

Models to Predict Solubility in Ternary Solvents Based on Sub-binary Experimental Data

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The capability of the extended forms, of two well established cosolvency models, *i.e.* the combined nearly ideal binary solvent/Redlich–Kister equation and the modified Wilson model, used to predict the solute solubility in non-aqueous ternary solvent mixtures is presented. These predictions are based on the measured solubilities of anthracene in binary solvent mixtures. As a result the values of average percent deviations were less than 2% for the anthracene solubility in ternary mixtures.

This work was also extended to other cosolvency models, *i.e.* the extended Hildebrand solubility approach and the mixture response surface method, which are also commonly used for correlating solubility data in ternary solvents. The accuracy of the models is compared with each other and also with a published solubility model for ternary mixtures. The results illustrate that all models produced comparable accuracy.

Key words solubility prediction; anthracene; cosolvency; combined nearly ideal binary solvent/Redlich–Kister; modified Wilson model; ternary solvent

Mixing of miscible solvents in order to enhance solubility of poorly soluble compounds is a very common method in chemical and pharmaceutical industries. The cosolvency phenomenon is important in liquid drug formulations, chemical separation, petroleum industry and environmental studies. In most cases, addition of one cosolvent to the main solvent, *e.g.* water in pharmaceutical applications, is not able to dissolve the compound in desired concentrations and one should add the second cosolvent.^{2–5)} Using two or more cosolvents in mixed solvent systems improves the solubility of the solute and also decreases the risk of toxicity. In pharmaceutical applications, the concentration of the cosolvents should be kept as low as possible, because of toxicity and cost effects. The often method to optimise the cosolvent concentration in pharmaceutical industries is based on trial and error approach. In order to present a rational method to optimise the cosolvents' concentrations in ternary solvent mixtures based on sub-binary data, anthracene solubility data in mixed solvents have been employed as a model system. It is obvious that one can employ the proposed procedure to calculate drug solubilities in aqueous ternary systems. Anthracene is a polycyclic aromatic hydrocarbon and solubility data of polycyclic aromatic hydrocarbons are becoming increasingly important in the petroleum industry, particularly in light of present trends towards heavier feedstock's and known carcinogenicity and/or mutagenicity of many of the larger polycyclic aromatic compounds.

In addition to the experimental measurements of solute solubility in mixed solvents, there are numerous models for calculating and/or correlating solubility data. We have previously summarised many of these models in and also compared their accuracy.⁶⁾ The final goal of developing cosolvency equations is that it enables researchers to predict the solute solubility in mixed solvents from a minimum number of experiments. Group contribution methods, such as universal functional group activity coefficient (UNIFAC), have proved fairly successful in estimating solid solubility in solvent mixtures from structural information. The predictive ability of the UNIFAC model for biphenyl solubilities in several binary mixed solvents was reported in a previous paper.⁷⁾

An alternative method to predict the solubility in mixed solvents is to use the correlative cosolvency models after training the models by employing measured solubilities at given cosolvent concentrations and predicting at other cosolvent concentrations by interpolation technique. It has been shown that solubility prediction in binary solvents based on trained models using insufficient experimental data points produced unacceptable errors.⁸⁾ On the other hand, Bustamante and co-workers⁹⁾ employed a modified form of the extended Hildebrand solubility approach to correlate structurally related drug solubility in binary solvent mixtures. The authors used the solute solubility in water and cosolvent, the solute solubility parameter, the Hildebrand solubility parameter of the solvent and the basic solubility parameter of the mixed solvent as independent variables. This approach is a useful solution to predict the solubility of the chemically related drugs which is often used in drug discovery studies where different derivatives of a drug/drug candidate are synthesised and evaluated. In a recent paper,¹⁰⁾ the applicability of the combined nearly ideal binary solvent/Redlich–Kister model for reproducing solubility data of structurally related drugs in binary solvents was presented. It was also shown that the prediction error of the later model is less than that of the modified form of the extended Hildebrand solubility approach.¹⁰⁾

In the present paper, the capability of the combined nearly ideal binary solvent/Redlich–Kister and the modified Wilson models for predicting solute solubility in ternary mixtures based on the model constants calculated by employing solubility data in sub-binary solvents, is presented. Usually, solubility data in binary solvents has been determined and in the case of inefficient solubilization by binary system, a possible solution is to use ternary solvent mixtures. The produced experimental binary data from the early stage can be used to predict solubility in ternary solvents as it has been shown in this report. Also, the published cosolvency models in binary solvents are extended in order to reproduce the solute solubility in ternary mixtures. Accuracy of the models is compared with that of an extended form of the combined nearly ideal binary solvent/Redlich–Kister equation.

Theoretical Background The combined nearly ideal bi-

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nary solvent/Redlich–Kister equation was suggested to reproduce the solubility profile in binary solvents, based upon the thermodynamic mixing model.¹¹⁾ Our previous reports have shown that the combined nearly ideal binary solvent/Redlich–Kister equation is the most accurate model for calculating and/or correlating solute solubility data in binary solvents.^{6,12)} It can be readily extended to describe solute solubility in ternary solvent mixtures. The obtained model represents the thermodynamic extension of the basic mixing model to a quaternary solution. For convenience, the equation is written in terms of the natural logarithm of the mole fraction solubilities of the solute. The fixed values of RT (R is the molar gas constant and T denotes absolute temperature of the solution) at a constant temperature are incorporated into the model constants. The extended form of the model is expressed by Eq. 1:

$$\ln X_m = f_1 \ln X_1 + f_2 \ln X_2 + f_3 \ln X_3 + f_1 f_2 \sum_{i=0}^p W_i (f_1 - f_2)^i + f_1 f_3 \sum_{i=0}^p W_i (f_1 - f_3)^i + f_2 f_3 \sum_{i=0}^p W_i (f_2 - f_3)^i \quad (1)$$

Where X_m is the solute mole fraction solubility in mixed solvent, f_1, f_2 and f_3 represent the solute free volume fraction of solvents 1, 2 and 3, respectively, X_1, X_2 and X_3 denote the solute mole fraction solubility in pure solvents 1, 2 and 3, W_i' and W_i'' are binary solvent–solute interaction terms which are calculated by employing binary solubility data *via* a least squares analysis (for details see appendix). In the Eq. 1 the value of p can be varied from 0–3.

An alternative equation is the modified Wilson model, which has been demonstrated as producing comparable results with the combined nearly ideal binary solvent/Redlich–Kister model.¹³⁾ It is possible to extend it for ternary solvent mixtures, such that:

$$\ln \left(\frac{X_s^i}{X_m} \right) = 1 - \frac{f_1 \left[1 - \ln \left(\frac{X_s^i}{X_1} \right) \right]}{f_1 + \lambda_{12} f_2 + \lambda_{13} f_3} - \frac{f_2 \left[1 - \ln \left(\frac{X_s^i}{X_2} \right) \right]}{\lambda_{21} f_1 + f_2 + \lambda_{23} f_3} - \frac{f_3 \left[1 - \ln \left(\frac{X_s^i}{X_3} \right) \right]}{\lambda_{31} f_1 + \lambda_{32} f_2 + f_3} \quad (2)$$

Where X_s^i is ideal mole fraction solubility of the solute and $\lambda_{12}, \lambda_{21}, \lambda_{13}, \lambda_{31}, \lambda_{23}$ and λ_{32} are the model constants, which are calculated from sub-binary solubility data.

In order to examine the applicability of these equations to real data, the prediction of anthracene solubility in ternary solvents, employed published solubility data in binary solvents and this allowed the calculation of the binary solvent–solute interaction constants. The binary interaction terms for the combined nearly ideal binary solvent/Redlich–Kister equation and the modified Wilson model were taken from the literature (for reference numbers, see Table 1). From these binary interaction terms, anthracene solubility in ternary solvents was predicted by using Eqs. 1 and 2.

In order to check the best fitness ability of various published models, the experimental data in ternary solvents were fitted to different equations. From this the correlative ability of the combined nearly ideal binary solvent/Redlich–Kister

model was compared with that of the excess free energy model, the extended form of a mixture response surface method and the modified form of the extended Hildebrand solubility model. These equations and the related extensions for correlating solubility data in ternary solvents, are briefly reviewed for the models.

Martin and co-workers¹⁴⁾ presented the extended form of the Hildebrand solubility approach to correlate experimental solubility of drugs in aqueous mixed solvents. Their equation was also applicable to non-aqueous solvents. The model was presented by Eq. 3:

$$-\ln X_m = -\ln X_s^i + \frac{V_s \phi_m^2 (\delta_m^2 + \delta_s^2 - 2WW)}{RT} \quad (3)$$

where V_s is the molar volume of the solute, ϕ_m denotes the volume fraction of the solvent in the solution which can be assumed equal to unity, δ_m and δ_s are mixed solvent and solute's solubility parameters, respectively and WW is the interaction term and is calculated by:

$$WW = \frac{\ln X_m - \ln X_s^i + \left(\frac{V_s \phi_m^2}{RT} \right) \delta_m^2 + \left(\frac{V_s \phi_m^2}{RT} \right) \delta_s^2}{2 \left(\frac{V_s \phi_m^2}{RT} \right)} \quad (4)$$

The authors correlated the experimental values of the interaction term to a power series of solvent's solubility parameter, δ_m :

$$WW = \sum_{i=0}^q A_i \delta_m^i \quad (5)$$

Where A_i is the curve-fit parameter. The numerical values of δ_m for ternary solvent mixtures are calculated by Eq. 6:

$$\delta_m = f_1 \delta_1 + f_2 \delta_2 + f_3 \delta_3 \quad (6)$$

In which δ_1, δ_2 and δ_3 are the solubility parameters of pure solvents 1, 2 and 3, respectively.

However, it is possible to use the solute free volume fraction of solvents instead of δ_m , to correlate experimental values of WW ¹⁵⁾:

$$WW = J_0 + J_1 f_1 + J_2 f_2 + J_3 f_3 + J_4 f_1^2 + J_5 f_2^2 + J_6 f_3^2 + J_7 f_1 f_2 + J_8 f_1 f_3 + J_9 f_2 f_3 \quad (7)$$

Where J_0 – J_9 are the curve-fit parameters. Equation 7 was obtained by substitution of δ_m values from Eq. 6 into Eq. 5 and then the appropriate rearrangements. This formalism allows us to reproduce solubility data in ternary solvents.

Williams and Amidon¹⁶⁾ presented the excess free energy approach to calculate the solute solubility in ternary solvent mixtures:

$$\ln X_m = f_1 \ln X_1 + f_2 \ln X_2 + f_3 \ln X_3 - A_{12} f_1 f_2 (2f_1 + 2f_2 - 1) (V_s/V_1) + A_{21} 2f_1 f_2 (f_1 + f_2) (V_s/V_2) - A_{13} f_1 f_3 (2f_1 + 1) (V_s/V_1) + A_{31} 2f_1^2 f_3 (V_s/V_3) - A_{32} f_2 f_3 (2f_3 - 1) (V_s/V_3) + A_{23} 2f_2 f_3^2 (V_s/V_2) - G_{123} V_s f_1 f_2 f_3 + G_{132} V_s f_1 f_2 + G_{133} V_s f_1 f_3 + G_{233} V_s f_2 f_3 + K V_s f_1 f_2 f_3 \quad (8)$$

Where A denotes binary solvent–solvent interaction terms in the absence of the solute, subscripts 1, 2 and 3 refer to solvents 1, 2 and 3, and s refers to the solute, V represents the molar volume, G stands for the binary solvent–solute interac-

tion constant, G_{123} is the ternary solvent–solvent interaction parameter in the absence of the solute and K is the ternary solvent–solute interaction constant. The solvent–solvent interaction constants (A , G_{123}) are obtained from the vapour–liquid equilibrium data. The binary solvent–solute interaction constants (G_{1s2} , G_{1s3} , and G_{s23} terms) are calculated by employing experimental solubility data in binary solvents (theoretically this may be calculated from one solubility experiment in each binary solvent) and the constant K is obtained from experimental solubility data in ternary solvents. Because A , V , G and K terms are constant values for a given ternary system, one can rearrange Eq. 8 as:

$$\ln X_m = f_1 \ln X_1 + f_2 \ln X_2 + f_3 \ln X_3 + M_1 f_1 f_1^2 f_2^2 + M_2 f_1 f_2 f_3 + M_3 f_1 f_2 + M_4 f_1^2 f_3 + M_5 f_1 f_3 + M_6 f_2 f_3^2 + M_7 f_2 f_3 \quad (9)$$

Where M_1 – M_7 are the model constants which are calculated via the least squares analysis by employing solubility data in ternary solvents.

The mixture response surface model is presented for reproducing solute solubility data in binary solvents.¹⁷⁾ The original five constant term model is expressed by:

$$\ln X_m = S_1 f_1' + S_2 f_2' + S_3 \left(\frac{1}{f_1'} \right) + S_4 \left(\frac{1}{f_2'} \right) + S_5 f_1' f_2' \quad (10)$$

Where $f' = 0.96f + 0.02$ and S_1 – S_5 are the model constants. One can extend the model to describe solute solubility in ternary solvents as:

$$\ln X_m = B_1 f_1' + B_2 f_2' + B_3 f_3' + B_4 \left(\frac{1}{f_1'} \right) + B_5 \left(\frac{1}{f_2'} \right) + B_6 \left(\frac{1}{f_3'} \right) + B_7 f_1' f_2' + B_8 f_1' f_3' + B_9 f_2' f_3' + B_{10} f_1' f_2' f_3' \quad (11)$$

Where B_1 – B_{10} denote the model constants.

To assess the prediction capability and the best fit ability of the models, we calculated percent deviation, %D, of back-calculated solubilities from experimental values by using Eq. 12:

$$\%D = \frac{100}{N} \sum \left(\frac{|(X_m)_{\text{Calc.}} - (X_m)_{\text{Exp.}}|}{(X_m)_{\text{Exp.}}} \right) \quad (12)$$

Where N is the number of data points in each set, $(X_m)_{\text{Calc.}}$ denotes back-calculated data and $(X_m)_{\text{Exp.}}$ represents experimental solubilities which are taken from published papers.

Computational Results and Discussion

Tables 1 and 2 show the details of anthracene solubilities in binary and ternary solvent systems collected from our published papers. The employed binary interaction terms and the produced prediction errors (%D) by Eqs. 1 and 2 are shown in Tables 3 and 4, respectively. Careful examination of these tables reveals that both Eqs. 1 and 2 provide accurate predictions for anthracene solubility in ternary solvent mixtures. The mean and standard deviation values of %D for 30 sets studied are 1.47 ± 0.47 and 1.42 ± 0.47 , respectively for Eqs. 1 and 2. The difference between two mean values is not significant (t -test, $p > 0.05$). Average %D values are less than 2% which is comparable to the experimental uncertainty, which suggests that both models can be employed to predict solute solubility in ternary solvents based on experimental

Table 1. The Details of Anthracene Solubility in Binary Solvent Mixtures

Solvent 1	Solvent 2	$\ln X_1$	$\ln X_2$	Ref. No.
1-Butanol	2-Butoxyethanol	-7.130	-5.577	18
1-Butanol	1-Propanol	-7.130	-7.434	19
1-Butanol	2-Propanol	-7.130	-7.797	19
2-Butanol	2-Butoxyethanol	-7.444	-5.577	18
2-Butanol	1-Propanol	-7.444	-7.434	19
2-Butanol	2-Propanol	-7.444	-7.797	19
Cyclohexane	1-Butanol	-6.468	-7.130	20
Cyclohexane	2-Butanol	-6.468	-7.444	21
Cyclohexane	2-Butoxyethanol	-6.468	-5.577	22
Cyclohexane	1-Propanol	-6.468	-7.434	20
Cyclohexane	2-Propanol	-6.468	-7.797	23
Heptane	1-Butanol	-6.456	-7.130	20
Heptane	2-Butanol	-6.456	-7.444	21
Heptane	2-Butoxyethanol	-6.456	-5.577	22
Heptane ^{a)}	Cyclohexane ^{a,b)}	-6.456	-6.468	24
Heptane	1-Propanol	-6.456	-7.434	20
Heptane	2-Propanol	-6.456	-7.797	23
1-Propanol	2-Butoxyethanol	-7.434	-5.577	18
2-Propanol	2-Butoxyethanol	-7.797	-5.577	18
2,2,4-Trimethylpentane	1-Butanol	-6.836	-7.130	20
2,2,4-Trimethylpentane	2-Butanol	-6.836	-7.444	21
2,2,4-Trimethylpentane	2-Butoxyethanol	-6.836	-5.577	22
2,2,4-Trimethylpentane ^{a,b)}	Cyclohexane ^{a,b)}	-6.836	-6.468	24
2,2,4-Trimethylpentane	1-Propanol	-6.836	-7.434	20
2,2,4-Trimethylpantane	2-Propanol	-6.836	-7.797	23

^{a)} The numerical values of the modified Wilson model constants (λ terms) used in Table 4 were computed using an in-house computer program²⁵⁾ (For details, see appendix). The other λ values were taken from the references. ^{b)} The anthracene solubility data in pure cyclohexane and 2,2,4-trimethylpentane were taken from ref. 22)

solubilities in pure solvents and sub-binary mixtures. From a computational standpoint, Eq. 1 is likely to be preferred because the binary solvent–solute interaction terms can be calculated by a simple least squares analysis which is provided by scientific calculators and commercial software. Equation 2 is an alternative model and the corresponding binary solvent–solute interaction constants can be estimated by a non-linear least squares analysis which is provided by most of the generally available statistical packages. It should be noted that there is a three-dimensional map for several parameter pairs against %D that describes the anthracene solubility within an acceptable error range. Any parameter set having a %D less than about 2% are sufficient for prediction purpose.

The numerical value of $X_s^i = 0.00984^{22)}$ used in Eqs. 2 and 3 was calculated from the molar enthalpy of fusion, ΔH_s^{fus} , at the normal melting point temperature of the solute, T_{mp} :

$$\ln X_s^i = \frac{-\Delta H_s^{\text{fus}}(T_{\text{mp}} - T)}{RTT_{\text{mp}}} \quad (13)$$

Attempts to eliminate X_s^i from Eq. 2 in favour of a simplified version ($X_s^i = 1$) however proved unsuccessful with the anthracene solubility data in non-aqueous binary solvents.²⁰⁾ In this study, the values of λ_{12} and λ_{21} were calculated by assuming $X_s^i = 1$ for sub-binary mixtures and the obtained %D is compared with that of original modified Wilson model.¹³⁾ There is no significant difference between the two %D values for binary mixtures. However, the predicted values of Eq. 2 for ternary solvent mixtures is more accurate than that of the simplified form of Eq. 2 ($X_s^i = 1$).

Table 5 shows the accuracy of Eqs. 1, 7, 9 and 11 to correlate experimental solubilities in ternary solvents. The results

Table 2. The Details of Solvents and the References

No.	Solvent 1	Solvent 2	Solvent 3	δ_1	δ_2	δ_3	Ref. No.
1	1-Butanol	Heptane	Cyclohexane	11.29	7.50	8.20	26
2	1-Butanol	2,2,4-Trimethylpentane	Cyclohexane	11.29	6.86	8.20	27
3	2-Butanol	Heptane	Cyclohexane	11.13	7.50	8.20	26
4	2-Butanol	2,2,4-Trimethylpentane	Cyclohexane	11.13	6.86	8.20	27
5	2-Butoxyethanol	Cyclohexane	1-Propanol	9.88	8.20	11.99	28
6	2-Butoxyethanol	Cyclohexane	2-Propanol	9.88	8.20	11.50	28
7	2-Butoxyethanol	Cyclohexane	Heptane	9.88	8.20	7.50	29
8	2-Butoxyethanol	Cyclohexane	2,2,4-Trimethylpentane	9.88	8.20	6.86	29
9	2-Butoxyethanol	Heptane	1-Propanol	9.88	7.50	11.99	28
10	2-Butoxyethanol	Heptane	2-Propanol	9.88	7.50	11.50	28
11	2-Butoxyethanol	1-Propanol	1-Butanol	9.88	11.99	11.29	30
12	2-Butoxyethanol	1-Propanol	2-Butanol	9.88	11.99	11.13	30
13	2-Butoxyethanol	2-Propanol	1-Butanol	9.88	11.50	11.29	30
14	2-Butoxyethanol	2-Propanol	2-Butanol	9.88	11.50	11.13	30
15	1-Propanol	1-Butanol	Cyclohexane	11.99	11.29	8.20	31
16	1-Propanol	1-Butanol	Heptane	11.99	11.29	7.50	32
17	1-Propanol	1-Butanol	2,2,4-Trimethylpentane	11.99	11.29	6.86	33
18	1-Propanol	2-Butanol	Cyclohexane	11.99	11.13	8.20	31
19	1-Propanol	2-Butanol	Heptane	11.99	11.13	7.50	32
20	1-Propanol	2-Butanol	2,2,4-Trimethylpentane	11.99	11.13	6.86	33
21	1-Propanol	Heptane	Cyclohexane	11.99	7.50	8.20	26
22	1-Propanol	2,2,4-Trimethylpentane	Cyclohexane	11.99	6.86	8.20	27
23	2-Propanol	1-Butanol	Cyclohexane	11.50	11.29	7.30	31
24	2-Propanol	1-Butanol	Heptane	11.50	11.29	7.50	32
25	2-Propanol	1-Butanol	2,2,4-Trimethylpentane	11.50	11.29	6.86	33
26	2-Propanol	2-Butanol	Cyclohexane	11.50	11.13	7.30	31
27	2-Propanol	2-Butanol	Heptane	11.50	11.13	7.50	32
28	2-Propanol	2-Butanol	2,2,4-Trimethylpentane	11.50	11.13	6.86	33
29	2-Propanol	Heptane	Cyclohexane	11.50	7.50	7.30	26
30	2-Propanol	2,2,4-Trimethylpentane	Cyclohexane	11.50	6.86	7.30	27

Table 3. The %D Values of Eq. 1 for the Sets Studied and the Constants Employed in the Calculations Taken from References

No. ^{a)}	%D	W_0	W_1	W_2	W'_0	W'_1	W'_2	W''_0	W''_1	W''_2
1	1.11	0.723	-0.004	0.201	0.741	-0.345	0.223	0.175	-0.126	0
2	1.49	0.536	-0.151	0.142	0.741	-0.345	0.223	0.050	0	0
3	1.74	1.225	0.292	0	1.260	-0.206	0	0.175	-0.126	0
4	2.05	1.070	0.213	0	1.260	-0.206	0	0.050	0	0
5	1.63	1.081	-0.863	0.565	1.222	-0.572	0.255	1.121	0.040	0.256
6	1.59	1.081	-0.863	0.565	1.550	-0.790	0.726	1.589	-0.143	0.248
7	3.22	1.081	-0.863	0.565	0.928	-0.488	0.123	0.175	0.126	0
8	1.21	1.081	-0.863	0.565	0.883	-0.548	0.198	0.050	0	0
9	1.48	0.928	-0.488	0.123	1.222	-0.572	0.255	1.098	-0.106	0.324
10	1.25	0.928	-0.488	0.123	1.550	-0.790	0.726	1.491	-0.587	0.566
11	1.20	1.222	-0.572	0.255	0.800	-0.319	0.185	0.117	-0.015	0
12	1.69	1.222	-0.572	0.255	1.155	-0.609	0.267	0	0	0
13	1.42	1.550	-0.790	0.726	0.800	-0.319	0.185	0.243	0.011	0
14	1.75	1.550	-0.790	0.726	1.155	-0.609	0.267	0.097	-0.013	0
15	1.34	0.117	-0.015	0	1.121	-0.040	0.256	0.741	-0.345	0.223
16	1.36	0.117	-0.015	0	1.098	0.106	0.324	0.723	-0.004	0.201
17	0.84	0.117	-0.015	0	0.825	0.103	0.291	0.536	-0.151	0.142
18	1.56	0	0	0	1.121	-0.040	0.256	1.260	-0.206	0
19	0.94	0	0	0	1.098	0.106	0.324	1.225	0.292	0
20	0.47	0	0	0	0.825	0.103	0.291	1.070	0.213	0
21	1.66	1.098	0.106	0.324	1.121	-0.040	0.256	0.175	-0.126	0
22	1.34	0.825	0.103	0.291	1.121	-0.040	0.256	0.050	0	0
23	1.55	0.243	0.011	0	1.589	0.143	0.248	0.741	-0.345	0.223
24	1.72	0.243	0.011	0	1.491	0.587	0.566	0.723	-0.004	0.201
25	1.22	0.243	0.011	0	1.193	0.369	0.333	0.536	-0.151	0.142
26	1.43	0.097	-0.013	0	1.589	0.143	0.248	1.260	-0.206	0
27	1.89	0.097	0.013	0	1.491	0.587	0.566	1.225	0.292	0
28	1.38	0.097	-0.013	0	1.193	0.369	0.333	1.070	0.213	0
29	0.99	1.491	0.587	0.566	1.589	0.143	0.248	0.175	-0.126	0
30	1.62	1.193	0.369	0.333	1.589	0.143	0.248	0.050	0	0
Mean	1.47									
S.D.	0.47									

a) Numbers are the same as in Table 2.

Table 4. The %D Values of Eq. 2 for the Sets Studied and the Constants Employed in the Calculations Taken from References

No. ^{a)}	%D	λ_{12}	λ_{21}	λ_{13}	λ_{31}	λ_{23}	λ_{32}
1	1.55	1.291	1.476	1.010	2.377	0.541	2.244
2	2.20	0.680	2.600	1.010	2.377	1.358	0.690
3	1.34	1.849	1.109	1.345	2.157	0.541	2.244
4	1.67	1.633	1.097	1.345	2.157	1.358	0.690
5	1.45	0.100	3.970	0.536	2.020	1.300	1.600
6	0.99	0.100	3.970	0.444	2.189	1.657	1.701
7	2.00	0.100	3.970	0.332	3.160	2.244	0.541
8	1.73	0.100	3.970	3.970	2.260	0.690	1.358
9	2.38	0.332	3.160	0.536	2.020	1.410	1.580
10	1.32	0.332	3.160	0.444	2.189	0.962	2.085
11	1.23	0.536	2.020	2.669	1.694	0.857	1.293
12	0.93	0.536	2.020	0.577	1.917	1.000	1.000
13	1.22	0.444	2.189	2.669	1.694	0.989	1.169
14	1.39	0.444	2.189	0.577	1.917	1.429	0.689
15	1.67	0.857	1.293	1.600	1.300	1.010	2.377
16	1.38	0.857	1.293	1.580	1.410	1.291	1.476
17	1.66	0.857	1.293	1.500	1.100	0.680	2.600
18	1.53	1.000	1.000	1.600	1.300	1.345	2.157
19	1.36	1.000	1.000	1.580	1.410	1.849	1.109
20	0.54	1.000	1.000	1.500	1.100	1.633	1.097
21	1.12	1.580	1.410	1.600	1.300	0.541	2.244
22	2.30	1.500	1.100	1.600	1.300	1.358	0.690
23	0.87	0.989	1.169	1.701	1.657	1.010	2.377
24	1.56	0.989	1.169	2.085	0.962	1.291	1.476
25	1.58	0.989	1.169	1.797	0.956	0.680	2.600
26	0.74	1.429	0.689	1.701	1.657	1.345	2.157
27	0.78	1.429	0.689	2.085	0.962	1.849	1.109
28	1.03	1.429	0.689	1.797	0.956	1.633	1.097
29	2.05	2.085	0.962	1.701	1.657	0.541	2.244
30	0.89	1.797	0.956	1.701	1.657	1.358	0.690
Mean	1.42						
S.D.	0.47						

a) Numbers are the same as in Table 2.

of analysis of variance indicate that the models produced comparable accuracy. It is suggested that this finding is acceptable, because it has been shown that all cosolvency models are identical from a mathematical point of view and one can convert the equations to a general form using simple algebraic manipulations.

Conclusion

The combined nearly ideal binary solvent/Redlich–Kister and the modified Wilson models are extended for predicting solute solubility in ternary (and higher multi-component) solvent mixtures based on the model constants calculated from solubility data in sub-binary solvents. Average %D values less than 2% illustrates that these models have a good prediction capability and one can use the models for solubility prediction in ternary or higher multi-component solvent mixtures in order to find the optimum solvent composition for solubilization or desolubilization of a solute. It is considered that the combined nearly ideal binary solvent/Redlich–Kister equation may be preferred by experimentalists because of its simplicity and availability for calculation by common software and scientific calculators. In the previous work it has been demonstrated that its application can be expanded to prediction of solubility in different temperatures³⁴⁾ and solubility of structurally related solutes in mixed solvents.¹⁰⁾

Table 5. The Accuracy of Models to Correlate Experimental Solubility Data in Ternary Solvents

No. ^{a)}	Eq. 1	Eq. 7	Eq. 9	Eq. 11
1	0.81	0.85	0.66	0.26
2	0.29	0.34	0.27	0.27
3	1.02	0.80	0.88	0.57
4	0.51	0.50	0.47	0.35
5	0.98	1.30	0.90	0.90
6	1.11	0.73	0.99	0.56
7	1.37	0.88	1.18	0.48
8	0.90	0.89	0.72	0.45
9	1.34	1.14	1.22	0.67
10	1.75	0.76	1.53	0.54
11	1.00	0.95	1.04	0.58
12	0.59	0.57	0.59	0.42
13	0.99	0.75	1.02	0.75
14	0.82	0.71	0.73	0.61
15	0.49	0.52	0.49	0.38
16	1.22	1.20	1.22	0.91
17	0.57	0.52	0.57	0.41
18	0.54	0.50	0.54	0.35
19	0.76	0.74	0.77	0.65
20	0.39	0.35	0.39	0.33
21	0.60	0.61	0.58	0.41
22	0.98	0.75	0.54	0.55
23	0.50	0.51	0.44	0.41
24	1.36	1.12	1.23	0.83
25	0.45	0.45	0.43	0.42
26	0.64	0.55	0.64	0.50
27	0.67	0.53	0.66	0.35
28	0.59	0.43	0.47	0.41
29	1.22	0.59	1.01	0.45
30	0.69	0.74	0.55	0.49
Mean	0.84	0.71	0.76	0.51
S.D.	0.35	0.25	0.31	0.17

a) Numbers are the same as in Table 2.

Appendix

The programs written in SPSS and GWBASIC environments for computing the sub-binary interaction terms are given here. It is obvious that, these types of calculations can be done in other software like Excel or Minitab.

The program file to calculate the binary interaction terms for anthracene solubility data in heptane+cyclohexane in SPSS environment is:

```
DATA LIST FREE /F1 XM
BEGIN DATA
0.0000 0.001552
0.1542 0.001608
0.3283 0.001642
0.4930 0.001640
0.6290 0.001651
0.7238 0.001605
1.0000 0.001571
END DATA
COMPUTE X1=0.001571
COMPUTE X2=0.001652
COMPUTE F2=1-F1
COMPUTE LX=LN(XM)
COMPUTE LX1=LN(X1)
COMPUTE LX2=LN(X2)
COMPUTE YLX=XM*(F1*X1+F2*X2)
COMPUTE W0=F1*F2
COMPUTE W1=(F1*F2)/(F1+F2)
COMPUTE W2=(F1*F2)/(F1+F2)
REGRESSION VARIABLES Y W0 W1 W2 ORIGIN /DEPENDENT Y /MET=0 END
```

The corresponding program file to compute the modified Wilson model constants in GWBASIC environment is:

```
10 REM *** CALCULATION OF MODIFIED WILSON PARAMETERS ***
20 REM ***** A. Jolyban-Charamaleki *****
30 REM *****
40 COLOR 2:14:CLS:COLOR 2:0:KEY OFF: N=7:AE=1000
50 STEP1=1:STEP2=1:MIN1=1:MIN2=1
60 LOCATE 10,15:INPUT "Enter maximum value of lambda1 (-30):" MAX1
70 LOCATE 12,15:INPUT "Enter maximum value of lambda2 (-4):" MAX2
80 COLOR 2:14:CLS:DIM H(10,MAX1):DIM C(10,MAX2):F1(10):NEXT C
90 FOR Q=1 TO 9:READ F1(Q),XM(Q),X1(Q),X2(Q),F2(Q):F1(Q):NEXT Q
100:COLOR 14:LOCATE 6:2:PRINT "Optimum Values:";COLOR 2:0:LOCATE 13,12:PRINT "Current Values:"
110:COLOR 0:7:LOCATE 19:2:PRINT "Final digit optimization of lambda1 and lambda2";COLOR 2:0
120:GOSUB 350
130:COLOR 0:7:LOCATE 19,12:PRINT "Second digit optimization of lambda1 and lambda2";COLOR 2:0
140:L=1:1-AJ=1:G1B=0:G1F1=L:MK=1:G2B=0:G2F1=L
150:MIN=G1R:AJ:MAX=G1H+AJ:STP1=(MAX-MIN)/10:MINJ=G2B:MK:MAXJ=G2B+MK:STEP2=(MAXJ-MINJ)/10
160:LOCATE 20:PRINT USING "lambda1 Min=###.### Max=###.### Step=#.#.#.#.### MinJ,MAXJ,STP1,AJ
170:LOCATE 21:PRINT USING "lambda2 Min=###.### Max=###.### Step=#.#.#.#.### MinJ,MAXJ,STEP2,MK
180:NN=NN+1:LOCATE 22:20:PRINT USING "No. of repetition=#:#;NNN
190:IF STEP1 < .001 AND STEP2 < .001 THEN 220
200:GOSUB 350
210:GOTO 140
```

```

230 AJ-G1B'D1 MK-C2B'D1 MINI-G1B-AJ MAXI-G1B-AJ STEP1=0001 MINJ=G7B.
MKMAXJ=C2B-MK-STEP2=0001
230 LOCATE 20,7 PRINT USING 'lamda1 Min=### Max=### Strp=### A:### lamda2:MINI(MAXI,STEP1,AJ
240 LOCATE 21,2 PRINT USING 'lamda2 Min=### Max=### Strp=### MK:### MINI(MAXJ,STEP2),YK
250 COLOR 0,7 LOCATEF 19,12 PRINT ' Fourth digit optimisation of lamda1 and lamda2 ' 'C:COLOR 2,0
260 S0GUB 250
270 CLOSE BEEP
280 DCLOR 2,1,14 CL6-CQ,OR 2,C LOCATE 10,15:PRN1 ' The opti med. mod. mod. Wilson model is:
290 LOCATE 12,15 PRINT ' F11-',PRN1 USING '###' F21-### LOG(1/X1(1)),LOG(1/X2(1))
300 LOCATE 13,15 PRINT 'lnX1 - 1-',STRING$(17,'96:','STRING$(17,'96:','
310 LOCATE 14,15 PRINT ' F' ' 'PRINT USING '###' F2 ' 'G1B.G2B
320 END
330 REM
340 REM ----- Minimisation of the PAE values -----
350 FOR G1 =MINI TO MAXI STEP STEP1
360 FOR G2 =MINJ TO MAXJ STEP STEP2
370 F=0:SE=0:ER=0:SPFR=0:QPER=C
380 FOR I=1 TO N
390 Y=1/EXP(1-(F1(1)+LOG(X1(1)))+(F1(1)+2(1)G1)-(F2(1)+LOG(X2(1)))+(F2(1)+F1(1)G2))
400 Q=1/EXP(1-(F1(1)+LOG(X1(1)))+(F1(1)+2(1)G2)-(F2(1)+LOG(X2(1)))+(F2(1)+F1(1)G1))
410 QER=ABS(100*(G-AM)/(X1(1)+X2(1)) QPER=Q/ER DER PER=ABS(100*(Y-XM)/(Y+XM)): SPFR=SPFR+QER
420 N=N-1
430 I=SPERN=N/OPERIN
440 IF E-PAE THEN COLOR 14,4 AE-C G1B-G2 LOCATEF 8,10 PRIN' USING 'PAE =### lamda1 =###
lamda2 =### AE:G1B.G2B:COLOR 2,0
450 IF W-PAE THEN COLOR 15,4 AE-W G1B-G2 G2B-G1 LOCATE 9,10 PRINT USING 'PAE =### lamda1 =###
lamda2 =### AE:G1B.G2B:COLOR 2,0
460 LOCATE 15,10 PRINT USING 'PAE =### lamda1 =### lamda2 =###:E:G1 G2
470 NEXT G2
480 NEXT G1
490 RETURN
500 REM -----
510 DATA 0.0000, 0.001552, 0.001571, 0.001582
520 DATA 0.1542, 0.001608, 0.001571, 0.001582
530 DATA 0.3283, 0.001642, 0.001571, 0.001582
540 DATA 0.4230, 0.001640, 0.001571, 0.001582
550 DATA 0.5290, 0.001621, 0.001571, 0.001582
560 DATA 0.7236, 0.001605, 0.001571, 0.001582
570 DATA 1.0000, 0.001571, 0.001571, 0.001582

```

After calculating the model constants in binary mixtures, the solubility in ternary mixtures have been predicted by Eqs. 1 and 2. As an example, the solubility of anthracene in 1-butanol-heptane-1-cyclohexane was predicted using a SPSS program file

```

DATA LIST FREE/F1 F2 XM
96GIN DATA
4099 7496 00:462
7147 0053 00:580
2948 1822 00:145
3228 4014 00:154
7475 0707 00:086
7687 137 00:071
1842 1127 00:1625
1616 1002 00:1075
6402 197 00:122
1232 1534 00:1643
1437 8183 00:158
233 078 00:1675
2798 6005 00:1642
1297 4223 00:1605
4874 9564 00:1368
5649 2963 00:1266
1308 3221 00:1623
4480 0721 00:1364
5535 0710 00:1293
ENG DATA
COMPUT X1=0.00080104
COMPUT X2=0.00571067
COMPUT X3=0.01555948
COMPUT X01=0.00564
COMPUT L12= 1.291
COMPUT L21= 1.478
COMPUT L13= 1.01
COMPUT L31= 2.377
COMPUT L123= 541
COMPUT L132= 2.244
COMPUT W012= 723
COMPUT W112= -704
COMPUT W212= 231
COMPUT W013= 741
COMPUT W113= -345
COMPUT W213= 223
COMPUT W023= 0.175
COMPUT W123= -1.26
COMPUT W223= 0
COMPUT F3=1-F1-F2
COMPUT F1=F12+F13
COMPUT F2=F21+F23
COMPUT F123=F12+F13+F23
COMPUT F123=F12+F13+F23
COMPUT Q12=(F1 F2)
COMPUT Q13=(F1 F3)
COMPUT Q23=(F2 F3)
COMPUT LX=M/LX/M
COMPUT LX2=LN(X2)
COMPUT LX1=X1/X1
COMPUT LX2=LN(X2)
COMPUT LX3=LN(X3)
COMPUT LXMEQ1=F1*X1+F2*X2+F3*X3+F12*W012+W112*W012+W212*W012
+F13*W013+W113*W013+F123*W013
COMPUT XMEQ1=EXP(LXMEQ1)
COMPUT PDED1=ABS(100*(XMEQ1-XM)/XM)
COMPUT LXMEQ2=F1*(F1+LN(X2)/X1)+F2*(F2+LN(X3)/X2)+F3*(F3+LN(X3)/X3)
-F12*LN(X2/X3)+F13*LN(X1/X3)+F23*LN(X1/X2)
COMPUT XMEQ2=X2*EXP(LXMEQ2)
COMPUT PDED2=ABS(100*(XMEQ2-XM)/XM)
DESCRIBE VAR=PAE PDED1 PDED2 STATISTICS MEAN

```

References and Notes

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