Extended Hildebrand Solubility Approach

Regular solution theory is largely limited to describing the solution behavior of nonelectrolytes in nonpolar solvents. The inadequacy, or inappropriate application, of the geometric mean assumption for the cohesive energy density of the solution is considered the reason why regular solution theory fails to describe other real solutions (Martin et al., 1985). It has been found that solutions that seemingly fit the criteria of regular solutions fail to yield a solubility predicted by regular solution equations. For example, solutions of benzene or simple substituted aromatics dissolved in alkane solvents were shown to deviate from behaviors predicted by literature solubility parameters and regular solution equations (Funk and Prausnitz, 1970; Hildebrand et al., 1970; Fung and Higuchi, 1971). Studies of these systems can frequently demonstrate that the deviation can be diminished by a correction factor applied to the geometric mean. Efforts have been made to generalize observed behaviors and to correct empirically for these deviations from predicted solubilities. In one method, the geometric mean is replaced with $k\delta_1\delta_2$, where k represents a constant (Walker, 1952). This has been applied with some success to pharmaceutical systems (Martin and Carstensen, 1981). It was found that the geometric mean rule could be relaxed empirically by inclusion of l_{12} (Funk and Prausnitz, 1970; Hildebrand et al., 1970) a binary constant that is small compared to unity:

$$C_{12} = \left(1 - l_{12}\right)\sqrt{C_{11}C_{22}} \tag{2.44}$$

such that Equation 2.42 would be rewritten as:

$$\ln \gamma_2 = \frac{\bar{V}_2\phi_1^2}{RT}\left[\left(\delta_1 - \delta_2\right)^2 + 2l_{12}\delta_1\delta_2\right] \tag{2.45}$$

An improvement in the prediction of androstanolone, nandrolone, and testosterone ester solubility in organic solvents was possible by including l_{12} in the calculations (James et al., 1976).

In the pharmaceutical literature, by far the most common means to account for the deviation from the geometric mean is the use of W, which is defined as follows:

$$W = K\delta_1\delta_2 \tag{2.46}$$

where K is a solute–solvent interaction factor that is not constant. The solubility equation used in this extended Hildebrand solubility approach (Adjei et al., 1980) is:

$$\ln X_2 = -\frac{\Delta\bar{H}_f}{RT_m}\left(\frac{T_m - T}{T}\right) - \frac{\bar{V}_2\phi_1^2}{RT}\left(\delta_1^2 - 2W + \delta_2^2\right) \tag{2.47}$$

This equation has been applied to data for caffeine (Adjei et al., 1980), theophylline (Martin et al., 1980), and satranidazole (Rathi, 2010) in a series of binary solvents consisting of water and dioxane; to data for testosterone in binary solvent systems consisting of chloroform and cyclohexane (Martin et al., 1982); and to polymorphs of mefenamic acid in a series of solvents involving ethanol and water or ethyl acetate and ethanol combinations necessary to cover a range of solvent solubility parameters (Romero et al., 1999). See Figure 2.4 for solubility data from Adjei et al. (1980). This approach is strictly empirical in that to assign values to W requires data for the solubility in a series of binary solvents consisting of two specific solvents in various proportions. The values of W for the solvent systems can be regressed as a power series in the solvent