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Pharmaceutics

The Science of Dosage Form Design

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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 (•)

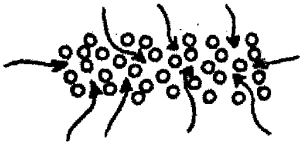
In gastrointestinal fluids, hard gelatin capsule shell dissolves, thereby exposing contents to fluids



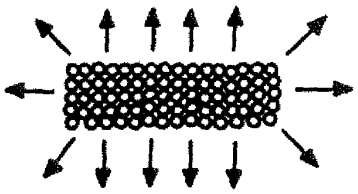
Contents remain as a capsule-shaped plug. Hydrophobic nature of contents impedes penetration of gastrointestinal fluids



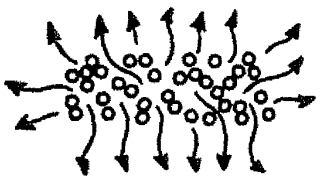
Particles of hydrophilic diluent dissolve in gastrointestinal fluids leaving a porous mass of drug



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.

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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

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