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Extended Hildebrand Solubility Approach: Methylxanthines in Mixed Solvents

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Abstract □ The solubility profiles of theobromine, theophylline, and caffeine at 25° were examined in binary solvent systems including dioxane–formamide, water–polyethylene glycol 400, and glycerin–propylene glycol. Theobromine solubility was studied in dioxane–water mixtures, a solvent system that was investigated earlier for the solubility of theophylline and caffeine. Solubilities were calculated in these polar systems by a regression method, based on an extension of the Hildebrand–Scatchard equation of regular solution theory. A linear relationship between the mixed solvent solubility parameter, δ_1, and dielectric constant, ϵ, was introduced earlier and was confirmed in the present study. In addition, it was observed that a regression of log(activity coefficient) on ϵ in a second or higher degree polynomial provides reasonable solubility values for the methylxanthines in mixed solvents. A direct regression of molal or mole fraction (but not molar) solubility against δ_1, ϵ, or against volume percent of one or the other solvent in a binary solvent mixture provided a suitable measure of solubility for these crystalline drugs in mixed polar solvents. The drug's solubility parameter as determined from peak solubility in mixed polar solvents varied somewhat, depending on the specific solvent system employed. It is suggested that a drug may exhibit one (or more) solubility parameters in nonpolar solutions and multiple solubility parameters in polar systems. The extended solubility approach serves for the back-calculation of solubilities in mixed solvent systems, even though the solubility parameter of the solute may vary from one solvent system to the next.

Keyphrases □ Methylxanthines—solubility profiles using extended Hildebrand–Scatchard equation □ Solubility—methylxanthines in mixed solvents, extended Hildebrand–Scatchard equation □ Hildebrand–Scatchard equation—modified, solubility profiles of methylxanthines in mixed solvents

Previous reports (1–3) introduced an approach to estimate the solubility of drugs in mixed and pure solvent systems. The method employs the equation:

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

or:

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

where X_2 is the mole fraction solubility of the drug, ΔS^f_m is the entropy of fusion, R is the molar gas constant, T_m is the melting point of the compound in Kelvin degrees, T is the absolute temperature at which the solubility is measured, V_2 is the molar volume of the drug as a hypothetical supercooled liquid solute at temperature T, ϕ_1 is the volume fraction of the solvent, δ_1 and δ_2 are the solubility parameters of the solvent and solute, and W is the solute–solvent interaction energy. Subscript 1 is used for solvent and subscript 2 for solute. The W value is computed for the drug in each solvent mixture, using Eq. 1*b*. It may, in turn, be back-calculated employing a power series regression in δ_1 to estimate mole fraction or molal solubilities. By knowing the density of the solution at a particular temperature, it is also possible to convert these calculations to molar solubilities. The term $V_2\phi_1^2/2.303RT$ is designated in this study by the symbol A. The present work tests the extended Hildebrand solubility approach (as this method is called) with various binary solvent mixtures.

EXPERIMENTAL

The sources and treatment of methylxanthines and some of the solvents used were given previously (2, 3)[1]. Additional solvents employed in the present study were propylene glycol[2], polyethylene glycol 400[2], and glycerin[2]. Pertinent physicochemical properties of the xanthine derivatives are recorded in Table I. The solubilities of the drugs were determined in a shaker bath employing 20-ml screw-capped vials containing an excess of the drug at 25 ± 0.2°. Equilibrium occurred well before 96 hr. Samples were withdrawn after 96 hr and filtered through a 0.22-μm filter, and aliquots were removed and diluted for spectrophotometric assay. Runs were carried out in quadruplicate, and the four results were averaged. Densities of the saturated solutions and of the solvent mixtures were determined in quadruplicate at 25 ± 0.2° in 10-ml pycnometers.

RESULTS AND DISCUSSION

Theobromine was dissolved in mixtures of dioxane and water at 25°. The solubility profile is shown in Fig. 1. Table II contains the data used to plot the back-calculation line of Fig. 1, including W_{calc} and A values. Solution densities and dielectric constants are also recorded in Table II.

Ideal Solubility in Relation to Maximum Solubility in Real Systems—The ideal mole fraction solubility of theobromine at 25° is 0.0029, a value well below the ideal solubilities of theophylline (0.0190) and caffeine (0.0685) at 25° (Table I and Fig. 1) because of the greater ΔH^f_m value and high melting point (348°) of theobromine. The peak solubility of theobromine in the best dioxane–water mixture (~70% dioxane) is well below ideal solubility (Fig. 1), as observed previously for caffeine and theophylline. This phenomenon was noted by Gordon and Scott (4) and by others (5, 6). Scatchard *et al.* (7) observed that the value of C_{12} (an-

[1] Reference 2 states that mean molar volumes of the binary solvent mixtures are calculated from Eq. 17, in which each molecular weight was multiplied by the mole fraction of that solvent in the mixture. This is an error; the quantity used in Refs. 2 and 3 and in the present study is volume fraction rather than mole fraction.
[2] Fisher Scientific.

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Table I—Properties of Theophylline, Caffeine, and Theobromine

Property	Theophylline	Caffeine	Theobromine
Heat of fusion[a] at melting point, cal/mole	7097	5044	9819
Melting point[b], °K	547.65	512.15	621.15
Molecular weight[c], g/mole	180.18	194.19	180.18
Molar volume[d] at 25°, ml/mole	124.0	144.0	124.0
Solubility parameter[e], $(cal/cm^3)^{1/2}$	14.0	13.8	14.0
Ideal mole fraction solubility, X_2^i at 25° [f]	0.01896	0.06845	0.00291
Solubility (mole/liter) in:			
Dioxane	0.03032	0.09656	0.00518
Water	0.04083	0.12438	0.00183
N,N-Dimethylformamide	0.20173	0.16433	0.00854
Hexane	0.00083	0.00003	0.00015
UV absorption spectra, λ_{max}[g]	270	273	273
Molar absorptivity[g], *E* 1%, 1 cm	530	519	550

[a] Determined by differential scanning calorimetry using Perkin-Elmer DSC model 1B. [b] Melting temperatures of the xanthines determined using Perkin-Elmer DSC model 1B. [c] Molecular weights of the xanthines obtained from the manufacturer's specifications and correlated with results using mass spectrometry. [d] Molar volume of the xanthines (ml/mole) determined using an arithmetic mean of the apparent molar volume in dioxane–water mixtures, and solute molar volumes from group contribution methods (Ref. 18). [e] Solute solubility parameters, $(cal/cm^3)^{1/2}$ calculated using a graphical solubility method (Ref. 22) and a group contribution method (Ref. 18). [f] $\log X_2^i = (\Delta S_m^f/R) \log (T/T_m)$. [g] Ref. 23.

other symbol used for W) was 5% greater than $\delta_1\delta_2$ for benzene in methanol at 0.5 mole fraction and 8% greater than $\delta_1\delta_2$ for carbon tetrachloride in methanol, signifying strong solute–solvent interaction in these mixtures. The mole fraction solubility of theobromine in the optimum water–dioxane mixture is 0.00075 or 74% below ideal (Fig. 1) suggesting self-association of solvent, solute, or both.

The differences, Δ, between ideal and actual interaction energies of the three methylxanthines in these optimum mixtures are given in Table III. The solute–solvent interaction energy, W, is included together with

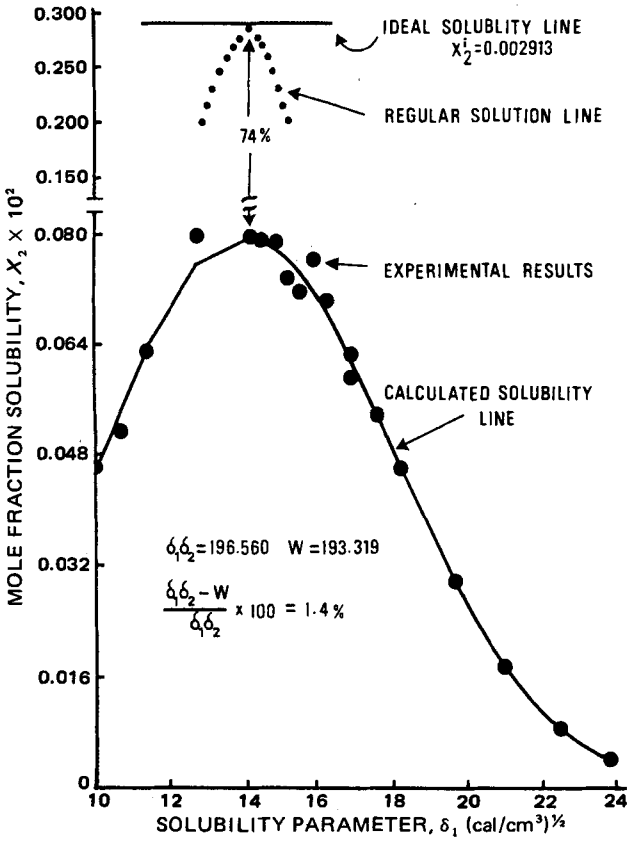

Figure 1—*Mole fraction solubility of theobromine in dioxane–water mixtures at 25°. Key: • • •, peak region of the regular solution curve; ●, observed solubilities; and —, back-calculated solubility using Eq. 2a of Table IV.*

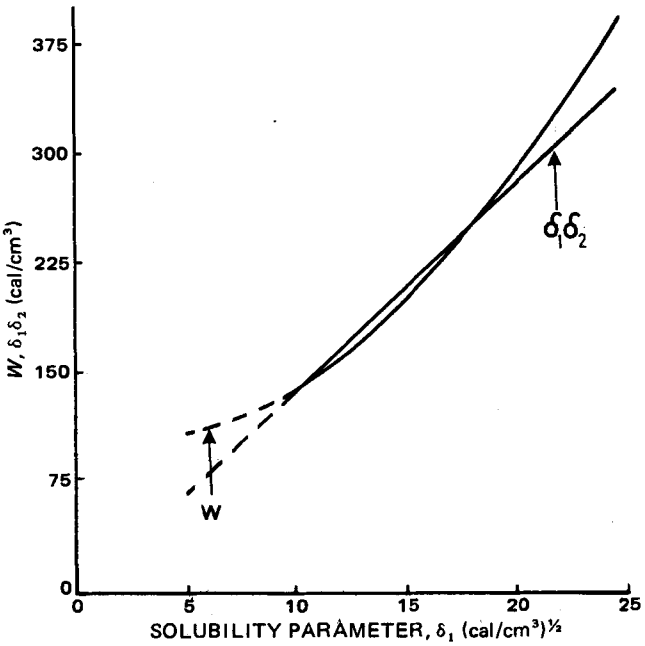

Figure 2—*Relationship of* W *and* $\delta_1\delta_2$, *for theophylline in dioxane* (δ_1 = *10.0) and water* (δ_2 = *23.5) mixture at 25°.*

$\delta_1\delta_2$, the interaction term that would be applicable if the systems behaved as regular solutions. The ratio, K, of W to $\delta_1\delta_2$ at peak solubility is found in the last column of Table III. These data indicate that a difference of 1.4% between the geometric mean $\delta_1\delta_2$ and W results in a 74% decrease in expected solubility for theobromine in dioxane–water.

Figure 2 shows the slightly curved line obtained when W is plotted against δ_1. The geometric mean, $\delta_1\delta_2$, is plotted on the same graph against δ_1 to depict graphically the relationship of W to $\delta_1\delta_2$ for theophylline across the mixtures of dioxane (δ_1 = 10.0) to water (δ_1 = 23.5). This small difference in interaction energy, ($\Delta = \delta_1\delta_2 - W$) of Eq. 1*a*, in xanthine–dioxane–water systems accounts for the fact that maximum solubility of the real system does not reach X_2^i, the ideal value of peak solubility.

The extended Hildebrand equation differs from the Hildebrand equation in the use of W to replace $\delta_1\delta_2$, and Fig. 2 provides a graphical demonstration of why the original Hildebrand approach cannot be used to estimate solubilities of drugs in polar solvent mixtures. In Fig. 2, $\delta_1\delta_2$

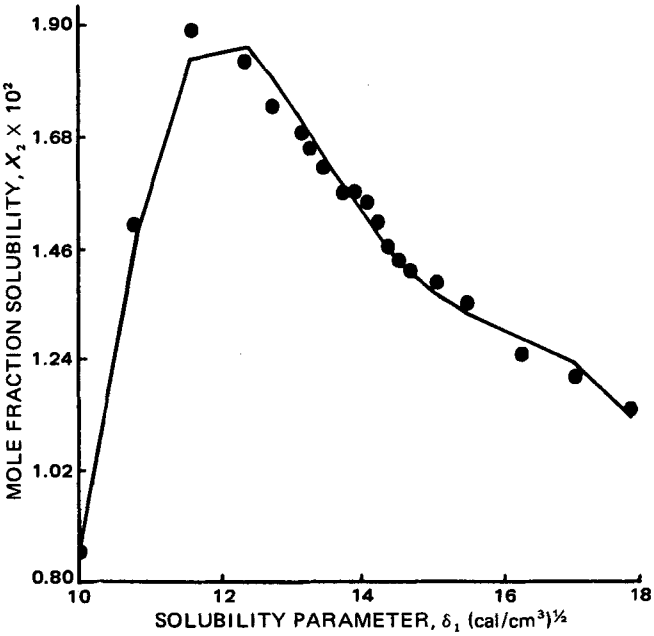

Figure 3—*Mole fraction solubility of caffeine in dioxane–formamide mixtures at 25°. Key: ●, observed solubilities; and —, back-calculated solubility based on Eqs. 5a and 5b of Table V.*

Table II—Observed [a] and Calculated [b] Solubilities of Theobromine [c] in Dioxane–Water Mixtures at 25°.

Volume Percent Water, $100\phi_w$	Solution Density	A [e]	δ_1 [f]	ϵ_1 [g]	W_{calc}	log α_2/A	$X_{2_{obs}} \times 10^6$ [a]	$X_{2_{calc}} \times 10^6$ [b]	Percent Difference
100	0.9976	0.09084	23.45	78.54	362.316	21.42037	33	33	−1.0
90	1.0808	0.09082	22.11	69.28	333.734	17.43588	76	77	−1.5
80	1.0148	0.09077	20.76	62.63	306.457	13.76552	164	157	4.6
70	1.0230	0.09072	19.42	52.02	280.888	11.21233	280	276	1.5
60	1.0293	0.09067	18.07	43.13	256.645	9.21972	425	428	−0.7
50	1.0350	0.09064	16.73	37.09	234.088	7.90106	560	582	−3.9
40	1.0388	0.09062	15.39	27.46	213.031	7.01479	674	699	−3.8
30	1.0381	0.09062	14.04	20.54	193.334	6.48362	753	746	1.0
20	1.0370	0.09065	12.70	12.52	175.289	6.51980	747	707	5.4
10	1.0336	0.09071	11.33	5.72	158.391	7.61277	594	595	−0.1
0	1.0290	0.09077	10.01	2.13	143.594	9.00030	444	452	−1.9

[a] Data selected from solubilities determined at 25° using 18 solvent mixtures. [b] Calculated solubilities obtained by regressing W *versus* δ_1 in a third-degree power series (cubic). The cubic equation is Eq. 3*a* of Table IV. Essentially the same $X_{2_{calc}}$ values are obtained by regressing W or log α_2/A on ϕ_w using Eq. 8*a* or 8*b* or by regressing W or log α_2/A on ϵ_1 (equations not shown). [c] $\delta_2 = 14.0$ (cal/cm^3)$^{1/2}$. [d] $X_2^i = 0.002913$, $-\log X_2^i = 2.5357$, $\Delta H_m^f = 9819$ cal/mole, $\Delta S_m^f = 15.81$ eu, and $V = 124$ ml/mole. [e] $V_2\phi_1^2/2.303RT$. [f] Solubility parameter obtained from Ref. 24 and by use of Eq. 14 of Ref. 2. [g] Experimentally determined dielectric constants of solvent mixtures at 25°.

is linear across the range of δ_1 values while the correct value, W, produces a curve that passes through the $\delta_1\delta_2$ line. Only at two points where the straight line intersects the curve may the Hildebrand $\delta_1\delta_2$ values be used satisfactorily to predict the drug solubility.

Predicting Solubility Using Regression Analysis—As with theophylline and caffeine, theobromine solubility may be depicted using the extended solubility approach, *i.e.*, the regression of W or log α_2/A on δ_1 in a power series as reported earlier (1–3). The appropriate second degree (quadratic), third degree (cubic), and fourth degree (quartic) equations for theobromine in dioxane–water at 25° are given in Table IV. The solid line in Fig. 1, representing back-calculated solubilities of theobromine in dioxane–water mixtures, was obtained with Eq. 2*a* and demonstrates a good fit to experimental data. As observed in Eqs. 2*a*, 3*a*, and 4*a* of Table IV, when regressing W *versus* δ_1, five or six places should be retained after the decimal point for satisfactory results. In the log α_2/A *versus* δ_1 equations (Eqs. 2*b*, 3*b*, and 4*b*), five or six places after the decimal points are also needed. The same remarks apply to Eqs. 5 and 6 of Table V. In Eqs. 8*a* and 8*b*, three places after the decimal point are adequate.

The question of when it is appropriate to use a quadratic *versus* a cubic or quartic equation is not easily answered without an analysis of variance. Statistical analysis of the solubility data will be presented in a separate report. Use of the extended solubility approach has shown that the data of some solubility studies (*e.g.*, theobromine in dioxane–water, Table II and Fig. 1) are satisfactorily reproduced with a quadratic equation. The solubility of caffeine in dioxane–water was better reproduced using a cubic equation and, for added refinement, a quartic equation (3). A fifth-degree equation was not necessary in any case studied thus far.

Methylxanthines in Other Solvent Systems—To examine the extended solubility approach in mixed solvents other than dioxane–water, solubilities of the three methylxanthines were measured at 25° in dioxane–formamide (Fig. 3), glycerin–propylene glycol (Fig. 4), and polyethylene glycol 400–water mixtures (Fig. 5). The quadratic regression equations of W *versus* δ_1 and log α_2/A *versus* δ_1 used to obtain the back-calculated curves of Figs. 3 and 4 are found in Table V (Eqs. 5 and 6).

The original Hildebrand equation (4, 8) predicts that the solubility of a compound, the solubility parameter of which lies between the δ values of the two solvents of a binary mixture, will exhibit a peak where the solubility parameter of the mixed solvent, δ_1, equals that of the solute, δ_2. When δ_2 of the solute is found on one side or the other of the solubility parameters of pure liquids that are combined to form the solvents, no peak is expected. For example, maximum solubility of theophylline is not found in the mixture of propylene glycol ($\delta_1 = 15.0$) and glycerin ($\delta_1 = 17.7$) since the solubility parameter of theophylline ($\delta_2 = 14.0$) does not fall between the δ values of these two solvents. However, this fact does not prevent the use of the extended Hildebrand solubility approach to calculate solubilities in solvent combinations such as glycerin and propylene glycol (Fig. 4).

Solvation—The solubilities of the three xanthines reach maxima below the ideal solubilities in dioxane–water mixtures. This failure to attain ideal solubility was attributed to solvent clustering (4), but a satisfactory explanation on a molecular basis has not been provided.

Solubility in excess of the ideal value is generally accepted as a manifestation of complexation between the solute and solvent and is commonly called solvation. Theophylline in the binary solvent of polyethylene glycol 400–water provides an example of solvation. Here the solubility rises to a maximum value of $X_2 = 0.0309$ (Fig. 5). In contrast to W values for the xanthines in dioxane–water mixtures (Table III), W for theophylline in polyethylene glycol 400–water is greater than $\delta_1\delta_2$ at maximum solubility. The K value, which is equal to $W/\delta_1\delta_2$, is 1.0074 in this case.

The percent difference between maximum actual and ideal mole fraction solubility for theophylline in polyethylene glycol 400–water is 63%, whereas the difference, $\Delta = \delta_1\delta_2 - W$, is only 0.7%. Comparison of these results with the values in Table III again demonstrates that a very small difference between $\delta_1\delta_2$ and W may result in a large difference between ideal and actual solubilities.

Thus, for real systems, drug solubility maxima in mixed solvents may be greater than, equal to, or less than ideal solubility, and $K = W/\delta_1\delta_2$ may have values greater than, equal to, or less than unity. When $K = 1.0$, a solution cannot necessarily be referred to as regular. In polar systems, the condition $W = \delta_1\delta_2$ may arise more or less by chance as observed in Fig. 2, where the $\delta_1\delta_2$ lines crosses W at two points owing, perhaps, to a balancing of opposing intermolecular forces; thus, the conditions set forth by Hildebrand (8) for a regular solution would not obtain.

For solubilities greater than ideal, the sign of the logarithmic activity coefficients becomes negative ($\alpha_2 < 1$), and the computer program used to obtain W_{calc} must take this fact into account. The W calculated by regression always yields a positive log α_2, and the computer is pro-

Table III—Comparison of Observed Peak and Ideal Solubility Values of Caffeine, Theophylline, and Theobromine in Dioxane–Water Mixtures at 25°

Compound	δ_2, (cal/cm^3)$^{1/2}$	Ideal Solubility X_2^i	Observed Peak Solubility X_2	$\frac{X_2^i - X_2}{X_2^i} \times 100\%$	$\delta_1\delta_2$ (cal/cm^3)	W, (cal/cm^3)	Δ [a] $= \delta_1\delta_2 - W$ (Percent Difference)	K [a] $= W/\delta_1\delta_2$
Caffeine	13.8	0.0685	0.0282	59%	193.200	191.715	1.485 (0.8%)	0.9923
Theophylline	14.0	0.0190	0.0144	24%	204.400	203.590	0.810 (0.4%)	0.9960
Theobromine	14.0	0.0029	0.00075	74%	196.000	193.319	2.681 (1.4%)	0.9863

[a] The quantity K was first suggested by E. Walker, J. Appl. Chem., 2, 470 (1952). The large differences between X_2 and X_2^i resulting from very small differences Δ between W and $\delta_1\delta_2$ were pointed out by Walker for polymer solutions.

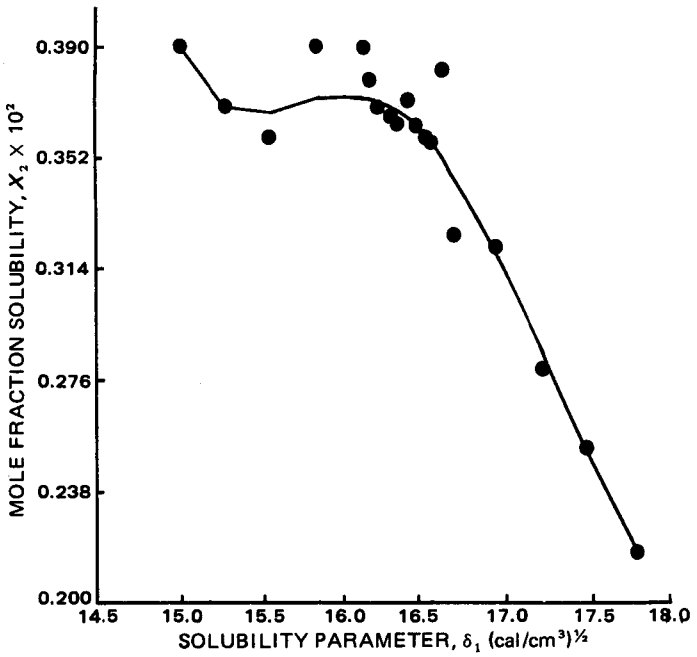

Figure 4—*Mole fraction solubility of theophylline in glycerin–propylene glycol mixtures at 25°. Key:* ●, *observed solubilities; and* —, *back-calculated solubility based on Eqs. 6a and 6b of Table V.*

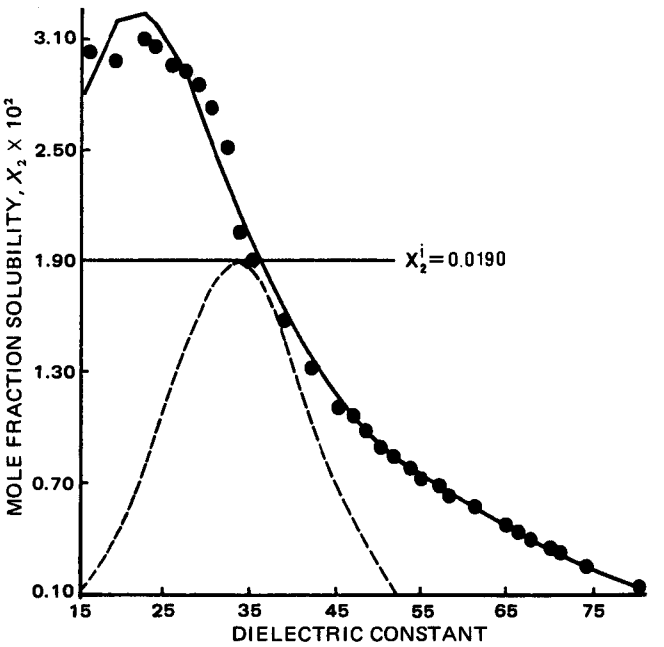

Figure 5—*Mole fraction solubility of theophylline in polyethylene glycol 400–water mixtures at 25°. Key:* ●, *observed solubilities;* —, *back-calculated solubility obtained by regressing* W *against solvent dielectric constant values based on Eqs. 7a and 7b of Table V; and* ---, *Hildebrand regular solution curve, which reaches a peak at* X_2^i *at a solubility parameter of 14.*

grammed to reverse this sign when the calculated solubility X_2 is greater than X_2^i.

Solubility Parameters and Dielectric Constant—Other investigators (9–12) studied the solubility of methylxanthines and other classes of drugs as a function of the dielectric constants, ϵ_1, of pure and mixed solvents. Employing 25 solvents of known δ_1 and ϵ_1 values, Paruta *et al.* (13) obtained:

$$\delta_1 = 7.5 + 0.22\epsilon_1 \qquad \text{(Eq. 9)}$$

to relate solvent solubility parameters to the solvent dielectric constant. The work leading to Eq. 9 (13) was repeated in the present study, regressing δ_1 values of 35 liquids from various classes against dielectric constants obtained from a standard reference source (14), and the following was obtained:

$$\delta_1 = 8.3 + 0.19\epsilon_1 \qquad \text{(Eq. 10)}$$

In the particular series used in the current solubility analysis, δ_1 values were regressed for each class of solvent against ϵ_1 values. The resulting expression, Eqs. 11–13, with appropriate coefficients are found in Table VI. These linear expressions allow the conversion from δ_1 to ϵ_1 and vice versa in mixed solvent systems when studying solubility profiles expressed in terms of either solubility parameters or dielectric constants. While Eqs. 9 and 10 do not provide exact correspondence between δ_1 and ϵ_1 in specific solvent systems as do Eqs. 11–13, they do afford simple relationships for quick conversion between δ_1 and ϵ_1.

Since δ_1 and ϵ_1 are linearly related, it should be possible to regress log α_2/A or W in a power series against ϵ_1; W and log α_2/A are regressed *versus* ϵ_1 for theophylline in polyethylene glycol 400–water mixtures (Eqs. 7, Table V). The back-calculated solubility curve, Eq. 7b, for theophylline in this mixed solvent system is shown in Fig. 5. Figure 5 demonstrates that results showing mole fraction or molal solubility plotted against dielectric constant may be calculated using the extended solubility approach. Eq. 7b gives better results than Eq. 7a.

Volume Fraction and Molar Volume—However, neither δ_1 nor ϵ_1 are necessary to predict solubility. An earlier report (3) demonstrated that W, δ_1, and δ_2 may be by-passed and that a drug's solubility in a binary solvent may be back-calculated at a particular temperature based only on the volume fraction or percent of one solvent in another. (Molar

Table IV—Equations Obtained from Regression of W and Log α_2/A in Second-(Quadratic), Third-(Cubic), and Fourth-Degree (Quartic) Power Series on δ_1 for Theobromine in Dioxane–Water Mixtures at 25°

	W *versus* δ_1	Equation	Log α_2/A *versus* δ_1	Equation
Quadratic	$78.761046 + 2.294693\delta_1 + 0.417790\delta_1^2$	2*a*	$38.477909 - 4.589386\delta_1 + 0.164419\delta_1^2$	2*b*
Cubic	$81.160844 + 1.827037\delta_1 + 0.446860\delta_1^2 - 0.000579\delta_1^3$	3*a*	$33.678312 - 3.654074\delta_1 + 0.106281\delta_1^2 + 0.001158\delta_1^3$	3*b*
Quartic	$65.378019 + 5.948237\delta_1 + 0.055798\delta_1^2 + 0.015432\delta_1^3 - 0.000239\delta_1^4$	4*a*	$65.243960 - 11.896473\delta_1 + 0.888405\delta_1^2 - 0.030865\delta_1^3 + 0.000478\delta_1^4$	4*b*

Table V—Caffeine, Theophylline, and Theobromine in Solvent Mixtures at 25°: Quadratic Equations Obtained from Regression of W and Log α_2/A *versus* δ, ϵ_1, and ϕ_w

Mixture	W *versus* δ_1	Equation	Log α_2/A *versus* δ_1	Equation
Caffeine in dioxane–formamide	$82.90558 + 1.36517\delta_1 + 0.44882\delta_1^2$	5*a*	$24.62885 - 2.73034\delta_1 + 0.10236\delta_1^2$	5*b*
Theophylline in glycerin–propylene glycol	$16.539654 + 9.924499\delta_1 + 0.182719\delta_1^2$	6*a*	$162.920693 - 19.848998\delta_1 + 0.634562\delta_1^2$	6*b*
Mixture	W *versus* ϵ_1	**Equation**	Log α_2/A *versus* ϵ_1	**Equation**
Theophylline in polyethylene glycol 400–water	$129.56925 + 1.29791\epsilon_1 + 0.02046\epsilon_1^2$	7*a*	$6.781325 - 0.347859\epsilon_1 + 0.005543\epsilon_1^2$	7*b*
Mixture	W *versus* ϕ_w (Volume Fraction of Water in Mixed Solvent)	**Equation**	Log α_2/A *versus* ϕ_w (Volume Fraction in Mixed Solvent)	**Equation**
Theobromine in Dioxane–Water	$143.453 + 143.768\phi_w + 75.088\phi_w^2$	8*a*	$9.164 - 18.042\phi_w + 30.184\phi_w^2$	8*b*

Table VI—Regression of δ_1 *versus* ϵ_1 for Solvent Mixtures at 25°

Mixed Solvent System	Regression Equation of δ_1 *versus* $\epsilon_{25°}$ for Mixed Solvents[a]	Equation	n	r^2
Dioxane–water	$\delta_1 = 10.332\ (\pm 0.182) + 0.171\ (\pm 0.016)\epsilon_1$	11	18	0.995
Glycerin–propylene glycol	$\delta_1 = 9.615\ (\pm 0.544) + 0.185\ (\pm 0.014)\epsilon_1$	12	11	0.986
Polyethylene glycol 400–water	$\delta_1 = 7.541\ (\pm 0.156) + 0.196\ (\pm 0.004)\epsilon_1$	13	20	0.999

[a] Values in parentheses are ±1 *SE*.

volume of the solvent mixture may also be regressed against log α_2/A to reproduce experimental solubilities.) For theobromine in pure dioxane, pure water, and mixtures of this solvent pair, an equation relating log α_2/A and ϕ_w, the volume fraction of water, is given as Eq. 8*b* in Table V. The log α_2/A and volume percent of water required for this calculation are found in Table II. With the value of A (Table II) at a solvent volume fraction, *e.g.*, 0.40 or 40% water, log $\alpha_{2_{calc}} = 0.61427$ is obtained. This term, together with $-\log X_2^1 = 2.5357$, yields $-\log X_2$. Changing the sign and taking the antilog provide the predicted solubility, $X_2 = 7.08 \times 10^{-4}$ at 25° for theobromine in water–dioxane mixtures having a δ_1 value fo 15.39 and a dielectric constant of 27.46 (40% water–60% dioxane); $X_{2_{obs}}$ is equal to 6.74×10^{-4}. If one wishes to obtain the drug's solubility at another temperature, both $-\log X_2^1$ and A will have new values. Densities of the solutions will also change with temperature.

If only molal or weight percent solubility data are accessible, together with volume percent of the liquids in a binary solvent, ideal solubility and A values being lacking, quadratic equations can be obtained by regressing concentrations *versus* δ_1, ϵ_1, or ϕ_w to give fairly accurate back-calculations of solubility across the entire range of the solvent mixture. If the solubility is expressed in molarity, however, the method cannot be used directly. Instead, densities must be used to convert molarity to molality or mole fraction before regression *versus* δ_1, ϵ_1, or the solvent volume fraction can be conducted.

Multiple Solubility Parameters of a Solute—The peak solubility of caffeine in dioxane–formamide (Fig. 3) is found at a solvent δ_1 value of 12, rather than the value of 13.8 observed for caffeine in dioxane–water systems. If the point of maximum solubility, where $\delta_1 \cong \delta_2$, is taken as a definition of δ_2 for the drug molecule, then two δ values (12.0 and 13.8) must be accepted for caffeine. Other workers observed more than one solubility parameter for a solute. Hildebrand and Scott (15) found it necessary to adjust the δ_2 value of iodine from 13.1 to 14.9 to account for variations in solute characteristics in some nonpolar and polar solvents; the solubility parameter ordinarily reported for iodine is 14.1. On investigating the solubility of sulfur in various solvents, Hildebrand and Scott (16) reported δ_2 values for sulfur from ~11.5 to 14.5, although most of the values were in the 12–13 range.

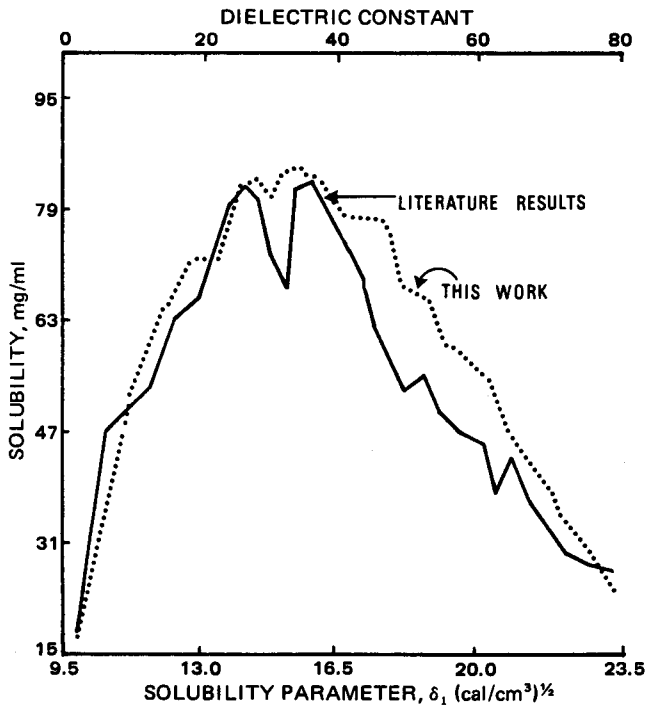

Figure 6—*Caffeine in dioxane–water mixtures at 25°. Solubility profiles were obtained from two studies (Ref. 2 is this work and Ref. 11 is literature results). The δ_2 value at peak solubility occurs at ~δ_1 = 15.*

Baker (17) found that solvents partitioned between amorphous and crystalline regions of semicrystalline polymers in solution. Based on solubility and swelling studies, he distinguished three distinct solubility parameters for a polymer. For example, the solubility parameters for butyl rubber at 25° were 7.15, 8.46, and 9.51. For atactic polypropylene at 40°, the δ_2 values were 7.01, 8.07, and 9.38. Other reports (11, 12) showed that methylxanthines in various binary solvent systems exhibited peak solubilities at different solvent dielectric constants. Therefore, it is not surprising that the δ_2 of caffeine obtained from peak solubilities in binary solvents varies according to the solvent mixture employed.

Although the studies reported here are preliminary, it appears from current work that drugs exhibit multiple solubility parameters (one or several for the solute in nonpolar and moderately polar solvents and multiple values in highly solvating and complexing solvents). Fortunately, multiple δ_2 values for a drug do not adversely affect the extended solubility approach. The appropriate δ_2 value is obtained from the method of Fedors (18), the maximum in the solubility profile for a dioxane–water system, or a regression method reported elsewhere (19, 20). The solute solubility parameter, δ_2, so determined is then used with W and δ_1 of the solvent mixture to back-calculate solubilities.

The physicochemical phenomenon on which multiple solute values are based is difficult to explain. Hoy (21) suggested that solutes may behave in a "chameleon-like" manner, adapting to the solvent environment in which they are found. For example, carboxylic acids interact through hydrogen bonds with alcohols and water in these highly polar solvents, whereas such acids self-associate in nonpolar solvents. Therefore, the solubility parameters of these solutes would be expected to have different values in various pure and mixed solvents.

The shape and position of the peak in a solubility profile are altered when solubility is plotted as molarity or milligrams per milliliter instead of mole fraction. The solubility profile for caffeine in dioxane–water mixtures, obtained in this work and from the literature (11), is plotted against δ_1 and ϵ_1 in Fig. 6. The solubility values from the two studies vary somewhat but produce essentially the same profiles. The δ_2 value from the peak solubility of a milligrams per milliliter *versus* δ_1 plot, as seen here, would be ~15, as contrasted to a value of 13.8 obtained from a plot of mole fraction solubility of caffeine in dioxane–water mixtures.

CONCLUSIONS

The extended solubility approach was shown to apply to three methylxanthines, theophylline, caffeine, and theobromine, in a number of binary solvent systems. It was suggested (1–3) that W, the solute–solvent interaction energy, may be regressed in a second, third, or fourth degree power series in terms of the pure or mixed solvent solubility parameter, δ_1, to reproduce the experimental solubility curve. Direct regression of log α_2/A on δ_1, together with a knowledge of A and the drug's ideal solubility at the temperature of the experiment, provides a method for accurately reproducing solubilities of drugs in binary solvent mixtures. In an earlier study (3), it was possible to regress log α_2/A on ϕ_i, where ϕ_i is the volume fraction of one of the two solvents in a binary solvent mixture. In the present report, the linear relationship between δ_1 and ϵ_1, first reported by Paruta *et al.* (13), was confirmed for various solvent systems. For the purpose of predicting solubility, it is possible to regress log α_2/A or W directly *versus* ϵ_1 in a quadratic or higher power series, as shown here. These various approaches yield back-calculated mole fraction solubility within experimental error.

The apparent success of the extended Hildebrand solubility approach to date suggests that Eq. 1, an extension of the Hildebrand equation without the restriction of the geometric mean, provides a satisfactory empirical representation for the solubility of drugs in polar binary solvent systems. In this method, W is obtained from solubility data and then back-calculated by regressing W against δ_1, ϕ_i, or ϵ_1. This technique may not appear to be fruitful in affording *ab initio* predictions of solubilities or providing fundamental information about solvent–solute interaction since solubility data are required for the method. However, the form of the empirical equation appears to be correct for handling relatively polar

as well as nonpolar systems. An effort is being made to obtain W without solubility data, with the possibility of finding a physicochemical basis for W and/or a group contribution method for estimating this solvent–solute interaction term.

It is interesting to observe in Table III and in Figs. 1 and 5 that small (fractional to 1 or 2%) differences between $\delta_1\delta_2$, the geometric mean, and W, the correct adhesive energy density, may cause large differences (25–75%) between ideal and real solubilities. It will challenge the investigator to measure and calculate energies within 5–50 cal/mole required for an independent measure of W for accurate estimation of solubilities. The prediction of solubility using W from group contributions would represent a step toward a better understanding of the behavior of drug molecules in polar and nonpolar solvent systems.

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Degradation Kinetics and Mechanism of Aminocephalosporins in Aqueous Solution: Cefadroxil

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Abstract □ The degradation kinetics and mechanism of a new, orally effective cephalosporin derivative, cefadroxil, in aqueous solution were investigated at pH 2.51–11.5 at 35° and ionic strength 0.5. The degradation rates were determined by high-pressure liquid chromatography. At constant pH and temperature, the degradation followed first-order kinetics and a log k–pH profile was presented. The shape of the rate–pH profile resembled that for cephalexin or cephradine under the same conditions. Citrate and phosphate buffers enhanced general acid and base catalysis of the degradation. In aqueous solution, cefadroxil was shown to degrade by three parallel reactions: (*a*) intramolecular aminolysis by the C-7 side-chain amino group on the β-lactam moiety, (*b*) water-catalyzed or spontaneous hydrolysis, and (*c*) β-lactam cleavage by the nucleophilic attack of hydroxide ion. In neutral and weak alkaline solutions, the main degradation products were two piperazine-2,5-diones and 3-hydroxy-4-methyl-2(5*H*)-thiophenone, the former being formed from Reaction *a*, while the latter arose *via* the degradation pathways of Reactions *b* and/or *c*.

Keyphrases □ Cefadroxil—degradation kinetics and mechanism, high-pressure liquid chromatography, pH–rate profile, intramolecular aminolysis to produce piperazinediones, buffer and temperature effects □ Degradation kinetics—cefadroxil, high-pressure liquid chromatography assay, pH–rate profile, intramolecular aminolysis to produce piperazinediones, buffer and temperature effects □ pH–rate profile—cefadroxil, degradation kinetics and mechanism, intramolecular aminolysis to produce piperazinediones, buffer and temperature effects □ Piperazinediones—cefadroxil degradation kinetics and mechanism, intramolecular aminolysis

A previous study (1) determined the degradation kinetics of a series of cephalosporins in aqueous solution at 35° and ionic strength 0.5. The degradation of cephalosporins possessing an α-amino group in their C-7 side chain, such as cephalexin, cephradine, and cephaloglycin, was facilitated by the intramolecular attack of the amino group to the reactive β-lactam moiety at neutral pH (1–4). The relative instability of cephaloglycin under physio-

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