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Prediction of the optimized solvent composition for solubilization of drugs in water-cosolvent mixtures

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The capability of the Jouyban-Acree model for predicting the optimized solvent composition of binary solvents for solubilization of drugs is shown employing solubility of drugs in aqueous mixtures of dioxane, ethanol and polyethylene glycol 400. The established model constants of the Jouyban-Acree model and solubility of drugs in water and cosolvent are used to predict the maximum solubility of in the binary solvent mixture ($\log X_{m(max)}$) and the corresponding solvent composition ($f_{1,max}$). The accuracy of the predicted $\log X_{m(max)}$ and $f_{1,max}$ is studied using average absolute error (AAE) of predicted and observed values. The AAEs were 0.10 ± 0.12 and 0.08 ± 0.10, respectively for $\log X_{m(max)}$ and $f_{1,max}$. The method provided acceptable predictions and is recommended for practical applications. The main advantage of the proposed method is its extension to temperatures higher/lower than room temperature.

1. Introduction

In drug discovery studies, solubility of a drug candidate is one of the main limiting factors and an ab initio prediction method is highly demanded. In the case of poor solubility of a drug, addition of a cosolvent is the main solubilization method and a number of models were presented for modeling the solubility data in binary solvent mixtures, including the log-linear (Yalkowsky and Roseman 1981), the extended Hildebrand solubility equation (Adjei et al. 1980), excess free energy approach (Williams and Amidon 1984), the Jouyban-Acree model (Acree 1992, 1996, Jouyban et al. 2006a), general single model (Barzegar-Jalali and Jouyban-Gharamaleki 1997), the modifed Wilson model (Jouyban-Gharamaleki 1998) and the model of Ruckenstein and Shulgin (2003). These models require a number of experimental data points to be trained and/or a number of physico-chemical properties for solubility prediction of drugs in water-cosolvent mixtures. The more reliable and simple cosolvency model, i.e. the log-linear model, requires the aqueous solubility of the drug and its logarithm of partition coefficient, while the Jouyban-Acree model requires the solubilities in mono-solvents as input data. The cosolvency models are usually used to calculate the solubility of a solute in different compositions of the solvents and compared with the corresponding experimental values. From this point of view, the Jouyban-Acree model (formerly known as the combined NIBS/Redlich-Kister model) is the most accurate among similar models (Jouyban-Gharamaleki et al. 1999) and is recommended for practical applications when accurate predictions are required. The model is able to represent the solubility of structurally related drugs (Jouyban-Gharamaleki et al. 1998), chameleonic effect (Jouyban-Gharamaleki and Acree 1998) and solubility of polymorphs (Jouyban and Clark 2002) in mixed solvents. The model was also able to predict the solubility of drugs in ternary solvents based on the model constants calculated from binary solvent data (Jouyban et al. 2006a).

The aim of this work was to present the applicability of the Jouyban-Acree model for reproducing the solubility profile of various drugs dissolved in a given binary solvent. The reported constants of the model for water-dioxane, water-ethanol and water-polyethylene glycol 400 (PEG 400) mixtures were used to reproduce the solubility data in the binary solvents at various temperatures. Then the maximum solubility of the drug and the optimized solvent composition to achieve the maximum solubility were calculated. The calculated maximum solubility and optimized solvent composition were compared with the corresponding experimental data taken from the literature.

2. Investigations, results and discussion

2.1. Theoretical treatment

The Jouyban-Acree model was used to correlate solubility of drugs in mixed solvent systems (Acree 1996; Jouyban et al. 2006a). Its basic form to calculate a solute solubility in water-cosolvent mixture is:

$$\ln X_m = f_1 \ln X_1 + f_2 \ln X_2 + f_1 f_2 \sum_{i=0}^{2} A_i (f_1 - f_2)^i \qquad (1)$$

where X_m is the solubility of the solute in solvent mixture, f_1 and f_2 are the fractions of cosolvent and water in the absence of the solute, X_1 and X_2 denote the solubilities in solvents 1 and 2, respectively, and A_i are the model coefficients computed using a no-intercept least square analysis (Jouyban-Gharamaleki and Hanaee 1997) for each binary solvent system. Subscript 1 of f and X terms

represent the fraction of solvent and solute solubility in solvent with higher solubility and for all solvent systems $X_1 > X_2$. As examples, for solubility of acetanilide in water-ethanol, ethanol is the solvent 1 and water is solvent 2, whereas for solubility of alanine in water-ethanol, water is the solvent 1 and ethanol is the solvent 2. The A_i coefficients are functions of two-body and three-body interaction energies that describe the interactions between the various molecules in solution (Acree 1992). In the case of a drug dissolved in water-cosolvent mixtures, the basic thermodynamic model from which Eq. (1) was derived included all six possible two-body (c-c, w-w, d-d, c-w, c-d and w-d) and all ten possible three-body (c-c-c, w-w-w, d-d-d, c-c-w, c-w-w, c-c-d, c-d-d, w-w-d, w-d-d and c-w-d) molecular interactions between water (w), cosolvent (c) and drug (d) molecules. Equation (1) was derived by differentiating the integral excess Gibbs energy of mixing equation for the mixture containing components c, w and d, expressed in terms of two-body and three-body interaction energies, with respect to the number of moles of drug. Raoult's law was used for the entropic contribution in the integral Gibbs energy of mixing equation. For more details of the derivation of the Jouyban-Acree model, readers are refered to a previous paper (Acree 1992). The applicability of the model was also extended to calculate the solubility of drugs in binary solvents at various temperatures (Jouyban-Gharamaleki and Acree 1998) as:

$$\ln X_{m,T} = f_1 \ln X_{1,T} + f_2 \ln X_{2,T} + f_1 f_2 \sum_{i=0}^{2} \frac{J_i (f_1 - f_2)^i}{T} \quad (2)$$

where $X_{m,T}$, $X_{1,T}$ and $X_{2,T}$ are the solubility of the solute in solvent mixture, solvents 1 and 2 in the absence of the solute at temperature (T, °K) and J_i are the model constants.

2.2. Computational methods

The reported model constants of the Jouyban-Acree model for water-cosolvent mixtures are:
For water-dioxane data (Jouyban 2007):

$$\log X_{m,T} = f_1 \log X_{1,T} + f_2 \log X_{2,T} + f_1 f_2 \times \left[\frac{958.44}{T} + \frac{509.45\,(f_1 - f_2)}{T} + \frac{867.44\,(f_1 - f_2)^2}{T} \right] \quad (3)$$

For water-ethanol data (Jouyban and Acree 2006):

$$\log X_{m,T} = f_1 \log X_{1,T} + f_2 \log X_{2,T} + f_1 f_2 \times \left[\frac{724.21}{T} + \frac{485.17\,(f_1 - f_2)}{T} + \frac{194.41\,(f_1 - f_2)^2}{T} \right] \quad (4)$$

For water-PEG 400 (Jouyban 2006):

$$\log X_{m,T} = f_1 \log X_{1,T} + f_2 \log X_{2,T} + f_1 f_2 \times \left[\frac{394.82}{T} - \frac{355.28\,(f_1 - f_2)}{T} + \frac{388.89\,(f_1 - f_2)^2}{T} \right] \quad (5)$$

Equations (3)–(5) require experimental solubility data of the drug in neat solvents 1 and 2 at the temperatures of interest and are able to reproduce a solubility profile in binary solvents at various temperatures. The numerical values of f_1 and f_2 (from 0.00 to 1.00) with 0.01 intervals and X_1 and X_2 values of the drug were replaced in Eqs. (3), (4) or (5) and logarithm of maximum solubility ($\log X_{m(max)}$) and the corresponing fraction of solvent 1 ($f_{1,max}$) were predicted. To carry out these computations, various software could be employed. Here, the simplest available software (GW-BASIC) was used and the computations carried out using a small program listed as:

```
 10 'Solubility maxima in water-ethanol mixtures
 20 INPUT "Enter log solubility of drug in solvent 1: ";
    LX1
 30 INPUT "Enter log solubility of drug in solvent 2: ";
    LX2
 40 IF LX1 < LX2 THEN PRINT "CHANGE
    SOLVENTS' 1 AND 2 SOLUBILITY VALUES":
    PRINT: GOTO 20
 50 INPUT "Enter temperature of solution (K): ";T
 60 J0=724.21/T
 70 J1=485.17/T
 80 J2=194.41/T
 90 CLS: ZMAX=LX2
100 FOR F1=0 TO 1 STEP 0.01
110 F2=1-F1
120 Q1=F1-F2
130 Q2=(F1-F2)*(F1-F2)
140 Z=F1*LX1+F2*LX2+F1*F2*(J0+J1*Q1+J2*Q2)
150 IF Z>ZMAX THEN LSMAX=Z:
    F1MAX=F1:ZMAX=Z
160 NEXT F1
170 PRINT USING "Log of maximum
    solubility= ###.## at solvent 1 fraction of:
    #.##";LSMAX,F1MAX
```

The results of the proposed models are evaluated using absolute error (AE) and average absolute error (AAE) as accuracy criteria computed by:

$$AE = |\,\text{Predicted} - \text{Observed}\,|$$

$$AAE = \frac{\sum |\,\text{Predicted} - \text{Observed}\,|}{N}$$

Where N is the number of data sets studied.

2.3. Results and discussion

The maximum solubility of 40 available solubility data of drugs in water-dioxane mixtures at temperatures ranging

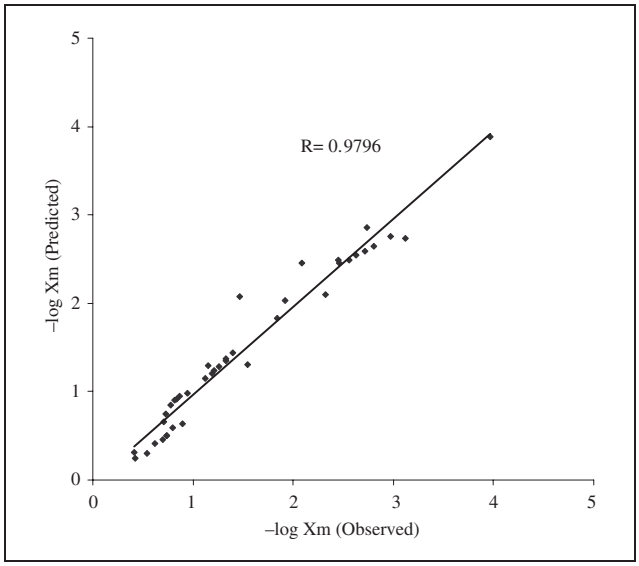

Fig. 1: Maximum predicted solubility of drugs using Eq. (3) versus observed values in dioxane-water mixtures (N = 40)

Table 1: Details of solubility data of drugs in water-dioxane (solvent 1) mixtures at various temperatures (T, K), the predicted and observed log $X_{m(max)}$ at volume fraction of solvent 1 ($f_{1,max}$), absolute error (AE) and average absolute error (AAE)

Solute	Reference	T	log X_1	log X_2	log $X_{m(max)}$	log $X_{m(max)}$		$f_{1,max}$	$f_{1,max}$	
					Predicted	Observed	AE	Predicted	Observed	AE
Acetanilide	Bustamante et al. 1998	293	−1.03	−3.15	−0.59	−0.80	0.21	0.83	0.90	0.07
Acetanilide	Bustamante et al. 1998	298	−0.92	−3.10	−0.50	−0.74	0.24	0.83	0.90	0.07
Acetanilide	Bustamante et al. 1998	303	−0.87	−3.05	−0.46	−0.70	0.24	0.83	0.80	0.03
Acetanilide	Bustamante et al. 1998	308	−0.79	−3.05	−0.41	−0.62	0.21	0.84	0.80	0.04
Acetanilide	Bustamante et al. 1998	313	−0.67	−2.96	−0.30	−0.54	0.24	0.84	0.80	0.04
Acetanilide	Pena et al. 2006	298	−0.92	−3.10	−0.50	−0.74	0.24	0.83	0.80	0.03
Benzocaine	Pena et al. 2006	298	−0.55	−4.00	−0.31	−0.41	0.10	0.88	0.90	0.02
Caffeine	Adjei et al. 1980	298	−2.07	−2.64	−1.31	−1.55	0.24	0.74	0.70	0.04
Nalidixic acid	Bustamante et al. 1998	283	−3.16	−5.74	−2.76	−2.97	0.21	0.84	0.85	0.01
Nalidixic acid	Bustamante et al. 1998	293	−3.00	−5.68	−2.65	−2.81	0.16	0.85	0.90	0.05
Nalidixic acid	Bustamante et al. 1998	298	−2.93	−5.62	−2.59	−2.72	0.13	0.85	0.90	0.05
Nalidixic acid	Bustamante et al. 1998	303	−2.87	−5.54	−2.54	−2.63	0.09	0.85	0.90	0.05
Nalidixic acid	Bustamante et al. 1998	308	−2.82	−5.44	−2.49	−2.56	0.07	0.85	0.85	0.00
Nalidixic acid	Bustamante et al. 1998	313	−2.78	−5.30	−2.45	−2.46	0.01	0.85	0.85	0.00
p-Hydroxybenzoic acid	Wu and Martin, 1983	298	−1.07	−3.22	−0.64	−0.90	0.26	0.83	0.90	0.07
Paracetamol	Bustamante et al. 1998	293	−1.61	−2.77	−0.98	−0.94	0.04	0.78	0.85	0.07
Paracetamol	Bustamante et al. 1998	298	−1.57	−2.72	−0.95	−0.87	0.08	0.78	0.85	0.07
Paracetamol	Bustamante et al. 1998	303	−1.53	−2.64	−0.92	−0.84	0.08	0.78	0.85	0.07
Paracetamol	Bustamante et al. 1998	308	−1.50	−2.59	−0.90	−0.82	0.08	0.78	0.85	0.07
Paracetamol	Bustamante et al. 1998	313	−1.45	−2.52	−0.85	−0.78	0.07	0.78	0.85	0.07
Paracetamol	Romero et al. 1996	298	−1.32	−2.72	−0.75	−0.73	0.02	0.79	0.85	0.06
Phenacetin	Bustamante and Bustamante, 1996	293	−1.85	−4.17	−1.44	−1.40	0.04	0.84	0.90	0.06
Phenacetin	Bustamante and Bustamante, 1996	298	−1.77	−4.09	−1.37	−1.33	0.04	0.84	0.90	0.06
Phenacetin	Bustamante and Bustamante, 1996	303	−1.67	−3.99	−1.28	−1.26	0.02	0.84	0.90	0.06
Phenacetin	Bustamante and Bustamante, 1996	308	−1.58	−3.93	−1.21	−1.19	0.02	0.84	0.90	0.06
Phenacetin	Bustamante and Bustamante, 1996	313	−1.51	−3.84	−1.15	−1.12	0.03	0.84	0.90	0.06
Phenacetin	Pena et al. 2006	298	−1.76	−4.00	−1.35	−1.33	0.02	0.83	0.90	0.07
Salicylic acid	Pena et al. 2006	298	−0.51	−3.70	−0.24	−0.42	0.18	0.87	0.90	0.03
Salmeterol xinafoate	Jouyban-Gharamaleki et al. 2001b	292	−2.37[a]	−5.55[a]	−2.08	−1.47[a]	0.61	0.87	0.90	0.03
Sulfadiazine	Bustamante et al. 1993	298	−3.30	−5.36	−2.86	−2.74	0.12	0.83	0.85	0.02
Sulfadimidine	Bustamante et al. 1993	298	−2.83	−5.52	−2.49	−2.45	0.04	0.85	0.90	0.05
Sulfamethizole	Reillo et al. 1995a	298	−3.02	−4.45	−2.46	−2.09	0.37	0.80	0.80	0.00
Sulfamethoxazol	Bustamante et al. 1993	298	−1.52	−4.64	−1.24	−1.21	0.03	0.87	0.85	0.02
Sulfanilamide	Reillo et al. 1993	298	−1.10	−3.19	−0.66	−0.71	0.05	0.83	0.85	0.02
Sulfapyridine	Reillo et al. 1995b	298	−4.47	−5.75	−3.88	−3.97	0.09	0.79	0.87	0.08
Sulfisomidine	Martin et al. 1985	298	−2.60	−4.00	−2.03	−1.92	0.11	0.79	0.80	0.01
Sulphamet-hoxypyridazine	Bustamante et al. 1993	298	−1.62	−4.43	−1.30	−1.15	0.15	0.86	0.86	0.00
Theobromine	Martin et al. 1981	298	−3.35	−4.48	−2.73	−3.12	0.39	0.78	0.70	0.08
Theophylline	Martin et al. 1980	298	−2.59	−3.13	−1.83	−1.84	0.01	0.74	0.70	0.04
Trimethoprim	Subrahmanyam et al. 1996	298	−2.52	−4.68	−2.10	−2.32	0.22	0.83	0.83	0.00
						AAE:	0.14		AAE:	0.043

[a] The solubility data of salmeterol xinafoate were reported in natural logarithm scale by a mistake in our previous paper (Jouyban-Gharamaleki et al. 2001b) and all data should be read in log scale instead of ln scale.

from 283–313 K collected from the literature were used to check the accuracy of Eq. (3) in predicting maximum solubility of a drug in water-dioxane mixtures and the optimized solvent composition. Details of the data sets, temperature, logarithms of drug solubilities in water and dioxane, logarithm of maxiumum solubilities predicted by Eq. (3) and the observed values, the corresponding solvent composition (predicted and observed values), AE and AAEs were listed in Table 1. The minimum AE (0.01) of log $X_{m(max)}$ was observed for acetanilide at 313 K whereas the maximum AE (0.61) was for salmeterol xinafoate at 292 K and the AAE (±SD) of log $X_{m(max)}$ was 0.14 ± 0.13. With the wide range of log X_m data (−3.97 to −0.51) AAE of 0.14 could be considered as an acceptable error. From a practical point of view, prediction of the best solvent composition to solubilize the maximum amount of the drug is more interesting. The proposed model was able to predict $f_{1,max}$, and the maximum and minimum AE values were 0.00 and 0.08 for nalidixic acid and theobromine data, respectively. The AAE (±SD) of $f_{1,max}$ was 0.04 ± 0.03 which means that the model is able to predict the best solvent composition of water-dioxane with overall error of 4%. Fig. 1 shows a good linear relationship ($R = 0.9796$, $N = 40$) between predicted and observed log $X_{m(max)}$ for the studied data sets.

Details of solubility data of drugs in water-ethanol mixtures were reported in Tables 2 and 3. Data of Table 2 were used to train the Jouyban-Acree model and obtain

Table 2: Details of solubility data of drugs in water-ethanol mixtures at various temperatures (T, K), the predicted and observed log $X_{m(max)}$ at volume fraction of solvent 1 ($f_{1,max}$), absolute error (AE) and average absolute error (AAE)

Solute	Reference	T	Solvent 1	log X_1	log X_2	log $X_{m(max)}$	log$X_{m(max)}$		$f_{1,max}$	$f_{1,max}$	
						Predicted	Observed	AE	Predicted	Observed	AE
Acetanilide	Stephen and Stephen, 1964	298	Ethanol	−3.07	−5.14	−2.88	−3.05	0.17	0.85	0.90	0.05
Alanine (Beta)	Greenstein and Winitz, 1961	298	Water	−0.82	−3.96	−0.76	−0.82	0.06	0.92	1.00	0.08
Alanine (DL)	Greenstein and Winitz, 1961	298	Water	−1.49	−4.35	−1.40	−1.49	0.09	0.90	1.00	0.10
Aminocaproic acid (ε)	Greenstein and Winitz, 1961	298	Water	−0.97	−3.95	−0.89	−0.97	0.08	0.91	1.00	0.09
Asparagine (L)	Greenstein and Winitz, 1961	298	Water	−2.47	−5.87	−2.43	−2.47	0.04	0.93	1.00	0.07
Aspartic acid (L)	Greenstein and Winitz, 1961	298	Water	−3.17	−6.17	−3.10	−3.17	0.07	0.91	1.00	0.09
Benoz [a] pyrene	Li and Yalkowsky, 1994	296	Ethanol	−2.24	−7.90	−2.24	−2.24	0.00	1.00	1.00	0.00
Caffeine	Bustamante et al. 2002	298	Water	−2.68	−2.77	−2.03	−1.83	0.20	0.67	0.60	0.07
Chrysene	Li and Yalkowsky, 1994	296	Ethanol	−2.78	−8.46	−2.78	−2.78	0.00	1.00	1.00	0.00
Furosemide	Jouyban-Gharamaleki et al. 2001a	298	Ethanol	−2.62	−5.64	−2.55	−2.62	0.07	0.91	1.00	0.09
Glycine	Greenstein and Winitz, 1961	298	Water	−1.25	−4.64	−1.21	−1.25	0.04	0.93	1.00	0.07
Glycylglycine	Greenstein and Winitz, 1961	298	Water	−1.52	−5.89	−1.52	−1.52	0.00	0.98	1.00	0.02
Hexachlorobenzene	Li and Yalkowsky, 1994	296	Ethanol	−2.50	−7.74	−2.50	−2.50	0.00	1.00	1.00	0.00
Leucine (L)	Greenstein and Winitz, 1961	298	Water	−2.50	−4.13	−2.24	−2.50	0.26	0.82	1.00	0.18
Nalidixic acid	Jouyban et al. 2002	298	Ethanol	−3.69	−5.62	−3.48	−3.56	0.08	0.84	0.85	0.01
Niflumic acid	Bustamante et al. 2002	298	Ethanol	−1.79	−5.26	−1.75	−1.79	0.04	0.94	1.00	0.06
Norleucine (DL)	Greenstein and Winitz, 1961	298	Water	−2.80	−4.21	−2.50	−2.80	0.30	0.80	1.00	0.20
Oxolinic acid	Jouyban-Gharamaleki et al. 2000	293	Ethanol	−5.16	−6.06	−4.74	−4.76	0.02	0.75	0.80	0.05
Oxolinic acid	Jouyban-Gharamaleki et al. 2000	298	Ethanol	−5.09	−5.97	−4.67	−4.68	0.01	0.75	0.80	0.05
Oxolinic acid	Jouyban-Gharamaleki et al. 2000	303	Ethanol	−4.98	−5.87	−4.57	−4.59	0.02	0.76	0.80	0.04
Oxolinic acid	Jouyban-Gharamaleki et al. 2000	308	Ethanol	−4.89	−5.79	−4.50	−4.48	0.02	0.76	0.80	0.04
Oxolinic acid	Jouyban-Gharamaleki et al. 2000	313	Ethanol	−4.79	−5.69	−4.41	−4.39	0.02	0.76	0.80	0.04
Paracetamol	Romero et al. 1996	298	Ethanol	−1.27	−2.72	−0.98	−1.10	0.12	0.80	0.85	0.05
Paracetamol	Bustamante et al. 1995	293	Ethanol	−1.28	−2.76	−0.98	−1.14	0.16	0.80	0.85	0.05
Paracetamol	Bustamante et al. 1995	298	Ethanol	−1.27	−2.72	−0.98	−1.10	0.12	0.80	0.85	0.05
Paracetamol	Bustamante et al. 1995	303	Ethanol	−1.21	−2.64	−0.92	−1.06	0.14	0.80	0.85	0.05
Paracetamol	Bustamante et al. 1995	308	Ethanol	−1.18	−3.02	−0.98	−1.01	0.03	0.84	0.85	0.01
Paracetamol	Bustamante et al. 1995	313	Ethanol	−1.15	−2.55	−0.88	−0.97	0.09	0.80	0.85	0.05
Pentachlorobenzene	Li and Yalkowsky, 1994	296	Ethanol	−1.08	−6.12	−1.08	−1.08	0.00	1.00	1.00	0.00
Perylene	Li and Yalkowsky, 1994	296	Ethanol	−3.33	−8.83	−3.33	−3.33	0.00	1.00	1.00	0.00
Salicylic acid	Jouyban et al. (2006a)	298	Ethanol	−0.89	−3.62	−0.79	−0.89	0.10	0.89	0.90	0.01
Sulphamethiazine	Bustamante et al. 1994	298	Ethanol	−3.13	−5.52	−2.99	−2.83	0.16	0.87	0.80	0.07
Sulphanilamide	Bustamante et al. 1994	298	Ethanol	−2.12	−3.19	−1.75	−1.90	0.15	0.77	0.80	0.03
Valine (DL)	Greenstein and Winitz, 1961	298	Water	−1.97	−4.13	−1.80	−1.97	0.17	0.86	1.00	0.14
							AAE:	0.08		AAE:	0.06

Table 3: Details of further solubility data of drugs in water-ethanol mixtures at various temperatures (T, K), the predicted and observed log $X_{m(max)}$ at volume fraction of solvent 1 ($f_{1,max}$), absolute error (AE) and average absolute error (AAE)

	Reference	T	Solvent 1	log X_1	log X_2	log $X_{m(max)}$	log $X_{m(max)}$		$f_{1,max}$	$f_{1,max}$	
						Predicted	Observed	AE	Predicted	Observed	AE
Acetaminophen	Jouyban et al. 2006b	298	Ethanol	2.15	1.18	2.55	2.32	0.23	0.76	0.80	0.04
Acetaminophen	Prakongpan and Nagai, 1984	303	Ethanol	2.31	1.32	2.69	2.39	0.30	0.76	0.80	0.04
Acetanilide	Stephen and Stephen, 1964	293	Ethanol	1.35	−0.28	1.62	1.42	0.20	0.82	0.84	0.02
Acetanilide	Pena et al. 2006	298	Ethanol	−1.09	−3.10	−0.90	−1.09	0.19	0.85	1.00	0.15
Acetanilide	Stephen and Stephen, 1964	303	Ethanol	1.46	−0.16	1.71	1.50	0.21	0.82	0.85	0.03
Amobarbital	Breon and Paruta, 1970	298	Ethanol	2.34	−0.25	2.46	2.36	0.10	0.88	0.96	0.08
Barbital	Breon and Paruta, 1970	298	Ethanol	1.97	0.86	2.33	2.08	0.25	0.77	0.88	0.11
Benzocaine	Pena et al. 2006	298	Ethanol	−0.82	−3.22	−0.68	−0.82	0.14	0.87	1.00	0.13
Benzoic acid	Pal and Lahiri, 1989	288	Ethanol	0.35	−1.70	0.56	0.35	0.21	0.84	1.00	0.16
Benzoic acid	Pal and Lahiri, 1989	293	Ethanol	0.40	−1.62	0.60	0.40	0.20	0.84	1.00	0.16
Benzoic acid	Pal and Lahiri, 1989	298	Ethanol	0.44	−1.55	0.64	0.44	0.20	0.84	1.00	0.16
Butabarbital	Breon and Paruta, 1970	298	Ethanol	1.92	−0.05	2.12	1.96	0.16	0.84	0.90	0.06
Butyrine (DL)	Greenstein and Winitz, 1961	298	Water	−1.44	−3.82	−1.30	−1.44	0.14	0.87	1.00	0.13
Cholordiazepoxide	Shokri, 2001	303	Ethanol	−2.47	−5.21	−2.38	−2.30	0.08	0.90	0.90	0.00
Clonazepam	Shokri, 2001	303	Ethanol	−2.99	−6.05	−2.93	−2.98	0.05	0.92	0.90	0.02
Diazepam	Shokri, 2001	303	Ethanol	−2.12	−5.48	−2.08	−2.07	0.01	0.93	0.90	0.03
Ketoprofen	Singhai et al. 1996	298	Ethanol	2.96	−0.97	2.97	2.96	0.01	0.96	1.00	0.04
Ketoprofen	Singhai et al. 1996	310	Ethanol	2.97	−0.88	2.98	2.97	0.01	0.97	1.00	0.03
Lorazepam	Shokri, 2001	303	Ethanol	−2.71	−5.46	−2.62	−2.57	0.05	0.90	0.90	0.00
Mefenamic acid (I)	Romero et al. 1999	298	Ethanol	−2.74	−5.49	−2.64	−2.74	0.10	0.89	1.00	0.11
Mefenamic acid (II)	Romero et al. 1999	298	Ethanol	−2.60	−5.35	−2.50	−2.60	0.10	0.89	1.00	0.11
Methobarbital	Breon and Paruta, 1970	298	Ethanol	1.62	0.30	1.94	1.71	0.23	0.79	0.88	0.09
Methyl p-hydroxybenzoate	Manzo, 1982	298	Ethanol	0.37	−1.84	0.53	0.37	0.16	0.86	1.00	0.14
Octadecanoic acid	Stephen and Stephen, 1964	298	Ethanol	0.92	−1.47	1.06	0.92	0.14	0.87	1.00	0.13
Pentobarbital	Breon and Paruta, 1970	298	Ethanol	2.40	−0.30	2.50	2.40	0.10	0.89	1.00	0.11
Phenacetin	Pena et al. 2006	298	Ethanol	−1.84	−5.00	−1.78	−1.76	0.02	0.92	0.90	0.02
Phenobarbital	Breon and Paruta, 1970	298	Ethanol	2.07	0.08	2.27	2.12	0.15	0.84	0.92	0.08
Phenyl salicylate	Stephen and Stephen, 1964	298	Ethanol	1.54	−1.82	1.59	1.54	0.05	0.93	1.00	0.07
Propyl p-hydroxybenzoate	Manzo, 1982	298	Ethanol	0.43	−2.68	0.49	0.43	0.06	0.92	1.00	0.08
Salicyclic acid	Pena et al. 2006	298	Ethanol	−0.85	−3.70	−0.76	−0.85	0.09	0.90	1.00	0.10
Thimylal	Breon and Paruta, 1970	298	Ethanol	2.21	−1.30	2.25	2.21	0.04	0.94	1.00	0.06
Thiopental	Breon and Paruta, 1970	298	Ethanol	1.75	−1.10	1.84	1.99	0.15	0.90	0.94	0.04
Triglycine	Greenstein and Winitz, 1961	298	Water	−2.24	−7.21	−2.24	−2.24	0.00	1.00	1.00	0.00
Tyrosine	Nozaki and Tanford, 1971	298	Ethanol	−1.35	−3.28	−1.13	−1.35	0.22	0.84	1.00	0.16
Vinbarbital	Breon and Paruta, 1970	298	Ethanol	1.79	−0.16	2.00	1.80	0.20	0.84	0.94	0.10
							AAE:	0.13		AAE:	0.08

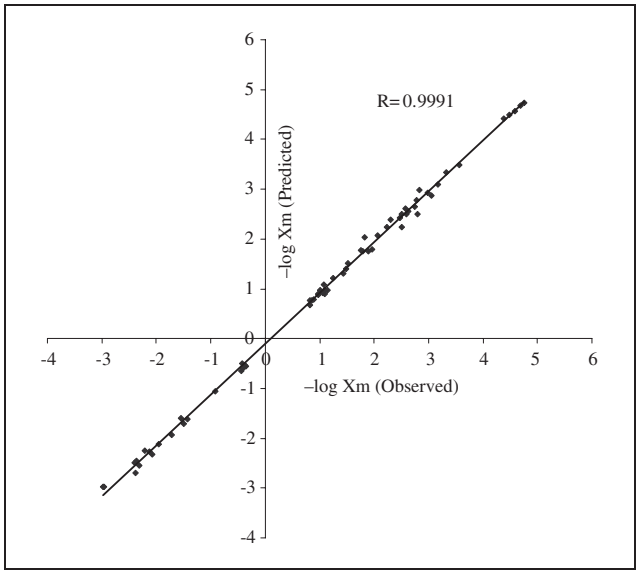

Fig. 2: Maximum predicted solubility of drugs using Eq. (4) versus observed values in ethanol-water mixtures (N = 65)

Eq. (4) and the maximum and minimum of AEs for $\log X_{m(max)}$ were for benz[a]pyrene (and also a number of data sets) (0.00) and norleucine (0.30) and the AAE ($\pm$SD) of $\log X_{m(max)}$ was 0.08 ± 0.08. The minimum, maximum of AEs and AAE ($\pm$SD) for $f_{1,max}$ were 0.00, 0.20 and 0.06 ± 0.05. Data sets of Table 3 were not used in the training process of Eq. (4) and produced the similar results as data sets of Table 2. The AAE ($\pm$SD) for $\log X_{m(max)}$ and $f_{1,max}$ were 0.13 ± 0.08 and 0.08 ± 0.05, respectively. Excellent agreement between predicted and oberserved $\log X_{m(max)}$ for data sets in water-ethanol mixtures is shown in Fig. 2. The wide range of solubility data varying from -8.83 to 2.97 reveals that the model provided acceptable predictions and could be used in pharmaceutical industry, where the maximum solubility in a water-cosolvent mixture and also the optimized solvent composition are highly demanded. Different solubility expressions from mole fraction to gram per liter data have been predicted using Eq. (4) employing various solvent composition expressions from volume fraction to weight fraction. The independence of the proposed method from

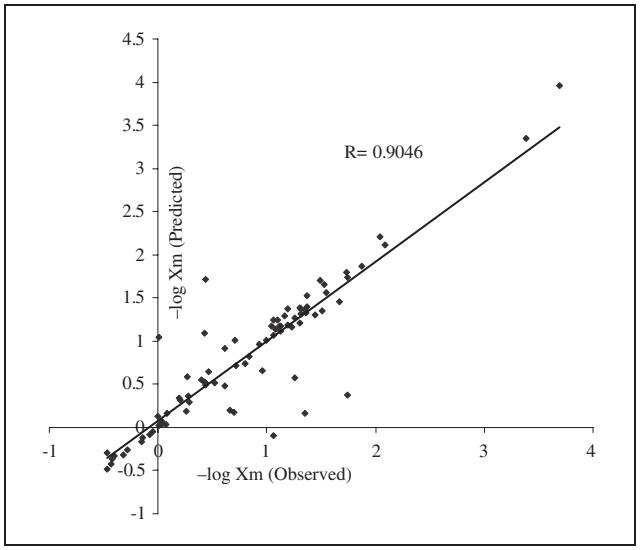

Fig. 3: Maximum predicted solubility of drugs using Eq. (5) versus observed values in PEG 400-water mixtures (N = 81)

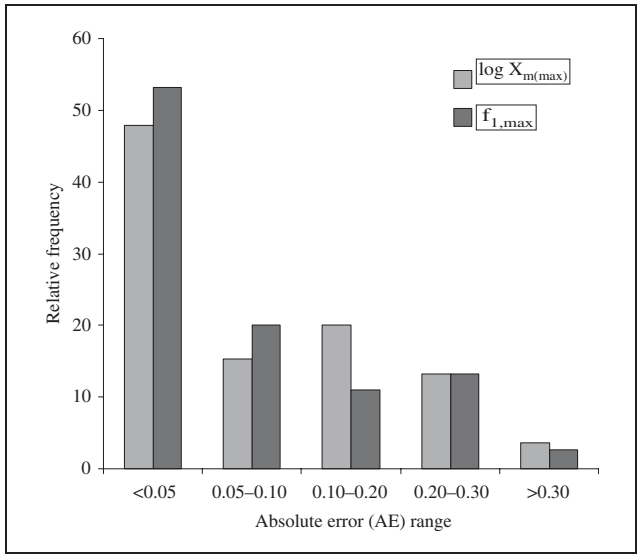

Fig. 4: Relative frequency of absolute errors sorted in five subgroups for predicted $\log X_{m(max)}$ and $f_{1,max}$ of solubility of drugs in water-cosolvent mixtures

solubility and solvent composition expressions facilitates its practical applications. In addition, it predicts the solubility at various temperatures which is quite beneficial in practice. The only limitation of the model is its input data (i.e. solubility of drug in neat water and ethanol), however, aqueous solubility is usually available in early stage of the drug discovery studies. Therefore, by determining only one solubility data in ethanol for each solute, its solubility profile in water-ethanol could be accurately reproduced using Eq. (4).

Equation (5) produced $\log X_{m(max)}$ in water-PEG 400 mixtures with maximum AE of 0.64 for methylparaben and AAE ($\pm$SD) of 0.07 ± 0.13. The corresponding values for $f_{1,max}$ were 0.62 for aminopyrine and 0.12 ± 0.14. Relatively higher AAEs for water-PEG 400 data sets is due to the wide range of solubility data and a limited number of data points in each set. The experimental data were reported at $f_1 = 0.00$, 0.25, 0.50, 0.75 and 1.00 in the reference (Rytting et al. 2005), and for most of drugs $f1 = 0.75$ or 1.00 showed the maximum solubility. However, one cannot assure that the real solubility maximum is 0.75 or 1.00 or at a solvent composition between 0.75 to 1.00. Fig. 3 shows the predicted $\log X_{m(max)}$ versus observed values. The correlation coefficient is 0.9046, and a number of drugs produced relatively high deviation.

AEs for $\log X_{m(max)}$ and $f_{1,max}$ values sorted in five subgroups, i.e. $\leq$0.05, 0.05–0.10, 0.10–0.20, 0.20–0.30 and $>$0.30 and the relative frequencies of the AEs for 186 data sets in three studied solvent systems are shown in Fig. 4. The overall AE distribution was acceptable and the probability of AE $\leq$0.20 for $\log X_{m(max)}$, was 0.83 and for $f_{1,max}$ was 0.84. This means that for a new drug dissolved in the aqueous mixtures of the studied solvent systems, one can predict $\log X_{m(max)}$ and $f_{1,max}$ with acceptable errors by determining its solubility in water and the neat cosolvent of interest.

As a general conclusion, the proposed method provided acceptable predictions and the AAEs ($\pm$SD) of $\log X_{m(max)}$ and $f_{1,max}$ for the available data sets studied were 0.10 ± 0.12 and 0.08 ± 0.10, respectively. The proposed method is able to predict solubilities in different solubility expressions. By using input data, i.e. X_1 and X_2, in mole per liter, the model is able to predict the solubilities in

Table 4: Details of solubility data of drugs in water-PEG 400 mixtures at 296 K[a], the predicted and observed $\log X_{m(max)}$ at volume fraction of solvent 1 ($f_{1,max}$), absolute error (AE) and average absolute error (AAE)

Solute	Solvent 1	$\log X_1$	$\log X_2$	$\log X_{m(max)}$	$\log X_{m(max)}$		$f_{1,max}$	$f_{1,max}$	
				Predicted	Observed	AE	Predicted	Observed	AE
Acetazolamide	PEG 400	−1.32	−2.44	−1.31	−1.11	0.20	0.96	0.75	0.21
Adenine	PEG 400	−1.34	−2.05	−1.30	−1.14	0.16	0.87	0.75	0.12
Adenosine	PEG 400	−1.64	−1.70	−1.26	−1.16	0.10	0.29	0.75	0.46
p-Aminobenzoic acid	PEG 400	0.30	−0.99	0.30	0.30	0.00	0.98	0.75	0.23
Aminopyrine	PEG 400	−0.59	−1.04	−0.47	−0.59	0.12	0.38	1.00	0.62
Ampicillin	Water	−1.65	−3.11	−1.65	−1.35	0.30	1.00	0.75	0.25
Aspirin	PEG 400	−0.13	−1.68	−0.13	−0.13	0.00	1.00	1.00	0.00
Atropine	PEG 400	−1.34	−2.18	−1.31	−1.25	0.06	0.91	0.75	0.16
Azathioprine	PEG 400	−1.39	−3.28	−1.39	−1.39	0.00	1.00	0.75	0.25
Benzamide	PEG 400	−0.56	−1.07	−0.48	−0.19	0.29	0.40	0.50	0.10
Benzoic acid	PEG 400	0.22	−1.60	0.22	0.32	0.10	1.00	0.75	0.25
Bumetanide	PEG 400	−0.52	−4.12	−0.52	−0.52	0.00	1.00	0.75	0.25
Butamben	PEG 400	0.47	−3.05	0.47	0.48	0.01	1.00	1.00	0.00
Butylparaben	PEG 400	0.43	−2.96	0.43	0.43	0.00	1.00	1.00	0.00
Carbamazepine	PEG 400	−0.86	−3.16	−0.86	−0.74	0.12	1.00	0.75	0.25
Chloramphenicol	PEG 400	−0.32	−1.94	−0.32	−0.32	0.00	1.00	1.00	0.00
Chlorthalidone	PEG 400	−0.88	−3.34	−0.88	−0.82	0.06	1.00	0.75	0.25
Chlorzoxazone	PEG 400	−0.49	−2.87	−0.49	−0.49	0.00	1.00	1.00	0.00
Cimetidine	PEG 400	−0.80	−1.07	−0.56	−0.52	0.04	0.33	0.75	0.42
Clofazimine	PEG 400	−1.72	−6.22	−1.72	−1.72	0.00	1.00	1.00	0.00
Cortisone	PEG 400	−1.66	−3.18	−1.66	−1.66	0.00	1.00	1.00	0.00
Dapsone	PEG 400	−0.75	−3.07	−0.75	−0.17	0.58	1.00	0.75	0.25
Deoxycorticosterone	PEG 400	−0.96	−3.59	−0.96	−0.96	0.00	1.00	1.00	0.00
Dexamethasone	PEG 400	−1.37	−3.68	−1.37	−1.37	0.00	1.00	1.00	0.00
Diflunisal	PEG 400	−1.33	−4.11	−1.33	−1.21	0.12	1.00	0.75	0.25
Diosgenin	PEG 400	−2.11	−5.08	−2.11	−2.11	0.00	1.00	1.00	0.00
Disopyramide	PEG 400	−0.34	−1.75	−0.34	−0.34	0.00	1.00	1.00	0.00
Equilin	PEG 400	−1.19	−5.00	−1.19	−1.19	0.00	1.00	1.00	0.00
Estradiol-17-alpha	PEG 400	−1.37	−5.31	−1.37	−1.37	0.00	1.00	1.00	0.00
Estriol	PEG 400	−1.34	−4.09	−1.34	−1.32	0.02	1.00	0.75	0.25
Estrone	PEG 400	−1.87	−5.25	−1.87	−1.87	0.00	1.00	0.75	0.25
Ethylparaben	PEG 400	0.24	−2.29	0.24	0.26	0.02	1.00	0.75	0.25
Fenbufen	PEG 400	−1.01	−4.14	−1.01	−1.01	0.00	1.00	1.00	0.00
Flufenamic acid	PEG 400	−1.07	−4.41	−1.07	−1.07	0.00	1.00	1.00	0.00
Flurbiprofen	PEG 400	0.10	−3.86	0.10	0.10	0.00	1.00	1.00	0.00
Glafenine	PEG 400	−1.36	−4.54	−1.36	−1.36	0.00	1.00	1.00	0.00
Griseofulvin	PEG 400	−0.16	−4.56	−0.16	−0.16	0.00	1.00	1.00	0.00
Guaifenesin	PEG 400	−0.31	−0.96	−0.26	−0.03	0.23	0.86	0.75	0.11
Guanine	Water	−4.07	−4.24	−3.76	−3.96	0.20	0.31	0.25	0.06
Hydrochlorothiazide	PEG 400	−1.07	−2.78	−1.07	−0.66	0.41	1.00	0.75	0.25
Hydrocortisone	PEG 400	−1.85	−3.03	−1.85	−1.46	0.39	0.97	0.75	0.22
Hydroflumethiazide	PEG 400	−1.48	−3.09	−1.48	−1.33	0.15	1.00	0.75	0.25
Ibuprofen	PEG 400	0.08	−3.63	0.08	0.08	0.00	1.00	1.00	0.00
Indapamide	PEG 400	−0.62	−3.70	−0.62	−0.48	0.14	1.00	0.75	0.25
Indoprofen	PEG 400	−1.27	−4.31	−1.27	−1.27	0.00	1.00	1.00	0.00
Iopanoic acid	PEG 400	−0.57	−5.48	−0.57	−0.57	0.00	1.00	1.00	0.00
Ketoprofen	PEG 400	−0.02	−3.28	−0.02	−0.02	0.00	1.00	1.00	0.00
Mefenamic acid	PEG 400	−1.05	−5.18	−1.05	−1.05	0.00	1.00	1.00	0.00
Methylparaben	PEG 400	−0.84	−2.06	−0.84	−0.20	0.64	0.97	0.75	0.22
Metronidazole	Water	−1.13	−1.16	−0.73	−1.01	0.28	0.28	0.25	0.03
Minoxidil	PEG 400	−1.84	−1.94	−1.49	−1.30	0.19	0.29	0.50	0.21
Nadolol	Water	−1.01	−1.12	−0.66	−0.91	0.25	0.30	0.25	0.05
Nalidixic acid	PEG 400	−2.21	−3.50	−2.21	−2.21	0.00	0.98	1.00	0.02
Naphthalene	PEG 400	0.05	−3.67	0.05	0.05	0.00	1.00	1.00	0.00
2-Naphthol	PEG 400	−0.14	−2.27	−0.14	−0.03	0.11	1.00	0.75	0.25
Naproxen	PEG 400	−0.29	−3.79	−0.29	−0.29	0.00	1.00	1.00	0.00
Norethisterone	PEG 400	−1.56	−4.66	−1.56	−1.56	0.00	1.00	1.00	0.00
Norfloxacin	PEG 400	−1.69	−2.76	−1.68	−1.70	0.02	0.95	1.00	0.05
Paracetamol	PEG 400	−0.06	−1.08	−0.05	0.17	0.22	0.94	0.75	0.19
Phenacetin	PEG 400	−0.53	−2.35	−0.53	−0.53	0.00	1.00	1.00	0.00
Phenolphthalein	PEG 400	−1.13	−5.00	−1.13	−1.09	0.04	1.00	0.75	0.25
Phenylbutazone	PEG 400	−0.72	−4.13	−0.72	−0.72	0.00	1.00	0.75	0.25
Prednisolone	PEG 400	−1.22	−3.18	−1.22	−1.18	0.04	1.00	0.75	0.25
Primidone	PEG 400	−1.63	−2.36	−1.59	−1.53	0.06	0.88	0.75	0.13
Progesterone	PEG 400	−1.40	−4.17	−1.40	−1.40	0.00	1.00	1.00	0.00
Propylparaben	PEG 400	0.12	−2.74	0.12	0.12	0.00	1.00	1.00	0.00
Quinidine	PEG 400	−1.17	−2.77	−1.17	−1.17	0.00	1.00	1.00	0.00
Quinine	PEG 400	−0.36	−2.43	−0.36	−0.36	0.00	1.00	1.00	0.00

Table 4: Continued

Solute	Solvent 1	log X_1	log X_2	log $X_{m(max)}$	log $X_{m(max)}$		$f_{1,max}$	$f_{1,max}$	
				Predicted	Observed	AE	Predicted	Observed	AE
Salicylamide	PEG 400	0.33	−1.77	0.33	0.33	0.00	1.00	1.00	0.00
Salicylic acid	PEG 400	0.36	−1.86	0.36	0.36	0.00	1.00	1.00	0.00
Sulfadiazine	PEG 400	−1.17	−3.60	−1.17	−1.17	0.00	1.00	1.00	0.00
Sulfamethazine	PEG 400	−1.29	−2.86	−1.29	−1.29	0.00	1.00	1.00	0.00
Sulfamethoxazole	PEG 400	−0.07	−2.85	−0.07	−0.07	0.00	1.00	1.00	0.00
Sulfanilamide	PEG 400	−0.73	−1.41	−0.69	−0.64	0.05	0.87	0.50	0.37
Sulfathiazole	PEG 400	−0.16	−2.18	−0.16	−0.16	0.00	1.00	1.00	0.00
Tenoxicam	PEG 400	−1.80	−3.94	−1.80	−1.80	0.00	1.00	1.00	0.00
Thiamphenicol	PEG 400	−0.56	−1.86	−0.56	−0.55	0.01	0.98	0.75	0.23
Triamcinolone	PEG 400	−1.85	−3.61	−1.85	−1.74	0.11	1.00	0.75	0.25
1,2,3-Trichlorobenzene	PEG 400	−0.38	−5.47	−0.38	−0.38	0.00	1.00	1.00	0.00
Trimethoprim	PEG 400	−1.25	−2.35	−1.24	−1.25	0.01	0.95	1.00	0.05
Xanthine	PEG 400	−3.78	−3.87	−3.42	−3.35	0.07	0.29	0.75	0.46
					AAE:	0.07		AAE:	0.12

[a]All solubility data in water-PEG 400 taken from Rytting et al. (2005).

mole per liter and so on. Considering the temperature parameter, using two solubility data points (at the lowest and highest temperature of interest) for each solubility set, it is possible to predict the solubility by van't Hoff plot and using an interpolation method.

References

Acree Jr WE (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. Thermochim Acta 198: 71–79.

Acree Jr WE (1996) Comments concerning 'Models for solubility estimation in mixed solvent systems'. Int J Pharm 127: 27–30.

Adjei A, Newburger J, Martin A (1980) Extended Hildebrand approach. Solubility of caffeine in dioxane-water mixtures. J Pharm Sci 69: 659–661.

Barzegar-Jalali M, Jouyban-Gharamaleki A (1997) A general model from theoretical cosolvency models. Int J Pharm 152: 247–250.

Breon TL, Paruta AN (1970) Solubility profiles for several barbiturates in hydroalcoholic mixtures. J Pharm Sci 59: 1306–1313.

Bustamante C, Bustamante P (1996) Nonlinear enthalpy-entropy compensation for the solubility of phenacetin in dioxane-water solvent mixtures. J Pharm Sci 85: 1109–1111.

Bustamante P, Escalera B, Martin A, Selles E (1993) A modification of the extended Hildebrand approach to predict the solubility of structurally related drugs in solvent mixtures. J Pharm Pharmacol 45: 253–257.

Bustamante P, Ochoa R, Reillo A, Escalera JB (1994) Chameleonic effect of sulfanilamide and sulfamethazine in solvent mixtures. solubility curves with two maxima. Chem Pharm Bull 42: 1129–1133.

Bustamante P, Romero S, Reillo A (1995) Thermodynamics of paracetamol in amphiprotic and amphiprotic-aprotic solvent mixtures. Pharm Sci 1: 505–507.

Bustamante P, Romero S, Pena A, Escalera B, Reillo A (1998) Enthalpy-entropy compensation for the solubility of drugs in solvent mixtures: Paracetamol, acetanilide and nalidixic acid in dioxane-water. J Pharm Sci 87: 1590–1596.

Bustamante P, Navarro J, Romero S, Escalera B (2002) Thermodynamic origin of the solubility profile of drugs showing one or two maxima against the polarity of aqueous and nonaqueous mixtures: Niflumic acid and caffeine. J Pharm Sci 91: 874–883.

Greenstein JP, Winitz M (1961) Chemistry of Amino Acids, Vol. 1, John Wiley & Sons, New York, p. 547.

Jouyban A (2006) Solubility prediction of drugs in water-PEG 400 mixtures. Chem Pharm Bull 54: 1561–1566.

Jouyban A (2007) In silico prediction of drug solubility in water-dioxane mixtures using Jouyban-Acree model. Pharmazie 62: 46–50.

Jouyban A, Clark BJ (2002) Describing solubility of polymorphs in mixed solvents by CNIBS/R-K equation. Pharmazie 57: 861–862.

Jouyban A, Acree Jr WE (2006) In silico prediction of drug solubility in water-ethanol mixtures using Jouyban-Acree model. J Pharm Pharmaceut Sci 9: 262–269.

Jouyban A, Romero S, Chan HK, Clark BJ, Bustamante P (2002) A cosolvency model to predict solubility of drugs at several temperatures from a limited number of solubility measurements. Chem Pharm Bull 50: 594–599.

Jouyban A, Chew NYK, Chan HK, Khoubnasabjafari M, Acree Jr WE (2006a) Solubility predicton of salicylic acid in water-ethanol-propylene glycol mixtures using the Jouyban-Acree model. Pharmazie 61: 318–321.

Jouyban A, Chan HK, Chew NYK, Khoubnasabjafari M, Acree Jr WE (2006b) Solubility predicton of paracetamol in in binray and ternary solvent mixtures using Jouyban-Acree model. Chem Pharm Bull 54: 428–431.

Jouyban-Gharamaleki A, Hanaee J (1997) A novel method for improvement of predictability of the CNIBS/R-K equation. Int J Pharm 154: 245–247.

Jouyban-Gharamaleki A (1998) The modified Wilson model and predicting drug solubility in water-cosolvent mixtures. Chem Pharm Bull 46: 1058–1059.

Jouyban-Gharamaleki A, Acree Jr WE (1998) Comparison of models for describing multiple peaks in solubility profiles. Int J Pharm 167: 177–182.

Jouyban-Gharamaleki A, Barzegar-Jalali M, Acree Jr WE (1998) Solubility correlation of structurally related drugs in binary solvent mixtures. Int J Pharm 166: 205–209.

Jouyban-Gharamaleki A, Valaee L, Barzegar-Jalali M, Clark BJ, Acree Jr WE (1999) Comparison of various cosolvency models for calculating solute solubility in water-cosolvent mixtures. Int J Pharm 177: 93–101.

Jouyban-Gharamaleki A, Romero S, Bustamante P, Clark BJ (2000) Multiple solubility maxima of oxolinic acid in mixed solvents and a new extension of Hildebrand solubility approach. Chem Pharm Bull 48: 175–178.

Jouyban-Gharamaleki A, Dastmalchi S, Chan HK, Hanaee J, Javanmard A, Barzegar-Jalali M (2001a) Solubility prediction for furosemide in water-cosolvent mixtures using the minimum number of experiments. Drug Dev Ind Pharm 27: 577–583.

Jouyban-Gharamaleki A, York P, Hanna M, Clark BJ (2001b) Solubility prediction of salmeterol xinafoate in water-dioxane mixtures. Int J Pharm 216: 33–41.

Li A, Yalkowsky SH (1994) Solubility of organic solutes in ethanol-water mixtures. J Pharm Sci 83: 1735–1740.

Manzo RH (1982) Effects of solvent medium on solubility. A linear free energy relationship treatment. J Pharm Pharmacol 34: 486–492.

Martin A, Newburger J, Adjei A (1980) Extended Hildebrand solubility approach: Solubility of theophylline in polar binary solvents. J Pharm Sci 69: 784–491.

Martin A, Paruta AN, Adjei A (1981) Extended Hildebrand solubility approach: Methylxanthines in mixed solvents. J Pharm Sci 70: 1115–1120.

Martin A, Wu PL, Velasquez T (1985) Extended Hildebrand solubility approach. Sulfonamides in binary and ternary solvents. J. Pharm. Sci. 74: 277-282.

Nozaki Y, Tanford C (1971) The solubility of amino acids and two glycine peptides in aqueous ethanol and dioxane solutions. J Biol Chem 246: 2211–2217.

Pena MA, Reillo A, Escalera B, Bustamante P (2006) Solubility parameter of drugs for predicting the solubility profile type within a wide polarity range in solvent mixtures. Int J Pharm 321: 155–161.

Prakongpan S, Nagai T (1984) Pharmaceutical interactions in dosage forms and processing .45. Solubility of acetaminophen in cosolvents. Chem Pharm Bull 32: 340–343.

Reillo A, Escalera B, Selles E (1993) Prediction of sulfanilamide solubility in dioxane-water mixtures. Pharmazie 48: 904–907.

Reillo A, Cordoba M. Escalera B, Selles E, Cordoba Jr M (1995a) Prediction of sulfamethiazine solubility in dioxane-water mixtures. Pharmazie 50: 472–475.

Reillo A, Bustamante P, Escalera B, Jimenez MM, Selles E (1995b) Solubility parameter-based methods for predicting the solubility of sulfapyridine in solvent mixtures. Drug Dev Ind Pharm 21: 2073–2084.

Romero S, Reillo A, Escalera B, Bustamante P (1996) The behaviour of paracetamol in mixtures of aprotic and amphiprotic-aprotic solvents. Relationship of solubility curves to specific and nonspecific interactions. Chem Pharm Bull 44: 1061–1064.

Romero S, Escalera B, Bustamante P (1999) Solubility behavior of polymorphs I and II of mefenamic acid in solvent mixtures. Int J Pharm 178: 193–202.

Ruckenstein E, Shulgin I (2003) Solubility of drugs in aqueous solutions – Part 2: Binary nonideal mixed solvent. Int J Pharm 260: 283–291.

Rytting E, Lentz KA, Chen XQ, Qian F, Venkatesh S (2005) Aqueous and cosolvent solubility data for drug-like organic compounds. AAPS J 7: E78–E105.

Singhai AK, Jain S, Jain NK (1996) Cosolvent solubilization and formulation of an aqueous injection of ketoprofen. Pharmazie 51: 737–740.

Shokri J (2001) PhD Dissertation, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

Stephen H, Stephen T (1964) Solubilities of Inorganic and Organic Compounds, Vol. 2, MacMillan, New York, pp. 1169-1170, 1190, 1200.

Subrahmanyam CVS, Ravi Prakash K, Gundu Rao P (1996) Estimation of the solubility parameter of trimethoprim by current method. Pharm Acta Helv 71: 175–183.

Williams NA, Amidon GL (1984) Excess free energy approach to the estimation of solubility in mixed solvent systems I. Theory. J Pharm Sci 73: 9–13.

Wu PL, Martin A (1983) Extended Hildebrand solubility approach: p-Hydroxybenzoic acid in mixtures of dioxane and water. J Pharm Sci 72: 587–595.

Yalkowsky SH, Roseman T (1981) In: Yalkowsky SH (Ed), Solubilization of Drugs by Cosolvents. Marcel Dekker, New York, pp. 91–134.