



Fig. 2 pH solubility plot of imiquimod in water. (Graph constructed from data published by Chollet et al., 1999.)

will simply mimic the Henderson–Hasselbach equation. An example of this is imiquimod (Chollet et al., 1999), the pH solubility profile of which is shown in Fig. 2.

Streng and Yu (1998) have published a computer program for prediction of stability curves based on the pK_a value of the compound in question.

4.2. Nonionizable Substances

For hydrophobic, (virtually) nonionizable substances (i.e., those that show no ionic species of significance in the pH range 1 to 10, e.g., diazepam), solubility can usually be improved by addition of nonpolar solvents. Aside from solubility, stability is also affected by solvents either in a favorable or in an unfavorable direction (Bakar and Niazi, 1983). Theoretical equations for solubility in water (Yalkowsky and Valvani, 1983) and in binary solvents (Acree and Rytting, 1983) have been reported in the literature, but in general the approach in preformulation is pseudoempirical. Most often the solubility changes as the concentration of nonpolar solvent, C_2 , increases. For binary system, it may simply be a monotonical increasing function (Carstensen et al., 1971), as shown in Fig. 3.

The solubility is usually tied to the dielectric constant, and in a case such as that shown in curve A, the solubility is often log-linear when plotted as a function of inverse dielectric constant, ϵ , that is,

$$\ln S = - \frac{e_1}{\epsilon + e_2} \quad (9.4)$$

where ϵ is the dielectric constant and the e terms are constants (Underberg and Lingeman, 1983).