The pH solubility curve can now be constructed simply by determining the solubility of HA (at low pH) and A^- (e.g., of NaA) at high pH (e.g., at pH 10).

4. SOLUBILITY

One important goal of the preformulation effort is to devise a method for making solutions of the drug. Frequently, the drug is not sufficiently soluble in water itself to allow for the desired concentrations, for example for injection solutions. Solubilities are determined by exposing an excess of solid to the liquid in question, and assaying after equilibrium has been established. This usually is in the range 60 to 72 h, and to establish that equilibrium indeed has been established, sampling at earlier points is necessary. Unstable solutions pose a problem in this respect and will be dealt with in more detail later. Solubilities cannot be determined by precipitative methods (e.g., by solubilizing an acid in alkali and then lowering the pH to the desired pH) because of the so-called metastable (solubility) zone (Rodriguez-Hornedo, 1984). In the writing to follow, drug substances are subdivided into two categories: (1) ionizable substances, and (2) (virtually) nonionizable substances.

Solubility determinations are necessary both for stability reasons and for formulation reasons. It was noted, in the chapter dealing with stability of solids in the presence of water, that the solubility term becomes part of a rate constant. Since preformulation occurs in the early stage of development, the optimization of stability by way of compound selection (correct salt) is of importance, and often a drug product can be stabilized by keeping the solubility of the drug substance low. In the limit this, however, might affect bioavailability.

Probably among the most well-known examples of such stabilization are that of procaine penicillin and that of potassium clavulanate. In the latter case, the sodium salt, for instance, is unstable to such an extent that it cannot be utilized. The decrease in solubility of the potassium salt renders the product machinable (although low humidities must be observed in manufacturing).

4.1 Use of Salt Formation to Increase Solubility

It is noted that at a given pH the amount in solution in a solubility experiment is

$$S = S_{HA} + C_{A^-} \tag{9.3}$$

where S denotes solubility. The last term can be determined from knowledge of the pK_a, the pH, and the use of Eq. (2).

For drugs that are amines, the free base is frequently poorly soluble, and in this case the $pK_{(a)}$ is often estimated by performing the titration is a solvent containing some organic solvent (e.g., ethanol). By doing this at different organic solvent concentrations (e.g., 5%, 10%, 15%, 20%), extrapolation can be carried out to 0% solvent concentration to estimate the aqueous $pK_{(a)}$.

Usually, alkali metal salts of acids are more soluble than the free acids, and in the case of basic (e.g., amine type) drugs, the solubility of the acid addition salts are more soluble than the free bases. At times (e.g., in the case of enalipril) the compound is amphoteric. The acid addition salt is soluble, the free base is less soluble, and the sodium salt is, again, more soluble. In simple cases, the solubility curve