Solubility prediction of caffeine in aqueous N,N-dimethylformamide mixtures using the Extended Hildebrand Solubility Approach

M. Angeles Herrador *, A. Gustavo González

Department of Analytical Chemistry, University of Seville, Seville 41012, Spain

Abstract

The solubilities of caffeine in several water–N,N-dimethylformamide mixtures have been determined. The data were treated on the basis of the Extended Hildebrand Solubility Approach and the results were discussed according to association phenomena between solute and solvent blend. An equation has been obtained for predicting the mole fraction solubility of caffeine in the studied mixtures. © 1997 Elsevier Science B.V.

Keywords: Extended Hildebrand Solubility Approach; Caffeine; Solubility; N,N-Dimethylformamide

1. Introduction

In a previous paper (González et al., 1994), the Extended Hildebrand Solubility Approach (Adjei et al., 1980) was applied to predict the solubilities of theophylline in mixtures of water and N,N-dimethylformamide (DMF). DMF is a very interesting cosolvent to study the interrelation between drug solubility and medium polarity because it is aprotic and completely miscible with water. Water–DMF mixtures are strongly non ideal and can act in the solute–solvation process via hydrophobic interactions and preferential solvation (Asuero et al., 1993; Sindreu et al., 1994). In terms of polarity, water–DMF mixtures cover a wide range of Hildebrand solubility parameters from 12.4 (pure DMF) to 23.45.

The Extended Hildebrand Solubility Approach enables us to predict the solubility of semipolar crystalline drugs in irregular solutions involving self-association and hydrogen bonding, like occurs in pure solvents or in solvent blends. The key relationship may be written as (James, 1986)

$$-\log x_2 = -\log x_2^{\text{id}} + \frac{\Phi_1^2 V_2 (\delta_1^2 + \delta_2^2 - 2W)}{2.303 RT} \quad (1)$$

* Corresponding author.

where W is an interaction term for estimating energy between solute and solvent for an irregular solution. This 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. 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 Carstensen (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.

Martin et al. (1980, 1982a,b), Martin and Carstensen (1981) expand the empirically evaluated W values as a power series in δ_1 utilizing mixed solvents. By using these polynomial fits the mole fraction solubility of solutes may be predicted in good agreement with the experimental values. This procedure may be applied for calculating solubilities of missing data by interpolation.

When the solvent studied is a mixed one, there are a series of parameters to be calculated: the solubility parameter, the volume fraction and the mean molar volume of mixed solvents.

The solubility parameter δ_1 for the mixture of two solvents DMF and water, W, is averaged in terms of volume fractions using the expression

$$\delta_1 = \frac{\delta_{DMF}\Phi_{DMF} + \delta_W\Phi_W}{\Phi_{DMF} + \Phi_W} \qquad (2)$$

where $\Phi_1 = \Phi_{DMF} + \Phi_W$ is the total volume fraction of the two solvents which can be calculated from

$$\Phi_1 = \frac{(1 - x_2) V_1}{(1 - x_2) V_1 + x_2 V_2} \qquad (3)$$

where x_2 is the mole fraction solubility of the solute in the mixed solvent and V_1 is the molar volume of the binary solvent. For each mixed solvent composed of water and DMF in various proportions:

$$V_1 = \frac{x_{DMF}M_{DMF} + (1 - x_{DMF}) M_W}{d_1} \qquad (4)$$

Here, x_i and M_i are the mole fraction and the molecular weight of the particular solvent in the mixture, respectively and d_1 is the density of the solvent mixture at the experimental temperature.

Caffeine is a sparingly water soluble drug which acts as a CNS, respiratory and cardiac stimulant widely used in pharmaceutical formulations. The solubilities of Caffeine in water–DMF mixtures have been determined for applying the Extended Hildebrand Approach.

2. Materials and methods

2.1. Apparatus

Absorbance measurements were made on a Hewlett Packard 8452A photodiode array spectrophotometer. Matched quartz cuvettes of 10-mm pathlength were used in all measurements.

To control the temperature of solutions, a Techne Tempette TE-8D thermostat assembled to a Techne RB-5 refrigerated bath circulator was utilized.

Solute–solvent equilibrations were carried out on water-jacketed titration vessels (Metrohm) thermostated at 25 ± 0.1°C under magnetic stirring using a Selecta Agimatic N magnetic stirrer.

Densities of liquids and solutions were determined using a Paar DMA 60 densimeter fitted with a Paar DT 100-20 densitothermometer joined to a Tecam 1000 heat interchanger and a Techne C-400 circulator.

2.2. Reagents

N,N-Dimethylformamide (Merck, analytical 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). Milli-Q (Millipore) treated water (resistivity greater than 18 M$\Omega\cdot$cm) was used throughout.

Anhydrous caffeine (Merck) was used as received.

Table 1
Mole fraction solubility of caffeine (x_2) and other related parameters against the volume fraction of DMF (Φ_{DMF})

Φ_{DMF}	x_2	δ_1	ϕ_1	V_1	$\delta_1\delta_2$	W
0	0.00226	23.45	0.996	18.05	323.610	362.630
0.1	0.00261	22.32	0.999	24.29	308.016	337.132
0.2	0.00294	21.19	0.998	30.54	292.422	312.797
0.3	0.00330	20.06	0.997	36.81	276.828	289.731
0.4	0.00382	18.93	0.997	43.06	261.234	268.025
0.5	0.00495	17.80	0.996	49.32	245.640	247.832
0.6	0.00614	16.66	0.991	55.38	229.908	228.613
0.7	0.01132	15.53	0.989	61.44	214.314	211.775
0.8	0.01395	14.40	0.986	65.98	198.720	195.319
0.9	0.01386	13.27	0.988	71.93	183.126	179.678
1.0	0.01194	12.14	0.989	77.40	167.532	164.994

The values for δ_1, Φ_1 and V_1 are calculated from Eqs. (2)–(4), respectively. W is calculated from Eq. (1).

2.3. Determination of solubilities

Solubilities of caffeine ($\delta_2 = 13.8$) were determined in mixed solvent consisting of DMF ($\delta_{DMF} = 12.4$) and water ($\delta_W = 23.45$). 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°C and under continuous magnetic stirring) containing excess caffeine and agitation was maintained for 72 h. Prior assays showed that equilibration is attained before this period.

After equilibration, the solution was microfiltered (0.45 μm) and the filtrate was then diluted to carry out the spectrophotometric determination. The solutions were analyzed by second derivative spectrophotometry (Martínez and Giménez, 1981) by measuring the distance between the second derivative signals at 296 and 284 nm. Calibration graphs of caffeine in each solvent blend were previously established with correlation coefficients greater than 0.9992. The working concentration range was from 3 to 25 mg/l caffeine.

The densities of the blends as well as the filtrates of saturated solutions were determined by injecting the previously degassed solution (by sonication) into the densitometer at 25°C. Once the densities of solutions are known, the solubilities can be expressed in molar, molal of mole fraction scale.

3. Results and discussion

The molar volume (V_2) and the solubility parameter of caffeine were previously estimated by using the group contribution approach of van Krevelen (1990), giving 135 cm³/mol and 13.5 cal¹/² cm³/². The ideal solubility of caffeine was calculated by Adjei et al. (1980) using the equation

$$-\log x_2^{id} = \frac{\Delta S_m^f}{R} \log \frac{T_m}{T} \qquad (5)$$

where ΔS_m^f is the entropy of fusion of the crystalline drug molecule at its melting point T_m. T is the temperature in Kelvin at which the solubility was determined. The value of ΔS_m^f was evaluated by the authors as $\Delta H_m^f/T_m$ ($\Delta H_m^f = 5044$ cal/mol, $T_m = 512$ K) giving 9.85 cal/(mol K). Thus, the ideal mole fraction solubility of caffeine is $-\log x_2^{id} = 1.1646$.

The mole fraction solubility of caffeine in water–DMF mixtures and other parameters of interest (δ_1, V_1, Φ_1) are collected in Table 1. The plot of these experimental solubilities versus the solubility parameter of mixtures, δ_1 is shown in Fig. 1. The solubility of caffeine was far from its ideal value in both pure solvents (DMF, water) as well as in the mixtures. The maximum solubility, although lower than ideal occurred at a $\delta_1 = 13.8$, very close to the calculated δ_2 for caffeine. According to James et al. (1976), a differential
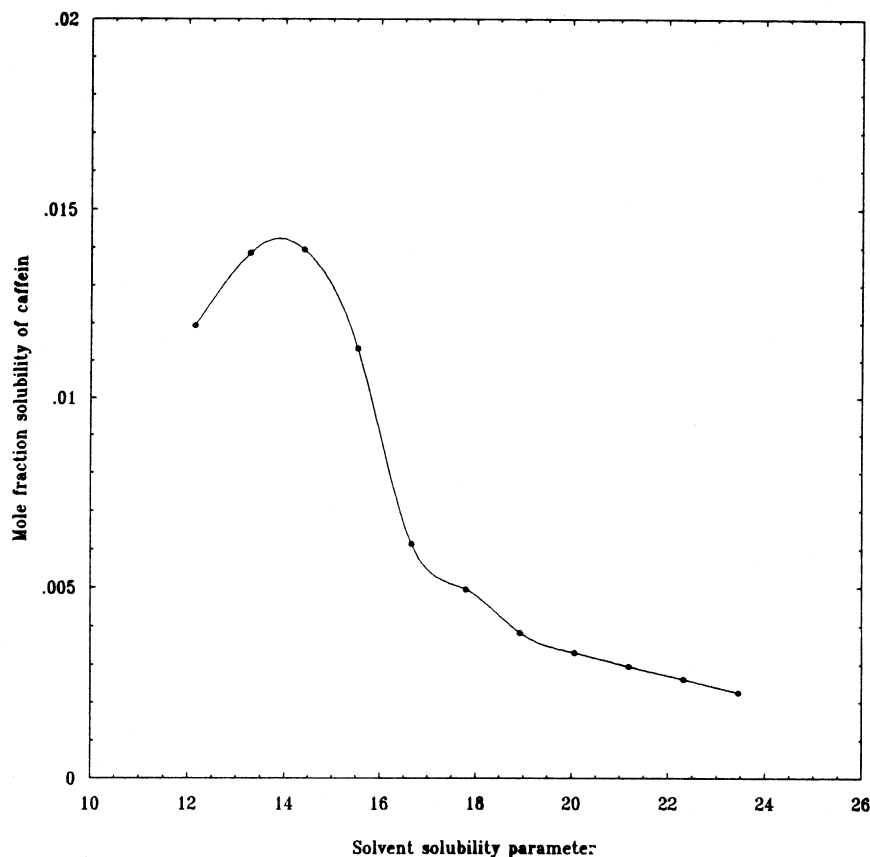
Fig. 1. Plot of the mole fraction solubility of caffeine against the solubility parameter of the water–DMF blend.

method was applied to estimate the value of the solubility parameter of caffeine, δ_2 as the maximum of the curve x_2 versus δ_1. From two neighbour points $j > i$, (x_{2i}, δ_{1i}) and (x_{2j}, δ_{1j}) the following values are calculated: $(\Delta x_2 / \Delta \delta_1)_i = (x_{2i} - x_{2j})/(\delta_{1i} - \delta_{1j})$ and $(\delta_1)_i = (\delta_{1i} + \delta_{1j})/2$. Thus, a derivative curve was obtained by plotting $(\Delta x_2 / \Delta \delta_1)_i$ against $(\delta_1)_i$. In the vicinity of the intersection point of the derivative curve and the x axis, the derivative curve behaves as a straight line. In our case the linear portion follows the equation $(\Delta x_2 / \Delta \delta_1) = 0.0276 - 0.002\delta_1$. Accordingly, when $(\Delta x_2 / \Delta \delta_1) = 0$ the maximum is reached at $\delta_1 = \delta_2 = 13.8$ in good agreement with the calculated value, 13.5, using the van Krevelen group contribution method.

The interaction term W can be calculated from Eq. (1) at each experimental point (x_2, δ_1). The results are also presented in Table 1. The W values may be expanded in a power series of δ_1 from polynomial regression. The goodness of the fit is improved by raising the order k of the polynomial and evaluating the regression variance v_{reg} (González et al., 1994). In passing from the kth to the $(k + 1)$th order, the F-test is applied to both regression variances, namely $F = v_{\text{reg}}(k)/v_{\text{reg}}(k + 1)$.

If the ratio so obtained proves be smaller than the critical tabulated F value at a selected significance level, the order of the polynomial should not be raised any more. For our case study, the best fit corresponds to a third degree polynomial as can be seen in Table 2. The significance of polynomial coefficients (b_i) once its standard deviation is known $(s(b_i))$, is carried out according the Student's t-test: $t = b_i/s(b_i)$.

Table 2
Optimization of the order of the fitted polynomial

k	d.f.	v_{reg}	r	F ratio	F crit
1	9	39.4764	0.99586	—	—
2	8	0.1987	0.99998	198.67	3.38
3	7	0.1024	0.99999	1.94	3.73

k, order of polynomial; d.f., degrees of freedom; v_{reg}, regression variance; r, correlation coefficient.
The significance level for the one-tailed critical F value is 0.05.

If this value is less than the critical tabulated t value at a given significance level, the coefficient is non-significant and the corresponding term drops out from the model equation, and the remaining significant coefficients, recalculated (Akhnazarova and Kafarov, 1984). In our case, the following fit was obtained: $W = 48.051 + 8.2584\delta_1 + 0.0094\delta_1^3$.

If we insert this equality in Eq. (1), we can predict the solubility of caffeine. The back-calculated logarithmic solubilities, $\log x_{2\,calc}$ are recorded in Table 3, together with the experimental values of $\log x_2$ and their differences. The plot of $\log x_{2\,calc}$ against $\log x_2$ gives a straight line passing through the origin with a slope of 1.000 ± 0.007.

A careful scrutiny of the behaviour of the solutions of caffeine in water–DMF mixtures may be performed comparing the value of the interaction term W at each experimental point com-

Table 3
Logarithmic values of experimental and calculated mole fraction solubilities and their residuals (Δ)

$-\log x_2$	$-\log x_{2\,calc}$	Δ
2.646	2.588	0.058
2.583	2.629	−0.046
2.532	2.593	−0.061
2.481	2.509	−0.028
2.418	2.394	0.024
2.305	2.260	0.045
2.212	2.116	0.096
1.946	1.997	−0.051
1.855	1.909	−0.054
1.858	1.872	−0.014
1.923	1.896	0.027

pared with the regular value $W = \delta_1\delta_2$. This comparison is presented also in Table 1. As can be observed, for volume fractions of DMF from 0 to 0.5, $W > \delta_1\delta_2$. However, for volume fractions of DMF from 0.6 to 1.0, $W < \delta_1\delta_2$. It may be assumed that caffeine solutions can behave as regular solutions at some point ($W = \delta_1\delta_2$) within 0.5–0.6 DMF volume fraction.

Thus, in water-rich mixtures it seems to be some kind of association between caffeine and the solvent mixture according to $W > \delta_1\delta_2$. This could be explained considering the hydrophobic hydration (HH). HH is featured by an enhanced hydrogen bonding between water molecules in the neighbourhood of non polar groups in water. When adding DMF, HH breaks down. The endothermic shift of the enthalpies of solution upon small additions of aprotic cosolvents ($\Phi_W > 0.6$) to water is known to appear for hydrophobic solutes (Balk and Somsen, 1985) like caffeine.

Conversely, in water poor mixtures self association of solvent, solute or both is expected because $W < \delta_1\delta_2$. It is well known that N,N-disubstituted amides exhibit 'head-to-tail' self-association leading to low values of permittivity by cancellation of dipole moments according to the geometrical arrangement (Yonezawa and Morishima, 1966). This behaviour may remain in rich DMF blends, and, therefore, the corresponding caffeine solubilities are less than regular one. Moreover, as Adjei et al. (1980) pointed out, caffeine may also undergo self-association by forming polymer chains.

4. Conclusion

The Extended Hildebrand Approach applied to the solubility data of caffeine in water–DMF mixtures leads to an expansion of the W interaction term as a third degree power series in δ_1 which reproduces the caffeine solubility within the accuracy ordinarily achieved in such measurements. The procedure can be used to predict the solubility of caffeine in pure water or DMF and in any water–DMF mixtures.

References

Adjei, A., Newburger, J., Martin, A., 1980. Extended Hildebrand Solubility Approach: solubility of caffeine in dioxane–water mixtures. J. Pharm. Sci. 69, 659–661.

Akhnazarova, S., Kafarov, V., 1984. Correlation and Regression Analysis. Experiment Optimization in Chemistry and Chemical Engineering, ch. 4. Mir, Moscow, pp. 123–149.

Asuero, A.G., Herrador, M.A., González, A.G., 1993. Estimation of pH and autoprotolysis constants in mixtures of aliphatic amides with water: medium effect on the 4-aminoazobenzene system. Talanta 40, 479–484.

Balk, R.W., Somsen, G., 1985. Preferential solvation and hydrophobic hydration of polyols in mixtures of water and *N*,*N*-dimethylformamide. J. Phys. Chem. 89, 5093–5097.

González, A.G., Herrador, M.A., Asuero, A.G., 1994. Solubility of theophylline in aqueous in aqueous *N*,*N*-dimethylformamide mixtures. Int. J. Pharm. 108, 149–154.

González, A.G., Rosales, D., Gómez-Ariza, J.L., Fernández Sanz, J., 1990. Solvent effects on dissociation of aliphatic carboxylic acids in water–*N*,*N*-dimethylformamide mixtures. Anal. Chim. Acta 228, 301–306.

James K.C., 1986. Regular solutions/nearly regular solutions. In: Solubility and Related Properties. Marcel Dekker, New York, Ch. 5, pp. 149–212 and Ch. 6, pp. 213–233.

James, K.C., Ng, C.T., Noyce, P.R., 1976. Solubilities of testosterone propionate and related esters in organic solvents. J. Pharm. Sci. 65, 656–659.

Martin, A., Carstensen, J., 1981. Extended Hildebrand solubility approach: solubility parameters for crystalline solid compounds. J. Pharm. Sci. 71, 170–172.

Martin, A., Newburger, J., Adjei, A., 1980. Extended Hildebrand solubility approach: Solubility of theophylline in polar binary solvents. J. Pharm. Sci. 69, 487–491.

Martin, A., Wu, P.L., Adjei, A., Lindstrom, R.E., Elworthy, P.H., 1982a. Extended Hildebrand solubility approach and the log linear solublility equation. J. Pharm. Sci. 71, 849–856.

Martin, A., Wu, P.L., Adjei, A., Mehdizadeh, M., James, K.C., Metzler, M., 1982b. Extended Hildebrand solubility approach: Testosterone and testosterone propionate in binary solvents. J. Pharm. Sci. 71, 1334–1340.

Martínez, D., Giménez, M.P., 1981. Determination of benzodiazepines by derivative spectroscopy. J. Anal. Toxicol. 5, 10–13.

Sindreu, R.J., Moyá, M.L., Sánchez Burgos, F., González, A.G., 1994. Solvent effects on the dissociation of aliphatic carboxylic acids in water–*N*,*N*-dimethylformamide mixtures: correlation between acidity constants and solvatochromic parameters. J. Solvent Chem. 23, 1101–1109.

Yonezawa, T., Morishima, I., 1966. NMR studies of the intermolecular interaction of amides and some other related dipolar molecules. Bull. Chem. Soc. Jpn. 39, 2346–2351.

van Krevelen, D.W., 1990. Properties of Polymers: Their Correlation with Chemical Structure; their Numerical Estimation and Prediction from Additive Group Contribution, third ed. Elsevier, Amsterdam.

.