

# 1

## What is clinical pharmaceuticals?

This chapter promotes the view that the fundamentals of pharmaceuticals 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 pharmaceuticals 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 pharmaceuticals is more important than other subjects, but there are at least three aspects of pharmaceuticals 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*.

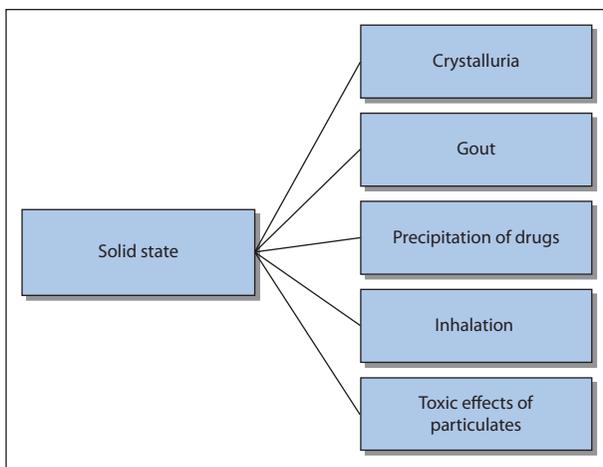
## Physical concepts

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.

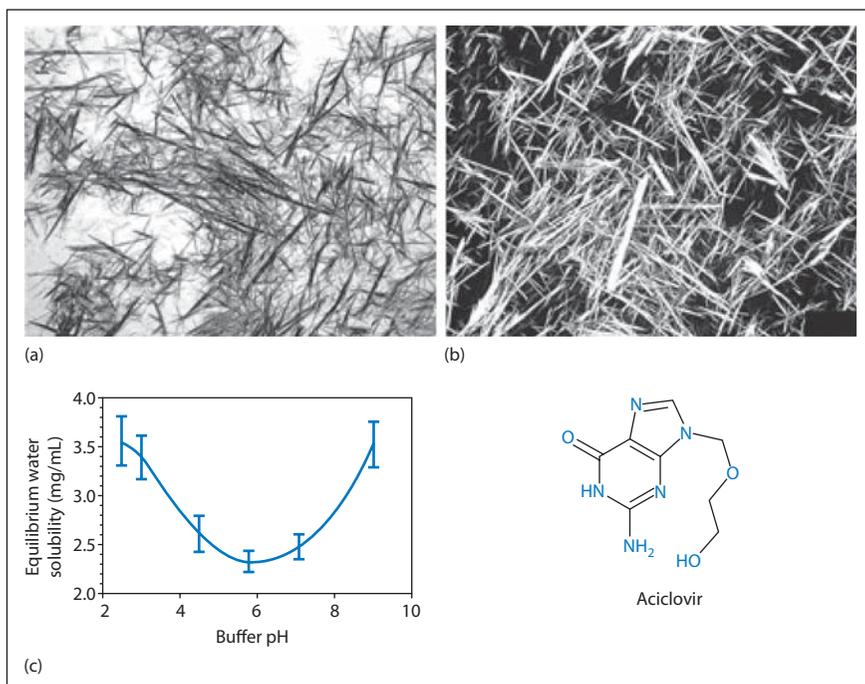
### Crystallisation

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<sup>1</sup> 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** The structure of aciclovir is shown above. (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. (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).<sup>2</sup> The concentration of aciclovir in human urine after *oral* administration of 200 mg reaches 7.5 µg/mL,<sup>3</sup> 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.

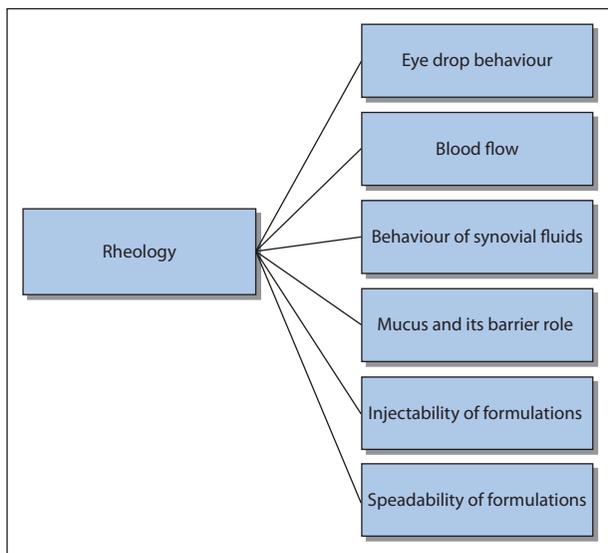
While crystallisation of drugs *in vivo* will be discussed later, this case illustrates that a knowledge of the solution properties of drugs and the pH at which drugs might precipitate or become saturated in body fluids and compartments is essential if we are to make contributions to patient care

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*<sup>4</sup> 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.<sup>5</sup> Solutions of hyaluronic acid (HA) with molecular weights greater than  $3 \times 10^5$  Da have been found to be effective, while HA with a molecular weight of  $5.5 \times 10^4$  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;<sup>6</sup> 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

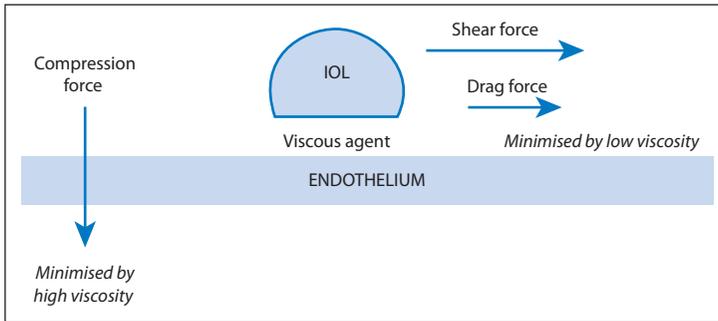
**Box 1.1** *Rheological terms and descriptors*

- **Newtonian and non-Newtonian liquids:**  
Viscosity  $\eta = \text{shear stress } (\tau) / \text{rate of shear } (\dot{\gamma})$ .  
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<sup>7</sup> 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.<sup>8</sup> *In vivo*, HA with a higher viscosity has been found to be more effective in lubricating joints.<sup>9</sup> 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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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:<sup>12</sup> 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  $4 \times 10^6$  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.<sup>13</sup>

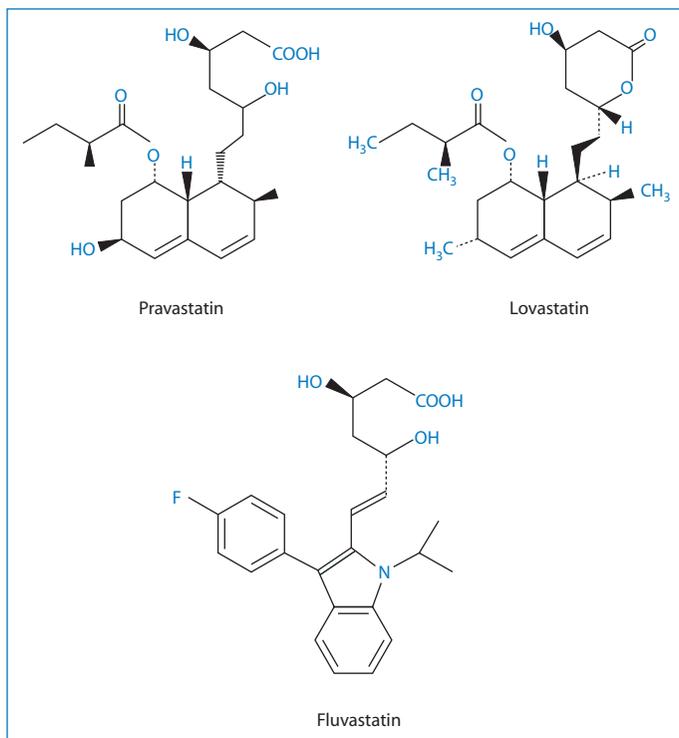
### *Effect of drug lipophilicity on blood rheology*

High dose intravenous (IV) immunoglobulin therapy increases blood viscosity to an extent that can impair blood flow.<sup>14</sup> 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.<sup>15</sup> This work<sup>15</sup> 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  $\approx$  cerivastatin  $>$  lovastatin  $\approx$  fluvastatin  $\approx$  atorvastatin  $\gg$  pravastatin. Pravastatin is 70–300 times more hydrophilic than the other statins.<sup>16</sup>



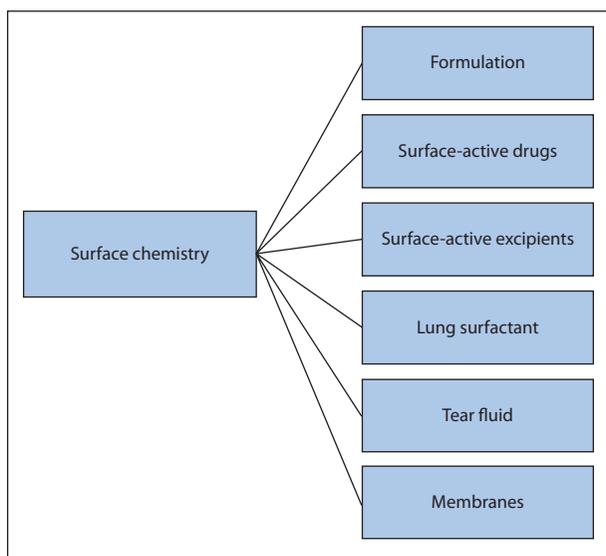
The relative hydrophobicities of drug molecules cannot always be determined visually from their structures, as there are other determinants of solubility such as hydrogen bonding and the cohesion of the crystals. Lovastatin's methyl substituent instead of a pravastatin's hydroxyl is one clue; the structure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



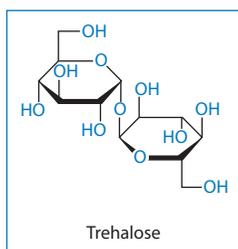
**Figure 1.5** A simplified version of the diagram shown in the Introduction (p. xiii). Surface chemistry is important directly in formulation, in understanding surfactants and surface-active drugs and excipients, natural surfactants as in the lung and in tears, and the manner in which drugs and excipients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

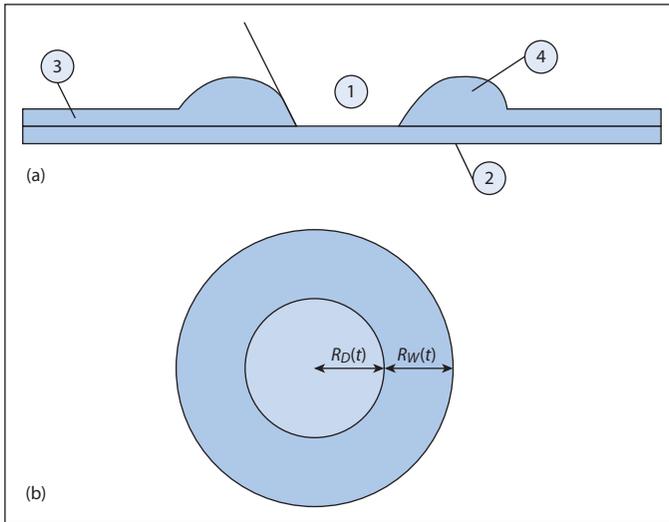
### Tear fluid

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<sup>17</sup> (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.<sup>18</sup>

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<sup>19</sup> 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  $\sim 2$  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.



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



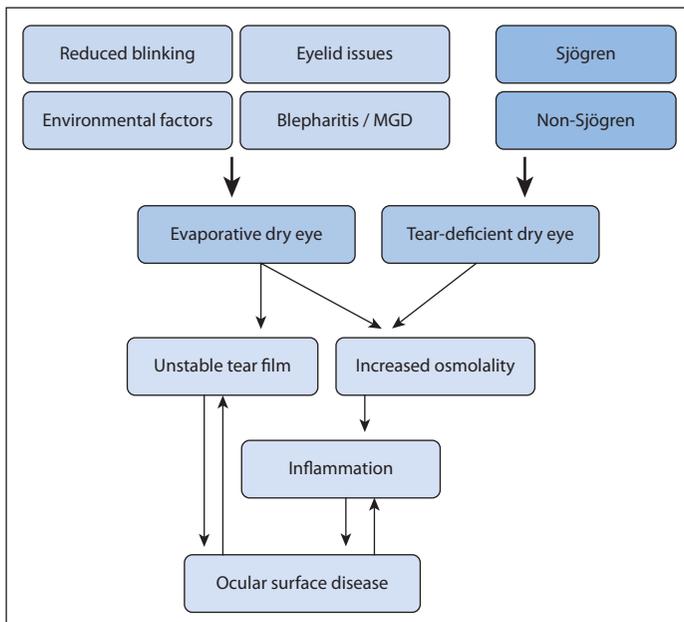
**Figure 1.6** (a) Simplified diagram showing a thin liquid film (3) on a surface such as the cornea (2). When the film reaches a critical thickness, instability causes the film to rupture and surface forces pull the film away from that point, leaving an exposed surface (1). The liquid in the film is 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.<sup>20</sup>

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.<sup>21</sup> This incomplete blinking<sup>22</sup> 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



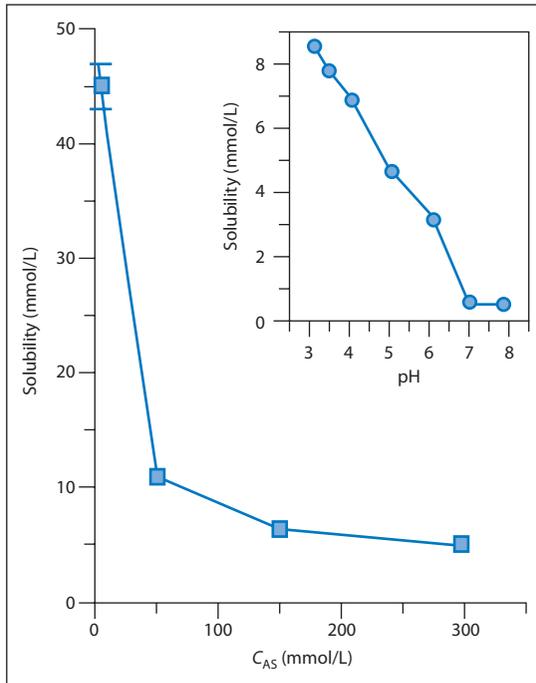
**Figure 1.7** Diagram showing the causes of dry eye, through reduced blinking, problems with eye lids (evaporative dry eye) or Sjögren's tear deficiency (tear-deficient dry eye). (From [www.lowvision.com](http://www.lowvision.com).) MGD, meibomian gland dysfunction.

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).

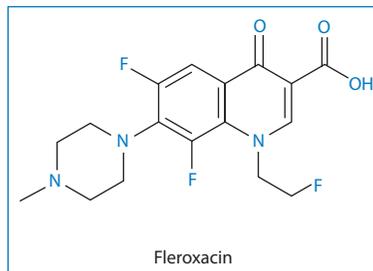
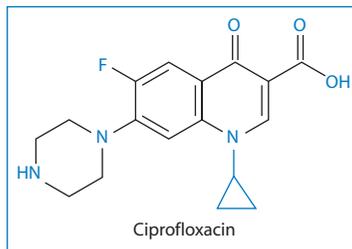
### Drugs and tear films

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.<sup>23</sup> 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,<sup>24</sup> as can be seen from Figure 1.8.<sup>25</sup> 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.



### *Eye drops and surface tension*

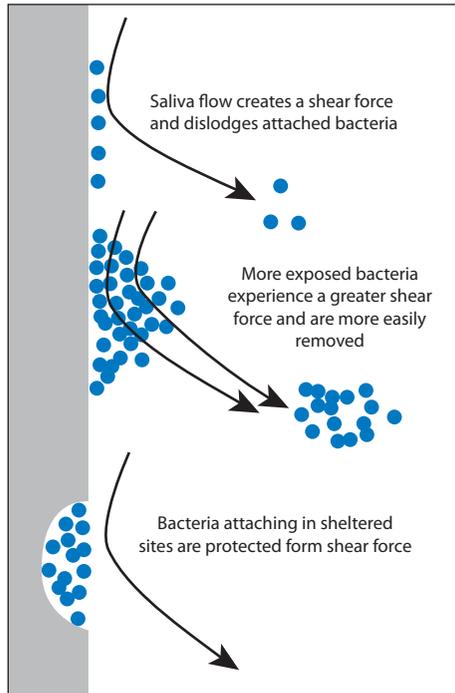
Conventional eye dropper devices deliver drops with a volume between 25 and 70  $\mu\text{L}$ . It has been argued<sup>26</sup> from many points of view, not least the biopharmaceutical one, that volumes of 5–15  $\mu\text{L}$  should be instilled in the eye. The surface tension of the solutions to be 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  $\mu\text{L}$  for a solution with a surface tension of 71.9 mN/m to 25  $\mu\text{L}$  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.<sup>27</sup> 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.

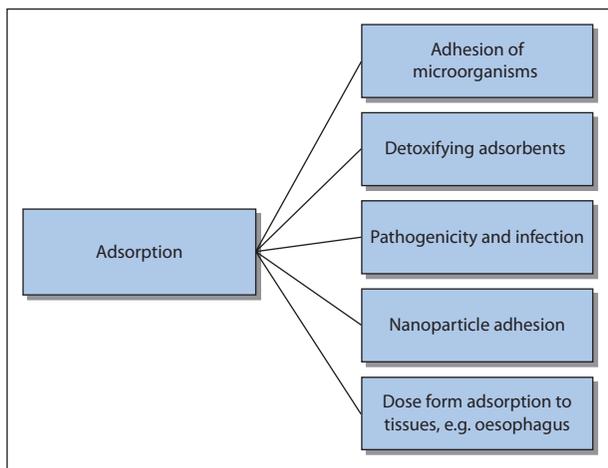


**Figure 1.9** Diagram of the effect of salivary flow in the normal mouth, dislodging bacteria adsorbed on teeth. Different situations are shown, with more exposed bacteria and bacteria in sheltered sites such as crevices.

## 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.<sup>28</sup> 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,<sup>29</sup> in surgical and dental materials, in polymers<sup>30</sup> 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<sup>28</sup> 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 glycocalyxes 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*

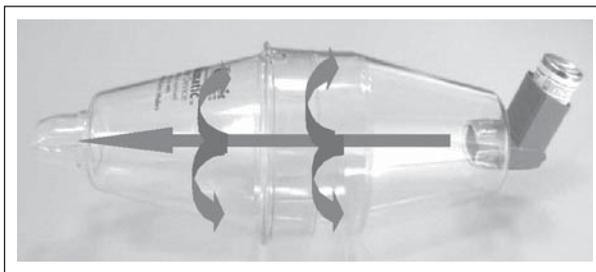
Electrostatics deals with phenomena that result from stationary electric charges on non-conducting surfaces. The build-up of charge on the surface of objects after contact with other surfaces is important pharmaceutically. In powder handling on the large scale, accumulation of charge can lead to sudden 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%.<sup>31</sup> 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*

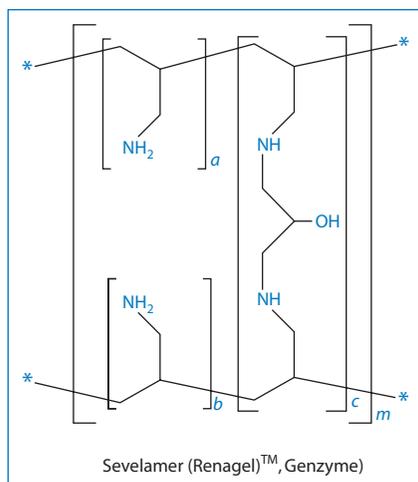
Highly adsorbent charcoal is used to reduce free toxin in the case of orally administered overdoses, deliberate or accidental. Patients who have to undergo haemodialysis are prone to hyperphosphataemia as the excretion of phosphate by dialysis is poor and renal function is impaired. Calcium as its carbonate 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<sub>2</sub> 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.<sup>32</sup> 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.



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.

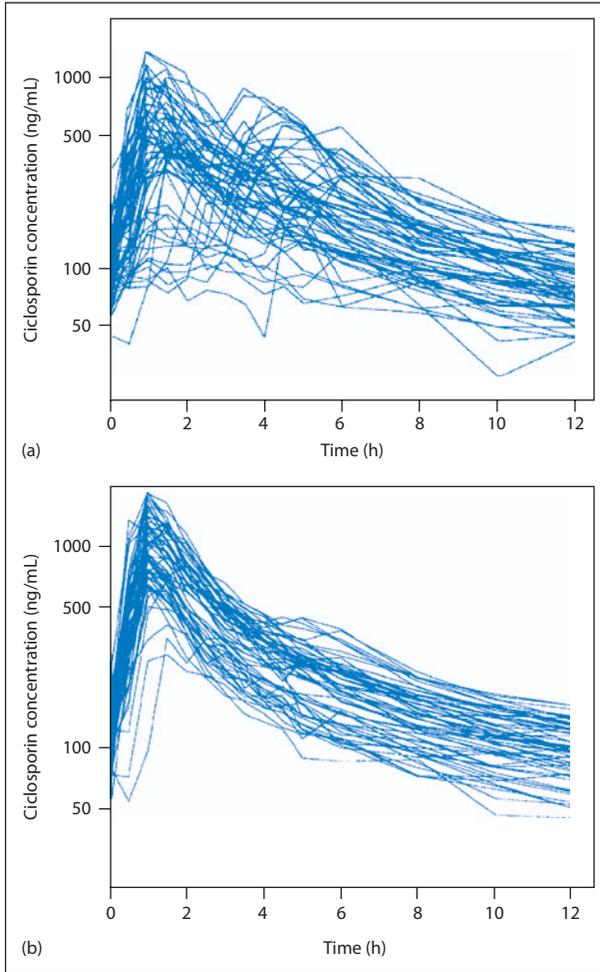
It is clear from knowledge of biopharmaceutics that dosage forms can considerably influence medication outcomes.<sup>33</sup> The development of controlled-release dosage forms is a good example of that influence, where the properties of the dosage form have been adjusted to ensure an optimal release 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

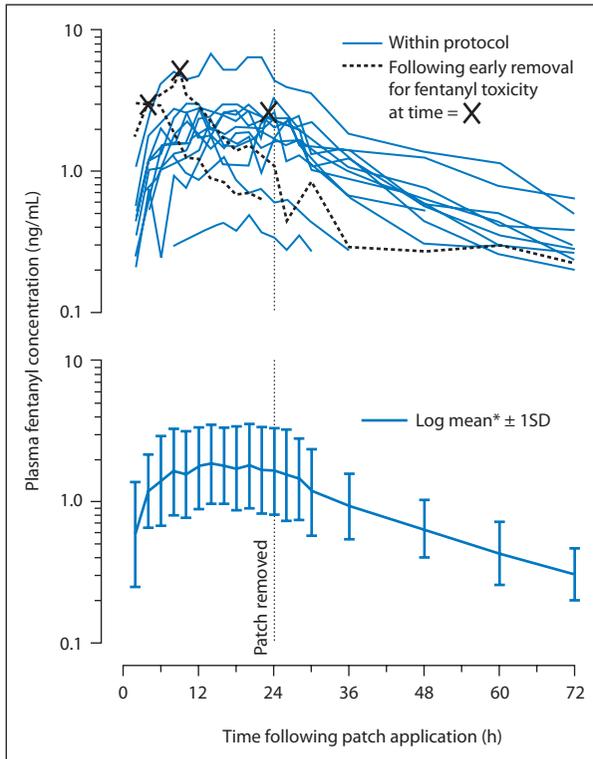
The quality of the clinical effect of medicines is often a pharmaceutical concern. As one example shows, considerable advances have been made with ciclosporin formulations to reduce the inter- and intra-patient variability in plasma levels. This is vital because appropriate levels are crucial in the 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 cyclosporin 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 cyclosporin 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.<sup>34</sup>



**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*<sup>35</sup> 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.<sup>36</sup> 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.<sup>37</sup>

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  $6\alpha$ -hydroxypaclitaxel by cytochrome P450 (CYP) 2C8. This is the major route of detoxification of paclitaxel.<sup>38</sup> This surfactant has also been found to decrease the accumulation of the hydroxyl derivative in cells and decrease the ratio of  $6\alpha$ -hydroxypaclitaxel to paclitaxel. To complicate matters, it also contributes to the non-linear kinetics of the drug.

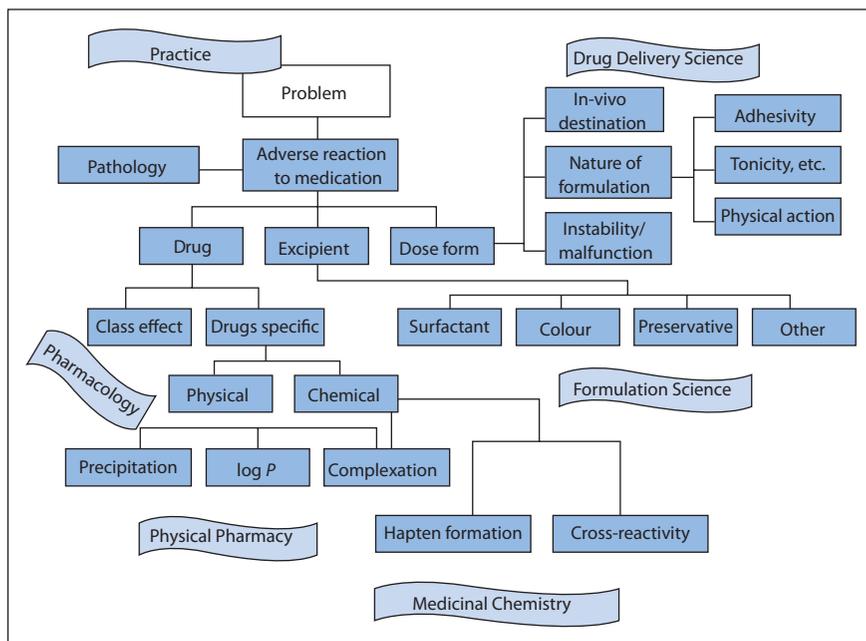
Clearly, Cremophor EL is more than a substance that simply increases the solubility of the drug. When observing the effect of a drug on adverse events we need always to consider the question: does the formulation itself or ingredients in the formulation play a part in the behaviour of the medicine or 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 thorough knowledge of pharmacology and therapeutics and key pharmacological 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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