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SOLUBILITY PARAMETER-BASED METHODS FOR PREDICTING THE SOLUBILITY OF SULFAPYRIDINE IN SOLVENT MIXTURES

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ABSTRACT

Sulfapyridine is used to test the extended Hildebrand approach for predicting solubility in dioxane-water mixtures. The method provided good agreement with the experimental data. A modification of this method, that directly relates the logarithm of the mole fraction solubility with the solubility parameter of the solvent mixture (δ_1) gave results comparable to that of the extended Hildebrand approach. This suggests that the volume fraction of the solvent can be disregarded in the solubility equation. The modified method does not require the knowledge of the ideal solubility of the drug. A single equation based on the solubilities of several sulfonamides is able to accurately calculate the solubility profile of sulfapyridine from 0 to 70% water in dioxane. Beyond 70% water, the extended Hildebrand method or its simplified form provide less errors, but these methods require 12-14 experimental

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solubilities, whereas the single equation only needs two experimental solubilities.

INTRODUCTION

Models for predicting solubility of drugs in solvent mixtures have an important practical application in drug formulation. Solvent mixtures are widely used in pharmacy, and theoretical and semiempirical approaches save experiments that are often expensive and time-consuming. The knowledge of solubility is particularly important in liquid dosage forms since drugs are often sparingly soluble in water and other solvents of pharmaceutical interest (1).

The solubility parameter and the theory of regular solutions (2-4) provide useful qualitative criteria for solvent selection. However, this theory is only able to quantitatively predict solubility in solutions where only dispersion forces are important. Martin et al. (5) proposed the extended Hildebrand method to apply the solubility parameter to semipolar compounds in polar solvent mixtures:

$$-\ln X_2 = -\ln X_2^i + A(\delta_1^2 + \delta_2^2 - 2W) \qquad \text{eq.1}$$

$$A = V_2\Phi_1^2/RT \qquad \text{eq.2}$$

$$\Phi_1 = V_1(1-X_2)/V_1(1-X_2) + V_2X_2 \qquad \text{eq.3}$$

where X_2 is the solubility mole fraction, X_2^i is the ideal solubility, δ is the solubility parameter, V is the molar volume, R is the gas constant, T is the absolute temperature of the experiment, and Φ_1, the volume fraction of the solvent. The subscripts, 1 and 2 refer to the solvent and the drug, respectively. In Eq. 1, W is less restrictive than the product $\delta_1\delta_2$ of the Hildebrand equation, and is defined as:

$$W = K\delta_1\delta_2 \qquad \text{eq.4}$$

where K is a proportionality factor relating W to the geometric mean $\delta_1\delta_2 = (\delta_1^2\delta_2^2)^{1/2}$ (6).

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The ideal solubility, X_2^i, (Eq. 1) can be calculated from the molar heat of fusion of and temperature of fusion of the drug:

$$- \ln X_2^i = \Delta H_m^f / RT(T_m - T/T_m) \quad \text{eq.5}$$

In the extended Hildebrand method, the W values, as calculated from experimental solubilities and Eq 1, are related to the solubility parameter of the solvent mixture through a n^{th} degree polynomial:

$$W = c_0 + c_1\delta_1 + c_2\delta_1^2 + \ldots + c_n\delta_1^n \quad \text{eq.6}$$

The predicted values, W_{calc}, from Eq. 6 are used in Eq. 1 to back-calculate solubilities. The values of $\ln \alpha_2/A$, in which α_2 is the activity coefficient of the drug, can also be regressed in a power series on the solubility parameters of the solvent mixture, δ_1 (5):

$$(\ln (X_2^i/X_2))/A = \ln \alpha_2/A = a_0 + a_1\delta_1 + \ldots + a_n\delta_1^n \quad \text{eq.7}$$

Equations 6 and 7 give similar calculated solubilities, usually within 20% or less error.

The extended Hildebrand method was modified to directly relate $\ln X_2$ to δ (7):

$$\log X_2 = b_0 + b_1\delta_1 + b_2\delta_1^2 + \ldots + b_n\delta_1^n \quad \text{eq.8}$$

Eq. 8 does not require the experimental determination of the ideal solubility of the solute, and eliminates the volume fraction of the solvent, used in the extended Hildebrand method. Furthermore, an empirical model was proposed to predict the solubility of several related drugs in water-cosolvent mixtures:

$$\log X_2 = b_0 + b_1 \log X_{2(c)} + b_2 \log X_{2(w)} + b_3\delta_1\delta_2 + b_4\delta_1^2 + b_5\delta_1^3 + b_6\delta_{1b} \quad \text{eq.9}$$

where $X_{2(c)}$ and $X_{2(w)}$ are the mole fraction solubilities of the drug in water (w) and the pure cosolvent (c), and δ_{1b} is the partial solubility parameter of the solvent mixture. This parameter was proposed by Karger et al. (1976) as a measure of the Lewis-base properties of the solvent. The solubility parameters, δ and δ_b, of the solvent mixtures are calculated from the expression:

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$$\delta_{(mix)} = \Sigma \phi_i \delta_i \qquad \text{eq.10}$$

where δ_i is the solubility parameter or partial solubility parameter of the pure solvent and ϕ_i is the volume fraction of the solvent in the solvent mixture.

The extended Hildebrand method as well as the solubility parameter-based approaches for single solutes (Eq. 8) and several related solutes (Eq. 9) are tested in this work with the experimental data of an antibacterial drug, sulfapyridine, in dioxane-water mixtures. Sulfapyridine is amphoteric (pK_{a1} = 8.43, pK_b = 11.42, isoelectric point, 4.25) (9). The pK_a of sulfonamides is attributed to the ionization of the N(1) sulfamido nitrogen and ranges from 5.74 for sulfamethoxazole to 8.4 for sulfapyridine, whereas the pK_b is due to the ionization of the anilino NH_2 group and is quite constant among sulfonamides (9). The dioxane-water mixtures serve as a model system of water-Lewis base cosolvents to test solubility models, because it provides a wide polarity range in which are included most solvent mixtures used in manufacturing processes. It should be noted that dioxane is toxic and it cannot be used for oral or parenteral dosage forms.

EXPERIMENTAL

- Reagents: Crystalline Sulfapyridine (Sigma). Spectrophotometric quality Dioxane (Panreac, Monplet and Esteban, Barcelona, Spain) and distilled water.

- Ideal Solubility Determination: The melting point and the heat of fusion, determined in a differential scanning calorimeter (Mettler DSC 30) are 464.6 K and 8496.36 Cal/Mole respectively.

- Determination of experimental solubility: Sulfapyridine solubility is determined in different proportions of a mixture composed of dioxane and distilled water. An excess of solute was placed in a measuring flask

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with a specific amount of solvent mixture; the flask was sealed and placed in a temperature-controlled bath at 25 ± 0.2°C and constantly shaken until solution saturation. The equilibrium saturation was attained within three days. Samples were taken and filtered through 0.2 μm pore Fluoropore membranes. After appropiate dilution with methanol, samples were spectrophotometrically determined at the maximum wavewlength, 269 nm in a double beam spectrophotometer (Bausch Lomb 2000).

- The density of the saturated solutions and of all the dioxane-water mixture proportions was determined at 25 ± 0.2°C in 10 ml pycnometers. The density is needed to convert the results obtained spectrophotometrically (molarity) to mole fraction.

- All determinations were performed in triplicate.

RESULTS AND DISCUSSION

The molar volume of the solute and its solubility parameter were calculated according to the Fedors method (10), based on group contributions. The calculated values are V_2 = 149.2 cm^3/ mol and δ_2 = 12.67 $(cal/cm^3)^{1/2}$. Table 1 gives the percentage of dioxane used, solubility parameters of the solvent mixture and experimental solubilities X_2. The solubility determined in water at 25 °C (1.78×10^{-5}) is in good agreement to the value reported by Regosz et al. (11), $X_2 = 1.94 \times 10^{-5}$. For all models tested, the choice of the best equation was based on the r^2 and residual analysis, according to the criteria of Jeng and Martin (12).

Using the extended Hildebrand method (Eq. 6), the best equation is a polynomial in the third degree:

$$W = 30{,}959387 + 8{,}844509\delta_1 - 0{,}036954\delta_1^2 + 0{,}00976\delta_1^3 \quad \text{eq.11}$$

$n = 17$, $r^2 = 0.9999$, $s = 0.35$, $F = 156329$, $F(3,13, 0.01) = 5.74$.

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TABLE 1

Experimental and calculated solubilities of sulfapyridine in dioxane-water mixtures.

% Dioxane	δ_1 (cal/cm)$^{1/2}$	K	X_{2exp}[a]	X_{2cal}[b]	X_{2cal}[c]	X_{2cal}[d]	X_{2cal}[e]
0	23.45	1.157	1.7768×10^{-5}	1.1327×10^{-15}	1.9448×10^{-5}	1.9331×10^{-5}	0.1370×10^{-5}
20	20.76	1.089	5.2066×10^{-5}	4.0549×10^{-10}	4.2145×10^{-5}	4.1937×10^{-5}	1.2200×10^{-5}
40	18.07	1.032	1.6017×10^{-4}	3.7914×10^{-6}	1.5330×10^{-4}	1.5288×10^{-4}	9.5130×10^{-5}
50	16.73	1.010	2.7515×10^{-4}	9.2307×10^{-5}	2.9595×10^{-4}	2.9543×10^{-4}	2.2238×10^{-4}
60	15.39	0.993	4.5279×10^{-4}	9.0846×10^{-4}	5.2456×10^{-4}	5.2409×10^{-4}	4.3990×10^{-4}
65	14.69	0.987	6.0976×10^{-4}	2.0932×10^{-3}	6.6800×10^{-4}	6.6733×10^{-4}	5.8935×10^{-4}
70	14.04	0.982	7.4579×10^{-4}	3.6421×10^{-3}	7.9735×10^{-4}	7.9660×10^{-4}	7.2364×10^{-4}
75	13.37	0.978	8.2768×10^{-4}	5.1596×10^{-3}	9.0436×10^{-4}	9.0379×10^{-4}	8.3342×10^{-4}
80	12.70	0.977	9.2980×10^{-4}	5.8335×10^{-3}	9.6063×10^{-4}	9.5997×10^{-4}	8.9535×10^{-4}
85	12.03	0.979	1.0335×10^{-3}	5.2645×10^{-3}	9.4715×10^{-4}	9.4593×10^{-4}	8.9277×10^{-4}
87	11.76	0.980	1.0743×10^{-3}	4.7392×10^{-3}	9.2029×10^{-4}	9.1869×10^{-4}	8.7548×10^{-4}
90	11.33	0.982	9.9777×10^{-4}	3.7176×10^{-3}	8.5289×10^{-4}	8.5157×10^{-4}	8.7748×10^{-4}
92	11.07	0.983	9.6181×10^{-4}	3.0685×10^{-3}	7.9979×10^{-4}	7.9845×10^{-4}	8.1063×10^{-4}
94	10.82	0.985	8.6300×10^{-4}	2.4699×10^{-3}	7.4138×10^{-4}	7.4041×10^{-4}	7.5897×10^{-4}
96	10.55	0.986	7.2208×10^{-4}	1.8862×10^{-3}	6.7211×10^{-4}	6.7158×10^{-4}	6.6980×10^{-4}
98	10.27	0.987	5.7877×10^{-4}	1.3711×10^{-3}	5.9665×10^{-4}	5.9650×10^{-4}	6.2019×10^{-4}
100	10.01	0.983	3.3935×10^{-4}	9.8356×10^{-4}	5.2479×10^{-4}	5.2539×10^{-4}	5.4295×10^{-4}

[a] Experimental solubility values; [b] Calculated from the Hildebrand equation.; [c] Calculated from Eq.12.; [d] Calculated from Eq.13.; [e] Calculated from Eq.14.

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Using the other form of the extended Hildebrand method (eq.7) a third-degree polynomial is also obtained:

$$\ln \alpha_2/A = 98.610126 - 17.689018\delta_1 + 1.073908\delta_1^2 - 0.019519\delta_1^3 \quad \text{eq.12}$$

$n = 17$, $r^2 = 0.9758$, $s = 0.71$, $F = 215.6$, $F(3,13,0.01) = 5.74$.

Table 1 shows that the predicted solubilities from the extended Hildebrand method (Eq. 12) are in excellent agreement with the experimental data, most values being within 15 % error, except the solubility predicted for the pure solvent, dioxane which is 55 % in error. It should be noted that expressing the residuals as percentage often overemphasizes error. The value, $X_{2exp} = 3.4 \times 10^{-4}$ versus $X_{2cal} = 5.24 \times 10^{-4}$ can be actually considered a fairly good result. Similar differences can be found among experimental data from different laboratories.

The results are similar using Eqs. 11 and 1. Eq. 12 was also tested introducing a correction term, $\ln (V_2/V_1) - 1 + (V_2/V_1)$, to account for differences of size of the solute and the solvent, but this term did not improve solubility prediction, differently from what occurs with other drugs like sulfathiazole (13).

Table 1 includes the values calculated with the original Hildebrand equation for regular solutions, which gives poor results in most cases, with errors larger than 100%. Sulfapyridine forms irregular solutions in dioxane-water mixtures, and the interaction term W deviates from the geometric mean $\delta_1\delta_2$. As shown in Figure 1, W is not linearly related to δ_1, as would occur for regular solutions.

Instead, W fits a polynomial in δ_1, as given in Eq. 11. Table I includes the values of K, as calculated with Eq. 4, which are used together with X_2^i to characterize solute-solvent interactions. Only for regular solutions K is equal to unit; small deviations from unity, as found in Table I, yields large errors in the calculated solubilities. Between 0-

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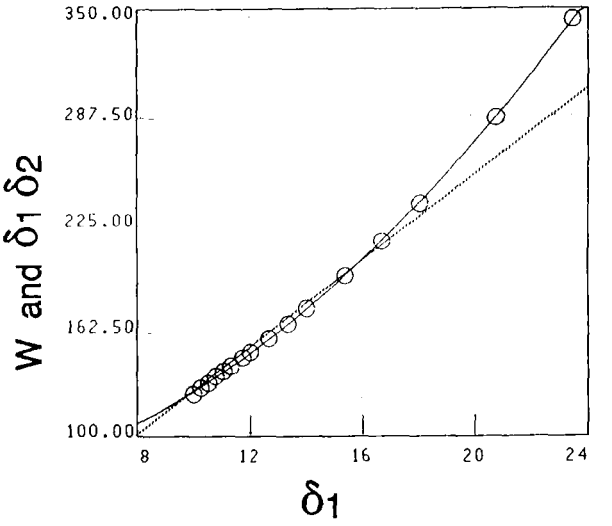

FIGURE 1.

Deviation of experimental W values (◯) from the geometric mean, $\delta_1\delta_2$ (dotted line). The solid line is calculated with equation 11, a third degree polynomial in δ_1.

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50% dioxane in water, K is larger than one, that is, the experimental solubility is greater than the solubility calculated with the Hildebrand equation, possibly because solute-solvent interactions are larger that expected from the geometric mean assumption. For the other solvent mixtures, K ranges from 0.993 to 0.987, and the actual solubilities are smaller than that calculated with the Hildebrand equation. Ionization of the drug can contribute to solubility increase in the mixtures of larger water content. The pH of the solvent mixtures ranges about one unit from the isoelectric point of the drug and ionization alone does not account for the solubility increase. The actual aqueous solubility is larger than the predicted value from the Hildebrand equation by a factor of 10^{10} (Table 1). Sulfapyrazine is also able to hydrogen bond with water and this may also contribute to increase solubility in water. However, the

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solvation effect of the solvent mixture is weak because the actual solubilities fall below the ideal solubility value (Figure 2).

The simplified model for single solutes, eq. 8, is also tested. The best result is a third degree polynomial in δ, as with the extended Hildebrand method:

$$\log X_2 = -13.055147 + 1.942046\delta_1 - 0.117901\delta_1^2 + 0.002143\delta_1^3 \quad \text{eq.13}$$

$n = 17$, $r^2 = 0.9757$, $s = 0.08$, $F = 215.135$, $F(3,13,0.01) = 5.74$.

The solubilities predicted with eq. 13 (Table 1) are comparable to that obtained with the extended Hildebrand method (eqs. 11, 1 and 12); most of them are within 15 % error whereas the largest error is obtained in dioxane. Figure 2 shows that eq. 13 closely calculates the experimental solubility curve. These results provide further evidence that for a single drug, the volume fraction of the solvent mixture as well as the ideal solubility can be disregarded in the solubility model. Eq. 13 allows direct calculation of X_2 in other solvent compositions without requiring an iterative procedure, as needed in the extended Hildebrand method to estimate the two unknown, X_2 and ϕ_1. The model (Eq. 8) gave also good results in other sulfonamides with mole fraction solubilities ranging between 3×10^{-6} and 0.007, where the value of A, which includes the volume fraction of the solvent (Eq. 2), showed a quite large variation (between 0.0098 and 0.113). For sulfapyridine, A ranges from 0.2509 to 0.2519, corresponding to mole fractions between 1.78×10^{-5} to 1.07×10^{-3}.

The model for related solutes (Eq. 9) is applied to sulfapyridine. According to this model, the regression coefficients are common for several drugs showing similar solute-solvent interactions. In earlier work, the solubility curves of several sulfonamides in dioxane-water were

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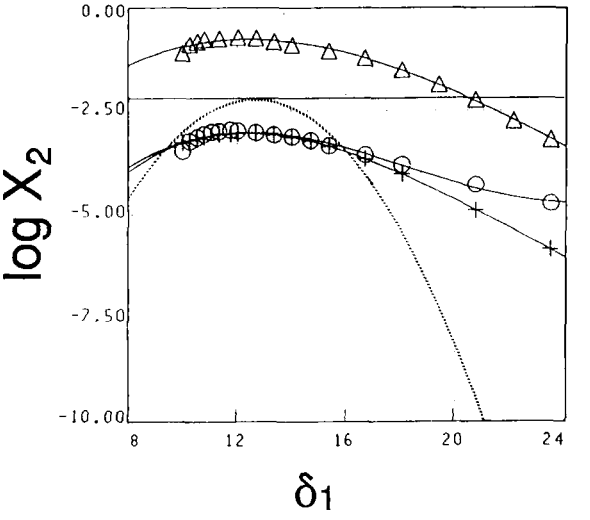

FIGURE 2.

Experimental and calculated solubilities of sulfapyridine in dioxane-water mixtures: (○) experimental values, (....) calculated with the Hildebrand equation; (+) predicted with equation 14. The figure shows for comparison the experimental solubilities of sulfadimidine (△) (ref. 7). The solid lines are obtained from polynomials of log X_2 in the third degree in δ_1 (Eq. 8). The solid straight line represents logX_2^i of sulfapyridine.

predicted by a single equation (7):

$$\log X_2 = 0.167822 + 1.146939 \log X_{2(diox)} + 0.2851214 \log X_{2(w)} + \\ + 0.03848\delta_1\delta_2 - 0.0872\,\delta_1^2 + 0.001335\,\delta_1^3 + \\ + 0.5813937\,\delta_{1b} \qquad \text{eq. 14}$$

To apply this model, the only experimental values needed for sulfapyridine are the solubility of the drug in the pure solvents, dioxane and water. The solubility parameter of the drug was obtained from the method of Fedors (10), that is only based in the structural formula of the drug. Table 1 shows that most calculated solubilities agree with the

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experimental values within 15 % error. The equation is able to very closely predict a major part of the experimental curve, as observed in Figure 2. The largest deviations are obtained for solvent mixtures containing more than 70% water, for which the equation only gives roughly order of magnitudes (Table 1). The extended Hildebrand equation and its simplified form (eq. 8) give less error for the largest water concentrations but both methods require 12-14 experimental solubilities to obtain the best polynomial, whereas eq. 14 only requires two experimental measurements. Eq. 14 does not include either the ideal solubility of the drug nor the volume fraction of the solvent mixtures, similarly to Eq. 8.

CONCLUSIONS

The experimental results of sulfapyridine, a drug which forms irregular solutions, provide further evidence that the volume fraction of the solvent can be disregarded in models relating solubility to solubility parameter. The use of a model including several related solutes allows reasonable prediction of the solubility of sulfapyridine in dioxane-water from only two experimental determinations. This suggests that this method can be applied to other drugs, provided they show similar solute-solvent interactions, to significantly reduce the number of experiments to predict the solubility profile of other related drugs in the solvent mixture.

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