as the solubility parameter and was developed from Hildebrand's regular solution theory in the Scatchard–Hildebrand equation (Hildebrand and Scott 1950, 1962):

$$-\log X_2 = \frac{\Delta H_f}{2.303RT}\left(\frac{T_m - T}{T_m}\right) + \frac{V_2\Phi_1^2}{2.303RT}(\delta_1 - \delta_2)^2 \tag{9.2}$$

where X_2 is the mole fraction of solute, ΔH_f is the heat of fusion of the solute, R is the gas constant, T is the absolute temperature of the solution, T_m is the melting point of the solid solute in absolute degrees, V_2 is the molar volume of the supercooled liquid solute, and Φ_1 is the volume fraction of the solvent. The second term to the right of the equal sign represents the decrease in solubility owing to intermolecular interaction differences of the solute and solvent molecules. Even though this represented advancement in the understanding of solubility (Gordon and Scott 1952; Chertkoff and Martin 1960; Restaino and Martin 1964), there are drawbacks to the regular solution theory. Rubino (1984) summarized these as being that the use of this equation is limited to one solute and one solvent, the equation is valid only for solutions where the solute and solvent are of comparable size, but most importantly, this equation is technically only applicable for solutions where the intermolecular forces between the solute and solvent consist of London dispersion forces.

Because of the need for better predictability in more aqueous cosolvent systems, the Scatchard–Hildebrand equation was modified into the Extended Hildebrand equation (Martin 1979, 1980):

$$-\log X_2 = \frac{\Delta H_f}{2.303RT}\left(\frac{T_m - T}{T_m}\right) + \frac{V_2\Phi_1^2}{2.303RT}(\delta_1^2 + \delta_2^2 - 2W)^2 \tag{9.3}$$

where W term is the potential energy or interaction energy between the solute and the solvent. While the Extended Hildebrand equation has been demonstrated in several cosolvent systems of varying polarity (Martin et al. 1979, 1980, 1981; Adjei et al. 1980; Martin and Miralles 1982), it suffers because calculation of the W term requires nonlinear regression of solubility data of the drug in the cosolvent system of interest. Therefore, it is not predictive.

To improve further on this equation, three-dimensional solubility parameters were proposed (Beerbower and Hansen 1971; Martin et al. 1981; Barton 1983) to account for more specific interactions that can occur, such as hydrogen bonding. The solubility parameter was divided into three components:

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \tag{9.4}$$

where δ_t^2 is the total cohesive energy density, δ_d^2 is the contribution to the cohesive energy density due to London dispersion forces, δ_p^2 is the contribution to the cohesive energy density due to polar interactions, and δ_h^2 is the contribution to the cohesive energy density due to hydrogen bonding. The cohesive energy density for dispersive forces can be calculated through a nonpolar homomorph or all three terms can be estimated through group contribution approaches (Martin et al. 1981).

The solubility parameter approach was subsequently expanded from three to four terms with the division of the hydrogen-bonding parameter into acidic and basic solubility parameters to quantify electron-donor and electron-acceptor properties (Beerbower et al. 1984; Martin et al. 1984). However, the expansion of these solubility parameter terms did not make the equation any easier to use for the *a priori* prediction of solubility in cosolvent systems.

Other attempts at characterizing the deviation from ideal solubility theory have been made. Anderson et al. (1980) showed that solubilities that could not be rationalized from the regular solution theory could be rationalized by assuming the formation of specific solute–solvent complexes. Yalkowsky et al. (1975) and Amidon et al. (1974) showed that the deviation from the ideal solubility equation could be expressed in terms of interfacial tension and surface area. In equation form,

$$-\log X_2 = \frac{\Delta H_f}{2.303RT}\left(\frac{T_m - T}{T_m}\right) + \frac{A\gamma_{12}}{2.303RT} \tag{9.5}$$