quadratic equation for application to semipolar drugs. For polar drugs, the addition of a less polar solvent tends to decrease the solubility of that compound. Therefore, their solubility curves show decreasing solubility with increasing cosolvent content.

Gould et al. (1984) studied the solubility relationships of polar, semipolar, and nonpolar drugs in mixed cosolvent systems. As expected, the nonpolar compound showed a log-linear increase in solubility with increasing cosolvent content. The semipolar compound showed parabolic log solubility curves. The polar compound showed a log-linear decrease in solubility with addition of cosolvent.

Comparisons between the Extended Hildebrand solubility approach and the log-linear solubility equation have been made (Martin et al. 1982; Wu and Martin 1983). However, the key to understanding when the log-linear solubility equation will apply is in understanding the relative polarities of the cosolvent(s) and solute.

Other methods of calculating solubility in cosolvent systems have included the UNIFAC group contribution method (Grunbauer et al. 1986) and the UNIQUAC local composition model (Grant and Higuchi 1990). In general, both approaches use the contributions of functional groups to estimate or predict the solubility of a nonelectrolyte in a cosolvent system. Both approaches require the use of tabulated parameters and at least one experimentally determined solubility of drug in pure water to predict a solubility profile. These are excellent methods for the computer-aided design of pharmaceutical dosage forms with increased solubility. The reader is referred to references for more details (Grunbauer et al. 1986; Grant and Higuchi 1990).

Rubino and Yalkowsky (1987) have reviewed cosolvency and cosolvent polarity. In this study, they related slopes, σ, of solubility plots, by means of linear or multiple linear regression, to indexes of polarity such as dielectric constant, solubility parameter, surface tension, interfacial tension, and octanol–water partition coefficients. Two other indexes were investigated: hydrogen-bond donor densities (HBD) and hydrogen-bond acceptor densities (HBA). These terms can be calculated by multiplying the number of proton donor groups for HBD or number of nonbonding electron pairs for HBA by the density of the cosolvent by 1000, then dividing by the molecular weight of the cosolvent. Those indexes that reflect the cohesive properties of the solvents, for example, solubility parameter and interfacial tension, resulted in the highest correlations with the slopes, σ. Therefore, these are better indexes for comparing polarity of compounds.

EMPIRICAL METHODS

The previous section discussed specific theoretical approaches to characterizing solubility in cosolvent systems. While this is extremely useful for understanding the theory behind solubilization, more empirical methods of characterizing the solubility of cosolvent systems can be utilized with the aid of statistical experimental design. Advantages to this approach are that one can add additional excipients, for example, surfactants, without having to consider assumptions used in the derivation of equations and their validity to the systems studied. Another advantage is that typically these studies provide very accurate predictions of solubilities within the design space studied. This allows determination of optimal mixtures of excipients for maximum solubility. Disadvantages to this approach are that it gives no scientific insight as to the mechanism of solubilization. Therefore, the scientist must still interpret the meaning behind data from such studies.

Although factorial designs are very useful for studying multiple variables at various levels, typically they will not be applicable to cosolvent solubility studies because of the constraint that all of the components must add to 100%. For this reason, mixtures of experimental designs are typically used. The statistical theory behind mixture designs has been extensively published (Scheffé 1957, 1963; Cornell 1975, 1990, 1991). There are also multiple examples of the use of mixture designs for solubility studies of pharmaceutical systems (Anik and Sukumar 1981; Moustafa et al. 1981; Belloto et al. 1985; Ochsner et al. 1985; Lewis and Chariot 1991; Vojnovic et al. 1995, 1996, 1997; Wells et al. 1996).