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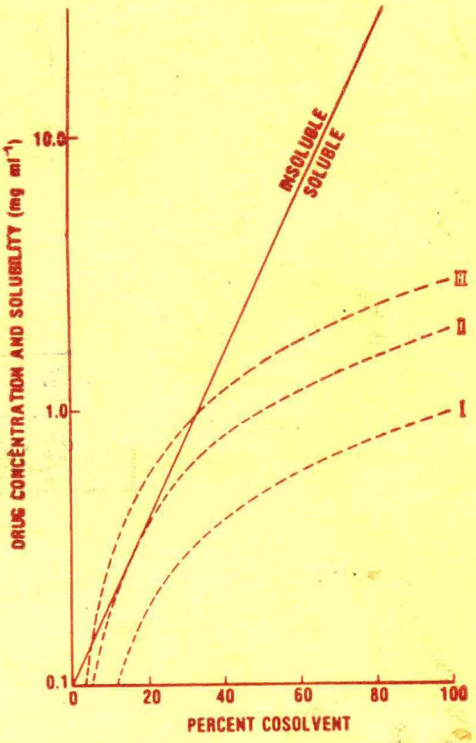
Techniques of Solubilization of Drugs



edited by Samuel H. Yalkowsky

TECHNIQUES OF SOLUBILIZATION OF DRUGS

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Foreword

The addition of drugs and other organic substances to various liquids, to produce solutions, is a very common procedure in all aspects of drug research and production. Although putting drugs into solution, particularly aqueous solution, increases the chances for chemical reactivity, and possible drug instability, the use of solutions as drug delivery systems has significant advantages. Certainly, in intravenous preparations it is the only approach which generally can be used. Thermodynamic stability which exists for molecules in solution, as opposed to the thermodynamic instability of suspensions or other disperse systems, is an important consideration for providing a reasonable guarantee of accurate dosage, particularly when small amounts of drug are to be delivered. Controlling the dissolution of drugs administered as solids, to optimize therapeutic activity is also an important reason for improving our understanding of solubilization. Nowhere is this more critical than when we deal with aqueous systems where complex organic molecules are most "unwelcome" from an energetic point of view.

For the formulator of pharmaceutical dosage forms, the task of optimizing solubility is made difficult because drug design does not generally include concern for a particular level of solubility, as well as other aspects of drug delivery. It would be extremely advantageous if one could design drugs with some a priori idea of the desired level of solubility in water and other solvents, and the structural components needed to accomplish this. It is fitting, therefore, that this book begins with a chapter which addresses the fundamental relationships among chemical structure, physical properties, and solubility.

Although our current state of knowledge does not allow exact prediction of solubility from chemical structure, the correlations developed here for a very wide range of nonelectrolytes is a major contribution toward that goal.

The options open to those who must produce a desired level of solubility are, indeed, quite extensive, yet the constraints brought about because of predetermined therapeutic and biopharmaceutical requirements and potential toxicity considerations can be significant. To this we should add the ever-present cost factor. The manipulation of molecules chemically to produce prodrugs presents an element of uncertainty since we must now rely on metabolic factors to produce the desired level of active species. Yet clearly, as described in this book, the significant improvement in solubilization of some highly insoluble drugs so as to make a difference in therapy more than offsets any such uncertainty. Going from chemical modification, we have the option to modify the solid-state properties of our drug in order to promote solubility. Here we see tremendous potential either by manipulating crystal forms or by adding agents which would tend to form and stabilize higher-energy solid forms. The critical uncertainty is that such high-energy forms can revert prematurely and cause unanticipated solubility problems. Fundamental knowledge of the solid state, as described in this book, will go a long way in helping to eliminate the uncertainties inherent in altering the solid state, and improve our use of this approach in formulations.

The major part of this book is devoted to the use of formulation ingredients, such as cosolvents, surfactants, and complexing agents, to promote solubility. Considering the widespread use of cosolvents, and to a lesser extent surfactants and complexing agents, to improve solubility, it is remarkable how little is really understood at a fundamental level. More important, perhaps, are the empirical and often naive approaches toward their use which are still in effect. What do you do when you have a drug to be solubilized in water for IV injection at a relatively high dose and you are severely limited by aqueous solubility and by the pH range to be used? What materials are available and how can one maximize the efficiency of solubilization before and after administration? The chapters dealing with cosolvents, micellar solubilization, and complexation as a means of promoting solubilization will be useful in pulling all of these principles into focus for critical examination and decision by the formulator.

In conclusion, a book which systematically brings together basic knowledge concerned with techniques of drug solubilization is a welcome tool for those who must deal with the complexities of drug product

formulation and manufacture. It is through such basic knowledge that the scientific approach to formulation will flourish. Ultimately, this will reap benefits in improving both the performance and economic aspects of drug delivery systems.

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Preface

It is well known that drug efficacy can be severely limited by poor aqueous solubility. It is also known that the side effects of some drugs are the result of their poor solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficacy and/or reducing side effects for certain drugs. This is true for parenterally, topically, and orally administered solutions. This book was developed in an attempt to provide a comprehensive guide to the techniques available for solubilizing drugs in aqueous vehicles.

There are a number of well-written books available which deal with solubilization by surfactants. Since surfactant solubilization is extremely important in pharmaceutical systems and is by far the most studied of the techniques covered, it will be discussed in the greatest detail in this book. There are several additional techniques which can be used to solubilize drugs. Although they tend to be less frequently utilized, they can be potentially more powerful than surfactant solubilization for increasing aqueous solubility.

Solubilization by cosolvents, complexing agents, crystal modification, and prodrug formation can individually or in combination be an extremely valuable means of solubilizing drugs. Each of these techniques is discussed from both the theoretical and practical points of view. For each technique, a wide variety of examples is provided along with rational guidelines for application to new and unstudied drugs.

It is hoped that Techniques of Solubilization of Drugs will serve as a useful guide to aid the pharmaceutical scientist in understanding, selecting, and utilizing all of the available means of overcoming solubility problems.

Samuel H. Yalkowsky

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Solubility and Solubilization of Nonelectrolytes

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Introduction

It is obvious from the following chapters that there are a variety of ways to solubilize a drug. To decide whether a particular drug can be solubilized to a specified extent, and if so, what technique of solubilization will be most effective, requires an understanding of why the drug is insoluble. Before considering the various means of solubilizing a drug, it is worthwhile to consider what factors cause the drug to be insoluble and the general ways in which these factors can be altered to increase aqueous solubility.

Factors Influencing Aqueous Solubility

The aqueous solubility of a drug is governed by three major factors [1]:

1. The entropy of mixing which favors complete miscibility of all components.
2. The difference between the sum of the drug-drug (DD) and water-water (WW) interactions on the one hand and the drug-water (DW) interactions on the other. This difference is related to the activity coefficient of the drug in water γ_w by

$$RT \ln \gamma_w = DD + WW - 2DW \quad (1)$$

If,

$$DD + WW - 2DW > 0 \quad (2)$$

as is usually the case for nonelectrolytes in water, there will be less than complete mixing and the drug will have a finite solubility in water. The greater the difference between the adhesive and cohesive interactions, the lower the solubility.

3. The additional drug-drug interactions that are associated with the lattice energy of crystalline drugs (DD). This effect is measured as the ideal solubility of a crystalline solute X_i^c. The ideal solubility will be shown to be dependent upon the melting point and other thermodynamic properties of fusion. The ideal solubility represents the solubility of a solute in a perfect solvent, i.e., a solvent for which the activity coefficient is equal to unity.

Mathematically, the observed solubility of a solute X_w is related to the ideal solubility and the activity coefficient by

$$\log X_w = \log X_i - \log \gamma_w \quad (3)$$

Both crystalline structure effects as reflected by X_i and solution interactions as reflected by γ_w can contribute to the insolubility of a solute. Also, both these factors can be modified as a means of solubilizing the drug. The remainder of this chapter will be devoted to assessing the relative roles of X_i and γ_w and to deciding which of these parameters needs to be altered in order to attain a desired degree of aqueous solubility.

Aqueous Solubility of Liquid Solutes

For a liquid solute the ideal mole fractional solubility is equal to unity so that the observed aqueous solubility is simply equal to the reciprocal of the aqueous activity coefficient.

$$\log X_w^1 = -\log \gamma_w \tag{4}$$

At present there are no well-established schemes for the estimation of the aqueous activity coefficients of nonelectrolytes. In order to develop such a scheme, it would be convenient to find an organic solvent for which γ_0 can be estimated and for which solvent/water mole fraction partition coefficients PC^x can also be estimated. This would enable the estimation of γ_w by

$$\log \gamma_w = \log PC^x - \log \gamma_0 \tag{5}$$

Fortunately, the solvent octanol satisfies both these requirements. It is an excellent solvent for most organic liquids, and the octanol-water system is the most studied of all partitioning systems. According to Hildebrand and Scott [2], a solute of similar size will be completely miscible with octanol if

$$(\delta_1 - \delta_2)^2 V < 2kT \tag{6}$$

where δ_0 is 10.3 the solubility parameter of octanol, δ_2 is the solubility parameter of the solute, and V is the average molar volume of the solute and octanol. For solutes of comparable size to octanol we can use 155 cm^3 for V. Upon substitution of the above values and rearrangement, Eq. (6) becomes

$$|10.3 - \delta_2| < 2.8 \tag{7}$$

which indicates that any solute for which $7.5 \leq \delta_2 \leq 13.1$ will be completely miscible with octanol. This range includes nearly all organic compounds less polar than ethanol and thus nearly all nonelectrolyte drugs. The solubility parameters of a number of common solutes are given in Table 1 for reference. This enables us to approximate X_0 and therefore γ_0 by a value of unity. Thus, log γ_0 in Eq. (5) vanishes, and we find that the aqueous activity coefficient of organic liquids is essentially equal to the octanol/water partition coefficient which is expressed in mole fractional units.

Ideal Solubility of Solid Solutes

Due to the efforts of Leo et al. [3], Hansch et al. [4], Nys, and Rekker [5], and others, it is possible to estimate the octanol/water partition coefficient of virtually any organic nonelectrolyte by a variety of group contribution schemes. Table 2 gives a set of substituent constants (f values) which have been found to work very well for this purpose.

TABLE 1 Solubility Parameters

Compound	Solubility parameter (δ)
n-Hexane	7.3
n-Heptane	7.5
n-Hexadecane	8.0
Cyclohexane	8.2
Carbon tetrachloride	8.6
Toluene	8.9
Ethyl acetate	9.1
Benzene	9.2
Chloroform	9.3
Aniline	9.8
Phenanthrene	9.8
Acetaldehyde	9.9
Naphthalene	9.9
Anthracene	9.9
Carbon disulfide	10.0
Dioxane	10.0
Nitrobenzene	10.0
t-Butyl alcohol	10.6
Benzoic acid	11.3
n-Propyl alcohol	11.9
Ethyl alcohol	13.0
Acetic acid	13.2
Iodine	14.1
Methyl alcohol	14.5
Glycerin	16.5
Water	23.4

Source: Adapted from A. Martin, Physical Pharmacy, Lea & Febiger, Philadelphia, 1960.

TABLE 2 Nys and Rekker f Values for Some Common Atoms and Groups

Substituent	f Value
Hydrocarbon	
CH_3	0.70
CH_2	0.53
CH (saturated)	0.24
CH (unsaturated)	0.36
C (saturated)	0.14
C (unsaturated)	0.16*
H	0.20
CH CH_2	0.93
C_6H_5	1.90
C_6H_4	1.73
C_6H_4	1.48
C_5H_4N	1.22

Nonhydrocarbon	Aliphatic	Aromatic
F	-0.41	0.43
Cl	0.06	0.93
Br	0.24	1.17
I	0.59	1.46
S	-0.51	0.14
SH	0.00	0.62
O	-1.54	-0.46
OH	-1.44	-0.37
OCH_3	-0.83	0.24
COO	-1.28	-0.40
COOH	-1.00	0.00
C=O	-1.69	-0.99
N	-2.13	-1.07
NH	-1.86	-0.93
NH_2	-1.38	-0.91
NO_2	-1.06	-0.09
$CONH_2$	-1.99	-1.26
C=N	-1.13	-0.20

*0.30 for carbon atom shared by two aromatic rings.

Source: From Ref. 11. Reproduced with permission of the copyright owner (Academic).

The log PC of the molecule is obtained by adding the f values for all of its constituents groups since

$$\log PC = \sum_{\substack{\text{all} \\ \text{groups}}} f_{\text{group}} \tag{8}$$

Conventional octanol/water partition coefficients refer to the distribution of the drug between equal volumes of octanol and water. It is necessary to convert conventional partition coefficients to mole fractional partition coefficients before they can be used in Eq. (5). This is accomplished by accounting for the molar volumes and density of both phases by

$$PC^x = PC \frac{\dfrac{\text{density of octanol}}{\text{molecular weight of octanol}}}{\dfrac{\text{density of water}}{\text{molecular weight of water}}} \tag{9}$$

which works out to

$$\log PC^x = \log PC + 0.94 \tag{10}$$

Substituting Eq. (5) and Eq. (10) into Eq. (4) gives

$$\log X_w^1 = -\log PC - 0.94 \tag{11}$$

which expresses the aqueous solubility as a linear function of the conventional octanol/water partition coefficient. This relationship has been tested by Valvani et al. [6], who showed that for 104 organic liquids (see Fig. 1)

$$\log X_w^1 = -1.08 \log PC - 1.04 \tag{12}$$

$r = 0.955 \quad s = 0.350$

which is in excellent agreement with Eq. (11)

The ideal mole fractional solubility of a solute is given by [2]

$$\log X_i = \frac{-\Delta H_f(T_f - T)}{T_f 2.303RT} - \frac{\Delta C_p}{R}\left[\frac{\Delta H_f(T_f - T)}{2.303T} + \log \frac{T_f}{T}\right] \tag{13}$$

where T and T_f are the temperature and freezing point, respectively, in degrees Kelvin. ΔH_f is the molar heat of fusion, and ΔC_p is the heat capacity difference between the crystalline and molten forms of the drug. Equation (13) can be simplified by replacing $(\Delta H_f/T_f)$ by ΔS_f,

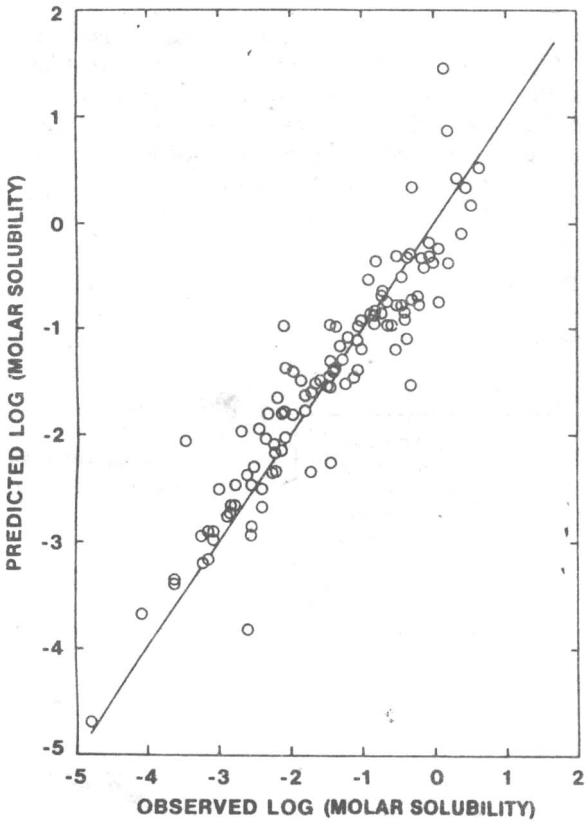

FIGURE 1 Predicted versus observed solubility of organic liquids in water. [From Ref. 6. Reproduced with permission of the copyright owner (J. Pharm. Sci.).]

the entropy of fusion, by assuming that ΔC_p is small compared to ΔS_f, by converting to degrees Celsius, and by assuming that T = 298K (25°C) to give [1]

$$\log X_i = \frac{-\Delta S_f}{1364} (MP - 25) \tag{14}$$

where MP is the melting point in degrees Celsius.

The estimation of ideal solubility now requires only a knowledge of the solute's melting point and entropy of fusion. Alternatively, the ideal solubility can be estimated from a knowledge of the melting point and a reasonable estimate of the entropy of fusion.