PART THREE

BIOPHARMACEUTICAL PRINCIPLES OF DRUG DELIVERY

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15
Introduction to biopharmaceutics

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CHAPTER CONTENTS

WHAT IS BIOPHARMACEUTICS?

Biopharmaceutics can be defined as the study of how the physicochemical properties of drugs, dosage forms and routes of administration affect the rate and extent of drug absorption.

The relationship between the drug, its dosage form and the route by which it is administered governs how much of the drug and how fast it enters the systemic circulation. For a drug to be effective, enough of it needs to reach its site(s) of action and stay there long enough to be able to exert its pharmacological effect. This depends upon the route of administration, the form in which it is administered and the rate at which it is delivered.

Background

Apart from the intravenous route, where a drug is introduced directly into the bloodstream, all other routes of administration where a systemic action is required, involve the absorption of the drug into the blood from the route of administration. Once the drug reaches the bloodstream it partitions between the plasma and the red blood cells, the erythrocytes. Drug in the plasma partitions between the plasma proteins (mainly albumin) and the plasma water. It is this free or unbound drug in plasma water, and not the drug bound to the proteins, that can pass out of the plasma through the capillary endothelium and reach other body fluids and tissues and hence the site(s) of action.

A dynamic equilibrium exists between the concentration of the drug in the blood plasma and the drug at its site(s) of action. This is termed ***distribution***, the degree of which will depend largely on the physicochemical properties of the drug, in particular its lipophilicity. As it is often difficult to access the drug at its site(s) of action, its concentration in the plasma is often taken as a surrogate for its concentration at its

site(s) of action. Even though the unbound drug in the plasma would give a better estimate of the concentration of the drug at its site(s) of action, this requires a much more complex and sensitive assay than a measurement of the total concentration of the drug (i.e. the sum of the bound and unbound drug) within the blood plasma. Thus it is this total drug concentration within the plasma that is usually measured for clinical purposes. Therefore, plasma protein binding is a critical parameter to consider when investigating the therapeutic effect of a drug molecule.

The concentration of the drug in blood plasma depends on numerous factors. These include the amount of an administered dose that is ***absorbed*** and reaches the systemic circulation; the extent of ***distribution*** of the drug between the systemic circulation and other tissues and fluids (which is usually a rapid and reversible process); and the rate of ***elimination*** of the drug from the body. The drug can either be eliminated unchanged or be enzymatically cleaved or biochemically transformed, in which case it is said to have been ***metabolized***. The study and characterization of the time course of drug **a**bsorption, **d**istribution, **m**etabolism and **e**limination (ADME) is termed ***pharmacokinetics***. Pharmacokinetics is used in the clinical setting to enhance the safe and effective therapeutic management of individual patients.

Figure 15.1 illustrates some of the factors that can influence the concentration of the drug in the blood plasma and also at its site(s) of action. Biopharmaceutics is concerned with the first stage, getting the drug from its route of administration to the blood.

THE CONCEPT OF BIOAVAILABILITY

If a drug is given intravenously it is administered directly into the blood, and therefore we can be sure that all the drug reaches the systemic circulation. The drug is therefore said to be 100% ***bioavailable***. However, if a drug is given by another route there is no guarantee that the whole dose will reach the systemic circulation intact. The fraction of an administered dose of the drug that reaches the systemic circulation in the unchanged form is known as the ***bioavailable dose***. The relative amount of an administered dose of a particular drug that reaches the systemic circulation intact and the rate at which this occurs is known as the ***bioavailability***. Bioavailability is therefore defined as the rate and extent of drug absorption. The bioavailability exhibited by a drug is thus very important in determining whether a therapeutically effective concentration will be achieved at the site(s) of action.

In defining bioavailability in these terms it is assumed that the intact drug is the therapeutically active form. This definition would not be valid in the

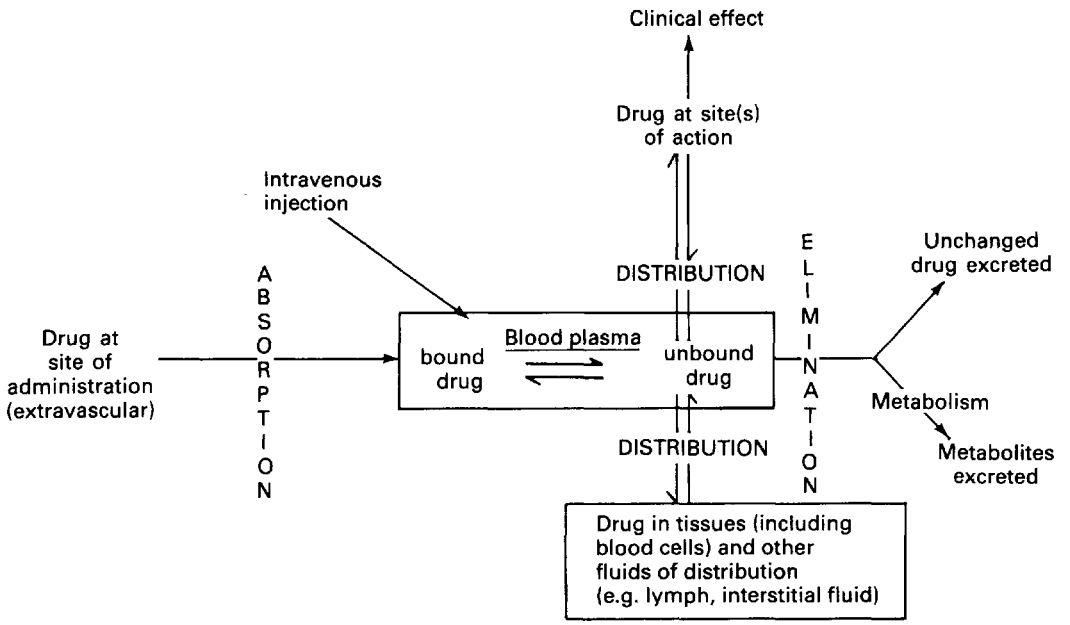


Fig. 15.1 Schematic representation of drug absorption, distribution and elimination.

case of prodrugs, whose therapeutic action normally depends on their being converted into a therapeutically active form prior to or on reaching the systemic circulation. It should also be noted that, in the context of bioavailability, the term systemic circulation refers primarily to venous blood (excluding the hepatic portal vein, which carries blood from the gastrointestinal tract to the liver in the absorption phase) and the arterial blood, which carries the intact blood to the tissues.

Therefore, for a drug which is administered orally to be 100% bioavailable, the entire dose must move from the dosage form to the systemic circulation. The drug must therefore be:

- completely released from the dosage form
- fully dissolved in the gastrointestinal fluids.
- stable in solution in the gastrointestinal fluids
- pass through the gastrointestinal barrier into the mesenteric circulation without being metabolized
- pass through the liver into the systemic circulation unchanged.

Anything which adversely affects either the release of the drug from the dosage form, its dissolution into the gastrointestinal fluids, its permeation through and stability in the gastrointestinal barrier or its stability in the hepatic portal circulation will influence the bioavailability exhibited by that drug from the dosage form in which it was administered.

THE CONCEPT OF BIOPHARMACEUTICS

Many factors have been found to influence the rate and extent of absorption, and hence the time course of a drug in the plasma and therefore at its site(s) of action. These include the foods eaten by the patient, the effect of the disease state on drug absorption, the age of the patient, the site(s) of absorption of the administered drug, the coadministration of other drugs, the physical and chemical properties of the administered drug, the type of dosage form, the composition and method of manufacture of the dosage form, the size of the dose and the frequency of administration.

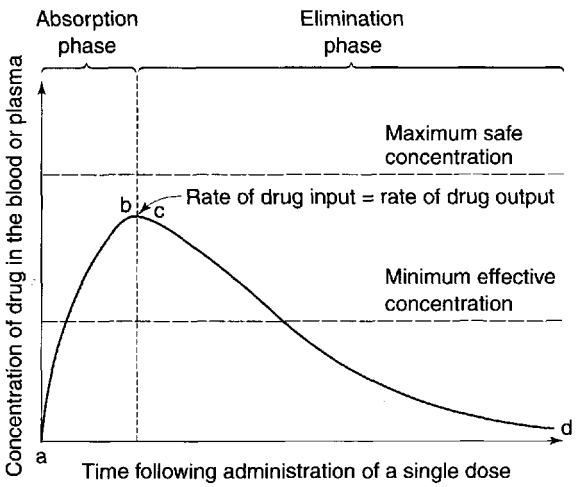
Thus, a given drug may exhibit differences in its bioavailability if it is administered:

- in the same type of dosage form by different routes of administration, e.g. an aqueous solution of a given drug administered by the oral and intramuscular routes;
- by the same routes of administration but different types of dosage form, e.g. a tablet, a hard gelatin capsule and an aqueous suspension administered by the peroral route;
- in the same type of dosage form by the same route of administration but with different formulations of the dosage form, e.g. different formulations of an oral aqueous suspensions.

Variability in the bioavailability exhibited by a given drug from different formulations of the same type of dosage form, or from different types of dosage forms, or by different routes of administration, can cause the plasma concentration of the drug to be too high and therefore cause side effects, or too low and therefore the drug will be ineffective. Figure 15.2 shows the plasma concentration–time curve following a single oral dose of a drug, indicating the parameters associated with a therapeutic effect.

Poor biopharmaceutical properties often result in:

- poor and variable bioavailability
- difficulties in toxicological evaluation
- difficulties with bioequivalence of formulations
- multi-daily dosing
- the requirement for a non-conventional delivery system
- long and costly development times.



a–b rate of drug absorption > rate of drug elimination
c–d rate of drug elimination > rate of drug absorption

Fig. 15.2 A typical blood plasma concentration–time curve obtained following the peroral administration of a single dose of a drug in a tablet.

CONCLUDING COMMENTS

The following chapters (Chapters 16 and 17) deal in more detail with the physiological factors, dosage form factors and intrinsic properties of drugs that influence the rate and extent of absorption. Chapter 18 looks at means of assessing the biopharmaceutical properties of compounds.

A thorough understanding of the biopharmaceutical properties of a candidate drug are important both in the discovery setting, where potential drug candidates are being considered, and in the development setting, where it is important to anticipate formulation problems and assess whether the drug is a candidate for a controlled-release formulation.

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The gastrointestinal tract – physiology and drug absorption

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CHAPTER CONTENTS

The factors that influence the rate and extent of absorption depend upon the route of administration. As stated in Chapter 15, the intravenous route offers direct access to the systemic circulation and the total dose administered via this route is available in the plasma for distribution into other body tissues and the site(s) of action of the drug. Other routes will require an absorption step before the drug reaches the systemic circulation. Factors affecting this absorption will depend on the physiology of the administration site(s) and the membrane barriers present at those site(s), that the drug needs to cross in order to reach the systemic circulation. A summary of some of the properties of each route of administration is given in Chapter 1.

The GI tract is discussed in detail in this chapter and a detailed description of the physiology of some of the other more important routes of administration is given in Part 4. The oral route of delivery is by far the most popular, mainly because it is natural and convenient for the patient and because it is relatively easy to manufacture oral dosage forms. Oral dosage forms do not need to be sterilized, are compact, and can be produced in large quantities by automated machines. This chapter and the next will therefore be confined to discussing the biopharmaceutical factors (that is, physiological, dosage form and drug factors) that influence oral drug absorption.

PHYSIOLOGICAL FACTORS INFLUENCING ORAL DRUG ABSORPTION

The gastrointestinal tract is complex. Figure 16.1 shows a diagram of the gastrointestinal tract, outlining some of the key structures involved in and key physiological parameters that affect oral drug absorption. In order to gain an insight into the numerous factors that can potentially influence the

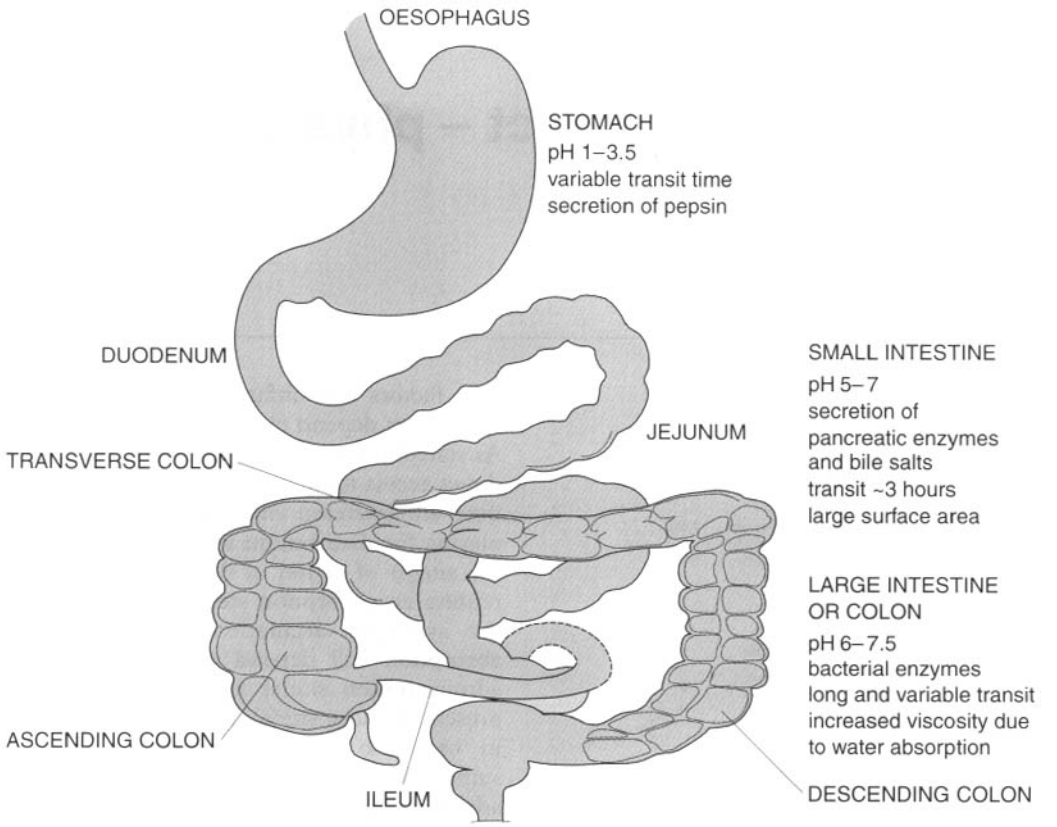

Fig. 16.1 The gastrointestinal tract.

rate and extent of drug absorption into the systemic circulation, a schematic illustration of the steps involved in the release and absorption of a drug from a tablet dosage form is presented in Figure 16.2. It can be seen from this that the rate and extent of appearance of intact drug in the systemic circulation depends on a succession of kinetic processes.

The slowest step in this series, which is known as the ***rate-limiting step***, controls the overall rate and extent of appearance of intact drug in the systemic circulation. The particular rate-limiting step will vary from drug to drug. For a drug which has a very poor aqueous solubility the rate at which it dissolves in the gastrointestinal fluids is often the slowest step, and the bioavailability of that drug is said to be ***dissolution-rate limited***. In contrast, for a drug that has a high aqueous solubility its dissolution will be rapid and the rate at which the drug crosses the gastrointestinal membrane may be the rate-limiting step (permeability limited). Other potential rate-limiting steps include the rate of release of the drug from the dosage form (this can be by design in the case of controlled-release dosage forms), the rate at which the stomach empties the drug into the small intestine, the rate at which the drug is metabolized by enzymes in the intestinal mucosal cells during its passage through them into the mesenteric blood vessels, and the rate of metabolism of drug during its initial passage through the liver, often termed the ***'first-pass' effect***.

PHYSIOLOGY OF THE GASTROINTESTINAL TRACT

The gastrointestinal tract is a muscular tube approximately 6 m in length with varying diameters. It stretches from the mouth to the anus and consists of four main anatomical areas: the oesophagus, the stomach, the small intestine and the large intestine or colon. The luminal surface of the tube is not smooth but very rough, thereby increasing the surface area for absorption.

The wall of the gastrointestinal tract is essentially similar in structure along its length, consisting of four principal histological layers (Fig. 16.3):

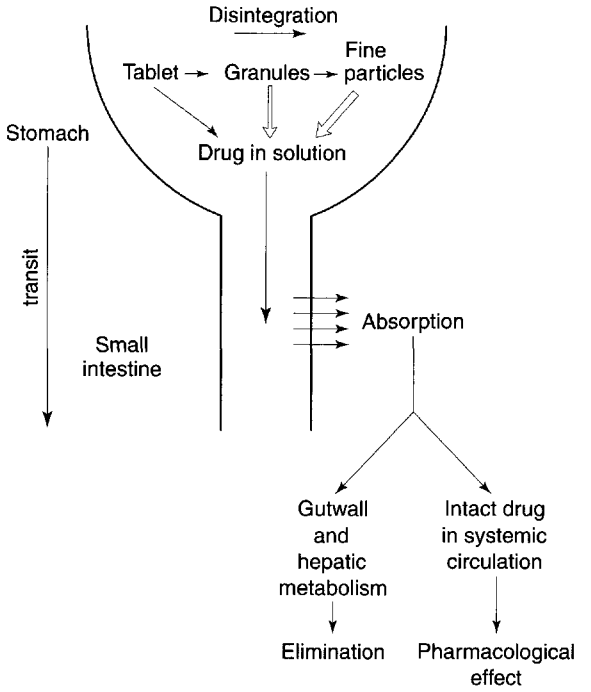

Fig. 16.2 Steps involved prior to a pharmacological effect after administration of a rapidly disintegrating tablet.

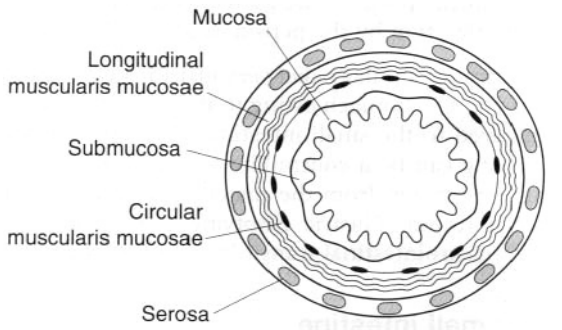

Fig. 16.3 Cross-section through the gastrointestinal tract.

1. The serosa, which is an outer layer of epithelium and supporting connective tissue;
2. The muscularis externa, which contains two layers of smooth muscle tissue, a thinner outer layer which is longitudinal in orientation, and a thicker inner layer, whose fibres are oriented in a circular pattern. Contractions of these muscles provide the forces for movement of gastrointestinal contents;
3. The submucosa, which is a connective tissue layer containing some secretory tissue and which is richly supplied with blood and lymphatic vessels. A network of nerve cells, known as the submucous plexus, is also located in this layer;
4. The mucosa, which is essentially composed of three layers, the muscularis mucosa, which can alter the local conformation of the mucosa, a layer of connective tissue known as the lamina propria, and the epithelium.

The majority of the gastrointestinal epithelium is covered by a layer of mucus. This is a viscoelastic translucent aqueous gel that is secreted throughout the gastrointestinal tract, acting as a protective layer and a mechanical barrier. Mucus is a constantly changing mix of many secretions and exfoliated epithelial cells. It has a large water component (~95%). Its other primary components, which are responsible for its physical and functional properties, are large glycoproteins called mucins. Mucins consist of a protein backbone approximately 800 amino acids long and oligosaccharide side chains that are typically up to 18 residues in length.

The mucus layer ranges in thickness from 5 μm to 500 μm along the length of the gastrointestinal tract, with average values of around 80 μm. The layer is thought to be continuous in the stomach and duodenum, but may not be so in the rest of the small and large intestines.

Mucus is constantly being removed from the luminal surface of the gastrointestinal tract through abrasion and acidic and enzymatic breakdown, and is continually replaced from beneath. Turnover time has been estimated at 4–5 hours, but this may well be an underestimate and is liable to vary along the length of the tract.

The oesophagus

The mouth is the point of entry for most drugs (so-called peroral – via the mouth – administration). At this point contact with the oral mucosa is usually brief. Linking the oral cavity with the stomach is the oesophagus. This is composed of a thick muscular layer approximately 250 mm long and 20 mm in diameter. It joins the stomach at the gastro-oesophageal junction, or cardiac orifice as it is sometimes known.

The oesophagus, apart from the lowest 20 mm which is similar to the gastric mucosa, contains a well differentiated squamous epithelium of non-proliferative cells. Epithelial cell function is mainly protective: simple mucous glands secrete mucus into the narrow lumen to lubricate food and protect the lower part of the oesophagus from gastric acid. The pH of the oesophageal lumen is usually between 5 and 6.

Materials are moved down the oesophagus by the act of swallowing. After swallowing, a single peristaltic

wave of contraction, its amplitude linked to the size of the material being swallowed, passes down the length of the oesophagus at the rate of 20–60 mm per second, speeding up as it progresses. When swallowing is repeated in quick succession, the subsequent swallows interrupt the initial peristaltic wave and only the final wave proceeds down the length of the oesophagus to the gastrointestinal junction, carrying material within the lumen with it. Secondary peristaltic waves occur involuntarily in response to any distension of the oesophagus and serve to move sticky lumps of material or refluxed material to the stomach. In the upright position the transit of materials through the oesophagus is assisted by gravity. The oesophageal transit of dosage forms is extremely rapid, usually of the order of 10–14 seconds.

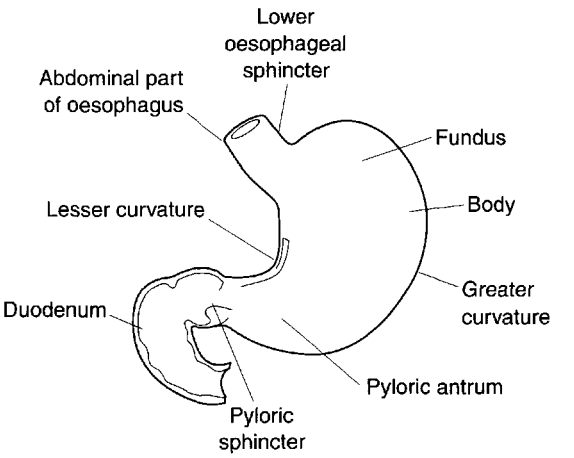

Fig. 16.4 The anatomy of the stomach.

The stomach

The next part of the gastrointestinal tract to be encountered by both food and pharmaceuticals is the stomach. The two major functions of the stomach are:

- to act as a temporary reservoir for ingested food and to deliver it to the duodenum at a controlled rate;
- to reduce ingested solids to a uniform creamy consistency, known as chyme, by the action of acid and enzymatic digestion. This enables better contact of the ingested material with the mucous membrane of the intestines and thereby facilitates absorption.

Another, perhaps less obvious, function of the stomach is its role in reducing the risk of noxious agents reaching the intestine.

The stomach is the most dilated part of the gastrointestinal tract and is situated between the lower end of the oesophagus and the small intestine. Its opening to the duodenum is controlled by the pyloric sphincter. The stomach can be divided into four anatomical regions (Fig. 16.4), namely the fundus, the body, the antrum and the pylorus.

The stomach has a capacity of approximately 1.5 L, although under fasting conditions it usually contains no more than 50 mL of fluid, which is mostly gastric secretions. These include:

- acid secreted by the parietal cells, which maintains the pH of the stomach between 1 and 3.5 in the fasted state;
- the hormone gastrin, which itself is a potent stimulator of gastric acid production. The release of gastrin is stimulated by peptides, amino acids and distension of the stomach;
- pepsins, which are secreted by the peptic cells in the form of its precursor pepsinogen. Pepsins are peptidases which break down proteins to peptides at low pH. Above pH 5 pepsin is denatured;
- mucus, which is secreted by the surface mucosal cells and lines the gastric mucosa. In the stomach the mucus protects the gastric mucosa from autodigestion by the pepsin–acid combination.

Contrary to popular belief very little drug absorption occurs in the stomach owing to its small surface area compared to the small intestine. The rate of gastric emptying can be a controlling factor in the onset of drug absorption from the major absorptive site, the small intestine. Gastric emptying will be discussed under gastrointestinal transit later in this chapter.

The small intestine

The small intestine is the longest (4–5 m) and most convoluted part of the gastrointestinal tract, extending from the pyloric sphincter of the stomach to the ileocaecal junction where it joins the large intestine. Its main functions are:

- digestion: the process of enzymatic digestion, which began in the stomach, is completed in the small intestine.
- absorption: the small intestine is the region where most nutrients and other materials are absorbed.

The small intestine is divided into the duodenum, which is 200–300 mm in length, the jejunum, which is approximately 2 m in length, and the ileum, which is approximately 3 m in length.

The wall of the small intestine has a rich network of both blood and lymphatic vessels. The gastrointestinal circulation is the largest systemic regional vasculature and nearly a third of the cardiac output flows through the gastrointestinal viscera. The blood vessels of the small intestine receive blood from the superior mesenteric artery via branched arterioles. The blood leaving the small intestine flows into the hepatic portal vein, which carries it via the liver to the systemic circulation. Drugs that are metabolized by the liver are degraded before they reach the systemic circulation: this is termed hepatic presystemic clearance, or first-pass metabolism.

The wall of the small intestine also contains lacteals, which contain lymph and are part of the lymphatic system. The lymphatic system is important in the absorption of fats from the gastrointestinal tract. In the ileum are areas of lymphoid tissue close to the epithelial surface which are known as Peyer's patches. These cells play a key role in the immune response as they transport macromolecules and are involved in antigen uptake.

The surface area of the small intestine is increased enormously, by about 600 times that of a simple cylinder, to approximately 200 m^2 in an adult, by several adaptations which render the small intestine such a good absorption site:

- Folds of Kerckring: these are submucosal folds which extend circularly most of the way around the intestine and are particularly well developed in the duodenum and jejunum. They are several millimetres in depth.
- Villi: these have been described as finger-like projections into the lumen (approximately 0.5–1.5 mm in length and 0.1 mm in diameter). They are well supplied with blood vessels. Each villus contains an arteriole, a venule and a blind-ending lymphatic vessel (lacteal). The structure of a villus is shown in Figure 16.5.
- Microvilli: approximately 600–1000 of these brush-like structures (~ 1 μm in length and 0.1 μm in width) cover each villus, providing the largest increase in surface area. These are covered by a fibrous substance known as glycocalyx.

The luminal pH of the small intestine increases to between about 6 and 7.5. The sources of the secretions that produce these pH values in the small intestine are:

- Brunner's glands, which are located in the duodenum and are responsible for the secretion of bicarbonate which neutralizes the acid emptied from the stomach;

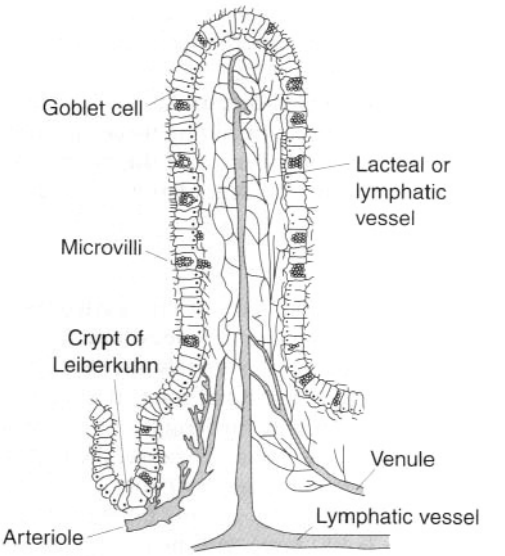

Fig. 16.5 Structure of a villus.

- intestinal cells, which are present throughout the small intestine and secrete mucus and enzymes. The enzymes, hydrolases and proteases, continue the digestive process;
- pancreatic secretions. The pancreas is a large gland which secretes about 1–2 L of pancreatic juice per day into the small intestine via a duct. The components of pancreatic juice are sodium bicarbonate and enzymes. The enzymes consist of proteases, principally trypsin, chymotrypsin and carboxypeptidases, which are secreted as inactive precursors or zymogens and converted to their active forms in the lumen by the enzyme enterokinase. Lipase and amylase are both secreted in their active forms. The bicarbonate component is largely regulated by the pH of chyme delivered into the small intestine from the stomach;
- bile, which is secreted by hepatocytes in the liver into bile canaliculi, concentrated in the gallbladder and hepatic biliary system by the removal of sodium ions, chloride and water, and delivered to the duodenum. Bile is a complex aqueous mixture of organic solutes (bile acids, phospholipids, particularly lecithin, cholesterol and bilirubin) and inorganic compounds (plasma electrolytes; sodium and potassium). Bile pigments, the most important of which is bilirubin, are excreted in the faeces, but the bile acids are absorbed by an active process in the terminal ileum. They are returned to the liver via the hepatic portal vein and, as they have a high

hepatic clearance, are resecreted in the bile. This process is known as enterohepatic recirculation. The main functions of the bile are promoting the efficient absorption of dietary fat, such as fatty acids and cholesterol, by aiding its emulsification and micellar solubilization, and the provision of excretory pathways for degradation products.

The colon

The colon is the final part of the gastrointestinal tract. It stretches from the ileocaecal junction to the anus and makes up approximately the last 1.5 m of the 6 m of the gastrointestinal tract. It is composed of the caecum (~85 mm in length), the ascending colon (~200 mm), the hepatic flexure, the transverse colon (usually greater than 450 mm), the splenic flexure, the descending colon (~300 mm), the sigmoid colon (~400 mm) and the rectum, as shown in Figure 16.6. The ascending and descending colons are relatively fixed, as they are attached via the flexures and the caecum. The transverse and sigmoid colons, however, are much more flexible.

The colon, unlike the small intestine has no specialized villi. However, the microvilli of the absorptive epithelial cells, the presence of crypts, and the irregularly folded mucosae serve to increase the surface area of the colon by 10–15 times that of a simple cylinder. The surface area nevertheless remains approximately 1/30th that of the small intestine.

The main functions of the colon are:

- the absorption of sodium ions, chloride ions and water from the lumen in exchange for bicarbonate and potassium ions. Thus the colon has a significant homeostatic role in the body.
- the storage and compaction of faeces.

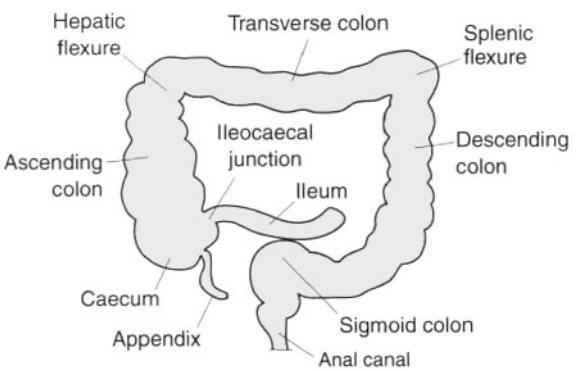

Fig. 16.6 The anatomy of the colon.

The colon is permanently colonized by an extensive number (about 10^{12} per gram of contents) and variety of bacteria. This large bacterial mass is capable of several metabolic reactions, including hydrolysis of fatty acid esters and the reduction of inactive conjugated drugs to their active form. The bacteria rely upon undigested polysaccharides in the diet and the carbohydrate components of secretions such as mucus for their carbon and energy sources. They degrade the polysaccharides to produce short-chain fatty acids (acetic, proprionic and butyric acids), which lower the luminal pH, and the gases hydrogen, carbon dioxide and methane. Thus the pH of the caecum is around 6–6.5. This increases to around 7–7.5 towards the distal parts of the colon.

Recently there has been much interest in the exploitation of the enzymes produced by these bacteria with respect to targeted drug delivery to this region of the gastrointestinal tract.

THE TRANSIT OF PHARMACEUTICALS IN THE GASTROINTESTINAL TRACT

As the oral route is the one by which the majority of pharmaceuticals are administered, it is important to know how these materials behave during their passage through the gastrointestinal tract. It is known that the small intestine is the major site of drug absorption, and thus the time a drug is present in this part of the gastrointestinal tract is extremely significant. If sustained- or controlled-release drug delivery systems are being designed, it is important to consider factors that will affect their behaviour and, in particular, their transit times through certain regions of the gastrointestinal tract.

In general, most dosage forms, when taken in an upright position, transit through the oesophagus quickly, usually in less than 15 seconds. Transit through the oesophagus is dependent both upon the dosage form and posture.

Tablets/capsules taken in the supine position, especially if taken without water, are liable to lodge in the oesophagus. Adhesion to the oesophageal wall can occur as a result of partial dehydration at the site of contact and the formation of a gel between the formulation and the oesophagus. The chances of adhesion will depend on the shape, size and type of formulation. Transit of liquids, for example, has always been observed to be rapid, and in general faster than that of solids. A delay in reaching the stomach may well delay a drug's onset of action or

cause damage or irritation to the oesophageal wall, e.g. potassium chloride tablets.

Gastric emptying

The time a dosage form takes to traverse the stomach is usually termed the ***gastric residence time, gastric emptying time*** or ***gastric emptying rate***.

Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence times usually range between 5 minutes and 2 hours, although much longer times (over 12 hours) have been recorded, particularly for large single units. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle, or migrating myoelectric complex (MMC) as it is known – governs its activity and hence the transit of dosage forms. It is characterized by a repeating cycle of four phases.

Phase I is a relatively inactive period of 40–60 minutes with only rare contractions occurring. Increasing numbers of contractions occur in phase II, which has a similar duration to phase I. Phase III is characterized by powerful peristaltic contractions which open the pylorus at the base and clear the stomach of any residual material. This is sometimes called the ***housekeeper wave***. Phase IV is a short transitional period between the powerful activity of phase III and the inactivity of phase I. The cycle repeats itself every 2 hours until a meal is ingested and the fed state or motility is initiated. In this state, two distinct patterns of activity have been observed. The proximal stomach relaxes to receive food and gradual contractions of this region move the contents distally. Peristalsis – contractions of the distal stomach – serve to mix and break down food particles and move them towards the pyloric sphincter. The pyloric sphincter allows liquids and small food particles to empty while other material is retropulsed into the antrum of the stomach and caught up by the next peristaltic wave for further size reduction before emptying.

Thus in the fed state liquids, pellets and disintegrated tablets will tend to empty with food, yet large sustained or controlled release dosage forms can be retained in the stomach for long periods of time. In the fasted state the stomach is less discriminatory between dosage form types, with emptying appearing to be an exponential process and being related to the point in the MMC at which the formulation is ingested.

Many factors influence gastric emptying, as well as the type of dosage form and the presence of food: these include the postural position, the composition of the food, the effect of drugs and disease state. In general, food, particularly fatty foods, delays gastric emptying and hence the absorption of drugs. Therefore, a drug will reach the small intestine most rapidly if it is administered with water to a patient whose stomach is empty. Metoclopramide, which is a drug that increases gastric emptying rate, has been shown to increase the rate of absorption of paracetamol, whereas propranthelline, a drug which delays gastric emptying, has been shown to delay its rate of absorption (Nimmo et al 1973).

Small intestinal transit

There are two main types of intestinal movement, propulsive and mixing. The propulsive movements primarily determine the intestinal transit rate and hence the residence time of the drug or dosage form in the small intestine. As this is the main site of absorption in the gastrointestinal tract for most drugs, the small intestinal transit time (that is, the time of transit between the stomach and the caecum) is an important factor with respect to drug bioavailability.

Small intestinal transit has been found to be relatively constant, at around 3 hours. In contrast to the stomach, the small intestine does not discriminate between solids and liquids, and hence between dosage forms, or between the fed and the fasted state.

Small intestinal residence time is particularly important for dosage forms that release their drug slowly (e.g. controlled- sustained- prolonged-release systems) as they pass along the length of the gastrointestinal tract; enteric-coated dosage forms which release drug only when they reach the small intestine; drugs that dissolve slowly in intestinal fluids; and drugs that are absorbed by intestinal carrier-mediated transport systems.

Colonic transit

The colonic transit of pharmaceuticals is long and variable and depends on the type of dosage form, diet, eating pattern and disease state.

Contractile activity in the colon can be divided into two main types:

- Propulsive contractions or mass movements, which are associated with the aboral (away from the mouth) movement of contents;
- Segmental or haustral contractions, which serve to mix the luminal contents and result in only small aboral movements. Segmental contractions are brought about by contraction of the circular

muscle and predominate, whereas the propulsive contractions, which are due to contractions of the longitudinal muscle, occur only 3–4 times daily in normal individuals.

Colonic transit is thus characterized by short bursts of activity followed by long periods of stasis. Movement is mainly aboral, i.e. towards the anus. Colonic transit can vary from anything between 2 and 48 hours. In most individuals mouth-to-anus transit times are longer than 24 hours.

BARRIERS TO DRUG ABSORPTION

Some of the barriers to absorption that a drug may encounter once it is released from its dosage form and has dissolved into the gastrointestinal fluids are shown in Figure 16.7. The drug needs to remain in solution and not become bound to food or other material within the gastrointestinal tract. It needs to be chemically stable in order to withstand the pH of the gastrointestinal tract, and it must be resistant to enzymatic degradation in the lumen. The drug then needs to diffuse across the mucous layer, without binding to it, across the unstirred water layer, and subsequently across the gastrointestinal membrane, its main cellular barrier. After passing through this cellular barrier the drug encounters the liver before it reaches the systemic circulation. Any of these barriers can prevent some or all of the drug reaching the systemic circulation, and can therefore have a detrimental effect on its bioavailability.

The environment within the lumen

The environment within the lumen of the gastrointestinal tract has a major effect on the rate and extent of drug absorption.

Gastrointestinal pH

The pH of fluids varies considerably along the length of the gastrointestinal tract. Gastric fluid is highly acidic, normally exhibiting a pH within the range 1–3.5 in healthy people in the fasted state. Following the ingestion of a meal the gastric juice is buffered to a less acidic pH, which is dependent on meal composition. Typical gastric pH values following a meal are in the range 3–7. Depending on meal size the gastric pH returns to the lower fasted-state values within 2–3 hours. Thus only a dosage form ingested with or soon after a meal will encounter these higher pH values. This may be an important consideration in terms of the chemical stability of a drug, or in achieving drug dissolution or absorption.

Intestinal pH values are higher than gastric pH values owing to the neutralization of the gastric acid with bicarbonate ions secreted by the pancreas into the small intestine. There is a gradual rise in pH along the length of the small intestine from the duo-

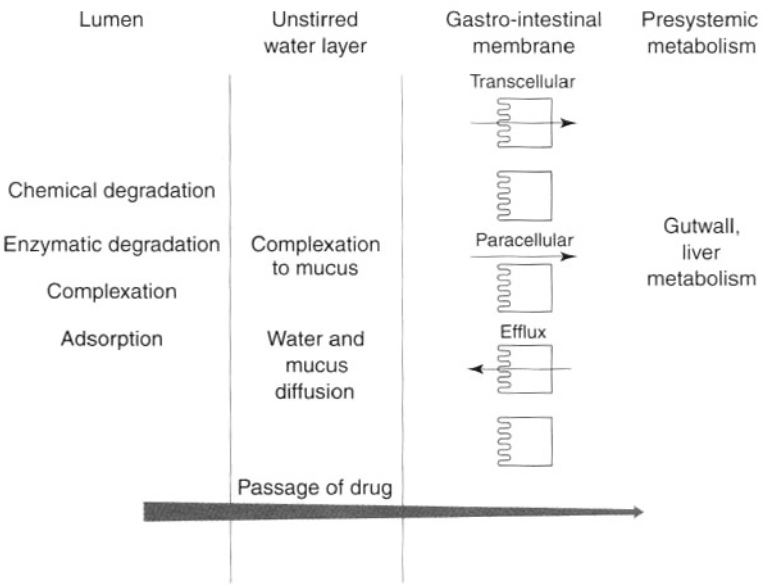

Fig. 16.7 Barriers to absorption.

Table 16.1 pH in the small intestine in healthy humans in the fasted and fed states

Location	Fasted state pH	Fed state pH
Mid-distal duodenum	4.9	5.2
	6.1	5.4
	6.3	5.1
	6.4	
Jejunum	4.4–6.5	5.2–6.0
	6.6	6.2
Ileum	6.5	6.8–7.8
	6.8–8.0	6.8–8.0
	7.4	7.5

Data from Gray and Dressman 1996.

denum to the ileum. Table 16.1 summarizes some of the literature values recorded for small intestinal pH in the fed and fasted states. The pH drops again in the colon, as the bacterial enzymes, which are localized in the colonic region, break down undigested carbohydrates into short-chain fatty acids; this lowers the pH in the colon to around 6.5.

The gastrointestinal pH may influence the absorption of drugs in a variety of ways. It may influence the chemical stability of the drug in the lumen, its dissolution or its absorption, if the drug is a weak electrolyte.

Chemical degradation due to pH-dependent hydrolysis can occur in the gastrointestinal tract. The result of this instability is incomplete bioavailability, as only a fraction of the administered dose reaches the systemic circulation in the form of intact drug. The extent of degradation of penicillin G (benzylpenicillin), the first of the penicillins, after oral administration depends on its residence time in the stomach and gastric pH. This gastric instability tends to preclude its oral use. The antibiotic erythromycin and proton pump inhibitors (e.g. omeprazole) degrade rapidly at acidic pH values and therefore have to be formulated as enteric-coated dosage forms to ensure good bioavailability (see Chapter 17).

The effects of pH on the drug dissolution and absorption processes are also discussed in Chapter 17.

Luminal enzymes

The primary enzyme found in gastric juice is pepsin. Lipases, amylases and proteases are secreted from the pancreas into the small intestine in response to ingestion of food. These enzymes are responsible for most of nutrient digestion. Pepsins and the proteases are responsible for the degradation of protein and peptide drugs in the lumen. Other drugs that resemble nutrients, such as nucleotides and fatty acids, may also be susceptible to enzymatic degradation. The lipases may also affect the release of drugs from fat/oil-containing dosage forms. Drugs that are esters can also be susceptible to hydrolysis in the lumen.

Bacteria, which are mainly localized within the colonic region of the gastrointestinal tract, also secrete enzymes which are capable of a range of reactions. These enzymes have been utilized when designing drugs or dosage forms to target the colon. Sulphasalazine, for example, is a prodrug of 5-aminosalicylic acid linked via an azo bond to sulphapyridine. The sulphapyridine moiety makes the drug too large and hydrophilic to be absorbed in the upper gastrointestinal tract, and thus permits its transport intact to the colonic region, where the bacterial enzymes reduce the azo bond and release the active drug, 5-aminosalycylic acid, for local action in colonic diseases such as inflammatory bowel disease.

Influence of food in the gastrointestinal tract

The presence of food in the gastrointestinal tract can influence the rate and extent of absorption, either directly or indirectly via a range of mechanisms.

Complexation of drugs with components in the diet Drugs are capable of binding to components within the diet. In general this only becomes an issue (with respect to bioavailability) where an irreversible or an insoluble complex is formed. In such cases the fraction of the administered dose that becomes complexed is unavailable for absorption. Tetracycline, for example, forms non-absorbable complexes with calcium and iron, and thus it is advised that patients do not take products containing calcium or iron, such as milk, iron preparations or indigestion remedies, at the same time of day as the tetracycline. However, if the complex formed is water soluble and readily dissociates to liberate the 'free' drug, then there may be little effect on drug absorption.

Alteration of pH In general, food tends to increase stomach pH by acting as a buffer. This is liable to decrease the rate of dissolution and subsequent absorption of a weakly basic drug and increase that of a weakly acidic one.

Alteration of gastric emptying As already mentioned, some foods, particularly those containing a high proportion of fat, and some drugs, tend to reduce gastric emptying and thus delay the onset of action of certain drugs.

Stimulation of gastrointestinal secretions Gastrointestinal secretions (e.g. pepsin) produced in

response to food may result in the degradation of drugs that are susceptible to enzymatic metabolism, and hence in a reduction in their bioavailability. The ingestion of food, particularly fats, stimulates the secretion of bile. Bile salts are surface active agents and can increase the dissolution of poorly soluble drugs, thereby enhancing their absorption. However, bile salts have been shown to form insoluble and hence non-absorbable complexes with some drugs, such as neomycin, kanamycin and nystatin.

Competition between food components and drugs for specialized absorption mechanisms In the case of those drugs that have a chemical structure similar to nutrients required by the body for which specialized absorption mechanisms exist, there is a possibility of competitive inhibition of drug absorption.

Increased viscosity of gastrointestinal contents The presence of food in the gastrointestinal tract provides a viscous environment which may result in a reduction in the rate of drug dissolution. In addition, the rate of diffusion of a drug in solution from the lumen to the absorbing membrane lining the gastrointestinal tract may be reduced by an increase in viscosity. Both of these effects tend to decrease the bioavailability of drug.

Food-induced changes in presystemic metabolism Certain foods may increase the bioavailability of drugs that are susceptible to presystemic intestinal metabolism by interacting with the metabolic process. Grapefruit juice, for example, is capable of inhibiting the intestinal cytochrome P450 (CYP3A family) and thus, taken with drugs that are susceptible to CYP3A metabolism, is likely to result in their increased bioavailability. Clinically relevant interactions exist between grapefruit juice and the antihistamine terfenadine, the immunosuppresant cyclosporin, the protease inhibitor saquinavir and the calcium channel blocker verapamil.

Food-induced changes in blood flow Blood flow to the gastrointestinal tract and liver increases shortly after a meal, thereby increasing the rate at which drugs are presented to the liver. The metabolism of some drugs (e.g. propranolol, hydralazine, dextropropoxyphene) is sensitive to their rate of presentation to the liver: the faster the rate of presentation the larger the fraction of drug that escapes first-pass metabolism. This is because the enzyme systems responsible for their metabolism become saturated by the increased rate of presentation of the drug to the site of biotransformation. For this reason, the effects of food serve to increase the bioavailability of some drugs that are susceptible to first-pass metabolism.

It is evident that food can influence the absorption of many drugs from the gastrointestinal tract by a variety of mechanisms. Drug–food interactions are often classified into five categories: those that cause reduced, delayed, increased and accelerated absorption, and those on which food has no effect. The reader is referred to reviews by Fleischer et al. (1999), Welling (1996) and Evans (2000) for more detailed information on the effect of food on the rate and extent of drug absorption.

Disease state and physiological disorders

Disease states and physiological disorders associated with the gastrointestinal tract are likely to influence the absorption and hence the bioavailability of orally administered drugs. Local diseases can cause alterations in gastric pH that can affect the stability, dissolution and/or absorption of the drug. Gastric surgery can cause drugs to exhibit differences in bioavailability than that in normal individuals. For example, partial or total gastrectomy results in drugs reaching the duodenum more rapidly than in normal individuals. This increased rate of presentation to the small intestine may result in an increased overall rate of absorption of drugs that are primarily absorbed in the small intestine. However, drugs that require a period of time in the stomach to facilitate their dissolution may show reduced bioavailability in such patients.

The unstirred water layer

The unstirred water layer or aqueous boundary layer is a more or less stagnant layer of water, mucus and glycocalyx adjacent to the intestinal wall. It is thought to be created by incomplete mixing of the luminal contents near the intestinal mucosal surface, and to be around 30–100 μm in thickness. This layer can provide a diffusion barrier to drugs. Some drugs are also capable of complexing with mucus, thereby reducing their availability for absorption.

The gastrointestinal membrane

The structure of the membrane

The gastrointestinal membrane separates the lumen of the stomach and intestines from the systemic circulation. It is the main cellular barrier to the absorption of drugs from the gastrointestinal tract. The membrane is complex in nature, being composed of lipids, proteins, lipoproteins and polysaccharides, and has a bilayer structure (Fig. 16.8). The barrier has the characteristics of a semipermeable membrane, allowing the rapid transit of some materials and impeding

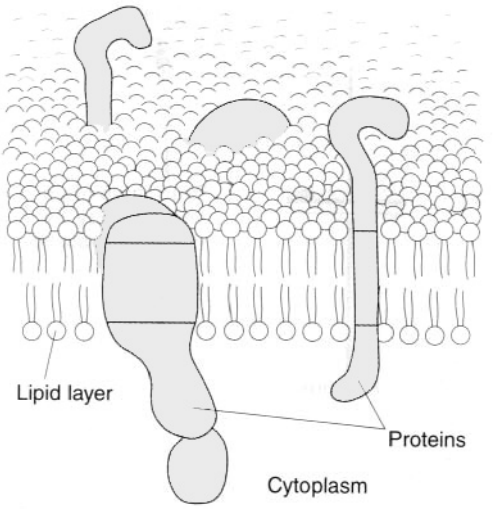

Fig. 16.8 Structure of the membrane.

or preventing the passage of others. It is permeable to amino acids, sugars, fatty acids and other nutrients, and impermeable to plasma proteins. The membrane can be viewed as a semipermeable lipoidal sieve, which allows the passage of lipid-soluble molecules across it and the passage of water and small hydrophilic molecules through its numerous aqueous pores. In addition there are a number of transporter proteins or carrier molecules that exist in the membrane and which, with the help of energy, transport materials back and forth across it.

Mechanisms of transport across the membrane

There are two main mechanisms of drug transport across the gastrointestinal epithelium: transcellular, i.e. across the cells, and paracellular, i.e. between the cells. The transcellular pathway is further divided into simple passive diffusion, carrier-mediated transport (active transport and facilitated diffusion) and endocytosis. These pathways are illustrated in Figure 16.9.

Transcellular pathways

Passive diffusion This is the preferred route of transport for relatively small lipophilic molecules and thus many drugs. In this process, drug molecules pass across the lipoidal membrane via passive diffusion from a region of high concentration in the lumen to a region of lower concentration in the blood. This lower concentration is maintained primarily by blood flow. The rate of transport is determined by the physicochemical properties of the drug, the nature of the membrane and the concentration gradient of the drug across the membrane. The process initially involves the partitioning of the drug between the aqueous fluids within the gastrointestinal tract and the lipoidal-like membrane of the lining of the epithelium. The drug in solution in the membrane then diffuses across the epithelial cell/cells within the gastrointestinal barrier to blood in the capillary network in the lamina propria. Upon reaching the blood the drug will be rapidly distributed, so maintaining a much lower concentration than that at the absorption site. If the cell membranes and fluid regions making up the gastrointestinal–blood barrier can be considered as a single membrane, then the stages involved in gastrointestinal absorption could be represented by the model shown in Figure 16.10.

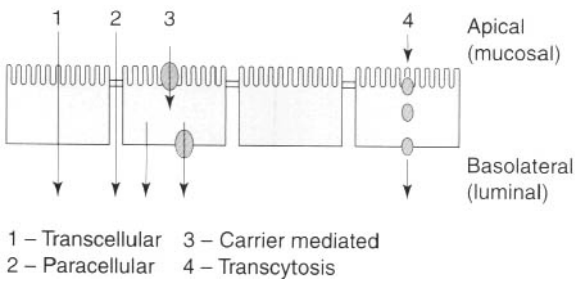

Fig. 16.9 Mechanisms of permeability (absorptive).

Passive diffusion of drugs across the gastrointestinal–blood barrier can often be described mathematically by Fick's first law of diffusion. This states that the rate of diffusion across a membrane (dC/dt) is proportional to the difference in concentration on each side of that membrane. Therefore, the rate of appearance of drug in the blood at the absorption site is given by:

$$dC/dt = k(C_g - C_b) \qquad (16.1)$$

where dC/dt is the rate of appearance of drug in the blood at the site of absorption, k is the proportionality constant, C_g is the concentration of drug in solution in the gastrointestinal fluid at the absorption site, and C_b is the concentration of drug in the blood at the site of absorption.

The proportionality constant k incorporates the diffusion coefficient of the drug in the gastrointestinal membrane (D), and the thickness (h) and surface area of the membrane (A).

$$k = \frac{DA}{h} \qquad (16.2)$$

These equations indicate that the rate of gastrointestinal absorption of a drug by passive diffusion depends on the surface area of the membrane that is

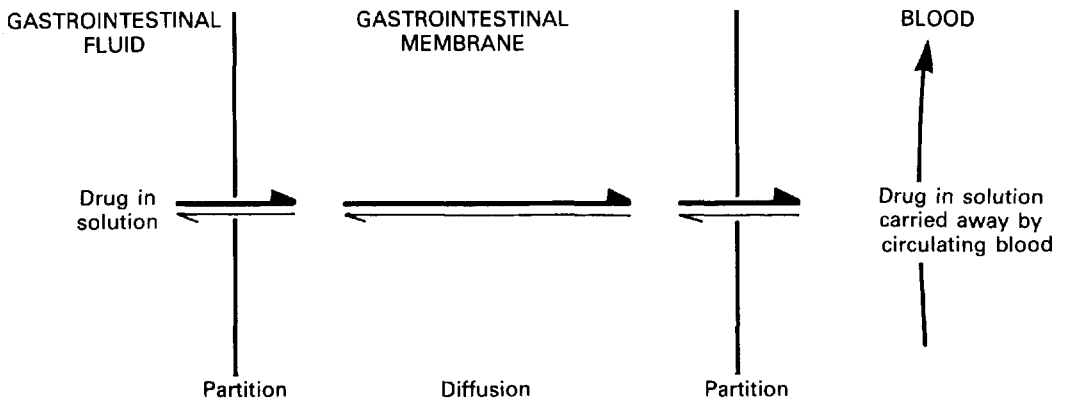

Fig. 16.10 Diagrammatic representation of absorption via passive diffusion.

available for drug absorption. Thus the small intestine, primarily the duodenum, is the major site of drug absorption, owing principally to the presence of villi and microvilli which provide such a large surface area for absorption (see earlier).

Equation 16.1 also indicates that the rate of drug absorption depends on a large concentration gradient of drug existing across the gastrointestinal membrane. This concentration gradient is influenced by the apparent partition coefficients exhibited by the drug with respect to the gastrointestinal membrane/fluid interface and the gastrointestinal membrane/blood interface. It is important that the drug has sufficient affinity (solubility) for the membrane phase that it can partition readily into the gastrointestinal membrane. In addition, after diffusing across the membrane the drug should exhibit sufficient solubility in the blood such that it can partition readily out of the membrane phase into the blood.

On entering the blood in the capillary network in the lamina propria, the drug will be carried away from the site of absorption by the rapidly circulating gastrointestinal blood supply and will become diluted by distribution into a large volume of blood (i.e. the systemic circulation), distribution into body tissues and other fluids, and by metabolism and excretion. In addition, the drug may bind to plasma proteins in the blood which will further lower the concentration of free (i.e. diffusable) drug in the blood. Consequently, the blood acts as a 'sink' for absorbed drug and ensures that the concentration of drug in the blood at the site of absorption is low in relation to that in the gastrointestinal fluids at the site of absorption, i.e. $C_g >> C_b$. The 'sink' conditions provided by the systemic circulation ensure that a large concentration gradient is maintained across the gastrointestinal membrane during the absorption process.

The passive absorption process is driven solely by the concentration gradient of the diffusable species of the drug that exists across the gastrointestinal–blood barrier. Thus Eqns 16.1 and 16.2 can be combined and written as:

$$dC / dt = \frac{DAC_g}{h} \qquad (16.3)$$

and because for a given membrane D, A and h can be regarded as constants, Eqn 16.3 becomes:

$$dC/dt = kC_g \qquad (16.4)$$

Equation 16.4 is an expression for a first-order kinetic process (see Chapter 7) and indicates that the rate of passive absorption will be proportional to the concentration of absorbable drug in solution in the gastrointestinal fluids at the site of absorption, and therefore that the gastrointestinal absorption of most drugs follows first-order kinetics.

It has been assumed in this description that the drug exists solely in one single absorbable species. Many drugs, however, are weak electrolytes that exist in aqueous solution as two species, namely the unionized species and the ionized species. Because it is the unionized form of a weak electrolyte drug that exhibits greater lipid solubility compared to the corresponding ionized form, the gastrointestinal membrane is more permeable to the unionized species. Thus the rate of passive absorption of a weak electrolyte is related to the fraction of total drug that exists in the unionized form in solution in the gastrointestinal fluids at the site of absorption. This fraction is determined by the dissociation constant of the drug (i.e. its pK_a value) and by the pH of the aqueous environment, in accordance with the Henderson–Hasselbalch equations for weak acids and bases (see Chapters 3 and 8). The gastrointesti-

nal absorption of a weak electrolyte drug is enhanced when the pH at the site of absorption favours the formation of a large fraction of the drug in aqueous solution that is unionized. This forms the basis of the pH-partition hypothesis (see Chapter 17).

Carrier-mediated transport As already stated, the majority of drugs are absorbed across cells (i.e. transcellularly) via passive diffusion. However, certain compounds and many nutrients are absorbed transcellularly by a carrier-mediated transport mechanism, of which there are two main types, ***active transport*** and ***facilitated diffusion*** or ***transport***.

Active transport In contrast to passive diffusion, active transport involves the active participation by the apical cell membrane of the columnar absorption cells. A carrier or membrane transporter is responsible for binding a drug and transporting it across the membrane by a process illustrated in Figure 16.11.

Carrier-mediated absorption is often explained by assuming a shuttling process across the epithelial membrane. The drug molecule or ion forms a complex with the carrier/transporter in the surface of the apical cell membrane of a columnar absorption cell; the drug–carrier complex then moves across the membrane and liberates the drug on the other side of the membrane. The carrier (now free) returns to its initial position in the surface of the cell membrane adjacent to the gastrointestinal tract, to await the arrival of another drug molecule or ion.

Active transport is a process whereby materials can be transported against a concentration gradient across a cell membrane, i.e. transport can occur from a region of lower concentration to one of higher concentration. Therefore, active transport is an energy-consuming process. The energy arises either from the hydrolysis of ATP or from the transmembranous sodium gradient and/or electrical potential.

There are a large number of carrier-mediated active transport systems or membrane transporters in the small intestine, which can be present either on the apical (brush border) or on the basolateral membrane. These include the peptide transporters, the nucleoside transporters, the sugar transporters, the bile acid transporters, the amino acid transporters, the organic anion transporters and the vitamin transporters.

Many nutrients, such as amino acids, sugars, electrolytes (e.g. sodium, potassium, calcium, iron, chloride, bicarbonate), vitamins (thiamine (B_1), nicotinic acid, riboflavin (B_2), pyroxidine (B_6) and B_{12}) and bile salts are actively transported. Each carrier system is generally concentrated in a specific segment of the gastrointestinal tract. The substance that is transported by that carrier will thus be absorbed preferentially in the location of highest carrier density. For example, the bile acid transporters are only found in the lower part of the small intestine, the ileum. Each carrier/transporter has its own substrate specificity with respect to the chemical structure of the substance that it will transport. Some carriers/transporters have broader specificity than others. Thus if a drug structurally resembles a natural substance which is actively transported, then the drug is also likely to be transported by the same carrier mechanism.

Many peptide-like drugs, such as the penicillins, cephalosporins, angiotensin-converting enzyme inhibitors (ACE) inhibitors and renin inhibitors, rely on the peptide transporters for their efficient absorption. Nucleosides and their analogues for antiviral and anticancer drugs depend on the nucleoside transporters for their uptake. L-dopa and α-methyldopa are transported by the carrier-mediated process for amino acids. L-dopa has a much faster

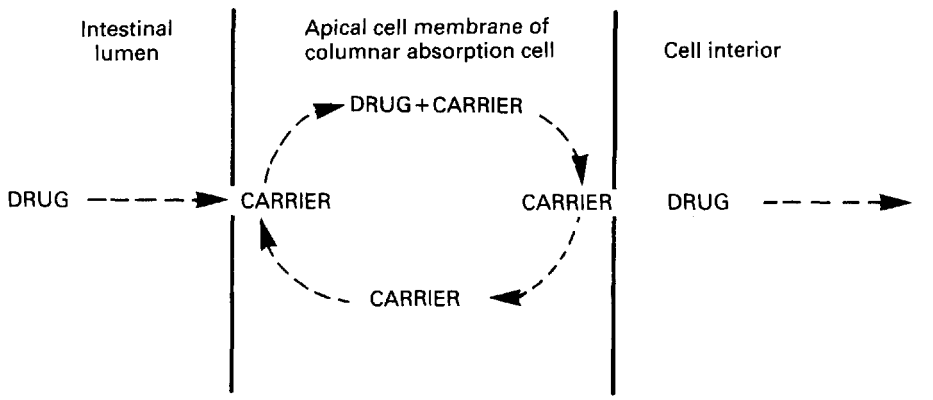

Fig. 16.11 Diagrammatic representation of active transport of a drug across a cell membrane.

permeability rate than methyldopa, which has been attributed to the lower affinity of methyldopa for the amino acid carrier.

Unlike passive absorption, where the rate of absorption is directly proportional to the concentration of the absorbable species of the drug at the absorption site, active transport proceeds at a rate that is proportional to the drug concentration only at low concentrations. At higher concentrations the carrier mechanism becomes saturated and further increases in drug concentration will not increase the rate of absorption, i.e. the rate of absorption remains constant. Absorption rate–concentration relationships for active and passive processes are compared in Figure 16.12.

Competition between two similar substances for the same transfer mechanism, and the inhibition of absorption of one or both compounds, are other characteristics of carrier-mediated transport. Inhibition of absorption may also be observed with agents such as sodium fluoride, cyanide or dinitrophenol, which interfere with cell metabolism.

Some substances may be absorbed by simultaneous carrier-mediated and passive transport processes. For example, certain pyrimidines, such as uracil and thymine, are absorbed both passively and via a carrier-mediated process. The contribution of the carrier-mediated process to the overall absorption rate decreases with concentration, and at a sufficiently high concentration is negligible.

In summary, active transport mechanisms:

- must have a carrier molecule;
- must have a source of energy;
- can be inhibited by metabolic inhibitors such as dinitrophenol;
- show temperature dependence;
- can be competitively inhibited by substrate analogues.

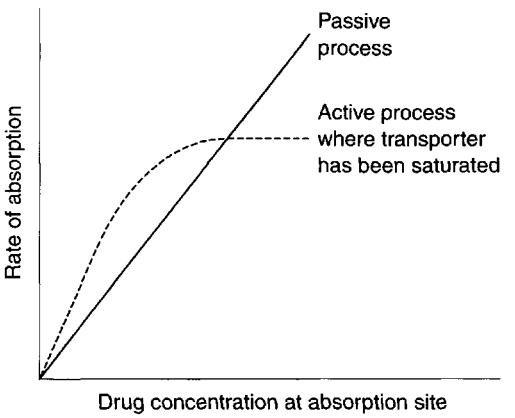

Fig. 16.12 Relationship between rate of absorption and concentration at the absorption site for active and passive processes.

Active transport also plays an important role in the intestinal, renal and biliary excretion of many drugs.

Facilitated diffusion or transport This carrier-mediated process differs from active transport in that it cannot transport a substance against a concentration gradient of that substance. Therefore, facilitated diffusion does not require an energy input but does require a concentration gradient for its driving force, as does passive diffusion. When substances are transported by facilitated diffusion they are transported down the concentration gradient but at a much faster rate than would be anticipated based on the molecular size and polarity of the molecule. The process, like active transport, is saturable and is subject to inhibition by competitive inhibitors. In terms of drug absorption, facilitated diffusion seems to play a very minor role.

More information on carrier-mediated transport of drugs within the intestines can be obtained from reviews by Oh et al. (1999), Tsuji and Tamia (1996) and Yang et al. (1999).

Endocytosis Endocytosis is the process by which the plasma membrane of the cell invaginates and the invaginations become pinched off, forming small intracellular membrane-bound vesicles that enclose a volume of material. Thus material can be transported into the cell. After invagination the material is often transferred to other vesicles or lysosomes and digested. Some material will escape digestion and migrate to the basolateral surface of the cell, where it is exocytosed. This uptake process is energy dependent. Endocytosis can be further subdivided into four main processes: fluid-phase endocytosis or pinocytosis; receptor-mediated endocytosis; phagocytosis; and transcytosis. Endocytosis is thought to be the primary mechanism of transport of macromolecules. The process and pathways of endocytosis are complex.

Pinocytosis Fluid-phase endocytosis or pinocytosis is the engulfment of small droplets of extracellular fluid by membrane vesicles. The cell will internalize material regardless of its metabolic importance to that cell. The efficiency of this process is low. The fat-soluble vitamins A, D, E and K are absorbed via pinocytosis.

Receptor-mediated endocytosis Many cells within the body have receptors on their cell surfaces that are capable of binding with suitable ligands to form ligand–receptor complexes on the cell surface. These complexes cluster on the cell surface and then invaginate and break off from the membrane to form coated

vesicles. The binding process between the ligand and the receptor on the cell surface is thought to trigger a conformational change in the membrane to allow this process to occur. Once within the cytoplasm of the cell the coated vesicles rapidly lose their coat, and the resulting uncoated vesicles will promptly deliver their contents to early endosomes. Within the endosomes the ligands usually dissociate from their receptors many of which are then recycled to the plasma membrane. The dissociated ligands and solutes are next delivered to prelysosomes and finally to lysosomes, the end-stage of the endocytic pathway. Lysosomes are spherical or oval cell organelles surrounded by a single membrane. They contain digestive enzymes which break down bacteria and large molecules, such as protein, polysaccharides and nucleic acids, which have entered the cell via endocytosis.

Phagocytosis Phagocytosis can be defined as the engulfment by the cell membrane of particles larger than 500 nm. This process is important for the absorption of polio and other vaccines from the gastrointestinal tract.

Transcytosis Transcytosis is the process by which the material internalized by the membrane domain is transported through the cell and secreted on the opposite side.

Paracellular pathway

The paracellular pathway differs from all the other absorption pathways as it is the transport of materials in the aqueous pores between the cells rather than across them. The cells are joined together via closely fitting tight junctions on their apical side. The intercellular spaces occupy only about 0.01% of the total surface area of the epithelium. The tightness of these junctions can vary considerably between different epithelia in the body. In general, absorptive epithelia, such as that of the small intestine, tend to be leakier than other epithelia. The paracellular pathway decreases in importance down the length of the gastrointestinal tract, and as the number and size of pores between the epithelial cells decrease.

The paracellular route of absorption is important for the transport of ions such as calcium and for the transport of sugars, amino acids and peptides at concentrations above the capacity of their carriers. Small hydrophilic and charged drugs that do not distribute into cell membranes cross the gastrointestinal epithelium via the paracellular pathway. The molecular weight cut-off for the paracellular route is usually considered to be 200 Da, although some larger drugs have been shown to be absorbed via this route.

The paracellular pathway can be divided into a convective ('solvent drag') and diffusive component. The convective component is the rate at which the compound is carried across the epithelium via the water flux.

Efflux of drugs from the intestine

It is now known that there are countertransport efflux proteins that expel specific drugs back into the lumen of the gastrointestinal tract after they have been absorbed. One of the key countertransport proteins is P-glycoprotein. P-glycoprotein is expressed at high levels on the apical surface of columnar cells (brush border membrane) in the jejunum. It is also present on the surface of many other epithelia and endothelia in the body, and on the surface of tumour cells. P-glycoproteins were originally discovered because of their ability to cause multidrug resistance in tumour cells by preventing the intracellular accumulation of many cytotoxic cancer drugs by pumping the drugs back out of the tumours. Certain drugs with wide structural diversity (Table 16.2) are susceptible to efflux from the intestine via P-glyocprotein. Such efflux may have a detrimental effect on drug bioavailability. These countertransport efflux proteins pump

Table 16.2 Examples of transport mechanisms of commonly used drugs across the gastrointestinal absorptive epithelia (adapted from Brayden 1997)

Route	Examples	Therapeutic class
Transcellular passive diffusion	Propranol	β-Blocker
	Testosterone	Steroid
	Ketoprofen	Non-steroidal anti-inflammatory
	Cisapride	Antispasmodic
	Oestradiol	Sex hormone
	Naproxen	Non-steroidal anti-inflammatory
Paracellular	Cimetidine	H_2 antagonist
	Loperamide	Antidiarrhoeal
	Atenolol	β-Blocker
	Mannitol	Sugar used as paracellular marker
	Tiludronate	Bisphosphonate
Carrier mediated	Cephalexin	Anti-bacterial
	Captopril	ACE inhibitor
	Bestatin	Anticancer
	Levodopa	Dopaminergic
	Foscarnet	Antiviral
Transcellular diffusion subject to P-glycoprotein efflux	Cyclosporine	Immunosuppressant
	Nifedipine	Calcium channel blocker
	Verapamil	Calcium channel blocker
	Paclitaxel	Anticancer
	Celiprolol	β-Blocker
	Digoxin	Cardiac glycoside

drugs out of cells in a similar way to which nutrients, and drugs are actively absorbed across the gastrointestinal membrane. This process therefore requires energy, can work against a concentration gradient, can be competitively inhibited by structural analogues or be inhibited by inhibitors of cell metabolism, and is a saturable process.

Table 16.2 summarizes the main mechanisms of drug transport across the gastrointestinal epithelia for a number of commonly used drugs.

Presystemic metabolism

As well as having the ability to cross the gastrointestinal membrane by one of the routes described, drugs also need to be resistant to degradation/metabolism during this passage. All drugs that are absorbed from the stomach, small intestine and upper colon pass into the hepatic portal system and are presented to the liver before reaching the systemic circulation. Therefore, if the drug is going to be available to the systemic circulation it must also be resistant to metabolism by the liver. Hence, an oral dose of drug could be completely absorbed but incompletely available to the systemic circulation because of ***first-pass*** or ***presystemic*** metabolism by the gut wall and/or liver.

Gut-wall metabolism

It is only relatively recently that the full extent of gut-wall metabolism has been recognized. Watkins and co-workers were the first to report that a major cytochrome P450 enzyme, CYP3A, that is present in the liver and is responsible for the hepatic metabolism of many drugs, is present in the intestinal mucosa and that intestinal metabolism may be important for substrates of this enzyme (Watkins et al. 1987, Kolars et al. 1992). This effect can also be known as ***first-pass metabolism*** by the intestine. One drug that is susceptible to extensive gut metabolism that results in a significant reduction in its bioavailability is cyclosporin (Benet et al, 1996).

Hepatic metabolism

The liver is the primary site of drug metabolism and thus acts as a final barrier for oral absorption. This first pass of absorbed drug through the liver may result in extensive metabolism of the drug, and a significant portion may never reach the systemic circulation, resulting in a low bioavailability of those drugs which are rapidly metabolized by the liver. The bioavailability of a susceptible drug may be reduced to such an extent as to render the gastrointestinal route of administration ineffective, or to necessitate an oral dose which is many times larger than the intravenous dose, e.g. propranolol. Although propranolol is well absorbed, only about 30% of an oral dose is available to the systemic circulation owing to the first-pass effect. The bioavailability of sustained-release propranolol is even less as the drug is presented via the hepatic portal vein more slowly than from an immediate-release dosage form, and the liver is therefore capable of extracting and metabolizing a larger portion. Other drugs which are susceptible to a large first-pass effect are the anaesthetic lidocaine, the tricyclic antidepressant imipramine and the analagesic pentazocine.

SUMMARY

There are many physiological factors that influence the rate and extent of drug absorption; these are initially dependent on the route of administration. For the oral route the physiological and environmental factors of the gastrointestinal tract, the gastrointestinal membrane and presystemic metabolism can all influence drug bioavailability.

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17

Bioavailability – physicochemical and dosage form factors

Marianne Ashford

CHAPTER CONTENTS

As discussed in Chapter 16, the rate and extent of absorption are influenced by the physiological factors associated with the structure and function of the GI tract. This chapter discusses the physicochemical properties of the drug and dosage form factors that influence bioavailability. For a drug to be absorbed it needs to be in solution and, secondly, to pass across the membrane; in the case of orally administered drugs this is the gastrointestinal epithelium. The physicochemical properties of the drug that will influence its passage into solution and transfer across membranes include its dissolution rate, pK_a, lipid solubility, chemical stability and complexation potential.

PHYSICOCHEMICAL FACTORS INFLUENCING BIOAVAILABILITY

Dissolution and solubility

Solid drugs need to dissolve before they can be absorbed. The dissolution of drugs can be described by the Noyes–Whitney equation (Eqn 17.1). This equation, first proposed in 1897, describes the rate of dissolution of spherical particles when the dissolution process is diffusion controlled and involves no chemical reaction:

$$dC / dt = \frac{DA(C_s - C)}{h} \qquad (17.1)$$

where dC/dt is the rate of dissolution of the drug particles, D is the diffusion coefficient of the drug in solution in the gastrointestinal fluids, A is the effective surface area of the drug particles in contact with the gastrointestinal fluids, h is the thickness of the diffusion layer around each drug particle, C_s is the saturation solubility of the drug in solution in the diffusion layer and C is the concentration of the drug in the gastrointestinal fluids.

Table 17.1 Physicochemical and physiological factors affecting drug dissolution in the gastrointestinal tract (adapted from Dressman et al, 1998)

Factor	Physicochemical parameter	Physiological parameter
Effect surface area of drug	Particle size, wettability	Surfactants in gastric juice and bile
Solubility in diffusion layer	Hydrophilicity, crystal structure, solubilization	pH, buffer capacity, bile, food components
Amount of drug already dissolved		Permeability, transit
Diffusivity of drug	Molecular size	Viscosity of luminal contents
Boundary layer thickness		Motility patterns and flow rate
Volume of solvent available		Gastrointestinal secretions, co-administered fluids

The limitations of the Noyes–Whitney equation in describing the dissolution of drug particles are discussed in Chapter 2. Despite these limitations, the equation serves to illustrate and explain how various physicochemical and physiological factors can influence the rate of dissolution in the gastrointestinal tract. These are summarized in Table 17.1 and are discussed in more detail in the next section.

Figure 17.1 illustrates the dissolution of a spherical drug particle in the gastrointestinal fluids.

Physiological factors affecting the dissolution rate of drugs

The environment of the gastrointestinal tract can affect the parameters of the Noyes–Whitney equation (Eqn 17.1) and hence the dissolution rate of a drug. For instance, the diffusion coefficient, D, of the drug in the gastrointestinal fluids may be decreased by the presence of substances that increase the viscosity of the fluids. Hence the presence of food in the gastrointestinal tract may cause a decrease in dissolution rate of a drug by reducing the rate of diffusion of the drug molecules away from the diffusion layer surrounding each undissolved drug particle. Surfactants in gastric juice and bile salts will affect both the wettability of the drug, and hence the effective surface area, A, exposed to gastrointestinal fluids, and the solubility of the drug in the gastrointestinal fluids via micellization. The thickness of the diffusion layer, h, will be influenced by the degree of agitation experienced by each drug particle in the

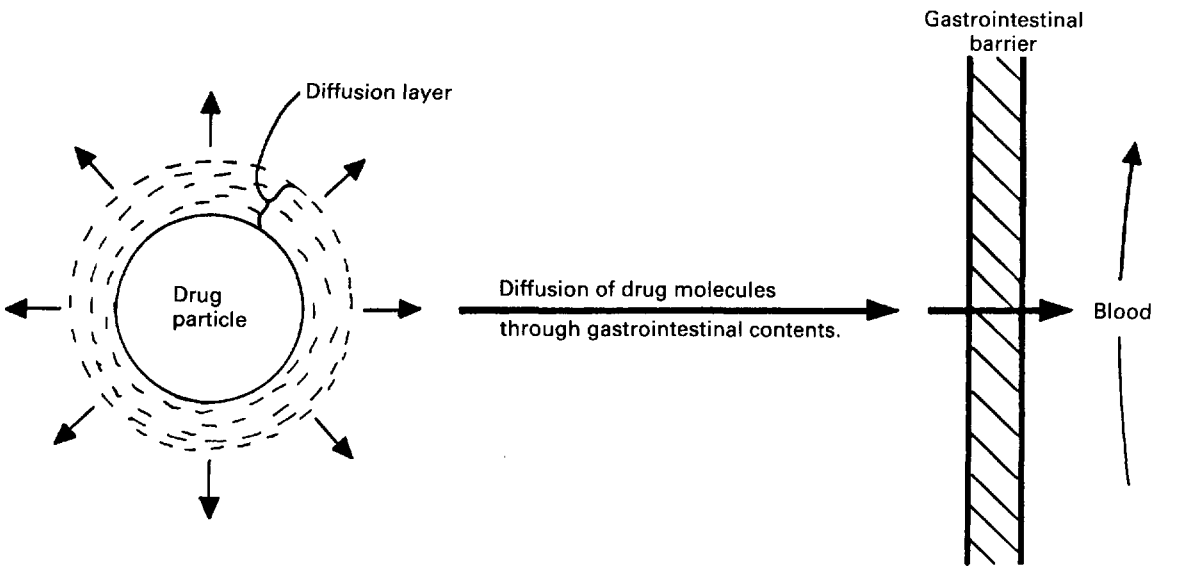


Fig. 17.1 Schematic representation of the dissolution of a drug particle in the gastrointestinal fluids.

gastrointestinal tract. Hence an increase in gastric and/or intestinal motility may increase the dissolution rate of a sparingly soluble drug by decreasing the thickness of the diffusion layer around each drug particle. The concentration, C, of drug in solution in the bulk of the gastrointestinal fluids will be influenced by such factors as the rate of removal of dissolved drug by absorption through the gastrointestinal–blood barrier, and by the volume of fluid available for dissolution, which will be dependent on the position of the drug in the gastrointestinal tract and the timing with respect to meal intake. In the stomach the volume of fluid will be influenced by the intake of fluid in the diet. According to the Noyes–Whitney equation a low value of C will favour more rapid dissolution of the drug by virtue of increasing the value of the term $(C_s - C)$. In the case of drugs whose absorption is dissolution-rate limited, the value of C is normally kept very low by absorption of the drug. Hence dissolution occurs under sink conditions, that is, under conditions such that the value of $(C_s - C)$ approximates to C_s. Thus for the dissolution of a drug from the gastrointestinal tract under sink conditions the Noyes–Whitney equation can be expressed as:

$$dC / dt = \frac{DAC_S}{h} \qquad (17.2)$$

Drug factors affecting dissolution rate

Drug factors that can influence the dissolution rate are the particle size, the wettability, the solubility and the form of the drug (whether a salt or a free form, crystalline or amorphous).

Surface area and particle size According to Eqn 17.1, an increase in the total surface area of drug in contact with the gastrointestinal fluids will cause an increase in dissolution rate. Provided that each particle of drug is intimately wetted by the gastrointestinal fluids, the effective surface area exhibited by the drug will be directly proportional to the particle size of the drug. Hence the smaller the particle size, the greater the effective surface area exhibited by a given mass of drug, and the higher the dissolution rate. Particle size reduction is thus likely to result in increased bioavailability, provided the absorption of the drug is dissolution-rate limited.

One of the classic examples of particle size effects on the bioavailability of poorly soluble compounds is that of griseofulvin, where a reduction of particle size from about 10 μm (specific surface area = 0.4 $m^2 g^{-1}$) to 2.7 μm (specific surface area = 1.5 $m^2 g^{-1}$) was shown to produce approximately double the amount of drug absorbed in humans. Many poorly soluble, slowly dissolving drugs are routinely presented in micronized form to increase their surface area.

Examples of drugs where a reduction in particle size has been shown to improve the rate and extent of oral absorption and hence bioavailability are shown in Table 17.2. Such improvements in bioavailability can result in an increased incidence of side-effects, thus for certain drugs it is important that the particle size is well controlled, and many Pharmacopoeia state the requirements of particle size.

For some drugs, particularly those that are hydrophobic in nature, micronization and other dry particle size-reduction techniques can result in aggregation of the material, with a consequent reduction in the effective surface area exposed to the gastrointestinal fluids and hence their dissolution rate and bioavailability. Aspirin, phenacetin and phenobarbitone are all prone to aggregation during particle size reduction; one approach that may overcome this problem is to micronize or mill the drug with a wetting agent or hydrophilic carrier. To overcome aggregation and to achieve particle sizes in the nanosize region, wet milling in the presence of stabilizers has been used. The relative bioavailability of danazol has been increased 400% by administering particles in the nano- rather than the micrometre size range.

As well as milling with wetting agents the effective surface area of hydrophobic drugs can be increased by the addition of a wetting agent to the formulation. The presence of polysorbate-80 in a fine suspension of phenacetin (particle size less than 75 μm) greatly improved the rate and extent of absorption of the phenacetin in human volunteers compared to the

Table 17.2 Examples of drugs where a reduction in particle size has led to improvements in bioavailability

Drug	Therapeutic class
Digoxin	Cardiac glycoside
Nitrofurantoin	Antifungal
Medoxyprogesterone acetate	Hormone
Danazol	Steroid
Tolbutamide	Antidiabetic
Aspirin	Analgesic
Sulphadiazine	Antibacterial
Naproxen	Non-steroidal anti-inflammatory
Ibuprofen	Non-steroidal anti-inflammatory
Phenacetin	Analgesic

same-size suspension without a wetting agent. Polysorbate-80 helps by increasing the wetting and solvent penetration of the particles and by minimizing aggregation of suspended particles, thereby maintaining a large effective surface area. Wetting effects are highly drug specific.

If an increase in the effective surface area of a drug does not increase its absorption rate it is likely that the dissolution process is not rate limiting. For drugs such as penicillin G and erythromycin, which are unstable in gastric fluids, their chemical degradation will be minimized if they remain in the solid state. Thus particle size reduction would not only serve to increase their dissolution rate, but would also increase chemical degradation and therefore reduce the amount of intact drug available for absorption.

Solubility in the diffusion layer, C_S The dissolution rate of a drug under sink conditions, according to the Noyes–Whitney equation, is directly proportional to its intrinsic solubility in the diffusion layer surrounding each dissolving drug particle, C_s. The aqueous solubility of a drug is dependent on the interactions between molecules within the crystal lattice, intermolecular interactions with the solution in which it is dissolving, and the entropy changes associated with fusion and dissolution. In the case of drugs that are weak electrolytes, their aqueous solubilities are dependent on pH (see Chapter 2). Hence in the case of an orally administered solid dosage form containing a weak electrolyte drug, the dissolution rate of the drug will be influenced by its solubility and the pH in the diffusion layer surrounding each dissolving drug particle. The pH in the diffusion layer – the microclimate pH – for a weak electrolyte will be affected by the pK_a and solubility of the dissolving drug and the pK_a and solubility of the buffers in the bulk gastrointestinal fluids. Thus differences in dissolution rate will be expected in different regions of the gastrointestinal tract.

The solubility of weakly acidic drugs increases with pH, and so as a drug moves down the gastrointestinal tract from the stomach to the intestine, its solubility will increase. Conversely, the solubility of weak bases decreases with increasing pH, i.e. as the drug moves down the gastrointestinal tract. It is important therefore for poorly soluble weak bases to dissolve rapidly in the stomach, as the rate of dissolution in the small intestine will be much slower. The antifungal drug ketoconazole, a weak base, is particularly sensitive to gastric pH. Dosing ketoconazole 2 hours after the administration of the H_2 blocker cimetidine, which reduces gastric acid secretion, results in a significantly reduced rate and extent of absorption (van der Meer et al 1980). Similarly, in the case of the antiplatelet dipyrimidole, pretreatment with the H_2 blocker famotidine reduces the peak plasma concentration by a factor of up to 10 (Russell et al 1994).

Salts The dissolution rate of a weakly acidic drug in gastric fluid (pH 1–3.5) will be relatively low. If the pH in the diffusion layer could be increased, then the solubility, C_s, exhibited by the acidic drug in this layer, and hence its dissolution rate in gastric fluids, would be increased even though the bulk pH of gastric fluids remained at the same low value. The pH of the diffusion layer would be increased if the chemical nature of the weakly acidic drug were changed from that of the free acid to a basic salt, for example the sodium or potassium form of the free acid. The pH of the diffusion layer surrounding each particle of the salt form would be higher (e.g. 5–6) than the low bulk pH (1–3.5) of the gastric fluids because of the neutralizing action of the strong anions (Na^+ or K^+) ions present in the diffusion layer (Fig. 17.2).

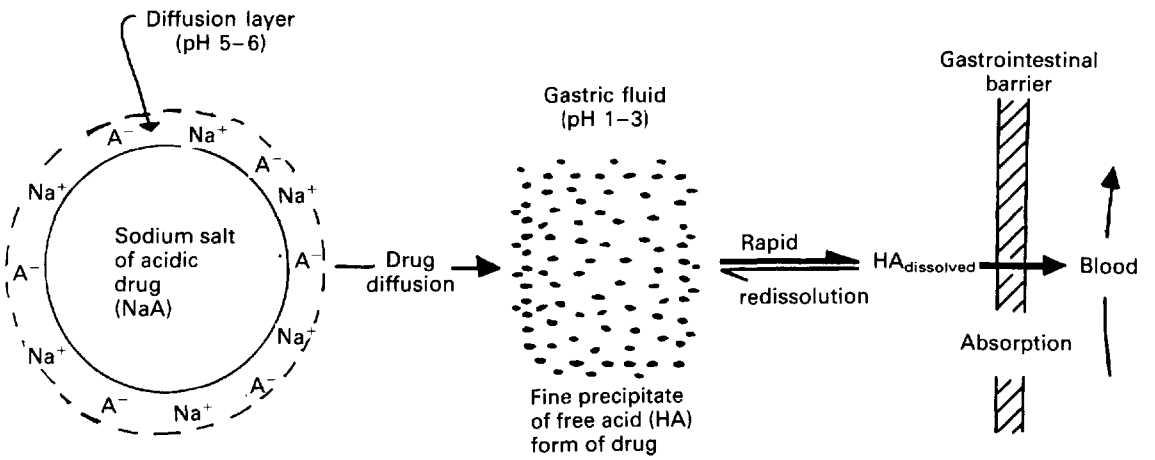


Fig. 17.2 Schematic representation of the dissolution process of a salt form of a weakly acidic drug in gastric fluid.

Because the salt form of the weakly acidic drug has a relatively high solubility at the elevated pH in the diffusion layer, dissolution of the drug particles will take place at a faster rate. When dissolved drug diffuses out of the diffusion layer into the bulk of the gastric fluid, where the pH is lower than that in the diffusion layer, precipitation of the free acid form is likely to occur. This will be a result of the overall solubility exhibited by the drug at the lower bulk pH. Thus the free acid form of the drug in solution, which is in excess of its solubility at the bulk pH of gastric fluid, will precipitate out, leaving a saturated (or near-saturated) solution of free acid in gastric fluid. Often this precipitated free acid will be in the form of very fine, non-ionized wetted particles which exhibit a very large total effective surface area in contact with gastric fluids. This large total effective surface area will facilitate rapid redissolution of the precipitated particles of free acid when additional gastric fluid becomes available as a consequence of either dissolved drug being absorbed, additional fluid accumulating in the stomach, or the fine precipitated particles being emptied from the stomach to the intestine. This rapid redissolution will ensure that the concentration of free acid in solution in the bulk of the gastric fluids will be at or near to saturation.

Thus the oral administration of a solid dosage form containing a strong basic salt of a weakly acidic drug would be expected to give a more rapid rate of drug dissolution and (in the case of drugs exhibiting dissolution rate limited absorption) a more rapid rate of drug absorption than the free acid form of the drug.

Many examples can be found of the effects of salts improving the rate and extent of absorption. The dissolution rate of the oral hypoglycaemic tolbutamide sodium in 0.1 M HCl is 5000 times faster than that of the free acid. Oral administration of a non-disintegrating disc of the more rapidly dissolving sodium salt of tolbutamide produced a very rapid decrease in blood sugar level (a consequence of the rapid rate of drug absorption), followed by a rapid recovery. In contrast, a non-disintegrating disc of the tolbutamide free acid produced a much slower rate of decrease of blood sugar (a consequence of the slower rate of drug absorption) that was maintained over a longer period of time. The barbiturates are often administered in the form of sodium salts to achieve a rapid onset of sedation and provide more predictable effects.

The non-steroidal anti-inflammatory drug naproxen was originally marketed as the free acid for the treatment of rheumatoid and osteoarthritis. However, the sodium salt (naproxen sodium) is absorbed faster and is more effective in newer indications, such as mild to moderate pain (Sevelius et al 1980).

Conversely, strongly acidic salt forms of weakly basic drugs, for example chlorpromazine hydrochloride, dissolve more rapidly in gastric and intestinal fluids than do the free bases (e.g. chlorpromazine). The presence of strongly acidic anions (e.g. Cl^- ions) in the diffusion layer around each drug particle ensures that the pH in that layer is lower than the bulk pH in either the gastric or the intestinal fluid. This lower pH will increase the solubility of the drug C_s in the diffusion layer. The oral administration of a salt form of a weakly basic drug in a solid oral dosage form generally ensures that dissolution occurs in the gastric fluid before the drug passes into small intestine, where pH conditions are unfavourable. Thus the drug should be delivered to the major absorption site, the small intestine, in solution. If absorption is fast enough, precipitation of the dissolved drug is unlikely to significantly affect bioavailability. It is important to be aware that hydrochloride salts may experience a common ion effect owing to the presence of chloride ions in the stomach (see Chapter 8). The in vitro dissolution of a sulphate salt of an HIV protease inhibitor analogue is significantly greater in hydrochloric acid than that of the hydrochloride salt. The bioavailability of the sulphate salt is more than three times greater than that of the hydrochloride salt. These observations are attributed to the common ion effect of the hydrochloride (Loper et al 1999).

The sodium salts of acidic drugs and the hydrochloride salts of basic drugs are by far the most common. However, many other salt forms are increasingly being employed (see Chapter 8). Some salts have a lower solubility and dissolution rate than the free form, for example aluminium salts of weak acids and palmoate salts of weak bases. In these cases insoluble films of either aluminium hydroxide or palmoic acid are found to coat the dissolving solids when the salts are exposed to a basic or an acidic environment, respectively. In general, poorly soluble salts delay absorption and may therefore be used to sustain the release of the drug. A poorly soluble salt form is generally employed for suspension dosage forms.

Although salt forms are often selected to improve bioavailability, other factors, such as chemical stability, hygroscopicity, manufacturability and crystallinity, will all be considered during salt selection and may preclude the choice of a particular salt. The sodium salt of aspirin, sodium acetylsalicylate, is much more prone to hydrolysis than is aspirin,

acetylsalicylic acid, itself. One way to overcome chemical instabilities or other undesirable features of salts is to form the salt in situ or to add basic/acidic excipients to the formulation of a weakly acidic or weakly basic drug. The presence of the basic excipients in the formulation of acidic drugs ensures that a relatively basic diffusion layer is formed around each dissolving particle. The inclusion of the basic ingredients aluminium dihydroxyaminoacetate and magnesium carbonate in aspirin tablets was found to increase their dissolution rate and bioavailability.

Crystal form

Polymorphism Many drugs can exist in more than one crystalline form, e.g. chloramphenicol palmitate, cortisone acetate, tetracyclines and sulphathiazole. This property is referred to as ***polymorphism*** and each crystalline form is known as a polymorph (see Chapter 9). As discussed in Chapter 2, a metastable polymorph usually exhibits a greater dissolution rate than the corresponding stable polymorph. Consequently, the metastable polymorphic form of a poorly soluble drug may exhibit an increased bioavailability compared to the stable polymorphic form.

A classic example of the influence of polymorphism on drug bioavailability is provided by chloramphenicol palmitate. This drug exists in three crystalline forms designated A, B and C. At normal temperature and pressure A is the stable polymorph, B is the metastable polymorph and C is the unstable polymorph. Polymorph C is too unstable to be included in a dosage form, but polymorph B, the metastable form, is sufficiently stable. The plasma profiles of chloramphenicol from orally administered suspensions containing varying proportions of the polymorphic forms A and B were investigated. The extent of absorption of chloramphenicol increases as the proportion of the polymorphic form B of chloramphenicol palmitate is increased in each suspension. This was attributed to the more rapid in vivo rate of dissolution of the metastable polymorphic form, B, of chloramphenicol palmitate. Following dissolution, chloramphenicol palmitate is hydrolysed to give free chloramphenicol in solution, which is then absorbed. The stable polymorphic form A of chloramphenicol palmitate dissolves so slowly and consequently is hydrolysed so slowly to chloramphenicol in vivo that this polymorph is virtually ineffective. The importance of polymorphism to the gastrointestinal bioavailability of chloramphenicol palmitate is reflected by a limit being placed on the content of the inactive polymorphic form, A, in Chloramphenicol Palmitate Mixture.

Amorphous solids In addition to different polymorphic crystalline forms, a drug may exist in an amorphous form (see Chapter 9). Because the amorphous form usually dissolves more rapidly than the corresponding crystalline form(s), the possibility exists that there will be significant differences in the bioavailabilities exhibited by the amorphous and crystalline forms of drugs that show dissolution-rate limited bioavailability.

A classic example of the influence of amorphous versus crystalline forms of a drug on its gastrointestinal bioavailability is provided by that of the antibiotic novobiocin. The more soluble and rapidly dissolving amorphous form of novobiocin was readily absorbed following oral administration of an aqueous suspension to humans and dogs. However, the less soluble and slower-dissolving crystalline form of novobiocin was not absorbed to any significant extent. The crystalline form was thus therapeutically ineffective. A further important observation was made in the case of aqueous suspensions of novobiocin. The amorphous form of novobiocin slowly converts to the more thermodynamically stable crystalline form, with an accompanying loss of therapeutic effectiveness. Thus unless adequate precautions are taken to ensure the stability of the less stable, more therapeutically effective amorphous form of a drug in a dosage form, then unacceptable variations in therapeutic effectiveness may occur.

Several delivery technologies for poorly soluble drugs rely on stabilizing the drug in its amorphous form to increase its dissolution and bioavailability.

Solvates Another variation in the crystalline form of a drug can occur if the drug is able to associate with solvent molecules to produce crystalline forms known as solvates. When water is the solvent, the solvate formed is called a hydrate. Generally the greater the solvation of the crystal, the lower are the solubility and dissolution rate in a solvent identical to the solvation molecules. As the solvated and non-solvated forms usually exhibit differences in dissolution rates, they may also exhibit differences in bioavailability, particularly in the case of poorly soluble drugs that exhibit dissolution-rate limited bioavailability.

A valuable example is that of the antibiotic ampicillin: the faster-dissolving anhydrous form of ampicillin was absorbed to a greater extent from both hard gelatin capsules and an aqueous suspension than was the slower-dissolving trihydrate form. The anhydrous form of the hydrochloride salt of an HIV protease inhibitor, an analogue of indinavir, has a much faster dissolution rate than the hydrated form in water; this

is reflected by a significantly greater rate and extent of absorption and overdoubling of the bioavailability of the anhydrous form (Loper et al 1999).

Factors affecting the concentration of drug in solution in the gastrointestinal fluids

The rate and extent of absorption of a drug depend on the effective concentration of that drug, i.e. the concentration of drug in solution in the gastrointestinal fluids which is in an absorbable form. Complexation, micellar solubilization, adsorption and chemical stability are the principal physicochemical properties that can influence the effective drug concentration in the gastrointestinal fluids.

Complexation Complexation of a drug may occur within the dosage form and/or in the gastrointestinal fluids, and can be beneficial or detrimental to absorption.

Mucin, a normal component of gastrointestinal fluids, complexes with some drugs. The antibiotic streptomycin binds to mucin, thereby reducing the available concentration of the drug for absorption. It is thought that this may contribute to its poor bioavailability. Another example of complexation is that between drugs and dietary components, as in the case of the tetracyclines, which is discussed in Chapter 16.

The bioavailability of some drugs can be reduced by the presence of excipients within the dosage forms. The presence of calcium (e.g. from the diluent dicalcium phosphate) in the dosage form of tetracycline reduces its bioavailability via the formation of a poorly soluble complex. Other examples of complexes that reduce drug bioavailability are those between amphetamine and sodium carboxymethylcellulose, and between phenobarbitone and polyethylene glycol 4000. Complexation between drugs and excipients probably occurs quite often in liquid dosage forms.

Complexation is sometimes used to increase drug solubility, particularly of poorly water-soluble drugs. One class of complexing agents that is increasingly being employed is the cyclodextrin family. Cyclodextrins are enzymatically modified starches. They are composed of glucopyranose units which form a ring of either six (α-cyclodextrin), seven (β-cyclodextrin) or eight (γ-cyclodextrin) units. The outer surface of the ring is hydrophilic and the inner cavity is hydrophobic. Lipophilic molecules can fit into the ring to form soluble inclusion complexes. The ring of β-cyclodextrin is the correct size for the majority of drug molecules, and normally one drug molecule will associate with one cyclodextrin molecule to form reversible complexes, although other stoichiometries are possible. For example the antifungal miconazole shows poor oral bioavailability owing to its poor solubility. However, in the presence of cyclodextrin the solubility and dissolution rate of miconazole are significantly enhanced (by up to 55- and 255-fold, respectively). This enhancement of dissolution rate resulted in a more than doubling of the oral bioavailability in a study in rats (Terjarla et al 1998). There are numerous examples in the literature of drugs whose solubility and hence bioavailability have been increased by the use of cyclodextrins: they include piroxicam, itraconazole, indamethacin, pilocarpine, naproxen, hydrocortisone, diazepam and digitoxin. The first product on the UK market containing a cyclodextrin is the poorly soluble antifungal itraconazole, which has been formulated as a liquid dosage form with the more soluble derivative of β-cyclodextrin, hydroxypropyl-β-cyclodextrin.

Micellar solubization Micellar solubilization can also increase the solubility of drugs in the gastrointestinal tract. The ability of bile salts to solubilize drugs depends mainly on the lipophilicity of the drug (Naylor et al 1995). Further information on solubilization and complex formation can be found in Florence and Attwood (1998).

Adsorption The concurrent administration of drugs and medicines containing solid adsorbents (e.g. antidiarrhoeal mixtures) may result in the adsorbents interfering with the absorption of drugs from the gastrointestinal tract. The adsorption of a drug on to solid adsorbents such as kaolin or charcoal may reduce its rate and/or extent of absorption, owing to a decrease in the effective concentration of the drug in solution available for absorption. A consequence of the reduced concentration of free drug in solution at the site of absorption will be a reduction in the rate of drug absorption. Whether there is also a reduction in extent of absorption will depend on whether the drug–absorbent interaction is readily reversible. If the absorbed drug is not readily released from the solid absorbent in order to replace the free drug that has been absorbed from the gastrointestinal tract, there will also be a reduction in the extent of absorption from the gastrointestinal tract.

Examples of drug–adsorbent interactions that give reduced extents of absorption are promazine–charcoal and linomycin–kaopectate. The adsorbent properties of charcoal have been exploited as an antidote in drug intoxification.

Care also needs to be taken when insoluble excipients are included in dosage forms to check that the

drug will not adsorb to them. Talc, which can be included in tablets as a glidant, is claimed to interfere with the absorption of cyanocobalamin by virtue of its ability to adsorb this vitamin.

Further details of the biopharmaceutical implications of adsorption can be found in Florence and Attwood (1998).

Chemical stability of the drug in the gastrointestinal fluids If the drug is unstable in the gastrointestinal fluids the amount of drug that is available for absorption will be reduced and its bioavailability reduced. Instability in gastrointestinal fluids is usually caused by acidic or enzymatic hydrolysis. When a drug is unstable in gastric fluid its extent of degradation would be minimized (and hence its bioavailability improved) if it exhibited minimal dissolution in gastric fluid but still rapid dissolution in intestinal fluid. The concept of delaying the dissolution of a drug until it reaches the small intestine has been employed to improve the bioavailability of erythromycin in the gastrointestinal tract. Enteric coating of tablets containing the free base erythromycin is one method that has been used to protect this drug from gastric fluid. The enteric coating resists gastric fluid but disrupts or dissolves at the less acid pH range of the small intestine (see later and Chapter 28). An alternative method of protecting a susceptible drug from gastric fluid, which has been employed in the case of erythromycin, is the administration of chemical derivatives of the parent drug. These derivatives, or prodrugs, exhibit limited solubility (and hence minimal dissolution) in gastric fluid but, once in the small intestine, liberate the parent drug to be absorbed. For instance, erythromycin stearate, after passing through the stomach undissolved, dissolves and dissociates in the intestinal fluid, yielding the free base erythromycin that is absorbed.

Instability in gastrointestinal fluids is one of the reasons why many peptide-like drugs are poorly absorbed when delivered via the oral route.

Poorly soluble drugs

Poorly water-soluble drugs are increasingly becoming a problem in terms of obtaining the satisfactory dissolution within the gastrointestinal tract that is necessary for good bioavailability. It is not only existing drugs that cause problems, but it is the challenge of medicinal chemists to ensure that new drugs are not only active pharmacologically but have enough solubility to ensure fast-enough dissolution at the site of administration, often the gastrointestinal tract. This is a particular problem for certain classes of drugs, such as the HIV protease inhibitors, the glycoprotein IIb/IIIa inhibitors, and many anti-infective and anticancer drugs. Medicinal chemists are using approaches such as introducing ionizable groups, reducing melting points, changing polymorphs or introducing prodrugs to improve solubility. Further information on these approaches can be obtained from reviews by Lipinski et al (1997) and Panchagnula and Thomas (2000). Pharmaceutical scientists are also applying a wide range of formulation approaches to improve the dissolution rate of poorly soluble drugs. These include formulating in the nano-size range; formulating in a solid solution or dispersion or self-emulsifying drug delivery system; stabilizing the drug in the amorphous form or formulating with cyclodextrins. Many drug delivery companies thrive on technologies designed to improve the delivery of poorly soluble drugs.

Drug absorption

Once the drug has successfully passed into solution it is available for absorption. In Chapter 16 many physiological factors were shown to influence drug absorption. Absorption, and hence the bioavailability of a drug once in solution, is also influenced by many drug factors, in particular its pK_a, lipid solubility, molecular weight, the number of hydrogen bonds in the molecule and its chemical stability.

Drug dissociation and lipid solubility

The dissociation constant and lipid solubility of a drug, and the pH at the absorption site, often influence the absorption characteristics of a drug throughout the gastrointestinal tract. The interrelationship between the degree of ionization of a weak electrolyte drug (which is determined by its dissociation constant and the pH at the absorption site) and the extent of absorption is embodied in the pH-partition hypothesis of drug absorption, first proposed by Overton in 1899. Although it is an oversimplification of the complex process of absorption, the pH-partition hypothesis provides a useful framework for understanding the transcellular passive route of absorption, which is that favoured by the majority of drugs.

pH-partition hypothesis of drug absorption According to the pH-partition hypothesis, the gastrointestinal epithelia acts as a lipid barrier towards drugs which are absorbed by passive diffusion, and those that are lipid soluble will pass across the barrier. As most drugs are weak electrolytes, the unionized form of weakly acidic or basic drugs (i.e. the lipid-soluble

form) will pass across the gastrointestinal epithelia, whereas the gastrointestinal epithelia is impermeable to the ionized (i.e. poorly lipid-soluble) form of such drugs. Consequently, according to the pH-partition hypothesis, the absorption of a weak electrolyte will be determined chiefly by the extent to which the drug exists in its unionized form at the site of absorption.

The extent to which a weakly acidic or basic drug ionizes in solution in the gastrointestinal fluid may be calculated using the appropriate form of the Henderson–Hasselbalch equation (see Chapter 3). For a weakly acidic drug having a single ionizable group (e.g. aspirin, phenylbutazone, salicylic acid) the equation takes the form of:

$$\log \frac{[A^-]}{[HA]} = pH - pK_a \qquad (17.3)$$

where pK_a is the negative logarithm of the acid dissociation constant of the drug, and [HA] and [A^-] are the respective concentrations of the unionized and ionized forms of the weakly acidic drug, which are in equilibrium and in solution in the gastrointestinal fluid. pH refers to the pH of the environment of the ionized and unionized species, i.e. the gastrointestinal fluids.

For a weakly basic drug possessing a single ionizable group (e.g. chlorpromazine) the analogous equation is:

$$\log \frac{[BH^+]}{[B]} = pK_a - pH \qquad (17.4)$$

where [BH^+] and [B] are the respective concentrations of the ionized and unionized forms of the weak basic drug, which are in equilibrium and in solution in the gastrointestinal fluids.

Therefore, according to these equations a weakly acidic drug, pK_a 3.0, will be predominantly unionized in gastric fluid at pH 1.2 (98.4%) and almost totally ionized in intestinal fluid at pH 6.8 (99.98%), whereas a weakly basic drug, pK_a 5, will be almost entirely ionized (99.98%) at gastric pH of 1.2 and predominantly unionized at intestinal pH of 6.8 (98.4%). This means that, according to the pH-partition hypothesis, a weakly acidic drug is more likely to be absorbed from the stomach where it is unionized, and a weakly basic drug from the intestine where it is predominantly unionized. However, in practice, other factors need to be taken into consideration.

Limitations of the pH-partition hypothesis The extent to which a drug exists in its unionized form is not the only factor determining the rate and extent of absorption of a drug molecule from the gastrointestinal tract. Despite their high degree of ionization, weak acids are still quite well absorbed from the small intestine. In fact, the rate of intestinal absorption of a weak acid is often higher than its rate of absorption in the stomach, even though the drug is unionized in the stomach. The significantly larger surface area that is available for absorption in the small intestine more than compensates for the high degree of ionization of weakly acidic drugs at intestinal pH values. In addition, a longer small intestinal residence time and a microclimate pH, that exists at the surface of the intestinal mucosa and is lower than that of the luminal pH of the small intestine, are thought to aid the absorption of weak acids from the small intestine.

The mucosal unstirred layer is another recognized component of the gastrointestinal barrier to drug absorption that is not accounted for in the pH-partition hypothesis. During absorption drug molecules must diffuse across this layer and then on through the lipid layer. Diffusion across this layer is liable to be a significant component of the total absorption process for those drugs that cross the lipid layer very quickly. Diffusion across this layer will also depend on the relative molecular weight of the drug.

The pH-partition hypothesis cannot explain the fact that certain drugs (e.g. quaternary ammonium compounds and tetracyclines) are readily absorbed despite being ionized over the entire pH range of the gastrointestinal tract. One suggestion for this is that the gastrointestinal barrier is not completely impermeable to ionized drugs. It is now generally accepted that ionized forms of drugs are absorbed in the small intestine but at a much slower rate than the unionized form. Another possibility is that such drugs interact with endogenous organic ions of opposite charge to form an absorbable neutral species – an ***ion pair*** – which is capable of partitioning into the lipoidal gastrointestinal barrier and be absorbed via passive diffusion.

Another, physiological, factor that causes deviations from the pH-partition hypothesis is ***convective flow*** or ***solvent drag***. The movement of water molecules into and out of the gastrointestinal tract will affect the rate of passage of small water-soluble molecules across the gastrointestinal barrier. Water movement occurs because of differences in osmotic pressure between blood and the luminal contents, and differences in hydrostatic pressure between the lumen and the perivascular tissue. The absorption of water-soluble drugs will be increased if water flows from the lumen to the blood, provided that the drug and water are using the same route of absorption; this will have greatest effect in the jejunum, where water movement is at its greatest. Water flow also effects the absorption of lipid-soluble drugs. It is

thought that this is because the drug becomes more concentrated as water flows out of the intestine, thereby favouring a greater drug concentration gradient and increased absorption.

Lipid solubility A number of drugs are poorly absorbed from the gastrointestinal tract despite the fact that their unionized forms predominate. For example, the barbiturates, barbitone and thiopentone, have similar dissociation constants – pK_a 7.8 and 7.6, respectively – and therefore similar degrees of ionization at intestinal pH. However, thiopentone is absorbed much better than barbitone. The reason for this difference is that the absorption of drugs is also affected by the lipid solubility of the drug. Thiopentone, being more lipid soluble than barbitone, exhibits a greater affinity for the gastrointestinal membrane and is thus far better absorbed.

An indication of the lipid solubility of a drug, and therefore whether that drug is liable to be transported across membranes, is given by its ability to partition between a lipid-like solvent and water or an aqueous buffer. This is known as the drug's ***partition coefficient***, and is a measure of its lipophilicity. The value of the partition coefficient P is determined by measuring the drug partitioning between water and a suitable solvent at constant temperature. As this ratio normally spans several orders of magnitude it is usually expressed as the logarithmn. The organic solvent that is usually selected to mimic the biological membrane, because of its many similar properties, is octanol.

$$\text{Partition coefficient} = \frac{\text{concentration of drug in organic phase}}{\text{concentration in aqueous phase}} \quad (17.5)$$

The effective partition coefficient, taking into account the degree of ionization of the drug, is known as the ***distribution coefficient*** and again is normally expressed as the logarithm (log D); it is given by the following equations for acids and bases:

For acids:

$$D = \frac{[HA]_{org}}{[HA]_{aq} + [A^-]_{aq}} \quad (17.6)$$

$$\log D = \log P - [1 + \text{antilog}\,(pH - pK_a)] \quad (17.7)$$

For bases:

$$D = \frac{[B]_{org}}{[B]_{aq} + [BH^+]_{aq}} \quad (17.8)$$

$$\log D = \log P - [1 + \text{antilog}\,(pK_a - pH)] \quad (17.9)$$

The lipophilicity of a drug is critical in the drug discovery process. Polar molecules, i.e. those that are poorly lipid soluble (log $P < 0$) and relatively large, such as gentamicin, ceftriaxone, heparin and streptokinase, are poorly absorbed after oral administration and therefore have to be given by injection. Smaller molecules that are poorly lipid soluble, i.e. hydrophilic in nature, such as the β-blocker atenolol, can be absorbed via the paracellular route. Lipid-soluble drugs with favourable partition coefficients (i.e. log $P > 0$) are usually absorbed after oral administration. Drugs which are very lipid soluble (log $P >$ 3) tend to be well absorbed but are also more likely to be susceptible to metabolism and biliary clearance. Although there is no general rule that can be applied across all drug molecules, within a homologous series drug absorption usually increases as the lipophilicity rises. This has been shown for a series of barbiturates by Schanker (1960) and for a series of β-blockers by Taylor et al (1985).

Sometimes, if the structure of a compound cannot be modified to yield lipid solubility while maintaining pharmacological activity, medicinal chemists may investigate the probability of making lipid prodrugs to improve absorption. A prodrug is a chemical modification, frequently an ester of an existing drug, which converts back to the parent compound as a result of metabolism by the body. A prodrug has no pharmocological activity itself. Examples of prodrugs which have been successfully used to improve the lipid solubility and hence absorption of their parent drugs are shown in Table 17.3.

Molecular size and hydrogen bonding Two other drug properties that are important in permeability are the number of hydrogen bonds within the molecule and the molecular size

For paracellular absorption the molecular weight should ideally be less than 200 Da; however, there are examples where larger molecules (up to molecular weights of 400 Da) have been absorbed via this

Table 17.3 Prodrugs with improved lipid solubility and oral absorption

Parent drug	Prodrug	Ester
Ampicillin	Pivampicillin	Pivaloyloxymethyl
Ampicillin	Bacampicillin	Carbonate
Carbenicillin	Indanylcarbenicillin	Indanyl
Cefuroxime	Cefuroxime axetil	Acetylethyl
Enalaprilat	Enalapril	Ester of 1-carboxylic acid
Terbutaline	Ibuterol	Dibutyl

route. Shape is also an important factor for paracellular absorption.

In general, for transcellular passive diffusion a molecular weight of less than 500 Da is preferable. Drugs with molecular weights above this may be absorbed less efficiently. There are few examples of drugs with molecular weights above 700 Da being well absorbed.

Too many hydrogen bonds within a molecule are detrimental to its absorption. In general, no more than five hydrogen bond donors and no more than 10 hydrogen bond acceptors (the sum of nitrogen and oxygen atoms in the molecule is often taken as a rough measure of hydrogen bond acceptors) should be present if the molecule is to be well absorbed. The large number of hydrogen bonds within peptides is one of the reasons why peptide drugs are poorly absorbed.

Summary

There are many properties of the drug itself that will influence its passage into solution in the gastrointestinal tract and across the gastrointestinal membrane, and hence its overall rate and extent of absorption.

DOSAGE FORM FACTORS INFLUENCING BIOAVAILABILITY

Introduction

The rate and/or extent of absorption of a drug from the gastrointestinal tract have been shown to be influenced by many physiological factors and by many physicochemical properties associated with the drug itself. The bioavailability of a drug can also be influenced by factors associated with the formulation and production of the dosage form. Increasingly many dosage forms are being designed to affect the release and absorption of drugs, for example controlled-release systems (see Chapter 20) and delivery systems for poorly soluble drugs. This section focuses on summarizing how the type of dosage form and the excipients used in conventional oral dosage forms can affect the rate and extent of drug absorption.

Influence of the type of dosage form

The type of dosage form and its method of preparation or manufacture can influence bioavailability. Thus, whether a particular drug is incorporated and administered in the form of a solution, a suspension or solid dosage form can influence its rate and/or extent of absorption from the gastrointestinal tract. The type of oral dosage form will influence the number of possible intervening steps between administration and the appearance of dissolved drug in the gastrointestinal fluids, i.e. the type of dosage form will influence the release of drug into solution in the gastrointestinal fluids (Fig. 17.3).

In general, drugs must be in solution in the gastrointestinal fluids before absorption can occur. Thus the greater the number of intervening steps, the greater will be the number of potential obstacles to absorption and the greater will be the likelihood of that type of dosage form reducing the bioavailability

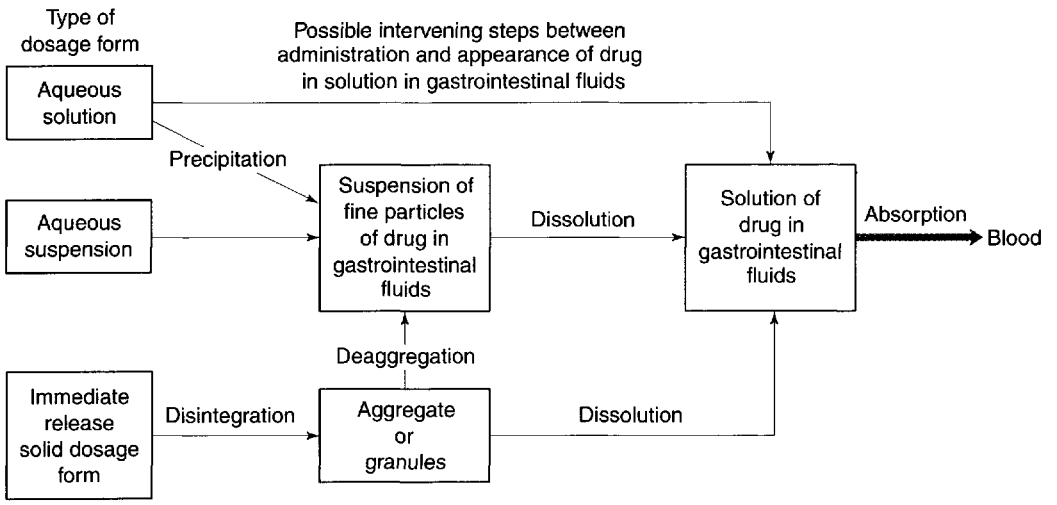


Fig. 17.3 Schematic outline of the influence of the dosage form on the appearance of drug in solution in the gastrointestinal tract.

exhibited by the drug. Hence the bioavailability of a given drug tends to decrease in the following order of types of dosage form: aqueous solutions > aqueous suspensions > solid dosage forms (e.g. hard gelatin capsules or tablets). Although this ranking is not universal, it does provide a useful guideline. In general, solutions and suspensions are the most suitable for administering drugs intended to be rapidly absorbed. However, it should be noted that other factors (e.g. stability, patient acceptability etc.) can also influence the type of dosage form in which a drug is administered via the gastrointestinal route.

Aqueous solutions

For drugs that are water soluble and chemically stable in aqueous solution, formulation as a solution normally eliminates the in vivo dissolution step and presents the drug in the most readily available form for absorption. However, dilution of an aqueous solution of a poorly water-soluble drug whose aqueous solubility had been increased by formulation techniques such as cosolvency, complex formation or solubilization can result in precipitation of the drug in the gastric fluids. Similarly, exposure of an aqueous solution of a salt of a weak acidic compound to gastric pH can also result in precipitation of the free acid form of the drug. In most cases the extremely fine nature of the resulting precipitate permits a more rapid rate of dissolution than if the drug had been administered in other types of oral dosage forms, such as aqueous suspension, hard gelatin capsule or tablet. However, for some drugs this precipitation can have a major effect on bioavailability. The same dose of an experimental drug was given to dogs in three different solution formulations, a polyethlyene glycol solution and two different concentrations of hydroxypropyl-β-cyclodextrin. Bioavailabilities of 19%, 57% and 89% were obtained for polyethylene glycol, the lower concentration and the higher concentration of hydroxypropyl-β-cyclodextrin, respectively. The difference in bioavailability of the three solutions was attributed to the difference in precipitation rates of the candidate drug from the three solutions on dilution. The experimental drug was observed to precipitate most quickly from the polyethylene glycol solution, and slowest from the most concentrated hydroxypropyl-β-cyclodextrin solution.

Factors associated with the formulation of aqueous solutions that can influence drug bioavailability include:

- The chemical stability exhibited by the drug in aqueous solution and the gastrointestinal fluids;
- Complexation, i.e. the formation of a complex between the drug and an excipient included to increase the aqueous solubility, the chemical stability of the drug or the viscosity of the dosage form;
- Solubilization, i.e. the incorporation of the drug into micelles in order to increase its aqueous solubility;
- The viscosity of a solution dosage form, particularly if a viscosity-enhancing agent has been included.

Information concerning the potential influence of each of the above factors was given earlier. Further details concerning the formulation of oral solution dosage forms are given in Chapter 21.

Aqueous suspensions

An aqueous suspension is a useful dosage form for administering an insoluble or poorly water-soluble drug. Usually the absorption of a drug from this type of dosage form is dissolution-rate limited. The oral administration of an aqueous suspension results in a large total surface area of dispersed drug being immediately presented to the gastrointestinal fluids. This facilitates dissolution and hence absorption of the drug. In contrast to powder-filled hard gelatin capsule and tablet dosage forms, dissolution of all drug particles commences immediately on dilution of the suspension in the gastrointestinal fluids. A drug contained in a tablet or hard gelatin capsule may ultimately achieve the same state of dispersion in the gastrointestinal fluids, but only after a delay. Thus a well formulated, finely subdivided aqueous suspension is regarded as being an efficient oral drug delivery system, second only to a non-precipitating solution-type dosage form.

Factors associated with the formulation of aqueous suspension dosage forms that can influence the bioavailabilities of drugs from the gastrointestinal tract include:

- The particle size and effective surface area of the dispersed drug;
- The crystal form of the drug;
- Any resulting complexation, i.e. the formation of a non-absorbable complex between the drug and an excipient such as the suspending agent;
- The inclusion of a surfactant as a wetting, flocculating or deflocculating agent;
- The viscosity of the suspension.

Information concerning the potential influence of the above factors on drug bioavailability is given in earlier sections. Further information concerning the

formulation and uses of suspensions as dosage forms is given in Chapter 23.

Liquid-filled capsules

Liquids can be filled into capsules made from soft or hard gelatin. Both types combine the convenience of a unit dosage form with the potentially rapid drug absorption associated with aqueous solutions and suspensions. Drugs encapsulated in liquid-filled capsules for peroral administration are dissolved or dispersed in non-toxic, non-aqueous vehicles. Such vehicles may be water immiscible (i.e. lipophilic) or water miscible (i.e. hydrophilic). Vegetable oils are popular water-immiscible vehicles, whereas polyethylene glycols and certain non-ionic surfactants (e.g. polysorbate-80) are water miscible. Sometimes the vehicles have thermal properties such that they can be filled into capsules while hot, but are solids at room temperature.

The release of the contents of gelatin capsules is effected by dissolution and splitting of the flexible shell. Following release, a water-miscible vehicle disperses and/or dissolves readily in the gastrointestinal fluids, liberating the drug (depending on its aqueous solubility) as either a solution or a fine suspension, which is conducive to rapid absorption. In the case of gelatin capsules containing drugs in solution or suspension in water-immiscible vehicles, release of the contents will almost certainly be followed by dispersion in the gastrointestinal fluids. Dispersion is facilitated by emulsifiers included in the vehicle, and also by bile. Once dispersed, the drug may end up as an emulsion, a solution, a fine suspension or a nano/microemulsion. Well formulated liquid-filled capsules aimed at improving the absorption of poorly soluble drugs will ensure that no precipitation of drug occurs from the nano- or microemulsion in the gastrointestinal fluids. If the lipophilic vehicle is a digestible oil and the drug is highly soluble in the oil, it is possible that the drug will remain in solution in the dispersed oil phase and be absorbed (along with the oil) by fat absorption processes. For a drug that is less lipophilic or is dissolved in a non-digestible oil, absorption probably occurs following partitioning of the drug from the oily vehicle into the aqueous gastrointestinal fluids. In this case the rate of drug absorption appears to depend on the rate at which drug partitions from the dispersed oil phase. The increase in interfacial area of contact resulting from dispersion of the oily vehicle in the gastrointestinal fluids will facilitate partition of the drug across the oil/aqueous interface. For drugs suspended in an oily vehicle release may involve dissolution in the vehicle, diffusion to the oil/aqueous interface and partition across the interface.

Many poorly water-soluble drugs have been found to exhibit greater bioavailabilities from liquid-filled capsule formulations. The cardiac glycoside digoxin, when formulated as a solution in a mixture of polyethylene glycol, ethanol and propylene glycol in a soft gelatin capsule, has been shown to be absorbed faster than the standard commercial tablets.

More recently, far more complex capsule formulations have been investigated to improve the absorption of poorly soluble drugs. Cyclosporin is a hydrophobic drug with poor solubility in gastrointestinal fluids. It showed low and variable oral bioavailability from its original liquid-filled soft gelatin capsule formulation (Sandimmun) and was particularly sensitive to the presence of fat in diet and bile acids. In its new formulation (Sandimmun Neoral), which is a complex mixture of hydrophilic and lipophilic phases, surfactants, cosurfactants and a cosolvent, it forms a non-precipitating microemulsion on dilution with gastrointestinal fluids. It has a significantly improved bioavailability with reduced variability that is independent of the presence of food (Drewe et al 1992).

Many protease inhibitors (antiviral drugs) are peptidomimetic in nature. They have high molecular weights and low aqueous solubility, are susceptible to degradation in the lumen and extensive hepatic metabolism, and consequently have poor bioavailability (Barry et al 1997). Saquinavir has recently been reformulated from a powder-filled hard gelatin capsule (Invirase) to a complex soft gelatin formulation (Fortovase). The latter shows a significant improvement in bioavailability (3–4 times) over the standard hard gelatin formulation, and as a consequence, a significantly greater viral load reduction (Perry and Noble 1998)

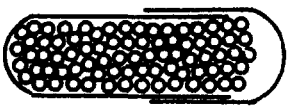
Factors associated with the formulation of liquid-filled gelatin capsules which can influence the bioavailabilities of drugs from this type of dosage form include:

- the solubility of the drug in the vehicle (and gastrointestinal fluids);
- the particle size of the drug (if suspended in the vehicle);
- the nature of the vehicle, i.e. hydrophilic or lipophilic (and whether a lipophilic vehicle is a digestible or a non-digestible oil);
- the inclusion of a surfactant as a wetting/emulsifying agent in a lipophilic vehicle or as the vehicle itself;
- the inclusion of a suspending agent (viscosity-enhancing agent) in the vehicle;
- the complexation, i.e. formation, of a non-absorbable complex between the drug and any excipient.

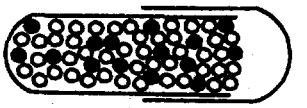
Powder-filled capsules

Generally the bioavailability of a drug from a well formulated powder-filled hard gelatin capsule dosage form will be better than or at least equal to that from the same drug in a compressed tablet. Provided the hard gelatin shell dissolves rapidly in the gastrointestinal fluids and the encapsulated mass disperses rapidly and efficiently, a relatively large effective surface area of drug will be exposed to the gastrointestinal fluids, thereby facilitating dissolution. However, it is incorrect to assume that a drug formulated as a hard gelatin capsule is in a finely divided form surrounded by a water-soluble shell, and that no bioavailability problems can occur. The overall rate of dissolution of drugs from capsules appears to be a complex function of the rates of different processes, such as the dissolution rate of the gelatin shell, the rate of penetration of the gastrointestinal fluids into the encapsulated mass, the rate at which the mass deaggregates (i.e. disperses) in the gastrointestinal fluids, and the rate of dissolution of the dispersed drug particles.

The inclusion of excipients (e.g. diluents, lubricants and surfactants) in a capsule formulation can have a significant effect on the rate of dissolution of drugs, particularly those that are poorly soluble and hydrophobic. Figure 17.4 shows that a hydrophilic diluent (e.g. sorbitol, lactose) often serves to increase the rate of penetration of the aqueous gastrointestinal fluids into the contents of the capsule, and to aid the

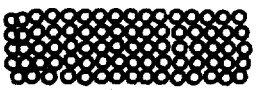


Hard gelatin capsule containing only hydrophobic drug particles

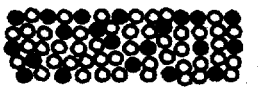


Hard gelatin capsule containing hydrophobic drug particles (o) and hydrophilic diluent particles (•)

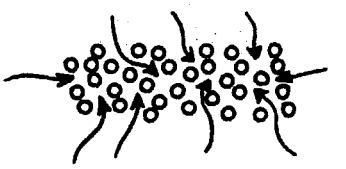
In gastrointestinal fluids, hard gelatin capsule shell dissolves, thereby exposing contents to fluids



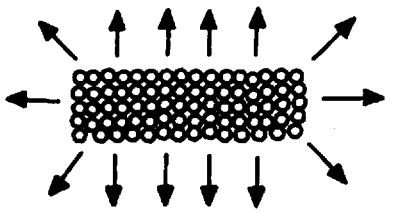
Contents remain as a capsule-shaped plug. Hydrophobic nature of contents impedes penetration of gastrointestinal fluids



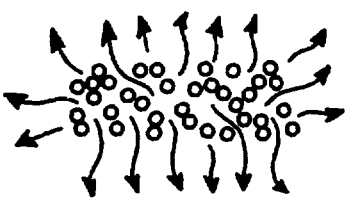
Particles of hydrophilic diluent dissolve in gastrointestinal fluids leaving a porous mass of drug



Gastrointestinal fluids can penetrate porous mass



Dissolution of drug occurs only from surface of plug-shaped mass. Relatively low rate of dissolution



Effective surface area of drug and hence dissolution rate is increased

Fig. 17.4 Diagrammatic representation of how a hydrophilic diluent can increase the rate of dissolution of a poorly soluble, hydrophobic drug from a hard gelatin capsule.

dispersion and subsequent dissolution of the drug in these fluids. However, the diluent should exhibit no tendency to adsorb or complex with the drug, as either can impair absorption from the gastrointestinal tract.

Both the formulation and the type and conditions of the capsule-filling process can affect the packing density and liquid permeability of the capsule contents. In general, an increase in packing density (i.e. a decrease in porosity) of the encapsulated mass will probably result in a decrease in liquid permeability and dissolution rate, particularly if the drug is hydrophobic, or if a hydrophilic drug is mixed with a hydrophobic lubricant such as magnesium stearate. If the encapsulated mass is tightly packed and the drug is hydrophobic in nature, then a decrease in dissolution rate with a concomitant reduction in particle size would be expected, unless a surfactant had been included to facilitate liquid penetration.

In summary, formulation factors that can influence the bioavailabilities of drugs from hard gelatin capsules include:

- the surface area and particle size of the drug (particularly the effective surface area exhibited by the drug in the gastrointestinal fluids);
- the use of the salt form of a drug in preference to the parent weak acid or base;
- the crystal form of the drug;
- the chemical stability of the drug (in the dosage form and in gastrointestinal fluids);
- the nature and quantity of the diluent, lubricant and wetting agent;
- drug–excipient interactions (e.g. adsorption, complexation);
- the type and conditions of the filling process;
- the packing density of the capsule contents;
- the composition and properties of the capsule shell (including enteric capsules);
- interactions between the capsule shell and its contents.

Tablets

Uncoated tablets Tablets are the most widely used dosage form. When a drug is formulated as a compressed tablet there is an enormous reduction in the effective surface area of the drug, owing to the granulation and compression processes involved in tablet making. These processes necessitate the addition of excipients, which serve to return the surface area of the drug back to its original precompressed state. Bioavailability problems can arise if a fine, well dispersed suspension of drug particles in the gastrointestinal fluids is not generated following the administration of a tablet. Because the effective surface area of a poorly soluble drug is an important factor influencing its dissolution rate, it is especially important that tablets containing such drugs should disintegrate rapidly and completely in the gastrointestinal fluids if rapid release, dissolution and absorption are required. The overall rate of tablet disintegration is influenced by several interdependent factors, which include the concentration and type of drug, diluent, binder, disintegrant, lubricant and wetting agent, as well as the compaction pressure (see Chapter 27).

The dissolution of a poorly soluble drug from an intact tablet is usually extremely limited because of the relatively small effective surface area of drug exposed to the gastrointestinal fluids. Disintegration of the tablet into granules causes a relatively large increase in effective surface area of drug and the dissolution rate may be likened to that of a coarse, aggregated suspension. Further disintegration into small, primary drug particles produces a further large increase in effective surface area and dissolution rate. The dissolution rate is probably comparable to that of a fine, well dispersed suspension. Disintegration of a tablet into primary particles is thus important, as it ensures that a large effective surface area of a drug is generated in order to facilitate dissolution and subsequent absorption.

However, simply because a tablet disintegrates rapidly this does not necessarily guarantee that the liberated primary drug particles will dissolve in the gastrointestinal fluids, and that the rate and extent of absorption are adequate. In the case of poorly soluble drugs the rate-controlling step is usually the overall rate of dissolution of the liberated drug particles in the gastrointestinal fluids. The overall dissolution rate and bioavailability of a poorly soluble drug from an uncoated conventional tablet is influenced by many factors associated with the formulation and manufacture of this type of dosage form. These include:

- the physicochemical properties of the liberated drug particles in the gastrointestinal fluids, e.g. wettability, effective surface area, crystal form, chemical stability;
- the nature and quantity of the diluent, binder, disintegrant, lubricant and any wetting agent;
- drug–excipient interactions (e.g. complexation), the size of the granules and their method of manufacture;
- the compaction pressure and speed of compression used in tabletting;
- the conditions of storage and age of the tablet.

Because drug absorption and hence bioavailability are dependent upon the drug being in the dissolved

state, suitable dissolution characteristics can be an important property of a satisfactory tablet, particularly if it contains a poorly soluble drug. On this basis, specific in vitro dissolution test conditions and dissolution limits are included in the *British Pharmacopoeia* for tablets (and hard gelatin capsules) containing certain drugs, e.g. digoxin. That a particular drug product meets the requirements of a compendial dissolution standard provides a greater assurance that the drug will be released satisfactorily from the formulated dosage form in vivo and be absorbed adequately (see also Chapter 18).

Coated tablets Tablet coatings may be used simply for aesthetic reasons to improve the appearance of a tablet or to add a company logo, or may be employed to mask an unpleasant taste or odour or to protect an ingredient from decomposition during storage. Currently the most common type of tablet coat is film; however, several older preparations, such as vitamins and ibuprofen, still have sugar coats. The presence of a coating presents a physical barrier between the tablet core and the gastrointestinal fluids: coated tablets therefore not only possess all the potential bioavailability problems associated with uncoated conventional tablets, but are subject to the additional potential problem of being surrounded by a physical barrier. In the case of a coated tablet which is intended to disintegrate and release drug rapidly into solution in the gastrointestinal fluids, the coating must dissolve or disrupt before these processes can occur. The physicochemical nature and thickness of the coating can thus influence how quickly a drug is released from a tablet.

In the process of sugar coating the tablet core is usually sealed with a thin continuous film of a poorly water-soluble polymer such as shellac or cellulose acetate phthalate. This sealing coat serves to protect the tablet core and its contents from the aqueous fluids used in the subsequent steps of the sugar-coating process. Hence the presence of this water-impermeable sealing coat can potentially retard drug release from sugar-coated tablets. In view of this potential problem, annealing agents such as polyethylene glycols or calcium carbonate, which do not substantially reduce the water impermeability of the sealing coat during sugar coating, but which dissolve readily in gastric fluid, may be added to the sealer coat in order to reduce the barrier effect to rapid drug release.

The coating of a tablet core by a thin film of a water-soluble polymer, such as hydroxypropyl methylcellulose, should have no significant effect on the rate of disintegration of the tablet core and subsequent drug dissolution, provided that the film coat dissolves rapidly and independently of the pH of the gastrointestinal fluids. However, if hydrophobic water-insoluble film-coating materials, such as ethylcellulose or certain acrylic resins, are used (see Chapter 28), the resulting film coat acts as a barrier which delays and/or reduces the rate of drug release. Thus these types of film-coating materials form barriers which can have a significant influence on drug absorption. Although the formation of such barriers would be disadvantageous in the case of film-coated tablets intended to provide rapid rates of drug absorption, the concept of barrier coating has been used (along with other techniques) to obtain more precise control over drug release than is possible with conventional uncoated tablets (see Chapter 20). In this context, film coating has been used to provide limited control over the site at which a drug is released from a tablet into the gastrointestinal tract.

Enteric-coated tablets The use of barrier coating to control the site of release of an orally administered drug is well illustrated by enteric-coated tablets. An enteric coat is designed to resist the low pH of gastric fluids but to disrupt or dissolve when the tablet enters the higher pH of the duodenum. Polymers such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, the copolymers of methacrylic acid and their esters and polyvinyl acetate phthalate, can be used as enteric coatings. These materials do not dissolve over the gastric pH range but dissolve rapidly at the less acid pH (about 5) values associated with the small intestine. Enteric coating should preferably begin to dissolve at pH5 in order to ensure the availability of drugs which are absorbed primarily in the proximal region of the small intestine. Enteric coating thus provides a means of delaying the release of a drug until the dosage form reaches the small intestine. Such delayed release provides a means of protecting drugs which would otherwise be destroyed if released into gastric fluid. Hence, enteric coating serves to improve the oral bioavailability exhibited by such drugs from uncoated conventional tablets. Enteric coating also protects the stomach against drugs which can produce nausea or mucosal irritation (e.g. aspirin, ibuprofen) if released at this site.

In addition to the protection offered by enteric coating, the delayed release of drug also results in a significant delay in the onset of the therapeutic response of a drug. The onset of the therapeutic response is largely dependent on the residence time of the enteric-coated tablet in the stomach. Gastric emptying of such tablets is an all-or-nothing process, i.e. the tablet is either in the stomach or in the duodenum. Consequently, drug is either not being released or being released. The residence time of an intact enteric-coated tablet in the stomach can vary from about 5 minutes to several hours (see Chapter 16).

Hence there is considerable intra- and intersubject variation in the onset of therapeutic action exhibited by drugs administered as enteric-coated tablets.

The formulation of an enteric-coated product in the form of small individually enteric-coated granules or pellets (multiparticulates) contained in a rapidly dissolving hard gelatin capsule or a rapidly disintegrating tablet, largely eliminates the dependency of this type of dosage form on the all-or-nothing gastric emptying process associated with intact (monolith) enteric coated tablets. Provided the coated granules or pellets are sufficiently small (less than 1 mm diameter), they will be able to empty from the stomach with liquids. Hence enteric-coated granules and pellets exhibit a gradual but continual release from the stomach into the duodenum. This type of release also avoids the complete dose of drug being released into the duodenum, as occurs with an enteric-coated tablet. The intestinal mucosa is thus not exposed locally to a potentially toxic concentration of drug.

Further information on coated tablets and multiparticulates is given in Chapter 28.

Influence of excipients for conventional dosage forms

Drugs are almost never administered alone but rather in the form of dosage forms that generally consist of a drug (or drugs) together with a varying number of other substances (called ***excipients***). Excipients are added to the formulation in order to facilitate the preparation, patient acceptability and functioning of the dosage form as a drug delivery system. Excipients include disintegrating agents, diluents, lubricants, suspending agents, emulsifying agents, flavouring agents, colouring agents, chemical stabilizers etc. Although historically excipients were considered to be inert in that they themselves should exert no therapeutic or biological action, or modify the biological action of the drug present in the dosage form, they are now regarded as having the ability to influence the rate and/or extent of absorption of the drug. For instance, the potential influence of excipients on drug bioavailability has already been illustrated by virtue of the formation of poorly soluble, non-absorbable drug–excipient complexes between tetracyclines and dicalcium phosphate, amphetamine and sodium carboxymethylcellulose, and phenobarbitone and polyethylene glycol 4000.

Diluents

The classic example of the influence that excipients employed as diluents can have on drug bioavailability is provided by the Australian outbreak of phenytoin intoxication which occurred in epileptic patients as a consequence of the diluent in sodium phenytoin capsules being changed. Many epileptic patients who had been previously stabilized with sodium phenytoin capsules containing calcium sulphate dihydrate as the diluent, developed clinical features of phenytoin overdosage when given sodium phenytoin capsules containing lactose as the diluent even though the quantity of drug in each capsule formulation was identical. It was later shown that the excipient calcium sulphate dihydrate had been responsible for decreasing the gastrointestinal absorption of phenytoin, possibly because part of the administered dose of drug formed a poorly absorbable calcium–phenytoin complex. Hence, although the size of dose and frequency of administration of the sodium phenytoin capsules containing calcium sulphate dihydrate gave therapeutic blood levels of phenytoin in epileptic patients, the efficiency of absorption of phenytoin had been lowered by the incorporation of this excipient in the hard gelatin capsules. Hence, when the calcium sulphate dihydrate was replaced by lactose without any alteration in the quantity of drug in each capsule, or in the frequency of administration, an increased bioavailability of phenytoin was achieved. In many patients the higher plasma levels exceeded the maximum safe concentration for phenytoin and produced toxic side-effects.

Surfactants

Surfactants are often used in dosage forms as emulsifying agents, solubilizing agents, suspension stabilizers or wetting agents. However, surfactants in general cannot be assumed to be 'inert' excipients as they have been shown to be capable of either increasing, decreasing or exerting no effect on the transfer of drugs across biological membranes.

Surfactant monomers can potentially disrupt the integrity and function of a biological membrane. Such an effect would tend to enhance drug penetration and hence absorption across the gastrointestinal barrier, but may also result in toxic side-effects. Inhibition of absorption may occur as a consequence of a drug being incorporated into surfactant micelles. If such surfactant micelles are not absorbed, which appears usually to be the case, then solubilization of a drug may result in a reduction of the concentration of 'free' drug in solution in the gastrointestinal fluids that is available for absorption. Inhibition of drug absorption in the presence of micellar concentrations of surfactant would be

expected to occur in the case of drugs that are normally soluble in the gastrointestinal fluids, i.e. in the absence of surfactant. Conversely, in the case of poorly soluble drugs whose absorption is dissolution-rate limited, the increase in saturation solubility of the drug by solubilization in surfactant micelles could result in more rapid rates of dissolution and hence absorption.

The release of poorly soluble drugs from tablets and hard gelatin capsules may be increased by the inclusion of surfactants in their formulations. The ability of a surfactant to reduce the solid/liquid interfacial tension will permit the gastrointestinal fluids to wet the solid more effectively, and thus enable it to come into more intimate contact with the solid dosage forms. This wetting effect may thus aid the penetration of gastrointestinal fluids into the mass of capsule contents that often remains when the hard gelatin shell has dissolved, and/or reduce the tendency of poorly soluble drug particles to aggregate in the gastrointestinal fluids. In each case, the resulting increase in the total effective surface area of drug in contact with the gastrointestinal fluids would tend to increase the dissolution and absorption rates of the drug. It is interesting to note that the enhanced gastrointestinal absorption of phenacetin in humans resulting from the addition of polysorbate-80 to an aqueous suspension of this drug was attributed to the surfactant preventing aggregation and thus increasing the effective surface area and dissolution rate of the drug particles in the gastrointestinal fluids.

The possible mechanisms by which surfactants can influence drug absorption are varied and it is likely that only rarely will a single mechanism operate in isolation. In most cases the overall effect on drug absorption will probably involve a number of different actions of the surfactant (some of which will produce opposing effects on drug absorption), and the observed effect on drug absorption will depend on which of the different actions is the overriding one. The ability of a surfactant to influence drug absorption will also depend on the physicochemical characteristics and concentration of the surfactant, the nature of the drug and the type of biological membrane involved.

Lubricants

Both tablets and capsules require lubricants in their formulation to reduce friction between the powder and metal surfaces during their manufacture. Lubricants are often hydrophobic in nature. Magnesium stearate is commonly included as a lubricant during tablet compression and capsule-filling operations. Its hydrophobic nature often retards liquid penetration into capsule ingredients, so that after the shell has dissolved in the gastrointestinal fluids a capsule-shaped plug often remains, especially when the contents have been machine-filled as a consolidated plug (Chapter 29). Similar reductions in dissolution rate may be observed when magnesium stearate is included in tablets. However, these effects can usually be overcome by the simultaneous addition of a wetting agent (i.e. a water-soluble surfactant) and the use of a hydrophilic diluent.

Disintegrants

Disintegrants are required to break up capsules, tablets and granules into primary powder particles in order to increase the surface area of the drug exposed to the gastrointestinal fluids. A tablet that fails to disintegrate or disintegrates slowly may result in incomplete absorption or a delay in the onset of action of the drug. The compaction force used in tablet manufacture can affect disintegration: in general, the higher the force the slower the disintegration time. Even small changes in formulation may result in significant effects on dissolution and bioavailability. A classic example is that of tolbutamide, where two formulations, the commercial product and the same formulation but with half the amount of disintegrant, were administered to healthy volunteers. Both tablets disintegrated in vitro within 10 minutes meeting pharmacopoeial specifications, but the commercial tablet had a significantly greater bioavailability and hypoglycaemic response.

Viscosity-enhancing agents

Viscosity-enhancing agents are often employed in the formulation of liquid dosage forms for oral use in order to control such properties as palatability, ease of pouring and, in the case of suspensions, the rate of sedimentation of the dispersed particles. The viscosity-enhancing agent is often a hydrophilic polymer.

There are a number of mechanisms by which a viscosity-enhancing agent may produce a change in the gastrointestinal absorption of a drug. Complex formation between a drug and a hydrophilic polymer could reduce the concentration of drug in solution that is available for absorption. The administration of viscous solutions or suspensions may produce an increase in viscosity of the gastrointestinal contents. This could lead to a decrease in dissolution rate and/or a decrease in the rate of movement of drug molecules to the absorbing membrane.

Normally, a decrease in the rate of dissolution would not be applicable to solution dosage forms unless dilution of the administered solution in the gastrointestinal fluids caused precipitation of the drug.

In the case of suspensions containing drugs with bioavailabilities that are dissolution-rate dependent, an increase in viscosity could also lead to a decrease in the rate of dissolution of the drug in the gastrointestinal tract.

Summary

As well as physiological and drug factors, the dosage form can play a major role in influencing the rate and extent of absorption. Often this is by design. However, even with conventional dosage forms it is important to consider whether changing the dosage form or excipients will affect the bioavailability of the drug. Some drugs will be more susceptible to changes in rate and extent of absorption through dosage form changes than others: this will depend on the biopharmaceutical properties of the drug (see Chapter 18).

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18

Assessment of biopharmaceutical properties

Marianne Ashford

CHAPTER CONTENTS

INTRODUCTION

Biopharmaceutics is involved with factors that influence the rate and extent of drug absorption. As discussed in Chapters 16 and 17, the factors that affect the release of a drug from its dosage form, its dissolution into physiological fluids, its stability within those fluids, its permeability across the relevant biological membranes and its presystemic metabolism will all influence its rate and extent of absorption (Fig. 18.1). Once the drug is absorbed into the systemic circulation, its distribution within the body tissues (including to its site of action), its metabolism and elimination are described by the pharmacokinetics of the compound. The pharmacokinetics of the compound influence the length and magnitude of the therapeutic effect or the response of the compound, i.e. its pharmacodynamics (see Chapter 15).

The key biopharmaceutical properties that can be quantified and therefore give an insight into the absorption of a drug are its:

- release from its dosage form into solution at the absorption site;
- stability in physiological fluids;
- permeability;
- susceptibility to presystemic clearance.

As most drugs are delivered via the mouth, these properties will be discussed with respect to the peroral route. The bioavailability of a compound is an overall measure of its availability in the systemic circulation, and so the assessment of bioavailability will also be discussed. Other methods of assessing the performance of dosage forms in vivo will also be briefly mentioned. The Biopharmaceutical Classification Scheme, which classifies drugs according to two of their key biopharmaceutical properties, solubility and permeability, is outlined.

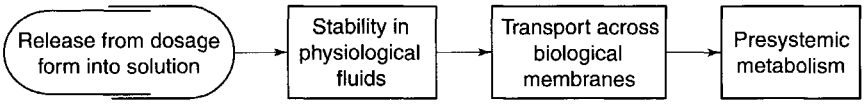

Fig. 18.1 Key biopharmaceutical properties affecting drug absorption.

MEASUREMENT OF KEY BIOPHARMACEUTICAL PROPERTIES

Release of drug from its dosage form into solution

As discussed in the Chapter 17 and Part 4 of this book, a dosage form is normally formulated to aid the release of drug from it. For example, for an immediate-release tablet, the tablet needs to disintegrate to give the primary drug particles. Further, a suspension should not be so thick that it impedes the diffusion of dissolving drug away from the solid particles.

The solubility of a drug across the gastrointestinal pH range will be one of the first indicators as to whether dissolution is liable to be rate limiting in the absorption process. A knowledge of the solubility across the gastrointestinal pH range can be determined by measuring the equilibrium solubility in suitable buffers or by using an acid or a base titration method.

Methods of measuring the dissolution rate of both a drug itself (intrinsic dissolution rate) and of various dosage forms are discussed in Chapters 8 and 2, respectively.

The aim of dissolution testing is to find an in vitro characteristic of a potential formulation that reflects its in vivo performance. Historically, dissolution tests have been developed mainly for quality control purposes and as a guide in the development of new formulations, rather than to predict the in vivo performance of the product. The tests tend to be carried out with standard procedures (volumes, agitation rates etc.) and under sink conditions. These conditions are not representative of physiological conditions and are therefore liable to correlate poorly with the in vivo situation.

When designing a dissolution test to assess drug release from a biopharmaceutical perspective, it is important to mimic as closely as possible the conditions of the gastrointestinal tract. Clinical scientists increasingly want to rely on dissolution tests to establish in vitro/in vivo correlations between the release of drug from the dosage form and its absorption. If this can be successfully achieved, it is possible that the dissolution test could replace some of the in vivo studies that need to be performed during product development and registration. Such correlations should have the benefit of reducing both the use of animals to evaluate formulations and the size and number of costly clinical studies to assess bioavailability.

An in vitro/in vivo correlation may only be possible for those drugs where dissolution is the rate-limiting step in the absorption process. Determining full dissolution profiles of such drugs in a number of different physiologically representative media will aid the understanding of the factors affecting the rate and extent of dissolution. The profiles can also be used to generate an in vitro/in vivo correlation. To achieve this, at least three batches that differ in their in vivo as well as their in vitro behaviour should be available. The differences in the in vivo profiles need to be mirrored by the formulations in vitro. Normally, the in vitro test conditions can be modified to correspond with the in vivo data to achieve a correlation. Very often a well designed in vitro dissolution test is found to be more sensitive and discriminating than the in vivo test. From a quality assurance perspective a more discriminative dissolution method is preferred because the test will indicate possible changes in the product before the in vivo performance is affected.

A dilute hydrochloric acid-based solution at pH 1.2 can simulate gastric fluid, and phosphate-buffered solution at pH 6.8 can mimic intestinal fluid. However, dissolution media more closely representing physiological conditions may well provide more relevant conditions. Dressman et al (1998) studied in detail a range of physiological parameters and suggested four more appropriate media for simulated gastric and intestinal conditions in the fed and fasted states. Each of these media takes into account not only the pH of the fluids in the different states, but their ionic composition, surface tension, buffer capacity and bile and lecithin contents. The proposed composition for gastric fluid in the fasted state and intestinal fluids in the fed and fasted states are shown in Tables 18.1–18.3.

In the fed state the conditions in the stomach are highly dependent on the composition of the meal eaten and therefore difficult to simulate. In trying to produce an in vitro/in vivo correlation it has been suggested that a more appropriate way of simulating the fed-state gastric fluids is to homogenize the meal to be used in clinical studies and then dilute it with

Table 18.1 Dissolution medium to simulate gastric conditions in the fasted state (proposed by Dressman et al 1998)

Component	Concentration/amount
Hydrochloric acid	0.01–0.05 M
Sodium lauryl sulphate	2.5 g
Sodium chloride	2 g
Distilled water	qs to 1000 mL

Table 18.2 Dissolution medium to simulate intestinal conditions in the fasted state (proposed by Dressman et al 1998)

Component	Concentration/amount
Potassium dihydrogen phosphate	0.029 M
Sodium hydroxide	qs to pH 6.8
Sodium taurocholate (bile salt)	5 mM
Lecithin	1.5 mM
Potassium chloride	0.22 M
Distilled water	qs to 1000 mL

pH = 6.8, osmolarity = 280–310 mOSm.
Buffer capacity = 10 ± 2 mEq/L/pH.

Table 18.3 Dissolution medium to simulate intestinal conditions in the fed state (proposed by Dressman et al 1998)

Component	Concentration/amount
Acetic acid	0.144 M
Sodium hydroxide	qs to pH 5
Sodium taurocholate (bile salt)	15 mM
Lecithin	4 mM
Potassium chloride	0.19 M
Distilled water	qs to 1000 mL

pH = 5, osmolarity = 485–535 mOSm.
Buffer capacity = 76 ± 2 mEq/L/pH

water. Long-life milk has also been used to simulate gastric conditions in the fed state.

It has been proposed that the duration of the dissolution test should depend on the site of absorption of the drug and its timing of administration. Thus, in designing a dissolution test some knowledge or prediction of the permeability properties of the drug is beneficial. If, for example, the drug is absorbed from the upper intestine and is likely to be dosed in the fasted state, the most appropriate dissolution conditions may be a short test (~ 15–30 minutes) in a medium simulating gastric fluid in the fasted state (see Table 18.1). Alternatively, if it is advised that a drug should be administered with food, and it is known to be well absorbed throughout the length of the gastrointestinal tract, a far longer dissolution test, perhaps several hours in duration, with a range of media such as, initially, simulated gastric fluid for the fed state, simulated intestinal fluid for the fed and then the fasted states, may be more appropriate.

The volumes in, and agitation of, the stomach and intestines vary enormously, particularly between the fed and the fasted states, and so it is difficult to choose a representative volume and degree of agitation. The latest Guidance for Industry on the dissolution testing of immediate-release solid oral dosage forms from the Food and Drug Administration (1997) suggests volumes of 500, 900 or 1000 mL and gentle agitation conditions.

Stability in physiological fluids

The stability of drugs in physiological fluids (in the case of orally administered drugs, the gastrointestinal fluids) depends on two factors: the chemical stability of the drug across the gastrointestinal pH range, i.e. the drug's pH–stability profile between pH 1 and pH 8, and its susceptibility to enzymatic breakdown by the gastrointestinal fluids. Means of assessing the chemical stability of a drug are discussed in Chapters 7 and 8. The stability of a drug in gastrointestinal fluids can be assessed by simulated gastric and intestinal media or by obtaining gastrointestinal fluids from humans or animals. The latter provides a harsher assessment of gastrointestinal stability but is more akin to the in vivo setting. In general the drug is incubated with either real or simulated fluid at 37°C for a period of 3 hours and the drug content analysed. A loss of more than 5% of drug indicates potential instability. Many of the permeability methods described below can be used to identify whether gastrointestinal stability is an issue for a particular drug.

For drugs that will still be in the gastrointestinal lumen when they reach the colonic region, resistance to the bacterial enzymes present in this part of the intestine need to be considered. The bacterial enzymes are capable of a whole host of reactions. There may be a significant portion of a poorly soluble drug still in the gastrointestinal tract by the

time it reaches the colon. If the drug is absorbed along the length of the gastrointestinal tract, and is susceptible to degradation or metabolism by the bacterial enzymes within the tract, its absorption and hence its bioavailability is liable to be reduced. Similarly, for sustained- or controlled-release products that are designed to release their drug along the length of the gastrointestinal tract, the potential of degradation or metabolism by bacterial enzymes should be assessed. If the drug is metabolized to a metabolite which can be absorbed the potential toxicity of this metabolite should be considered.

Permeability

There is a wealth of techniques available for either estimating or measuring the rate of permeation across membranes that are used to gain an assessment of oral absorption in humans. These range from computational (in silico) predictions and both physicochemical and biological methods. The biological methods can be further subdivided into in vitro, in situ and in vivo methods. In general, the more complex the technique the more information that can be gained and the more accurate is the assessment of oral absorption in humans. The range of techniques is summarized in Table 18.4. Some of the more popular ones are discussed below.

Partition coefficients

One of the first properties of a molecule that can be predicted or measured is its partition coefficient between an oil and a water phase (log *P*). This gives

Table 18.4 Some of the models available for predicting or measuring drug absorption

Model type	Model	Description
Computational	cLog*P*	Commercial software that calculates octanol/water partition coefficient based on fragment analysis, known as the Leo–Hansch method
	mLog*P*	Method of calculating log *P*, known as the Moriguchi method (see text)
Physicochemical	Partition coefficient	Measure of lipophilicity of drug, usually measured between octanol and aqueous buffer via a shake-flask method
	Immobilized artificial membrane	Measures partition into more sophisticated lipidic phase on an HPLC column
Cell culture	Caco-2 monolayer	Measures transport across monolayers of differentiated human colon adenocarcinoma cells
	HT-29	Measures transport across polarized cell monolayer with mucin-producing cells
Excised tissues	Cells	Measures uptake into cell suspensions, e.g. erythrocytes
	Freshly isolated cells	Measures uptake into enterocytes; however, the cells are difficult to prepare and are short-lived
	Membrane vesicles	Measures uptake into brush border membrane vesicles prepared from intestinal scrapings or isolated enterocytes
	Everted sacs	Measures uptake into intestinal segments/sacs
	Everted intestinal rings	Studies the kinetics of uptake into the intestinal mucosa
	Isolated sheets	Measures the transport across sheets of intestine
In situ studies	In-situ perfusion	Measures drug disappearance from either closed or open loop perfusate of segments of intestine of anaesthetized animals
	Vascularly perfused intestine	Measures drug disappearance from perfusate and its appearance in blood
In vivo studies	Intestinal loop	Measures drug disappearance from perfusate of loop of intestine in awake animal
Human data	Loc-I-Gut	Measures drug disappearance from perfusate of human intestine
	High-frequency capsule	Non-invasive method; measures drug in systemic circulation
	InteliSite capsule	Non-invasive method; measures drug in systemic circulation.
	Bioavailability	Deconvolution of pharmacokinetic data

a measure of the lipophilicity of a molecule, which can be used as a prediction as to how well it will be able to cross a biological membrane. As discussed in Chapter 17, octanol is usually chosen as the solvent for the oil phase as it has similar properties to biological membranes. If the aqueous phase is at a particular pH, the distribution coefficient at that pH is measured (log *D*); this then accounts for the ionization of the molecule at that pH. In the case of a weakly acidic or a weakly basic drug, the log *D* measured at an intestinal pH (e.g. 6.8) is liable to give a better prediction of the drug's ability to cross the lipid gastrointestinal membrane than its partition coefficient, log *P*, which does not take the degree of ionization into account.

One of the most common ways of measuring partition coefficients is to use the shake flask method. This relies on the equilibrium distribution of a drug between an oil and an aqueous phase. Prior to the experiment the aqueous phase should be saturated with the oil phase and vice versa. The experiment should be carried out at constant temperature. The drug should be added to the aqueous phase and the oil phase which, in the case of octanol, as it is less dense than water, will sit on top of the water. The system is mixed and then left to reach equilibrium (usually at least 24 hours). The two phases are separated and the concentration of drug is measured in each phase and a partition coefficient calculated (Fig. 18.2). As discussed in Chapter 17, within a homologous series increasing lipophilicity (log *P*/*D*) tends to result in greater absorption. A molecule is unlikely to cross a membrane (i.e. be absorbed via the transcellular passive route) if it has a log *P* less than 0.

Instead of measuring log *P* computational methods can be used to estimate it, and there are a number of software packages available to do this. There is a reasonably good correlation between the calculated and the measured values. Log *P* can be estimated by breaking down the molecule into fragments and calculating the contribution of each fragment to overall lipophilicity (often called the cLog*P*). Another method used to calculate log *P* is the Moriguchi method, which uses 13 parameters for hydrophobic and hydrophilic atoms, proximity effects, unsaturated bonds, intramolecular bonds, ring structures, amphoteric properties and several specific functionalities to obtain a value for the partition coefficient. This is often called the mLog*P*. The advantages of these methods are in drug discovery, where an estimate of the lipophilicity of many molecules can be obtained before they are actually synthesized.

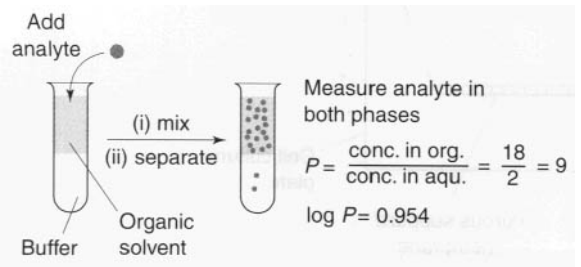

Fig. 18.2 Diagram of the shake-flask method for determining partition coefficient.

Another more sophisticated physicochemical means of gaining a view as to how well a drug will partition into a lipophilic phase is by investigating how well the molecule can be retained on a high-performance liquid chromatography column (HPLC). HPLC columns can be simply coated with octanol to mimic octanol–aqueous partition, or more elaborately designed to mimic biological membranes, for example the Immobilized Artificial Membrane (IAM). This technique provides a measure of how well a solute (i.e. the drug) in the aqueous phase will partition into biological membranes (i.e. be retained on the column). Good correlations between these methods and biological in vitro methods of estimating transcellular passive drug absorption have been obtained.

Cell culture techniques

Cell culture techniques for measuring the intestinal absorption of molecules have been increasingly used over recent decades and are now a well accepted model for absorption.

The cell line that is most widely used is Caco-2. Caco-2 cells are a human colon carcinoma cell line that was first proposed and characterized as a model for oral drug absorption by Hidalgo in 1989. In culture, Caco-2 cells spontaneously differentiate to form a monolayer of polarized enterocytes. These enterocytes resemble those in the small intestine, in that they contain microvilli and many of the transport systems present in the small intestine, for example those for sugars, amino acids, peptides and the P-glycoprotein efflux transporter. Adjacent Caco-2 cells adhere through tight junctions. However, the tightness of these junctions is more like those of the colon than those of the leakier small intestine.

There are many variations on growing and carrying out transport experiments with Caco-2 monolayers. In general the cells are grown on porous supports, usually for a period of 15–21 days in typical cell

culture medium, Dulbecco's Modified Eagle Medium supplemented with 20% fetal bovine serum, 1% non-essential amino acids and 2mM L-glutamine. The cells are grown at 37°C in 10% carbon dioxide at a relative humidity of 95%. The culture medium is replaced at least twice each week. Transport experiments are carried out by replacing the culture medium with buffers, usually Hanks Balanced Salt Solution adjusted to pH 6.5 on the apical surface and Hanks Balanced Salt Solution adjusted to pH 7.4 on the basolateral surface (Fig. 18.3).

After a short incubation period – usually about 30 minutes – when the cells are maintained at 37°C in a shaking water bath, the buffers are replaced with fresh buffers and a dilute solution of drug is introduced to the apical chamber. At regular intervals the concentration of the drug in the basolateral chamber is determined. The apparent permeability coefficient across cells can be calculated as follows:

$$P_{app} = dQ/dt(1/C_0A) \qquad (18.1)$$

where P_{app} is the apparent permeability coefficient (cm/s), dQ/dt is the rate of drug transport (μg/s), C_0 is the initial donor concentration (μg/mL) and, A is the surface area of the monolayer (cm^2).

To check that the monolayer has maintained its integrity throughout the transport process, a marker for paracellular absorption, such as mannitol, which is often radiolabelled for ease of assay, is added to the apical surface. If less than 2% of this crosses the monolayer in an hour then the integrity of the monolayer has been maintained. Another way to check the integrity of the monolayer is by measuring the transepithelial resistance, or TEER.

To use the Caco-2 cells as an absorption model a calibration curve needs to be generated. This is done for compounds for which the absorption in humans is known. Figure 18.4 shows the general shape of the curve of fraction absorbed in humans versus the apparent permeability coefficient in Caco-2 cells. As cells are biological systems, and as small changes in their source, method of culture and the way in which the transport experiment is carried out will affect the apparent permeability of a drug, this curve can shift significantly to the right or left or alter its steepness. Therefore, when carrying out Caco-2 experiments it is important always to standardize the procedure within a particular laboratory, and ensure that this procedure is regularly calibrated with a set of standard compounds.

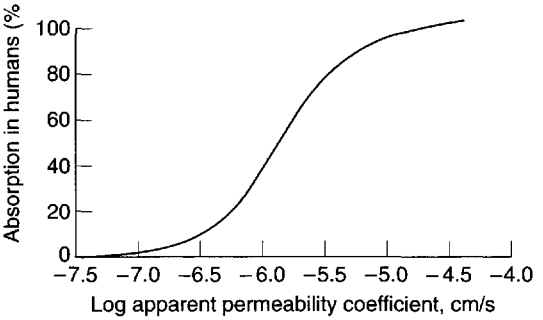

Fig. 18.4 The relationship between the fraction absorbed in humans and the apparent permeability coefficient in Caco cells.

Caco-2 monolayers can also be used to elucidate the mechanism of permeability. If the apparent permeability coefficient is found to increase linearly with increasing concentration of drug (i.e. the transport is not saturated), is the same whether the drug transport is measured from the apical to basolateral or the basolateral to apical direction, and is independent of pH, it can be concluded that the transport is a passive and not an active process. If the transport in the basolateral to apical direction is significantly greater than that in the apical to basolateral direction, then it is likely that the drug is actively effluxed from the cells by a countermembrane transporter such as P-glycoprotein. If the transport of the drug is

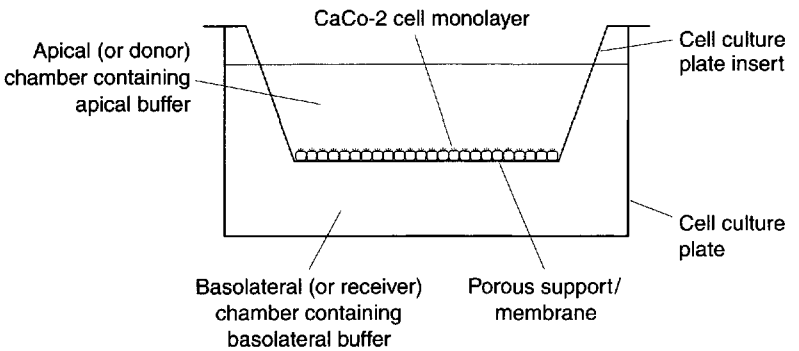

Fig. 18.3 Diagram of a Caco-2 cell culture system for determining apparent permeability.

also inhibited by the presence of compounds that are known inhibitors of P-glycoprotein, such as verapamil, this gives a further indication that the drug is susceptible to P-glycoprotein efflux.

To help elucidate whether other membrane transporters are involved in the absorption of a particular drug, further competitive inhibition studies can be carried out with known inhibitors of the particular transporter. For example, the dipeptide glycosylsarcosine can be used to probe whether the dipeptide transporter is involved in the absorption of a particular drug.

To evaluate whether a compound is absorbed via the paracellular or the transcellular pathway, the tight junctions can be artificially opened with compounds such as EDTA, which chelates calcium. Calcium is involved in keeping the junctions together. If the apparent permeability of a compound is not affected by the opening of these junctions, which can be assessed by using a paracellular marker such as mannitol, one can assume the drug transport is via a transcellular pathway.

If the disappearance of drug on the apical side of the membrane is not mirrored by its appearance on the basolateral side, and/or the mass balance at the end of the transport experiment does not account for 100% of the drug, there may be a problem with binding to the membrane porous support. This will need investigation, or the drug may have a stability issue. The drug could be susceptible to enzymes secreted by the cells and/or to degradation by hydrolytic enzymes as it passes through the cells, or it may be susceptible to metabolism by cytochrome P450 within the cell. Thus the Caco-2 cells are not only capable of evaluating the permeability of drugs but have value in investigating whether two of the other potential barriers to absorption, stability and presystemic metabolism, are likely to affect the overall rate and extent of absorption.

Caco-2 cells are very useful tools for understanding the mechanism of absorption of drugs and have furthered significantly our knowledge of the absorption of a variety of drugs. Other advantages of Caco-2 cells are that they are a non-animal model, require only small amounts of compound for transport studies, can be used as a rapid screening tool to assess the permeability of large numbers of compounds in the discovery setting, and can be used to evaluate the potential toxicity of compounds to cells.

The main disadvantages of Caco-2 monolayers as an absorption model are that, because of the tightness of the monolayer, they are more akin to the paracellular permeability of the colon rather than that of the small intestine, and that they lack a mucus layer. HT-29-18C1, a subclone of a human intestinal adenocarcinoma cell line, can differentiate in culture to produce both absorptive cells containing a microvillus structure and mucus secreting goblet cells. It also has a resistance similar to that of the small intestine, and so it can be argued that this cell line is preferable to Caco-2 in that it will give better information about the transcellular and paracellular routes of absorption. However, this cell line has yet to be well characterized as an absorption model, and therefore its use is not widespread.

Further information on the use of Caco-2 monolayers as an absorption model can be obtained from Artusson et al (1996).

Tissue techniques

A range of tissue techniques have been used as absorption models (Table 18.4). Two of the more popular ones are the use of isolated sheets of intestinal mucosa and of everted intestinal rings. These are discussed in more detail below.

Isolated sheets of intestinal mucosa are prepared by cutting the intestine into strips; the musculature is then removed and the sheet mounted and clamped in a diffusion chamber or an Ussing chamber filled with appropriate biological buffers (Fig. 18.5). The transepithelial resistance is measured across the tissue to check its integrity. The system is maintained at 37°C and stirred so that the thickness of the unstirred water layer is controlled and oxygen provided to the tissue. The drug is added to the donor chamber and

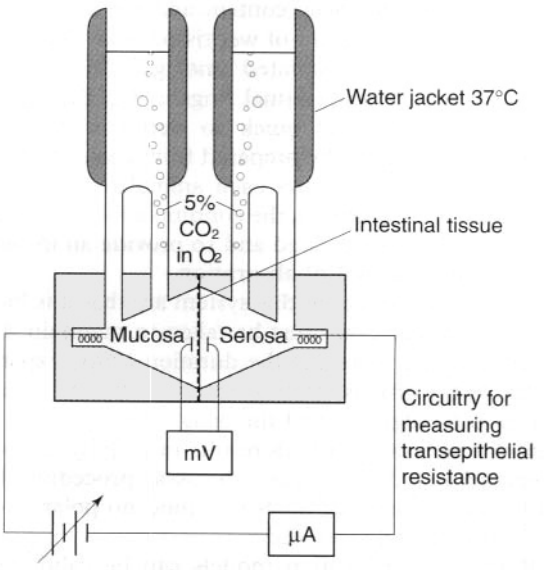

Fig. 18.5 Diagram of a diffusion chamber.

the amount accumulating in the receiver chamber is measured as a function of time. The permeability across the tissue can then be calculated.

Similar to cell monolayers, the two sides of the tissue can be sampled independently and thus fluxes from mucosal to serosal and from serosal to mucosal can be measured. Any pH dependence of transport can be determined by altering the pH of the buffers in the donor and/or receiver chambers. This system can also therefore be used to probe active transport.

One advantage of this technique over cell culture techniques is that permeability across different regions of the intestine can be assessed. It is particularly helpful to be able to compare permeabilities across intestinal and colonic tissue, especially when assessing whether a drug is suitable for a controlled-release delivery system. In addition, different animal tissues can be used, which permits an assessment of permeability in different preclinical models. The rat intestine is usually preferred for absorption studies as its permeability correlates well with that of human intestine. Human tissue and cell monolayers have also been used in this system.

Everted intestinal rings use whole intestinal segments rather than just sheets. The musculature is therefore intact. Intestinal segments are excised, again usually from rats; the segment is then tied at one end and carefully everted by placing it over a glass rod, and cut into small sections or rings. These rings are incubated in stirred oxygenated drug-containing buffer at 37°C. After a set period of time, drug uptake is quenched by quickly rinsing the ring with ice-cold buffer and carefully drying it. The ring is then assayed for drug content and the amount of drug taken up per gram of wet tissue over a specific period of time is calculated (mol g^{-1} $time^{-1}$). The advantage of using intestinal rings is that the test is relatively simple and quick to perform. A large number of rings can be prepared from each segment of intestine, which allows each animal to act as its own control. In addition, the conditions of the experiment can be manipulated and so provide an insight into the mechanisms of absorption.

The disadvantages of this system are that it is biological and that care must be taken to maintain the viability of the tissue for the duration of the experiment. As the drug is taken up into the ring, the tissue needs to be digested and the drug extracted from it before it is assayed, which results in lengthy sample preparation and complicates the assay procedure. In addition, as this is an uptake method no polarity of absorption can be assessed.

Both these absorption models can be calibrated with a standard set of compounds similar to the Caco-2 model. A similarly shaped curve for the percentage of drug absorbed in humans versus apparent permeability or uptake (mole per weight of tissue) for the isolated sheet and everted ring methods, respectively, is obtained.

Perfusion studies

Many variations of intestinal perfusion methods have been used as absorption models over the years. Again, in general, because of its relative ease of use and similarity to the permeability of the human intestine, the rat model is preferred. In situ intestinal perfusion models have the advantage that the whole animal is used, with the nerve, lymphatic and blood supplies intact, and therefore there should be no problem with tissue viability and all the transport mechanisms present in a live animal should be functional.

The animal is anaesthetized and the intestine exposed. In the open loop method a dilute solution of drug is pumped slowly through the intestine and the difference in drug concentration between the inlet and outlet concentrations is calculated (Fig. 18.6). An absorption rate constant or effective permeability coefficient across the intestine can be calculated as follows:

$$P_{eff} = Q \,.\, \ln (C_i - C_0)/2\pi rl \qquad (18.2)$$

where P_{eff} is the effective permeability coefficient (cm/s), Q is the flow rate in mL/s, C_i is the initial drug concentration, C_0 is the final drug concentration, r is the radius of the intestinal loop (cm), and, l is the length of intestinal loop (cm).

In the closed loop method a dilute solution of drug is added to a section of the intestine and the

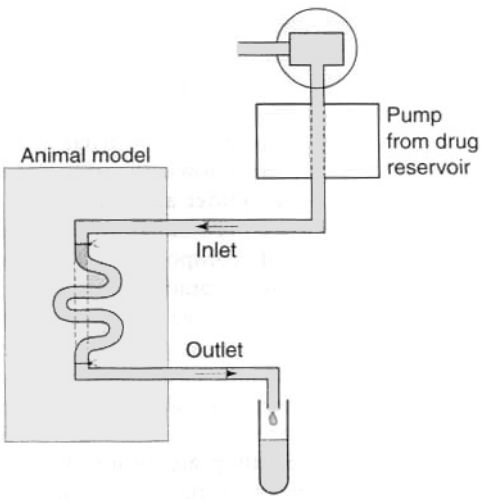

Fig. 18.6 Diagram of an in situ rat perfusion.

intestine closed. The intestine is then excised and drug content analysed immediately and after an appropriate time or time intervals, depending on the expected rate of absorption. Again, assuming a first-order rate process and hence an exponential loss of drug from the intestine, an absorption rate constant and effective permeability can be calculated. Like the intestinal ring method, the closed loop in situ perfusion model requires a lengthy digestion, extraction and assay procedure to analyse the drug remaining in the intestinal loop.

There is a lot of fluid moving in and out of the intestine, and so the drug concentrations in both these in situ perfusion methods need to be corrected for fluid flux. This is normally done by gravimetric means or by using a non-absorbable marker to assess the effect of fluid flux on the drug concentration. As with other absorption models, correlations have been made with standard compounds where the fraction absorbed in humans is known, and similar-shaped curves have been obtained (Fig. 18.4). In these models the 'absorption rate' is calculated by measuring the disappearance of the drug from the lumen and not its accumulation in the plasma. It is therefore important to check that the drug is not degraded in the lumen or intestinal wall, as drug that has disappeared will be erroneously assumed to have been absorbed.

More sophisticated techniques are those involving vascular perfusion. In these techniques, either a pair of mesenteric vessels supplying an intestinal segment or the superior mesenteric artery and portal vein perfusing almost the entire intestine are cannulated. The intestinal lumen and sometimes the lymph duct are also cannulated for the collection of luminal fluid and lymph, respectively. This model, although complicated, is very versatile as drug can be administered into the luminal or the vascular perfusate. When administered to the intestinal lumen, drug absorption can be evaluated from both its disappearance from the lumen and its appearance in the portal vein. Using this method both the rate and extent of absorption can be estimated, as well as carrier-mediated transport processes. Collection of the lymph allows the contribution of lymphatic absorption for very lipophilic compounds to be assessed. One of the other advantages of this system is the ability to determine whether any intestinal metabolism occurs before or after absorption.

A further extension of this model is to follow the passage of drugs from the intestine through the liver, and several adaptations of rat intestinal–liver perfusion systems have been investigated. Such a combined system gives the added advantage of assessing the first-pass or presystemic metabolism through the liver, and determining the relative importance of the intestine and liver in presystemic metabolism.

The disadvantages of these perfusion systems is that as they become more complex, a larger number of animals are required to establish suitable perfusion conditions and the reproducibility of the technique. However, in general, as the complexity increases so does the amount of information obtained.

Assessment of permeability in humans

Intestinal perfusion studies Until relatively recently the most common way to evaluate the absorption of drugs in humans was by performing bioavailability studies and deconvoluting the data available to calculate an absorption rate constant. This rate constant, however, is dependent on the release of the drug from the dosage form, and is affected by intestinal transit and presystemic metabolism. Therefore, very often it does not reflect the true intrinsic intestinal permeability of a drug.

Extensive studies have been carried out using a regional perfusion technique which has afforded a greater insight into human permeability (Loc-I-Gut). The Loc-I-Gut is a multichannel tube system with a proximal and a distal balloon (Fig. 18.7). These balloons are 100 mm apart and allow a segment of intestine 100 mm long to be isolated and perfused. Once the proximal balloon passes the ligament of Treitz both balloons are filled with air thereby preventing mixing of the luminal contents in the segment of interest with other luminal contents. A non-absorbable marker is used in the perfusion solution to check that the balloons work to occlude the region of interest. A tungsten weight is placed in front of the distal balloon to facilitate its passage down the gastrointestinal tract.

Drug absorption is calculated from the rate of disappearance of the drug from the perfused segment. This technique has afforded greater control in human intestinal perfusions, primarily because it isolates the

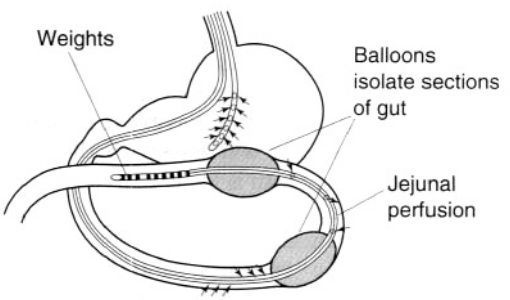

Fig. 18.7 Diagram of the Loc-I-Gut.

luminal contents of interest, and has greatly facilitated the study of permeability mechanisms and the metabolism of drugs and nutrients in the human intestine (Knutson et al 1989, Lennernas et al 1992).

Non-invasive approaches There is concern that the invasive nature of perfusion techniques can affect the function of the gastrointestinal tract, in particular the fluid content, owing to the intubation process altering the absorption and secretion balance. To overcome this problem, several engineering-based approaches have been developed to evaluate drug absorption in the gastrointestinal tract. These include high-frequency (HF) capsules (Fuhr et al 1994) and the InteliSite capsule (Wilding 1997).

The transit of the high-frequency capsule down the gastrointestinal tract is followed by X-ray fluoroscopy. Once the capsule reaches its desired release site drug release is triggered by a high-frequency signal, which leads to rupturing of a latex balloon that has been loaded with drug. Concerns about X-ray exposure and the difficulties of loading the drug into the balloon have limited the use of this technique.

The InteliSite capsule is a more sophisticated system for measuring drug absorption. Either a liquid or a powder formulation can be filled into the capsule, the transit of which is followed by gamma-scintigraphy (see later). Once the capsule reaches its desired release site it is activated by exposure to a radiomagnetic field, which induces a small amount of heat in the capsule's electronic assembly. The heat causes some shape-memory alloys to straighten, rotating the inner sleeve of the capsule with respect to an outer sleeve and allowing a series of slots in the two sleeves to become aligned and the enclosed drug to be released. For both these systems blood samples need to be taken to quantify drug absorption.

Presystemic metabolism

Presystemic metabolism is the metabolism that occurs before the drug reaches the systemic circulation. Therefore, for an orally administered drug this includes the metabolism that occurs in the gut wall and the liver. As discussed above, perfusion models that involve both the intestines and the liver allow an evaluation of the presystemic metabolism in both organs. In other models it is sometimes possible to design mass balance experiments that will assess whether presystemic intestinal metabolism is likely to occur.

Intestinal cell fractions, such as brush border membrane preparations which contain an abundance of hydrolytic enzymes, and homogenized preparations of segments of rat intestine, can also be used to determine intestinal presystemic metabolism. Drugs are incubated with either brush border membrane preparations or gut wall homogenate at 37°C and the drug content analysed.

Various liver preparations, for example subcellular fractions such as microsomes, isolated hepatocytes and liver slices, are used to determine hepatic metabolism in vitro. Microsomes are prepared by high-speed centrifugation of liver homogenates (100 000 *g*) and are composed mainly of fragments of the endoplasmic reticulum. They lack cystolic enzymes and cofactors and are therefore only suitable to evaluate some of the metabolic processes the liver is capable of, known as phase I metabolism. Hepatocytes must be freshly and carefully prepared from livers and are only viable for a few hours. It is therefore difficult to obtain human hepatocytes. Hepatocytes are very useful for hepatic metabolism studies as it is possible to evaluate most of the metabolic reactions, i.e. both phase I and II metabolism. Whole liver slices again have the ability to evaluate both phase I and II metabolism. Because they are tissue slices rather than cell suspensions, and because they do not require enzymatic treatment in their preparation, this may be why a higher degree of in vivo correlation can be achieved with liver slices than with hepatocytes and microsomes. The reader is referred to a review by Carlile et al (1997).

ASSESSMENT OF BIOAVAILABILITY

The measurement of bioavailability gives the net result of the effect of the release of drug into solution in the physiological fluids at the site of absorption, its stability in those physiological fluids, its permeability and its presystemic metabolism on the rate and extent of drug absorption by following the concentration–time profile of drug in a suitable physiological fluid. The concentration–time profile also gives information on other pharmacokinetic parameters, such as the distribution and elimination of the drug. The most commonly used method of assessing the bioavailability of a drug involves the construction of a blood plasma concentration–time curve, but urine drug concentrations can also be used and are discussed below.

Plasma concentration–time curves

When a single dose of a drug is administered orally to a patient, serial blood samples are withdrawn and the plasma assayed for drug concentration at specific periods of time after administration, a plasma concentration–time curve can be constructed.

Figure 18.8 shows a typical plasma concentration–time curve following the administration of an oral tablet.

At zero time, when the drug is first administered, the concentration of drug in the plasma will be zero. As the tablet passes into the stomach and/or intestine it disintegrates, the drug dissolves and absorption occurs. Initially the concentration of drug in the plasma rises, as the rate of absorption exceeds the rate at which the drug is being removed by distribution and elimination. Concentrations continue to rise until a maximum (or peak) is attained. This represents the highest concentration of drug achieved in the plasma following the administration of a single dose, and is often termed the $C_{P_{max}}$. It is reached when the rate of appearance of drug in the plasma is equal to its rate of removal by distribution and elimination.

The ascending portion of the plasma concentration–time curve is sometimes called the ***absorption phase***. Here the rate of absorption outweighs the rate of removal of drug by distribution and elimination. Drug absorption does not usually stop abruptly at the time of peak concentration, but may continue for some time into the descending portion of the curve. The early descending portion of the curve can thus reflect the net result of drug absorption, distribution, metabolism and elimination, but in this phase the rate of drug removal from the blood exceeds the rate absorption. Therefore, the concentration of the drug in the plasma declines.

Eventually drug absorption ceases when the bioavailable dose has been absorbed, and the concentration of drug in the plasma is now controlled only by its rate of elimination by metabolism and/or excretion. This is sometimes called the elimination phase of the curve. It should be appreciated, however, that elimination of a drug begins as soon as it appears in the plasma.

Several parameters based on the plasma concentration–time curve which are important in bioavailability studies are shown in Figure 18.9, and are discussed below.

Minimum effective (or therapeutic) plasma concentration It is generally assumed that some minimum concentration of drug must be reached in the plasma before the desired therapeutic or pharmacological effect is achieved. This is called the ***minimum effective*** (or ***therapeutic***) ***plasma concentration***. Its value not only varies from drug to drug but also from individual to individual, and with the type and severity of the disease state. In Figure 18.9 the minimum effective concentration is indicated by the lower line.

Maximum safe concentration The concentration of drug in the plasma above which side-effects or toxic effects occur is known as the maximum safe concentration.

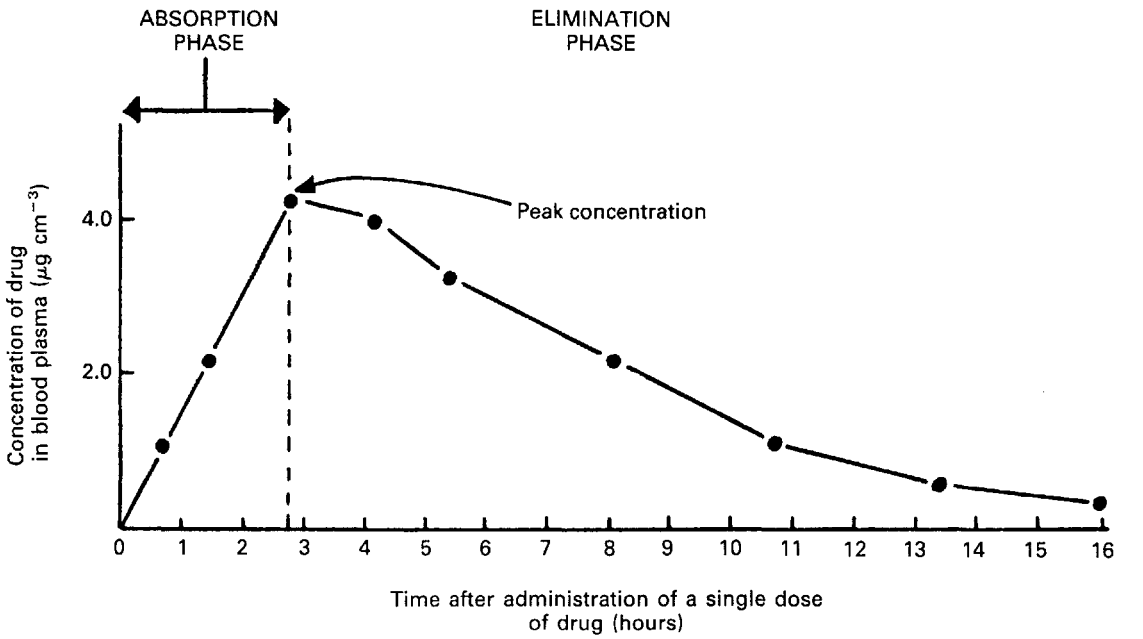

Fig. 18.8 A typical blood plasma concentration–time curve obtained following the peroral administration of a single dose of a drug in a tablet.

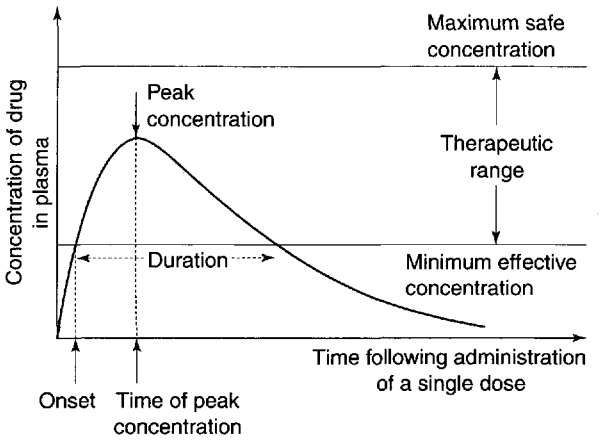

Fig. 18.9 Relationship between the plasma concentration–time curve obtained following a single extravascular dose of a drug and parameters associated with the therapeutic or pharmacological response.

Therapeutic range or window A range of plasma drug concentrations is also assumed to exist, over which the desired response is obtained yet toxic effects are avoided. This range is called the **therapeutic range** or **window**. The intention in clinical practice is to maintain plasma drug concentrations within this range.

Onset The onset may be defined as the time required to achieve the minimum effective plasma concentration following administration of the dosage form.

Duration The duration of the therapeutic effect of the drug is the period during which the concentration of drug in the plasma exceeds the minimum effective plasma concentration.

Peak concentration This represents the highest concentration of the drug achieved in the plasma, which is often referred to as the $C_{p_{max}}$.

Time of peak concentration This is the period of time required to achieve the peak plasma concentration of drug after the administration of a single dose. This parameter is related to the rate of absorption of the drug and can be used to assess that rate. It is often referred to as the T_{max}.

Area under the plasma concentration–time curve This is related to the total amount of drug absorbed into the systemic circulation following the administration of a single dose, and is often known as the AUC. However, changes in the area under the plasma concentration–time curve need not necessarily reflect changes in the total amount of drug absorbed, but can reflect modifications in the kinetics of distribution, metabolism and excretion.

The use of plasma concentration–time curves in bioavailability studies

In order to illustrate the usefulness of plasma concentration–time curves in bioavailability studies to assess the rate and extent of absorption, the administration of single equal doses of three different formulations, A, B and C, of the same drug to the same healthy individual by the same route of administration on three separate occasions can be considered. The assumption is made that sufficient time was allowed to elapse between the administration of each formulation such that the systemic circulation contained no residual concentration of drug and no residual effects from any previous administrations. It is also assumed that the kinetics and pattern of distribution of the drug, its binding phenomena, the kinetics of elimination and the experimental conditions under which each plasma concentration–time profile was obtained, were the same on each occasion. The plasma concentration–time profiles for the three formulations are shown in Figure 18.10. The differences between the three curves are attributed solely to differences in the rate and/or extent of absorption of the drug from each formulation.

The three plasma profiles in Figure 18.10 show that each of the three formulations (A, B and C) of the same dose of the same drug results in a different peak plasma concentration. However, the areas under the curves for formulation A and B are similar, and this indicates that the drug is absorbed to a similar extent from these two formulations. Consideration of the times at which the peak plasma concentrations occur for formulations A and B show that the drug is absorbed faster from A than from B, meaning that formulation A shows a fast onset of therapeutic action, but as its peak plasma concentration exceeds the maximum safe concentration it is likely that this formulation will result in toxic side-effects. Formulation B, which gives a slower rate of absorption than A, shows a slower therapeutic onset than A, but its peak plasma concentration lies within the therapeutic range. In addition, the duration of action of the therapeutic effect obtained with formulation B is longer than that obtained with A. Hence formulation B appears to be superior to formulation A from a clinical viewpoint, in that its peak plasma concentration lies within the therapeutic range of the drug and the duration of the therapeutic effect is longer.

Formulation C gives a much smaller area under the plasma concentration–time curve, indicating that a lower proportion of the dose has been absorbed.

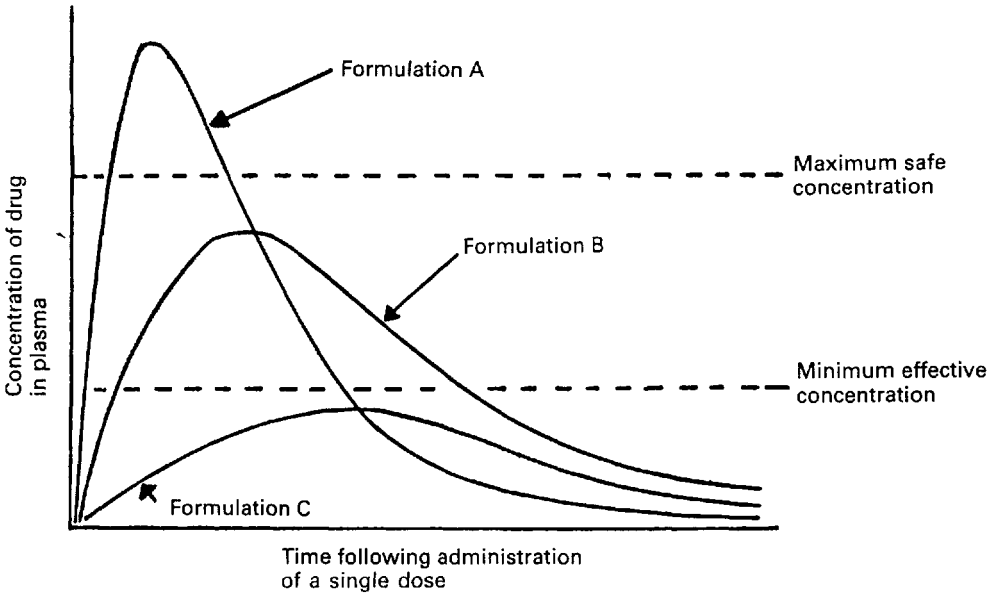

Fig. 18.10 Plasma concentration–time curves for three different formulations of the same drug administered in equal single doses by the same extravascular route.

This, together with the slower rate of absorption from formulation C (the time of peak concentration is longer than for formulations A and B), results in the peak plasma concentration not reaching the minimum effective concentration, i.e. formulation C does not produce a therapeutic effect and consequently is clinically ineffective as a single dose.

This simple hypothetical example illustrates how differences in bioavailability exhibited by a given drug from different formulations can result in a patient being either over, under, or correctly medicated.

It is important to realize that the study of bioavailability based on drug concentration measurements in the plasma (or urine or saliva) is complicated by the fact that such concentration–time curves are affected by factors other than the biopharmaceutical factors of the drug product itself. Factors such as body weight, sex and age of the test subjects, disease states, genetic differences in drug metabolism, excretion and distribution, food and water intake, concomitant administration of other drugs, stress and time of administration of the drug are some of the variables that can complicate the interpretation of bioavailability studies. As far as possible, studies should be designed to control these factors.

Although plots such those in as Figure 18.10 can be used to compare the relative bioavailability of a given drug from different formulations, they cannot be used indiscriminately to compare different drugs. It is quite usual for different drugs to exhibit different rates of absorption, metabolism, excretion and distribution, different distribution patterns and differences in their binding phenomena, all of which would influence the concentration–time curve. Therefore it would be extremely difficult to attribute differences in the concentration–time curves obtained for different drugs presented in different formulations to differences in their bioavailabilities.

Cumulative urinary drug excretion curves

Measurement of the concentration of intact drug and/or its metabolite(s) in the plasma can also be used to assess bioavailability.

When a suitable specific assay method is not available for the intact drug in the urine, or the specific assay method available for the parent drug is not sufficiently sensitive, it may be necessary to assay the principal metabolite or intact drug plus its metabolite(s) in the urine to obtain an index of bioavailability. Measurements involving metabolite levels in the urine are only valid when the drug in question is not subject to metabolism prior to reaching the systemic circulation. If an orally administered drug is subject to intestinal metabolism or first-pass liver metabolism, then measurement of the principal metabolite, or of intact drug plus metabolites, in the urine would give an overestimate of the systemic availability of that drug. It should be remembered that the definition of

bioavailability is in terms of the extent and the rate at which intact drug appears in the systemic circulation after the administration of a known dose.

The assessment of bioavailability by urinary excretion is based on the assumption that the appearance of the drug and/or its metabolites in the urine is a function of the rate and extent of absorption. This assumption is only valid when a drug and/or its metabolites are extensively excreted in the urine, and where the rate of urinary excretion is proportional to the concentration of the intact drug in the blood plasma. This proportionality does not hold if:

- the drug and/or its metabolites are excreted by an active transport process into the distal kidney tubule;
- the intact drug and/or its metabolites are weakly acidic or weakly basic (i.e. their rate of excretion is dependent on urine pH);
- the excretion rate depends on the rate of urine flow.

The important parameters in urinary excretion studies are the cumulative amount of intact drug and/or metabolites excreted, and the rate at which this excretion takes place. A cumulative urinary excretion curve is obtained by collecting urine samples (resulting from total emptying of the bladder) at known intervals after a single dose of the drug has been administered. Urine samples must be collected until all drug and/or its metabolites has been excreted (this is indicated by the cumulative urinary excretion curve becoming parallel to the abscissa) if a comparison of the extent of absorption of a given drug from different formulations or dosage forms is to be made. A typical cumulative urinary excretion curve and the corresponding plasma concentration–time curve obtained following the admission of a single dose of a given drug by the oral route to a subject is shown in Figure 18.11.

The initial segments (X–Y) of the curves reflect the 'absorption phase' (i.e. where absorption is the dominant process) and the slope of this segment of the urinary excretion curve is related to the rate of absorption of the drug into the blood. The total amount of intact drug (and/or its metabolite) excreted in the urine at point Z corresponds to the time at which the plasma concentration of intact drug is zero and essentially all the drug has been eliminated from the body. The total amount of drug excreted at point Z may be quite different from the total amount of drug administered (i.e. the dose), either because of incomplete absorption on because of the drug being eliminated by processes other than urinary excretion.

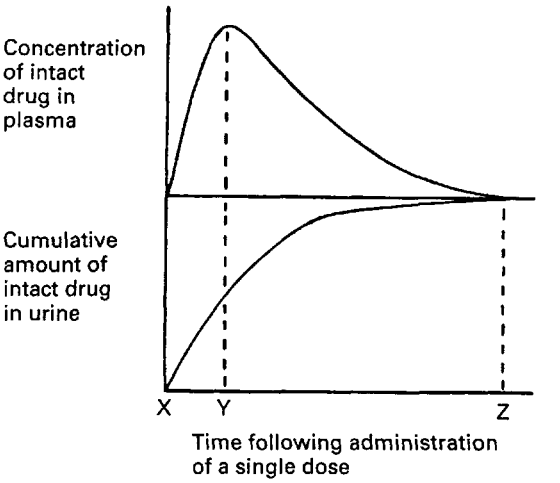

Fig. 18.11 Corresponding plots showing the plasma concentration–time curve (*upper curve*) and the cumulative urinary excretion curve (*lower curve*) obtained following the administration of a single dose of a drug by the peroral route

The use of urinary drug excretion curves in bioavailability studies

In order to illustrate how cumulative urinary excretion curves can be used to compare the bioavailabilities of a given drug from different formulations, let us consider the urinary excretion data that would have been obtained following the administration of single equal doses of the three different formulations, A, B and C, of the same drug to the same healthy individual by the same extravascular route on three different occasions, and giving the plasma concentration–time curves shown in Figure 18.10. The corresponding cumulative urinary excretion curves are shown in Figure 18.12.

The cumulative urinary excretion curves show that the rate at which drug appeared in the urine (i.e. the slope of the initial segment of each urinary excretion curve) from each formulation decreased in order A > B > C. Because the slope of the initial segment of the urinary excretion curve is related to the rate of drug absorption, the cumulative urinary excretion curves indicate that the rates of absorption of drug from the three formulations decrease in the order A > B > C. Inspection of the corresponding plasma concentration–time curves in Figure 18.10 shows that this is the case, i.e. peak concentration times (which are inversely related to the rate of drug absorption) for the three formulations increase in the order A > B > C. Although Figure 18.12 shows that the rate of appearance of drug in the urine from formulation A is faster than from B, the total amount of drug eventually

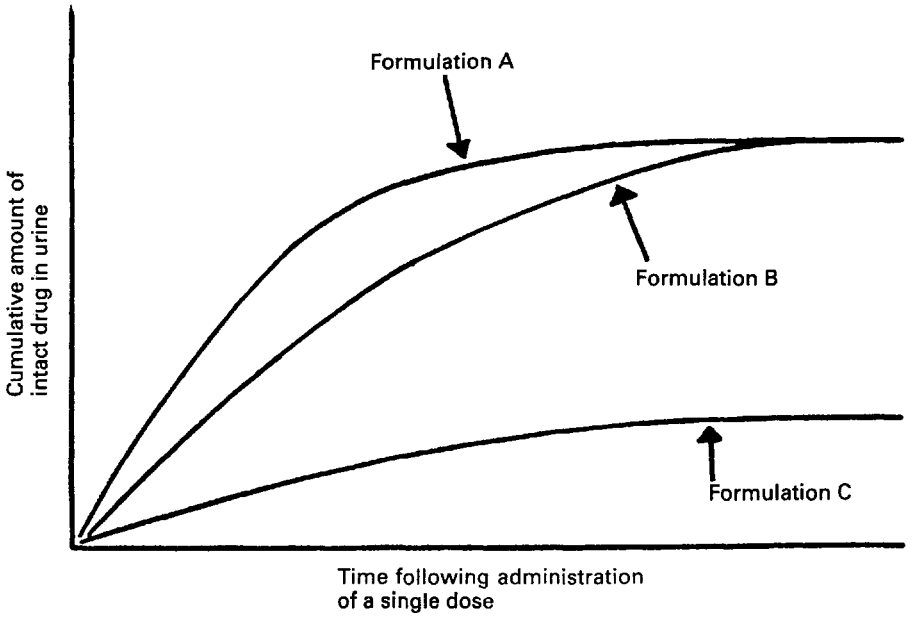

Fig. 18.12 Cumulative urinary excretion curves corresponding to the plasma concentration–time curves shown in Fig. 18.10 for three different formulations of the same drug administered in equal single doses by the same extravascular route.

excreted from these two formulations is the same, i.e. the cumulative urinary excretion curves for formulations A and B eventually meet and merge. As the total amount of intact drug excreted is assumed to be related to the total amount absorbed, the cumulative urinary excretion curves for formulations A and B indicate that the extent of drug absorption from these two formulations is the same. This is confirmed by the plasma concentration–time curves for formulations A and B in Figure 18.10, which exhibit similar areas under their curves.

Thus both the plasma concentration–time curves and the corresponding cumulative urinary excretion curves for formulations A and B show that the extent of absorption from these formulations is equal, despite being at different rates from the respective formulations.

Consideration of the cumulative urinary excretion curve for C shows that this formulation not only results in a slower rate of appearance of intact drug in the urine, but also that the total amount of drug that is eventually excreted is much less than from the other two formulations. Thus the cumulative urinary excretion curve suggests that both the rate and extent of drug absorption are reduced in the case of formulation C. This is confirmed by the plasma concentration–time curve shown in Figure 18.10 for formulation C, i.e. formulation C exhibits a longer peak concentration time and a smaller area under the curve than do formulations A and B. Thus one can conclude that cumulative urinary excretion curves may be used to compare the rate and extent of absorption of a given drug presented in different formulations, provided that the conditions mentioned previously apply.

Absolute and relative bioavailability

Absolute bioavailability

The absolute bioavailability of a given drug from a dosage form is the fraction (or percentage) of the administered dose which is absorbed intact into the systemic circulation. Absolute bioavailability may be calculated by comparing the total amount of intact drug that reaches the systemic circulation after the administration of a known dose of the dosage form via a route of administration, with the total amount that reaches the systemic circulation after the administration of an equivalent dose of the drug in the form of an intravenous bolus injection. An intravenous bolus injection is used as a reference to compare the systemic availability of the drug administered via different routes, because when a drug is delivered intravenously the entire administered dose is introduced directly into the systemic circulation, i.e. it has no absorption barriers to cross and is therefore considered to be totally bioavailable.

The absolute bioavailability of a given drug using plasma data may be calculated by comparing the total areas under the plasma concentration–time curves obtained following the administration of equivalent doses of the drug via an absorption site and via the intravenous route in the same subject on different occasions. Typical plasma concentration–time curves obtained by administering equivalent doses of the same drug by the intravenous route (bolus injection) and the gastrointestinal route are shown in Figure 18.13.

For equivalent doses of administered drug:

$$\text{absolute bioavailability} = \frac{(\text{AUC}_\text{T})_{\text{abs}}}{(\text{AUC}_\text{T})_{\text{iv}}} \qquad (18.3)$$

where $(AUC_T)_{abs}$ is the total area under the plasma concentration–time curve following the administration of a single dose via an absorption site and $(AUC_T)_{iv}$ is the total area under the plasma concentration–time curve following administration by rapid intravenous injection.

If different doses of the drug are administered by both routes, a correction for the sizes of the doses can be made as follows:

$$\text{absolute bioavailability} = \frac{(\text{AUC}_\text{T})_{\text{abs}} / D_{\text{abs}}}{(\text{AUC}_\text{T})_{\text{iv}} / D_{\text{iv}}} \qquad (18.4)$$

where D_{abs} is the size of the single dose of drug administered via the absorption site, and D_{iv} is the size of the dose of the drug administered as an intravenous bolus injection. Sometimes it is necessary to use different dosages of drugs via different routes. Often the dose administered intravenously is lower to avoid toxic side-effects and for ease of formulation. Care should be taken when using different dosages to calculate bioavailability data, as sometimes the pharmacokinetics of a drug are non-linear and different doses will then lead to an incorrect figure for the absolute bioavailability calculated using a simple ratio, as in Eqn 18.4.

Absolute bioavailability using urinary excretion data may be determined by comparing the total cumulative amounts of unchanged drug ultimately excreted in the urine following administration of the drug via an absorption site and the intravenous route (bolus injection), respectively, on different occasions to the same subject.

For equivalent doses of administered drug:

$$\text{absolute bioavailability} = \frac{(X_\text{u})_{\text{abs}}}{(X_\text{u})_{\text{iv}}} \qquad (18.5)$$

where $(X_U)_{abs}$ and $(X_U)_{iv}$ are the total cumulative amounts of unchanged drug ultimately excreted in the urine following administration of equivalent

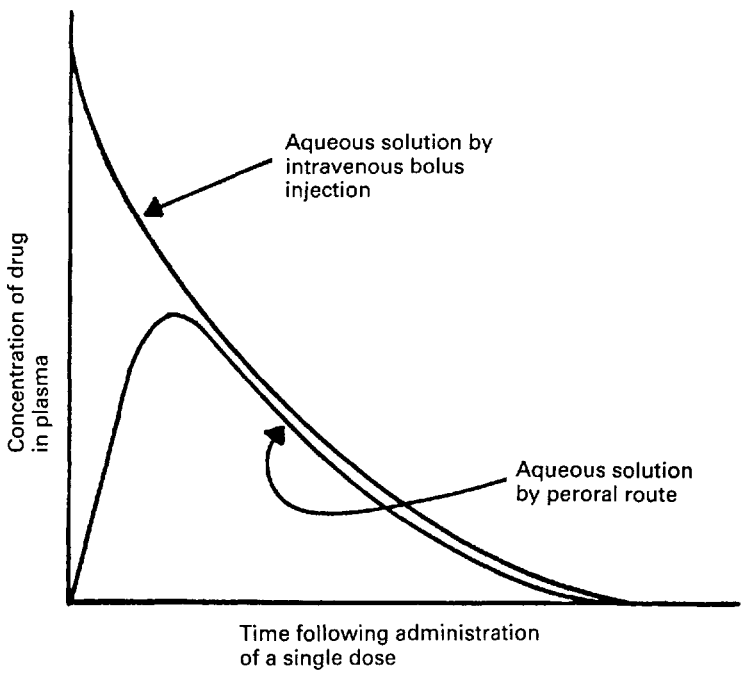

Fig. 18.13 Typical plasma concentration–time curves obtained by administering equivalent doses of the same drug by intravenous bolus injection and by the peroral route.

single doses of drug via an absorption site and as an intravenous bolus injection, respectively.

If different doses of drug are administered,

$$\text{absolute bioavailability} = \frac{(X_u)_{abs} / D_{abs}}{(X_u)_{iv} / D_{iv}} \quad (18.6)$$

The absolute bioavailability of a given drug from a particular type of dosage form may be expressed as a fraction or, more commonly, as a percentage.

Measurements of absolute bioavailability obtained by administering a given drug in the form of a simple aqueous solution (that does not precipitate on dilution with gastrointestinal fluids) by both the oral and the intravenous routes provide an insight into the effects that factors associated with the oral route may have on bioavailability, e.g. presystemic metabolism by the intestine or liver, the formation of complexes between the drug and endogenous substances (e.g. mucin) at the site of absorption and drug stability in the gastrointestinal fluids.

It should be noted that the value calculated for the absolute bioavailability will only be valid for the drug being examined if the kinetics of elimination and distribution are independent of the route and time of administration, and also of the size of dose administered (if different doses are administered by the intravenous route and absorption site). If this is not the case, one cannot assume that the observed differences in the total areas under the plasma concentration–time curves or in the total cumulative amounts of unchanged drug ultimately excreted in the urine are due entirely to differences in bioavailability.

Relative bioavailability

In the case of drugs that cannot be administered by intravenous bolus injection, the relative (or comparative) bioavailability is determined rather than the absolute bioavailability. In this case the bioavailability of a given drug from a 'test' dosage form is compared to that of the same drug administered in a 'standard' dosage form, which is either an orally administered solution (from which the drug is known to be well absorbed) or an established commercial preparation of proven clinical effectiveness. Hence relative bioavailability is a measure of the fraction (or percentage) of a given drug that is absorbed intact into the systemic circulation from a dosage form relative to a recognized (i.e. clinically proven) standard dosage form of that drug.

The relative bioavailability of a given drug administered as equal doses of a test dosage form and a recognized standard dosage form, respectively, by the same route of administration to the same subject on different occasions, may be calculated from the corresponding plasma concentration–time curves as follows:

$$\text{relative bioavailability} = \frac{(AUC_T)_{test}}{(AUC_T)_{standard}} \quad (18.7)$$

where $(AUC_T)_{test}$ and $(AUC_T)_{standard}$ are the total areas under the plasma concentration–time curves following the administration of a single dose of the test dosage form and of the standard dosage form, respectively.

When different doses of the test and standard dosage forms are administered, a correction for the size of dose is made as follows:

$$\text{relative bioavailability} = \frac{(AUC_T)_{abs} / D_{test}}{(AUC_T)_{standard} / D_{standard}} \quad (18.8)$$

where D_{test} and $D_{standard}$ are the sizes of the single doses of the test and standard dosage forms, respectively.

Like absolute bioavailability, relative bioavailability may be expressed as a fraction or as a percentage.

Urinary excretion data may also be used to measure relative bioavailability as follows:

$$\text{relative bioavailability} = \frac{(X_u)_{test}}{(X_u)_{standard}} \quad (18.9)$$

where $(X_u)_{test}$ and $(X_u)_{standard}$ are the total cumulative amounts of unchanged drug ultimately excreted in the urine following the administration of single doses of the test dosage form and the standard dosage form, respectively.

If different doses of the test and standard dosage forms are administered on separate occasions, the total amounts of unchanged drug ultimately excreted in the urine per unit dose of drug must be used in the above equation.

It should be noted that measurements of relative and absolute bioavailability based on urinary excretion data may also be made in terms of either the total amounts of principal drug metabolite or of unchanged drug plus its metabolites ultimately excreted in the urine. However, the assessment of relative and absolute bioavailability in terms of urinary excretion data is based on the assumption that the total amount of unchanged drug (and/or its metabolites) ultimately excreted in the urine is a reflection of the total amount of intact drug entering the systemic circulation (as discussed in the earlier section on cumulative urinary excretion curves).

Relative bioavailability measurements are often used to determine the effects of dosage form differences on

the systemic bioavailability of a given drug. Numerous dosage form factors can influence the bioavailability of a drug. These include the type of dosage form (e.g. tablet, solution, suspension, hard gelatin capsule), differences in the formulation of a particular type of dosage form, and manufacturing variables employed in the production of a particular type of dosage form. A more detailed account of the influence of these factors on bioavailability is given in Chapter 17.

Bioequivalence

An extension of the concept of relative bioavailability, which essentially involves comparing the total amounts of a particular drug that are absorbed intact into the systemic circulation from a test and a recognized standard dosage form, is that of determining whether test and standard dosage forms containing equal doses of the same drug are equivalent or not in terms of their rates and extents of absorption (i.e. systemic availabilities). This is called ***bioequivalence***.

Two or more chemically equivalent products (i.e. products containing equal doses of the same therapeutically active ingredient(s) in identical types of dosage form which meet all the existing physicochemical standards in official compendia) are said to be bioequivalent if they do not differ significantly in their bioavailability characteristics when administered in the same dose under similar experimental conditions. Hence in those cases where bioavailability is assessed in terms of plasma concentration–time curves, two or more chemically equivalent drug products may be considered bioequivalent if there is no significant difference between any of the following parameters: maximum plasma concentrations (C_{max}), time to peak height concentration (T_{max}) and areas under the plasma concentration–time curves (AUC).

In conducting a bioequivalence study it is usual for one of the chemically equivalent drug products under test to be a clinically proven, therapeutically effective product which serves as a standard against which the other 'test' products may be compared. If a test product and this standard product are found to be bioequivalent then it is reasonable to expect that the test product will also be therapeutically effective, i.e. the test and the reference products are therapeutically equivalent. Bioequivalence studies are therefore important in determining whether chemically equivalent drug products manufactured by different companies are therapeutically equivalent, i.e. produce identical therapeutic responses in patients.

If two chemically equivalent drug products are absolutely bioequivalent, their plasma concentration–time and/or cumulative urinary excretion curves would be superimposable. In such a case there would be no problem in concluding that these products were bioequivalent. Nor would there be a problem in concluding bioinequivalence if the parameters associated with the plasma concentration–time and/or cumulative urinary excretion profiles for the test differed from the standard product by, for instance, 50%. However, a problem arises in deciding whether the test and standard drug products are bioequivalent when such products show relatively small differences in their plasma concentration–time curves and/or cumulative urinary excretion curves.

The problem is how much of a difference can be allowed between two chemically equivalent drug products and still permit them to be considered bioequivalent. Should this be 10%, 20%, 30% or more? The magnitude of the difference that could be permitted will depend on the significance of such a difference on the safety and therapeutic efficacy of the particular drug. This will depend on such factors as the toxicity, the therapeutic range and the therapeutic use of the drug. In the case of a drug with a wide therapeutic range, the toxic effects of which occur only at relatively high plasma concentrations, chemically equivalent products giving quite different plasma concentration–time curves (Fig. 18.14) may still be considered satisfactory from a therapeutic point of view, although they are not strictly bioequivalent.

In the case of the hypothetical example shown in Figure 18.14, provided that the observed difference in the rates of absorption (as assessed by the times of peak plasma concentration), and hence in the times of onset, for formulations X and Y is not considered to be therapeutically significant, both formulations may be considered to be therapeutically satisfactory. However, if the drug in question was a hypnotic, in which case the time of onset for the therapeutic response is important, then the observed difference in the rates of absorption would become more important.

If the times of peak plasma concentration for formulations X and Y were 0.5 and 1.0 hour, respectively, it is likely that both formulations would still be deemed to be therapeutically satisfactory despite a 100% difference in their times of peak plasma concentration. However, if the times of peak plasma concentration for formulations X and Y were 2 and 4 hours, respectively, these formulations might no longer be regarded as being therapeutically equivalent even though the percentage difference in their peak plasma concentration was the same.

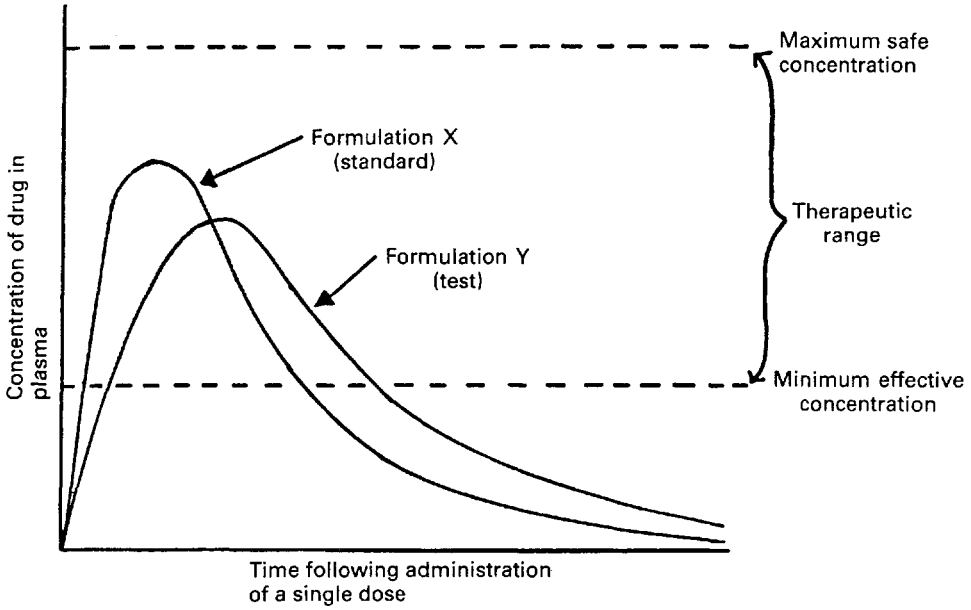

Fig. 18.14 Plasma concentration–time curves for two chemically equivalent drug products administered in equal single doses by the same extravascular route.

It is difficult to quote a universally acceptable percentage difference that can be tolerated before two chemically equivalent drug products are regarded as being bioinequivalent and/or therapeutically inequivalent. In the case of chemically equivalent drug products containing a drug which exhibits a narrow range between its minimum effective plasma concentration and its maximum safe plasma concentration (e.g. digoxin), the concept of bioequivalence is fundamentally important, as in such cases small differences in the plasma concentration–time curves of chemically equivalent drug products may result in patients being overmedicated (i.e. exhibiting toxic responses) or undermedicated (i.e. experiencing therapeutic failure). These two therapeutically unsatisfactory conditions are illustrated in Figure 18.15a & b respectively.

Despite the problems of putting a value on the magnitude of the difference that can be tolerated before two chemically equivalent drug products are deemed to be bioinequivalent, a value of 20% for the tolerated difference used to be regarded as suitable as a general criterion for determining bioequivalence. Thus if all the major parameters in either the plasma concentration–time or cumulative urinary excretion curves for two or more chemically equivalent drug products differed from each other by less than 20%, these products would have been judged to be bioequivalent. However, if any one or more of these parameters differed by more than 20% then there might have been a problem with the bioequivalence of the test product(s) with respect to the standard product. However, recently some regulatory authorities have been adopting more stringent requirements for bioequivalence, involving statistical models and considerations of average, population and individual pharmacokinetics.

A further crucial factor in establishing bioequivalence, or in determining the influence of the type of dosage form, the route of administration etc., have on the bioavailability of a given drug, is the proper design, control and interpretation of such experimental studies.

ASSESSMENT OF SITE OF RELEASE IN VIVO

There are many benefits of being able to assess the fate of a dosage form in vivo and the site and release pattern of the drug. Particularly for drugs that show poor oral bioavailability, or in the design and development of controlled- or sustained-release delivery systems, the ability to follow the transit of the dosage form and the release of drug from it is advantageous. The technique of gamma scintigraphy is now used extensively and enables a greater knowledge and understanding of the transit and fate

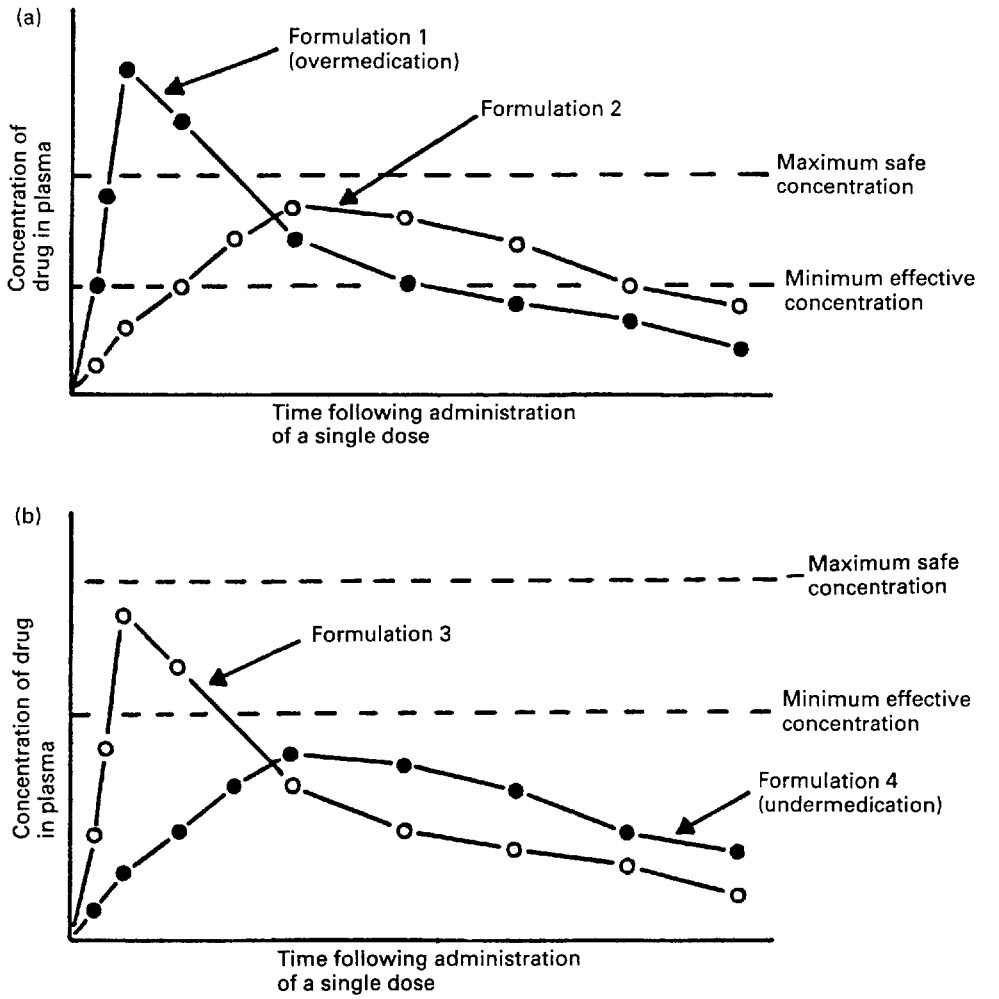

Fig. 18.15 Plasma concentration–time curves for chemically equivalent drug products administered in equal single doses by the same extravascular route, showing potential consequences of bioinequivalence for a drug having a narrow therapeutic range, i.e., (a) overmedication and (b), undermedication. (After Chodos and Di Santo 1973.)

of pharmaceuticals in the gastrointestinal tract to be gained.

Gamma scintigraphy is a versatile, non-invasive and ethically acceptable technique which is capable of obtaining information both quantitatively and continuously. The technique involves the radiolabelling of a dosage form with a gamma-emitting isotope of appropriate half-life and activity. Technetium-99m is often the isotope of choice for pharmaceutical studies because of its short half-life (6 hours). The radiolabelled dosage form is administered to a subject who is positioned in front of a gamma camera. Gamma radiation emitted from the isotope is focused by a collimator and detected by a scintillation crystal and its associated circuitry. The signals are assembled by computer software to form a two-dimensional image of the dosage form in the gastrointestinal tract. The anatomy of the gastrointestinal tract can be clearly seen from liquid dosage forms, and the site of disintegration of solid dosage forms identified. The release of the radiolabel from the dosage form can be measured by following the intensity of the radiation. By co-administration of a radiolabelled marker and a drug in the same dosage form, and simultaneous imaging and taking of blood samples, the absorption site and release rate of a drug can be determined (for example with the InteliSite capsule; see earlier). When used in this way, the technique is often referred to as ***pharmacoscintigraphy***.

THE BIOPHARMACEUTICAL CLASSIFICATION SCHEME

A biopharmaceutical classification scheme has been proposed which classifies drugs into four classes according to their solubility across the gastrointestinal pH range and their permeability across the gastrointestinal mucosa (Amidon et al 1995). Two of the four potential barriers to absorption are thus addressed by the scheme (see Fig. 18.1).

The scheme was originally proposed for the identification of immediate-release solid oral products for which in vivo bioequivalence tests may not be necessary, but it is also useful to classify drugs and predict bioavailability issues that may arise during the various stages of the development process. The four classes are:

- Class I: high solubility/low permeability
- Class II: low solubility/high permeability
- Class III: high solubility/low permeability
- Class IV: low solubility/low permeability.

A drug is considered to be highly soluble where the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range 1–8. The volume is derived from the minimum volume anticipated in the stomach when a dosage form is taken in the fasted state with a glass of water. If the volume of aqueous media taken to dissolve the drug in pH conditions ranging from 1 to 8 is greater than 250 mL then the drug is considered to have low solubility. The classification therefore takes into account the dose of the drug as well as its solubility. A drug is considered to be highly permeable when the extent of absorption in humans is expected to be greater than 90% of the administered dose. Permeability can be assessed using one of the methods discussed earlier which has been calibrated with known standard compounds or by pharmacokinetic studies.

Class I drugs Class I drugs will dissolve rapidly when presented in immediate-release dosage forms, and are also rapidly transported across the gut wall. Therefore, unless they form insoluble complexes, are unstable in gastric fluids or undergo presystemic clearance, it is expected that such drugs will be rapidly absorbed and thus show good bioavailability. Examples of class I drugs are the β-blockers propranolol and metoprolol.

Class II drugs In contrast, for drugs in class II the dissolution rate is liable to be the rate-limiting step in oral absorption. For class II drugs, therefore, it should be possible to generate a strong correlation between in vitro dissolution and in vivo absorption (see earlier). Examples of class II drugs are the non-steroidal anti-inflammatory drug ketoprofen and the antiepileptic carbamazepine. This class of drug should be amenable to formulation approaches to improve the dissolution rate and hence oral bioavailability.

Class III drugs Class III drugs are those that dissolve rapidly but which are poorly permeable; examples are the H_2-antagonist ranitidine and the β-blocker atenolol. It is important that dosage forms containing class III drugs release them rapidly, in order to maximize the amount of time these drugs, which are slow to permeate the gastrointestinal epithelium, are in contact with it.

Class IV drugs Class IV drugs are those that are classed as poorly soluble and poorly permeable. These drugs are liable to have poor oral bioavailability, or the oral absorption may be so low that they cannot be given by the oral route. The diuretics hydrochlorothiazide and frusemide are examples of class IV drugs. Forming prodrugs of class IV compounds or finding an alternative route of delivery are approaches that have to be adopted to significantly improve their absorption into the systemic circulation.

SUMMARY

This chapter discusses the range of current approaches to assessing the biopharmaceutical properties of drugs that are intended for oral administration. Methods of measuring and interpreting bioavailability data are described. The concepts of bioequivalence and the biopharmaceutical classification of drugs are introduced. It is imperative that the biopharmaceutical properties of drugs are fully understood, both in the selection of candidate drugs during the discovery process and in the design and development of efficacious immediate- and controlled-release dosage forms.

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19
Dosage regimens

Stuart Proudfoot (updated by John Collett)

CHAPTER CONTENTS

DOSAGE REGIMENS: THEIR INFLUENCE ON THE CONCENTRATION–TIME PROFILE OF A DRUG IN THE BODY

The subject of dosage regimens is concerned with the dose, time of administration and drug plasma levels factors associated with ***multiple*** dosing of a drug. The influence that physiological factors, the physicochemical properties of a drug and dosage form factors can have in determining whether a therapeutically effective concentration of a drug is achieved in the plasma following peroral administration of a ***single*** dose of drug has been discussed previously in Chapters 16, 17 and 18.

Some drugs, such as hypnotics, analgesics and antiemetics, may provide effective treatment following the administration of a single dose. However, the duration of most illnesses is longer than the therapeutic effect produced by the administration of a single dose of a drug in a conventional dosage form, i.e. a dosage form which is formulated to give rapid and complete drug release. In such cases doses are usually administered on a repetitive basis over a period of time determined by the nature of the illness. For instance, one 250 mg ampicillin capsule may be administered every 6 hours for a period of 5 days to treat a bacterial infection. Such a regimen, in which the total dose of drug (i.e. in this example 5 g) administered over 5 days is given in the form of multiple doses (i.e. each of 250 mg) at given intervals of time (i.e. every 6 hours) is known as a ***multiple-dosage regimen***.

The proper selection of both the dose size and the frequency of administration is an important factor that influences whether a satisfactory therapeutic plasma concentration is achieved and maintained over the prescribed course of treatment. Thus the design of a multiple-dosage regimen is crucial to successful drug therapy.

ONE-COMPARTMENT OPEN MODEL OF DRUG DISPOSITION IN THE BODY

In order to understand how the design of a dosage regimen can influence the time course of a drug in the body, as measured by its plasma concentration–time curve, consider that the complex kinetic processes of drug input, output and distribution in the body may be represented by the pharmacokinetic model of drug disposition, the one-compartment open model, shown in Figure 19.1. In this case the drug is considered to be distributed instantly throughout the whole body following its release and absorption from the dosage form. Thus the body behaves as a single compartment in which absorbed drug is distributed so rapidly that a concentration equilibrium exists at any given time between the plasma, other body fluids, and the tissues into which the drug has become distributed.

To assume that the body behaves as one-compartment open model does not necessarily mean that the drug concentrations in all body tissues at any given time are equal. The model does assume, however, that any changes that occur in the plasma reflect quantitatively changes occurring in the concentration of drug at the site(s) of action.

Rate of drug input versus rate of drug output

In a one-compartment open model, the overall kinetic processes of drug input and drug output are described by first-order kinetics. In the case of a perorally administered dosage form, the process of drug input into the body compartment involves drug release from the dosage form and passage of the drug across the cellular membranes constituting the gastrointestinal barrier. The rate of input or absorption represents the net result of all these processes. The rate of input (absorption) at any given time is proportional to the concentration of drug, which is assumed to be in an absorbable form, in solution in the gastrointestinal fluids at the site(s) of absorption, i.e. the effective concentration, C_e, of drug at time t. Hence:

$$\text{rate of drug input at time } t \propto C_e \qquad (19.1)$$

and

$$\text{rate of drug input at time } t = -k_a C_e \qquad (19.2)$$

where k_a is the apparent absorption rate constant.

The negative sign in Eqn 19.2 indicates that the effective concentration of drug at the absorption site(s) decreases with time. The apparent absorption rate constant gives the proportion (or fraction) of drug that enters the body compartment per unit time. Its units are time^{-1}, e.g. h^{-1}.

Unlike the rate of drug input into the body compartment, the apparent absorption rate constant, k_a, is independent of the effective concentration of drug at the absorption site(s). Because the rate of drug input is proportional to the effective drug concentration, it will be maximal following the administration of a dose contained in a peroral dosage form which gives rapid and complete drug release. The rate of drug input will decrease gradually with time as a consequence of the effective drug concentration at the absorption site(s) decreasing progressively with time, chiefly as a result of absorption into the body compartment. Other processes, such as chemical degradation and movement of drug away from the absorption site(s), will also contribute to the gradual decrease in the effective drug concentration with time.

In the case of a one-compartment open model, the rate of drug output or elimination is a first-order process. Consequently, the magnitude of this parameter at any given time is dependent on the concentration of drug in the body compartment at that time. Immediately following administration of the first dose of a peroral dosage form, the rate of drug output from the body will be low as little of the drug will have been absorbed into the body compartment. However, as absorption proceeds – initially at a higher rate than the rate of drug output – the net concentration of drug in the body will increase with time. Likewise, the rate of drug output from the

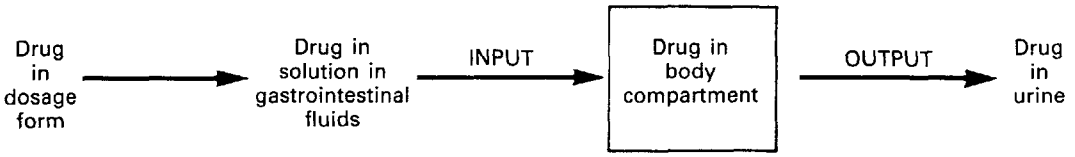


Fig. 19.1 One-compartment open model of drug disposition for a perorally administered drug.

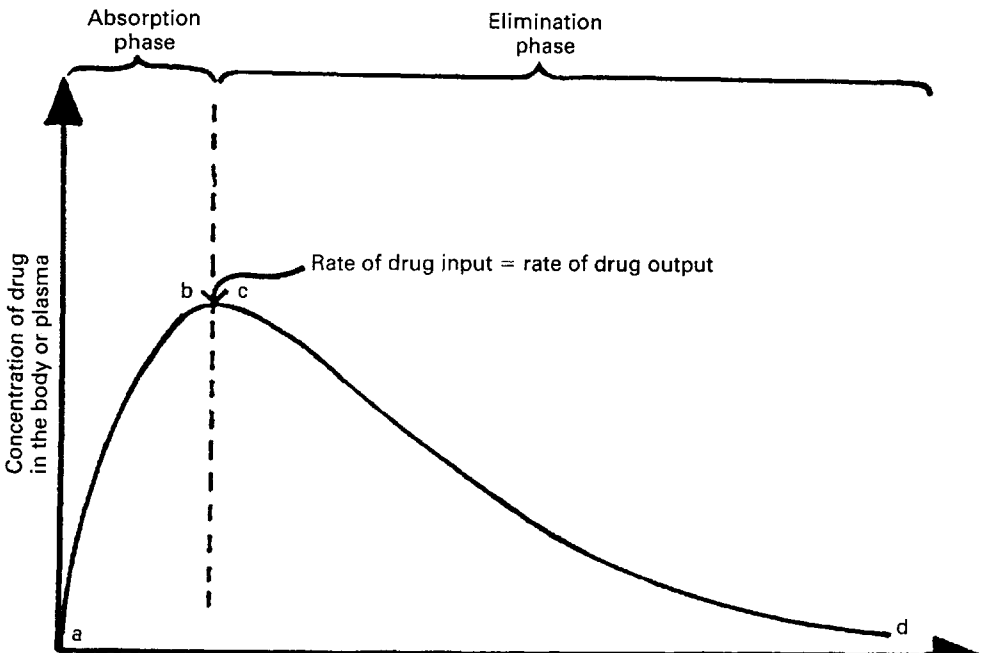
body compartment will also increase with time. As the rate of drug output is increasing with time while the rate of input into the body compartment is decreasing with time, the situation is eventually reached when the rate of drug output just exceeds that of drug input. Consequently, the net concentration of drug in the body compartment will reach a peak value and then begin to fall with time. The ensuing decreases in the net concentration of drug in the body will also cause the rate of drug output to decrease with time.

These changes in the rates of drug input and output relative to each other with time are responsible for the characteristic shape of the concentration–time course of a drug in the body shown in Figure 19.2 following peroral administration of a single dose of drug.

It is evident from the above discussion and Figure 19.2, that the greater the rate of drug input relative to that of drug output from the body compartment over the net absorption phase, the higher will be the peak concentration achieved in the body or plasma following peroral administration of a single dose of drug. This interplay explains why increases in dose size and formulation changes in dosage forms which produce increases in the effective concentration of drug at the absorption site(s), result in higher peak plasma and body concentrations being obtained for a given drug. It should also be noted that any unexpected decrease in the rate of drug output relative to that of drug input, which may occur as the result of renal impairment, is also likely to result in higher plasma and body concentrations of drug than expected, and the possibility of the patient exhibiting undesirable side-effects. The adjustment of dosage regimens in cases of patients having severe renal impairment is considered later in this chapter.

Elimination rate constant and biological half-life of a drug

In the case of a one-compartment open model the rate of elimination or output of a drug from the body compartment follows first-order kinetics (Chapter 7) and is related to the concentration of drug, C_t,



a – b rate of drug absorption > rate of drug elimination
c – d rate of drug elimination > rate of drug absorption

Fig. 19.2 Concentration–time course of a drug in the body following peroral administration of a single dose of drug which confers one-compartment open model characteristics on the body.

remaining in the body compartment at time t, by the following equation:

$$\text{rate of elimination at time } t = -k_e C_t \qquad (19.3)$$

where k_e is the apparent elimination rate constant. The negative sign in Eqn 19.3 indicates that elimination is removing drug **from** the body compartment.

The apparent elimination rate constant of a drug gives the proportion or fraction of that drug which is eliminated from the body per unit time. Its units are in terms of time^{-1}. The apparent elimination constant of a given drug therefore provides a quantitative index of the persistence of that drug in the body.

An alternative parameter used is the biological or elimination half-life of the drug, $t_{1/2}$. This is the time required for the body to eliminate 50% of the drug that it contained. Thus, the larger the biological half-life exhibited by a drug, the slower will be its elimination from the body or plasma.

For a drug whose elimination follows first-order kinetics, the value of its biological half-life is independent of the concentration of drug remaining in the body or plasma. Hence, if a single dose of a drug having a biological half-life of 4 hours was administered perorally, then after the peak plasma concentration had been reached the plasma concentration of drug would fall by 50% every 4 hours until all the drug had been eliminated or a further dose was administered. The relationship between the numbers of half-lives elapsed and the percentage of drug eliminated from the body following administration of a single dose is given in Table 19.1.

An appreciation of the relationship between the percentage of drug eliminated from the body and the number of biological half-lives elapsed is useful when considering how much drug is eliminated from the body over the time interval between successive doses in a multiple-dosage regimen. Biological half-life varies from drug to drug and, even for a given drug, from patient to patient. Some biological half-lives for various drugs are given in Table 19.2.

Table 19.1 Relationship between the amount of drug eliminated and the number of half-lives elapsed

Number of half-lives elapsed	Percentage of drug eliminated
0.5	29.3
1.0	50.0
2.0	75.0
3.0	87.5
3.3	90.0
4.0	94.0
4.3	95.0
5.0	97.0
6.0	98.4
6.6	99.0
7.0	99.2

Table 19.2 The biological half-life ranges for phenobarbitone, digoxin and theophylline

Drug	Biological half-life (h)
Phenobarbitone	50–120
Digoxin	36–51
Theophylline	3–8

For a drug whose elimination follows first-order kinetics, the biological half-life, $t_{1/2}$, is related to the apparent elimination rate constant, k_e, of that drug according to the following equation:

$$t_{1/2} = \frac{0.693}{k_e} \qquad (19.4)$$

Thus the biological half-life of a drug will be influenced by any factor that influences the apparent elimination rate constant of that drug. This explains why factors such as genetic differences between individuals, age and disease can affect the biological half-life exhibited by a given drug. Biological half-life is an important factor that influences the plasma concentration–time curve obtained following peroral administration of a multiple-dosage regimen.

Concentration–time curve of a drug in the body following the peroral administration of equal doses of a drug at fixed intervals of time

In discussing how the design of multiple peroral dosage regimen can influence the concentration–time course of a drug in the body, the following assumptions have been made:

1. The drug confers upon the body the characteristics of a one-compartment open model.
2. The values of the apparent absorption rate and apparent elimination rate constants for a given drug do not change during the period for which the dosage regimen is administered to a patient.
3. The fraction of each administered dose which is absorbed by the body compartment remains constant for a given drug.

4. The aim of drug therapy is to achieve promptly and maintain a concentration of drug at the appropriate site(s) of action which is both clinically efficacious and safe for the desired duration of treatment. This aim is assumed to be achieved by the prompt attainment and maintenance of plasma concentrations of drug which lie within the therapeutic range of that drug.

If the interval between each perorally administered dose is longer than the time required for complete elimination of the previous dose, then the plasma concentration–time profile of a drug will exhibit a series of isolated single-dose profiles, as shown in Figure 19.3.

Consideration of the plasma concentration–time profile shown in Figure 19.3 in relation to the minimum effective and maximum safe plasma concentrations (MEC and MSC, respectively) for the drug reveals that the design of this particular dosage regimen is unsatisfactory. The plasma concentration only lies within the therapeutic concentration range of the drug for a relatively short period following the administration of each dose, and the patient remains undermedicated for relatively long periods. If the dosing time interval is reduced so that it is now shorter than the time required for complete elimination of the previous dose, then the resulting plasma concentration–time curve exhibits the characteristic profile shown in Figure 19.4.

Figure 19.4 shows that at the start of this multiple-dosage regimen the maximum and minimum plasma concentrations of drug observed during each dosing time interval tend to increase with successive doses. This increase is because the time interval between successive doses is less than that required for complete elimination of the previous absorbed dose. Consequently, the total amount of the drug remaining in the body compartment at any time after a dose is equal to the sum of that remaining from all the previous doses. The accumulation of drug in the body and plasma with successively administered doses does not continue indefinitely. Provided drug elimination follows first-order kinetics, the rate of elimination will increase as the average concentration of drug in the body (and plasma) rises. If the amount of drug supplied to the body compartment per unit dosing time interval remains constant, then a situation is eventually reached when the overall rate of elimination from the body over the dosing time interval becomes equal to the overall rate at which drug is being supplied to the body compartment over that interval, i.e. the overall rate of elimination has effectively caught up with the overall rate of supply. This effect

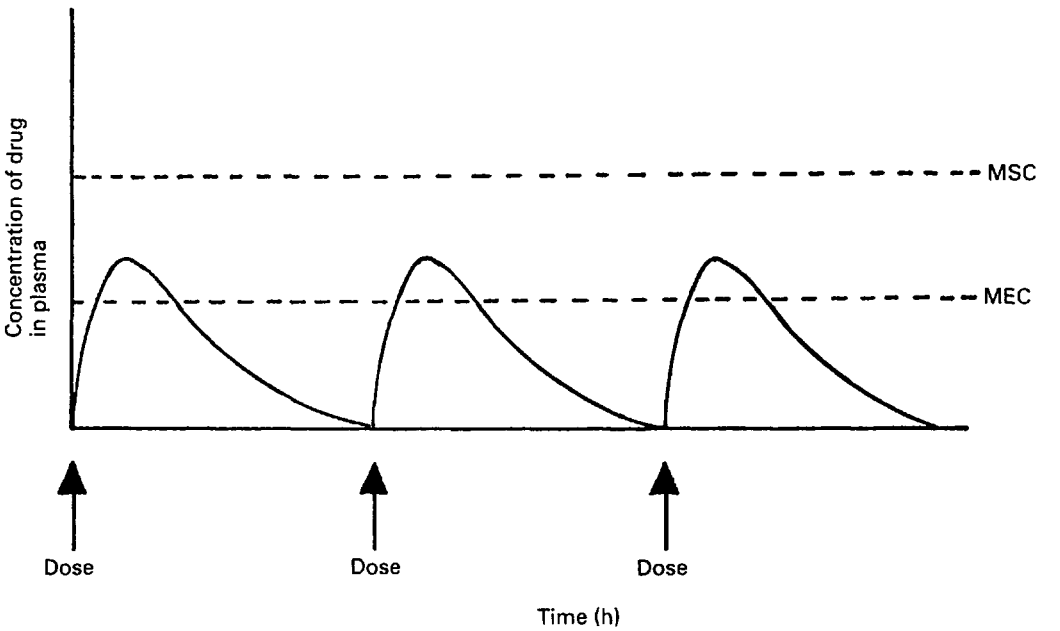


Fig. 19.3 Plasma concentration–time curve following peroral administration of equal doses of a drug at time intervals that allow complete elimination of the previous dose. (MSC, maximum safe plasma concentration of the drug; MEC, minimum effective plasma concentration of the durg.)

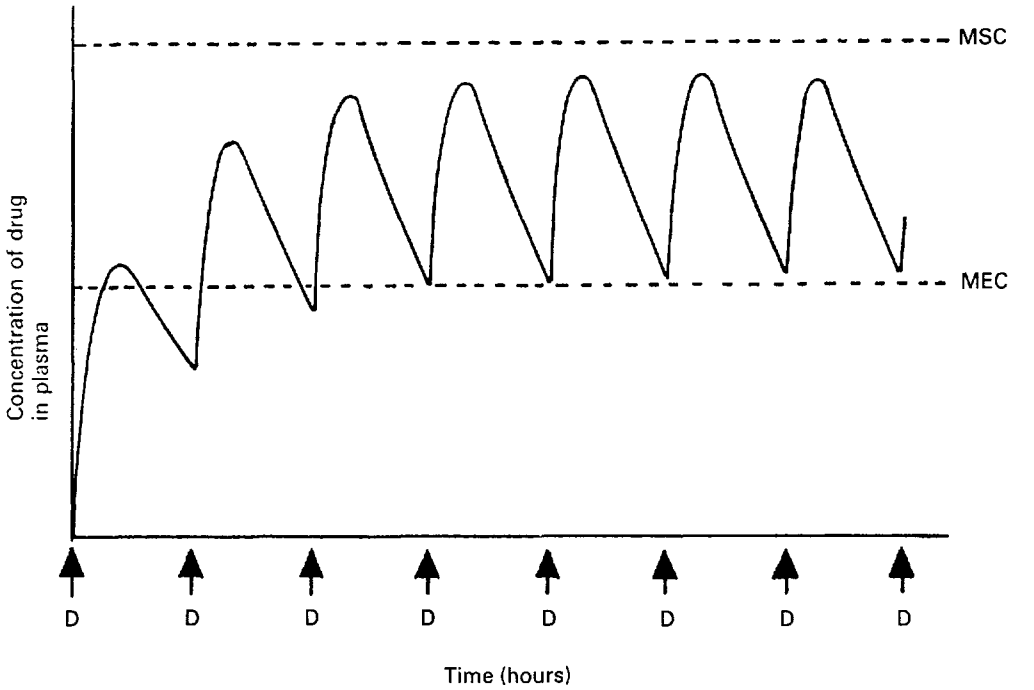


Fig. 19.4 Plasma concentration–time curve following peroral administration of equal doses, *D*, of a drug every 4 hours. (MSC, maximum safe plasma concentration of the drug; MEC, minimum effective plasma concentration of the drug.)

is due to the elimination rate increasing as the residual concentration of drug in the plasma rises (as elimination is first order here).

When the overall rate of drug supply equals the overall rate of drug output from the body compartment, a ***steady state*** is reached with respect to the average concentration of drug remaining in the body over each dosing time interval. At steady state, the amount of drug eliminated from the body over each dosing time interval is equal to the amount that was absorbed into the body compartment following administration of the previous dose.

Figure 19.5 shows that the amount of drug in the body, as measured by the plasma concentration, fluctuates between maximum and minimum values which remain more or less constant from dose to dose. At steady state the average concentration of drug in the plasma, $C^{ss}_{average}$, over successive dosing time intervals remains constant.

For a drug administered repetitively in equal doses and at equal time intervals, the time required for the average plasma concentration to attain the corresponding steady-state value is a function only of the biological half-life of the drug, and is independent of both the size of the dose administered and the length of the dosing time interval. The time required for the average plasma concentration to reach 95% of the steady-state value corresponding to the particular multiple dosage regimen is 4.3 times the biological half-life of the drug. The corresponding figure for 99% is 6.6 times. Therefore, depending on the magnitude of the biological half-life of the drug being administered, the time taken to attain the average steady-state plasma concentration may range from a few hours to several days.

From a clinical viewpoint the time required to reach steady state is important, because for a properly designed multiple-dosage regimen the attainment of steady state corresponds to the achievement and maintenance of maximal clinical effectiveness of the drug in the patient.

It should be noted that for a drug such as phenytoin, whose elimination is not described by first-order kinetics, the peroral administration of equal doses at fixed intervals may not result in the attainment of steady-state plasma levels. If the concentration of such drug in the body rises sufficiently following repetitive administration, the pathway responsible for its elimination may become saturated. If this occurred the rate of elimination would become maximal and could not increase to cope with any further rises in the average concentration of drug in the body. Hence the overall rate of elimination would not become equal to the overall rate of

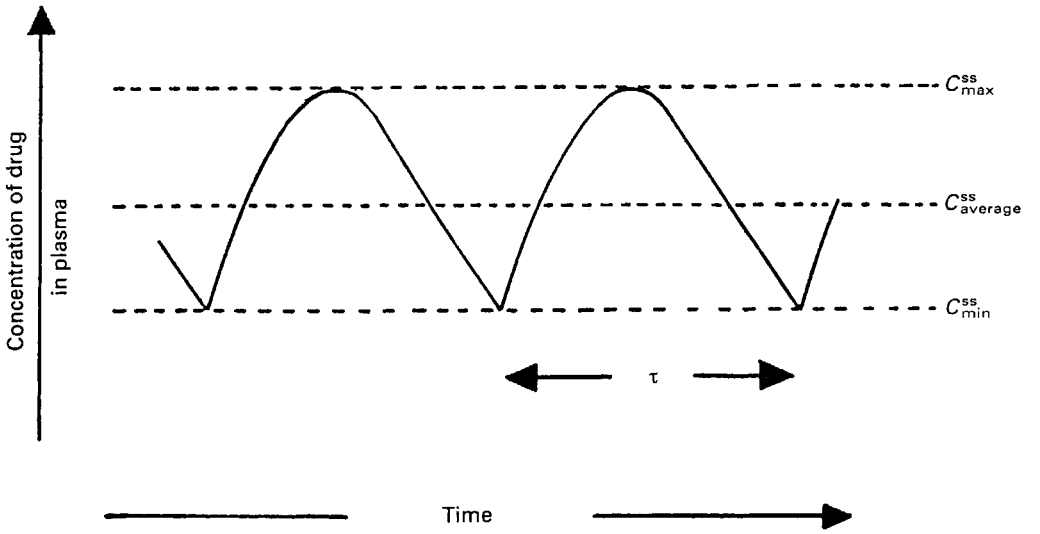


Fig. 19.5 Fluctuation of concentration of drug in the plasma at steady state resulting from repetitive peroral administration of equal doses, D, of drug at a fixed interval of time, τ. C^{ss}_{max}, C^{ss}_{min} and $C^{ss}_{average}$ represent the maximum, minimum and average plasma concentrations of drug, respectively, achieved at steady state.

supply over each dosing time interval, and the condition necessary for the attainment of steady state would not be achieved. If repetitive administration continued at the same rate, the average concentration of drug in the body and plasma would tend to continue to accumulate, rather than to reach a plateau.

IMPORTANT FACTORS INFLUENCING STEADY-STATE PLASMA DRUG CONCENTRATIONS

Dose size and frequency of administration

In designing a multiple-dosage regimen that balances patient convenience with the achievement and maintenance of maximal clinical effectiveness, only two parameters can be adjusted for a given drug: the size of dose and the frequency of administration. Consider how the maximum, minimum and average steady-state plasma concentrations of drug are influenced by these parameters.

Size of dose

Figure 19.6 illustrates the effects of changing the dose size on the concentration of drug in the plasma following repetitive administration of peroral doses at equal intervals of time. As the size of the administered dose is increased, the higher are the corresponding maximum, minimum and average plasma drug levels, C^{ss}_{max}, C^{ss}_{min} and $C^{ss}_{average}$, respectively, achieved at steady state. What may not be so well appreciated is that the larger the dose the larger is the fluctuation between C^{ss}_{max} and C^{ss}_{min} during each dosing time interval. Large fluctuations between C^{ss}_{max} and C^{ss}_{min} can be hazardous, particularly with a drug such as digoxin, which has a narrow therapeutic range. In such cases, it is possible that C^{ss}_{max} could exceed the maximum safe plasma concentration. Figure 19.6 also illustrates that the time required to attain steady-state plasma concentrations is independent of the size of the administered dose.

Interval between successive equal doses

Figure 19.7 illustrates the effects of constant doses administered at various dosing intervals, which are multiples of the biological half-life of the drug $t_{1/2}$. The uppermost plasma concentration–time curve in Figure 19.7 shows that the repetitive administration of doses at a time interval which is less than the biological half-life of the drug results in higher steady-state plasma drug concentrations being obtained. This is a consequence of the extent of elimination of the drug from the body over a dosing time interval equal to 0.5 $t_{1/2}$ being smaller than that which is eliminated when the dosing time interval is equal to $t_{1/2}$ (see Table 19.1).

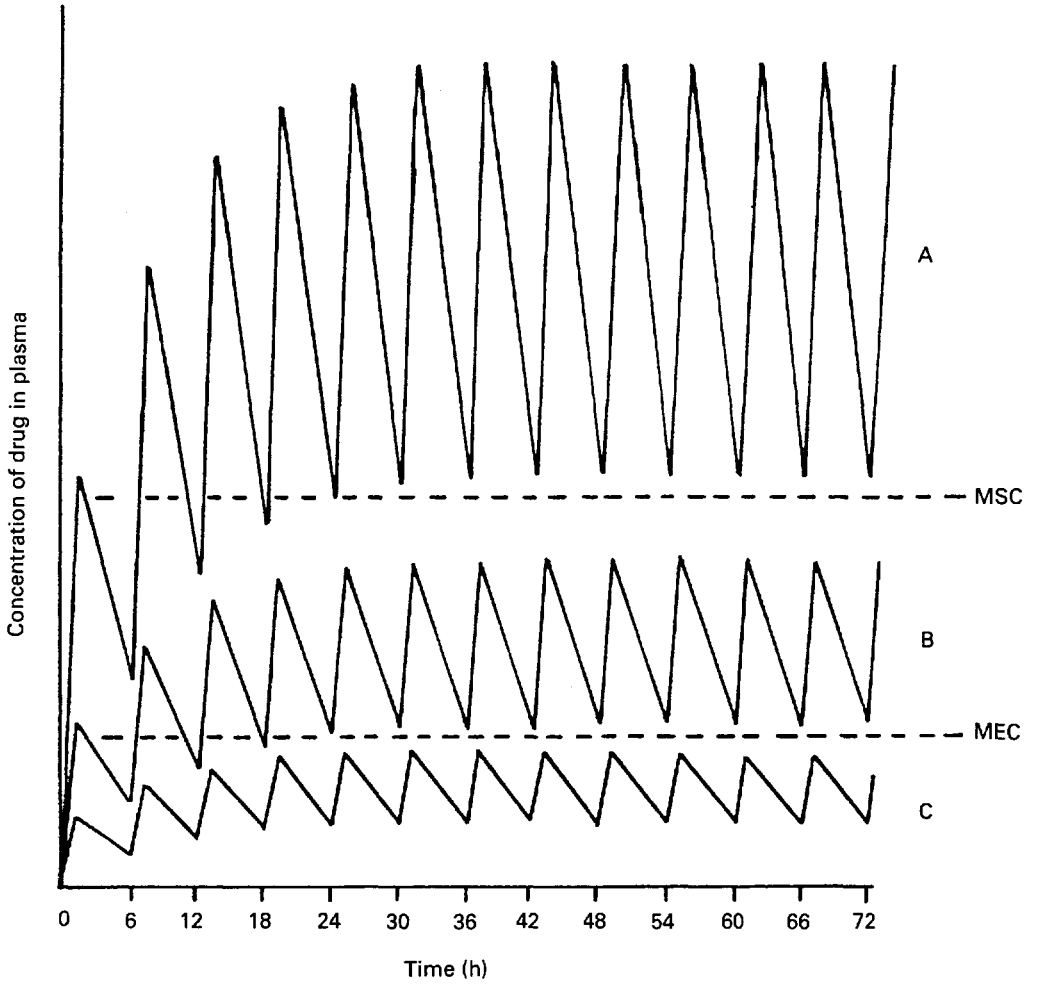


Fig. 19.6 Diagrammatic representation of the effect of dose size on the plasma concentration–time curve obtained following peroral administration of equal doses of a given fixed drug at fixed intervals of time equal to the biological half-life of the drug. Curve A, dose = 250 mg. Curve B, dose = 100 mg. Curve C, dose = 40 mg.

Figure 19.7 also shows that repetitive administration of doses at intervals greater than the biological half-life of the drug results in the lower steady-state plasma drug concentrations being obtained. This is a consequence of a greater proportion of the drug being eliminated over a dosing time interval equal to $2t_{1/2}$, compared to that which is eliminated when the dosing time interval is equal to $t_{1/2}$.

Summary of the effects of dose size and frequency of administration

Consideration of the effects of dose size and the dosage interval on the amount of a given drug achieved in the body, as measured by the plasma concentration, following repetitive peroral administration of equal doses, have revealed the following relationships:

1. The magnitude of the fluctuations between the maximum and minimum steady-state amounts of drug in the body is determined by the size of dose administered or, more accurately, by the amount of drug absorbed following each dose administered.
2. The magnitude of the fluctuations between the maximum and minimum steady-state plasma concentrations are an important consideration for any drug that has a narrow therapeutic range, e.g. digoxin. The more frequent administration of smaller doses is a means of

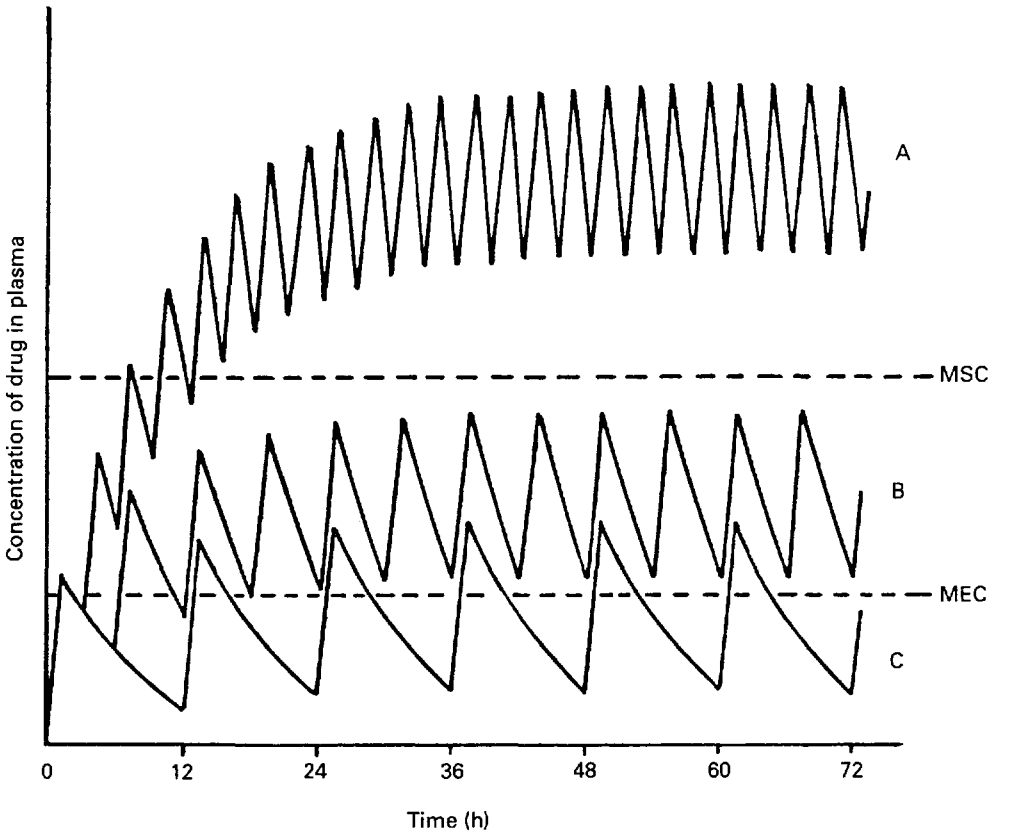


Fig. 19.7 Diagrammatic representation of the effect of changing the dosing time interval, τ, on the plasma concentration–time curve obtained following repetitive peroral administration of equal size doses of a given drug. Curve A, dosing time interval = 3 hours ($0.5t_{\frac{1}{2}}$). Curve B, dosing time interval = 6 hours ($t_{\frac{1}{2}}$). Curve C, dosing time = 12 hours ($2t_{\frac{1}{2}}$).

reducing the steady-state fluctuations without altering the average steady-state plasma concentration. For example, a 500 mg dose given every 6 hours will provide the same $C^{ss}_{average}$ value as a 250 mg dose of the same drug given every 3 hours, whereas the C_{max} and C_{min} fluctuation for the latter dose will be decreased by half.

3. The average maximum and minimum amounts of drug achieved in the body at steady state are influenced by either the dose size, the dosage time interval in relation to the biological half-life of the drug, or both. The greater the dose size and the smaller the dosage time interval relative to the biological half-life of the drug, the greater are the average, maximum and minimum steady-state amounts of drug in the body.
4. For a given drug, the time taken to achieve steady state is independent of dose size and dosage time interval.
5. If the maximum safe and minimum effective plasma drug concentrations are represented by the dashed lines shown in Figures 19.6 and 19.7, respectively, then it is evident that the proper selection of dose size and dosage time interval are important with respect to achieving and maintaining steady-state plasma concentrations that lie within the therapeutic range of the particular drug being administered.

It is evident from the preceding discussion that the proper selection of the dose size and the dosage time interval is crucial in ensuring that a multiple-dosage regimen provides steady-state concentrations of drug in the body which are both clinically efficacious and safe.

Mathematical relationships that predict the values of the various steady-state parameters achieved in the body following repetitive administration of doses at constant intervals of time have been used to assist

the design of clinically acceptable multiple dosage regimens. For example, a useful equation for predicting the average amount of drug achieved in the body at steady state, $D^{ss}_{average}$, following repetitive peroral administration of equal doses, D, at a fixed time interval, τ is:

$$D^{ss}_{average} = \frac{F \cdot D \cdot t_{1/2} \cdot 1.44}{\tau} \qquad (19.5)$$

where F is the fraction of drug absorbed following the administration of a dose, D, of drug; thus $F \cdot D$ is the bioavailable dose of drug, and $t_{1/2}$ is the biological half-life of that drug. The average amount of a given drug in the body at steady state, $D^{ss}_{average}$ is related to the corresponding average plasma concentration of the drug by the factor known as the ***apparent volume of distribution***, i.e.:

$$D^{ss}_{average} = V_d \, C^{ss}_{average} \qquad (19.6)$$

where V_d is the apparent volume of distribution of the drug and $C^{ss}_{average}$ is the average steady-state plasma concentration. Equation 19.5 can be rewritten in terms of the average steady-state plasma concentration of the drug as follows:

$$C^{ss}_{average} = \frac{F \cdot D \cdot t_{1/2} \cdot 1.44}{\tau \cdot V_d} \qquad (19.7)$$

If the value of the average body amount or the average plasma concentration of a given drug at steady state which gives a satisfactory therapeutic response in a patient is known, then Eqns 19.5 or 19.7 can be used respectively to estimate either the size of dose that should be administered repetitively at a preselected constant dosage time interval, or the dosage time interval at which a preselected dose should be administered repetitively. In order to illustrate a dosage regimen calculation, based on the average steady-state plasma concentration of a drug, consider the following worked example.

An antibiotic is to be administered on a repetitive basis to a male patient weighing 76 kg. The antibiotic is commercially available in the form of tablets, each containing 250 mg of the drug. The fraction of the drug that is absorbed following peroral administration of one 250 mg tablet is 0.9. The antibiotic has been found to exhibit a biological half-life of 3 hours and the patient has an apparent volume of distribution of 0.2 L kg^{-1} of body weight. What dosage time interval should be selected to administer this drug on a repetitive basis so that a therapeutic average steady-state plasma concentration of 16 mg L^{-1} will be achieved?

Using Eqn 19.7:

$$C^{ss}_{average} = \frac{F \cdot D \cdot t_{1/2} \cdot 1.44}{\tau \cdot V_d} \qquad (19.8)$$

where the average steady-state plasma concentration of drug, $C^{ss}_{average}$, is 16 mg L^{-1}, the fraction of each administered dose absorbed, F = 0.9, the size of administered dose, D = 250 mg, the biological half-life of the drug, $t_{1/2}$ = 3 h, and the apparent volume of distribution, V_d = 0.2 L kg^{-1} of patient's body weight.

Hence, for a patient weighing 76 kg the value of

$$V_d = 0.2 \times 76 \text{ L}$$
$$= 15.2 \text{ L}.$$

To calculate the dosage time interval, τ, requires substitution of the above values into Eqn 19.7, which gives:

$$16 = \frac{0.9 \times 250 \times 3 \times 1.44}{\tau \times 15.2}$$

$$\tau = \frac{0.9 \times 250 \times 3 \times 1.44}{16 \times 15.2}$$

$$= \frac{972.0 \text{h}}{243.2}$$

$$\approx 4 \text{h}.$$

Thus one 250 mg tablet should be administered every 4 hours in order to achieve the required averaged average steady-state plasma concentration.

Mathematical equations which predict the maximum or minimum steady-state plasma concentrations of a drug achieved in the body followed by repetitive administration of equal doses at a fixed interval of time are also available for drugs whose time course in the body is described by the one-compartment open pharmacokinetic model.

The concept of 'loading doses'

As discussed earlier, the time required for a given drug to reach 95% of the average steady-state plasma concentration is 4.3 biological half-lives, when equal doses of the drug are administered repetitively at equal intervals of time. Thus, for a drug with a long half-life of 24 hours it would take more than 4 days for the average concentration in the plasma to reach 95% of its steady-state value. Because the attainment of steady-state plasma concentrations is normally associated with the attainment of maximal clinical effectiveness of the drug, it is conceivable that a number of days could elapse before a patient experienced the full therapeutic benefit of a drug having a long half-life. To reduce the time required for onset of the full therapeutic effect, a large single dose of the drug may be admin-

istered initially in order to achieve a peak plasma concentration that lies within the therapeutic range of the drug and is approximately equal to the value of C^{ss}_{max} required. This is known as the ***loading dose*** or ***priming dose***.

Thereafter smaller, equal doses are administered repetitively at suitable fixed intervals so as to maintain the plasma concentrations of drug at the maximum, minimum and average state levels that provide the patient with the full therapeutic benefit. These are known as ***maintenance doses***. As a general rule, the loading dose should be twice the size of the maintenance dose if the selected dosage time interval corresponds to the biological half-life of the drug.

Figure 19.8 illustrates how rapidly therapeutic steady-state plasma concentrations of drug are achieved when the dosage regimen consists of an initial loading dose followed by equal maintenance doses at fixed intervals, compared to a 'simple' multiple-dosage regimen consisting of doses that are equal in size and are administered at the same dosage time intervals as the maintenance doses.

Influence of changes in the apparent elimination rate constant of a drug: the problem of patients with renal impairment

Whereas the loading dose, maintenance dose and dosage time interval may be varied in order to design a clinically efficacious multiple dosage regimen, one factor cannot normally be adjusted. This is the apparent elimination rate constant exhibited by the particular drug being administered. However, the elimination rate constant of a given drug does vary from patient to patient, and is influenced by whether the patient has normal or impaired renal function.

Figure 19.9 indicates the effects produced by changes in the apparent elimination rate constant on the plasma concentration–time curve obtained following repetitive, peroral administration of equal doses of a given drug at equal intervals of time. Any reduction in the apparent elimination rate constant will produce a proportional increase in the biological half-life exhibited by the drug. This reduction, in turn, will result in a greater degree of accumulation of the drug in the body following repetitive administration

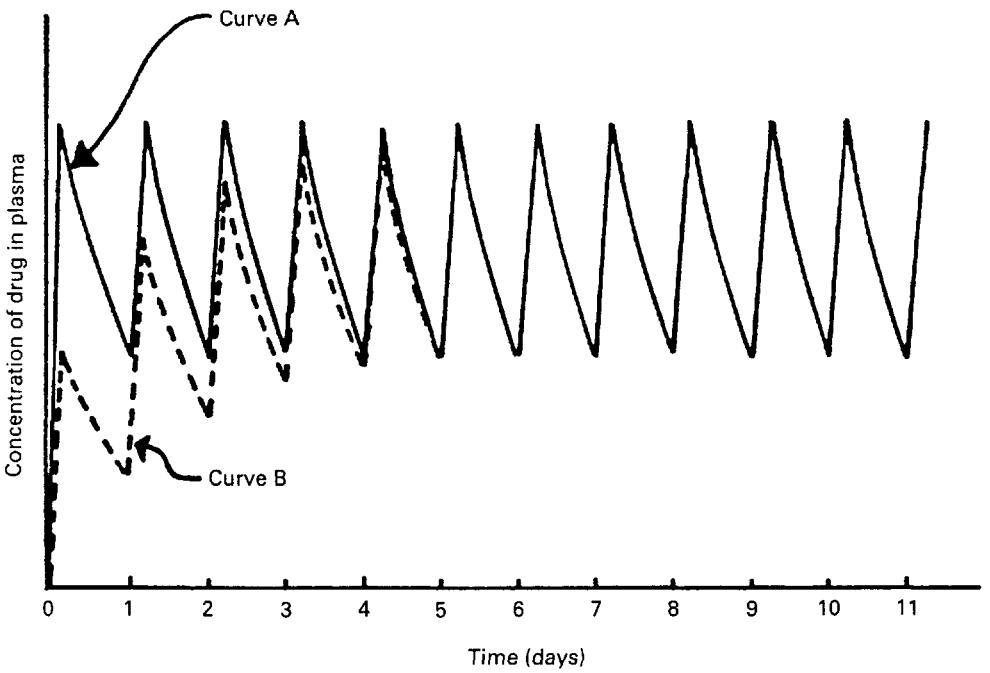


Fig. 19.8 Diagrammatic representation of how the initial administration of a loading dose followed by equal maintenance doses at fixed intervals of time ensure rapid attainment of steady-state plasma levels for a drug having a long biological half-life of 24 hours. Curve A represents the plasma concentration–time curve obtained following peroral administration of a loading dose of 500 mg followed by a maintenance dose of 250 mg every 24 hours. Curve B represents the plasma concentration–time curve obtained following peroral administration of a 250 mg dose every 24 hours.

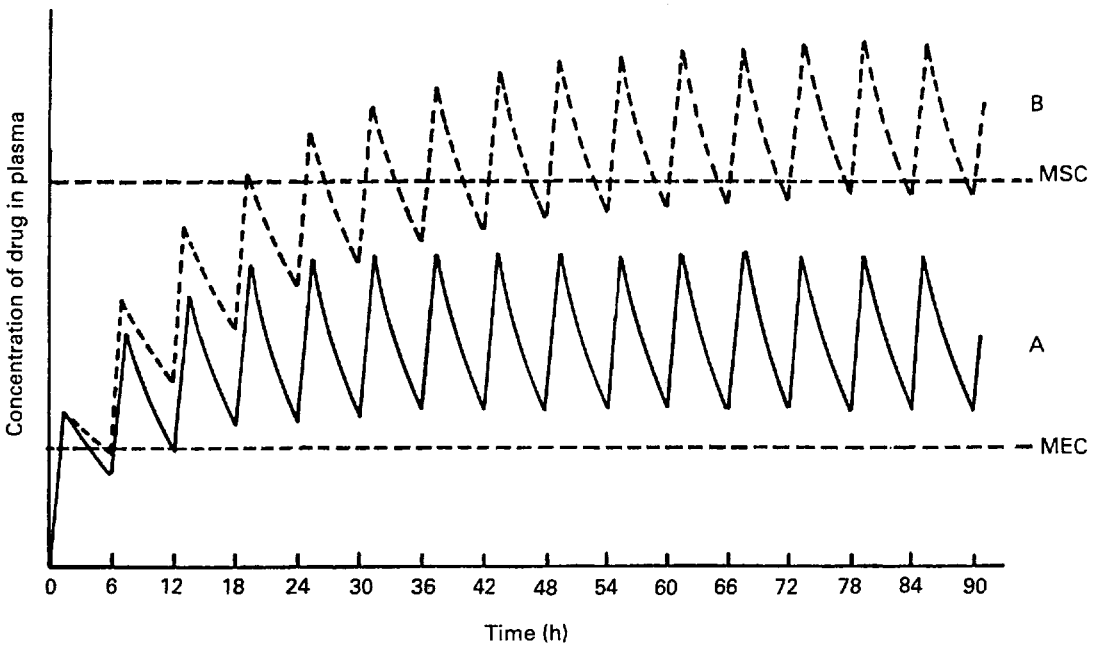


Fig. 19.9 Diagrammatic representation of the effect of changing the biological half-life of a given drug on the plasma concentration–time curve exhibited by the drug following peroral administration of one 250 mg dose every 6 hours. Curve A, biological half-life of drug = 6 hours. Curve B, biological half-life of drug = 12 hours.

before steady-state drug levels are achieved. The greater degree of drug accumulation is a consequence of a smaller proportion of the drug being eliminated from the body over each fixed dosage time interval when the biological half-life of the drug is increased.

Patients who develop severe renal impairment normally exhibit smaller apparent elimination rate constants and consequently longer biological half-lives for drugs which are eliminated substantially by renal excretion than do patients with normal renal function. For instance, the average apparent elimination rate constant for digoxin may be reduced from 0.021 h^{-1} in patients with normal renal function to 0.007 h^{-1} severe renal impairment. The average steady-state amount of drug in the body is only achieved and maintained when the overall rate of supply equals the overall rate of elimination over successive dosing time intervals. Any reduction in the overall rate of elimination of a drug as a result of renal disease, without a corresponding compensatory reduction in the overall rate of supply, will result in increased steady-state amounts of drug in the body. This effect in turn may lead to side-effects and toxic effects if the increased steady-state levels exceed the maximum safe concentration of the drug.

In order to illustrate this concept, consider that curves A and B in Figure 19.9 correspond to the plasma concentration–time curves obtained for a given drug in patients having normal renal function and severe renal impairment, respectively, and that the upper and lower dashed lines represent the maximum safe and minimum effective plasma concentrations, respectively. It is thus evident that the administration of a drug according to a multiple-dosage regimen which produces therapeutic steady-state plasma levels in patients with normal renal function, will give plasma concentrations that exceed the maximum safe plasma concentration of the drug in patients with severe renal impairment. Hence the adjustment of multiple-dosage regimens in terms or dose size, frequency of administration or both is necessary if patients suffering with renal disease are to avoid the possibility of overmedication.

Influence of the 'overnight no-dose period'

So far we have considered that multiple-dosage regimens comprise of doses being administered at uniform time intervals around the clock, but in practice this is unusual. If a multiple-dosage regimen

requires a dose to be administered 'four times a day' it is unlikely that a dose will be administered at 6-hourly intervals around the clock. Instead, the four doses are likely to be administered during 'waking' hours, e.g. 10 am–2 pm –6 pm–10 pm or 9 am–1 pm–5 pm–9 pm. The significant feature of both these schedules is that the patient will experience an overnight no-dose period of 12 hours. Although this will undoubtedly give the patient periods of undisturbed sleep, it may also cause problems in maintaining therapeutic steady-state plasma concentrations of drug in the body.

It is conceivable that overnight no-dose periods of 8–12 hours could result in substantial decreases in the amount of a drug in the plasma and body, particularly for drugs having biological half-lives which are relatively short compared to the overnight no-dose period. For instance, in the case of a drug having a biological half-life of 4 hours, an overnight no-dose period of 12 hours would correspond to the elapse of three biological half-lives and consequently a large reduction in the amount of drug in the body.

The potential problems of overnight no-dose periods with respect to maintaining therapeutic steady-state drug levels is illustrated in Figure 19.10. This shows that for a drug having a biological half-life of 4 hours, a multiple-dosage regimen comprising one 60 mg dose administered perorally four times each day according to the timetable 9 am–1 pm–5 pm–9 pm does not permit a true steady state to be attained. Thus the concentration of drug in the plasma does not fluctuate between constant maximum and minimum values over successive dosage time intervals, as would occur if the doses were administered every 4 hours around the clock.

Furthermore, Figure 19.11 shows that even if a loading dose of 120 mg were included in the dosage regimen to ensure that a true steady state was obtained before the first overnight no-dose period, the steady state would not be re-established after the first overnight no-dose period. If the upper and lower dashed lines in Figures 19.10 and 19.11 represent the therapeutic range of the drug, then the patient would experience periods during which the level of drug in the plasma and body would fall below that necessary to elicit the therapeutic effect. Hence, unless the therapeutic range of the drug is sufficiently large to accommodate the fluctuations in concentration associated with overnight no-dose periods, problems could arise with regard to maintaining therapeutic drug levels in patients. The potential problems associated with overnight no-dose periods are even further complicated by patients who forget to take one of their daytime doses.

Concluding comments

This chapter explains the interrelationship between the rate at which drug enters the body and the rate at which it leaves. It also discusses how, in turn, this balance influences the concentration of drug in the plasma at any given time. It is clearly important for pharmaceutical scientists to come to terms with this problem and then overcome it by finding ways of

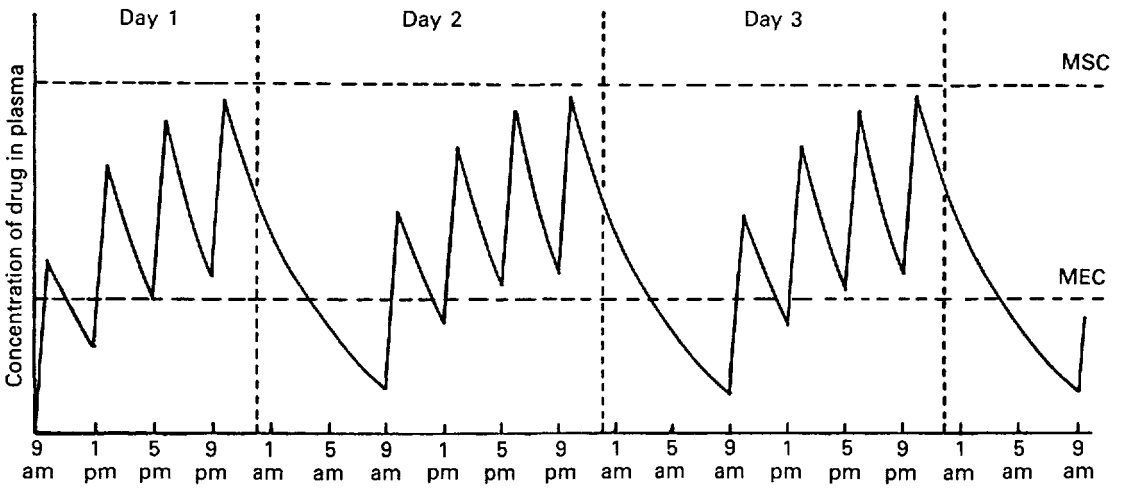


Fig. 19.10 Diagrammatic representation of the variation in the concentration of a drug in the plasma accompanying the peroral administration of a single dose of 60 mg four times a day according to the time schedule 9 am–1 pm–5 pm–9 pm. The biological half-life of the drug is 4 hours.

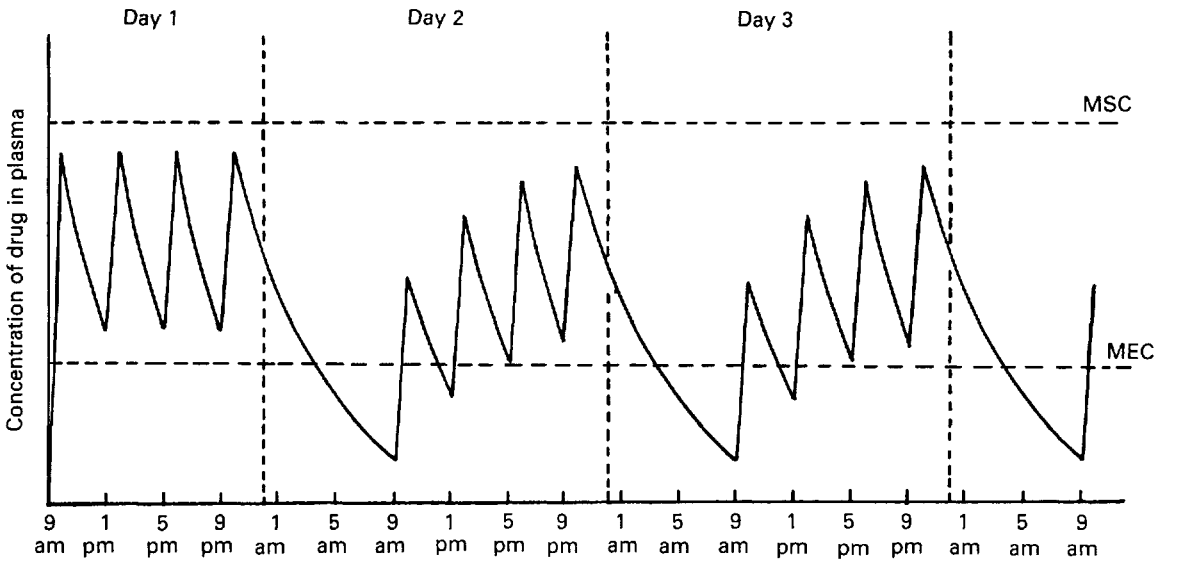


Fig. 19.11 Diagrammatic representation of the variation in the concentration of drug in the plasma accompanying the peroral administration of a loading dose of 120 mg followed by single maintenance doses of 60 mg four times a day according to the time schedule 9 am–1 pm–5 pm–9 pm. The biological half-life of the drug is 4 hours.

maintaining therapeutic drug levels appropriate to a particular disease state. This can be achieved by the careful design of the appropriate drug delivery system. This aspect of the design and formulation of modified-release drug delivery systems is discussed fully in Chapter 20.

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Modified-release peroral dosage forms

John Collett, Chris Moreton

CHAPTER CONTENTS

MAINTENANCE OF THERAPEUTIC DRUG CONCENTRATIONS BY MODIFIED-RELEASE PERORAL DOSAGE FORMS

For many disease states the ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site(s) of action is attained immediately and is then maintained constant for the desired duration of the treatment. It is evident from the preceding chapter that, provided dose size and frequency of administration are correct, therapeutic 'steady-state' plasma concentrations of a drug can be achieved promptly and maintained by the repetitive administration of conventional peroral dosage forms. However, there are a number of potential limitations associated with this. In the context of this section a 'conventional' peroral oral dosage form is assumed to be one that is designed to release rapidly the complete dose of drug contained therein immediately following administration. In addition, the released drug is assumed to be in a form which is therapeutically active and immediately available for absorption into the systemic circulation.

These limitations are:

1. The concentration of drug in the plasma and hence at the site(s) of action of the drug fluctuates over successive dosing intervals, even when the so-called 'steady-state' condition is achieved. Hence it is not possible to maintain a therapeutic concentration of drug **which remains constant** at the site(s) of action for the duration of treatment. At best, the mean value of the maximum and minimum plasma concentrations associated with each successive dose remains constant for the period of drug treatment.
2. The inevitable fluctuations of steady-state concentrations of drug in the plasma, and hence at the site(s) of action, can lead to a patient being over- or undermedicated for periods of time if the values of C^{ss}_{max} and C^{ss}_{min} (Chapter 19) rise or fall, respectively, beyond the therapeutic range of the drug.
3. For drugs with short biological half-lives frequent doses are required to maintain steady-state plasma concentrations within the therapeutic range. For such drugs the maintenance of therapeutic plasma concentrations is particularly susceptible to the consequence of forgotten doses and the overnight no-dose period. Lack of patient compliance, which is more likely in the case of regimens requiring frequent administration of conventional dosage forms, is often an important reason for therapeutic inefficiency or failure. Clearly, not even a peroral dosage regimen which has been designed to perfection can achieve and maintain clinically efficacious concentrations of a drug at its site(s) of action if the patient does not comply with it.

These limitations and requirements led pharmaceutical scientists to consider presenting therapeutically active molecules in 'extended-release' preparations. In reality the scientists were attempting to take the control of medication away from the patient, and to some extent the physician, and to place it in the drug delivery system.

Over the years there has been an enormous amount of work put into designing drug delivery systems that can eliminate or reduce the cyclical plasma concentrations seen after conventional drug delivery systems are administered to a patient according to a specified dosage regimen.

One of the first commercially available products to provide sustained release of a drug was Dexedrine Spansules®, made by Smith Kline & French. After this many more sustained-release products came to the market, some successful, others potentially lethal. Each delivery system was aimed at eliminating the cyclical changes in plasma drug concentration seen after the administration of a conventional delivery system. A variety of terms was used to describe these systems:

- ***Delayed release*** indicates that the drug is not being released immediately following administration but at a later time, e.g. enteric-coated tablets, pulsatile-release capsules.
- ***Repeat action*** indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.
- ***Prolonged release*** indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.
- ***Sustained release*** indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period.
- ***Extended release*** (ER) dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hours).

- ***Controlled release*** (CR) dosage forms release drug at a constant rate and provide plasma concentrations that remain invariant with time.
- ***Modified release*** (MR) dosage forms are defined by the USP as those whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional forms, whereas an extended-release (ER) dosage form allows a twofold reduction in dosing frequency or increase in patient compliance or therapeutic performance. It is interesting to note that the USP considers that the terms controlled release, prolonged release and sustained release are interchangeable with extended release. From a biopharmaceutical perspective this is not strictly a concern.

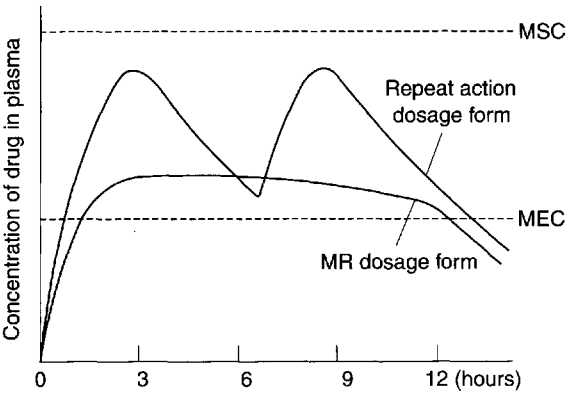

Fig. 20.1 Plasma concentration–time curves obtained following peroral administration of (a) one repeat-action dosage form containing two doses, and (b) one MR dosage form containing the same drug. MSC = maximum safe concentration, MEC = minimum effective concentration (see Chapter 19).

Repeat-action versus sustained-action drug therapy

A repeat-action tablet or hard gelatin capsule may be distinguished from its sustained-released counterpart by the fact that the repeat-action product does not release the drug in a slow controlled manner, and consequently does not give a plasma concentration–time curve which resembles that of a sustained-release product. A repeat-action tablet usually contains two doses of drug, the first being released immediately following peroral administration in order to provide a rapid onset of the therapeutic response. The release of the second dose is delayed, usually by means of an enteric coat. Consequently, when the enteric coat surrounding the second dose is breached by the intestinal fluids, the second dose is released immediately. Figure 20.1 shows that the plasma concentration–time curve obtained following the administration of one repeat-action preparation exhibits the 'peak and valley' profile associated with the intermittent administration of conventional dosage forms. The primary advantage provided by a repeat-action tablet over a conventional one is that two (or occasionally three) doses are administered without the need to take more than one tablet.

Modified release

The term modified release (MR) will be used in this chapter to describe peroral dosage forms that continuously release drugs at rates which are sufficiently controlled to provide periods of prolonged therapeutic action following each administration of a 'single dose'. Although all MR products could be described literally as controlled-release systems, the term 'controlled release' will only be used in this chapter to describe a peroral sustained-release product which is able to maintain a constant therapeutic steady-state concentration of drug in the plasma, the tissues, or at the site of action. This use of the term is in accordance with the proposals of Chien (1995).

The degree of precision of control over the rate of drug release from an MR dosage form varies according to the particular formulation technique employed. Consequently, depending on the degree of control over release (and consequently over drug absorption) that is achieved, peroral MR products are generally designed to provide either:

1. the prompt achievement of a plasma concentration of drug that remains essentially constant at a value within the therapeutic range of the drug for a satisfactorily prolonged period of time, or
2. the prompt achievement of a plasma concentration of drug which, although not remaining constant, declines at such a slow rate that the plasma concentration remains within the therapeutic range for a satisfactorily prolonged period of time.

Typical drug plasma concentration–time profiles corresponding to the above criteria for modified-release products are shown in Figure 20.2.

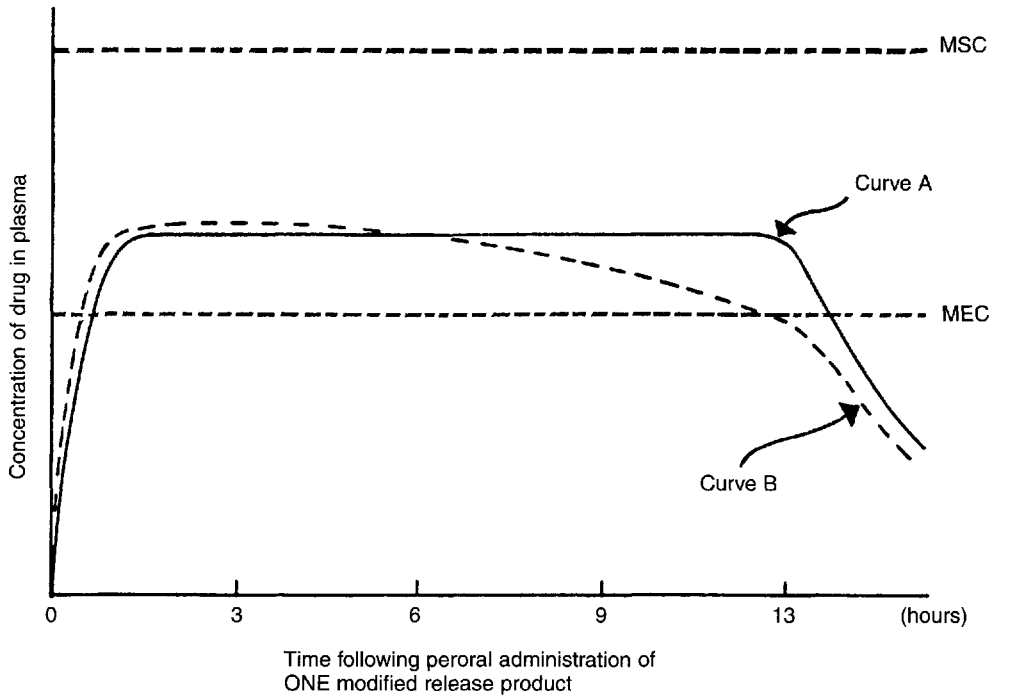

Fig. 20.2 Typical plasma concentration – time profiles for MR peroral products which, following rapid attainment of a therapeutic plasma concentration of drug, provide a period of prolonged therapeutic action by either (a) maintaining a *constant* therapeutic plasma concentration (curve A) or, (b) ensuring that the plasma concentration of drug remains within the therapeutic range for a satisfactorily prolonged period of time (curve B).

Kinetic pattern of drug release required for the ideal modified controlled-release peroral dosage form

If it is assumed that the drug which is to be incorporated into the ideal MR dosage form confers upon the body the characteristics of a one-compartment open model, then the basic kinetic design of such a product may be represented diagrammatically as shown in Figure 20.3.

To achieve a therapeutic concentration promptly in the body and then to maintain that concentration for a given period of time requires that the total drug in the dosage form consists of two portions, one that provides the **initial** priming/loading dose, D_i, and one that provides the **maintenance** or sustained dose, D_m.

The initial priming dose of drug D_i is released rapidly into the gastrointestinal fluids immediately following administration of the MR dosage form (see step 1 in Fig. 20.3). The released dose is required to be absorbed into the body compartment rapidly following a first-order kinetic process that is characterized by the apparent absorption rate constant, $k^1{}_a$ (see step 2 in Fig. 20.3). The aim of this initial rapid release and subsequent absorption of the initial priming dose is the rapid attainment of a therapeutic concentration of drug in the body. This priming dose provides a rapid onset of the desired therapeutic response in the patient.

Following this period of rapid drug release, the portion D_m of drug remaining in the dosage form is released at a slow but defined rate (see step 3 in Fig. 20.3). In order to maintain a constant plasma level of drug, the maintenance dose, D_m, must be released by the dosage form according to zero-order kinetics. It thus follows that the rate of release of drug will remain constant and be independent of the amount of the maintenance dose remaining in the dosage form at any given time. The rate of release of the maintenance dose may be characterized by the zero-order rate constant k^o_m.

Two further conditions must be fulfilled in order to ensure that the therapeutic concentration of drug in the body remains constant.

1. The zero-order rate of release of drug from the maintenance dose must be rate determining with respect to the rate at which the released drug is subsequently absorbed into the body.

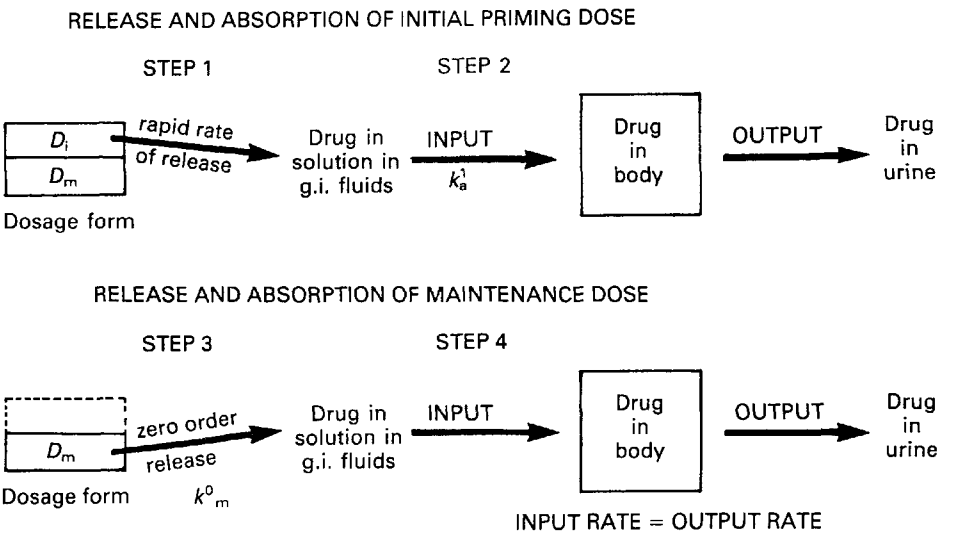

Fig. 20.3 A one-compartment open model of drug disposition in which the source of drug input is an *ideal* MR peroral drug product. D_i is the initial priming dose of drug in dosage form; D_m is the maintenance dose of drug in the dosage form; k^1_a is the first-order apparent absorption rate constant of drug from the priming dose; k^0_m is the zero-order release rate constant of drug from the maintenance dose.

The kinetics of absorption of the maintenance dose will thus be characterized by the same zero-order release rate constant, k^0_m (step 3 in Fig. 20.3).

2. The rate at which the maintenance dose is released from the dosage form, and hence the rate of absorption (input) of drug into the body, must be equal to the rate of drug output from the body when the concentration of drug in the body is at the required therapeutic value (see step 4 in Fig. 20.3).

In practice, the design of an ideal modified- or controlled-release product, which is capable of releasing the maintenance dose at a precise controlled rate which is in mass balance with the rate of drug elimination corresponding to the required therapeutic concentration of drug in the plasma, is difficult to achieve. There are problems in achieving and maintaining zero-order release and absorption of the maintenance dose of drug in the presence of all the variable physiological conditions associated with the gastrointestinal tract (see Chapter 16). In addition, the apparent elimination rate constant of a given drug varies from patient to patient, depending on such factors as genetic differences, age differences and differences in the severity of disease. Consequently it is likely that most peroral MR products in current use will not fall into the category of ideal MR/controlled-release peroral dosage forms. However, such products may be referred to simply as MR products and may be differentiated from their ideal counterparts by the following definition. A modified-release product/dosage form is a system in which a portion (the initial priming dose) of the drug is released immediately in order to achieve the desired therapeutic response promptly. The remaining dose of drug (the 'maintenance' dose) is then released slowly, thereby resulting in a therapeutic drug/tissue drug concentration which is prolonged but not maintained constant.

Formulation methods of achieving modified drug release

It is evident from the preceding discussion that formulation techniques that permit rapid release of the priming dose, followed by slow release of the maintenance dose, are required in order to design peroral MR products. All MR formulations use a chemical or physical 'barrier' to provide slow release of the maintenance dose. Many formulation techniques have been used to 'build' the barrier into the peroral dosage form. These include the use of coatings, embedding of the drug in a wax or plastic matrix, microencapsulation, chemical binding to ion-exchange resins, and incorporation in an osmotic pump. The initial rapidly releasing priming dose may be provided by incorporating that portion of the drug in a separate, rapidly releasing form in the dosage form, for instance as uncoated, rapidly releas-

ing granules or pellets in a tablet or hard gelatin capsule. Alternatively, immediate and rapid release of the priming dose has been achieved by that portion of the drug being positioned at the surface of a porous wax or plastic matrix.

Potential advantages of modified-release dosage forms over conventional dosage forms

1. Improved control over the maintenance of therapeutic plasma drug concentration of drugs permits:
   (a) improved treatment of many chronic illnesses where symptom breakthrough occurs if the plasma concentration of drug drops below the minimum effective concentration, e.g. asthma, depressive illnesses;
   (b) maintenance of the therapeutic action of a drug during overnight no-dose periods, e.g. overnight management of pain in terminally ill patients permits improved sleep;
   (c) a reduction in the incidence and severity of untoward systemic side-effects related to high peak plasma drug concentrations;
   (d) a reduction in the total amount of drug administered over the period of treatment. This contributes to the reduced incidence of systemic and local side-effects observed in the cases of many drugs administered in MR formulations.
2. Improved patient compliance, resulting from the reduction in the number and frequency of doses required to maintain the desired therapeutic response, e.g. one peroral MR product every 12 hours contributes to the improved control of therapeutic drug concentration achieved with such products.
3. There is a reduction in the incidence and severity of localized gastrointestinal side-effects produced by 'dose dumping' of irritant drugs from conventional dosage forms, e.g. potassium chloride. The more controlled, slower release of potassium chloride from its peroral MR formulations minimizes the build-up of localized irritant concentrations in the gastrointestinal tract. Consequently, potassium chloride is now administered perorally almost exclusively in MR form.
4. It is claimed that cost savings are made from the better disease management that can be achieved with MR products.

Potential limitations of peroral modified-release dosage forms

1. Variable physiological factors, such as gastrointestinal pH, enzyme activities, gastric and intestinal transit rates, food and severity of disease, which often influence drug bioavailability from conventional peroral dosage forms, may also interfere with the precision of control of release and absorption of drugs from peroral MR dosage forms. The achievement and maintenance of prolonged drug action depends on such control.
2. The rate of transit of MR peroral products along the gastrointestinal tract limits the maximum period for which a therapeutic response can be maintained following administration of a 'single dose' to approximately 12 hours, plus the length of time that absorbed drug continues to exert its therapeutic activity.
3. MR products, which tend to remain intact, may become lodged at some site along the gastrointestinal tract. If this occurs, slow release of the drug may produce a high localized concentration that causes local irritation to the gastrointestinal mucosa. MR products which are formulated to disperse in the gastrointestinal fluids are less likely to cause such problems.
4. There are constraints on the types of drugs that are suitable candidates for incorporation into peroral MR formulations. For instance, drugs having biological half-lives of 1 hour or less are difficult to formulate for modified release. The high rates of elimination of such drugs from the body mean that an extremely large maintenance dose would be required to provide 8–12 hours of continuous therapy following a single administration. Apart from the potential hazards of administering such a large dose, the physical size of the MR dosage form could make it difficult to swallow. Drugs having biological half-lives between 4 and 6 hours make good candidates for inclusion in MR formulations. Factors other than the biological half-life can also preclude a drug from being formulated as an MR product. Drugs that have specific requirements for their absorption from the gastrointestinal tract are poor candidates. In order to provide a satisfactory period of prolonged drug therapy, a drug is required to be well absorbed from all regions as the dosage form passes along the gastrointestinal tract.
5. MR products normally contain a larger total amount of drug than the single dose normally

administered in a conventional dosage form. There is the possibility of unsafe overdosage if an MR product is improperly made and the total drug contained therein is released at one time or over too short a time interval. Consequently, it may be unwise to include very potent drugs in such formulations.

6. As a general rule, MR formulations cost more per unit dose than conventional dosage forms containing the same drug. However, fewer 'unit doses' of an MR formulation should be required.

DESIGN OF PERORAL MODIFIED-RELEASE DRUG DELIVERY SYSTEMS

Factors influencing design strategy

Having made the decision that a drug is to be included in a modified-release delivery system intended for oral administration, it is necessary to take account of the physiology of the gastrointestinal tract; the physicochemical properties of the drug; the design of the dosage form; the drug release mechanism; the particular disease factors; and the biological properties of the drug. All of these can influence or interact with one another.

The physiology of the gastrointestinal tract and drug absorption

The influence of gastrointestinal physiology on drug delivery is discussed in detail in Chapter 16. It should also be noted that the residence time of a dosage form in the gastrointestinal tract is influenced by both stomach emptying time and intestinal transit time. It has been reported that:

- solution and pellets (<2 mm) leave the stomach rapidly;
- single dose units (>7 mm) can stay in the stomach for up to 10 hours if the delivery system is taken with a heavy meal;
- the transit time through the small intestine is approximately 3 hours.

Physicochemical properties of the drug

Several physicochemical properties of the active drug can influence the choice of dosage form. This is discussed fully in Chapter 17; these properties include aqueous solubility and stability; pK_a; partition coefficient (or, more appropriately, permeability values) and salt form.

The aqueous solubility and intestinal permeability of drug compounds are of paramount importance. A classification has been made (Amidon et al 1995) whereby drugs can be considered to belong to one of four categories:

- high solubility and high permeability (best case);
- high solubility and low permeability;
- low solubility and high permeability;
- low solubility and low permeability (worst case).

This is now codified as the Biopharmaceutical Classification System (see Chapter 18 for further details).

Consider first the influence of solubility. A drug that is highly soluble at intestinal pH and absorbed by passive diffusion (i.e. not site-specific absorption) would probably present the ideal properties for inclusion in an MR dosage form. However, there may be some problems associated with the choice of actual formulation. At the other end of the scale, compounds that have a low aqueous solubility (<1 mg mL^{-1}) may already posses inherent sustained-release potential as a result of their low solubility. The innate advantages of low aqueous solubility in relation to modified release would be negated if the drug also had low membrane permeability.

Having achieved dissolution of the drug in the gastrointestinal tract then permeability considerations become important. An indication of drug permeability values can be obtained using Caco-2 tissue culture models (see Chapter 18). More than 90% absorption in vivo may be expected for compounds with permeability, P, values $> 4 \times 10^{-6}$ mm s^{-1}, whereas less than 20% absorption is expected when P is $<0.5 \times 10^{-6}$ mm s^{-1} (Bailey et al 1996). Drug candidates with a permeability $<0.5 \times 10^{-6}$ mm s^{-1} are likely to be unsuitable for presentation as MR preparations.

Drug compounds that satisfy the solubility and permeability requirements should also ideally have:

- a biological half-life of between two and six hours so that accumulation in the body does not occur
- a lack of capability to form pharmacologically active metabolites by, for example, first-pass metabolism. Modified release is actually used for drugs which undergo first-pass metabolism but this should not be to such an extent that only inactive metabolites are left after absorption
- a dosage not exceeding 125–325 mg in order to limit the size of the delivery system. There are a few examples where this dose is exceeded, e.g. Brufen Retard.

Choice of the dosage form

The first decision to be made is whether to formulate the active ingredient as a single or a multiple unit system. Single-unit dosage forms include tablets, coated tablets, matrix tablets and some capsules. A multiple-unit dosage form includes granules, beads, capsules and microcapsules.

Modified-release dosage forms include inert insoluble matrices, hydrophilic matrices, ion-exchange resins, osmotically controlled formulations and reservoir systems.

The selection of the appropriate dosage form will need to take account of an acceptable level of variability of performance, the influence of GI tract structure and function on the delivery system, and the release mechanism and release profile of the dosage form.

Drug-release mechanisms

The two basic mechanisms controlling drug release are dissolution of the active drug component and the diffusion of dissolved or solubilized species. Within the context of these mechanisms there are four processes operating:

- Hydrating of the device (swelling of the hydrocolloid or dissolution of the channelling agent)
- Diffusion of water into the device
- Dissolution of the drug
- Diffusion of the dissolved (or solubilized) drug out of the device.

These mechanisms may operate independently, together or consecutively.

Drug delivery systems can be designed to have either continuous release, a delayed gastrointestinal transit while continuously releasing, or delayed release. Drug release may be constant, declining or bimodal.

Constant release The general belief has been that the ideal MR system should provide and maintain constant drug plasma concentrations. This led to considerable effort being put into developing systems that release drugs at a constant rate. (Although with the advent of chronotherapy, i.e. drug delivered at both the appropriate time *and* rate, zero-order release may not be such a desirable goal in the future.) In general these systems rely on diffusion of the drug or, occasionally, osmosis.

Declining release Drug release from these systems is commonly a function of the square root of time or follows first-order kinetics. These systems cannot maintain a constant plasma drug concentration but can provide sustained release.

Bimodal release Although constant drug release may be ideal, this may not always be the case. If the gastrointestinal tract behaves as a one-compartment model (Chapter 19), i.e. the different segments are homogeneous, then the situation is ideal. However, we know from Chapter 16 that absorption rate is not invariant along the gastrointestinal tract. So, whatever happens, the rate of release from the dosage form must regulate drug absorption – in other words, release rate must always be slower than absorption rate. This situation may not be easy to achieve: a release rate suited to absorption from the intestine may be far too great for that required in the stomach or colon. One possible solution to this problem is to prepare a dosage form that provides a rapid initial delivery of drug followed by a slower rate of delivery and then an increased rate at a later time.

FORMULATION OF MODIFIED-RELEASE DOSAGE FORMS

For convenience of description oral modified release delivery systems can be considered under the following headings:

- Monolithic or matrix systems
- Reservoir or membrane-controlled systems
- Osmotic pump systems.

These are the main classes of delivery system and they are considered in turn below. However, there are other systems and the above is not an exhaustive list.

There is a basic principle that governs all these systems. In a solution, drug diffusion will occur from a region of high concentration to a region of low concentration. This concentration difference is the driving force for drug diffusion out of a system. Water diffuses into the system in an analogous manner. There is an abundance of water in the surrounding medium and the system should allow water penetration. The inside of the system normally has a lower water content initially than the surrounding medium.

Components of a modified-release delivery system

These include:

- active drug;
- release-controlling agent(s): matrix formers, membrane formers;

Table 20.1 Suitable excipients for modified-release dosage forms categorized as inert, lipid or hydrophilic

Inert excipients
Dibasic calcium phosphate
Ethyl cellulose
Methacrylate copolymer
Polyamide
Polyethylene
Polyvinyl acetate
Lipid excipients
Carnauba wax
Cetyl alcohol
Hydrogenated vegetable oils
Microcrystalline waxes
Mono- and triglycerides
PEG monostearate
PEG
Hydrophilic excipients
Alginates
Carbopol
Gelatin
Hydroxypropylcellulose
Hydroxypropyl methylcellulose
Methylcellulose

- matrix or membrane modifier, such as channelling agents for wax matrices and solubilizers, and wicking agents for hydrophilic matrices;
- solubilizer, pH modifier and/or density modifiers;
- lubricant and flow aid, such as magnesium stearate, stearic acid, hydrogenated vegetable oil, sodium stearyl fumarate, talc, colloidal silicon dioxide;
- supplementary coatings to extend lag time, further reduce drug release, etc.;
- density modifiers (if required).

These types of components are virtually the same for all oral solid MR dosage forms. The differences are in the excipients, how they are incorporated into the formulation and what role they play.

The delivery systems may also be classified as inert, lipid or hydrophilic, depending on the nature of the excipients used. Suitable excipients for modified-release dosage systems are listed in Table 20.1.

Monolithic matrix delivery systems

These systems can be considered as two groups:

- Those with drug particles dispersed in a soluble matrix, with drug becoming available as the matrix dissolves or swells and dissolves (***hydrophilic colloid matrices***);
- Those with drug particles dispersed in an insoluble matrix, with drug becoming available as a solvent enters the matrix and dissolves the particles (***lipid matrices*** and ***insoluble polymer matrices***).

Drugs dispersed in a soluble matrix rely on a slow dissolution of the matrix to provide sustained release. Excipients used to provide a soluble matrix often are those used to make soluble film coatings. Alternatively, slowly dissolving fats and waxes can be used. Synthetic polymers, such as polyorthoesters and polyanhydrides, have been used. These undergo surface erosion with little or no bulk erosion. If the matrix is presented with a conventional tablet geometry, then on contact with dissolution media the surface area of the matrix decreases with time, with a concomitant decrease of drug release.

Drug particles may be incorporated into an insoluble matrix. Drug release from these matrices follows penetration of fluid, followed by dissolution of the drug particles and diffusion through fluid-filled pores. This type of delivery system would not be suitable for the release of compounds that are insoluble or which have a low aqueous solubility.

Excipients used in the preparation of insoluble matrices include hydrophobic polymers, such as polyvinyl acetate, ethylcellulose and some waxes.

It is useful to consider each of the matrix systems mentioned above separately.

Lipid matrix systems

Principle of design Wax matrices are a simple concept. They are easy to manufacture using standard direct compression, roller compaction or hot-melt granulation.

The matrix compacts are prepared from blends of powdered components. The active compound is contained in a hydrophobic matrix that remains intact during drug release. Release depends on an aqueous medium dissolving the channelling agent, which leaches out of the compact so forming a porous matrix of tortuous capillaries. The active agent dissolves in the aqueous medium and, by way of the water-filled capillaries, diffuses out of the matrix.

Wax matrices are a simple unsophisticated delivery system with a fairly coarse control of rate and extent of drug release. The release is generally not zero order and there are few opportunities to modify it.

These matrices are not now in common usage, but the concept is worth considering. A typical formulation consists of:

- active drug
- wax matrix former

- channelling agent
- solubilizer and pH modifier
- antiadherent/glidant
- lubricant.

Matrix formers Hydrophobic materials that are solid at room temperature and do not melt at body temperature are used as matrix formers. These include hydrogenated vegetable oils, cottonseed, oil, soya oil, microcrystalline wax and carnauba wax. In general such waxes form 20–40% of the formulation.

Channelling agents Channelling agents are chosen to be soluble in the gastrointestinal tract and to leach from the formulation, so leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released. The drug itself can be a channelling agent, but a water-soluble pharmaceutically acceptable solid material is more likely to be used. Typical examples include sodium chloride, sugars and polyols. The choice will depend on the drug and the desired release characteristics. These agents can be 20–30% of the formulation.

Solubilizers and pH modifiers It is often necessary to enhance the dissolution of the drug. This may be achieved by the inclusion of solubilizing agents, such as PEGs, polyols or surfactants. If the drug is ionizable then the inclusion of buffers or counter-ions may be appropriate. On occasions the dissolution enhancer may also be the channelling agent.

Antiadherent/glidant Heat generated during compaction of the matrix can cause melting of the wax matrix-forming compound and sticking to the punches. Something is needed to cope with the sticking; suitable antiadherents include talc and colloidal silicon dioxide.

These materials also act as glidants and improve the flow of formulations on the tablet machine. The typical amounts used will depend on the antiadherent used, for example 0.5–1% for colloidal silicon dioxide and 4–6% for talc.

This type of formulation usually does not need a lubricant per se, as the fats are themselves liquid-film lubricants (i.e. they melt during compaction). Magnesium stearate, if added, can also act as an antiadherent.

Insoluble polymer matrix systems

An inert matrix system is one in which a drug is embedded in an inert polymer which is not soluble in the gastrointestinal fluids. Drug release from inert matrices has been compared to the leaching from a sponge. The release rate depends on drug molecules in aqueous solution diffusing through a network of capillaries formed between compacted polymer particles. The concept of using inert matrices as drug delivery systems was considered in the late 1950s and led to the development of Duretter (Astra Hassle) and Gradumet (Abbott) technologies, and products such as Ferro-Gradumet (Abbott). There have been concerns that residual catalysts and initiators used in the preparation of the polymer(s) of the matrix could be leached along with active drug. The matrices remain intact during gastrointestinal transit, and there have also been concerns that impaction may occur in the large intestine and that patients may be concerned to see the matrix 'ghosts' in stools. More recently there has been renewed interest in this type of matrix, and polymers such as ethylcellulose are finding favour.

The release rate of a drug from an inert matrix can be modified by changes in the porosity and tortuosity of the matrix, i.e. its pore structure. The addition of pore-forming hydrophilic salts or solutes will have a major influence, as can the manipulation of processing variables. Compression force controls the porosity of the matrix, which in turn controls drug release. Generally a more rigid and less porous matrix will release drug more slowly than a less consolidated matrix.

The addition of excipients, such as lubricants, fillers etc., is a necessary part of the formulation process. However, the presence of excipients is likely to influence drug release. It may be anticipated that water-soluble excipients will enhance the wetting of the matrix, or increase its tortuosity and porosity on dissolution. Insoluble excipients will tend to decrease the wettability of the matrix and reduce the penetration of the dissolving medium.

The particle size of the insoluble matrix components influences release rate, larger particles leading to an increase in release rate. This is attributed to these coarser particles producing matrices with a more open pore structure.

An increase in drug loading tends to enhance release rate, but the relationship between the two is not clearly defined. One possible explanation may be a decrease in the tortuosity of the matrix. As may be expected, release rate can be related to drug solubility.

Drug release from insoluble matrices The release of drugs from insoluble matrices has been investigated and four types of drug matrix system can be considered:

- Drug molecularly dissolved in the matrix and drug diffusion occurs by a solution–diffusion mechanism;
- Drug dispersed in the matrix and then, after dissolution of the drug, diffusion occurs via a solution–diffusion mechanism;

- Drug dissolved in the matrix and diffusion occurs through water-filled pores in the matrix;
- Drug dispersed in the matrix and then, after dissolution, diffusion occurs through water-filled pores.

The amount of drug released from matrix dosage forms is normally proportional to the square root of the time of exposure to the dissolution medium:

$$M_t = Kt^{0.5} \quad (20.1)$$

where M_t is the amount of drug released with time t, and K is a constant.

The amount of drug released decreases with time of exposure to the dissolution medium. The reason for this is that the drug is released initially from the surface region, and there is then only a short diffusion pathway. As the period of dissolution progresses, the area of drug exposed to dissolution medium decreases. Also, an ever-increasing 'zone of depletion' is formed within the matrix as the drug dissolves, and so the diffusion pathway increases in length.

A simple exponential relationship has been used to characterize drug release from non-swelling delivery systems:

$$\frac{M_t}{M_\alpha} = Kt^n \quad (20.2)$$

where M_t/M_α is the fractional solute release, K is a constant and n is the diffusional exponent.

The numerical value of the diffusional exponent is indicative of the release mechanism and is influenced by the matrix aspect ratio (i.e. diameter:length ratio). If the matrix is presented as a thin film a value of $n = 0.5$ would be indicative of Fickian diffusion, whereas values of n not equal to 0.5 are indicative of anomalous or non-Fickian process. Zero-order release is considered to be happening if $n = 1.0$. In other words, the rate of surface erosion is controlling the rate of drug release and not its rate of diffusion within the matrix.

Hydrophilic colloid matrix systems

These delivery systems are also called swellable–soluble matrices. In general they comprise a compressed mixture of drug and water-swellable hydrophilic polymer. The systems are capable of swelling, followed by gel formation erosion and dissolution in aqueous media. Their behaviour is in contrast to a true hydrogel, which swells on hydration but does not dissolve.

Principle of design of hydrophilic matrices The system comprises a mixture of drug, hydrophilic colloid, any release modifiers and lubricant/glidant. On contact with water the hydrophilic colloid components swell to form a hydrated matrix layer. This then controls the further diffusion of water into the matrix. Diffusion of the drug through the hydrated matrix layer controls its rate of release. The outer hydrated matrix layer will erode as it becomes more dilute; the rate of erosion depends on the nature of the colloid.

Hydrophilic colloid gels can be regarded as a network of polymer fibrils that interlink in some way. There is also a continuous phase in the interstices between the fibrils through which the drug diffuses. These interstices connect together and are analogous to the tortuous capillaries seen in wax matrices.

The tortuosity of the diffusion path and the 'microviscosity' and interactions within the interstitial continuum govern the diffusion of the drug through the hydrated gel layer, and hence the release of the drug.

Types of hydrophilic matrix

True gels These systems interact in the presence of water to form a crosslinked polymeric structure with a continuous phase trapped in the interstices of the gel network. The crosslinks are more than just random hydrogen bonds between adjacent polymer chains (e.g. alginic acid in the presence of di or trivalent cations, gelatin): here they limit the mobility of the polymer chains and give a structure to the gel (Fig. 20.4). The crosslinks can be chemical bonds or physical bonds, e.g. triple-helix formations in gelatin gels which are based on hydrogen bonds. The portions of the polymer chains between crosslinks can move, but the crosslinks restrict the overall movement of the chains.

Viscous or 'Viscolized' matrices Not all matrix systems form 'true' gels: in reality some are more

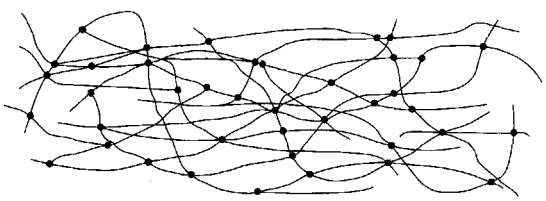

Fig. 20.4 Representation of a 'true' gel matrix.

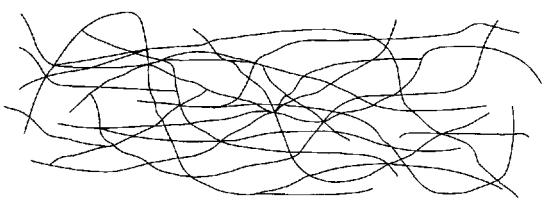

Fig. 20.5 Representation of a 'viscolized' matrix.

Table 20.2 Comparison of different types of hydrocolloid matrix

True gels	Viscous matrices
The diffusion pathway is via the continuous phase in the interstices of the gel	The diffusion pathway is via the continuous phase trapped between the adjacent polymeric chains
The crosslinks are more or less 'fixed' after the gel has formed	There are no 'fixed' cross-links
The bulk viscosity of the gel is derived from the structure of the crosslinked polymeric chains with a contribution from the continuous phase	The bulk viscosity is related to the entanglement of adjacent polymer chains which are free to move within the continuous phase
Bulk viscosity generally does not correlate well with diffusion	Bulk viscosity may correlate with diffussion
Diffusion in the gel correlates with 'microviscosity'	

properly described as very viscous solutions. In the presence of water these systems form a matrix in which the increased viscosity occurs as a result of simple entanglement of adjacent polymer chains, but without proper crosslinking (Fig. 20.5). It is a dynamic structure. The chains are able to move relative to one another and the drug diffuses through the interstitial continuum, but the pathway is not fixed. Examples are hydroxypropyl methylcellulose and sodium alginate in water.

Comparison of different types of hydrocolloid matrix
The differences between the various different types of hydrocolloid matrix are summarized in Table 20.2. It should be appreciated that these are simplifications. In general bulk viscosity is not a good test for the functionality of either system. It may be satisfactory as a quality control test for the matrix-forming materials.

Advantages of hydrophilic matrix systems
- Comparatively simple concept;
- Excipients are generally cheap and are usually GRAS (generally regarded as safe);
- Capable of sustaining high drug loadings;
- Erodible, so reducing the possibility of 'ghost' matrices;
- Easy to manufacture using commonly available equipment, by direct compression, wet granulation or roller compaction;
- Well established technology;
- Uses readily available pharmaceutical manufacturing equipment;
- Possible to obtain different types of release profile: zero order, first order, biomodal etc.

Disadvantages of hydrophilic matrix delivery systems
- Release of the drug is dependent on two diffusion processes, penetration of the water through the hydrated matrix into the non-hydrated core, and diffusion of the dissolved drug through the hydrated matrix.
- If the outer layer of the hydrated matrix erodes, this can complicate the release profile.
- Requires batch-to-batch consistency in the matrix-forming materials, other components and process parameters.
- Scale-up of manufacture can be a problem.
- Need optimal rate-controlling polymers for different actives.

These matrices are comparatively simple in concept. However, the events following hydration can be quite complex.

The key is that there are two diffusion processes (water in and then drug out). The drug will only diffuse through a hydrated gel layer. This really only applies to drugs that are solid at room temperature. Liquid drugs may diffuse in the non-hydrated state and would not be suitable for some types of system.

Components of hydrophilic matrix delivery systems
- Active drug
- Hydrophilic colloid(s)
- (Matrix modifier)
- (Solubilizer and/or pH modifier)
- Compression aid
- Lubricant
- (Glidant).

Those components listed in parentheses are optional and not always necessary.

Matrix-forming agents for hydrophilic matrices
Hydrophilic colloids which, on contact with water, form a hydrated gel that remains 'sufficiently intact' during passage through the gastrointestinal tract are suitable matrix-forming agents for hydrophilic matrices. Examples of hydrophilic colloids include:
- Hydroxypropyl methylcellulose (high-viscosity grades)
- Sodium carboxymethyl cellulose
- Alginates
- Xanthan gum
- Xanthan gun/locust bean gum combinations
- Carbopol.

These agents generally occupy 20–80% of the mass; the actual amount will depend on the drug and the desired release characteristics.

Hydration and swelling are the key factors in the functioning of a hydrophilic matrix, as has already been stated.

Gel modifiers for hydrophilic matrix delivery systems These are materials that are incorporated into the matrix to modify the diffusional characteristics of the gel layer, very often to enhance drug diffusion and hence release of the drug. Examples include sugars, polyols and soluble salts.

The type of modifier will depend very much on the chemical nature of the hydrocolloid(s) used. They may also modify the rate and extent of hydration of the hydrophilic matrix material.

Gel modifiers can have a number of other functions. For example, they may act:

- to allow more complete, more uniform hydration of the gel matrix;
- to allow more rapid hydration of the gel matrix;
- to associate with the matrix molecules and thus to influence the interactions at a molecular level, e.g. crosslinking;
- to modify the environment in the interstices of the gel, either to speed up or slow down diffusion;
- to suppress or promote the ionization of ionizable polymers.

Few materials will have only a single action. It is more likely that they will work in several ways.

Solubilizers and pH modifiers for drugs in hydrophilic matrices Many drugs will not dissolve sufficiently in gastrointestinal fluids to allow them to be released from a hydrophilic colloid matrix. Dissolution can be improved by the inclusion of solubilizing agents (e.g. PEGs, polyols, surfactants etc.). The only restriction is that the formulation can be formed into a tablet and that the material is acceptable. Many drugs are ionizable. The inclusion of appropriate counter-ions can facilitate release from the system. Some materials can act as both dissolution enhancer and matrix modifier: the amount of excipient needed will be determined by the amount of drug.

The above relates to the drug molecule, rather than the matrix material. It is necessary for any drug to be in solution for diffusion to occur. For insoluble drugs, solubilization is therefore an important consideration.

With some gel materials the use of certain ions causes changes in the nature of the gel matrix.

The solubilizers and pH modifiers might also influence the release process through a direct effect on the matrix. Different materials could augment crosslinking, whereas others might perhaps weaken the crosslinks.

Lubricants for hydrophilic delivery systems As with any tablet compacted on a tablet machine, a lubricant is necessary. Lubricants can have four functions:

- Reduce interparticulate friction during compression and compaction;
- Reduce die-wall friction;
- Prevent sticking to the punches;
- Improve flow of the formulation on to the machine and into the die.

The requirement for lubricants for hydrophilic matrix tablets are no different from those for any other tablet, and are thus analogous to those for conventional immediate-release tablets and capsules. Generally the choice is not governed by the same constraints as in immediate release. For example, overblending or excess magnesium stearate may not be a major problem here.

It is not essential that the lubricant is soluble. Such lubricants are available but are generally not very effective and tend to be reserved for effervescent products.

Suitable lubricants and recommended concentrations to be included in the formulation are listed in Table 20.3.

Drug release from hydrophilic colloid matrices The classic description of the events following immersion of a matrix in aqueous media are as follows:

- Surface drug (if water soluble) dissolves and gives a 'burst effect'.
- The hydrophilic polymer hydrates and an outer gel layer forms.
- The gel layer becomes a barrier to uptake of further water and to the transfer of drug.

Table 20.3 Concentration of lubricants used in hydrophilic matrix systems

Lubricants	%
Hydrophobic lubricants	
Magnesium stearate	0.25–2
Calcium stearate	0.25–2
Stearic acid	1–4
Hydrogenated vegetable oil	1–4
Hydrophilic lubricants (the latter two examples are only partially soluble in water)	
Glyceryl palmitostearate	0.5–5
Glyceryl behenate	2–5
Sodium stearyl fumarate	0.25–2
Inorganic lubricants	
Colloidal silicon dioxide	0.05–0.25 as glidant 0.2–0.5 as antiadherent
Talc	1–4 as antiadherent

- Drug (if soluble) release occurs by diffusion through the gel layer; insoluble drug is released by erosion followed by dissolution.
- Following erosion the new surface becomes hydrated and forms a new gel layer.

It may be anticipated that the relative importance of each release mechanism will depend on the physicochemical properties of the gel layer; the aqueous solubility of the drug; and the mechanical attrition of the matrix in the aqueous environment.

When a drug/glassy polymer matrix is placed in an aqueous environment, the water penetrates the polymer network. As the amount of water increases a transition from a glassy to a rubbery state occurs as the glass transition temperature is decreased by the presence of water to the temperature of the medium. The intake of solvent (water) induces stresses within the matrix polymer. Eventually the matrix polymer relaxes, and this manifests itself as swelling. It is possible to differentiate three 'fronts' during hydration: eroding, diffusing and swelling.

The actual drug release mechanism depends on the relative contributions of swelling and dissolution. Drug release from swellable, soluble matrices is constant when swelling and eroding fronts synchronize, but is non-linear when this is not the case. The release of sodium diclofenac from PVA and from HPMC matrices has been investigated. It was noted that if the fronts synchronized then the gel layer thickness was constant and zero-order release was observed. When synchronization did not take place the gel layer tended to increase in thickness and there was a decrease in the amount released, providing non-linear kinetics.

Membrane-controlled drug delivery systems

Membrane-controlled delivery systems function as follows. The rate-controlling part of the system is a membrane through which the drug must diffuse. To allow the drug to diffuse out, the membrane has to become permeable, e.g. through hydration by water normally present in the gastrointestinal tract, or by the drug being soluble in a membrane component, such as the plasticizer. Unlike hydrophilic matrix systems, the membrane polymer does not swell on hydration to form a hydrocolloid matrix, and does not erode.

A drug reservoir, e.g. a tablet or multiparticulate pellet, is coated with a membrane. The drug should not diffuse in the solid state, although loading of the membrane might be an advantage if an initial release on contact with dissolution medium is desired. Aqueous medium diffusing into the system and forming a continuous phase through the membrane initiates drug diffusion and release.

The essential difference between a membrane and a matrix system is that in the former the polymer membrane is only at the surface of the system, whereas in the latter the polymer is throughout the whole system. In both cases the hydration of the polymer is the step that allows the drug to diffuse. With the classic membrane system there are the two diffusion processes: 'water in' followed by 'drug out'.

The delivery systems may be presented either as single or as multiple unit.

Components of a membrane-controlled system

Core

- Active drug
- Filler or substrate
- (Solubilizer)
- Lubricant/glidant.

The exact composition of the core formulation will depend on the formulation approach adopted.

Coating

- Membrane polymer
- Plasticizer
- (Membrane modifier)
- (Colour/opacifier).

Single-unit systems

This is essentially a tablet formulation, but with differences from conventional dosage forms in that modified-release tablet cores should not disintegrate but dissolve; and a formulation is required that allows water to penetrate and the drug to dissolve so that diffusion can occur.

Core formulation for single-unit systems Generally, water-insoluble materials that compact by brittle fracture are not suitable if used alone. Suitable fillers include lactose, microcrystalline cellulose, dextrose, sucrose and polyols (mannitol, sorbitol, xylitol etc.).

Care is needed in the choice of soluble fillers to minimize osmotic effects. An inappropriate choice will result in increased internal osmotic pressure followed by rupture of the release-controlling membrane. The choice of solubilizer (if required) will be governed by the solubility characteristics of the drug. Materials that have been used include buffers, surfactants, polyols and PEGs.

Because single-unit cores are most often compressed tablets, a satisfactory lubricant system will

also be required. Again, this is the same as for any tablet except that soluble lubricants may not be necessary. Suitable lubricants are listed in Table 20.3.

Multiple-unit systems

As the name implies, this type of dosage unit comprises more than one discrete unit. Typically, such systems comprise coated spheroids (pellets approximately 1 mm in diameter) filled into a hard gelatin capsule shell or, less commonly, compressed into a tablet.

There are two main approaches that can be adapted to the manufacture of drug-containing multiple units:

- The use of inert sugar spheres ('nonpareils') coated first with drug and then with the release-controlling membrane;
- The formulation of small spheroids containing the drug using an extrusion/spheronization process (see Chapter 25). This approach is better if a high drug loading is required.

Typical formulations comprise drug with combinations of lactose and microcrystalline cellulose. Other materials can be used. A typical formulation for a wet mass for extrusion/spheronization might comprise:

	Parts by weight
Active drug	1–20
Lactose	60
Microcrystalline cellulose	40
Binder	2–4
Water	40

After spheronization the material is dried prior to coating.

Release-controlling membrane The membrane is a critical part of the formulation as it controls the release of the drug. The requirement is that the polymer remain intact for the period of release, i.e. there should be no swelling or subsequent erosion, as seen in hydrophilic matrices. Typical polymers used include ethyl cellulose, acrylic copolymers, e.g. Eudragit RL and RS grades, shellac and zein. Shellac and zein are natural products and their quality can vary.

The release-controlling polymer is film-coated on to the system. For the coating to be successful the coating droplets must coalesce. The plasticizer is used to lower the glass transition temperature (T_g) of the film (see Chapter 28). The choice of plasticizer will depend on the polymer used, the active drug and the desired release characteristics. In addition, the plasticizer may modify the diffusional characteristics of the membrane with respect to the drug. The final choice of plasticizer will probably be a compromise of all these different requirements.

Examples of suitable plasticizers for ethyl cellulose films include dibutyl phthalate, diethyl phthalate, dibutyl sebecate and citric acid esters. These are water-insoluble materials; a water-soluble plasticizer might increase the permeability of the membrane excessively. The amount of plasticizer required will depend on the several factors mentioned above, but is typically 10–25% of the polymer dry weight.

The smallest amount of plasticizer is used that will produce the most consistent result, i.e. complete coalescence of the droplets to form the film without making it too elastic, plastic, soft or permeable. The plasticizer is not present only for processing but is added to have an effect on the mechanical properties of the film, i.e. film flexibility should be induced and maintained. Plasticizers should be permanent to avoid stability problems.

It may be necessary to add components to the coating formulation to modify the release characteristics of the film, particularly to increase the rate of release. Typically this will be a less hydrophobic, water-soluble component. Examples of such materials include polyethylene glycols, propylene glycol, glycerol or other polyols, and water-soluble polymers. Some of these may also act as plasticizers. It is important to recognize that many materials can have different functions in a formulation, and also to understand what the implications of these different functionalities are for the finished product.

Advantages of membrane-controlled systems

- For multiple-unit systems the gastrointestinal transit of small particulates is more consistent than that of a larger single-unit system.
- Multiple-unit systems are also less likely to suffer from the problems associated with total dose dumping due to overall catastrophic failure of a film around a monolith (tablet), which would then release the whole dosage.
- In addition, multiple-unit systems allow the release mechanism to be optimized for individual drugs in a system delivering two or more active components.

Disadvantages of membrane-controlled systems

- Dose dumping can occur from single-unit system as a result of film failure.
- Multiple-unit systems can be difficult to retain in the higher gastrointestinal tract.
- The control of the membrane characteristics in film-coated membranes can be difficult.
- Filling of the multiunit spheroids into capsules can be a problem owing to build-up of static charge.

Osmotic pump systems

In one sense osmotic pump systems are another form of membrane-controlled release drug delivery system and work in the following way. A drug is included in a tablet core which is water soluble, and which will solubilize (or suspend) the drug in the presence of water. The tablet core is coated with a semipermeable membrane which will allow water to pass through into the core, which then dissolves. As the core dissolves, a hydrostatic pressure builds up and forces (pumps) drug solution (or suspension) through a hole drilled in the coating. The rate at which water is able to pass in through the membrane, and how quickly the drug solution (or suspension) can pass out of the hole, govern the rate of release.

The rate at which the drug solution/suspension is forced out can be modified by changes in the viscosity of the solution formed inside the system. The essential difference between an osmotic pump system and a 'classic' membrane-controlled system is that for the osmotic pump only one diffusion process is required (in this case, 'water in'). As mentioned above, in the 'classic' system two processes are key: water in, drug out.

Components of osmotic pump systems

Core This consists of the active drug, a filler or substrate, a (viscosity modifier), (solubilizer) and, lubricant/glidant.

Coating Coatings contain a membrane polymer, a plasticizer, a (membrane modifier) and (colour/opacifier).

This is the same list of components as for matrix-controlled systems, and the types of excipient used are essentially similar. However, it is important to remember that the diffusing species is only water; an agent must be included in the core which is soluble enough to generate the osmotic pressure; and there must be a hole through which the drug solution/suspension can be pumped out. Otherwise, the same considerations apply for the formulation of the core as with other membrane-controlled systems. The coating must also be fully coalesced and be free from unintentional pinholes, and it should act as a semipermeable membrane.

Advantages of osmotic pump systems

- They are well characterized and understood.
- The diffusing species is water.
- Modification of the rate of water diffusion is more straightforward than for many drugs.
- The release mechanism is not dependent on the drug.
- They are suitable for a wide range of drugs.
- The coating technology is straightforward.
- They typically give a zero-order release profile after an initial lag.

Disadvantages of osmotic pump systems

- Size of hole is critical.
- Laser drilling is capital intensive.
- Integrity and consistency of the coating is essential:
  - If the coating process is not well controlled there is a risk of film defects, which could result in dose dumping.
  - The film droplets or particles must be induced to coalesce into a film with consistent properties.

Delivery systems for targeting to specific sites in the gastrointestinal tract

Systems that target specific sites in the gastrointestinal tract are a form of modified-release delivery system and are considered briefly here. Targeting of drugs in the gastrointestinal tract is considered useful as a means of taking advantage of and/or overcoming efflux systems (Chapter 16) and intestinal cell metabolism; specific carrier mechanisms; and cell recognition sites. It can be achieved by gastric retentive delivery systems and by colonic drug delivery systems.

Gastric retentive systems

The advantages of using these drug delivery systems include reduced variability of drug release, local drug delivery and action, and enhanced bioavailability for those drugs with a restricted absorption window in the gastrointestinal tract.

Methods to achieve gastric retention are:

- the addition of passage-delaying agents, such as food material, for example triethanolamine myristate, or drugs, for example propantheline;
- the use of high-density materials: high-density particles (>2.5g/cm^3) have prolonged gastric residence times. This can be achieved by the addition of materials such as barium sulphate;
- modification of the size/shape of delivery system by the use of unfolding polymer sheets, swelling hydrogel balloons, or polymer units that are too large to pass through the pyloric sphincter.
- bioadhesive systems. Systems have been used which will adhere to surfaces such as the mucosa. The problems when these systems are used for gastrointestinal delivery are that first, high local

concentrations of drug may result, and second, there is a turnover of mucosa, leading to detachment of the delivery system;
- the use of floating dosage forms. These systems resist gastric emptying by floating on the stomach contents. They should not alter the intrinsic emptying rate of the stomach and their specific gravity should be less than that of the stomach contents. Systems used are (a) hydrodynamically balanced systems; (b) carbon dioxide-generating systems; (c) freeze-dried systems.

Colonic delivery systems

Applications for these systems include local delivery for the treatment of inflammatory diseases, infections, and diarrhoea; and systemic delivery.

Design principles for these delivery systems make use of:

- the specific pH of the colon: pH-sensitive polymers are used in their manufacture, e.g. combinations of Eudragit 100-55 (pH 5.5) with Eudragit S (pH 7.0). The principle is that drug is released at a specific pH environment;
- small-intestine transit time. These depend on timed release of the active drug;
- colonic bacteria. The principle here is to coat the drug/delivery system with a polymer that is sensitive to bacteria in the colon. Degradation of the polymer permits release of the active drug. Polymers used include glassy amylase (mixed with ethylcellulose); or pectin as a thick compression coat, crosslinked with calcium, with different degrees of methoxylation or amidation, or mixed with ethylcellulose.

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ACKNOWLEDGEMENT

The authors wish to thank, Dr L.G. Martini and Dr P.B. Geraghty (Glaxo SmithKline Pharmaceuticals, Harlow, UK) for their assistance and advice in the preparation of this chapter.

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