METHODS OF PREDICTING SOLUBILITY IN COSOLVENTS

Theoretical Methods

Rubino (1984) has reviewed the progression of approaches for predicting solubility in cosolvents. One of the first advances beyond empirical trial-and-error was the use of the dielectric constant ($\in$) to optimize cosolvent systems. The dielectric constant is a dimensionless parameter because it is the ratio of the capacitance of a condenser filled with the material of interest versus a vacuum. Cosolvents that are more polar have larger dielectric constants. Much work has been done around the use of the dielectric constant for optimizing pharmaceutical cosolvent systems (Moore 1958; Paruta et al. 1962, 1964; Sorby et al. 1963, 1965; Gorman and Hall 1964; Paruta 1964, 1966a,b, 1969; Paruta and Irani 1965; Paruta et al. 1965a,b; Paruta and Sheth 1966; Kato and Ohuchi 1972; Amirjahed and Blake 1974, 1975; Neira et al. 1980; Chien, 1984; Ibrahim and Shawky 1984). Simply speaking, the optimal cosolvent system should have a dielectric constant analogous to the solute being dissolved. In general, it has been recognized that the $\in$ of a mixture of two or more solvents is directly proportional to the fraction of the individual solvents (Yalkowsky and Roseman 1981). In this method, to calculate $\in$ of a solvent mixture, one needs to know the $\in$ of the pure solvents. The $\in$ of a solvent mixture is calculated based on a simplified Onsager–Kirkwood equation shown in the following:

$$\text{D.C.} = \sum (\text{fraction of solvent } A \times \text{D.C. of solvent } A) + (\text{fraction of solvent } B \times \text{D.C. of solvent } B) \tag{9.1}$$

The method of calculating ϵ of complex mixtures using the above-mentioned equation would theoretically be correct only if the mixture behaves like an ideal solution. Since most solvent mixtures may exhibit a high degree of intermolecular association, a $\in$ of such systems would lead to a deviation from the experimental data. The simplified Onsager–Kirkwood equation provides only a good approximate dielectric constant for mixed solvent systems.

Owing to ease of use, volume/volume fraction system is used more frequently in mixing of two or more solvents over percent weight/weight fractions system. In case of percent volume/volume fraction system, one needs to recognize that the final volume of miscible solvents may not attain 100%. Sorby et al. (1963) have measured dielectric constant of mixtures containing water–ethanol–glycerin and water–ethanol–propylene glycol and compared them with the calculated dielectric constant of mixtures using Onsager–Kirkwood method. They observed large deviations for the measured values of dielectric constant from those calculated using Onsager–Kirkwood's simplified approach. They also noted that deviations of such a magnitude were also observed for binary systems. Another observation was noted that even though there was a poor agreement between calculated and measured dielectric constants, "the nature of the curves does indicate that dielectric constants in these systems are apparently some type of linear function of the concentration of the various components expressed on a volume basis; however, because of the various complexities of these systems, no simple relationship appears to exist between dielectric constants of the mixtures and those of the pure components, which would allow computation by the simplified form of the Onsager–Kirkwood equation." Furthermore, there was no advantage of using weight fractions over volume fractions.

Rubino (1984) cited the shortcoming of the dielectric constant as being the inability of this individual molecular polarity parameter to reflect the summation of all attractive forces that surround a molecule leading to an inability to predict solubilities in different solvent systems.

A better estimate of all attractive forces surrounding a molecule was found in the use of the solubility parameter, δ (Hildebrand 1916, 1919). Hancock et al. (1997) has reviewed the use of solubility parameters in pharmaceutical dosage form design. The solubility parameter is used as a measure of the internal pressures of the solvent and solute in nonideal solutions. Cosolvents that are more polar have larger solubility parameters. The square root of the cohesive energy density, that is, the square root of the energy of vaporization per unit volume of substance, is known