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Extended Hildebrand Solubility Approach: Solubility of Tolbutamide, Acetohexamide, and Sulfisomidine in Binary Solvent Mixtures

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Abstract □ The extended Hildebrand approach for predicting solubilities of crystalline compounds in solvent mixtures was tested using tolbutamide, acetohexamide, and sulfisomidine in mixed solvents consisting of hexane–absolute ethanol and 95% (v/v) ethyl alcohol–aqueous buffer. The solubility of these drugs was determined at 25 ± 0.2° and then back-calculated using the adhesive energy term, W, to account for solute–solvent interaction. Solubilities were predicted within 13% for tolbutamide, 31% for acetohexamide, and 43% for sulfisomidine, and with considerably better accuracy in most solvent mixtures.

Keyphrases □ Hildebrand solubility approach, extended—tolbutamide, acetohexamide, and sulfisomidine in binary solvent mixtures □ Tolbutamide—solubility in binary solvent mixtures, extended Hildebrand approach □ Acetohexamide—solubility in binary solvent mixtures, extended Hildebrand approach □ Sulfisomidine—solubility in binary solvent mixtures, extended Hildebrand approach

The Hildebrand–Scatchard theory (1) for crystalline solids in regular solution is expressed by:

$$-\log X_2 \simeq \frac{\Delta H_m^f}{2.303\,RT}\left(\frac{T_m - T}{T_m}\right) + \frac{V_2\,(\phi_1)^2}{2.303\,RT}(\delta_1 - \delta_2)^2 \quad \text{(Eq. 1)}$$

where X_2 is the mole fraction solubility, ΔH_m^f is the heat of fusion, T_m is the melting point of the solute expressed in absolute degrees, T is the absolute temperature of the solution, R is the gas constant expressed in cal/°Kmole, V_2 is the molar volume of the solute as a hypothetical supercooled liquid, δ_1 and δ_2 are the solubility parameters of the solvent and the solute, respectively, and ϕ_1 is the volume fraction of the solvent.

An approach (2) was suggested recently to extend regular solution theory to semipolar drugs in pure solvents and in polar binary solvent mixtures (2–4). The extended Hildebrand solubility equation may be written as:

$$-\log X_2 = -\log X_2^i + \frac{V_2\,(\phi_1)^2}{2.303\,RT}(\delta_1^2 + \delta_2^2 - 2W_{calc}) \quad \text{(Eq. 2)}$$

where X_2^i is the ideal solubility of the solute expressed in mole fraction, W_{calc} is the potential energy of solute–solvent interaction, and all other terms are identical with those in Eq. 1. The square of the solubility parameters are referred to as cohesive energy densities, and W may be referred to as an adhesive energy density since it involves both solute and solvent. The units of energy densities are calories per cubic centimeter (cal/cm^3) and for solubility parameters they are the square root of the same unit [(cal/cm^3)$^{1/2}$]. The ideal solubility term, $-\log X_2^i$, constitutes the first right-hand term of Eq. 1. Log X_2^i may be taken as roughly equal to $-\Delta H_m^f/2.303\,RT\,[(T_m - T)/T_m]$ as seen in Eq. 1, or as $\Delta S_m^f/R\,[\log (T/T_m)]$ as used in earlier studies (2–4). Although it has not been established which is more correct, either form provides satisfactory results

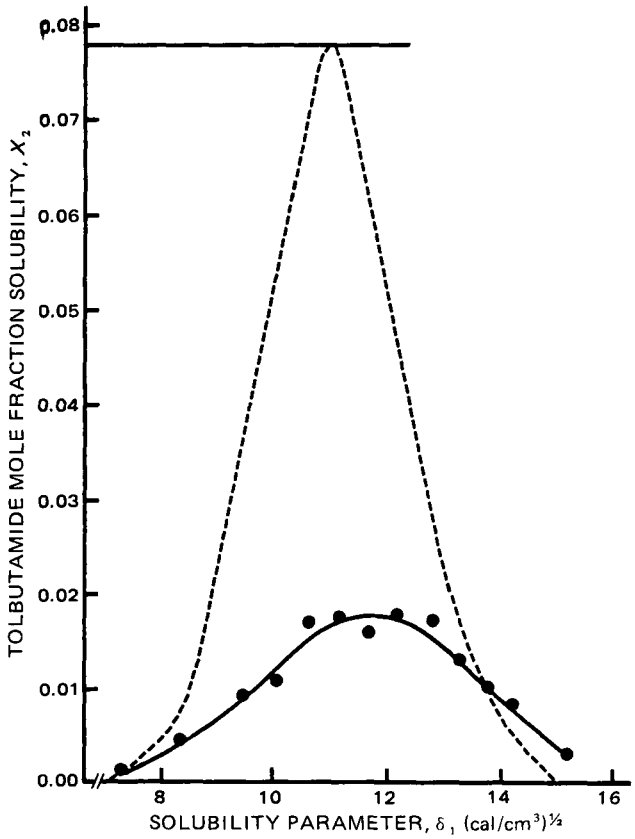

Figure 1—*Solubility profile of tolbutamide in* n*-hexane–absolute ethanol and 95% ethanol–aqueous buffer systems at 25°; δ_2 = 10.98, X_2^i = 0.07218. Key: (- - -) regular solution (Eq. 1); (—) calculated solubility (Eqs. 3*a *and* b*). The horizontal line intersecting the regular solution curve at its peak is the ideal solubility, X_2^i = 0.07218.*

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Table I—Melting Point, Heat of Fusion, Ideal Solubility, Molar Volume, and Solubility Parameters of I, II, and III

Compound	T_m, °K	ΔH_m^f, cal/mole[a]	X_2^i, (25°)	log X_2^{ib}, (25°)	V_2^c, cm³/mole (25°)	δ_2^c, cal/cm$^{3\ 1/2}$ (25°)
Tolbutamide (I)	404.8	6122	0.072180	−1.1416	209.9	10.98
Acetohexamide (II)	457.0	9819	0.003146	−2.5022	234.4	11.64
Sulfisomidine (III)	515.6	10781	0.000463	−3.3344	181.9	12.80

[a] Determined by differential scanning calorimetry. [b] Calculated from the equation, $-\log X_2^i = (\Delta H_m^f)/2.303\,RT\,[(T_m - T)/T_m]$. [c] Obtained from the method of Fedors (Ref. 5).

Table II—Mole Fraction Solubility of I in *n*-Hexane–Absolute Ethanol and 95% (v/v) Ethanol–Aqueous Buffer Systems at 25°[a]

Solvent Composition	δ_1, cal/cm$^{3\ 1/2}$	Solution Density, g/cm³	V_1, cm²/mole	A	W_{obs}	W_{calc}	log α_2/A (obs)	log α_2/A (calc)	X_{2obs}	X_{2calc}	Percent Error in X_2
100% hexane	7.30	0.6559	131.35	0.15324	81.1643	81.2637	11.5219	11.3230	0.001238	0.001328	−7.27
80 hexane in absolute ethanol	8.39	0.6862	113.12	0.15119	91.5510	91.3535	7.8504	8.2454	0.004694	0.004091	12.85
60% hexane in absolute ethanol	9.48	0.7248	96.67	0.14777	102.2015	102.1887	6.0279	6.0533	0.009283	0.009202	0.87
50% hexane in absolute ethanol	10.03	0.7366	89.26	0.14621	107.7655	107.9390	5.6303	5.2833	0.010845	0.012188	−12.38
40% hexane in absolute ethanol	10.58	0.7608	81.49	0.14099	114.0233	113.8790	4.4502	4.7787	0.017021	0.015499	8.94
30% hexane in absolute ethanol	11.12	0.7705	75.66	0.13979	119.8956	119.8957	4.4235	4.4234	0.017380	0.017380	0.00
20% hexane in absolute ethanol	11.63	0.7895	69.40	0.13964	125.5801	125.7461	4.6570	4.3251	0.016148	0.017966	−11.26
10% hexane in absolute ethanol	12.17	0.8039	62.75	0.13706	132.0865	132.1185	4.4963	4.4324	0.017464	0.017820	−2.04
100% absolute ethanol	12.76	0.8182	58.28	0.13606	139.4080	139.2900	4.5620	4.7980	0.017287	0.016055	7.13
95% (v/v) ethanol	13.24	0.8375	54.96	0.13986	145.2214	145.2856	5.4151	5.2868	0.012620	0.013153	−4.22
95% ethanol in aqueous buffer	13.72	0.8492	52.01	0.14143	151.4441	151.4258	5.9105	5.9473	0.010531	0.010405	1.20
90% ethanol in aqueous buffer	14.20	0.8597	49.38	0.14357	157.8167	157.7104	6.5771	6.7795	0.008206	0.007675	6.47
80% ethanol in aqueous buffer	15.15	0.8838	44.05	0.14357	170.5180	170.5750	9.0469	8.9328	0.003225	0.003354	−4.00

[a] $X_2^i = 0.07218$; $V_2 = 209.9$; $\delta_2 = 10.98$.

in the back-calculation method of the extended solubility approach.

To further test the extended solubility approach for drugs in mixed solvents, solubilities of the hypoglycemic agents, tolbutamide (I) and acetohexamide (II), and a structurally related compound, sulfisomidine (III), were determined in mixtures of *n*-hexane–absolute ethanol, and 95% (v/v) ethanol in an aqueous buffer. The W values of the extended solubility equation are obtained from experimental X_2 using Eq. 2, and then W_{calc} is obtained by regressing W on δ_1 for the solvent mixture in a second degree or higher power series. Log α_2/A may also be regressed against δ_1 to obtain logα_2/A_{calc}.

EXPERIMENTAL

Materials—Tolbutamide[1], acetohexamide[2], sulfisomidine[3], *n*-hexane[4], absolute ethanol[5], 95% ethanol[6], sodium hydroxide[6], and methanol[6] were tested for identity and purity, and otherwise used as received.

Solubility Determination—The solubility of I (δ_2 = 10.98) and II (δ_2 = 11.64) was determined in mixed solvents consisting of *n*-hexane (δ_{1a} = 7.30) and absolute ethanol (δ_{1b} = 12.76), and in 95% ethanol (δ_{1c} = 13.24) mixed with aqueous buffer (δ_{1d} = 22.77, pH = 2.59) in different proportions. The solubility of III (δ_2 = 12.80) was determined in mixed solvents consisting of *n*-hexane and absolute ethanol, and 95% ethanol–aqueous buffer (δ_{1c} = 22.34, pH = 4.9).

About 20 ml of the pure solvent or solvent mixture was introduced into screw-capped vials containing an excess of the drug being studied. The vials were agitated for ~72 hr in a shaker bath maintained at 25 ± 0.2°. After equilibrium was obtained, a filtered aliquot was pipetted, using an automatic micropipette, into a volumetric flask and appropriately diluted with methanol. The solutions were analyzed in a spectrophotometer[7] at 264 nm for I, 247 nm for II, and 281.5 nm for III. The densities of the saturated solutions and solvent mixtures were determined at 25 ± 0.2° using a 10-ml pycnometer. All determinations were made in triplicate.

Water Content—The water content of absolute ethanol and ethanol labeled 95% (v/v) was determined by direct titration[8].

Aqueous Buffer Preparation—The pH of the distilled water used in the preparation of the solvent mixtures was adjusted so that the drugs existed predominantly in their nonionized form; thus, solubility as the ion was not involved. The pH of the buffer solution was measured after preparation and at several intervals to be sure that changes in pH did not occur in the solutions alone or after the drug was added.

Heat of Fusion of I, II, and III—A differential scanning calorimeter[9] was used to determine the heats of fusion of the drugs. The technique and equations utilized in the determination were reported earlier (3).

Solubility Parameter and Molar Volume—The solubility parameters and molar volumes of I, II, and III were calculated using the functional group contribution method of Fedors (5). The solubility parameters of the solutes were verified using the data from solubility studies of the drugs in binary systems (4). The solubility parameter (δ_2) was obtained at peak solubility and was assumed to be equal to the solubility parameter of the solvent mixture (δ_1). In polar solvent mixtures this procedure yields somewhat different solubility parameters depending on the solvent system used.

Other quantities required in predicting the solubility of a drug in solvent mixtures (molar volumes, V; volume fraction of the solvent mixtures, ϕ_1; mole fraction solubility of the solute, X_2; ideal solubility of the solute expressed in mole fraction, X_2^i; solute activity coefficients, α_2; and the adhesive energy density, W) were calculated as described previously (3). The solubility parameters and the molecular weights of absolute ethanol

[1] Upjohn, Kalamazoo, Mich.
[2] Eli Lilly, Indianapolis, Ind.
[3] Sigma Chemical, St. Louis, Mo.
[4] Aldrich Chemical, Wilwaukee, Wis.
[5] Commercial Solvent, Terre Haute, Ind.
[6] Fisher Scientific, Fair Lawn, N.J.
[7] Beckman Model 25 spectrophotometer.
[8] Aquatrator, Precision Scientific Co.
[9] Model 1B, Perkin-Elmer.

Table III—Regression Equations of W_{calc} and log α_2/A_{calc} for I, II, and III in Hexane–Absolute Ethanol and 95% Ethanol–Aqueous Buffer Systems at 25°. [a]

Compound	Equations	
Tolbutamide (I)	$W_{calc} = 32.9064\ (\pm 0.8420) + 4.3342\ (\pm 0.1528)\ \delta_1 + 0.3137\ (\pm 0.0067)\ \delta_1^2$	(Eq. 3a)
	$n = 13 \quad R^2 = 0.999 \quad s = 0.12663 \quad F = 265172 \quad F_{(2,10,0.01)} = 7.56$	
	$\log \alpha_2/A_{calc} = 54.7567\ (\pm 1.6842) - 8.6700\ (\pm 0.3056)\ \delta_1 + 0.3726\ (\pm 0.0135)\ \delta_1^2$	(Eq. 3b)
	$n = 13 \quad R^2 = 0.988 \quad s = 0.25330 \quad F = 420 \quad F_{(2,10,0.01)} = 7.56$	
Acetohexamide (II)	$W_{calc} = 43.0479\ (\pm 1.8180) + 3.7634\ (\pm 0.3300)\ \delta_1 + 0.3460\ (\pm 0.0146)\ \delta_1^2$	(Eq. 4a)
	$n = 10 \quad R^2 = 0.999 \quad s = 0.25268 \quad F = 53040 \quad F_{(2,7,0.01)} = 9.55$	
	$\log \alpha_2/A_{calc} = 49.4027\ (\pm 3.6367) - 7.5282\ (\pm 0.6601)\ \delta_1 + 0.3081\ (\pm 0.0291)\ \delta_1^2$	(Eq. 4b)
	$n = 10 \quad R^2 = 0.962 \quad s = 0.50544 \quad F = 90 \quad F_{(2,7,0.01)} = 9.55$	
Sulfisomidine (III)	$W_{calc} = 93.8825\ (\pm 6.5207) - 5.7575\ (\pm 1.6683)\ \delta_1 + 1.1189\ (\pm 0.1366)\ \delta_1^2 - 0.0186\ (\pm 0.0036)\ \delta_1^3$	(Eq. 5a)
	$n = 12 \quad R^2 = 0.999 \quad s = 0.33165 \quad F = 49488 \quad F_{(3,8,0.01)} = 7.59$	
	$\log \alpha_2/A_{calc} = -23.9294\ (\pm 13.0437) + 11.5170\ (\pm 3.3371)\ \delta_1 - 1.2380\ (\pm 0.2732)\ \delta_1^2 + 0.0371\ (\pm 0.0072)\ \delta_1^3$	(Eq. 5b)
	$n = 12 \quad R^2 = 0.984 \quad s = 0.66342 \quad F = 166 \quad F_{(3,8,0.01)} = 7.59$	

[a] The statistical parameters under each regression equation are n, the number of solvent mixtures used; R^2, the squared multiple correlation coefficient; s, the standard deviation of the sample; F, the Fisher F ratio, which is followed by the tabular value of F with degrees of freedom k and $n - k - 1$ at the 99% level. The value k is the number of independent variables in the equation.

and 95% ethanol were corrected relative to their water content [0.57% (v/v) for absolute ethanol and 5.06% (v/v) for ethanol labeled 95%].

RESULTS AND DISCUSSION

Experimental melting points (T_m), obtained with a capillary apparatus[10], heat of fusion (ΔH_m^f), ideal solubilities (X_2^i), solubility parameters, and molar volumes for I, II, and III are reported in Table I.

The values of observed and calculated solubilities (Eq. 2) of I in hexane–absolute ethanol and 95% ethanol–aqueous buffer are compared in Table II. Solution densities are included to allow calculations of solubilities in mole/liter or gram/cm^3. The experimental solubilities of I, II, and III, expressed as mole fraction *versus* the solubility parameters of the solvent mixtures, are plotted in Figs. 1–3. The ideal solubilities, X_2^i, and the regular solution curve obtained using Eq. 1 are also shown. The regression equations and statistics for W_{calc} and log α_2/A_{calc} are shown in Table III. Earlier studies (3, 4) employed 20–30 data points for regression analysis. The present study shows that about 12 points are adequate for back-calculating the solubility curve.

The regular solution curves of Figs. 1, 2, and 3, do not coincide with the experimentally determined solubilities, indicating that the mixtures do not follow regular solution theory. In contrast, the lines obtained by using the extended Hildebrand approach for the drugs investigated reproduced the solubility of I, II, and III in the solvent mixtures satisfactorily (Figs. 1, 2, and 3). The ideal solubilities of I and II are higher than the peak solubility in mixtures of *n*-hexane–absolute ethanol and 95% ethanol–aqueous buffer. For III the ideal solubility is lower than the experimental solubility in aqueous ethanol, presumably because of solvation of the drug by the mixed solvent.

At the maximum of the solubility curve, the experimental points for II fall below the predicted solubility using the extended Hildebrand approach, but the discrepancy is not great. This may be explained by the presence of small peaks and valleys in the solubility profile of II that the empirical expression for W cannot be expected to reproduce. The presence of peaks and valleys around the maximum solubility is not an uncommon occurrence; prominent peaks were first observed by Paruta and Irani (6) in the solubility of caffeine in a mixture of dioxane and water.

The solubility parameters for I, II, and III were used to position the maxima of the regular solution lines of Figs. 1–3. The maxima do not coincide exactly with the peaks of the experimental curves. Although an accurate knowledge of the solubility parameters of the drugs is important for an understanding of physicochemical properties, the extended solubility method—being a back-calculation procedure—does not depend on absolute values of δ_2 for its success. As reported earlier (3) the method may, in fact, bypass W and δ_2 and yield X_{2calc} by regression of logα_2/A on δ_1, as shown in Table III. In the present study, the results obtained using the Fedors method (5) were accepted as a first approximation as the solubility parameters of the three drugs.

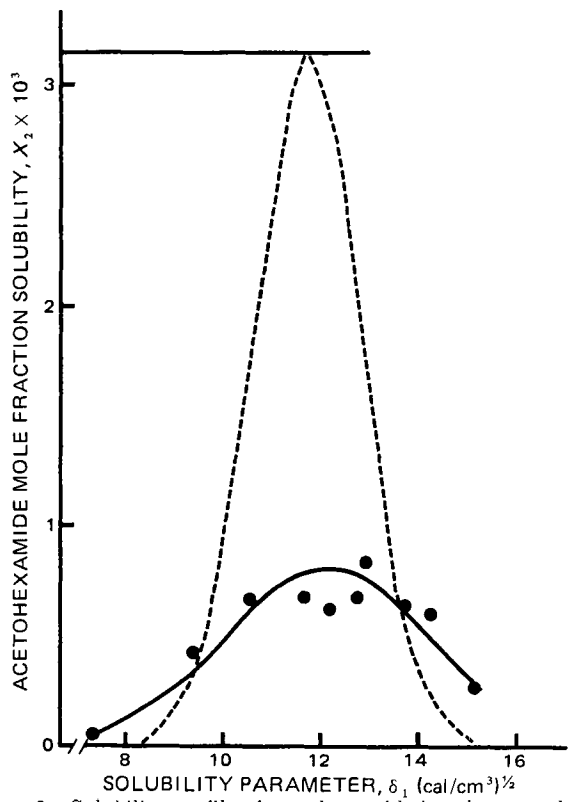

Figure 2—*Solubility profile of acetohexamide in* n*-hexane–absolute ethanol and 95% ethanol–aqueous buffer at 25°; $\delta_2 = 11.64$, $X_2^i = 0.00314$. Key: (- - -) regular solution (Eq. 1); (—) calculated solubility (Eqs. 4a and b). The horizontal line intersecting the regular solution curve at its peak is the ideal solubility, $X_2^i = 0.00314$.*

[10] Thomas Hoover capillary melting point apparatus, A. H. Thomas Co.

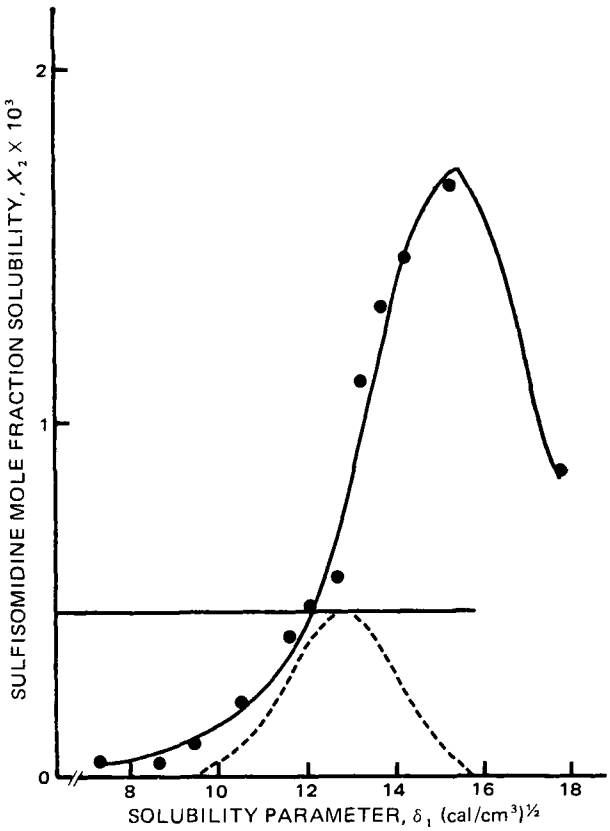

Figure 3—*Solubility profile of sulfisomidine in n-hexane–absolute ethanol and 95% ethanol–aqueous buffer systems at 25°; δ_2 = 12.80. Key: (- - -) regular solubility (Eq. 1); (—) calculated solubility (Eqs. 5a and b). The horizontal line intersecting the peak of the regular solution curve signifies the ideal mole fraction solubility, $X_2^i = 0.463 \times 10^{-3}$.*

CONCLUSIONS

The extended Hildebrand solubility approach (1–3) was tested for its ability to reproduce solubilities of tolbutamide, acetohexamide, and sulfisomidine in mixtures of *n*-hexane–absolute ethanol and 95% ethanol–aqueous buffer. Power series regression (quadratic for I and II and cubic for III) in δ_1 was used to back-calculate W, and from W to calculate solubilities.

Workers in various industries, including the pharmaceutical and cosmetic sciences, have not been able to rely on the Hildebrand equation (Eq. 1) for estimating solubilities in polar solvent systems. According to regular solution theory the solubility of I is predicted to be much larger than actual solubility at $\delta_1 = \delta_2 = 10.98$ (Fig. 1). Conversely, for III the solubility predicted by the Hildebrand approach is grossly underestimated (Fig. 3). The Hildebrand theory provides reasonable, although not always accurate, estimates of solubility in nonpolar solvents but is not successful for polar systems.

The extended Hildebrand solubility approach, replacing the geometric mean $\delta_1\delta_2$ by an adhesive energy density W, and regressing W against the solvent solubility parameter to obtain back-calculated values of solubility, shows one reason why the Hildebrand method (Eq. 1) fails in binary mixtures of polar solvents. Surprisingly, small differences between W and $\delta_1\delta_2$ result in large differences between actual and ideal solubility. For I at $\delta_1 = 11.12$, $\delta_1\delta_2 = 122.0976$, and $W = 119.8957$; $X_2 = 0.017380$, and $X_2^i = 0.072180$. The difference of as little as 1.8% between W of the extended approach and $\delta_1\delta_2$ of the Hildebrand theory yields a 315% solubility difference between experimental solubility and that calculated by the Hildebrand method. In the same mixed solvent, 30% hexane in ethanol, the extended Hildebrand solubility method calculates the correct solubility, $X_{2calc} = 0.01738$ (0.0% error).

Both the Hildebrand and its extended method yield unsatisfactory estimates for solubilities of crystalline drugs in single polar solvents. Unlike binary mixtures, individual solvents show wide differences in molar volume, acid–base characteristics, and other properties. It will be necessary to devise new approaches, such as that suggested by the Hansen partial solubility parameters (7), in order to describe complex drug molecules in single solvents of high, low, and intermediate polarity.

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