

Solubility and pharmacological importance

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Abstract - The solution properties of some compounds of pharmaceutical interest are described. Attention is drawn to the dependence of solubility on chain-length. The prediction of solubility from group contribution parameters is introduced. Transfer thermodynamics are outlined and their relevance for pharmaceuticals described.

Solutions of drugs can almost never be regarded as ideal. Moreover the solutions of interest frequently involve mixed and heterogeneous solvent systems (emulsions, micelles, liposomes, tissue/bacterial cell systems, etc.). Thus discussions of solution theory as presently understood, in the context of pharmaceutical sciences is likely to be of limited practical use and this view is endorsed by survey of the literature. This is not to imply that disregard of solution theory is appropriate or, indeed, that "no good will come of it".

Problems abound in the study of solutions of drugs - not only mixed solvents and heterogeneous solvent systems but, in practice, also problems associated with ionisation, presence of other solutes (formulation components etc), aggregation phenomena, and in vivo the problems associated with metabolism, transport, etc. are present.

Moreover it is possible that it is not the simple property of solubility that is important but perhaps the related properties of rate of solution and, for solid drugs, wettability.

There have, of course, been many attempt of predict solubility - commencing notably with the Hildebrand solubility parameter (see Barton, 1975).

Solubilisation in mixed solvents has become important since dissolution testing has become mandatory in most pharmacopoeias. The need for mixed solvent systems is of course a consequence of the poor aqueous solubility of many drugs. There has therefore been a serious effort made to understand the predict solubility in such solvent systems. The studies of Taft, Kamlet and Abraham do not require any other than the parametric values of the correlation equation in the selected solvent system to allow prediction of solubility. Gould (1984) has also attempted some semi-theoretical analysis.

Solubility parameters may be used to estimate the co-solubility of material through simple comparison of their δ values e.g. methylparaben, $\delta = 11.98$ is quite soluble in butylene glycol, $\delta = 13.70$ and in hexyl alcohol, $\delta = 10.50$ but is poorly soluble in glycerin, $\delta = 16.26$ and in butyl stearate $\delta = 7.68$. Co-solubilisers can be identified by their occupancy of some intermediate status between two relatively immiscible materials.

Further applications of these concepts allows calculation of the ideal mole fraction solubility of a crystal X as (Hildebrand and Scott, 1962):

$$\ln X_i = \frac{-\Delta f_{us}H}{R} \left[\frac{T_m - T}{T_m T} \right] + \frac{\Delta C_p}{R} \left[\left[\frac{T_m - T}{T} \right] - \ln \frac{T_m}{T} \right] \quad (1)$$

where $\Delta f_{us}H$ is the enthalpy of fusion of the solid; R the gas constant; T_m and T are the absolute melting point and T the temperature of interest; ΔC_p the difference in heat

capacity between solid and molten forms of the drug. Frequently (although ΔC_p values are not widely available in the literature) ΔC_p is small and also since $\frac{T_m - T}{T} \approx \ln \frac{T_m}{T}$ then this last equation can be written as the approximation.

$$\ln X_i \approx \frac{\Delta f_{us}^H}{RT_m} \left[\frac{T_m - T}{T} \right] \quad (2)$$

This equation has been modified (Yalkowsky and Valvani, 1980) to:-

$$\log X_i = \frac{\Delta_{fus} S}{1364} (T_m - 298) \quad (3)$$

since $\frac{f_{us}^H}{T_m} = f_{us}^S$ and setting $T = 298K$.

Using a "conventional" temperature scale and introducing the activity coefficient to once again permit consideration of "real" aqueous solubilities produces

$$\log X_i = \frac{-\Delta_{fus} S}{1364} (MP - 25) - \log y_w \quad (4)$$

This equation it is claimed will allow realistic estimates of aqueous solubilities to be made for crystalline solutes. Yalkowsky and Valvani (1980) describe methods for estimating $\Delta_{fus} S$ and y_w and proceed to show good correlation between the observed and experimental solubilities for a wide range of crystalline organic non-electrolytes. The final equation (see original paper for details) is given as

$$\log S_w \approx - \log PC - 1.11 \frac{\Delta_{fus} S (MP - 25)}{1364} + 0.54 \quad (5)$$

where PC is the octanol-water partition coefficient.

The equation above, proposed by Yalkowsky and Valvani (1980), is a modification of equations of the type

$$\log X_i = - \log y_{sat} + \frac{\Delta_{fus} S}{2.3R} \left[\frac{T_m - T}{T} \right] \quad (6)$$

which have been discussed in detail by Hildebrand and Scott (1962) and by Hollenbeck (1980). The Yalkowsky-Valvani equation has been widely applied but, it is claimed (Tomlinson and Hafkenscheid, 1986), is subject to many problems: the equation does not hold for solutes that can self-associate in one of the phases of associate with one of the solvents employed in the partition; methods for experimentally obtaining PC are tedious; calculation of PC via group contributions (Leo et al., 1975) or fragmental constants (Rekker, 1977) is not simple; and no approach deals adequately with mixed solvents; this may be regarded as a most severe limitation. James (1984) in discussing the calculation of solubilities from molecular surface areas has observed "...frequently all that is required is an indication of where a solubility lies at ambient temperature. A simple method for estimating approximate aqueous solubilities is therefore desirable".

This view, which is commonly held, has pervaded the pharmaceutical literature. It seems to imply that understanding of the forces and interactions which determine solubility is secondary to the establishment of a correlation which associates solubility, through some parameterised equation, with some other easy-to-measure- or-estimate property. However close inspection of most of the equations does indicate clear concern for those factors which contribute to solubility and its limits. It is, however, with the parameters of regression equations that there appears little concern as to "significance".

Solubility parameter approaches to the estimation of solubility in a wide range of solvent systems continues to be of great interest. For example Martin et al. (1984) have taken an expanded solubility approach to investigate the solubility of p-hydroxybenzoic acid and fo methyl p-hydroxybenzoate in individual solvents. In general these approaches have been based upon values of δ .

$$\delta_o = \frac{\Delta_{vap} U}{V} = \frac{(\Delta_{vap} H - RT)d}{Mr} \quad (7)$$

where $V = - Mr/d$.

This overall solubility parameter is further factored into contributions from dispersion forces, δ_D , from dipole-dipole interactions, δ_P , and from hydrogen bonding forces δ_H as

$$\delta_o = (\delta_D^2 + \delta_P^2 + \delta_H^2)^{1/2} \quad (8)$$

frequently δ_P is small and ignored. Much attention (Martin et al. 1984 and references cited therein) is given to methods for the assessment of δ_X values. Such δ_o values have been correlated with other system parameters. δ_o has also been correlated (Schott, 1984) with the hydrophilic-lipophilic balance of non-ionic surfactants (HLB) where

$$HLB = \frac{E+P}{5} \quad (9)$$

and E is the percent (w/w) of polyoxyethylene and P the percent (w/w) of polyhydric alcohols in the surfactant molecule. The result of this study (Schott, 1984) was that HLB is a reasonable parameter to characterise the emulsifying efficiency of non-ionic surfactants.

The problem of predicting real solubilities i.e. for non-ideal systems is still however profound. As indicated above "real" systems are accommodated through consideration of activities and activity coefficients in place of concentration terms. Thus

$$\ln X = - \ln y - \frac{\Delta f_{usH}}{RT} \left[\frac{T}{T_m} - 1 \right] \quad (10)$$

and y is an implicit function of X and T. The universal functional group activity coefficient (UNIFAC) approach relies upon a quasi chemical (Guggenheim, 1966) theory of liquid mixtures and yields a semitheoretical equation for excess Gibbs energy of liquid mixtures through the introduction of the 'local area fraction' as the primary concentration variable. The resulting equation is called the Universal Quasi Chemical (UNIQUAC) equation and uses only 2 adjustable parameters per binary. Grunbauer and Tomlinson (1984) have illustrated the application and basis of this approach to correlate mutual solubilities in binary and ternary systems and distribution coefficients including, importantly, study of some mixed solvent systems (i.e. water-organic solvent mixtures). Tomlinson (Grunbauer and Tomlinson, 1984) concludes that the results are "comparable to those of previous empirical correlation studies and much better than those produced by the solubility parameter concept". The empirical equations used for comparison are the familiar ones of the form:

$$\log Y = A \log X + B \quad (11)$$

where A and B are regression constants and Y and X some parameters describing the systems e.g. partition coefficient, solubility, retention time etc. Further support of the UNIQUAC approach has recently come from Basu et al. (1986) who used it to predict the solubility of long-chain hydrocarbons in several solvents. Tomlinson (de Meere et al. 1986) has pressed the application of this model to the problem of differentiation of hydrophobic fragmental constants. It is claimed that the analysis permits the identification of a non-specific size term within the fragmental constant which is due to the spatial arrangement of that fragment and of specific interaction effects both with water and with an organic phase.

The development of equations related to the initial Hildebrand solubility parameter (for a collection of δ values see Barton, 1975) is dependent upon the model used to formulate the equation. The models usually involve, in part, the creation of a cavity in the solvent (i.e. bonds are broken, order in the solvent is disturbed) into which the solute can fit. δ_H can be seen to be a measure of the energy required to separate solvent molecules from one another. Thus it is not surprising that solubility correlations have been proposed with solute surface area/volume. For recent reviews of this material see; Pearlman 1986; Yalkowsky et al. 1976; Lee 1985.

These simple and briefly outlined approaches have, in general based solvent effects upon single indicators e.g. δ_o , surface area. A better approach to estimating solubilities may be arrived at by averaging multiple normalised solvent effects on a variety of properties involving many diverse types of indicators. Thus Taft and Kamlet have proposed equations of the type

$$XYZ = XYZ_o + \text{cavity term} + \text{dipolar term} + \text{hydrogen bonding term(s)}$$

where large numbers of solubility and solvent dependent properties, XYZ are well correlated by equations that include linear combinations of Gibbs energy or enthalpy contributions (Taft et al. 1985; Kamlet et al. 1981; 1983; 1985). The cavity term includes the solute molar volume and δ_H ; the dipolar term includes solute-solvent, dipole-dipole, dipole-induced dipole and dispersion interactions. The latter term is evaluated through the use of solvatochromic parameters; (π^*) measures of the ability of a compound to

stabilise a neighbouring change or dipole by virtue of its dielectric effect. The hydrogen bonding term(s) describe complexation between hydrogen bond donor solvents (α_1) and hydrogen bond acceptor solutes (β_m)₂ (and vice versa). Thus

$$XYZ = XYZ_0 + A(\delta_H^2)_1 V_2/100 + B\pi_1^*\pi_2^* + c\alpha_1(\beta_m)_2 + D\beta_1(\alpha_m)_2 \quad (12)$$

subscript 1 refers, conventionally, to the solvent and subscript 2 to the solute. Full details can be found in the references cited - as can tabulated values of the solvatochromic parameters for a wide range of systems. The (Kamlet et al. 1986) published data is then, finally, of the form for example

$$\log S_w = (0.59 \pm 0.13) - (3.35 \pm 0.10) V_2/100 + (0.46 \pm 0.11)\pi_2^* + (5.08 \pm 0.12) (\beta_m)_2$$

$$n = 50, \quad r = 0.9944, \quad SD = 0.152. \quad (13)$$

This equation correlates the aqueous solubility (S_w) of nonprotonic liquid aliphatic nonelectrolytes in water at 298K in terms of fundamental physicochemical properties of the solutes (for the first time it is claimed (Kamlet et al. 1986)). Further analysis of equations of this type leads to discussion of the principal factors affecting solubility e.g. for the solutes described by the above equation the leading terms is the exergic effect of hydrogen bonding between water as the donor and the solutes as the acceptors; the next most important term is that for the endoergic cavity formation process and the dipolarity-polarisability term reflects only a second order exoergic dependence on these interactions. The equations are, however, correlations and there is as yet little physical significance attached to the regression parameters A, B, C, D. Thus whilst there is much to be gained from these equations, solubilities in solvents (not just water), insight into some aspects of the physicochemical basis of the process the meanings of the regression parameters is still obscure. This form of linear solvation energy relationship has been used to derive a correlation for octanol-water partition coefficients (Taft et al. 1985) which has a satisfactory statistical basis. It has, too, the advantages of describing the solubilities and interactions in the separate solvent systems in addition to simply describing a correlation between PC and some properties of the partitioning system itself. Not surprisingly these equations meet criticism and modifications are proposed (Leahy, 1986; Fuchs and Stephenson, 1983). Leahy (1986) has returned to calculations of van der Waals or intrinsic volume (Pearlman, 1986) instead of molar volume as a measure of the cavity term in the basic form of the solvatochromic correlation equation claiming at least as good correlation and obviating the need to insert empirical "correction factors" and alicyclic solutes.

One objection to these correlation schemes is, of course, the need for a large body of data on which to establish the correlations. Another has already been referred to and is that of the significance of the parameters of regression. Indeed consideration mixed solvent systems (note they are present in all experimental partition coefficient measurements) has of course been attempted previously (e.g. Manzo, 1982; Yalkowsky et al. 1976) but can also be met in this new solvatochromic approach provided sufficient data exists to establish the correlation. An important feature will, therefore, be the discovery of any significance in relative values of parameters of regression. These, like the parameters of the Collander equation

$$\ln PC_{\text{sysI}} = a + b \ln PC_{\text{sysII}} \quad (14)$$

may be treated as only of qualitative significance. Recently, however, it has been shown (Beezer et al. 1987) that a thermodynamic analysis of this equation allows physical significance to be attached to the parameters a and b.

The problems that remain are however, formidable, not all systems are regular. Some years ago Yalkowsky (Yalkowsky et al. 1972) showed that chain length in solutes produced variation in solubility and in other physicochemical phenomena. Newton (Hansford et al. 1980) has shown that attempts to measure wettability of powders (griseofulvin) by extrapolation of contact angle measurements from alcohol/water mixtures to pure water indicated, not surprisingly, a dependence upon the properties of alcohol/water systems. More recently Beezer et al. (1985) have measured solubilities and enthalpies of solution of some solutes in water/alcohol systems (alcohol = MeOH to octan-1-ol) where the {alcohol} = 0.00316M, the saturating concentration of octan-1-ol in water. The data showed breaks in behaviour which could be related to the molar volumes of the alcohol and the solute.

Thus whilst considerable progress has been made in correlating behaviour in solutions through, consideration of factored forces; cavity, polarisability, H-bonding etc. considerable uncertainties attend the interpretation of these equations. These uncertainties, not surprising involve "real" systems i.e. mixed solvent systems and our capacity to

discriminate between them. Thus the capacity to predict solubility (and PC) from consideration of the forces operating in solutions has improved but we await the development of methods to describe and interpret data for complex systems.

Not surprisingly other components of solid formulations which are used to improve physico-chemical properties e.g. wetting, solubility, etc. complicate the picture.

Interestingly the relationship between solubility and wetting has been little explored. Recently Buckton et al., (Buckton et al. 1986, 1988) have studied the wetting of pharmaceutical powders under a variety of environmental conditions. The studies are, initially, directed at the derivation of quantitative structure activity relationships.

Overall, therefore, there is great concern in the pharmaceutical world for solubility - but approached mainly from the applied interest. The consequences of this are vigorous attempts to interpret and use the relationships derived and explored by physical chemists. Unsurprisingly the problems of anything beyond ternary systems has not been considered but yet it is in such very heterogeneous systems that the "real" problems lie.

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