will be fully ionized (and vice versa for a basic drug) (see Fig. 3.1).

The degree of ionization will affect solubility because ionized species are more freely soluble in water. Taking the acid-species Henderson-Hasselbalch equation as an example (i.e. Eqn 3.15), since $[A^-]$ represents the saturated concentration of ionized drug (S_i) and [HA] represents the saturated concentration of unionized drug (i.e. the intrinsic solubility, S_o) then the equation may be re-written as:

$$pK_a = pH + \log\frac{S_o}{S_i} \tag{23.10}$$

At any given pH, the observed total solubility (S_t) must be the sum of the solubilities of unionized and ionized fractions, i.e.:

$$S_t = S_o + S_i \tag{23.11}$$

Note that in this chapter, the alternative symbol S (with appropriate subscript) is used for the specific concentration of solution that corresponding to the saturated concentration or 'solubility. This is equally acceptable and is presented here, and later in the discussion of intrinsic dissolution rate, as an alternative to annotation used elsewhere. This annotation is particularly useful when discussing various types of solubility, as here.

Rearranging Equation 23.11 gives:

$$S_i = S_t - S_o \tag{23.12}$$

Substituting in Equation 23.10 gives:

$$pK_a = pH + \log\frac{S_o}{S_t - S_o} \tag{23.13}$$

Or, in antilog form:

$$S_t = S_o[1 + \text{antilog}(pH - pK_a)] \tag{23.14}$$

Equation 23.14 allows calculation of the total solubility of an acidic drug as a function of pH. Total solubility will be equal to the intrinsic solubility at pH values below pK_a and will increase significantly at pH values above pK_a. In theory, Equation 23.14 predicts an infinite increase in solubility when pH >> pK_a. In practice this is not attained, primarily because real systems exhibit non-ideal behaviour. Nevertheless, Equation 23.14 is a useful approximation over narrow, but useful, pH ranges.

A similar derivation can be made for weak bases following the same logic, resulting in:

$$S_t = S_o[1 + \text{antilog}(pK_a - pH)] \tag{23.15}$$

Equation 23.15 implies that, for weak bases, total solubility will be equal to the intrinsic solubility at pH values above pK_a and will increase significantly at pH values below pK_a.

Measurement of pK_a

Modern automated instrumentation is available that can determine pK_a values with very small (typically 10–20 mg) amounts of drug. This is extremely useful in the context of preformulation where material is scarce. Usually this instrumentation is based upon a potentiometric pH titration. The drug is dissolved in water, forming either a weakly acidic or weakly basic solution. Acid or base (as appropriate) is titrated and the solution pH recorded. A plot of volume of titrant solution added versus pH allows graphical determination of the pK_a, since when pH = pK_a the compound is 50% ionized. This method has the significant advantage of not requiring an assay.

Alternative methods for determining pK_a include conductivity, potentiometry and spectroscopy. However, if the intrinsic solubility has been determined, measurement of solubility at a pH where the compound is partially ionized will allow calculation of pK_a from the Henderson-Hasselbalch equations.

Partitioning

No solute has complete affinity for either a hydrophilic or a lipophilic phase. In the context of preformulation, it is important to know early in the development stage how a molecule (or charged ion) will distribute between aqueous and fatty environments (e.g. between gut contents and lipid biological bilayers in the surrounding cell walls). When a solute is added to a mixture of two (immiscible) solvents it will usually dissolve in both to some extent and a