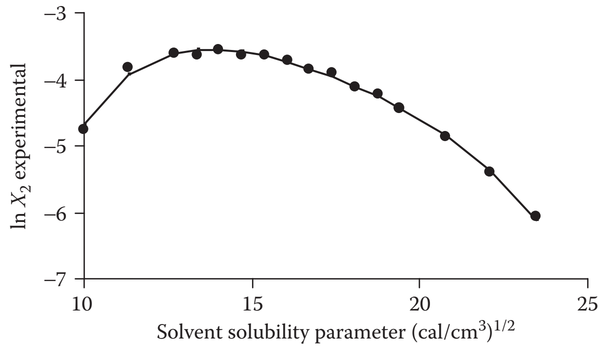

FIGURE 2.4 Caffeine solubility in dioxane-water binary solvents. The curve is an interpolation between calculated values. (From Adjei, A. et al.: Extended Hildebrand approach: Solubility of caffeine in dioxane-water mixtures. *Journal of Pharmaceutical Sciences*. 1980. 69. 659–661. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

solubility parameter, using the following equation to calculate the solvent solubility parameter for the binary solvent system:

$$\delta_{13} = \frac{\phi_1\delta_1 + \phi_3\delta_3}{\phi_1 + \phi_3} \tag{2.48}$$

where the subscripts 1 and 3 are assigned to the first and second solvent. The δ_{13} solvent solubility parameter would replace the δ_1 found in Equation 2.47. In the case of caffeine (Adjei et al., 1980), acetaminophen (Subrahmanyam et al., 1992), and mefenamic acid (Romero et al., 1999) in cosolvent–water systems, the *W* values were regressed as a fourth-order polynomial in the solvent solubility parameter to achieve a close fit to the experimental data (Figure 2.4). The fit can be excellent because it is possible to fit any data set using a polynomial if there are enough adjustable parameters (Grant and Higuchi, 1990). Each new term in the polynomial introduces another adjustable parameter.

Lin and Nash (1993) have proposed an equation to estimate the Hildebrand solubility parameter of a solute strictly from its mole fraction solubility in *n* different solvents and the corresponding solvent solubility parameter:

$$\delta_2 = \frac{\sum_{i=1}^{n} X_{2,i}\delta_{1,i}}{\sum_{i=1}^{n} X_{2,i}} \tag{2.49}$$

where $X_{2,i}$ refers to the mole fraction solubility of the solute in a particular solvent and $\delta_{1,i}$ is the solubility parameter of that particular solvent. This equation has been applied to benzoic acid, theophylline, and methylparaben data by Lin and Nash (1993) and to polymorphs of mefenamic acid data by Romero et al. (1999) with some success. The estimated solubility parameters for the two polymorphs of mefenamic acid were quite similar. This is to be expected since the solute interactions in solution would not depend on the solid characteristics defined by the polymorphic form. Indeed, it has been reported that the difference in solubility between different polymorphs is usually less than one order of magnitude (Huang and Tong, 2004) or might even be less than a factor of 2 (Pudipeddi and Serajuddin, 2005).

Grant and Higuchi (1990) noted that, although this approach can be used to correlate and condense data, its use as a predictive method is questionable. It would be more promising if *W* could be related to polar characteristics, but to date there is no means to estimate it based on the physicochemical properties of the solute or solvent (Adjei et al., 1980). The value of this approach is that the regression equation can be used to interpolate the magnitude of *W* for a binary solvent from the same system that has not been investigated experimentally. Therefore, it has a direct application in the investigation of solubility in cosolvent mixtures, as will be discussed later.