Hansen Approach

Attempts have been made to extend the solubility parameter approach to include polar systems. Compensation for hydrogen bonding (Burrell, 1955a, 1955b; Crowley et al., 1966; Karger et al., 1976) and polar contributions (Hildebrand and Scott, 1962; Blanks and Prausnitz, 1964; Harris and Prausnitz, 1969; Karger et al., 1976) refined the application, but a more successful approach was to acknowledge that the cohesive energy density is the sum of intermolecular forces consisting of dispersion forces (*D*), polar forces involving permanent dipoles (*P*), and hydrogen bonding (*H*) (Hansen, 1967). Each of these components can be represented in a three-dimensional solubility parameter:

$$\delta_T^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \tag{2.50}$$

where δ_T is the one-dimensional solubility parameter, previously given the symbol δ and considered earlier in this chapter. Each of the component solubility parameters is expressed in the same units as the conventional solubility parameter. Three-dimensional solubility parameters have been the subject of much investigation, and tables of these solubility parameters, in particular for common solvents, are available (Beerbower and Dickey, 1969; Hansen and Beerbower, 1971; Hansen, 1972, 2007; Barton, 1983).

The solubility of the drug is determined in multiple solvents that possess different functional groups, both nonpolar and polar, to allow each of the three-dimensional solubility parameters to be estimated. A typical means to arrive at the values of the component solubility parameters is the use of multiple regression analysis (Thimmasetty et al., 2009). Alternatively, each of the three-dimensional solubility parameters can be estimated using group contribution methods, as described in the following paragraphs.

Tentatively, water was assigned $\delta_D = 7.0$, $\delta_P = 8.0$, and $\delta_H = 20.9$ hildebrands, which agrees with extrapolations for dispersion and polar components generated from the solubility and molar volume data for alcohols, and for the hydrogen-bonding contribution if one considers water as having two alcohol hydrogen atoms. Use of these values in calculations for organic solvent–water binary systems have met with success (Hansen, 1967). A recently reported set of parameters for water based on the energy of evaporation is still quite similar to those tentatively proposed: $\delta_D = 7.58$, $\delta_P = 7.82$, and $\delta_H = 20.7$ hildebrands (Hansen, 2007).

The dispersion solubility parameter can be estimated using the classical one-dimensional solubility parameter of a homomorph (Blanks and Prausnitz, 1964; Hansen, 1969; Barton, 1983). The homomorph of a polar molecule is defined as a nonpolar molecule having very nearly the same molecular size and shape. Alternatively, the dispersion contributions can be estimated using functional group contributions, $F_{D,i}$, and the formula:

$$\delta_D = \frac{\sum F_{D,i}}{\bar{V}} \tag{2.51}$$

The other components can also be estimated using additive functional group contributions, and tables of group contributions for dispersion, and polar and hydrogen-bonding contributions are available (Hansen and Beerbower, 1971; Van Krevelen and Hoftyzer, 1976; Barton, 1983; Hansen, 2007; Abbott and Hansen, 2010; Just et al., 2013). If we label the polar functional group contributions $F_{P,i}$, the polar contributions are summed in this fashion:

$$\delta_P = \frac{\sqrt{\sum F_{P,i}^2}}{\bar{V}} \tag{2.52}$$