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Solubility of theophylline in aqueous *N,N*-dimethylformamide mixtures

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Abstract

The solubilities of theophylline in several water-N,N-dimethylformamide mixtures have been determined and found to show non-regular behaviour. The results were treated on the basis of the extended Hildebrand solubility approach, considering interaction terms. An equation has been obtained for predicting the solubility of theophylline in *N,N*-dimethylformamide, water and their mixtures, allowing the interpolation of new or missing solubilities in these blends.

Key words: Solubility prediction; Extended Hildebrand solubility approach; Theophyline; Aqueous *N,N*-dimethylformamide mixture

1. Introduction

Water-miscible cosolvents are widely used in the pharmaceutical design and formulation of preparations based on sparingly water soluble drugs. Aliphatic amides appear to be an optimal class of water-miscible cosolvents to study the interrelations between the solubility of drugs and the permittivity of the medium (Rodewald and Möldner, 1973). *N,N*-Dimethylformamide (DMF) appears to be a suitable cosolvent, since it is aprotic and fully miscible with water. Water-DMF mixtures are strongly non-ideal and can act in the solute-solvation process according to two different solvation mechanisms: via hydrophobic interactions and via hydrogen-bonding preferential solvation (González et al., 1991).

Theophylline is a sparingly water soluble drug which acts a stimulator of the central nervous system and is used in medicine especially in the treatment of bronchial asthma and apnoea. The solubilities of theophylline in water-DMF mixtures have been determined in order to apply the extended Hildebrand solubility approach for predicting solubilities of crystalline compounds according to the procedure developed by Martin et al. (1980, 1982a,b).

2. Theory

Martin et al. (1980) have extended the Hildebrand-Scatchard solubility approach for solubility

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predictions of semipolar crystalline drugs in pure solvents and in polar binary mixtures according to the equation

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

where X_2 is the mole fraction solubility of the crystalline solute at temperature T on the Kelvin scale, ΔS_m denotes the entropy of fusion of the crystalline drug molecule at its melting point T_m, R is the molar gas constant, V_2 represents the molar volume of the solute and ϕ_1 the volume fraction of the pure or mixed solvent. The solubility parameters for the solute and solvent are δ_2 and δ_1, respectively. The W expression is an interaction term that will be discussed below. Eq. 1 may be rewritten as (James, 1986):

$$-\log X_2 = \log a_2 + \frac{V_2\phi_1^2}{2.303RT}(\delta_1^2 + \delta_2^2 - 2W) \quad (2)$$

where a_2 is the activity of the solute on the mole fraction scale (ideal mole fraction solubility). Eq. 2 may be also expressed in the form:

$$\log f_2 = A(\delta_1^2 + \delta_2^2 - 2W) \quad (3)$$

in which f_2 denotes the activity coefficient of the solute and A is $\phi_1^2 V_2/2.303RT$. The interaction parameter W accurately quantifies the cohesive energy density between solute and solvent. When $W = \delta_1\delta_2$ the solution is said to be regular. $W > \delta_1\delta_2$ appears when the blended solvents are able to hydrogen bond with each other but not with their own kind. Accordingly, the calculated regular solubility is less than the experimental value. The case of $W < \delta_1\delta_2$ occurs when like molecules associate and unlike molecules do not, such as for non-polar media in water.

Although W cannot be theoretically evaluated, Martin and Carstersen (1981) assumed that when a range of similar solvents are used for dissolving a fixed solute, $W = K\delta_1\delta_2$, where K is a proportionality constant. Accordingly, Eq. 3 leads to:

$$\frac{\log f_2}{A} = \delta_2^2 - 2K\delta_1\delta_2 + \delta_1^2 \quad (4)$$

which is a power series in δ_1. James (1986), Martin et al. (1980, 1982a,b) and Martin and Carstensen (1981) utilized these polynomial fits to estimate the mole fraction solubilities in good agreement with the experimental values. This procedure may be applied for calculating the solubilities of missing data of a related class of solutes by interpolation or extrapolation, i.e., for predicting solubilities.

3. Materials and methods

3.1. Apparatus

Absorbance (and its derivatives) measurements were made on a Hewlett Packard model 8452A diode array spectrophotometer. Matched silica cuvettes of 10 mm path length were used in all measurements. A Techne Tempette TE-8D thermostat assembled to a Techne Refrigerated bath RB-5 circulator were utilized for controlling the temperature of solutions.

Solute-solvent equilibrations were performed in water-jacketed titration vessels (Metrohm) thermostatically controlled at 25 ± 0.1°C under continuous magnetic stirring using a Selecta Agimatic-N model magnetic stirrer.

In the determination of densities, a Paar DMA 60 densimeter fitted with a Paar DT 100-20 densitothermometer in assembly with a Tecam 1000 heat interchanger and a Techne C-400 circulator were employed.

3.2. Reagents

N,N-Dimethylformamide (Merck analytical-reagent grade) was stored over 4 Å molecular sieves for at least 1 week. The solvent was shown to be free from acidic impurities by titration with 0.1 M tetrabutylammonium hydroxide in benzene-methanol (González et al., 1990). Glass-distilled deion-

ized water (with a conductivity lower than 1 μmho cm^{-1}) was used throughout and was boiled to remove carbon dioxide before use. Anhydrous theophylline (Sigma) was used as received.

3.3. Procedures

3.3.1. Solubility determinations

The solubility of theophylline ($\delta_2 = 14.0$) was determined in mixed solvents consisting of DMF ($\delta_{1,DMF} = 12.4$) and water ($\delta_{1,w} = 23.45$). Solvent blends were made covering 0–100% DMF (v/v). About 25 ml of the mixed solvent was placed into a capped titration vessel (thermostated at 25 ± 0.1°C under continuous magnetic stirring as indicated above) containing excess theophylline and agitation was maintained for 48 h. A preliminary study showed that equilibration is attained before this period.

After equilibration, the solution was filtered out through a microfilter unit by using a disposable syringe. The filtrate was then adequately diluted to perform the spectrophotometric analysis. The solutions were analyzed by second derivative spectrophotometry (Martínez and Giménez, 1981), by measuring the distance between the second derivative signals at 294 and 284 nm. Calibration graphs of theophylline in each solvent blend were established previously with correlation coefficients greater than 0.9994. The dynamic concentration range was from 3 to 25 mg/l of theophylline.

The densities of the solvent mixtures and of the filtrates of the saturated solutions were determined by injecting the previously degassed solutions into the Paar DMA 60 densitometer at 25 ± 0.1°C. Once the density of each solution is known, it is possible to express the solubilities of theophylline in units of molal, molar, or mole fraction concentrations.

3.3.2. Solubility parameter of mixed solvents

The solubility parameter δ_1 for the solvent blend was calculated according to Barton (1975) as $\delta_1 = f_{DMF}\delta_{1,DMF} + (1 - f_{DMF})\delta_{1,w}$ where f_{DMF} is the volume fraction of DMF in the mixed solvent.

3.3.3. Mean molar volume and total volume fraction of mixed solvents

The mean molar volume (V_1) of solvent blends composed of DMF and water in various proportions was calculated from:

$$V_1 = \frac{X_{DMF} M_{DMF} + (1 - X_{DMF}) M_w}{d_1}$$

where X_i and M_i are the mole fraction and the molecular weight, respectively, of each particular solvent in the mixture and d_1 denotes the density of the mixture.

The total volume fraction (ϕ_1) of the mixed solvent was calculated using the expression:

$$\phi_1 = \frac{(1 - X_2)V_1}{(1 - X_2)V_1 + X_2 V_2}$$

where X_2 is the mole fraction solubility of the solute drug.

4. Results and discussion

Both the molar volume (V_2) and the solubility parameter (δ_2) of theophylline have been calculated using the group contribution approach of Fedors (1974), giving 124 cm^3/mol and 14.0 respectively, as previously obtained by Martin et al. (1980). The authors also gave the values of ΔS_m (12.96 cal/mol per K) and T_m (547.7 K) which permit calculation of the activity or ideal mole fraction solubility of theophylline, yielding $a_2 = 0.01896$.

The mole fraction solubility of theophylline in water-DMF mixtures and other parameters of interest (δ_1, V_1, ϕ_1) are collected in Table 1. Fig. 1 shows the plot of these experimental solubilities vs the solubility parameter of mixtures, δ_1. As can be observed, the experimental points did not exhibit regular solution behaviour. The solubility of theophylline attained was far from its ideal solubility in both pure solvents (DMF, water) and the solvent mixtures studied. The maximum solubility, although lower than ideal, occurred at $\delta_1 \sim 14$, the calculated value of δ_2 for theophylline.

The interaction term W may be calculated using Eq. 4 once all the involved parameters are

Table 1
Solubility mole fractions of theophylline and other related parameters against the volume fraction of cosolvent

f	X_2	ϕ_1	V_1	δ_1	W
0.0	0.00074	0.995	18.05	23.45	365.111
0.1	0.00090	0.999	24.29	22.32	339.745
0.2	0.00105	0.998	30.54	21.19	315.527
0.3	0.00127	0.998	36.81	20.06	292.672
0.4	0.00159	0.997	43.06	18.93	271.176
0.5	0.00198	0.995	49.32	17.80	250.942
0.6	0.00307	0.992	55.38	16.66	232.338
0.7	0.00547	0.990	61.44	15.53	215.533
0.8	0.00750	0.986	65.98	14.40	199.375
0.9	0.00722	0.987	71.93	13.27	183.654
1.0	0.00580	0.989	77.40	12.14	168.772

known. The results are also depicted in Table 1. The W values were assigned to undergo expansion in a power series of δ_1 by means of polynomial regression methods. The goodness of fit is improved by raising the order of the polynomial and evaluating the regression variance (v_{reg}). In passing from the k-th to the $(k+1)$-th order, the F-test is applied to the corresponding regression variances, namely,

$$F = v_{reg}(k)/v_{reg}(k+1)$$

If the ratio so obtained proves smaller than the F tabulated value for the selected significance

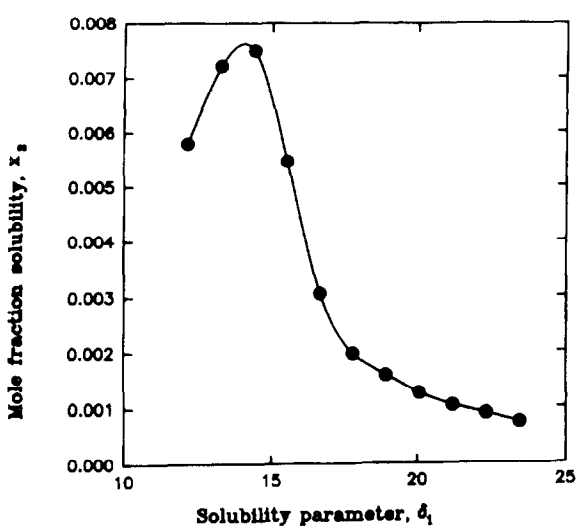

Fig. 1. Plot of the mole fraction solubility of theophylline vs the value of the solubility parameter of the aqueous *N,N*-dimethylformamide mixture.

Table 2
Optimization of the order of the fitted polynomial

k	d.f.	v_{reg}	r	F ratio	F tab
1	9	42.6760	0.995871		
2	8	0.3437	0.999967	124.17	3.38
3	7	0.1441	0.999988	2.38	3.73

k, order of polynomial; d.f., degrees of freedom; v_{reg}, variance of regression; r, correlation coefficient. The significance level for the one-tailed tabulated value of F is 5%.

level, the order of the polynomial should not be raised any more. In our case, the best fit is obtained for a third-degree polynomial, as indicated in Table 2. For testing the polynomial coefficients (c_i), the experimental ratio:

$$t = c_i/s(c_i)$$

was calculated where $s(c_i)$ is the standard error associated with the coefficient c_i. If this value is less than the tabulated value of the Student's t-test, at the chosen significance level, then the corresponding coefficient is deleted from the polynomial model equation, since it is non-significant and the remaining significant coefficients are recalculated (Akhnazarova and Kafarov, 1982). Accordingly, the following third-degree equation for W was obtained:

$$W = 52.840 + 8.2106\delta_1 + 0.00930\delta_1^3$$

The W values calculated from the cubic polynomial substituted in Eq. 1 provide a means for predicting the solubility of theophylline. The back-calculated logarithmic solubilities, $\log X_{2\,calc}$ are recorded in Table 3, together with the experimental values and their differences. In order to validate the prediction of solubilities, a regression analysis was applied: The plot of $\log X_{2\,calc}$ against $\log X_2$ gives a straight line with a non-significant intercept. Accordingly, by using a regression line passing through the origin, a slope of 0.999 ± 0.007 was obtained. These results indicate that the predicted values do not differ, statistically speaking, from those observed (Thompson, 1990).

From Eq. 4, and according to the polynomial expansion of W, we can obtain the following expression for $\log f_2/A$:

$$\log f_2/A = 90.320 - 16.4211\delta_1 + \delta_1^2 - 0.0186\delta_1^3$$

Table 3
Logarithmic values for the experimental and calculated mole fraction solubility and their differences (Δ, expressed as absolute values)

$-\log X_2$	$-\log X_{2\,calc}$	Δ
3.130	3.095	0.035
3.046	3.088	0.042
2.979	3.019	0.040
2.896	2.906	0.010
2.799	2.767	0.032
2.703	2.614	0.089
2.513	2.460	0.053
2.262	2.325	0.063
2.125	2.221	0.096
2.141	2.164	0.023
2.237	2.168	0.069

Remembering that $K = W/\delta_1\delta_2$, the parameter K may also be expressed as a function of the solubility parameters:

$$K = \left(52.840 + 8.2106\delta_1 + 0.00930\delta_1^3\right)/\delta_1\delta_2$$
$$= 3.7743/\delta_1 + 0.5865 + 6.64 \times 10^{-4}\delta_1^2$$

Taking into account that δ_1 ranges from 12.4 for pure DMF to 23.45 for pure water, the corresponding values of K lie within the interval 0.90–0.76, indicating as above, that the solubility of theophylline in DMF-water mixtures is less than regular, and the solute or solvent, or both, can be considered as self-associated. Effectively, apart from the association between water molecules and the strongly basic carbonyl group of DMF (Mahmood and Islam, 1977), the repulsive interaction between the hydrophobic methyl groups and water results in a cluster distribution of water molecules (Cilense et al., 1983).

5. Conclusion

The Hildebrand equation accounting for regular solution behaviour cannot be used to represent the solubility of theophylline in water-DMF mixtures. Nevertheless, the extended Hildebrand equation considering the interaction term W does reproduce accurately the solubility of theophylline in DMF, water and their mixtures, and allows us to predict or to interpolate new or missing solubilities in these blends from the value of the solubility parameter δ_1.

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