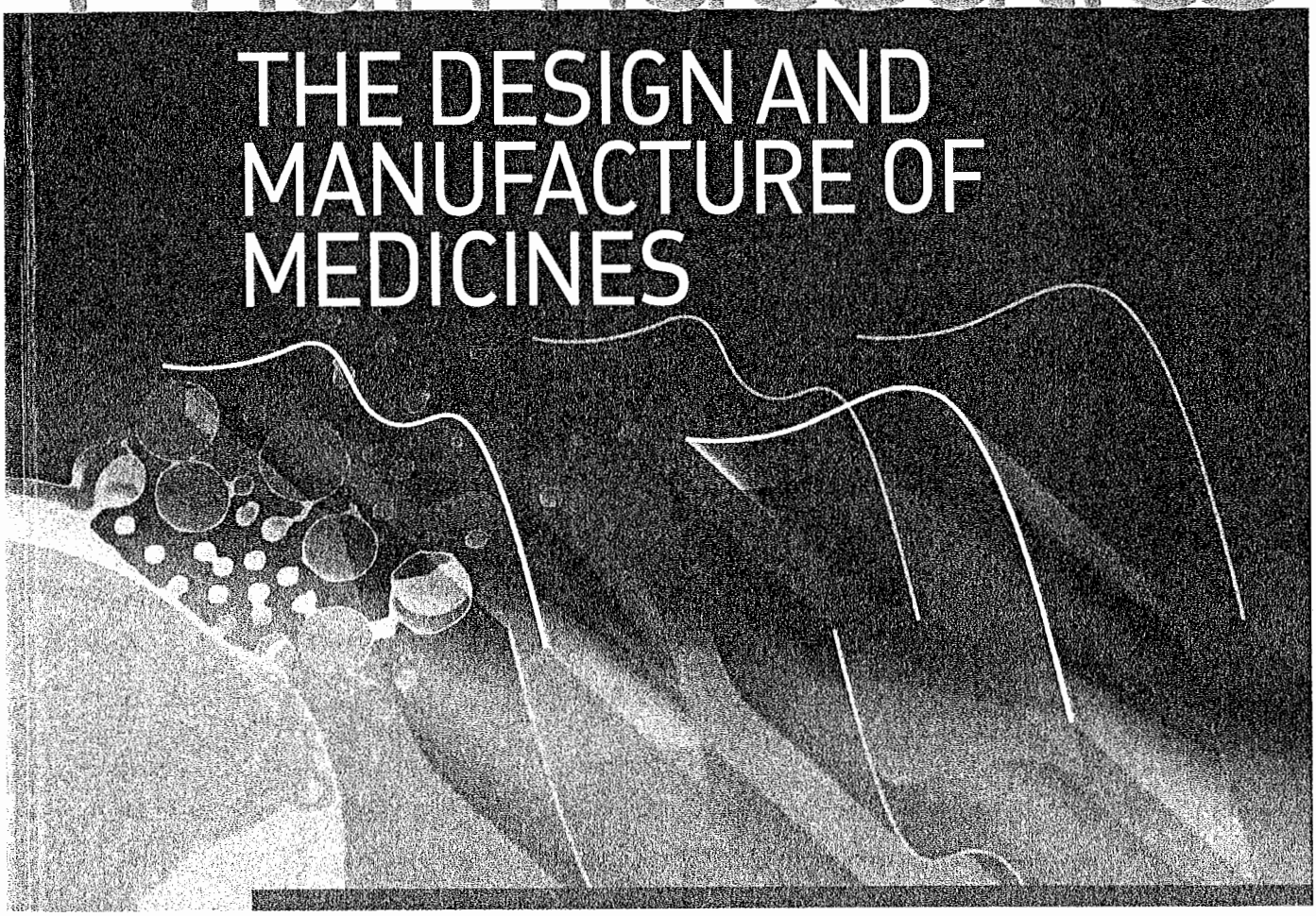
THIRD EDITION

Aulton's Pharmaceutics

THE DESIGN AND MANUFACTURE OF MEDICINES



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Bioavailability – physicochemical and dosage form factors

M. Ashford

CHAPTER CONTENTS

INTRODUCTION

As discussed in Chapter 20, the rate and extent of absorption are influenced by the physiological factors associated with the structure and function of the GI tract. This chapter discusses the physicochemical properties of the drug and dosage form factors that influence bioavailability. For a drug to be absorbed, it needs to be in solution and to be able to pass across the membrane. In the case of orally administered drugs, this is the gastrointestinal epithelium. The physicochemical properties of the drug that will influence its passage into solution and transfer across membranes include its dissolution rate, pK_a, lipid solubility, chemical stability and complexation potential.

PHYSICOCHEMICAL FACTORS INFLUENCING BIOAVAILABILITY

Dissolution and solubility

Solid drugs need to dissolve before they can be absorbed. The dissolution of drugs can be described by the Noyes–Whitney equation (Eqn 21.1). This equation, first proposed in 1897, describes the rate of dissolution of spherical particles when the dissolution process is diffusion controlled and involves no chemical reaction:

$$dC/dt = \frac{DA(C_S - C)}{h} \qquad (21.1)$$

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

The limitations of the Noyes–Whitney equation in describing the dissolution of drug particles are discussed

Table 21.1 Physicochemical and physiological factors affecting drug dissolution in the gastrointestinal tract (adapted from Dressman et al 1998)

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

in Chapter 2. Despite these limitations, the equation serves to illustrate and explain how various physicochemical and physiological factors can influence the rate of dissolution in the gastrointestinal tract. These are summarized in Table 21.1 and are discussed in more detail in the next section.

Figure 21.1 illustrates the dissolution of a spherical drug particle in the gastrointestinal fluids.

Physiological factors affecting the dissolution rate of drugs

The environment of the gastrointestinal tract can affect the parameters of the Noyes–Whitney equation (Eqn 21.1) and hence the dissolution rate of a drug. For instance, the diffusion coefficient, D, of the drug in the gastrointestinal fluids may be decreased by the presence of substances that increase the viscosity of the fluids. Hence the presence of food in the gastrointestinal tract may cause a decrease in dissolution rate of a drug by reducing the rate of diffusion of the drug molecules away from the diffusion layer surrounding each undissolved drug particle. Surfactants in gastric juice and bile salts will affect both the wettability of the drug, and hence the effective surface area, A, exposed to gastrointestinal fluids, and the solubility of the drug in the gastrointestinal fluids via micellization. The thickness of the diffusion layer, h, will be influenced by the degree of agitation experienced by each drug particle in the gastrointestinal tract. Hence an increase in gastric and/or intestinal motility may increase the dissolution rate of a sparingly soluble drug by decreasing the thickness of the diffusion layer around each drug particle.

The concentration, C, of drug in solution in the bulk of the gastrointestinal fluids will be influenced by such factors as the rate of removal of dissolved drug by absorption

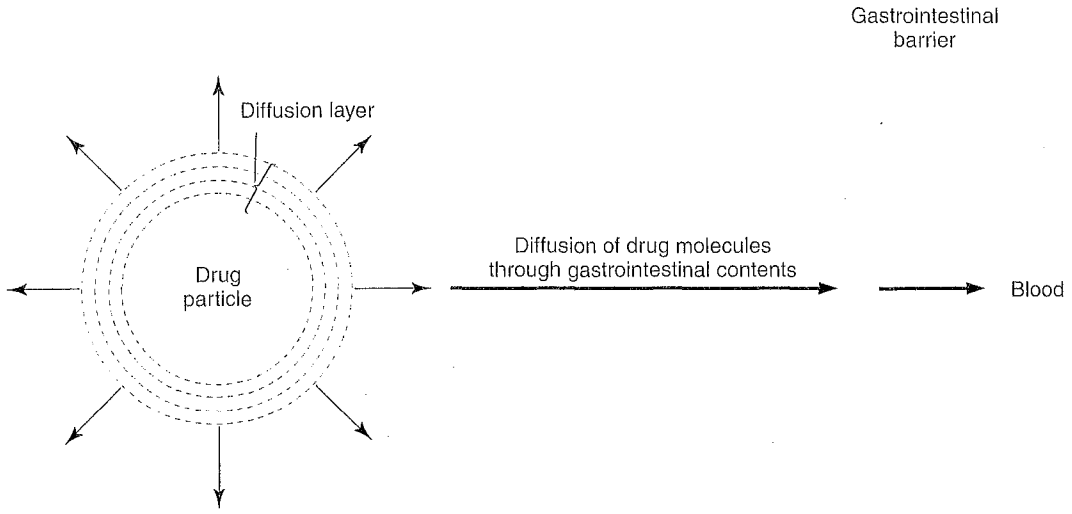

Fig. 21.1 Schematic representation of the dissolution of a drug particle in the gastrointestinal fluids.

through the gastrointestinal–blood barrier and by the volume of fluid available for dissolution, which in turn will be dependent on the position of the drug in the gastrointestinal tract and the timing with respect to meal intake. In the stomach, the volume of fluid will be influenced by the intake of fluid in the diet. According to the Noyes–Whitney equation, a low value of C will favour more rapid dissolution of the drug by virtue of increasing the value of the term $(C_S - C)$. In the case of drugs whose absorption is dissolution rate limited, the value of C is normally kept very low by absorption of the drug. Hence dissolution occurs under sink conditions; that is, under conditions such that the value of $(C_S - C)$ approximates to C_S. Thus for the dissolution of a drug from the gastrointestinal tract under sink conditions, the Noyes–Whitney equation can be expressed as:

$$dC/dt = \frac{DAC_S}{h} \qquad (21.2)$$

Drug factors affecting dissolution rate

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

Surface area and particle size According to Eqn 21.1, an increase in the total surface area of drug in contact with the gastrointestinal fluids will cause an increase in dissolution rate. Provided that each particle of drug is intimately wetted by the gastrointestinal fluids, the effective surface area exhibited by the drug will be directly proportional to the particle size of the drug. Hence the smaller the particle size, the greater the effective surface area exhibited by a given mass of drug and the higher the dissolution rate. Particle size reduction is thus likely to result in increased bioavailability, provided that the absorption of the drug is dissolution rate limited.

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

Examples of drugs where a reduction in particle size has been shown to improve the rate and extent of oral absorption and hence bioavailability are shown in Table 21.2. Such improvements in bioavailability can result in an increased incidence of side-effects; thus for certain drugs it is important that the particle size is well controlled, and many pharmacopoeia state a requirement for particle size.

Table 21.2 Examples of drugs where a reduction in particle size has led to improvements in bioavailability

Drug	Therapeutic class
Digoxin	Cardiac glycoside
Nitrofurantoin	Antifungal
Medroxyprogesterone	Hormone acetate
Danazol	Steroid
Tolbutamide	Antidiabetic
Aspirin	Analgesic
Sulfadiazine	Antibacterial
Naproxen	Non-steroidal antiinflammatory
Ibuprofen	Non-steroidal antiinflammatory
Phenacetin	Analgesic

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

As well as milling with wetting agents, the effective surface area of hydrophobic drugs can be increased by the addition of a wetting agent to the formulation. The presence of polysorbate 80 in a fine suspension of phenacetin (particle size less than 75 µm) greatly improved the rate and extent of absorption of the phenacetin in human volunteers compared to the same-size suspension without a wetting agent. Polysorbate 80 helps by increasing the wetting and solvent penetration of the particles and by minimizing aggregation of suspended particles, thereby maintaining a large effective surface area. Wettability effects are highly drug specific.

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

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