related to the properties of the apical cell membrane of the columnar absorption cell and thus gastrointestinal absorption becomes a special case of the general biological phenomenon of membrane transport (Levine, 1971). The apical cell membrane exhibits the characteristic trilaminar membrane structure upon electron microscopic examination and is composed largely of protein and lipid. Although the precise molecular structure of a cell membrane is not known, the apical cell membrane of the columnar absorption cell appears to behave, with respect to the absorption of drugs and nutrients, as a 'lipoidal' membrane penetrated periodically by submicroscopic aqueous filled channels or pores. Water-soluble substances of small molecular size (radius less than 0.4 nm), such as urea, are absorbed by simple diffusion through the water filled channels. Most drug molecules, however, are too large to pass through these channels and the apical cell membrane (and hence the gastrointestinal/blood barrier) behaves like a 'lipoidal sieve' with respect to the absorption of drugs. Thus the barrier allows the passage of lipid-soluble drugs in preference to lipid-insoluble drugs. The majority of drugs appear to cross the apical cell membrane of the lining epithelium (and other cell membranes within the gastrointestinal/blood barrier) by the mechanism known as passive diffusion. This and other mechanisms by which some drugs are absorbed will be considered.

Passive diffusion

In this process the apical cell membrane of a columnar absorption cell plays a passive role and does not participate actively in the transport process. The rate of drug transport is determined by the physicochemical properties of the drug, the nature of the membrane and the concentration gradient of drug across the membrane. The process of passive diffusion, shown in Fig. 9.4, initially involves partition of a drug between the aqueous fluid in the gastrointestinal tract and the lipoidal-like cell membrane of the lining epithelium. The drug in solution in the membrane then diffuses across the membrane followed by a second partition of drug between the membrane and the aqueous fluids within the columnar absorption cells. The drug would cross the other cell membranes in the gastrointestinal/blood barrier by this sequence of steps and thus would eventually enter the blood of the capillary network in the lamina propria. If we considered that the cell membranes and fluid regions making up the gastrointestinal/blood barrier could be represented by a single 'membrane', the gastrointestinal membrane, separating the aqueous gastrointestinal fluid from the capillary blood supply in the lamina propria, then the stages involved in the gastrointestinal absorption of a drug by passive diffusion could be represented by the model shown in Fig. 9.4.

Passive diffusion of drugs across the gastro-

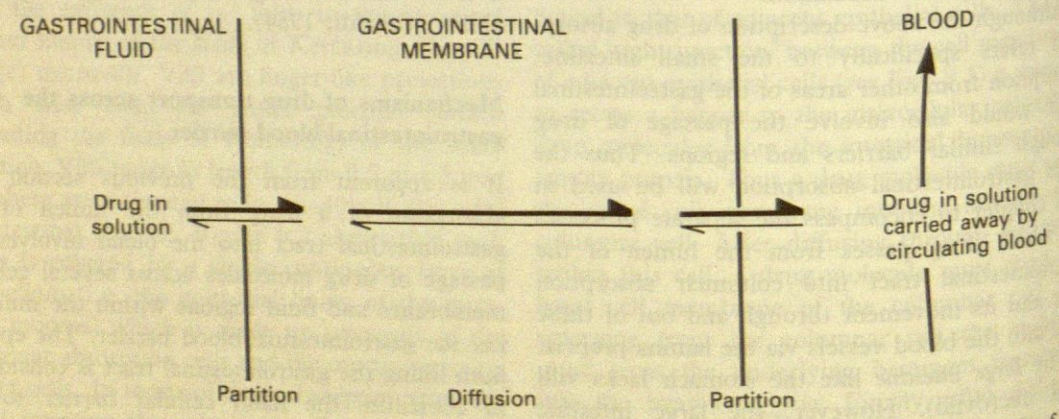


Fig. 9.4 Diagrammatic representation of gastrointestinal absorption via passive diffusion (bold arrows indicate direction of net movement of drug)

intestinal/blood barrier can often be described mathematically by Fick's first law of diffusion. Accordingly the rate of appearance of drug in the blood at the site of absorption is given by

$$\frac{dm}{dt} = \frac{D\,A\,(K_1C_g - K_2C_b)}{h} \qquad (9.1)$$

where dm/dt is the rate of appearance of drug in the blood at the site of absorption, D is the effective diffusion coefficient of the drug in the gastrointestinal (g.i.) 'membrane', A is the surface area of the gastrointestinal 'membrane' available for absorption by passive diffusion, K_1 is the apparent partition coefficient of the drug between the gastrointestinal 'membrane' and the gastrointestinal fluid i.e.

$$K_1 = \frac{\text{concentration of drug inside 'membrane' at g.i. fluid/membrane interface}}{\text{concentration of drug in g.i. fluid}}$$

C_g is the concentration of drug in solution in the gastrointestinal fluid at the site of absorption, K_2 is the apparent partition coefficient of the drug between the gastrointestinal 'membrane' and the blood, C_b is the concentration of drug in the blood at the site of absorption, and h is the thickness of the gastrointestinal 'membrane'.

Hence K_1C_g and K_2C_b represent the concentrations of drug inside the gastrointestinal membrane at the g.i. fluid/membrane interface and g.i. membrane/blood interface respectively. The expression

$$\frac{(K_1C_g - K_2C_b)}{h}$$

represents the concentration gradient of drug across the 'membrane'.

Eqn 9.1 indicates that the rate of gastrointestinal absorption of a drug by passive diffusion depends on the surface area of the 'membrane' that is available for drug absorption. This is compatible with the observation that the small intestine, particularly the duodenum, is the major site for drug absorption due principally to the presence of villi and microvilli which provide an enormous surface area for absorption. Eqn 9.1 also indicates that the rate of drug absorption depends on a large concentration gradient of drug existing across the gastrointestinal 'membrane'. It is of interest to note that the concentration gradient of drug across the membrane is influenced by the apparent partition coefficients exhibited by the drug with respect to the g.i. 'membrane'/g.i. fluid interface and the g.i. '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', i.e. K_1 should exceed unity. In addition, after diffusing across the 'membrane' the drug should exhibit sufficient solubility for the blood such that it can partition readily out of the 'membrane' phase into the blood, i.e. K_2 should be less than 1. Drug on entering the blood in the capillary network in the lamina propria will be carried away from the site of absorption by the rapidly circulating gastrointestnal blood supply and will become diluted by

1 distribution in a large volume of blood, i.e. the systemic circulation,
2 distribution into body tissue and other fluids of distribution, and
3 by metabolism and excretion.

In addition, proteins in the blood may bind drug molecules and thereby further lower the concentration of 'free' (diffusible) 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 the concentration of drug in solution in the gastrointestinal fluids at the site of absorption, i.e. $C_g \gg C_b$. The 'sink' conditions provided by the systemic circulation ensures 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 diffusible species of the drug which exists across the gastrointestinal/blood barrier. Under such conditions that $K_1C_g \gg K_2C_b$ and thus $(K_1C_g - K_2C_b)$ approximates to K_1C_g, Eqn 9.1 may be rewritten in the form

$$\frac{dm}{dt} = \frac{D\,A\,K_1C_g}{h} \qquad (9.2)$$

For a given drug and 'membrane' under specified conditions, D, A, K_1 and h may be regarded as constants which can be incorporated into a combined constant known as the permeability constant, P. Hence Eqn 9.2 becomes

$$\frac{dm}{dt} = P\,C_g \qquad (9.3)$$

where

$$P = \frac{D\,A\,K_1}{h}$$

Eqn 9.3 is an expression for a first order kinetic process and indicates that the rate of passive drug absorption will be proportional to the concentration of absorbable drug in solution in the gastrointestinal fluids at the site of absorption. In practice, the gastrointestinal absorption of most drugs by passive diffusion follows first order kinetics.

It has been assumed that the drug in aqueous solution on each side of the gastrointestinal/blood barrier (see Fig. 9.4) existed entirely in the form of a single absorbable (via passive diffusion) species which exhibited definite partition coefficients for distribution between

1 the aqueous gastrointestinal fluids and the lipoidal 'membrane', and
2 the blood and the lipoidal 'membrane'.

However, many drugs are weak electrolytes which exist in aqueous solution as two species, namely the unionized and ionized species. Since it is the unionized form of a weak electrolyte drug which exhibits greater lipid solubility compared to the corresponding ionized form, the gastrointestinal 'membrane' (like other membranes) is permeable preferentially to the unionized species. Thus the rate of passive absorption of weak electrolyte drugs 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 its aqueous environment in accordance with the Henderson–Hasselbalch equations for weak acids and bases. The gastrointestinal 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. These observations form the basis of the pH–partition hypothesis (see later in this chapter).

Carrier-mediated transport

Active transport Most drugs are absorbed from the gastrointestinal tract by passive diffusion. However, a few lipid-insoluble drugs (such as 5-fluorouracil) and many substances of nutritional interest are absorbed by active transport mechanisms. In contrast to passive diffusion, active transport involves active participation by the apical cell membrane of the columnar absorption cell (and presumably also by the other cell membranes constituting the gastrointestinal/blood barrier) in the gastrointestinal absorption of a drug. A 'carrier' which may be an enzyme or some other component of the cell membrane is responsible for effecting the transfer of drug by a process which is represented in Fig. 9.5.

Figure 9.5 shows that the drug molecule or ion forms a complex with the 'carrier' in the surface of the apical cell membrane of a columnar absorption cell involved in the active transport of the particular drug. 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 lumen of 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 absorption process. In the case of the gastrointestinal absorption of drugs by active transport, transfer of drug occurs in the direction of the gastrointestinal lumen to the blood and not normally in the reverse direction, i.e. drug absorption by active transport across the gastrointestinal/blood barrier does not normally occur against a concentration gradient of the drug. The carrier system is generally a 'one-way' transport system.

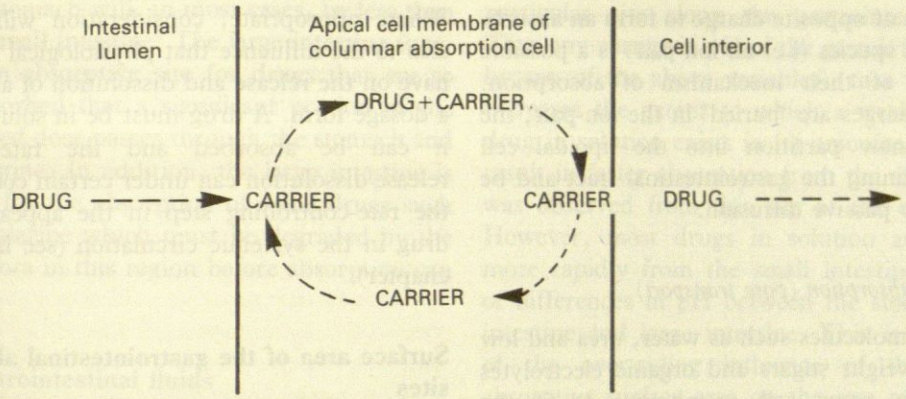


Fig. 9.5 Diagrammatic representation of active transport of a drug across a cell membrane

There appear to be several carrier-mediated active transport systems in the small intestine. Each carrier appears to be highly selective with respect to the chemical structure of the substance which it will transport. Thus if a drug structurally resembles a natural substance which is actively transported then that drug is also likely to be transported by the same carrier mechanism. For instance the drug levodopa, which is structurally related to the amino acids tyrosine and phenylalanine, is absorbed by the same active transport system that is used to transport these amino acids from the lumen of the small intestine into the blood. Each carrier system is generally concentrated in a specific segment of the gastrointestinal tract. The substance which is transported by that carrier will thus be absorbed preferentially in the location of highest carrier density. For instance, more riboflavin is absorbed from the proximal portion of the small intestine than from the large or upper intestine.

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 which 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.

Many body nutrients such as sugars and L-amino acids are transported across the gastrointestinal 'membrane' by active transport processes. Vitamins such as thiamine, nicotinic acid, riboflavin and B_6 require an active transport system. The anticancer drug 5-fluorouracil, methyldopa and nicotinamide are absorbed by active transport. Active transport also plays an important role in the renal and biliary excretion of many drugs and metabolites.

Facilitated diffusion or transport This is also a carrier-mediated transport system which 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 it does require a concentration gradient for its driving force (as does passive diffusion). In terms of drug absorption, facilitated diffusion seems to play a very minor role.

Ion-pair absorption

This mechanism of absorption has been proposed to explain how certain drugs such as quaternary ammonium compounds and tetracyclines, which are ionized over the entire gastrointestinal pH range, are absorbed from the gastrointestinal tract. Such drug ions are considered to be too lipid insoluble to partition directly into the lipoidal apical cell membrane of the columnar absorption cells lining the gastrointestinal tract. In addition, these water-soluble drug ions are too large to pass through the aqueous filled pores or channels which are considered to exist in the cell membrane lining the gastrointestinal tract. However, the interaction of such drug ions with endogenous

organic ions of opposite charge to form an absorbable neutral species (i.e. an ion-pair) is a possible explanation of their mechanism of absorption. Since the charges are 'buried' in the ion-pair, the latter can now partition into the lipoidal cell membrane lining the gastrointestinal tract and be absorbed by passive diffusion.

Convective absorption (pore transport)

Very small molecules such as water, urea and low molecular weight sugars and organic electrolytes are able to cross cell membranes as if the membrane contained aqueous filled channels or pores. The effective radius of these channels has been estimated to be of the order of 0.4 nm. As a result of molecular size limitations, this mechanism of absorption appears to be of minor importance with respect to the gastrointestinal absorption of large water-soluble drug molecules or ions. However, convective absorption is involved in the renal excretion of drugs and the uptake of drugs into the liver.

Pinocytosis

Pinocytosis is the only mechanism of absorption in which the material does not have to be in aqueous solution in order to be absorbed. The mechanism is comparable to phagocytosis and involves invagination of the material by the apical cell membrane of the columnar absorption cells lining the gastrointestinal tract to form vacuoles containing the material. These vacuoles then cross the columnar absorption cells. This mechanism of absorption appears to be of little importance for drugs but is important for the absorption of macromolecules such as proteins.

PHYSIOLOGICAL FACTORS INFLUENCING DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

In discussing how various physiological properties of the gastrointestinal tract may influence drug absorption, it should be noted that it is assumed (unless otherwise stated) that the drug is in solution in the appropriate gastrointestinal fluid. Where appropriate, consideration will be given also to the influence that physiological factors can have on the release and dissolution of a drug from a dosage form. A drug must be in solution before it can be absorbed and the rate of drug release/dissolution can under certain conditions be the rate-controlling step in the appearance of a drug in the systemic circulation (see later in this chapter).

Surface area of the gastrointestinal absorption sites

The biological environments and the areas of membrane available for absorption in the stomach, the small intestine and the large intestine are quite different and these differences give rise to variations in the rate and extent of absorption of a drug from these anatomical regions.

As previously discussed, the presence of (a) folds in the mucosa, (b) villi and (c) microvilli is responsible for the small intestine having the largest effective surface area available for absorption. Consequently the small intestine is the region of maximum absorption for the majority of drugs even though the pH of the intestinal fluid does not provide optimum conditions for the absorption of all drugs, e.g. weak acidic drugs. In addition to its large absorptive surface area the small intestine is the most important region for carrier-mediated drug absorption, i.e. the small intestine is the location of highest 'carrier' density.

In contrast to the small intestine, the absorptive surface areas of the stomach and the large intestine are relatively small since neither of these regions possess villi or microvilli. Despite the relatively small absorptive surface area available in the stomach, certain drugs (e.g. weak acidic drugs in solution which are unionized) are absorbed in this region. It should be noted that following oral ingestion of a drug in solution a major part of the stomach's absorptive area will be immediately in contact with dissolved drug and, providing that the intrinsic physicochemical properties of the drug permit permeation of the gastrointestinal/blood barrier, good absorption may occur. However, because the absorptive surface area in the stomach is so small compared to that in the small intestine, the rate and extent of absorption of a given drug

from the stomach will, in most cases, be less than from the small intestine. The large intestine functions as an absorptive site for drugs that are so slowly absorbed that a significant portion of the administered dose passes through the stomach and small intestine. In addition, the large intestine is important for the absorption of some drugs such as sulphasalazine which must be degraded by the bacterial flora in this region before absorption can occur.

pH of gastrointestinal fluids

The pH of the fluids varies considerably along the length of the gastrointestinal tract. Gastric fluid is highly acidic, exhibiting a pH within the range 1–3.5. The fluid in the small intestine is generally considered to have a pH in the range 5–8, generally from a pH range of 5–6 in the duodenum to about pH 8 in the lower ileum. The fluid in the large intestine is generally considered to have a pH of about 8. Considerable variations within the above pH ranges may occur in an individual. For instance, there appears to be a diurnal cycle of gastric acidity, the fluids becoming more acidic at night and fluctuating during the day primarily in response to food ingestion. Gastric fluid pH generally increases when food is ingested and then slowly decreases over the following few hours. There is also considerable intersubject variation in gastrointestinal pH depending on such factors as:

1 the general health of the individual,
2 the presence of localized disease conditions (e.g. gastric and duodenal ulcers) along the gastrointestinal tract,
3 the types and amounts of food ingested, and
4 drug therapy.

In the case of drug therapy, anticholinergic drugs inhibit or reduce gastric secretion and the oral administration of antacids usually elevates gastric pH for a short period of time.

Gastrointestinal pH may influence drug absorption in a variety of ways. The degree to which a given weak electrolyte drug ionizes in solution in the gastrointestinal fluids is a function of pH (and pK_a of the drug). In general the unionized form of a drug in solution will be absorbed faster than the ionized form of the same drug at any particular site along the gastrointestinal tract. Thus any change in pH of the gastric fluid (caused by any of the above variables), to a value which increases the extent to which a weak electrolyte drug in solution exists in its unionized form, will result in faster absorption from the stomach than was observed from this site at the original pH. However, most drugs in solution are absorbed more rapidly from the small intestine regardless of differences in pH between the stomach, small intestine and large intestine. This is a reflection of the over-riding influence of the available absorptive surface area on the rate of absorption of drugs in solution from these sites.

Since the aqueous solubility of a weak electrolyte drug is influenced by pH, the rate of dissolution of such a drug from a solid dosage form will be pH dependent. In the case of a poorly soluble weak electrolyte drug administered in a solid dosage form, the rate of drug dissolution in the gastrointestinal fluids may be the rate-limiting step for the absorption of such a drug. Hence gastrointestinal pH would be expected to exert a major influence on the dissolution rate and hence the overall absorption rate of such a drug administered in a solid dosage form such as a tablet or a hard gelatin capsule. Consequently a poorly soluble weak acidic drug, which only exhibits a high dissolution rate in an alkaline aqueous environment, will only be expected to be rapidly absorbed from a solid dosage form when the drug passes through the acid environment of the stomach and reaches the more alkaline intestinal fluids where rapid drug dissolution can occur. In contrast, a poorly aqueous-soluble weak basic drug, which only exhibits a high dissolution rate in an acidic aqueous environment, must first dissolve in the acidic gastric fluid before it reaches the small intestine in order to be rapidly absorbed from the small intestine. Any undissolved weak basic drug which reaches the small intestine would be expected to exhibit a relatively low absorption rate since its dissolution rate in the relatively alkaline intestinal fluids would be low (Mayersohn, 1979).

A further way by which gastrointestinal pH can influence drug absorption is in the case of drugs which exhibit limited chemical stability in either acidic or alkaline environments. The influence

that the chemical stability exhibited by a drug in the gastrointestinal fluids can have on the absorption of such a drug from the gastrointestinal tract is discussed later in this chapter.

Gastric emptying rate

Most drugs are optimally absorbed from the small intestine following peroral administration. Hence any reduction in the rate at which a drug in solution leaves the stomach and enters the duodenum (i.e. the gastric emptying rate) is likely to reduce the overall rate of drug absorption and therefore delay the onset of the therapeutic response of the drug. In addition the intensity of the therapeutic response may be reduced. The rate of gastric emptying is also important for drugs which are prone to chemical degradation in the stomach by virtue of the low pH or enzyme activity associated with the gastric fluid. The longer the time that a susceptible drug spends in the stomach, the more likely the drug is to be degraded with an accompanying reduction in its effective concentration and hence bioavailability. Drugs contained in enteric-coated dosage forms, which are formulated so as to prevent drug release into gastric fluid but to allow release into the fluid in the duodenum, will show a delayed onset of therapeutic activity if the gastric emptying rate is suppressed.

The gastric emptying of fluids and small particles appears to be an exponential process (Bechgaard and Christensen, 1982). Standard low bulk meals and liquids are transferred from the stomach into the duodenum in an apparent first order rate process, i.e. the rate of gastric emptying is proportional to the volume of the material remaining in the stomach. Gastric emptying rate is influenced by a large number of factors. Factors promoting gastric emptying rate include hunger, anxiety, the patient's body position (i.e. lying on the right side), the intake of liquids and the antiemetic drug, metoclopramide (Gibaldi, 1984). Gastric emptying rate is retarded by factors such as fatty foods, a high bulk (viscous) diet, mental depression, gastric ulcers, pyloric stenosis, hypothyroidism, the patient's body position (lying on the left side) and drugs such as anticholinergics, tricyclic antidepressants, aluminuim hydroxide and alcohol (Mayersohn, 1979). In view of these numerous factors which can influence gastric emptying rate, it is not surprising that this is a highly variable parameter both among different individuals and within any one individual at different times. It is likely that such variation in gastric emptying rate contributes to the intersubject and intrasubject variation observed in the bioavailability of a given drug.

The gastric emptying of solution-type dosage forms and suspensions of fine drug particles is generally much faster and less variable than that of solid, non-disintegrating unit dosage forms and lumpy masses of aggregrated particles. For instance the gastric emptying times of single non-disintegrating tablets (diameter 10–16 mm) range from 0.5 to 4.5 hours whereas dosage forms which disintegrate into small subunits (e.g. granules, pellets) are emptied gradually from the stomach with a mean time of 1.5 hours (Bechgaard and Christensen, 1982). It is thus not surprising to find that the gastric emptying times of enteric-coated tablets, which are designed to remain intact in the stomach, are very erratic and this contributes to the unusually large intersubject variability found in the absorption of drugs from this type of dosage form (Gibaldi, 1984).

In general, the presence of food in the stomach reduces the gastric emptying rate and thus can delay the absorption of drugs which are normally absorbed from the small intestine. Hence, unless a drug is irritating to the gastric mucosa, a drug should not be administered with or immediately after a bulky meal. In general a drug will reach the small intestine most rapidly if it is administered with water to a patient whose stomach is empty of food. However, effects of food on drug absorption from the gastrointestinal tract are quite variable and are considered in greater detail later in this chapter.

Whilst the above discussion suggests that a decrease in gastric emptying rate will be disadvantageous with respect to the overall rate of absorption of many drugs, the opposite may also be true. An example is the case of a solid dosage form containing a poorly soluble drug which must first dissolve in gastric fluid prior to being absorbed rapidly from the small intestine. Such would be the case for a poorly soluble weak basic drug since

any of this drug which reached the small intestine in the undissolved state would be expected to dissolve (and hence be absorbed) slowly. This is a consequence of the reduced solubility exhibited by such drugs at intestinal pH conditions. Hence a decrease in gastric emptying rate would permit a longer time in which dissolution of such a drug could occur in the more favourable acidic pH conditions of the stomach. A greater proportion of the administered dose of drug would dissolve and thus be in an absorbable form when it passed into the duodenum. The enchanced bioavailability exhibited by the poorly soluble drug nitrofurantoin in the presence of food was considered to be a result of the accompanying decreased gastric emptying rate which permitted a greater proportion of the drug to dissolve in the gastric fluids before passing into the duodenum from where it is optimally absorbed (Rosenberg and Bates, 1976).

Intestinal motility

Once a drug empties from the stomach and enters the small intestine it will be exposed to an environment which is totally different from that of the stomach. Since the small intestine is the primary site of drug absorption, the longer the residence time in this region the greater is the potential for efficient drug absorption assuming that the drug is stable in the intestinal fluids and does not react with endogenous materials to form poorly absorbable 'complexes' (Mayersohn, 1979).

There are two types of intestinal movements, propulsive and mixing. The propulsive movements primarily determine the intestinal transit rate and thus the residence time of a drug or a dosage form in the small intestine. The greater the intestinal motility, the shorter the residence time and the less time there is for dissolution and absorption of drugs to occur. Under normal circumstances, peristaltic waves propel the intestinal contents relatively slowly, i.e. it takes 3–10 hours to move a meal in the form of chyme along the entire length of the small intestine (Mayersohn, 1979). The residence time in the small intestine, as determined by intestinal motility, may be an important factor with respect to drug bioavailability. The longer a drug is in contact with the absorption site(s) the greater the amount of drug absorbed (Bates and Gibaldi, 1970). Intestinal residence time will thus be important for

1 dosage forms which release drug slowly (e.g. controlled/sustained/prolonged release dosage forms) as they pass along the entire length of the gastrointestinal tract,
2 enteric-coated dosage forms which release drug only when they reach the small intestine,
3 drugs which dissolve slowly in the intestinal fluids and
4 drugs which are absorbed by intestinal carrier-mediated transport systems.

Mixing movements of the small intestine bring drug which is in solution in the intestinal contents into intimate contact with the large epithelial absorptive surface area of the small intestine. The mixing movements thus increase the area of contact between drug in solution and the gastrointestinal 'membrane'. In addition, the mixing movements will also increase the dissolution rate of drugs from solid dosage forms and this will be particularly significant in the case of poorly soluble drugs which exhibit dissolution rate-limited absorption.

Drug stability in the gastrointestinal tract

Absorption is not the only process that can occur as a drug in solution passes along the gastrointestinal tract. A drug may be chemically degraded and/or metabolized in the gastrointestinal tract. The consequence of this is usually incomplete bioavailability since only a fraction of the administered dose reaches the systemic circulation in the form of intact drug. Chemical degradation, particularly pH-dependent reactions such as hydrolysis, can occur in the fluids of the gastrointestinal tract. For instance, erythromycin undergoes acid-catalysed hydrolysis in gastric fluid. Drugs which resemble nutrients such as polypeptides, nucleotides or fatty acids may be especially susceptible to enzymic hydrolysis in the gastrointestinal tract. In addition to enzymic metabolism in the gastrointestinal fluids, drugs may be metabolized by enzymes located in the intestinal mucosa. For instance, intestinal metabolism accounts for orally administered isoproter-

enol being 1000 times less active than intravenously administered isoproterenol (Gibaldi, 1984). Other drugs which appear to be metabolized in the gastrointestinal mucosa include chlorpromazine, L-dopa, stilboestrol, progesterone and testosterone. The metabolic potential of the gastrointestinal microflora is also now recognized (Mayersohn, 1979).

It would seem that metabolism and degradation of a drug in the gastrointestinal tract would serve primarily to reduce the extent of its bioavailability. However, in some instances these processes may be essential for drug absorption to occur. Many pro-drugs such as erythromycin stearate and chloramphenicol palmitate depend on degradation in the gastrointestinal tract in order to release the therapeutically active parent molecule.

Hepatic metabolism

All drugs that are absorbed from the stomach, small intestine and colon pass into the hepatic portal system and are presented to the liver before reaching the systemic circulation. The liver is the primary site of drug metabolism. Hence this first pass of absorbed drug through the liver may result in extensive metabolism of the drug and a significant proportion of the absorbed dose of intact drug may never reach the systemic circulation. This phenomenon is known as the *first pass effect* and results in a decrease in bioavailability of those drugs which are rapidly metabolised by the liver. The bioavailability of a susceptible drug may be reduced to such an extent so as to render the gastrointestinal route of administration ineffective (as in the case of lignocaine where 70% of the oral dose is metabolized by the intestinal wall and liver) or to necessitate an oral dose which is many times larger than the intravenous dose (e.g. propranolol). Other drugs which are subject to the first pass effect include alprenolol, pethidine, organic nitrates and propoxyphene.

Influence of food and diet

There is considerable evidence that the rate and/or extent of drug absorption can be influenced by the presence of food in the gastrointestinal tract (Welling, 1980). Food may influence drug bioavailability by means of the following mechanisms.

Alteration in the rate of gastric emptying

For instance, solid meals (particularly those which are hot and contain a high proportion of fat) tend to decrease gastric emptying rate and can thus delay the onset of therapeutic action of some drugs. Further information on the potential consequences of reduced gastric emptying rate on drug bioavailability has been given earlier in this chapter.

Stimulation of gastrointestinal secretions

Gastrointestinal secretions (e.g. gastric hydrochloric acid, pepsin) secreted in response to the presence of food may result in the degradation of drugs which are susceptible to chemical hydrolysis or enzymic metabolism. This would lead to a reduction in drug bioavailability. In the case of stable drugs, the stimulation of gastrointestinal secretions may increase bioavailability by assisting drug dissolution. The ingestion of food, especially fat, stimulates the secretion of bile. Bile salts are surface-active agents and can increase the dissolution of some poorly soluble drugs thereby enhancing their absorption. For instance the enhanced absorption exhibited by griseofulvin when fatty meals are ingested may be due to the solubilizing effect of bile salts secreted in response to the fatty components of the meal. However bile salts have been shown to form insoluble, non-absorbable complexes with such drugs as neomycin, kanamycin and nystatin.

Competition between food components and drugs for specialized absorption mechanisms

In the case of those drugs which have a chemical structure similar to nutrients required by the body for which specialized absorption mechanisms exist, there is the possibility of competitive inhibition of drug absorption. One example appears to be L-dopa whose absorption may be inhibited

by certain amino acids resulting from the breakdown of ingested proteins.

Complexation of drugs with components in the diet

The gastrointestinal absorption of tetracyline is reduced by virtue of the formation of a non-absorbable complex with calcium present in dairy foods. Foods containing a high iron content also reduce the bioavailability of tetracycline due to complex formation. In general, complexation is only important (with respect to bioavailability) when an irreversible or an insoluble complex is formed. In such cases the fraction of the administered dose of drug which becomes complexed is unavailable for absorption. Consequently the effective concentration of drug in solution in the gastrointestinal fluids is reduced and both the rate and/or extent of drug absorption is reduced. If the complex formed is water soluble and readily dissociates to liberate the 'free' (absorbable) drug, then little or no effect of complexation on drug absorption is noted. The rate at which the complex dissociates determines whether drug absorption is as rapid and/or complete as in the absence of complex formation. Further information on the effects of complexation on drug absorption is given later in this chapter.

Increased viscosity of gastrointestinal contents

The presence of food in the gastrointestinal tract will provide a viscous environment which may result in a reduction in the rate of drug dissolution in the gastrointestinal contents. 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 will tend to decrease the bioavailability of drug.

Food-induced changes in blood flow to the liver

Blood flow to the gastrointestinal tract and liver increases shortly after a meal. This increased blood flow to the liver will increase 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 greater the rate of presentation of such drugs to the liver, the larger the fraction of drug that escapes first pass metabolism. This is because the enzyme systems responsible for their metabolism become 'swamped' (i.e. saturated) by the increased rate of presentation of drug to the site of biotransformation. Under these circumstances food, by virtue of causing a transient increase in hepatic blood flow, can increase the amounts of such drugs that reach the systemic circulation intact.

It is thus evident that food can influence the absorption of drugs from the gastrointestinal tract by a variety of mechanisms. A summary of the influences that food may have on the absorption of a number of drugs is given in Table 9.1. Whilst food has been reported to increase or decrease the rate and/or extent of absorption of numerous drugs, it should be noted that the absorption of some drugs does not appear to be influenced by food ingestion. Drugs whose absorption is reported to be unaffected by food include chlorpropamide, oxazepam and prednisolone (Welling, 1980).

Miscellaneous physiological factors influencing gastrointestinal absorption

Disease states and physiological disorders associated with the gastrointestinal tract are likely to influence the absorption and hence bioavailabilities of drugs administered via this route. Local disease states can cause alterations in gastric pH. For instance, the pH of gastric fluid is elevated (up to pH 6.9) in patients with gastric cancer. The various ways by which alterations in gastric pH can influence drug bioavailability have been discussed earlier in this chapter. Gastric surgery can cause drugs to exhibit different bioavailabilities in such patients compared to normal individuals. Partial or total gastrectomy results in drugs reaching the duodenum more rapidly than in the case of normal individuals. This increased rate of presentation of drug to the small intestine may result in an increased overall rate of absorption of drugs which are best absorbed from this segment of the gastrointestinal tract. However, drugs

Table 9.1 The influence of food on the gastrointestinal absorption of some drugs (Mayersohn, 1979)

Drug	*Influence of food on absorption*	*Comments*
Aspirin	Reduction in rate but not in extent of absorption	Reduced rate of gastric emptying gives delayed onset of analgesia
Barbiturates	Reduction in rate but not in extent of absorption	Reduced rate of gastric emptying gives delayed hypnotic response
Cephalosporins	Reduction in rate but not in extent of absorption	Reduced rate of gastric emptying gives lower peak plasma concentrations
Griseofulvin	Absorption increased when fatty meal ingested	Solubilizing effect of bile salts secreted in response to fatty meal
Nitrofurantoin	Reduced rate but increased extent of absorption gives higher urinary concentrations	Prolonged residence in stomach gives improved dissolution in gastric fluids
Penicillins (benzylpenicillin, methicillin, oxacillin)	Rate and extent of absorption reduced	Prolonged residence in stomach causes increased loss of those penicillins which are sensitive to acid hydrolysis
Hydralazine	Extent of absorption increased	Reduction in first pass degradation
Tetracyclines (tetracycline, oxytetracycline)	Extent of absorption decreased	Formation of non-absorbable complex with calcium ions present in dairy products

which require a period of time in the stomach in order to facilitate their dissolution may show reduced bioavailabilities in such patients. Diarrhoeal conditions may reduce drug bioavailability by virtue of reducing the drug's residence time in the small intestine.

Other factors which may influence the bioavailabilities of drugs from the gastrointestinal tract include age (i.e. children, adults and elderly patients), stress (e.g. stress induced through illness) and whether a patient is bedridden or not.

PHYSICOCHEMICAL FACTORS INFLUENCING DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

In the previous section, drug absorption has been shown to be influenced by many physiological factors. The absorption and hence the bioavailability of a drug is also influenced by many of its physicochemical properties, notably pK_a, lipid solubility, dissolution rate, chemical stability and complexation.

Drug dissociation constant and lipid solubility

The dissociation constant and lipid solubility of a drug and the pH at the absorption site often dictate 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 drug absorption is embodied in the pH-partition hypothesis of drug absorption.

pH-partition hypothesis of drug absorption

According to this hypothesis, the gastrointestinal/blood barrier acts as a lipid barrier towards weak electrolyte drugs which are absorbed by passive diffusion. The gastrointestinal/blood barrier is thus impermeable to the ionized (i.e. poorly lipid-soluble) form of a weak acidic or basic drug but relatively permeable to the non-ionized (i.e. more lipid-soluble) form of such a drug. Consequently, according to the pH-partition hypothesis, the absorption of a weak electrolyte drug will be determined chiefly by the extent to which the drug exists in its unionized form at the site of absorption.

In order to illustrate the concept of the pH-partition hypothesis, let us consider the distribution of weak acidic and basic drugs across the gastrointestinal barrier between the gastric fluid and the blood. The extent to which a weak acidic

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

$$\log \frac{[A^-]}{[HA]} = pH - pK_a \qquad (9.4)$$

where pK_a is the negative logarithm of the acid dissociation constant of the drug, [HA] and $[A^-]$ are the respective concentrations (mol dm^{-3}) of the unionized and ionized forms of the weak acidic drug, which are in equilibrium and in solution either the gastric fluid or the blood. pH refers to the pH of the environment of the ionized and unionized species of the weak acidic drug, i.e. gastric fluid or blood.

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

$$\log \frac{[BH^+]}{[B]} = pK_a - pH \qquad (9.5)$$

where $[BH^+]$ and [B] are the respective concentrations (mol dm^{-3}) of the ionized and unionized forms of the weak basic drug which are in equibilibrium and in solution in either the blood or gastric fluid.

Absorption of a weak acidic drug Consider the distribution of a weak acidic drug having a pK_a of 3.0 between the blood and gastric fluid. For the purposes of this calculation, assume that the pH of gastric fluid is 1.2 and the pH of blood is 7.4. Equation 9.4 may be used to calculate the ratios of the concentrations of the ionized form (A^-) and unionized form (HA^-) of the weak acidic drug which exist in equilibrium in solution in gastric fluid and blood, respectively. In gastric fluid, pH 1.2

$$\log \frac{[A^-]}{[HA]} = pH - pK_a$$
$$= 1.2 - 3.0 = -1.8$$

Therefore,

$$\frac{[A^-]}{[HA]} = \text{antilog}\,(-1.8) = 0.016$$

Thus the ratio of the concentrations of the ionized and unionized forms of the weak acidic drug ($pK_a = 3.0$) in solution in gastric fluid (pH 1.2) is 0.016 : 1, respectively. The vast majority (98.4%) of the drug in solution in gastric fluid exists therefore in the ionized (absorbable) form. Thus the vast majority of the drug in solution in gastric fluid will be absorbed passively through the gastrointestinal barrier and enter the blood. On partitioning into the blood, the drug will experience a pH of 7.4. The extent of ionization of the weak acidic drug ($pK_a = 3.0$) in the blood (pH 7.4) may be calculated using Eqn 9.4 as follows:

$$\log \frac{[A^-]}{[HA]} = pH - pK_a$$
$$= 7.4 - 3.0 = 4.4$$

Therefore,

$$\frac{[A^-]}{[HA]} = \text{antilog}\,(4.4)$$
$$= 25\,119$$

Thus the ratio of the concentrations of the ionized and unionized forms of the weak acidic drug in solution in the blood is 25 119 : 1, respectively. It is evident that the weak acidic drug, once present in the blood, will exist almost entirely (99.996%) in its ionized form, A^-. Thus irrespective of the sink conditions provided by the systemic circulation to absorbed drug, there will be virtually no tendency for the weak acidic drug in the blood to be absorbed back into the stomach since only 0.004% of the drug in the blood exists in the absorbable, unionized form.

If the stomach and blood are considered to be two enclosed compartments separated by the gastrointestinal barrier, which is freely permeable to the unionized form of the weak acidic drug but impermeable to the ionized form of the drug, then the unionized form of the drug (HA) will distribute between the gastric fluid and the blood until equilibrium is reached, i.e. the concentrations of unionized drug on each side of the gastrointestinal barrier are equal. However, because the pH on each side of the gastrointestinal barrier is different and the barrier is assumed to

be impermeable to the ionized form of the drug, the concentration of the ionized form on each side of the membrane when this equilibrium is attained, may not be equal. The equilibrium distribution of the weak acidic drug ($pK_a = 3.0$) between gastric fluid (pH 1.2) and blood (pH 7.4) may be represented as shown in Fig 9.6.

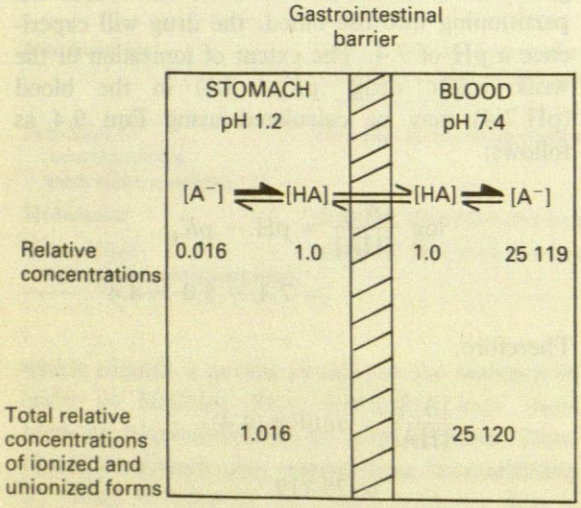


Fig. 9.6 Diagrammatic representation of the equilibrium distribution of a weak acidic drug (pK_a 3.0) between the stomach and the blood

For this particular example the total relative equilibrium concentrations of weak acidic drug in the stomach and the blood are in the ratio of 1.016 : 25 120 respectively. The total equilibrium concentration of weak acidic drug is thus approximately 25 000 times greater in the blood than in the stomach. Hence according to the pH-partition hypothesis drugs such as weak acidic drugs which exist predominantly in the unionized form at gastric pHs will be well absorbed from the stomach.

Absorption of a weak basic drug Let us now consider how a weak basic drug having a pK_a of 5.0 becomes distributed between the gastric fluid (pH = 1.2) and the blood (pH = 7.4). Eqn 9.5 may be used to calculate the ratios of the unionized (B) and ionized (BH^+) forms of the drug which exist in equilibrium in solution in the gastric fluid and in the blood, respectively.

In gastric fluid, pH 1.2,

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

$$= 5.0 - 1.2 = 3.8$$

Therefore,

$$\frac{[BH^+]}{[B]} = \text{antilog } (3.8)$$

$$= 6309.6$$

Hence, in gastric fluid (pH 1.2) the ratio of the equilibrium concentrations of the ionized and unionized forms of the weak basic drug ($pK_a = 5.0$) is 6309.6 : 1, respectively. The vast majority of the drug (i.e. 99.98%) in solution exists in the ionized, unabsorbable form.

In blood, pH 7.4,

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

$$= 5.0 - 7.4 = -2.4$$

Therefore,

$$\frac{[BH^+]}{[B]} = \text{antilog } (-2.4)$$

$$= 0.004$$

Hence in blood (pH 7.4) the ratio of the equilibrium concentrations of the ionized and unionized forms of the weak basic drug ($pK_a = 5.0$) is 0.004 : 1, respectively. It is thus evident that any of the weak basic drug which is absorbed from the stomach into the blood will exist predominantly (i.e. 99.6%) in the unionized form. If we consider that the blood and stomach are enclosed compartments separated by the gastrointestinal barrier which is freely permeable to the unionized species (B) but impermeable to the ionized species (BH^+) of the weak basic drug, then the unionized species will distribute between these two compartments until its concentration on each side of the barrier is equal. The equilibrium distribution of the weak basic drug ($pK_a = 5.0$) between the stomach and blood may be represented as shown in Fig. 9.7.

For this particular example, Fig. 9.7 shows that the total relative equilibrium concentrations of weak basic drug in solution in the gastric fluid and

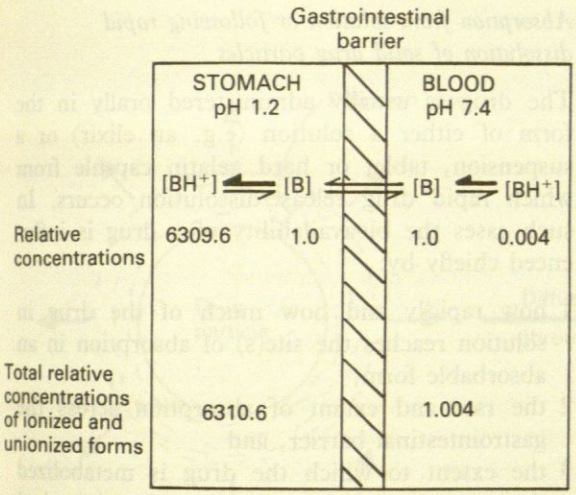


Fig. 9.7 Diagrammatic representation of the equilibrium distribution of a weak basic drug ($pK_a = 5.0$) between the stomach and the blood

the blood are in the ratio of 6310.6 : 1.004, respectively. At equilibrium the total concentration of the weak basic drug in the stomach is approximately 6300 times greater than that in the blood. Thus according to the pH-partition hypothesis, drugs such as weak basic drugs which are predominantly ionized at gastric pHs will be poorly absorbed from the stomach.

Limitations of the pH-partition hypothesis In calculating the distribution of a typical weak acidic drug and a typical weak basic drug between the stomach and blood, it has been assumed that an equilibrium distribution is attained. In practice such an equilibrium will rarely (if ever) be achieved since the stomach and the blood are not closed, static compartments. Drug is removed from the stomach into the intestine by the normal contractions of the stomach. Drug which enters the blood is removed from the site of absorption by circulation of the blood and is removed from the blood by distribution into tissues, by glomerular filtration and by metabolism. However, despite the above criticism, absorption from the stomach, as determined by direct measurements, generally conforms qualitatively to the pH-partition hypothesis. Weak organic acids are relatively well absorbed since they are all almost completely unionized at gastric pHs. Strong organic acids ($pK_a < 1$) which are ionized even in the acid conditions of the stomach are not well absorbed. Weak bases, which are ionized at gastric pHs tend to be only absorbed negligibly but their absorption can be increased, as expected, by raising the pH of the gastric fluid. For more detailed informaiton concerning the influence of pK_a and pH on the gastric absorption of weak basic and acidic drugs the reader should refer to the work of Hogben *et al.* (1957), Schanker *et al.* (1957), Shore *et al.* (1957) and Brodie (1964).

The pH range of the small intestinal fluids is less acid than that of the stomach. Thus, in accordance with the pH-partition hypothesis, the absorption of weak bases generally tends to be favoured over weak acids since a larger fraction of a weak basic drug in solution will be in the unionized form. However, the extent to which a drug exists in the unionized form is not the sole criterion determining the extent of absorption of a drug form the small intestine. For instance, it is found that 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 drug is often higher than its rate of absorption from the stomach even though the drug will be unionized in the stomach. The existence of an effective pH at the surface of the intestinal mucosa (the so-called 'virtual membrane pH' of about pH 5.3), which is lower than the bulk pH in the lumen of the small intestine, has been proposed to account for the unexpectedly high rate of absorption of weak acids from this segment of the gastrointestinal tract. However, it is likely that the larger mucosal surface area available for absorption in the small intestine more than compensates for the low degree of unionization of weak acidic drugs at intestinal pHs.

A further illustration that the absorption of a drug from the gastrointestinal tract is not soley dependent on the drug being unionized, is provided by the observation that a number of drugs are poorly absorbed from certain areas of the gastrointestinal tract despite the fact that their unionized forms predominate in such areas. For instance barbitone (pK_a 7.8), which is almost totally unionized at gastric pHs, is only poorly absorbed from the stomach. However thiopen-

tone, which has a similar pK_a value (i.e. pK_a 7.6) is much better absorbed from the stomach than barbitone. The reason for this difference is that the absorption of drugs is also affected by the lipid solubility exhibited by the unionized form. Thus the unionized form of thiopentone, being more lipid soluble than the unionized form of barbitone, exhibits a greater affinity for the gastrointestinal 'membrane' and is thus better absorbed than barbitone from the stomach. The importance of lipid solubility to the gastrointestinal absorption of barbiturates has been demonstrated by Schanker (1960).

A further observation which cannot be explained by the pH-partition hypothesis is that certain drugs (e.g. quaternary ammonium compounds and tetracyclines) are absorbed readily despite being ionized over the enter pH range of the gastrointestinal tract. For more detailed discussions on the limitations of the pH-partition hypothesis of drug absorption, the reader is referred to articles by Benet (1973), Wagner and Sedman (1973) and Florence and Attwood (1981a).

To summarize, the gastrointestinal absorption characteristics of drugs which are weak electrolytes cannot be explained completely on the basis of their degree of ionization at any particular site of absorption. However, in general, the unionized form of drug in aqueous solution will be absorbed faster than the ionized form of the same drug at any particular site in the gastrointestinal tract. Since the absorptive surface area of the small intestine is so large in comparison to the stomach, this region is accepted as the major site of absorption for both weak acids and bases. Hence the rate of absorption of a given weak electrolyte drug from the small intestine will be greater than form the stomach even if the drug is ionized in the intestine and unionized in the stomach. Despite its limitations, the pH-partition hypothesis remains a useful guide in predicting general trends in drug absorption as a function of pH and pK_a within a specific region of the gastrointestinal tract.

Dissolution rate of drugs

Most drugs are absorbed and reach the systemic circulation by one of the following processes.

Absorption from solution or following rapid dissolution of solid drug particles

The drug is usually administered orally in the form of either a solution (e.g. an elixir) or a suspension, tablet or hard gelatin capsule from which rapid drug release/dissolution occurs. In such cases the bioavailability of a drug is influenced chiefly by:

1 how rapidly and how much of the drug in solution reaches the site(s) of absorption in an absorbable form,
2 the rate and extent of absorption across the gastrointestinal barrier, and
3 the extent to which the drug is metabolized during passage through the gastrointestinal barrier and/or the liver.

Absorption following the slow dissolution of solid drug particles

In those cases where a sparingly soluble drug* is administered in the form of a suspension, a tablet or a hard gelatin capsule, the rate at which the solid drug particles dissolve in the gastrointestinal fluids may be the slowest step in the sequence of events leading to the appearance of intact drug in the systemic circulation (refer back to Fig. 9.1). In such cases, drug absorption and hence bioavailability is dependent on how fast the drug dissolves in the gastrointestinal fluids, i.e. drug bioavailability is dissolution rate limited. Hence factors which influence the rate of dissolution of the drug in the gastrointestinal fluids will also influence the bioavailability of the drug.

Factors influencing the dissolution rates of drugs in the gastrointestinal tract

A schematic outline of the dissolution of a spherical drug particle in the gastrointestinal fluids is shown in Fig. 9.8.

* The term sparingly soluble refers to the solubility exhibited by a drug in the gastric and/or intestinal contents. A drug which was administered as an aqueous solution could still exhibit dissolution rate-limited absorption if the drug was precipitated by the conditions in the gastrointestinal tract and the dissolution rate exhibited by the precipitated drug was sufficiently low.

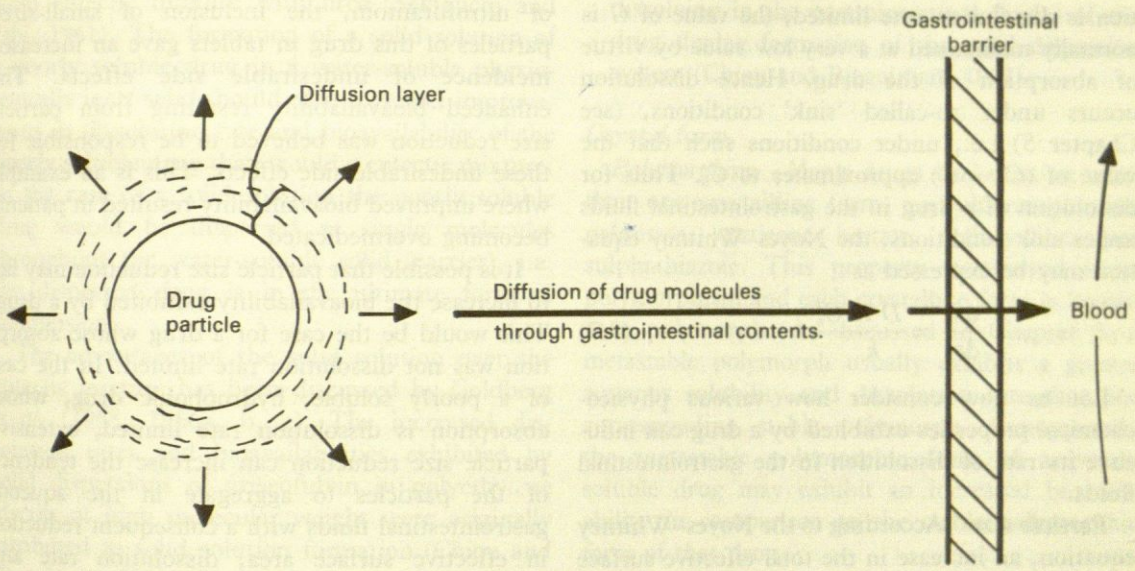


Fig. 9.8 Schematic representation of the dissolution of a drug particle in the gastrointestinal fluids

An equation which describes this process of dissolution is the Noyes–Whitney equation. This equation, which describes the rate of dissolution of spherical drug particles when the dissolution process is diffusion controlled and involves no chemical reaction, may be written

$$\frac{dm}{dt} = \frac{D\,A}{h}\,(C_s - C) \qquad (9.6)$$

where dm/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 the diffusion layer, and C is the concentration of drug in solution in the bulk of the gastrointestinal fluids.

The limitations of the Noyes–Whitney equation in describing the dissolution of drug particles are discussed in Chapter 5. Despite its limitations, the Noyes–Whitney equation serves to illustrate and explain how various physicochemical and physiological factors can influence the rate of dissolution of drugs in the gastrointestinal tract.

Physiological conditions In this context, it is of interest to consider how certain parameters in the Noyes–Whitney equation (and hence the dissolution rate of a drug) may be influenced by the physiological conditions in the gastrointestinal tract. For instance, the diffusion coefficient, D, of the drug in the gastrointestinal fluids may be decreased by the presence of substances which increase the viscosity of the fluids. Hence the presence of food in the gastrointestinal tract may cause a decrease in the dissolution rate of a drug by virtue of reducing the rate of diffusion of drug molecules away from the diffusion layer surrounding each undissolved drug particle. The thickness of the diffusion layer, h, will be influenced by the degree of agitation experienced by each drug particle in the gastrointestinal tract. Hence, an increase in gastric and/or intestinal motility may increase the dissolution rate of a sparingly soluble drug by virtue of 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. 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 rapid dissolution of the drug by virtue of increasing the value of the term $(C_s - C)$. In the case of drugs whose absorp-

tion is dissolution rate limited, the value of C is normally maintained at a very low value by virtue of absorption of the drug. Hence dissolution occurs under so-called 'sink' conditions, (see Chapter 5) i.e., under conditions such that the value of $(C_s - C)$ approximates to C_s. Thus for dissolution of a drug in the gastrointestinal fluids under sink conditions, the Noyes–Whitney equation may be expressed as

$$\frac{dm}{dt} = \frac{D\,A\,C_s}{h} \qquad (9.7)$$

Let us now consider how various physicochemical properties exhibited by a drug can influence its rate of dissolution in the gastrointestinal fluids.

Particle size According to the Noyes–Whitney equation, an increase in the total effective 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 porportional 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 will be the dissolution rate. Particle size reduction is thus likely to result in increased bioavailability provided that absorption of the drug is dissolution rate limited.

A striking example of this effect is provided by griseofulvin. A reduction in 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 by Atkinson *et al.* (1962) to produce an approximate doubling in the amount of griseofulvin absorbed in humans. Duncan *et al.* (1962) also demonstrated that particle size reduction of griseofulvin permitted similar blood levels of this drug to be obtained in humans with half the original dose, i.e. a dose of 0.25 g instead of 0.5 g of griseofulvin.

Other drugs whose bioavailabilities have been enhanced by particle size reduction include sulphadiazine, phenothiazine, tolbutamide, spironolactone, aspirin, nitrofurantoin, digoxin and bishydroxycoumarin (Fincher, 1968; Shaw *et al.*, 1973; Florence *et al.*, 1974; Nash *et al.*, 1974/75). It is interesting to note that in the case of nitrofurantoin, the inclusion of small-sized particles of this drug in tablets gave an increased incidence of undesirable side effects. The enhanced bioavailability resulting from particle size reduction was believed to be responsible for these undesirable side effects. This is an example where improved bioavailability resulted in patients becoming overmedicated.

It is possible that particle size reduction may fail to increase the bioavailability exhibited by a drug. This would be the case for a drug whose absorption was not dissolution rate limited. In the case of a poorly soluble, hydrophobic drug, whose absorption is dissolution rate limited, extensive particle size reduction can increase the tendency of the particles to aggregate in the aqueous gastrointestinal fluids with a consequent reduction in effective surface area, dissolution rate and hence bioavailability. Certain drugs such as penicillin G and erythromycin are unstable in gastric fluids. Thus chemical degradation will be minimized if such a drug does not dissolve readily in gastric fluids. Hence particle size reduction would not only produce an increased rate of drug dissolution in gastric fluid but also an increase in the extent of drug degradation. This would result in a decrease in the amount of intact drug available for absorption from the small intestine.

Solid dispersions A unique approach to presenting a poorly soluble drug in an extremely fine state of subdivision to the gastrointestinal fluids, is the administration of the drug in the form of a solid eutectic mixture. Such a mixture consists of a microcrystalline dispersion of the poorly soluble drug (e.g. sulphathiazole) in a matrix consisting of a physiologically inert, readily water-soluble solid such as urea. The water-soluble solid is often referred to as the 'carrier'. Exposure of this type of solid dispersion system to the gastrointestinal fluids results in dissolution of the water-soluble matrix (carrier). As the matrix dissolves it exposes the dispersed poorly soluble drug, which is in an extremely fine state of subdivision, to the aqueous gastrointestinal fluids. Hence the poorly soluble drug is presented to the aqueous fluids in a form which facilitates its dissolution rate and bioavailability. It is interesting to note that the bioavailability of sulphathiazole was found to be increased when this drug was presented in the form of a

solid eutectic mixture with urea (Sekiguchi and Obi, 1961). The formation of a solid solution of a poorly soluble drug in a water-soluble physiologically inert solid should offer a greater improvement in dissolution rate and bioavailability of the poorly soluble drug than would a eutectic mixture. In the case of a solid solution the poorly soluble drug would be dispersed as single molecules throughout the water-soluble solid (carrier), i.e. the dispersed drug is in the ultimate form of subdivision.

The advantages of the solid solution over the eutectic mixture has been discussed by Goldberg *et al.* (1965, 1966a, b, c). The increased dissolution rates and bioavailabilities exhibited by solid dispersions of griseofulvin in polyethylene glycols of high molecular weight were originally attributed to solid solution formation (Chiou and Riegelman, 1971). However, later work by Chiou (1977) and Kaur *et al.* (1980) suggested that griseofulvin had negligible or very limited solubility in polyethylene glycol dispersion systems. The marked enhancement of dissolution and absorption rate of griseofulvin dispersed in such systems seemed to be primarily the result of the reduced size of the griseofulvin crystals, i.e. griseofulvin was in the form of microcrystals. In addition to this reduction in crystal size, other factors may also contribute to the improved dissolution rate and bioavailability exhibited by a drug presented in the form of a solid dispersion system. These factors are:

1 an increase in aqueous solubility of the drug because of its extremely small particle size,
2 a possible solubilization effect on the drug by the 'carrier' in the diffusion layer surrounding each dissolving drug particle in the gastrointestinal fluids,
3 a reduction or absence of aggregation and agglomeration of the drug particles exposed to the gastrointestinal fluids,
4 excellent wettability and dispersibility of the exposed drug particles in the gastrointestinal fluids (factors 3 and 4 will ensure that the effective surface area of the drug in contact with the gastrointestinal fluids is very large), and
5 possible formation of metastable polymorphic forms (which are more soluble and rapidly dissolving in the gastrointestinal fluids) of the drug during formation of the solid dispersion system (Chiou and Riegelman, 1971).

Crystal form

Polymorphism Many drugs can exist in more than one crystallline 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. As discussed in Chapter 5, a metastable polymorph usually exhibits a greater aqueous solubility and dissolution rate than the corresponding stable polymorph. Consequently the metastable polymorphic form of a poorly soluble drug may exhibit an increased bioavailability in comparison to the stable polymorphic form of that drug.

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. The unstable polymorphic form of chloramphenicol palmitate is too unstable to be included in a dosage form. However, the metastable form is sufficiently stable to permit its incorporation in a dosage form. The mean blood serum levels and urinary excretion rates of chloramphenicol from orally administered suspensions containing varying proportions of the polymorphic forms A and B of chloramphenicol palmitate were studied by Augiar *et al.* (1967). The extent of absorption of chloramphenicol increased as the proportion of polymorphic form B of chloramphenicol palmitate 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 without biological activity. The importance of polymorphism to the gastrointestinal bioavailability of chloramphenicol palmi-

tate is reflected by a limit being placed on the content of the inactive polymorphic form, A, in Chloramphenicol Palmitate Mixture BP.

Amorphous solids In addition to different polymorphic crystalline forms, a drug may exist in an amorphous form. Since the amorphous form is usually more soluble and rapidly dissolving than the corresponding crystalline form(s), the possibility exists that there will be significant differences in the bioavailabilities exhibited by the amorphous and crystalline form(s) of a given poorly soluble drug. A classic example of the influence of amorphous versus crystalline form of a drug on its gastrointestinal bioavailability is provided by the work of Mullins and Macek (1960) on the antibiotic drug, novobiocin. The more soluble and more 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 did not appear to be 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.

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 in the crystal, the lower is the solubility and dissolution rate in a solvent identical to the solvation molecules. Since the solvated and non-solvated forms of a drug usually exhibit differences in solubility and dissolution rates, it is reasonable to expect that such forms may also exhibit differences in bioavailability particularly in the case of a poorly soluble drug which exhibits dissolution rate-limited bioavailability.

Poole *et al.* (1968) showed that the more aqueous soluble and rapidly dissolving anhydrous form of ampicillin was absorbed to a greater extent from hard gelatin capsule or aqueous suspension dosage forms administered to humans or dogs than was the less soluble, slower dissolving trihydrate form of ampicillin. However, it is possible that the observed difference may not have been due entirely to the state of solvation of ampicillin but also due to formulation differences within each type of dosage form tested.

Solubility of the drug in the diffusion layer (salt forms) According to the Noyes–Whitney equation (referred to earlier in this chapter) the dissolution rate of a drug in the gastrointestinal fluids is influenced by the solubility (C_s) that the drug exhibits in the diffusion layer surrounding each dissolving drug particle. In the case of drugs which are weak electrolytes, their overall aqueous solubilities are dependent on pH (see Chapter 5). 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 hence the pH in the diffusion layer surrounding each dissolving drug particle. It should be noted that the pH in the diffusion layer is not necessarily equal to the pH in the bulk of the gastrointestinal fluids. The dissolution rate of a weak acidic drug in gastric fluid (pH 1–3) will be relatively low. This is a consequence of the low solubility (C_s) exhibited by the drug in the diffusion layer because of the low pH in this layer. If the pH in the diffusion layer could be increased, then the solubility (C_s) exhibited by the weak acidic drug in this layer and hence the dissolution rate of the drug in the gastric fluids would be increased even though the bulk pH of the gastric fluids remained at the same low value. The pH of the diffusion layer would be increased if the chemical nature of the weak acidic drug was changed from that of the free acid to a strong alkali salt form of the free acid, e.g. the sodium or potassium salt form of the free acid. The pH in the diffusion layer surrounding each particle of the salt form would be higher (e.g. pH 5–6) than the low bulk pH (pH 1–3) of the gastric fluids because of the neutralizing action of the strong alkali cations (e.g. K^+ or Na^+ ions) present in the diffusion layer (see Fig. 9.9).

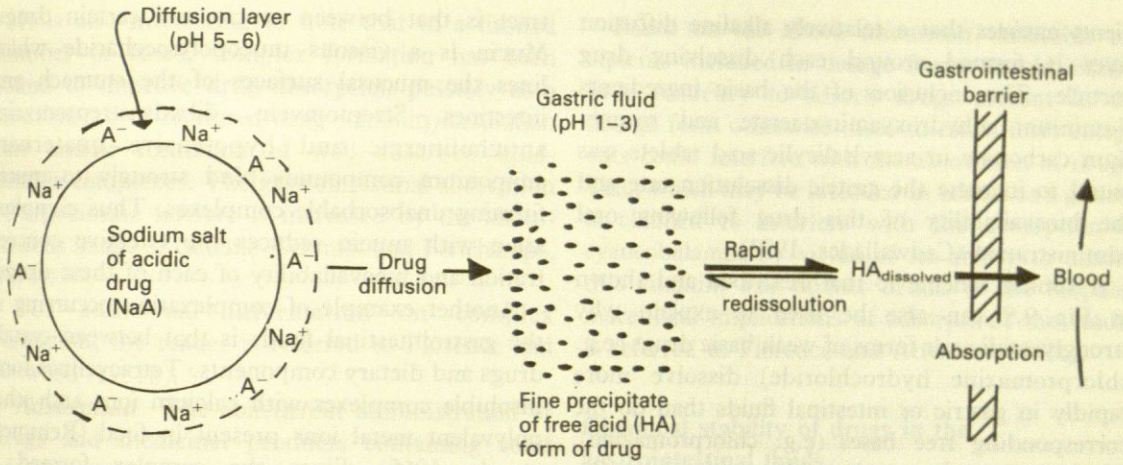


Fig. 9.9 Schematic representation of the dissolution process of a salt form of a weak acidic drug in gastric fluid. (After Cadwallader, 1973)

Since the salt form of the weak 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 of the drug is likely to occur. This will be a result of the lower 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 the gastric fluid, will precipitate out leaving a saturated (or near saturated) solution of free acid in the gastric fluid. It is considered that the precipitated free acid will be in the form of very fine, non-ionized, wetted drug particles which exhibit a very large total effective surface area in contact with the gastric fluids (much larger than would have been obtained if the free acid form of the drug had been administered). 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

1 dissolved drug being absorbed,
2 additional fluid accumulating in the stomach, or
3 the fine precipitated particles being emptied from the stomach into 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 (at the bulk pH conditions prevailing in the stomach).

Thus the oral administration of a solid dosage form containing a strong alkali salt of a weak 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 if the free acid form of the drug itself had been included in the dosage form. This is well illustrated by the work of Nelson *et al* (1962) who showed that 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 more slowly dissolving tolbutamide base produced a much slower rate of decrease of blood sugar level (a consequence of the slower rate of drug absorption) but the lower sugar level was maintained for a longer period of time. It is interesting to note that the gradual but prolonged decrease in blood sugar levels, and not the sharp dip and recovery is the preferred clinical response to oral hypoglycaemic drugs (Cadwallader, 1973).

An alternative method of increasing the dissolution rate of a weak acidic drug in gastric fluid is the inclusion of non-toxic basic substances in a solid dosage form containing the free acid form of the drug. The presence of the basic ingre-

dients ensures that a relatively alkaline diffusion layer is formed around each dissolving drug particle. The inclusion of the basic ingredients aluminium dihydroxyaminoacetate and magnesium carbonate in acetylsalicylic acid tablets was found to increase the gastric dissolution rate and the bioavailability of this drug following oral administration (Cadwallader, 1973).

A similar scheme to that described and shown in Fig. 9.9 can also be used to explain why strongly acidic salt forms of weak basic drugs (e.g. chlorpromazine hydrochloride) dissolve more rapidly in gastric or intestinal fluids than do the corresponding free bases (e.g. chlorpromazine). The presence of strongly acidic cations (e.g. Cl^- ions) in the diffusion layer formed around each dissolving acidic salt particle of drug ensures that the pH in that layer is lower than the bulk pH in either gastric or 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 weak basic drug in a solid dosage form generally ensures that dissolution of the drug occurs in the gastric fluid before the drug passes into the small intestine where the pH conditions are less favourable to the dissolution of weak bases. Hence the use of strong acidic salt forms of weak basic drugs generally ensures that stomach emptying (and not dissolution rate) is the rate-determining step for the absorption of such drugs from the small intestine (Notari, 1980).

For further information concerning the usefulness and limitations of salt forms of drugs, the reader is referred to the review by Berge *et al.* (1977).

Complexation The rate and extent of absorption of a drug depends 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 is one of the principal types of physicochemical interactions which can influence the effective drug concentration in the gastrointestinal fluids. The other types of interaction are adsorption and micellar solubilization. Complexation of a drug may occur within the dosage form and/or in the gastrointestinal fluids.

An example of complexation between a drug and a normal component of the gastrointestinal tract is that between mucin and certain drugs. Mucin is a viscous mucopolysaccharide which lines the mucosal surfaces of the stomach and intestines. Streptomycin, dihydrostreptomycin, anticholinergic and hypotensive quaternary ammonium compounds bind strongly to mucin forming unabsorbable complexes. Thus complexation with mucin reduces the effective concentration and bioavailability of each of these drugs.

Another example of complexation occurring in the gastrointestinal fluids is that between certain drugs and dietary components. Tetracyclines form insoluble complexes with calcium ions and other polyvalent metal ions present in food (Remmers *et al.*, 1965). Since the complex formed is insoluble in the gastrointestinal fluids, that fraction of the antibiotic which has become complexed is unavailable for absorption. Consequently tetracyclines tend to show reduced absorption if taken with milk or dairy products which contain calcium ions. In addition antacids containing Ca^{2+}, Mg^{2+} or Al^{3+} ions and iron preparations (particularly those containing ferrous sulphate) also reduce the bioavailabilities exhibited by tetracyclines via the formation of insoluble complexes.

Tetracyclines also provide an example of drugs whose bioavailabilities are reduced by the formation of poorly soluble complexes with excipients present in dosage forms. The extent of absorption of tetracycline is reduced if dicalcium phosphate is included as a diluent in a tablet or hard gelatin capsule containing this antibiotic. Other examples of complexes which give reduced drug bioavailability are those between amphetamine and sodium carboxymethylcellulose and between phenobarbitone and polyethylene glycol 4000. Complexation between drugs and excipients such as cellulose derivatives, polyols, gums and surfactants probably occurs quite often in liquid dosage forms; complexation is sometimes used to increase drug stability or solubility.

In many cases the drug–excipient complexes are soluble in the gastrointestinal fluids and rapidly dissociate to liberate the 'free' drug. In such cases, little or no effect of complexation on drug absorption is noted. Hence the rate at which a complex dissociates will determine whether absorption of the drug is as rapid and/or complete as in the absence of complex formation.

It is also interesting to note that in a limited number of cases, complex formation has been found to improve drug absorption possibly as a consequence of increased drug solubility/dissolution rate and/or formation of well absorbed lipid-soluble complexes. The gastrointestinal absorption of ergotamine tartrate is increased by the simultaneous intake of caffeine (Schmidt and Fonchamps, 1974).

For additional information on complex formation, the reader is referred to Florence and Attwood (1981b).

Adsorption The concurrent administration of drugs and medicinal products containing solid adsorbents (e.g. antidiarrhoeal mixtures) may result in the adsorbents interfering with the absorption of such drugs from the gastrointestinal tract. The adsorption of a drug onto solid adsorbents such as kaolin, attapulgite or charcoal may reduce the rate and/or extent of drug absorption from the gastrointestinal tract. A decrease in the effective concentration of drug in solution which is available for absorption will occur if a significant proportion of the administered dose of drug is adsorbed to the solid adsorbent at the site(s) of absorption of that drug. A consequence of the reduced concentration of 'free' (i.e. absorbable) drug in solution at the site(s) of absorption will be a reduction in the rate of drug absorption. Whether or not there will also be a reduction in the extent of drug absorption will depend on whether or not the drug–adsorbent interaction is readily reversible. If the adsorbed drug is not readily released from the solid adsorbent in order to replace that 'free' drug which has been absorbed from the gastrointestinal tract, then there will be a reduction in the extent of absorption of that drug.

Examples of drug–adsorbent interactions which give reduced extents of drug absorption are promazine/charcoal and lincomycin/kaopectate. In contrast the adsorption of promazine by the solid adsorbent, attapulgite, only produces a reduction in the rate but not extent of absorption of promazine in humans. This is because the adsorbed promazine is readily released from attapulgite in order to replace that 'free' promazine which has been absorbed from the gastrointestinal tract (Sorby, 1965).

Based on the above discussion, insoluble excipients included in dosage forms should exhibit little tendency to adsorb drugs present in the dosage form otherwise these so-called inert excipients could interfere with the absorption of drugs. Talc, which may be included in tablets as a glident is claimed to interfere with the absorption of cyancobalamin by virtue of its ability to adsorb this vitamin. For further details of the biopharmaceutical implications of adsorption, the reader is referred to Florence and Attwood (1981c).

Chemical stability of drugs in the gastrointestinal fluids

Poor bioavailability usually results if a drug undergoes extensive acid or enzyme hydrolysis in the gastrointestinal tract. For instance, both penicillin G and erythromycin are susceptible to acid-catalysed hydrolysis and the extent of absorption of these drugs is thus influenced by the time that they reside in the stomach and on the gastric pH. When a drug is unstable in gastric fluid, its extent of degradation would be minimized (and hence its bioavailability would be improved) if it exhibited minimal dissolution in gastric fluid and 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 exhibited by erythromycin from the gastrointestinal tract. Enteric coating of tablets containing the free base, erythromycin, is one method which 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. Hence the drug is not liberated until the coated tablet reaches the small intestine (further details concerning enteric coating may be found later in this chapter and in Chapters 18 and 40). However, despite the protection offered to susceptible drugs from gastric fluid by enteric coating, the bioavailability exhibited by drugs from enteric-coated tablets is potentially more variable than from any other type of dosage form (see later in this chapter).

Pro-drugs 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 derivations of the

parent drugs. These derivatives (called pro-drugs) 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 yeilding the free base, erythromycin, which is absorbed. In the case of erythromycin estolate, which is the lauryl sulphate salt of the ester erythromycin propionate, the improved bioavailability exhibited by this pro-drug is achieved in two ways. First, the poorly soluble lauryl sulphate salt remains undissolved and is thus not degraded during its passage through the stomach. Once in the small intestine, the lauryl sulphate salt dissolves and dissociates to give the ester, erythromycin propionate. Second, erythromycin propionate by virtue of its increased lipid solubility is better absorbed than the free base erythromycin. Once present in the blood, erythromycin propionate hydrolyses to liberate erythromycin, the active form of the antibiotic.

DOSAGE FORM FACTORS INFLUENCING DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

The rate and/or extent of absorption of a drug from the gastrointestinal tract has been shown to be influenced by many physiological factors associated with this route of drug administration and by many physicochemical properties associated with the drug itself. The bioavailability of a drug administered in a dosage form can also be influenced by factors associated with the formulation and production of the dosage form. This aspect of biopharmaceutics will now be considered.

Influence of excipients

Drugs are almost never administered alone to patients but in the form of dosage forms. A dosage form generally consists of a drug (or drugs) together with a varying number of other substances (called excipients) that have been 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. Excipients are also referred to as adjuvants, additives or inert ingredients. Although excipients were considered to be inert in that they, themselves, should not exert any therapeutic or biological action or modify the biological action of the drug present in the dosage form, it is now recognized that excipients can potentially influence the rate and/or extent of absorption of the drug. For instance, the potential influence of excipients on drug bioavailability has already been implicated by virtue of the formation of poorly soluble, non-absorbable drug–excipients complexes between tetracyclines and dicalcium phosphate, amphetamine and sodium carboxymethylcellulose and phenobarbitone and polyethylene glycol 4000.

Diluents

A dramatic 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 being changed in sodium phenytoin capsules (Tyler *et al.*, 1970). 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 has 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 of such capsules, the accompanying improved bioavailability resulted in higher plasma levels of phenytoin. In many patients, the higher plasma levels exceeded the maximum safe concentration for phenytoin and produced toxic side effects. This case is also discussed in Chapter 19.

Surfactants

Surfactants are often employed as emulsifying agents, solubilizing agents, suspension stabilizers or as wetting agents in dosage forms. However, surfactants in general cannot be assumed to be 'inert' excipients since they have been shown to be capable of either increasing, decreasing or exerting no effect on the transfer of drugs across biological membranes. In addition, surfactants might also be able to produce significant changes in the biological activity of drugs by perhaps exerting an influence on drug metabolizing enzymes or on the binding of drugs to receptor proteins (Florence, 1981).

Many studies aimed at elucidating the mechanisms by which surfactants can influence drug absorption have involved simple animal models of drug absorption such as the gill membrane of the goldfish, the isolated rabbit gastric mucosa and the ligated gastric fundic pouch of the dog. Although it is not clear to what extent such animal studies can be extrapolated to humans, some potential ways in which surfactants might influence drug absorption from the gastrointestinal tract in humans are as follows. Surfactant monomers can potentially disrupt the integrity and function of a membrane. Hence, such a membrane-disrupting effect would tend to enhance drug penetration and hence absorption across the gastrointestinal barrier. Inhibition of drug absorption may occur as a consequence of a drug being incorporated into surfactant micelles. If such surfactant micelles are not absorbed, which appears to be usually the case, then solubilization of a drug may result in a reduction of the concentration of 'free' drug in solution in the gastrointestinal fluids which 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 which are normally soluble in the gastrointestinal fluids, i.e. in the absence of surfactant. However, 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 drug dissolution and hence absorption. Very high concentrations of surfactant in excess of that required to solubilize the drug could decrease drug absorption by decreasing the chemical potential of the drug.

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 more effectively and 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 which 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 drugs.

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 (Prescott *et al.*, 1970).

It is also possible that surfactants could influence drug absorption by exerting a physiological action of their own on the gastrointestinal tract, for instance by altering the gastric residence time of a drug.

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 over-riding 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 on the type of biological membrane involved. Reviews on the effects of surfactants on drug absorption are provided by Gibaldi (1970), Gibaldi and Feldman (1970) and Florence (1981).

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 but many sugars serve the dual function of sweetening and viscosity-enhancing agents.

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 which is available for drug absorption (see earlier in this chapter). The administration of viscous solutions or suspensions may produce an increase in viscosity of the gastrointestinal contents. Such an increase in viscosity could lead to the following general effects:

1 a decrease in gastric emptying rate, i.e. an increase in gastric residence time,
2 a decrease in intestinal motility,
3 a decrease in dissolution rate of the drug, and
4 a decrease in the rate of movement of drug molecules to the absorbing membrane.

Normally, effect 3 would not be applicable to solution dosage forms unless dilution of the administerted solution in the gastrointestinal fluids caused precipitation of the drug. Levy and Jusko (1965) suggested that effects 1, 2 and 4 would lead to a decrease in the rates of absorption of drugs from viscous solutions. Studies in which increased viscosity was found to produce reductions in the rates of absorption of drugs from solutions include the effects of sucrose solutions on the induction time of phenobarbitone sodium (Malone *et al.*, 1960), methylcellulose on the absorption of solutions of sodium salicylate (Davison *et al.*, 1961) and salicylic acid (Levy and Jusko, 1965), different gums on the urinary excretion rate of sodium salicylate solution (Bachynsky *et al.*, 1976) and sodium alginate on the bioavailability of phenolsulphonphathalein (Ashley and Levy, 1973).

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. Thus the observation by Seager (1968) that methylcellulose reduced the rate and extent of absorption of nitrofurantoin from aqueous suspensions of this drug could have been due to effects 1, 2, 3 and 4. In addition, nitrofurantoin may form complexes with methylcellulose which could also tend to reduce the absorption of this drug (Shah and Sheth, 1976).

The potential absorption-enhancing effects of increased viscosity have been considered by Barzegar-Jalali and Richards (1979). An extended gastric residence time, or a slower intestinal transit time produced by an increase in viscosity, would allow a longer period in which drug dissolution could occur in the gastrointestinal tract and this could lead to an increase in the extent of absorption of a drug from a suspension. In addition, the increase in gastric residence time caused by an increase in viscosity could also enhance the amount of absorption of drugs with pK_a values that permit absorption of those drugs from the stomach. Similarly an increase in intestinal transit time would favour an increase in the amount of absorption of the majority of drugs since the intestine is the optimal site of absorption of most drugs. The net effect of increased viscosity on the absorption of a particular drug from the gastrointestinal tract will thus depend on whether or not the absorption-enchancing effects outweigh the absorption-reducing effects of increased viscosity. It is interesting to note that the absorption-enhancing effects of increased viscosity appeared to outweigh the absorption-reducing effects in studies on the effects of various macromolecular

suspending agents on the bioavailabilities of aspirin and salicylic acid in the rabbit (Barzegar-Jalali and Richards, 1979).

The above examples serve to illustrate that so-called 'inert' excipients can often markedly influence the bioavailabilities of drugs administered in dosage forms via the gastrointestinal route.

Influence of the type of dosage form

In addition to the amount and physicochemical nature of each so-called 'inert' excipient included in a formulation, 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 suspension, a hard gelatin capsule or a tablet can influence the rate and/or extent of absorption of that drug from the gastrointestinal tract. The type of oral dosage form will influence the number of possible intervening steps between administration of the dosage form 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. A simplified scheme depicting this is shown in Fig. 9.10.

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 drug absorption and the greater will be the likelihood of that type of dosage form reducing the bioavailability 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 > hard gelatin capsules > uncoated tablets > coated tablets. Whilst the number of intervening steps between administration and the appearance of a drug in solution in the gastrointestinal fluids may be equal in the case of the hard gelatin capsule and tablet dosage forms (see Fig. 9.10), the fine particles of drug in a hard gelatin capsule are not normally subjected to high compression forces and the subsequent reduction in effective drug surface area as a consequence of the tablet manufacturing process and to the difficulty in regenerating well dispersed drug particles after administration. Hence, particularly in the case of a poorly soluble drug, the rate of appearance of a given drug in solution in the gastrointestinal fluids is likely to be slower from a tablet than from a hard gelatin capsule. Although the above

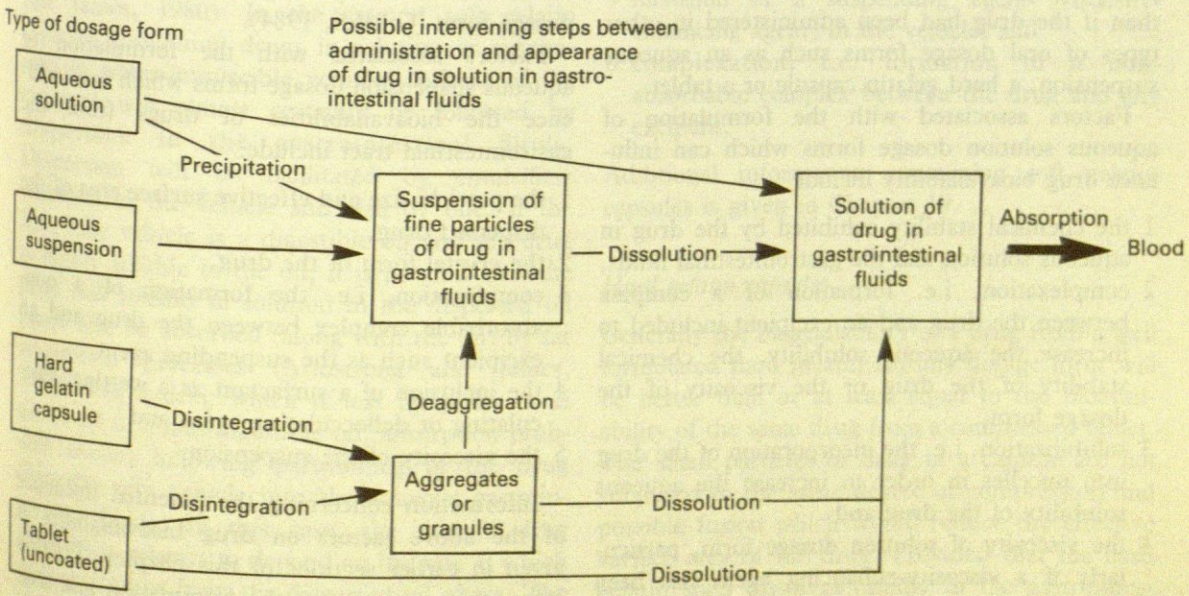


Fig. 9.10 Schematic outline of the influence of the dosage form on the appearance of a drug in solution in the gastrointestinal fluids

ranking of the types of oral dosage form is not universal, it does provide a useful guideline. In general solution and suspension dosage forms are 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 which 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 (Rees, 1974). However, dilution of an aqueous solution of a poorly soluble drug (whose aqueous solubility has been increased by means of formulation techniques such as cosolvency, complex formation or solubilization) in the gastric fluids can result in precipitation of the drug. 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. However, in most cases, the extremely fine nature of the precipitate permits a more rapid rate of dissolution than if the drug had been administered in other types of oral dosage forms such as an aqueous suspension, a hard gelatin capsule or a tablet.

Factors associated with the formulation of aqueous solution dosage forms which can influence drug bioavailability include

1 the chemical stability exhibited by the drug in aqueous solution and the gastrointestinal fluids,
2 complexation, i.e. 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,
3 solubilization, i.e. the incorporation of the drug into micelles in order to increase the aqueous solubility of the drug and
4 the viscosity of solution dosage form, particularly if a viscosity-enhancing agent has been included.

Information concerning the potential influence of each of the above factors on drug bioavailability from the gastrointestinal tract is given in earlier sections of this chapter. Further details concerning the formulation of oral solution dosage forms are given in Chapter 14.

Aqueous suspensions

An aqueous suspension is a useful dosage form for administering an insoluble or poorly aqueous soluble drug. Usually the absorption of a drug from this type of dosage form is dissolution rate limited. Oral administration of a dose of an aqueous suspension results in a large total surface area of dispersed drug being immediately presented to the gastrointestinal fluids. This large surface area facilitates dissolution and hence absorption of the drug. In contrast to hard gelatin capsule and tablet dosage forms, dissolution of all drug particles commences immediately on dilution of the dose of 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 time lag. Thus a well formulated, finely subdivided aqueous suspension is regarded as being an efficient oral drug delivery system, second in efficiency only to the solution-type dosage form (Gibaldi, 1984).

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

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

Information concerning the potential influence of the above factors on drug bioavailability is given in earlier sections of this chapter. Further information concerning the formulation and uses of suspensions as dosage forms is given in Chapter 15.

Soft gelatin capsules

Soft gelatin capsules combine the convenience of a unit dosage form with the potentially rapid drug absorption associated with aqueous solution and suspension types of dosage forms (Rees, 1974). Drugs encapsulated in soft gelatin capsules for peroral administration are dissolved or dispersed in a non-toxic, non-aqueous vehicle. Such vehicles may be water immiscible (i.e. lipophilic) or water miscible (i.e. hydrophilic). Vegetable oils are popular water-immiscible vehicles whilst polyethylene glycols and certain non-ionic surfactants (e.g. polysorbate 80) are employed as water-miscible vehicles.

Release of the contents of a soft gelatin capsule 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 a solution or a fine suspension in the gastrointestinal fluids. The drug is thus liberated in a form which is conducive to rapid absorption. Many poorly water-soluble drugs have been found to exhibit greater bioavailabilities from soft gelatin capsules containing water-miscible vehicles than from aqueous suspensions, hard gelatin capsules or tablets (Armstrong and James, 1980). In the case of soft 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 will be facilitated by emulsifiers included in the vehicle and also by bile. 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 (Armstrong and James, 1980). For a drug which 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 a drug which is suspended in an oily vehicle, drug release may involve dissolution in the vehicle, diffusion to the oil/aqueous interface, and partition across the interface. It is also possible that release could involve the passage of solid drug particles across the oil/aqueous interface followed by dissolution in the gastrointestinal fluids. This latter mechanism has been proposed by de Blaey and Polderman (1980) as a model for drug release from lipophilic suppository vehicles containing suspended drug.

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

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

Additional information concerning soft gelatin capsules is given in Chapter 19.

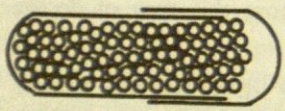
Hard gelatin capsules

Generally the bioavailability of a drug from a well formulated hard gelatin capsule dosage form will be better than or at least equal to the bioavailability of the same drug from a compressed tablet. The small particles of drug in a capsule are not subjected to the same degree of compression and possible fusion which would reduce the effective surface area of the drug. Provided that the hard gelatin shell dissolves rapidly in the gastrointestinal fluids and the encapsulated mass disperses rapidly and efficiently, a relatively large effective

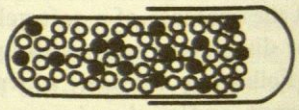
surface area of drug will be exposed to the gastrointestinal fluids thereby facilitating drug dissolution. However, it is incorrect to assume that because a drug formulated as a hard gelatain capsule is in a finely divided form surrounded by a water-soluble shell, no bioavailability problems can occur (Rees, 1974). The overall rate of dissolution of drugs from capsules appears to be a complex function of the rates of different processes such as:

1 the dissolution rate of the gelatin shell,
2 the rate of penetration of the gastrointestinal fluids into the encapsulated mass,
3 the rate at which the mass deaggregates (i.e. disperses) in the gastrointestinal fluids, and
4 the rate of dissolution of the dispersed drug particles (Finholt, 1974).

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 which are poorly soluble and hydrophobic. Figure 9.11 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 disper-

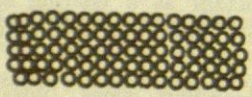


Hard gelatin capsule containing only hydrophobic drug particles

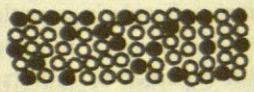


Hard gelatin capsule containing hydrophobic drug particles (o) and hydrophilic diluent particles (•)

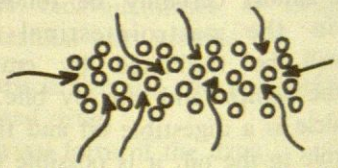
In gastrointestinal fluids, hard gelatin capsule shell dissolves, thereby exposing contents to fluids



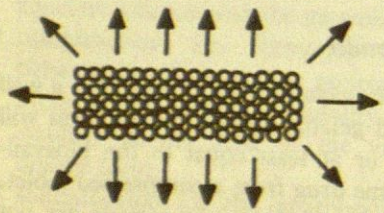
Contents remain as a capsule-shaped plug. Hydrophobic nature of contents impedes penetration of gastrointestinal fluids



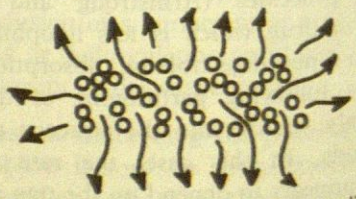
Particles of hydrophilic diluent dissolve in gastrointestinal fluids leaving a porous mass of drug



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

sion and subsequent dissolution of the drug in these fluids. However, the diluent should exhibit no tendency to adsorb or complex with the drug since either can impair absorption from the gastrointestinal tract. For instance, the bioavailability of tetracycline is reduced if dicalcium phosphate is included as the diluent in capsules of this antibiotic. A poorly soluble, non-absorbable calcium–tetracycline complex is formed as the contents of the capsule dissolve in the gastrointestinal fluids.

Magnesium stearate is commonly included as a lubricant for the capsule-filling operation. Its hydrophobic nature often retards liquid penetration so that a capsule-shaped plug often remains after the shell has dissolved in the gastrointestinal fluids, especially when the contents have been machine-filled as a consolidated plug (Rees, 1974). However, this effect can usually be overcome by the simultaneous addition of a wetting agent (i.e. a water-soluble surfactant) and a hydrophilic diluent to the contents.

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 (Newton, 1972). 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. Granulation can increase the dissolution rate of a micronized hydrophobic drug by increasing the liquid permeability of the encapsulated mass (Newton, 1972).

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

1 surface area and particle size of drug (particularly the effective surface area exhibited by the drug in the gastrointestinal fluids),
2 use of the salt form of a drug in preference to the parent weak acid or base,
3 crystal form of the drug,
4 the chemical stability of the drug (in the dosage form and gastrointestinal fluids),
5 the natures and quantities of the diluent, lubricant and wetting agent,
6 drug–excipient interactions (e.g. adsorption, complexation),
7 the type and conditions of the filling process,
8 the packing density of the capsule contents,
9 the composition and properties of the capsule shell (including enteric capsules), and
10 interactions between the capsule shell and contents.

Further information concerning the hard gelatin capsule as a dosage form is given in Chapter 19.

Tablets

Uncoated tablets When a drug is formulated as a compressed tablet, there is an enormous reduction in the effective surface area of the drug due to the granulation and compression processes involved in tablet making (see Chapters 37 and 39). These processes also necessitate the addition of excipients which themselves may alter the release of a drug from a tablet. Many bioavailability problems are associated with this reduction in effective surface area of drug and with the problems of generating a fine, well dispersed suspension of drug particles in the gastrointestinal fluids following administration of a tablet. Since 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 drug release, dissolution and absorption is 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 18).

A diagrammatic representation of the disintegration and dissolution steps that normally occur with a tablet prior to drug absorption are shown in Fig. 18.1. 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 drug 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 of the drug. The dissolution rate is probably comparable to that of a fine, well dispersed suspension of drug (Gibaldi 1984). Disintegration of a tablet into primary drug particles is thus important since it ensures that a large effective surface area of poorly soluble drug is generated in order to facilitate dissolution and subsequent absorption of the drug (Wells and Rubinstein, 1976).

However, simply because a tablet disintegrates rapidly does not necessarily guarantee that the liberated primary drug particles will dissolve rapidly in the gastrointestinal fluids and that the rate and extent of drug absorption will be adequate. In the case of poorly soluble drugs, the rate-controlling step for drug absorption 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 (Finholt, 1974). These factors include:

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

Since 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.

Further information on formulation and release of drugs from tablets is given in Chapter 18.

Coated tablets The most common of the various types of coated tablets are sugar-coated and film-coated tablets. The presence of a coating around a tablet presents a physical barrier between the tablet core and the gastrointestinal fluids. Hence coated tablets 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 (see Chapter 40). This sealing coat serves to protect the tablet core and its contents from the aqueous coating 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 dissolve readily in gastric fluid, may be added to the sealer coat in order to reduce the 'barrier' effect of this coat to rapid drug release.

The coating of a tablet core by a thin film coat of a water-soluble polymer such as hydroxy-