example, many (about 75%) drugs are weak bases or their salts. These drugs dissolve more rapidly in the low pH of the acidic stomach. However, there will be little or no absorption of the drug there as it will be too ionized. Drug absorption normally will have to wait until the more alkaline intestine where the ionization of the dissolved weak base is reduced
- the stability of many drugs
- body tissues (both extremes of pH are injurious).

These implications have great consequence during peroral drug delivery as the pH experienced by the drug could range from pH 1 to 8 at it passes down the gastrointestinal tract. The interrelationship between degree of ionization, solubility and pH is discussed below in this chapter. The biopharmaceutical consequences are discussed in Chapter 20.

Dissociation (or ionization) constants; pK_a and pK_b

Many drugs are either weak acids or weak bases. In solutions of these drugs, equilibria exist between undissociated molecules and their ions. In a solution of a weakly acidic drug HA, the equilibrium may be represented by Equation 3.7:

$$\mathrm{HA} \leftrightarrow \mathrm{H}^+ + \mathrm{A}^- \tag{3.7}$$

Similarly, the protonation of a weakly basic drug B can be represented by Equation 3.8:

$$\mathrm{B} + \mathrm{H}^+ \leftrightarrow \mathrm{BH}^+ \tag{3.8}$$

In solutions of most salts of strong acids or strong bases in water, such equilibria are shifted strongly to one side of the equation because these compounds are virtually completely ionized. In the case of aqueous solutions of weaker acids and bases, the degree of ionization is much more variable and indeed, as will be seen, controllable.

The *ionization constant* (or *dissociation constant*) K_a of a partially ionized weakly acid species can be obtained by applying the Law of Mass Action to yield Equation 3.9 in which $[I^+]$ and $[I^-]$ represent the concentrations of the dissociated ionized species and $[U]$ is the concentration of the unionized species.

$$K_a = \frac{[I^+][I^-]}{[U]} \tag{3.9}$$

For the case of a weak acid this can be written (from Eqn 3.7) as:

$$K_a = \frac{[\mathrm{H}^+][\mathrm{A}^-]}{[\mathrm{HA}]} \tag{3.10}$$

Taking logarithms of both sides of Equation 3.10 yields:

$$\log_{10} K_a = \log_{10}[\mathrm{H}^+] + \log_{10}[\mathrm{A}^-] - \log_{10}[\mathrm{HA}] \tag{3.11}$$

The signs in this equation may be reversed to give Equation 3.12:

$$-\log_{10} K_a = -\log_{10}[\mathrm{H}^+] - \log_{10}[\mathrm{A}^-] + \log_{10}[\mathrm{HA}] \tag{3.12}$$

The symbol pK_a is used to represent the negative logarithm of the acid dissociation constant K_a in an analogous way that pH is used to represent the negative logarithm of the hydrogen ion concentration (as Eqn 3.6). Therefore:

$$\mathrm{p}K_a = -\log_{10} K_a \tag{3.13}$$

Now Equation 3.12 may therefore be rewritten as Equation 3.14:

$$\mathrm{p}K_a = \mathrm{pH} + \log_{10}[\mathrm{HA}] - \log_{10}[\mathrm{A}^-] \tag{3.14}$$

or

$$\mathrm{p}K_a = \mathrm{pH} + \log_{10}\frac{[\mathrm{HA}]}{[\mathrm{A}^-]} \tag{3.15}$$

or even

$$\mathrm{pH} = \mathrm{p}K_a + \log_{10}\frac{[\mathrm{A}^-]}{[\mathrm{HA}]} \tag{3.16}$$

Equations 3.15 and 3.16 are known as the Henderson–Hasselbalch equations for a weak acid.