CHAPTER II

REVIEW OF LITERATURE

In a pharmaceutical formulation, it is often desirable to prepare a clear liquid dosage form (40). This is because a clear solution avoids the disadvantages inherent in other dosage forms, such as nonuniform dose, caking of solid drug and possible slow release of the medicament (17). Studying the solubility of a drug is very important in the area of pharmaceutical preparations. Also, the theory of solutions is one of the most challenging and least understood branches of physical chemistry (10). This theory is valuable in the design of liquid formulations for topical, oral and parenteral administration. The Hildebrand-Scatchard theory of regular solution is a pioneer approach in this field. In recent years the solubility parameter concept has been extended to practical areas of industrial and commercial paints, inks, polymers, plastics, insecticides and pharmaceuticals. As reported recently, the Hildebrand-Scatchard equation has been successfully modified and solubilities of several drugs are estimated in binary solvents in attempt to design of improved dosage forms and drug delivery systems.

Generally, water is always the solvent of choice in pharmaceutical preparations. However, when it is not possible for physical and chemical reasons (such as limited solubility and hydrolytic reactions) to use a wholly aqueous system, techniques of solubilization

become important. In general, the aqueous solubility of a drug can be increased by a variety of techniques. The choice of a method, however, depends upon the nature of the drug, and degree of solubilization required. Some of these techniques are :

1. Complexation This method utilizes complexing agents (also called ligand e.g. EDTA, citric acid, caffeine, etc.) to associate with a drug. The application of this technique is quite limited with some problems. First,if complexation is rapid and total reversible process, it may result in precipitation upon dilution. A second problem associated with complexation is the necessary presence of the ligand. Since the ligand will normally be present in molar ratios equivalent to and often much greater than the drug. This may cause some undesirable effects. The final limiting factor is the fact that, the apparent solubility increased by this technique is an order of magnitude or less. When solubility increased of 10^2 or 10^3 are required, other approaches are probably best consideration.

2. Micellar solubilization By adding of a surfactant, the solubility of insoluble or poorly soluble drug is increased by the presence of surfactant-micelles. Non-ionic surfactants are frequently included in a dosage formulation in different amounts depending on the role they play in this form (4). It is generally accepted that a drug solubilized in micelles is not available for absorption. This is because the drug absorption process from micellar solutions is usually explained on the basis of a pseudo-phase-separation model in which two phases are considered; the dispersed micellar phase and the continuous aqueous phase. The drug is partitioned between

these two phases with a constant partition ratio. Therefore, micellar solubilization would have a negative effect on drug absorption. Moreover, the possible short or long term adverse effect of the surfactant on the body, the concomitant solubilization of other ingredients such as preservatives, coloring agents, flavoring agents which may result in alterations in stability and effectiveness of drug product make this technique to be limited. However, this method is better than the previous one because of its higher degree of increased solubility.

3. Using mixed solvents (cosolvents) The solubility of a drug can be increased by selecting some nonaqueous solvents to form a binary or ternary mixed solvent with water. The solubility of many drugs have often been interpreted on the basis of polarity differences between solutes and solvents. It results principally from interactions between solute and solvent molecules. Mixed solvent can provide proper polarity of each drug by varying the ratio of aqueous and nonaqueous solvents. Additionally, the selection of appropriate mixed solvents can ensure the solubility of all compounds in the formulation and minimize the potential for precipitation which may result from cooling or from diluting with blood aqueous fluids or other kinds of solution. Consequently, this may ensure minimal tissue irritation at the site of administration. However, the selection of nonaqueous solvent for a drug vehicle is a compromise among influencing factors, such as its chemical and physical properties, its pharmacological and physiological properties in the body. Today, mixed solvents are commonly used for solubilizing drugs in many preparations including injections for intravenous and intramuscular administration. The most

Table I : Some Parenteral Products Containing Mixed Solvents*

Tradename	Manufacturer	General name	Mixed Solvents
Dramamine	Searle	Dimenhydrinate	50% Propylene glycol
Apresoline	Ciba	Hydralazine HCl	10% Propylene glycol
MVI	USV	Multivitamin infusion	30% Propylene glycol
Nembutal	Abbott	Phenobarbital sodium	10% Ethanol, 40% propylene glycol
Luminal	Winthrop	Pentobarbital sodium	67.8% Propylene glycol
Dilantin	Parke-Davis	Phenytoin sodium	10% Ethanol, 40% propylene glycol
DHE 45	Sandoz	Dihydroergotamine mesylate	6.1% Ethanol, 15% glycerine
Cedilanid	Sandoz	Deslanoside	9.8% Ethanol, 15% glycerine
Robaxin	Robbins	Methocarbamol	50% Polyethylene glycol
Serpasil	Ciba	Reserpine	10% Dimethylacetamide, 5% polyethylene glycol
Ativan	Wyeth	Lorazepam	80% Propylene glycol, 20% polyethylene glycol
Librium	Roche	Chlordiazepoxide	20% Propylene glycol
Valium	Roche	Diazepam	10% Ethanol, 40% propylene glycol
Lanoxin	Burroughs Wellcome	Digoxin	10% Ethanol, 40% propylene glycol

*Yalkowsky, S.H., Techniques of Solubilization of Drugs, p. 131, Marcel Dekker Inc., New York, 1981.

frequently used mixed solvents are propylene glycol, ethanol, glycerine and polyethylene glycol in water. The major pharmaceutical and pharmacological properties of these and other water-miscible cosolvents have been reviewed by Speigel and Noseworthy (17). Some marketed formulations utilizing mixed solvents are listed in Table I.

4. Other methods By using some chemical reactions such as making the drug in the form of prodrugs or by solid dispersion process, the solubility of a drug may be increased.

Since technique of mixed solvent was chosen to solubilize indomethacin in this experiment, its details will be discussed.

The activity of a solute in a solution is directly proportional to the concentration of solute ($a_2 \alpha\ x_2$). When the concentration is given in mole fraction (x_2), the activity is expressed in equation as

$$a_2 = x_2\gamma_2 \qquad \text{(Eq. 1)}$$

in which γ_2 is the rational activity coefficient and subscript 2 refers to solute. Converting to logarithms, we have

$$\log a_2 = \log x_2 + \log \gamma_2 \qquad \text{(Eq. 2)}$$

In an ideal solution $\gamma_2 = 1$, 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 (26). 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 considerations 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, Tm 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 solute and R is the molar gas constant.

From Eq. 2 when $\gamma_2 = 1$, $\log \gamma_2 = 0$ 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 log form, becomes

$$-\log x_2 = \frac{\Delta Hf}{2.303\ RT}\left[\frac{Tm - T}{Tm}\right] + \log \gamma_2 \qquad \text{(Eq. 5)}$$

Nonideal solutions are devided into two types; regular and irregular solutions. The properties of regular solution 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 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

$$\log \gamma_2 = \frac{V_2 \phi_1^2}{2.303\ RT} (w_{22} + w_{11} - 2w_{12}) \qquad \text{(Eq. 6)}$$

in which V_2 is the molar volume of solute as a hypothetical supercooled liquid and ϕ_1 is 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. 6 can be rewritten as

$$\log \gamma_2 = \frac{V_2 \phi_1^2}{2.303\ RT} \{(w_{11})^{\frac{1}{2}} - (w_{22})^{\frac{1}{2}}\}^2 \qquad \text{(Eq. 7)}$$

The $(w)^{\frac{1}{2}}$ terms are known as solubility parameters and designated by the symbols δ_1 and δ_2 for solvent and solute, respectively. Hence, Eq. 7 is written as

$$\log \gamma_2 = \frac{V_2 \phi_1^2}{2.303\ RT} (\delta_1 - \delta_2)^2 \qquad \text{(Eq. 8)}$$

When Eq. 8 is substituted in Eq. 5, the mole fraction solubility of a nonpolar or moderately polar solute is obtained as

$$-\log x_2 = \frac{\Delta Hf}{2.303\ RT} \left[\frac{Tm - T}{Tm} \right] + \frac{V_2 \phi_1^2}{2.303\ RT} (\delta_1 - \delta_2)^2 \qquad \text{(Eq. 9)}$$

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

The solubility parameter is the square root of cohesive energy density which is the energy required to break all intermolecular contacts within the mixture (10,18). It has been shown that the solubility parameter is connected to other physical properties such as HLB values and dielectric constants (19,20).

The solubility parameter of solvent, δ_1, is obtained as suggested by Hildebrand and Scott (10). Using the relationship

$$\delta_1 = \left[\frac{\Delta Ev}{V_1} \right]^{\frac{1}{2}} = \left[\frac{\Delta Hv - RT}{V_1} \right]^{\frac{1}{2}} \qquad \text{(Eq. 10)}$$

where ΔEv is the molar energy of vaporization, ΔHv is the molar heat of vaporization, and V_1 is the molar volume of the solvent.

The solubility parameter of solid is difficult to obtain, and few values are available in the literature (21,22), since many organic compounds decompose above their melting points (11,21,22). Fedors (23) has proposed a method of group contributions for estimating the total solubility parameters for compound such as drug molecules that are difficult to achieve. The atoms and chemical groups contribution to ΔE and ΔV, as provided by Fedors, are summed to yield.

$$\delta^2 = \frac{\Sigma \Delta E}{\Sigma \Delta V} \qquad \text{(Eq. 11)}$$

As seen in Eq. 9 the term $(\delta_1 - \delta_2)^2$ can lead only to positive values (or zero), that mean the heat must be absorbed when the solute is mixed with the solvent to form a regular solution. When the solubility parameter of the solute is equal to that of the solvent, then $\delta_1 - \delta_2 = 0$ and the last term of the equation becomes zero. The solubility of the solute then depends solely on the ideal solubility term of equation.

Several investigators, including Hildebrand, (11,22, 24) have recommended that expression in the form of Eq. 9 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 refered 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. A total activity coefficient, log γ_2, must be written consisting of the term representing physical or van der Waals forces, log γ_v and an additional term, log γ_R, representing residual forces presumably stronger forces

$$\log \gamma_2 = \log \gamma_v + \log \gamma_R \qquad \text{(Eq. 12)}$$

The total activity coeffient suggested by Hildebrand is

$$\log \gamma_2 = A (\delta_1^2 + \delta_2^2 - 2W) \qquad \text{(Eq. 13)}$$

where W is the interaction energy between the solute and solvent in an irregular solution and A stands for $V_2\phi_1^2/2.303\ RT$. From Eq. 9 the term on the right side, $A (\delta_1 - \delta_2)^2$, involved van der Waals forces and can be written as

$$\log \gamma_v = A (\delta_1 - \delta_2)^2 \qquad \text{(Eq. 14)}$$

Employing Eqs. 12,13,14, one obtains for the residual term.

$$\log \gamma_R = 2A (\delta_1\delta_2 - W) \qquad \text{(Eq. 15)}$$

Hence, the logarithm of the total activity coefficient may be written for irregular solution as :

$$\log \gamma_2 = A(\delta_1 - \delta_2)^2 + 2A\,(\delta_1\delta_2 - W) \qquad \text{(Eq. 16)}$$

and the modified Hildebrand solubility equation becomes :

$$-\log x_2 = \frac{\Delta Hf}{2.303\ RT}\left[\frac{Tm - T}{Tm}\right] + \frac{V_2\phi_1^2}{2.303\ RT}\,(\delta_1^2 + \delta_2^2 - 2W) \qquad \text{(Eq. 17)}$$

This equation is used to predict drug solubility in pure or mixed solvent liquid solution.

The final step utilized in the Extended Hildebrand Solubility Approach, the interaction energy, W, will be calculated using Eq. 17 from knowing other terms obtained experimentally. The observed W, are regressed versus a polynomial expression in the solubility parameter of mixed solvents (10,15,24,25) using an equation

$$W = a + b\delta_1 + c\delta_1^2 \qquad \text{(Eq. 18)}$$

in which a, b and c are coefficients. Then, back-calculating W and substituting into Eq. 17 allows calculation of predicted mole fraction solubility of the drug in the mixed solvents.

The solubility parameter for a mixture of two solvents a, b, is calculated using an equation.

$$\delta_1 = \frac{\phi_a\delta_a + \phi_b\delta_b}{\phi_a + \phi_b} \qquad \text{(Eq. 19)}$$

where ϕ_a and ϕ_b are volume fractions of pure solvent a, b used to form mixed solvents, δ_a and δ_b are solubility parameters of pure solvent a, b, respectively.

The total volume fraction of mixed solvent (ϕ_1) is calculated using an equation

$$\phi_1 = \frac{(1-X_2)V_1}{(1-X_2)V_1 + X_2V_2} \qquad \text{(Eq. 20)}$$

in which V_1 is the mean molar volume of mixed solvents, obtained using the relationship

$$V_1 = \frac{X_a M_a + X_b M_b}{\rho_1} \qquad \text{(Eq. 21)}$$

where X_i and M_i are the mole fraction and molecular weight of the individual solvent (a, b) in the mixture, respectively and ρ_1 is the density of mixed solvent at the experimental temperature determined using a pycnometer.

The ability to predict drug solubility in a solvent is of great value in the design of improved dosage forms and drug delivery systems. At present, the Extended Hildebrand Solubility Approach is acceptably used and results obtained are satisfactory(10-16).

The molar heat of fusion, ΔHf, is the energy that must be supplied to break a large fraction of the secondary valence force between neighboring chains as the substance melts (24). The ΔHf values for a number of drugs are presented elsewhere. All these molar heat of fusions are determined experimentally (11,27). The accurate and precise values are obtained using a differential scanning calorimeter (DSC) and caluculated employing an equation.

$$\Delta Hf(\text{sample}) = \left[\frac{\text{Sensitivity for sample} \times \Delta Hf(\text{std}) \times \text{Std wt.}}{\text{Sensitivity for std} \times \text{sample wt.} \times \text{Std MW}} \times \frac{\text{sample peak area} \times \text{sample MW}}{\text{Std peak area}} \right]$$

when the equipment is not available, the values of ΔHf are simply determined in a laboratory (27). The method starts at an equation for the solubility of solute in an ideal solution

$$-\log x_2^i = \frac{\Delta Hf}{2.303\ RT}\left[\frac{Tm - T}{Tm}\right] \qquad \text{(Eq. 4)}$$

Rearranging, Eq. 4 can be written as

$$-\log x_2^i = \frac{\Delta Hf}{2.303\ RTm} - \frac{\Delta Hf}{2.303\ R} \cdot \frac{1}{T} \qquad \text{(Eq. 4.1)}$$

$$-\log x_2^i = \frac{-\Delta Hf}{2.303\ RTm} \cdot \frac{1}{T} + \text{constant} \qquad \text{(Eq. 4.2)}$$

Eq. 4.2 is a linear regression form ($y = a + bx$). When $\log x_2^i$ is plotted against reciprocal of absolute temperature, ^{o}K, a slope of the graph is $\frac{-\Delta Hf}{2.303\ R}$. Assuming that the solution is ideal, the ΔHf value of the drug can be calculated from slope of the line.