

# PHARMACEUTICALS AND MEDICINES

# 01



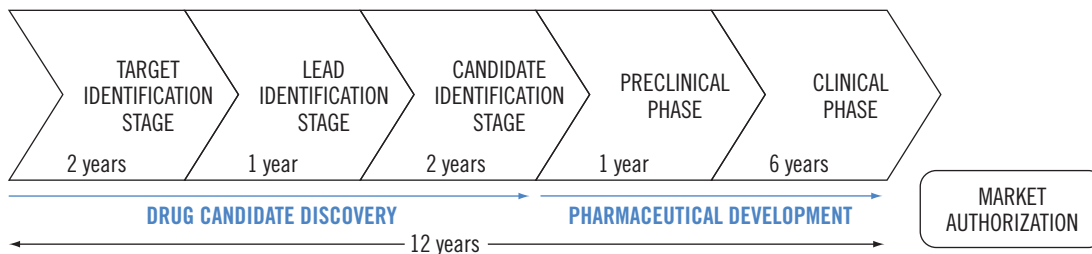
## Learning objectives

Having studied this chapter, you should be able to:

- understand the terms **pharmaceutical, medicine, active pharmaceutical ingredient, drug substance and excipient**
- appreciate the chemical nature of pharmaceuticals
- broadly understand the role of pharmaceutical excipients
- understand the terms **drug delivery and dosage form**
- describe the various pharmaceutical dosage forms and routes of administration
- appreciate the factors that must be considered when selecting an appropriate dosage form and route of administration for a drug substance
- understand what the term **physicochemical properties** means and why these properties are important.

## 1.1 INTRODUCTION TO THE ESSENTIAL PROPERTIES OF PHARMACEUTICALS

The overall goal of pharmaceutical research is to identify molecules with pharmacological activity to treat, prevent or alleviate disease and illness. To successfully progress through the highly regulated drug development process (Fig. 1.1), these molecules must possess certain attributes. Firstly, they must have a proven pharmacological efficacy. Secondly, they must demonstrate an acceptable safety profile. Numerous compounds fail during development or are withdrawn from the market post-approval due to adverse effects. Reliability of pharmacological activity is a third essential criterion. A pharmaceutical product will only be approved by national and international regulatory bodies when these three quality attributes have been demonstrated.



**FIGURE 1.1** Schematic diagram of the drug development process (adapted from Food and Drug Administration (FDA), (2004)).

### 1.1.1 Some key concepts

We begin with an overview of some of the key terms and concepts that will be used in this book. **Physicochemical** is the adjective used to describe the properties relating to both the physical and chemical behaviour of a substance. A good understanding of physical chemistry is required to understand these properties. Physical chemistry is the application of physical concepts to particulate, macroscopic, microscopic, atomic and subatomic phenomena in chemical systems. Table 1.1 lists some key molecular and crystalline physicochemical properties of particular interest to the efficacy of pharmaceutical compounds.

#### The components of medicines

Pharmaceutical compounds can be divided into **drug substances** [also referred to as **active pharmaceutical ingredients (APIs)**] and **excipients**. Excipients are pharmacologically inert materials that are combined with APIs to aid their processing into dosage forms (e.g. tablets, injections and ointments) and to facilitate API administration to patients. As well as being pharmacologically inert, excipients are also required to be chemically and physically inert. A more detailed classification of APIs is given in Section 1.2. The physicochemical properties of these materials can influence their performance during processing, storage and subsequent administration to the patient. Alterations in the performance of these compounds can undermine the required quality attributes of **efficacy, safety and reliability**. (The **efficacy** of a drug is the maximum possible pharmacological effect it can achieve.) It is an essential pre-requisite for medicinal chemists and pharmaceutical scientists to possess a fundamental understanding of these physicochemical properties in relation to pharmaceutical compounds. The aim of this text is to explain the fundamental theories behind key physicochemical properties and how they impact upon the biological behaviour of pharmaceutical compounds.

APIs exert their desired pharmacological effect by interacting with specific **biological targets**. In modern pharmacy, APIs are rarely administered to patients in their pure form. Normally they are combined with excipients via one or more processing steps to produce a **dosage form**. The primary goal in transforming an API into a dosage form is to facilitate delivery of that API to the biological target. The delivery of an API to a biological target is commonly referred to as **drug delivery**.

**TABLE 1.1** Molecular and crystalline physicochemical properties related to pharmaceutical compounds.

Scale of scrutiny	Physicochemical properties
Molecular	Structure
	Molecular weight
	Dissociation constant
	Equilibrium solubility
	Partition coefficient
Crystalline	Polymorphism/solvates
	Crystalline or amorphous state
	Thermal behaviour
	Surface energy
	Dissolution rate
	Crystal strength
	Particle-size distribution
	Morphology
	Compressibility
	Density

Physicochemical properties of pharmaceutical compounds, both APIs and excipients, can have a significant influence on the drug-delivery process. A basic knowledge of the classes of pharmaceutical compounds, the drug-delivery process, **routes of drug administration** and types of dosage forms is required. The remaining sections of this chapter provide this basic knowledge.

## 1.2 CLASSES OF PHARMACEUTICAL COMPOUNDS

By definition, pharmaceuticals are the chemicals used in pharmacy – that is, they are the chemical constituents of medicines. These chemicals can be further divided into APIs, and excipients. These groupings can be further subclassified in a number of ways, for instance on the basis of chemical structure. However, it is most common to classify pharmaceuticals on the basis of activity or function, and that basis will be used here.

### 1.2.1 Active pharmaceutical ingredients

APIs can be categorized into four major classes, as follows.

#### Psychopharmacological agents, or compounds acting on the central nervous system

The central nervous system, or CNS, consists of the brain and the spinal cord. The CNS controls thought processes, emotions, senses and motor functions. Drugs that act on the CNS include antidepressants, antipsychotics, anxiolytics, psychomimetics, anticonvulsants, sedative-hypnotics, analgesics, and anti-Parkinsonian agents.

#### Pharmacodynamic agents

These are drugs that interact with the normal dynamic process of the body, for example circulation of blood. Included are antiarrhythmics, antianginals, vasodilators, anti-hypertensives, antithrombotics, antiallergy agents, and drugs that interact with the gastrointestinal system.

#### Chemotherapeutic agents

These are agents that are selectively more toxic for disease-causing microorganisms than for the host. As such, this category includes antibiotics, antiparasitics, antivirals and antifungals. Cancer-controlling compounds are also usually included in this category.

#### Agents acting on metabolic diseases and endocrine function

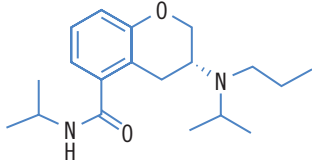
This group includes drugs for the treatment of diabetes, inflammation, atherosclerosis and arthritis. Also included are drugs not falling under any of the previous categories, for example hormones.

An appreciation of molecular structure and function is required to understand the physicochemical properties of these compounds. A thorough review of drug structure is beyond the scope of this book. However, Fig. 1.2 gives the molecular structures of a representative selection from each of the above categories. The following general points should be noticed.

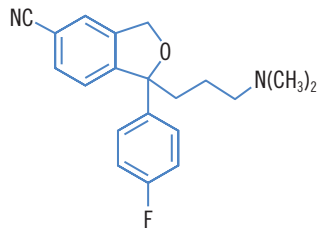
- The great majority of the examples are molecular organic compounds. The molecular masses of these compounds usually lie within the approximate range of 300 to 1200 atomic mass units. These compounds are often referred to as 'low to medium weight' compounds, or even as 'small molecule' drugs. Simple inorganic compounds are represented, for example lithium carbonate. Organometallic drugs are also known, for example oxaliplatin. Larger molecular weight biomolecules are also represented, for example salmon calcitonin, a peptide with 32 amino acid residues.

**FIGURE 1.2** (*opposite*) Molecular structures of a representative selection of (a) psychopharmacological agents, (b) pharmacodynamic agents, (c) chemotherapeutic agents, and (d) other agents. In (d), the structure of salmon calcitonin uses the following abbreviations for amino acids: Cys (cysteine), Ser (serine), Asn (asparagine), Leu (leucine), Thr (threonine), Val (valine), Gly (glycine), Lys (lysine), Gln (glutamine), Glu (glutamic acid), His (histidine), Tyr (tyrosine), Pro (proline), Arg (arginine); for further information on amino acids and proteins, see Patrick (2005) under Further Reading at the end of the chapter.

(a) Psychopharmacological agents



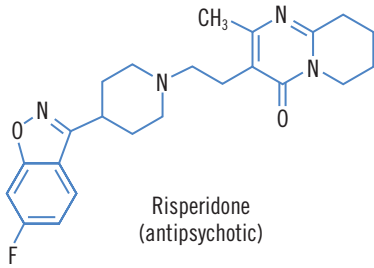
Ebalzotan  
(antidepressant)



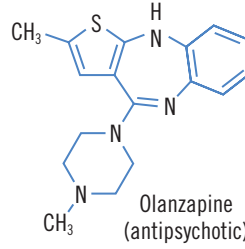
Citalopram  
(antidepressant)



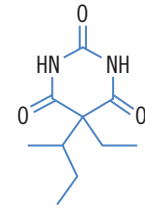
Lithium carbonate  
(mood stabilizer)



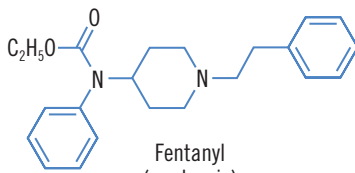
Risperidone  
(antipsychotic)



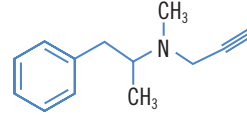
Olanzapine  
(antipsychotic)



Pentobarbital  
(sedative-hypnotic)

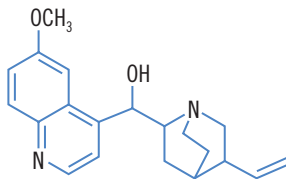


Fentanyl  
(analgesic)

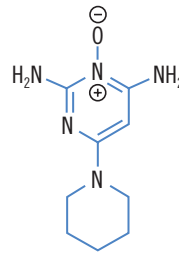


Selegiline  
(antiParkinsonian)

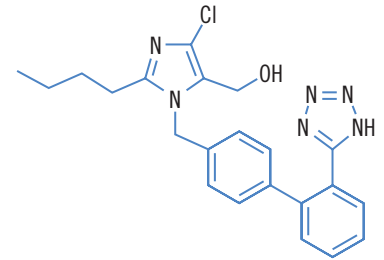
(b) Pharmacodynamic agents



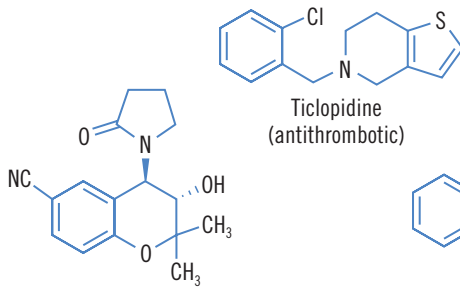
Quinidine  
(antiarrhythmic)



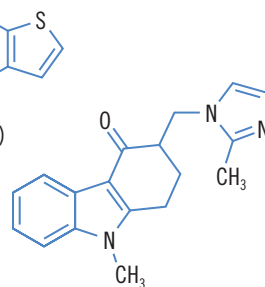
Minoxidil  
(vasodilator)



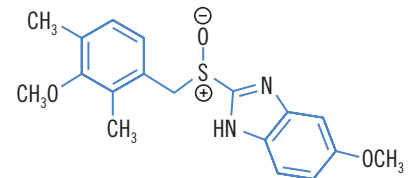
Losartan  
(antihypertensive)



Cromakalim  
(antihypertensive)



Ondansetran  
(antiemetic)



Omeprazole  
(gastrointestinal agent)

## (c) Chemotherapeutic agents

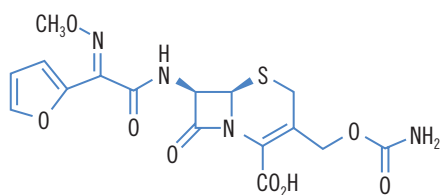
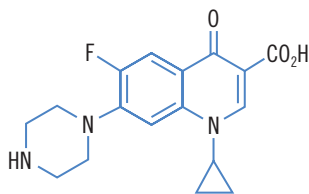
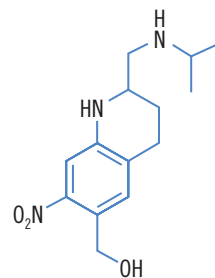
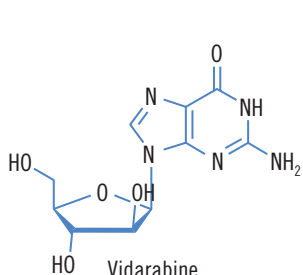
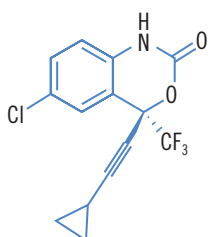
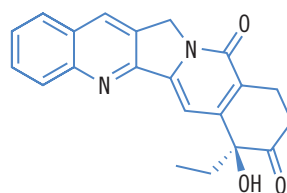
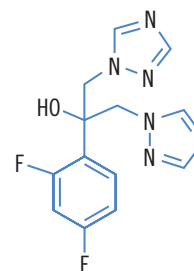
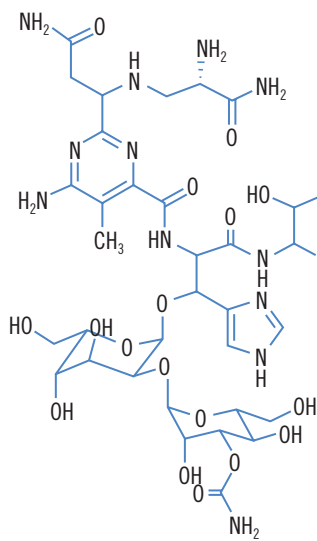
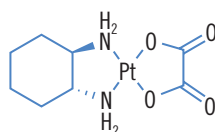
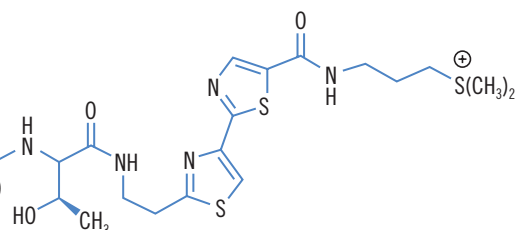
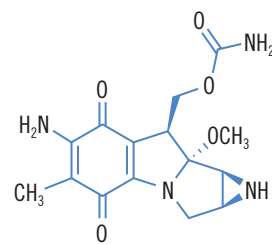
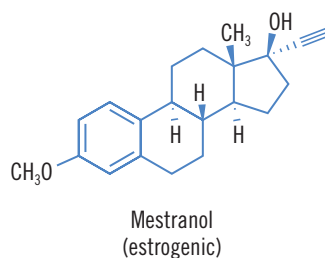
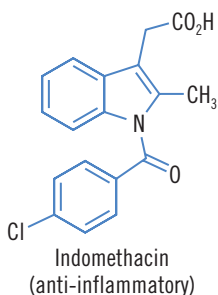
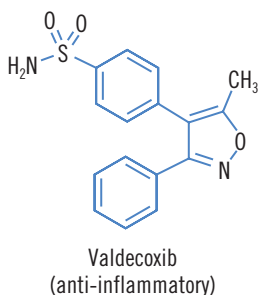
Cefuroxime  
(antibiotic)Ciprofloxacin  
(antibiotic)Oxamniquine  
(antiparasitic)Vidarabine  
(antiviral)Efavirenz  
(antiviral)Camptothecin  
(anticancer)Fluconazole  
(antifungal)Bleomycin A<sub>2</sub>  
(anticancer)Oxaliplatin  
(anticancer)Mitomycin C  
(anticancer)

FIGURE 1.2 Continued

(d) Other agents



Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-  
Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH<sub>2</sub>  
Salmon Calcitonin  
(osteoarthritis treatment)

FIGURE 1.2 Continued

- Cyclic systems (for example benzene rings) are very well represented. Carbocyclic and heterocyclic systems are ubiquitous in drug structure. Five- and six-membered rings are the most common, but small ring systems occur with reasonable frequency, (for example, the cyclopropane ring in ciprofloxacin and the aziridine ring in mitomycin C). Of the five- and six-membered systems, the majority are aromatic or pseudo-aromatic. Hence, substituted benzene rings are very common, and heterocycles such as pyridines, furans, thiophenes, imidazoles, isoxazoles and others occur commonly in drug structure.
- Polar functional groups are very common. These include ethers, amines, amides, esters, carboxylic acids, nitriles, halides, alcohols, thiols, *N*-oxides, sulfoxides, sulfonamides and others. Many of these functional groups are also acidic or basic to some extent. This especially applies to carboxylic acids, phenols, thiols, sulfonamides, amines and other nitrogen-containing functional groups such as amidines. Such groups are capable of existing in both un-ionized or ionized forms. This possibility is often of great pharmaceutical importance, as it allows drugs to travel through different types of environment in the body (see Chapter 7). For example, many of the drug compounds shown in Fig. 1.2 are used as salt forms, rather than as the un-ionized forms shown.

### 1.2.2 Excipients

Excipients are the chemical components of medicines other than the active ingredients. The most convenient classification of excipients is in terms of the functions they perform in dosage formulations.

#### Diluents (or fillers)

These are used to increase the bulk volume of material, especially for tablet and capsule formation. Examples include carbohydrates such as glucose, sucrose, lactose, sorbitol, mannitol, cellulose and starch. Calcium phosphates and carbonates are also used.

### Surfactants

These are used to aid formation of suspensions, emulsions or solutions. Surfactants are amphipathic compounds, that is, they contain both hydrophobic and hydrophilic regions. The hydrophobic regions are generally long alkyl chains. The hydrophilic regions can be either 'ionic' or 'non-ionic'. The ionic groups are positively or negatively charged functional groups. The non-ionic groups are most commonly polyethers, in particular, polyethylene glycol.

### Lubricants

These are used to reduce friction between powders and metal surfaces during tablet manufacture. Examples include paraffin, magnesium stearate, polyethylene glycol and sodium dodecyl sulfate.

### Disintegrants

Disintegrants are added to aid break up of solid dosage forms such as tablets. Examples include cellulose and cellulose derivatives, and croscarmellose sodium.

### Viscosity enhancers

These can be added to liquid formulations to control properties such as ease of pouring and sedimentation of suspensions. An example would be xanthan gum.

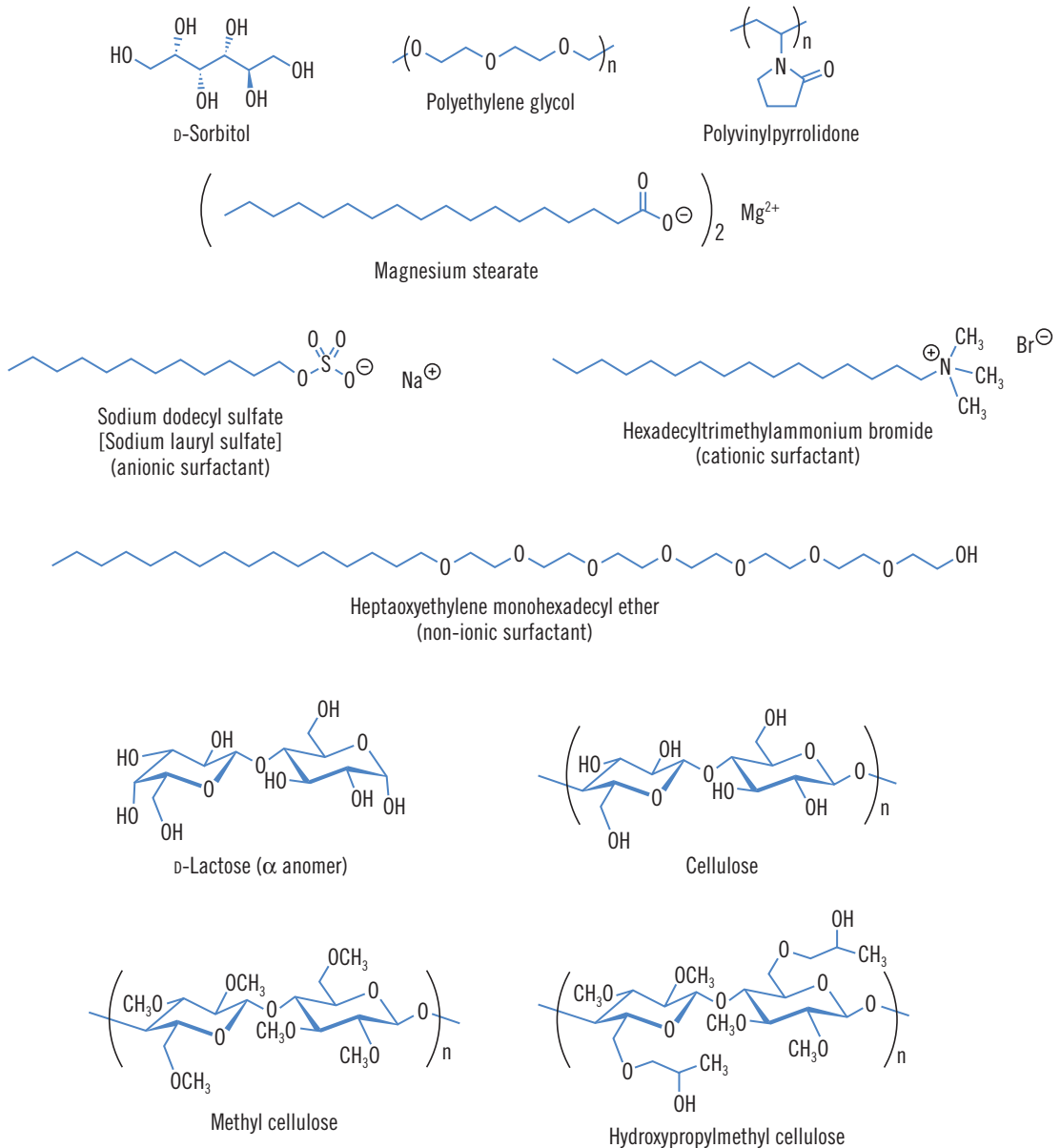
### Binders (or adhesives)

These are added to give adherence to powder mixtures for manufacture of solid-state dosage forms such as tablets. Examples include cellulose derivatives, polyvinylpyrrolidone and polyethylene glycol.

Figure 1.3 gives the molecular structures of a selection of excipients. While some of these are small to medium molecular weight molecules, many are high molecular weight polymers. Most of the structures shown have hydrophilic groups, for example alcohol groups, polyether segments or ionized groups. Some, such as the surfactants, also have hydrophobic groups. It should be noted that the cellulose derivatives often do not have very uniform repeating structures. The structures shown in Fig. 1.3 at best illustrate representative portions of these derivatives. Excipients such as calcium phosphate are not molecular in nature and possess complex mineral structures.

## 1.3 DRUG DELIVERY: GETTING THE ACTIVE PHARMACEUTICAL INGREDIENT TO THE SITE OF ACTION

Dosage forms are also referred to as '**drug-delivery systems**' and '**finished drug product**'. An ideal dosage form should reliably deliver the specified level of drug substance, to the specified biological target, for the specified duration. It should minimize exposure of the drug substance to other receptors that might result in the patient experiencing adverse effects. The inconvenience or discomfort associated with administering a dosage form should not outweigh its therapeutic benefits. For example, a patient may be willing to have an analgesic



**FIGURE 1.3** Molecular structures of selected excipients.

drug administered via intravenous infusion to treat severe pain but this form of treatment may not be tolerated to treat a minor headache, despite its effectiveness.

During release of the drug substance from the dosage form and its delivery to the target receptor, the pharmaceutical compounds (drug substance and excipients) are required to change from one phase to another. For example, a drug substance may change from a solid phase to a solution phase or from an aqueous solution phase to a lipid solution phase. In order to understand drug delivery and the design of effective dosage forms, a

basic understanding of these phase changes is essential. An explanation of these phase changes is given in Chapter 3.

### 1.3.1 Routes of administration

Before an active pharmaceutical ingredient (API) can reach its specific biological target, the patient must first be administered a dosage form containing the API. At the start of this section the ideal properties of a dosage form are described. In Section 1.3.2, the wide variety of dosage forms used to deliver APIs are described. The route by which a dosage form is administered to a patient is referred to as the 'route of administration'. Numerous possible routes of administration can be used and Table 1.2 gives a list of some of the main routes of administration along with examples of drugs delivered by each route. A comprehensive list of routes of administration is given in Appendix A1. General terms are used in relation to routes of administration. The term **parenteral** refers to administration via injection, infusion or implantation. **Peroral** refers to administration through the mouth. The meaning of the term **enteral** varies widely. It can refer to direct administration

**TABLE 1.2** A list of some of the main routes of administration with examples of drug substances delivered by each route and their indication.

Term	Description	Example of	Indication
Otic	to the ear	Gentamicin	Infection of the ear
Ophthalmic	to the eye	Cromolyn	Conjunctivitis
Nasal	to the nose	Betamethasone	Inflammation of the nose
Oral	to or by way of the mouth	Paracetamol	General analgesia
Buccal	toward the cheek	Prochlorperazine	Vertigo
Sublingual	beneath the tongue	Glyceryl trinitrate	Angina pectoris
Rectal	to the rectum	Meloxicam	Rheumatoid arthritis
Topical	to the outer surface of the body	Benzoyl peroxide	Acne vulgaris
Subcutaneous	beneath the skin	Insulin	Diabetes mellitus
Transdermal	through the dermal layer to systemic circulation	Fentanyl	Analgesia
Implantation	by implanting	Estradiol	Hormone-replacement therapy
Intravenous	within a vein	Gentamicin	Systemic infections
Intramuscular	within a muscle	Lorazepam	Acute anxiety states
Vaginal	into the vagina	Clotrimazole	Candidal vaginitis
Intrapulmonary	within the lungs or its bronchi	Salbutamol	Asthma

to the intestines. It is also given the more general meaning of administration to any point of the gastrointestinal tract, from the mouth to the rectum.

The administration of a dosage form via these routes can result in either local or systemic (via the blood stream) delivery or both. The choice of route of administration is primarily influenced by location of the biological target.

### Local delivery

If the target receptor is external or easily accessed then local delivery of the medication can be a feasible and effective approach. For example, conjunctivitis, an infection of the conjunctiva, can be treated by the local delivery of eye drops to the surface of the eye. The delivery of bronchodilators to the lungs via inhalers for the treatment of asthma is another example of local delivery. Due to advances in surgical techniques and biomaterials, more sophisticated dosage forms are now available for local delivery. Carmustine, a drug effective at treating cancerous brain tumours, can now be delivered locally to the tumour site. A biodegradable wafer containing carmustine is placed under the skull by surgical implantation. Due to its site-specific delivery characteristics, local delivery is generally the preferred approach. Site-specific delivery minimizes the exposure of non-target biological receptors to the drug substance and thereby reduces the risk of adverse effects.

### Systemic delivery

When the target receptor cannot be easily accessed systemic delivery is required. Blood is carried throughout the body through a network of veins, arteries and capillaries. The function of the blood system is to transport materials to and from the tissues throughout the body. Therefore, it is an ideal delivery pathway for a drug substance. The drug substance can enter the systemic circulation via the majority of routes of administration.

Dosage forms can be administered directly into the systemic circulation via veins (**intravenous administration**) or less frequently via arteries (**interarterial administration**). Systemic delivery can also be achieved indirectly by the administration of the dosage form via a less invasive route such as an **oral, transdermal** or **pulmonary route**. Indirect systemic drug delivery usually requires the release of a drug substance from the dosage form before it can travel across the biological barrier membranes into the blood system. The process by which it crosses the biological barrier into the blood stream is termed **absorption**. The drug substance is required to change phase during the absorption process, for example change from a solid to a liquid phase. These phase transitions are influenced by the particular physicochemical properties of the drug substance. Greater detail regarding these phase transitions is given in Chapter 3.

Compared to local delivery, a major limitation of systemic delivery is the reduced capability for site-specific delivery and increased potential for associated adverse effects. More sophisticated targeted dosage forms and advanced drug substances are being developed to overcome this limitation.

## 1.3.2 Pharmaceutical dosage forms

Pharmaceutical dosage forms are designed to facilitate the administration of drug substances. The majority of dosage form types can be classified as solid, semisolid, liquid and

TABLE 1.3 Main types of dosage forms.

Class	Type	Specific types
Solid	Powder	for solution, for suspension, for topical application
	Granule	for solution, for suspension, modified release, effervescent,
	Bead	implantable
	Pellet	modified release, implantable
	Minitablets	modified release, implantable, modified release, multilayered
	Tablet	chewable, modified release, effervescent, for solution, for suspension, multilayered, orally disintegrating
	Capsule	powder filled, liquid filled, semisolid filled, containing pellets, with modified release coating
Semisolid	Ointment	API dissolved, solid API suspended
	Cream	oil in water, water in oil, API dissolved, solid API suspended
	Gel	API dissolved, solid API suspended
Liquid	Solution	API dissolved
	Disperse systems	API solubilized in micelles, API solubilized in liposomes
	Suspensions	solid API suspended
	Emulsions	oil in water, water in oil, API dissolved, solid API suspended
	Foam	API dissolved liquid phase, solid API suspended
Gaseous	Medical gases	API gas at room temperature, API volatile liquid at room temperature
	Aerosols	solid API suspended, API solution droplets suspended

gaseous at room temperature. Semisolid dosage forms possess certain liquid and certain solid properties. **Ointments, creams and gels** are examples of semisolid dosage forms. At room temperature, semisolid materials behave like solids and do not flow or flow very slowly when low forces are applied. However, when high forces are applied, semisolid materials flow in a manner similar to liquids. Common pharmaceutical dosage forms are listed according to the classification in Table 1.3.

Dosage forms can be composed of more than one phase; these are termed **disperse systems** and are explained in greater detail in Chapters 5 and 6:

- solid material dispersed in liquid, e.g. pharmaceutical suspension
- solid material dispersed in gas, e.g. dry powder inhalers
- liquid dispersed in gas, e.g. nebulized solution
- one liquid dispersed in an immiscible liquid, e.g. pharmaceutical emulsion.

### Controlled-release dosage forms

Having looked at the different types of dosage forms, we now consider the ways by which the release of drug substance from these dosage forms can be controlled after administration. The release or liberation of the drug substance from the dosage form can be controlled in certain types of dosage form. Release can be controlled in two ways, (1) the drug substance is released at a specified rate or (2) the drug substance is released at a specified location. These dosage forms are termed **modified release dosage forms**. In Table 1.3 the dosage form types with modified release capability are indicated.

Extended release and delayed release are the most common type of modified release dosage forms. **Extended release** dosage forms allow the rate of drug-substance release to be controlled in such a manner as to allow a reduction in dosing frequency. The rate of drug-substance release is controlled by the inclusion of excipients that retard drug-substance release. Certain designs of delayed release dosage forms contain functional excipients that release the drug substance in response to a stimulus, such as the presence of a specific enzyme, biological substrate or pH. The remainder of this section describes the different solid, semisolid, liquid and gaseous dosage forms.

### Solid dosage forms

The majority of solid dosage forms are composed of **powders** processed to some degree to change their form. These include **granules, beads, pellets** and **tablets**. However, simply blending together powders of one or more drug substance and excipients can constitute a simple solid dosage form, a **pharmaceutical powder**.

Pharmaceutical powders can be administered orally or applied topically. Single doses of oral powders are generally wrapped or filled into sachets for ease of administration by the patient. However, oral powders have been largely replaced by tablet and capsule dosage forms. Medicated dusting powders applied topically are used to treat surface skin conditions. They are required to be sterile when designed for application to open wounds.

**Granules** are composed of solid particles and to the human eye they can look the same as pharmaceutical powders. However, the difference between a granule and a powder can be observed when viewed under a microscope. The granule particles, on close examination, are composed of a number of individual powder particles stuck together. The powder, on the other hand, consists only of solid particles. If we imagine each powder particle the size of a rice crispie then the granule particles would appear like rice crispie buns. The individual rice crispies, like the individual powder particles, are visible but stuck together in groups by a binding material, in this case chocolate. Granules can be manufactured as an intermediate process step in the production of tablets, capsules, pellets or beads. However, they can constitute a dosage form in their own right. Like powders they can be administered orally or topically. Due to their superior flow properties, uniformity of drug content and size and their reduced dustiness they are often preferred to powders as an oral dosage form.

In addition to direct administration of oral powders and granules, they can be dispersed or dissolved in a liquid prior to administration. **Effervescent** granules contain bicarbonate and citric or tartaric acid. These granules effervesce, releasing CO<sub>2</sub>, when in

contact with water, (for example, vitamin C tablets often comprise effervescent granules). Effervescence enhances the rate of disintegration and dissolution of the granule in liquid prior to oral administration.

**Multiparticulate solid dosage forms** include beads, pellets and **minitablets**. These multiparticulate dosage forms can be packaged in an outer capsule shell for oral administration. Beads and pellets can be mixed with other excipients and compressed into a tablet dosage form. Sterile multiparticulate dosage forms can be administered by injection or by implantation. Bead and pellet dosage forms can be used for administration of drug substances to wounds and pathological cavities.

**Oral tablets** are the most common type of dosage form marketed. Tablets are generally manufactured by compression of powders, granules, beads or pellets with the aid of other excipients. In addition to compression, orally dispersible tablets can be manufactured by moulding and freeze drying. Tablets are moulded by pouring a molten mixture containing the drug substance into pre-formed moulds where they solidify into a tablet shape. Many throat lozenges are prepared in this manner. Freeze-dried tablets are prepared by freezing a solution of the drug substance and excipients in pre-formed tablet moulds and removing water from frozen solution under vacuum. The remaining material after drying is a highly porous tablet-shaped solid. Freeze drying is often used to prepare tablets that are required to disintegrate rapidly in the mouth.

Tablets can be taken into the mouth intact or dispersed in water prior to administration. Tablets that are taken into the mouth intact can be designed to be chewed, sucked, dispersed, dissolved sublingually (under the tongue), buccally (between the cheek and gum) or swallowed. Tablets that are swallowed intact release the drug substance in the gastrointestinal tract where it is absorbed into the blood system.

**Capsules** are defined as a solid dosage form comprising a shell with filling. The shell can be a single sealed enclosure (soft capsules) or can comprise two halves that fit together (hard capsules). The capsule's shell is usually comprised of gelatine but it can also be composed of a starch- or cellulose-based material. The filling of the capsule can be liquid, semisolid or solid. Solid fillings can be powders, granules, beads, pellets or minitablets.

Capsules are generally administered orally and swallowed intact. Capsule dosage forms are also designed so that the contents are emptied or extruded from the shell prior to administration. For example, Creon® capsules that contain a pancreatin enzyme supplement; can be opened and their contents mixed with soft food prior to oral administration.

All solid dosage forms can be designed with modified release properties. Film coatings with modified release properties can be applied externally to a solid core. The drug substance is normally located in the core but in some circumstances can be located in the coat. Alternatively, modified release excipients can be added to the powder mix during the production of tablets, beads, pellets, minitablets and granules. By mixing with the modified release excipients, the drug-substance particles become entrapped in a matrix of excipients that then control the drug's release. Tablets containing these modified release excipients can be administered less frequently than conventional tablets. The reduction in frequency of dosing helps patients to remember to take tablets when prescribed and improves patient compliance with medication. Figure 1.4 gives some examples of solid dosage forms (tablets and capsules) and solid dosage forms reconstituted with liquid (injection and oral suspension) prior to administration.



**FIGURE 1.4** Solid dosage forms (tablets and capsules) and solid dosage forms reconstituted with liquid (injection and oral suspension) prior to administration.

### Semisolid dosage forms

Semisolid dosage forms can exist as single-phase systems (the drug substance in solution in the semisolid material) or as more complex two-phase or multiphase systems. An example of a complex multiphase system is an oil in water emulsion with suspended solid particles. The majority of semisolid dosage forms are applied topically to skin or accessible mucous membranes such as the interior of the nose or rectum. If applied to open wounds or lesions, sterile semisolid dosage forms are required.

Semisolid dosage forms can be divided into a range of different types of preparations. Ointments consist of a waxy, hydrophobic semisolid base to which one or more drug substances can be dispersed or dissolved. Ointment bases are generally composed of hydrocarbons, fixed oil bases or silicones. The term ‘paste’ is used to describe an ointment in which a large percentage of solid material (20–50%) is dispersed.

Creams are semisolid dosage forms containing two or more phases. They consist of water droplets dispersed in an oil phase or oil droplets dispersed in a water phase. They can be classified as **emulsion** systems, which are discussed in greater detail in Chapters 5 and 6. The drug substance can be dispersed or dissolved in the cream base. Dissolved drug substance can be located in the oil phase, the aqueous phase or both phases of the cream.

Pharmaceutical **gels or jellies** are semisolid dosage forms composed of a liquid phase within a network structure of a solid gelling agent. It is the nature of the network of the gelling agent around the liquid phase that provides the gel with stiffness. Gelling agents can be small inorganic particles, such as aluminium hydroxide, or large organic molecules, polymers. When water is the liquid phase, gels are termed ‘hydrogels’. The drug substance can be dispersed or dissolved in the liquid phase in the gel system.

Rigid hydrogels with a low liquid content are referred to as **films**. More detail relating to pharmaceutical gels is given in Chapter 6.

Gel dosage forms can be designed with a particular shape and texture to facilitate administration of drug substances to specific body orifices such as the nose, ear, rectum or vagina. When administered vaginally they are termed **pessaries**; when administered rectally they are termed **suppositories**.

In addition to gel-based systems, other suppository bases can be used. Glyceride-type fatty bases release the drug substance by melting or softening at body temperature. Water-soluble bases release the drug substance by dissolving in the aqueous physiological fluids. The drug substance can be dispersed or dissolved in the suppository base.

Chewing gum can be used as a dosage form to facilitate oral drug delivery. As for confectionary chewing gum, pharmaceutical chewing gum consists of a sweetened and flavoured insoluble plastic material that liberates the drug substance when chewed in the oral cavity.

Modified release semisolid dosage forms can be designed if they contain dispersed solid drug substance with modified release properties. Alternatively, the viscosity and consistency of the semisolid dosage form can be modified to increase or decrease the rate of drug-substance release by modifying the diffusion rate of the drug substance through the semisolid carrier material. The factors that influence this diffusion rate are explained in more detail in Section 3.3.3.

### Liquid dosage forms

Compared to semisolid substances, liquids are pourable and conform to the shape of the container they are stored in at room temperature. **Pharmaceutical solutions** are liquid dosage forms that are clear, homogeneous and single-phase systems. They contain one or more drug substance dissolved in one or more solvents. While aqueous solutions are generally preferred for parenteral administration, oil based injections are also used.

Liquid dispersions are two-phase liquid systems. This means that they are composed of one phase dispersed throughout a second phase. The dispersed phase can be solid particles (ranging in size from nanometres to millimetres), **micelles**, **liposomes**, oil droplets (**oil in water emulsion**) and water droplets (**water in oil emulsion**). **Suspensions** are disperse systems containing the drug substance as solid particles suspended in a suitable liquid vehicle. The structure and characteristics of liquid dispersions are covered in more detail in Chapters 5 and 6. Modified release liquid dispersions can be designed by the inclusion of a solid disperse phase with modified release characteristics. **Foams** can also be classified as two-phase liquid dispersion as they consist of a gas phase dispersed within a liquid. Pharmaceutical foams are useful for the topical, rectal and vaginal delivery of drug substances.

Pharmaceutical solutions and dispersions can be supplied pre-prepared or to be prepared prior to administration by reconstitution with a suitable solvent or vehicle. Liquid dosage forms can be administered by all routes. Liquid dosage forms for parenteral administration are required to be sterile. In addition to sterility, liquid dosage forms for intravenous and intra-arterial administration are required to be free of particles greater than 5  $\mu\text{m}$ . Liquid dosage forms for topical administration must have a viscosity suitable for spreading over the area of administration. The sensory perception (taste and

**TABLE 1.4** Various terms used in relation to liquid dosage forms.

Term	Description	Route of administration
Lotion	liquid emulsion, non-greasy	for cutaneous administration
Elixir	liquid solution, clear, flavoured, may contain ethanol	for oral administration
Enema	liquid aqueous solution	for rectal administration
Irrigant	liquid sterile aqueous solution	for topical administration to bathe or flush open wounds or body cavities
Mouthwash	liquid aqueous solution	for oropharyngeal administration
Shampoo	liquid soap or detergent	for administration to the scalp, used as a vehicle for dermatologic agents
Paint	liquid solution or suspension	for cutaneous administration and less frequently to mucous membranes
Collodion	liquid solution of pyroxylin in ether and ethanol	for cutaneous administration, dries on the skin to form a flexible film at the site of administration
Linctus	liquid solution, viscous with high proportion of sucrose, other sugars or polyhydric alcohols	for oral administration in the treatment or relief of cough
Liniment	liquids solution	for cutaneous administration to the unbroken skin with friction

mouth feel) are critical considerations in the formulation of oral liquids. Table 1.4 lists terms commonly used in describing pharmaceutical liquid dosage forms.

Examples of some common liquid dosage forms are shown in Fig. 1.5.

### Gaseous dosage forms

Gaseous medical products consist of medical gases and aerosols. Medical gases are ideal for intrapulmonary administration via inhalation generally through a breathing apparatus. Medical gases do not require incorporation of the drug substance into a dosage form to facilitate administration. Aerosols also can be considered as gaseous dosage forms. In aerosols the gaseous phase is the vehicle for administration of the drug substance. Aerosols are stable dispersions of solid particles or liquid droplets in a gaseous medium.

Compared to other dosage forms, aerosols exhibit a high degree of physical instability with time. Therefore, aerosols are generated immediately prior to administration via an aerosol-generating device. The three primary aerosol-generating devices are **metered dose, dry powder inhalers**, and **nebulizers**. Metered dose aerosol devices are used for delivery topically to the skin, into the nose, mouth or lungs. Dry powder inhalers and nebulizers are used primarily for administration to the lungs. More detail in relation to aerosols is given in Chapter 6.



FIGURE 1.5 Some liquid dosage forms.

### 1.3.3 Factors influencing dosage form choice

The factors that influence the choice of dosage form for a particular drug substance include the patient type, illness type and drug substance's physicochemical properties. Let's consider each of these in turn.

#### Patient-type factors

Age, cognitive understanding of dosing regimen, consciousness and living conditions must be considered when selecting an appropriate dosage form. Elderly patients and children under the age of 6 years can have difficulties swallowing solid dosage forms. For these patients oral liquids, dispersible tablets and suppositories are preferable. A child's physiology undergoes development up to puberty. The organs and enzyme systems of children can function differently from those of healthy adults. During development, differences in the physiology of routes of administration, such as skin, lungs and gastrointestinal tract, can result in specific dosage form requirements for children compared to adults. The geriatric population will also exhibit differences in physiology due to aging that may require alterations in dosage forms compared to the younger healthy adults.

Visual impairment and arthritic conditions are common ailments of the elderly population and can complicate their self-administration of a number of dosage forms. Dosage forms that require a degree of manual dexterity and accurate vision, such as drawing up liquid to a set volume in a syringe, instillation of eye drops and use of metered

dose inhalers, may not be best choice of dosage forms for this patient group. Patients with cognitive impairment may have difficulties in complying with dosage regimes that require regular administration. In such cases, **extended release** dosage forms are often favoured. Sustained release intramuscular injections of fluphenazine decanoate, used in the treatment of schizophrenia, have a half-life of seven to ten days and therefore can be administered at two-week intervals. In situations where the patient is unconscious or in a coma, injections, infusions, transdermal patches or suppositories may be required to replace oral dosage forms.

It also should be considered as to whether the medication will be self-administered by the patient or administered by a carer or healthcare professional. Many dosage forms are relatively simple to administer but others require the patient to undergo a level of training or instruction to ensure correct administration. Patients should receive verbal or written instructions before administering drug substances using dosage forms such as inhalers, nebulizers, eye, nose, ear drops, sublingual tablets, suppositories and pessaries. There are a selection of dosage forms that must be administered by trained healthcare professionals. These include the majority of parenteral dosage forms, implants and drug-eluting devices.

### Illness-type factors

The type of illness that the drug substance is administered to treat or alleviate will also influence the choice of a suitable dosage form. For example, nitroglycerin is used in the treatment of chest pain due to ischaemic heart disease and is available in a range of dosage forms. The intravenous injection, sublingual tablet and spray dosage forms are recommended to treat chest pain and prevent chest pain caused by exertion because of their advantageous rapid onset of action (1–2 min). However, these preparations are unsuitable for long-term maintenance and prophylaxis due to their short duration of action. Nitroglycerin oral extended release tablets and transdermal patches are more suitable for these indications. While they have a slower onset of action, their duration of action is longer.

The severity of the illness or disease for which the drug substance is indicated can also influence the dosage form selected. Paclitaxel, a widely indicated anticancer agent, is formulated as a solution for intravenous injection. Due to its poor water solubility, Cremophor® EL, a non-ionic surfactant is incorporated in the dosage form as a solubility increasing agent. Cremophor® EL is associated with severe allergic reactions when administered intravenously. So severe and distressing is this allergic reaction that it is commonplace that patients are required to be administered steroids prior to administration of the paclitaxel injection to prevent the occurrence of an allergic reaction. These adverse effects may be tolerated in the treatment of cancer but it is difficult to imagine a patient tolerating them for a more minor ailment. For minor ailments the adverse effects experienced due to the dosage form might outweigh the relief achieved by its administration.

The vast proportion of oral dosage forms on the market compared to parenteral forms indicates patients' preference for oral dosage forms over the more invasive parenteral dosage forms. However, where an alternative effective oral dosage form is not available, patients will tolerate repeated daily subcutaneous injections, as is the case of insulin for the treatment of diabetes.

**TABLE 1.5** Physicochemical properties associated with poor absorption outlined in Lipinski's Rule of Five.

Property	Value
Molecular weight	Greater than 500
Partition coefficient $\text{Log } P_{\text{octanol/water}}$	Greater than 5
Number of H-bond donors	Greater than 5
Number of H-bond acceptors	Greater than 10

### Active pharmaceutical ingredient physicochemical properties

The physicochemical properties of the drug substance play a significant role in the choice of dosage form and route of administration. **Lipinski's Rule of Five** (ROF) was developed as a general guide to the physicochemical properties that can cause problems with respect to aqueous solubility in physiological fluids after release from the dosage form and permeability of biological barriers during absorption (Lipinski 2001). The rule states that problems with absorption can be avoided when any two of the four rules listed in Table 1.5 are avoided. The explanation of why these problems occur will be explored in more detail in Chapters 2, 7 and 8.

The Rule of Five is a useful general guide to identifying compounds with API-like properties: aqueous solubility, permeability and chemical and enzymatic stability. It does not address the specific differences in physicochemical requirements for compounds delivered by different routes of delivery to various sites in the body, i.e. across the blood brain barrier or to the lungs. The physicochemical requirements of individual routes are dealt with in greater detail in Chapter 7. The suboptimal physicochemical properties of the active pharmaceutical ingredient can be altered or compensated for by intelligent dosage form design. Simple examples would be in the inclusion of surfactants to increase the solubility of poorly soluble drug substances and more sophisticated approaches would include liposomal formulations detailed in Chapter 6. The remaining chapters of this book will highlight the theory behind these physicochemical properties and how these influence dosage form design, manufacture and performance.

## 1.4 SUMMARY

- Pharmaceuticals are the chemical constituents of medicines. Pharmaceuticals can be divided into two categories: active pharmaceutical ingredients (APIs) and excipients. APIs are the actual drug substances that give medicines their therapeutic properties. The main classes of APIs are psychopharmacological agents, pharmacodynamic agents, chemotherapeutic agents, and agents acting on metabolic diseases and endocrine function. The majority of APIs are organic compounds. Many contain one or more cyclic systems in their molecular structures. They also often contain polar functional groups.

- Excipients are the chemical components of medicines other than APIs. They are combined with the API to make dosage forms, or medicines, which can deliver the API to the required site of action in the body. The excipients may act as diluents, surfactants, lubricants, disintegrants, viscosity enhancers, or binders.
- Dosage forms may be administered to the patient by a variety of routes of administration. These include administration by the mouth (oral), by the surface of the body (topical) and by other routes. Delivery may be local or systemic. Types of dosage form include ointments, creams, gels, capsules, granules, beads, pellets and tablets. Two-phase dosage forms include micelles, liposomes, foams and suspensions. The choice of dosage form may depend on patient factors and illness factors.
- The key physical and chemical properties of importance for the activity of pharmaceutical compounds are known as their physicochemical properties.

## REFERENCES

- FDA (Food and Drug Administration). (2004). Innovation or stagnation: Challenge and opportunity on the critical path to new medical products.
- Lipinski, C. A. *et al.* (2001). *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings*. *Advanced Drug Delivery Review*, 46, 3–26.

## FURTHER READING

- Aulton M. E. (ed.) (2002). *Pharmaceutics, the science of dosage form design* (2nd edn). Edinburgh: Churchill Livingstone.
- Florence, A. T. and Attwood, D. (2006). *Physicochemical principles of pharmacy* (4th edn). London: Pharmaceutical Press.
- Patrick, G. L. (2005). *An Introduction to Medicinal Chemistry* (3rd edn). Oxford: Oxford University Press.