hence charge, lipid solubility, molecular weight, the number of hydrogen bonds in the molecule and its chemical stability.

Drug dissociation and lipid solubility

The dissociation constant and lipid solubility of a drug and the pH at the absorption site often influence 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 absorption is embodied in the pH-partition hypothesis of drug absorption, first proposed by Overton in 1899. Although it is an oversimplification of the complex process of absorption, the pH-partition hypothesis still provides a useful framework for understanding the transcellular passive route of absorption, which is that favoured by the majority of drugs.

pH-partition hypothesis of drug absorption. According to the pH-partition hypothesis, the gastrointestinal epithelium acts as a lipid barrier to drugs which are absorbed by passive diffusion, and those that are lipid soluble will pass across the barrier. As most drugs are weak electrolytes, the unionized form of weakly acidic or basic drugs (i.e. the lipid-soluble form) will pass across the gastrointestinal epithelium, whereas it is impermeable to the ionized (i.e. poorly lipid-soluble) form of such drugs. Consequently, according to the pH-partition hypothesis, the absorption of a weak electrolyte will be determined chiefy by the extent to which the drug exists in its unionized form at the site of absorption.

The extent to which a weakly acidic or basic drug ionizes in solution in the gastrointestinal fuid may be calculated using the appropriate form of a Henderson-Hasselbalch equation (discussed further in Chapter 3). For a weakly acidic drug having a single ionizable group (e.g. aspirin, phenobarbital, ascorbic acid (vitamin C)), the equation takes the form of:

$$\log\frac{[A^-]}{[HA]} = pH - pK_a \qquad (20.5)$$

This is a slightly rearranged form of Equation 3.16 where pK_a is the negative logarithm of the acid dissociation constant of the drug, and [HA] and [A^-] are the respective concentrations of the unionized and ionized forms of the weakly acidic drug, which are in equilibrium and in solution in the gastrointestinal fluid. pH refers to the pH of the environment of the ionized and unionized species, i.e. the gastrointestinal fuids.

For a weakly basic drug possessing a single ionizable group (e.g. chlorpromazine, erythromycin, morphine), the analogous equation is:

$$\log\frac{[BH^+]}{[B]} = pK_a - pH \qquad (20.6)$$

This is a slightly rearranged form of Equation 3.19 where [BH^+] and [B] are the respective concentrations of the ionized and unionized forms of the weak basic drug, which are in equilibrium and in solution in the gastrointestinal fuids.

Therefore, according to these equations, a weakly acidic drug, pK_a 3.0, will be predominantly (98.4%) unionized in gastric fuid at pH 1.2 and almost totally (99.98%) ionized in intestinal fuid at pH 6.8, whereas a weakly basic drug, pK_a 5, will be almost entirely (99.98%) ionized at gastric pH of 1.2 and predominantly (98.4%) unionized at intestinal pH of 6.8. This means that, according to the pH-partition hypothesis, a weakly acidic drug is more likely to be absorbed from the stomach where it is unionized and a weakly basic drug from the intestine where it is predominantly unionized. However, in practice, very little absorption occurs in the stomach and many other factors need to be taken into consideration.

Limitations of the pH-partition hypothesis. The extent to which a drug exists in its unionized form is not the only factor determining the rate and extent of absorption of a drug molecule from the gastrointestinal tract. 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 is often higher than its rate of absorption in the stomach, even though the drug is unionized in the stomach. The significantly larger surface area that is available for absorption in the small intestine more than compensates for the high degree of ionization of weakly acidic drugs at intestinal pH values. In addition, a longer small intestinal residence time and a microclimate pH (that exists at the surface of the intestinal mucosa and is lower than that of the luminal pH of the small