Extended Hildebrand Approach: Solubility of Caffeine in Dioxane–Water Mixtures

A. ADJEI, J. NEWBURGER, and A. MARTIN ˣ

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Abstract □ The solubility of caffeine in various dioxane–water mixtures was analyzed in terms of solute–solvent interactions using a modified version of the Hildebrand treatment for regular solutions. The solubility equation employs a term (W) to replace the geometric mean $(c_1c_2)^{1/2}$, where c_1 and c_2 are the cohesive energy densities for the solvent and solute, respectively. The new equation provides an accurate prediction of solubility once the interaction energy, W, is obtained. In this case, the energy term is regressed against a polynomial in δ_1 of the binary mixture. A quartic expression of W in terms of the solvent solubility parameter was found for predicting the solubility of caffeine in dioxane–water mixtures. The expression yields an error in mole fraction solubility of <3%, a value approximating that of the experimentally determined solubility. The one exception to a good fit is near the maximum solubility, where a depression or valley occurs between the two peaks in solubility data; at this point, the theoretical equation predicts the solubility within ~9%. The new model also may be used to estimate the solubility of drug molecules employing the volume fraction of water in the solvent mixture instead of the composite solubility parameter, δ_1. The method has potential usefulness in preformulation and formulation studies during which solubility determination is important for drug design.

Keyphrases □ Caffeine—solubility in water–dioxane mixtures, extended Hildebrand approach, mathematical prediction of solute–solvent solubilities □ Solubility—caffeine in water–dioxane mixtures, prediction of solubility, extended Hildebrand approach □ Hildebrand solubility equation, modified—caffeine in water–dioxane mixtures, solubility predictions

In previous reports (1, 2), the Hildebrand–Scatchard solubility approach (3) to the prediction of solubility was extended to semipolar crystalline drugs in pure solvents and in polar binary solvent mixtures. The equation for calculating the solubility of drug molecules in polar and nonpolar solvents is (2):

$$-\log X_2 = \frac{\Delta S_m^f}{R}\log\frac{T_m}{T} + \frac{V_2\phi_1^2}{2.303RT}(\delta_1^2 + \delta_2^2 - 2\delta_1\delta_2) + \frac{V_2\phi_1^2}{2.303RT}(2\delta_1\delta_2 - 2W) \quad \text{(Eq. 1}a\text{)}$$

or:

$$-\log X_2 = \frac{\Delta S_m^f}{R}\log\frac{T_m}{T} + \frac{V_2\phi_1^2}{2.303RT}(\delta_1^2 + \delta_2^2 - 2W) \quad \text{(Eq. 1}b\text{)}$$

where X_2 is the mole fraction solubility of the crystalline solute at temperature T on the Kelvin scale; ΔS_m^f is the entropy of fusion of the crystalline drug molecule at its melting point, T_m; R is the molar gas constant; V_2 is the molar volume of the solute, and ϕ_1 is the volume fraction of the pure or mixed solvent. The solubility parameters for the solvent (subscript 1) and the solute (subscript 2) are δ_1 and δ_2, respectively. The W expression is an interaction term which, in regular solution theory, is taken to be equal to a geometric mean, $(c_1c_2)^{1/2}$, where c_1 is the cohesive energy density of the solvent (δ_1^2) and c_2 is the cohesive energy density of the solute (δ_2^2).

The first right-hand term of Eq. 1b is the negative logarithm of the ideal solubility ($-\log X_2^i$), and the second term is the logarithmic solute activity coefficient ($\log \alpha_2$). In Eq. 1a, $\log \alpha_2$ is divided into the regular solution term for van der Waals interaction energies ($\log \alpha_v$) and a final term ($\log \alpha_R$) representing residual solute–solvent interactions (2). The quantities $V_2\phi_1^2/(2.303RT)$ will be represented by A.

In the present approach, W is evaluated from knowledge of the other terms in Eq. 1, obtained experimentally or found in the literature. In polar systems, W equals the geometric mean $(c_1c_2)^{1/2}$ only at points A and B along the solubility profile (Fig. 1) where the real solubility line crosses the regular solution line. This fact emphasizes that the Hildebrand–Scatchard equation (3), written in terms of cohesive energy densities:

$$-\log X_2 = \frac{\Delta S_m^f}{R}\log\frac{T_m}{T} + \frac{V_2\phi_1^2}{2.303RT}\{c_1 + c_2 + 2(c_1c_2)^{1/2}\} \quad \text{(Eq. 2)}$$

correctly calculates the solubility of drugs in mixed polar solvents only at these two points in Fig. 1.

A better approach is not to restrict the interaction term W to a geometric mean but rather to evaluate it experimentally from the solubility of the solute in various solvent concentrations in a binary mixture employing Eq. 1b. An empirical equation for W as a function of solubility parameters of the solvent mixture remains to be discovered. Then, back-calculating W and substituting into Eq. 1 permit the mole fraction solubility of a drug (solute) to be predicted in essentially any solvent mixture.

EXPERIMENTAL

The solubility of crystalline caffeine[1] in dioxane, water, and mixtures of dioxane and water was determined as described for theophylline solutions (2). The other quantities required for predicting drug solubility in mixed solvents also were discussed (2). The solubility parameter, δ_2, for caffeine may be obtained from the peak solubility (Fig. 1), where the solvent δ_1 value should approximate the δ_2 value as required by Eq. 2. A more accurate determination (4) may be obtained by a differential method, plotting $\Delta X_2/\Delta\delta_1$ *versus* δ_1 (Fig. 2) and reading δ_2 as the δ_1 value at the apex of this curve.

RESULTS AND DISCUSSION

To obtain the ideal solubility of caffeine, the procedures described under *Experimental* were employed; the following values were obtained: ΔH_m^f, 5044 cal/mole; T_m, 512°K; and $\Delta S_m^f = \Delta H_m^f/T_m$, 9.85 cal/mole/degree. The ideal mole fraction solubility of caffeine was calculated from these values: $X_2^i = 0.06845$ ($\log X_2^i = -1.1646$). The molar volume of caffeine is 144 cm³/mole, which may be obtained as an average of the apparent molar volume in the mixtures (5). It also may be estimated by the group contribution method of Fedors (6).

The experimental solubility of caffeine at 25 ± 0.1° in dioxane–water mixtures is plotted in Fig. 1 *versus* the solubility parameter, δ_1, of the various mixed solvent systems. Also shown in Fig. 1 are the ideal solubility ($X_2^i = 0.06845$) and the regular solution curve (Eq. 2). The solubility of caffeine ($\delta_2 = 13.8$) in pure dioxane ($\delta_1 = 10.0$), pure water ($\delta_1 = 23.5$), and in the mixture of the two solvents is represented by the solid circles in Fig. 1. The maximum solubility of caffeine in the mixture is X_2 =

[1] Knoll Chemicals.

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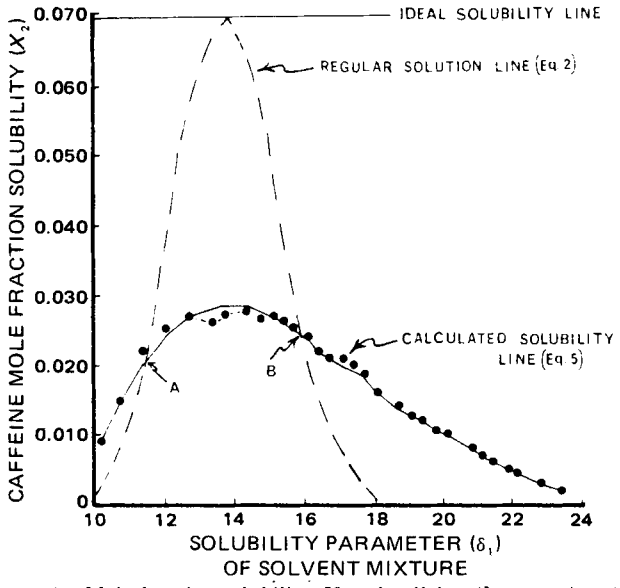

Figure 1—*Mole fraction solubility, X_2, of caffeine (δ_2 = 13.8) at 25° in dioxane, water, and dioxane–water mixtures. Key: A and B, points where real solubility equals regular solution solubility and $W = (c_1c_2)^{1/2} = \delta_1\delta_2$; ●, experimental points; and ··· ● ···, valley between two peaks in the caffeine solubility profile.*

0.0282 and occurs at δ_1 = 13.8. This value is well below the ideal solubility, X_2^i = 0.06845, as predicted from regular solution theory. The discrepancy between the results using the original Hildebrand equation and the experimental points demonstrates that Eq. 2 cannot be used to predict drug solubility in polar solvent systems.

Solubility Prediction Using Regression of *W versus* δ_1—Equation 1, differing from Eq. 2 in that the geometric mean is not used, provides an accurate prediction of solubility once W is obtained. Although W presently cannot be estimated based on fundamental physicochemical properties of the solute and solvent, W may be regressed against a polynomial in δ_1 of the solvent mixtures as described previously (1, 2). The following quadratic, cubic, and quartic equations were obtained using the experimental solubility data for caffeine in dioxane–water mixtures:

$$W = 79.4113802 + 1.8685725\delta_1 + 0.4356481\delta_1^2 \quad \text{(Eq. 3)}$$

$$W = 66.3515007 + 4.3901982\delta_1 + 0.2792065\delta_1^2 + 0.0031281\delta_1^3 \quad \text{(Eq. 4)}$$

$$W = 15.0752785 + 17.6279025\delta_1 - 0.9668266\delta_1^2 + 0.0539120\delta_1^3 - 0.0007578\delta_1^4 \quad \text{(Eq. 5)}$$

The W values calculated using these expressions compared favorably

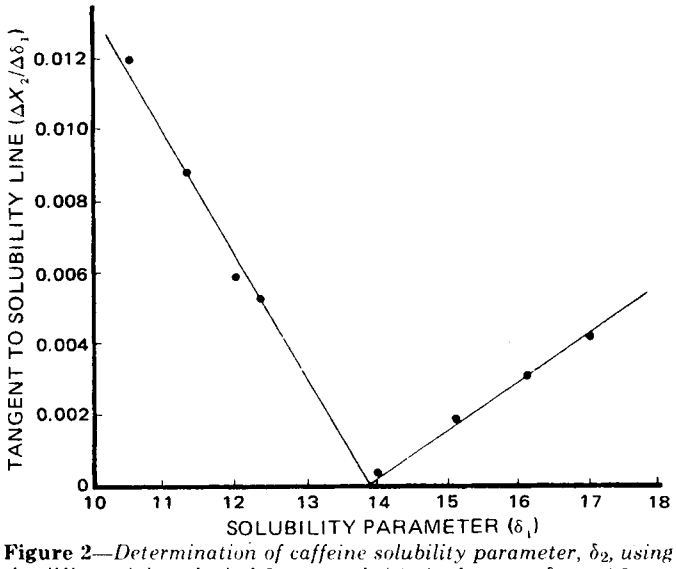

Figure 2—*Determination of caffeine solubility parameter, δ_2, using the differential method of James* et al. *(4). At the apex, δ_2 = 13.8.*

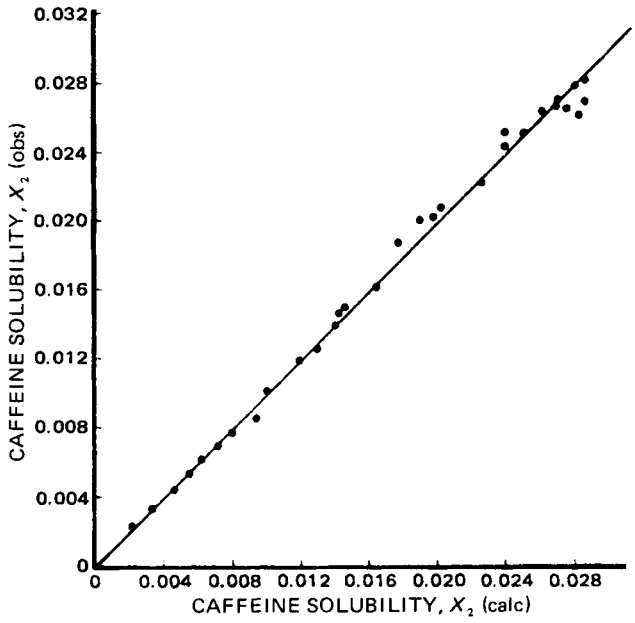

Figure 3—*Comparison of 31 observed caffeine solubilities in dioxane–water systems at 25° with solubilities predicted by the extended Hildebrand approach. The intercept of the line is 0.001, and the slope is 0.999. The correlation coefficient, r^2, is 0.989 for* n = 31.

with the original W values computed using Eq. 1. The solid line plotted in Fig. 1 was obtained employing the quartic expression (Eq. 5). This calculated solubility curve fits the experimental data points quite well (Figs. 1 and 3), predicting the solubility of caffeine in dioxane–water mixtures at most points within an error of ~3%, a value approximating the error in experimentally determined solubility values.

One notable exception to the fit is near the peak solubility where a depression or valley occurs between two peaks in the solubility data. Here the theoretical equation cannot reproduce the exact solubility and results in an error of 8.6%. Paruta *et al.* (7) first reported the peaks and valleys in solubility data and demonstrated essentially the same profile for caffeine as shown in Fig. 1. These workers (7) attributed the decreased solubility of caffeine in the dioxane–water mixture at this solvent composition to solvation or to the possible self-association of caffeine into polymeric forms as reported previously (8).

Equations 3–5 are empirical expressions and cannot be expected to reproduce the acute change in solubility represented by small peaks and

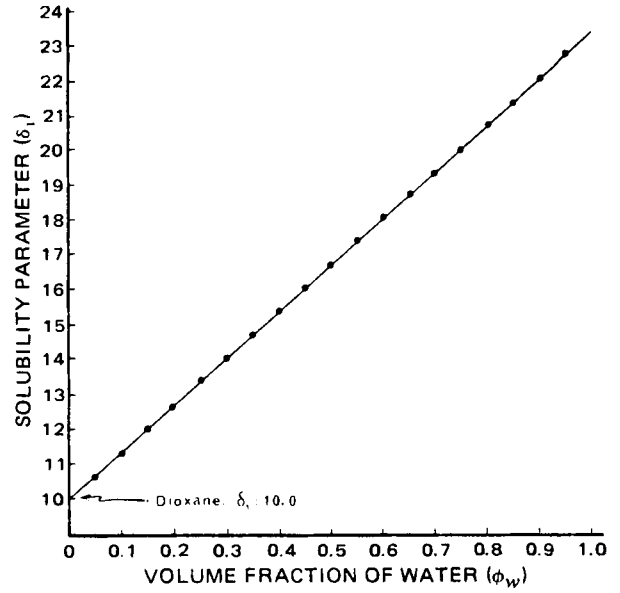

Figure 4—*Solvent solubility parameter, δ_1, in relation to the composition, ϕ, of the dioxane–water mixture as calculated from Eq. 6. The intercept of the line is 10.00, and the slope is 23.45. The number of data sets,* n, *is 31.*

Table I—Comparisons of Observed [a] and Calculated Solubilities of Caffeine (δ_2 = 13.8) in Dioxane–Water Systems at 25° ($-\log X_2^i$ = 1.1646); X_2^i = 0.06845; V_2 = 144 cm³/mole

Volume Percent of Water ($100\phi_w$)	Solution Density	A [b]	δ_1	X_2 (obs)	X_2 (calc)	Percent Solubility Difference
0	1.0337	0.10257	10.01	0.00849	0.00939	10.6
10	1.0440	0.09714	11.33	0.02255	0.01976	12.4
20	1.0516	0.09467	12.70	0.02698	0.02696	0.1
25	1.0532	0.09454	13.37	0.02605	0.02830	8.6
30	1.0542	0.09310	14.04	0.02823	0.02866	1.5
35	1.0556	0.09323	14.71	0.02647	0.02762	4.3
40	1.0542	0.09269	15.39	0.02628	0.02606	0.8
45	1.0516	0.09294	16.06	0.02429	0.02388	1.7
50	1.0506	0.09369	16.73	0.02137	0.02138	0.0
55	1.0481	0.09374	17.40	0.01997	0.01904	4.7
60	1.0443	0.09520	18.07	0.01617	0.01641	1.5
65	1.0399	0.09543	18.75	0.01465	0.01420	3.1
70	1.0346	0.09653	19.42	0.01195	0.01194	0.1
80	1.0254	0.09837	20.76	0.00780	0.00796	2.1
90	1.0095	0.10020	22.11	0.00453	0.00466	2.9
100	1.0024	0.10179	23.45	0.00229	0.00222	3.1

[a] Data selected from the 31 solubility points shown in Fig. 1. Calculated solubilities were obtained with the help of Eq. 8 as described in the text. [b] $A = V_2\phi_1^2/(2.303RT)$ in Eqs. 1 and 2.

valleys in a solubility profile. The calculated solubility line (solid line of Fig. 1), representing the quartic expression (Eq. 5), passes smoothly through the points about the peak solubility, ignoring the slight depression (dotted line at the peak in Fig. 1) at the maximum solubility. This kind of second-order deviation in drug solubility in polar solvents requires additional investigation and a considerably refined model for its characterization.

Predicting Drug Solubility from Solvent Concentration—The solubility parameter, δ_1, against which W is regressed to calculate solubility is calculated for a mixture of two solvents, a and b, using:

$$\delta_1 = \frac{\phi_a\delta_a + \phi_b\delta_b}{\phi_a + \phi_b} \quad \text{(Eq. 6)}$$

where the total volume fraction of the two solvents is given by:

$$\phi_1 = \phi_a + \phi_b \quad \text{(Eq. 7)}$$

Therefore, it is possible to express δ_1 in terms of the volume fraction (or volume percent) of either binary solvent species. The solubility parameter, δ_1, is plotted in Fig. 4 against the volume fraction of water in the mixture. A straight line is obtained, which suggests the possibility of bypassing W and δ_1 and back-calculating $\log \alpha_2/A$ by regressing it directly against the volume fraction of water, ϕ_w, in the solvent mixture. The quartic regression equation becomes:

$$\log \alpha_2/A = 8.409751 - 38.419518\phi_w + 109.607554\phi_w^2 - 114.353521\phi_w^3 + 49.383099\phi_w^4 \quad \text{(Eq. 8)}$$

Equation 8 yields the calculated solubility data found in Table I. For example, at 65% water, a volume fraction, ϕ_w, of 0.65 is substituted in Eq. 8, which yields 7.157 for $\log \alpha_2/A$. This value is multiplied by A to obtain $\log \alpha_2$ or 0.68299. Log α_2 then is added to $-\log X_2^i$, which is 1.1646, to obtain the negative logarithm of the solubility, $-\log X_2$. The sign is changed and the antilog is calculated to obtain X_2 = 0.01420. This result is within 3.1% of X_2 (obs) = 0.01465. The procedure is shown more clearly as:

$$\log \alpha_2 - \log X_2^i = -\log X_2 \quad \text{(Eq. 9a)}$$

$$0.68299 + 1.1646 = 1.84759 = -\log X_2 \quad \text{(Eq. 9b)}$$

$$\text{antilog}\,(-1.84759) = X_2 = 0.01420 \quad \text{(Eq. 9c)}$$

CONCLUSIONS

The extended Hildebrand approach to solubility employs a power series (quartic) equation in δ_1 to back-calculate W, which reproduces the solubility of caffeine in dioxane–water mixtures within the accuracy ordinarily achieved in experimental solubility results.

Hildebrand *et al.* (9) made the following observations: "Plato asserted that heavenly bodies move in circles because a circle is the most perfect geometrical figure. He was wrong: the most perfect geometrical construct is a straight line between two axes; one which expresses theory, the other which states the facts" (9). To test this Hildebrand hypothesis, Fig. 3 was drawn, and an almost straight line of zero intercept was obtained, r^2 = 0.989.

The close correlation of calculated results with experimental solubility is gratifying, although the extended method cannot be called a theory. At best, the method is semiempirical, because one uses solubilities originally to obtain the W values. Then W (or $\log \alpha_2/A$) is regressed in terms of solvent δ values or volume fractions of a solvent in the mixture to back-calculate solubilities. It is surprising that such good fits of the data have been obtained both with theophylline (2) and with caffeine in binary solvent systems. However, dioxane–water mixtures are relatively well behaved, producing fairly uniform bell-shaped solubility profiles; other solvent pairs may not perform as well. Limited experience with the solubility of drugs in pure solvents shows that the extended Hildebrand approach will prove useful for pure solvent systems only if a technique more fundamental than power series regression on δ_1 is found.

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