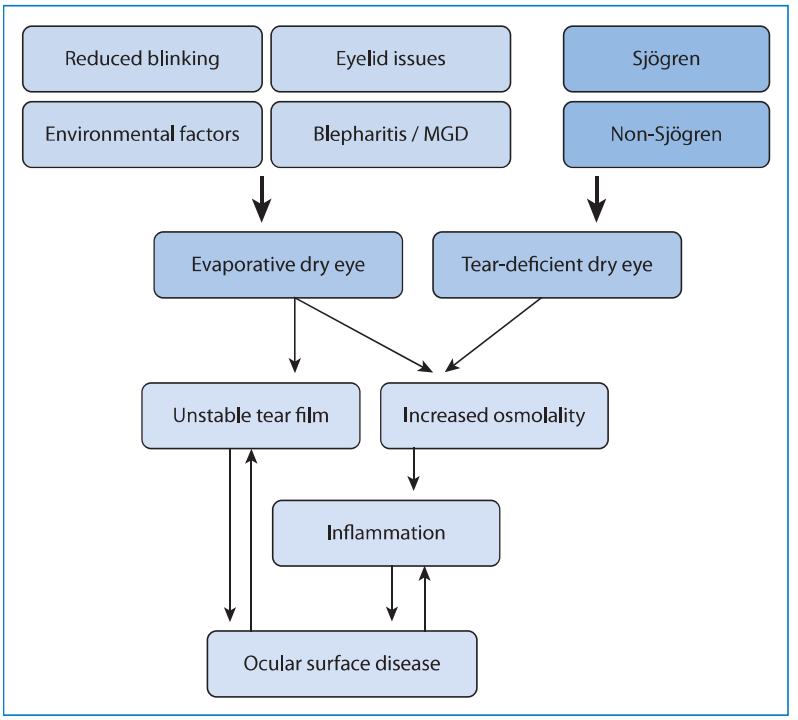


Figure 1.7 Diagram showing the causes of dry eye, through reduced blinking, problems with eye lids (evaporative dry eye) or Sjögren's tear deficiency (Tear-deficient dry eye). MGD, meibomian gland dysfunction.

the likelihood of bacterial adhesion to the corneal surface. This is similar to the case with saliva, which removes bacteria on teeth (see Xerostomia below).

Drugs and tear films

Drugs administered to the eye may affect the functioning of tear fluid. One aspect, connected with the earlier discussion on crystallisation, has been the solubility characteristics of drugs applied to the eye. Tear pH is dominated by the pH of the formulation. Immediately after instillation ciprofloxacin 0.3% has been shown to precipitate in the eye, driven by supersaturation as the pH changes.[23] In this case the pH was found to drop initially to 4.7 (the formulation has a pH of 4.5), normalising after 15 minutes to around 6.8. The solubility of ciprofloxacin is at a minimum at pH 7,[24] as can be seen from Figure 1.8.[25] Hence, drug that is in solution in the formulation will precipitate in the tear fluid. There is 100-fold reduction in ciprofloxacin solubility as the pH increases from 4.8 to 6.8.

Fleroxacin has a 10-fold greater solubility at pH 7 than ciprofloxacin, although this is not immediately obvious from comparing the structures of the two drugs. Each drug must of course be considered on the basis of its complete physical chemistry and its dose/solubility ratio. As a consequence, at equal doses one would not expect fleroxacin to precipitate to the same extent as ciprofloxacin.

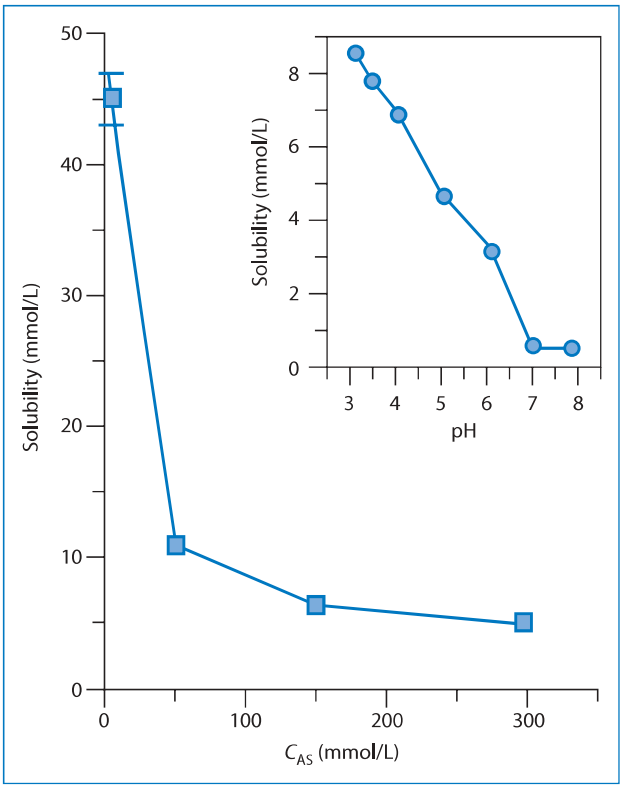
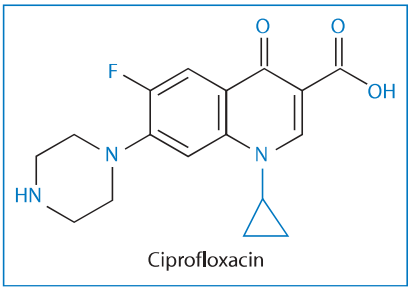
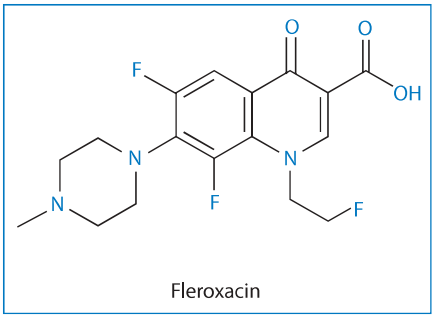


Figure 1.8 Ciprofloxacin solubility as a function of pH (inset) and as a function of the concentration of added salt (ammonium sulfate) (c_{AS}) from reference 25.



Ciprofloxacin



Fleroxacin

Eye drops and surface tension

Conventional eye dropper devices deliver drops with a volume between 25 and 70 µL. It has been argued[26] from many points of view, not least the biopharmaceutical one, that volumes of 5–15 µL should be instilled in the eye. The surface tension of the solutions to be instilled obviously has an effect on droplet size. The lower the surface tension, the smaller the drop delivered for a given expulsion pressure. Drops range from 44 µL for a solution with a surface tension of 71.9 mN/m to 25 µL for a solution with a surface tension of 32 mN/m. As has been mentioned, many drugs and some excipients are surface active, as we will discuss in Chapter 3. Tetracaine hydrochloride at a concentration of 16.6 mmol/L has a surface tension of 50.5 mN/m. Benzalkonium chloride 0.01% lowers the surface tension of water to 45 mN/m. The effect of lowering droplet size is relevant also in intravenous giving sets.

Xerostomia

Another syndrome that requires replacement or supplementation of a natural fluid with an artificial substance is xerostomia ('dry mouth'). Normal saliva function and control are compromised in this condition. Saliva is a clear, usually alkaline and somewhat viscous secretion from the parotid, submaxillary, sublingual and smaller mucous glands of the mouth.[27] In some cases xerostomia is caused by medication, especially with anticholinergics. Chemotherapeutic agents can also have a direct effect on salivary glands, reducing saliva output. Saliva consists primarily of water but contains enzymes and other proteins and electrolytes. It has a surface tension of around 58 mN/m. Saliva is essential for the normal 'feel' of the mouth and it assists lubrication, possesses antimicrobial activity and aids mucosal integrity. Saliva provides protection by constantly flushing non-adhered microbes, their toxins and nutrients from the mouth. It is also been suggested that the flow of saliva detaches adsorbed microbes from the teeth or prevents their adhesion, as shown in Figure 1.9. Saliva contains a wide spectrum of agents such as lactoferrin, lysozyme, histatins, cystatins, mucins, agglutinins, secretory leukocyte proteinase inhibitor, tissue inhibitors of proteinases, chitinase, peroxidases, and calprotectin.

Dry mouth can be treated with artificial saliva, although these solutions, as can be imagined from the list of components of natural saliva, rarely truly mimic the properties of the natural lubricant and wetting material. Designed to behave as far as possible like natural saliva, commercially available artificial salivas mostly contain agents such as carboxymethylcellulose and hydroxyethylcellulose to increase viscosity.

The rheological properties of saliva are quite complex, but these polymer additives do at least increase the residence time of the fluid. Gels that can prolong contact between the fluid and the oral mucosa are sometimes preferred.

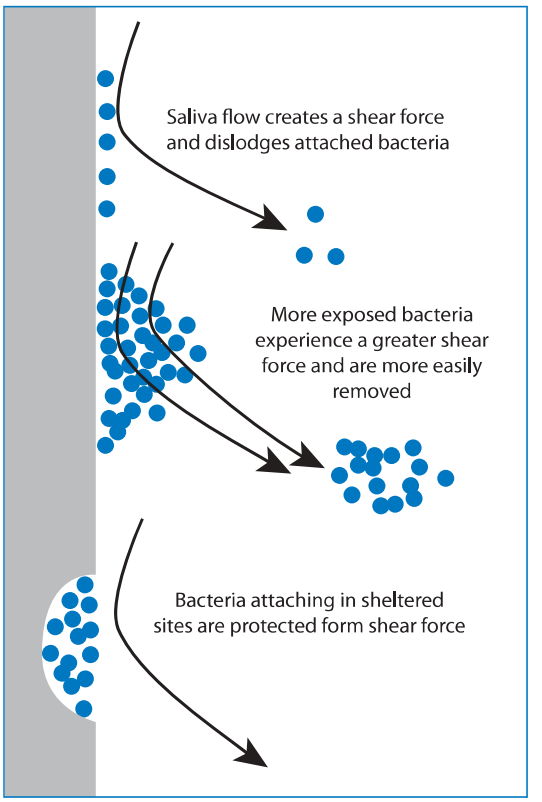


Figure 1.9 Diagram of the effect of salivary flow in the normal mouth, dislodging bacteria adsorbed on teeth. Different situations are shown, with more exposed bacteria and bacteria in sheltered sites such as crevices.

Adhesion and adsorption

Adsorption usually refers to the process whereby small or large molecules attach themselves to surfaces, whereas the term adhesion is usually applied when two macrosurfaces or crystals come into close contact. Adhesion of solids and adsorption of molecules to surfaces are topics often discussed in basic pharmaceutics. Adsorption by definition involves deposition of molecules on surfaces. There are many surfaces to consider: biological surfaces or membranes, glass, plastics, teeth and so on. Figure 1.10 deals with some of the effects of adhesion ranging from the use of adsorbents to removing toxins in overdose to pathogenicity and infection. There are aspects of adhesion that are important in medication, as we will see later in relation to the unintended capture of dose forms in the oesophagus.

Bacterial adhesion to catheters can be reduced if the properties of both the organism and the plastic or other materials of the catheter are known. Box 1.2 gives the summary from a paper by Homma and colleagues.[28] One can speculate why these effects are exhibited. Surface hydrophobicity and surface charge are both important: it is interesting that the anionic heparinised catheters were free from biofilms of the negatively charged *Escherichia coli* and

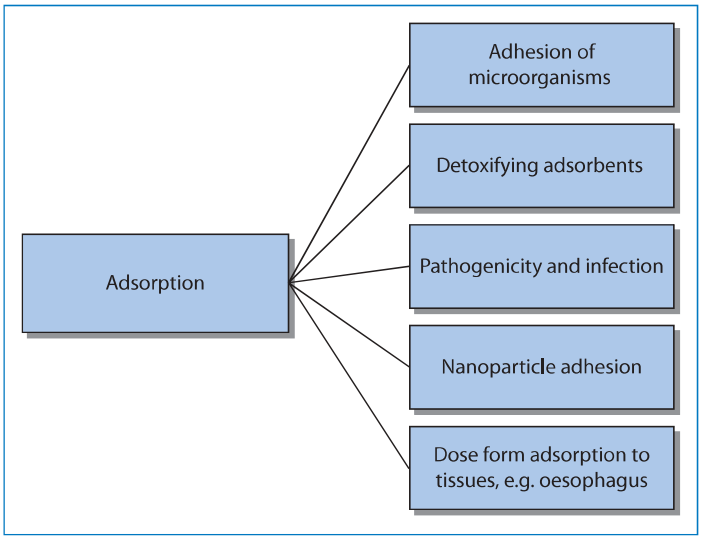


Figure 1.10 A schematic linking various branches of the topics of adsorption and adhesion, from adhesion of microorganisms leading to pathogenicity and infection, the adsorption of toxins on material such as charcoal, nanoparticle adhesion, and dose form adhesion to tissues such as the oesophagus.

Staphylococcus aureus, suggesting of course that the bacteria are repelled from the surface by electrostatic forces.

The role of hydrophobic interactions between bacteria and surfaces is important, for example, in the oral cavity, in contact lenses,[29] in surgical and dental materials, in polymers[30] for pharmaceutical and food use and in food itself. The adhesion of crystalline drugs to carrier particles such as lactose in aerosol suspensions can determine their effectiveness: too strong adhesion

Box 1.2 Bacterial adhesion

The inhibitory effects on bacterial adhesion of a new hydrophilic heparinised catheter to be used in patients with malignant obstructive jaundice, has been investigated in a randomised controlled study[28] of indwelling endoprostheses using either implantable port-connected heparinised catheters ($n = 25$) or silicone catheters ($n = 21$). Catheters withdrawn from patients were cultured for bacteria and examined for the presence of adherent organisms. Examination of the two types of catheters exposed to suspensions of *E. coli* and *Staph. aureus* showed the formation of a biofilm coated with glycocalyces in the silicone catheters, but not in the heparinised catheters. There was little bacterial adhesion to the heparinised surface, but significant formation of biofilm on the silicone surface. Anionic heparinised catheters have inhibitory effects on bacterial adhesion.

means that the drug will not free itself from the carrier. The adhesion of suspension particles to glassware is an unwanted effect, and in low-dose systems can reduce the amount of drug delivered.

Electrostatics and adhesion

Electrostatics deals with phenomena that result from stationary electric charges on non-conducting surfaces. The build-up of charge on the surface of objects after contact with other surfaces is important pharmaceutically. In powder handling on the large scale, accumulation of charge can lead to sudden discharge and explosions. On the smaller scale, electrostatics is important particularly when plastic surfaces are involved. Plastic (e.g. polycarbonate) spacers used with pressurised inhalers can acquire charges and attract aerosol particles to their surface. This can reduce drug availability by up to 50%.[31] The simple expedient of washing the spacer, such as a Volumatic (see Figure 1.11), with a detergent (surfactant) solution can reduce electrostatic charge and, as a consequence, improve performance.

The effect of the surfactant is to change the nature of the surface, so that the particle 'sees' the surfactant rather than the polymer. The nature of the induced charge on polymers depends on the nature of the polymer. Such interactions between drug and spacer are probably more important with steroids, but with beta-agonists the dosage is less critical and adsorption might not have significant clinical effects that can be measured.

When lactose is used as a carrier for the drug in aerosol formulations, lactose–drug interactions can occur and lead to the drug being released less readily from the lactose.

Charcoal, calcium carbonate and sevelamer

Highly adsorbent charcoal is used to reduce free toxin in the case of orally administered overdoses, deliberate or accidental. Patients who have to undergo haemodialysis are prone to hyperphosphataemia as the excretion of phosphate by dialysis is poor and renal function is impaired. Calcium as its carbonate or acetate is a phosphate-binding agent that is administered orally

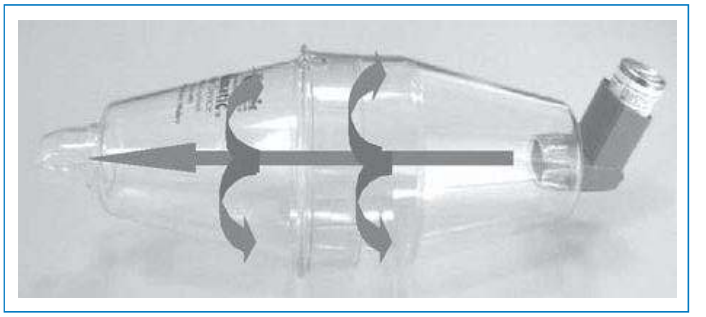
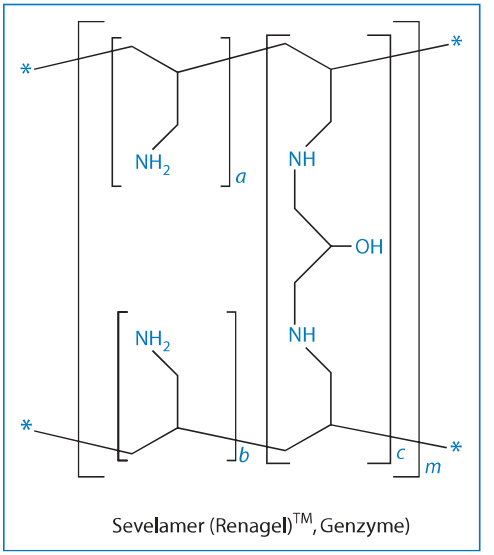


Figure 1.11 Volumatic spacer showing hypothetical trajectories of particles attracted electrostatically to the plastic internal surface of the device.

to reduce phosphate ion levels. A polymeric ion exchange resin, sevelamer (see structure) is also used. It is a copolymer of 2-(chloromethyl)oxirane (epichlorohydrin) and prop-2-en-1-amine. The marketed form is a partial hydrochloride salt, being present as ~40% amine·HCl and 60% sevelamer base. The amine groups of sevelamer become partially protonated in the intestine and interact with phosphorus molecules through ionic and hydrogen bonding.

The structure shows the exposed binding site for phosphates – the repeating and adjacent NH_2 groups. The dose both of calcium salts and of sevelamer is high, being 1.25 g for Calcichew tablets and 800 mg for the sevelamer, and patients who are already on several medications have reported problems with compliance.[32] The sevelamer tablets are large and one patient reports 'the tablets are so disgusting, their consistency is so disgusting – so disgusting that you don't want to take [them]'. Here the concept is good with the agents used, but they are insufficiently powerful adsorbents or ion exchangers to allow dosage reduction. Tablets not taken are a negation of therapeutics.



Sevelamer (Renagel)™, Genzyme)

So far, the selected examples have touched on the importance in a range of circumstances of surface tension, wetting, de-wetting, precipitation, pH–solubility relationships, adhesion, adsorption and viscosity. These were related variously to xerophthalmia, synovial fluid supplementation, the behaviour of drugs in eye drops and crystalluria. Other examples will follow in later chapters. We now discuss some introductory examples of the nature of the formulation (dose form) and events and outcomes in the clinic.

The nature of the dosage form and outcomes

Formulations on shelves sooner or later become formulations in patients, unless, as referred to above with phosphate-binding agents, patients forget or refuse to take their medication. Many changes in products can occur as a

result of the sudden change of environment when the medicine is administered. Drugs precipitate from injection solutions after administration; infusion pumps become blocked when the proteins they are delivering aggregate; some oral dose forms adhere to oesophageal membranes; the ghosts of insoluble matrix tablets can accumulate in gut diverticula; and eye drops can not only irritate but may deliver lethal doses in the very young.

It is clear from knowledge of biopharmaceutics that dosage forms can considerably influence medication outcomes.[33] The development of controlled-release dosage forms is a good example of that influence, where the properties of the dosage form have been adjusted to ensure an optimal release of active to reduce the frequency of administration by prolonging the therapeutic levels of drug, and to reduce peak plasma levels that contribute to toxic effects.

The era of personalised medicines will bring great challenges for the development of products for groups of patients identified by their physiological, pathological and even genetic status, rather than as now when, apart from dosage adjustments, all patients may receive the same product that has been designed for the average patient. Aspects of personalised medicines are discussed in Chapter 8.

Quality of effect

The quality of the clinical effect of medicines is often a pharmaceutical concern. As one example shows, considerable advances have been made with ciclosporin formulations to reduce the inter- and intra-patient variability in plasma levels. This is vital because appropriate levels are crucial in the suppression of rejection following transplantation. Comparison of the former product Sandimmune with Neoral (microemulsion) demonstrates (Figure 1.12) improvements in the consistency of plasma levels with the latter, although there is still considerable patient-to-patient variability in both C_{max} and t_{max}. But the point is clear: formulation can influence outcomes.

The variability of many non-disintegrating controlled-release formulations taken orally is the result not of differences in the nature of the dosage form but of variability in their gastrointestinal transit times in different patients or in the same patient at different times. However, such effects are felt mainly with non-disintegrating dosage forms such as oral osmotic pumps and matrix tablets. Transit times vary considerably and the challenge for the future is to take these differences into account in the design of formulations. It is clear that if mouth-to-anus transit times are of the order of 2 hours in one individual and 12 hours in another, then a product that releases its content over 8 hours will not perform well in the former patient. Ideally we need to have available dose forms that accommodate the extremes for the future when personalised medicine is more accepted and catered for.

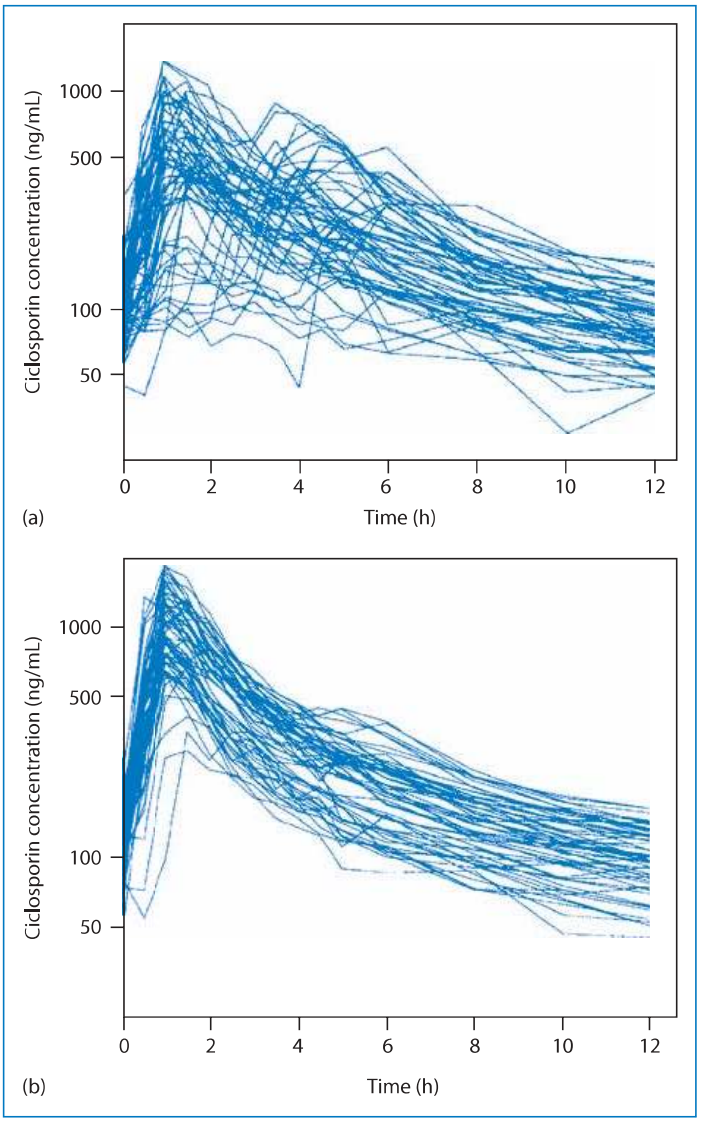


Figure 1.12 Plasma levels of ciclosporin after administration of Sandimmune (a) and Neoral (b), showing the reduction (but not elimination) of patient-to-patient variability. The logarithmic scales conceal to an extent the very considerable variability even with the improved formulation. Variability of ciclosporin and other immunosuppressives has an extremely important effect on outcomes following transplants. Neoral is a concentrate which on dilution produces a microemulsion.

Transdermal products *in situ* enjoy a more static environment. But variability of performance of transdermal patches has been demonstrated many times. Patches do of course modulate the intra-individual differences in absorption, but only to an extent that is determined by the transport properties of the drug through the polymer membrane separating the reservoir from the skin surface. Patches do not generally control the onward movement of drug. An example in Figure 1.13 makes this point, showing the variability in plasma levels attained from fentanyl patches from a commercial system.[34]

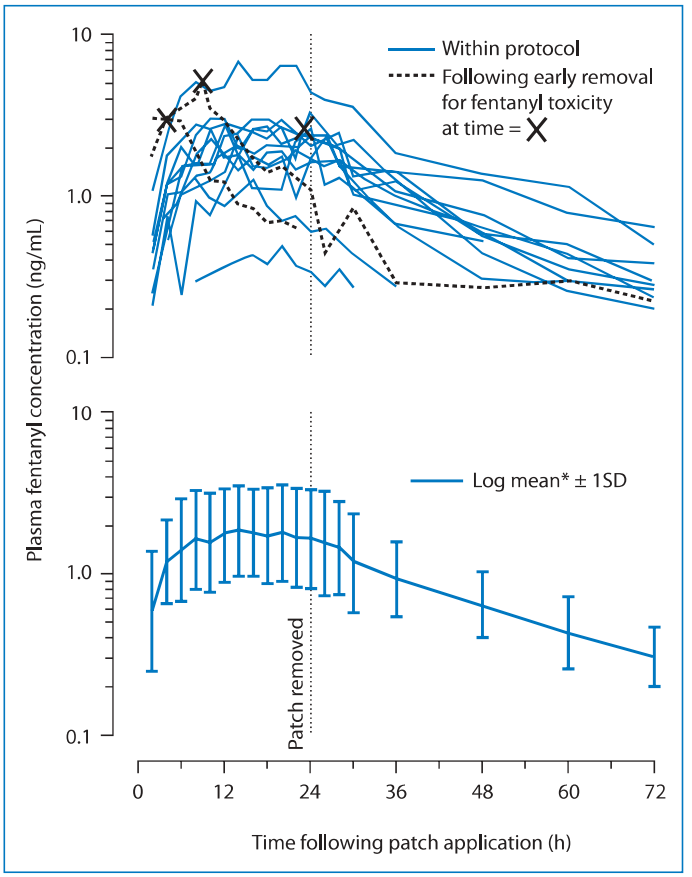


Figure 1.13 Plasma levels of fentanyl administered via a Cygnus transdermal device. This shows clearly the wide variability of levels. (From reference 34.)

Modes of injection and formulation

An editorial in the *British Medical Journal*[35] pointed out the importance of injecting vaccines into muscle in the deltoid or the anterolateral aspect of the thigh. As the article indicates, 'injecting a vaccine into the layer of subcutaneous fat, where poor vascularity may result in slow mobilisation and processing of antigen is a cause of vaccine failure for example in hepatitis B, rabies and influenza vaccines.' The use of a standard size of needle will not guarantee successful intramuscular injection in all patients; hence thought must be given to choice of needle length and bore. It is in such apparently minor details that success or failure can reside, or at least on which less favourable or more favourable outcomes depend. Some years ago, the dispersion of diazepam after intramuscular injection was found to depend on whether a doctor or a nurse administered the dose; plasma levels varied more and mean levels less when the nurse carried out the injection, because of the variation in the site and mode of injection. The sex of the patient can affect responses to antibiotic injections owing to differences in the distribution of fatty tissues in men and women, since women have greater lipidic deposits in the gluteal region.

Ingredients in dosage forms and their influence on outcomes

Just as important as the physical form of the delivery system are its ingredients, the excipients, which although chosen to be inert, are not always so.[36] This is principally the subject of Chapter 2. Transdermal patches can cause adverse effects on the skin as the adhesive employed may cause irritation. Solubilisers such as Cremophor EL in injection formulations of paclitaxel can initiate anaphylactic reactions, while a battery of excipients, from dyes and stabilisers to preservatives, can in sensitive individuals cause unwanted effects.[37]

Excipients are rarely totally inert as we will see in Chapter 2. Most excipients are substances that are foreign to the body and hence can elicit adverse effects. These may occur even if the excipients are insoluble. The effect of inhaled powders that can cause a cough reflex may be one example. Paradoxical bronchoconstriction has been described in inhaler formulations for the treatment of asthma, for example. The precipitation of drugs from injection vehicles can be the cause of pain and thrombophlebitis. Hence dosage forms must be chosen with care. They must also be used with care.

Influence of a surfactant on the behaviour of paclitaxel

A specific example is given here of the effects of one excipient type, namely a non-ionic surfactant, Cremophor EL, an ethoxylated castor oil used as a solubiliser in many formulations. Cremophor EL, a component of Taxol (paclitaxel) injections, not only solubilises the drug, but also inhibits the metabolism of the drug to the 6α-hydroxypaclitaxel by cytochrome P45 (CYP) 2C8. This is the major route of detoxification of paclitaxel.[38] This surfactant has also been found to decrease the accumulation of the hydroxyl derivative in cells and decrease the ratio of 6α-hydroxypaclitaxel to paclitaxel. To complicate matters, it also contributes to the non-linear kinetics of the drug.

Clearly, Cremophor EL is more than a substance that simply increases the solubility of the drug. When observing the effect of a drug on adverse events we need always to consider the question: does the formulation itself or ingredients in the formulation play a part in the behaviour of the medicine or indeed other medicines given concomitantly?

In the following chapters we will elaborate on some of these issues, using cases that have been reported as the starting point to refresh collective memories of the pharmaceutics involved. The examples can only be selected cases. What should be developed is a sense of asking questions about the nature of medication that may (or may not) have affected an outcome, or caused an adverse event, or have suited one patient more than another. Pharmacists can only play a useful independent clinical role if they bring to the ward,

the bedside and the community interface the additional knowledge that is embodied in subjects with which physicians and nurses are less well versed. It goes without saying that pharmaceutics must of course be coupled with a through knowledge of pharmacology and therapeutics and key pharmaco-chemical facts.

Conclusion

To conclude this introduction to clinical pharmaceutics, we can use Figure 1.14 to illustrate the case when considering adverse events. It emphasises the need for a comprehensive synthesis of the disciplines of pharmacy to interpret complex events intelligently. Here the cause may be the drug, excipients or the nature of the dosage form itself. If it is the drug, we ask: Is it a class effect or is it compound specific? Is it a chemical or physical problem, arising from precipitation, lipophilicity or complexation? Does the chemical structure or reactivity of the drug result in hapten formation or cross-reactivity with other drugs? Excipient effects may be due to surfactants, dyes, preservatives or antioxidants. The dosage form may affect drug distribution or precipitation, and the nature of the dosage form itself (size, adhesivity) may cause problems in the oesophagus or intestine. Even tonicity, viscosity and density may in some rare cases cause problems with drug administration.

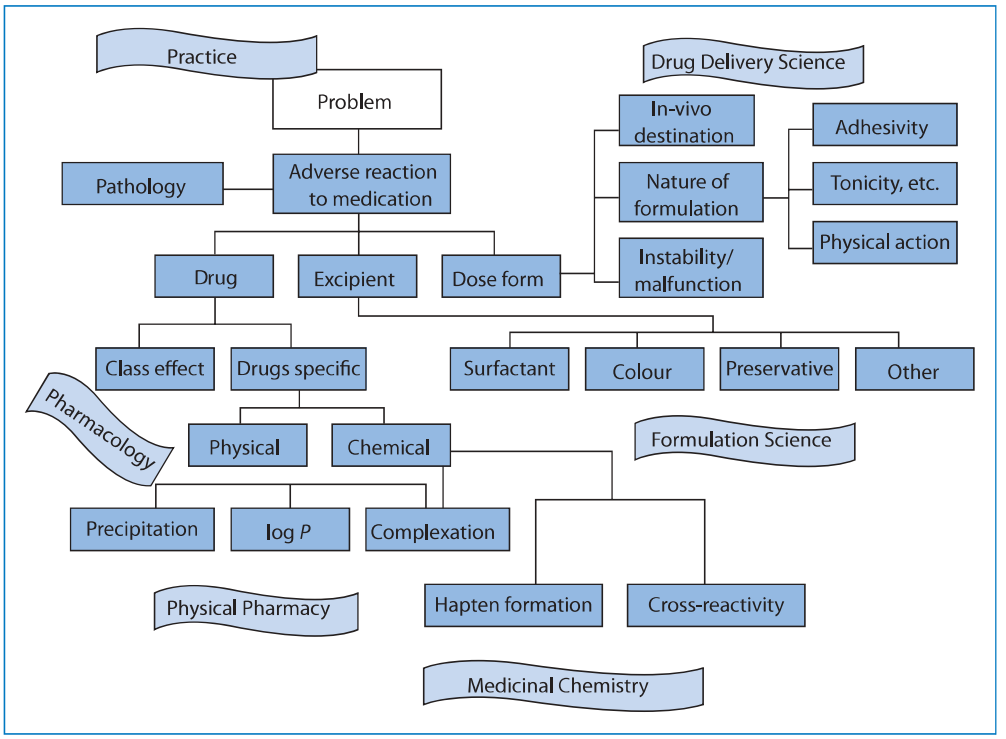


Figure 1.14 Scheme showing the relationship between a problem in practice – in this example an adverse event or reaction – and the physical, pharmacological and chemical sciences. Adverse reactions to formulations are discussed in Chapter 5.

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2

Excipients: Not always inert

Introduction

Excipients are components of formulations other than the drug or other active ingredient. Their functions are many, variously to aid processing, to aid dissolution of solid dose forms or conversely to retard release of the drug, to stabilise the formulation or to protect the drug from adverse environments both *in vitro* and *in vivo*. Excipients are the dominant material in many tablet and capsule formulations as sometimes their main role is to provide sufficient bulk for a low-dose drug to be administered safely. This chapter deals with the potential for excipients to influence outcomes of medication. Excipients are not always the inert substances that we presume. Some cases and reports of the adverse action of excipients are discussed here. While labelling requirements insist on the listing of ingredients in some products, the plethora of trade names (e.g. for surfactants, polymers, lipids and other excipients) can make accurate identification of materials a difficult task. (The European Commission guidelines requires that all excipients need to be declared on the labelling if the product is an injectable, or a topical (for skin, for inhalation, delivery to the vaginal, nasal or rectal mucosae) or an eye preparation.) Batch-to-batch variation of many excipient raw materials adds another layer of complexity in tracking down and comparing case histories. One problem we face is that products available in one national market may have different formulations from those marketed in another. Papers do not always detail the formulations or brands used in clinical studies.

Usually but not always inert

Excipients are intended to be inert, but they are not always so in all patients.[1] In a review on the safety of pharmaceutical excipients, Figure 2.1 was used.[2] This summarised the main requirements of excipients: to be of high quality, to be safe and to have a high degree of functionality, that is, fitness for use.

Fitness for use in one application may not mean fitness for use in another, for example by another route of administration. Even though adverse reactions to excipients might be relatively rare, it is for this reason that the

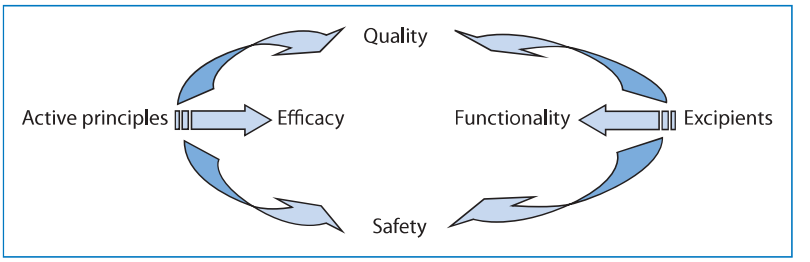


Figure 2.1 The main requirements of excipients: high quality, safety and functionality, the property of being in effect fit for purpose. (From reference 2.)

possibility that an excipient might be the cause of any adverse event should be kept in mind. Fillers like lactose bulk out a low dose (milligrams or micrograms) so that the resulting tablet or capsule can be manufactured and is of a sufficient size to be handled. Lactose is also used in dry powder inhaler formulations as a carrier for the drug. There may be lubricants such as magnesium stearate to aid the flow of powders and their subsequent tabletting or filling into capsules.

Preservatives and dyes are listed in Tables 2.1 and 2.2, the result of surveys of these ingredients and their frequency of use,[3] albeit not in the UK. These figures are used here to give an impression of the excipients most likely to be encountered.

Relatively simple molecules are used as excipients in formulations, from substances such as lactose or magnesium stearate through surfactants, preservatives, colours and flavours to macromolecules. Macromolecules (polymers) may be soluble, swellable or insoluble. With small molecules,

Table 2.1 Preservatives found in liquid pharmaceutical formulations ($n = 73$)

Preservatives	% of formulations
Methylparaben	45.2
Propylparaben	35.6
Sodium benzoate	32.8
Sodium metabisulfite	11
Benzoic acid	8
Hydroxyparabenzoate	4
Potasssium sorbate	2
Hydroxyparabenzoic acid	1
No preservatives	2

From reference 3.

Table 2.2 Dyes found in pharmaceutical formulations ($n = 73$)

Dyes	% of formulations
Dusk Yellow (FD&C #6)	15
Tartrazine Yellow (FD&C #5)	9.5
Erythrosine	6.8
Ponceau 4R Red	5.4
Caramel	4.1
Red #40	4.1
Food Red	4.1
Bordeaux S Red	2.7
Quinoline Yellow	2.7
Yellow #10	2.7
Blue #1	1.3
Red #10	1.3
Iron oxide	1.3

From Reference 3.

such as the *para*-aminobenzoic acid esters (parabens), we can know whether the compound is pure, and know exactly what we are dealing with. It is not possible to generalise about the effects of excipients with all their structural diversity and uses. With polymers and other macromolecules one needs to know their molecular weight, or more likely their molecular weight distribution, or about the presence of impurities, such as catalysts and peroxides, the latter in polysorbate 80 for example. Cremophor EL, which is used in paclitaxel formulations is 'cleaned' rather than pure. Unpurified material causes some instability in the paclitaxel, possibly due to the presence of carboxylate anions.[4] Excipients are rarely produced to the extremely high standards of purity that apply to drug substances. Hence the presence of impurities rather than the material itself might be the cause of any adverse event, perhaps by inducing degradation of the drug. There may be batch differences or brand differences in excipients, which are confusing. A mutein is a protein with its amino acid sequence altered usually sufficiently to alter its properties. Oxidised IL-2 mutein forms in the presence of a high-peroxide-value polysorbate sample to a greater extent than with a low-peroxide-value sample.[5] Some polymeric materials are complex, not only because of the existence in any one sample of a range of molecular

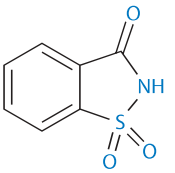
weights, but also because many contain plasticisers to adjust their physical properties or agents to aid production. Plasticisers such as diethyl phthalate leach out from plastic giving sets into infusions, particularly those that have ingredients (such as surfactants) that might aid the solubilisation of the phthalate. Dioctyl phthalate and dioctyl adipate have been found in some silicone tubing.

Problems with excipients to which the American Academy of Pediatrics have drawn attention are shown in Table 2.3. Note that the route of administration and sometimes the mode of administration (for example, a particular device such as a nebuliser) and the concentration will affect the appearance or severity of many adverse effects.

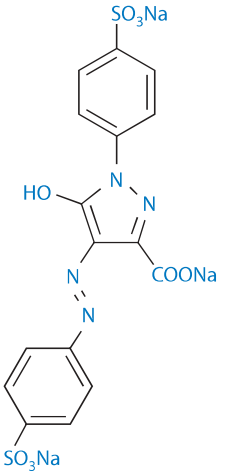
Table 2.3 Excipients that have caused problems in paediatric and adult medicines

Excipient or class	Selected observed reactions
Sulfites	Wheezing, dyspnoea, anaphylactoid reactions
Benzalkonium chloride	Paradoxical bronchoconstriction, reduced forced expiry volume
Aspartame	Headache, hypersensitivity
Saccharin[a]	Dermatological reactions; avoid in children with sulfa allergies
Benzyl alcohol	In high concentrations can cause neonatal death
Various dyes	Reactions to tartrazine[b] similar to aspirin intolerance; patients with the 'classic aspirin triad' reaction (asthma, urticaria, rhinitis) may develop similar reactions from other dyes such as amaranth, erythrosin, indigo, carmine, Ponceau, Sunset Yellow, Brilliant Blue
Lactose	Problem in lactose-sensitive patients (lactase deficiency)
Propylene glycol	Localised contact dermatitis topically; lactic acidosis after absorption

[a] Saccharin is an *o*-toluene sulfonamide:



[b] Tartrazine:



E-numbers

From Table 2.2 it is clear that there are many ways of referring to additives. A classification system has been developed that codifies additives both in food and in pharmaceuticals in terms of E-numbers. Box 2.1 gives the general numbering system for several classes of ingredients found in food. It is useful when trying to detect cross-reactivity and sensitivities to know the E-numbers of colours, preservatives, and other ingredients. Each additive has a number within the classifications shown in Box 2.1.

Further deconstruction of E-numbers might be useful in identifying possible causes of adverse events. E100–109 are yellow dyes; for example, tartrazine (F&DC Yellow 5) is E102. E140-149 are green dyes. E430–439 are polyoxyethylene derivatives such as polysorbate, 80 which is E433. E210–219 are benzoates. E230–239 are phenols and methanoates. E220–220 are sulfites (e.g. sodium metabisulfite has an E number of 223).

One case report[6] reads as follows:

> During the 1999/2000 influenza outbreak, a 53-year-old man consulted because of a persistent productive cough that followed flu-like illness. The patient was examined and prescribed erythromycin (Erymax™, Elan). He made it clear that he had a previous history of aspirin allergy and was reassured that there was no known cross-sensitivity between erythromycin and aspirin. Two days later, the patient's wife came into the surgery; she was angry and upset because shortly after taking the erythromycin capsules, her husband had developed some tingling and swelling of his fingers and feet similar to the symptoms he had previously experienced with aspirin. They were both disturbed to find the following warning in the patient information leaflet: '*Capsules contain the colouring agent E110. This can cause allergic-like reactions including asthma. You are more likely to have a reaction if you are also allergic to aspirin*'.

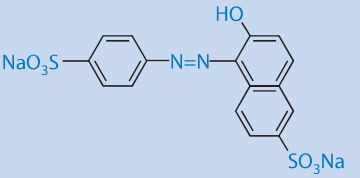
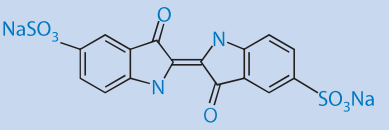
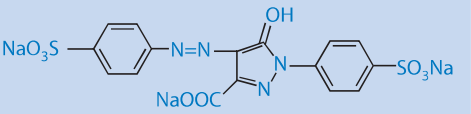
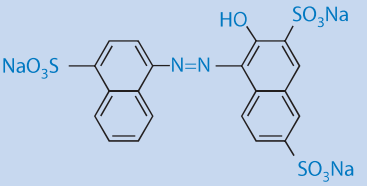
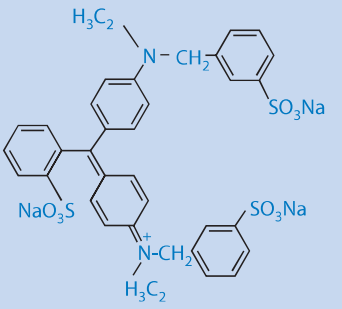
This case raised many issues. Was the patient allergic to E110 (Sunset Yellow FCF, Orange Yellow S, FD&C Yellow 6), or was the patient allergic to

Box 2.1 General system of E-numbers

E100–E199 (colours)
E200–E299 (preservatives)
E300–E399 (antioxidants, acidity regulators)
E400–E499 (thickeners, stabilisers, emulsifiers)
E500–E599 (acidity regulators, anti-caking agents)
E600–E699 (flavour enhancers)

erythromycin itself? The physician concerned was unaware both of the presence of E110 in the formulation and of the apparent cross-reactivity between aspirin and this colouring agent, there being no mention of either in the physician's BNF or in the Pharmaceutical Data Sheet Compendium. To be able to foresee such interactions requires that the structures of the molecules concerned be known and this is a tall order. However, understanding after the event is a reasonable goal for avoiding future occurrences. The structures of some of these dyes are quite complex, as can be seen in Table 2.4, and perhaps

Table 2.4 Adverse effects of dyes and colouring agents

Compound	Structure	Adverse effects
Sunset Yellow		Urticaria exacerbation
Indigo carmine		Urticaria exacerbation
Tartrazine		Headache, gastrointestinal disturbance, exacerbation of asthma, dangerous in aspirin-intolerant individuals
Amaranth		Potential carcinogenicity (banned)
Brilliant Blue		Hypersensitivity reactions

From reference 2.

not surprisingly, some do have pharmacological effects, which are listed in Table 2.4.

Another report[7] discussed patients with reactions to E102 (tartrazine (F&DC Yellow 5)) in oxytetracycline tablets and to E131(Patent Blue V) in a doxycycline formulation.

Azo dyes (those with the –N=N– linkage) account for 60–70% of dyes used in food and textile manufacture. Their acute toxicity is low but some azo dyes have been banned from foods because of the toxicity of dye breakdown products rather than the dye itself. The mechanisms by which tartrazine causes allergic reactions is not fully understood.

Cross-reactivity

Cross-reactivity can be defined as a reaction to different compounds which may or may not have some structural similarity. Often the immune system is involved. Cross-reactions between different azo dyes and *para*-amino compounds have been studied[8] in azo-dye-sensitive subjects, in the clinical aspects of azo dye dermatitis, and to attempt to relate the pattern of cross-sensitisations to the chemical structure of the different dyes. Out of 6203 consecutively tested patients, 236 were sensitised to at least 1 of 6 azo compounds employed as textile dyes. One hundred and seven subjects reacted to Disperse Orange 3 (DO3), 104 to Disperse Blue 124 (DB124), 76 to *para*-aminoazobenzene (PAAB), 67 to Disperse Red 1 (DR1), 42 to Disperse Yellow 3 (DY3), and 31 to *p*-dimethylaminoazobenzene (PDAAB). Co-sensitisations to *para*-phenylenediamine were present in most subjects sensitised to DO3 (66%) and PAAB (75%), in 27% and 36% of DR1 and DY3-sensitive subjects, and in only 16% of subjects sensitised to DB124. After the hands and the face, the neck and the axillae were the most frequently involved skin sites. Cross-sensitisations between azo dyes and *para*-amino compounds can partially be explained on the basis of structural affinities.

Dyes used in lymph node identification

Dyes are used for lymphatic mapping and sentinel lymph node biopsy in patients with breast cancer and other malignant tumors.[9] Some are shown in Figure 2.2.[10] Reports of anaphylactic reactions have become more frequent, although mechanisms remain unclear. Blue dyes administered by a variety of routes can results in the skin of patients turning blue.[11]

Non-ionic surfactants

Non-ionic surfactants are widely used in formulations as wetting agents and solubilising agents. As discussed in Chapter 3, because surfactants are by structure and nature surface active they will accumulate at interfaces, the

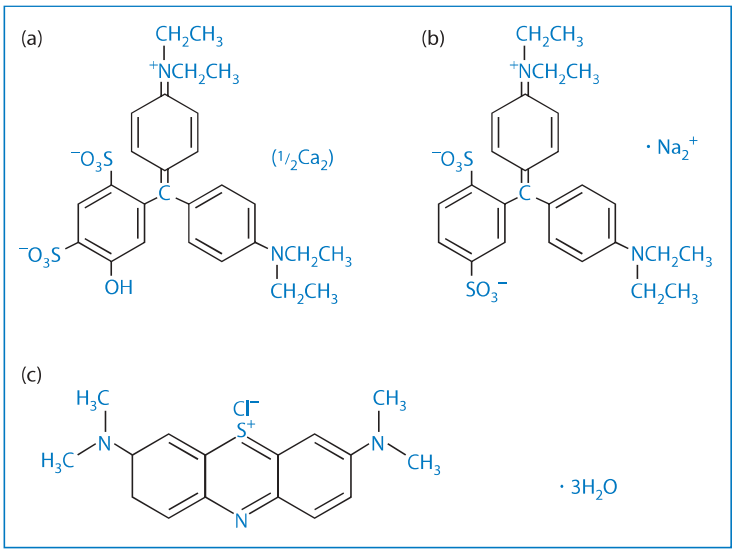
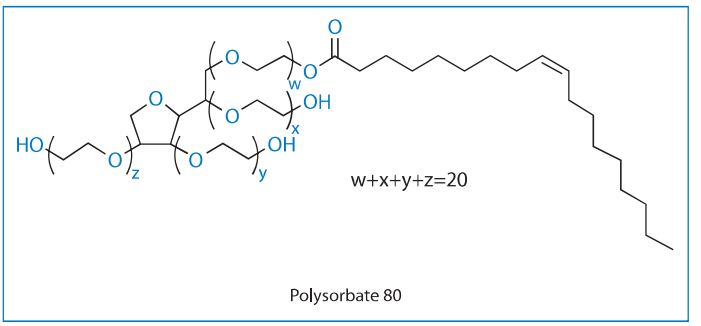


Figure 2.2 Structural formulae of dyes commonly used for sentinel lymph node localisation: (a) Patent Blue V; (b) Isosulfan Blue; (c) Methylene Blue. (Used with permission from reference 10.)

air–water interface and the oil–water interface as well as the membrane–water interface. At membranes they can influence the fluidity of the membrane, and at higher concentrations, generally above their critical micelle concentrations (CMCs), they can cause membrane damage because they can solubilise structural lipids and phospholipids. While non-ionic surfactants allow poorly water-soluble drugs to be formulated as injectables, some have side-effects that are by now well known. The two most commonly used, and therefore cited as causing adverse events, are polysorbate 80 (Tween 80; E433) and a polyoxyethylated castor oil (Cremophor EL). Anaphylactic reactions are the most frequently cited, although they occur in a minority of patients. Hence it is useful, should such reactions to injections occur in new or experimental formulations, that their presence be recognised. Some products that contain Cremophor EL include teniposide, ciclosporin and paclitaxel formulations; docetaxel contains polysorbate 80, as does etoposide. The pharmacological effects of formulation vehicles have been discussed in detail elsewhere.[12] Different formulations of these drugs exist in different countries, hence the true composition must be ascertained in assessing outcomes.



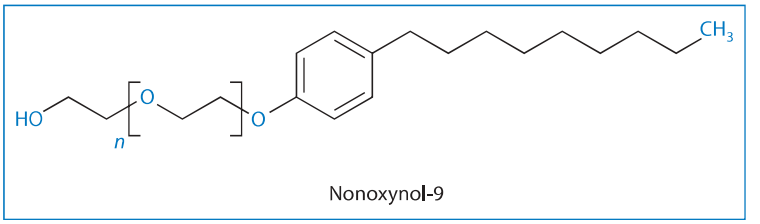
Polyoxyethylene glycols (PEGs)

Polyoxyethylene glycols (PEGs) (macrogols) when used as suppository bases are not surface-active as they are completely hydrophilic with no hydrophobic domains, but they exert an adverse effect through being hygroscopic. They absorb water from the rectal tissues and cause irritation, but this can be minimised by first moistening the PEG base before insertion. This affinity for water is the result of the interaction of water molecules with the oxygen of the repeating $–CH_2CH_2O–$ units; a macrogol of molecular weight 44 500 has approximately 1000 such ethylene oxide units, each interacting with up to four H_2O molecules. Macrogols 4000 and 3350 are used to sequester water in the bowels (Idrolax (Ipsen) or Laxido (Galen). As the BNF states, 'giving fluids with macrogols may reduce the dehydrating effect sometimes seen with osmotic laxatives.'

Paediatric powder formulations of PEGs are available for faecal impaction and constipation (Movicol Paediatric, Norgine) with a dose of 6.563 g of Macrogol 3350. Sodium dodecyl (lauryl) sulfate is also an ingredient of an osmotic laxative, Relaxit Micro-enema. Usually it is found as a wetting agent in pharmaceuticals. Its presence in laxative formulations is most likely to aid the penetration of water into the faecal mass.

Adjuvants as therapeutic substances

Nonoxynol-9 is similar to many non-ionic surfactants used as excipients to increase wetting and entry of water into dosage forms as well as solubilisers. It is used as a spermicide because, being membrane active, it interacts with spermatozoa and reduces their mobility. It has also some activity against HIV. However it also is suspected to increase HIV access through the vaginal wall as it can damage biomembranes. It also increases rectal infection by the herpes simplex virus. The microscopic evidence is clear that the compound damages the epithelial wall as shown in Figure 2.3 in the case of rectal tissue.[13]



Nonoxynol-9

Poloxamers are ABA block copolymer surfactants; in designating them, A is the hydrophilic polyoxyethylene chain and B is the hydrophobic polyoxypropylene chain. The properties of the poloxamers depend of the length of each chain. ABA block copolymer surfactants such as poloxamer 199 have many pharmaceutical uses, as wetting, solubilising and emulsifying agents,

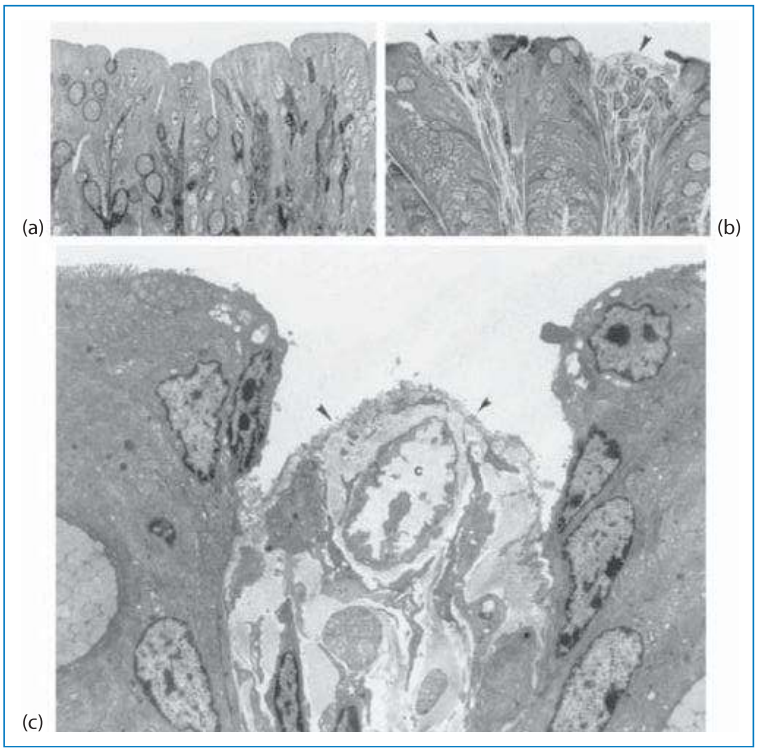


Figure 2.3 Light micrographs of the rectal epithelium and lamina propria of mice treated for 10 min with phosphate buffered saline (PBS) (a) and nonoxynol-9. (b). Control (PBS-treated) tissue is characterised by a continuous epithelium of columnar and goblet cells. In tissue treated with nonoxynol-9, epithelial cells appear necrotic. In some areas the epithelium is missing and connective tissue is directly exposed to the rectal lumen (arrows). In the transmission electron micrograph shown in (c), connective tissue (arrows) appears to be exposed to the rectal lumen. Epithelial cells are missing microvilli. A capillary is shown in (c). (From reference 13 by permission of Elsevier.)

but some like poloxamer 188 (Pluronic F68) have interesting pharmacology. Poloxamer 118 has some haemorheological, antithrombotic and neutrophil-inhibiting properties, although studies in a canine model have not proved exciting.[14] However, it improves microvascular blood flow by reducing blood viscosity, particularly in low-shear conditions. Its mechanism of action is not clear, but it is suggested that the surfactant binds to cells hydrophobically leaving the polyoxyethylene chains to provide a hydrated barrier reducing cell–cell, cell–protein and protein-protein interactions in the blood.[15]

Poloxamer 188 has also been studied as a cell repair agent or membrane sealant (Figure 2.4).[16] Researchers are investigating whether poloxamer 188 can help keep muscle cells intact in muscular dystrophy. It can have a protective effect on damaged heart muscle cells. Purified poloxamer 188 also has a beneficial effect on the treatment of sickle cell disease,[17] perhaps because of decreased adhesion of sickle cells to the microvasculature.

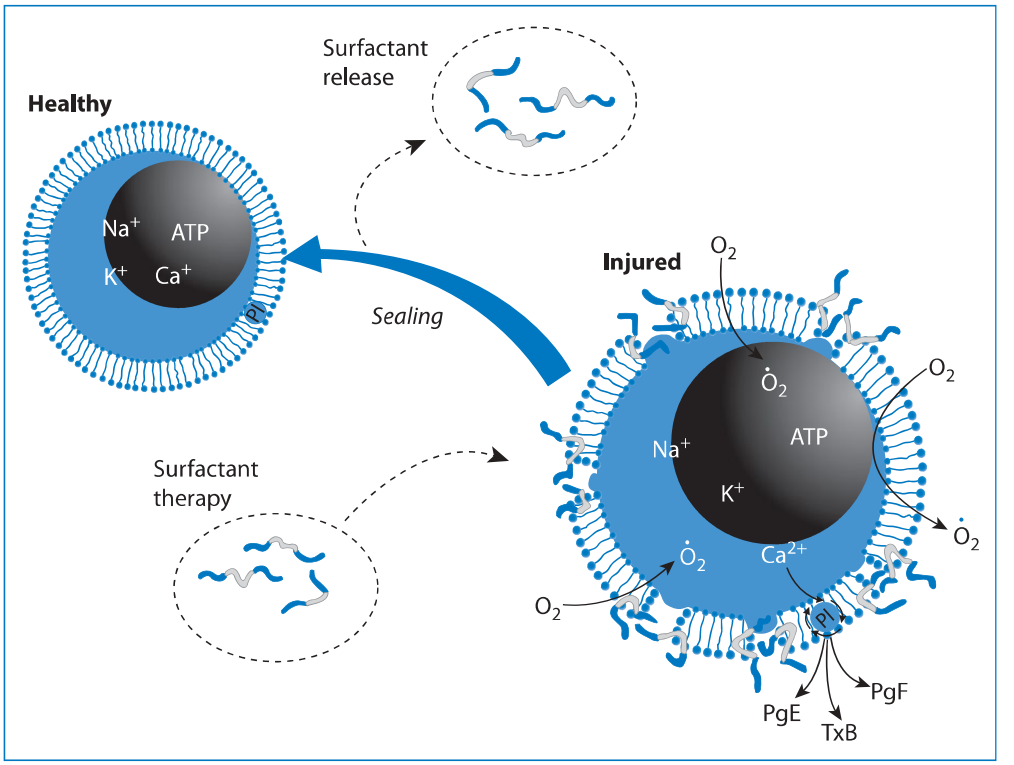


Figure 2.4 Suggested mechanism of action of poloxamer 188 operating at a cell membrane, acting as a sealant. The surfactant shown with its hydrophobic portion in light grey and hydrophilic part in blue interacts with the injured cell 'sealing' the membrane and returning it to normal. ATP, adenosine triphosphate; PgE, PgF, prostaglandin E and F, respectively; T × B, thrombozane B. (From reference 16.)

Talc as therapeutic agent and excipient

Talc is hydrated magnesium silicate; there are variable amounts of calcium, magnesium and iron present in different samples of talc. Its particle size can vary considerably. Humble talc is used not only in baby care but also as a lubricant in the manufacture of tablets and also as a lubricant for surgical gloves.

There is one less well known use of talc, which is as a therapeutic agent rather than as an excipient. This is in the procedure of pleurodesis, when the membranes around the lung adhere. Talc prevents the build-up of fluid between the membranes. An irritant such as bleomycin, tetracycline or talc powder is instilled inside the pleural cavity to instigate an inflammatory response that 'tacks the two pieces together'.[18] Talc is one of the most effective agents to achieve the desired outcome, but there have been concerns about side-effects, especially acute respiratory distress syndrome (ARDS), assumed to be related to both the particle size and perhaps the shape of the talc particles.[19] Particle size has been found to be key in determining the distribution of talc in the body.[20] Marchi *et al.* point out

that absorption of pleural fluid and particles from the pleural space occurs 'through stomas described on the parietal pleura of animals (in rats the medium cross section area of the stomas is $12.9 \pm 10.3\,\mu m^3$, suggesting the possibility of migration of talc through the lymphatics).' When 85% of the talc particles are greater than 10 µm, talc has been seen in several organs.[21]

In the USA, talc used in this procedure has a smaller particle size than in European samples, and it is in the USA that most cases of ARDS seem to occur. It has been shown[22] in comparing two sizes of talc (normal and large) that they both elicit the same benefit in pleurodesis but the smaller sizes have greater pulmonary and systemic deposition of talc particles and greater pleural inflammation. This is another example where the physical properties of a material influence its biological effect.

Small particles, once they gain entry, can in fact translocate throughout the body, depending on their size and surface properties, an issue discussed briefly in Chapter 8 in the section on pharmaceutical nanotechnology. The smaller the particles, the farther they can travel; hence there is real concern about the migration of such particles whether inhaled, swallowed or inadvertently placed in contact with open wounds, for example.

Freedom from talc on medical gloves

The FDA guidance on surgical and other gloves that come into contact with patients includes the following:[23]

> Donning lubricants such as cornstarch and silicone may make it easier to put on medical gloves. Powdered lubricants are also called *donning powders* or *dusting powders*. Powder from medical gloves directly contacts wounds, body cavities, and skin and can contaminate both the patient's and the user's environment. FDA believes it is important to minimize the amount of powder on finished gloves.
>
> **Examination Gloves.** Cornstarch that meets the specification for absorbable donning or dusting powder in the United States Pharmacopeia (U.S.P.) is a commonly used lubricant for examination gloves. Any powder used for lubricating examination gloves should meet the U.S.P. monograph for absorbable dusting powder or be equivalent in terms of safety and effectiveness. The type, specifications, and source of powder or other donning lubricant used on the gloves [should be specified]. You should not use talc, cotton flock, and other non-absorbable materials as a lubricating, dusting, or donning powder. Recognized consensus standards specify that the inside and outside surface of medical gloves be free of talc.

Active excipients in multiple therapies

When an excipient in one formulation affects, say, P-glycoproteins (P-gp), and is administered along with another product whose absorption is P-gp-dependent, then interpretation of interactions can be obscured if the excipients in both products are not taken into account. Examples might include paclitaxel formulations with Cremophor EL and polysorbate 80 when used along with other formulations. Several non-ionic surfactants have been found to inhibit P-gp-mediated transport *in vitro*;[24] in one system the descending order of effect was Tocopheryl Polyethylene Glycol 1000 Succinate (TPGS) > Pluronic PE8100 > Cremophor EL > Pluronic PE6100 ≈ Tween 80. These surfactants had no effect on MRP2 (multiple drug resistance protein 2) function, suggesting specificity.

The well-known effects of surfactants on absorption enhancement have in the past been thought to be mainly due to direct interactions of the surfactant with biomembranes, at low concentrations causing increased fluidity and transport and at high concentrations causing solubilisation of key membrane components. Sometimes surfactants affect absorption in multiple ways, by interacting with the barrier membrane, by forming a microemulsion and thus aiding dispersal of lipophilic drugs or by affecting intestinal secretory transit.[25]

Conclusions

From these few examples it can be seen that excipients are not always just bystanders in formulations. The field is made more complex by the use of many trade names for dyes and surfactants, so identifying causative agents of adverse events, or positive events such as absorption enhancement, is not always straightforward. Batch-to-batch variation in excipients may be a problem: different amounts of certain impurities such as catalysts may be present depending on the batch and mode of manufacture.

More examples of how excipients contribute to the properties of the finished dose form are discussed in Chapter 6.

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3

Thinking chemically

In this chapter we consider the value of remembering more about the chemistry of drugs, that is, both their organic and their physical chemistry. Chemistry has a large part to play in applying pharmaceutics. There is no pharmaceutics proper without a consideration of the issues in this chapter. However, in the context of this book we cannot go far into the field of medicinal chemistry as such.

Introduction

The representation of a drug molecule by a structural formula, especially a space-filling model, should convey several important messages about the molecule, about its size, shape and nature, frequently determined by the reactive groups and side-chains. Structures often show clearly the relationship to other drugs. Equations used in physical chemistry should convey a meaning also, but when one is faced with both formulae and equations the relevance does not always shine through. One cannot retain in one's memory the structures of all drugs and excipients one has come across. There are particular problems with the structures of proteins and oligopeptides, which do not lend themselves to detailed representation in the same way as for smaller molecules. Nonetheless, there are things to be learned from a knowledge of the primary, secondary and tertiary structures of proteins and other macromolecules and constructs. Even the comprehension of the size and molecular volume of these molecules can be valuable, especially in relation to their absorption.

It is not so much the knowledge of one particular compound that is of utmost importance, but the recognition of similarities between molecules and between classes of molecules; for example, to allow prediction of whether or not a new drug is likely to have similar pharmacological effects and side-effects to an established one with similar structure.

The chemistry of drugs and clinical pharmaceutics

Pharmaceutics would not exist without taking into account the chemistry of drugs and other therapeutic agents. Although chemistry is part and parcel of each pharmacy course, the clinical practice of pharmacy is hampered by the neglect of structural knowledge. For all the chemistry that is taught, sometimes the knowledge of drug properties and especially structure that remains in the memory at the end of a course is wanting. Yet the chemistry of a drug tells us much more than the manner of its synthesis and manufacture, important as these are, or about its mode of analysis; it hints at its stability, its methods of detection *in vivo*, its metabolism and its potential to form toxic, long-lasting or even active metabolites. Does drug X form adducts with proteins to cause adverse reactions? Are there indeed structural similarities between drug A and drug B. If so, this might allow us to define similarities in primary activity and also in side-effects. It is in these situations that a knowledge of chemistry allows pharmacists to be more scientific in their evaluation of drugs, drug actions and side-effects.

Remembering chemistry

Some feel that chemical formulae are really not important. Of course if one has never been convinced of their importance, chemical knowledge such as this fades and clearly will not be used in practice: this is a vicious cycle. In interviews I have had with a range of final-year students over three years, too many had difficulty showing that they were at ease with the chemistry of drugs, even at a superficial level. Getting them to recognise the generic structure of a given tricyclic compound (Figure 3.1a) (that is, that it was a tricyclic compound) or a tetracyclic compound (b) (that is, that it was a tetracycle) or a steroid (c) was sometimes painful. The question was not 'What is the INN (International Non-proprietary Name) of this compound whose structure is shown here?', but 'Can you comment on what you see?'. The structures are shown in Figure 3.1.

There were also problems in differentiating macromolecules and smaller organic molecules. A feeling for the order of magnitude of the molecular weight of, say, insulin was far from universal. Some believed that this was around 600, perhaps in line with the expressed belief that steroids are macromolecules. Knowing the INN or chemical names of drugs, but not having a feeling for their structures or properties tells only part of the story. If one can remember the pharmacological action or therapeutic use of a drug but can convey little of what the compound is like chemically, the opportunities to contribute over and above the common knowledge of other health care providers will be lost. This is especially true when we are discussing comparisons between drugs in the same pharmacological class with different chemistries, or those that are in different classes but which have similar chemistry.

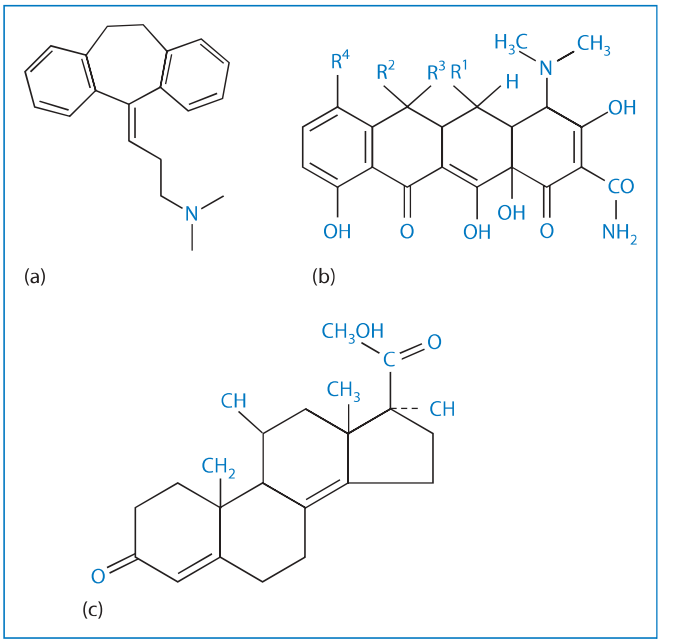


Figure 3.1 (a) A tricyclic compound; (b) a tetracyclic compound; (c) a steroid used in questions.

Some peptides

Having said this, the structure of most oligopeptides and proteins and drugs such as vancomycin (see Figure 3.2) could never be memorized, so other strategies have to be adopted when dealing with these: knowledge of molecular size is important. Molecular size is key in relation to absorption and diffusion. The larger the molecule, all other things being equal, the lower is the

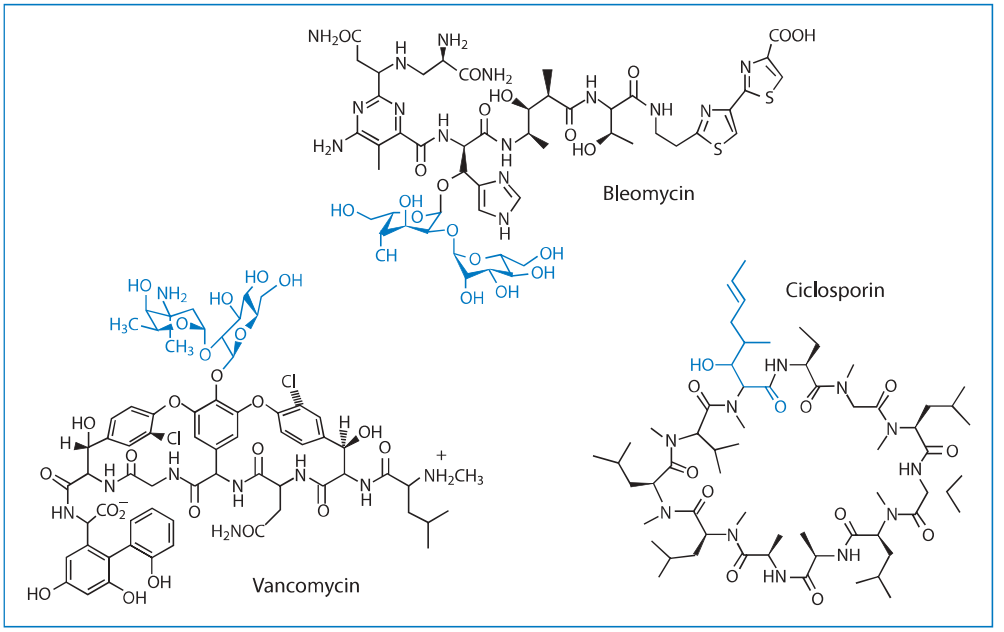


Figure 3.2 Bleomycin, vancomycin and ciclosporin structures.

absorption reduced. Diffusion is inversely related to the radius of a molecule or a particle. Ciclosporin is a peptide yet it is absorbed orally to the extent of around 15% in simple formulations (and more in optimised systems). It is a cyclic peptide and it is also lipophilic: these features contribute to its stability in the gut and its absorption characteristics. The formulation of ciclosporin in lipid vehicles is discussed in Chapter 4.

Knowing the basic structure of the β-lactam antibiotics, one will recall why penicillin can be destroyed by enzymes, but also how impurities in penicillin can lead to allergic reactions, through cleavage of the β-lactam ring and the formation of polymers that have a characteristic peptide linkage (as we will discuss).

Bleomycin (Figure 3.2) is not administered orally; its systemic absorption ranges from 40% to 80% after intrapleural or intraperitoneal administration. The pharmacokinetics of large single intramuscular (IM) or intravenous (IV) injections are almost identical. Vancomycin (Figure 3.2) is a complex molecule with six pK_a values: 7.75 (the NH_2) and 8.89 (NH-Me) (basic) and 2.18 (the carboxyl), 9.59, 10.4 and 12 (the phenolic OH groups) (acidic).[1] Vancomycin is given both intravenously and orally. Because of its size and relative hydrophilicity it is poorly absorbed after oral administration, but as it is used to treat colitis its effect is local and not systemic. Nonetheless, significant absorption has been reported in a patient with bowel inflammation caused by *Clostridium difficile*.[2] The permeability of the epithelium is enhanced in a variety of inflammatory bowel conditions. A 23-month-old child has also been reported to have experienced 'red man syndrome' after oral vancomycin for *C. difficile* colitis, usually experienced after high parenteral doses.[3] Red man syndrome (flushing of the upper body) is often associated with rapid infusion of the first dose of vancomycin. It was initially attributed to impurities in vancomycin preparations, but reports of the syndrome persist after improvement in vancomycin purity. Other antibiotics or other drugs that stimulate histamine release can result in the red man syndrome.

Peptide structures can be rendered in different ways: the conventional two-dimensional structure, and a three-dimensional form that is often useful. This is illustrated for two depictions of octreotide in Figure 3.3.

The logarithm of the partition or distribution coefficient of octreotide at neutral pH (log *P*) is cited as −0.49.[4] Ciclosporin has a log *P* of 2.96. These data may explain the differences in absorption and in routes of administration.

Desmopressin (see the structure in Figure 3.4) has a very low log *P* (of around −4.0 to −5.0). It is a large, clearly hydrophilic molecule with a volume of 768 $Å^3$, yet it is available in oral tablet form (as well as a nasal spray and as sublingual tablets). The fact that an oral form is available is perhaps confusing, but the bioavailability (in the range of 0.08–0.16%) must be one of the lowest that has been accepted for oral administration.

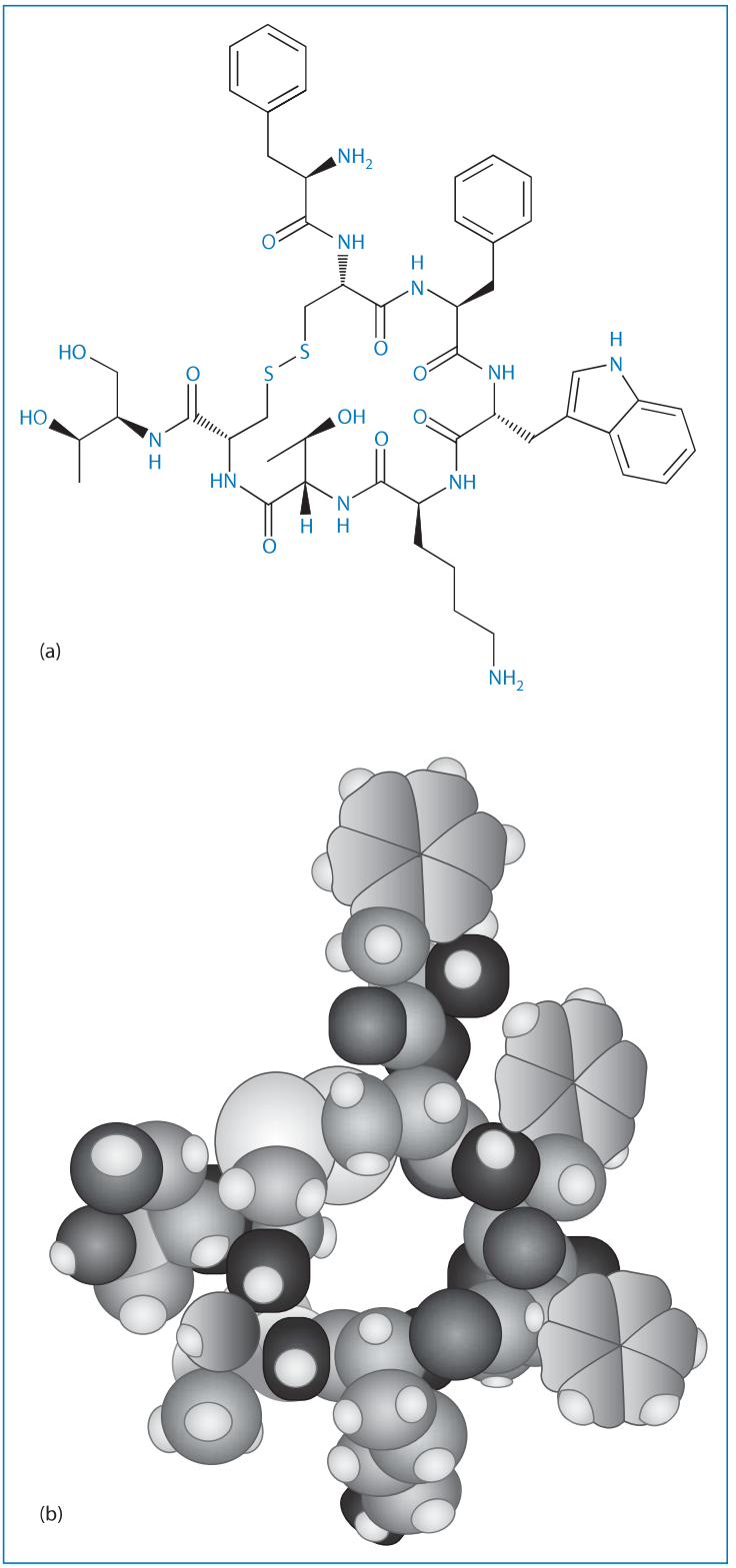


Figure 3.3 Octreotide structure in 2D and 3D modes. The molecule has a volume of 751.35 Å^3.

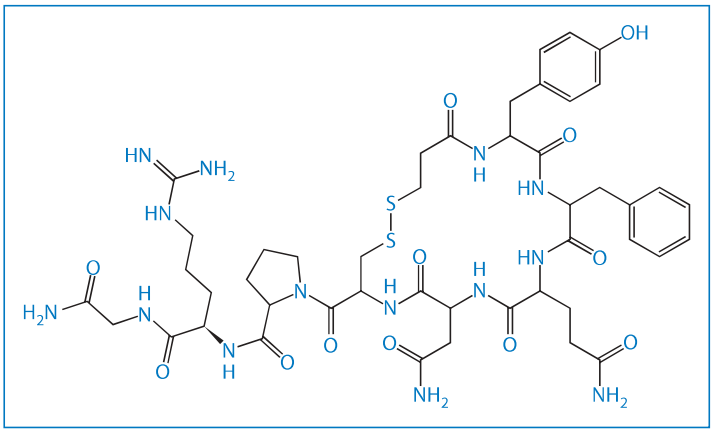


Figure 3.4 Desmopressin: its hydrophilic character can be readily seen in this structural diagram. It is used as the acetate trihydrate.

Molecular size is related to diffusion in tissues, and also to absorption across biological membranes (see Box 3.1). With generic versions of recombinant proteins, some detailed knowledge of the effect of amino acid substitution is important if we wish to understand potential differences between so-called biosimilars (see Chapter 7).

The formulation of peptides, proteins and other macromolecules to a large extent determines the pharmacokinetics of the agent. An example would be octreotide as Sandostatin LAR, in which the drug is dispersed in 30 μm poly(D,L-lactic-co-glycolic acid) (PLGA) particles; these release drug into the body over a period of 4 weeks.

Monoclonal antibodies

Monoclonal antibodies are large structures whose introduction into medicine has been a slow process. To give an example of complexity, the

Box 3.1 Molecular size and diffusion

For spherical molecules and particles the Stokes–Einstein equation applies. The diffusion coefficient, D, is related to the radius (r) of the system diffusing by this equation, where η is the viscosity of the liquid in which the molecule diffuses:

$$D = kT/6\pi\eta r$$

For asymmetric molecules, whether linear or branched or planar, the radius is the so-called hydrodynamic radius, which reflects the effective radius of the molecule in tumbling motion.

molecular weight of infliximab (which binds to the soluble and transmembranous forms of TNFα) is 144 190 Da and its atomic composition is $C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$, which reveals little apart from its sheer size. However, its size perhaps explains both the time to reach a maximum serum concentration (some 7 days[5] after subcutaneous (SC) administration) and its plasma half-life of 9.5 days. The crystalline form of infliximab used in the study was developed for SC administration and shows an extended serum pharmacokinetic profile and high bioavailability compared with the soluble form delivered intravenously.[6]

Chemical nomenclature

The INN names chosen for drugs naturally indicate something about their structure and therapeutic class. Excipients are classified in a less formalised way. If we consider for discussion a compound that is not a drug but is an active formulation component, benzalkonium chloride (see Figure 3.5), it is clear from its name alone that it has a benzyl group, an alkyl group (hydrophobic) and an 'onium' group (hydrophilic). The space-filling model clearly exhibits the form of a surface-active agent. Even if it can be sketched out only roughly, it will be evident that it is a molecule with a hydrophobic portion and hydrophilic entity. It is in fact a cationic surfactant.

Benzalkonium chloride is often found as a mixture of alkyl derivatives of different chain lengths, but it is shown in Figure 3.5 as dodecyl dimethyl

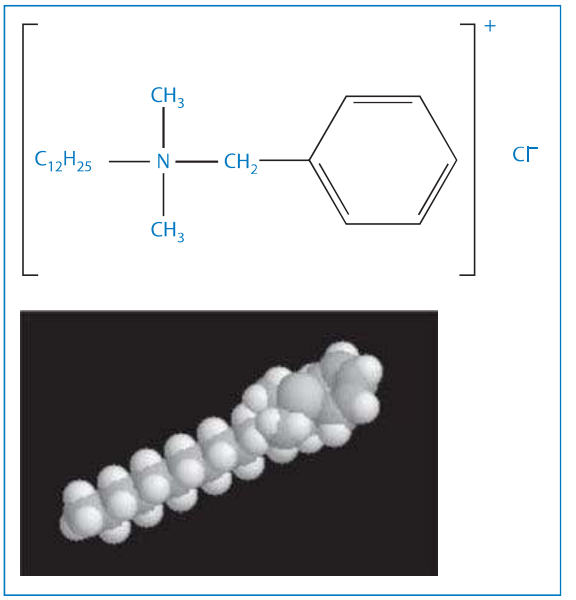


Figure 3.5 Benzalkonium chloride: conventional representation above and space-filling representation below.

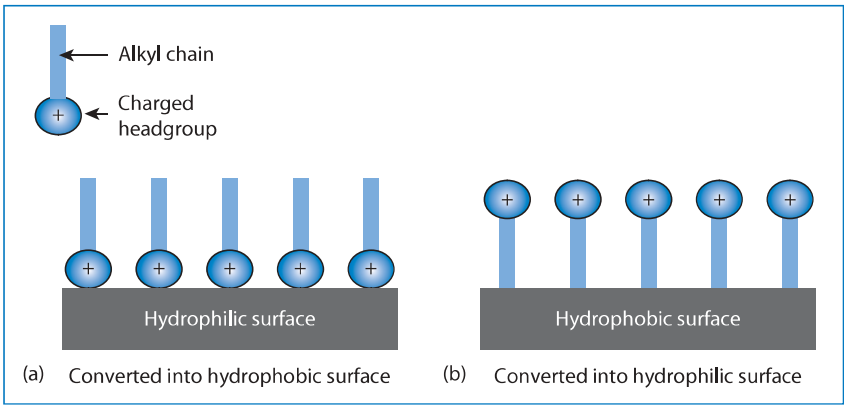


Figure 3.6 Diagrammatic representation of the effects of the adsorption at low concentrations of a cationic surfactant or bactericide (a) by charge–charge interactions with a polar hydrophilic surface and (b) by hydrophobic interactions with a non-polar surface.

benzyl ammonium chloride: conventional representation above and space-filling diagram below). The compound is often a mixture of alkyl chain lengths. The fact that the substance is known as a benzyl-alkyl compound – rather than say a benzyl-dodecyl compound – reflects the fact that it contains a mixture of alkyl derivatives.

Apart from its antibacterial properties, not unrelated to its surface activity, it will adsorb onto all surfaces including biological membranes, contact lenses and glassware; it will lower surface tension, and will change hydrophobic surfaces into hydrophilic surfaces and hydrophilic surfaces into hydrophobic surfaces (Figure 3.6).

Benzalkonium chloride is used as a preservative against microbial contamination in eye drops during use. It might exert other effects: adsorbing onto contact lens material, and concentrating in hydrogel lenses, it can cause irritation to the wearer. It also can have an effect on the tear film itself: if it adsorbs through charge effects onto the hydrophilic negatively charged corneal surface, it can create a hydrophobic region (as shown diagrammatically in Figure 3.6); hence de-wetting will occur and dry spots will give rise to dry eye syndrome at points on the corneal surface (see Chapter 1). Other cationic surfactants are antibacterial. Cetrimide (cetylpyridinium chloride) and CTAC (cetyltrimethylammonium chloride) are two examples, whose structures are shown in Figure 3.7. All those discussed are cytotoxic at high concentrations.

Having looked at the surface-active bactericides, it is reasonable perhaps to expect that even non-ionic surfactants may have biological activity, which indeed they do. The non-ionic nonoxynol has both anaesthetic activity and spermicidal activity. Chemistry therefore sheds light on physical properties, and common properties such as amphipathic structures can lead to intelligent speculation about a compound's behaviour.

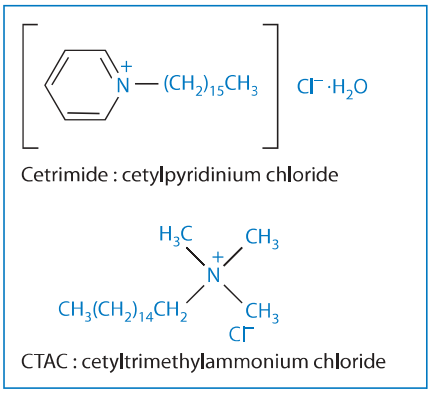


Figure 3.7 Cetrimide (cetylpyridinium chloride) and CTAC (cetyltrimethylammonium chloride).

Surface-active drugs

Many drugs have properties of surfactant molecules[7], possessing in their structure both clearly differentiated hydrophobic and hydrophilic groups. Examples include chlorpromazine, tetracaine, oxprenolol, sodium fusidate, nortriptyline and amphotericin B. The structures of some of these are given in Figure 3.8 to demonstrate the individual structural features necessary for surface activity.

Does surface activity really matter? Given the wide range of actions of surfactant molecules, the possession of this characteristic implies membrane-activity in the case of drug molecules. Critical micellar concentrations of most surface-active drugs are higher than the concentrations they attain *in vivo*, so micellar properties are unlikely to be an issue except in concentrates. The abilities of molecules in dilute solution to decrease surface tension, cause haemolysis, adsorb onto glassware or interact with membranes are all properties of surface-active agents.

Acids and bases

Knowledge of the acidic and basic, zwitterionic or non-ionic properties of drugs allows us to approach answers to questions such as:

1. Is absorption of drug A affected by H_2-blockers, antacids or achlorhydria?
2. Will an increase in pH of the drug solution cause an increase or decrease in the solubility of the drug?
3. Will the drug precipitate when mixed with this fluid?
4. Will alkalinisation of the urine increase or decrease tubular reabsorption?

and so on.

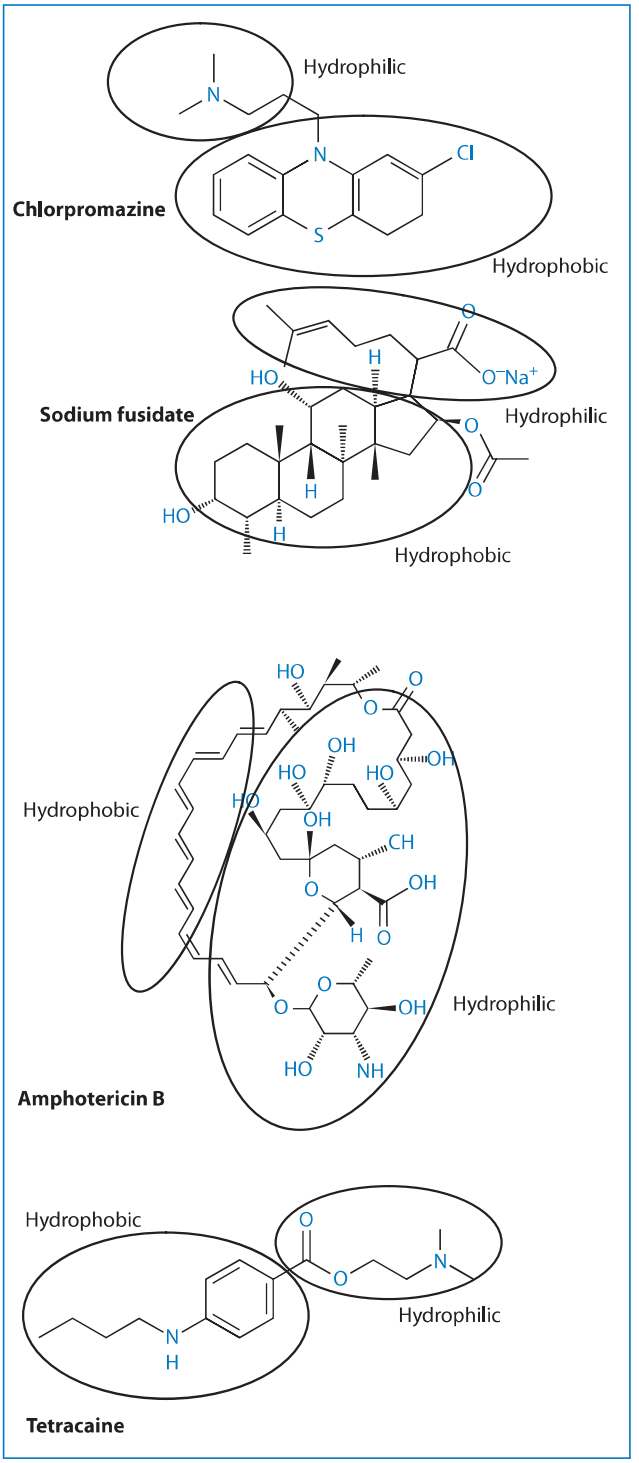


Figure 3.8 Chlorpromazine, sodium fusidate, amphotericin B and tetracaine, showing the hydrophilic and hydrophobic moieties that confer surface-active properties to the molecules.

We cannot really opt for omitting fundamental pieces of pharmaceutical knowledge. We cannot predict under what circumstances, or when, these stored pieces of information will become vital, even if only once in a lifetime. They may save someone's life.

Solubility of acidic and basic drugs

One of the most important relationships in pharmacy, and one that has many ramifications in practice, is that linking pH, pK_a and solubility for acids and bases (see Box 3.2). This is mostly relevant in predicting precipitation of drugs or the outcome of mixing drugs in IV fluids and giving sets. Even in very complex molecules one can look for the appropriate chemical groups, which are those that ionise, confer solubility in aqueous or lipid environments, or lead to breakdown or metabolism. It has to be admitted that in some cases, for example vancomycin, which we have seen has six ionisable groups, it is not simple to predict solubility at different pH values. But solubility experiments are quite straightforward to carry out to determine whether precipitation occurs, for example.

From the equations in Box 3.2, the solubility, S, can be calculated if S_0 is known and the pK_a of the drug is known. One unit change in pH causes a 10-fold change in solubility. Many solutions used in IV therapy, such as dextrose, have pH specifications that vary over at least this range.

Examples of unwanted precipitation of drugs are discussed in Chapter 1. Precipitation can occur when the equilibrium solubility of a compound in solution is exceeded, when the pH of the medium changes either because of addition of buffers or addition of an acidic or basic drug, or owing to electrostatic interactions between an acidic and a basic drug where both are in the ionised state.

Box 3.2 pH, pK_a and solubility

The equation relating pH, pK_a and solubility of acidic drugs, where S is the solubility at any given pH and S_0 is the solubility of the undissociated form of the drug takes the following forms.

For *acidic* drugs:

$$\text{pH} - \text{p}K_a = \log\left[(S - S_0)/S_0\right]$$

For *basic* drugs:

$$\text{pH} - \text{p}K_a = \log\left[S_0/(S - S_0)\right]$$

In the first case the equation can be used in the form

$$S = S_0[\text{antilog}\,(\text{pH} - \text{p}K_a) + 1]$$

and the analogous expression in the second case.

(For further details, see AT Florence and D Attwood, *Physicochemical Principles of Pharmacy*, 4th edn, Pharmaceutical Press, London, 2006, pp. 150–155 and D Attwood and AT Florence, *Physical Pharmacy*, Pharmaceutical Press, London, 2008, pp. 14–19.)

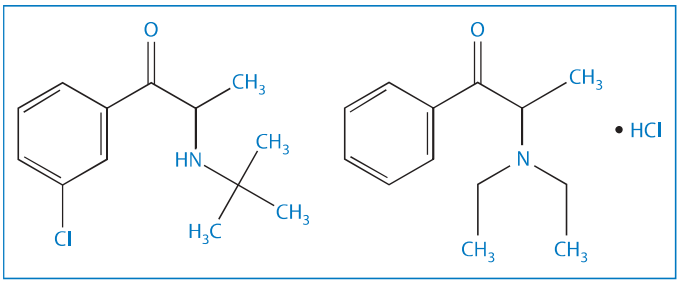


Figure 3.9 Bupropion (left) and diethylpropion·HCl (right).

Structural similarities between drugs

Bupropion and diethylpropion

It has been suggested that the structure of bupropion – a drug with antidepressant properties used primarily as an aid in smoking cessation – is 'almost identical to' that of the controlled drug diethylpropion. The question that this raised is why the two are treated differently in their legal classification. The structures of the drugs are shown in Figure 3.9. Is there indeed the pharmacological effect that one would expect from such analogues? Diethylpropion (Tenuate) is used in the pharmacotherapy of obesity; bupropion (Zyban) has also been studied as an aid to weight loss. One report[8] states that 'there is a serious risk of incorrectly identifying bupropion as only a therapy for nicotine withdrawal without taking the precaution of exploring possible psychiatric co-morbidity.' Diethylpropion also can induce psychotic episodes, but rarely does so at normal doses.

Cross-reactivity

Cross-reactivity relates to the observation of similar pharmacological, immunological or adverse effects of a drug that has structural similarities to another causative agent. The topic of cross-reactivity (generally in the adverse event sense) is a good example of how we need a chemical basis to understand this aspect of medicine. Shenfield and Jackal[9] discuss the possibility of the cross-reactivity between sulfonamides and structurally related drugs such as the sulfonylureas. They refer to a suggestion that sulfonylureas were not recommended in patients with a history of adverse drug reactions (ADRs) to sulfonamides was unwarranted. They provide some evidence that this is true. Why indeed should there be such suggestions in the first place? Some structures of sulfonamides and sulfonylureas given in Figure 3.10 and Table 3.1 suggest why.

Cross-reactivity of sulfonamides

Understanding cross-reactivity is a powerful aid to prediction and explanation of adverse events. As we can see from Figure 3.10, the structural feature

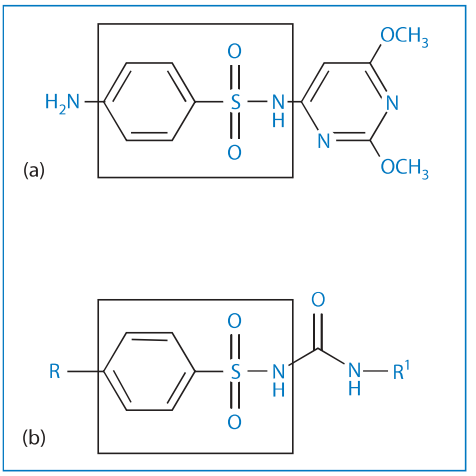
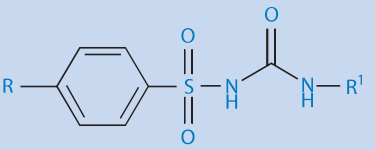
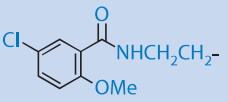
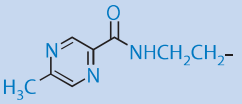
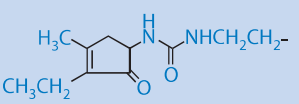
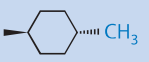


Figure 3.10 Structures of sulfonamides and sulfonylureas. (a) and (b) show the overlapping structures in sulfonamides (a) and sulfonylureas (b).

Table 3.1 The structures of some common sulfonylureas



Name	R	R^1
Tolbutamide	$-CH_3$	$-CH_2CH_2CH_2CH_3$
Chlorpropamide	–Cl	$-CH_2CH_2CH_3$
Tolazamide	$-CH_3$	
Acetohexamide		
Glibenclamide		
Glipizide		
Glimepiride		

within a drug that makes it a 'sulfonamide' is present in many different drugs. Some sulfonamides are anti-infectives and are used in combination with pyrimethamine as antimalarial/antiprotozoal drugs, as anti-infectives in eye-drops (sulfacetamide), or in combination with trimethoprim (sulfamethoxazole in co-trimoxazole). Other drugs also contain a sulfonamide structure (celecoxib, sulfamethoxazole, glibenclamide (glyburide); see Figure 3.11) but not the sulfanilamide structure as in anti-infectives and have no anti-infective capacity.

To investigate the cross-reactivity within different sulfonamide derivatives, T-cell clones (TCCs) obtained from patients with sulfamethoxazole allergy were generated and analysed.[10] The TCCs showed a quite high diversity in their ability to respond to different sulfonamide derivatives. On the one hand, one-half of the clones were highly specific and could be stimulated by sulfamethoxazole only. On the other hand, several clones showed a broad cross-reactivity, responding to up to nine different compounds sharing only a small structural similarity of the side-chain.[10] But all cross-reactive compounds had the sulfanilamide-core structure in common.

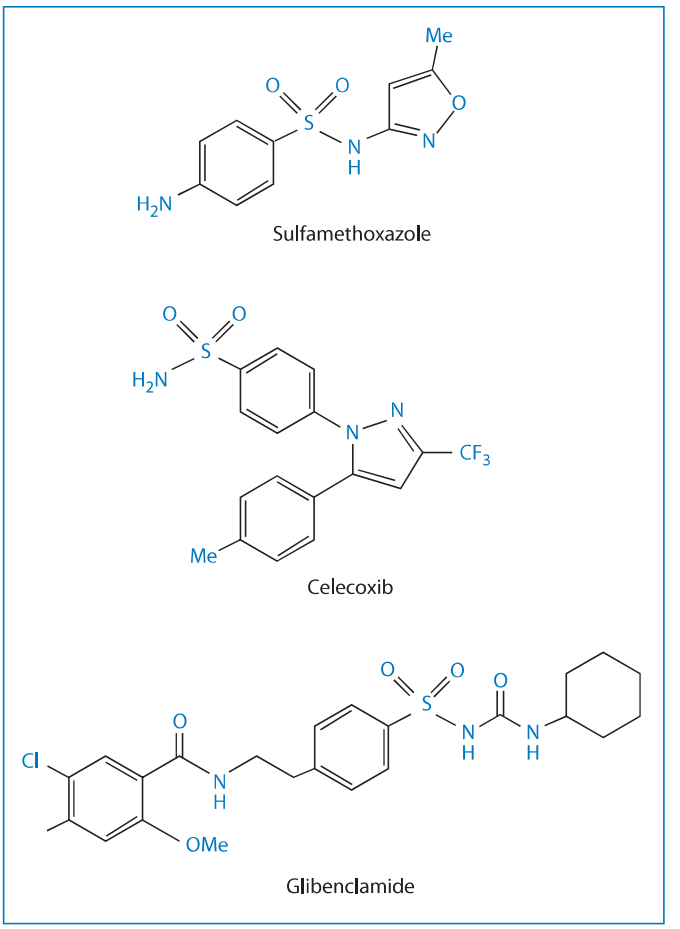


Figure 3.11 Sulfamethoxazole, celecoxib and glibenclamide.

Table 3.2 Classification of allergy due to topical corticosteroids

Group	Agent
A	Hydrocortisone (see structure in Figure 3.12a), hydrocortisone acetate, cortisone acetate, tixocortol pivalate (see structure in Figure 3.12a), prednisolone, meprednisone
B	Triamcinolone acetonide, triamcinolone alcohol, amcinomide, budenoside, desonide, fluocinonide, flucinolone acetonide (see structure in Figure 3.12b), halcinonide
C	Betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone
D	Hydrocortisone 17-butyrate, hydrocortisone 17-valerate, alclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasol 17-butyrate, clobetasol 17-propionate, fluocortolone caproate, fluocortolone pivalate, fluprenidene acetate

Cross-reactivity of topical steroids

Contact dermatitis and testing for topical reactivity are discussed in Chapter 5. Here we refer to the observed cross-reactivity in allergies to topically applied corticosteroids. A classification of allergy due to steroids[11] is given in Table 3.2, but it is not easy to understand from a simple structural point of view (see Figure 3.12)! The table is included here to demonstrate that not all explanations have a straightforward chemical basis.

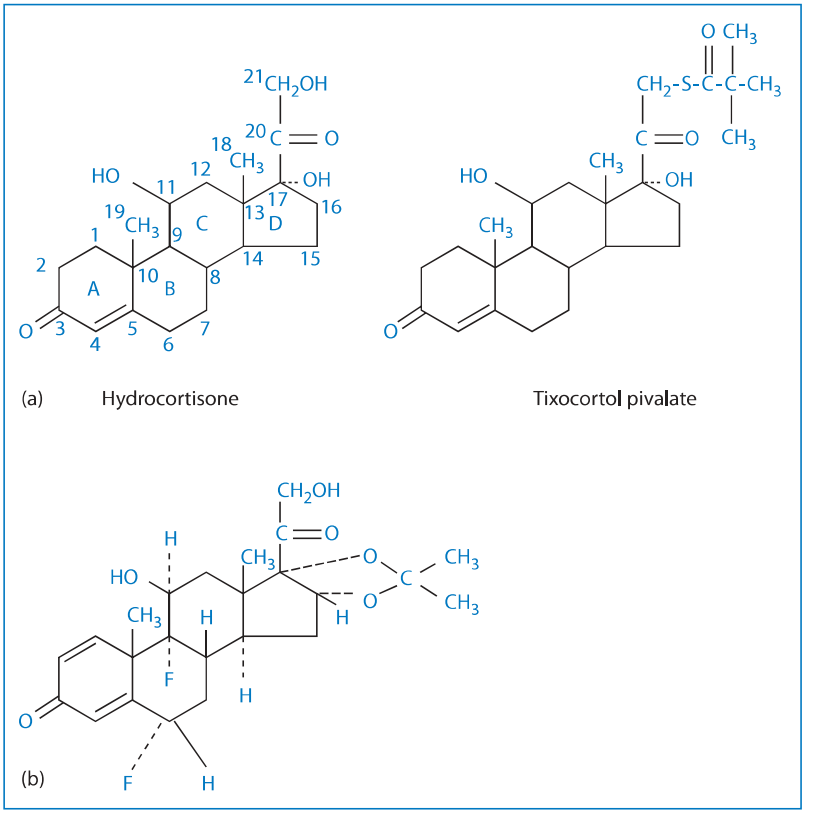


Figure 3.12 (a) Hydrocortisone and tixocortol pivalate, two compounds from Group A steroids. (b) Fluocinonide acetonide: a steroid from Group B. (See Table 3.2)

All these structures of the steroids would need examination along with their physical properties to begin to appreciate their activity. This is the dilemma. However, a neglect of structure will not aid the process and the table will remain a list to be memorised without a solid basis.

Beta-lactam antibiotics and the formation of oligomers

It is clear from the basic structure of the β-lactam antibiotics (see Figure 3.13[12]) how these compounds can be degraded through cleavage of the β-lactam ring and form polymers that have a characteristic peptide linkage. This is what causes these oligomers, dimers, trimers, etc. to have allergic potential.

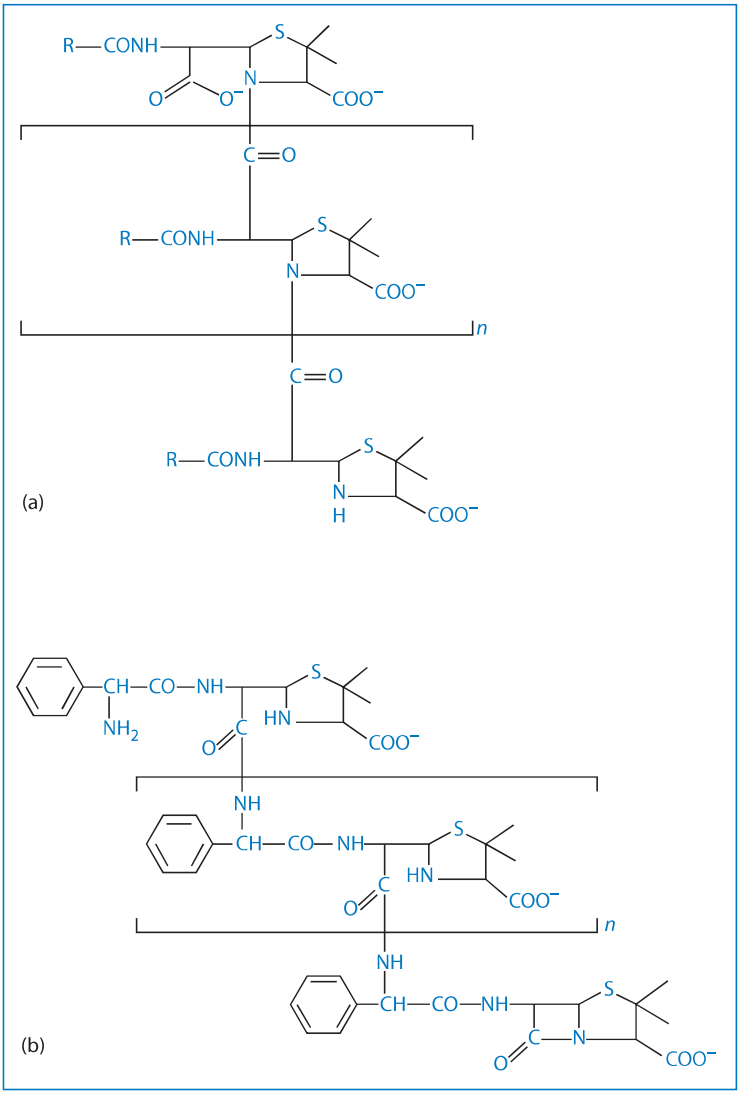
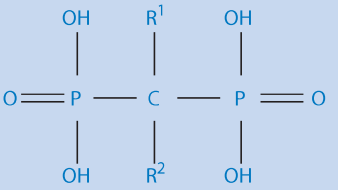


Figure 3.13 Structures of (a) benzylpenicillin polymers (R = benzyl) and (b) ampicillin polymers. In the latter the terminal β-lactam ring may be intact or open. (From reference 12.)

The bisphosphonates

The bisphosphonates are used in osteoporosis to inhibit the resorption of bone by osteoclasts. Their structure gives them a high affinity for bone. They are structurally similar to pyrophosphoric acid and their structural features important to activity are shown in Table 3.3.[13] The binding to hydroxyapatite and the biological action of bisphosphonates depends on the P–C–P group and the structure of the R^1 and R^2 side-chains As one might imagine from their hydrophilic properties, in spite of various modifications to the R^1 and R^2 side-chains, they are generally very poorly absorbed after oral administration. They are administered as their sodium salts, and have bioavailabilities as

Table 3.3 Bisphosphonate structures.



Bisphosphonate	R^1 side-chain	R^2 side-chain
Etidronate[a]	OH	CH_3
Clodronate[b]	Cl	Cl
Pamidronate[b]	OH	$CH_2CH_2NH_2$
Alendronate[a]	OH	$(CH_2)_3NH_2$
Risedronate[a]	OH	CH_2-3-pyridine
Tiludronate[a]	H	CH_2-S-phenyl-Cl
Ibandronate[b]	OH	$CH_2CH_2N(CH_3)$(pentyl)
Zoledronate[b]	OH	CH_2-imidazole
YH 529	OH	CH_2-2-imidazo-pyridinyl
Incadronate	H	N-(cyclclo-heptyl)
Olpadronate	OH	$CH_2CH_2N(CH_3)_2$
Neridronate	OH	$(CH_2)_5NH_2$
EB-1053	OH	CH_2-1-pyrrolidinyl

[a] Bisphosphonates approved for use in non-malignant conditions.

[b] Bisphosphonates approved for use in malignancy for one or more indications.

Other agents are only available for experimental purposes.

(Modified from reference 13 and other sources.)

low as 1%. The instructions for use by patients are to take the products with copious water because the bisphosphonates are irritant to the oesophageal tissues and one must avoid oesophageal capture which results in oesophageal pain and dysphagia.[14] For further examples of this, see Chapter 5 on adverse reactions to formulations.

Hydrophobic and hydrophilic statins

Statins lower blood cholesterol and are prescribed for patients with hypercholesterolaemia or hyperlipidaemia. There are two main types of statins, classified on the basis of their physical properties.[15] These are the hydrophobic statins such as simvastatin or atorvastatin, and hydrophilic statins such as pravastatin (Figure 3.14). The pharmacokinetics of individual statins are

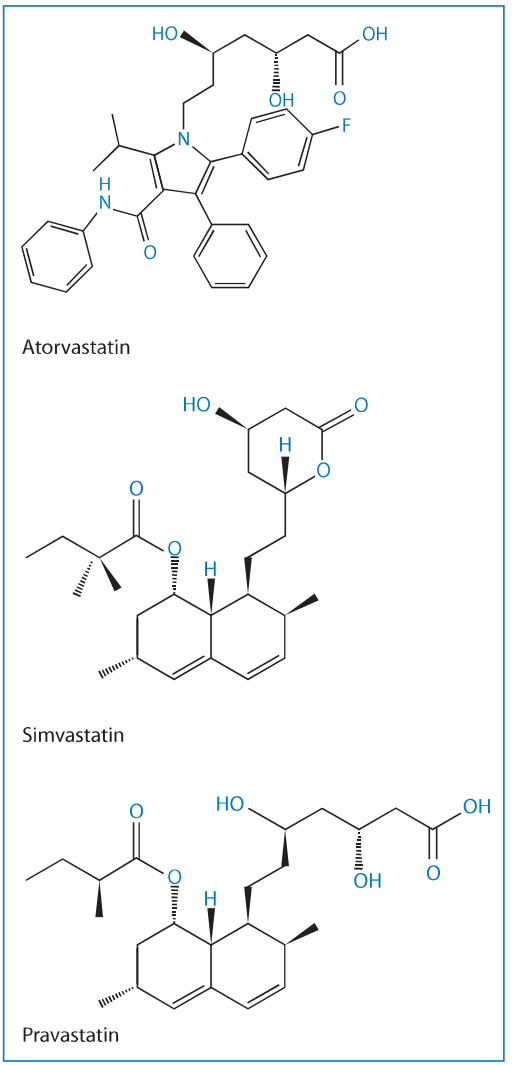


Figure 3.14 Atorvastatin, simvastatin and pravastatin.

influenced by their hydrophobicity. The hydrophobic compounds are transported by passive diffusion and are better substrates for both the P450 (CYP) family of enzymes and transporters involved in biliary excretion. The more hydrophilic pravastatin requires active transport into the liver, is less metabolised by the cytochrome CYP family, and exhibits more pronounced active renal excretion.

Hydrophobic statins can enter extrahepatic and hepatic cells by passive diffusion. Hydrophilic statins are distributed more selectively in hepatic cells. It has been suggested that the former inhibit not only cholesterol synthesis but also the production of essential substances in many extrahepatic tissues and hence cause additional side-effects.

Statins act by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, thereby reducing cholesterol synthesis (see structures in Figure 3.15). Differences in statin structure and binding characteristics contribute to differences in potency of HMG-CoA reductase inhibition and other pharmacological properties.

X-ray crystallographic studies[16] show that the HMG-like moiety built into statin molecules occupies the HMG binding site of the enzyme. Hydrophobic groups of the statins occupy a binding site exposed by movement of flexible helices in the enzyme catalytic domain. In addition to bonds formed by the HMG-like moiety, statins exhibit different binding interactions in association with their structural differences. Type 1 statins (e.g. simvastatin) exhibit binding via a decalin ring structure, and type 2 statins (e.g., rosuvastatin, atorvastatin, fluvastatin) exhibit additional binding via their fluorophenyl group. Rosuvastatin and atorvastatin exhibit hydrogen bonds absent from other type 2 statins; rosuvastatin forms a unique bond through its electronegative sulfone group (see Figure 3.15).

Photochemical reactions and photoinduced reactions

First, it is essential to define a variety of light-induced effects. These include:

- *Photoallergy*: an acquired immunological reactivity dependent on antibody- or cell-mediated hypersensitivity.
- *Photosensitivity*: a broad term used to describe an adverse reaction to light after drug administration, which may be photoallergic or phototoxic in nature.
- *Phototoxicity*: the conversion of an otherwise non-toxic chemical or drug to one that is toxic to tissues after absorption of electromagnetic radiation.
- *Photodynamic effects*: photoinduced damage requiring the presence of light, photosensitiser and molecular oxygen.

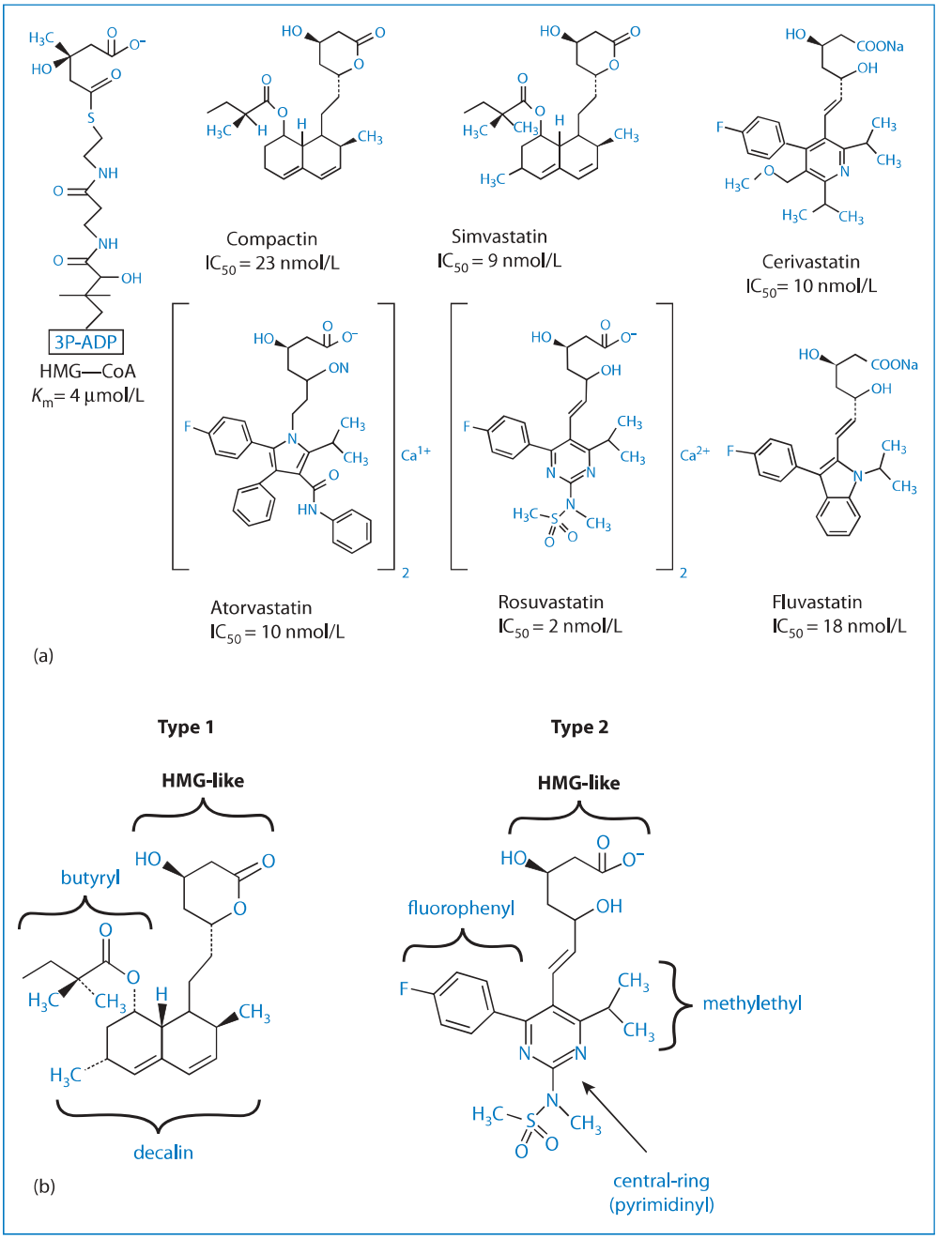


Figure 3.15 (a) The structure of HMG-CoA is shown at the left side of the diagram. Type 1 statins including compactin and simvastatin, and type 2 statins including atorvastatin and fluvastatin are shown. (b) The diagrams of the two types show some of the chemical differences between the them. The similarities between the HMG-like portions of the molecules are clear. The hydrophobic sites are indicated. (From reference 16.)

- *Photodynamic therapy (PDT)*: therapy in which photoactive drugs inactive in the unexcited state are administered and activated at particular sites in the body.

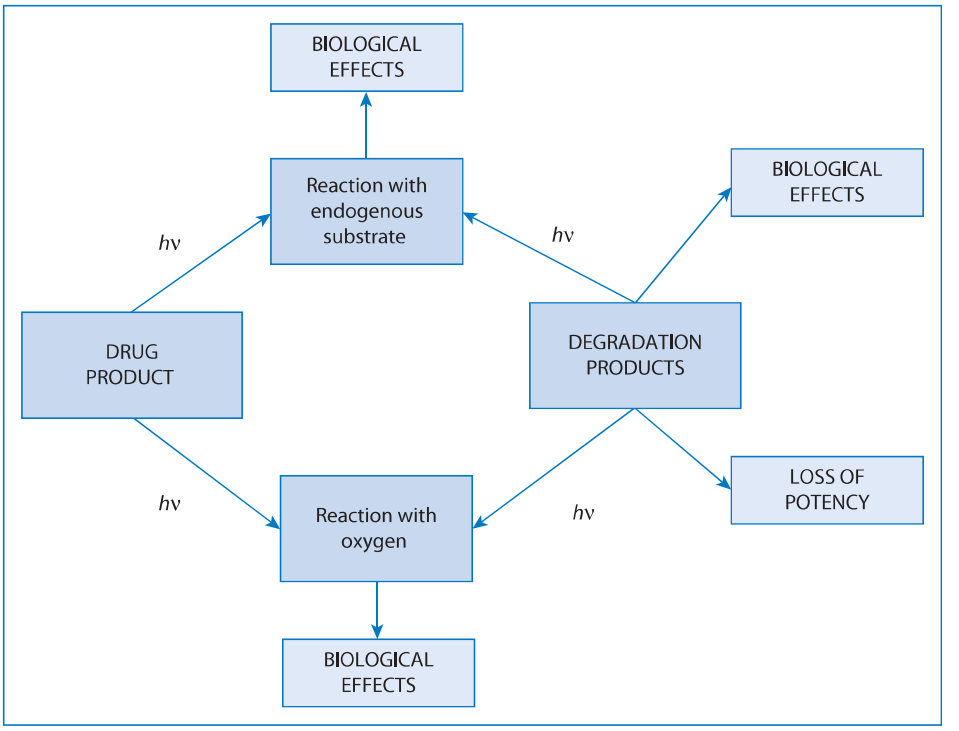


Figure 3.16 The consequences for a light-sensitive drug of interaction with light energy, causing biological effects and loss of potency depending on the compounds involved. (Redrawn from reference 17.)

Many drugs decompose *in vitro* after exposure to light, but the consequences depend on the nature of the breakdown products (Figure 3.16)[17]. Some derivatives of nifedipine have a very short photochemical half-life, sometimes of the order of a few minutes, while others decompose only after several weeks' exposure. A drug may not decompose after exposure to light, but may be the source of free radicals or of phototoxic metabolites *in vivo*. Adverse reactions occur when the drug or metabolites are exposed to light and the absorption spectrum of the drug coincides with the wavelength of light to which it is exposed. (The wavelengths of UV-A are 320–400 nm; of UV-B 280–320 nm; and of UV-C 200–290 nm.) To behave as a photoallergen, a drug or chemical must be able to absorb light energy present in sunlight and on absorption of the light generate a chemical species capable of binding to proteins in the skin, either directly or after metabolism.[18]

How do photosensitisers work?

In photodynamic therapy, drugs that may be activated by light are administered intravenously. The drug remains inactive until exposed to light with a wavelength that can penetrate the skin but is not completely attenuated by the

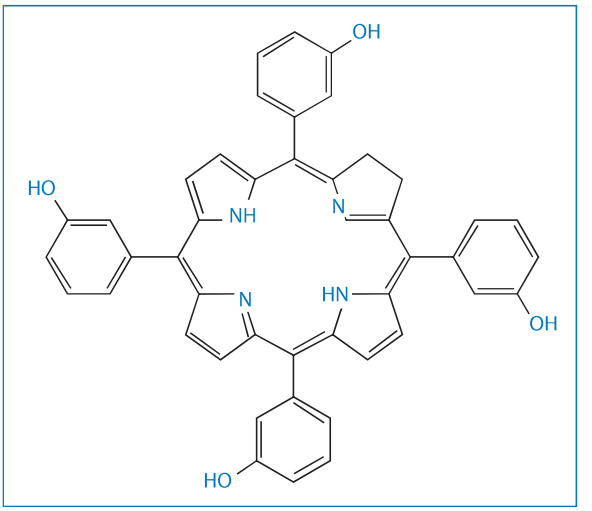


Figure 3.17 Temoporfin.

blood. Most photosensitive drugs respond best to blue or green light *in vitro*, but these wavelengths can pass through only a thin layer of human skin. Red blood cells absorb blue and green light, making it impossible for most photosensitisers to work in deep or bloody places. Texaphyrins, on the other hand, respond best to a specific red light that passes through blood. Light energy is directed to the required site through a fibre-optic device. When activated, the drug – usually a porphyrin derivative – creates oxygen radicals that destroy tissue in its vicinity. Principal side-effects of drugs like Photofrin are a skin sensitivity to light for up to 6 weeks as the drug is available systemically and partitions into lipid layers.

Other drugs cause light sensitivity; these are those that deposit in the skin and either interact with light or degrade to form coloured complexes. Coloration is not always sign of pathological change.

Temoporfin (Foscan; see Figure 3.17) and porfimer sodium (Photofrin) are used in PDT of various tumours. Activated by laser light they produce a cytotoxic effect in the tissues in which they accumulate. Temoporfin is licensed in the UK for the therapy of advanced head and neck cancers, while porfimer sodium is used in the PDT of non-small-cell lung cancer and oesophageal cancer. The cautions given in the BNF for porfimer are to 'avoid exposure of the skin to direct sunlight or bright indoor light for at least 30 days', and for temoporfin 'for at least 15 days' but to avoid prolonged exposure of the injection site to direct sunlight for 6 months after administration.

Chemical photosensitivity

In chemical photosensitivity, patients develop redness, inflammation, and sometimes brown or blue discoloration in areas of skin that have been

Table 3.4 Some substances that sensitise skin to sunlight

Type	Examples
Anxiolytics	Alprazolam, chordiazepoxide
Antibiotics	Quinolones, sulfonamides, tetracyclines, trimethoprim
Antidepressants	Tricyclics
Antifungals (oral)	Griseofulvin
Antihypertensives	Sulfonylureas
Antimalarials	Chloroquine, quinine
Antipsychotics	Phenothiazines
Diuretics	Furosemide, thiazides
Chemotherapeutics	Dacarbazine, fluorouracil, methotrexate, vinblastine
Anti-acne drugs (oral)	Isotretinoin
Cardiovascular drugs	Amiodarone, quinidine
Skin preparations	Chlorhexidine, hexachlorophene, coal tar, fragrances, sunscreens

exposed to sunlight for a brief period. This reaction occurs after ingestion of drugs, such as tetracycline, or the application of compounds topically in consumer products such as perfumes or aftershaves. These substances (Table 3.4) may make some skin more sensitive to the effects of ultraviolet (UV) light. Some develop hives with itching, which indicates a type of drug allergy triggered by sunlight.

Burns after photodynamic therapy

Problems have been reported during a clinical trial with Foscan. This contains temoporfin as its active ingredient. In the trial it was alleged that a high proportion of patients suffered burns.[19] The manufacturer of the product complained that the results were at odds with more extensive trials of the product.[20] It subsequently emerged that in the trials the formulation of the product was different from that of the marketed product. It was claimed that a new solvent had been added so that the drug would be more soluble and less painful to administer. Here was the scenario: trial data are disputed, there is some confusion or inadequate reporting of the formulation used (there are many instances of this including the problems that arise

with the different formulations of amphotericin) and an underlying effect of the active substance, a porphyrin. Later, two of the physicians involved in the trial[21] admitted that there may have been a connection between the leakage and the effect of the solvent as the active agent had spread from the point of administration. The adverse events were not due to extravasation injury itself as they occurred only after photoactivation.[22] This is a good example of the interlocking effects of drug, formulation and the nature of clinical trials, where the influence of the formulation was underestimated or neglected.

Chelation and tetracyclines

It is well known that tetracyclines chelate with divalent or trivalent ions, forming coloured compounds. The tetracyclines also chelate with growing teeth, so that children who have been prescribed tetracyclines can develop discoloured dentition. The colour of the complex depends on the tetracycline concerned. A tetracycline can be chosen that chelates only poorly or that does not form a strongly coloured product. The three potential chelation sites of doxycycline are shown in Figure 3.18. Chelation can also reduce the absorption of the tetracycline as the complexes formed have twice the molecular weight of the single drug molecule, as seen in see Figure 3.18b.

Sugammedex: a cyclodextrin derivative

Sugammedex (Figure 3.19) is an example of a modified excipient that is used therapeutically. It is a γ-cyclodextrin derivative which, when administered intravenously, complexes with rocuronium and other neuromuscular blocking agents (Figure 3.20) and thus reduces the levels of the anaesthetic, acting as an antagonist.[23] The complex is excreted mainly in the urine. The concept has been described as the 'doughnut and the hole' approach.[24]

The negative charge on the sugammedex (it is used as the sodium salt) attracts the positive charge of the rocuronium. Clearly sugammedex has affinities with other similar anaesthetic molecules such as vecuronium, but not atracurium which, as can be seen in Figure 3.20, has bulky benzylisoquinolinium groups that cannot be accommodated into the cavity of the cyclodextrin. Hence, levels of atracurium will not be changed by administration of sugammedex, but vecuronium levels are reduced. Although its affinity for the sugammedex is weaker, it is itself seven times more potent than rocuronium, so that fewer molecules are present. Vecuronium blockage can thus be successfully achieved. The possibilities of forming complexes with other steroidal molecules such as aldosterone and glucocorticoids have been found to be insignificant.

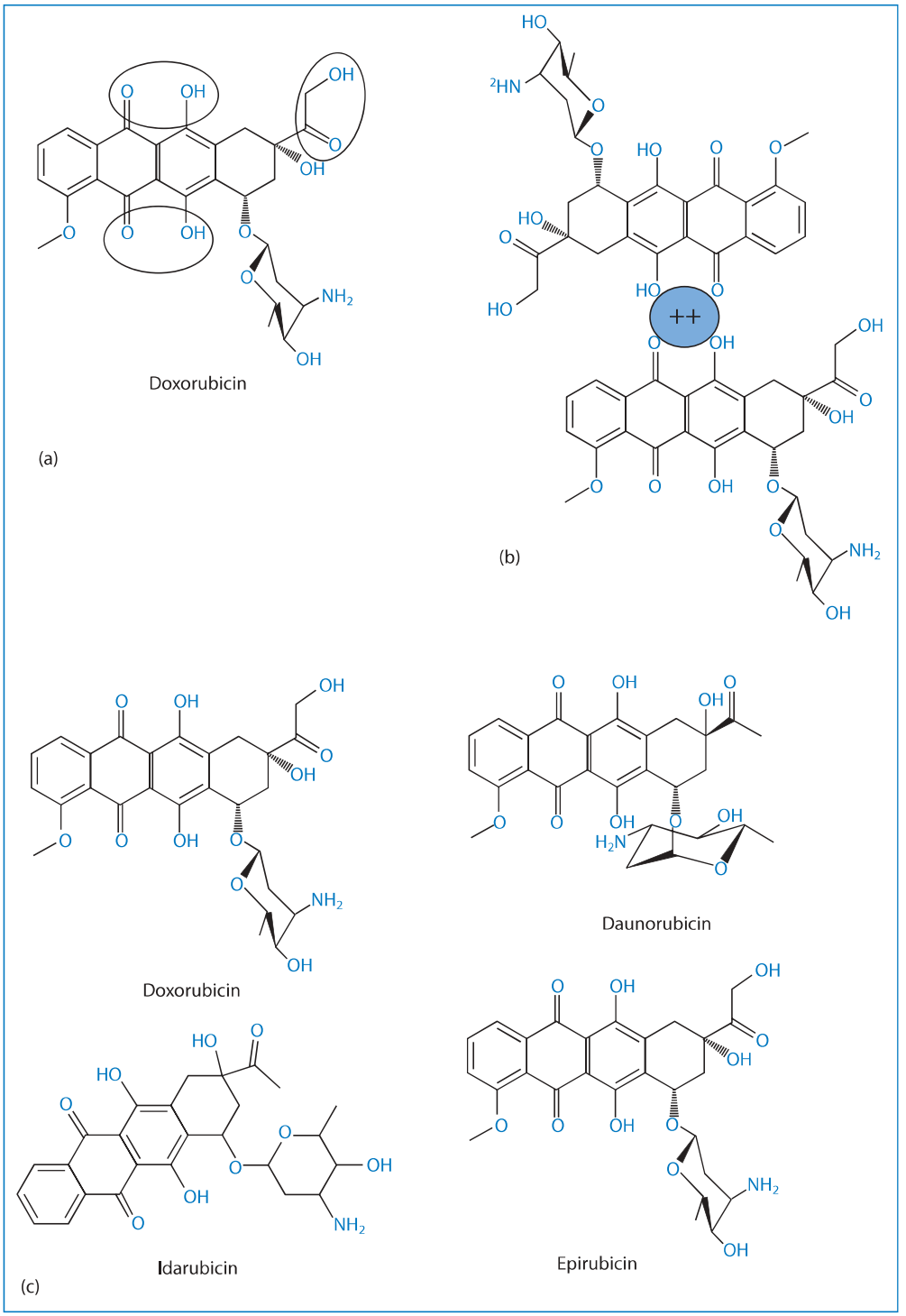


Figure 3.18 (a) Doxorubicin. (b) A 2:1 complex of doxycycline with a divalent ion, e.g. calcium. (c) Tetracycline derivatives: doxorubicin, daunorubicin, idarubicin and epirubicin do not all have the same ability to chelate with divalent or trivalent ions.

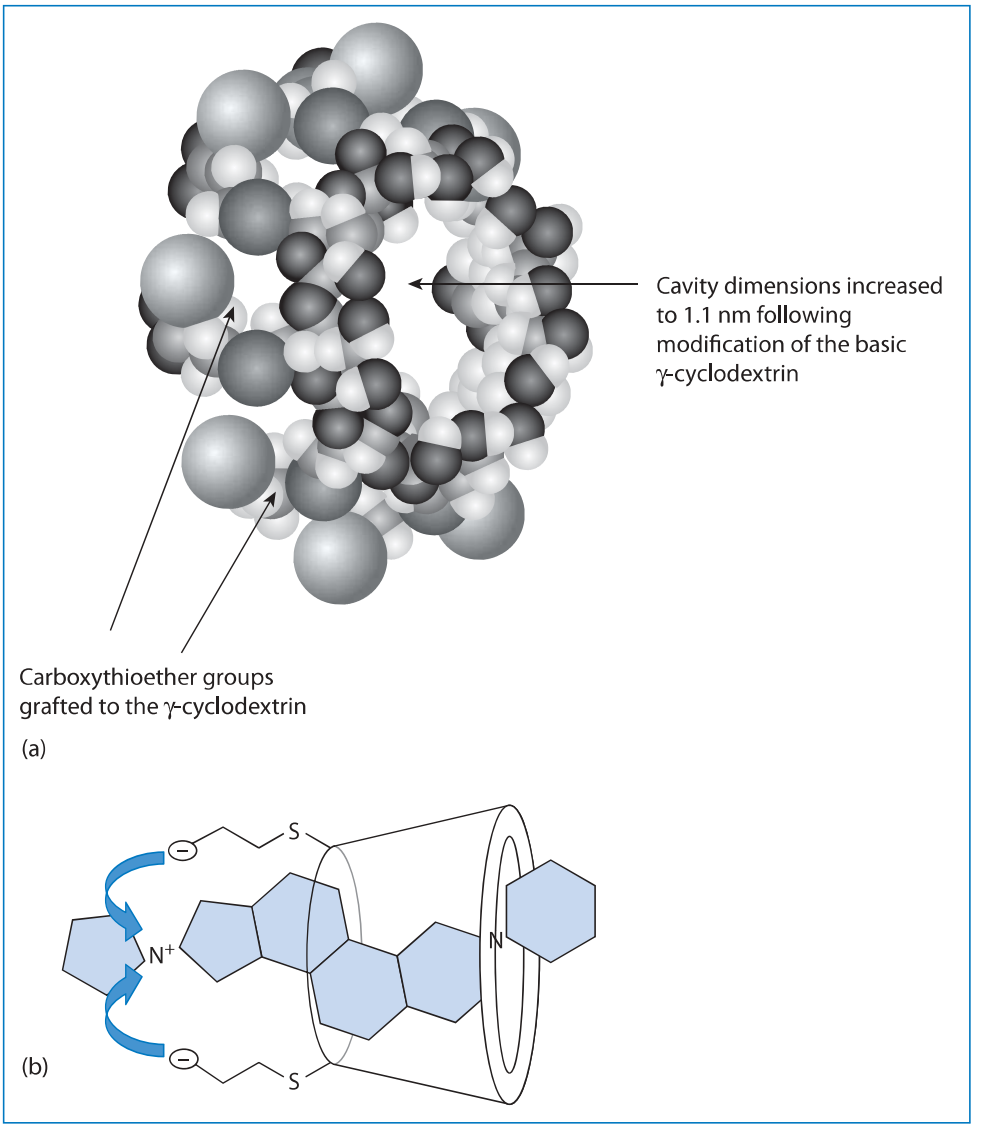


Figure 3.19 (a) Perspective and (b) schematic view of the interaction of sugammedex.

Conclusions

This chapter has drawn attention to some of the issues that may be encountered in practice where the chemistry of the drug can be of crucial importance in understanding the event in question and of avoiding it in the future if the event is an adverse one. Of course, not all drug actions and results of drug intake can be explained by chemistry alone. One also has always to remember that the metabolite or metabolites of a drug, or its degradation products, may be the molecule or molecules to be concerned with. Thinking chemically gives an added dimension to the knowledge that pharmacists can bring to patient care. It does not require us to know every drug structure by heart, but it does require practice to think of a therapeutic agent as a molecule in a product – a

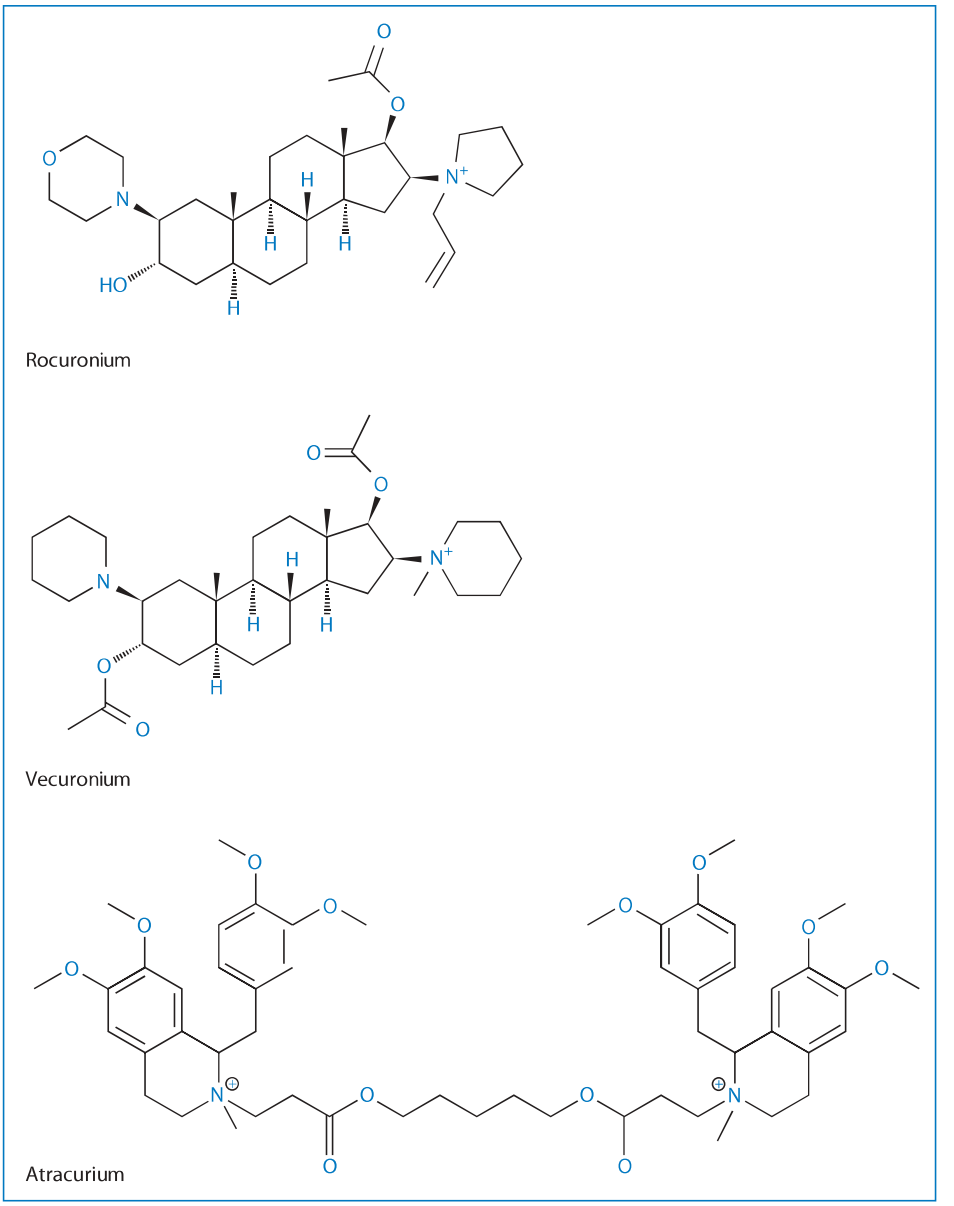


Figure 3.20 Neuromuscular blocking agents: rocuronium, vecuronium and atracurium.

molecule that degrades, that may photosensitise, that may complex with proteins, that may precipitate, and all the other possibilities dealt with in this short chapter. This forces us to look at drug structures and, where this is difficult, as with biological products, nevertheless to think of issues of overall size and charge and stability. In short, when faced with a problem concerning therapy, it is worth asking 'could it be the drug structure that holds the clue?'

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4

Looking at formulations

Introduction

In this chapter some formulations are examined to explore the variety of ways devised to deliver drugs by a variety of routes. Some techniques have solved problems of delivery of 'difficult' drugs, that is, drugs which are insoluble or unstable or are macromolecules which are unstable *in vivo*. Some formulations utilise newer technologies to achieve improved pharmacokinetics and ultimately enhanced patient benefit. Formulation is, of course, still carried out by pharmacists, not only in industry but also in 'specials' laboratories and in many hospital settings. Modern technologies might also allow its return to community pharmacy in the promised era of personalised medicines.

A selection of systems, both as types or as specific formulations, is described here, but it is by no means exhaustive. The purpose is to alert us to recognise issues that might arise with their administration, their admixture, their use and their activity. Some of the effects that are influenced by the nature of the formulation or its ingredients are indeed subtle. One instance that reminds us of this fact is given by the case we discuss later of propofol (Diprivan) injections and the role of lidocaine addition to the formulation. This results in a marked reduction in the pain of injection. It might be expected that a local anaesthetic would act in this way but, as discussed later, it is not so straightforward and this is at least in part due to the effect of the additive on the pH of the preparation.

A general caution is that the formulations of some branded products differ depending on the country of source. We cannot assume that a European formulation is the same as that available in the USA (although most are). This, coupled with the fact that many clinical papers are not specific about the formulation of drugs used, makes the interpretation of the literature somewhat difficult.

Of new drug types, apart from those that are poorly soluble, small ('conventional') organic molecules (molecules up to about 600 Da), proteins and other fragile, poorly absorbed molecules are increasingly part of the pharmaceutical armamentarium. We begin by considering some general aspects of protein formulations.

Protein drugs and formulations

The complexity of proteins as drugs is well known. Peptides and proteins are subject to a variety of chemical and physical instabilities in aqueous solution and at interfaces, and can also suffer during the stresses of some manufacturing processes.

Issues with protein generics

Now that the protein therapeutic market has matured, generic versions of protein drugs are becoming available (see Chapter 7). The source and mode of production of the protein therapeutic is an important issue. With the so-called 'follow-on' protein drugs,[1] compound or product identicality cannot always be demonstrated as it can with conventional molecules. Even with the latter there are often small regulated amounts of impurities, such as dimers, breakdown products and products of side-reactions. The impurities in proteins are often very similar to the parent compound and, although present in low concentrations, may be pharmacologically or immunologically active. Small changes in manufacturing processes may lead to final products that are not identical to the originator's product. Aggregation, protein folding and glycosylation may be affected, any of which can lead to differences in pharmacokinetics, immunogenicity or indeed efficacy. The formulation may or may not influence outcomes. One example has been seen with recombinant human erythropoietin (Eprex). A change of stabiliser from albumin to sorbitol caused the formation of anti-erythropoietin antibodies revealed in pure red cell aplasia.[2]

Pegylated therapeutic proteins

For many years now, proteins have been modified by the covalent addition of polyoxyethylene (PEG, polyethylene glycol) chains to their structures (the process of PEGylation or pegylation). While the intrinsic activity of the protein is generally unaffected, other parameters change so that a pegylated protein must be considered to be a new chemical entity. Pegylation of therapeutic proteins changes their pharmacokinetics and dynamics. It improves the performance of therapeutic proteins, providing them with a longer circulation time *in vivo*, and a reduction in immune responses. There is often also enhanced solubility of the peptide or protein (as might be expected from the addition of these very hydrophilic chains) or improved stability. Increased circulation time decreases the dose of protein necessary for biological action. Reduced antigenicity, immunogenicity and proteolysis are some of the benefits claimed for pegylated over non-pegylated forms of proteins and peptides.

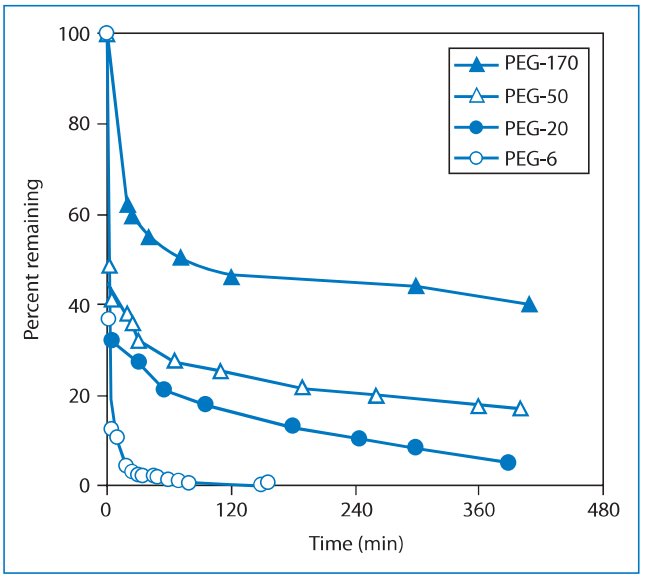


Figure 4.1 The percentage of polyethylene glycols remaining in the circulation as a function of their size (molecular weight: 6 = 6 kDa, 20 = 20 kDa etc.). (From reference 3.)

Why is this? The barrier produced by the PEG chains is both a physical and a thermodynamic one. The polyoxyethylene molecules shield the protein, reducing uptake and loss by the reticuloendothelial system. The resulting larger size of the molecule may, however, confer slower diffusional characteristics on the molecules. The addition of these water-soluble entities not only increases solubility but can also decrease the pH-dependency of protein solubility. Above all, the PEG layer shields the protein from opsonisation *in vivo* and thus the molecules are not scavenged by the reticuloendothelial system (RES) and hence circulation times are enhanced. As might be anticipated, the length of the PEG chain is important: the longer the chain, the longer the circulation time. Figure 4.1 shows the kinetics of unattached PEG molecules as a function of molecular size.[3]

Pegfilgastim is a pegylated recombinant methionyl human granulocyte-stimulating factor indicated in the reduction of the duration of neutropenia and incidence of febrile neutropenia during cancer chemotherapy. It is administered by intramuscular (IM) injection.

PEG-Intron (Peginterferon alfa) (see Figure 4.2) is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. Compared to standard interferon alfa, this modified molecule has a longer half-life after injection, allowing once-weekly injections and superior antiviral efficacy in the treatment of hepatitis C when used in combination with ribavirin. A case of a local blistering reaction developing in a patient receiving pegylated interferon alfa-2b has been reported.[4] Dalmau *et al.*[5] state that although injection site pain is infrequent (2–3%), site inflammation

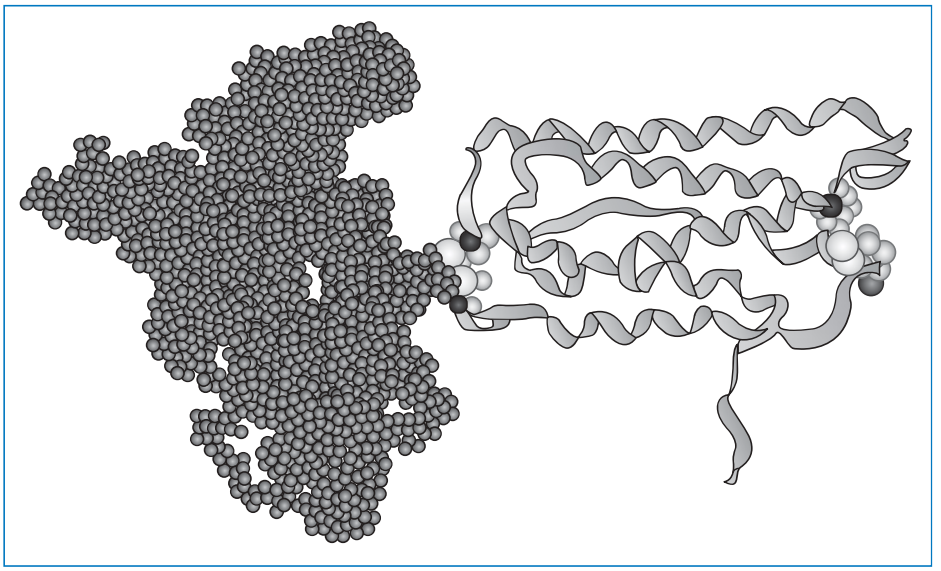


Figure 4.2 Pegylated interferon (Mire Zloh, The School of Pharmacy, University of London). The right-hand portion of the molecule represents the interferon while the left-hand part represents the polyoxyethylene chains.

and skin reactions (e.g. bruises, itchiness, irritation) occur at approximately twice the incidence with pegylated interferon alfa-2b treatment (in up to 75% of patients) compared with ordinary recombinant interferon alfa-2b. Dalmau and co-workers suggest that 'because pegylated interferon alfa-2b has almost completely replaced interferon for its most frequent indications, increased awareness of the possibility of cutaneous necrosis is necessary for early diagnosis to prevent continuation of pegylated interferon alfa-2b injections at the involved area.' There are hints that the pegylated interferon is more toxic at the site of injection than the unpegylated form. This might be due to its higher molecular weight and slower diffusion from the site.

Methoxy polyethylene glycol-epoetin beta (pegzerepoetin alfa; Mircera) is given by subcutaneous injection or intravenous infusion. Its half-life is extended over other forms of epoetin alfa or epoetin beta, as shown in Figure 4.3.

Pegvisomat (Somavert), a pegylated analogue of human growth hormone (hGH) structurally altered to act as a growth hormone (GH) receptor antagonist, comprises 191 amino acids with an average of 4–6 PEG molecules covalently bound to lysine residues and one bound to the terminal phenylalanine. It acts by binding to GH receptors on cell surfaces. The molecular weight of the protein is 21 998 Da and the molecular weight of each PEG chain is 5000 Da; hence there are three predominant molecular sizes in the product with molecular weights of 42 000, 47 000 and 52 000 Da. Thus it is not a homogeneous product, but it should be a *consistent* product in terms of the ratios of the

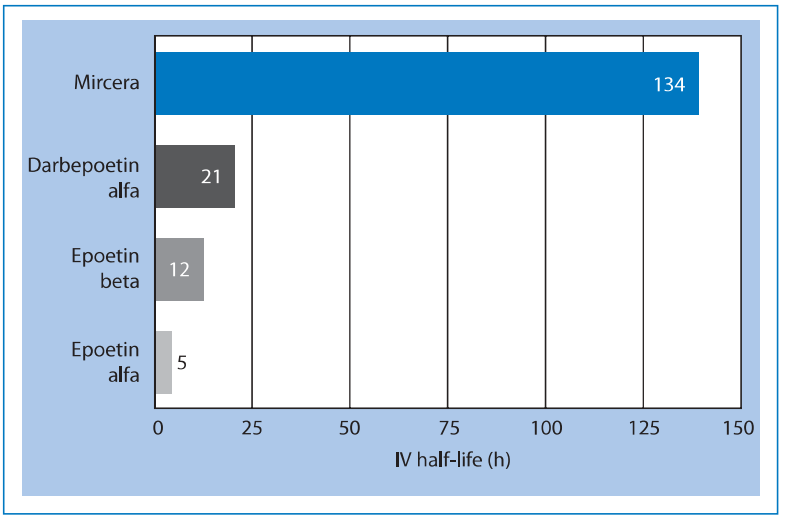


Figure 4.3 The half-life of pegzerepoetin alfa (Mircera) compared with darbepoetin alfa, epoetin alfa and epoetin beta.

predominant species. Clearly, when generic versions become available, information on the molecular weight species will be an important parameter. Peak concentrations after subcutaneous (SC) administration are achieved 33–77 hours after administration, a result likely to be due to its high molecular weight.

Monoclonal antibodies (MAbs)

There are now many monoclonal antibody products available for clinical use. They are most often given by the intravenous (IV) route, but when larger and more frequent doses are required the SC route is preferred. The MAb products, Rituxan (rituximab) and Herceptin (trastuzumab) are administered by the IV route. Treatments with high doses of antibody (>1 mg/kg or 100 mg per dose) require solution formulations at concentrations above 100 mg/mL, given the small volume (around 1.5 mL) that can be administered subcutaneously.[6] Proteins have a tendency to aggregate at high concentrations and there are as well limits to solubility. Aggregation of proteins can affect activity, pharmacokinetic behaviour and immunology. Not least, the viscosity of formulations can increase through aggregation. As the viscosity increases, the force required for injection increases. Even without aggregation there can be a marked temperature dependence of viscosity of MAbs, as shown in Figure 4.4.[7] The appearance of solutions may be indicative of excessive aggregation; opacity usually means that aggregation has occurred.

While proteins (and also RNA and DNA, which can be used therapeutically) require special formulations and handling, there is a range of drugs that have provided challenges and require more or less complex techniques for their delivery. Some of these are discussed here.

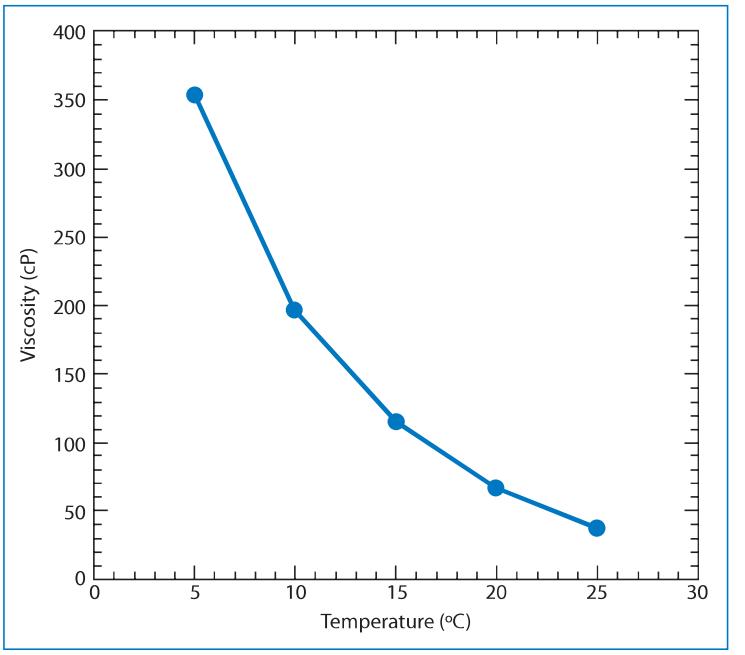
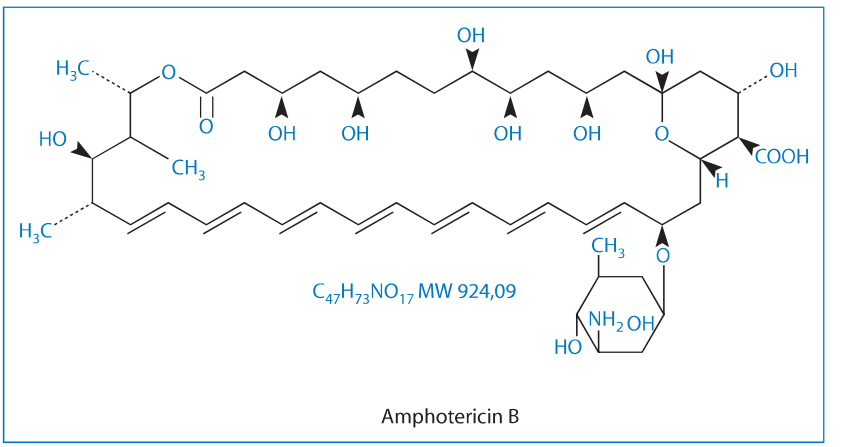


Figure 4.4 The temperature dependence of the viscosity of a solution of a monoclonal antibody in clinical development. The refrigerated product had a very high viscosity which falls markedly on warming. (From reference 7.)

Amphotericin B formulations

Amphotericin B is used in the treatment of severe systemic fungal infections. It is poorly soluble in water and hence a variety of lipid-based and non-lipid formulations have been developed to deliver the drug. Because of the range of types of formulation and trade names, confusion of the nature of the formulation can occur.

A news item in the *British Medical Journal* of 8 September 2007[8] reported on the National Patient Safety Agency's warning about the risk of dosing error following the death of two cancer patients receiving amphotericin. Confusion



Amphotericin B

Table 4.1 Pharmacokinetic properties of amphotericin B formulations

Formulation	Dose (mg/kg per day)	Maximum concentration (μg/mL)	Area under the curve (μg × h/mL)	Volume of distribution (L/kg)	Clearance (mL/h per kg)
AMB desoxycholate	1	2.9	36	1.1	28
Abelcet	5	1.7	14	131	436
Amphotec	5	3.1	43	4.3	121
AmBisome	5	83	555	0.1	11

From reference 9.

between the lipid and non-lipid formulations, it stated, can lead to a dose that is too high or a dose that is too low. The item stated (*in error*) that the patients died after being prescribed the non-lipid form of amphotericin, stated to be AmBisome, but were treated with Fungizone, described as the lipid formulation.

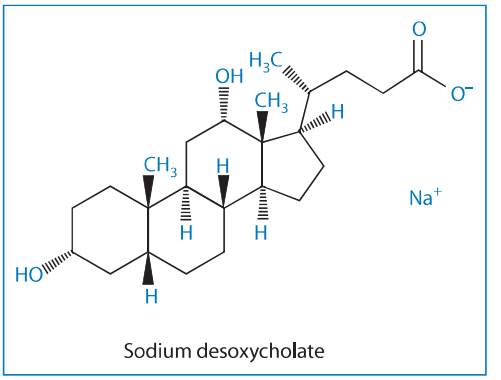
Of course, as will be seen below, Fungizone is the non-lipid formulation while AmBisome is a lipid (liposomal) formulation, which is less toxic than the former. The formulations are described below. This report demonstrated (1) that formulation matters, not least because of differences in the doses of the products but also because of their different pharmacokinetics; (2) that knowledge of formulation matters; and (3) that confusion can arise when there are several formulations of the same drug available that are not bioequivalent.

The various formulations have different doses, clearance rates and bioavailabilities even by the IV route (see Table 4.1 [9]). If the drug is sequestered in lipidic systems such as liposomes, then it is clear that the pharmacokinetics of the drug will be affected. Micellar systems (such as Fungizone) tend not to change significantly the pharmacokinetics of the drug they contain, as micelles have a shorter existence than liposomes and complexed systems.

Fungizone

Fungizone is the original clinical formulation of amphotericin B. It employs sodium desoxycholate (see below) as a micelle-forming bile salt, to solubilise the drug. The formulation is termed the 'conventional' amphotericin B in Martindale (35th edition, page 473). Each vial contains a sterile lyophilised cake or powder containing 50 mg amphotericin B and 41 mg sodium desoxycholate with 20.2 mg sodium phosphate as buffer. It forms a clear colloidal solution, which is then further diluted before administration with 5% dextrose injection with a pH above 4.2. The use of any diluent other than those recommended, or the presence of bacteriostatic compounds such as benzyl

alcohol in any such diluent, may cause the precipitation of the amphotericin B. The side-effects of Fungizone have resulted in the development of the lipid-based systems.



Sodium desoxycholate

Abelcet

This formulation, introduced by the Liposome Company in 1995, is an amphotericin B–lipid complex, the lipids being dimyristoyl phosphatidylcholine and dimyristoyl phosphatidylglycerol. These complexes, illustrated in Figure 4.5, are described as ribbon-like and have dimensions of 500–5000 nm.

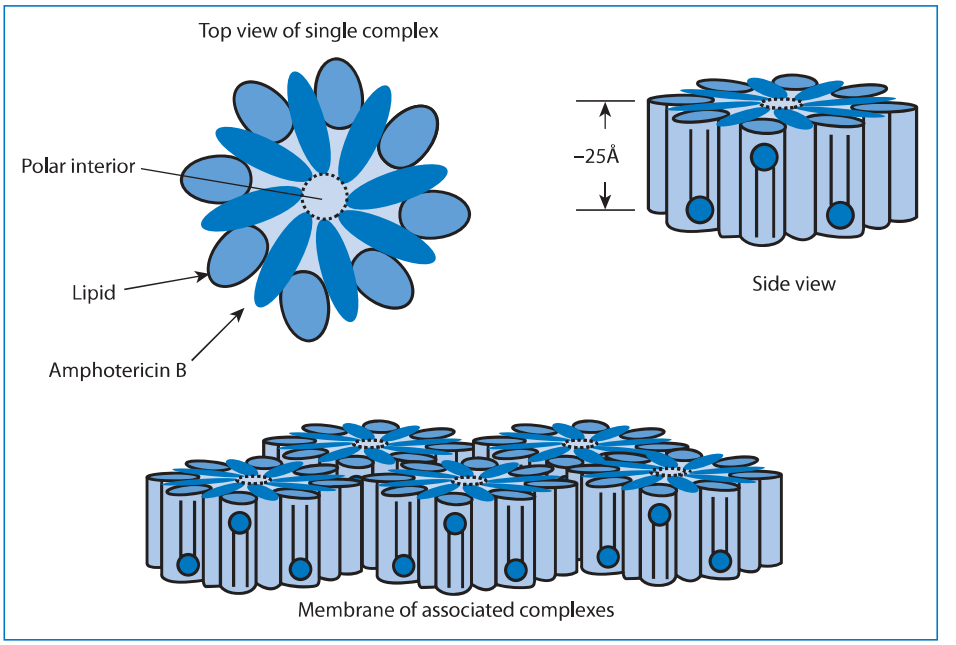


Figure 4.5 The structures of Abelcet in diagrammatic form showing the amphotericin lipid complex from the top and from the side. The lower diagram shows the membrane-associated complexes. (The Liposome Co.)

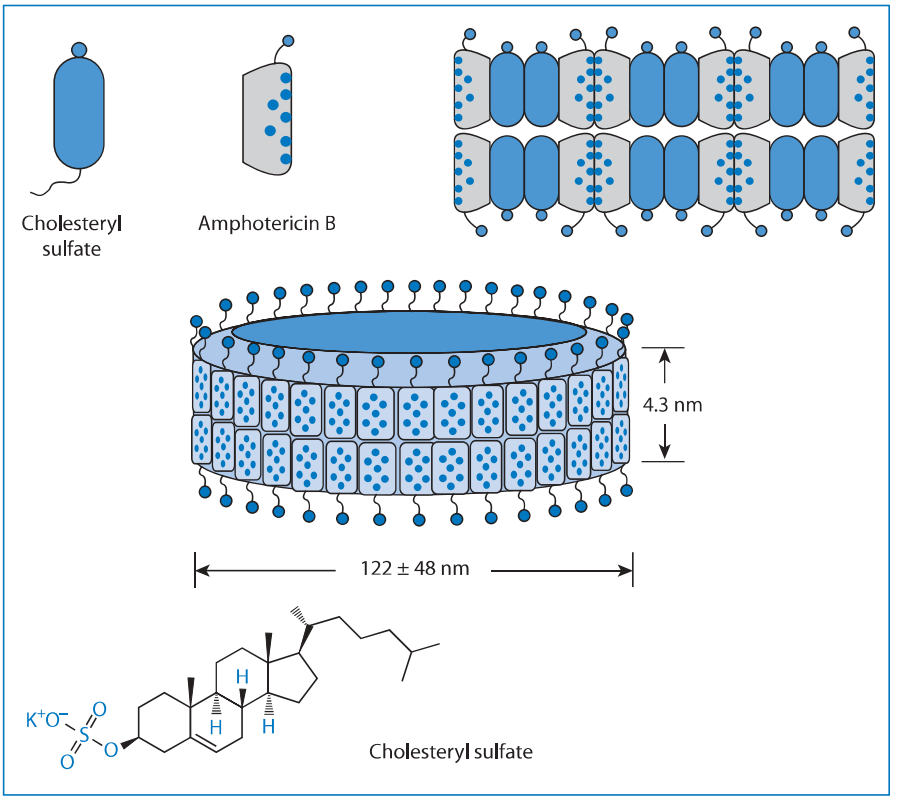


Figure 4.6 Cartoon illustration of the nature of the amphotericin B–cholesteryl sulfate complex and its dimensions, 122 ± 48 nm by 4.3 nm. (Sequus Pharmaceuticals Inc.)

Amphotec

Amphotec was introduced by Sequus Pharmaceuticals in the USA in 1996. It is a sodium cholesteryl sulfate complex, forming disc-like aggregates with a mean diameter of 125 nm (Figure 4.6).

Amphocil (UK)

This is another formulation of amphotericin B as a sodium cholesteryl sulfate complex.

AmBisome

A liposomal formulation of amphotericin B was first marketed by Fujisawa USA and NeXstar Pharmaceuticals in 1997. The liposomes are unilamellar, spherical vesicles with a mean diameter of 90 nm. The liposomes comprise soy phosphatidylcholine, cholesterol and distearoyl phosphatidylglycerol.

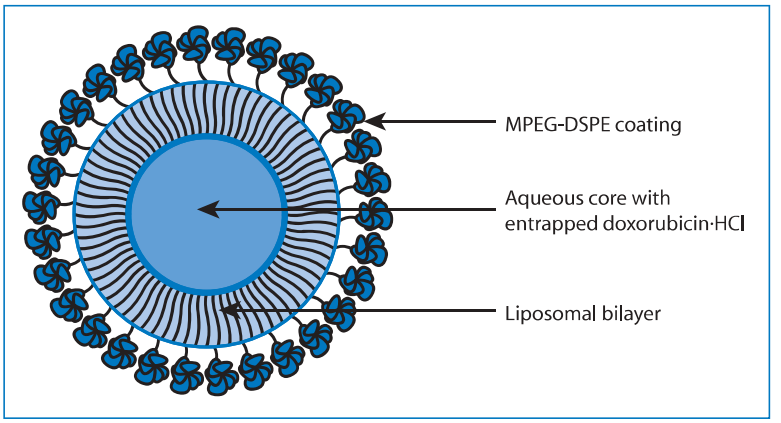


Figure 4.7 Representation of a cross-section of a doxorubicin Stealth™ liposome. MPEG-DSPE, methylpolyethylene glycol conjugate of distearoyl phosphatidyl ethanolamine.

A doxorubicin formulation: Doxil

Doxil is a formulation containing so-called Stealth liposomes encapsulating doxorubicin hydrochloride (see Figure 4.7). Surface-grafted PEG chains allow longer circulation *in vivo* (analogous to the effect of PEG chains on proteins and peptides). Hence there is a greater statistical chance of uptake by tumour tissues. Doxil has a longer plasma half-life than doxorubicin at an equivalent dose; it is less cardiotoxic, myelotoxic and nephrotoxic than doxorubicin (Adriamycin) because of its changed biodistribution patterns.[10]

Nonetheless, generic stealth liposomes differ from conventional liposomes and clearly the formulation differs from simple doxorubicin injections. Hypersensitivity reactions occur in about 45% of patients. Complement activation may play a part,[11] but the mechanism has not yet been elucidated. The long circulation times are related to another often significant problem that is exhibited by pegylated liposomal doxorubicin, that of plantar–palmar erythrodysaesthesia (hand–foot syndrome).[12] Its occurrence is related to prolonged exposure to the drug, in this case because of the prolonged half-life, for example in the sweat glands of the hands. Local cooling reduces the problem, possibly due to vasoconstriction leading to lower extravasation into surrounding tissues.[13]

A propofol formulation: Diprivan

Diprivan is a brand of propofol (2,6-diisopropylphenol; its structure is shown in Figure 4.8) formulated as an oil-in-water emulsion. There are also other branded and generic formulations. There have been some changes to the formulation in the USA, with the addition of EDTA and sulfite to prevent bacterial contamination.

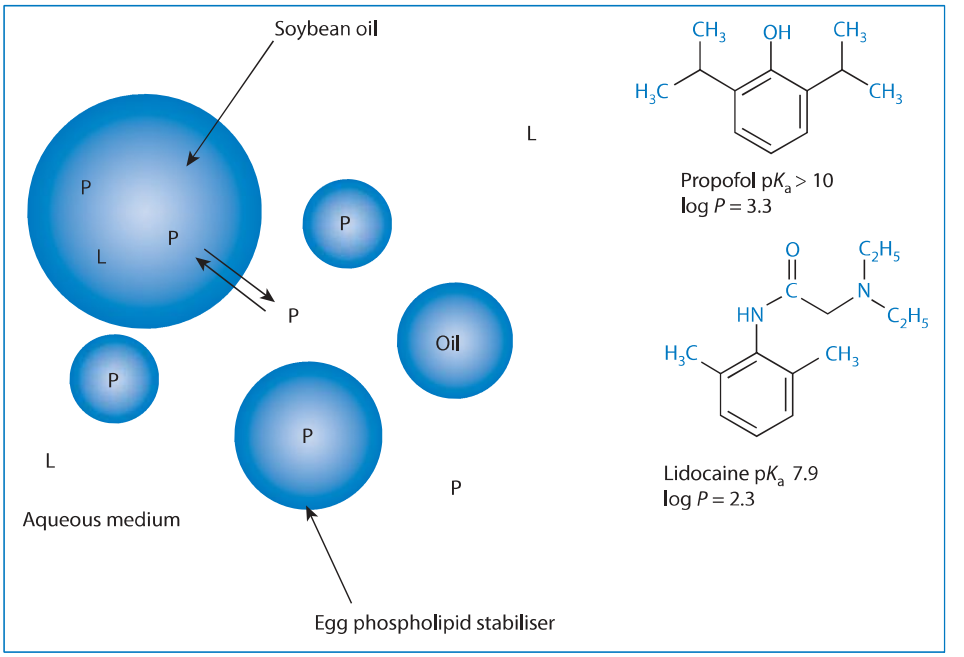


Figure 4.8 Representation of the emulsion formulation of propofol (P) with added lidocaine (L) and the structures of both propopol and lidocaine and their pK_a and log *P* values.

Pain on injection

Propofol has the disadvantage of causing pain on injection. Not unexpectedly lidocaine (lignocaine) reduces this pain. However, it is not a straightforward effect. In one study[14] the conclusions were as follows:

> When propofol partitions into the aqueous phase of the preparation there is a higher incidence of pain on injection. The addition of 1% lignocaine to propofol reduces pain. The low concentration of this local anaesthetic and the rapid pain relief observed indicates that mechanisms other than local anaesthesia are involved... A clinical study was performed to investigate the influence of lignocaine and pH on pain during injection of 1% Diprivan. Ten parts of 1% Diprivan were mixed with one part of saline, 1% lignocaine or hydrochloric acid to achieve the same pH as that after addition of lignocaine. Diprivan 1% mixed with 1% lignocaine and with hydrochloric acid gave mean pain ratings (1–10) of 0.32 (SD 0.75) ($n = 25$) and 0.88 (1.30) ($n = 24$), respectively. These ratings were significantly lower than ratings after injection of a saline-Diprivan mixture (2.18 (2.06), $n = 22$). The pH of the 1% Diprivan formulation decreased after mixing with 1% lignocaine. The concentration of propofol in the aqueous phase was lower when 1% Diprivan was mixed with 1% lignocaine (0.376 g litre^{-1}) or HCI (0.392 g litre^{-1}) compared with 1% Diprivan and saline (0.476 g litre^{-1}) mixed in the same proportion.

It is thus clear that pH changes may modify propofol-induced pain on injection by a mechanism different from the effects of the local anaesthetic on the vascular endothelium. The results may explain why lidocaine mixed with propofol causes less pain than injection of lidocaine followed by propofol.

Figure 4.8 diagrammatically illustrates the situation and shows the structures of both propofol and lidocaine.

Other formulations of propofol

There are other formulations of propofol:[15] a brief report [16] described the effect of a 'new' emulsion formulation of propofol on the severity of pain on IV injection when compared with Diprivan (AstraZeneca, Wilmington, DE, USA). A generic formulation of propofol containing a different preservative (sodium metabisulfite) (Baxter, Chicago, IL, USA) is apparently associated with less severe pain on injection than an EDTA-containing Diprivan formulation.[17] So again it is important to ensure that the components of formulations described in the literature are the same as those in the formulation of interest.

Long-acting depot injections

Long-acting oily neuroleptic formulations

Long-acting depot injections of drugs such as fluphenazine decanoate (Modecate) or flupentixol decanoate (Depixol) function because the long-chain ester (e.g. decanoate) is very hydrophobic and soluble almost exclusively in the oil phase (e.g. sesame oil). Table 4.2 [18] lists some of the oil phases used in such preparations. The oil has some affinity for water and thus allows penetration of water; the ester is hydrolysed at the surface of the

Table 4.2 Vehicles in depot antipsychotic formulations

Preparation	Group	Vehicle	$t_{1/2}$
Fluphenazine decanoate	Phenothiazine	Sesame oil	14 days
Flupentixol decanoate	Thioxanthene	Viscoleo[a]	17 days
Zuclopentixol decanoate	Thioxanthene	Viscoleo	19 days
Pipothiazine palmitate	Phenothiazine	Coconut oil	15–16 days
Haloperidol decanoate	Butyrophenone	Sesame oil	21 days
Fluspirilene	Phenylbutyl-piperidine	Aqueous suspension	>72 hours

From reference 18.

[a] Viscoleo is a fractionated coconut oil.

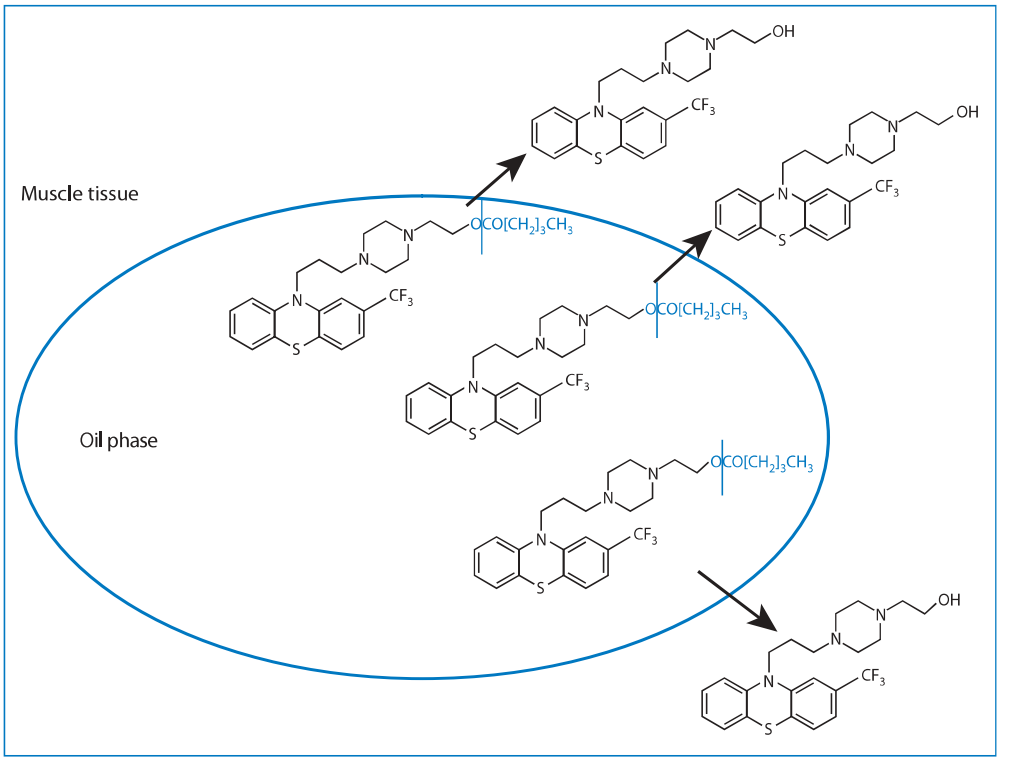


Figure 4.9 Diagrammatic representation of the release of fluphenazine from oily depots of long-chain esters in muscle tissue. Hydrolysis occurs at or near the oil–tissue interface.

droplet. Figure 4.9 is a diagrammatic scheme of the formulation and its action. The total surface area of the droplet can influence the release rate and hence affect the pharmacokinetics of the drug. Depot droplet dimensions and total surface area be influenced by (a) the force of injection, (b) the viscosity and surface tension (interfacial tension) of the oil phase, and (c) the size of the needles and the environment in which the injection finds itself. As several oils are used in these formulations, it is useful to consider the viscosity of some as given in Table 4.3.[19] Oils can be mixed with other oils to reduce the viscosity and so ease administration. The oils disappear from the injection site slowly over a period of a month. In one study[20] the more viscous arachis oil (35.2 cP) had a half-life of 27 days after subcutaneous injection compared with 9 days for ethyl oleate (3.9 cP). There is apparently little difference between the half-life of the oil after IM or SC injection. Note that there will be differences between the half-life of therapeutic substances at the site of injection and the half-life of the oily depots.

Fluphenazine itself in its un-ionised state is quite lipophilic. The log *P* value of the drug between sesame oil and water is 2.58 and between isopropyl myristate and water is 2.80. Contrast these values for fluphenazine enanthate with values at pH 7.4, of 6.3 and 6.5, respectively.[21] The rate of hydrolysis is not thought to be rate determining,[22] but hydrolysis of the drug can occur

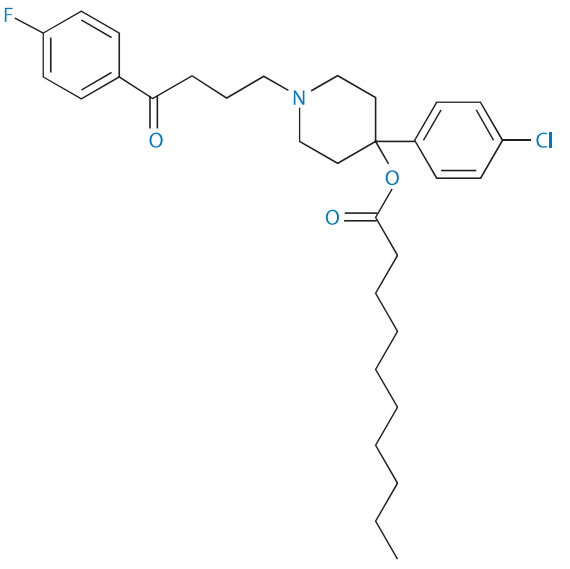
Table 4.3 Viscosity of oils used in depot injections

Oil	Viscosity (cP)
Ethyl oleate	3.9
Viscoleo	12
Sesame oil	33
Arachis oil	35.2
Peanut oil	38
Castor oil	283
Viscoleo/sesame 50:50	23
Viscoleo/castor oil 75:25	27
Sesame/castor oil 50:50	55

From reference 19 with added data from reference 20.

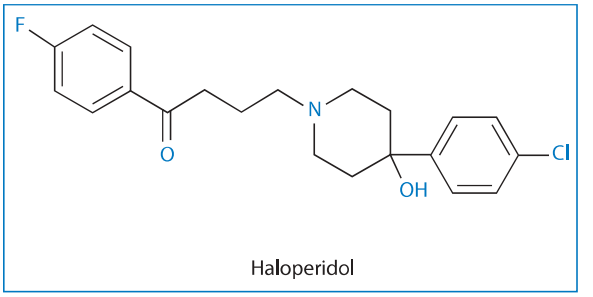
during long-term storage and lead to high and toxic peak levels when the de-esterified compound is released rapidly. Bursts of exercise, as in football-playing patients, have been known to raise plasma levels, most probably by increasing the surface area of the droplets.

Other long-chain antipsychotic drugs include formulations of haloperidol decanoate (Haldol) (see structures of haloperidol and its decanoate below), pipothiazine palmitate (Piportil Depot) and zuclopenthixol decanoate



Haloperidol long chain (decanoate) ester as in Haldol decanoate ™

(Clopixol). When administered by deep intramuscular injection, all of these provide therapeutic cover over periods of 2–4 weeks which is thus the interval between injections.



Haloperidol

Long-acting depot steroid injections

A number of steroids are formulated in the same manner as the neuroleptics, as oil-soluble esters dispersed in oils such as sesame oil or arachis oil. For example, nandrolone decanoate (Deca-Durabolin) is a long-acting anabolic steroid formulation. This formulation also contains benzyl alcohol (which acts as a solvent and an analgesic).

Testosterone enanthate, testosterone propionate (Sustanon 100 and 250) and the undecanoate (Nebido) and the cypionate (the 3-cyclopentyl-1-oxopropoxyl ester) are available for intramuscular injection. Depo-Testosterone contains testosterone cypionate, benzyl benzoate (as a solubilisation aid), cottonseed oil (the main carrier) and benzyl alcohol as a preservative, as shown below:

Depo-Testosterone formula (10 mg/mL product)	
Testosterone cypionate	100 mg
Benzyl benzoate	0.1 mL
Cottonseed oil	736 mg
Benzyl alcohol	9.45 mg

Soft capsules of testosterone undecanoate (Restandol) in an oil are used in the treatment of androgen deficiency by oral administration.

Raft-producing oral formulations

Gaviscon and related products Algicon, Gastrocote, Gaviscon Advance, Mylanta, Peptac and Rennie Duo are antacid formulations used in the treatment of gastric oesophageal reflux disease (GORD). The formulations have

Table 4.4 Alginate raft resilience measurements

Product	Raft resilience (range) (min)
Algicon	0–0
Gastrocote	2–10
Gaviscon Advance	60–60
Gaviscon Liquid	10–30
Gaviscon Regular Strength[a]	0–0
Gaviscon Extra Strength[a]	0–0
Mylanta Heartburn Relief	2–5
Peptac	2–10
Rennie Duo	0–2

[a] US products.

the ability to form a buoyant alginate raft to prevent oesophageal reflux of acidic gut contents. A variety of techniques including gamma-scintigraphy, radiography and MRI scanning have shown that alginates do form physical rafts on the stomach contents after ingestion. Techniques have been developed to measure raft strength,[23] including their 'resilience', a measure used to compare a variety of raft-forming products in terms of speed of raft formation, flotation potential and coherence. Table 4.4 shows some of the resilience data. The higher the value the stronger the raft.

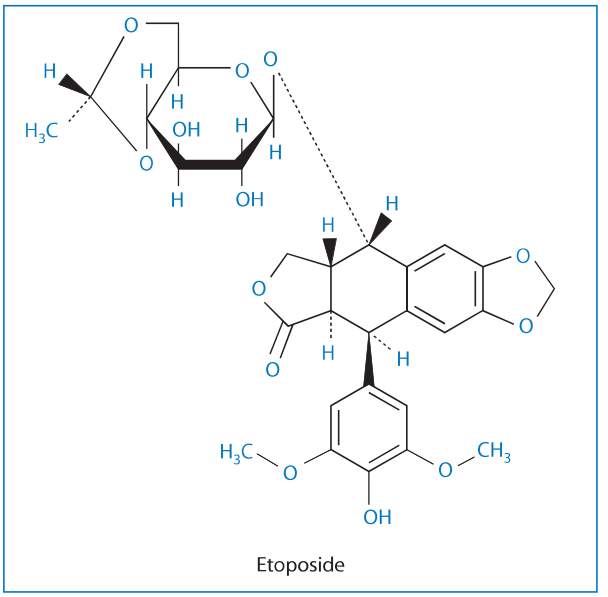
Etoposide (Vepesid, VP 16 and etoposide phosphate)

Etoposide is a widely used cytotoxic drug with poor water solubility. It thus requires solubilisers to prevent its precipitation at clinical concentrations of the IV formulation. Etoposide concentrate for IV infusion (Vepesid) contains polysorbate 80, ethanol and benzyl alcohol. This is diluted for intravenous use.

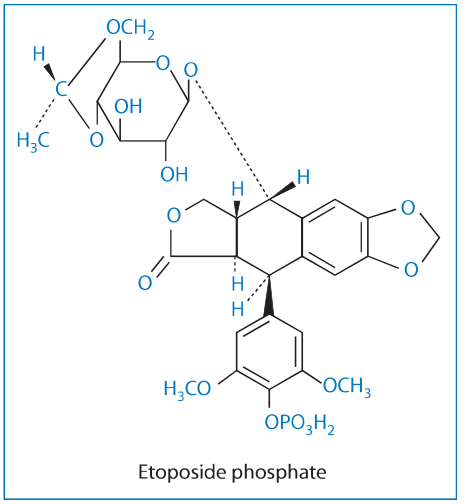
Note that polysorbate 80, like other micelle-forming non-ionic surfactants in other formulations, may enhance the leaching of plasticizers such as DEHP (di-(2-ethylhexyl) phthalate) from PVC bags and tubing.[24] Thus non-PVC tubing and sets are recommended.

An alternative product, Etophos uses etoposide phosphate, a water-soluble prodrug of etoposide, as a powder for reconstitution.

A product containing etoposide, polysorbate 80 and polyethylene glycol has been compared with etoposide phosphate and found to be pharmacokinetically virtually equivalent, although the phosphate provides slightly higher



Etoposide

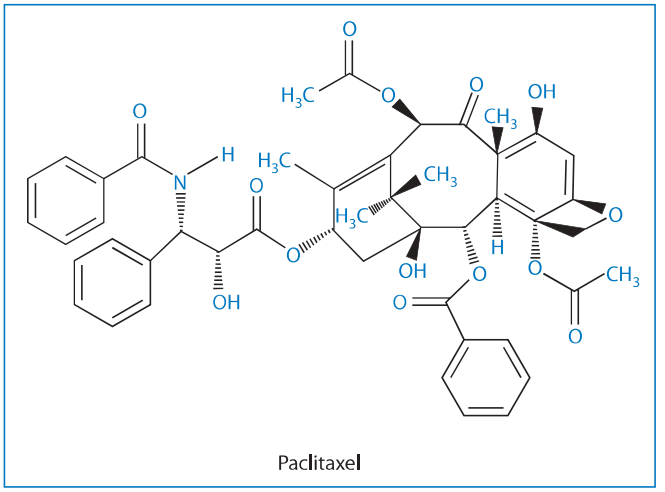


Etoposide phosphate

peak levels.[25] Surfactants present in formulations in solubilising drugs can sometimes lead to a slightly slower release of drug *in vivo*, although the influence of agents such as polysorbate 80 and Cremophor EL are complex, as was discussed in Chapter 2.

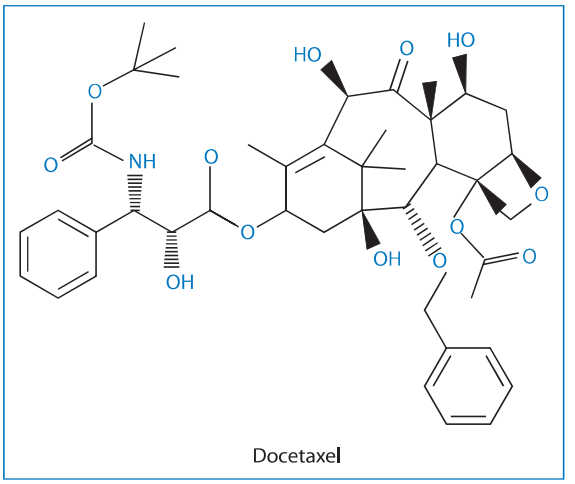
Data on the stability of diluted concentrates of etoposide can be contradictory. Before the literature can be useful, it is essential that the formulation and brand of the product in source literature and that in the pharmacy are identical, as minor formulation differences can influence outcomes.

Paclitaxel



Paclitaxel

Paclitaxel and its close relative docetaxel are poorly water-soluble anticancer drugs. Paclitixel has been formulated both as a generic preparation and as the branded Taxol as a concentrate containing high concentrations of Cremophor EL for addition to infusion fluids such as 5% glucose or 0.9% sodium chloride. The solvent for the concentrate (6 mg/mL paclitaxel) is a 50:50 mixture of Cremophor EL and ethanol. The surfactant alone would be too viscous for manipulation and would disperse only slowly on addition to aqueous infusion fluids. The ethanol reduces the viscosity and aids the dispersal of the concentrate in an infusion fluid. This is best done in stages, however, to prevent gel formation. On dilution of the concentrate to final paclitaxel concentrations of 0.3–1.2 mg/mL, the micellar solution formed solubilises the paclitaxel sufficiently to prevent the precipitation of the drug. Other taxanes are similarly formulated in polysorbate 80–ethanol mixtures. Taxotere is a 40 mg/mL concentrate of docetaxel and uses polysorbate 80 in its formulation. Some claim that Cremophor EL induces more adverse events than does polysorbate



Docetaxel

80, but both surfactants in fact can induce adverse reactions (see Chapters 2 and 5). Whichever surfactant is used, the infusion, which is given over 3 hours, should not be administered via PVC sets, as the surfactant can solubilise plasticisers from the giving sets.

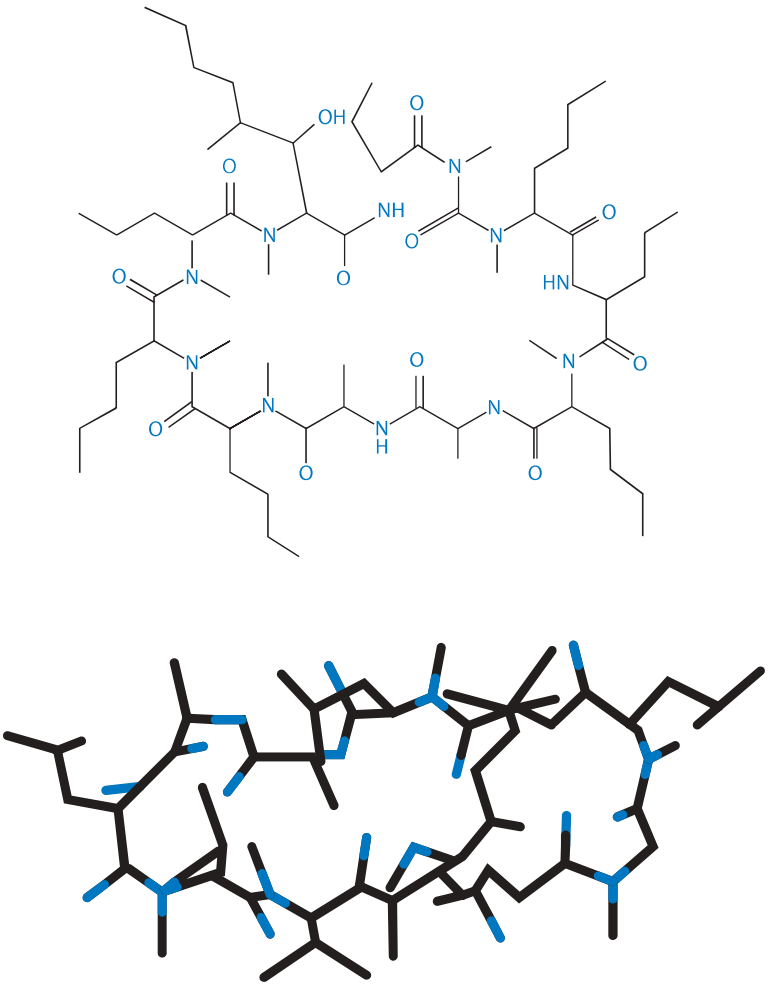
Eutectic mixtures of local anaesthetics

EMLA is a eutectic mixture of the local anaesthetics lidocaine and prilocaine in a 1:1 mixture (2.5%, 2.5%). It can be used, for example, to prevent the pain of injection or catheter insertion. Lidocaine and prilocaine bases are two structurally related solids with respective melting points of 66–69°C and 36–30°C. The combination of the two compounds forms a eutectic mixture. A eutectic is a mixture of often similar materials whose melting point is below that of either individual component; in this case it is lowered to 16°C. The result is an oil that can be formulated as an oil-in-water emulsion where the disperse phase is the anaesthetic mixture; or it can be incorporated into a cream or formulated as a patch. A 5% EMLA cream when applied to the oral mucosa achieves maximum concentrations of 418 ng/mL for lidocaine and 223 ng/mL for prilocaine.[26] Patents exist for eutectic mixtures of other drugs.

Ciclosporin (cyclosporin)

Ciclosporin is an immunosuppressant cyclic peptide that has an oral bioavailability of around 15% in its amorphous and unformulated form. This is in contrast to the majority of (non-cyclic) peptides, which have little or no oral availability. Ciclosporin, being poorly water-soluble, is difficult to formulate as an oral product. It has been available in several innovative forms: an emulsion-forming (Sandimmun) and a microemulsion-forming product (Neoral).[27] Figure 4.10 shows the variability of absorption after oral administration of Sandimmun and also with the improved microemulsion system Neoral. The latter is less variable, that is, it improves the quality of effect. Reproducibility of effect is extremely important in transplantation patients to avoid under-dosing and transplant rejection. In transplantation patients, initial treatment is by way of intravenous dosing and later maintenance through the oral route.

It is logical to assume that the absorption of the drug would be improved by its formulation in a microemulsion form, where the lipid droplets are in the nanometre rather than micrometre size range. A simple surface area effect would operate – the smaller droplets, having a larger surface area per unit weight, present a greater surface from which the ciclosporin can diffuse directly into intestinal absorbing tissue. It has been suggested that with the microemulsion, inhibition of metabolism in the gut wall leads to higher availability. Several formulations of ciclosporin are available. The BNF 55



Different representations of the structure of ciclosporin (Commons.Wikimedia.org/wiki/File/ciclosporin.svg)

(page 476) states that 'because of differences in bioavailability, the brand of oral ciclosporin to be dispensed should be specified by the prescriber.'

Ingredients:[28] Neoral oral solution contains in addition to ciclosporin, DL-α-tocopherol, ethanol, polyoxyethylated 40, hydrogenated castor oil, maize oil (corn oil mono-, di-, tri-glycerides) and propylene glycol. (The listing in one document (Novartis, Canada) does not mention polyoxyethylated hydrogenated castor oil.) The oral solution should be diluted in orange juice or apple juice to improve its taste, or with water immediately before dosing. The concentrate forms a microemulsion. Neoral soft gelatin capsules also contain the above excipients and this also forms a microemulsion *in vivo*.

Sandimmun IV concentrate for solution for infusion contains ciclosporin 50 mg/mL, ethanol 278 mg/mL and [sic] castor oil 650 mg/mL (the Novartis information states 'polyoxyethylated castor oil'). The variety of formulations

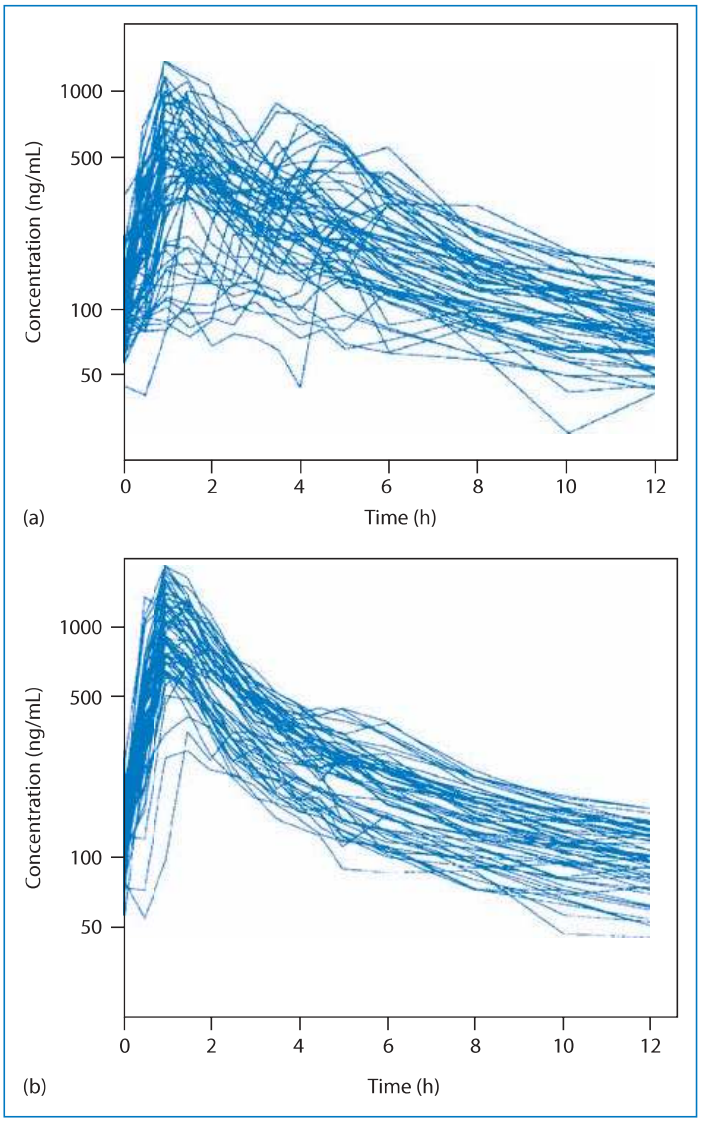


Figure 4.10 Plasma concentrations of ciclosporin after (a) Sandimmune and (b) Neoral, showing the improvement in average performance of the latter.

now available from other manufacturers makes the elucidation of pharmacokinetics, bioavailability, dosing and adverse reactions complex. Not all the preparations are available in all countries, hence literature reports have to be scanned carefully to determine which formulation has been used.

Inadequate mixing of ciclosporin formulations

One report[29] in 1995 referred to anaphylactoid reactions during a Phase I/II clinical trial of high-dose IV preparations of ciclosporin in children. The problem was ascribed to the presence of Cremophor EL. However, it was exacerbated by the inadequacy of mixing of the formulation with the

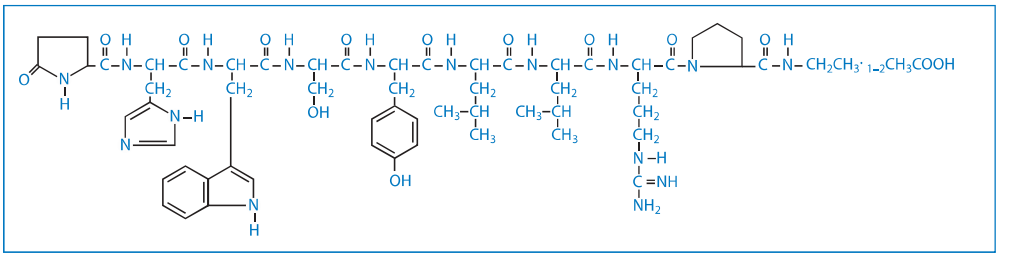


Figure 4.11 Leuprorelin structure.

intravenous fluid. Improper mixing led to a bolus dose of Cremophor EL, which sank to the bottom of the vial. Efficient mixing avoids problems when a formulation must be diluted or added to other fluids whose densities differ and when the additive perhaps disperses slowly.

Topical preparations and inhaled formulations of ciclosporin have been used, as well as an ophthalmic ointment for the treatment of dry eye.

Lupron Depot, Prostap SR and Prostap 3

Lupron and Prostap are sustained-release formulations of leuprolide (INN leuprorelin), an analogue of luteinising hormone-releasing hormone (LHRH). The drug is dispersed in PLGA (poly(D,L-lactic-co-glycolic acid)) microspheres, which slowly degrade after intramuscular injection (the peptide is not active orally) to release the hormone, achieving a depot effect. Leuprorelin has greater potency than the natural hormone. Figure 4.11 shows the structural formula of leuprorelin.

Intramuscular injection of the depot formulations provides plasma concentrations of leuprolide over a period of one month with Prostap SR, and three months with Prostap 3.

Lupron Depot and Prostap are available in prefilled dual-chamber syringes containing sterile lyophilised microspheres which, when mixed with diluent, form a suspension. The first chamber of the 3.75 mg product contains leuprolide acetate (3.75 mg), purified gelatin (0.65 mg), PLGA (33.1 mg), and D-mannitol (6.6 mg). The second chamber with the diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, and glacial acetic acid to control pH.

Zoladex

Zoladex is an injectable implant containing goserelin acetate, the nonapeptide luteinising hormone-releasing hormone analogue (LHRHa).[30] It prevents the production of testosterone and oestrogen. It is used to treat hormone-sensitive cancers of the prostate and breast (in pre- or peri-menopausal women) and some benign gynaecological disorders. Zoladex is available in a 28-day form and a long-acting 3-month formulation. The product is administered using the Zoladex SafeSystem (Figure 4.12) designed to protect from the risk of

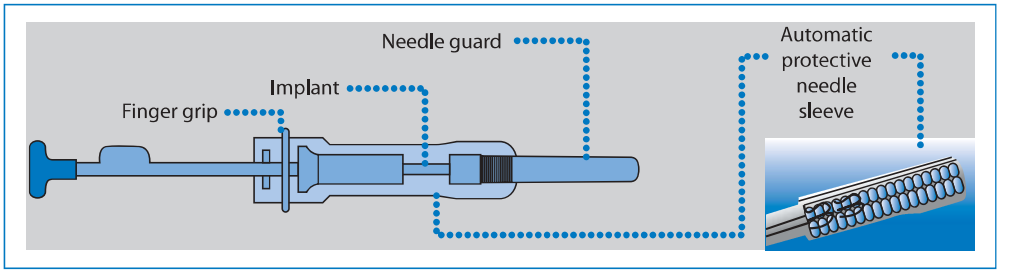


Figure 4.12 Zoladex SafeSystem. (From www.prostateinfo.com.)

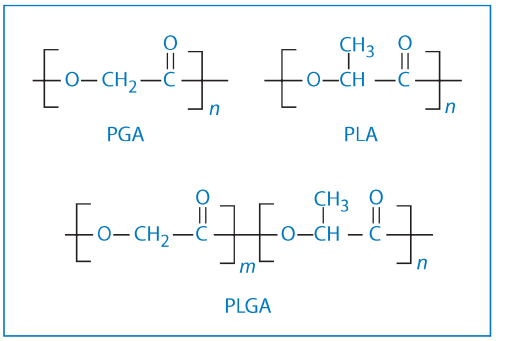


Figure 4.13 Chemical structures of poly(glycolic acid) (PGA), poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA).

needle-stick injury. Both depots are used for the treatment of prostate cancer, endometriosis and uterine fibroids but only the 28-day depot is approved for breast cancer, endometrial thinning and assisted reproduction. Zoladex was first launched in 1987;[31] Zoladex SafeSystem was launched in 2003. The design of the formulation was discussed in 1990 by scientists[32] involved in the work at the then ICI Pharmaceuticals (now Astra-Zeneca), Macclesfield, UK. Controlled release of the goserelin is dependent on the molecular weight of the PLGA and the ratio of the lactic acid and glycolic acid monomers in the polymer (see structures of the monomers and polymers in Figure 4.13). Particle size, and hence the surface area of the particles, is optimised. The higher the molecular weight of the PLGA the slower the release, facilitated by degradation of the polymer chains and by entry of water into the system.

Fluoroquinolone eye drops

How do different fluoroquinolones behave in tears? In one study, three fluoroquinolone solutions were evaluated:[33] ciprofloxacin 0.3% (Ciloxan), norfloxacin (Chibroxin) and ofloxacin 0.3% (Ocuflox). The pH of the tear film for the first 15 minutes after instillation of each of the drugs is determined by the pH of its formulation. Rapid precipitation of ciprofloxacin was seen in a model system 8 minutes after dosing of ciprofloxacin owing to the supersaturation of the drug in tears, while the tear concentration of ofloxacin and norfloxacin remained below saturation solubility at all pH values studied. These findings may explain the reports of pre-corneal deposits following use

of ciprofloxacin. Figure 4.14 shows the solubility–pH plots for the three drugs, which explain the problem that occurs with Ciloxan in the model tear system when drug tear concentrations exceed drug solubility. One can see that solubility line crosses the concentration line in the diagram for Ciloxan).

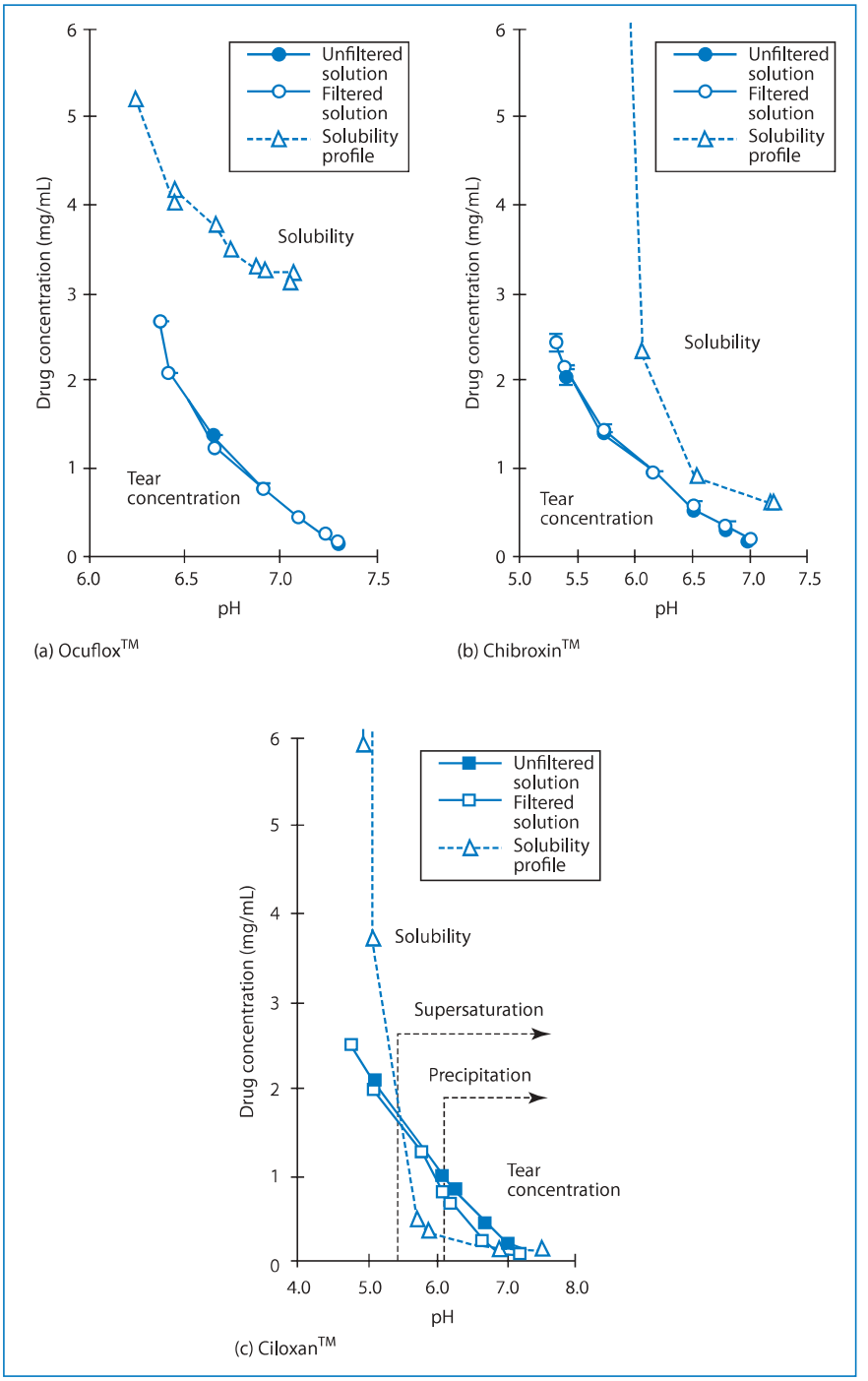


Figure 4.14 Relationship between the drug concentration in a tear turnover model and drug solubility (dashed lines). (From reference 33.)

The pH–solubility profiles of the fluoroquinolones up to pH 7.2 are typical of a base. Solubility decreases with increasing pH, with a minimum in solubility around pH 7. If the pH were to increase above 7.5, solubility would increase again as the compound possesses a carboxyl group. The pH of tear fluids is just over 6.8. When the solubility curve falls below the concentration curve, precipitation can be anticipated, a quick way of predicting the occurrence of precipitation.

Ionsys: Iontophoretic transdermal device for fentanyl

Ionsys is an iontophoretic device comprising an electronic controller and two hydrogel reservoirs, one of which contains 40 mg fentanyl hydrochloride in a gel formulation for on-demand delivery.[34] It is used for the management of acute moderate to severe postoperative pain in hospital settings only – a potentially dangerous amount of fentanyl remains in the Ionsys system after use. Figure 4.15 shows some pharmacokinetic data comparing fentanyl levels from the Ionsys product and an IV injection.

The many ingredients of the system should not be of consequence in intact systems. For interest and to emphasise the complexity, they comprise the following: in the housing assembly, glycol-modified polyethylene terephthalate; in the anode hydrogel, purified water, sodium hydroxide, polacrilin and polyvinyl alcohol; in the cathode hydrogel, sodium citrate, polyvinyl alcohol, anhydrous citric acid, cetylpyridinium chloride, purified water and sodium chloride. The skin adhesive contains polybutene resin ester.

Parenterals

The administration of many formulations parenterally leads to the possibility of drug precipitation in the blood because of the dilution of the solvent systems that solubilise the drug in the vial. The effect of this on pain and on the fate of the precipitated particles can be discussed. Above all, the issue of solubility and its pH dependence has to be revisited[35] (see Chapter 3). Many of the problems with parenterals occur before administration and result from the addition of one product to intravenous fluids such as dextrose and physiological saline and subsequent precipitation of the active due to pH changes or to interaction with a second drug.

Solubility considerations

A query raised by a nurse on Levaquin (levofloxacin) and Lasix (furosemide):[36]

> The patient was on Levaquin i.v. and was prescribed a Lasix i.v. push. I stopped the Levaquin, ran the saline line at 100 for 25–30. Then I proceeded to push the Lasix. I drew back and the *syringe* contents

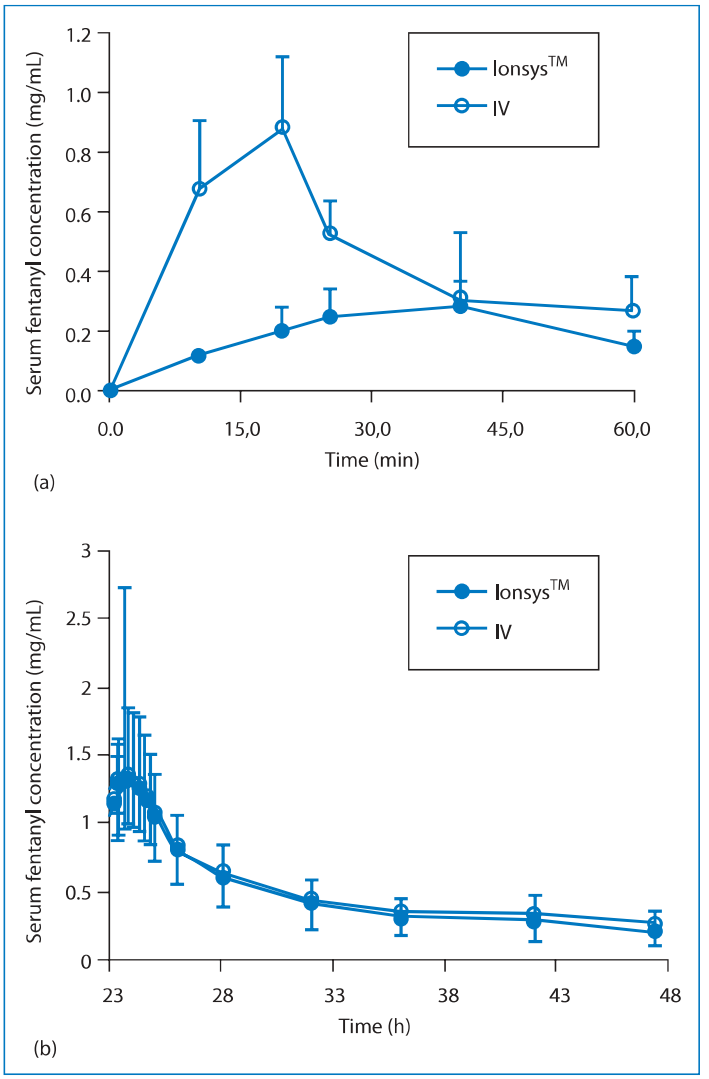
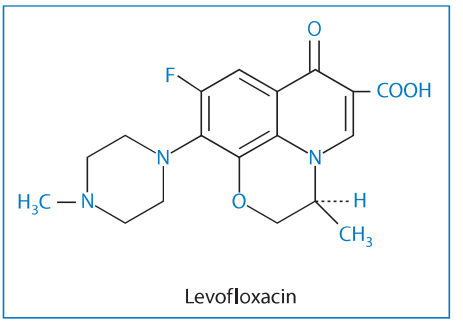


Figure 4.15 Pharmacokinetic data comparing fentanyl levels from the Ionsys product and an IV injection. (a) First hour of a representative treatment. (b) Last hour and upon termination of a representative treatment. The treatments were: *Ionsys*, 40 µg, two sequential doses over 20 minutes every hour for 23 hours 20 minutes. *IV*, 80 µg dose over 20 minutes every hour for 23 hours 20 minutes. (Source: FDA, http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021338lbl.pdf.)

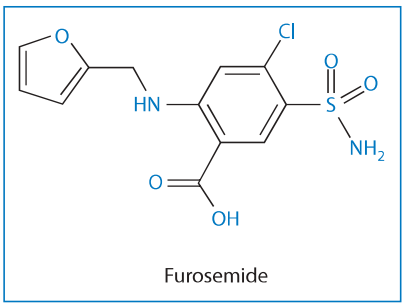
> looked a little cloudy. I had never seen a drug precipitate (I thought it would have crystallized immediately). I started to push it but then second guessed myself and stopped. I turned off the pump immediately and took the line off the patient. Only then did I see the crystallization. Did I need to flush for longer or should I have gotten a new saline bag and pushed it through a new line? I worry that some of the [sic] contaminated fluid entered the patient.

This shows that not everyone is clear about the nature of precipitates and crystallisation. We should remember that not all interactions lead to visible

crystals, and we should be aware of changes in the appearance of fluids. From the structures given below can you identify the reasons for the precipitation referred to by the nurse in question?



Levofloxacin



Furosemide

Chloramphenicol

Chloramphenicol is available as 250 mg capsules or as a liquid (125 mg/5 mL). In some countries, chloramphenicol is sold as chloramphenicol palmitate ester. Chloramphenicol palmitate ester is inactive, and is hydrolysed to active chloramphenicol in the small intestine. There is no difference in bioavailability between chloramphenicol and chloramphenicol palmitate. The IV preparation of chloramphenicol is the succinate ester, because chloramphenicol itself does not dissolve in water. This creates a problem: chloramphenicol succinate ester is an inactive prodrug and must first be hydrolysed to chloramphenicol. The hydrolysis process is incomplete and 30% of the dose is lost unchanged in the urine; therefore, serum concentrations of chloramphenicol are only 70% of those achieved when chloramphenicol is given orally. For this reason, the chloramphenicol dose needs to be increased to 75 mg/kg per day when administered intravenously in order to achieve levels equivalent to the oral dose. The oral route is therefore preferred to the intravenous route.

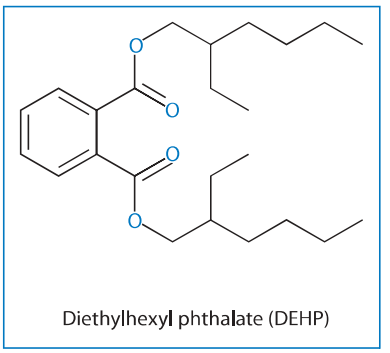
Materials used in drug delivery

Plasticised PVC Bags

(The information in this section was derived from a web page by Inga Rustamova, PSIV, University of California, San Francisco.[37])

Figure 4.16 Plasticised PVC bag.

Plasticised polyvinyl chloride (PVC) is one of the most widely used polymeric materials in medical and related fields. In the medical field, flexible PVC is used for blood storage bags, tubing used during haemodialysis, endotracheal tubes, intravenous solution dispensing sets, as well as for drug product storage and packaging (Figure 4.16). PVC is a rigid polymer, so plasticisers are added to increase its flexibility. Phthalic acid esters, mainly di-(2-ethylhexyl) phthalate (DEHP), are the preferred plasticisers used in the medical field. Since these additives are not covalently bound to the polymer, there is a possibility for migration of the plasticiser from the matrix. The migration of DEHP (structure below) from PVC bags into the solution has been a major concern for many years. The toxicity of DEHP and PVC has raised serious questions about their use[38].



Diethylhexyl phthalate (DEHP)

Plasticised bags allow evaporation of water and sorption and loss of drug. Kowaluk *et al.* examined interactions between 46 injectable drug products and Viaflex (PVC) infusion bags. Study results showed that: (a) sorption increases as drug concentration increases; (b) loss is negligible for ionised or polar drugs (apparent octanol–water partition coefficient < 5). Migration of drug into plastic may lead to subtherapeutic drug concentrations of, for example, insulin, vitamin A acetate, diazepam and nitroglycerin.[39] Influencing factors include (a) pH, (b) temperature, (c) structure of the plastic, (d) the volume/surface area ratio, (e) storage time. Formulations may alter the properties of plastic, for example, fat emulsions and the presence of surfactants like polysorbate and Cremophor as we have discussed. The benefits of DEHP include (a) increased flexibility of PVC, and (b) increased survival time of platelets. Indeed no specific toxicity in humans has been reported.

Leakage of plasticisers into the solution is influenced by (1) shaking, although it has been found[40] that agitation had no effect on rate or the amount of DEHP leached into D5 injection, ethanol 25 %, and polysorbate 80 1% solutions; (2) storage time and temperature; (3) pH; (4) drug concentration; (5) manufacturing processes that involve, for example, thermal exposure; (6) formulations with surfactants (DEHP is leached by polysorbate 80, polyoxyethylated castor oil and formulations which normally contain surfactants, such as ciclosporin, miconazole, teniposide, and etoposide). In total parenteral nutrition (TPN) mixtures[41] 0–3 mg DEHP/mL (depending on lipid concentration and storage condition) was found in products administered 24 to 36 hours after admixture. Total DEHP exposure range was 0–9 mg.

It has been suggested that decreasing plasticiser migration by coating PVC bags with hydrophilic polymers, using polymeric plasticisers or grafting molecules such as polyethylene glycol, improves blood compatibility. Other plasticisers include tri-(2-ethylhexyl)trimellitate (TOTM). Specific toxicity from exposure to DEHP has not been well established in humans.[42] Most toxicity studies were carried out in rats, making extrapolation of toxicity data to human toxicity unreliable. There is not enough scientific data to completely or partially ban use of DEHP and PVC in medical or related fields. The balance of opinion is to suspend use of PVC administration sets and containers with formulations that are known to leach DEHP. This would limit the potential DEHP exposure as much as possible until further studies establish DEHP toxicity.

Conclusions

Only a selection of formulations has been covered in this chapter. Each example has been chosen to display some facet of formulation and how it might impinge on the performance of the medicine in question. Other formulations will be dealt with in other chapters according to other themes. The

object has been not only to draw attention to the ingenuity of formulators, but also to heighten awareness of what to look for in formulations, especially when problems arise before or after their administration, or when formulations behave in a manner other than anticipated. It is not always simple to determine compositions of formulations, and this hampers fuller understanding of their properties. However, there are key questions to be posed when considering the influence of formulations.

First ask whether the product contains:

- A surfactant
- A surface-active bactericide
- Dyes that might cause allergic reactions
- Stabilisers
- Flavours
- Viscosity-enhancing agents
- Benzyl alcohol
- Solvents such as ethanol
- Another additive?

Then one must consider whether or not any observed event may be caused by one of these ingredients or whether the whole formulation has changed because of precipitation or the other phenomena discussed.

The next chapter deals with adverse events associated with formulations, where we examine more closely some of the activities of materials used in formulations, following on from Chapter 2. These of course can include synergistic effects.

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5

Adverse events and formulations and devices

Introduction

It is generally assumed when an adverse reaction or adverse event occurs (see Box 5.1) that the drug is the causative agent. So what is the connection between pharmaceutics and adverse reactions to medications? It is generally the case that the drug is the culprit, but there are instances when formulation factors come into play. Sometimes, as we discussed in Chapter 2, excipients have their own biological effect; sometimes the way in which the product is constructed and behaves may cause the drug to have enhanced toxicity.

This chapter summarises the potential for formulations, their form or the ingredients that they contain, to precipitate adverse reactions or events. Figure 5.1 shows both product and patient factors in the causation of adverse events. Errors of choice of product or drug aside, when the correct drug and formulation has been administered, there are still many opportunities for matters to go awry. These include effects which are the result of:

- Abnormal bioavailability (both large and small) caused by a product or manufacturing defect
- Sensitivities to formulation ingredients (discussed in Chapter 2)
- Reactions to impurities and breakdown products
- Aggregation of protein drugs in devices
- Device failure, for example with medicated stents or infusion pumps
- The nature of the formulation, for example adhesive tablets lodging in the oesophagus or drug precipitation from injections.

Figure 5.1[1] elaborates on these cases, dividing adverse events into those dependent on patient factors and those related to medicinal formulations and devices. Adverse events include allergic reactions, local toxicities, systemic effects or idiosyncratic reactions. It is not the place here to recount

Box 5.1 Adverse events and adverse drug reactions

Adverse reactions following administration of a medicine or use of a device can be discussed in terms of adverse events (where the causality is not known) or adverse drug reactions (where the causative factor is the drug itself).

When both drug and formulation are involved, or when an excipient is implicated, the term adverse event is possibly the more accurate.

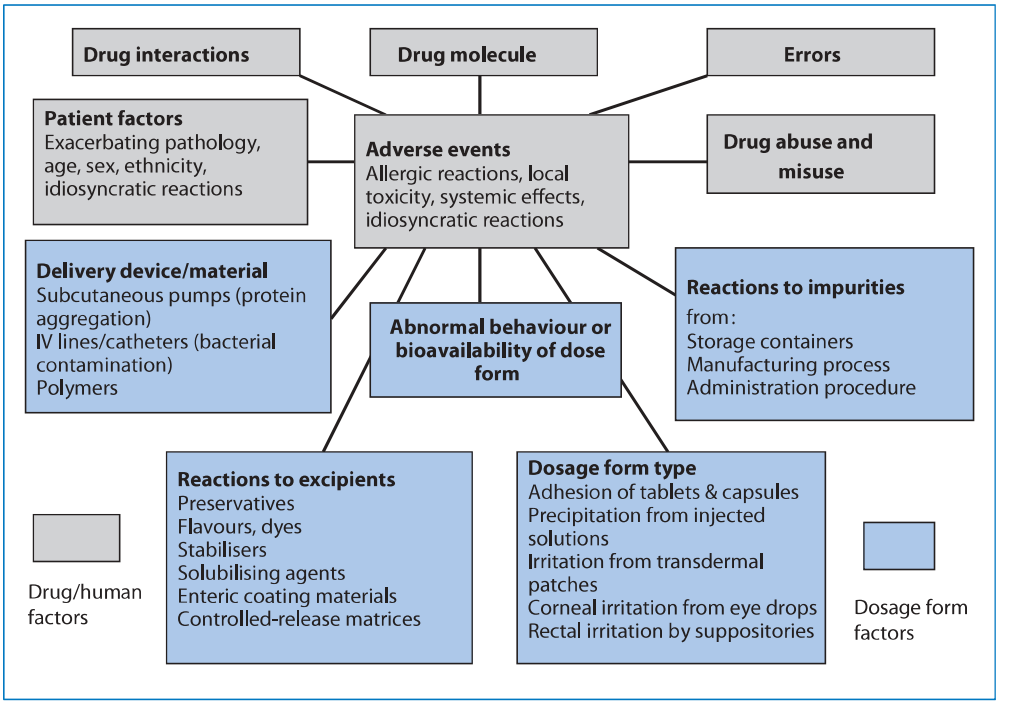


Figure 5.1 Drug/human factors and dosage form factors in adverse events following medication administration. (Modified from reference 1.)

patient-related factors in detail, although there are of course dose form–patient interactions that make these of interest. Changed physiology in the postnatal growth period, in childhood and in the elderly can mean that dose forms may behave differently in certain patient groups (see Chapter 6). Some factors include exacerbating pathology, age, sex and ethnicity. The following sections deal with some product-related adverse effects.

The variety of adverse events that have occurred in the recent past is illustrated in Table 5.1.

Table 5.1 Some `classic' adverse events as a result of use of formulations

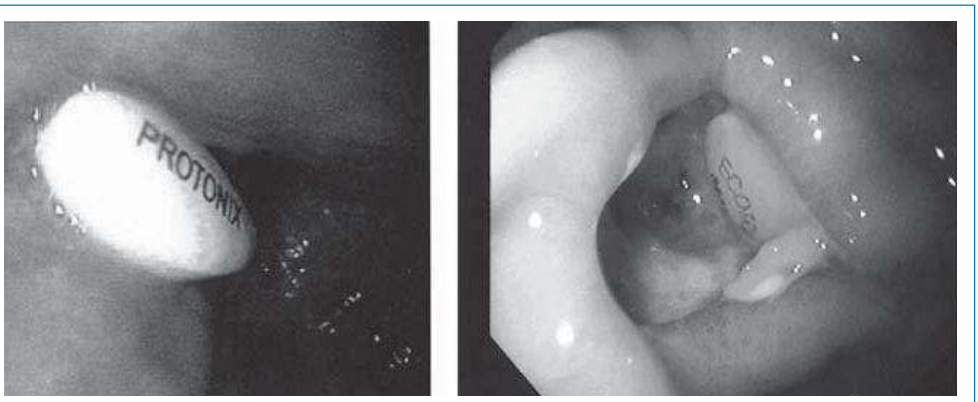
Dosage form	Trade name	Adverse event
Indometacin osmotic minipump tablets	Osmosin	Intestinal perforation
Fluspirilene IM injection	Redeptin	Tissue necrosis at site of injection
Epidural injection of prednisolone injection containing benzyl alcohol as preservative	Depo Medrol	Mild paralysis
Inhalation of nebulised ipratropium bromide solution containing benzalkonium chloride as preservative	Atrovent	Bronchoconstriction
Vaginal application of povidone iodine solution		Anaphylactoid reaction
Application of timolol eye drops	Timoptic	Bronchoconstriction
Fentanyl transdermal patch	Duragesic	Respiratory depression and death

From reference 1.

Dosage form type

Adhesion and trapping of tablets

Oesophageal damage caused by tablets is discussed later, but it is worth considering here a recent and graphic case that has been described[2] in a patient (a 57-year-old woman) with oesophageal dysmotility. A tablet of pantoprazole (Protonix) was seen 'perched' (Figure 5.2a) in the oesophagus of this patient with diffuse bronchiolar disease that required hospitalisation. The photograph in Figure 5.2b shows an enteric-coated aspirin tablet, its coating



(a) (b)

Figure 5.2 Tablets adhering to the oesophageal mucosa. (a) Pantoprazole (Protonix™). (From reference 2.) (b) An enteric-coated aspirin tablet with coating still intact within an ulcer of the gastric antrum of a 76-year-old woman. (From reference 3.)

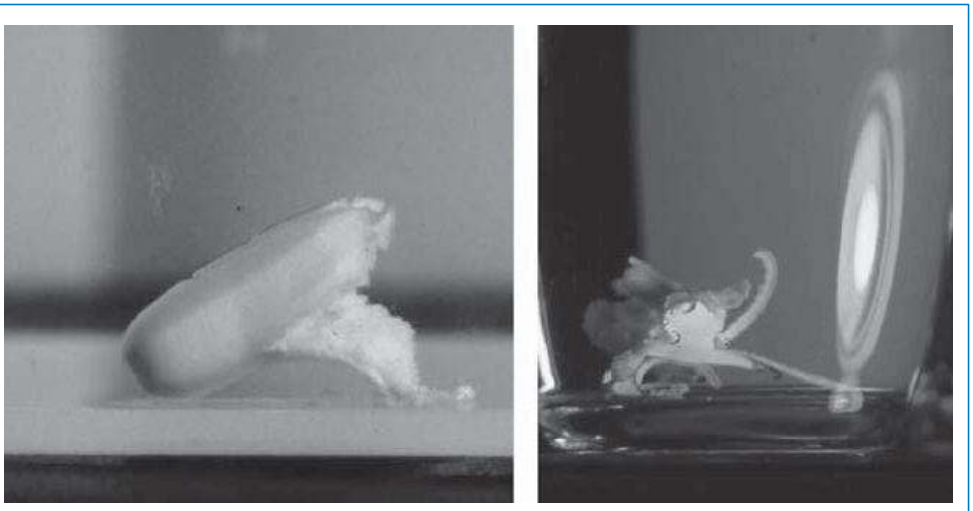


Figure 5.3 Two tablets disintegrating in an aqueous medium at room temperature. Both show the splitting of the coating layer on the tablets, but (b) shows a now-discontinued dose form of emepromium bromide (Cetiprin) that is unravelling to expose the core of pure drug, irritant to the oesophageal lining. (From reference 4.)

still intact, in an ulcer in the gastric antrum of another patient.[3] Thus, adhesion or simply entrapment in diverticula may be an issue.

In these cases a combination of pathology and dose form conspired to cause a problem. Adverse events are rarely simple. The manner in which dose forms behave in the presence of small or larger amounts of aqueous media, which may be found respectively in the oesophagus or later in the stomach, are varied. Simple *in vitro* studies can be illuminating, as Figure 5.3 illustrates.[4] This shows the unusual disintegration properties of two tablet formulations, the lower example being an extreme case typical of emepromium bromide tablets once marketed as Cetiprin for the treatment of nocturnal enuresis. The Cetiprin tablet is seen to break apart, exposing a core of pure drug, which has surfactant properties. If this occurred in the oesophagus, pain and damage would result and this indeed was the case. Given its indication, many patients took the tablets with insufficient water and many cases of dysphagia were reported. The product was withdrawn from the market.

In this case the combination of adherence and the presence of a potentially irritant drug is the problem. Close connection between epithelia and product leads to high concentrations of drug and to damage. The oesophagus is a primary site for such adverse events, since tablets and capsules will generally not have disintegrated during their oesophageal transit and retain their bulk. Small uncoated tablets may also cause problems in the oesophagus because they can adhere firmly to the mucosal surface. A range of drugs have been reported to cause oesophageal injury (Table 5.2).

Table 5.2 Some drugs that cause oesophageal injury

- Alendronate
- Alprenolol
- Aspirin
- Clindamycin
- Doxycycline
- Emepromium bromide
- Ferrous salts
- Indometacin
- Potassium chloride
- Risendronate
- Tetracycline
- Thioridazine

We may ask what, if any, are the common features of the drugs listed in this table? What might be the main reason or reasons for each to cause injury? These include the acidity of the concentrated solutions of some of the drugs (aspirin, alendronate and risendronate); the proximity of high concentrations of drugs such as doxycycline which chelate calcium and hence disrupt the epithelial lining; the surface activity of agents such as emepromium bromide; or high electrolyte concentrations from the inorganic drugs. If these agents are in dose forms that are swallowed with sufficient water and do not lodge in the oesophagus, damage will not be caused.

Dose forms have other effects and influences in modulating or causing adverse events. Precipitation of drugs from injection solutions is one prime example which was discussed in Chapter 1. Figure 5.1 reminds us of others: irritation from the adhesives of transdermal patches, corneal irritation from eye drops and rectal irritation from the use of suppository bases (such as the polyoxyethylene glycols, PEGs) that extract water from the mucosa.

Reactions to impurities

Reactions to impurities generally refer to the effect of breakdown products of the drug, which may be initiated by interactions with moisture or acidity or with excipients or materials from containers and packaging. The manufacturing process may contribute some impurities, although these will be limited by the marketing authorisation, but the validity of these requirements and limitations will depend on the same route of synthesis and production being adhered to.

Heparin

In January 2008, Baxter Healthcare Corporation withdrew batches of nine lots of heparin sodium in the USA[5] because around 700 acute allergic-type adverse reactions had been reported after their use. The number of deaths was 19. The source of the active ingredient for this product was the Scientific Protein Laboratories (SPL) in Changhzou, China. The FDA found that the heparin batches associated with the reactions contained 5–20% of a heparin-like compound as a contaminant. It was later identified as over-sulfated chondroitin sulfate (OSCS) (see Figure 5.4). More than 80 adverse reactions were also reported in Germany with products where the heparin was again sourced from China, although from another company in Changzhou. Methods were developed rapidly to determine the quantities of OSCS in heparin preparations.[6]

This example illustrates that the name of a respected manufacturer does not always guarantee the safety of products if the raw material has been sourced from another company. In-house testing of the incoming material should have detected that there was a problem, given the high percentage of the impurities, but it is difficult to cater for previously unknown impurities. Another case is illustrated by the recent reports of melamine-contaminated milk powder products in China (levels ranged from 0.1 to

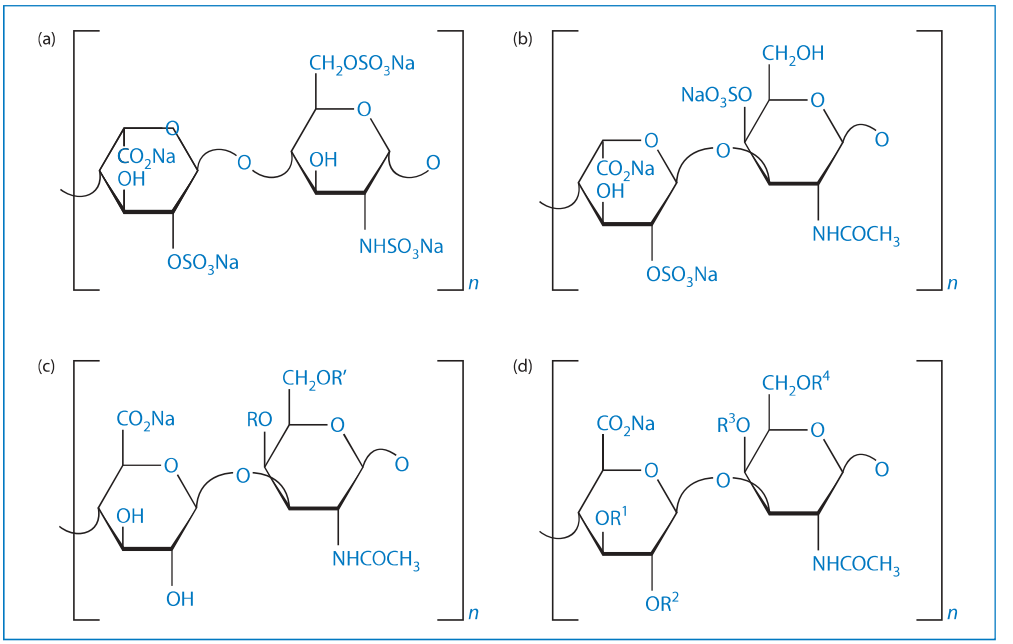


Figure 5.4 Structural formulae of heparin (a), dermatan sulfate (b), chondroitin sulfate A and C (c), and oversulfated chondroitin sulfate (OSCS) (d). For chondroitin sulfate A, group R represents the sulfated moiety, as for chondroitin sulfate C the residual group R′ is sulfated. For OSCS, R^1–R^4 label possibly sulfated moieties. The dermatan in heparin preparations is a signal of poor purification methods. (From reference 6.)

2500 ppm).[7] The melamine was added criminally to increase the measured but not actual protein content. Children consuming the product developed nephrolithiasis.[8]

A detailed discussion of the outbreak of adverse reactions as a result of the use of contaminated heparin is provided by Blossom *et al.*[9]

Hyaluronic acid

The use of hyaluronic acid (HA) in osteoarthritis as a synovial fluid supplement was discussed in Chapter 1. It has also been used in ophthalmic surgery. *In vivo* metabolic degradation of HA by hyaluronidase is one of the determinants of its biological half-life. HA can be sourced from bacteria, from rooster combs or from human umbilical cord, and the resulting HA products contain different impurities.[10] Several commercially available products in one study did not degrade on digestion with hyaluronidase, clearly indicating that biological half-life will not be the same. Vigilance is necessary and, where problems arise, the provenance of biological products must be determined. Sources might vary from batch to batch as discussed in Chapter 4. Source matters, processing matters, purification matters and, of course, proving this by the application of the highest-quality analytical technology is essential. Finding out about such problems before damage is done or suspected is certainly difficult. We must be prepared to ask the obvious questions of suppliers when problems are suspected. It is not always possible to wait for final proof.

Oligomeric impurities in penicillins

Acute sensitivity to penicillins occurs in a minority of patients, but the reaction is well known in practice. Nevertheless, the source of at least some of the adverse reactions is not always appreciated. Impurities in penicillins have been blamed for sensitivities and allergies to this class of drug. The number of impurities found in samples of amoxicillin is quite remarkable.[11] Amoxicillin's structure is shown in Figure 5.5.

Impurities in amoxicillin samples can include 2-hydroxy-3-(4-hydroxyphenyl)pyrazine, 4-hydroxyphenylglycine, 4-hydroxyphenylglyclamoxicillin,

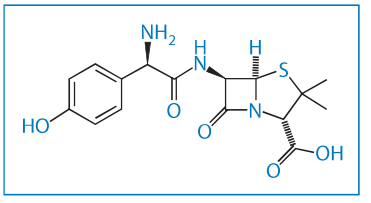


Figure 5.5 Structure of amoxicillin.

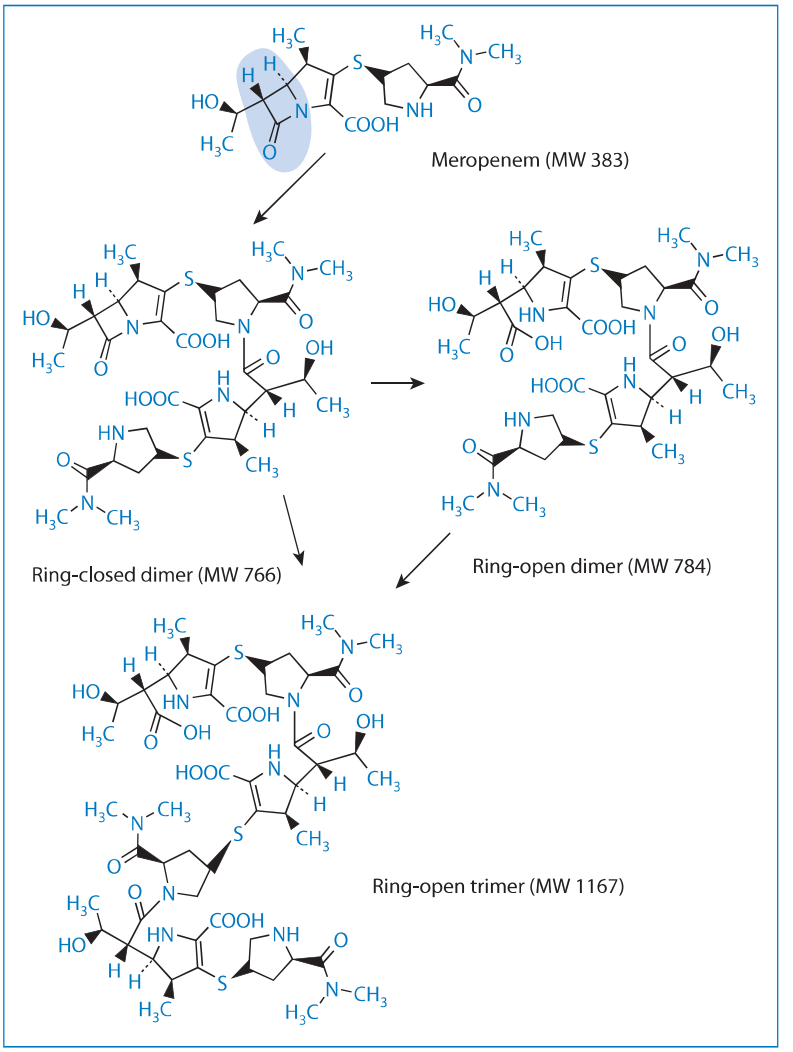


Figure 5.6 Ring-opened and ring-closed dimers and a ring-open trimer. The ring in question, the β-lactam ring, is highlighted.

6-aminopenicillanic acid, amoxicilloic acid and seven others not including the dimer and the trimer (see Figure 5.6) These and other oligomers are possibly prime culprits in penicillin allergies as they are formed with peptide bonds and resemble peptides.

Contamination of products from containers

Sensitisation of the skin to topical products may not always be the result of the drug or of the excipients. There is the potential for contamination by substances that have leached from the containers. The aluminium tube is still the most widely used container for topical creams and ointments; the tubes are lacquered to prevent direct interaction between product and aluminium. Epoxy resins are used as the protective layer in most cases, particularly

bisphenyl A diglycidyl ether (BADGE)-based resins. Leaching of BADGE and its congeners depends to an extent on the formulation and the mechanical stresses applied to the tubes.[12] Adverse effects due to these leachables have not been assessed but they are a potential cause, for example, of contact dermatitis.

Delivery devices and materials

There is an increasing number of devices and biomaterials that are used to deliver drugs, genes and vaccines. Issues can arise with the materials used in such devices, which include syringes and giving sets, or with the manner in which the device as a whole behaves (system plus active material). There might also be technical failure of a pump or reservoir, or conditions in the device that destabilise the drug, especially if it is a protein.

Insulin pumps

A good example of problems that arise through system–drug interactions is the phenomenon of protein aggregation in insulin pumps.[13] Insulin aggregation is accompanied by a significant loss of biological activity. Various problems have been encountered with insulin pumps: obstruction in the infusion set or leakage at the infusion set connection or from the infusion site. Insulin aggregation (when insulin fibrils form after heating) can also occur owing to agitation of the pump during wear and to temperature fluctuations. The stability is influenced by the type of insulin, the solvent and the concentration.[14] Metal ion contamination has also been implicated and the use of EDTA has been recommended to sequester ions.[15] Insulin aggregates will at times block delivery channels.

Figure 5.7 illustrates the different deposition patterns of insulin in solution following administration by pen injector, a jet injector and an external insulin pump. The diffusion of insulin from sites of administration is important for its activity; retention of insulin and its degradation at the site of deposition might reduce biological activity. Pharmacokinetic differences between these modes of administration might also be found.

In one study of bovine zinc-insulin, aggregation occurred only when agitation and hydrophobic surfaces were present.[16] Other proteins also degrade physically in pumps; interleukin 2 can lose 90% of its activity over a 24-hour period of infusion. Adsorption, which is a precursor of aggregate formation in some insulin systems, does not occur with interleukin 2, but irreversible structural changes can occur.[17] Methods of maintaining the physical stability of protein solutions are discussed by Lougheed *et al.*[18]

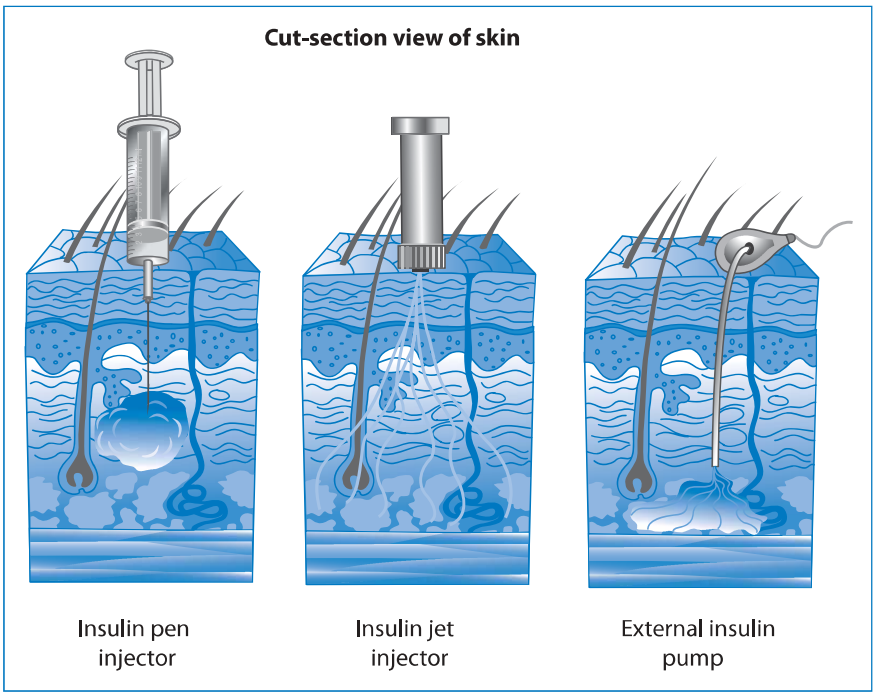


Figure 5.7 Different distribution patterns after administration of insulin by injector pen, jet injector and external insulin pump. (From http://adam.about.com/care/diabetes.)

Adsorption of proteins onto solid surfaces is a well-known phenomenon. Insulin adsorbs to glass, so that in low concentrations drug can be lost. Figure 5.8 shows the rate at which Asp^{B25} insulin adsorbs onto a silanated silica wafer surface.[19] At the higher concentrations adsorption is rapid, as one

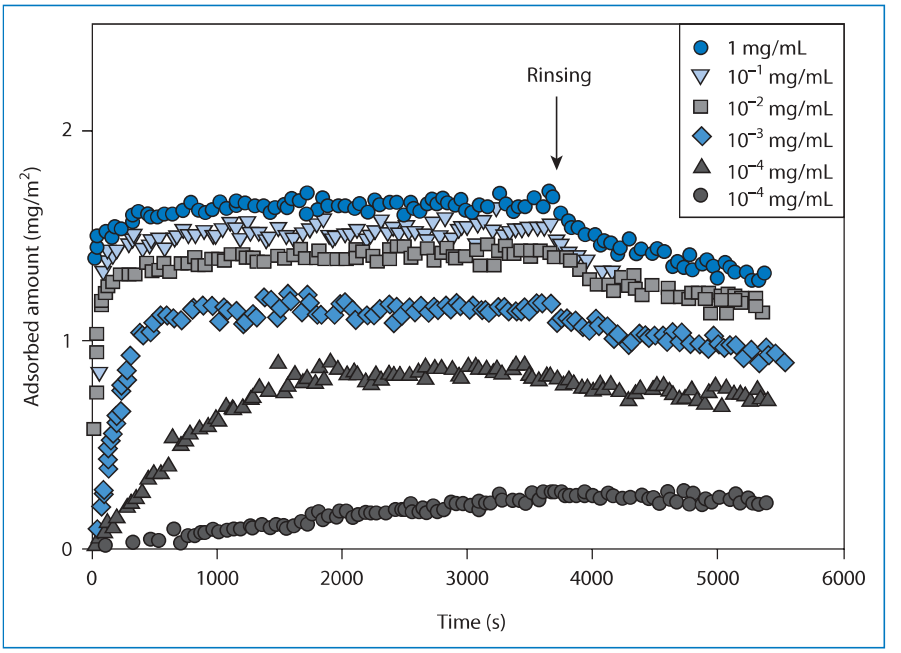


Figure 5.8 Adsorption onto silanised silica surfaces of Asp^{B25} insulin, showing the influence of concentration, (From reference 19.)

might expect from diffusion-controlled kinetics. One technique to avoid loss of insulin by adsorption is to add small amounts of albumin to the infusion; the albumin adsorbs first and inhibits further adsorption of the active.

Stents

Drug-eluting stents have made an impact in the therapy of restenosis but there have been many reports of adverse events ranging to death due to early and late stent thrombosis.[20] It has been suggested that many of the problems have been due to the polymer used in the stent coating.[21] Many variants have been studied: changing the polymer[22] and including the use of biodegradable polymers[23] and also designs with non-polymeric systems. Figure 5.9 shows a stent in place in a coronary artery close to plaque; the figure to the right (b) represents the release of drug from a polymer coating on the stent structure.

The components of a drug-eluting stent comprise a platform (the stent), a carrier (usually a polymer) and an agent (a drug).[24] Stents allow the local delivery of the active agent to the area of vascular injury, averting the need to deliver high doses systemically. The device must have mechanical resistance to abrasion during implantation, resist sterilisation, control drug release, and not damage the vessel wall and tissue. Various coatings have been developed, including phosphorylcholine; biocompatible non-erodible, biodegradable, or bioabsorbable polymers, as well as ceramic layers. Polymers are the most commonly used carriers. Clinical trials of safety and efficacy are required for each device.

Problems that have arisen with drug-eluting stents have been reviewed from an FDA perspective.[25] Some relate to the reports of subacute thrombosis and 60 associated deaths (up to 2004). While it was not possible to determine whether the adverse events are more common in drug-eluting or bare metal

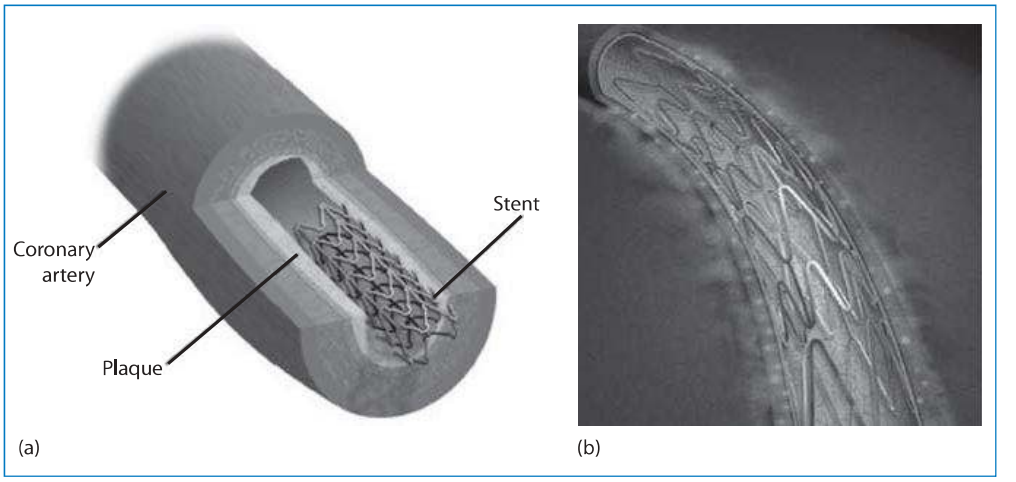


Figure 5.9 (a) A cartoon of a stent in a coronary artery (www.csmc.edu/images). (b) The release of active agent from the polymer coating on the stent (Boston Scientific Corporation).

stents, some are related to problems with failure of the stent to deflate after deployment (Taxus Express). This problem has been ascribed to issues in the manufacturing process that could have led to a weakening of the outer lumen of the delivery catheter. The resistance of the stent to withdrawal has been ascribed to 'stickiness'. One suggestion was that it was due to the friction between the stent delivery balloon and the drug–polymer coating on the stent.

Catheters

Intravascular catheter-related infections can be an important source of bloodstream infections in patients who are critically ill.[26] It is said that more than 250 000 vascular catheter-related bacterial or fungal infections occur each year in the USA, with mortalities in critical ill patients of up to 25%. Bacteria can adhere to and form biofilms on catheter surfaces. Preventive stratagems include cutaneous antisepsis, use of sterile barriers during insertion, application of chlorhexidine-impregnated sponges and the use of antimicrobial, antibiotic-coated or silver-impregnated catheters. Urinary catheters also suffer from bacterial film formation, and there are several points of entry of bacteria in such systems, as seen in Figure 5.10. This is clearly an area of great importance, but some of the issues are outside the scope of this book. What is clear is that antibiotic-coated catheters are drug delivery devices and that bacterial biofilms that form on catheters are the result of an adhesion process, two areas that are outwith our scope (although we should never be concerned in practice about such boundaries).

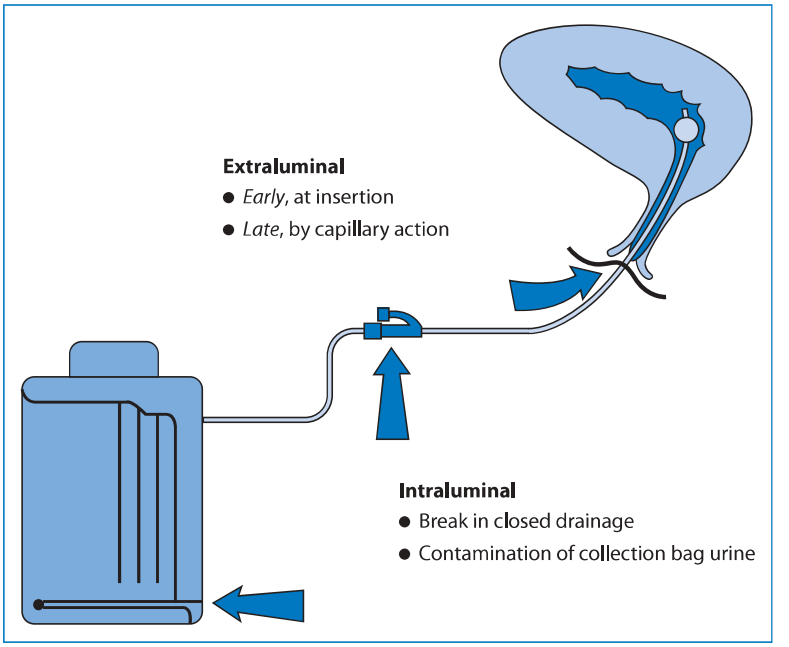


Figure 5.10 A schematic of the arrangement of a urinary catheter. Sources of infection are indicated by arrows.

Table 5.3 Contact angles of different *Pseudomonas* spp.

Strain number and name	Contact angle (°)
Pseudomonas fluorescens	21.2
Pseudomonas aeruginosa	25.7
Pseudomonas putida	38.5
Pseudomonas sp strain 26-3	20.1
Pseudomonas sp strain 52	19.0
Pseudomonas sp. strain 80	29.5

Values for other organisms can range up to 60° for an *Arthrobacter* sp. strain 177 and 70° for a *Corynebacter* sp. strain 125.

Bacteria adhere to solid surfaces. Bacterial hydrophobicity can be correlated with the adhesion of bacteria to experimental surfaces such as negatively charged polystyrene. Different bacteria have different hydrophobic properties; the contact angles of water with bacterial surfaces correlate with hydrophobicity. The higher the contact angle, the higher the hydrophobicity and the greater the adsorption.[27] Different strains of bacteria, e.g. of pseudomonads, behave differently as can be seen in Table 5.3. However, it is generally unlikely that only one parameter correlates with bacterial adsorption onto a wide range of surfaces, which are not always smooth as in experimental systems. Nonetheless, knowing the surface properties of bacteria and of the catheter material can be valuable in understanding problems.

Transdermal patches as devices?

Transdermal patches can be considered devices. Problems that have arisen with these include adverse reactions to the adhesive used to adhere the patch to the skin. Allergic contact dermatitis from hydroxymethylcellulose has been reported with an estradiol patch.[28] Mishaps related to use of transdermal patches include many involving patches falling off under a variety of conditions, including subsequent adhesion to another person! Other events include swelling and itching at the application site; too strong adhesion, leading to pain on removal; excessive adhesion of the plastic backing to the adhesive layer, leading to tearing of the patch; inflexible patches that do not flex with the skin; and cases of drug crystals being seen on patches.[29] Cases of burning have been reported when medicated patches containing even small amounts of aluminium are worn during magnetic resonance imaging, as a result of overheating in the area of the patch.[30]

Abnormal bioavailability, high or low

Classical examples where the bioavailability has changed after a period when patients have been stabilised and physicians are accustomed to responses from a particular dose form or brand include digoxin (Lanoxin). In the 1970s a change in the manufacturing process led to a marked difference in bioavailability through an increase in particle size. A change in the main excipient from calcium carbonate to lactose in a brand of phenytoin sodium led to a marked increase in bioavailability and overdosing. The calcium was clearly forming a calcium salt of the drug, decreasing its solubility and rate of dissolution. Its removal led to faster absorption and toxic effects in titrated patients.

Testing for adverse effects

Can pharmacists become more involved in searching for the causes of adverse effects? One example might be our own experience in the University of Strathclyde working with the Contact Dermatitis Unit at Belvidere Hospital Glasgow some years ago, where we explored modes of measurement of skin reactions to substances applied to the skin. The aim was to replace more subjective clinical scoring when pharmacists had an opportunity to assess reactions scientifically. Contact dermatitis is a term for a skin reaction resulting from exposure to allergens (allergic contact dermatitis) or irritants (irritant contact dermatitis). Phototoxic dermatitis occurs when the allergen or irritant is activated by sunlight. Contact dermatitis can occur from contact with jewellery but also from drugs and devices (e.g. transdermal patch adhesives).

Contact dermatitis testing

Suspected contact dermatitis is usually tested for by application of a series of patches containing putative causative agents. The formulation of these materials has often been fairly crude (for example by dispersing nickel sulfate in a paraffin base) and this might affect the outcome. Poor attention to pharmaceutical principles of release, poor choice of vehicle and lack of consideration of particle size all contribute to imprecision.[31] Proprietary patch formulations are available. Test results are often evaluated against a control or controls by clinical scoring of reactions from severe (+++), through (++), (+), 0 and equivocal (<+). Skin reflectance measurements were evaluated as a measure of skin haemoglobin content and correlated well with clinical scoring.[32] The following is an example of a study conducted some time ago.[31]

> A group of 43 patients with a clinical history of nickel allergy who exhibited an equivocal or no allergic reaction to a patch test at 48 h were further challenged using several different formulations of nickel

sulphate. This experimental test battery comprised aqueous, dimethyl sulphoxide (DMSO) and propylene glycol (PG) solutions of nickel sulphate, and nickel sulphate incorporated into Cetomacrogol cream and yellow soft paraffin (PMF). Although some of these vehicles were irritant, a formulation-dependent test response was observed, such that in terms of the number of responses per unit weight of nickel sulphate applied to the skin, the vehicles could be ranked: DMSO greater than PG greater than aqueous solution greater than Cetomacrogol cream greater than PMF preparations. This ranking could be correlated with the relative ease with which nickel sulphate could be dialysed from each vehicle in vitro. This study demonstrates that for nickel sulphate, the vehicle can influence the outcome of patch testing apparently by modifying the quantity of nickel released into the skin for elicitation of the allergic response.

(Cetomacrogol is a non-ionic surfactant with a C_{16} hydrocarbon chain and an average 24-unit polyoxyethylene oxide hydrophilic chain.)

Release of nickel sulfate from the test preparations varied considerably, as shown in Figure 5.11. The correlation between skin blood flow (plotted in Figure 5.12 as the Hb (haemoglobin index) and clinical scoring is good. The response is often a weal which reflects increased blood flow and, of

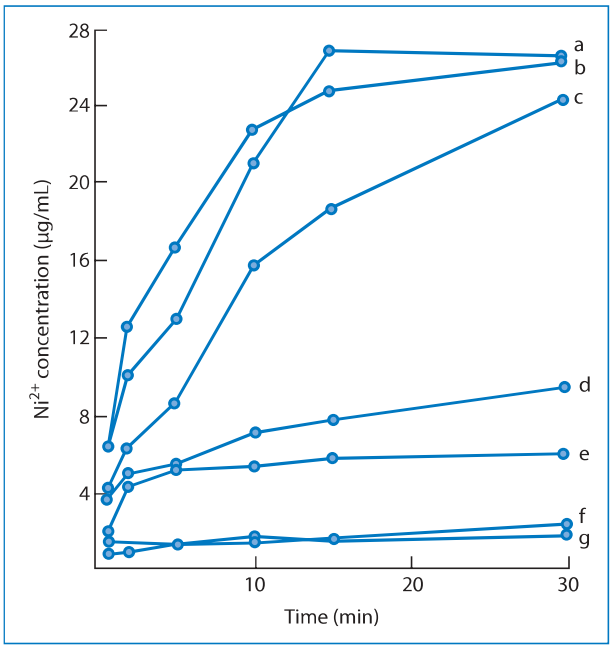


Figure 5.11 *In vitro* release of nickel sulfate from various vehicles at 37°C using a dialysis technique. Curve a, an aqueous solution of nickel sulfate ($NiSO_4$); curve b, propylene glycol solution; curve c, dimethyl sulfoxide (DMSO) solution; curve d, Cetomacrogol cream; curve e, 2.5% $NiSO_4$ in yellow soft paraffin (proprietary formulation); curve f, yellow soft paraffin; curve g, 5% $NiSO_4$ in yellow soft paraffin (proprietary formulation). (From reference 31.)

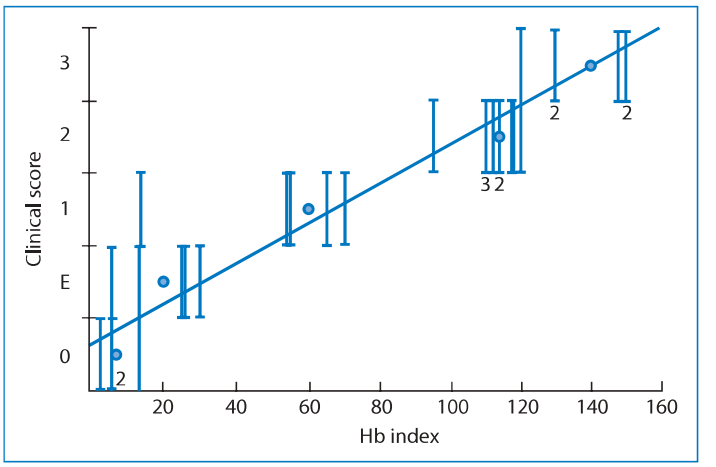


Figure 5.12 Correlation between clinical scores of patient responses to a variety of proprietary test patches and the haemoglobin (Hb) index derived from a skin reflectance technique. The individual test patches contained separately nickel, chromium, colophony fragrances, thiomersal, benzoic acid, parabens, neomycin and a range of other materials implicated in contact dermatitis. (From reference 32.)

course, heat output. Infra-red thermography has also been used.[33] This is a convenient non-invasive technique that employs an infra-red (IR) camera and can be used to discriminate between irritant and allergic responses and to quantify the latter.

Figure 5.13 shows some results after application of the contact dermatitis test patches, both the appearance of the reactions to different formulations and the results when assessed using the IR camera. The IR thermograms, which detect the increased blood flow and heat profiles, show not only the intensity but also the spread of the reaction on the skin.

Nanosystems

The next few years will see the advent in medicine and pharmacy of many particulate systems. There are several reasons why we should be concerned and observant about potential toxicity. The first is that nanosystems, although they have been around in pharmacy since the mid 1970s, have not been widely used. The second is that their small size allows them to translocate in the body and end up in higher concentrations in organs such as the liver and spleen that larger particles cannot access. Lastly, their small size leads to large surface areas per unit weight and this can bring its own problems with regard to interaction with blood components and with tissues. Figure 5.14 illustrates some of the nanosystems now available experimentally from polymer particles, fullerenes, dendrimers and gold sols, and also their potential for interactions *in vivo:* interactions with blood components, interaction with and effects on immune cells, accumulation in the reticuloendothelial system and immunogenicity.[34]

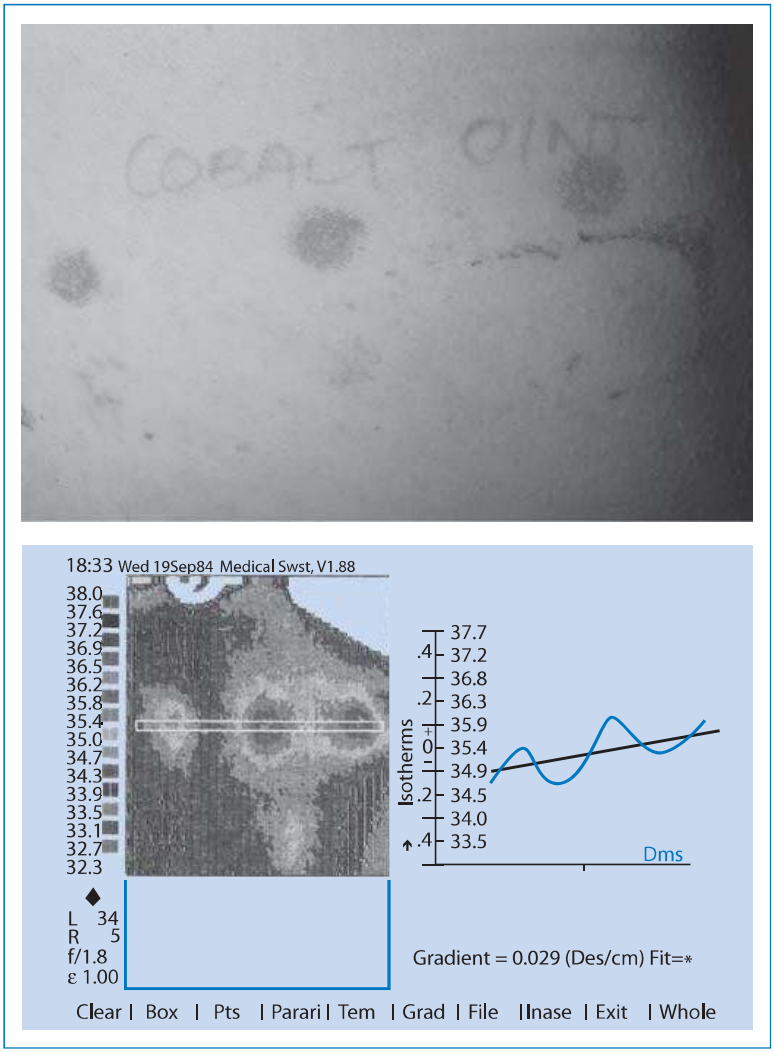


Figure 5.13 (a) Typical appearance of positive reactions to contact with patch tests on the back of a subject. (b) An infrared thermogram of the back of a (different) patient who has been assessed for contact dermatitis to nickel with three formulations of nickel sulfate. The image shows not only differences in intensity but also difference in the spread of the response. These thermograms are more informative than physicians' scoring systems.

Undoubtedly new adverse effects will arise from the use of nanosytems after their widespread use. Inhaled systems will reach sensitive lung tissue, but like other inhaled medicines, material swallowed will end up in the gut and it is known that small quantities of nanoparticles can be absorbed intact through the M-cells of the gut-associated lymphoid tissue (GALT) and also through enterocytes.[34] Much has still to be learned about the potential down sides of nanomedicines and assurances on the safety of the materials from which they are made is not always sufficient to instil confidence in the safety of the nanoparticles. Because of the vast array of possible systems, it is impossible to generalise. Each system will have to be examined and tested on its merits.

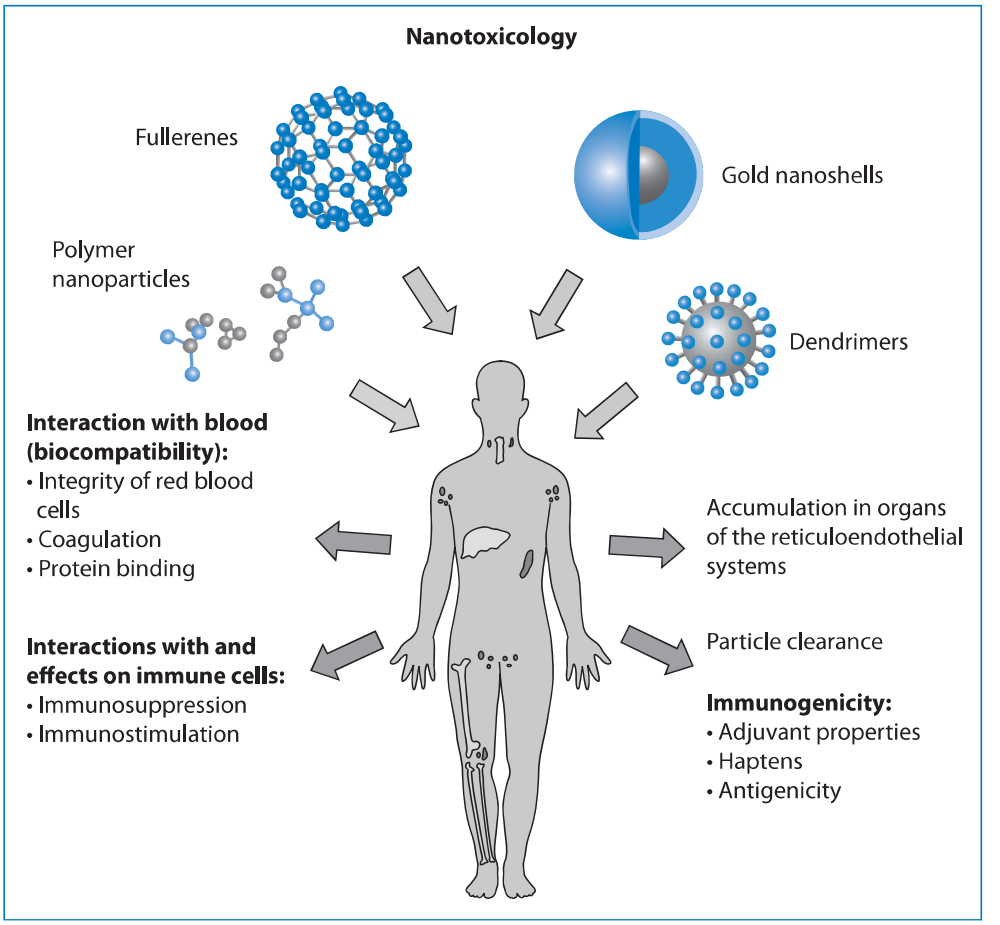


Figure 5.14 Mechanisms of toxicity of nanosystems.

Conclusions

Detecting the causes of adverse events is not an easy task, especially when drugs or drug products are novel. It is essential that we look for analogies, reports on closely related drugs, and similar formulations, perhaps identical excipients.

Potential mechanisms should be proposed and the following questions asked:

- Is the event due to the drug?
- Is it an excipient effect?
- Is it a result of the dosage form?

and of course:

- Is it unrelated to the medication?

This requires a breadth of knowledge of similar events recorded in the literature or from experience. The few examples noted in this chapter may assist in

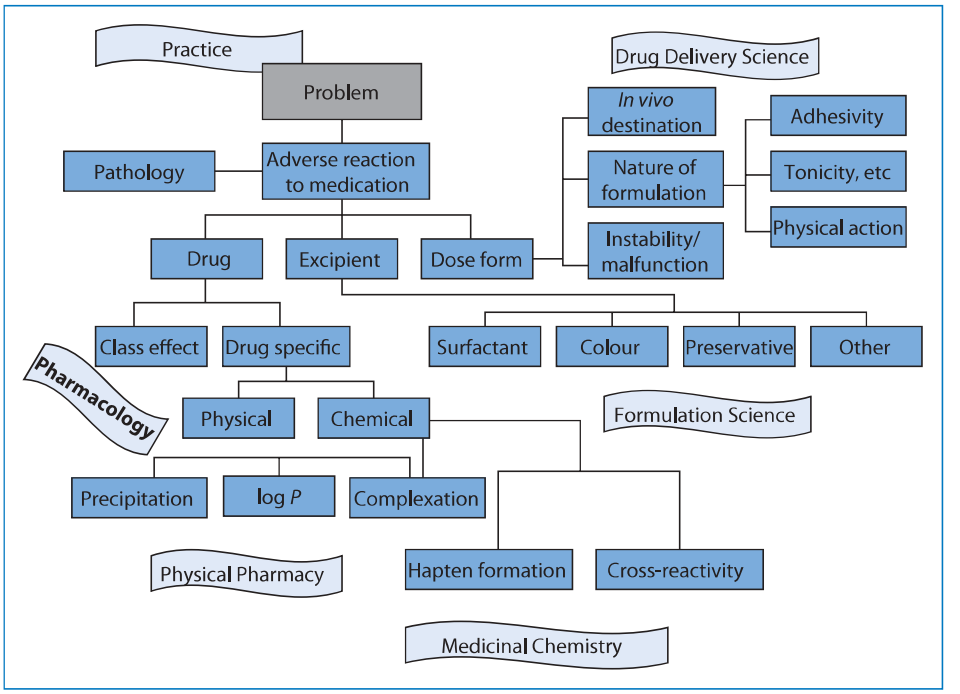


Figure 5.15 Charting the causes of adverse reactions to medications. The many causes are shown in relation to drug, excipient, nature of formulation, the dosage form or device and whether there are physical or chemical causes.

asking the right questions. The concluding illustration (Figure 5.15) summarises how one might approach the issues. A fuller record of adverse events and the involvement of delivery systems (up to 1996) can be read:[1] the older literature should not be discarded as there may be clues there which might have relevance to new medicines and treatments.

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6

Paediatric, geriatric and special formulations

This chapter covers some aspects of formulation in paediatric and geriatric practice, a branch of pharmacy in which personalised medication comes into its own. We deal with the need for special formulations for individual cases and some of the more general needs of the population at the different ends of the age spectrum. This has been termed 'age-specific' medicine. We will deal also with medication and enteral delivery by feeding tubes, in both children and the elderly.

Introduction

If there was ever a case of continued emphasis on pharmaceutics it is the need to design patient-specific medicines both nationally, in specialist units in hospitals and, one would hope, in community pharmacies in the future. The possibility of errors in medication increases with the number of manipulations and calculations required; hence even simple technologies that provide dosing systems to avoid the large dilutions that are frequently necessary in paediatric care would be of benefit. In the 1950s and 1960s, extemporaneous formulations were the norm even if the drugs and ingredients they contained were inferior to today's. We now have a wider range of excipients and active agents available and also a much broader range of methods of formulation and modes of delivery of drugs. We can now also characterise and manipulate materials in a superior way. Unfortunately, many formulations for children are perforce prepared from products designed for adults; the same applies for the elderly, who may have difficulties in swallowing or have problems that demand modified approaches to medication. We do not deal here with the differences in the pharmacokinetic and pharmacodynamic or metabolic aspects of drugs in the different categories of patients. These often necessitate the use of sustained-release (SR) or modified-release (MR) formulations or individualised therapies, but are covered in detail in other texts. However, formulations are not chosen in isolation. There are age-related developmental

changes in the pharmacokinetics[1,2] and pharmacodynamics[3] of drugs. Changes occur in gastric acidity, drug clearance and receptor expression, as discussed in an article by Kearns *et al.*[4] Many of these changes are relevant to drug absorption. Neonatal stomachs are achlorhydric soon after birth, so the absorption of, for example, acid-labile drugs may be increased. The rate of gastric emptying falls as infants get older, being faster in the neonate than in adults, but slower in infants and children than in adults. This has consequences with some formulations. Because the liver takes up a relatively large percentage of body volume in infants, clearance rates often exceed those in adults. It is clear then that extrapolation of data from adult data sets in terms of absorption or the behaviour of both drugs and dose forms is hazardous. Many of these issues are discussed in more detail in a review on the topic of developing paediatric medicines.[5] One problem with assessing the literature on the use of medicines in children is that journals 'permit inadequate formulation information in pediatric drug trials ... impairing their validity and reliability'.[6] Full formulation information should be provided in all paediatric clinical trial reports and in other publications.

Extemporaneous formulations

Extemporaneous formulation would not be so daunting were it not for the reluctance of manufacturers to provide pure drug samples for human administration. Hence, formulations are frequently prepared from tablets, capsules and injections to produce medicines suitable for an individual child or for groups of children. This should be considered unacceptable in the twenty-first century, as much as the need for the elderly to have to cut tablets in half. Nonetheless, it is pharmacy's role to provide appropriate medicine for individuals.

Figure 6.1 illustrates some of the basic approaches used when converting existing formulations of tablets, capsules and injections into alternative forms. It may be that the contents of an injection can be incorporated directly into a suitable vehicle. The same may be true of soft-gelatin capsules, whose contents may be amenable to emulsification depending on their nature. In a survey of extemporaneously prepared dosage forms in NHS trusts in Yorkshire, NE England, and in London, it was found that 66% were aqueous suspensions, 22% solutions, 4% powders, 1.2% oils and 0.2% capsules.[7] Most were for use in paediatric patients, and included drugs such as midazolam, vancomycin, clonidine hydrochloride, diazoxide, clobazam and warfarin. Yet in this study it was found that 28% of extemporaneously prepared products had neither chemical nor microbiological supporting data and close to 8% had their formulae and expiry dates taken from the literature. Much of the data was not on file.

Often the issue is dose reduction, but it is also frequently to provide a dosage form that aids swallowing in both the young and the elderly. The

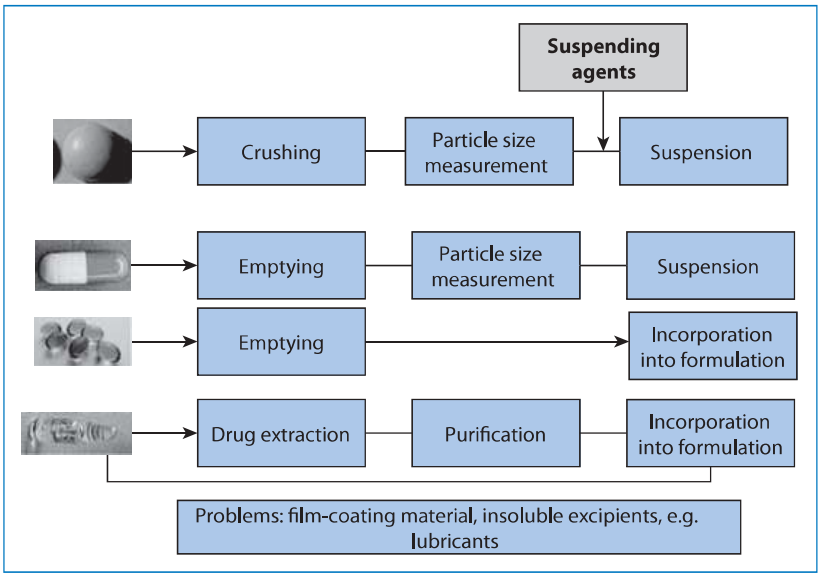

Figure 6.1 Stratagems applied when there is a necessity to convert existing adult dosage forms (tablets, hard- and soft-gelatin capsules and injections) for use in children or the elderly. Drug substance may also be sourced from chemical manufacturers, but must undergo strict quality control before use.

pharmacokinetic and metabolic differences in patients are clearly also among the drivers of formulation choice, as outlined in Figure 6.2.

The problem in the extemporaneous formulation of medicines 'that children can take', as Nunn[8] has put it, is that many products used have inadequate data on stability and shelf-life, let alone bioavailability, and have an unpleasant taste. He calls for a national standard for extemporaneously dispensed medicines. Solid dosage forms are usually more stable than liquid

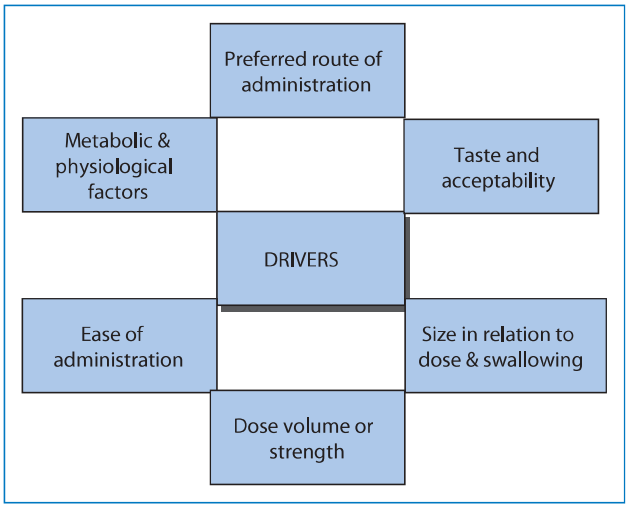

Figure 6.2 The matrix of drivers for special formulations.

formulations. The use of mini-tablets, 3 mm in diameter, to aid swallowing has been investigated in children aged from 2 to 6 years.[9]

In a discussion of the development of an oral captopril formulation for paediatric patients it has been pointed out that the stability of the liquid products was variable, partly as a result of variability of the purity of the captopril used.[10] But even with a single source of drug, stability after one month at room temperature ranged from 71.5% to 100%, although with storage at $5 \pm 3^{\circ}C$ the range was from 82% to 99.7%. At the latter storage temperatures, the formulation is stable for two years. Captopril oxidation is catalysed by metal ions, hence the value of the presence of EDTA for a stable formulation and the avoidance of contact with metal ions, which might come from use of drug substances extracted for other formulations. Apparently, a variety of unlicensed captopril products were used in 13 tertiary paediatric cardiac centres in the UK and 13 large hospitals referring patients to these centres: four hospitals dispensed captopril tablets by crushing and dissolving in water before administration, and the other 22 used nine different liquid formulations. As the authors conclude,[11] this degree of inconsistency raises 'issues about optimal captopril dosing and potential toxicity, such that its use may influence paediatric cardiac surgical and interventional outcomes'. This is an indictment of modern pharmacy.

Effect of formulation and presentation: a case from the literature

Isoniazid absorption in two young children

The abstract of a paper by Notterman *et al.* reads in full:[12]

> In an 8-month-old infant with tuberculosis meningitis treatment with isoniazid was unsuccessful and was associated with lower than expected plasma concentrations of isoniazid (measured concentration 0.1 microgram/mL). The infant had received isoniazid as a crushed tablet admixed with apple sauce. Oral administration of the parenteral solution of isoniazid (Nydrazid, Squibb) mixed in apple juice produced a higher isoniazid concentration (2.9 micrograms/mL) and the child improved clinically. Pharmacokinetic studies in two subjects were performed following intramuscular injection of isoniazid and oral administration of (1) an isoniazid tablet crushed and mixed with apple sauce, (2) parenteral isoniazid solution mixed with apple juice, and (3) a commercially available syrup containing isoniazid and pyridoxine (P-I-N Forte, Lannett). Of the three oral preparations, the syrup produced the highest peak concentrations (8.3 and 6.9 micrograms/mL). The crushed tablet in apple sauce produced the lowest peak concentrations (1.4 and 2.4 micrograms/mL).

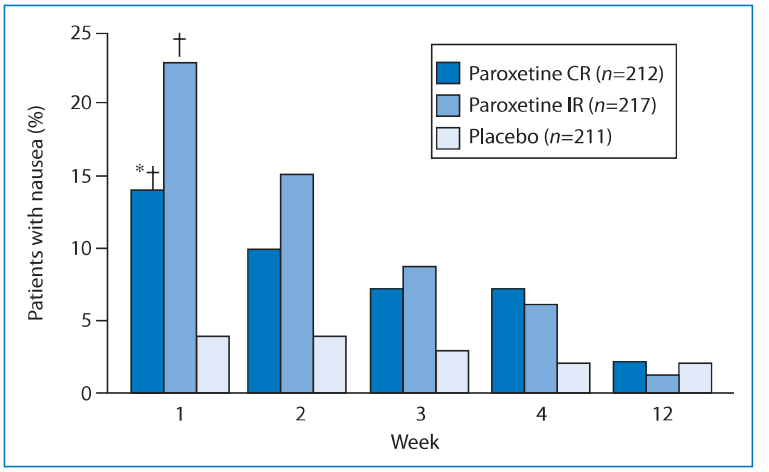

Figure 6.3 The number of patients with nausea as a function of the nature of the dosage form versus placebo. CR, controlled-release; IR, immediate-release. * $p \leq 0.05$ vs paroxetine IR; † $p \leq 0.05$ vs placebo. (From reference 13.)

> Administration of crushed isoniazid tablets with food may be associated with impaired gastrointestinal absorption, lower than expected isoniazid concentrations, and treatment failure.

There are issues of the particle size or granule size in the case of the crushed tablets and of the effect of the apple sauce, as suggested, on gastrointestinal (GI) absorption. One of the key issues when using crushed tablets or the contents of capsules is the determination of particle size distributions so that different batches at least consist of the same size as far as possible.

Formulation of paroxetine and reduction of nausea

Controlled-release formulations have long been used not only to prolong the effectiveness of drugs, but also to reduce side-effects. As one example, Figure 6.3 [13] shows the effectiveness of controlled-release formulations versus immediate-release formulations in reducing the incidence of nausea after paroxetine administration. There is an interesting time-dependence of the effect.

Developing paediatric medicines: liquid or solid oral forms?

Children are far from being a homogeneous group. As patients they may range from pre-term newborn infants (premature) with an average weight of less than 3.4 kg, through full-term infants (neonates) (0–27 days), infants and toddlers (28 days to 23 months) with weights of 3.4–12.4 kg, children from 2 to11 years (12.4–39 kg) and adolescents from 12 to 16/18 years weighing on average 39–72 kg for males and 60 kg for females.

In devising formulations for this variable group, note has to be taken of the issue of excipient biological activity, discussed in Chapter 2 and Chapter 5.

Liquid formulations are often favoured because of the ease of administration and acceptability to the child. Some researchers have actually studied methods of teaching children as young as 6 years to swallow tablets.[14] Taste masking is more of an issue with liquid formulations, but solid dose forms can be difficult to swallow and may lodge in the young oesophagus. Liquid formulations suffer somewhat from variability of measurement of dose, although oral injectors can reduce this frequent domestic error. The teaspoon is far from a standard measure, delivering in use between 2.5 and 9 mL according to a 1975 study.

The conversion from liquid to solid formulations of antiretrovirals is of interest.[15] There are problems with liquid formulations other than measurement of dose in practice: the daily dose volumes for a 20 kg child are 40 mL for stavudine, 22 mL for zidovudine 16 mL for abacavir and 12 mL for didanosine, for example,[8] and there are other practical issues in terms of bulk drug. Stavudine is available as a powder for reconstitution. In a single month, 18 packs would be required, needing as many reconstitutions. Three boxes of capsules hold equivalent treatments to the injection.

Itraconazole

Itraconazole is used in children with invasive fungal infections following chemotherapy. The drug is highly lipophilic and capsules have been reported to have variable absorption; a liquid itraconazole formulation employing a cyclodextrin as a solubilising agent has a bioavailability 60% higher than that of the capsules.[16]

Extemporaneous formulations and performance

If tablets are crushed to provide drug for extemporaneous formulations (avoiding of course the crushing of sustained-release forms), the process must be standardised as far as possible and the particle size distribution must be evaluated as minimal quality procedures.

There are commercial devices on sale for crushing tablets. Frequently these do not instruct patients or carers not to crush controlled-release tablets. Even if they did so, patients and carers would not be able to tell which were and which were not controlled-release systems.

The elderly and their medication

There are many reasons why medicines are required for use in the elderly patient. There are changes with ageing of the oral cavity and oesophagus, gastric and intestinal changes, let alone the problems of co-morbidity and polypharmacy that complicate their pharmaceutical care.[17] Prescribing

appropriately for the elderly is discussed in some detail elsewhere.[18] Xerostomia (see also Chapter 1) and delayed oesophageal emptying may have relevance for the use of certain oral medications, such as fast-dissolving dosage forms or buccal and sublingual forms. Here paucity of fluid intake may slow the release of drug in the oral cavity. The relationship between dose forms and oesophageal damage is dealt with in Chapter 5. The elderly are more susceptible to the lodging of tablets and capsules in the oesophagus than are younger patients. This is not necessarily the fault of the dose form, but can be the result of taking the tablet with no or too little water. The variability of water intake in 108 female subject in a trial of a film-coated placebo tablet when they were free to use whatever volume they wished is shown in Figure 6.4.[19]

The incidence of achlorhydria is found to be up to 20% in elderly patients and hypochlorhydria in 20% of patients over 70 years of age. Around 11% of the elderly have a median fasting gastric pH of above 5.[20] Intestinal transit may be slowed in the elderly. The effects of these many changes may be self-cancelling or may be significant. Much will depend on the drug and it is difficult to predict largely because the individual patients data are not available. More prosaic problems such as difficulty of patients in opening child-proof containers are well known.

Difficulties in swallowing are a problem not only in the young but also in the elderly[21] with dysphagia and those in particular with dementia. Patients

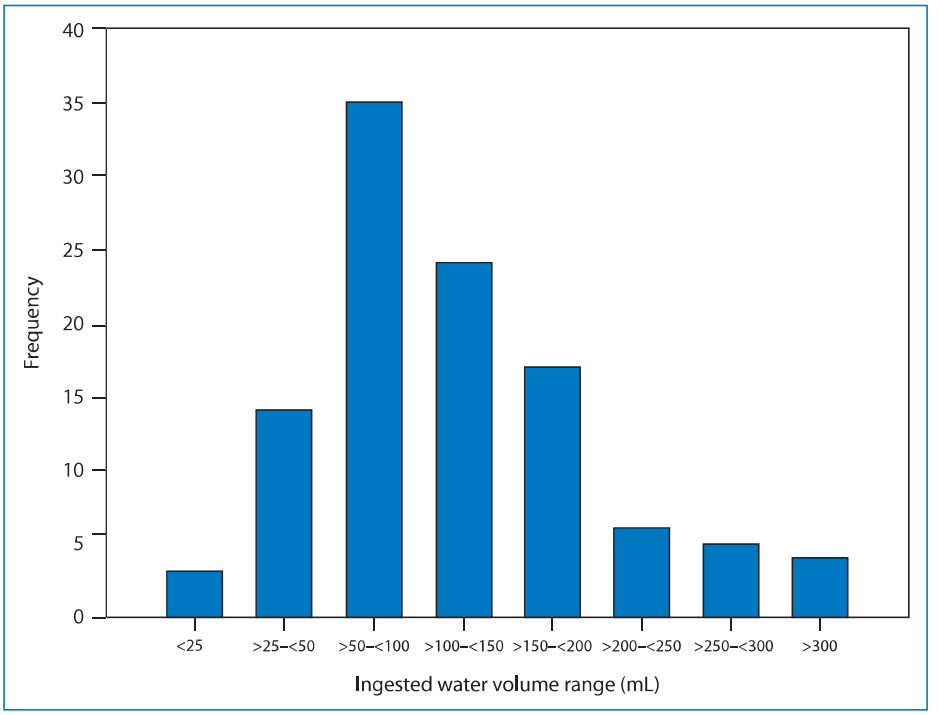

Figure 6.4 Distribution of volume of water ingested by participants swallowing a film-coated placebo tablet in a study of oesophageal transit (From reference 19 with permission.)

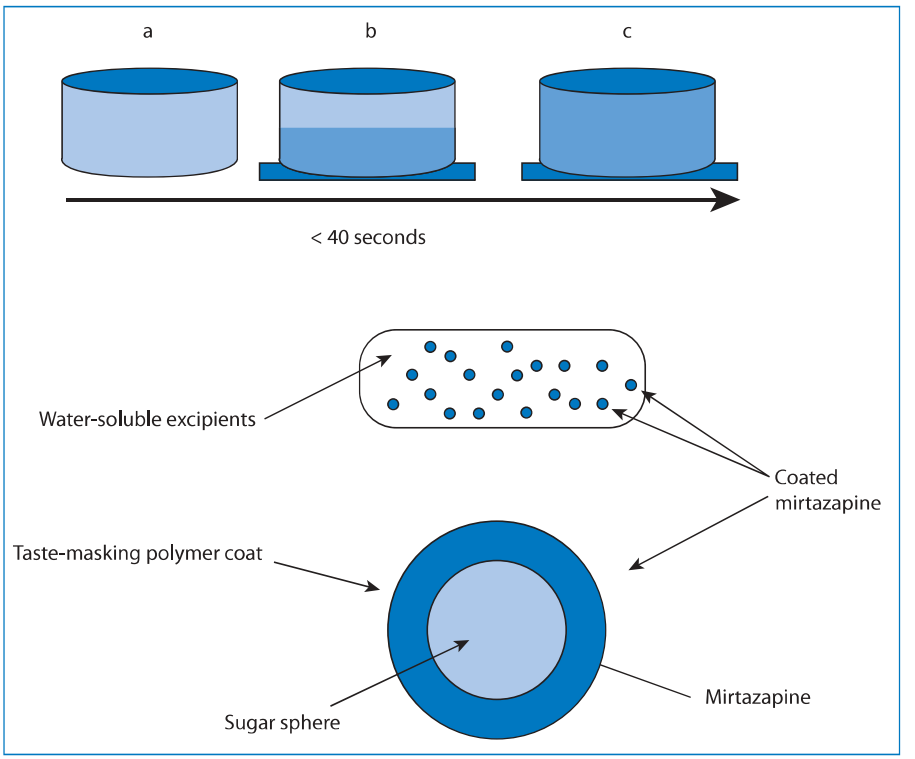

Figure 6.5 Top: the process of dissolution of mirtazapine SolTab in the saliva of the oral cavity: the penetration of water (stages a, b c) takes less than 40 seconds. Bottom: the structure of these fast-dissolving systems. (From reference 22 with permission.)

may simply refuse to take their oral solid medications. Fast-dissolving formulations administered sublingually can be one solution to the problem (see Figure 6.5); such formulations are frequently bioequivalent to the conventional oral forms. The problems of xerostomia, mentioned above, may, however, compromise outcomes somewhat. The benefits have been emphasised of having available for administration a range of different drug formulations, not least in psychopharmacology.[22]

Alternative routes of administration may be employed. The transdermal route has been promoted for use in the older population. There are apparently few differences in the permeability of the skin: the need to adapt doses for use in the elderly relate more to changes in cardiovascular, renal and hepatic change.[23]

Enteral feeding

While the main use of enteral feeding is to enhance nutrition in patients unable to take food normally, enteral feeding tubes also allow the administration of drugs to such patients.[24] This poses many pharmaceutical problems, however. Different feeding tubes have different destinations (Figure 6.6) and hence it is important to choose the correct site for the administration of the drug,

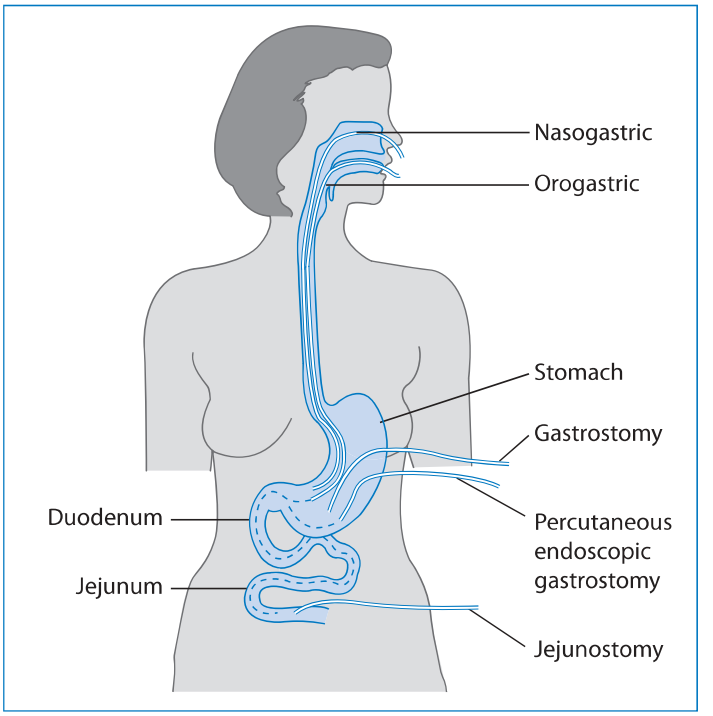

Figure 6.6 Different types of feeding tubes leading to the stomach. Nasoduodenal, nasojejunal and percutaneous jejunostomy tubes extend to the small intestine.

depending on the characteristics of the medication. Even though drugs may be absorbed maximally in the intestine, bypassing the stomach may result in poor absorption as the drug will not have the opportunity to dissolve in the acidic environment of the stomach.

Liquid formulations and solid dosage forms can be administered this way, and with caution several medications can be given at the same time. Nevertheless, drug–nutrient interactions can take place, there can be problems with the osmolality of the liquids administered, and there can be blockage of the tubes (see Table 6.1).

Table 6.1 Some liquid medications that are physically incompatible with most enteral fluids

- Brompheniramine (Dimetane Elixir, Wyeth, USA)
- Calcium gluconate (Rugby, USA)
- Ferrous sulfate (Feosol Elixir, GSK, UK)
- Guaifenesin (Robitussin Liquid, Wyeth, USA)
- Lithium citrate (Cibalith-S syrup, CIBA, USA)
- Potassium chloride liquid (Wyeth, USA)
- Pseudoephedrine hydrochloride (Sudafed Syrup, Pfizer, USA)

Osmolality

The osmolality of enteral feeding formulae is important because of its influence on the GI tract. Osmolality is expressed in mOsm/kg,[25] and is affected by the concentration of amino acids, carbohydrates and electrolytes. If quantities of a liquid with a higher osmolality than the gut contents are administered, water is drawn into the intestine; such a process leads to diarrhoea, nausea and distension. The osmolality of normal body fluids is 300 mOsm/kg and isotonic formulations have values close to this. Table 6.2 taken from Dickerson and Malnik[26] lists liquid medications that have osmolalities greater than 300 mOsm/kg. The exact osmolalitites will vary with the exact formulations used and will often differ between various brands of a formulation.

There are some liquid preparations that are not suitable for administration by enteral feeding tubes. Some may be too viscous and may occlude the tubes. Syrups with pH values below 4 often produce incompatibility with the enteral nutrition (EN) formulations, which may result in clumping, increase in viscosity and clogging of the tubes. Not all syrups produce this effect.

Solid conventional-release dose forms can be crushed for administration with EN fluids. The finely ground tablet is added as a suspension in water (15–30 mL). The contents of liquid gelatin capsules are often viscous and it is not easy to remove all of the contents from a single capsule. Delayed-release pancreatic enzyme capsules that contain enteric-coated beads[27] can be mixed with apple sauce or juice for administration via feeding tube. It has been suggested that the soft-gelatin capsule can be dissolved in hot water and the whole contents administered. Extended-release tablets and capsules have to be treated as special cases: the contents of capsules containing coated pellets

Table 6.2 Some liquid medications with osmolalities greater than 300 mOsm/kg[a]

- Acetominophen (paracetamol) elixir, 65 mg/mL
- Amantadine HCl solution, 10 mg/mL
- Chloral hydrate syrup, 50 mg/mL
- Cimetidine solution, 60 mg/mL
- Docusate sodium syrup, 3.3 mg/mL
- Lactulose syrup, 0.67 mg/mL
- Metoclopramide HCl syrup, 1 mg/mL
- Promethazine HCl syrup, 1.25 mg/mL

From reference 26.

[a] The exact osmolalities will vary with the exact formulations used and will often differ between various brands of a formulation.

can be mixed with EN fluids, but there can be a tendency for these to clump and block narrow-bore feeding tubes.

Drug interactions with nutrient formulations

Certain drugs have been found to interact with nutrient solutions. It is not surprising, given the nature of these solutions, that drugs may bind to proteins or be affected by electrolytes. Phenytoin, carbamazepine, warfarin and some fluoroquinolones have been reported to have lowered bioavailability because of various interactions. Phenytoin absorption has been reported to be reduced by up to 70% on co-administration with enteral feeds.[28,29]

Conclusions

This chapter has covered many of the areas in which drug formulation is important clinically. Special formulations for paediatric and geriatric patients form a group of products that are key to optimising therapy in these vulnerable age groups. Some wider issues are also discussed, including enteral feeding, interactions of drugs with nutritional fluids and the osmolalities of liquid formulations. These are only snapshots but further searching of the literature should provide many more examples of special formulations.

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7

Generic medicines: Conventional drugs and biologicals

Introduction

Generic forms of conventional (i.e. small-molecule) medicines contain the same drug as the original brand leader, although the details of the formulation may be different. The issue of generic equivalence and performance thus certainly lies within the domain of pharmaceutics. It is too simple to say that, as the drug is the same, only the formulation may differ, because as we will discuss in this chapter there can be differences in the purity of a drug even when it is within pharmacopoeial limits. The formulation and manufacturing process may indeed influence the stability of the drug and perhaps its physical form. Generic drugs are subject to strict guidelines for licensing so that, within the limits possible with modern analytical techniques and the variability of subjects, they will be bioequivalent, again with certain limits. One problem is that a generic product will be tested against the brand leader and there is no requirement to test generic versus generic. This is where there problems can arise, as we will see.

We distinguish here between so-called conventional, small-molecule drugs and those proteins and other macromolecules that are more complex. Generic forms of biologicals, especially of recombinant proteins, present other issues as the active molecule may contain, say, subtle differences in amino acid sequence due to often inevitable differences in the mode of production and processing. The term 'biosimilars' has evolved for generic forms of such biologicals; alternative terms include follow-on biologics (FOBs) or biogenerics. We deal first with small-molecule chemical medicines and issues related to branded and generic versions of a medicine. It should be noted that many generic products carry brand names, so in fact the discussion is centred around

the orginator's branded product and those products that follow from expiry of patents, and the issue of substitution of a generic for a branded product or one generic for another.

A 2007 survey of recent (Australian) pharmacy graduates' knowledge of generic medicines[1] found that more than 80% believed generic medicines to be inferior, to be less effective and to produce more side-effects when compared with branded medicines. When one considers that many generic medicines are manufactured by companies such as Pfizer, Sandoz, GSK and Merck, whose primary occupation is the development of branded innovative products, one wonders where this perception comes from. There are of course differences in formulation between many generics and their branded equivalents and sometimes, as we have discussed in Chapters 2 and 5, these differences can be important for patients, but for the majority of conventional (normal) release products of most drugs there are few problems. There are some therapeutic categories where one might choose to continue with a product on which the patient has been stabilised, as with antiepileptic drugs; clearly, this is where professional intelligence has to be applied.

Regulatory statements on generic products[2]

A generic drug should be identical or bioequivalent to a brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. The US and European authorities adopt similar approaches. To gain approval, a generic drug must:

- Contain the same active ingredients as the innovator drug (inactive ingredients may vary).
- Be identical in strength, dosage form, and route of administration.
- Have the same use indications.
- Be bioequivalent.
- Meet the same batch requirements for identity, strength, purity, and quality.
- Be manufactured under the same strict standards of good manufacturing practice (GMP) regulations required for innovator products.

The question of bioavailability has to be looked at in several ways (Figure 7.1). Products can be bioequivalent yet not therapeutically equivalent, perhaps because the rate of absorption of the drug differs in the first 30 minutes or so. If bioavailability is measured by the area under the plasma concentration–time curve (AUC) over 24 or 48 hours, then these measures of bioavailability might not show up subtle differences.

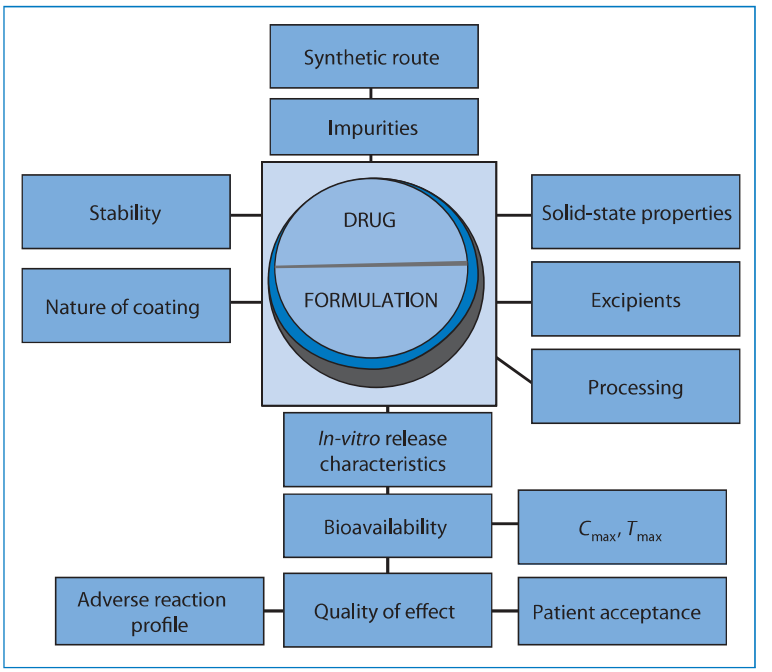


Figure 7.1 The range of issues in determining the equivalence or essential similarity of formulations.

Generics: A question of quality

Equivalence between medicinal products can be thought of at two levels, namely:

1 *Chemical equivalence*, which refers to dosage forms containing the same amount of the same drug in similar dose forms.
2 *Therapeutic equivalence*, which refers to medicines having not only the same bioavailability (as measured by the AUC), but the same clinical effects.

Figures 7.2 and 7.3 demonstrate the limits of bioequivalence and non-bioequivalence. Figure 7.3 shows how, while two generic products may be equivalent to the first brand product, the two generics may not be equivalent to each other, which may pose problems in practice.

Essential similarity of dose forms of the same drug focuses on the essential similar of purity of the drug substance as well as similarity of release rates. Chemical equivalence is ensured by pharmaceutical processes and quality assurance and is one prerequisite for therapeutic equivalence. Limits are set for drug substance; for example, tetracycline hydrochloride contains not less than 96% and not more than 102.0% of the drug. As far as therapeutic equivalence is concerned, the product should have essentially the same safety profile as the comparator product. Regulations do not speak of *identicality* between products, but *essential similarity*. One reason is that drug substances

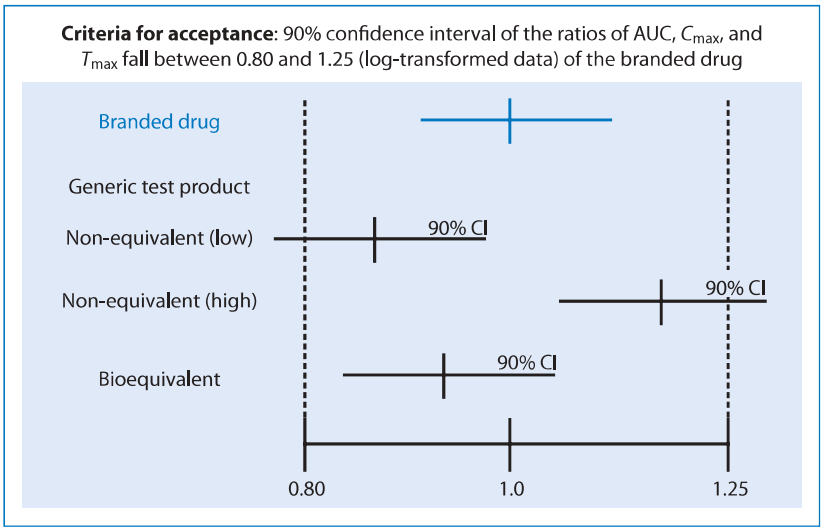


Figure 7.2 The issue of variability in branded and generic products with their 90% confidence limits and the definition of non-equivalence and equivalence in visual form. (From Medscape.)

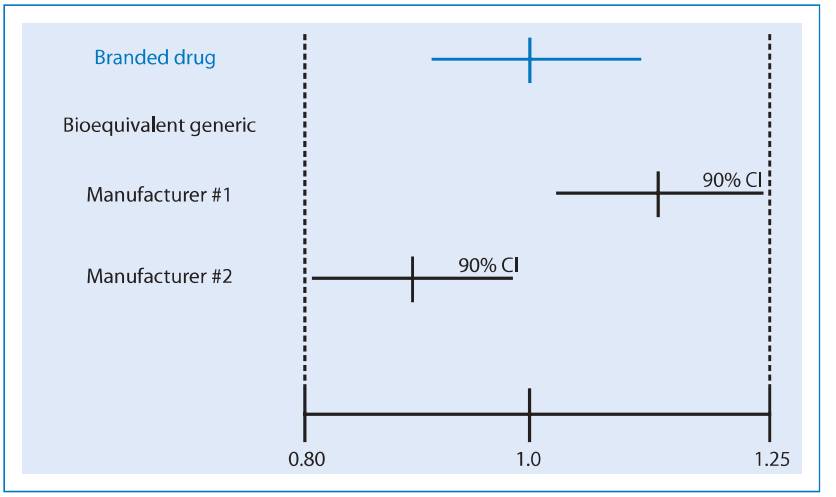


Figure 7.3 Visual demonstration of bioequivalence between generics and branded drugs, which demonstrates clearly that while generic 1 can be equivalent to the brand, generic 2 may not be equivalent to generic 1.

can vary in purity within pharmacopoeial guidelines, and there are variations in the amount of drug within each unit of product, again within limits. On top of this there are interpatient and intrapatient variability. This does not excuse differences and indeed sometimes exacerbates differences. Many drugs are absorbed readily and raise no concerns when generic versions become available. It is with drugs that have proven bioavailability problems or that require special formulation techniques that the issue of similarity becomes real. Drugs with a narrow therapeutic index have to be considered with care. On the other hand, solutions and syrups do not need such scrutiny. Simple formulations of soluble drugs for injection are unlikely to cause concern. The only concern

Table 7.1 Relative potential of oral medicines to display bioavailability problems

High	Intermediate	Low
Enteric-coated tablets	Suspensions	Solutions
Sustained-release tablets	Chewable tablets	
Complex formulations	Capsules	
Slowly disintegrating tablets		

might be with drug purity. Pharmacopoeias of course provide limits on undesirable impurities in the drug substance. Toxic 4-epi-anhydrotetracycline is limited in tetracycline products. Even if the limit is very low (say 0.005%), there may be three products (or the same product in different batches) with levels of such an impurity at 0.0048%, 0.004% and 0.002%. Are these identical? Much depends on the nature and activity of the impurity.

For conventional tablets, solutions, simple injections and suspensions, generic versions can be used without qualms. However, once we enter the field of formulation modification, as with sustained-release products, the picture becomes more complex. One knows that towards the end of the patent life of conventional products, modified-release forms (or sometimes new polymorphs of the drug substance) are introduced to delay the introduction of generics and to retain brand loyalty. The relative potential of oral dosage forms to exhibit bioavailability problems are listed in Table 7.1. It is obvious that the more complex formulations can rarely be identical in originators and branded preparations. Among the 'complex' formulations, one might include liposomes and microparticle and nanoparticulate systems.

There are generic versions of some sustained-release formulations, but within a given class of sustained-release product of a given drug, such as theophylline, there will be a spectrum of release rates. The proliferation of sustained- and modified-release forms of branded products at the end of the patent life of a product results not necessarily from the prospect of improved clinical outcomes but for the very reason that generic versions are difficult to produce. Generic modified-release products themselves are therefore usually branded. Having said this, the benefit of having a range of formulations is recognised.[3]

Specific conditions and generics

There is just the chance that in the treatment of some conditions differences in the performance of products are relevant. There are also some conditions where particular care has to be taken in titrating patients and maintaining therapeutic levels closely throughout treatment. Such is the case with

antiepileptic drugs. While generic medicines have been an issue at least since the 1970s, problems with antiepileptic drugs are still current,[4,5] as we discuss below. There are reports on the re-emergence of psychotic symptoms after conversion (a study with $n = 7$) from a brand-name clozapine to a generic formulation.[6] However, the problem with such reports is that they are often specific to a country; the results will depend on which brand and which generic are being studied. Papers do not always give full pharmaceutical information and hence their value is diminished. The difficulty in extrapolating results across borders is exhibited by clozapine. It has been found that generic preparations of the drug licensed in the UK are bioequivalent with the branded Clozaril: as the author[7] states: 'There was no evidence of clinical deterioration or the need to higher use higher doses. Generic clozapine is not inferior to Clozaril.' Some US reports suggest that there are problems in substituting the originators' product with a generic. But another study in the USA of a generic clozapine (Mylan) and Clozaril. (Novartis)[8] concluded that they were therapeutically equivalent.

Antiepileptic drugs: Clinical experience and the literature

There is, however, a relative shortage of literature comparing generic substitutions for antiepileptic drugs (AEDs). Most of the case reports, letters to the editor and some papers deal with three drugs, carbamazepine, phenytoin and valproate. These reports document breakthrough seizures or adverse events when switching from a branded antiepileptic drug to a generic version. Of around 300 US neurologists, 56% reported adverse events, and 68% reported breakthrough seizures in at least *one* patient when medication was switched from a branded to a generic AED. Burkhardt *et al.*[9] identified eight adult patients whose seizures worsened after switching from branded phenytoin to generic phenytoin. The few blinded, controlled studies reported in the literature have evaluated relative pharmacokinetics of a brand versus generic formulations. Sometimes only one generic version was studied (note Figure 7.2). No controlled studies have mirrored practice by evaluating safety, efficacy, and compliance with the therapeutic regimen when multiple generic versions are used in succession.

The American Academy of Neurology (AAN) has produced a number of recommendations regarding generic substitution for AEDs:[10,11]

- Such substitutions can be approved only if the safety and efficacy of treatment is not compromised.
- Specific pharmacokinetic information about each AED generic should be made available to physicians, who should avoid switching between formulations of AEDs.

- Labelling should identify specific manufacturers.
- Pharmacists should be required to inform patients and physicians when switching a product between manufacturers.
- Organisations that encourage or mandate substitution of AEDs should evaluate their responsibility for any problems arising from their policies.

Because changing from one formulation of an AED to another can usually be accomplished, and risks minimised, if physicians and patients monitor blood levels, seizures and toxicity, it is maintained in the USA that the individual and physician should be notified and should give their consent before a switch in medications is made, whether it involves either generic substitution for brand name products, or generic-to-generic substitutions.

Reading and deconstructing the literature on bioequivalence

If pharmacokinetic data are available, one needs to ask whether the analytical methodology was up to the task. Was the study sound? The literature can be biased because studies supported by manufacturers of products under study (both generic and branded)[8] might not be published if the results, say, show inequivalence in the former case or equivalence in the latter. In one case, with levothyroxine, it was estimated that analytical techniques commonly used were not sufficiently precise to ascertain equivalence. Figure 7.4 shows data on the levels of thyroxine in plasma after administration of doses from 400 to 600 μg, without taking into account baseline thyroxine concentrations.[12] Such a method would not be able to distinguish between generics if it cannot distinguish between the doses over the range given. The lower figure shows the data taking baseline levels into account. The latter method would be adequate.

The other issue is whether active and active metabolites are being measured, as with risperidone whose active metabolite, 9-hydroxy-risperidone has a much longer half-life than the parent drug.

Antiretroviral drugs

It is always difficult to generalise from single studies on generic equivalence or non-equivalence. Comparisons of generic and branded anti-HIV products containing the three drugs stavudine, lamivudine and nevirapine have been made in HIV-infected adults.[13] Stavudine levels were found to be significantly lower using the generic formulation. A similar but larger study, also in infected adults, found that generic fixed-dose combinations of these drugs were efficacious and safe.[14] Two generic fixed-dose combinations of these

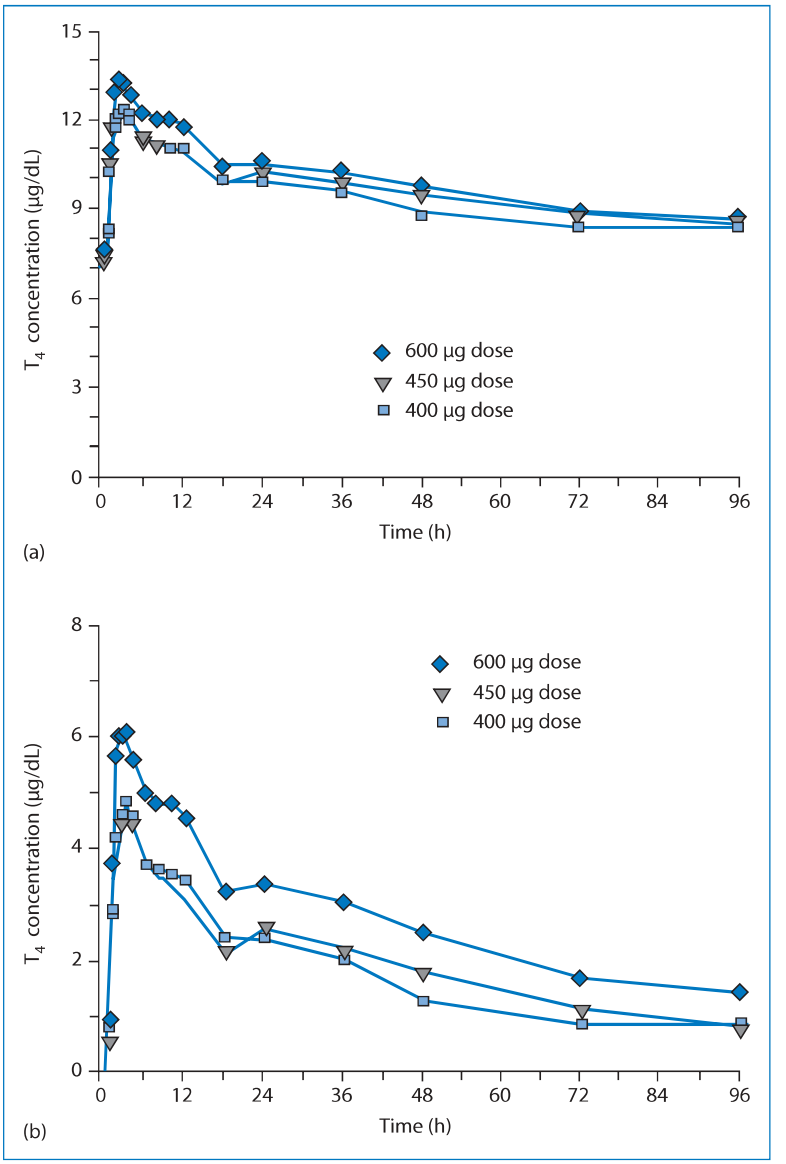


Figure 7.4 Thyroxine levels in plasma as a function of time. (a) Mean levothyroxine concentration time profiles on study day 1 following a single-dose administration of levothyroxine sodium, uncorrected for baseline levothyroxine concentrations. (b) Figures corrected for baseline levothyroxine concentrations. (From reference 12.)

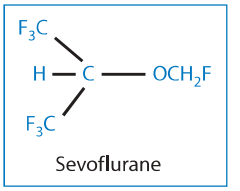
drugs for children (Pedimune Baby and Pedimune Junior, Cipla Pharmaceuticals) have been found to be similar to the branded products when tested in healthy adults.[15] As with many products, the true measure of quality is not minor differences in peak plasma levels or AUCs but therapeutic outcome. Never more so than in developing countries. The stark facts are that after the introduction of cheaper antiretroviral therapies in Southern India, the numbers using these products increased and death rates decreased from 25 to 5 deaths per 100 persons between 1997 and 2003.[16]

Bioequivalence of ophthalmic products

It is difficult to assess the bioequivalence of ophthalmic products. There have been issues, however,[17] one being high rates of precipitation in a generic prednisone formulation. Some products will employ different excipients, which might lead to subtle differences in behaviour of the preparation; a generic timolol gel-forming product possessed a different 'feel' from the branded product. This also apparently gave the impression that the generic formulation was less efficacious.

The case of sevoflurane

The apparent simplicity of molecule of the anaesthetic sevoflurane masks differences in synthetic methods and degradation that may be significant in deciding between products.



Sevoflurane

Sevoflurane is available in the USA from two manufacturers as Ultane (Abbott Laboratories, Inc.) and a generic product, Sevoflurane Inhalation Anesthetic (Sevoness) (Baxter Healthcare Corp.). These products are rated therapeutically equivalent by the Food and Drug Administration, but there are some differences. Ultane is made in a single-step synthetic process and generic sevoflurane is manufactured using a three-step process, as described by Baker.[18] In the UK sevoflurane is a non-proprietary product. As there is only one UK product, the question of differences will arise only if there are several manufacturers. In the USA, as Baker points out, Ultane contains >300 ppm water and generic sevoflurane contains ≤130 ppm water. Ultane is supplied in a plastic poly(ethylene naphthalate) polymer bottle, while generic sevoflurane is supplied in lacquer-lined aluminium bottles. Here then is an example that typifies some generics issues. The products have different manufacturing processes (see Figure 7.5) and hence different impurities, have different containers, and have potential differences in the rate or extent of sevoflurane degradation.

The significance of the containers has been discussed[18] and relates to the discovery that sevoflurane can be unstable in glass bottles in which the anaesthetic was originally supplied. Reports of a cloudy product with an strong odour appeared. Such batches were found to contain HF in concentrations up to 863 ppm as well as a pH below unity. This was linked to Lewis-acid defluorination of the drug. (Lewis acids are usually metal–containing

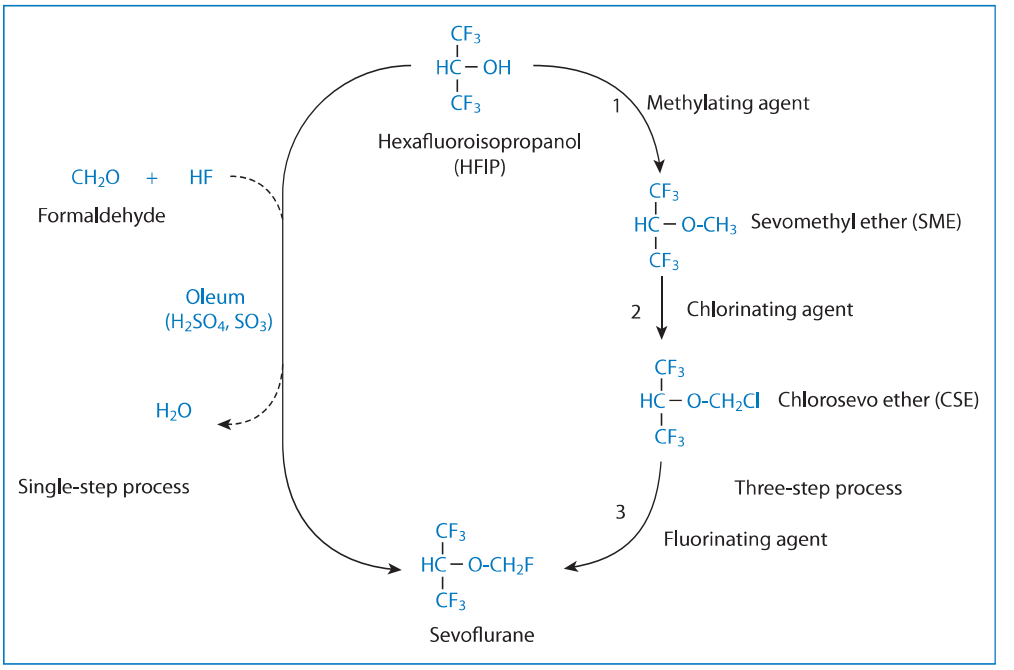


Figure 7.5 Pathways for the single-step and three-step syntheses of sevoflurane from the starting compound hexafluoroisopropanol. The potential impurity from the single-step method is formaldehyde, and from the three step process is sevomethyl ether (SME) and chlorosevo ether (CSE). (From reference 18.)

compounds that accept electrons from Lewis bases and result in Lewis base degradation. There are many Lewis acids such as metal halides and metal oxides including Al_2O_3). The Lewis acid in this case was identified as rust (iron oxide) on a valve on a bulk shipping container. The drug is especially susceptible to degradation because of the monofluoroalkyl ether group. The whole story can be read in Baker's paper.[18]

The base-catalysed conversion of sevoflurane to 'compound A' is as shown in Figure 7.6. Figure 7.7 shows a range of degradation pathways for the anaesthetic.[19]

Carbon dioxide absorption enables the use of low-flow anaesthesia, and a decreased consumption of medical gases and halogenated anaesthetics, as well as reduced pollution. Chemical absorbents (soda lime and barium hydroxide lime (Baralyme) may produce toxic compounds: carbon monoxide with all halogenated anaesthetics and 'compound A' with sevoflurane

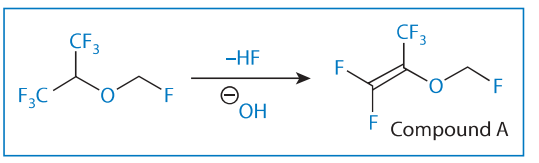


Figure 7.6 Base-catalysed conversion of sevoflurane to so-called compound A.

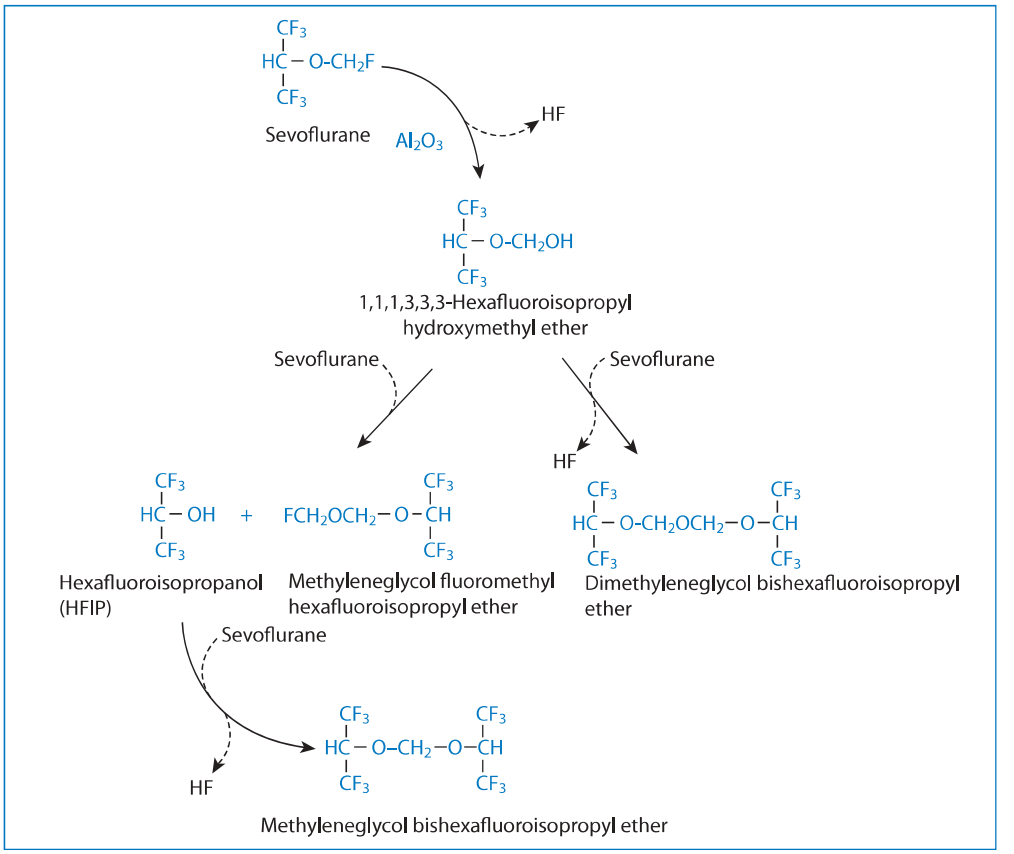


Figure 7.7 Potential pathways of degradation and the products of degradation of sevoflurane on reaction with alumina (Al_2O_3). The degradation products are detected at very low concentrations in low-flow, long-duration anaesthesia. (From reference 19.)

(see Figure 7.6). Simple measures against desiccation of the lime prevent carbon monoxide production. The toxicity of compound A, shown in the rat, has not been demonstrated in clinical anaesthesia. Recent improvements in manufacturing processes have decreased the powdering of lime. Moreover, filters inserted between the anaesthesia circuit and the patient abolish the risk for powder inhalation.

A Japanese product is marketed as Sevofrane (Maruishi Pharmaceutical Co, Osaka, Japan)[20] and is available there along with Sevoness. Both products studied contain over 99.998% sevoflurane and fluoride concentrations were the same at around 0.43 ppm. The formation and toxicity of anaesthetic degradation products can be an issue.[21] Soon after its introduction in 1935 there were reports of neuropathies following trichloroethylene anaesthesia. These were attributable to the formation of dichloroacetylene through base-catalysed elimination of HCl from the compound.

The common cause of their formation is the reaction of the anaesthetic with the bases in adsorbents in the circuit. (These include sodium hydroxide (soda lime) barium hydroxide lime, KOH-free soda lime, calcium hydroxide

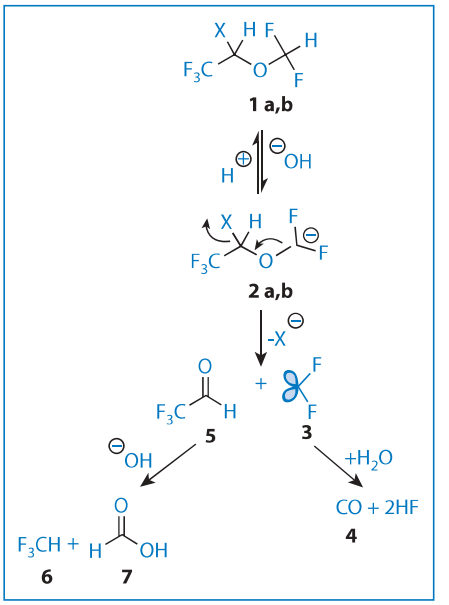


Figure 7.8 Base-catalysed conversion of desflurane and isoflurane (**1a** and **1b**) to CO (**4**). Note also trifluroacetaldehyde (**5**) and trifluoromethane (**6**) and formic acid (**7**).

and non-caustic lime. These have different reactivities: sodium hydroxide > soda lime > KOH-free soda lime > calcium hydroxide.) Understanding the nature of these reactions that affect trichloroethylene, desflurane (Figure 7.8), norflurane and enflurane has helped towards the safe use of these agents.

Although these examples are of a specialised use of these agents, nevertheless the potential formation of very low concentrations of degradants by whatever means can lead to adverse events or certainly to differences in the behaviour of products.

Generic biologicals (biologics)

A generic is, as stated above, a product that has been shown to be 'essentially similar' to the originator's product. However, biological products (biologics, biologicals, biopharmaceuticals) are more complicated than drugs that are small or relatively small organic molecules. Because of their labile nature and the fact that the products may be dependent on the mode of manufacture, it is important to remember that it is has been stated that a process 'cannot be exactly duplicated by another manufacturer'.[22] Methods used to show that small-molecule therapeutics are nearly identical to each other are clearly not sufficient for biologicals. Bioequivalence is usually defined in terms of areas under the curve (AUCs), but this is only part of the story with biological products. The nature of impurities is different. These might be analogues with a single amino acid difference, yet be potent. If the impurity is potent, this can lead to clinical problems. Impurities might be more difficult to detect in

biological products if they are analogues of the main agent, so there is the risk of immunological and other side-effects. It is also possible, as we recounted in Chapter 4, that the formulation may cause there to be differences in protein products as with recombinant human erythropoietin (Eprex). A change of stabiliser from albumin to sorbitol resulted in the formation of anti-erythropoietin antibodies and hence pure red cell aplasia.[23]

Figure 7.9 summarises the issues that must be considered when dealing with biological generics.[24] The most appropriate description for generic biologicals is that they are 'biosimilar'.

The European Medicines Agency (EMEA) has stated that the generic route is not appropriate for biologics, and the FDA stated in September 2006 that it 'has not determined how interchangeability can be established for complex proteins'. Note, however, that for biologics such as insulin the transfer of patients from one product to another of the same insulin type is commonplace, though carried out with circumspection.

Why do these products have such specific problems? The molecules are large and often prepared in cell-based systems; they have complex tertiary and quaternary structures related to their activity; and they may be glycosylated. They are very sensitive to stresses such as temperature and even to shear forces

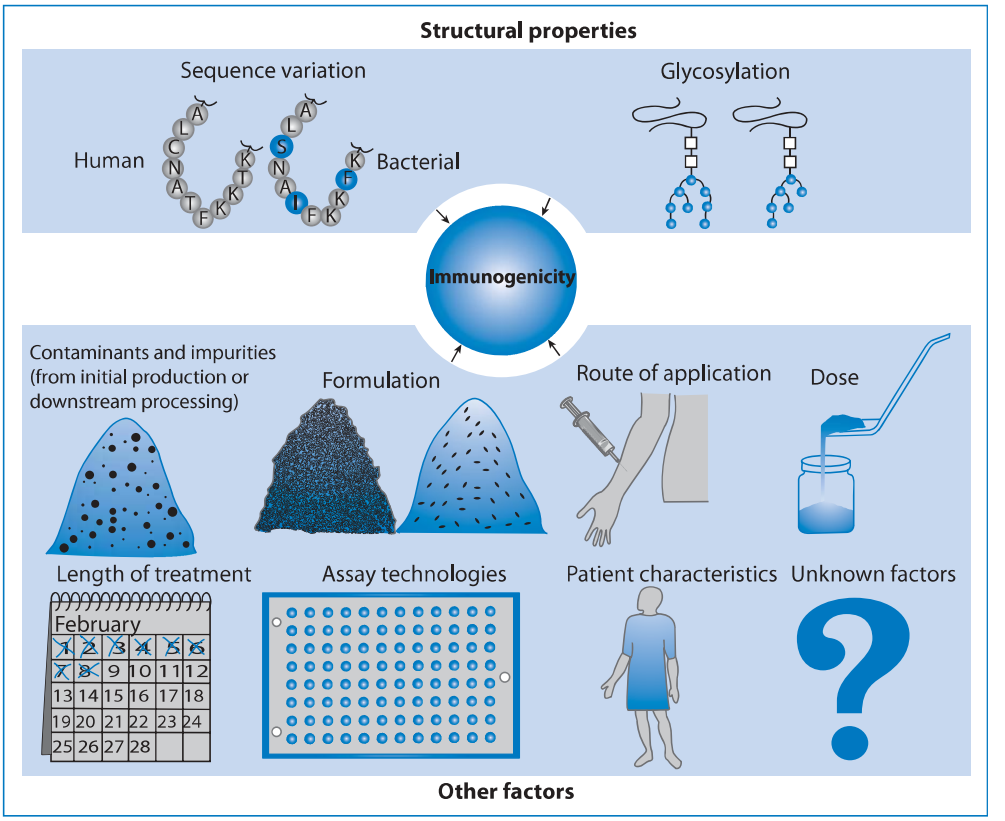


Figure 7.9 Areas of importance in determining the bioequivalence and the immunogenicity of biopharmaceuticals. (From reference 24.)

that might be used in their production. DNA, for example, suffers from degradation due to shear forces. A practical pharmacy aspect is the use of International Non-propriety Names (INNs) for such products. With conventional drugs an identical INN means a bioequivalent product and the same drug substance within pharmacopoeial or other limits. There are dangers if INNs are used for biogenerics that are subtly different.

Regulatory views on biosimilar biologicals

The FDA acknowledges that 'biosimilars have not been demonstrated to be interchangeable through any scientific process'. A different naming scheme for these products might involve utilising a different level of granularity, which may be more detailed or less detailed. If the outcome of assigning the same INN to two products with highly similar ingredient(s) creates the implication that the two products are pharmacologically interchangeable *and* there were no scientific data to support that finding, then the FDA would have serious concerns about such an outcome, especially with more complicated proteins. At present, the FDA has not determined how interchangeability can be established for complex proteins.

This initiative reinforces the EMEA communication on biosimilar medicines and recognises the uniqueness of these products. It states that they cannot be classified as 'generics' in the same way that chemical compounds may be, owing to the differences stemming from the variability of the active biotechnological substances and manufacturing processes. Further, the EMEA document clarifies that 'since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional'. This is effective advice against automatic substitution of one biological medicine over another ostensibly the same.

Pegylated proteins

Some pegylated proteins are discussed in Chapter 5. Attachment of long-chain polyoxyethylene glycols (PEGs) to proteins is the basis of pegylation. This can increase the circulation time of proteins with short half-lives and can reduce immunogenicity; however, there are cases[25] where the process can reduce the functional activity of the protein by blocking access to receptors. These modified proteins are clearly not biosimilar to the parent proteins and are essentially new molecules.

Conclusions

For many medicinal products the initial brand and the subsequent generic products are therapeutically equivalent. There are of course effects of

differences such as the colour of capsules and tablets or the appearance of liquids, which can prejudice patients. There are drugs that have a narrow therapeutic index and that are perhaps poorly soluble, which perhaps suggests that they might not be used interchangeably, but these are few in number; experts are not agreed even with drugs such as the antiepileptic agents. There is a greater practical problem in that while biostudies might have shown generic 1 to be bioequivalent to the brand leader, and generic 2 is also bioequivalent, as we have discussed, generic 1 is not necessarily equivalent to generic 2. Pharmacists have thus to be aware of the source of generics.

With generic versions of biologicals or biosimilars the issues are somewhat more complex. Development in analytical methods and other tests might assist in elucidating the similarity or otherwise of this growing array of drugs in the future. With both conventional drugs and biological drugs, wherever a formulation has been devised to alter the rate of release or delivery of the active agent, it is not automatic that generic versions will produce identical results. Table 7.2 lists some of the diverse classes of recombinant proteins that have been approved for clinical use.[26] To be able to make informed decisions, pharmacists and drugs and therapeutics committees need access to the facts about such products and in particular their biopharmaceutical profiles in patients or volunteers.

Table 7.2 Classes of approved recombinant protein drugs

Class	Examples
Hormones	Insulin (e.g. Humulin), glucagon (e.g. Glucagen), human growth hormone (e.g. Humatrope), erythropoietin (e.g. Epogen)
Cytokines	Interferon alfa (e.g. Roferon-A)
Clotting factors	Factor VII (NovoSeven)
Monoclonal antibodies	Antibodies to vascular endothelial growth factor (bevacizumab [Avastin]), epidermal growth factor receptor (cetuximab [Erbitux]). TNF-α (e.g. infliximab [Remicade])
Vaccines	Hepatitis B surface antigen (e.g. Recombivax HB)
Enzymes	Glucocerebrosidase (Cerezyme), DNase (Pulmozyme), thrombolytics (e.g. alteplase [Activase])
Synthetic proteins	Fusion proteins, e.g. soluble TNF receptor linked to IgG Fc
Conjugates	Pegylated proteins: interferon such as peginterferon alfa 2a (Pegasys), granulocyte colony-stimulating factor (pegfilgrastin [Neulastal]). Covalently attached metal chelators (ibritomab)

From reference 26.

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8

The future: Delivery systems for modern therapeutics

Introduction

The nature of therapeutic interventions will undoubtedly change in the next decade. Already there are many additions to the medicinal armamentarium, with many biological molecules, including recombinant proteins, nucleic acids (both DNA and RNA), monoclonal antibodies and cell-based therapies. The question that must be addressed is: What will be the role of pharmacy in relation to these products, particularly those related to cell therapy? When in the future some of these therapies become more commonplace, will they be distributed, dispensed and monitored through pharmacy channels in the way in which conventional drugs are, or will they be deemed too 'technical'? The topic of delivery systems for modern therapeutics is certainly in the domain of clinical pharmaceutics, as the nature of the delivery systems used will be an important component of therapy. We need to think more imaginatively of pharmacy's role in the future. Pharmaceutical precepts of safety, quality and efficacy must be emphasised in experimental clinical procedures, as this did not always occur with early clinical studies of, say, liposomes. In particular, the consistency of the drug and the formulation, and their freedom from impurities, must be ensured. The concept of impurities in cell therapy is likely to be different from our current experience.

Personalised medicine and medicines

While tablets and capsules might remain the most popular and most used dosage forms in the future, there must be changes in the way we deliver drugs and the facility to alter doses in perhaps a continuous (e.g. 1–10 mg) rather than multiple (e.g. 2.5, 5.0, 10 mg) manner in the future. That is, dosing must change. No human population can be classified with regard to the important parameters of drug distribution (body weight, body fat, creatinine clearance), in a stepwise fashion, so why should doses? For practicality of manufacturing only, according to current paradigms. Hence the need to explore newer means

of fashioning delivery systems. The core of personalised medicine is that patients will receive medications tailored for them rather than receiving the same drug at the same dose, which is the norm for most products prescribed and dispensed today. It could be argued that for many agents, such as a number of antibiotics, precision dosing is not necessary. In spite of increased specificity of many new drugs, such an approach is surely counterintuitive. The post-genomic era has promised much through a better understanding of pharmacogenetics. Through genetic profiling of patients involved in clinical trials, more valuable data will be obtained for the treatment of individual groups likely to respond well (e.g. to Herceptin (trastuzumab)) or to suffer adverse reactions. But there are other issues to contend with apart from the drug, matters we explore now.

Drug delivery and personalised medicines

The focus in discussions on personalised medicine has been on the drug itself, rather than on the mode of delivery. A report on personalised medicines emanating from the Royal Society[1] neglects to mention delivery systems. This is perhaps understandable because the emphasis has been on the drug and its suitability for a given group or subgroups of patients. There is of course a question of delivery systems: pharmaceutics (as well as pharmacokinetic analysis) has a large part to play in ensuring that appropriate formulations are available for appropriate drugs.

The MHRA[2] has recognised the need for a multiplicity of dosage form:

> Personalised medicine can occur on the basis of dose adjustment for side effects, dose adjustment for efficacy, dose adjustment for concomitant medication, metabolising rate and renal excretion, drug choice due to allergic potential, drug choice due to resistance profile of the infecting organism, drug choice due to biological target, and drug choice according to the personal wishes of a patient.
>
> Increasingly accurate and specific medical information on each individual patient is becoming available to provide prescribers with more and more information from increasingly sensitive physical methods and the wider application of biomarkers (for instance to identify drug metabolising characteristics of each individual patient). This will result in future medicines needing to be available to provide a greater range of doses for prescribers; there will be fewer numbers of patients in the target indication at the time of product registration due to better use of inclusion and exclusion criteria; medicines will be safer, more effective and have fewer side effects as the dose will be adjusted to ensure that the most appropriate dose is prescribed to each patient.

A comprehensive report, *Priority Medicines for Europe and the World*[3] published by the World Health Organization in 2004, highlights many of the issues in the war against relatively neglected diseases such as malaria. For such, insufficient research and development efforts worldwide have led and still lead to loss of life on an unthinkable scale. There is a reminder in the report of the importance of drug delivery. The authors conclude that 'there is a wide range of existing evidence-based, very often off-patent technologies that are heavily under-utilised. Such technologies could be used to improve the 'patient-friendly' performance of a number of existing medicines'. These one might claim to be the neglected technologies, invented but discarded because funding bodies or the market will not pay for them, or because a worthy application has not been found.

In all parts of the world, there are at least two identifiable and disparate patient groups for whom there is a need for personalised medicines or personalised formulations. The latter will sound strangely familiar to pharmacists of an older generation used to preparing medicines extemporaneously for individual patients. Children and the elderly, neither of whom comprise homogeneous sets, could be considered to be neglected patients. As we have discussed in Chapter 6, children exhibit rapid changes in metabolism and physiological functions in their progression from the neonatal state through infancy and early and late childhood. The elderly also experience changes in body fat distribution, renal clearance and gastrointestinal function, and treatment is often because of concomitant pathologies.

Figure 8.1 illustrates the categories of patients for whom personalised medicines will be designed. One might include everyone if the true meaning of the phrase is considered, but this is unrealistic. The divisions are not mutually exclusive categories of age-related, disease-related and genetically determined maladies.

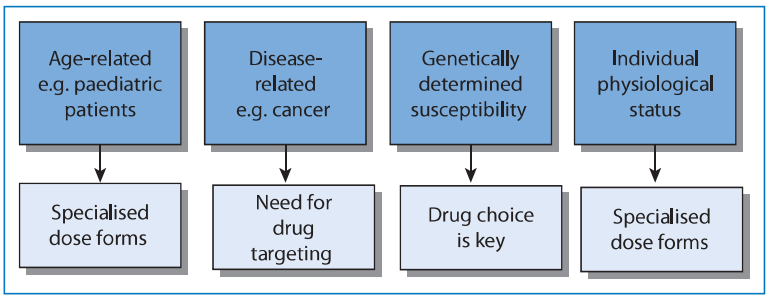

Figure 8.1 An attempt to categorise patients in terms of personalised medicine in its broadest sense. These are not exclusive categories. In the case of genetically determined susceptibility to drugs, drug choice is the key; but in the other categories drug delivery systems are likely to play a prominent part in optimising treatment.

Paediatric cardiovascular medications have been discussed elsewhere[4] and general paediatric formulations in practice are reviewed[5] in the textbook, *Paediatric Drug Handling*.[6] Paediatric medicine provision, as discussed in Chapter 6, is not necessarily a question of high-technology solutions. One of the most distressing consequences of the use of adult dosage forms in paediatric practice is the necessity for large dilutions and thus the enhanced opportunity for error. Errors of 10-fold excess or under-dosing are often the root cause of serious outcomes. It should not be beyond our wit to devise foolproof devices that make such errors difficult to commit. An alternative might be to have access to more appropriate formulations that contain doses relevant for the patient group in question.

It could be argued that individualised medicine is available now through specialised dose forms for the very young, although in many cases this is not so.[7] Genetics aside, we have not been able as a community to devise and market systems suitable for children and the elderly. We certainly have not solved the issue of the safety of dosing in these cases. Tuleu[8] states that in addition to legislative and formulary developments, innovations in pharmaceutical formulations should improve the ease in which children can access medicines. Innovative modified-release preparations represent one need. The following areas, Tuleu suggests, are also ripe for future developments and research:

- New routes of administration such as oral–transmucosal (buccal strips), intranasal and transdermal products(for neonates mainly).
- More research into alternative safe excipients for children, such as natural polymers (e.g. cyclodextrins to mask the taste of drugs, to improve solubility or to protect drugs/patient).
- Children's ability to swallow and their preferences. This will direct future formulation research towards mini-tablets, chewable tablets, dispersible tablets or more oral liquids.

Although new and innovative formulations are urgently needed, work on extemporaneous formulation should not be disregarded.

The provision of flexible dose products is key. In the twenty-first century, splitting tablets hardly seems a reasonable approach, but mini-tablets that can be administered in multiples can have a role. Self-regulating and pulsatile delivery systems, and means of delivering doses flexibly, are some of the possibilities discussed here. An important development might be the re-introduction of pharmacy-based product manufacture. Extemporaneous dispensing is not dead. In the USA, pharmaceutical compounding in community pharmacies is a thriving if controversial activity. Discussed below are several potential technological solutions for the preparation and presentation of new dose forms as well as a brief outline of pharmaceutical nanotechnology.

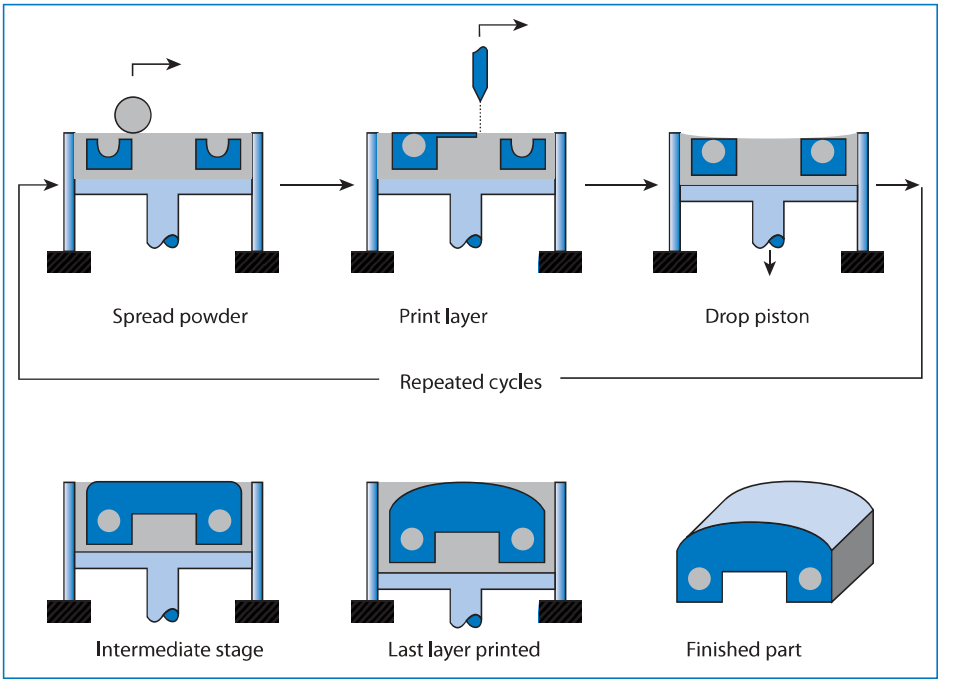

Figure 8.2 The process of three-dimensional printing (3DP) demonstrated with a ceramic process. Deposition of material, e.g. drug or coating materials, is controlled by the control of droplet size as in a bubble-jet printer.

Technologies

Three-dimensional printing

With the invention of three-dimensional printing (3DP) techniques the possibility probably now exists for the individual and batch production of either implants[9] or oral dose forms.[10] The basis of the technique of 3DP as shown in Figure 8.2 is that the finished product design is elaborated on a computer. Much depends on the particle size of active, the nature of the binder such as its viscosity, and also the potential for diffusion of drug between layers and subsets of the structure. In effect, the release rate and pattern of the active(s) can be predetermined by the possibility of placing the active in different regions of the structure. Figure 8.3 shows data demonstrating the control of release profiles of levofloxacin from a variety of implants with different geometries. A proposed 'breakaway' tablet prepared by 3DP (Figure 8.4) that breaks into two parts after the dissolution of the fixative joining the parts together is only one example of the possibilities.

Low-dose and flexible-dose products

Products with readily variable dose levels are required. Methods for depositing drugs in solution onto biosoluble and biodegradable matrices also offer the possibility of ready fabrication in hospital and community pharmacies. A

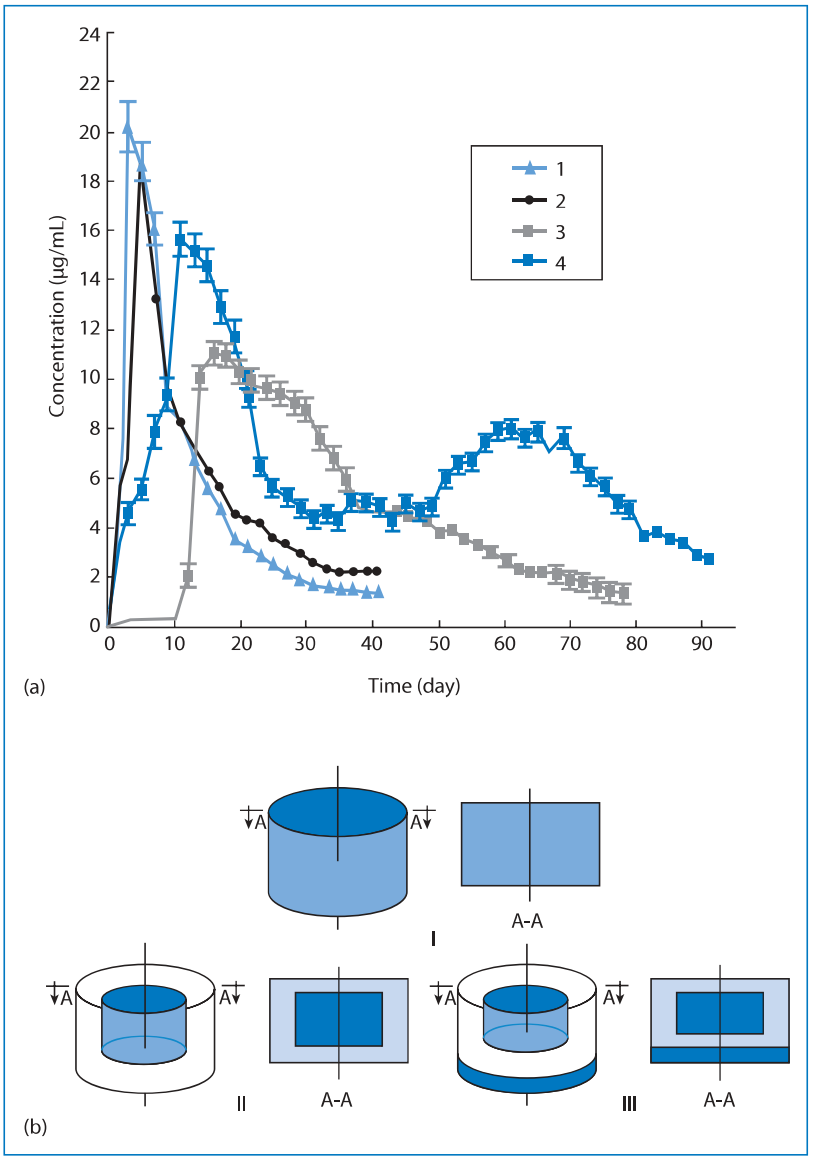

Figure 8.3 (a) *In vitro* release of levofloxacin from implants: curve 1, implant I made by 3DP; curve 2, implant I made by a conventional process; curve 3, implant II made by 3DP; and curve 4, implant III made by 3DP. (b) The design of the three implant systems I, II and III. (From reference 9.)

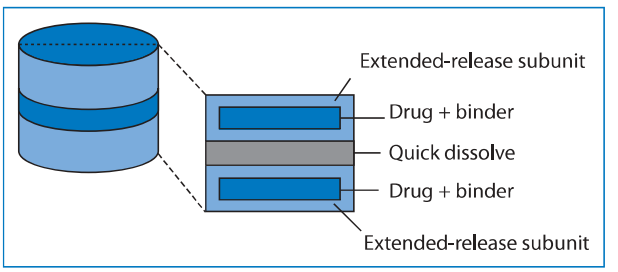

Figure 8.4 Cartoon of a conjoined tablet containing fast-release and slow-release elements, which allows two drugs to be administered at two different rates.

matrix platform for such products is required. Developments in bubble-jet devices exemplified by Hamamatsu micro-droplet technology suggest the possibility of the adsorption of the smallest doses onto suitable matrices for delivery, say, to neonates by oral or buccal routes. Microfabricated electrokinetic pumps can be used to deliver water, polar organic solvents, and biomacromolecules.[11] A new delivery system for inner-ear infections involves a microcatheter delivering gentamicin driven by an electronic micropump.[12]

Flexible dosage systems

Liquid formulations are possibly the form that most easily allow continuous increments in dosing, but they sometimes suffer from instability or simply from the fact that the drug might not be soluble in a suitable solvent. The Chinese once used rice paper impregnated with drugs as a delivery system. It is possible with modern technology to dose matrices of a variety of dimensions with accurate amounts of drug in solution, in suspension and in micro- or nanoparticulate form. Ink-jet technology has much to teach. Figure 8.5 is a simple cartoon of the possibility of dosing of a matrix for drug delivery.

Suspensions are more difficult to formulate than solutions because of the possibility of particle agglomeration, sticking and blocking of needles, but there are solutions: the SonicSyringe (Sono-Tek Corporation, USA), for example, uses ultrasonic energy to accurately and uniformly coat nanoparticles onto a surface. Hence there is no excuse for not having at our disposal a more flexible system of dosing the patient population from birth to extreme old age. Various pumps can of course provide graded dosing, often on command. Many systems (e.g. the Medtronic Synchromed infuser) are too large for implantation. Smaller devices (e.g. the Duros osmotic pump, and Gliadel implantable wafers) often do not have the flexibility to allow variable dosing.

A variety of micromachined delivery systems now exist using micropumps. Microneedles for transdermal delivery are represented in Figure 8.6. Drug is released into the epidermis and dermis through 150 microneedles from a chip 25 mm in length; the short length of the microneedles avoids the pain receptors of the skin.

Microfluidic systems

Microfluidic devices are increasingly used in analytical procedures when small quantities of materials have to be mixed and analysed. Figure 8.7 illustrates such a device. It can be envisioned either that two drugs could be mixed by proper routing of the channels or that drugs could be administered in small quantities, say in a pulsatile manner, if the droplets in the diagram represent a drug and the fluid carrier is an inactive excipient.

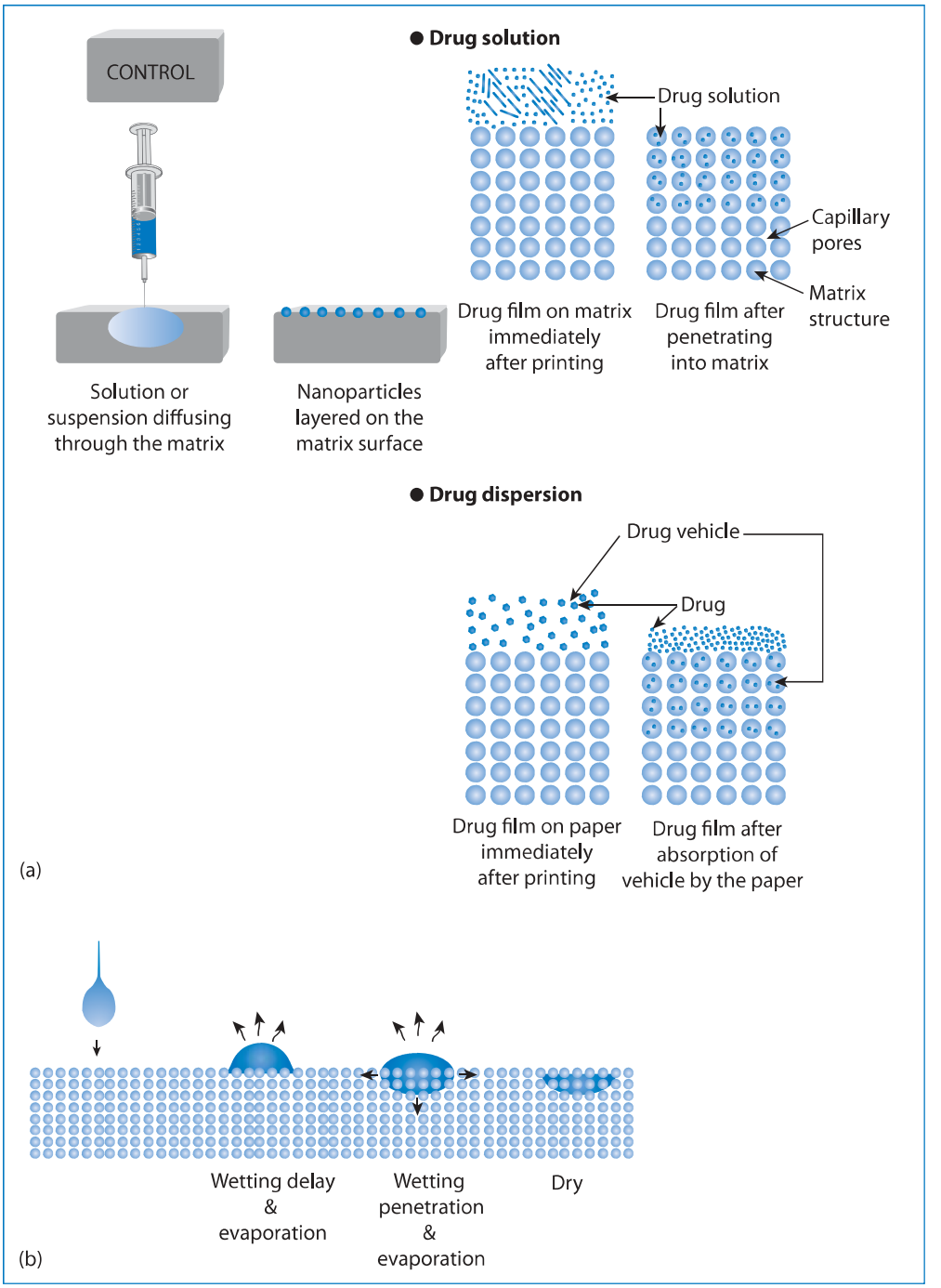

Figure 8.5 (a) A simplified set-up for dosing a matrix for drug delivery. The distribution of the drug within the matrix will depend on the nature of the matrix, the drug and its solution or suspension state. Also shown to the right is the possibility of deposition of nanoparticles of drug or polymer–drug mixtures to provide a very accurate and low-dose product. (b) Modes of penetration into a paper matrix and deposition patterns that might result from changes in the state of the applied droplets.

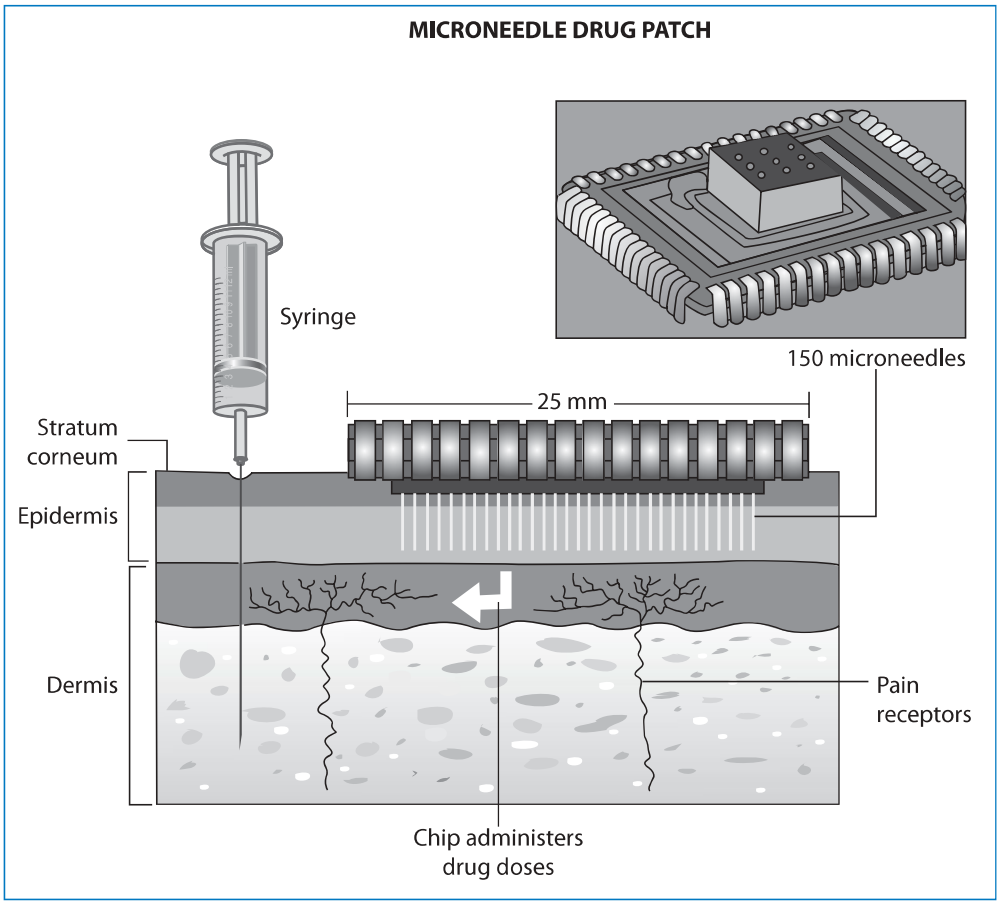

Figure 8.6 Microneedle-based drug patch for transdermal use. Drug output is controlled by the chip.

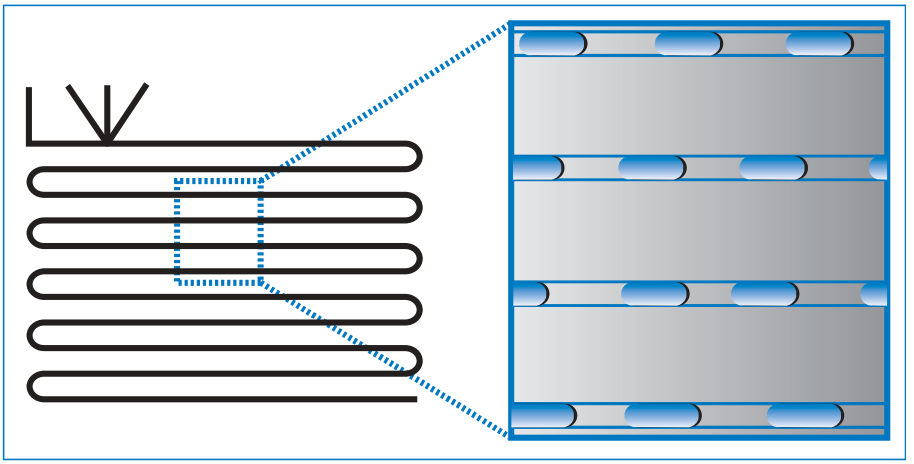

Figure 8.7 A microfluidic device with multiple channels showing droplets (or microspheres or nanosuspensions) of drug. The channels can be fabricated in any pattern and materials can be driven through the narrow capillaries into the body to provide pulsatile release. Different drugs and carriers can be mixed to provide versatile delivery systems.

Combination dose systems

Christine Ford[13] states that 'according to the FDA, a combination product is one composed of two or more regulated components – any combination of a drug and device; biological product and device; drug and biological product; or drug, device, and biological product'.

For many years combination products have been frowned on by the FDA and other regulatory authorities largely because of their inflexibility in dosing fixed ratios of two or more drugs. The treatment of AIDS has highlighted the need for combination tablets. If the drug/dose ratio required depends more than on pharmacogenetics, then this is the opportunity for three-dimensional printing approaches exemplified in Figure 8.4 or for other ways of making flexible dose forms to be adopted.

The FDA's definition is quite inclusive, encompassing drug-coated devices, drugs packaged with delivery devices in medical kits, and drugs and devices packaged separately but intended to be used together. The FDA have developed a categorisation scheme for combination products in which a product a product is placed into one of nine categories, which include:

- Prefilled drug or biologic delivery device/system
- Device, coated/impregnated or otherwise combined with drug
- Device, coated or otherwise combined with biologic
- Drug–biologic combination
- Other type of combination product.

It is interesting after the widespread use of tablets and capsules in the past that the difficulty in making combination products has been acknowledged.[14] It is, in a way, encouraging that the traditional pharmaceutics of tablet manufacture was considered in 2006 to be an underrated topic.

Mini-tablets

Matrix mini-tablets based on starch–microcellulose wax mixtures have been described by De Brabander and colleagues.[15,16] The possibility with these systems is that different dose levels can be administered by choice of the number of mini-tablets within a capsule for adults or using single units for children.

Nanotechnology

Nanotechnology is the science that deals with particles or constructs that have dimensions ranging from several nanometres to around 100–150 nm (Figure 8.8[17]), although more commonly the upper limit is stretched to 200 nm. It is not possible here to cover the whole gamut of nanotechnology or even

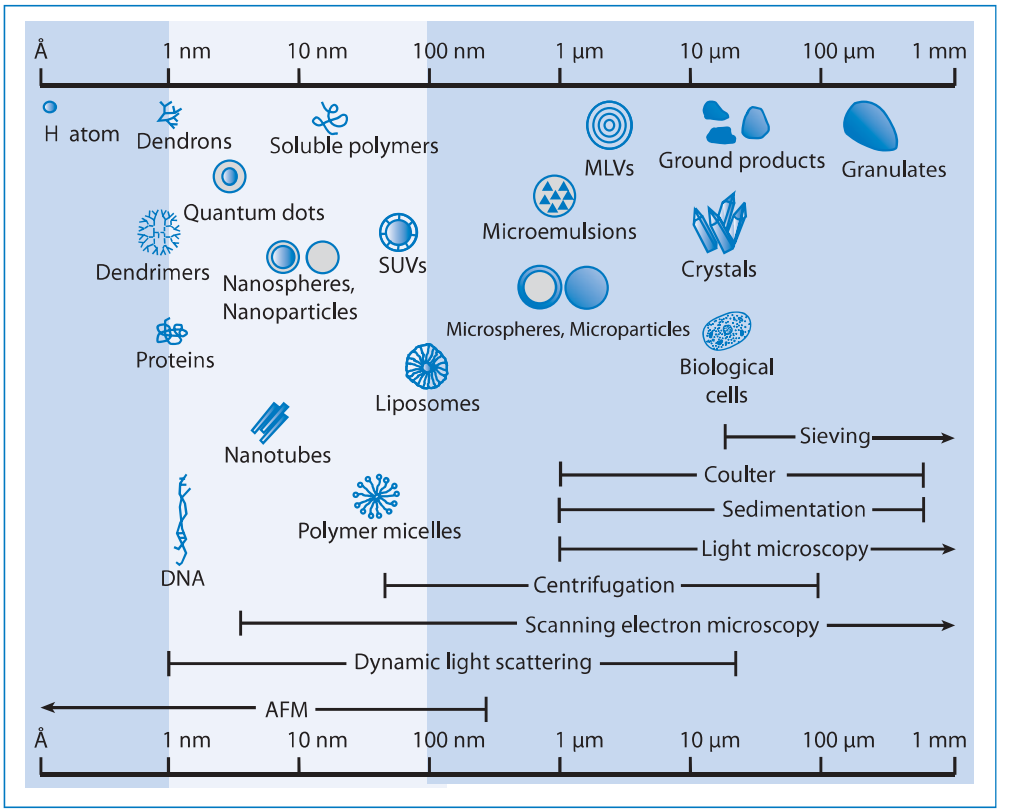

Figure 8.8 The size spectrum of nanoparticles and other nanosystems in the context of microparticulates and macrosystems. SUV, small unilamellar vesicle; MLV, multilamellar vesicle; AFM, atomic force microscopy. (Diagram from reference 17.)

pharmaceutical aspects of the subject in all its manifestations. As a discipline, nanotechnology has already spawned several journals dealing with the physics, the biology, the toxicology, the engineering and the pharmaceutical applications, as well as many books,[18,19,20,21] chapters and reviews and a rapidly growing number of papers and consensus papers.[22,23]

Figure 8.8 illustrates the size spectrum of different systems from the macroscopic, through microscopic to the nanoscopic and the modes of measurement of particle size distribution. It can be seen that dendrimers, small spherical or quasi-spherical synthetic polymers, are at the particle–molecule interface and represent irreducibly small delivery agents. Quantum dots are a form of nanocrystal made from semiconductor materials (e.g. zinc sulfide, cadmium selenide) that have applications in sensors and tracking (imaging) at the nanoscale.

Figure 8.9 illustrates the domains of nanomedicine, which can be considered to cover nanodevices, nanocarriers, nature's own nanovehicles such as low-density lipoprotein (LDL) particles[24,25] (as carriers of cholesterol), viruses (as carriers of DNA) and transmitter vesicles (as carriers of neurotransmitters). Diagnostic devices and techniques employing nanoparticles are

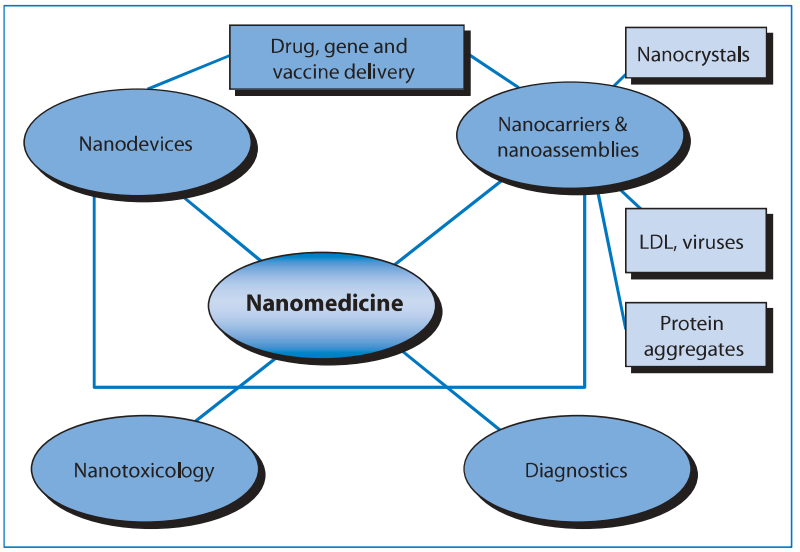

Figure 8.9 The domains of nanomedicine.

part of the scene. Nanopharmacy or pharmaceutical nanotechnology comprises, but is not limited to, the topics shown in Figure 8.10. These encompass the manipulation and processing of nanosystems in the 2–150 nm size range, their physicochemical characterisation, applications and biological evaluation. One warning: it is dangerous to try to generalise about nanosystems or nanotoxicology as so much depends not only on particle size and surface characteristics but also on physical form.

Typical pharmaceutical carrier systems in the domain of nanotechnology include nanoparticles, nanosuspensions, nano- (micro-) emulsions, nanocrystals, dendrimers and dendriplexes and carbon nanotubes as well as the smallest liposomes. Figure 8.10 suggests the main areas of focus in pharmaceutical nanotechnology and summarises the wide range of means of characterising nanosystems through investigation of their drug loading rate and capacity, release rate, chemical and physical stability of both drug and carrier, particle size and size distribution, surface charge and character (hydrophilic, hydrophobic), nanoparticle diffusion and rheology. Biological evaluation of nanosystems involves a knowledge of the absorption of the drug and the carrier with its encapsulated or adsorbed drug, distribution of both carrier and drug, as well as component excretion and metabolism.

The whole topic, however, is determined by the size and size range of the systems concerned. Small size brings with it certain advantages and disadvantages. Advantages include the ability to diffuse farther into biological tissues and to be taken up more readily by cells than microparticles. The disadvantages include the greater ability to aggregate because of their large surface area.

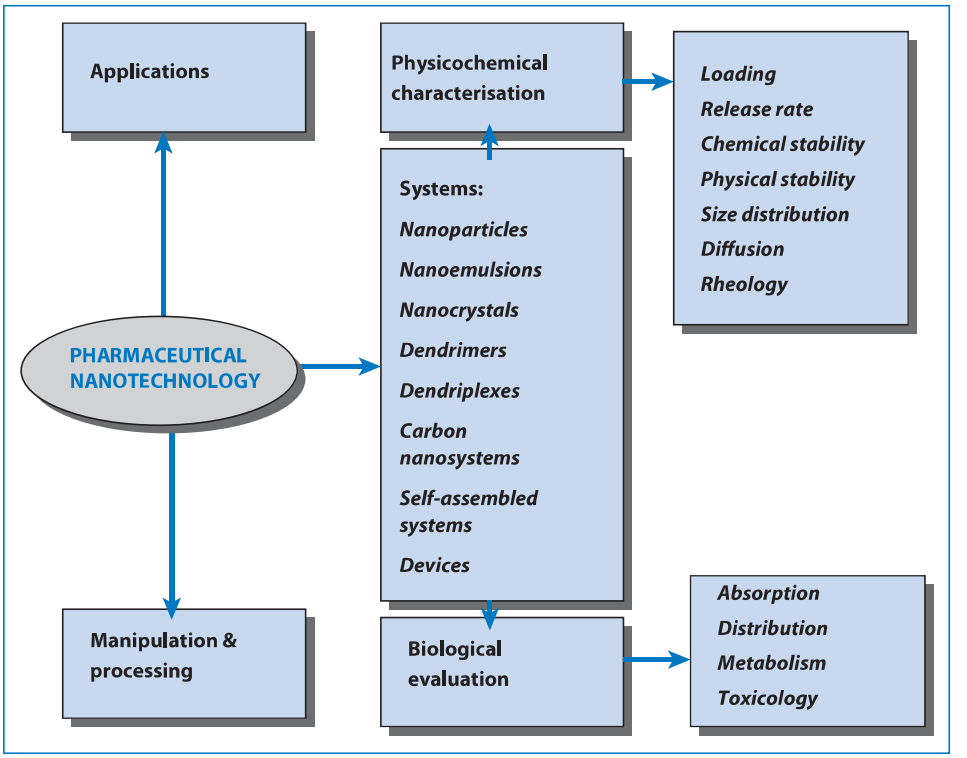

Figure 8.10 Pharmaceutical nanotechnology's main areas of focus: applications, manipulation and processing, the physicochemical characterisation of a variety of systems, their biological evaluation, particularly an understanding of the interaction between the physicochemical properties of these systems and biological barriers and environments. Absorption, distribution, metabolism and toxicology refer to both the drug once released from the delivery system and the delivery system itself, while being aware of possible synergistic effects between the two.

Nanoparticles in pharmacy

The main use of nanoparticles in pharmacy so far has been as carriers of drugs, DNA and vaccines. The nanoparticles serve several functions: (1) protecting the actives from hostile environments, (2) determining the fate of agents that are still encapsulated; and (3) acting as potential targeting moieties when the particles are decorated with ligands for appropriate proteins and receptors.

Although the descriptor *nanotechnology* came to the fore in the late 1980s, it has a somewhat longer pedigree in pharmacy, since, in fact, Professor Peter Speiser and his colleagues in Zurich prepared and investigated 'nanoparts' and 'nanocapsules' in the 1970s, as discussed in an historical perspective.[26] Surfactant micelles[27] which have diameters of some 1–3 nm, have also been studied for many decades as solubilisers of poorly water-soluble drugs,[28,29] for example, and would be considered in today's parlance to be nanosystems. Microemulsions, a descriptor coined by Schulman in 1959, have in fact droplets in the nanoscale, as produced by dilution of Neoral (see Chapter 4). It is claimed that the first commercial microemulsion was introduced in 1928.

Application of nanoparticles in drug delivery

Nanoparticles can in principle be used to deliver drugs, genes and radiolabels by a variety of routes listed here. References to individual papers that apply to the route in question are cited here as examples only. Routes of administration include:

- Ocular[30]
- Oral[31]
- Intravenous[32], intraperitoneal[33], intraluminal[34], subcutaneous[35] or intramuscular[36]
- Nasal[37]
- Respiratory tract[38]
- Intratumoral[39]
- Delivery to the brain[40]
- Delivery to the lymphatics.[41]

Some of these routes are discussed below, but the references to all will provide further information.

In ocular delivery to the cul-de-sac of the eye, nanoparticles in suspension can prolong the action of the drug both by slow release and by their slower escape by way of the punctae compared with a solution, and perhaps also the adhesive qualities of some nanosystems[42] will assist.

Oral delivery is a potential means to deliver vaccines, to provide slow release of drugs, or through bioadhesive nanoparticles to achieve uptake for systemic activity, although to date the evidence for significant uptake is limited.[43] Bioadhesive nanoparticles have been advocated to assist adhesion of the carriers to the mucosa and thus increase the probability of arrest, as well as to provide time for the transfer of drug from the carriers or the particles themselves into the gut wall. The importance of the lymphoid tissue in the gut, the gut-associated lymphoid tissue (GALT), is crucial to the understanding of some of these possibilities. The M-cells and lymphoid tissues of other anatomical regions can be important in particle delivery; for example the nasal lymphoid tissue (NALT), the bronchial tissue (BALT) and other sites (omentum, OALT) provide the possibility of access of particles in small quantities. Such small quantities may be sufficient for immunisation with oral vaccines.

Intravenous delivery allows the particles to enter the circulation immediately, but the fate of the particles so administered is not necessarily simple, as the flow properties of the particles and their interactions with blood components can be complex. Figure 8.11, much simplified, lists some of the factors that determine the success or otherwise of drug targeting using nanosystems. The idea of targeting drugs to the extent of 100% of the dose is a far-off hope.

As particle size is key in the delivery of particulates to the lung, there are possibilities for using nanoparticles, although the sizes lie below those derived

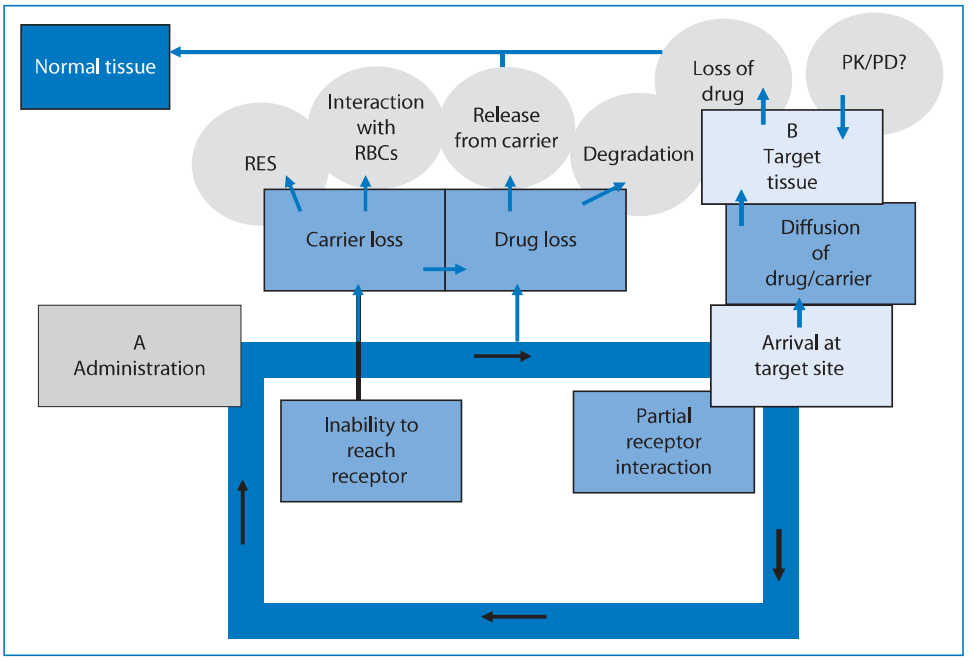

Figure 8.11 A much-simplified diagram pointing out the reasons for less-than-quantitative targeting of drugs and genes to particular sites within the body. Carrier can be lost in the reticuloendothelial system (RES), or by interaction with erythrocytes; drug can be lost through premature release from the carrier, or by degradation. Drug freed from the carrier will reach normal tissues. Interactions with receptors is a statistical process; particles that do interact then have to be taken up and diffuse through multiple cells in the tissue concerned. PK, pharmacokinetics; PD, pharmacodynamics; RBC, red blood cell.

for particulates for optimal deposition in the bronchial tree. Deposition of nanoparticles of C_{60} fullerene has been found to be 50% greater than that of microparticles.[44]

Pegylation of carriers

Surface modification of proteins to prolong their circulation was introduced after the finding that covering the surface of hydrophobic nanoparticles could change their biodistribution. The diagram in Figure 8.12[45] nicely illustrates the transformation of the surface and why the surface would inhibit the adsorption of opsonins, thus preventing extensive uptake by the reticuloendothelial system and prolonging particle circulation, enhancing the opportunity for targeting.

Cell-based therapies

After the biological 'revolution' in therapeutics has come the exploration of cell-based therapy and, of much longer provenance, gene therapy. Cell-based interventions include stem cell therapy and the use of dendritic cells and

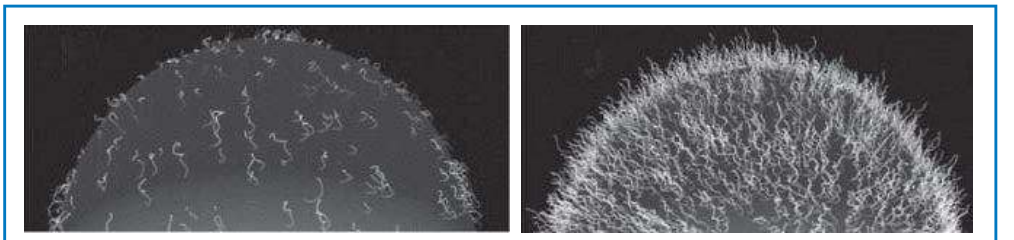

Figure 8.12 Polyethylene glycol chains on the surface of a nanoparticle: (a) light coverage; (b) complete coverage. The chains in (b) limit opsonisation and capture of the particles by the Kupffer cells of the liver and spleen (From reference 45 with permission.)

neural cells for parkinsonism. The issues in gene therapy are not least those of delivery of the labile plasmid DNA or oligonucleotides into the nucleus. There is much debate over the relative merits of viral and non-viral vectors as carriers for genetic material. The former are more efficient but there are safety issues, while the latter suffer fewer potential adverse effects but are less efficient in transfection. One question to be asked is to what extent pharmacists are to be involved with either. There are many links to pharmaceutics in the delivery of cell therapy, not only in the design of matrices for some cells but also because cells *in vivo* behave like colloidal systems, chief of which pharmaceutically would be fine dispersions or suspensions of microspheres, for example. Stem cells have been used themselves as vehicles for targeted delivery to lung metastases in the treatment of breast carcinoma.[46]

The pharmaceutics of cell delivery

There are certainly traditional pharmaceutical concepts involved in the administration of cell-based therapies: the definition of dose, the quality control of the cells, their 'purity', and their mode of delivery and their fate in the body. Conceptually the main issues are the same as with conventional therapies, but the products are somewhat more fragile and complex.

How is the dose of a cell type defined? How do we ensure purity and absence of viral load? How do we deliver cells to the right locus and avoid their deposition in unwanted sites? One study[47] on the delivery of mesenchymal stem cells showed that after intravenous administration (to rats) much of the dose of donor cells was trapped in the lungs. Within 4 hours only 1% of the cells had migrated to the myocardial epithelium.

Rosen has rightly asked[48] 'Are stem cells drugs?' Referring to stem cell therapy of cardiovascular disease, it is suggested that progress has not been fast. Questions include 'Can we really expect that after we inject stem cells into a region of the heart directly intramyocardially or via a coronary artery, they will stay in place without a subset migrating to other sites in the body?' The other key question reflects the problems with a naive approach to drug

targeting which suggests that because nanoparticles or other constructs have surface ligands that bind to epithelial receptors, they somehow 'home' to their target. Rosen also asks 'When stem cells are injected into a peripheral vein and expected to follow a 'homing signal' to regions of the heart in need, will they faithfully cluster at such a site?' While many cells do remain at the site, others, in his words, 'either die or wander off.'

The administration of cells to the body should draw on the experience of the administration of microspheres and nanoparticles: intravenously administered microsystems will accumulate rapidly in the lung, indeed within seconds. Hence there is a low efficiency in delivering cells to the heart after IV infusion and cells find themselves other than at the target sites. Aggregation of cells will occur under some conditions during intracoronary infusion, and this can of course cause problems: microvascular obstruction can be caused by cell 'sludging' and this may lead to microinfarctions.[49]

Routes of administration of cells in cardiology

As might be anticipated, a variety of points of entry and delivery of cells in cardiovascular disease have been studied (Figure 8.13[50]).

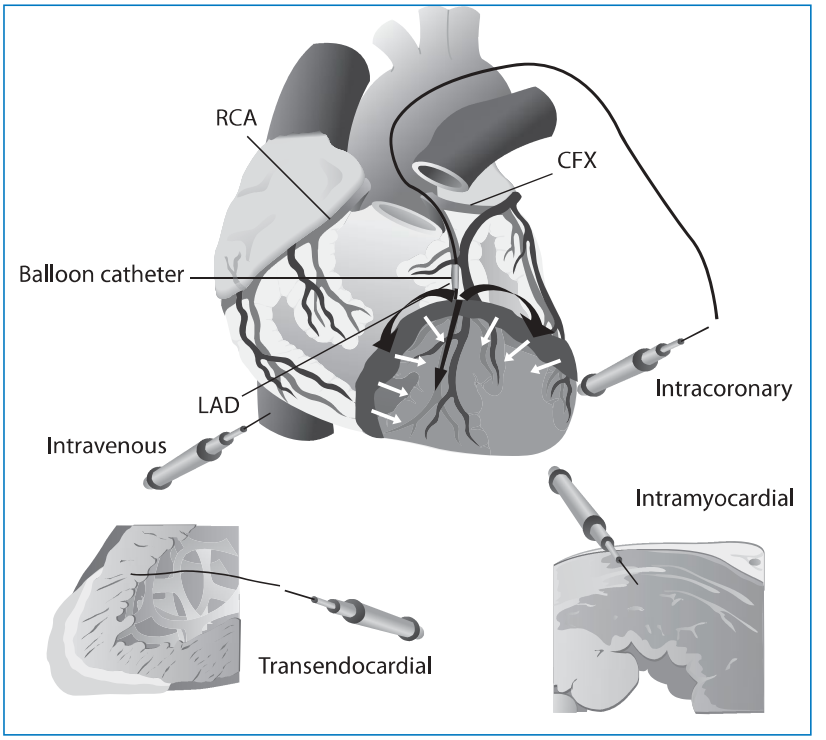

Figure 8.13 Routes of injection of cells in cardiovascular disease. CFX, circumflex artery; LAD, left anterior descending coronary artery; RCA, right coronary artery. (From reference 50.)

Cardiovascular treatment may involve[51]

- Systemic delivery, which may not be optimal for the reasons stated above.
- Local delivery, which can be achieved by direct injection at time of surgery or by percutaneous catheter-guided intracoronary infusion.
- Surgical delivery for intramyocardial injection to infarct borders.
- Catheter delivery involving a range of percutaneous catheter techniques for delivery to the myocardium.

Studies suggest that at best only 30–40% of particulates are retained in the myocardium after successful endomyocardial injections.[52]

Cell delivery for cartilage and bone regeneration

When skeletal tissue is being engineered using autologous cells, delivery is effected by polymeric bioresorbable scaffolds. These maintain the three-dimensional shape required and allow nutrient supply by diffusion.[53] Cells are usually mixed with polymers, which subsequently gel. The materials used are well known in pharmacy: materials such as collagen, hyaluronates, agarose, alginates and chitosan. There is a desire for delivery systems that can be used with minimally invasive procedures. Thermoreversible materials that gel *in vivo* (*in situ*) have been explored. Polymer-based systems have been used for the delivery of growth factors in tissue regeneration.[54] Cell scaffolds often contain a mixture of cell adhesion molecules and other tissue factors. This is mixture formulation in a microcosm and possibly requires future work to ensure that the rates of release and stability of the materials in combination are sufficient and reproducible.

Gene therapy

Although adenoviruses and other viral forms (even synthetic viral particles) have been used to deliver DNA into the nuclei of cells to achieve genetic modification, only non-viral vectors will be discussed briefly here. A variety of constructs have been used in attempt to deliver DNA to the nucleus of cells and hence effect transfection. Mainly cationic systems are preferred because of their interaction with the negatively charged DNA. Such cationic nanoparticles and anionic DNA condense to form compact complexes, whose size, overall charge and lipophilicity can all affect uptake into cells, and subsequent behaviour in the cells. Figure 8.14 is one scheme for the process. Transport through the cytoplasm is an issue that is being explored actively. The cytoplasm is a complex mixture that is said to be 'molecularly crowded' with complex barriers such as the actin–myosin scaffolds, proteins and highly concentrated macromolecules, a hostile environment for ready diffusion of even the smallest constructs.

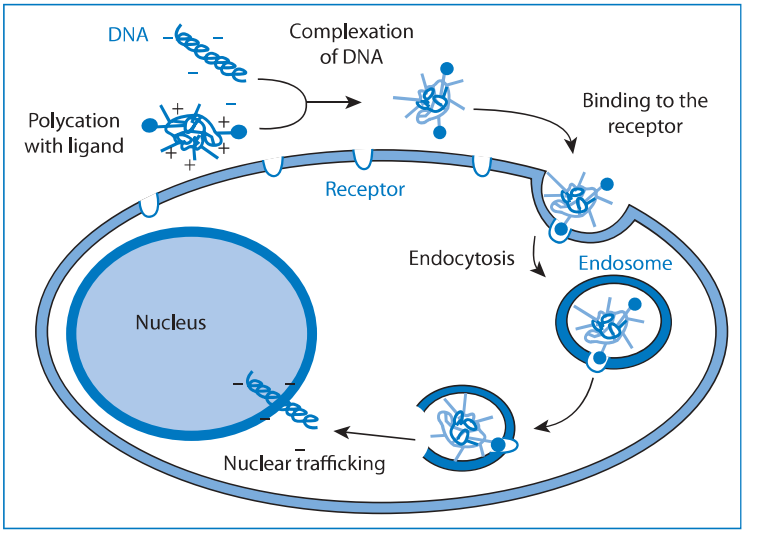

Figure 8.14 Schematic representation of complexation of DNA with a polycation (which could be a cationic dendrimer, a polycationic polymer, liposome or nanoparticle): complexation, binding to receptors, endocytotic uptake into endosomes and nuclear trafficking by way of the nuclear pore membrane. (From www.nano-lifesciences.com.)

Conclusions

With so many new materials and new means of transforming them into novel structures of a variety of shapes and sizes and surface characteristics, there is much scope for finding new means of delivering new and complex drugs in this post-genomic period. On the other hand, simple technologies may provide the answer to many of the problems of dosing individual patients. There are many opportunities for pharmacists to be involved in ensuring that the systems used in the clinic are well characterised, stable and reproducible so that we do not repeat the errors of the past. It is a dangerous exercise to attempt to predict the future, but one thing is guaranteed: if we probe the body even with new therapeutic agents based on endogenous species and transport them to sites where they are not naturally found, there will be unusual side-effects to look out for and to explain on the basis of the nature of the materials themselves, their biodistribution, and their biodegradation. There are exciting prospects.

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