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A Modification of the Extended Hildebrand Approach to Predict the Solubility of Structurally Related Drugs in Solvent Mixtures

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Abstract—A modification of the extended Hildebrand equation is proposed to estimate the solubility of an organic drug in solvent mixtures. The equation accurately reproduces the solubility of four sulphonamides in dioxane–water mixtures without requiring the heat of fusion of the solute. A single equation is obtained for predicting the solubility of related drugs using the solubilities of the drugs in the pure solvents, dioxane and water, and solute–solvent interaction terms consisting of the solubility parameter, δ_2, of the solute and the solubility parameter, δ_1, and basic partial solubility parameter, δ_{1b}, of the solvent mixture. By this procedure a single equation was obtained to estimate the solubilities of three xanthines in dioxane–water and another equation to obtain the solubilities of four sulphonamides. The equation obtained for sulphonamides is able to predict the experimental solubilities of two parent compounds, sulphasomidine and sulphathiazole, and the solubilities of a drug of different structure, *p*-hydroxybenzoic acid. This suggests that the intermolecular solute-solvent interaction of sulphonamides and *p*-hydroxybenzoic acid are similar. The results indicate that the solubility behaviour of drugs having different structures may be modelled using a common equation provided that they show similar solute-solvent interactions.

Liquid dosage forms of a drug require solubilization of the agent in an individual solvent or mixture of solvents. Most often the drug to be dissolved is a complex organic compound and a suitable theoretical basis for predicting the solubility behaviour of these compounds has not yet been attained. Until recent years only limited attention had been paid to the study of solubility principles as applied to the pharmaceutical sciences. James (1986), Grant & Higuchi (1990) and Yalkowsky & Banerjee (1992) have reviewed principles and methods for predicting solubility.

This report centres on the extended Hildebrand approach (Martin et al 1979, 1982; Martin & Miralles 1982; Wu & Martin 1983) for predicting the solubility of single or several related organic drug compounds in mixed solvents.

The mole fraction solubility of a drug in a non-ideal solution is given as $a_2/X_2=\gamma_2$ or:

$$-\log X_2 = -\log a_2 + \log \gamma_2 \qquad (1)$$

where a_2 is the activity and γ_2 is the activity coefficient of the drug. For an ideal solution of a solid in a liquid solvent, $\gamma_2=1$, therefore $a_2=X_2^i$, and from thermodynamic considerations:

$$a_2 = X_2^i \simeq \frac{\Delta H_m^f}{2{\cdot}303RT}\left(\frac{1}{T_m}-\frac{1}{T}\right) \qquad (2)$$

where ΔH_m^f is the heat of fusion of the solid solute at the melting point, T_m is the melting temperature, T is the temperature under study (Kelvin degrees) and X_2^i is the mole fraction of the solute in an ideal solution. Hildebrand & Scott (1950) derived an expression to predict the activity coefficient γ_2 involving the solubility parameter, δ, defined as the square root of the cohesive energy density. Accordingly, equation 1 is rewritten as:

$$-\log X_2 = -\log X_2^i + A(\delta_1^2+\delta_2^2-2\delta_1\delta_2) \qquad (3)$$

in which

$$A = V_2\phi_1^2/2{\cdot}303RT \qquad (4)$$

V is the molar volume (mL mol^{-1}), ϕ_1 is the volume fraction of the solvent (dimensionless), and R is the gas constant (cal K^{-1} mol^{-1}). The subscripts, 1 and 2, refer to the solvent and solute, respectively. The units of the solubility parameter are $(cal\ mL^{-1})^{1/2}$. Equation 3 applies to the so-called regular solution (Hildebrand & Scott 1950), where only van der Waals forces are present. For regular solutions the assumption of a geometric mean of δ_1^2 and δ_2^2, that is, $\delta_1\delta_2=(\delta_1^2\delta_2^2)^{1/2}$ in equation 3 is valid.

In the extended Hildebrand solubility approach (Martin et al 1979, 1982; Martin & Miralles 1982; Wu & Martin 1983), the term $\delta_1\delta_2$ is replaced by W in order to correct the geometric mean assumption:

$$-\log X_2 = -\log X_2^i + A(\delta_1^2+\delta_2^2-2W) \qquad (5)$$

For drugs in polar solvent mixtures, the solute–solvent interaction term, W, is related to the solubility parameter of the solvent mixture through a polynomial,

$$W = c_0 + c_1\delta_1 + c_2\delta_1^2 + \ldots + c_n\delta_1^n \qquad (6)$$

Equation 5 may be rearranged as:

$$[\log (X_2^i/X_2)]/A = \log \gamma_2/A = (\delta_1^2+\delta_2^2-2W) \qquad (7)$$

From equations 6 and 7, the values of $\log \gamma_2/A$ for a given drug can be regressed in a power series on the solubility parameters of the solvent mixture, δ_1:

$$[\log (X_2^i/X_2)]/A = \log \gamma_2/A = a_0 + a_1\delta_1 + \ldots + a_n\delta_1^n \qquad (8)$$

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Usually, a polynomial in the second or third degree (i.e. n is 2 or 3 in equation 8) is enough to reproduce accurately the experimental solubilities.

In this report, a modified extended Hildebrand method is used to predict the solubility of sulphonamides in dioxane–water mixtures. Furthermore, an approach based on the Hildebrand solubility parameter combined with the basic partial solubility parameter of the solvent mixture δ_{1b}, introduced by Hansen (1967), is developed to obtain a single equation for predicting the solubility of several related drugs in solvent mixtures.

Materials and Methods

The solubility of sulphamethoxypyridazine, sulphadiazine, sulphadimidine and sulphamethoxazole (Interchimia, Hamburg, Germany) in mixtures composed of dioxane (spectrophotometric grade, Panreac, Monplet and Esteban, Barcelona, Spain) and water was determined at 25±0·2°C. The drugs were tested for purity by determination of the melting point and the heat of fusion in a differential scanning calorimeter Mettler TA 3000. An excess of drug was brought to equilibrium with the mixed solvent in a constant temperature shaker bath for 3 days. Preliminary experiments showed that this time period was enough to ensure saturation at 25°C. The excess of solute was separated by centrifugation and the solutions were filtered through Durapore filters. Samples were diluted with methanol and analysed in a double beam spectrophotometer (Bausch Lomb 2000). The densities of the solvent mixtures and solutions were determined in 10 mL picnometers. All the results are the average of at least 4 measurements. The data were analysed using the statistical package NCSS (Hintze 1990).

Results and Discussion

Sulphonamides in dioxane–water solvent mixtures

Equation 8 of the extended Hildebrand solubility approach may be written as:

$$-\log X_2 = -\log X_2^i + Aa_0 + Aa_1\delta_1 + Aa_2\delta_1^2 + \ldots + Aa_n\delta_1^n \quad (9)$$

In the extended Hildebrand method, a different A value for each case is used because the term A includes the square of the volume fraction of the solvent (eqn 4). The ϕ_1 values are related to the mole fraction X_2 as follows:

$$\phi_1 = \frac{V_1(1-X_2)}{V_1(1-X_2)+V_2X_2} \quad (10)$$

The term A could be considered roughly as a constant because it varies in a narrow range compared with the variation of the independent variable, δ_1. For the mole fractions X_2 of the sulphonamides used in this work, the A values vary between 0·092–0·113 for sulphamethoxypyridazine, 0·112–0·113 for sulphadiazine, 0·143–0·146 for sulphadimidine and 0·098–0·130 for sulphamethoxazole. The δ_1 values vary between 10·01 and 23·45. The assumption of a constant A value provided good results for naphthalene in individual solvents (Bustamante et al 1991) and it is tested here with solvent mixtures. Provided that A is a constant, it can be included in the regression coefficients and equation 9 may be written as a multiple linear regression equation in the form:

$$\log X_2 = b_0 + b_1\delta_1 + b_2\delta_1^2 + \ldots + b_n\delta_1^n \quad (11)$$

Equation 11 directly relates the log mole fraction solubility to the partial solubility parameters thus avoiding the use of

Table 1. Solubility parameters of dioxane–water mixtures and experimental solubilities of sulphonamides.

ϕ_D[a]	δ_1[b] (cal mL^{-1})$^{1/2}$	δ_{1b}[c] (cal mL^{-1})$^{1/2}$	log X_2[d] Sulphamethoxypyridazine	Sulphadimidine	Sulphadiazine	Sulphamethoxazole
0	23·45	32	−4·4287	−5·5192	−5·3563	−4·6350
0·10	22·11	29·56	−3·7804	−5·1783	−4·8397	−3·9974
0·20	20·76	27·12	—	−4·6135	−4·2164	−3·3549
0·30	19·42	24·68	−2·8324	−4·1209	−3·8637	−2·7566
0·40	18·07	22·24	−2·4198	−3·7248	−3·6779	−2·5178
0·50	16·73	19·8	−1·9458	−3·3648	−3·2577	−2·0962
0·55	16·06	18·58	−1·8040	—	—	—
0·57	15·79	18·09	−1·7318	—	—	—
0·60	15·39	17·36	−1·5939	−3·0150	−3·0750	−1·7803
0·65	14·71	16·14	—	−2·8478	—	—
0·70	14·04	14·92	−1·4139	−2·7554	−2·8981	−1·5528
0·75	13·37	13·7	−1·2685	−2·6165	−2·7915	−1·3791
0·80	12·7	12·48	−1·2143	−2·5426	−2·7544	−1·2759
0·85	12·03	11·26	−1·1495	−2·4589	−2·7432	−1·2126
0·86	11·89	11·02	−1·1547	—	—	—
0·87	11·76	10·77	—	—	−2·7526	—
0·90	11·33	10·04	−1·1922	−2·4458	−2·7894	−1·2158
0·92	11·07	9·55	—	−2·4455	—	—
0·94	10·8	9·06	−1·2600	−2·4521	−2·8660	−1·2548
0·96	10·55	8·58	−1·2954	−2·5096	−2·9644	−1·2834
0·98	10·27	8·09	−1·3778	−2·5613	−3·1120	—
0·99	10·14	7·84	—	−2·6855	—	—
1·00	10·01	7·6	−1·6248	−2·8254	−3·3039	−1·5228

[a] Volume fraction of dioxane in the mixture dioxane–water. [b] Calculated from equation 17 using ϕ_1 values of 1st column, δ_1(water)=23·4 and δ_1(dioxane)=10·01 (cal mL^{-1})$^{1/2}$. [c] Calculated from equation 17 using ϕ_1 values of 1st column, δ_{1b}(water)=32 and δ_{1b}(dioxane)=(7·6 cal mL^{-1})$^{1/2}$. [d] Sulphamethoxypyridazine, δ_2=11·89 (cal mL^{-1})$^{1/2}$, V_2=174·6 mL mol^{-1}; sulphadimidine, δ_2=12·58 (cal mL^{-1})$^{1/2}$, V_2=199·6 mL mol^{-1}; sulphadiazine, δ_2=13·20 (cal mL^{-1})$^{1/2}$, V_2=154·2 mL mol^{-1}; sulphamethoxazole, δ_2=11·60 (cal mL^{-1})$^{1/2}$, V_2=177·9 mL mol^{-1}.

an iterative procedure to predict the log X_2 values as needed with the extended Hildebrand solubility approach (eqn 8).

The experimental solubility of the four sulphonamides in dioxane–water mixtures and the solubility parameters of the solvent mixtures are listed in Table 1. Sulphonamides were chosen as drug models because of the possibility of their interaction with the solvent by several kinds of forces, including hydrogen bonds. Dioxane is toxic and, of course, could not be used in pharmaceutical preparations; but the dioxane–water mixtures have the advantage over other solvent mixtures in this study in that they provide a very wide range of polarity. Dioxane is used here as a model of a basic cosolvent, capable of accepting protons to form hydrogen bonding, to test several models for predicting solubility. Equation 11 was applied individually to each sulphonamide. The regression equation for sulphamethoxypyridazine is:

$$\log X_2 = -11{\cdot}37241 + 1{\cdot}932651\delta_1 - 0{\cdot}1122836\delta_1^2 + 0{\cdot}001818\delta_1^3$$
$$n = 18,\ r^2 = 0{\cdot}9953,\ \text{s.d.} = 0{\cdot}007 \qquad (12)$$

For sulphadiazine,

$$\log X_2 = -11{\cdot}47519 + 1{\cdot}551219\delta_1 - 0{\cdot}0840\delta_1^2 + 0{\cdot}001242\delta_1^3$$
$$n = 17,\ r^2 = 0{\cdot}9862,\ \text{s.d.} = 0{\cdot}102 \qquad (13)$$

For sulphadimidine,

$$\log X_2 = -11{\cdot}21735 + 1{\cdot}71877\delta_1 - 0{\cdot}1034113\delta_1^2 + 0{\cdot}001726\delta_1^3$$
$$n = 19,\ r^2 = 0{\cdot}9951,\ \text{s.d.} = 0{\cdot}075 \qquad (14)$$

For sulphamethoxazole,

$$\log X_2 = -3{\cdot}80076 + 0{\cdot}4613005\delta_1 - 0{\cdot}0212\delta_1^2$$
$$n = 15,\ r^2 = 0{\cdot}9935,\ \text{s.d.} = 0{\cdot}096 \qquad (15)$$

As observed in equations 12–15, sulphamethoxypyridazine, sulphadiazine and sulphadimidine required a polynomial in the third degree whereas for sulphamethoxazole (eqn 15) a polynomial in the second degree is enough to reproduce the experimental solubilities. The residuals are in most cases within 0·1 log units and all the regression coefficients are significant ($P < 0{\cdot}01$). Fig. 1 demonstrates the close correspondence between the experimental and calculated log X_2 curves for each sulphonamide as a function of δ_1. These results show that it is possible to relate log X_2 to δ_1 directly, making the assumption of a constant A value.

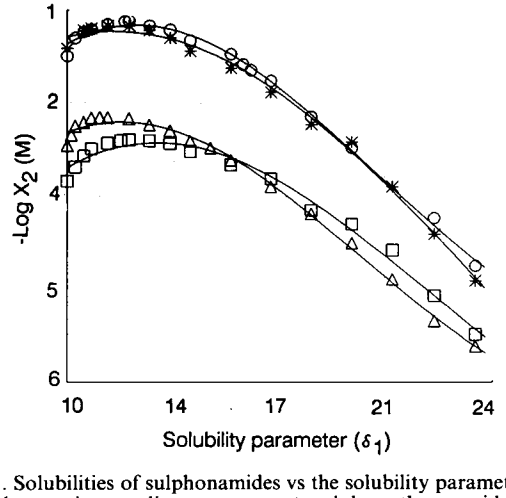

FIG. 1. Solubilities of sulphonamides vs the solubility parameter of the solvent mixture, dioxane–water. ○ sulphamethoxypyridazine, * sulphamethoxazole, △ sulphadimidine, □ sulphadiazine. Solid lines are calculated curves for each sulphonamide from equations 12–15.

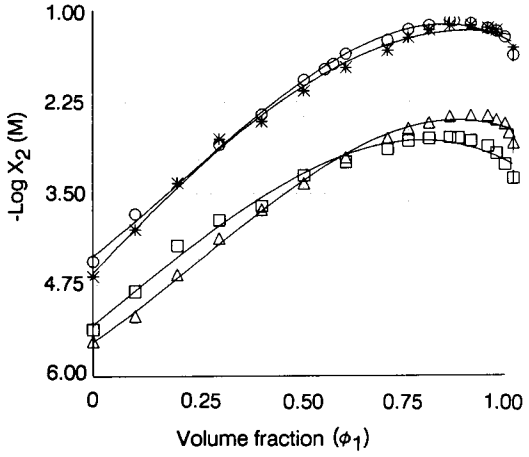

FIG. 2. Solubilities of sulphonamides vs the volume fraction of the solvent mixture, dioxane–water. ○ Sulphamethoxypyridazine, * sulphamethoxazole, △ sulphadimidine, □ sulphadiazine. The solid lines are calculated using polynomials in ϕ_1 in the fourth degree for each sulphonamide.

The same types of curves are obtained when log X_2 is plotted against the volume fraction ϕ_1 of the cosolvent, dioxane. A polynomial in the fourth degree is required when volume fraction is used (Fig. 2). Solubility parameters are preferred rather than volume fraction of the cosolvent because δ is related to intermolecular interactions, providing a more physical meaning than the volume fraction of the solubility phenomena. The equations obtained do not require the experimental determination of the heat of fusion to calculate the ideal solubility, X_2^i. Since this term is a constant for each sulphonamide it need not be included among the variables in the equations. The heat of fusion is needed in the extended Hildebrand equation introduced in earlier work (eqn 8) to compute (log γ_2)/A, the dependent variable. In the present study, the variation of the solubility for a particular drug is a function only of the solubility parameter of the solvent mixture.

Multiple drug solubility in dioxane–water mixtures

An attempt was made to obtain a single equation for predicting the solubility of structurally related drugs in dioxane–water mixtures. Such an equation would allow one to predict the solubility of a new related compound in this solvent blend. An empirical model is proposed in the form:

$$\log X_2 = b_0 + b_1 \log X_{2(\text{diox})} + b_2 \log X_{2(w)} + b_3\delta_1\delta_2 + b_4\delta_1^2 + b_5\delta_1^3 + b_6\delta_{1b} \qquad (16)$$

Equation 16 includes solute–solvent interaction parameters represented by the solubility parameters, δ_1 and δ_2, the partial basic solubility parameter, δ_{1b}, of the solvent mixture and the associated regression coefficients. Dispersion, dipolar and hydrogen bonding partial solubility parameters were introduced by Hansen (1967) and the hydrogen bonding parameter was later divided into acidic δ_a and basic δ_b

parameters (Karger et al 1976). These parameters have been found to be useful to differentiate the solvent action of solvents with a similar Hildebrand solubility parameter. They have been used in polymer science (Peiffer 1980) and for predicting the solubility of drugs in individual solvents (Beerbower et al 1984). The partial solubility parameter, δ_{1b}, has not been used before in solvent mixtures and it is tested here to characterize the basic properties of the solvent system. The units of δ_1 and δ_{1b} are (cal $mL^{-1})^{1/2}$. The solubility parameters δ_1 as well as the basic partial solubility parameters δ_{1b} of the solvent mixtures to be used in equation 16 are calculated from the expression,

$$\delta_i(\text{mix}) = \Sigma \phi_i \delta_i \qquad (17)$$

where δ_i is the solubility parameter or the basic partial solubility parameter of the pure solvent and ϕ_i is the volume fraction of the solvent in the mixture. Thus, for a 60:40 dioxane–water mixture by volume, $\delta_1 = (0{\cdot}6 \times 10{\cdot}01) + (0{\cdot}4 \times 23{\cdot}45) = 15{\cdot}39$, and $\delta_{1b} = (0{\cdot}6 \times 6{\cdot}5) + (0{\cdot}4 \times 32) = 16{\cdot}7$. The solubility parameters and basic partial solubility parameters of the dioxane–water mixtures used for the sulphonamides are listed in Table 1.

Williams & Amidon (1988) used the solubility of the organic solute in water and in the cosolvent in their solubility equation. In order to account for different solutes, equation 16 includes the solubility parameter of the drug, δ_2, and the solubilities in the pure solvents, dioxane and water, as variables in the equation. Equation 16 was tested using the four sulphonamides together in a single equation:

$$\log X_2 = 0{\cdot}1678822 + 1{\cdot}146939 \log X_{2(\text{diox})} + 0{\cdot}2851214 \log X_{2(W)} + 0{\cdot}03848\delta_1\delta_2 - 0{\cdot}0872\delta_1^2 + 0{\cdot}001335\delta_1^3 + 0{\cdot}5813937\delta_{1b}$$
$$n = 69,\ r^2 = 0{\cdot}9917,\ \text{s.d.} = 0{\cdot}110 \qquad (18)$$

The same model (eqn 16) was tested with published solubility data of the methylxanthines, caffeine ($\log X_{2(\text{diox})} = -2{\cdot}0711$, $\log X_{2(W)} = -2{\cdot}6402$, $\delta_2 = 13{\cdot}8$, $V_2 = 144$), theophylline ($\log X_{2(\text{diox})} = -2{\cdot}5857$, $\log X_{2(W)} = -3{\cdot}1299$, $\delta_2 = 14$, $V_2 = 124$) and theobromine ($\log X_{2(\text{diox})} = -3{\cdot}3526$, $\log X_{2(W)} = -4{\cdot}4815$, $\delta_2 = 14$, $V_2 = 124$), in dioxane–water mixtures (solubility data from Adjei et al (1980) and Martin et al (1980, 1981)). The single equation obtained for the three xanthines is:

$$\log X_2 = 5{\cdot}15332 + 2{\cdot}388403 \log X_{2(\text{diox})} - 2{\cdot}563509 \log X_{2(W)} - 0{\cdot}1100082\delta_1\delta_2 - 0{\cdot}0615\delta_1^2 + 0{\cdot}000909\delta_1^3 + 1{\cdot}502413\delta_{1b}$$
$$n = 32,\ r^2 = 0{\cdot}9826,\ \text{s.d.} = 0{\cdot}118 \qquad (19)$$

All the regression coefficients of equations 18 and 19 are statistically significant at the 0·01 level. As shown in Fig. 3 the single equation for the sulphonamides (eqn 18) accurately reproduces the four solubility curves, one for each sulphonamide. In the same way, the single equation for the xanthines (eqn 19) describes well the three experimental solubility curves for the xanthines. The errors using individual equations for each sulphonamide (eqns 12–15) are of course smaller. However, equations 12–15 have a more limited predictive capacity than equation 18 since they cannot be applied to more than the one drug.

Equations 18 and 19 may be used to predict the solubility curve of related compounds in dioxane–water mixtures. The experimental data needed are the solubilities of the new drug in dioxane and water. The solubility parameters and partial basic solubility parameters of the solvent mixture can be calculated from equation 17, using the values for the pure components of the mixture, which may be found in the literature. The solubility parameter of the drug δ_2 can be estimated from a group contribution method (Fedors 1974). Most of the solubility parameters of the drugs range between 10 and 14. Equation 18 was tested for predicting the solubility of two drugs which have not been used to obtain equation 18, sulphasomidine and sulphathiazole. The equation reproduces the experimental solubility curve for a δ_2 value of 13·5 for sulphasomidine and 13·4 for sulphathiazole (Fig. 4). Furthermore, equations 18 and 19 are used to predict the solubility of a different compound, *p*-hydroxybenzoic acid in dioxane–water mixtures. It is interesting to observe how closely equation 18 reproduces the experi-

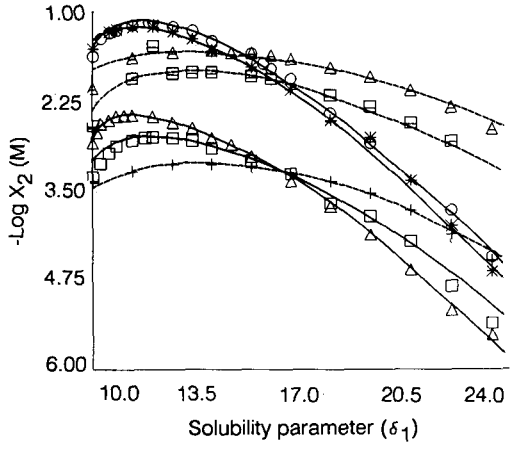

FIG. 3. Solubilities of sulphonamides and xanthines in dioxane–water mixtures. ○ Sulphamethoxypyridazine, * sulphamethoxazole, △ sulphadimidine, □ sulphadiazine, △ caffeine, □ theophylline, + theobromine. —— Calculated curves for sulphonamides from equation 18. – – – Calculated curves for xanthines using equation 19.

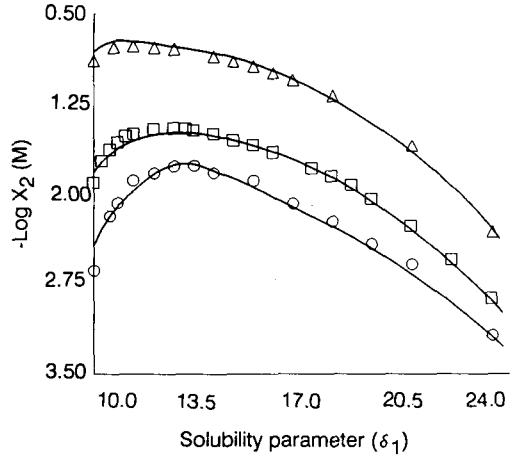

FIG. 4. Solubilities of sulphathiazole in dioxane–water mixtures (○) (data from this laboratory), sulphasomidine in dioxane–water mixtures (□) (data from Martin & Miralles (1982)), and *p*-hydroxybenzoic acid (△) (data from Wu & Martin (1983)) in dioxane–water mixtures. The solid lines are calculated using equation 18.

mental curve for *p*-hydroxybenzoic acid using a δ_2 value of 12 (Fig. 4). However, equation 19, obtained for xanthines, is not able to reproduce the solubility curve of *p*-hydroxybenzoic acid. This indicates that the solute–solvent interactions of *p*-hydroxybenzoic acid in dioxane–water mixtures are similar to those of the sulphonamides, and equation 18 has a predictive capacity not limited to the sulphonamides.

Conclusions

The extended Hildebrand solubility equation was modified to relate directly the mole fraction solubility to the solubility parameters of the solvent mixture, provided that the A values vary in a range of 0·098 to 0·113, corresponding to mole fractions of 3×10^{-6}–0·07 for the sulphonamides used in this work. This rather wide solubility range suggests that the extended Hildebrand solubility approach may be simplified, allowing the application of this method without the need to determine the heat of fusion and avoiding the use of an iterative procedure to calculate X_2 as required by the extended Hildebrand solubility approach.

The results obtained with the empirical model proposed, equation 16, show that it is possible to combine the solubility of several related drugs in a common equation to be used for new predictions. This equation is able to fit the experimental solubilities of two series of structurally related compounds, sulphonamides and xanthines. The equation obtained for sulphonamides, equation 18, closely reproduces the solubility curve of two parent compounds, sulphasomidine and sulphathiazole, and the solubility curve of a drug of different structure, *p*-hydroxybenzoic acid. The results suggest that the equation could model the behaviour of drugs having a different chemical structure but showing similar solute–solvent interactions. Additional work is needed to test this approach for other structurally related drugs.

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