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

Influence of the type of dosage form

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

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

DOSAGE FORM FACTORS INFLUENCING BIOAVAILABILITY

Introduction

The rate and/or extent of absorption of a drug from the gastrointestinal tract have been shown to be
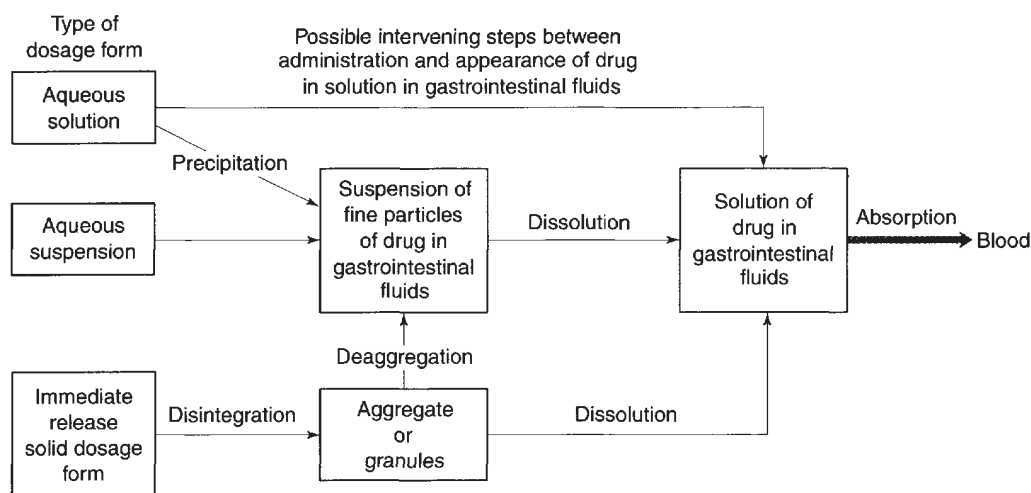

Fig. 17.3 Schematic outline of the influence of the dosage form on the appearance of drug in solution in the gastrointestinal tract.

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

Aqueous solutions

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

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

- The chemical stability exhibited by the drug in aqueous solution and the gastrointestinal fluids;

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

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

Aqueous suspensions

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

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

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

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

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

Liquid-filled capsules

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

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

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

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

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

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

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

Powder-filled capsules

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

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

Hard gelatin capsule containing only hydrophobic drug particles

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

In gastrointestinal fluids, hard gelatin capsule shell dissolves, thereby exposing contents to fluids
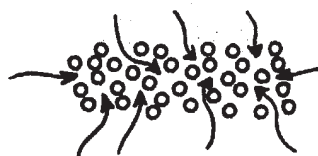
Contents remain as a capsule-shaped plug. Hydrophobic nature of contents impedes penetration of gastrointestinal fluids
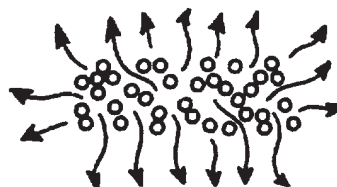
Particles of hydrophilic diluent dissolve in gastrointestinal fluids leaving a porous mass of drug

Gastrointestinal fluids can penetrate porous mass
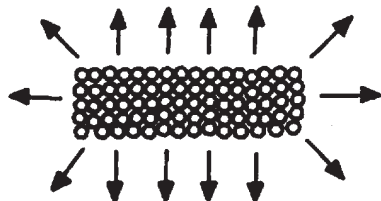
Dissolution of drug occurs only from surface of plug-shaped mass. Relatively low rate of dissolution

Effective surface area of drug and hence dissolution rate is increased

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

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

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

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

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

Tablets

Uncoated tablets   Tablets are the most widely used dosage form. When a drug is formulated as a compressed tablet there is an enormous reduction in the effective surface area of the drug, owing to the granulation and compression processes involved in tablet making. These processes necessitate the addition of excipients, which serve to return the surface area of the drug back to its original precompressed state. Bioavailability problems can arise if a fine, well dispersed suspension of drug particles in the gastrointestinal fluids is not generated following the

administration of a tablet. Because the effective surface area of a poorly soluble drug is an important factor influencing its dissolution rate, it is especially important that tablets containing such drugs should disintegrate rapidly and completely in the gastrointestinal fluids if rapid release, dissolution and absorption are required. The overall rate of tablet disintegration is influenced by several interdependent factors, which include the concentration and type of drug, diluent, binder, disintegrant, lubricant and wetting agent, as well as the compaction pressure (see Chapter 27).

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

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

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

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

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

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

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

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

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

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

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

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

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

Influence of excipients for conventional dosage forms