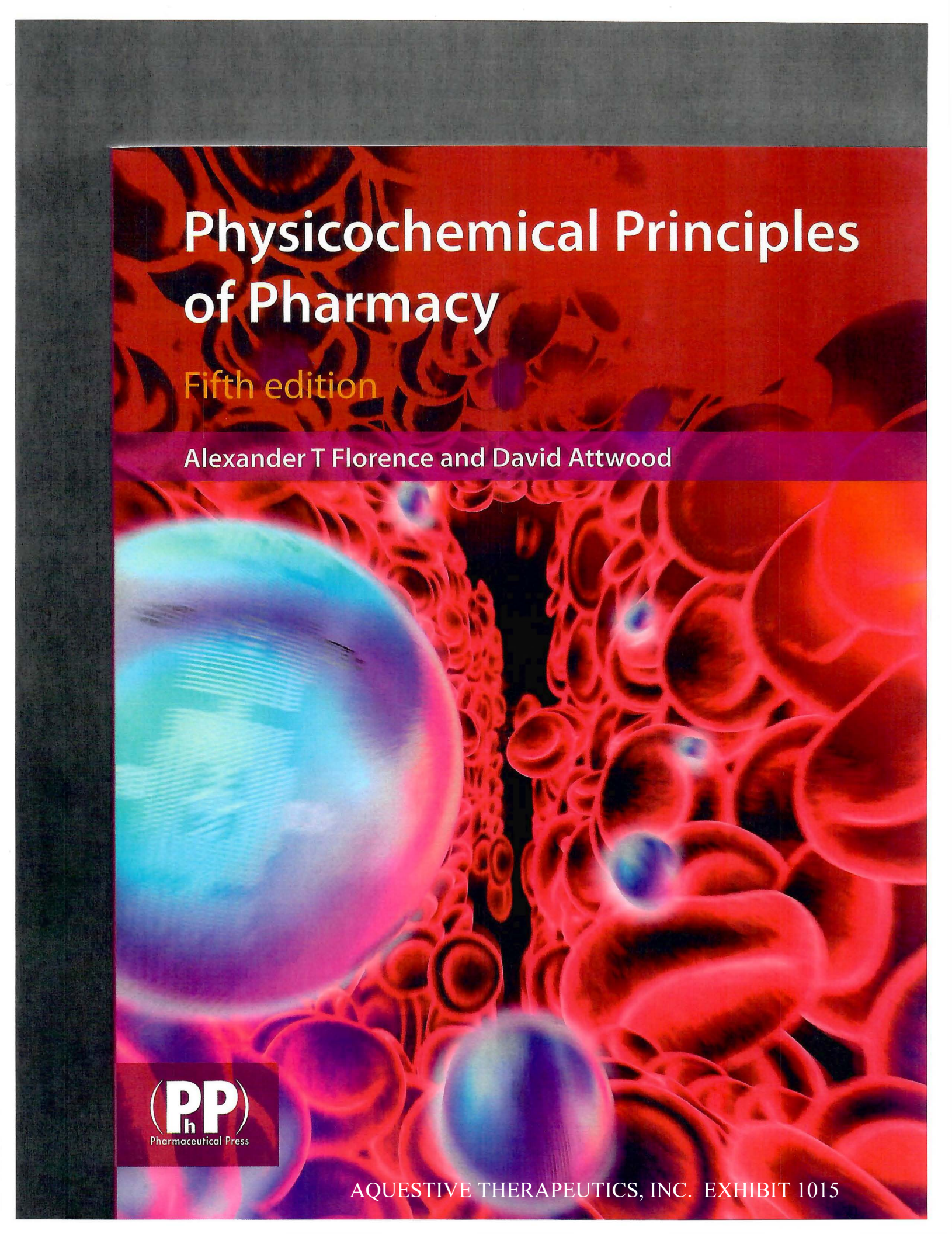




Physicochemical Principles of Pharmacy

Fifth edition

Alexander T Florence and David Attwood

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Physicochemical Principles of Pharmacy

FIFTH EDITION

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9

Drug absorption and the oral route

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This chapter provides basic information on the physicochemical mechanisms of drug absorption and how the processes of absorption are affected by the physicochemical properties of the drug and its formulation, and importantly by the interaction of the drug with the aqueous phase. The nature of the barrier membranes varies, however, and while they share the same basic structures, differences in detail can determine the extent of absorption at different sites in the gastrointestinal (GI) tract. The oral route, as the most frequently used and most acceptable route of drug administration, is discussed here in some detail. The influence of the following intertwined parameters in determining bioavailability should become clear:

- The rate and extent of dissolution of the drug, an essential prelude to absorption
- The rate of gastric emptying and its importance in the dynamics of the absorption process
- The site of absorption, especially in relation to the influence of pH

The pH of the contents of the GI tract and the effect of pH on the ionisation of the drug (discussed also in section 4.2.4) are crucial. The application of the so-called pH-partition hypothesis – and its limitations – should be understood, so that the effects of the nature of the drug and the medium on absorption can be assessed. In the case of the oral route, the effect of concomitant medication (e.g. H_2 antagonists, antacids), which might alter the pH of the gut contents, can be approximated by calculating the change in the drug ionisation. The word ‘approximated’ is used deliberately because the multiple factors involved in absorption from the GI tract means that the theoretical equations can only explain each process in part.

Absorption, whether it is from the GI tract, the buccal mucosa or the rectal cavity, generally requires the passage of the drug in a molecular form across one or more barrier membranes and tissues. Most drugs are presented to the body as solid or semisolid dosage forms and obviously these must first release the drug contained within them. Tablets or capsules will disintegrate, and the drug will then dissolve either completely or partially and at a greater or lesser rate. Many tablets contain granules or drug particles that deaggregate to facilitate the solution process. If the drug has the appropriate physicochemical properties, it will pass by passive diffusion from a region of high concentration to a region of low concentration across the membrane separating the site of absorption from tissues containing the blood

supply. Soluble drugs can, of course, also be administered as solutions, but it should be remembered that drugs can precipitate from solution formulations as they interact with biological fluids.

The special features of the different routes of administration are dealt with in Chapter 10. A brief summary of the general properties of biological membranes and drug transport, knowledge of which is important in understanding all absorption processes, is given here. Where attempts have been made to quantify absorption, equations are presented, but the derivations of most equations have been omitted.

9.1 Biological membranes and drug transport

Biological membranes confine the aqueous contents of cells and separate them from an aqueous exterior phase. To achieve this, membranes are lipoidal in nature. To allow nutrients to pass into the cell and waste products to move out, biological membranes are selectively permeable. Membranes have specialised transport systems to assist the passage of water-soluble materials and ions through their lipid interior. Lipid-soluble substances can pass by passive diffusion through the membrane from a region of high concentration to one of low concentration. Biological membranes differ from polymer membranes in that they are composed of small amphipathic molecules, phospholipids

(see Fig. 9.1) with two hydrophobic chains and cholesterol or other related structures, which associate into lipoidal bilayers in aqueous media. Embodied in the matrix of lipid molecules are proteins, which are generally hydrophobic in nature, embedded in the matrix of lipid molecules. Glycoproteins provide a hydrophilic element to the external membrane; cells have a net negative surface charge.

Cholesterol is a major component of most mammalian biological membranes. Cholesterol forms complexes with phospholipids and its presence reduces the permeability of phospholipid membranes to water, cations, glycerol and glucose. The shape of the cholesterol molecule allows it to fit closely in bilayers with the hydrocarbon chains of unsaturated fatty acids (Fig. 9.1). Cholesterol condenses and rigidifies membranes without

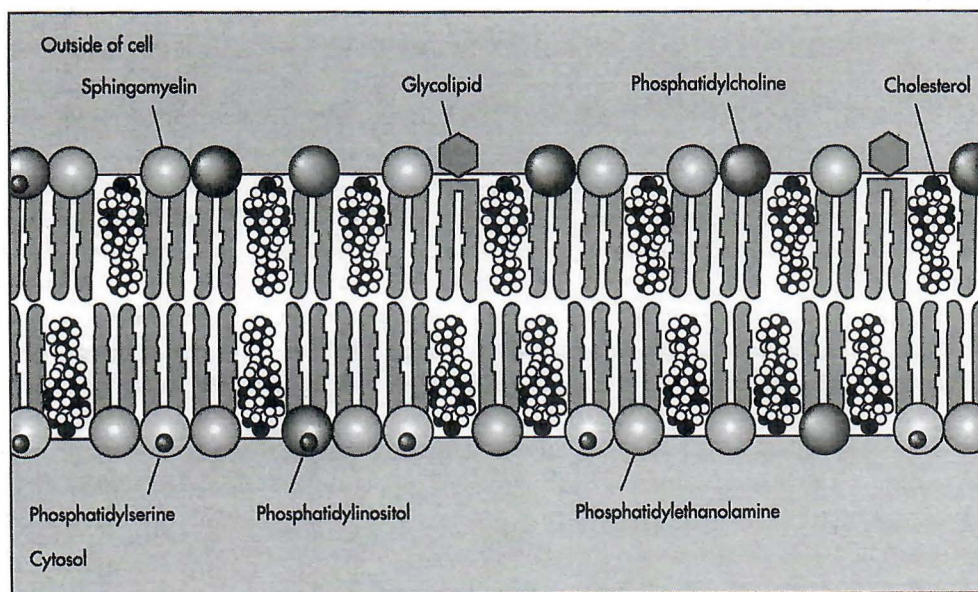


Figure 9.1 Model of a biological membrane showing the different compositions of the interior and exterior sides. Glycolipids are seen on the outside, while phosphatidylserine and phosphatidylinositol predominate on the cytosolic side. See Figure 9.2 for an impression of the membrane surface appearance.

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solidifying them. Its removal causes the membrane to lose its structural integrity and to become highly permeable. The flexibility of biological membranes is one of their important features, giving them their ability to reform and to adapt to changed environments, a vital part of their function. The dynamic characteristics of biological membranes are due to their unique construction from small amphipathic molecules. On stretching (as with a soap film), the molecules at the surfaces become less concentrated in the bilayer but then are rapidly replenished from the bulk phase to maintain the original tension. That is, they are dynamic structures. Figure 9.2 shows a diagram of the 'fluid mosaic' model of a biological membrane.

Although most of the data on permeation of non-electrolytes across biological membranes can be explained on the basis of the membrane behaving as a continuous hydrophobic phase, a fraction of the membrane may be composed of aqueous channels. These are effectively pores that offer a pathway parallel to the diffusion pathway through the lipid. In the absence of flow of water in one direction or the other, these pores play a minor part in the transfer of most drugs, although in the case of ions and charged drugs such as the quaternary ammonium compounds the pore pathway must be important. The fluid mosaic model of membranes allows the protein-lipid complexes to form either hydrophilic or hydrophobic 'gates' to allow transport of materials with different characteristics.

Overall, membrane permeability is controlled by the nature of the membrane, its degree of internal bonding

and rigidity, its surface charge and the nature of the drug (solute) being transported. There are some similarities between solute transport in biological membranes and in synthetic membranes. As we have discussed in Chapter 7, the permeation of drugs and other molecules through hydrophobic membranes made of polydimethylsiloxane, for example, depends primarily on the solubility of the drug in the membrane. Drugs with little affinity for the membrane are unlikely to permeate, although in porous membranes, such as those of cellophane or collagen, even drugs with little affinity for the polymer may be transported through the pores.

Most biological membranes bear a surface negative charge, so one would imagine that this might influence permeation. Membranes with un-ionised surfaces (such as cellophane) or positively charged surfaces such as collagen have different permeability characteristics for ionic drugs. Crucially, anionic solutes permeate faster than cationic solutes. With amphoteric drugs such as sulfisomidine and sulfamethizole, a similar order of permeation may be observed depending on the pH of the medium, namely: un-ionised > anionic > cationic form. In acidic media the membrane is positively charged and cationic drugs will therefore be repelled from the surface.

In biological membranes, one might expect some preference for cationic drugs, other things being equal, but we have to remember that biological membranes are more complex and more dynamic than synthetic membranes and there are many confounding factors. One of these, which is outside the scope of this book, is the existence of efflux mechanisms centred on P-glycoproteins (P-gp) 'pumps'. Some drugs are ejected from cells by the efflux pump, so that these drugs have a lower apparent absorption than predicted on physicochemical grounds. Some excipients (e.g. surfactants such as polysorbate 80) interact with these proteins, so both drug and excipients must be studied for their effect on the efflux pump activity.

In Chapter 4 we examined some relationships between the lipophilicity of drugs and their activity, controlled by their ability to pass across lipid barriers. Although of the same basic construction, biological membranes in different sites in the body serve different functions and thus one might expect them to have different compositions and physicochemical properties, as indeed they do. Tissues derived from the ectoderm (the epidermis, the epithelium of nose and mouth and

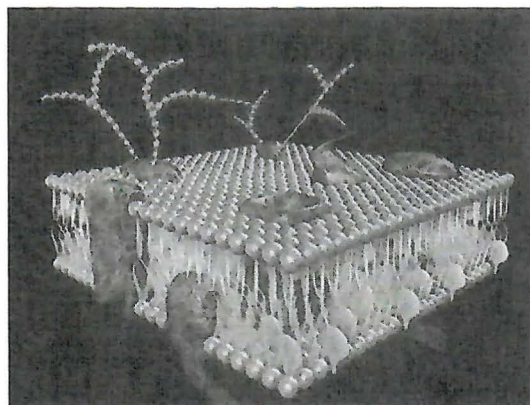


Figure 9.2 Representation of the 'fluid mosaic' model of a biological membrane, showing embedded protein and protruding glycoproteins.

From Funhouse Films.

the anus, and the tissues of the nervous system) have protective and sensory functions. Tissues evolved from the endoderm, such as the epithelium of the gastrointestinal (GI) tract, have evolved mainly to allow absorption.

9.1.1 Lipophilicity and absorption

If one measures the absorption of a sufficiently wide range of substances in a series, one generally finds that there is an optimal point in the series for absorption. In other words, a plot of percentage absorption versus $\log P$ would be parabolic with the optimum value designated as $\log P_o$ (Fig. 9.3). By noting the values of optimal partition coefficient for different absorbing membranes and surfaces, one can deduce something about their nature. Some values are given in Table 9.1.

The parabolic nature of activity- $\log P$ plots is due to a combination of factors: with drugs with high $\log P$ values, protein binding, low solubility and binding to extraneous sites cause a lower measured activity than if it were possible to take the drug and place it at the receptor without it having to traverse the various lipid and aqueous hurdles that it has to overcome on its way to the site of action.

Molecular weight and drug absorption

The larger drug molecules are, the poorer will be their ability to traverse biological membranes. The change of permeability with increasing molecular size is shown in Fig. 9.4.

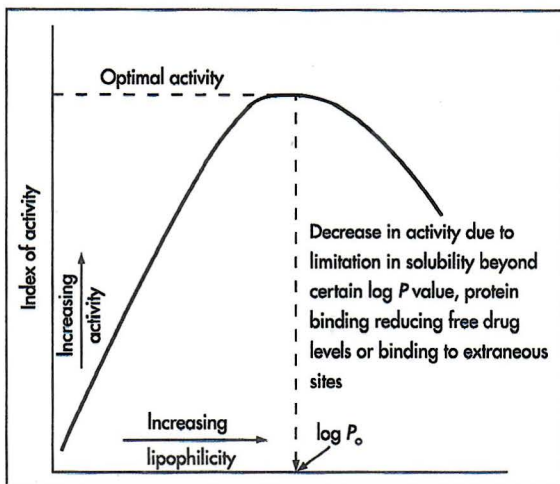


Figure 9.3 Parabolic nature of a typical activity- $\log P$ plot: the decrease in biological activity beyond the optimal $\log P_o$ is probably due to the factors listed.

System	Solute or drug	$\log P_o$ (octanol/water) for maximal transport
Buccal cavity (human)	Bases	5.52 (undissociated)
		3.52 (dissociated)
	Acids	4.19 (undissociated)
Epidermis (human)	Steroids	3.34
Whole skin (rabbit)	Non-electrolytes	2.55
Small Intestine (rat)	Sulfonamides	2.56–3.33
Stomach (rat)	Barbiturates	2.01
	Acids	1.97
Cornea (rabbit)	Steroids	2.8
Biliary excretion	Sulfathiazoles	0.60
Milk/plasma	Sulfonamides	0.53
Prostatic/plasma ratio	Sulfonamides	0.23

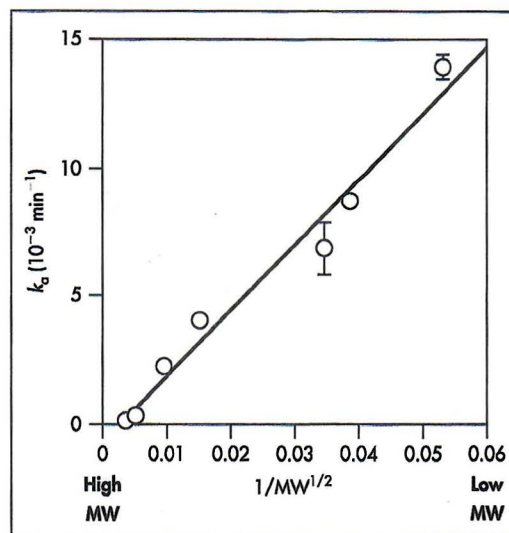


Figure 9.4 The relationship between the molecular weight of compounds and absorption rate constant. The membrane studied is the rat kidney surface, but similar plots hold for other sites. Reproduced from Nishida K et al., *Eur J Pharm Biopharm*, 2004; 58, 705–711.

In a survey of over 2000 drugs only 11% had molecular weights above 500 Da, and only 8% had molecular weights above 600 Da. Lipinski¹ devised the so-called 'Rule of 5' which refers to drug-like properties of molecules. It states that *poor* oral absorption is more likely when the drug molecule:

- Has more than five hydrogen-bond donors (–OH groups or –NH groups)
- Has a molecular weight >500 Da
- Has a log *P* > 5
- Has more than 10 H-bond acceptors

Note that all the numbers are factors of 5, hence the name of the rule. Compounds that are substrates for transporters are exceptions to the rule.

9.1.2 Permeability and the pH-partition hypothesis

If, in the first instance, the plasma membrane is considered to be a strip of lipoidal material, homogeneous in nature and with a defined thickness, one must assume that only lipid-soluble agents will pass across this barrier. As most drugs are weak electrolytes it is to be expected that the un-ionised form (U) of either acids or bases, the lipid-soluble species, will diffuse across the membrane, while the ionised forms (I) will be rejected. This is the basis of the *pH-partition hypothesis* in which the pH dependence of drug absorption and solute transport across membranes is considered. The equations of Chapters 2 and 4 are relevant here.

For weakly acidic drugs such as acetylsalicylic acid (aspirin) and indometacin, the ratio of ionised to un-ionised species is given by the equation

$$\begin{aligned} \text{pH} - \text{pK}_a &= \log \frac{[\text{ionised form}]}{[\text{un-ionised form}]} \\ &= \log \frac{[\text{I}]}{[\text{U}]} \end{aligned} \quad (9.1)$$

For weak bases the equation takes the form

$$\begin{aligned} \text{pK}_a - \text{pH} &= \log \frac{[\text{ionised form}]}{[\text{un-ionised form}]} \\ &= \log \frac{[\text{I}]}{[\text{U}]} \end{aligned} \quad (9.2)$$

One can calculate from these equations (and equations 2.71 and 2.72) the relative amounts of absorbable and nonabsorbable forms of a drug

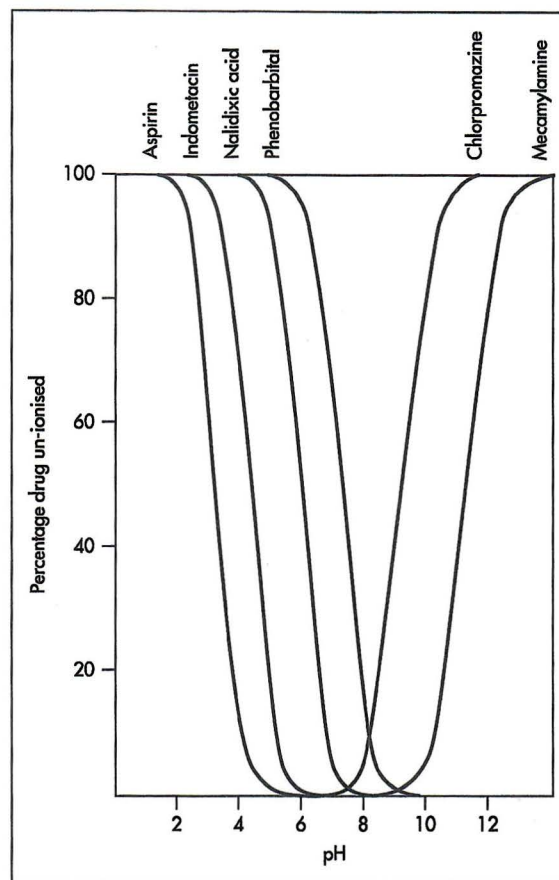


Figure 9.5 Plot of percentage drug un-ionised (that is, in its lipid-soluble form) as a function of solution pH, for the acidic drugs aspirin, indometacin, nalidixic acid and phenobarbital, and for the basic drugs chlorpromazine and mecamylamine.

substance ([U] and [I], respectively), given the prevailing pH conditions in the lumen of the gut or the site of absorption. The profiles for un-ionised drug (%) versus pH for several drugs are given in Fig. 9.5. In very broad terms, one would expect acids to be absorbed from the stomach and bases from the intestine.

A comparison of the intestinal absorption of several acids and bases at various pH values (Table 9.2) indicates the expected trend. Surprisingly, however, it will be seen that salicylic acid is absorbed from the rat intestine at pH 8, although with a *pK_a* of 3.0 it is virtually completely ionised at this pH. There are two explanations: one is that absorption and ionisation are both dynamic processes and that the small amount of un-ionised drug absorbed is replenished; the second is that the bulk pH is not the actual pH at the membrane. Nevertheless, instilling solutions of different pH directly

into the lumen of the rat stomach indicates the correct qualitative trends of absorption (62% absorption at pH 1 for salicylic acid and 13% at pH 8). Similarly, Box 9.1 shows that the absorption of acetylsalicylic acid is much greater than one would expect from a calculation of the pH dependency of its ionisation.

In attempts to explain away discrepancies between theoretical prediction and observed results we have already hinted that a local pH exists at the membrane surface that differs from the bulk pH (see below). This local pH is due to the attraction of hydrogen ions by the negative groups of membrane components so that, in the intestine, while the bulk pH is around 7 the surface pH is nearer 6. A 'virtual' surface pH can be calculated, which will allow results such as those in Table 9.2 to be explained. If we take as another example salicylic acid, again calculating the percentage of un-ionised species by equation (9.1), we obtain the following figures (taken from Table 9.2):

pH	4	5	7	8
Percentage un-ionised	9.09	0.99	0.0099	0.001
Percentage absorbed	64	35	30	10

Box 9.1 Calculation of percentage ionisation

Absorption values for acetylsalicylic acid at pH 4, 5, 7 and 8 are quoted in Table 9.2. The amount of drug in the un-ionised form at these pH values is obtained from equation (9.1). For example, at pH 4,

$$4 - 3.5 = \log \frac{[I]}{[U]}$$

$$\therefore \frac{[I]}{[U]} = 3.162$$

Percentage un-ionised

$$= \frac{[U] \times 100}{[U] + [I]} = \frac{100}{1 + \frac{[I]}{[U]}}$$

$$= \frac{100}{1 + 3.162} = \frac{100}{4.162} = 24.03\%$$

In the same way, we find 3.07% un-ionised at pH 5; 0.032% at pH 7; and less than 0.009% un-ionised at pH 9. Absorption is much greater than one would expect, being 41% at pH 4 and 27% at pH 5, although the trend is as predicted.

Table 9.2 Intestinal absorption of acids and bases in the rat at several pH values^a

Acid/base	pK _a	Percentage absorption			
		pH 4	pH 5	pH 7	pH 8
Acids					
Salicylic acid	3.0	64	35	30	10
Acetylsalicylic acid (aspirin)	3.5	41	27	–	–
Benzoic acid	4.2	62	36	35	5
Bases					
Amidopyrine	5.0	21	35	48	52
Quinine	8.4	9	11	41	54

^a Reproduced from Brodie BB, in: Bonns, ed., *Absorption and Distribution of Drugs*, Edinburgh: Livingstone; 1964.

To have 30% of this compound in its un-ionised form when the bulk pH is 7 would require a surface pH of about 3.4, which is lower than anticipated. Again, however, we must remember that absorption and ionisation processes are dynamic processes. As the un-ionised species are absorbed, so the level of [U] in the bulk falls and, because of a shift in equilibrium, more of the un-ionised species appears in the bulk. In fact, if a pH of 5.3 is taken as the pH of the absorbing surface, the results in Table 9.2 become more explicable, as we discuss in the next section.

9.1.3 Problems with the quantitative application of the pH-partition hypothesis

There are several reasons why the pH-partition hypothesis cannot be applied quantitatively in practical situations. Some are discussed here.

Variability in pH conditions

The variation in the stomach pH in human subjects is remarkable, bearing in mind that each pH unit represents a 10-fold difference in hydrogen ion concentration. While the normally quoted range of stomach pH

is 1–3, studies using pH-sensitive radiotelemetric capsules have shown a greater spread of values, ranging up to pH 7 as seen in Fig. 11.2 in Chapter 11. This means that the dissolution rate of many drugs will vary markedly in individuals – this is indeed one of the reasons for individual-to-individual variation in drug availability.

The scope for variation in the small intestine is less, although in some pathological states the pH of the duodenum may be quite low owing to hypersecretion of acid in the stomach. Table 9.3 lists the normal pH of the blood and of different regions of the GI tract.

pH at membrane surfaces

Data on the relationship between absorption and pH of the intestinal contents on the one hand, and the percentage of drug in the un-ionised state on the other, can generally be rationalised if the apparent pH is reduced below the pH of the intestine. As described above, this pH 'shift' is due to the existence of a pH at the membrane surface lower than that of the bulk pH. One might expect that the hydrogen ion concentration at the surface would be greater (and hence pH lower) at the membrane surface as hydrogen ions would accumulate near anionic groups, leading to an effect that can be quantified by the equation

$$[H^+]_{\text{surface}} = [H^+]_{\text{bulk}} \exp \frac{-F\zeta}{RT} \quad (9.3)$$

where F is the Faraday constant, R is the gas constant, T is absolute temperature and ζ is the zeta potential of the surface (see Chapter 6). Thus, in terms of pH,

Table 9.3 pH of blood and contents of the human alimentary tract^a

Sample	pH
Blood	7.35–7.45
Buccal cavity	6.2–7.2
Stomach	1.0–3.0
Duodenum	4.8–8.2
Jejunum and ileum	7.5–8.0
Colon	7.0–7.5

^a Reproduced from Bowman WC et al., *Textbook of Pharmacology*, London: Blackwell; 1967

$$\text{pH}_{\text{surface}} = \text{pH}_{\text{bulk}} + \frac{\zeta}{60} \quad (9.4)$$

where ζ is expressed in millivolts.

The secretion of acidic and basic substances in many parts of the gut wall is also a complicating factor, as the local pH in the region of the microvilli of the small intestine will undoubtedly influence the absorption of weak electrolytes. A drug molecule in the bulk will diffuse towards the membrane surface and so meet different pH conditions from those in the bulk phase. Whether or not this influences the extent of absorption will depend on the pH changes and the pK_a of the drug in question. The negative charge on the membrane will attract small cations towards the surface and small anions will be repelled; one might thus expect some selectivity in the absorption process. The existence of this 'microclimate' has been questioned, but experimental evidence for its existence has been obtained from the use of micro-electrodes, which revealed the existence of a layer on the (rat) jejunum with a pH of 5.5 when the pH of the bathing buffer was 7.2. The existence of this more acid layer has also been demonstrated on the surface of the human intestine.

Other complications include convective water flow and unstirred layers, discussed below.

Convective water flow

The movement of water molecules into and out of the GI tract will affect the rate of passage of small molecules across the membrane. The reasons for water flow are the differences in osmotic pressure between blood and the contents of the lumen, and differences in hydrostatic pressure between lumen and perivascular tissue, resulting, for example, from muscular contractions. It can be appreciated that the absorption of water-soluble drugs will be increased if water flows from the lumen across the mucosa to the blood side, provided that drug and water are using the same route. Water movement is greatest within the jejunum.

Unstirred water layers

A layer of relatively unstirred water lies adjacent to all biological membranes. The boundary between the bulk water and this unstirred layer is indistinct but, nevertheless, it has a real thickness. During absorption, drug molecules must diffuse across this layer

and then on through the lipid layer. The overall rate of transfer is the result of the resistance in both water layer and lipid layer. The flux, J , for a substance across the unstirred layer is given by the expression

$$J = (C_1 - C_2) \frac{D}{\delta} \quad (9.5)$$

where C_1 and C_2 are the concentrations of the substance in the bulk water phase and in the unstirred water layer, respectively, D is the diffusion coefficient and δ is the effective thickness of the unstirred layer. The flux of molecules that pass by passive diffusion through the lipid membrane can be written as

$$J = C_2 P_c \quad (9.6)$$

where P_c is the permeability coefficient. The rate of absorption must equal the rate of transport across the unstirred layer; that is,

$$J = (C_1 - C_2) \frac{D}{\delta} = C_2 P_c \quad (9.7)$$

The rate of movement across the unstirred layer, as can be seen from the equations, is proportional to D/δ ; the rate of absorption is proportional to P_c . Compounds with a large permeability coefficient may be able to penetrate across cell membranes much faster than they can be transported through the unstirred layer. Under these circumstances diffusion through the water layer becomes the rate-limiting step in the absorption process. Neglect of the unstirred layer causes errors in the interpretation of experimental flux data.

Effect of the properties of the drug

Drugs must be in their molecular form before diffusional absorption processes take place. We would expect bases to be more soluble than acids in the stomach, but it is impossible to generalise in this way. Although the basic form of a drug as its hydrochloride salt should be soluble to some extent in this medium, this is not always so. Indeed the free bases of, for example, chlortetracycline, dimethylchlortetracycline and methacycline are more soluble than their corresponding hydrochlorides in the pH range of the stomach (see Chapter 4). It has been shown that mean plasma levels following administration of the free base and the hydrochloride of these tetracyclines reflect the

differences in solubility, the bases giving higher levels. The reason is most likely that discussed in section 4.7.2, namely the influence of high ionic strength on the solubility of the drug substance (the common ion effect). As absorption of the tetracyclines takes place mainly from the duodenum, it is vital that they reach the intestine in a dissolved or readily soluble form, as their solubility is low at the pH conditions prevailing in the duodenum (pH 4–5).

The presence of buffer components in the formulation also creates a pH microenvironment around dissolving particles that may aid drug dissolution. If dissolution is the rate-limiting step in the absorption process, this will be significant in determining absorption. Bulk pH will then give little help in calculating the solution rate on the basis of a knowledge of saturation solubilities in bulk conditions.

Other complicating factors

The very high area of the surface of the small intestine also upsets the calculation of absorption based on considerations of theoretical absorption across identical areas of absorbing surface. The sheer complexity of the situation precludes mathematical precision, yet the pH-partition hypothesis is useful especially in predicting what follows from a change in bulk pH – for example, on ingestion of antacids or drugs such as histamine receptor antagonists (H_2 blockers) that reduce gastric acid secretion. The extent of the change in pH after administration of one of the first in the class, cimetidine, can be seen from the diagram in Fig. 9.6, which shows a rise in resting pH from below 2 to near neutrality. The effect in turn depends on the formulation used. The fact that aspirin, an acid with a pK_a of 3.5, is absorbed from the small intestine is due partly to the massive surface area available for absorption which allows significant absorption to occur, even though the percentage of absorbable species is very low, and partly to the dynamics of the process referred to earlier.

A warning, however, about other complications: drugs that (1) are unstable in the GI tract (for example, erythromycin), (2) are metabolised on their passage through the gut wall, (3) are hydrolysed in the stomach to active forms (namely prodrugs), and (4) bind to mucin or form complexes with bile

Figure 9.7 shows clearly the effect of chloride ion and other anions such as methane sulfonate on the apparent partition coefficient of chlorpromazine.

The nature of the anion significantly affects the partitioning of the drug. Ion pairing in the GI tract obviously could influence absorption.



Key points

- Biological membranes are composed primarily of phospholipids and cholesterol forming a lipoidal bilayer in which proteins are embedded; as a consequence they have a hydrophilic negatively charged exterior and a hydrophobic interior. They are selectively permeable, allowing nutrients to pass into the cell and waste products to move out.
- Lipid-soluble agents can cross the membrane by passive diffusion; in addition there are pores that offer an alternative diffusion pathway that is particularly important for the transference of ions and charged drugs such as the quaternary ammonium compounds. Overall, the permeability is controlled by the nature of the membrane, its degree of internal bonding and rigidity, its surface charge and the nature of the solute being transported.
- A plot of percentage absorption versus $\log P$ for drugs within a series is generally parabolic; optimum absorption occurs at $\log P_0$. A relationship between the properties of a drug and its extent of absorption was devised by Lipinski, the 'Rule of 5'. Poor absorption is likely when the drug has a molecular weight >500 Da, more than 5 H-bond donors, a $\log P > 5$, and more than 10 H-bond acceptors.
- The pH-partition hypothesis assumes that only lipid-soluble agents will cross the membrane, which for simplicity is considered to be a strip of lipoidal material. It is therefore expected that un-ionised forms of either acidic or basic drugs will diffuse across the membrane, while the ionised forms will be rejected.
- Absorption is sometimes much greater than predicted from the pH-partition hypothesis. There are several possible reasons for this:
 - The pH of the stomach may be higher than the normally quoted range of 1–3.
 - The pH at the membrane surface is lower than the bulk pH; there may also be secretion of acidic and basic substances in parts of the gut wall.
 - The movement of water molecules, due to differences in osmotic pressure between blood and the contents of the lumen and differences in hydrostatic pressure between the lumen and the perivascular tissue, affects the rate of absorption of small molecules.
 - A layer of unstirred water lies adjacent to the membrane, which is an additional barrier across which molecules must diffuse during their absorption.
 - Although we would expect that bases would be more soluble than acids in the stomach, this may not always be the case because, for example, of the common ion effect.
 - A variety of other factors may complicate the absorption process, including the complex nature and very high area of the surface of the small intestine and the properties of the drug, for example its stability in the GI tract, its binding to mucin or complexation with bile salts, and the formation of ion pairs.

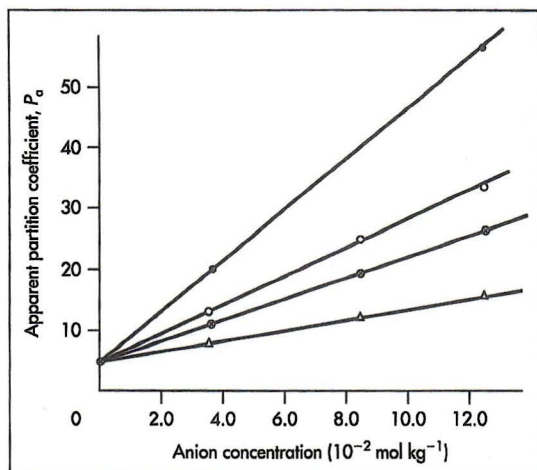


Figure 9.7 Apparent partition coefficients for chlorpromazine between *n*-octanol and aqueous buffers at pH 3.9, in the presence of various anions at 30°C: ○, chloride; ●, propanesulfonate; ⊗, ethanesulfonate; △, methanesulfonate.

Reproduced from Murthy LS, Zografi G, *J Pharm Sci*, 1970; 59: 1281.

9.2 The oral route and oral absorption

9.2.1 Drug absorption from the gastrointestinal tract

The oral route is the most popular and convenient route of drug administration for those drugs that can survive the acid of the stomach, that are resistant to enzymatic attack, and that are absorbed across GI membranes. The functions of the GI tract are the digestion and absorption of foods and other nutrients and it is not easy to separate these two functions from that of drug delivery. Indeed, the natural processes in the gut frequently influence the absorption of drugs. This is not surprising when it is considered that on average approximately 500 g of solid and up to 2.5 litres of fluid are ingested each day. As well as this oral intake, an estimated 30 litres of endogenous fluid are excreted each day into the intestine.

The pH of the gut contents and the presence of enzymes, foodstuffs, bile salts, fat and the microbial flora will all influence drug absorption. The complexity of the absorbing surfaces means that a simple physicochemical approach to drug absorption remains an approach to the problem and not the complete picture, as described above. Whatever the limitations

of theory – and one should not expect simple theories to hold in the complex and dynamic circumstances that are involved in drug absorption – theory provides a starting point in rationalising the behaviour of drugs in the GI tract. While most drugs are absorbed by passive diffusion across the lipid membranes separating the gut contents from the rest of the body, certain molecules that resemble naturally occurring substances are actively transported by special mechanisms.

We first consider the physiological situation that might impinge on passive drug absorption. The delivery of macromolecules, including peptides and proteins, is treated in Chapter 12.

Particulate absorption from the gut

While the general rule is that only drugs in solution are absorbed from the GI tract, colloidal particles, some viruses, bacteria and prion proteins can gain entry in low amounts to the lymphatic system after absorption by specialised cells (M-cells) in the gut-associated lymphoid tissue (GALT). A discussion of this route of uptake is outside the scope of this book, but it is a route that is likely to be increasingly explored as a means of delivering proteins and perhaps genes in carrier nanoparticles and for oral vaccination. It has yet to fulfil its promise.²

9.2.2 Structure of the gastrointestinal tract

We first consider the physiological situations and the structure and function of the GI tract that might impinge on passive drug absorption.

Figure 9.8 diagrammatically represents the GI tract and some of the factors involved in the process of drug absorption from this complex milieu. The stomach is not an organ that has evolved for absorption; the main site of absorption is the small intestine.

The stomach may be divided into its two main parts: (i) the body of the stomach which is in effect a receptacle or hopper, which includes pepsin- and HCl-secreting areas, and (ii) the pylorus (a churning chamber), the mucus-secreting area of the gastric mucosa. The stomach varies its luminal volume with the content of food and this is one reason why food intake can be so important in relation to drug absorption; the stomach of adults may contain a few millilitres or a litre or more of fluid. Hydrochloric acid is liberated

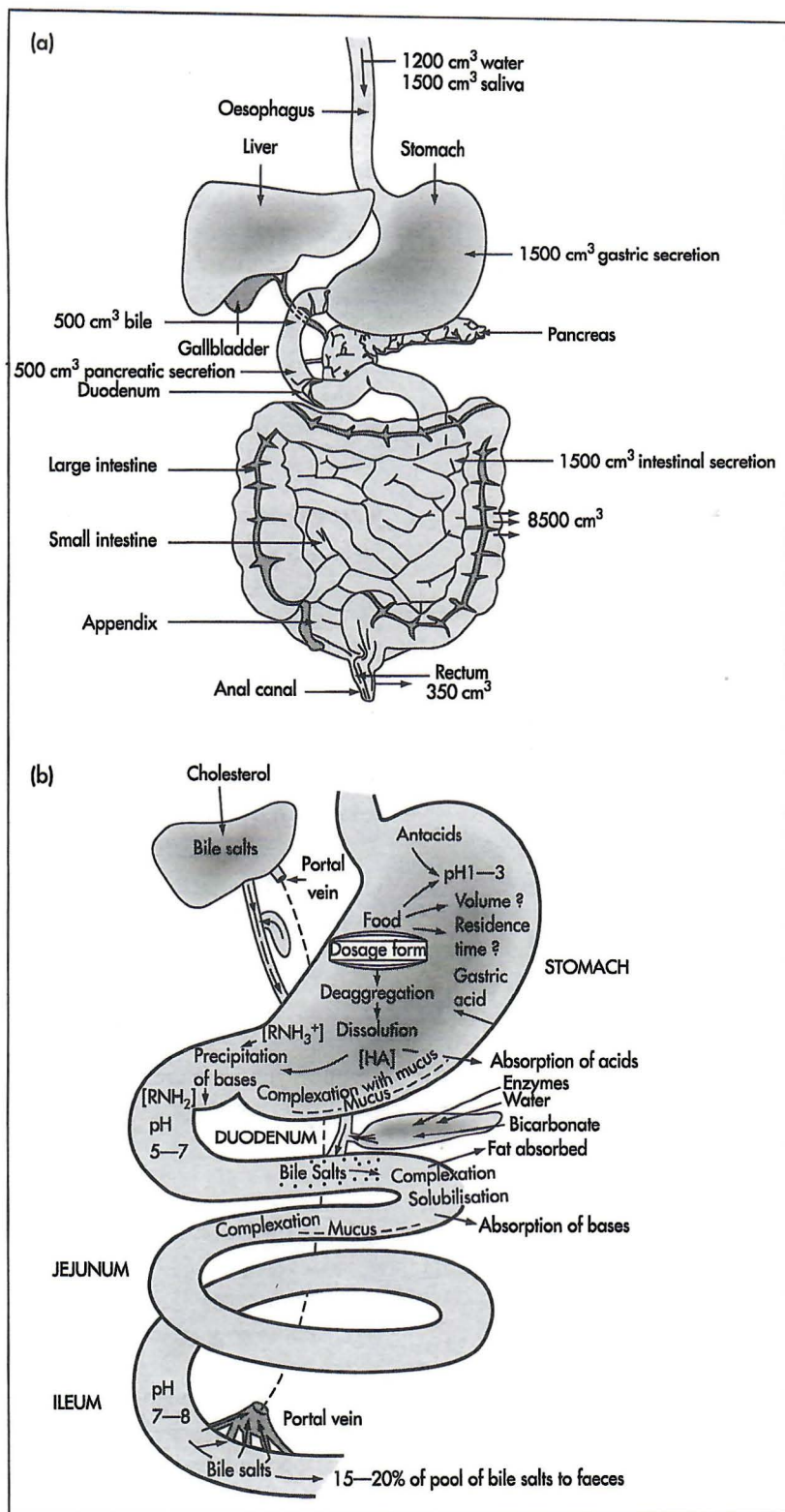


Figure 9.8 Representation of the processes occurring along the gastrointestinal tract, and of the factors that must be taken into account in considering drug absorption.

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from the parietal cells at a concentration of 0.58%, or 160 mmol dm^{-3} . The gastric glands produce some $1000\text{--}1500 \text{ cm}^3$ of gastric juice per day. It is in this somewhat chaotic environment that pharmaceutical dosage forms find themselves. Some of the events that result are shown in Fig. 9.8b.

The small intestine is divided anatomically into three sections: duodenum, jejunum and ileum. Histologically there is no clearly marked transition between these parts. All three are involved in the digestion and absorption of foodstuffs, absorbed material being removed by the blood and the lymph. The absorbing area is enlarged by surface folds in the intestinal lining that are macroscopically apparent: the surfaces of these folds possess villi and microvilli (Fig. 9.9). It has been calculated that with a maximum of 3000 microvilli per cell in the epithelial brush border (so called because of its physical appearance) the number of microvilli in the small intestine mucosa, even of the rat, is 2×10^8 per mm^2 . Although one would expect organic acids to be absorbed only from the stomach where they will exist in the un-ionised lipid-soluble and membrane-diffusible form, the enormous surface area in the intestine allows significant absorption of acidic drugs from the intestine even though (as noted earlier) the fraction of un-ionised molecules is very small.

Over the entire length of the large and small intestines and the stomach, the brush border has a uniform coating (3 nm thick) of mucopolysaccharides that consist of multibranched polymeric chains. This coating layer appears to act as a mechanical barrier to bacteria, cells or food particles, or as a filter. Whatever its function, the weakly acidic, sulfated mucopolysaccharides influence the charge on the cell membrane and complicate the explanations of absorption.

The goblet cells of the epithelium form mucus; secretions are stored in granule form in the apical cell region and are liquefied on contact with water to form mucus, which is composed of protein and carbohydrate and acts as a protective mechanism for the gut surface. Its role in the absorption of drugs is unclear.

The large intestine is concerned primarily with the absorption of water and the secretion of mucus to aid the intestinal contents to slide down the intestinal 'tube'. Villi are therefore completely absent from the large intestine, but there are deep crypts distributed over its surface.

Differences in the absorptive areas and volumes of gut contents in experimental animals are important when comparing experimental results on drug absorption in various species and in humans.³ The all-important extrapolation to the human animal is complex. The human small intestine has a calculated active surface area of approximately 100 m^2 . No analogous

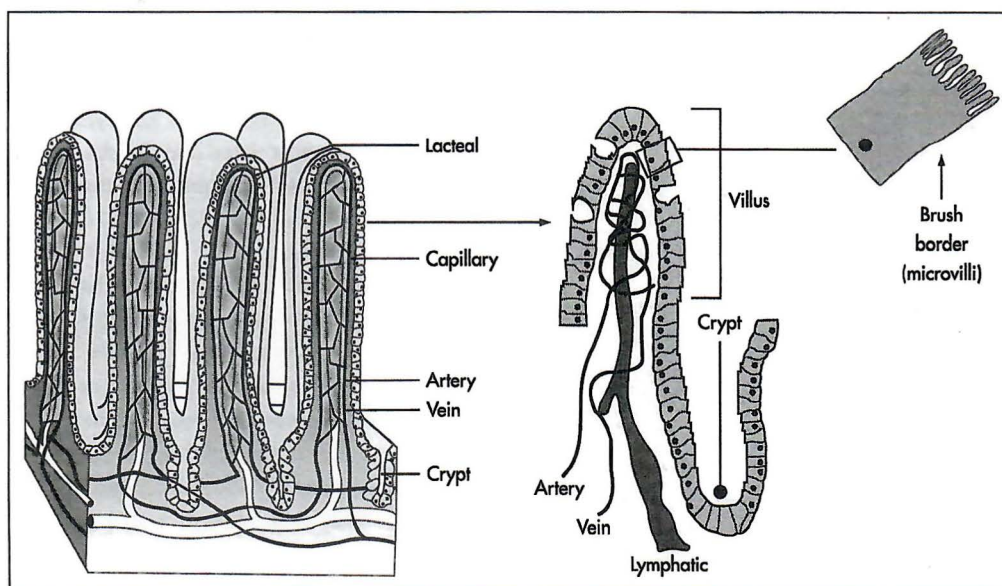


Figure 9.9 Representation of the epithelium of the small intestine at different levels of magnification. From left to right: the intestinal villi and microvilli that comprise the brush border.

calculations are available for the most commonly used laboratory animals, although the surface area of the small intestine of the rat is estimated to be 700 cm^2 .

Passive transport, carrier-mediated transport and specialised transport

In discussing the pH-partition hypothesis, it has been considered that drugs are absorbed by passive diffusion through epithelial cells – the enterocytes of the GI tract for example. In fact there is the possibility of some passage of drugs by way of the tight junctions (the paracellular route) and there are transcellular carrier-mediated uptake mechanisms as well as endocytosis. Figure 9.10 summarises these.

9.2.3 Bile salts and fat absorption pathways

Fat is absorbed by special mechanisms in the gut. The bile salts that are secreted into the jejunum are efficient emulsifiers and disperse fat globules, allowing the action of lipase at the much increased globule surface. Medium-chain triglycerides are thought to be directly absorbed. Long-chain triglycerides are hydrolysed, and the monoglycerides and fatty acids produced form mixed micelles with the bile salts and are absorbed either directly in the micelle or, more probably, brought to the microvillus surface by the micelle and transferred directly to the mucosal cells, the bile salts remaining in the lumen. The bile salts are reabsorbed in the ileum and transported via the portal vein back into the bile salt pool.

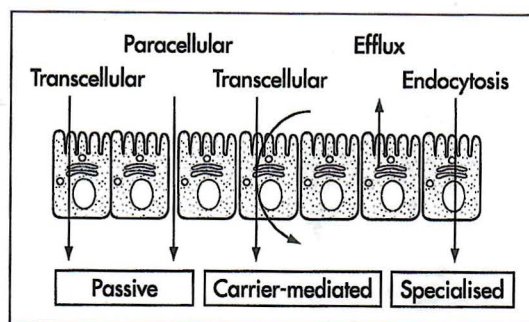


Figure 9.10 GI membrane transport. Transport through the enterocyte barrier can be divided into active, passive and specialised transport; and into the paracellular and transcellular routes. Efflux mechanisms can reduce absorption by these routes.

There have been suggestions that lipid-soluble drugs may be absorbed by fat absorption pathways. Certainly, administration of drugs in an oily vehicle can significantly affect absorption, increasing it in the case of griseofulvin and ciclosporin, but decreasing it in the case of vitamin D.

9.2.4 Gastric emptying, motility and volume of contents

The volume of the gastric contents will determine the concentration of a drug that finds itself in the stomach. The time the drug or dosage form resides in the stomach will determine many aspects of absorption. If the drug is absorbed lower down the gut, the residence time will determine the delay before absorption begins; if the drug is labile in acid conditions, longer residence times in the stomach will lead to greater stability; if the dosage form is non-disintegrating then retention in the stomach can influence the pattern of absorption. Gastroretentive dosage forms are designed to achieve that control.

The stomach empties liquids faster than solids. The rate of transfer of gastric contents to the small intestine is retarded by the activity of receptors sensitive to acid, fat, osmotic pressure and amino acids in the duodenum and the small intestine, and stimulated by material that has arrived from the stomach. Gastric emptying is a simple exponential or square-root function of the volume of a test meal – a pattern that holds for meals of variable viscosity. To explain the effect of a large range of substances on emptying, an osmoreceptor has been postulated that shrinks in hypertonic solutions and swells in hypotonic solutions.

Acids in test meals have been found to slow gastric emptying; acids with higher molecular weights (for example, citric acid) are less effective than those, such as HCl, with very low molecular weights. Natural triglycerides inhibit gastric motility, linseed and olive oils being effective. The formulation of a drug may thus influence drug absorption through an indirect physiological effect. The nature of the dose form – whether solid or liquid, whether acid or alkaline, whether aqueous or oily – may thus influence gastric emptying. The question of gastric emptying and transit down the GI tract has assumed further importance in relation to the design and performance of sustained-release preparations. The transit of pellets of different densities,^{4,5} for

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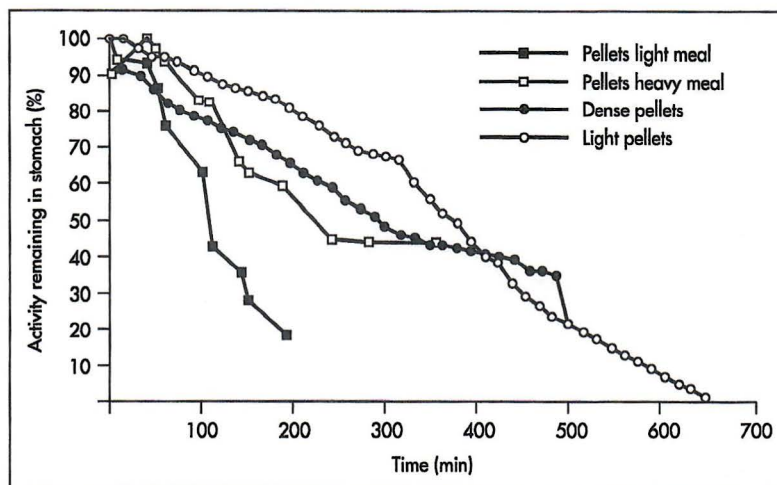


Figure 9.11 Gastric emptying of pellets of different density with various sizes of meal.

Reproduced from Wilson CG, Washington N, *Physiological Pharmaceutics*, Chichester: Ellis Horwood; 1989.

example, is shown in Fig. 9.11 and illustrates the influence of both density and food intake.

Food, then, affects not only transit but also pH. The effect of a meal on the hydrogen ion concentration of the stomach contents is shown in Fig. 9.12; the effect of two antacids on gastric volume and pH is shown in Table 9.4. When considering the effect of an antacid, therefore, the effect of volume change and pH change and the effect on gastric emptying must all

be considered. In designing delivery systems all these factors have ideally to be taken into account.



Key points

- The oral route is the most convenient route of drug administration for those drugs that can survive the acid of the stomach, that are resistant to enzymatic attack, and that are absorbed across GI membranes. Prediction of absorption rates is complicated, however, by the complexity of the absorbing surfaces, and the presence of enzymes, foodstuffs, bile salts, fat and microbial flora.
- Absorption is influenced by the volume of the gastric contents, the rate of gastric emptying, and the effect of food on the pH of the stomach contents.
- Although most drugs are absorbed by passive diffusion through epithelial cells, there is also the possibility of absorption by passage through tight junctions (paracellular absorption), by transcellular carrier-mediated uptake mechanisms and by endocytosis.
- Special mechanisms operate for the absorption of fat that involve mixed micelle formation with bile salts.

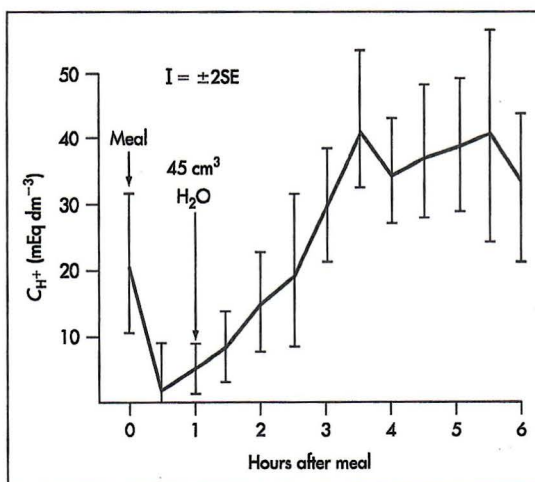


Figure 9.12 Hydrogen ion concentrations (C_{H^+}) at intervals after a test meal (mean results are shown $\pm 2SE$); the zero samples were taken just before the meal was begun, and the 1-hour sample just before 45 cm³ of water.

Modified from Fordtran J, *N Engl J Med*, 1966; 274: 921.

Table 9.4 Effects of antacids on gastric volume and pH in the rat^{a,b}

	Water	Maalox	Amphojel
Volume (cm ³)	0.29 ± 0.03	1.8 ± 0.3	4.0 ± 0.2
pH	2.2 ± 0.2	7.4 ± 0.1	4.7 ± 0.2

^a Reproduced from Hava M, Hurwitz A, *Eur J Pharmacol*, 1973; 22: 156.

^b Ten rats per group. Measurements on gastric contents made 20 minutes after the third hourly dose of 1 cm³ water or antacid by gastric intubation.

9.3 Oral dosage forms

A variety of modified-release oral dosage forms are discussed in other chapters of this book. Here we briefly touch on the conventional delivery systems used in the great majority of cases, namely tablets, capsules, suspensions and liquids. In the main, conventional – that is to say fast-release – products are used as a means of administering large and small doses of drugs in convenient forms, to provide stable systems and reliable dosing. For very low-dose drugs (such as oral contraceptives) there is the problem even today of ensuring that the drug is dispersed evenly in the bulk powder or granules used for tableting, because of the phenomenon of particle segregation. On the other hand, it is possible by appropriate design of the dosage form to alter the pharmacokinetics that the drug would otherwise exhibit. Modified-, sustained-,

delayed- or controlled-release forms (these descriptors are used interchangeably) can be used by the oral route to prolong the release and thus the action of drugs, so reducing the frequency of dosing with drugs having a short intrinsic half-life. One of the oldest forms of delayed-release product is the enteric-coated tablet or capsule. These have a polymer coat whose solubility is pH-dependent, this becoming porous or soluble in the lower intestine or colon. Other film coats and non-disintegrating matrix forms are dealt with in Chapter 7.

The preparation and formulation of tablets and capsules can be either straightforward or complex depending on the nature of the drug and the excipients. Particular problems arise with labile drugs that might be affected by moisture, low-dose drugs, and dose forms containing more than one active ingredient, with the potential for the interaction between the drugs themselves or with the excipient materials. A cartoon of a typical coated tablet is drawn in Fig. 9.13, which in a simple way illustrates the potential for problems.

9.3.1 The Biopharmaceutical Classification System (BCS)⁶

With the plethora of drugs now available and being tested, there was a need to assist drug developers to make decisions about the manner in which to deliver drugs by the oral route. Through the work of Gordon

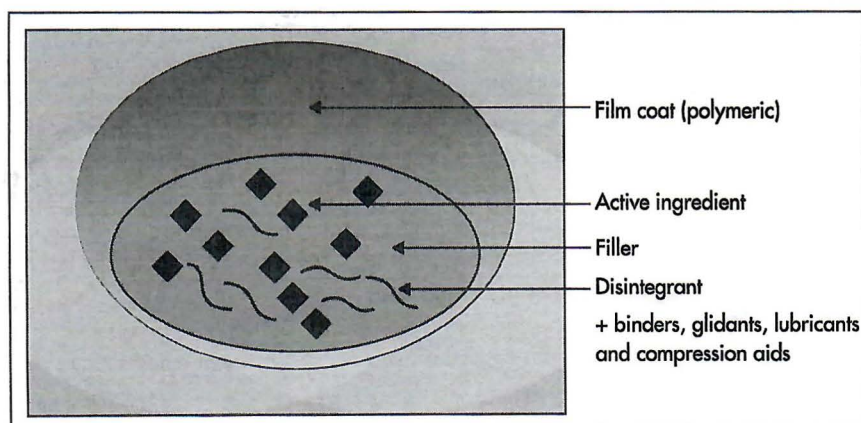


Figure 9.13 A cartoon of a conventional film-coated tablet, showing just some of the ingredients commonly found and the range of possibilities for interactions such as drug–excipient, excipient–excipient, and changes in the polymer film coat.

Table 9

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Table 9.5 The four BCS Drug Classes

Class I: High solubility, high permeability	Class II: Low solubility, high permeability
Class III: High solubility, low permeability	Class IV: Low solubility, low permeability

Amidon and colleagues, a valuable classification system was developed to relate drug intestinal absorption to the physical properties of drugs. Drugs were characterised into four types or classes, as shown in Table 9.5. The ideal drugs fall within Class I. Different strategies must be adopted to formulate drugs in other classes to achieve efficient oral absorption.

There are, of course, drugs that are at the boundaries of these classifications: it is clear too that properties will vary widely within classes. The commonly seen grid is as shown in Fig. 9.14, where GI permeability is plotted not against drug solubility itself but against the *dose/solubility ratio*. Very poorly soluble drugs may be therapeutically effective orally if their dose is very low. High-dose drugs with a low solubility present the greatest pharmaceutical challenge. The figure also shows some of the stratagems to be adopted to achieve better absorption.



Key points

- Conventional oral delivery systems such as tablets, capsules, suspensions and liquids are fast-release formulations. The release of drug can be prolonged in order to reduce the frequency of dosing by enteric coating or the use of non-disintegrating matrix forms.
- Particular problems arise in the formulation of oral dosage forms containing labile drugs that might be affected by moisture, low-dose drugs, and dose forms containing more than one active ingredient, with the potential for the interaction between the drugs themselves or with the excipient materials.
- The Biopharmaceutical Classification System (BCS)⁶ is a valuable aid in choosing a strategy for the formulation of oral dosage forms. Drugs are classified as high solubility, high permeability (Class I); low solubility, high permeability (Class II); high solubility, low permeability (Class III); and low solubility, low permeability (Class IV).

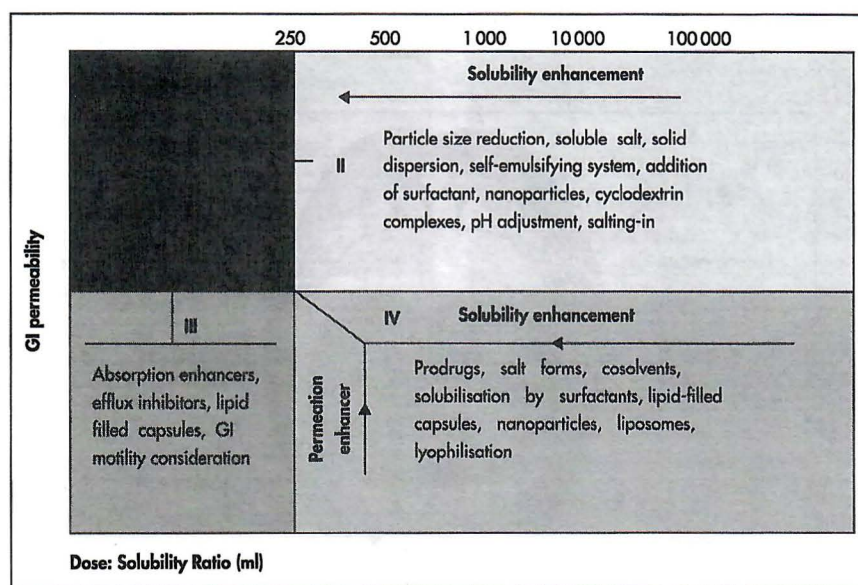


Figure 9.14 A BCS type plot of the four classes of drug with suggested techniques to enhance absorption. Class II compounds benefit from particle size reduction, soluble salt formation, solubilisation by surfactants, etc; Class III drugs require absorption enhancers and efflux inhibitors *inter alia*; Class IV drugs require a range of techniques to attempt to enhance absorption as shown.

9.4 Buccal and sublingual absorption

Mouthwashes, toothpastes and other preparations are introduced into the oral cavity for local prophylactic and therapeutic reasons. It is not known to what extent components of these formulations are absorbed and give rise to systemic effects. The absorption of drugs through the oral mucosa, however, provides a route for systemic administration that avoids exposure to the GI system. Drugs absorbed in this way bypass the liver and have direct access to the systemic circulation. The sublingual, buccal and gingival tissues are shown diagrammatically in Fig. 9.15. The oral mucosa functions primarily as a barrier, however, and it is not a highly permeable tissue, resembling skin more closely than the gut in this respect. Table 9.6 lists some commercially available sublingual and buccal delivery systems. Mucosal adhesive systems have been studied for administration of buprenorphine through the gingiva.

9.4.1 Mechanisms of absorption

The oral mucosa comprises

- A mucus layer over the epithelium,
- A keratinised layer in certain regions of the oral cavity

- An epithelial layer
- A basement membrane
- Connective tissue
- A submucosal region

While cells of the oral epithelium and epidermis are capable of absorbing material by endocytosis, it does not seem likely that drugs or other solutes would be transported by this mechanism across the entire stratified epithelium. It is also unlikely that active transport processes are operative in the oral mucosa. There is considerable evidence that most substances are absorbed by simple diffusion. The linear relationship between percentage absorption through the buccal epithelium and $\log P$ of a homologous series is seen in Fig. 9.16. For example, the buccal absorption of some basic drugs increases (Fig. 9.17), and that of acidic drugs decreases, with increasing pH of their solutions.

Nicotine in a gum vehicle when chewed is absorbed through the buccal mucosa; nicotine levels obtained are lower than those obtained by smoking cigarettes and the high peak levels are not seen. Buccal glyceryl trinitrate has been found to be an effective drug. The buccal route has the advantages of the sublingual route – the buccal mucosa is similar to sublingual mucosal tissue – but a sustained-release tablet can be held in the cheek pouch for several hours if necessary. Mucosal adhesive formulations can have obvious advantages.

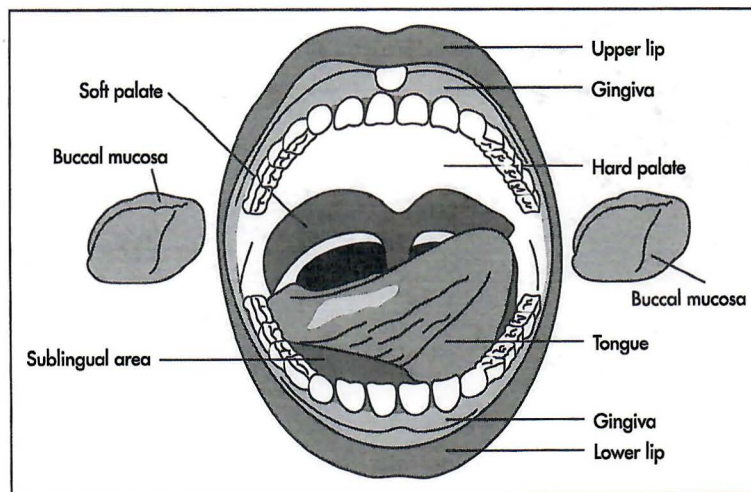


Figure 9.15 The anatomy of the oral cavity including the buccal, sublingual and gingival cavities.

From Kunth K *et al.*, *Adv Drug Deliv Rev*, 1993; 11: 137.

Table 9.6 Commercially available drug-delivery systems for systemic delivery by the oral mucosal route^a

Mucosal site	Drug	Proprietary name	Dosage form
Sublingual	Glyceryl trinitrate	Nitrostat	Tablets
		Lenitral spray	Spray
		Susadrin	Bloadhesive tablets
	Isosorbide dinitrate	Risordan	Tablets
		Sorbitrate	Chewable tablets
		Isocard spray	Spray
	Erythritol trinitrate	Cardiwell	Tablets
	Nifedipine	Adalat	Tablets
	Buprenorphine	Temgesic	Tablets
	Apomorphine HCl	Apomorphine	Tablets
Buccal	Prochlorperazine	Buccastem	Bloadhesive tablets
		Tementil	Solution
	Phloroglucinol	Spasfon-Lyoc	Lyocs
	Oxazepam	Seresta Expidet	Lyophilised tablets
	Lorazepam	Temesta Expidet	Lyophilised tablets
	Methyltestosterone	Metandren	Tablets
	Nicotine	Nicorette	Chewing-gum

^a Modified from Ponchel G, *Adv Drug Deliv Rev*, 1994; 13: 75.

Experiments with some analgesics showed that the highly lipid-soluble etorphine was absorbed several times more rapidly from the buccal cavity than the less lipid-soluble morphine.⁷ Impressive absorption has been obtained with glyceryl trinitrate (which exerts its pharmacological action 1–2 minutes after sublingual administration), methacholine chloride, isoprenaline, some steroids such as desoxycortisone acetate⁸

and 17 β -estradiol (at one-quarter of its normal oral dose), morphine, captopril and nifedipine.

It has been claimed that an oil/water partition coefficient in the range 40–2000 (log P of 1.6–3.3) is optimal for drugs to be used by the sublingual route. Drugs with a log P greater than 3.3 are so oil-soluble that it is difficult for sufficiently high levels of drug to be soluble in the aqueous salivary fluids. Drugs less lipophilic than those with a log P of 1 would not be absorbed to any great extent and would thus require large doses by this route. A comparison of the sublingual/subcutaneous dose ratio serves as an index of the usefulness of the route.⁹ For example, cocaine with a P of 28 requires a sublingual/subcutaneous dosage ratio of 2 to obtain equal effects; atropine with a P of 7 requires 8 times the subcutaneous dose; and for codeine ($P \sim 2$) over 15 times the subcutaneous dose must be given sublingually.



Key points

- Absorption of drugs through the oral mucosa provides a route for systemic administration that avoids exposure of the drug to the GI tract, and also metabolism in the liver.
- The oral mucosa functions primarily as a barrier and is not highly permeable. Most drugs are absorbed by simple diffusion.
- There is a linear relationship between percentage absorption through the buccal epithelium and log P for a homologous series of drugs. Buccal absorption of basic drugs increases and that of acidic drugs decreases with increasing pH of their solutions.
- The optimum log P for drugs to be administered by the sublingual route is between 1.6 and 3.3

Summary

We have considered the basic mechanisms of absorption that apply to all routes of administration, dealing

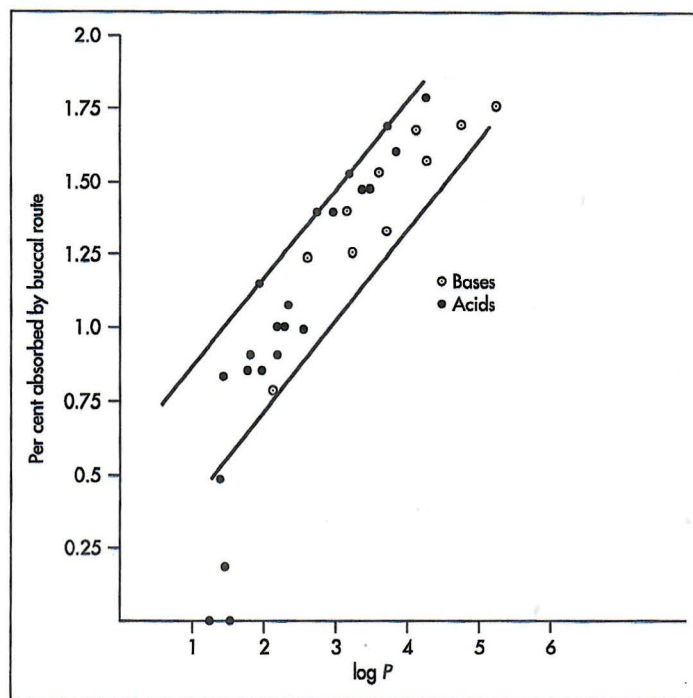


Figure 9.16 Relationship between the log P of solute and the percentage absorption through the buccal mucosa of human subjects for bases (○) and acids (●).

Plotted from data from Lien E et al., *Drug Intell Clin Pharm*, 1971; 5: 38.

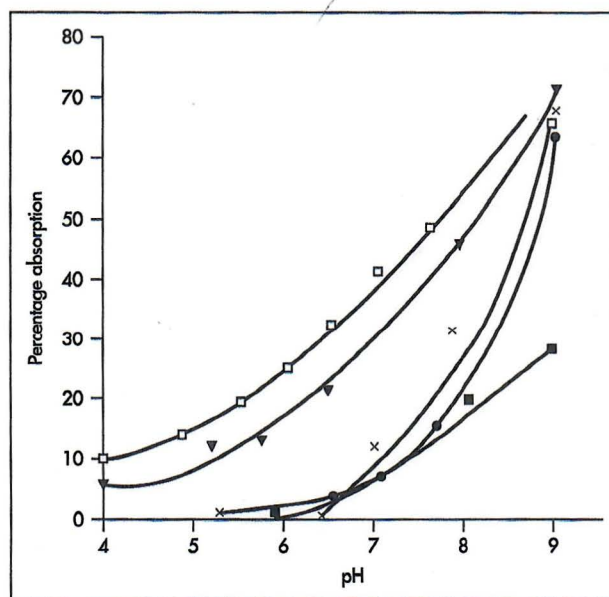


Figure 9.17 Buccal absorption of some basic drugs. The drugs were dissolved in buffered solutions of different pH and placed in the mouth of human subjects; absorption rates were determined from the decrease of drug concentration in expelled solutions: □, chlorphenamine ($pK_a = 8.99$); ▼, methadone ($pK_a = 8.25$); ×, amphetamine ($pK_a = 9.94$); ●, pethidine ($pK_a = 8.72$); ■, nicotine ($pK_a = 8.02$).

Reproduced from Beckett AH, Triggs EJ, *J Pharm Pharmacol*, 1976; 19: 315.

with the factors that depend on the drug itself, its chemical and physicochemical characteristics, the nature of the medium and the subtle differences in biological barriers that drugs experience. While the equations that relate to many of the processes are given, it is emphasised that the dynamic processes of drug absorption, dynamic in two senses in that the drug is moving down the GI tract at the same time as it is being absorbed, deny us a physicochemical 'theory of everything'. Nonetheless, estimates are valuable in understanding what is going on.

The emphasis on the oral route of delivery and sublingual and buccal delivery provided details of the underlying processes. The following chapter considers parenteral (non-oral) routes of drug administration. In all of these the actual processes of absorption of drug once it reaches the absorbing surface are the same as those discussed in the present chapter. Sometimes the route to that surface, such as after inhalation, is very tortuous, and sometimes as with topical preparations there is a more direct contact between the formulation and the barrier to be overcome. In all, there are at least three important factors: the drug, the route and the formulation.

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