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Drug solubility prediction by using solvatochromic parameters

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Summary

The advantages and possibilities for predicting solubilities by using linear combinations of solvatochromic parameters are discussed. A brief survey on drug solubility prediction is given.

It is well known that the poor solubility in water of many drugs has necessitated the use of water-miscible cosolvent mixtures to prepare solutions of these compounds (Rubino and Berryhill, 1986). Lipophilic solvents are required for lipid drugs that are to be administered in soft gelatin capsules, suppositories, topical preparations or injections. Bioavailability from suppositories, percutaneous absorption from topical preparations and duration of biological activity following intramuscular injection are all dependent on the degree of saturation of the drug in the solvent (James, 1986). Accordingly, the ability for predicting drug solubilities is important in order to select a suitable solvent giving the appropriate biological response. Estimated solubilities are of importance for correlations with other physical properties, as in quantitative structure-activity relationships (QSAR) (Hansch, 1978). These involve correlation between biological activities and various physical properties, and are used for predicting the potencies of known untested compounds and for suggesting new compounds of pharmaceutical interest.

This paper is devoted to the application of linear free energy relationships involving solvatochromic parameters in order to predict drug solubilities in solvents and solvents mixtures.

A primal concept for discussing solubilization by cosolvents is polarity. In the pharmacy world, the most commonly used measures of polarity are dielectric constant (ϵ), solubility parameter (δ) (Hildebrand and Scott, 1950) and surface tension (γ). Extending Hildebrand's solubility parameter theory to semipolar and polar systems and observing an empirical equation which links the dielectric constant and the solubility parameter

$$\delta = 7.5 + 0.22\epsilon \qquad (1)$$

Paruta et al. (1962) postulated that a maximum solubility of a given solute should occur within a particular narrow dielectric constant range, re-

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gardless of whether this dielectric constant is that of a pure solvent of that of an appropriate mixture. Eqn 1 correlates fortuitously with solvents of pharmaceutical interest. A more critical assessment found that ϵ and δ were related provided that the solvent systems were restricted to liquids exhibiting similar bonding characteristics. The procedure failed when there was a wide variation in the chemical nature of solvents (German and Hall, 1964). Dielectric constants therefore serve as a useful aid to select a suitable solvent for a given drug. They also provide a means for quantitating the selection of solvent blends. The influence of dielectric constants of binary or tertiary mixtures on the solubility of drugs was studied with the aid of an approximate dielectric constant (ADC) (Rohdewald and Möldner, 1973). Assuming that the dielectric constant of a mixture of two or more solvents is directly proportional to the concentration of the individual solvents, Moore (1958) calculated the ADC as a weighted mean

$$\mathrm{ADC} = \sum f_i \epsilon_i \tag{2}$$

where f is the volume fraction of each solvent. However, this equation applies when the solvent blend is an ideal solution, and therefore yields only approximate values with real systems (Sunwoo and Eisen, 1971).

In order to predict drug solubilities, Yalkowsky et al. (1972) introduced a log linear equation

$$\log S = \log S_w + \sigma f \tag{3}$$

which describes the solubility of some drugs in binary aqueous systems where S denotes the drug solubility in a solvent consisting of water and a non-aqueous cosolvent whose volume fraction is f, S_w represents the drug solubility in water and σ is a parameter representing the solubilizing power for the drug and depends on the polarity of the drug and the cosolvent. This latter parameter may be evaluated as the difference between the logarithm of the partition coefficient for octanol/water ($P_{o/w}$) and for the octanol/cosolvent ($P_{o/c}$) of the drug (Yalkowsky and Roseman, 1981).

The log linear solubility relationship as introduced in Eqn 3 gives a good linear fit for semipolar drugs in a number of water-cosolvent mixtures (Martin et al., 1982), but does not appear to be applicable for non-polar cosolvent systems.

According to the scaled particle theory (SPT) developed by Pierotti (1976), the solution process essentially consists of two energy-dependent steps: (i) the formation of a cavity in the solvent of suitable size to accommodate the solute; (ii) the introduction into the cavity of a solute species which interacts with the solvent. Unfortunately, SPT fits well only in the cases of nonpolar solutes in solvents and solvent mixtures nearly ideal (Brückl and Kim, 1981). The nature of interaction between solute and solvent may be electrostatic (changes in the macroscopic dielectric constant of solvent), dipolar (Keesom, Debye or London short-range interactions deriving from the Lennard-Jones potential) or specific (hydrogen bonding, chemical equilibria). In addition, specific solvation, homoconjugation process and particularly hydrophobic interactions can play substantial roles (Gonzalez et al., 1991). Accordingly, solubility predictions may be obscured.

In a landmark paper, Kamlet et al. (1986) show a relationship that allows one to predict solubilities with greater accuracy and for a wider range of substances than has hitherto been possible. Thus, many solubility and solvent-dependent properties represented by the term XYZ, depend on linear combinations of energy contributions of three types of terms:

$$XYZ = XYZ_0 + \text{cavity term} + \text{dipolar term} \\ + \text{hydrogen bonding term} \tag{4}$$

The cavity term measures the free energy input needed to separate the solvent molecules overcoming the cohesive forces. The cavity term depends on the solubility parameter δ of the solvent and the molar volume V of the solute. The dipolar term, which depends on the π^* parameter (Kamlet et al., 1977) of both solute and solvent, measures the effect of solute-solvent dipole-dipole and dipole-induced dipole interactions.

The hydrogen bonding terms measure the exoergic effects of complexation between hydrogen bond donor (HBD, α-scale) (Taft and Kamlet, 1976) and hydrogen bond acceptor (HBA, β-scale) (Kamlet and Taft, 1976) abilities of solvent and solute.

Accordingly, with the solvatochromic parameters included (subscript 1 refers to the solvent, subscript 2 corresponding to the solute), Eqn 4 becomes

$$XYZ = XYZ_0 + a\delta_1^2 V_2 + b\pi_1^* \pi_2^* + c\alpha_1\beta_2 + d\beta_1\alpha_2 \tag{5}$$

When dealing with the effects of different solvents on the properties of single solutes, the factor relating to the solute(s) may be subsumed into the constants in Eqn 5 giving

$$XYZ = XYZ_0 + A\delta_1^2 + B\pi_1^* + C\alpha_1 + D\beta_1 \tag{6}$$

Conversely, when dealing with solubilities of a set of different solutes in a single solvent,

$$XYZ = XYZ_0 + AV_2 + B\overset{*}{\pi}_2 + C\alpha_2 + D\beta_2 \tag{7}$$

These relationships enable us to predict solubilities in blood (S_b) and toxicities (LC_{50}) to the tathead minnow and golden orfe. The π^* parameter provides information regarding the mechanism of tadpole narcosis, toxicity to *Photobacterium phosphoreum*, and possibly the 'rapture of the deep' experienced by deep sea divers (Kamlet et al., 1986).

Some authors examined *XYZ* properties for their relationships to the solvent polarity indices of solvent mixtures, P_m being estimated using a linear combination rule (assuming the solvatochromic excess to be zero). Therefore, in the case of a water-cosolvent mixture

$$P_m = P_C f_C + P_W f_W \tag{8}$$

However, although these relationships may serve as a guide to the true behaviour, their use for predicting solubilities may lead to gross errors because of the strong non-ideality of a number of such mixtures. Hence, it is more advisable to estimate the appropriate solvatochromic parameters in the given solvent mixture according to the procedures available in the literature (Kamlet et al., 1986). Accordingly, Cheong and Carr (1988) have determined π^* values for aqueous mixtures of methanol, acetonitrile, 2-propanol and tetrahydrofuran from 0 to 100% v/v of cosolvent.

Once the corresponding solvatochromic parameters have been evaluated for the solvent mixture, Eqn 6 may be applied for predicting solubilities of organic non-electrolytes. This equation, however, still presents some drawbacks as described in the following: it fits well only for monofunctional solutes; no data base of solvatochromic parameters exists for ionic compounds; very weakly dipolar solutes show small deviations; and it does not apply to strong acids or strong base solutes and solvents.

Linear free energy relationships between some properties such as solubility and donor-acceptor parameters in non-aqueous solvents and their mixtures are not a new discovery (Ahmed, 1979; Kolling, 1982; Coetzee et al., 1990), however, the simple 'ground rules' for understanding and predicting solvation effects (Arnett, 1985) cannot be utilized seriously because driving forces not dependent upon the interaction between solutes and solvent may appear, such as hydrophobic interactions which can play a primary role (Ben-Naim, 1980; Aerts and Clauwaert, 1986).

At the present state of the art, the evaluation of solvatochromic parameters in solvent mixtures as well as the extension of Eqn 6 are important future objectives and accordingly, all efforts of workers within this realm should be directed toward these goals. Otherwise, the selection of solvent mixtures for dissolving a given solute will remain in the same place, being rather a matter of trial and error supported by the ancient saying, simila similibus solventur.

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