Theoretical Considerations

The effects of various factors such as pH, the common ion effect, and temperature on solubility will have a greater impact on formulation development for insoluble compounds than for soluble ones. The general solubility theory has been extensively discussed. To afford better understanding of the solubility behavior of insoluble compounds, the pertinent solubility theory and its practical implications will be reviewed here.

Definition of Solubility

The simplest definition of solubility is that the solubility, S_T, of a substance is the molarity of that substance (counting all solution species) in a solution that is at chemical equilibrium with an excess of the undissolved substance. This implies that there must also be a uniform temperature throughout the system, because S_T is typically temperature dependent (Ramette 1981).

pH Effect on Solubility—pH-Solubility Profile

The equilibrium for the dissociation of the monoprotonated conjugate acid of a basic compound may be expressed by:

$$BH^+ + H_2O \xrightleftharpoons{K'_a} B + H_3O^+ \tag{4.1}$$

where BH^+ is the protonated species, B is the free base, and K'_a is the apparent dissociation constant of BH^+ which is defined as follows:

$$K'_a = \frac{[H_3O^+][B]}{[BH^+]} \tag{4.2}$$

Generally, the relationships drawn in Equations 4.1 and 4.2 must be satisfied for all weak electrolytes in equilibrium irrespective of pH and the degree of saturation. At any pH, the total concentration of a compound, S_T, is the sum of the individual concentrations of its respective species:

$$S_T = [BH^+] + [B] \tag{4.3}$$

In a saturated solution of arbitrary pH, this total concentration, S_T, is the sum of the solubility of one of the species and the concentration of the other necessary to satisfy the mass balance.

At low pH where the solubility of BH^+ is limiting, the following relationship holds:

$$S_{T,\,\mathrm{pH}<\mathrm{pH}_{\max}} = [BH^+]_s + [B] = [BH^+]_s\left(1 + \frac{K'_a}{[H_3O^+]}\right) \tag{4.4}$$

where $\mathrm{pH}_{\max}$ refers to the pH of maximum solubility and the subscript $\mathrm{pH} < \mathrm{pH}_{\max}$ indicates that this equation is valid only for pH values less than $\mathrm{pH}_{\max}$. The subscript s indicates a saturated species. A similar equation can be written for solutions at pH values greater than $\mathrm{pH}_{\max}$ where the free base solubility is limiting:

$$S_{T,\,\mathrm{pH}>\mathrm{pH}_{\max}} = [BH^+] + [B]_s = [B]_s\left(1 + \frac{[H_3O^+]}{K'_a}\right) \tag{4.5}$$

Each of these equations describes an independent curve that is limited by the solubility of one of the two species.

The pH-solubility profile is non-uniformly continuous at the juncture of the respective solubility curves. This occurs at the precise pH where the species are simultaneously saturated, previously designated as the $\mathrm{pH}_{\max}$.