CHAPTER II

REVIEW OF LITERATURE

The wide application of liquid dosage forms used in pharmaceuticals is demonstrable proof of the importance of solutions in formulation. Therefore, studying the solubilities of pharmaceutical substances are very important in the area of pharmaceuticals (12). As reported previously (2 - 10, 14 - 26), there were many attempts to predict solubilities of solute in various solvents. These attempts emphasize the fact that it would be very essential to identify suitable approach(es) for prediction of solubilities of solute in various individual untested solvents. For this purpose, three approaches were used in this study, they are :

1. Regular Solution Theory (Scatchard-Hildebrand Equation)
2. The Extended Hildebrand Solubility Approach (EHS)
3. The Extended Hansen Solubility Approach

The detail of individual approach may be discussed as follows:

1. <u>The Regular Solution Theory</u> (1, 4 - 10)
<u>(Scatchard-Hildebrand Equation)</u>

The activity of a solute in a solution is directly proportional to the concentration of solute ($a \alpha X_2$). When the concentration is given in mole fraction (X_2), the activity is expressed in equation as

$$a_2 = X_2\alpha_2 \qquad \text{(Eq.1)}$$

in which α_2 is the rational activity coefficient and subscript 2 refers to the solute. Converting to logarithms, we have

$$\log a_2 = \log X_2 + \log \alpha_2 \qquad \text{(Eq.2)}$$

In an ideal solution, $\alpha_2 = 1$, since an ideal solution is one in which the presence of the solute molecules has no effect on the forces existing between the solvent molecules, and vice versa. Consequently, upon mixing there is no change in properties of the components other than dilution. When two liquids dissolve to give an ideal solution, there is no heat effect, and other properties, e.g., density, volume, refractive index, viscosity and vapor pressure, can be directly calculated by averaging the properties of the components of the solution (27). The solubility of a solid in an ideal solution depends on temperature, melting point of the solid and molar heat of fusion. Ideal solubility is not affected by the nature of the solvent and the equation derived from thermodynamic consideration is :

$$-\log X_2^i = \frac{\Delta Hf}{2.303\ RT}\left[\frac{Tm - T}{Tm}\right] \qquad \text{(Eq.3)}$$

in which X_2^i is the ideal solubility of the solute expressed in mole fraction, T_m is the melting point of solute in absolute degree, T is the absolute temperature of the solution, ΔHf is the molar heat of fusion of the solute and R is the molar gas constant.

From Eq.2 when $\alpha_2 = 1$, $\log \alpha_2 = 0$, so in an ideal solution the relationship exists as

$$-\log a_2 = -\log X_2^i = \frac{\Delta Hf}{2.303\ RT}\left[\frac{Tm - T}{Tm}\right] \qquad \text{(Eq.4)}$$

But most solute-solvent mixtures do not behave ideally, and solute mole fractional concentrations often differ greatly from their activities. Therefore, such solutions are called as nonideal solutions. The solubility of a solute in a nonideal solution, expressed in logarithmic

form, becomes

$$-\log X_2 = \frac{\Delta Hf}{2.303 \cdot RT}\left[\frac{Tm - T}{Tm}\right] + \log \alpha_2 \qquad \text{(Eq.5)}$$

or $$-\log X_2 = -\log X_2^i + \log \alpha_2 \qquad \text{(Eq.6)}$$

Nonideal solutions are classified into two types; regular and irregular solutions. The properties of regular solutions are similar to those of ideal solutions. The molecules exhibit complete freedom of motion and randomness of distribution in the solution as found in ideal solutions. There is no change in entropy but heat is absorbed when the components of a regular solution are mixed. Scatchard and Hildebrand studied the solubility of crystalline solids in regular solutions and found that the activity coefficient term of the solubility equation depends on temperature of solution, volume of the solute, the fraction of total volume of solvent and the work that must be done in removing a molecule from the solute phase and depositing it in the solvent. This work is obtained by summation total energy required in solubility processes which may be considered in three steps. The first step involves the removal of a molecule from the solute phase at a definite temperature. The gain in potential energy for this step is is W_{22} in which subscript $_{22}$ refers to the interaction between solute molecules. The second step involves the creation of a hole in the solvent just large enough to accept the solute molecule. The work required for this step is W_{11}, in which the subscript $_{11}$ refers to the energy of interaction between solvent molecules. In the last step, the solute molecule is placed in the hole in the solvent, and the total energy decreased in this step is $-2W_{12}$. The subscript $_{12}$ stands for

the interaction energy of the solute with the solvent.

In summary, the activity coefficient term of solubility equation reported by Scatchard and Hildebrand is

$$\log \alpha_2 = \frac{V_2\phi_1^2}{2.303\ RT}(W_{22} + W_{11} - 2W_{12}) \qquad \text{(Eq.7)}$$

in which V_2 is the molar volume of the solid solute taken as hypothetical supercooled liquid and ϕ_1 is the volume fraction of solvent. Since van der Waals force between molecules follow a geometric mean, thus, the interaction between different molecules is equal to the square root of the product of the attractions among similar molecules or $W_{12} = \sqrt{W_{11}W_{22}}$, then Eq.7 can be rewritten as

$$\log \alpha_2 = \frac{V_2\phi_1^2}{2.303\ RT}\{(W_{11})^{\frac{1}{2}} - (W_{22})^{\frac{1}{2}}\}^2 \qquad \text{(Eq.8)}$$

The $(W)^{\frac{1}{2}}$ terms are known as the solubility parameters and designated by the symbols δ_1 and δ_2 for solvent and solute, respectively. Hence Eq.8 is written as

$$\log \alpha_2 = \frac{V_2\phi_1^2}{2.303\ RT}(\delta_1 - \delta_2)^2 \qquad \text{(Eq.9)}$$

or

$$\log \alpha_2 = A(\delta_1 - \delta_2)^2 \qquad \text{(Eq.10)}$$

in which

$$A = \frac{V_2\phi_1^2}{2.303\ RT} \qquad \text{(Eq.11)}$$

and the volume fraction of solvent, ϕ_1, can be obtained using the relationship

$$\phi_1 = \frac{V_1(1 - X_2)}{V_1(1 - X_2) + V_2X_2} \qquad \text{(Eq.12)}$$

in which V_1 is the molar volume of the solvent. When Eq.9 is substituted in Eq.5, the mole fraction solubility of a nonpolar or moderately polar solute is obtained as

$$-\log X_2 = \frac{\Delta Hf}{2.303\ RT}\left[\frac{Tm - T}{Tm}\right] + \frac{V_2\phi_1^2}{2.303\ RT}(\delta_1 - \delta_2)^2 \quad \text{(Eq.13)}$$

or

$$-\log X_2 = -\log X_2^i + A(\delta_1 - \delta_2)^2 \quad \text{(Eq.14)}$$

The predicted value of X_2 is achieved by employing Eqs. 12, 11, and 14, respectively, begining with a value of 1.0 for ϕ_1 and iterating until X_2 or ϕ_1 no longer changes by more than some desired small value, say 1×10^{-5}.

This refers to the Scatchard-Hildebrand method. It is used to estimate solubility only for relatively nonpolar drugs in nonpolar solvents according to regular solution theory.

2. <u>The Extended Hildebrand Solubility Approach (EHS)</u> (1, 3-6, 10, 13-16)

This approach is extended from the Scatchard-Hildebrand equation (Eq.13 or 14) in regular solution theory. This is because several investigators, including Hildebrand (1,4,17), have found that expression in the form of Eq.13 is not a good representation of nonideality in solutions of polymers and various polar and semipolar compounds in polar and semipolar solvents. Since these solutions are quite irregular, often involving self-association or solvation. For irregular solutions, the Scatchard-Hildebrand equation must be modified and is referred to as the Extended Hildebrand Solubility Approach (EHS). The extended method allows one to calculate the solubility of polar and nonpolar solutes in solvents ranging from nonpolar hydrocarbons to highly polar

solvents such as alcohols, glycols and water. Hence, the modified Scatchard-Hildebrand solubility equation becomes

$$-\log X_2 = \frac{\Delta Hf}{2.303\ RT}\left[\frac{Tm-T}{Tm}\right] + \frac{V_2\phi_1^2}{2.303\ RT}(\delta_1^2+\delta_2^2-2W) \quad \text{(Eq.15)}$$

or

$$-\log X_2 = -\log X_2^i + A(\delta_1^2 + \delta_2^2 - 2W) \quad \text{(Eq.16)}$$

in which W is the interaction energy between the solute and the solvent in an irregular solution. This equation is used to predict drug solubility in pure and/or mixed solvent liquid solutions.

The interaction energy, W, will be calculated using Eq.15 from knowing other terms obtained experimentally. The observed W, are regressed versus a polynomial expression in the solubility parameters of each individual solvent (1,28,29) using an equation:

$$W = a + b\delta_1 + c\delta_1^2 \quad \text{(Eq.17)}$$

in which a, b and c are coefficients. Then, back-calculating W and substituting into Eq.16 allows calculation of X_2 in term of A.

The final step utilized in The Extended Hildebrand Solubility Approach, the predicted value of X_2 is achieved by employing Eqs. 12, 11, and 16, respectively, begining with a value of 1.0 for ϕ_1 and iterating until X_2 or ϕ_1 no longer changes by more than some desired small value, say 1×10^{-5}

3. <u>The Extended Hansen Solubility Approach</u> (1, 17 - 21)

Hildebrand and Scott(11) designated the energy of vaporization per cubic centimeter as the cohesive energy density (ced) which is the energy required to break all intermolecular contacts within the mixture, and its square root as the solubility parameter (δ) (8, 11, 17).

Thus, the solubility parameter of solvent (δ_1) is obtained using the relationship

$$\delta_1 = \left[\frac{\Delta E_v}{V_1}\right]^{\frac{1}{2}} = \left[\frac{\Delta H_v - RT}{V_1}\right]^{\frac{1}{2}} \qquad \text{(Eq.18)}$$

in which ΔE_v is the molar energy of vaporization, ΔH_v is the molar heat of vaporization, and V_1 is the molar volume of the solvent.

As suggested by Crowley(11), the unit $(cal/cm^3)^{\frac{1}{2}}$ is named as a "Hildebrand."

The solubility parameter of the solid is difficult to obtain, and few values are available in the literature (4,13,17). This is because many organic compounds decompose above their melting points (18, 20). Fedors (30) has proposed a method of group contributions for estimating the total solubility parameters for compound such as drug molecules that are difficult to achieve. In this technique, the atoms and chemical groups contribution to ΔE and ΔV, as provided by Fedors, are summed to yield

$$\delta^2 = \frac{\Sigma \Delta E}{\Sigma \Delta V} \qquad \text{(Eq.19)}$$

Hansen(11,13) partitioned the cohesive energies into a term for nonpolar or dispersion interactions, ΔE_D, a second for permanent dipole-permanent dipole interactions, ΔE_P, and a third for hydrogen bonding, ΔE_H. The hydrogen-bonding term actually includes all varieties of strong donor-acceptor interaction between solute and solvent and is not restricted to the classical meaning of hydrogen bonding.

The summation of these energy terms divided by molar volume gives the total cohesive energy density (1,11,13,17) :

$$\frac{\Delta E}{V} = \frac{\Delta E_D}{V} + \frac{\Delta E_P}{V} + \frac{\Delta E_H}{V} \qquad \text{(Eq.20)}$$

or $$\delta^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \qquad \text{(Eq.21)}$$

in which δ is the total, essentially the Hildebrand, solubility parameter, δ_D is the dispersion component of the total solubility parameter, δ_P is the polar component of the total solubility parameter, and δ_H is the hydrogen bonding component of the total solubility para meter. Values for δ_D^2 were determined by reference to a corresponding hydrocarbon called a homomorph, δ_P^2 and δ_H^2 were obtained by empirical method. The three partial solubility parameters, obtained by later improved methods are reported elsewhere.

Hildebrand and Scott (1)included the solubility parameters for a number of compounds in their books. A table of solubility parameters has also been compiled by Hansen and Beerbower(11). They used a semi-empirical method as well as nealy 10,000 experimental observations of solubility and pigment suspensions to provide a self-consistent set of three partial solubility parameters (δ_D, δ_P, δ_H) values in a three-dimensional system (13). These data may be used with the relation between X_2, X_2^i and α_2 as shown in Eq.6 as :

$$-\log X_2 = -\log X_2^i + \log \alpha_2 \qquad \text{(Eq.6)}$$

and the statistical method of multiple regression analysis and is referred to as the Extended Hansen Solubility Approach. Hence, the Extended Hansen Solubility equation may be expressed as (1,18-21,28,29):

$$\log\left[X_2^i/X_2\right] = \log \alpha_2 = C_0 + C_1A(\delta_{1D}-\delta_{2D})^2 + C_2A(\delta_{1P}-\delta_{2P})^2 + C_3A(\delta_{1H}-\delta_{2H})^2 \quad \text{(Eq.22)}$$

in which C_i (i = 0,1,2,3) are regression coefficients obtained using regression analysis; δ_{1D}, δ_{1P}, and δ_{1H} are the three partial solubility parameters for the solvent; and δ_{2D}, δ_{2P}, and δ_{2H} are the corresponding values for the solute. A is a term from regular solution theory obtained using Eqs.11 and 12 as mentioned above:

$$A = \frac{V_2\phi_1^2}{2.303\ RT} \quad \text{(Eq.11)}$$

$$\phi_1 = \frac{V_1(1 - X_2)}{V_1(1 - X_2) + V_2X_2} \quad \text{(Eq.12)}$$

The method starts with, first, the observed values of ϕ_1 and A will be calculated using Eqs.12 and 11, respectively, from knowing the observed values of X_2 obtained experimentally. The value of log X_2^i and the observed values of log $\left[X_2^i/X_2\right]$ or log α_2 will be calculated using Eqs.3 and 6, respectively. Then the observed values of log $\left[X_2^i/X_2\right]$ or log α_2 are regressed versus a multiple regression expression against $A(\delta_{1D} - \delta_{2D})^2$, $A(\delta_{1P} - \delta_{2P})^2$, and $A(\delta_{1H} - \delta_{2H})^2$ using Eq.22 from knowing partial solubility parameters obtained from the literature.

Results obtained from the computer output of multiple regression analysis are C_0, C_1, C_2, C_3 which will be substituted into Eq.22. Then, using the partial solubility parameters of each solvent (δ_{1D}, δ_{1P}, δ_{1H}) and solute (δ_{2D}, δ_{2P}, δ_{2H}) together with the value of log X_2^i from Eq.3 allows back-calculation of X_2 in term of A, and the predicted

value of A is calculated using Eq.11. Owing to the predicted value of ϕ_1 is unknown since it depends on the value of X_2 which is sought using Eq. 12. Thus, the predicted value of A is achieved by employing Eqs.12, 11, and 22 begining with a value of 1.0 for ϕ_1 and iterating until X_2 or ϕ_1 no longer changes by more than some desired small value, say 1×10^{-5}.

The final step employed in the Extended Hansen Solubility Approach, the predicted value of ϕ_1 obtained using an iterating procedure will be substituted into Eq.11 for A value. Using this iterated value of A in Eq.22 the method will allow calculation of predicted mole fraction solubility of the drug in various individual solvents.