

EVALUATING PREDICTION ABILITY OF DIFFERENT MODELS USED FOR SOLUTE SOLUBILITY CALCULATION IN BINARY SOLVENT SYSTEMS

ABOLGHASEM JOUYBAN-GHARAMALEKI*, HA-KIM CHAN* and MOHAMMAD BARZEGAR-JALALI**

*Faculty of Pharmacy, The University of Sydney, Sydney NSW 2006, Australia

** Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran.

ABSTRACT

The available theoretical and empirical models for expression a solute solubility in a binary solvent system as a function of the solvent concentration have been compared by the accuracy and predictability points of view. In order to evaluate the accuracy of the equations with different number of curve fitting parameters, 3 to 7 parameter models from the considered methods were employed using whole data points in each set. In addition, a minimum number of 3 and/or 5 data point was used to calculate the model parameters from which the whole data points in each set was predicted. Using the whole data in a set, it became evident that no single model was superior in all aspects of accuracy. However, one of the models in which the number of data expressed as percentage of all data points in all sets was adhered best whereas another model was the best when the percent overall average error for all the set was used as a measure of accuracy. When a minimum number of data in a set was employed to estimate model constants for evaluating the predictability, it became apparent that those produced accurate results when the whole data points did not yield satisfactory predictions and other models were superior in this respect.

Key words : Solubility; Binary solvent system; Cosolvency; Comparison of models

INTRODUCTION

The solubility of a solute in a solvent mixture (i.e. cosolvency) has a wide applications in different industries including pharmaceutical industry. One of the main use of the solvent mixture for influencing the solubility is in the formulation of the liquid dosage forms. The benefit of cosolvency modelling is to predict and calculate the solvent composition for an acceptable drug formulation.

Several cosolvency models are available. Some of them such as excess free energy model, EFE (1), the combined nearly ideal binary solvent/Redlich-Kister equations, CNIBS/R-K (2), a general single model, GSM, derived from EFE and CNIBS/R-K equations (3) are theoretical and others like extended Hildebrand approach, EHA (4), mixture response-surface methodology, MR-S, (5), linear double log-log models, LDL-L (6), double log-log, DL-L, double log-exponential, DL-E, modified EFE, M-EFE and modified CNIBS/R-K, M-CNIBS/R-K (7) are semiempirical or empirical in nature.

The purpose of this paper is to compare the accuracy and predictability of the models which express the relationship between the solute

solubility and the concentrations of the solvents in the mixture using 3 to 7 parameter models. A similar comprehensive study has not been reported. The criteria of comparison were percent average error, %A.E., and percent overall average error (7) produced by a model in all systems as well as a number of sets adhered best to a model expressed as percent of best adherence, %B.A., by model parameters obtained either from the whole data points or a minimum number of data in a set.

THEORETICAL TREATMENT

The theoretical EFE methods were two, three and four suffix equations expressed by the equations 1-3.

$$\log X_m = f_a \log X_a + f_b \log X_b + A_{1,3} f_a f_b (q_2/q_1) \quad 1$$

$$\log X_m = f_a \log X_a + f_b \log X_b - A_{1,3} f_a f_b (2f_a - 1)(q_2/q_1) + 2A_{3,1} f_a^2 f_b (q_2/q_3) + C_2 f_a f_b \quad 2$$

$$\log X_m = f_a \log X_a + f_b \log X_b - A_{1,3} f_a f_b (2f_a - 1)(q_2/q_1) + 2A_{3,1} f_a^2 f_b (q_2/q_3) + 3D_{13} f_a f_b^2 (q_2/q_3) + C_3 f_a f_b^2 (q_2/q_3) + C_1 f_a^2 f_b (q_2/q_1) \quad 3$$

where X_m is the solute solubility in the solvent mixture, f_a and f_b are the volume fractions of the solvents a and b in the mixture, X_a and X_b denote the solubility in the neat solvents a and b, $A_{1,3}$ and $A_{3,1}$ represent the vapour pressure

of the mixed solvent, q_1 , q_2 and q_3 are the molar volumes of the solvent a, the solute and solvent b, and C_1 - C_3 and D_{13} are the interaction terms between mixed solvent and the solute.

These equations could be simplified to the following forms, respectively:

$$\log X_m = f_a \log X_a + f_b \log X_b + K_1 f_a f_b \quad 4$$

$$\log X_m = f_a \log X_a + f_b \log X_b + K_1 f_a f_b + K_2 f_a^2 f_b \quad 5$$

$$\log X_m = f_a \log X_a + f_b \log X_b + K_1 f_a f_b + K_2 f_a^2 f_b + K_3 f_a f_b^2 + K_4 f_a^2 f_b^2 \quad 6$$

where $K_1 = [A_{1,3}(q_2/q_1)]$, $K_1 = [A_{1,3}(q_2/q_1) + C_2]$, $K_2 = 2[A_{3,1}(q_2/q_3) - A_{1,3}(q_2/q_1)]$, $K_1 = [A_{1,3}(q_2/q_1)]$, $K_2 = 2[A_{3,1}(q_2/q_3) - A_{1,3}(q_2/q_1)] + C_1(q_2/q_1)$, $K_3 = C_3(q_2/q_3)$ and $K_4 = [3D_{13}(q_2/q_3)]$.

The second theoretical model, i.e., CNIBS/R-K, in general form is:

$$\log X_m = f_a \log X_a + f_b \log X_b + f_a f_b \sum S_i (f_a - f_b)^i \quad 7$$

in which S_i is the model constant and i could be equal to 0-3 (2,8-9). Depending on the values of i four equations could be obtained from Eq. 7.

The general single model, GSM, which obtained from the two theoretical models EFE and CNIBS/R-K, is represented as:

$$\log X_m = \sum B_j (f_a)^j \quad 8$$

in which B_j is the model constant and $j=1-5$.

MR-S models are as follows:

$$\log X_m = W_1 f_a + W_2 f_b + W_3 f_a f_b \quad 9$$

$$\log X_m = W_1 f_a + W_2 f_b + W_3 (1/f_a) + W_4 (1/f_b) \quad 10$$

$$\log X_m = W_1 f_a + W_2 f_b + W_3 (1/f_a) + W_4 (1/f_b) + W_5 f_a f_b \quad 11$$

in which W_1 - W_3 , $W_1 - W_4$ and $W_1 - W_5$ are the models parameters and f_a and f_b are given by $f_a = 0.96 f_a + 0.02$ and $f_b = 0.96 f_b + 0.02$ (5).

The LDL-L method was expressed by Eqs. 12 and 13:

$$\log[\log(X_m/X_b)] = \text{Intercept} + \text{slope} \log(f_a/f_b) \quad \text{when } 0 < f_a < 0.5 \quad 12$$

$$\log[\log(X_a/X_m)] = \text{Intercept} + \text{slope} \log(f_b/0.5) \quad \text{when } 0 < f_b < 0.5 \quad 13$$

This method is used to linearize the solubility data, which has not been linearized by the log-linear model (6). The LDL-L method are applicable only to those cases where plot of solubility vs the solubility parameter of the solvent, δ_1 , lacks a maximum.

The DL-L and DL-E methods are given by Eqs. 14 and 15:

$$\log(-\log X_m) = \sum B_k (\log f_a)^k \quad (k = -3, -2, -1, 0, 1, 2, 3) \quad 14$$

$$\log(-\log X_m) = \sum A_q 10^{(q f_a)} \quad (q = -5, -3, -1, 0, 1, 3, 5) \quad 15$$

B_k and A_q are constants of the models.

The M-EFE and M-CNIBS/R-K are presented

by Eqs. 16-18 and Eq. 19, respectively:

$$\log X_m = M_1 f_a + M_2 f_b + M_3 f_a f_b \quad 16$$

$$\log X_m = M_1 f_a + M_2 f_b + M_3 f_a f_b + M_4 f_a^2 f_b \quad 17$$

$$\log X_m = M_1 f_a + M_2 f_b + M_3 f_a f_b + M_4 f_a^2 f_b + M_5 f_a f_b^2 + M_6 f_a^2 f_b^2 \quad 18$$

$$\log X_m = S_1 f_a + S_2 f_b + f_a f_b \sum S_i (f_a - f_b)^i \quad 19$$

where M_1 - M_3 , M_1 - M_4 , M_1 - M_6 , S_1 , S_2 and S_i are the models constants. The reasons for employing M_1 - M_3 , M_1 - M_4 , M_1 - M_6 , S_1 - S_2 instead of the original constants ($\log X_a$ and $\log X_b$) is provided in a previous paper (7).

COMPUTATIONAL RESULTS AND DISCUSSION

All the models with 3-7 parameters, except LDL-L method, have been applied to 88 data sets by references provided in Table 1. The percent average error, %A.E. for each model with the specified number of parameters was calculated by:

%A.E. = $1/Z \sum |100 [(X_m)_p - (X_m)_e] / (X_m)_p|$ where Z equals the number of data, N , in each system for models 1 and 3-7 and $(N-2)$ for the model 2, $(X_m)_p$ and $(X_m)_e$ denote the predicted and experimental values of X_m at fa. The percentage overall average error (% O.A.E.) was calculated by:

$$\% \text{ O.A.E.} = (\sum \% \text{ A.E.}) / 88$$

The corresponding %O.A.E. is shown in Fig. 1. As it is shown in the Figure 1, in each model with increase in the number of parameters there is an increase in the accuracy. Also, as the number of parameters increases, the difference in accuracy among the models generally becomes less apparent. Overall, M-CNIBS/R-K model, because of the least %O.A.E. values was found to be the best model. However, in a recent report (10) it is shown that the accuracy of the original CNIBS/R-K model is considerably improved, and becomes comparable to that of M-CNIBS/R-K model when the variables of this model is used in a new arrangement.

In term of %B.A., DL-L model is the best among all models and the maximum %B.A. occurs with $n=6$. Also, the CNIBS/R-K model exhibits a minimum value with $n=4$ and the pattern for other models does not obey a general trend (Fig. 2). The GSM derived from the theoretical models provided theoretical justifications for other semiempirical or empirical models (3), and was the least accurate model from both %O.A.E. and %B.A. points of view

Table 1 Systems used for comparison of the models

No.	Solute in solvent a + solvent b	Reference
1	Anthracene in benzene + cyclohexane	15
2	Anthracene in benzene + n-heptane	15
3	Anthracene in benzene + isooctane	15
4	Anthracene in cyclooctane + benzene	15
5	Anthracene in cyclooctane + cyclohexane	15
6	Anthracene in dibutyl ether + n-hexadecane	16
7	Anthracene in dibutyl ether + squalane	16
8	Anthracene in n-heptane + cyclohexane	15
9	Anthracene in n-hexane + benzene	15
10	Anthracene in n-hexane + cyclohexane	15
11	Anthracene in isooctane + cyclohexane	15
12	Anthracene in n-octane + cyclohexane	15
13	Benzil in carbon tetrachloride +isooctane	17
14	Benzil in cyclohexane + cyclooctane	17
15	Benzil in cyclohexane + n-heptane	17
16	Benzil in cyclohexane + isooctane	17
17	Benzil in cyclohexane + n-octane	17
18	Benzil in cyclooctane + carbon tetrachloride	17
19	Benzil in n-octane + carbon tetrachloride	17
20	Benzoic acid in cyclohexane + carbontetrachloride	18
21	p-Benzoquinone in cyclohexane +isooctane	19
22	p-Benzoquinone in cyclooctane +cyclohexane	19
23	p-Benzoquinone in n-dodecane + n-heptane	19
24	p-Benzoquinone in n-heptane + carbontetrachloride	19
25	p-Benzoquinone in n-heptane + cyclohexane	19
26	p-Benzoquinone in n-octane + carbontetrachloride	19
27	Butyl-p-aminobenzoate in propyleneglycol+water	20
28	Butyl-p-hydroxybenzoate in propyleneglycol+water	20
29	Caffeine in dioxane + water	21
30	Carbazole in dibutyl ether + chlorocyclohexane	22
31	Carbazole in dibutyl ether + 1-chlorohexane	23
32	Carbazole in dibutyl ether + 1-chlorooctane	22
33	Carbazole in dibutyl ether + 1-chlorotetradecane	22
34	Carbazole in dibutyl ether + cyclohexane	24
35	Carbazole in dibutyl ether + cyclooctane	24
36	Carbazole in dibutyl ether + n-heptane	24
37	Carbazole in dibutyl ether + n-hexadecane	16
38	Carbazole in dibutyl ether + n-hexane	24
39	Carbazole in dibutyl ether + isooctane	24
40	Carbazole in dibutyl ether + methyl-cyclohexane	24
41	Carbazole in dibutyl ether + n-octane	24
42	Carbazole in dibutyl ether + squalane	16
43	Carbazole in tetrahydropyran + t-butylcyclohexane	9
44	Carbazole in tetrahydropyran + cyclohexane	9
45	Carbazole in tetrahydropyran + n-heptane	9
46	Carbazole in tetrahydropyran + n-hexadecane	9
47	Carbazole in tetrahydropyran + n-hexane	9
48	Carbazole in tetrahydropyran + isooctane	9
49	Ethyl-p-aminobenzoate in propyleneglycol+water	20
50	Ethyl-p-hydroxybenzoate in propyleneglycol+water	20
51	p-Hydroxybenzoic acid in dioxane+water	25
52	Iodine in n-heptane + benzene	26
53	Iodine in n-hexadecane + n-heptane	27
54	Iodine in n-hexadecane + isooctane	27
55	Iodine in n-hexane + benzene	26
56	Iodine in isooctane + benzene	26
57	Methyl-p-aminobenzoate in propyleneglycol+water	20

58	Methyl-p-hydroxybenzoate in propyleneglycol+water	20
59	Naphthalene in acetonitrile + water	28
60	Naphthalene in ethylene glycol +water	28
61	Naphthalene in methanol + water	28
62	Paracetamol in ethyl acetate + methanol	29
63	Paracetamol in methanol + water	29
64	Propyl-p-aminobenzoate in propyleneglycol+water	20
65	Propyl-p-hydroxybenzoate in propyleneglycol+water	20
66	Sulphadiazine in dimethylformamide+water	30
67	Sulphamethazine in ethanol + water	31
68	Sulphamethazine in ethyl acetate+ethanol	31
69	Sulphanilamide in dioxane + water	32
70	Sulphanilamide in ethanol + water	31
71	Sulphanilamide in ethyl acetate+ethanol	31
72	Sulphisomidine in dioxane + water	32
73	Sulphamethoxypyridazine in ethanol+water, 20°C	33
74	Sulphamethoxypyridazine in ethanol+water, 25°C	33
75	Sulphamethoxypyridazine in ethanol+water, 30°C	33
76	Sulphamethoxypyridazine in ethanol+water, 35°C	33
77	Sulphamethoxypyridazine in ethanol+water, 40°C	33
78	Testosterone in chloroform + cyclohexane	4
79	Theobromine in dioxane + water	34
80	Theophylline in acetonitrile + water	29
81	Theophylline in dioxane + water	35
82	Theophylline in ethylene glycol+water	29
83	Theophylline in methanol + water	29
84	Tolbutamide in hexane + ethanol	36
85	p-Tolylacetic acid in cyclohexane+n-hexane	37
86	p-Tolylacetic acid in n-heptane+cyclohexane	37
87	p-Tolylacetic acid in isooctane+cyclohexane	37
88	p-Tolylacetic acid in n-octane +cyclohexane	37

due to the different arrangement of the variables. In the pharmaceutical industry for economical and practical considerations, a minimum number of solubility experiments are required. Therefore, a minimum number of data points which was equal to the number of constants in each model was used to calculate the model constants in order to verify the predictability of the models by using all possible combinations of the data points in 88 systems. It was found that at least in nearly 25 % of cases the %A.E. was greater than the acceptable 30% level (11-12) which was not satisfactory from practical point of view and indicated that the models were not reliable for this purpose of accuracy. However, the LDL-L model was proved to be the most accurate method for this purpose. It should be borne in mind that this model was applicable to cases where a plot of solubility vs solubility parameter of the solvent, δ_1 , do not show a maximum. This model together with other models outlined above were applied to systems No. 7, 27, 28, 34-41, 43-50, 57, 58, 64 and 65 cited in a previous paper (7) and a minimum number of 6 data points were used for calculation of models

constants in order to predict solubilities for whole data points in each systems. Percentage of all possible six data point combinations which produced %A.E. greater than 30% for LDL-L, NIBS/R-K, DL-E, M-EFE, M-CNIBS/R-K, DL-L and MR-S were 4.38, 4.55, 12.48, 13.17, 13.44, 20.20, 23.51 and 32.72, respectively.

Because of the possible toxicity of pharmaceutical cosolvents, their concentrations in the liquid dosage forms should be kept as low as possible and should not exceed 50% V/V (13). In addition, in the preformulation stage of a new drug due to the scarcity of the drug, a minimum number of solubility experiments should be carried-out in order to predict the solubility at other concentrations of the cosolvent. Thus, a minimum number of three data points were used to verify the predictability of the models up to 0.5 volume fraction of cosolvent for the 23 sets. Percent of all possible three data point combinations which produced %A.E. greater than 30% for DL-L, DL-E, LDL-L, CNIBS/R-K, M-CNIBS/R-K, M-EFE, EFE and MR-S models were 0.00, 1.83, 2.74, 4.35, 4.35, 4.35, 25.89 and 25.89, respectively.

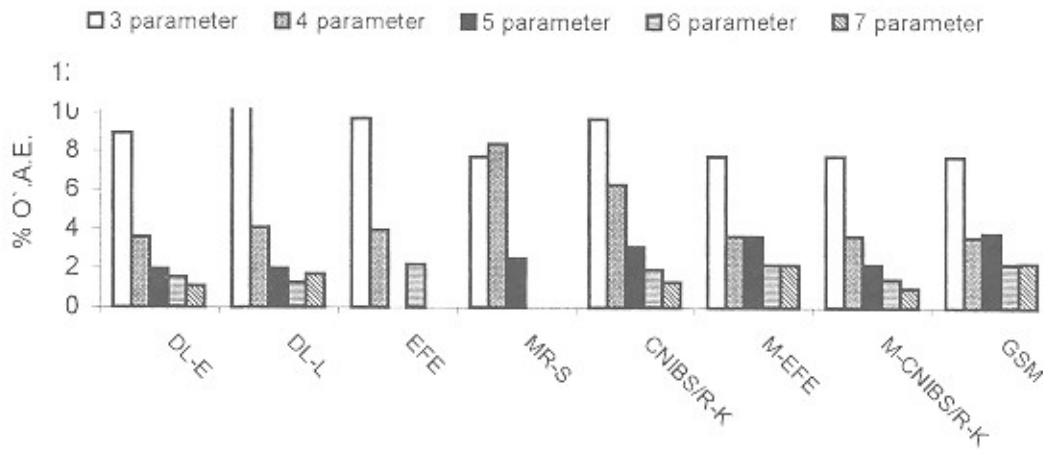


Figure 1 Comparison of predictability of various equations on the basis of percent overall average error, %O.A.E., with different number of parameters.

Some models i.e., EFE and M-EFE did not possess 5 and 7 parameter equations and MR-S lacked 6 and 7 parameter equations.

For 3-6 parameter DL-E models q was equal to $-1, 0, 1; -3, -1, 0, 1; -3, -1, 0, 1, 3$ and $-5, -3, -1, 0, 1, 3$, respectively.

For 3-6 parameter DL-L models q was equal to $-1, 0, 1; -2, -1, 0, 1; -2, -1, 0, 1, 2$ and $-3, -2, -1, 0, 1, 2$, respectively.

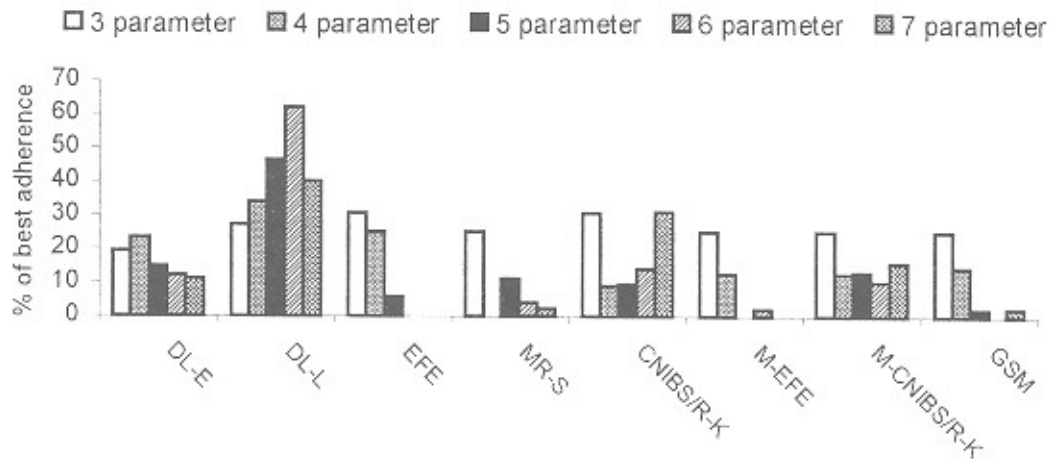


Figure 2 Number of data (as percentage of sum of all data points in 88 sets) adhered best to models with different number of parameters

Some models i.e., EFE and M-EFE did not possess 5 and 7 parameter equations and MR-S lacked 6 and 7 parameter equations.

For 3-6 parameter DL-E models q was equal to $-1, 0, 1; -3, -1, 0, 1; -3, -1, 0, 1, 3$ and $-5, -3, -1, 0, 1, 3$, respectively.

For 3-6 parameter DL-L models q was equal to $-1, 0, 1; -2, -1, 0, 1; -2, -1, 0, 1, 2$ and $-3, -2, -1, 0, 1, 2$, respectively.

CONCLUSIONS

The present investigation indicated that no single model is superior in all aspects of accuracy and prediction requirements. For example, employing whole data points in a set, M-CNIBS/R-K was the most accurate model in terms of %O.A.E. whereas DL-L model was superior to the other models from %B.A. point of view. Also, DL-L and LDL-L methods were the most accurate models when a minimum

number of data points in a set was used. These findings were in parallel with previous results (14) in which only three cosolvency models were compared by a limited number of experimental sets.

ACKNOWLEDGMENTS

The authors would like to thank the University of Sydney and the Tabriz University of Medical Sciences for their financial supports.

REFERENCES

- Williams, N.A. and Amidon, G.L. (1984) Excess free energy approach to the estimation of solubility in mixed solvent systems: I. Theory. *J. Pharm. Sci.* 73: 9-13.
- Acree, W.E., Jr. (1992) Mathematical representation of thermodynamic properties. Part 2. Derivation of the combined nearly ideal binary solvent (NIBS)/Redlich-Kister mathematical representation from a two-body and three-body interactional mixing model. *Thermochimica Acta* 198: 71-79.
- Barzegar-Jalali, M. and Jouyban-Gharamaleki, A. (1997) A general single model from theoretical cosolvency models. *Int. J. Pharm.* 152: 247-250.
- Martin, A., Wu, P.L., Adjei, A., Mehdizadeh, M., James, K.C. and Metzler, C. (1982) Extended Hildebrand solubility approach. Testosterone and testosterone propionate in binary solvents. *J. Pharm. Sci.* 71: 1334-1340.
- Ochsner, A.B., Belloto, R.J., Jr. and Sokoloski, T.D. (1985) Prediction of xanthine solubilities using statistical techniques. *J. Pharm. Sci.* 74: 132-135.
- Barzegar-Jalali, M. and Hanaee, J. (1994) Model for solubility estimation in mixed solvent systems. *Int. J. Pharm.* 109: 291-295.
- Barzegar-Jalali, M. and Jouyban-Gharamaleki, A. (1996) Models for calculating solubility in binary solvent systems. *Int. J. Pharm.* 140: 237-246.
- Acree, W.E., Jr. and Zvaigzne, A.I. (1991) Thermodynamic properties of nonelectrolyte solution. Part 4. Estimation and mathematical representation of solute activity coefficients and solubilities in binary solvents using the NIBS and modified Wilson equations. *Thermochimica Acta* 178: 151-167.
- Acree, W.E., Jr., McCargar, J.W., Zvaigzne, A.I. and Teng, I.L. (1991) Mathematical representation of thermodynamic properties. Carbazole solubilities in binary alkane+dibutyl ether and alkane + tetrahydropyran solvent mixtures. *Phys. Chem. Liq.* 23: 27-35.
- Jouyban-Gharamaleki, A. and Hanaee, J. (1997) A novel method for improvement of predictability of the CNIBS/R-K equation. *Int. J. Pharm.* 154: 245-247.
- Beerbower, A., Wu, P.L. and Martin, A. (1984) Expanded solubility approach I: Naphthalene and benzoic acid in individual solvents. *J. Pharm. Sci.* 73: 179-188.
- Reillo, A., Cordoba, M., Escalera, B., Selles, E. and Cordoba, M.Jr. (1995) Prediction of sulfamethiazole solubility in dioxane-water mixtures. *Pharmazie* 50: 472-475.
- Boylan, J.C., Fites, A.L. and Nail, S.L. (1996) Parenteral products. In: Banker, G.S. and Rhodes, C.T. (eds) *Modern Pharmaceutics*, Marcel Dekker, New York, p. 453.
- Barzegar-Jalali, M., Jouyban-Gharamaleki, A., Hanaee, J. and Chokhachzadeh-Moghaddam, M.H. (1996) Comparison of double log-log, mixture response-surface and combined NIBS/Redlich-Kister solubility models. *Int. J. Pharm.* 144: 127-130.
- Acree, W.E., Jr. and Rytting, J.H. (1983) Solubility in binary solvent systems: III. Predictive expressions based on molecular surface area. *J. Pharm. Sci.*, 72: 292-296.
- McCargar, J.W. and Acree, W.E., Jr. (1987) Thermochemical investigations of associated solutions: 4. Calculation of carbazole-dibutyl ether association constants from measured solubility in binary solvent mixtures. *J. Pharm. Sci.*, 76: 572-574.

17. Acree, W.E., Jr. and Rytting, J.H. (1982) Solubility in binary solvent systems : I. Specific versus non-specific interactions. *J.Pharm.Sci.*, 71: 201-204.
18. Acree, W.E., Jr. and Bertrand, G.L. (1981) Thermochemical investigations of nearly ideal binary solvents :VII . Monomer and dimer models for solubility of benzoic acid in simple binary and ternary solvents. *J.Pharm.Sci.*, 70: 1033-10
19. Acree, W.E., Jr. and Rytting, J.H. (1982) Solubilities in binary solvent systems : II. The importance of non-specific interactions. *Int.J.Pharm.*, 10: 231-238.
20. Rubino, J.T., and Obeng, E.K. (1991) Influence of solute structure on deviation from log-linear solubility equation in propylene glycol:water mixtures. *J.Pharm.Sci.*, 80: 479-483.
21. Adjei, A., Newburger, J. and Martin, A. (1980) Extended Hildebrand approach : Solubility of caffeine in dioxane-water mixtures. *J.Pharm.Sci.*, 69: 659-661.
22. McCargar, J.W. and Acree, W.E., Jr. (1989) Solubility of carbazole in binary chloroalkane + dibutyl ether solvent mixtures. *J.Solution Chem.*, 18: 151-158.
23. Acree, W.E., Jr. and McCargar, J.W. (1987) Thermochemical investigations of associated solutions: 5. Calculation of solute-solvent equilibrium constants from solubility in mixtures containing two complexing solvents. *J.Pharm.Sci.*, 76: 575-579.
24. McCargar, J.W. and Acree, W.E., Jr. (1987) Thermochemical investigations of associated solutions: 3. Effect of the inert cosolvent on solute-solvent association constants calculated from solubility measurements. *Phys.Chem.Liq.*, 17: 123-138.
25. Wu, P.L. and Martin, A. (1983) Extended Hildebrand solubility approach: p-Hydroxybenzoic acid in mixtures of dioxane and water. *J.Pharm.Sci.*, 72: 587-592.
26. Acree, W.E., Jr. (1983) Thermochemical investigations of associated solutions: II. Calculation of iodine-benzene equilibrium constants from solute solubility in binary solvent mixtures. *Int.J.Pharm.*, 15: 159-165.
27. Acree, W.E., Jr. and Bertrand, G.L. (1977) Thermochemical investigations of nearly ideal binary solvents: 3. Solubility in systems of non-specific interactions. *J.Phys.Chem.*, 81: 1170-1173.
28. Khossravi, D. and Connors, K.A. (1992) Solvent effects on chemical processes: I. Solubility of aromatic and heterocyclic compounds in binary aqueous-organic solvents. *J.Pharm.Sci.*, 81: 371-379.
29. Subrahmanyam, C., Sreenivasa Reddy, M., Venkata Rao, J. and Gaund Rao, P. (1992) Irregular solution behaviour of paracetamol in binary solvents. *Int.J.Pharm.*, 78: 17-24.
30. Martin, A., Wu, P.L., Adjei, A., Lindstrom, R.E. and Elworthy, P.H. (1982) Extended Hildebrand solubility approach and the log linear solubility equation. *J.Pharm.Sci.*, 71: 849-856.
31. Bustamante, P., Ochoa, R., Reillo, A. and Escalera, J.B. (1994) Chameleonic effect of sulfanilamide and sulfamethazine in solvent mixtures. Solubility curves with two maxima. *Chem.Pharm.Bull.*, 42: 1129-1133.
32. Reillo, A., Escalera, B. and Selles, E. (1993) Prediction of sulfanilamide solubility in dioxane-water mixtures. *Pharmazie*, 48: 904-907.
33. Bustamante, P. and Escalera, B. (1995) Enthalpy and entropy contributions to the solubility of sulfamethoxypyridazine in solvent mixtures showing two solubility maxima. *J. Pharm. Pharmacol.*, 47: 550-555.
34. Martin, A., Paruta, A.N. and Adjei, A. (1981) Extended Hildebrand solubility approach: Methylxanthines in mixed solvents. *J.Pharm.Sci.*, 70: 1115-1120
35. Martin, A., Newburger, J. and Adjei, A. (1980) Extended Hildebrand solubility approach: Solubility of theophylline in polar binary solvents. *J.Pharm.Sci.*, 69: 487-491.
36. Martin, A. and Miralles, M.J. (1982) Extended Hildebrand solubility approach: Solubility of tolbutamide, acetohexamide, and sulfisomidine in binary solvent system. *J.Pharm.Sci.*, 71: 439-442.
37. Judy, C.L. and Acree, W.E. Jr. (1985) Solubility in binary solvent systems: V. Monomer and dimer models for the solubility of p-tolylacetic acid in systems of non-specific interactions. *Int.J.Pharm.*, 27: 39-44.