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Predicting the Solubility of Drugs in Solvent Mixtures: Multiple Solubility Maxima and the Chameleonic Effect

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Abstract—An approach to reproduce the solubility profile of a drug in several solvent mixtures showing two solubility maxima is proposed in this work. The solubility of sulphamethoxypyridazine was determined at 25°C in several mixtures of varying polarity (hexane:ethyl acetate, ethyl acetate:ethanol and ethanol:water). Sulphamethoxypyridazine was chosen as a model drug because of its proton-donor and proton-acceptor properties. A plot of the mole fraction of the drug vs the solubility parameter of the solvent mixtures shows two solubility peaks. The two peaks found for sulphamethoxypyridazine demonstrate the chameleonic effect as described by Hoy and suggest that the solute-solvent interaction does not vary uniformly from one mixture to another. The different behaviour of the drug in mixtures of two proton-donor and proton-acceptor solvents (alcohol and water), and in mixtures of one proton acceptor (ethyl acetate) and one proton donor-proton acceptor (ethanol) is rationalized in terms of differences in the proton donor-acceptor ability of the solvent mixtures. An approach based on the acidic and basic partial solubility parameters together with the Hildebrand solubility parameter of the solvent mixtures is developed to reproduce the experimental results quantitatively. The equation predicts the two solubility maxima as found experimentally, and the calculated values closely correspond to the experimental values through the range composition of the solvent mixtures. These results show that the chameleonic effect can be described in a quantitative way in terms of Lewis acid-base interactions; this approach can assist the product formulator to choose the proper solvent mixture for a new drug. A good solvent blend should result in a solubility parameter close to that of the drug; the acidic and basic partial solubility parameter values should provide maximum acid-base interaction of the mixed solvent with the drug. The failure in one of these conditions results in decreased solubility. Solubility parameters as well as the acidic and basic parameters are tabulated or they can be obtained from group contribution methods, making easier the evaluation of the best solvent mixture for a drug.

Binary solvent mixtures are used in a number of fields to develop models for predicting solubility (Martin et al 1979, 1985a; Acree & Tucker 1985), and to increase the solubility of a drug. Deviations of the algebraic mixing rule in mixtures consisting of water and a cosolvent have been interpreted in terms of the interaction of the cosolvent with water and the water structuring effect on the nonpolar parts of the drug (Rubino & Obeng 1991). Several kinds of solubility curves may be obtained when the solubility of a drug in solvent mixtures is plotted against the volume fraction of the cosolvent or the solubility parameter, δ, defined as the square root of the cohesive energy density (Hildebrand et al 1970). A smooth curve is obtained which shows a peak solubility value.

In irregular solutions involving solvation or association, those systems of most interest in the pharmaceutical sciences, the solubility parameter of the solute is approximately equal to the solubility parameter of the solvent mixture, but the mole fraction solubility at the solubility peak does not ordinarily equal the ideal mole fraction solubility. Furthermore, a linear relationship rather than a curve may be obtained if the solubility parameter of the drug is outside the range of the solubility parameter of the solvent mixtures (Martin et al 1985a). The solubility curves showing only one maximum are well described using the extended Hildebrand method (Martin et al 1979; Wu & Martin 1983). This method predicts a maximum at a certain composition of the solvent mixture. Solubility curves with two or more solubility maxima cannot be described using the solubility parameter alone; the extended Hildebrand method must be applied separately to each part of the curve. In our earlier report (Bustamante et al 1993) a modification of the extended Hildebrand method was used to obtain a single equation for predicting the solubility of structurally related drugs in solvent mixtures composed of water and a proton-acceptor solvent, dioxane. The approach combines the solubility parameters, δ_1, and the basic partial solubility parameters, δ_{1b}, of the solvent mixture. The solubility of the drugs in the pure solvents, dioxane and water were also needed for this model. The basic partial solubility parameters express the proton acceptor or Lewis basicity of the solvent mixture. The model reproduced the solubility curves of sulphonamides and xanthines. The equation for sulphonamides was able to predict the solubility of other structurally related solutes in the solvent mixture. Following these lines, the acidic and basic partial solubility parameters were tested in this work to account in a quantitative way for the behaviour of a model drug, sulphamethoxypyridazine, in several solvent mixtures with different hydrogen-bonding abilities: mixtures of ethanol and water having both proton donor and proton acceptor characteristics; mixtures of one proton-donor/proton-acceptor and one proton-acceptor solvent (ethanol and ethyl acetate); and mixtures of a proton-acceptor (ethyl acetate) and a nonhydrogen-bonding solvent (hexane). Sul-

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Table 1. Solubility of sulphamethoxypyridazine at 25°C.

Solvent mixture	Ln X_2	Ln $X_{2(calc)}$ (eqn 7)	Residual[a]	δ_1[b]	δ_{1a}[b]	δ_{1b}[b]
Water:ethanol						
% Ethanol						
0	−10·1983	−10·3835	0·19	23·40	6·70	32·00
30	−8·1611	−7·7177	−0·44	20·26	7·18	24·05
50	−6·8120	−6·6896	−0·12	18·18	7·50	18·75
60	−6·4098	−6·3442	−0·06	17·13	7·66	16·10
65	−6·1695	−6·2356	0·06	16·61	7·74	14·78
70	−6·0044	−6·1726	0·17	16·09	7·82	13·45
75	−5·9327	−6·1320	0·20	15·57	7·90	12·13
80	−5·9096	−6·2547	0·35	15·09	7·98	10·80
85	−5·9533	−6·1364	0·18	14·52	8·06	9·48
90	−6·1502	−6·2103	0·06	14·00	8·14	8·15
93	−6·1610	−5·7350	−0·42	13·48	8·19	7·36
95	−6·2592	−6·8250	0·56	13·68	8·22	6·82
100	−6·5384	−6·4491	−0·08	12·96	8·30	5·50
Ethanol:ethyl acetate						
% Ethanol						
95	−6·3945	−6·0860	−0·31	12·70	8·15	5·32
90	−6·2296	−6·0202	−0·21	12·56	8·00	5·14
80	−5·8928	−5·6095	0·28	12·17	7·70	4·78
65	−5·4898	−5·3640	−0·13	11·58	7·25	4·24
60	−5·4115	−5·3074	−0·10	11·39	7·10	4·06
50	−5·3323	−5·2373	−0·09	11·00	6·80	3·70
40	−5·2816	−5·2339	−0·05	10·60	6·50	3·34
30	−5·2320	−5·3324	0·10	10·21	6·20	2·98
20	−5·3513	−5·5146	0·16	9·82	5·90	2·62
17	−5·4650	−5·5813	0·12	9·70	5·81	2·51
13	−5·6338	−5·6821	0·05	9·54	5·69	2·37
10	−5·7230	−5·7807	0·05	9·43	5·60	2·26
0	−6·1859	−6·1305	−0·05	9·04	5·30	1·90
Ethyl acetate:hexane						
% Hexane						
50	−9·5165	−9·8134	0·30	8·17	2·65	0·95
70	−11·7703	−11·6158	−0·15	7·82	1·59	0·57
100	−14·7937	−14·6778	−0·12	7·30	0·00	0·00

[a] Residual = ln X_2 − ln $X_{2(calc)}$. [b] Solubility parameters and partial solubility parameters are calculated for each solvent mixture from the expression: $\delta(mix) = \Sigma\delta_i\phi_i$, where δ_i is the value for the pure solvent and ϕ_i the volume fraction of the solvent in the solvent mixture.

phamethoxypyridazine was chosen as a model drug because of its proton-donor and proton-acceptor capabilities.

Materials and Methods

The solubilities of sulphamethoxypyridazine in ethanol–water, ethyl acetate–ethanol and hexane–ethyl acetate mixtures (Table 1) were determined at 25°C. The solute (Interchimia, Hamburg, Germany) and solvents (analytical or UV-IR grade, Pancreac, Monplet & Esteban, Barcelona, Spain) were used as received. The drug was tested for purity in a differential scanning calorimeter (DSC Mettler TA 3000). The melting point and the heat of fusion for sulphamethoxypyridazine are 180·4°C (453·6 K) and 8110 cal mol^{-1}, respectively. Twenty-millilitre samples containing an excess of solute were shaken for 72 h and allowed to reach equilibrium in a constant temperature bath held at 25 ± 0·1°C. Preliminary experiments showed that 72 h was sufficient to ensure saturation at the temperatures under study. The excess solute was eliminated by filtration through Durapore or Fluoropore filters (pore size < 1 μm), depending on the compatibility of the solvent with the filter. Four samples of each solution were diluted with methanol and assayed in a double-beam spectrophotometer (Bausch and Lomb 2000) at 268 nm. The small amount of solvent present after dilution with methanol did not affect the absorbance readings. The solvent, hexane, was evaporated before dilution with methanol. The concentration (molarity units) of the solute in methanol was determined from a Beer's law plot. The densities of the saturated solutions, needed to express the results in mole fraction, were measured in 10-mL pycnometers at 25°C. The results were the average of at least four solubility determinations. The experimental variation in solubility was less than 3% in replicated samples.

Results and Discussion

Fig. 1 shows the solubility profile of sulphamethoxypyridazine plotted against the solubility parameter of the solvent mixture. As ethanol was added to water the polarity of the solvent mixture decreased from $\delta_1 = 23{\cdot}4$ to $\delta_1 = 12{\cdot}96$. The solubility of the drug increased along a smooth curve, reaching a maximum at 80:20 v/v ethanol:water, corresponding to a solubility parameter of the solvent mixture, $\delta_1 = 15{\cdot}09$ (cal $cm^{-3})^{1/2}$. From this point the solubility decreased and showed a minimum at 100% ethanol ($\delta_1 = 12{\cdot}96$). As ethyl acetate was then added to ethanol the polarity decreased but the solubility of the drug increased to a second higher maximum at 30:70 ethanol:ethyl acetate ($\delta_1 = 10{\cdot}21$ (cal $cm^{-3})^{1/2}$). From this point the solubility

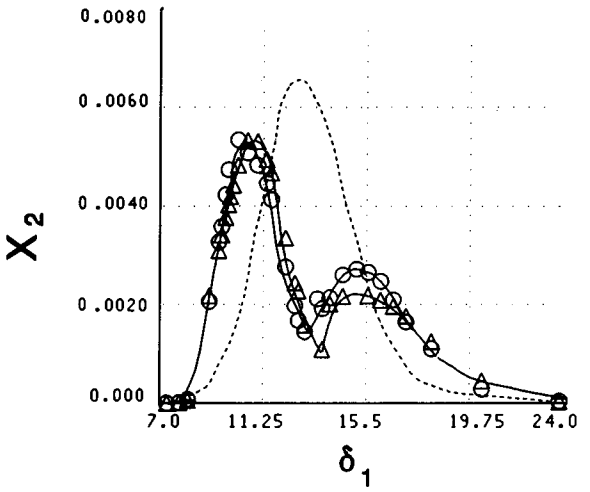

FIG. 1. Mole fraction solubility of sulphamethoxypyridazine in water:ethanol (δ_1 from 23·4 to 12·96), ethanol:ethyl acetate (δ_1 from 12·96 to 9·04) and ethyl acetate:hexane (δ_1 from 9·04 to 7·3). o Experimental values, Δ calculated from equation 7, - - - - calculated with the extended Hildebrand method, a third degree polynomial in δ_1.

decreased along a smooth curve to 100% ethyl acetate ($\delta_1 = 9{\cdot}04$). The polarity was further lowered by addition of hexane to ethyl acetate, and the solubility decreased as the concentration of hexane increased from zero to 100% ($\delta_1 = 7{\cdot}3$).

Chertkoff & Martin (1960) studied the solubility of benzoic acid in those same solvent mixtures and found a smooth curve with a unique solubility maximum at $\delta_1 = 11{\cdot}3$. The small peaks and valleys reported by Paruta et al (1965) for the solubility curve of xanthines in dioxane–water mixtures were not as high and clearly different as the two solubility maxima shown in Fig. 1. The two peaks found here for sulphamethoxypyridazine show the chameleonic effect described by Hoy (1970). According to Hoy, some compounds may exhibit more than one solubility parameter in an effort to adapt to the environment of the solvent medium. Thus, acetic acid acts as a monomer in water showing an apparent $\delta_2 = 13{\cdot}01$ as unassociated molecules and associates as dimers in solvents of lower polarity such as hexane, through intermolecular hydrogen bonding showing a smaller solubility parameter, $\delta_2 = 9{\cdot}19$. This chameleonic effect was observed by Martin et al (1985b) who called attention to the inconstancy of the solubility parameter of drug molecules such as theophylline in solvent mixtures. Thus, the solubility parameter of theophylline and other molecules increases with the polarity of the solvents in which they are determined. In the solvent mixtures used here, sulphamethoxypyridazine shows the chameleonic effect at the two solubility maxima of Fig. 1, having a higher solubility parameter $\delta_2 = 15{\cdot}09$ in the more polar mixture, ethanol:water and a smaller solubility parameter, $\delta_2 = 10{\cdot}21$ in the ethanol:ethyl acetate and ethyl acetate:hexane mixtures of lower polarity. The solubility parameter of sulphamethoxypyridazine, $\delta_2 = 12{\cdot}20$, as calculated from the group-contribution method of Fedors (1974) is very close to that obtained from the solubility peak found in dioxane:water mixtures (Bustamante et al 1993). The solubility parameters of benzoic acid range only from 13·2 in the highly polar solvents to 11·33 in the less polar mixtures. This smaller variation (1·87 units compared with 4·88 units found for sulphamethoxypyridazine) may be the result of cancellation of acid-base effects against water, ethanol and ethyl acetate, producing a unique maximum in these solvent mixtures. This is not the case for sulphamethoxypyridazine, which shows a larger sensitivity to the polarity of the solvent mixture. The chameleonic effect is quantitatively treated here in terms of the different capabilities of the functional groups of the solute to interact through hydrogen bonding with solvent mixtures having different donor-acceptor capacity. The ability to undergo Lewis acid-base interactions depends on the acidic and basic characteristics of both the solute and the solvent. Since sulphamethoxypyridazine shows both acidic and basic characteristics, the solubility curve demonstrates the drug's different behaviour toward solvent mixtures which are highly self-associated and have a high degree of structure; and solvent mixtures with a proton acceptor, that is, a less structured solvent, ethyl acetate. Hexane is an inert solvent and in the mixture, hexane-ethyl acetate, the sulphonamide only interacts through acid-base interactions with ethyl acetate and the curve does not show a maximum (Fig. 1).

The partial molar heat of mixing of a solute forming a true solution is given by the Hildebrand equation (Hildebrand et al 1970):

$$\overline{\Delta H_2} = V_2 \phi_1^2 (\delta_1 - \delta_2)^2 \qquad (1)$$

where δ_1 and δ_2 are the Hildebrand solubility parameters of the solvent and the solute, respectively, ϕ_1 is the volume fraction of the solvent and V_2 is the molar volume of the solute. Equation 1 predicts a zero or positive enthalpy of mixing. The equation assumes only dispersion forces and does not account for acid-base interaction (exothermic effects). If acid-base interaction occurs between the solute and the solvent, equation 1 may be written as:

$$\overline{\Delta H_2} = V_2 \phi_1^2 (\delta_1 - \delta_2)^2 + \overline{\Delta H_2^{ab}} \qquad (2)$$

where the first right hand term is the contribution of the Hildebrand solubility parameter to the dispersion forces and $\overline{\Delta H_2^{ab}}$ is the acid-base contribution to the heat of mixing. A similar equation was suggested by Fowkes (1984) for the partial molar heat of mixing of polymers showing acid-base interaction with the solvent. Fowkes suggested that the term $\overline{\Delta H_2^{ab}}$ be calculated using the Drago parameters (Drago & Wayland 1965; Drago et al 1971; Drago 1974). Unfortunately, the C and E values of Drago have not been determined for complex drug molecules such as sulphamethoxypyridazine. The term $\overline{\Delta H_2^{ab}}$ may be written as:

$$\overline{\Delta H_2^{ab}} = V_2 \phi_1^2 (\delta_{1a} - \delta_{2a})(\delta_{1b} - \delta_{2b}) \qquad (3)$$

where δ_a and δ_b are the acidic and basic partial solubility parameters first defined by Karger et al (1976) as a measure of the proton-donating and proton-accepting characteristics of a molecule. The subscripts 1 and 2 refer to the solvent and the solute, respectively. Equation 3 is a quantitative way to express the Small equation (Small 1953) for the effect of hydrogen bonding upon the heat of mixing. The Small equation is only qualitative in that it predicts the algebraic sign (exothermic or endothermic) of the heat of mixing. Acidic and basic partial solubility parameters are found in the literature (Beerbower et al 1984) allowing a semi-

quantitative use of equation 3. According to equation 3, equation 2 is written as:

$$\overline{\Delta H_2} = V_2\phi_1^2(\delta_1-\delta_2)^2 + V_2\phi_1^2(\delta_{1a}-\delta_{2a})\,(\delta_{1b}-\delta_{2b}) \quad (4)$$

Equation 4 accounts for the effect on solubility of the enthalpy of mixing. Solubility reflects free energy changes, and the free energy is composed of enthalpy and entropy terms. There is no general correlation of equilibrium constants and enthalpy; however, numerous examples of enthalpy-entropy compensation (linear relationships) have been reported for a particular set of either acids or bases (Drago et al 1971) and in solvent mixtures (Manzo & Ahumada 1990). If solvation effects are constant and the entropy is proportional to the enthalpy, $\ln X_2$ is proportional to the partial molar heat of mixing (eqn 4). This allows a quantitative expression of the relationship of solubility to the heat of acid-base interaction to explain the two maxima found in the experimental curve:

$$\ln X_2 = A(\delta_1-\delta_2)^2 + B(\delta_{1a}-\delta_{2a})\,(\delta_{1b}-\delta_{2b}) \quad (5)$$

where the first right hand term expresses the contribution of the Hildebrand solubility equation, which includes the energy of cavity formation and the nonspecific van der Waals interactions, and the second hand right term represents the Lewis acid-base interactions of the solute and solvents as shown in equation 3. A and B in equation 5 include the constant terms of equation 4. To test this approach with the experimental solubility data of Table 1, equation 5 is expanded and written as a regression equation:

$$\ln X_2 = c_o + c_1\delta_1 + c_2\delta_1^2 + c_3\delta_{1a} + c_4\delta_{1b} + c_5\delta_{1a}\delta_{1b} \quad (6)$$

When equation 6 is applied to a drug in different solvent mixtures, the solubility parameter δ_2 and partial solubility parameters δ_{2a} and δ_{2b} are constants and are therefore included together with the constants A and B of equation 5 in the regression coefficients of equation 6.

Using the experimental values found in Table 1, the equation obtained for sulphamethoxypyridazine in the three solvent mixtures is:

$$\ln X_2 = -16{\cdot}2400 + 1{\cdot}22431\delta_1 - 0{\cdot}1384\delta_1^2 + 1{\cdot}3653\delta_{1a} + 2{\cdot}6624\delta_{1b} - 0{\cdot}1929\delta_{1a}\delta_{1b} \quad (7)$$

$$r^2 = 0{\cdot}990,\ \text{s.d.} = 0{\cdot}24,\ n = 29$$

Table 1 lists the experimental and calculated $\ln X_2$ values and the residuals. The experimental mole fraction solubilities (X_2) and the calculated values using equation 7 are plotted in Fig. 1, which also shows the predicted curve using the extended Hildebrand method, a third degree polynomial in δ_1. A polynomial in δ_1 gives excellent results in solvent mixtures showing a unique maximum, but it is not able to reproduce the solubility curve of sulphamethoxypyridazine in solvent mixtures with two solubility maxima. Equation 7 reproduces the shape of the curve with the two maxima found in the different solvent mixtures. The calculated values are very close to the experimental values, except for the maximum found in ethanol-water, where the experimental maximum is higher than the predicted values. The result of the present study demonstrates that the proton-donating δ_{1a} and proton-accepting δ_{1b} capacities of the solvent mixtures can be used with the Hildebrand equation to describe complex solubility curves showing two maxima. Presumably, the acid-base interactions are responsible for the two solubility maxima found. The model is empirical, but the variables used are related to the different solute-solute, solvent-solvent and solute-solvent interactions that occur in solution. It should be noted that the signs of the regression coefficient are those expected. The terms representing solute-solvent interactions, δ_1 for van der Waals forces, and δ_{1a} and δ_{1b} for acid-base interactions are positive and increase the solubility, since they make $\ln X_2$ less negative. The regression coefficients on the variables representing solvent-solvent interactions, δ_1^2 for van der Waals and $\delta_{1a}\delta_{1b}$ are negative and result in decreased solubility. The equation does not require the heat of fusion of the solute, but only the solubility parameters of the solvent mixture and the acidic and basic partial solubility parameters of the solvent mixture. They can easily be calculated from the values of the pure solvents and the volume fraction of the solvent mixture (see footnote in Table 1).

Using this approach there is no need to obtain solubility parameter values for the drug in each solvent mixture; a common equation can be used for the three solvent mixtures. The two solubility maxima are explained by the terms in δ_a and δ_b, which express the different contribution of donor-acceptor properties of each solvent mixture to the partial molar heat of mixing.

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