Ionization constants of both acidic and basic drugs are usually expressed in terms of pK_a. The equivalent acid dissociation constant (K_a) for the protonation of a weak base is given (from Eqn 3.8) by Equation 3.17. Note the equation appears to be inverted, but it is written in terms of K_a rather than K_b (the base dissociation constant):

$$K_a = \frac{[H^+][B]}{[BH^+]} \tag{3.17}$$

Taking negative logarithms yields Equation 3.18:

$$-\log_{10} K_a = -\log_{10}[H^+] - \log_{10}[B] + \log_{10}[BH^+] \tag{3.18}$$

or

$$pK_a = pH + \log_{10}\frac{[BH^+]}{[B]} \tag{3.19}$$

or

$$pH = pK_a + \log_{10}\frac{[B]}{[BH^+]} \tag{3.20}$$

Equations 3.19 and 3.20 are known as the Henderson–Hasselbalch equations for a weak base.

Link between pH, pK_a, degree of ionization and solubility of weakly acidic or basic drugs

There is a direct link for most polar ionic compounds between the degree of ionization and aqueous solubility. As has been shown above, in turn, the degree of ionization is controlled by the pK_a of the molecule and the pH of its surrounding environment. This interrelationship is shown diagrammatically in Figure 3.1.

Taking the weak acid line first, it can be seen that at high pH the drug is fully ionized and at its maximum solubility. Under low pH conditions the opposite is true. The shape of the curve is defined by the Henderson–Hasselbalch equation for weak acids (Equation 3.15) that shows the link between pH, pK_a and degree of ionization for a weakly acidic drug. It can also be seen from Figure 3.1 that when the pH is equal to the pK_a of the drug, that drug is 50% ionized. This is also predicted from the Henderson–Hasselbalch equation.

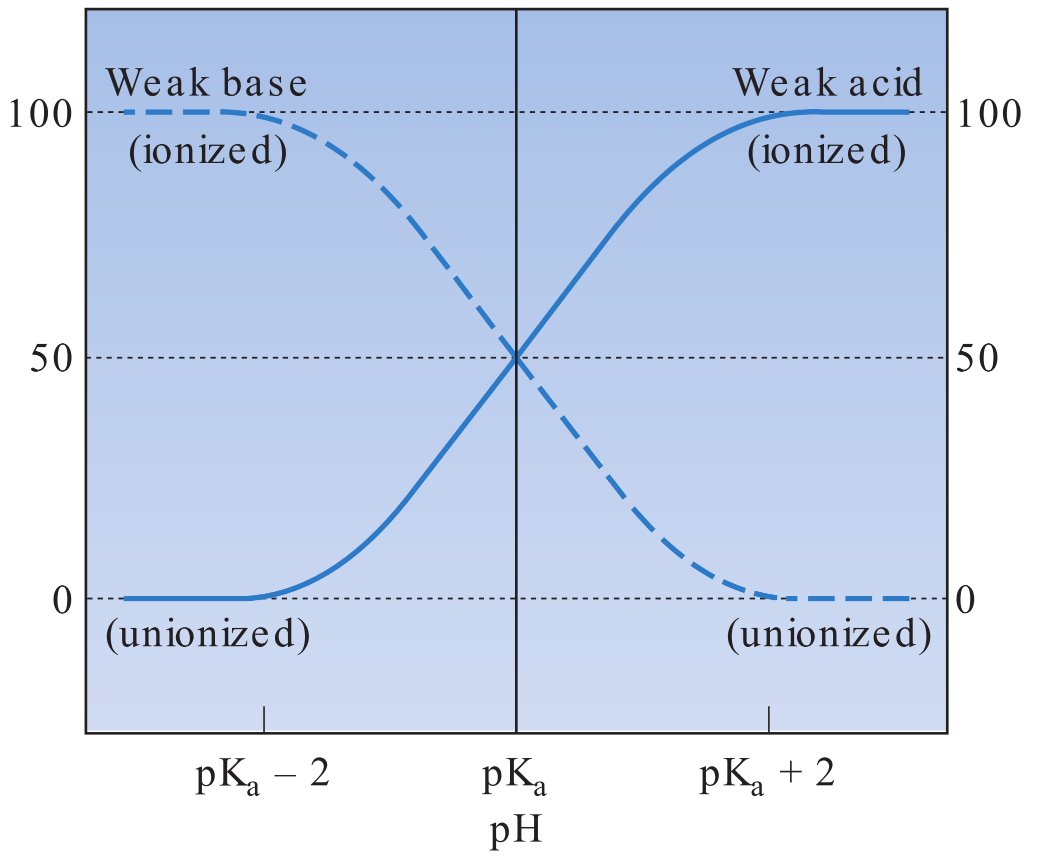

Fig. 3.1 • Change in degree of ionization and relative solubility of weakly acidic and weakly basic drugs as a function of pH.

Equation 3.16 shows that when [A$^-$] = [HA], log ([A$^-$]/[HA]) will equal log 1 (i.e. zero) and thus pH = pK_a. Put another way, when the pH of the surrounding solution equals the pK_a, then the concentration of the ionized species [A$^-$] will equal the concentration of the unionized species [HA], i.e. the drug is 50% ionized. The Henderson–Hasselbalch equations also show that a drug is almost completely ionized or non-ionized (as appropriate) when two pH units away from its pK_a.

Examination of the equivalent line for a weak base will indicate that it is probably not a coincidence that most drugs for peroral delivery are weak bases. A weak base will be ionized and at its most soluble in the acidic stomach and non-ionized and therefore will be more easily absorbed in the more alkaline small intestine. The choice of the pK_a for a drug is thus of paramount importance in peroral drug delivery.

Use of the Henderson–Hasselbalch equations to calculate degree of ionization of weakly acidic or basic drugs

Various analytical techniques, e.g. spectrophotometric and potentiometric methods, may be used to determine ionization constants, but the temperature at which the determination is performed should be specified because the values of the constants vary with temperature.