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A model to represent solvent effects on the chemical stability of solutes in mixed solvent systems

A. Jouyban [a,*], H.K. Chan [b], M. Barzegar-Jalali [a], W.E. Acree Jr [c]

[a] *School of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran*
[b] *Faculty of Pharmacy, The University of Sydney, Sydney, NSW 2006, Australia*
[c] *Department of Chemistry, University of North Texas, Denton, TX 76203-5070, USA*

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Abstract

The applicability of the combined nearly ideal binary solvent/Redlich–Kister (CNIBS/R–K) equation for quantification of solvent effects on the stability of a solute is shown employing the experimental data of three solutes in different aqueous binary solvents. The proposed model provides a simple computational method to correlate/predict the instability rate constant of a drug in mixed solvent systems. The accuracy of the model is compared with that of a model proposed by Connors and co-workers employing various methods including mean percentage deviation (MPD) as comparison criteria. The obtained overall MPD values for the proposed model to correlate and predict the instability rate constants are 2.05 ± 1.44 and $4.41 \pm 3.21\%$, respectively, where the corresponding values for Connors' model are 4.34 ± 3.28 and $10.74 \pm 9.86\%$. The results suggest that by using only five experimental instability rate constants at different concentrations of the cosolvent in a binary mixture, it is possible to predict unmeasured values falling between data points within an acceptable error range.

Keywords: Chemical stability; Solvent effects; Mixed solvents; Mathematical model

1. Introduction

The use of water miscible solvents in the formulation of aqueous drug dosage forms affects among another properties the solubility and chemical stability of drugs as well as the excipients. In order to mathematically represent the solvent effects on the solubility of solutes, the combined nearly ideal binary solvent/Redlich–Kister (CNIBS/R–K) equation has been suggested (Acree, 1992) and evaluated employing experimental solubility data of polycyclic aromatic hydrocarbons in binary non-aqueous solvent systems (Acree, 1995). Further investigations showed that the CNIBS/R–K model is the most accurate model among similar models to calculate drug solubilities in water–cosolvent mixture (Jouyban-Gh et al., 1999). The model is able to calculate solubility of chemically related drugs in a given binary solvent (Jouyban-Gh et al., 1998) and solubility of a drug in a binary solvent at different temperatures (Jouyban-Gh and Acree,

* Corresponding author. Tel.: +98-411-334-1315; fax: +98-411-3344-798
E-mail address: jouyban@tbzmed.ac.ir (A. Jouyban).

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1998). The aim of this communication is to introduce the applicability of the CNIBS/R–K model for describing the effects of different concentrations of a cosolvent in a binary solvent mixture on the chemical stability of a drug. The accuracy of the proposed model has been evaluated and compared with that of the phenomenological model (Skwierczynski and Connors, 1994) by employing experimental data collected from the literature. Using the model, researchers are able to predict the instability rate constants at different solvent compositions falling between measured data points after carrying out a minimum number of experiments in order to train the model. Due to infinite number of possible solvent compositions from a binary mixture, the prediction method could be beneficial to speed up the process of solvent mixture optimization. In addition, the model provides a means of screening the experimental data for possible outliers in need of re-determination. Another versions of the CNIBS/R–K model provided accurate predictions for solubility of a solute in a binary solvent (Jouyban-Gh et al., 2001), for electrophoretic mobility of analytes in capillary zone electrophoresis (Jouyban-Gh et al., 2000) and for acid dissociation constants of analytes in a binary solvent mixture (Jouyban et al., 2002).

2. Theoretical treatment

The CNIBS/R–K model provides a simple method to correlate/predict the excess molar properties of a solute in a binary solvent in terms of weighted mole fraction average of solute properties in the pure solvents and contributions of solute–solvent and solvent–cosolvent interactions. The proposed model to calculate the instability rate constant of a solute in a mixed solvent system is expressed as:

$$\ln k_m = f_c \ln k_c + f_w \ln k_w + f_c f_w \sum_{j=0}^{3} M_j (f_c - f_w)^j \quad (1)$$

where k_m is the instability rate constant in the mixed solvent, f_c and f_w denote the concentrations of the cosolvent and water in the binary solvent mixture, k_c and k_w are the instability rate constants of the drug in pure cosolvent and water, respectively, and M_j is the model constant representing two-body and three-body interactional terms (Acree, 1992). The numerical values of j can be varied between 0–3 in order to present an accurate mathematical representation of experimental data. In some cases, the numerical value of k_c is not available and to overcome this, it is possible to consider $\ln k_c$ as a model constant, B, and rewrite Eq. (1) as Eq. (2):

$$\ln k_m = f_w \ln k_w + B f_c + f_c f_w \sum_{j=0}^{3} M_j (f_c - f_w)^j \quad (2)$$

The phenomenological model of solvent effects on chemical stability of drugs in aqueous–cosolvent mixture (Skwierczynski and Connors, 1994) is represented as:

$$-k_B T \ln k_m = -k_B T \ln k_w + \frac{\Delta g A^{\#} \gamma' \beta_1 f_c f_w + 2\Delta g A^{\#} \gamma' \beta_2 f_c^2}{f_w^2 + \beta_1 f_c f_w + \beta_2 f_c^2} \quad (3)$$

where k_B is Boltzmann's constant, T is the absolute temperature, $\Delta g A^{\#}$ is the difference between the curvature-corrected molecular surface areas of the cavities containing the transition state and the reactant, γ' is $(\gamma_w - \gamma_c)/2$ in which γ_w and γ_c are the bulk surface tensions of pure water and pure cosolvent, β_1 and β_2 denote the model parameters. These parameters and $\Delta g A^{\#}$ are computed by a non-linear regression method. Since $\Delta g A^{\#}$ and γ' possess the constant values for a given system, it is possible to rearrange Eq. (3) as:

$$-k_B T \ln k_m = -k_B T \ln k_w + \frac{a\beta_1 f_c f_w + b\beta_2 f_c^2}{f_w^2 + \beta_1 f_c f_w + \beta_2 f_c^2} \quad (4)$$

where a and b are unconstrained constants. This rearrangement which has also been proposed by Connors and coworkers (Khossravi and Connors, 1992) to calculate the solute solubility in binary solvents using another version of Eq. (3), makes the calculations easier and there is no need to know the numerical values of $\Delta g A^{\#}$ and γ' terms.

To assess the accuracy of the equations, the experimental k_m values were fitted into the equations and the mean percentage deviation (MPD) between experimental and calculated k_m values is considered as an accuracy criterion. MPD defined as:

$$\mathrm{MPD} = \left(\frac{100}{N}\right)\sum\left|\frac{k_m^{\mathrm{calculated}} - k_m^{\mathrm{observed}}}{k_m^{\mathrm{observed}}}\right| \quad (5)$$

where N is the number of experimental data points in each set. The mean value of MPDs is denoted as overall MPD (OMPD) and is given by:

$$\mathrm{OMPD} = \frac{\sum_1^{23} \mathrm{MPD}}{23} \quad (6)$$

The individual percentage deviation (IPD) is also calculated by:

$$\mathrm{IPD} = 100\left|\frac{k_m^{\mathrm{calculated}} - k_m^{\mathrm{observed}}}{k_m^{\mathrm{observed}}}\right| \quad (7)$$

Existence of outliers could affect MPD values. To assess the models from another viewpoint, the best adherence to a model, percent of best adherence (%BA), is calculated by Eq. (8).

$$\%\mathrm{BA} = 100\left(\frac{\text{Number of data producing less IPD in all sets of data}}{\text{Total number of data in all sets of data}}\right) \quad (8)$$

Table 1
Details of the collected data sets, number of data points (N) in each set and mean percentage deviations for correlative Eqs. (2) and (4)

Number	System	N	Eq. (2)				Eq. (4)
			$j=0$	$j=1$	$j=2$	$j=3$	
1	Aspartame in 1.0 M HCl + acetone	13	3.66	3.35	3.34	3.35	3.42
2	Aspartame in 1.0 M HCl + acetonitrile	13	4.14	1.72	0.93	0.94	3.13
3	Aspartame in 1.0 M HCl + dimethyl sulphoxide	13	2.20	0.77	0.69	0.56	0.70
4	Aspartame in 1.0 M HCl + dioxane	13	2.07	0.93	0.68	0.64	1.37
5	Aspartame in 1.0 M HCl + tetrahydrofuran	13	4.83	0.93	0.87	0.95	1.83
6	Aspartame in carbonate buffer + acetone	11	2.55	1.99	1.98	1.91	1.94
7	Aspartame in carbonate buffer + acetonitrile	14	5.30	3.25	3.30	3.26	3.26
8	Aspartame in carbonate buffer + dimethyl sulphoxide	11	7.76	6.48	6.57	6.15	7.32
9	Aspartame in carbonate buffer + dioxane	12	4.73	4.84	4.92	4.71	4.34
10	Aspartame in carbonate buffer + methanol	16	4.35	2.84	2.74	2.75	4.16
11	Aspartame in carbonate buffer + tetrahydrofuran	10	5.13	5.07	4.62	4.24	5.08
12	*N*-Chloroalanine in water + methanol	10	4.13	1.71	1.66	1.64	2.34
13	*N*-Chloroalanine in water + ethanol	9	1.63	1.18	1.17	1.05	5.59
14	*N*-Chloroalanine in water + 1-propanol	11	3.21	2.71	1.35	1.10	2.51
15	*N*-Chloroalanine in water + 2-propanol	18	6.12	2.74	1.90	1.94	6.45
16	*N*-Chloroalanine in water + ethylene glycol	11	1.22	0.80	0.65	0.61	0.60
17	*N*-Chloroalanine in water + propylene glycol	10	4.98	2.57	1.54	1.55	1.77
18	*N*-Chloroalanine in water + acetonitrile	13	2.25	2.24	1.59	1.48	13.99
19	*N*-Chloroalanine in water + dioxane	10	2.90	1.95	1.97	1.98	5.21
20	*N*-Chloroleucine in water + methanol	10	4.78	1.95	1.54	1.53	4.57
21	*N*-Chloroleucine in water + 2-propanol	12	11.50	4.54	2.12	2.31	9.31
22	*N*-Chloroleucine in water + ethylene glycol	11	2.37	1.62	1.01	0.75	1.34
23	*N*-Chloroleucine in water + acetonitrile	12	2.85	2.29	1.90	1.77	9.69

Data sets 1–11 were taken from Skwierczynski and Connors (1994) and 12–23 from Lepree and Connors (1996).

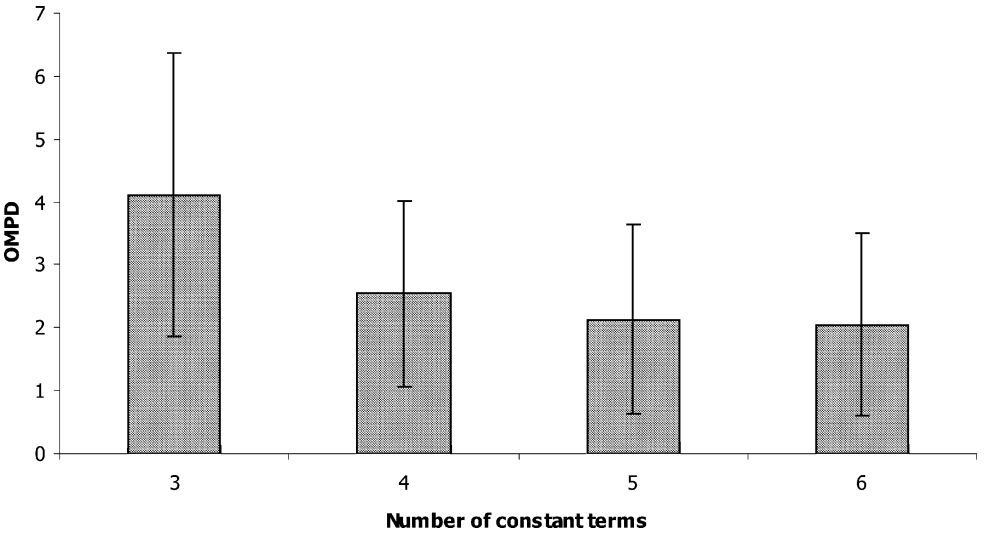

Fig. 1. The overall mean percentage deviation (OMPD) and standard deviations for the proposed model with different numbers of constant terms. The OMPD differences for various numbers of constant terms are statistically significant (paired t-test, $P < 0.01$).

3. Results and discussion

Table 1 shows details of the collected data sets and the MPD values for the proposed model with different constant terms and also Eq. (4) with five constant terms. In this set of analysis, whole data points in each set have been fitted to the model and the results show the correlation ability of the models. Therefore, these equations have been called correlative equations. As a general pattern for mathematical models containing constant terms, the more the number of constant terms the more accurate the results and this has been observed in this study. The OMPD and standard deviations for different numbers of curve-fitting parameters have been shown in Fig. 1. The improvement in accuracy with increase in the number of constants reaches a limiting value after the inclusion of about five or six constants.

In order to compare the accuracy of the proposed model with a previously published model (i.e. Eq. (4)), the MPD values have been computed for the k_m values back-calculated by Eq. (4). The OMPD values for Eq. (4) and the proposed one with the same number of constant terms ($j = 2$) have been shown in Fig. 2. The difference between the OMPD values for Eq. (4) and the proposed model is statistically significant (paired t-test, $P < 0.003$) showing that the proposed model provides more accurate calculations in comparison with the previous model.

The IPD values for correlative Eqs. (2) and (4) in different groups (IPD < 2, 2–4, 4–8, 8–12 and > 12%) have been shown in Fig. 3. The higher frequency has been observed for IPD < 2% which are 64.5 and 43.5%, respectively, for Eqs. (2) and (4). Overall distribution of relative frequency indicates that the expected IPD using Eq. (2) is lower than that of Eq. (4) and the proposed model is superior from this point of view. The %BA for the proposed model is 62.0% and for Eq. (4) is 29.3% where in 8.7% of the cases equal IPD values have been produced by both models.

The prediction capabilities of the models have been evaluated by employing 5 data points in each set as a training set to compute the models constants. These 5 points have been chosen with nearly constant f_c intervals to provide best interpolation results. Using the trained models which is called predictive equations, the k_m values at other solvent compositions (test set) have been predicted and then compared with experimental k_m. Table 2 summarized the MPD values for Eqs. (2) and (4) for 23 data sets studied. The OMPD and the standard deviations for Eqs. (2) and (4) are 4.41 ± 3.21 and $10.71 \pm 9.86\%$, respectively,

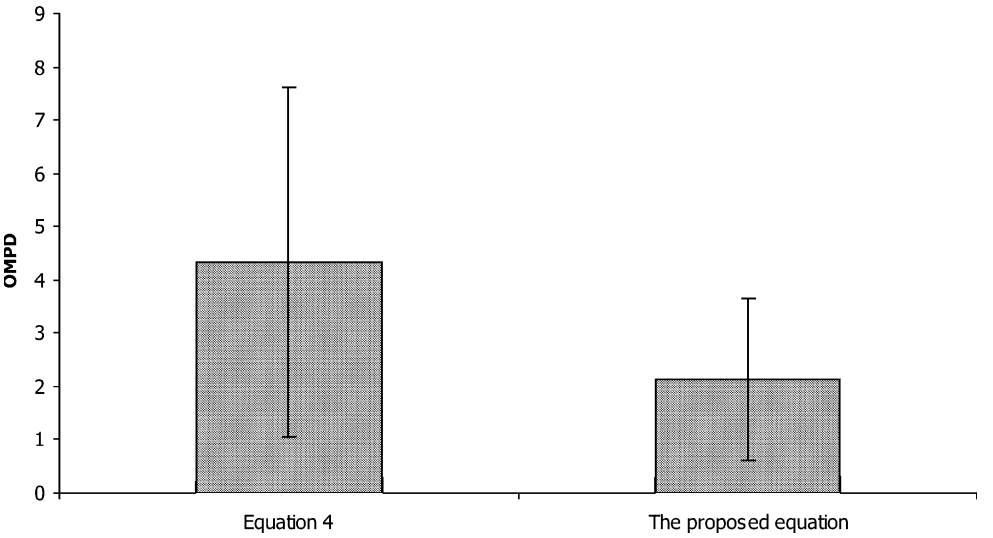

Fig. 2. The overall mean percentage deviation (OMPD) and standard deviations for correlative Eqs. (2) and (4) with five constant terms. The OMPD difference is statistically significant (paired t-test, $P < 0.003$).

and the mean difference is statistically significant (paired t-test, $P < 0.002$). This means that using just five experimental data, one is able to predict the k_m values at other solvent compositions and the mean expected prediction errors for Eqs. (2) and (4) are 4.41 and 10.71%, respectively. A 4.41% Prediction error could be considered as an acceptable error where the maximum experimental relative standard deviations reported in the literature are 13.4% (decomposition of *N*-chloroalanine in pure water) (Lepree and Connors, 1996), 6.1% (decomposition of *N*-chloroalanine in water-dioxane 50:50) (Lepree and Connors, 1996) and 4.1% (hydrolysis of aspartame in 1.0 M HCl–tetrahydrofuran 80:20) (Skwierczynski and Connors, 1994). Fig. 4 shows the prediction error distributions for the models using minimum number of training data points. The probability of predicting the k_m values with error less than 2% is around 0.34 and 0.22 for Eqs. (2) and (4), where the corresponding probability for prediction error $> 12\%$ are 0.09 and 0.23. The %BA for the predictive models 2 and 4 are 62.1 and 37.9%, respectively. Therefore, using Eq. (2) more accurate predictions are expected.

In conclusion, the proposed model shows accurate results from correlation and prediction points of view and it is suggested to be employed in the pharmaceutical industry whenever the optimization of the cosolvent concentration is the prime concern. As shown in Table 1, one can employ more constant terms to provide more accurate results whereas the phenomenological model contains only five constant terms. The predictions of a property in mixed solvents based on a minimum number of experiments provide a useful computational tool to speed up the process of formulation optimization.

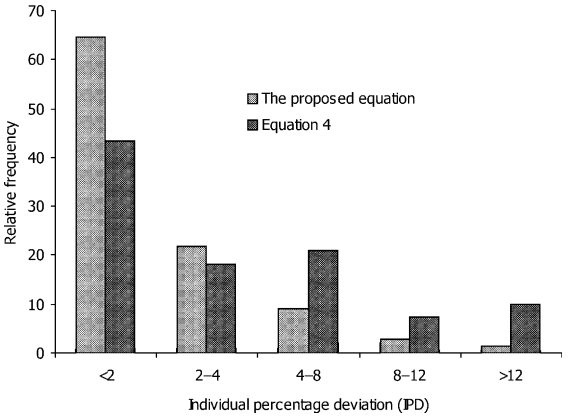

Fig. 3. Distribution of individual percentage deviations (IPD) for correlative Eqs. (2) and (4).

Table 2
Mean percentage deviations for predictive Eqs. (2) and (4)

Number	Eq. (2)	Eq. (4)	*N*
1	5.05	4.99	8
2	1.65	6.00	8
3	2.47	1.74	8
4	1.78	1.69	8
5	3.00	2.18	8
6	3.06	2.99	6
7	5.39	7.13	9
8	8.36	7.28	6
9	6.83	6.09	7
10	15.96	33.10	11
11	9.37	30.38	5
12	4.32	10.12	5
13	3.22	6.48	4
14	2.60	20.19	6
15	3.83	5.84	13
16	1.83	32.98	6
17	3.37	11.02	5
18	3.53	21.33	8
19	2.51	7.08	5
20	3.18	5.61	5
21	4.67	10.48	7
22	2.85	2.10	6
23	2.69	10.20	7
OMPD	4.41[a]	10.74[a]	
S.D.	3.21	9.86	

[a] The OMPD differences is statistically significant (paired *t*-test, $P < 0.002$).

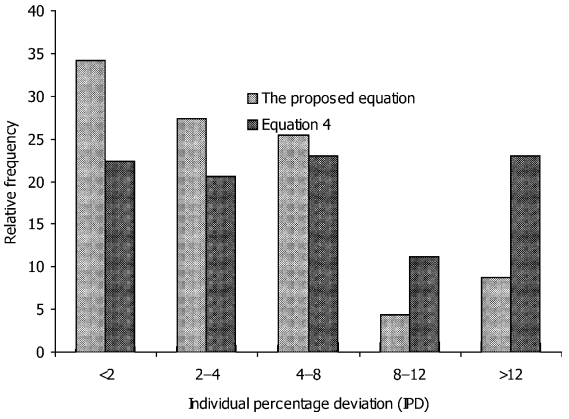

Fig. 4. Distribution of individual percentage deviations (IPD) for predictive Eqs. (2) and (4).

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