A Cosolvency Model to Predict Solubility of Drugs at Several Temperatures from a Limited Number of Solubility Measurements

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A cosolvency model to predict the solubility of drugs at several temperatures was derived from the excess free energy model of Williams and Amidon. The solubility of oxolinic acid, an antibacterial drug, was measured in aqueous (water+ethanol) and non-aqueous (ethanol+ethyl acetate) mixtures at several temperatures (20, 30, 35, 40 °C). Oxolinic acid displays a solubility maximum in each solvent mixture at solubility parameter values of 32 and 22 MPa$^{1/2}$. The temperature and heat of fusion were determined from differential scanning calorimetry. The solvent mixtures do not produce any solid phase change during the solubility experiments. The experimental results and those from the literature were employed to examine the accuracy and prediction capability of the proposed model. An equation was obtained to represent the drug solubility changes with cosolvent concentration and temperature. The model was also tested using a small number of experimental solubilities at 20 and 40 °C showing reasonably accurate predictions. This is important in pharmaceutics because it save experiments that are often expensive and time consuming.

Key words solubility; prediction; cosolvency; oxolinic acid; model

Solubility prediction based on a minimum number of experiments has not been comprehensively considered in the pharmaceutical literature. Predictions using a few experimental data can be employed in drug liquid formulations and preformulation studies of a new drug/drug candidate where only a small quantity of the drug is available. This is important in pharmaceutics because it reduces the number of required experiments that are often expensive and time consuming. A number of papers have been published in the past two decades regarding mathematical modelling of drug solubility in binary solvents at a single temperature.[1—9] However, the works dealing with solubility in mixed solvents at different temperatures and solubility prediction based on a minimum number of experiments are scarce. In this work, an extension of the excess free energy approach presented by Williams and Amidon[3] to correlate/predict solubility in binary solvents at different temperatures is proposed. Binary solvent systems are employed in drug formulation of water poorly soluble drugs, liquid–liquid extraction and re-crystallisation of drugs. The solubilities determined between of 20—40 °C are of particular interest because this range includes the physiological temperature and temperature variations that may occur during storage.

The accuracy and prediction capability of the proposed model are critically examined using the experimental solubilities of oxolinic acid (5-ethyl-5,8-dihydro-8-oxo-1,3-dioxo-[4,5-g]-quinoline-7-carboxylic acid) and published data in binary solvents at different temperatures. Oxolinic acid is an effective chemotherapeutic agent in the treatment of acute and recurrent urinary tract infections. This drug is structurally related to nalidixic acid, having a similar antibacterial spectrum and mechanism of action.

Theoretical

Williams and Amidon[3] derived relationships between solute activity coefficient, solute's Henry law constants in pure solvents, and solute free cosolvent and water volume fractions at a constant temperature. These models were used to predict solubility in binary solvents by employing the Wohl method.[3] The three-suffix equation for a binary solvent system is:

$$\ln x_m = \phi_1 \ln x_1 + \phi_2 \ln x_2 - A_{1-2}\phi_1\phi_2(2\phi_1 - 1)\left(\frac{V_s}{V_1}\right) + 2A_{2-1}\phi_1^2\phi_2\left(\frac{V_s}{V_2}\right) + C_s\phi_1\phi_2 \quad (1)$$

where x_m, x_1 and x_2 are the solubility mole fraction of the solute in the mixture and in the pure solvents 1 and 2, ϕ_1 and ϕ_2 are the solute free volume fractions of solvents 1 and 2, A_{1-2} and A_{2-1} stand for solvent–cosolvent interaction terms calculated from vapour–liquid equilibrium data, V_s, V_1 and V_2 are the molar volumes of the solute and solvents 1 and 2, respectively, and C_s is the solute–solvent interaction term. From a theoretical point of view, C_s is the only unknown constant. The C_s value can be calculated from one solubility measurement in a binary solvent mixture, or it can be estimated from a least square method setting the intercept equal to zero[3]:

$$\ln x_m - \phi_1 \ln x_1 - \phi_2 \ln x_2 + A_{1-2}\phi_1\phi_2(2\phi_1 - 1)\left(\frac{V_s}{V_1}\right) - 2A_{2-1}\phi_1^2\phi_2\left(\frac{V_s}{V_w}\right) = C_s\phi_1\phi_2 \quad (2)$$

In another paper, Williams and Amidon[10] suggested a single point estimation of the C_s term. In water+ethanol mixtures, the values used for the solvent–cosolvent interaction terms were $A_{1-2}=1.2160$ and $A_{2-1}=0.9093$. An important goal in mathematical modelling is to provide accurate quantitative relationships for correlating/predicting the experimental data points. The fitness (correlation) ability of a model

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can be used to identify outliers in order to re-determinate experimental data. The capability to provide accurate predictions distinguishes the good from the poor models. As shown in a recent work,[11] the numerical methods proposed by Williams and Amidon produced relatively high prediction errors. In order to provide more accurate predictions, and since the terms A_{1-2}, A_{2-1}, V_s, V_1, V_2 and C_s are constant for a solute in a given binary solvent, it is possible to rewrite Eq. 1 as:

$$\ln x_m = \phi_1 \ln x_1 + \phi_2 \ln x_2 + \left[A_{1-2}\left(\frac{V_s}{V_1}\right) + C_s \right]\phi_1\phi_2 + \left[2A_{2-1}\left(\frac{V_s}{V_2}\right) - 2A_{1-2}\left(\frac{V_s}{V_1}\right) \right]\phi_1^2\phi_2 \quad (3)$$

or

$$\ln x_m = \phi_1 \ln x_1 + \phi_2 \ln x_2 + M_1\phi_1\phi_2 + M_2\phi_1^2\phi_2 \quad (4)$$

where M_1 and M_2 are the model constants that can be computed by regressing $\ln x_m - \phi_1 \ln x_1 - \phi_2 \ln x_2$ against $\phi_1\phi_2$ and $\phi_1^2\phi_2$ using a no intercept least squares method. In the original derivation of Eq. 3,[12] the excess free energy term, g^E, was divided by RT where R is the gas constant. At constant temperature, RT may be included into the constants of the model. For different temperatures, Eq. 5 can be derived where R is included into the J_1 and J_2 terms.

$$\ln x_{m,T} = \phi_1 \ln x_{1,T} + \phi_2 \ln x_{2,T} + J_1\left(\frac{\phi_1\phi_2}{T}\right) + J_2\left(\frac{\phi_1^2\phi_2}{T}\right) \quad (5)$$

where $x_{m,T}$, $x_{1,T}$ and $x_{2,T}$ are the solute solubility in the binary mixture, the pure solvents 1 and 2 at temperature T, respectively and J_1 and J_2 are the constants of the model. Equation 5 is also derivable from a previously published model based on the combined nearly ideal binary solvent/Redlich–Kister model.[13] It should be noted that the model assumes a constant contribution from the solid phase, that is, the solvent mixtures do not induce significant solid phase changes (polymorphism or solvates). Therefore, the solid phase contribution is included as a constant value into the regression coefficients.

The correlation/prediction capability of the models is evaluated by the average relative error (ARE):

$$ARE = \frac{100}{N}\sum_1^N \left\{ \frac{|(x_m)_{observed} - (x_m)_{calculated}|}{(x_m)_{observed}} \right\} \quad (6)$$

where N is the number of data points obtained in each set which equals the number of different cosolvent ratios and temperatures used.

Experimental

Oxolinic acid was purchased from Sigma. The purity of the lot employed in this work (20H0315) was >99%. The solvents used were ethanol and ethyl acetate (spectrophotometric and analytical grade, respectively, Panreac, Monplet and Esteban, Barcelona, Spain) and double distilled water.

An excess amount of oxolinic acid was added to sealed flasks containing the pure solvents and solvent mixtures and shaken at four temperatures (20—40 °C) in a temperature-controlled bath (±0.1 °C, Heto SH 02/100). The binary mixtures were prepared by volume. When the saturation concentration was attained, the solid phase was removed by filtration (Durapore membranes, 0.2 μm pore size). The drug did not significantly adsorb onto the membranes as shown from the similar results obtained in preliminary experiments (centrifugation and filtration). For example, the solubility in water at 25 °C was 29.50±0.11 μg/ml (centrifugation) and 29.20±0.10 μg/ml (filtration). The solubilities in ethanol at 25 °C were 71.86±0.58 μg/ml (centrifugation) and 71.56±0.25 μg/ml (filtration). The clear solutions were diluted with ethanol 96% volume and assayed in a double beam spectrophotometer. The calibration line was obtained by preparing in triplicate with 14 concentrations ranging from 1 to 5.6 μg/ml and measuring the absorbance at the wavelength of maximum absorption, 260 nm. The relationship is linear at this concentration range: Absorbance=0.1297 (±0.006) Concentration+0.043 (±0.024), n=14, r^2=0.999, S.D.=0.003, F=40929. The intercept is not statistically different from zero. The molar absorptivity is 12.97×10^4 $l\,mol^{-1}\,cm^{-1}$. To test the accuracy, known concentrations of oxolinic acid (10, 20, 25, 30 μg/ml) were assayed at different days. Three dilutions were prepared in triplicate from these initial concentrations to obtain 2, 3 and 4 μg/ml (a total of 12 samples). The absorbance readings of these samples were converted into concentrations using the equation above. The coefficients of variation among replicated samples range between 0.06—2% and the differences between the known and the measured concentrations were less than 2% except for one case (2.7% error). The densities of the solutions were determined at each temperature in 10-ml pycnometers to convert molarity units into mole fraction units.

Differential scanning calorimetry (Mettler TA 4000) was performed on the solid phase before and after equilibration with the solvent mixtures at heating rates of 2 °C/min, 5 °C/min and 10 °C/min.

Results and Discussion

The onset melting temperature of oxolinic acid is 314 (±0.1) °C at 2 °C/min and 5 °C/min and 314.4 (±0.1) °C at 10 °C/min. These values agree with literature results (314 °C at 10 °C/min.[14]). The molar heat of fusion only varies 1.6—3% with the heating rate (2 °C/min, ΔH^F=42172 (±172) J/mol; at 5 °C/min, ΔH^F=43594 (±178) J/mol; at 10 °C/min, ΔH^F=42953 (±90.2) J/mol). It should be noted that decomposition starts during melting and an accurate determination of the heat of fusion is not possible, a fact that was also reported.[14] The differential scanning calorimetry (DSC) curves after equilibration with the saturated solutions do not show new thermal effects that could indicate solid-phase changes. To save journal space, the curves are not included.

The mole fraction solubilities of oxolinic acid in the solvent mixtures studied at 20, 25, 30, 35 and 40 °C are listed in Table 1 along with the coefficient of variation, CV=(S.D./mean)×100, of the replicated measurements to show the precision of the data. Among the 95 mean solubility values listed, 84 cases have CV values less than 1% and the remaining 11 solubilities have CV values between 1—2.5%, that is, very close to 1%. In our knowledge, the literature does not report any solubility data for oxolinic acid in solvent mixtures. The only value reported is the solubility in water at 20 °C (10±0.5 μg/ml).[14] We obtain 12±0.09 μg/ml at the same temperature. Figure 1 shows the experimental and predicted mole fraction solubilities for oxolinic acid versus solvent's solubility parameter at different temperatures.

The mixtures studied contain a common cosolvent (ethanol) and the polarity of the medium ranges from δ_1=48 $MPa^{1/2}$ (water) to δ_1=18 $MPa^{1/2}$ (ethyl acetate). The Hildebrand solubility parameter δ_1 is a measure of the overall polarity. From Fig. 1, the solubilization power of the less polar mixture (ethyl acetate–ethanol, δ_1=18—26 $MPa^{1/2}$) is larger than that of the amphiprotic mixture (ethanol–water, δ_1=26—48 $MPa^{1/2}$). The solubility of oxolinic acid in the pure solvents decreases from ethyl acetate (hydrogen bond acceptor)>ethanol (amphiprotic)>water (amphiprotic). Although these cosolvents are able to hydrogen bond with oxolinic acid, the solubility is low due to the high melting tem-

Table 1. Mole Fraction Solubility (x_m) of Oxolinic Acid in Ethanol+Water and Ethanol+Ethyl Acetate Mixtures between 20 and 40 °C[a)]

Ethanol % (v/v)	T				
	40 °C[b)]	35 °C[b)]	30 °C[b)]	25 °C[c)]	20 °C[b)]
	Water (solvent 2)+ethanol (solvent 1) mixtures				
0	2.0239×10^{-6} (0.47)	1.6262×10^{-6} (0.58)	1.3400×10^{-6} (0.50)	1.0785×10^{-6} (0.99)	8.6910×10^{-7} (0.73)
10	4.0432×10^{-6} (0.65)	3.6934×10^{-6} (1.09)	3.3067×10^{-6} (1.08)	2.9212×10^{-6} (0.71)	2.6436×10^{-6} (1.09)
20	7.6222×10^{-6} (0.24)	6.9258×10^{-6} (0.44)	6.0327×10^{-6} (0.26)	5.3991×10^{-6} (0.33)	4.7790×10^{-6} (0.74)
30	1.1087×10^{-5} (0.74)	9.6362×10^{-6} (0.78)	8.5378×10^{-6} (0.66)	7.4102×10^{-6} (0.46)	6.6149×10^{-6} (0.62)
40	1.5873×10^{-5} (0.62)	1.3482×10^{-5} 80.55)	1.1643×10^{-5} (0.91)	9.9686×10^{-6} (0.55)	8.8411×10^{-6} (0.61)
50	2.2126×10^{-5} (0.77)	1.8304×10^{-5} (0.71)	1.5412×10^{-5} (1.00)	1.2658×10^{-5} (0.82)	1.0698×10^{-5} (1.13)
60	2.9339×10^{-5} (0.57)	2.3903×10^{-5} (0.56)	1.9706×10^{-5} (0.58)	1.6336×10^{-5} (0.88)	1.4121×10^{-5} (0.35)
70	3.5493×10^{-5} (0.58)	2.9524×10^{-5} (0.57)	2.3253×10^{-5} (0.56)	2.0166×10^{-5} (0.84)	1.7127×10^{-5} (1.12)
80	4.0944×10^{-5} (0.61)	3.2843×10^{-5} (1.11)	2.5838×10^{-5} (0.86)	2.0990×10^{-5} (0.22)	1.7377×10^{-5} (0.53)
90	3.2119×10^{-5} (1.07)	2.6540×10^{-5} (0.41)	2.1113×10^{-5} (0.67)	1.6879×10^{-5} (0.93)	1.4073×10^{-5} (0.83)
100	1.6298×10^{-5} (0.45)	1.2907×10^{-5} (0.81)	1.0561×10^{-5} (0.76)	8.2357×10^{-6} (0.15)	6.8334×10^{-6} (0.40)
	Ethanol (solvent 1)+ethyl acetate (solvent 2) mixtures				
90	2.3899×10^{-5} (0.75)	1.9124×10^{-5} (0.75)	1.4964×10^{-5} (0.36)	1.1781×10^{-5} (0.26)	9.8744×10^{-6} (0.49)
80	3.2903×10^{-5} (0.82)	2.6539×10^{-5} (0.19)	2.0749×10^{-5} (0.19)	1.6534×10^{-5} (0.23)	1.3452×10^{-5} (1.05)
70	4.2799×10^{-5} (1.14)	3.4058×10^{-5} (0.91)	2.7848×10^{-5} (0.51)	2.2560×10^{-5} (0.29)	1.8206×10^{-5} (0.35)
50	6.3393×10^{-5} (0.88)	5.1237×10^{-5} (0.23)	4.1175×10^{-5} (0.71)	3.4887×10^{-5} (0.77)	2.9685×10^{-5} (0.52)
40	6.4468×10^{-5} (0.52)	5.3949×10^{-5} (0.94)	4.6038×10^{-5} (0.54)	3.8134×10^{-5} (0.87)	3.2916×10^{-5} (1.04)
30	6.9308×10^{-5} (0.86)	5.8886×10^{-5} (0.93)	4.9118×10^{-5} (0.35)	4.1588×10^{-5} (0.12)	3.4750×10^{-5} (0.85)
10	5.8387×10^{-5} (0.86)	4.9079×10^{-5} (0.59)	4.0771×10^{-5} (0.36)	3.4276×10^{-5} (1.25)	2.9980×10^{-5} (0.63)
0	4.2288×10^{-5} (0.17)	3.5456×10^{-5} (0.55)	2.9801×10^{-5} (0.89)	2.4502×10^{-5} (0.60)	2.0103×10^{-5} (0.20)

a) Coefficient of variation (CV=S.D./mean)×100 in parentheses. The results are the average of at list three replicate experiments. *b*) From this work. *c*) Data taken from a previous paper.[21)]

perature of the solute. The less ordered structure of the non-aqueous mixture may also explain the larger solubilities obtained for oxolinic acid in ethanol–ethyl acetate. Addition of ethanol to water enhances the solubility of the solute to a maximum (80% ethanol–in water, $\delta_1=32\ \mathrm{MPa}^{1/2}$). Ionization also contributes to the aqueous solubility of oxolinic acid. The total solubility of oxolinic acid is the sum of the intrinsic solubility of the non-ionized species and the concentration of the ionized species. As ethanol is added to water, the effect of ionization is expected to decrease. The overall solubility increase suggests a dominant contribution from the enhanced intrinsic solubility of the non-ionized species. The solubility maximum is not related to solid phase changes and it may be related to an optimal polarity value for the solute–solvent interactions. The nature of the cosolvent added to ethanol (water, electron donor/acceptor or ethyl acetate, electron donor) also plays an important role, in addition to polarity. Thus a higher solubility maximum is obtained in the ethanol–ethyl acetate mixture (40% ethanol–in ethyl acetate) at a smaller polarity value ($\delta_1=22\ \mathrm{MPa}^{1/2}$). Sulphonamides and paracetamol also show two solubility peaks at the same polarity range, one in each solvent mixture,[7,15,16)] whereas mefenamic acid displays a single maximum in the less polar mixture (ethanol–ethyl acetate).[17)]

Although oxolinic acid has polar groups and consequently it forms non-ideal solutions, the van't Hoff plots of the logarithm of the mole fraction solubility against the reciprocal of temperature are linear ($r^2\geq0.99$) for both mixtures at all cosolvent ratios, as shown in Fig. 2 for the pure solvents. Linear relationships are often observed for sparingly soluble drugs at the temperature range used in this study. This can be interpreted as a local linearity from a more general non-linear function. As the temperature range spans, it is expected to observe curved rather than linear relationships.[18)] However, from a practical point of view, the linear behaviour commonly observed allows to interpolate the results to pre-

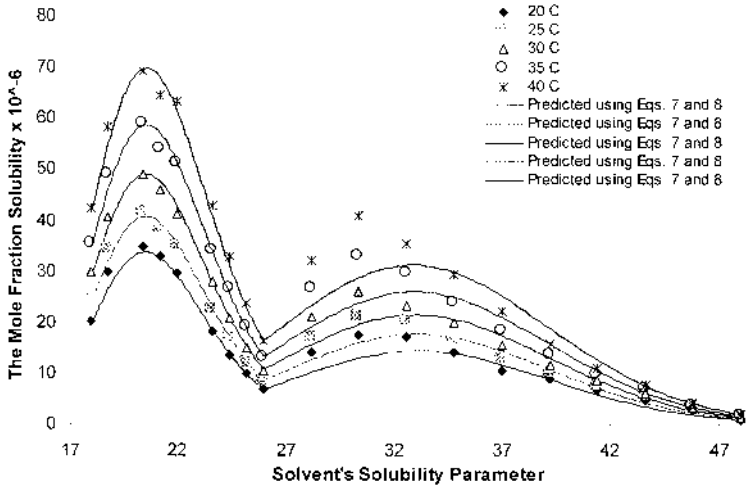

Fig. 1. The Experimental and Predicted Mole Fraction Solubility of Oxolinic Acid *vs.* Solvent's Solubility Parameter at Temperatures 20, 25, 30, 35 and 40 °C

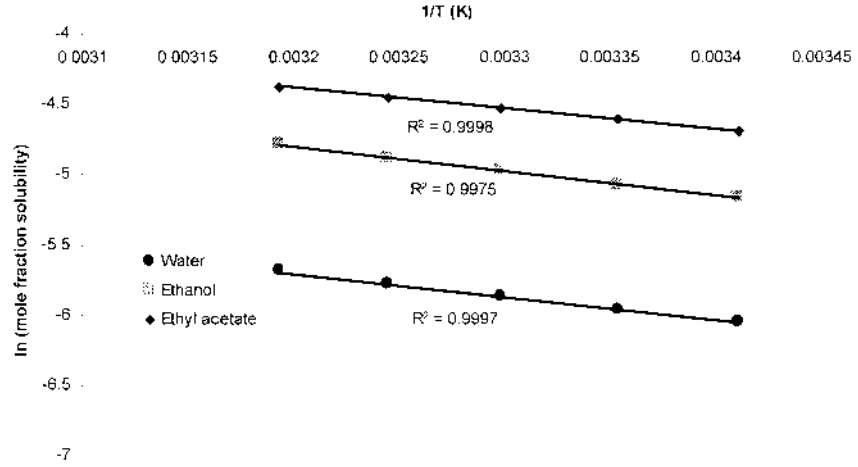

Fig. 2. Linear Relationship between ln x *vs.* $1/T$ in Pure Solvents 1—3

Table 2. Data Sets at Temperatures 20 to 40 °C, the References and Average Relative Error (*ARE*) Values Using Eq. 5 and a Previously Published Model[13)]

Solute and mixed solvent	Reference	Eq. 5	Published model	$N^{a)}$
Oxolinic acid in water+ethanol	This work and 21	12	4	55
Oxolinic acid in ethanol+ethyl acetate	This work and 21	2	2	45
Paracetamol in water+ethanol	15	16	16	35
Paracetamol in ethanol+ethyl acetate	15	16	13	35
Sulphamethoxypyridazine in water+ethanol	16	10	10	35
Sulphamethoxypyridazine in ethanol+ethyl acetate	16	6	6	25
Paracetamol in water+dioxane	22	17	11	60
Nalidixic aicd in water+dioxane	22	14	11	72
Acetanilide in water+dioxane	22	24	17	55
	Mean *ARE*	13	10	

a) N is the number of data points in each set.

dict solubility at the temperature range which is more relevant for pharmaceutical purposes.

The experimental solubilities were fitted to Eq. 5 and $x_{m,T}$ was back calculated by the trained model. The *ARE* value obtained from these calculations employing the whole data set in water+ethanol and ethanol+ethyl acetate were 12 and 2%. This analysis (fitting whole data points in each set and back-calculating solubility values) shows the correlation ability of the proposed model. As mentioned above, this numerical method could be employed to detect possible outliers where re-determination is required.

To further investigate the accuracy of the proposed model to correlate experimental solubilities, published solubility data sets in binary solvent mixtures at different temperatures

were collected from the literature. The results (Table 2) are less accurate than those obtained with a previously published model.[13] However, Eq. 5 employs less curve-fitting parameters and it is obvious that the larger the number of curve-fitting parameters, the more accurate the result is likely to be. The disadvantage for employing more curve-fitting parameters is that the model needs more experimental data whose collection is costly and time consuming. This is an important factor to be considered in pharmaceutical industry where often a limited amount of a new drug candidate is available. Using the same number of curve-fit parameters, it is expected that Eq. 5 would produce the same accuracy as the proposed equation,[13] because from a mathematical point of view the published model and Eq. 5 can be made equivalent by simple algebraic manipulations.

Equation 5 was also tested by calculating the model constants with a smaller number of experimental data, *i.e.* 8 values, using ϕ_1=0, 0.3, 0.6 (or 0.7) and 1 at 20 and 40 °C. The solubility at the remaining ϕ_1 and T values were predicted from the $x_{1,T}$ and $x_{2,T}$ values and the trained model. The *ARE* value for oxolinic acid in water+ethanol and ethanol+ethyl acetate mixtures were 14 and 2% (the number of predicted data points is N-14). There is no difference between *ARE* values obtained from back calculations using whole data points and predictions using 8 experimental data points. This means that instead of measuring the solute solubility in a large number of solvent compositions and temperatures, one may employ a smaller number of data points to reproduce the solubility in mixed solvents at different temperatures. Since there is a linear relationship between $\ln x$ and $1/T$ throughout the entire solvent composition, one can use the interpolated values of $\ln x_{1,T}$, $\ln x_{2,T}$ and $\ln x_{3,T}$ instead of real experimental values. Using this method, the following equations were obtained for the oxolinic acid data in water+ethanol mixtures:

$$\ln x_{m,T} = \left(1.732 - \frac{3993.207}{T}\right)\phi_1 + \left(-0.651 - \frac{3901.497}{T}\right)\phi_2 + 1720.50\left(\frac{\phi_1\phi_2}{T}\right) + 250.22\left(\frac{\phi_1^2\phi_2}{T}\right) \quad (7)$$

and for oxolinic acid in ethanol+ethyl acetate:

$$\ln x_{m,T} = \left(0.829 - \frac{3419.279}{T}\right)\phi_1 + \left(1.732 - \frac{3993.207}{T}\right)\phi_2 + 788.965\left(\frac{\phi_1\phi_2}{T}\right) + 574.798\left(\frac{\phi_1^2\phi_2}{T}\right) \quad (8)$$

It should be noted that these equations are useful for drug formulation and to predict drug solubility at physiological temperature because many sparingly soluble drugs show linear van't Hoff plots[18] at this temperature range. Using Eqs. 7 and 8, there is no need to measure the solubility in pure solvents at other temperatures in order to predict the solubility in the mixed solvent system. The *ARE* value for the predicted solubilities of oxolinic acid, which were not used to obtain the model in water+ethanol and ethanol+ethyl acetate were 14 and 3%, respectively. This means that it is possible to predict the drug solubility at different ϕ_1 and T values employing just 8 experimental data points collected from 2 cosolvent concentrations (the best ϕ_1 are 0.33 and 0.66) and the pure solvents at 2 different, preferably the lowest and the highest, temperatures. Figure 1 shows the calculated curves using Eqs. 7 and 8. The model gives excellent results in ethanol–ethyl acetate (left curve), and the errors are larger near the maximum in ethanol–water (right curve). However, these errors are acceptable for practical application taking into account the advantages of using a small number of experiments.

In conclusion, it has been shown that we can extend the applicability of the excess free energy model for calculating solute solubility in mixed solvents at various temperatures using a single equation. Because of the lack of theoretical knowledge on solute–solvent and solvent–solvent interactions, these terms should be estimated using experimental data. The possibility of estimation of these terms using solubility data at two temperatures and predicting solubility at other temperatures using interpolation technique is shown here. The mean *ARE* is around ((14+2)/2) 8%. For compounds showing low solubility, an estimation method can be considered accurate if solubility predictions are, on the average, within ±30% of the experimental values.[20] Therefore, this approach provides a rational drug formulation strategy rather than a trial and error approach when the optimisation of the cosolvent concentration at different temperatures is required. This is important in pharmaceutics because it saves experiments that are often expensive and time consuming. These computations are also applicable to re-crystallisation processes of drug/chemical compounds. The model employs the total solubility and does not differenciate the contribution from ionized and non-ionized species. For sparingly soluble drugs in solvent mixtures, the cosolvent effect on the non-ionized species seems to be dominant as shown from the initial solubility increase as the cosolvent is added to water.

Acknowledgements The authors would like to thank the Australian Department of Education, Training and Youth Affairs and the University of Sydney for providing the IPRS and IPA scholarships. The experimental data were obtained with the financial support of Ministerio de Educación y Cultura (project PM99-0127) and University of Alcalá (project E007/99). S. Romero acknowledges a grant provided by Comunidad de Madrid (683/96).

References

1) Adjei A., Newburger J., Martin A., *J. Pharm. Sci.*, **69**, 659—661 (1980).
2) Acree W. E., Jr., Rytting J. H., *Int. J. Pharmaceut.*, **10**, 231—238 (1982).
3) Williams N. A., Amidon G. L., *J. Pharm. Sci.*, **73**, 14—18 (1984).
4) Rubino J. T., Yalkowsky S. H., *Pharm. Res.*, **4**, 220—230 (1987).
5) Acree W. E., Jr., *Thermochim. Acta*, **198**, 71—79 (1992).
6) Khossravi D., Connors K. A., *J. Pharm. Sci.*, **81**, 371—379 (1992).
7) Bustamante P., Ochoa R., Reillo A., Escalera J. B., *Chem. Pharm. Bull.*, **42**, 1129—1133 (1994).
8) Barzegar-Jalali M., Jouyban-Gh. A., *Int. J. Pharmaceut.*, **152**, 247—250 (1997).
9) Jouyban-Gh. A., *Chem. Pharm. Bull.*, **46**, 1058—1061 (1998).
10) Williams N. A., Amidon G. L., *Pharm. Res.*, **5**, 193—195 (1988).
11) Jouyban A., Chan H. K., Romero S., Bustamante P., Manuscript in preparation.
12) Williams N. A., Amidon G. L., *J. Pharm. Sci.*, **73**, 9—13 (1984).
13) Jouyban-Gh. A., Acree W. E., Jr., *Int. J. Pharmaceut.*, **167**, 177—182 (1998).
14) Brazier M., Julien R., Ceolin R., Robert H., Khodadad P., *Pharm. Acta Helv.*, **66**, 226—229 (1991).
15) Bustamante P., Romero S., Reillo A., *Pharm. Sci.*, **1**, 505—507 (1995).
16) Bustamante P., Escalera B., *J. Pharm. Pharmacol.*, **47**, 550—555 (1995).

17) Romero S., Escalera B., Bustamante P., *Int. J. Pharmaceut.*, **178**, 193—202 (1999).
18) Grant D. J. W., Mehdizadeh M., Chow A. H. L., Fairbrother J. E., *Int. J. Pharmaceut.*, **18**, 25—38 (1984).
19) Barzegar-Jalali M., Jouyban-Gh. A., Hanaee J., Chookhachizadeh-Moghaddam M. H., *Int. J. Pharmaceut.*, **144**, 127—130 (1996).
20) Dickhut R. M., Armstrong D. E., Andren A. W., *Environ. Toxicol. Chem.*, **10**, 881—889 (1991).
21) Jouyban-Gh. A., Romero S., Bustamante P., Clark B. J., *Chem. Pharm. Bull.*, **48**, 175—178 (2000).
22) Bustamante P., Romero S., Pena A., Escalera B., Reillo A., *J. Pharm. Sci.*, **87**, 1590—1596 (1998).