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Comparison of various cosolvency models for calculating solute solubility in water–cosolvent mixtures

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Abstract

Previously published cosolvency models are critically evaluated in terms of their ability to mathematically correlate solute solubility in binary solvent mixtures as a function of solvent composition. Computational results show that the accuracy of the models is improved by increasing the number of curve-fit parameters. However, the curve-fit parameters of several models are limited. The combined nearly ideal binary solvent/Redlich–Kister, CNIBS/R–K, was found to be the best solution model in terms of its ability to describe the experimental solubility in mixed solvents. Also presented is an extension of the mixture response surface model. The extension was found to improve the correlational ability of the original model.

Keywords: Solubility; Cosolvency; Modeling; Combined nearly ideal binary solvent/Redlich–Kister; Excess free energy; Water–cosolvent mixtures

1. Introduction

Solubilization of a poorly water-soluble drug has an important role in the formulation of liquid pharmaceutical preparations. There are a number of methods which are used to affect the solubility. One of the most effective and readily available methods is to add a water miscible cosolvent which is called cosolvency. Today, in order to prepare a suitable drug formulation, the optimum concentration of the cosolvent, is obtained by experimental measurements. However, this method is time-consuming and costly. Cosolvency data modeling provides not only a means of screening experimental data sets for possible out-

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liers in need of redetermination, but also facilitates interpolation at other points falling between the measured data. Using this technique, the researcher can predict the optimum concentration of the cosolvent. Various solution models have been published in the pharmaceutical and chemical literature for mathematical representation of solubility data in binary solvents. The main objective of the current communication is to critically compare the accuracy of the various cosolvency models in terms of their ability to describe solute solubility as a function of cosolvent volume fraction.

2. Presentation of various cosolvency models considered

The previously published models are as follows:

Algebraic mixing rule or log-linear model, LL (Yalkowsky and Roseman, 1981)

$$\ln X_m = f_c \ln X_c + f_w \ln X_w \quad (1)$$

where X_m is the mole fraction solubility of the solute, f_c and f_w denote the initial volume fractions of cosolvent and water in the absence of the solute, and X_c and X_w refer to the solute mole fraction solubility in the neat cosolvent and water, respectively. Substitution of $1 - f_c$ for f_w in Eq. (1) gives the familiar log-linear equation:

$$\ln X_m = \ln X_w + (\ln X_c - \ln X_w)\cdot f_c \quad (2)$$

$$\ln X_m = \text{Intercept} + \text{Slope}\cdot f_c \quad (3)$$

Water–cosolvent systems encountered in the pharmaceutical industry often exhibit highly non-ideal behavior, and they do not necessarily conform to the underlying assumptions inherent in the log-linear equation (Li and Yalkowsky, 1994). In such cases the experimental drug solubility can differ significantly from the calculated value based upon the log-linear equation.

The excess free energy models, EFE (Williams and Amidon, 1984), which have additional terms to describe deviations from the log-linear equation, are:

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + A_{1-3} f_c f_w (q_s/q_c) \quad (4)$$

$$\ln X_m = f_c \ln X_c + f_w \ln X_w - A_{1-3} f_c f_w (2f_c - 1)(q_s/q_c) + 2A_{3-1} f_c^2 f_w (q_s/q_w) + C_2 f_c f_w \quad (5)$$

$$\ln X_m = f_c \ln X_c + f_w \ln X_w - A_{1-3} f_c f_w (2f_c - 1)(q_s/q_c) + 2A_{3-1} f_c^2 f_w (q_s/q_w) + 3D_{13} f_c^2 f_w^2 (q_s/q_w) + C_3 f_c f_w^2 (q_s/q_w) + C_1 f_c^2 f_w (q_s/q_c) \quad (6)$$

where A_{1-3}, A_{3-1}, C_2, D_{13}, C_3 and C_1 are solute–solvent or solvent–solvent interaction terms. The symbols q_c, q_s and q_w represent the molar volumes of cosolvent, solute and water, respectively.

These three equations can however be simplified to the following forms, respectively:

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + K_1 f_c f_w \quad (7)$$

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + K_1' f_c f_w + K_2' f_c^2 f_w \quad (8)$$

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + K_1'' f_c f_w + K_2'' f_c^2 f_w + K_3'' f_c f_w^2 + K_4'' f_c^2 f_w^2 \quad (9)$$

where $K_1 = [A_{1-3}(q_s/q_c)]$, $K_1' = [A_{1-3}(q_s/q_c) + C_2]$, $K_2' = 2[A_{3-1}(q_s/q_w) - A_{1-3}(q_s/q_c)]$, $K_1'' = [A_{1-3}(q_s/q_c)]$, $K_2'' = 2[A_{3-1}(q_s/q_w) - A_{1-3}(q_s/q_c)] + C_1(q_s/q_c)$, $K_3'' = C_3(q_s/q_w)$ and $K_4'' = [3D_{13}(q_s/q_w)]$.

Mixture response surface methods, MRS (Ochsner et al., 1985), are statistically based models which were proposed for predictive purposes. These models are as follows:

$$\ln X_m = \beta_1 f_c' + \beta_2 f_w' + \beta_3 f_c' f_w' \quad (10)$$

$$\ln X_m = \beta_1' f_c' + \beta_2' f_w' + (\beta_3'/f_c') + (\beta_4'/f_w') \quad (11)$$

$$\ln X_m = \beta_1'' f_c' + \beta_2'' f_w' + (\beta_3''/f_c') + (\beta_4''/f_w') + \beta_5'' f_c' f_w' \quad (12)$$

in which β_1 thru β_3, β_1' thru β_4', and β_1'' thru β_5'' are models' curve-fit parameters, and $f_c' = 0.96 f_c + 0.02$ and $f_w' = 0.96 f_w + 0.02$.

One can calculate the deviated solubility values, from the log-linear equation, by using the mixture response surface method. The extended equations, EMRS, are given by:

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + \alpha_1 f_c + \alpha_2 f_w + \alpha_3 f_c f_w \quad (13)$$

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + \alpha_1' f_c + \alpha_2' f_w + (\alpha_3'/f_c) + (\alpha_4'/f_w) \quad (14)$$

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + \alpha_1'' f_c + \alpha_2'' f_w + (\alpha_3''/f_c) + (\alpha_4''/f_w) + \alpha_5'' f_c f_w \quad (15)$$

where α_1 thru α_3, α_1' thru α_4', and α_1'' thru α_5'' are the model coefficients which are evaluated by regressing the term $[\ln X_m - f_c \ln X_c - f_w \ln X_w]$ versus f_c, f_w, $1/f_c$, $1/f_w$ and $f_c f_w$ using a no intercept regressional analysis. The latter two equations are applicable for $0 < f_c < 1$ and there is no need to change f_c and f_w into f_c' and f_w'.

Combined nearly ideal binary solvent/Redlich–Kister equations, CNIBS/R–K (Acree et al., 1991):

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + f_c f_w \Sigma W_i (f_c - f_w)^i \quad (16)$$

where W_i stands for the model constants, which are calculated via regressing $[\ln X_m - f_c \ln X_c - f_w \ln X_w]$ versus $f_c f_w (f_c - f_w)^i$ terms using a no intercept analysis (Jouyban-Gharamaleki and Hanaee, 1997). The CNIBS/R–K equation has been shown to accurately describe the solubility behavior of anthracene and pyrene in a large number of binary organic solvent mixtures with i ranging from $i = 0$ to $i = 3$ (Acree, 1994, 1995a,b; Zvaigzne and Acree, 1995; Powell et al., 1996, 1997). In the case of water–cosolvent mixtures one or two additional parameters may be needed (Barzegar-Jalali and Jouyban-Gharamaleki, 1996). The CNIBS/R–K method is also able to describe multiple solubility maxima, solubility at various temperatures (Jouyban-Gharamaleki and Acree, 1998) and solubility of structurally related drugs in mixed solvents (Jouyban-Gharamaleki et al., 1998).

Modified Wilson model, MW (Acree et al., 1991):

$$\ln(X_s^{id}/X_m) = 1 - \{f_c[1 - \ln(X_s^{id}/X_c)]/[f_c + f_w \Lambda_{cw}^{adj}]\} - \{f_w[1 - \ln(X_s^{id}/X_w)]/[f_c \Lambda_{wc}^{adj} + f_w]\} \quad (17)$$

or in simplified form, SMW (Jouyban-Gharamaleki, 1998):

$$-\ln X_m = 1 - \{f_c [1 + \ln X_c]/[f_c + f_w \lambda_{cw}^{adj}]\} - \{f_w[1 + \ln X_w]/[f_c \lambda_{wc}^{adj} + f_w]\} \quad (18)$$

where X_s^{id} denotes ideal mole fraction solubility of the solute, Λ_{cw}^{adj}, Λ_{wc}^{adj}, λ_{cw}^{adj} and λ_{wc}^{adj} are adjustable parameters of the models which can be evaluated via least-quares analysis. Eq. (17) has been used frequently to describe solubility in non-aqueous mixed solvents and several studies have shown that the MW model is comparable to Eq. (16) in terms of its ability to mathematically describe measured anthracene and pyrene solubilities (Acree, 1994, 1995a,b; Zvaigzne and Acree, 1995; Powell et al., 1996, 1997). For water–cosolvent systems significantly larger deviations are observed between the experimental solubilities and values back-calculated based upon Eq. (17). Jouyban-Gharamaleki (1998) recently proposed Eq. (18) for solutes dissolved in water–cosolvent mixtures. The author showed that Eq. (18) provided a reasonably accurate mathematical description of solute solubility behavior in binary aqueous–organic mixtures.

General single models, GSM (Barzegar-Jalali and Jouyban-Gharamaleki, 1997)

$$\ln X_m = L_0 + L_1 f_c + L_2 f_c^2 + L_3 f_c^3 + L_4 f_c^4 + \ldots \quad (19)$$

$$\ln X_m = \Sigma L_i (f_c)^j \quad (20)$$

where L_0 thru L_4, and L_j denote the model constants, which are determined by least-squares analysis. Although the model has been used as an empirical equation (Wu and Martin, 1983; Tarantino et al., 1994), a theoretical justification was provided by comparing the mathematical form to equations derived from more theoretically based solution models (Barzegar-Jalali and Jouyban-Gharamaleki, 1997).

3. Data and methods

The published solubility data in binary aqueous–organic solvent mixtures, containing more than ten experimental data points, were collected from the pharmaceutical literature. Water is the main solvent in biological and pharmaceutical sciences. Some of the selected cosolvents, such as dioxane, are toxic and are not used in pharmaceutical formations, but they can be used

Table 1
Details of the solubility data for select solutes dissolved in binary water–cosolvent mixtures

System no.	Cosolvent	Solute	n[a]	Reference
1	Acetonitrile	Theophylline	17	Khossravi and Connors (1992)
2	Dimethylformamide	Sulfadiazine	14	Martin et al. (1982)
3	Dioxane	Caffeine	16	Adjei et al. (1980)
4	Dioxane	*p*-Hydroxybenzoic acid	13	Wu and Martin (1983)
5	Dioxane	Paracetamol	17	Romero et al. (1996)
6	Dioxane	Phenacetin	13	Bustamante and Bustamante (1996)
7	Dioxane	Sulfadiazine	17	Bustamante et al. (1993)
8	Dioxane	Sulfadimidine	19	Bustamante et al. (1993)
9	Dioxane	Sulfamethizole	19	Reillo et al. (1995b)
10	Dioxane	Sulfamethoxazole	15	Bustamante et al. (1993)
11	Dioxane	Sulfapyridine	17	Reillo et al. (1995a)
12	Dioxane	Sulfamethoxypyridazine	19	Bustamante et al. (1993)
13	Dioxane	Sulfanilamide	16	Reillo et al. (1993)
14	Dioxane	Sulfisomidine	21	Martin et al. (1985)
15	Dioxane	Theobromine	11	Martin et al. (1981)
16	Dioxane	Theophylline	21	Martin et al. (1980)
17	Ethanol	Paracetamol	13	Romero et al. (1996)
18	Ethanol	Sulfamethazine	11	Bustamante et al. (1994)
19	Ethanol	Sulfanilamide	12	Bustamante et al. (1994)
20	Ethylene glycol	Naphthalene	18	Khossravi and Connors (1992)
21	Ethylene glycol	Theophylline	17	Khossravi and Connors (1992)
22	Methanol	Theophylline	13	Khossravi and Connors (1992)
23	Propylene glycol	Butyl *p*-aminobenzoate	11	Rubino and Obeng (1991)
24	Propylene glycol	Butyl *p*-hydroxybenzoate	11	Rubino and Obeng (1991)
25	Propylene glycol	Ethyl *p*-aminobenzoate	11	Rubino and Obeng (1991)
26	Propylene glycol	Ethyl *p*-hydroxybenzoate	11	Rubino and Obeng (1991)
27	Propylene glycol	Methyl *p*-aminobenzoate	11	Rubino and Obeng (1991)
28	Propylene glycol	Methyl *p*-hydroxybenzoate	11	Rubino and Obeng (1991)
29	Propylene glycol	Propyl *p*-aminobenzoate	11	Rubino and Obeng (1991)
30	Propylene glycol	Propyl *p*-hydroxybenzoate	11	Rubino and Obeng (1991)

[a] n is the number of data points in each data set.

Table 2
Mean and (±) standard deviation of % deviation values for the models with respect to the total number of constant terms

Constants[a]	LL	EFE	MRS	EMRS	CNIBS/R-K	SMW	MW	GSM
2	49.66 ± 20.53	–	–	–	–	–	–	–
3	–	22.25 ± 14.54	15.89 ± 9.65	–	22.25 ± 14.53	—	—	15.89 ± 9.65
4	–	10.72 ± 7.64	18.71 ± 8.92	–	10.72 ± 7.63	7.77 ± 5.37	28.41 ± 19.44	9.06 ± 5.62
5	–	–	6.33 ± 3.97	9.83 ± 6.63	5.92 ± 4.16	—	—	8.53 ± 4.96
6	–	5.92 ± 4.16	–	10.19 ± 7.16	4.23 ± 2.69	—	—	5.22 ± 2.83
7	–	–	–	4.35 ± 2.69	3.06 ± 1.74	—	—	5.06 ± 2.65

[a] Defined as the sum of the number of curve-fit coefficients. The number was increased by two if the equation required a prior knowledge of the solute solubilities in the two neat solvents.

as model cosolvents. The specific solutes and solvent systems selected, along with the literature references, are listed in Table 1.

To critically assess the accuracy of the various models to mathematically represent solubility behavior in water–cosolvent mixtures, the experimental data are fitted to the models and the models' curve-fit coefficients are calculated. In the case of Eqs. (17) and (18) the coefficients are taken from previous work (Jouyban-Gharamaleki, 1998). Differences between the experimental solubilities and back-calculated values, expressed as percentages:

$$\%\text{Dev.} = (100/N)\,\Sigma\left|X_m^{cal} - X_m^{exp}\right|/X_m^{exp} \qquad (21)$$

are taken as the measure of the model's descriptive ability (Barzegar-Jalali and Jouyban-Gharamaleki, 1996). The summation extends over the number of experimental data points in each set, N. The mean of %Dev. is calculated as a comparison criterion.

Analysis of variance and Duncan's multiple range test are used to assess the statistical significance between means of %Dev. for the various models considered. The ability of the models to mathematically describe the experimental data are compared taking into consideration both the number of curve-fit parameters and number of experimental data points that must be determined in order to use each model. Equal number of *total constant* and maximum number of *total constant* comparisons were made. To us this seems to be a fair method to compare the different mathematical representations in that several models use the calculated coefficients to describe the actual mole fraction solubilities, whereas other models have a much simpler task of describing only the deviations from an idealized volume fraction average of logarithm mole fraction solubilities in the two pure solvents. The latter models do require as input values the measured solubilities in the two pure solvents, and this then increases by two the total number of constants that must be evaluated from the available experimental data. All calculations were performed by the statistical package for social sciences (SPSS) in a Windows environment.

4. Results and discussion

Table 2 shows the mean and standard deviation values of %Dev. for various models with respect to the total number of constants contained in each model. Careful examination of the numerical entries reveals that the accuracy of the mathematical representation improves as more curve-fit parameters are introduced. There are two exceptions to this observation, i.e., MRS and EMRS models with four curve-fit parameters. The reason for this exception is that the mathematical form of both models does drastically change with the introduction of the fourth curve-fit coefficient. The term $\beta_3 f_c' f_w'$ is dropped from the three-parameter

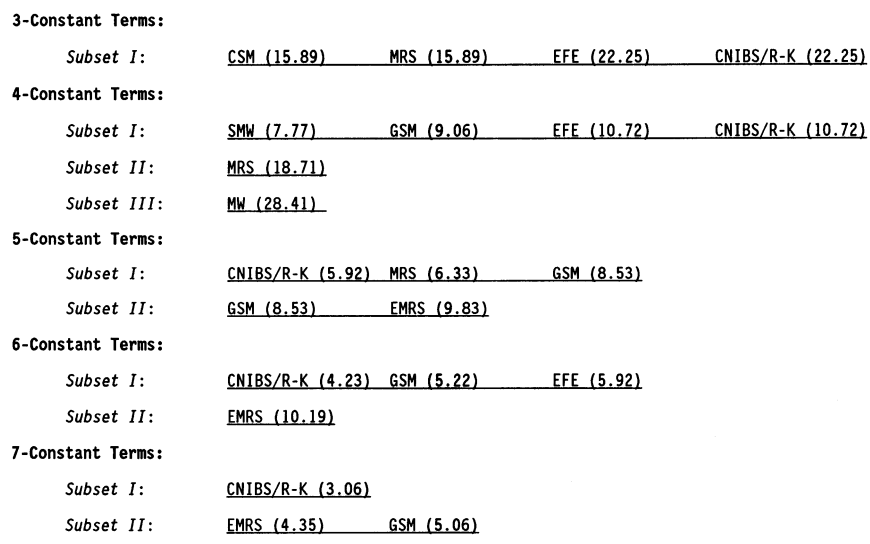

Fig. 1. Duncan's multiple range test for the various cosolvency models with respect to the number of constant terms.

representation of the MRS model and is replaced by the two additional terms $(\beta'_3/f_c') + (\beta'_4/f_w')$. Similarly, in the EMRS model $\alpha_3 f_c f_w$ is replaced by $(\alpha'_3/f_c) + (\alpha'_4/f_w)$. The other solution models simply introduce the additional term to the mathematical form already present. For these latter models the additional term must reduce the deviations between the observed and back-calculated solute solubilities. If not, the additional curve-fit coefficient will equal zero (or nearly zero) as calculated by the least-squares regressional analysis.

Several models such as LL, EFE and MRS have only two, three, four or five constants, whereas equations derived from other models, such as the CNIBS/R–K and GSM, can be extended indefinitely in order to provide a more accurate mathematical representation. However, it is obvious from this that more experimental determinations will be needed when the curve-fit parameters are increased. The most accurate mathematical representations for three, four, five or more than five constant expressions are achieved by GSM, SMW and CNIBS/R–K models. Fig. 1 depicts the results of analysis of variance and Duncan's multiple range test for the models with respect to the number of constants contained in the equation. It is suggested that the difference between the descriptive ability of the models as underlined are not significant.

The %Dev. for select models using the maximum number of constants are listed in Table 3. A second comparison is performed for the models without considering the number of constants. From this standpoint CNIBS/R–K is the most accurate model, which is followed by EMRS, GSM, EFE, MRS and SMW. The results of Duncan's analysis is shown in Fig. 2. Two of the seven-constant models, i.e. CNIBS/R–K and EMRS, provide the most accurate correlation and in this case the accuracy differences between these models and the other listed models are significant ($p < 0.01$).

The ability of the CNIBS/R–K to accurately describe solute solubility in binary organic solvent mixtures (Acree et al., 1991; Acree, 1994, 1995a,b; Zvaigzne and Acree, 1995; Powell et al., 1996, 1997) and aqueous–organic solvent systems (Acree, 1996; Barzegar-Jalali and Jouyban-Gharamaleki, 1996) is shown. This particular solution model has a theoretical basis (Acree, 1992) and can be applied to describe other situations such as solubility in ternary mixed solvents (Jouyban-Gharamaleki and Acree, 1998) or solubility of structurally related drugs in binary solvents (Jouyban-Gharamaleki et al., 1998). In comparison the

Table 3
Best fit % deviation of the different models for the 30 data sets studied

SN[a]	EFE	MRS	EMRS	CNIBS/R–K	SMW[b]	GSM
1	3.07	11.86	13.35	2.88	9.93	4.59
2	2.19	8.25	9.00	2.00	11.36	2.22
3	3.73	1.74	1.94	2.19	3.76	3.60
4	5.02	2.89	3.30	1.83	4.52	5.08
5	7.69	5.50	4.12	3.61	7.21	5.65
6	3.67	5.47	2.87	2.18	2.78	3.23
7	11.32	10.03	8.62	7.27	11.83	8.47
8	14.57	3.55	5.02	7.33	9.51	9.74
9	16.97	13.77	6.30	5.51	10.42	12.77
10	9.74	8.84	7.33	5.38	5.79	7.75
11	10.16	6.88	3.64	3.48	6.04	6.65
12	8.70	8.31	5.87	4.86	5.82	7.21
13	11.28	3.59	3.61	4.22	7.54	7.92
14	12.53	4.99	4.75	3.80	11.09	7.49
15	1.81	2.28	0.62	0.80	1.90	1.87
16	5.90	1.96	2.13	2.89	4.75	4.48
17	6.57	3.61	3.60	3.50	5.86	6.68
18	4.87	2.96	2.45	3.57	7.52	4.51
19	3.04	3.87	3.12	2.98	2.67	3.03
20	1.44	1.55	1.85	0.67	1.96	1.51
21	1.90	2.41	2.17	1.59	2.89	1.88
22	1.39	3.26	1.68	0.83	5.81	2.21
23	4.65	5.85	2.98	1.09	9.75	4.84
24	4.04	18.47	4.68	2.72	29.38	6.25
25	3.03	7.23	3.13	1.63	5.36	3.01
26	5.08	9.35	7.51	4.10	11.31	5.19
27	1.99	5.05	2.01	1.42	3.29	2.00
28	3.21	9.26	3.97	1.49	11.84	3.32
29	3.65	6.80	3.28	3.32	5.98	3.70
30	4.44	10.26	5.53	2.60	15.13	4.83
Mean	5.92	6.33	4.35	3.06	7.77	5.06

[a] SN is the system number.
[b] % deviation values are taken from an earlier paper (Jouyban-Gharamaleki, 1998).

MRS and EMRS models are strictly empirical in nature. The CNIBS/R–K and EFE equations do have a common theoretical basis, and equations based upon each model can be readily transformed into the GSM Eq. (20) (Barzegar-Jalali and Jouyban-Gharamaleki, 1997). The CNIBS/R–K model, because of the suitable arrangement of the independent variables, produces a slightly more accurate mathematical representation of solute solubilities for the 30 systems considered in this study. Published papers (Jouyban-Gharamaleki and Acree, 1998; Jouyban-Gharamaleki et al., 1998) have compared the predictive ability of the CNIBS/R–K model to various modified forms of the Hildebrand and extended Hildebrand equations. The above analyses suggest that CNIBS/R–K as being the best cosolvency model.

Fig. 2. Duncan's analysis for the various cosolvency models without considering the number of constant terms.

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