Biotechnology: Pharmaceutical Aspects

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Volume VI: *Solvent Systems and Their Selection in Pharmaceutics and Biopharmaceutics*
P. Augustijns, M.E. Brewster

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Springer

AAPS PRESS

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Library of Congress Control Number: 2007924356

ISBN-13: 978-0-387-69149-7 e-ISBN-13: 978-0-387-69154-1

Printed on acid-free paper.

9 8 7 6 5 4 3 2 1

springer.com

Dedication

We would like to dedicate this volume to Prof. David Grant, who passed away on December 9, 2005. Prof. Grant held the William and Mildred Peters Endowed Chair in the College of Pharmacy, Department of Pharmaceutics at the University of Minnesota. Prof. Grant was an internationally recognized authority on solid-state properties of drugs. His research directly impacted the ability to make safe and effective pharmaceutical agents with reproducible and predictable biopharmaceutical performance. Prof. Grant was a prolific scientist with more than 200 scientific articles to his credit. He also gave back to the scientific community in many ways, including his participation on the editorial boards of various scientific publications including the *Journal of Pharmaceutical Sciences*, where he served as Associate Editor, as well as *Pharmaceutical Development and Technology* and *The AAPS Journal* (formerly *AAPS Pharm Sci*). Prof. Grant was often singled out by his peers for his excellent contributions to science; he received such awards as the Pharmaceutics Award in Excellence from the Pharmaceutical Research and Manufacturers Association Foundation as well as the 2004 Dale E. Wurster Research Award, the highest recognition in his discipline from the American Association of Pharmaceutical Scientists (AAPS). The legacy left by Prof. Grant is substantial and transformational. We are indebted to him on so many levels, including his contribution to this monograph.

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Preface

Solvent systems are integral to drug development and pharmaceutical technology. This single topic encompasses numerous allied subjects running the gamut from recrystallization solvents to biorelevant media. The goal of this contribution to the **Biotechnology: Pharmaceutical Aspects** series is to generate both a practical handbook as well as a reference allowing the reader to make effective and informed decisions concerning the use of solvents and solvent systems. To this end, the monograph was created by inviting recognized experts from a number of fields to author relevant sections. Specifically, 14 chapters have been designed to cover the theoretical background of solubility, the effect of ionic equilibria and pH on solubilization, the use of solvents to effect drug substance crystallization and polymorph selection, the use of solvent systems in high throughput screening and early discovery, solvent use in preformulation, the use of solvents in biorelevant dissolution and permeation experiments, solvents and their use as toxicology vehicles, solubilizing media and excipients in oral and parenteral formulation development, specialized vehicles for protein formulation, and solvent systems for topical and pulmonary drug administration. The chapters are organized such that useful decision criteria are included together with the scientific underpinning for their application. In addition, trends in the use of solvent systems and a balance of current views make this monograph useful, we hope, to both the novice and experienced researcher and to scientists at all developmental stages from early discovery to late pharmaceutical operations.

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Principles of Solubility

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Introduction

Solubility is defined as the maximum quantity of a substance that can be completely dissolved in a given amount of solvent, and represents a fundamental concept in fields of research such as chemistry, physics, food science, pharmaceutical, and biological sciences. The solubility of a substance becomes especially important in the pharmaceutical field because it often represents a major factor that controls the bioavailability of a drug substance. Moreover, solubility and solubility-related properties can also provide important information regarding the structure of drug substances, and in their range of possible intermolecular interactions. For these reasons, a comprehensive knowledge of solubility phenomena permits pharmaceutical scientists to develop an optimal understanding of a drug substance, to determine the ultimate form of the drug substance, and to yield information essential to the development and processing of its dosage forms.

In this chapter, the solubility phenomenon will be developed using fundamental theories. The basic thermodynamics of solubility reveals the relation between solubility, and the nature of the solute and the solvent, which facilitates an estimation of solubility using a limited amount of information. Solubility-related issues, such as the solubility of polymorphs, hydrates, solvates, and amorphous materials, are included in this chapter. In addition, dissolution rate phenomena will also be discussed, as these relate to the kinetics of solubility. A discussion of empirical methods for the measurement of solubility is outside the scope of this chapter, but is reviewed elsewhere (Grant and Higuchi, 1990; Grant and Brittain, 1995).

Units for the Expression of Solubility

A discussion of the thermodynamics and kinetics of solubility first requires a discussion of the method by which solubility is reported. The solubility of a substance may be defined in many different types of units, each of which represents an expression of the quantity of solute dissolved in a solution at a given temperature. Solutions are said to be *saturated* if the solvent has dissolved the maximal amount of solute permissible at a particular temperature, and clearly an *unsaturated* solution is one for which the concentration is less than the saturated concentration. Under certain conditions, metastable solutions that are *supersaturated* can be prepared, where the concentration exceeds that of a saturated solution. The most commonly encountered units in pharmaceutical applications are molarity, normality, molality, mole fraction, and weight or volume percentages.

The *molarity* (abbreviated by the symbol M) of a solution is defined as the number of moles of solute dissolved per liter of solution (often written as mol/L or mol/dm^3), where the number of moles equals the number of grams divided by its molecular weight. A fixed volume of solutions having the same molarity will contain the same number of moles of solute molecules. The use of molarity bypasses issues associated with the molecular weight and size of the solute, and facilitates the comparison of different solutions. However, one must exercise caution when using molarity to describe the concentrations of ionic substances in solution, because the stoichiometry of the solute may cause the solution to contain more moles of ions relative to the number of moles of dissolved solute. For example, a 1.0 M solution of sodium sulfate (Na_2SO_4) would be 1.0 M in sulfate ions and 2.0 M in sodium ions.

The *normality* (abbreviated by the symbol N) of a solution is defined as the number of equivalents of solute dissolved per liter of solution, and can be written as eq/L or eq/dm^3. Normality has the advantage of describing the solubility of the ionic compounds since it takes into account the number of moles of each ion in the solution liberated upon dissolution of a given number of moles of solute. The number of equivalents will equal the number of grams divided by the equivalent weight. For ionic substances, the equivalent weight equals the molecular weight divided by the number of ions in the compound. Equivalent weight of an ion is the ratio of its molecular (atomic) weight and its charge. Therefore, a molar solution of Na_2SO_4 is 2 N with respect to both the sodium and the sulfate ion. Since the volume of solution is temperature dependent, molarity and normality can not be used when the properties of solution, such as solubility, is to be studied over a wide range of temperature.

Molality is expressed as the number of moles of solute dissolved per kilogram of solvent, and is therefore independent of temperature since all of the quantities are expressed on a temperature-independent weight basis. The molality of a solution is useful in describing solubility-related phenomena at various temperatures, and as the concentration unit of colligative property studies. When the density of the solvent equals unity, or in the case of dilute aqueous solutions, the molarity and the molality of the solution would be equivalent.

Expressing solution concentrations in terms of the *mole fraction* provides the ratio of the number of moles of the component of interest to the total number of moles of solute and solvent in the solution. In a solution consisting of a single solute and a single solvent, the mole fraction of solvent, X_A, and solute, X_B, is expressed as:

$$X_A = \frac{n_A}{n_A + n_B} \tag{1}$$

$$X_B = \frac{n_B}{n_A + n_B} \tag{2}$$

where n_A and n_B are the number of moles of solvent and solute, respectively. Obviously the sum of the mole fraction of the two components must equal one:

$$X_A + X_B = 1 \tag{3}$$

Since mole fractions provide quantitative information of a mixture that can be readily translated down to the molecular level, this unit is most commonly used in thermodynamic studies of solubility behavior.

Volume fraction is frequently used to define the composition of mixed solvent systems, or to express the solubility of one solvent in another. However, since the volumes of solutions exhibit a dependence on temperature, the expression of concentrations in terms of volume fraction requires a simultaneous specification of the temperature. In addition, since volume defects may occur during the mixing of the solvents, and since these will alter the final obtained volume, defining the solubility of a solution in terms of volume fraction can lead to inaccuracies that can be avoided through the use of other concentration parameters.

The concept of *percentage* is widely used as a concentration parameter in pharmaceutical applications, and is expressed as the quantity of solute dissolved in 100 equivalent units of solution. The *weight percentage* (typically abbreviated as % w/w) is defined as the number of grams of solute dissolved in 100 grams of solution, while the *volume percentage* (typically abbreviated as % v/v) is defined as the number of milliliters of solute dissolved in 100 mL of solution. A frequently encountered unit, the *weight-volume percentage* (typically abbreviated as % w/v) expresses the number of grams of solute dissolved in 100 mL of solution. The choice of unit to be used depends strongly on the nature of solute and solvent, so the solubility of one liquid in another is most typically expressed in terms of the volume percentage. The use of weight or weight-volume percentages is certainly more appropriate to describe the concentration or solubility of a solid in its solution.

For very dilute solutions, solubility is often expressed in units of parts per million (ppm), which is defined as the quantity of solute dissolved in 1,000,000 equivalent units of solution. As long as the same unit is used for both solute and solvent, the concentration in parts per million is equivalent to the weight, volume, or weight-volume percentages multiplied by 10,000. The descriptive terms of solubility that is expressed in units of parts of solvent required for each part of solute can be found in each edition of the United States Pharmacopeia (Table 1).

Descriptive term	Parts of solvent required for 1 part of solute
Very soluble	Solubility < 1
Freely soluble	1 < Solubility < 10
Soluble	10 < Solubility < 30
Sparingly soluble	30 < Solubility < 100
Slightly soluble	100 < Solubility < 1,000
Very slightly soluble	1,000 < Solubility < 10,000
Practically insoluble, or Insoluble	Solubility > 10,000

Table 1. Descriptive terms of solubility.

Reproduced from:

United States Pharmacopeia, 25th edition. United States Pharmacopeial Convention; Rockville, MD; 2002, p. 2363.

Thermodynamics of Solubility

The *equilibrium solubility* of a substance is defined as the concentration of solute in its saturated solution, where the saturated solution exists in a state of equilibrium with pure solid solute. As solutes and solvents can be gaseous, liquid, or solid, there are nine possibilities for solutions, although liquid-gas, liquid-liquid, and liquid-solid are of particular interest for pharmaceutical applications. Among these, the most frequently encountered solubility behavior involves solid solutes dissolved in liquid solvent, so systems of this type will constitute the examples of the following discussions.

For the particular system of a saturated solution, the dissolved solute in the solution and the undissolved solute of the solid phase are in a state of dynamic equilibrium. Under those conditions, the rate of dissolution must equal the rate of precipitation and hence the concentration of the solute in the solution remains constant (as long as the same temperature is maintained).

For two phases in equilibrium, the chemical potential, μ_i, of the component in the two phases must be equal:

$$\mu_{\text{solute}} = \mu_{\text{solid}} \tag{4}$$

The chemical potential, also known as the molar free energy, can be represented by:

$$\mu = \mu^\circ + RT \ln a \tag{5}$$

where μ° is the chemical potential of the solute molecule in its reference state, and a is the activity of the solute in the solution. Since both the dissolved solute and the undissolved solid must refer back to the same standard state, it follows

that the activities of the dissolved solute and that of the undissolved solid must be identical.

The activity of a component in a solution is defined as the product of its activity coefficient, γ, and its mole fraction, X:

$$a = \gamma X \tag{6}$$

For the solute **B** in a saturated solution:

$$a_{\text{solid}} = a_{\text{solute}} = \gamma_{\text{B}} X_{\text{B}} \tag{7}$$

or

$$X_{\text{B}} = \frac{a_{\text{solid}}}{\gamma_{\text{B}}} \tag{8}$$

According to equation (8), the solubility of a substance would be proportional to the activity of the undissolved solid, and inversely proportional to its activity coefficient. Although the activity of a substance in its standard state is defined as unity, the activity of the undissolved solid must depend on reference state. A hypothetical, supercooled liquid state of solute at the temperature of interest is commonly taken as the standard state, making the activity coefficient a more complicated term. The activity coefficient will depend on the nature of both the solute and solvent, as well as on the temperature of the solution.

Solubility in Ideal Solutions

In order to understand the thermodynamics of solubility, it is appropriate to begin with a simplified model of solution, namely that of an ideal solution. An ideal solution is defined as one where the activity coefficient of all components in the solution equals one. Under these stipulations, the activity of the dissolved solute, the activity of the solid, and the molar solubility of the dissolved solute would be equal.

$$a_{\text{solute}} = a_{\text{solid}} = X_{\text{B}} \tag{9}$$

As discussed above, the absolute activity of the solid depends on the chosen reference or standard state, and the usual practice is to take the supercooled liquid state of the pure solute at the temperature of solution as the standard state of unit activity. At temperatures lower than the melting point, the liquid state of the solute is less stable than its solid state, making the activity of the corresponding solid less than one.

An ideal solution requires that the scope of solute-solute, solvent-solvent, and solute-solvent intermolecular forces be all the same. Thus, the net energy change associated with breaking bonds between two solute molecules and two solvent molecules, and then forming new bonds between solute and solvent molecules must be zero. Moreover, the mixing process is ideal as well, so that the total volume of the solute/solvent system does not change during the mixing

process.

$$\Delta U_{mix} = 0 \tag{10}$$

$$\Delta H_{mix} = 0 \tag{11}$$

$$\Delta V_{mix} = 0 \tag{12}$$

where ΔU_{mix} is the energy of mixing, ΔH_{mix} is the enthalpy of mixing, and ΔV_{mix} is the volume change of mixing. The ideal entropy of mixing, ΔS_{mix}, can be derived from pure statistical substitution

$$\Delta S_{mix} = -R(n_A \ln X_A + n_B \ln X_B) \tag{13}$$

where n_A and n_B are the number of moles of the solvent (A) and the solute (B), respectively. Because the mole fractions of the solvent and the solute, X_A and X_B, are less than unity, it follows that ΔS_{mix} is always positive. From this analysis, one can conclude that the mixing processes associated with an ideal solution would be thermodynamically favored.

The dissolution of a solid in a solvent can be considered as consisting of two steps. The first step would be, in effect, a melting of the solid at the absolute temperature (T) of the solution, and the second step would entail mixing of the liquidized solute with the solvent. The enthalpy of solution (ΔH_s) is therefore equal to the sum of the enthalpy of fusion (ΔH_f^T) and the enthalpy of mixing (ΔH_{mix}). However, since the enthalpy of mixing must equal zero for an ideal solution, it follows that the enthalpy of solution must equal the enthalpy of fusion of the solid at the given temperature, T:

$$\Delta H_s = \Delta H_f^T \tag{14}$$

For those situations where the temperature of study is not the same as the melting point, then $\Delta H_f^T \neq \Delta H_f^m$, where now ΔH_f^m is the enthalpy of fusion at the melting point(T_m). If one makes the approximation that the enthalpy of fusion is constant over the temperature range in the vicinity of the melting point, then:

$$\Delta H_s = \Delta H_f^T \approx \Delta H_f^m \tag{15}$$

Applying the Clausius-Clapeyron equation to the solubility calculation yields:

$$\left(\frac{\partial \ln a}{\partial T}\right)_P = \frac{\Delta H_s}{RT^2} \tag{16}$$

Integration of equation (16) provides the relationship known as the van't Hoff equation, which expresses the temperature dependence of the solubility of a solid solute (identified as species B) in an ideal solution:

$$\ln X_B = \ln a_B = -\frac{\Delta H_s}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right) \tag{17}$$

By combining equations (15) and (17), one finds that the molar solubility of the solute in an ideal solution (expressed in natural logarithmic form) is given by:

$$\ln X_B = \ln a_B = -\frac{\Delta H_f^m}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right) \tag{18}$$

Since the solid solute and its corresponding molten solid must be in a state of equilibrium at the melting point, it follows that:

$$\Delta G_f^m = \Delta H_f^m - T_m \Delta S_f^m = 0 \tag{19}$$

where the enthalpy of fusion (ΔH_f^m) is equal to $T_m \Delta S_f^m$, where ΔS_f^m is the entropy of fusion at the melting temperature. Under these circumstances, equation (18) may also be written as:

$$\ln X_B = \ln a_B = -\frac{\Delta S_f^m}{R}\left(\frac{T_m}{T} - 1\right) \tag{20}$$

The enthalpy and entropy of fusion, and the melting temperature may all be measured through the use of differential scanning calorimetry (DSC), and therefore equations (18) and (20) provide a simple way to predict the solubility of a solute in an ideal solution.

To achieve a better prediction of the solubility of a solute, one must consider the temperature dependence of the enthalpy of fusion, which is described by the Kirchoff equation

$$\left(\frac{\partial \Delta H_f}{\partial T}\right)_P = \Delta C_p \tag{21}$$

where ΔC_p is the difference between the heat capacities of the supercooled liquid and that of the corresponding solid. Therefore:

$$\Delta H_f^T = \Delta H_f^m - \Delta C_p\,(T_m - T) \tag{22}$$

With the assumption that ΔC_p is independent of temperature, integration of equation (16) and the replacement of ΔH_s by ΔH_f^T, yields the Hildebrand equation

$$\ln X_B = \ln a_B = -\frac{\Delta H_f^m}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right) + \frac{\Delta C_p}{R}\frac{T_m - T}{T} - \frac{\Delta C_p}{R}\ln\frac{T_m}{T} \tag{23}$$

Equation (23) provides a better prediction of the solubility of a solute in an ideal solution.

Prediction of solubility in an ideal solution can also be performed using the entropy approach developed by Hildebrand and Scott (Hildebrand and Scott, 1962). Assuming that $\Delta H_s \approx T\Delta S_f^m \approx T\Delta C_p$, they found that:

$$\ln X_B = \ln a_B = -\frac{\Delta S_f^m}{R}\ln\frac{T}{T_m} \tag{24}$$

Equation (24) is similar to equation (20), except that $\ln(X_B)$ is correlated to $\ln(T)$ instead of $1/T$. The solubility prediction using equation (24) was found

to have a better tolerance for the non-ideality of the solution than that obtained using equation (20).

Several approaches have been used to predict the entropy of fusion required for the prediction of solubility. According to Walden's rule, the entropy of fusion (ΔS_f^m) is approximately equal to 13 cal/K·mol for most organic compounds (Walden, 1908). Use of this approximation reduces equation (20) to:

$$\ln X_B = \ln a_B = -\frac{\theta_m - 25}{298.15} \tag{25}$$

where θ_m is the melting point of the solute in degrees centigrade.

Yalkowsky proposed that the entropy of fusion of an organic compound is the sum of translational, rotational, and internal entropy changes when it is released from the crystal lattice (Yalkowsky, 1979):

$$\Delta S_f = \Delta S_{trans} + \Delta S_{rot} + \Delta S_{int} \tag{26}$$

while, the translational entropy change consists of the components associated with the expansion and change of position as the solid melts.

$$\Delta S_{trans} = \Delta S_{exp} + \Delta S_{pos} \tag{27}$$

Yalkowsky also proposed empirical values and limits for these components. Both the Walden and Yalkowsky models provide ways by which one can predict the entropy of fusion, and therefore predict the solubility of the solute in an ideal solution.

Over a small temperature range, the enthalpy of solution of a solid can be assumed to be independent of temperature. The van't Hoff equation shows that $\ln(X_B)$ increases with temperature, until the solid melts at $T = T_m$. At this condition, the solid forms a liquid in the absence of solvent, and since $X_B = 1$, the slope of the van't Hoff plot is equal to $(\Delta H_S/R)$. The degree of ideality associated with a given solution may therefore be tested by evaluating the degree of linear correlation between $\ln(X_B)$ and $1/T$. Figure 1 shows the ideal behavior of naphthalene dissolved in benzene and xylene, which is due to the similar nature of the molecules involved, and the strength of intermolecular interactions such as polarity, polarizability, molecular volume, and hydrogen-bonding characteristics (Grant and Higuchi, 1990). On the other hand, the molecular properties of ethanol are very different from those of naphthalene. Thus one finds that for solutions of naphthalene in ethanol, $\ln(X_B)$ does not exhibit a linear dependence on $1/T$, which is taken as an indication of the non-ideal character of the solution.

Typically, one finds that the solubility that would be predicted assuming the model of an ideal solution is normally much higher than the solubility that is actually measured for a non-ideal solution.

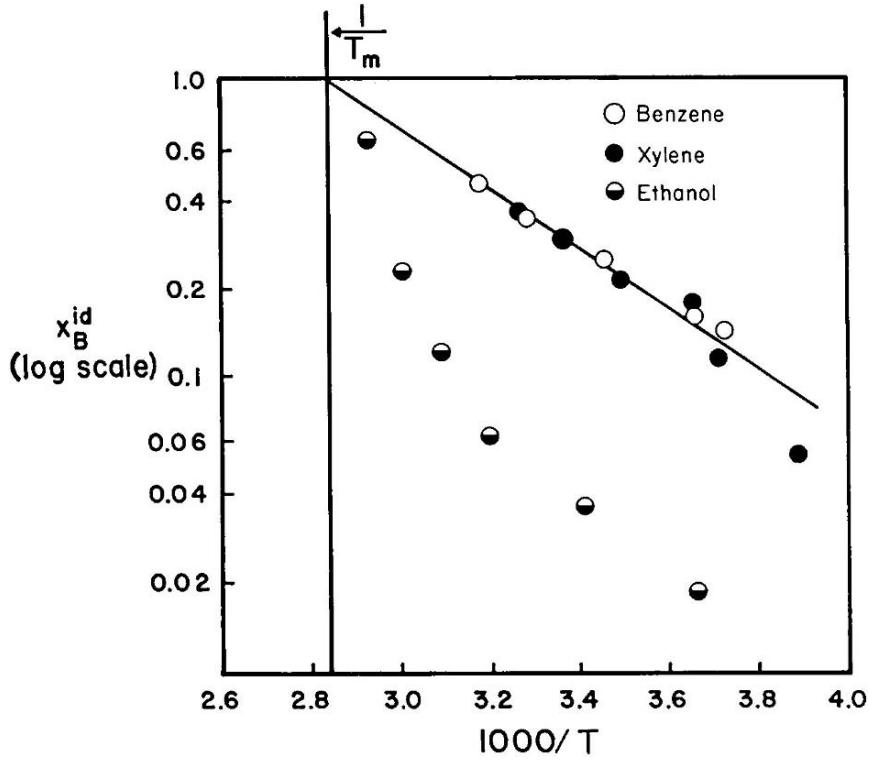

Figure 1. Van't Hoff plot of the molar solubility of naphthalene in benzene, xylene, and ethanol as a function of the reciprocal of the absolute temperature. The solid line corresponds to equation (17) for the ideal solubility of solid. Reproduced from DJW Grant, and T Higuchi, *Solubility Behavior of Organic Compounds*, John Wiley & Sons, New York, NY, 1990, p. 17.

Solubility in Regular Solutions

One rarely encounters ideal solutions in practice, and practically all solutions of pharmaceutical interest are non-ideal in character. For such non-ideal solutions, the activity coefficient (γ_B) of the solute does not equal one because the range of solute-solute, solvent-solvent, and solute-solvent interactions are significant. Therefore, one must consider the effect of the activity coefficient in order to predict the properties of non-ideal solutions:

$$X_B = \frac{a_B}{\gamma_B} \tag{28}$$

$$\ln X_B = \ln a_B - \ln \gamma_B \tag{29}$$

In equations (28) and (29), a_B is the activity of the dissolved solute and the undissolved solid, which may be evaluated using the hypothetical supercooled liquid as the standard state of unit activity. $\ln(a_B)$ may be expressed by equation

(17), as was the case for ideal solutions. Therefore:

$$\ln X_B = -\frac{\Delta H_s}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right) - \ln \gamma_B \tag{30}$$

The value of the activity coefficient depends on many factors, and for non-ideal solutions the activity coefficient may be predicted from knowledge of the nature of the solute and the solvent.

For the sake of simplicity, the prediction of activity coefficients in regular solutions, the simplest non-ideal solution, will be discussed. For a regular solution, the energy of mixing and the enthalpy of mixing are not negligible because the intermolecular solute-solute, solvent-solvent, and solute-solvent interactions are different. However, the total volume is still assumed to be unchanged during mixing.

The activity coefficient in a regular solution can be estimated by considering the changes in intermolecular interaction energies that accompany the mixing of solute and solvent. For this purpose, the solution process may be divided into the three steps illustrated in Figure 2. The first step would consist of the removal of a solute molecule from its pure solute phase into the vapor phase, the second step would be the creation of a hole in the solvent for incorporation of the solute molecule, and the third step is the process where the free solute molecule fills the hole created in the solvent (Higuchi, 1949; Hildebrand and Scott, 1950; Martin, 1993).

To begin the analysis, the potential energy of solute-solute, solvent-solvent, and solute-solvent pairs is identified as w_{BB}, w_{AA}, and w_{AB}. In the first step, an energy equal to $2w_{BB}$ must be absorbed to break the solute-solute interaction between two adjacent solute molecules in the solid. After the solute molecule

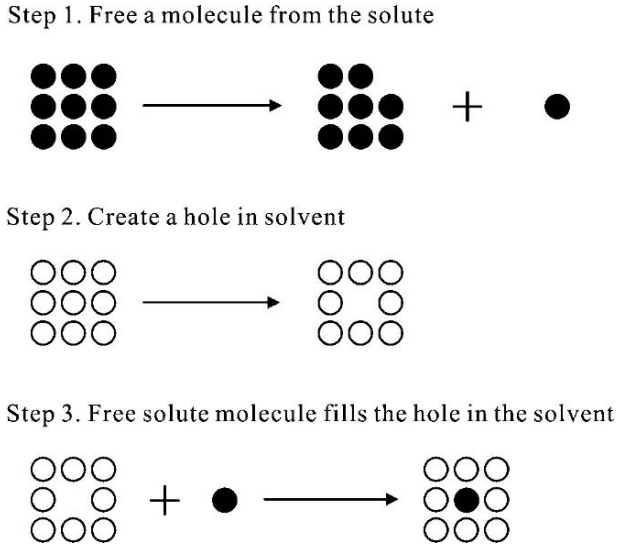

Figure 2. Hypothetical steps in solution process.

is removed to the vapor phase, the hole created in the solute closes, which releases an energy equal to w_{BB}, making the net energy change associated with liberation of a solute molecule equal to w_{BB}. In the second step, energy equal to w_{AA} is absorbed to separate a pair of solvent molecules, and to produce a hole in the solvent which the solute molecule may occupy. Finally, the solute molecule liberated from its solid phase is inserted in the hole in the solvent, forming two solute-solvent interactions and releasing an energy equal to $2w_{AB}$. The overall potential energy change, Δu, is therefore:

$$\Delta u = w_{AA} + w_{BB} - 2w_{AB} \tag{31}$$

Using this simplified model, Hildebrand and Wood (1933) proposed

$$\ln \gamma_B = (w_{AA} + w_{BB} - 2w_{AB}) \frac{V_B \Phi_A^2}{RT} \tag{32}$$

where V_B is the molar volume of the solute in the supercooled state, Φ_A is the volume fraction of the solvent in solution, R is the gas constant, and T is the absolute temperature of the solution.

The attractive interactions between pairs of solute and solvent molecules are assumed to be derived from van der Waals forces, so the solute-solvent interaction energy (w_{AB}) may be represented by the geometric mean of the solute-solute (w_{BB}) and the solvent-solvent (w_{AA}) interaction energies:

$$w_{AB} = \sqrt{w_{AA}\, w_{BB}} \tag{33}$$

Therefore, equation (32) becomes:

$$\ln \gamma_B = ((w_{AA})^{\frac{1}{2}} - (w_{BB})^{\frac{1}{2}})^2 \frac{V_B \Phi_A^2}{RT} \tag{34}$$

The square root of the interaction energy is defined as the solubility parameter, δ, and so equation (34) can be rewritten as:

$$\ln \gamma_B = (\delta_A - \delta_B)^2 \frac{V_B \Phi_A^2}{RT} \tag{35}$$

where δ_A and δ_B are the solubility parameters of the solvent and solute, respectively. In the case of a mixed solvent system, the total solubility parameter of the solvent mixture is given by:

$$\delta_A = \phi_1 \delta_1 + \phi_2 \delta_2 + \cdots \tag{36}$$

where δ_1 and δ_2 refer to the respective solvent parameters of pure solvents 1 and 2, and ϕ_1 and ϕ_2 are the respective volume fractions in the solvent mixture.

Introducing equation (35) into equation (30) yields the Hildebrand solubility equation describing regular solution behavior:

$$\ln X_B = -\frac{\Delta H_s}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right) - (\delta_A - \delta_B)^2 \frac{V_B \Phi_A^2}{RT} \tag{37}$$

According to equation (37), if the difference between δ_A and δ_B is very small, then the second term approaches zero. The implication of this is that a regular

solution would behave in an ideal manner when the solute and solvent have similar chemical properties. It may be seen that the Hildebrand solubility equation enables the prediction of solubility in regular solutions, as long as one has knowledge of the solubility parameters of both components in the solution.

Following the introduction of the Hildebrand model, the topic of solubility parameters has been extensively discussed (Hildebrand and Scott, 1962; Hildebrand et al., 1970; Kumar and Prausnitz, 1975; Barton, 1983), and values of δ can be found in these reference works. As a general rule, compounds having stronger London forces will be characterized by larger solubility parameters values.

Hildebrand and Scott (1950) proposed that the solubility parameters of similar molecules could be calculated using the enthalpy of vaporization (ΔH_v) and the molar volume of the liquid component (V_l) at the temperature of interest:

$$\delta = \left(\frac{\Delta H_v - RT}{V_l} \right)^{\frac{1}{2}} \tag{38}$$

Predictions of the solubility of non-polar solutes in non-polar solvents have been successfully achieved using the Hildebrand solubility equation (Davis et al., 1972). These solutions may be classified as regular solutions since the primary intermolecular interactions are London dispersion forces. However, the equation does not provide a good prediction of solubility for solutions involving polar components. When dipole-dipole, dipole-induced-dipole, charge transfer, and/or hydrogen-bonding interactions exist in the solution, $w_{AB} \neq \sqrt{w_{AA} w_{BB}}$, and with the presence of hydrogen bonding the entropy of mixing is no longer ideal. In addition, ΔV_{mix} will not equal zero if the dimensions of the solute and solvent molecules are very different.

Modifications to the Hildebrand solubility parameter model have been advanced in attempts to achieve better degrees of solubility prediction (Taft et al., 1969; Rohrschneider, 1973). Among these, the three-dimensional solubility parameter introduced by Hansen and Beerbower (1971) showed the most practical application. These workers calculated the total solubility parameter (δ_{total}) using three partial parameters, δ_D, δ_P, and δ_H:

$$\delta^2_{total} = \delta^2_D + \delta^2_P + \delta^2_H \tag{39}$$

where the parameters δ_D, δ_P, and δ_H account for dispersion, polar, and hydrogen-bonding interactions, respectively. Some of the values deduced for δ_D, δ_P, δ_H, and δ_{total} are listed in Table 2. Another modification of Hildebrand solubility parameter considered the effects of polar interaction and hydrogen bonding, and was found to yield good solubility predictions in many cases (Kumar and Prausnitz, 1975). However, the modified Hildebrand solubility equation can only be used empirically in predicting solubility in polar solvents, since the original assumptions associated with regular solutions do not apply in polar solvents (Grant and Higuchi, 1990).

In solvent systems where polar interactions exert a major role, the molecular and group-surface-area (MGSA) approach provides a better quality solubility prediction (Yalkowsky et al., 1972, 1976; Amidon et al., 1974, 1975). Instead of

Solvents	Solubility parameter $(cal/cm^3)^{1/2}$			
	δ_D	δ_P	δ_H	δ_{total}
n-Butane	6.9	0	0	6.9
n-Hexane	7.3	0	0	7.3
n-Octane	7.6	0	0	7.6
Diethyl ether	7.1	1.4	2.5	7.7
Cyclohexane	8.2	0	0.1	8.2
n-Butyl acetate	7.7	1.8	3.1	8.5
Carbon tetrachloride	8.7	0	0.3	8.7
Toluene	8.8	0.7	1.0	8.9
Ethyl acetate	7.7	2.6	3.5	8.9
Benzene	9.0	0	1.0	9.1
Chloroform	8.7	1.5	2.8	9.3
Acetone	7.6	5.1	3.4	9.8
Acetaldehyde	7.2	3.9	5.5	9.9
Carbon disulfide	10.0	0	0.3	10.0
Dioxane	9.3	0.9	3.6	10.0
1-Octanol	8.3	1.6	5.8	10.3
Nitrobenzene	9.8	4.2	2.0	10.9
1-Butanol	7.8	2.8	7.7	11.3
1-Propanol	7.8	3.3	8.5	12.0
Dimethylformamide	8.5	6.7	5.5	12.1
Ethanol	7.7	4.3	9.5	13.0
Dimethyl sulfoxide	9.0	8.0	5.0	13.0
Methanol	7.4	6.0	10.9	14.5
Propylene glycol	8.2	4.6	11.4	14.8
Ethylene glycol	8.3	5.4	12.7	16.1
Glycerin	8.5	5.9	14.3	17.7
Formamide	8.4	12.8	9.3	17.9
Water	7.6	7.8	20.7	23.4

Table 2. Solubility parameters for some common solvents.

Reproduced from:

Hansen C, and Beerbower A. Solubility Parameters. In: Standen A. *Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed. Supplement Volume.* New York, NY: Wiley; 1971. 889–910.

the potential energy term that was used in equation (32), a free energy model was used in the MGSA approach to represent the change of the interactions at mixing. The power of this approach is that changes in enthalpy and entropy are included:

$$\ln \gamma_B = (W_{AA} + W_{BB} - 2W_{AB}) \frac{V_B \phi_A^2}{RT} \tag{40}$$

In equation (40), W is reversible work which represents the internal free energy. Yalkowsky et al. (1976) used the molar surface area (A) and the surface tension (σ) to replace the molar volume (V) and reversible work. Under those circumstances, equation (40) becomes:

$$\ln \gamma_B = \frac{\sigma_{AB} A_B}{kT} \tag{41}$$

where σ_A and σ_B are the surface energies of the pure liquids A and B, while σ_{AB} is the interfacial energy between the two liquids. The interfacial tension can be experimentally measured for substances of different polarity, and therefore equation (41) better predicts solubility in polar solvents.

Intermolecular Interactions in Non-Ideal Solutions

Prediction of solubility using the regular solution theory usually fails when the solute and solvent are polar in character. The dipole-dipole, dipole-induced-dipole, charge-transfer, and hydrogen bonding interactions that exist between solute and solvent molecules may reduce the free energy of the solution, and increase the solubility. In these solutions, the activity coefficient may be less than one, a fact that cannot be explained using regular solution theory. The range of dipole-dipole, dipole-induced-dipole, and hydrogen bonding interactions in polar solutions may also lead to molecular orientation, which would tend to decrease the entropy of mixing. Clearly the nature of the forces involved in solution, and the influence of the forces on solubility, are important in order to arrive at a better understanding of solubility behavior.

Coulombic interaction is a valence force between counterions, and in extreme situations a cation-anion pair might form a strong ion-dipole interaction in solution. Such interactions would tend to be major for ionic substances dissolved in non-polar solvent systems, but less so in polar solvents where the forces of solvation serve to disrupt ion pairs into individual solvated ions. These trends provide an insight into why salts tend to be soluble in polar solvents, but not in non-polar solvents.

Van der Waals forces represent important intermolecular interactions between nonelectrolyte substances, and can be categorized into dipole-dipole, dipole-induced-dipole, and induced-dipole-induced-dipole forces. Polar molecules, by definition, will have a permanent dipole moment, and will interact with the oppositely charged portions or other molecules having permanent dipole moments. The dipole-dipole interaction is known as the orientation effect, or as the Keesom force.

Molecules having delocalized electron systems or large molar volumes often are characterized by high degrees of polarizability. Their interaction with polar molecules can induce shifts in electron density that result in the transient presence of induced dipole moments, and the charged portions of the induced dipoles can form an attractive interaction with the neighboring polar molecule. This type of interaction is termed the dipole-induced-dipole force, the induction effect, or the Debye force. It is found that Keesom and Debye forces provide efficient molecular packing in crystals, accounting for the high stability, low thermodynamic activity, and the high melting point of many organic crystals. These attractive effects may yield substantial lattice energies for such crystals, and therefore tend to reduce their solubility in potential solvents.

All molecules, whether polar or nonpolar, are also attracted to each other by induced-dipole-induced-dipole interactions, which are known as dispersion forces, or London forces.

Nonpolar molecules can only interact by dispersion forces, while the interactions of polar molecules are often dominated by the Keesom forces. However, under certain circumstances it is still possible that dispersion forces might predominate over the other forces, even for polar molecules such as HCl. The Debye forces are often stronger than the London forces for highly polar molecules, and would predominate over Keesom forces for weakly polar molecules. Debye forces are selective, and important in explaining why certain nonpolar but polarizible molecules can still be soluble in polar solvents (Krishnan and Fredman, 1971).

Hydrogen atoms are small in size, and would be positively polarized in molecules where it is bound adjacent to an electronegative atom, A. Should another strongly electronegative atom, B, approach the hydrogen atom at a short distance, a strong interaction may develop that is termed a hydrogen bond. The strongest hydrogen bonds are formed when the electronegative atoms involved are fluorine, oxygen, or nitrogen, although chlorine and sulfur are known to form weak hydrogen bonds in some molecules.

The strengths of hydrogen bonds are similar in magnitude to those of van der Waals forces, but is also directional in the manner of a covalent bond. Hydrogen bonding tends to stabilize molecular pairs and reduces the enthalpy, but also tends to orient the molecules involved and decrease the entropy. The effect of hydrogen bonding on solubility is complicated, and the analysis must proceed on a case-by-case basis. Extensive intermolecular hydrogen bonding in a crystal would tend to decrease the free energy, with this stabilization effect reducing the activity of the solute, and tending to reduce the solubility. However, the hydrogen bonds formed between solute and solvent molecules would tend to reduce the activity coefficient, and this effect would lead to increased solubility.

Influence of Temperature on Solubility

For ideal solutions, the van't Hoff relation of equation (17), and the Hildebrand relation of equation (24), state that the $\ln(X_B)$ term is linearly dependent on $1/T$ and on $\ln(T)$. The enthalpy of solution is equal to the enthalpy of melting

(*i.e.*, $\Delta H_s = \Delta H_f^T$), since the enthalpy of mixing is zero for an ideal solutions. Since ΔH_s for ideal solutions is always endothermic and positive, the solubility of an ideal solution would increase with increasing temperature.

In non-ideal solutions, however, the enthalpy of solution does not equal the enthalpy of melting because the enthalpy of mixing does not equal zero. Moreover, because the heat capacity of the solid is different from the heat capacity of the supercooled liquid, the ΔC_p term does not equal zero, and:

$$\Delta H_s = \Delta H_f^m - \Delta C_p(T_m - T) + \Delta H_{mix} \tag{42}$$

The strong solute-solvent interactions in solution may significantly reduce the free energy of the final solution compared to that of the pure solute and solvent. Despite the positive entropy of mixing, the enthalpy of mixing term may be negative, especially when the molecules in solution are oriented by the strong polar-polar, polar-induced-polar, and/or hydrogen-bonding interactions. Moreover, the second term in equation (42) may yield a negative contribution to the total enthalpy of solution. Therefore, the dissolution of a solute in a non-ideal solution might turn out to be an exothermic process, characterized by a negative ΔH_s. For those systems where ΔH_s is negative, it follows that the solubility would decrease with increasing temperature. The dissolution of carbon dioxide in water is characterized by a negative enthalpy of solution, and therefore carbonated waters go flat when their temperature is raised.

Grant et al. (1984) proposed an equation that better represents the temperature dependence of the molar solubility of polar organic compounds in water:

$$\ln X_B = -\frac{a}{R}\frac{1}{T} + \frac{b}{R}\ln T + c \tag{43}$$

In equation (43), a, b, and c are adjustable parameters, and this equation enables one to simulate the solubility of most solute-solvent combinations over a wide temperature range.

Solubility of Substances in Various Solid-State Forms

Many pharmaceutical solids are capable of existing in several different solid-state forms, such as polymorphs, solvatomorphs, and amorphous form (Brittain, 1999; Bernstein, 2002). *Polymorphism* is defined as the ability of a substance to exist in two or more crystalline phases that differ in the arrangement and/or conformation of the molecules in the crystal structure with the empirical formula of a polymorphic pair being identical. Polymorphism can arise from a different packing arrangement of molecules having the same conformation, or from the alternate assembly of different conformational states of the same molecule. *Solvatomorphism (pseudopolymorphism)* is defined as the ability of a substance to exist in two or more crystalline phases that differ in their empirical formulae with solvatomorphs being characterized by the presence of water (i.e., hydrates) or other solvent molecules (i.e., solvates) in the crystal structure. An *amorphous* solid

is characterized by a disordered arrangement of molecules, where intermolecular forces impose short range order and where there is no long range order in the solid.

The different internal energies of these structural types are manifested in different magnitudes of lattice energy, and hence lead to the existence of different solubilities for the various forms. The solubility difference may be understood using the solution models that have been developed in the previous sections. For dissolution to take place, the solute-solvent attractive forces must be stronger than the solute-solute and solvent-solvent attractive interactions so that the latter may be overcome by the former. As always, the free energy change associated with the process determines the ultimate equilibrium solubility of the solute in the solution. Details of the internal structure of the various solid-state forms will determine the respective enthalpies of solution, and the differing enthalpies of solution associated with the various different solid-state forms will lead to the existence of differing solubilities. These phenomena will be considered using the basic thermodynamic theory.

Solubility of Polymorphic Substances

The attraction force between two neighboring molecules of a solute is determined by the interactions existing in the crystal structure. Consequently, the internal energy (U) of a particular polymorph is equal to the sum of the individual energies of interaction between each pair of neighboring molecules as these are dictated by the details of the crystal structure. At constant pressure (P), the enthalpy (H) of a polymorph is defined as:

$$H = U + P \times V \tag{44}$$

where V is the volume of the crystal. The stability of the polymorph is determined by its free energy (G):

$$G = H - T \times S \tag{45}$$

where S is the entropy of the polymorph. The polymorph with the lowest free energy is termed the thermodynamically stable form, and the polymorphs having higher free energies are termed the metastable forms. Following accepted nomenclature, Form-I will be identified as the stable crystal form, and Form-II will be identified as the metastable form.

The solubility of the most stable crystal form in a polymorphic system is termed the *equilibrium solubility*. While the measurement of equilibrium solubility at a given temperature is a routine practice in pharmaceutical research (Grant and Brittain, 1995), evaluation of the solubility of a metastable polymorph is frequently more complicated owing to the tendency of metastable forms to undergo a phase transformation to the more stable polymorph in the medium of measurement. It is therefore prudent to include a determination of the phase at the completion of any solubility measurement to verify exactly which polymorphic form has been the subject of the measurement.

Several indirect methods have been proposed to determine the solubility of metastable polymorphs. Milosovish (1964) deduced the relative solubilities of metastable and stable polymorphs based on the measurement of intrinsic dissolution rates. Ghosh and Grant (1995) proposed an extrapolation technique to determine the solubility of a crystalline solid that undergoes a phase change upon contact with a solvent medium. Brittain (1996) used the time evolution of light scattering from aqueous suspensions of anhydrous theophylline as a means to evaluated its solubility, and also to study its phase transformation into its monohydrate solvatomorph.

In many systems, measurement of the solubility of a metastable form can be directly obtained if there is an energy barrier between the metastable polymorph and the stable polymorph that prevents interconversion during the lifetime of the measurement. If the free energy difference of the polymorphs, which is the driving force of the phase transformation, does not overcome the activation energy barrier, the metastable polymorph may stay unchanged for a sufficiently long period of time to permit a direct determination of solubility to be made.

Solubility of Solvatomorphic Substances

Solvatomorphs are formed when solvent molecules become incorporated into a crystalline solid, and occupy regular positions in the crystal lattice. In other cases, the crystal structure may contain channels having repetitive sites of hydrophilicity or hydrophobicity, and solvent molecules can become attached to those sites. Hydrates are those solvatomorphs where water molecules constitute an integral part of the crystal structure, and are typically contained in a defined ratio. Hydrates will be specifically discussed since those solvatomorphs are often of highest interest for pharmaceutical applications, but the results of the discussion apply equally well to solvatomorphs containing solvent molecules other than water.

In the presence of water, hydrated and anhydrous crystals can be considered as being in equilibrium:

$$\mathrm{A(solid)} + \mathrm{mH_2O} \overset{K_h}{\longleftrightarrow} \mathrm{A \cdot mH_2O(solid)} \tag{46}$$

where A(solid) and $\mathrm{A \cdot mH_2O(solid)}$ refer to the anhydrous and hydrated phase, respectively, **m** is the stoichiometry of the hydrate, and K_h is the equilibrium constant of hydration:

$$K_h = \frac{a[\mathrm{A \cdot mH_2O(solid)}]}{a[\mathrm{A(solid)}]\, a[\mathrm{H_2O}]^{\mathrm{m}}} \tag{47}$$

Equation (47) indicates that the activity ratio of the hydrated and anhydrous crystals depend on the activity of water. When $a[\mathrm{H_2O}]^{\mathrm{m}}$ is greater than $\{a[\mathrm{A} \cdot \mathrm{mH_2O(solid)}]/K_h \cdot a[\mathrm{A(solid)}]\}^{1/\mathrm{m}}$, the hydrated form is more stable than the anhydrous form (Zhu and Grant, 1996). Obviously when the value of

$\{a[A \cdot mH_2O(solid)]/K_h \cdot a[A(solid)]\}^{1/m}$, exceeds that of $a[H_2O]^m$, the anhydrate form would be more stable. The addition of a miscible cosolvent would reduce the water activity, and would move the position of equilibrium toward that of the anhydrous form.

As a rule of thumb, hydrated crystalline forms are usually less soluble in water than are the corresponding anhydrate crystalline forms (Grant, 1990), and thus solid solvates are usually less soluble in the solvating solvent than the original solid. However, the solubility of a solvate in a solvent that is miscible with the solvating solvent is higher than the corresponding non-solvated form. This phenomenon arises because the negative energy change of mixing associated with the solvents provides an additional contribution to the negative free energy of solution.

When $a[H_2O]$ equals zero, then $a[A \cdot mH_2O(solid)]/a[A(solid)]$ also equals zero. The consequence of this is that, thermodynamically speaking, the hydrated form is only stable in the presence of water. For this reason, the solubility of a hydrate crystal form can only be measured in water, as the solubility of a solvate can only be measured in the solvating liquid corresponding to the included solvate molecule. Similar to the metastable polymorphs, however, a solvate may be temporarily stable in absence of the solvating liquid due to a high energy barrier of desolvation.

Solubility of the Amorphous Form

As described above, amorphous solids are disordered in nature, and contain only short range order between the constituent molecules. Amorphous solids lack the stabilizing influence of lattice energy, and therefore are thermodynamically less stable than any of the corresponding crystalline forms of the substance. Since the amorphous form represents the most highly energetic solid state form of a material (Hancock and Zografi, 1996), it follows that amorphous materials exhibit the highest degree of solubility for a given substance.

In some instances, the relative solubilities of the amorphous and crystalline forms of a substance can be estimated using the same methodologies as would be used in the measurement of the solubility of polymorphic materials. Using a theoretical approach, Hancock and Parks (2000) proposed that the solubility advantage of the amorphous drug to its most stable crystalline form was about 16-fold to 1600-fold. The maximum concentration measured during the course of dissolution of the amorphous form was taken to represent the solubility of the amorphous form. However, the empirical data were less than that predicted, suggesting that the amorphous substances partially converted to a crystalline form during the lifetime of the solubility measurement. It is probably true that amorphous materials cannot achieve their maximum theoretical solubility under practical experimental conditions owing to phase transformations.

Sato et al. (1981) measured the solubility of amorphous substance by adding a nucleation inhibitor, but the measured solubility could have been affected by the presence of the nucleation inhibitor.

Dissolution Phenomena: Kinetics of Solubility

Systemic absorption of a drug substance from a particulate form takes place after the compound enters the dissolved state. If the dissolution rate of the substance is less than the diffusion rate to the site of absorption and the absorption rate itself, then the dissolution process will be the rate-determining step. This situation is characteristic of drug substances that have low degrees of aqueous solubility, and therefore low dissolution rates, and it has become an established tenet in pharmaceutics that one method to improve the dissolution rate of a relatively insoluble substance is to reduce the particle size of its component particles. As discussed above, the solubilities of polymorphs, solvatomorphs, and amorphous forms are different, and these differences may lead to differences in the dissolution rate, which in turn could lead to differences in bioavailability.

The mechanism of dissolution was proposed by Nernst (1904) using a film-model theory. Under the influence of non-reactive chemical forces, a solid particle immersed in a liquid experiences two consecutive processes. The first of these is solvation of the solid at the solid-liquid interface, which causes the formation of a thin stagnant layer of saturated solution around the particle. The second step in the dissolution process consists of diffusion of dissolved molecules from this boundary layer into the bulk fluid. In principle, one may control the dissolution through manipulation of the saturated solution at the surface. For example, one might generate a thin layer of saturated solution at the solid surface by a surface reaction with a high energy barrier (Mooney et al., 1981), but this application is not commonly employed in pharmaceutical applications.

In the majority of dissolution phenomena, the solvation step is almost instantaneous. The diffusion process is much slower and, therefore constitutes the rate limiting step. Noyes and Whitney (1897) developed an equation based on Fick's second law of diffusion to describe dissolution within the scope of their model, and report the relation:

$$\frac{dC}{dt} = \frac{DS}{h}(C_s - C) \tag{48}$$

where dC/dt is the rate of drug dissolution at time t, D is the diffusion coefficient, S is the surface area of the particle, h is the thickness of the stagnant layer, C_s is the concentration of the drug in the stagnant layer (usually taken as the equilibrium solubility), and C is the concentration of the drug in the bulk solvent. According to the Stock-Einstein equation for the small particles, the diffusion coefficient, D, is related to the viscosity of the liquid medium:

$$D = \frac{kT}{6\pi\eta r} \tag{49}$$

where k is the Boltzmann constant, T is the temperature, η is the viscosity of the solvent, and r is the radius of the particle.

According to the Noyes-Whitney equation (48), the dissolution rate of a drug substance is directly proportional to its equilibrium solubility. However, the nature of the dissolving solid and the dissolution medium also exert strong

influences on the dissolution rate. For example, metastable polymorphs will exhibit faster dissolution rates than would the thermodynamically stable polymorph, and amorphous materials will dissolve faster than any corresponding crystalline forms. Temperature may affect both the solubility and the diffusion coefficient, and in many cases the dissolution rate will increase with increasing temperature. Consequently, as was the case for solubility determinations, evaluation of drug dissolution must be conducted at a fixed and reported temperature.

The effect of particle size and dissolution rate has been known since the pioneering work of Noyes and Whitney (1897), and Hixson and Crowell (1931) subsequently derived a highly useful equation that expresses the rate of dissolution based on the cube root of the weight of the particles. When the Hixson-Crowell model is applied to micronized particles, for which the thickness of the aqueous diffusion layer around the dissolving particles is comparable to or larger than the radius of the particle, the change in particle radius with time is given by:

$$r^2 = r_0^2 - \frac{2DC_s t}{\rho} \tag{50}$$

where r_0 is the initial radius of the particle, r is the radius of the particle at time equal to t, D is the diffusion coefficient of the molecules dissolving from the particle, C_S is the equilibrium solubility of the substance, and ρ is the density of the solution.

A very useful relation is obtained for the time, T, which would be required to achieve complete dissolution of the particle, or the condition where $r^2 = 0$:

$$\mathrm{T} = \frac{\rho r_0^2}{2DC_s} \tag{51}$$

For most aqueous solutions, D is typically equal to 5×10^{-6} cm^2/sec, ρ is approximately equal to 1.0 g/mL, so the calculation of equation (51) can be performed if the equilibrium solubility of particles having a known initial particle size is known. Consider a substance whose equilibrium solubility is 1.0 mg/mL. For a particle whose initial diameter equals 10 μm, the time to achieve complete dissolution would be predicted to be 25 seconds (0.42 minutes). For the same substance, if the initial diameter instead equaled 50 μm, then the time to achieve complete dissolution would be predicted to be 625 seconds (10.4 minutes). For 100 μm particles of this substance, the time to achieve complete dissolution is calculated to be 2500 seconds (41.7 minutes). The relationship between particle size and the time required to completely dissolve particles of various sizes as defined in equation (51) has been illustrated in Figure 3.

This effect of particle size on dissolution rate of sparingly soluble drug substances has been demonstrated in many instances by the superior dissolution rates observed after size reduction. Examples of compounds studied in such work include methylprednisolone (Higuchi et al., 1963), 1-isopropyl-7-methyl-4-phenylquinazolin-2(1H)-one (Kornblum and Hirschorn, 1970), griseofulvin (Ullah and Cadawader, 1971), monophenylbutazone (Habib and Attia, 1985), nitrofurantoin (Eyjolfsson, 1999), and piroxicam (Swanepoel et al., 2000).

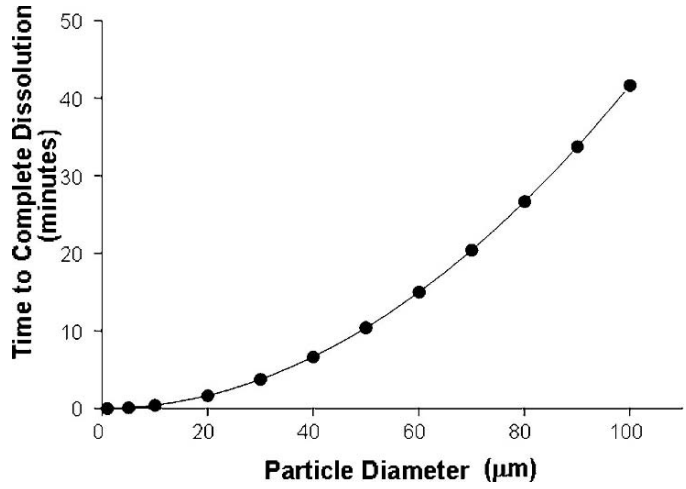

Figure 3. Relationship between particle size and the time required to completely dissolve particles of a given size.

Since the dissolution rate of a loosely suspended substance will depend on the particle size and surface area of the solid, the technique of intrinsic dissolution has been developed. In this method, the solid of interest is compressed into a die and embedded in a rotational disc where only one face of the compressed solid remains exposed to the dissolution medium. Under these circumstances, the area of the solid-liquid interface must remain constant during the dissolution process.

The dissolution rate (dm/dt) of a given solid is usually directly proportional to the wetted surface area (A) of the dissolving solid:

$$dC/dt = J \times A \tag{52}$$

where J is the mass flux, or the dissolution rate per unit surface area. J is usually termed the intrinsic dissolution rate. But since dC/dt is also defined according to the Noyes-Whitney equation (48), it follows that:

$$J = B \times (C_s - C) \tag{53}$$

where B is the mass transfer coefficient, defined as:

$$B = \frac{DS}{Ah} \tag{54}$$

At the earliest stage of an intrinsic dissolution study, $C << C_s$, so:

$$J_{t\to 0} = BC_s \tag{55}$$

It can therefore be concluded that if the surface area of the dissolving solid is kept constant, the intrinsic dissolution rate will be directly proportional to the equilibrium solubility.