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In silico prediction of drug solubility in water-dioxane mixtures using the Jouyban-Acree model

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A numerical method based on the Jouyban-Acree model was presented for prediction of drug solubility in water-dioxane mixtures at various temperatures. The method requires drug solubility in monosolvent systems, i.e. two data points for each temperature of interest. The mean percentage deviation (MPD) of predicted solubilities was calculated to show the accuracy of the predicted data and 27% was found as the average MPD for 36 data sets studied. The proposed numerical method reduced the number of required experimental data from five to two points and could also be extended to predict solubility at various temperatures.

1. Introduction

Dissolving a desired amount of a drug in a given volume of a solvent and/or a solvent mixture is still a challenging area in pharmaceutical industry. The history of systematic solubility studies in mixed solvent systems date back to a couple of decades ago. Paruta and his co-workers (1964) have studied the solubility of different drugs in water-cosolvent mixtures and tried to explain the solubility behavior based on variations of dielectric constant of the solvent which is assumed as an indicator of solvent's polarity (Paruta et al. 1964). In 1972, Yalkowsky and co-workers proposed the log-linear equation to represent the drug solubility in water-cosolvent mixtures using solute free volume fraction of the cosolvent (Yalkowsy and Roseman 1981). Martin et al. (1981) have extended the Hildebrand solubility approach to describe the solubility of polar/semi-polar drugs in aqueous mixtures of a model cosolvent, dioxane. The excess free energy approach (Williams and Amidon 1984), mixture response surface (Ochsner et al. 1985), the phenomenological model (Khossravi and Connors 1992), the combined nearly ideal binary solvent/Redlich-Kister equation, so-called the Jouyban-Acree model (Acree 1996; Jouyban-Gh et al. 1999; Jouyban et al. 2006), the modified Wilson model (Jouyban-Gh 1998) and fluctuation theory (Ruckenstein and Shulgin 2003) have also been employed to model drug solubility data in aqueous binary solvent mixtures. In addition to the models mentioned above, attempts have been made to build a general correlative/predictive equation for a group of structurally related drugs in a given aqueous binary solvents (Bustamante et al. 1993; Jouyban-Gh et al. 1998). Most of the models require relatively complex computational methods, a number of experimental data points to train the model and also a knowledge of physico-chemical properties such as molar volume, solubility parameters etc of the solute and solvents. In addition to the experimentally originated errors (as an example of such errors see Kishi and Hashimoto (1989)), any error in computations/determinations of these physico-chemical properties could be source of a major error in solubility calculations. As an example, different numerical values of solute's solubility parameters produced prediction errors between 58 and 30915% in prediction of the solubility of p-hydroxybenzoic acid in water-dioxane mixtures (Jouyban-Gh et al. 1998).

From these models, the log-linear equation of Yalkowsky has been preferred, because of its simplicity and applicability in pharmaceutical industry where researchers are more interested in models requiring simple and easy computational operations. However, the model is only applicable for solubility profiles showing no solubility maximum in mixed solvents. This is not the case for most of the drug solubility profiles in water-pharmaceutically interesting cosolvent mixtures and there is a number of solubility profiles, such as solubility in water-ethanol mixtures (as examples see Romero et al. 1996; Bustamante et al. 2002) which show solubility maximum. As previously reported (Li and Yalkowsky 1994) a couple of reasons could be provided to explain these deviations from log-linear relationship.

In prediction of a solute solubility in a given mixed solvent system showing no solubility maxima, reasonably acceptable predictions could be made using Yalkowsky's log-linear equation. In order to estimate the solubility of different solutes in a given binary solvent systems, Millard et al. (2002) reported the solubilization power of four common pharmaceutical cosolvents. From this correlation, each cosolvent has two constant values and the aqueous solubility of a drug and its partition coefficient are required as input data to predict the solubility in water-cosolvent mixtures. Machatha and Yalkowsky (2004) used half slope of the log-linear solubilization power ($\sigma_{0.5}$) to predict the cosolvent fraction giving the maximum solubility of a drug. The required data were partition coefficients of the cosolvent and the solute. The partition coefficient (logP) of a solute

could be determined experimentally or calculated using software like ClogP®, ACDlogP and KowWin® The logP data calculated using ClogP® software provided more accurate results (Machatha and Yalkowsky 2005). This prediction could help pharmaceutical industry to speed up the optimization of liquid drug formulations where the cosolvent fraction should be kept as low as possible, usually less than 0.5. Rytting et al. (2004) proposed quantitative structure-property relationships (QSPRs) to compute solubility of drug/drug like molecules in water-PEG 400 mixtures using molecular descriptors computed by Cerius software and different sets of model constants for each binary solvent composition. The most accurate prediction for all solvent systems could be achieved using the Jouyban-Acree model with a minimum number of experimental data as training set and prediction at other solvent compositions. This point has been discussed in more details in previous publications (Jouyban-Gh et al. 2001a, b). To broaden the prediction capability of the Jouyban-Acree model, it was used for prediction of the solubility of structurally related drugs in a given binary solvent system. This type of prediction could be more appropriate for extending the available solubility data of related drugs to predict the solubility of a new drug candidate from the same chemical group (Jouyban-Gh et al. 1998).

Solubility prediction of different solutes in various solvent systems with an acceptable error range is the ultimate goal of predictions in this area. The produced prediction errors for such models are relatively high and could not be recommended to be used in pharmaceutical industry and an accurate predictive model was not proposed so far. However, considering rapid growth in databases and also computational methods, it is expected to be presented in the near future. The aim of this work was to establish model constants of the Jouyban-Acree model for water-dioxane mixtures to predict the solubility of various solutes in a given water-dioxane mixture at different temperatures employing solubilities of the solute in mono-solvent systems. Dioxane is not a pharmaceutically acceptable cosolvent, however, since it is completely miscible with water and provides the widest polarity range, it is capable of dissolving poorly soluble drugs. It has been extensively used as a model cosolvent in cosolvency studies, therefore, the proposed method is checked using solubility data in water-dioxane mixtures.

2. Investigations, results and discussion

2.1. Computational methods

The Jouyban-Acree model was used to correlate different physico-chemical properties in mixed solvent systems which is briefly reviewed in a recent paper (Jouyban et al. 2005). Its basic form to calculate a solute solubility in water-cosolvent mixture is:

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + f_c f_w \sum_{i=0}^{2} A_i (f_c - f_w)^i \quad (1)$$

where X_m is the mole fraction solubility of the solute in solvent mixture, f_c and f_w the volume fractions of cosolvent and water in the absence of the solute, X_c and X_w the mole fraction solubilities in neat cosolvent and water, respectively, and A_i the solvent-solvent and solute-solvent interaction terms (Acree 1992) computed using a no-intercept least square analysis (Jouyban-Gh and Hanaee 1997) for each binary solvent system. The A_i coefficients in Eq. (1) do have theoretical signficance in that each coefficient is a function of two-body and three-body interaction energies that describe the attractions between the various molecules in solution (Acree 1992). In the case of a solute 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, s-s, c-w, c-s and w-s) and all ten possible three-body (c-c-c, w-w-w, s-s-s, c-c-w, c-w-w, c-c-s, c-s-s, w-w-s, w-s-s and c-w-s) molecular interactions between water (w), cosolvent (c) and solute (s) molecules. Equation (1) was derived by differentiating the integral excess Gibbs energy of mixing equation for the mixture containing components c, w and s, expressed in terms of the 16 fore-mentioned two-body and three-body interaction energies, with respect to the number of moles of solute. Raoult's law was used for the entropic contribution in the integral Gibbs energy of mixing equation. More details of the derivation of the model could be found in 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-Gh and Acree 1998):

$$\ln X_{m,T} = f_c \ln X_{c,T} + f_w \ln X_{w,T} + f_c f_w \sum_{i=0}^{2} \frac{J_i (f_c - f_w)^i}{T} \quad (2)$$

where $X_{m,T}$, $X_{c,T}$ and $X_{w,T}$ are the mole fraction solubility of the solute in solvent mixture, cosolvent and water in the absence of the solute at temperature (T, °K) and J_i is the model constant.

The mean percentage deviations (MPD) were used to check the accuracy of the prediction method and is calculated using eq. (3).

$$\mathrm{MPD} = \frac{100}{N} \sum \frac{|\mathrm{Calculated} - \mathrm{Observed}|}{\mathrm{Observed}} \quad (3)$$

in which N is the number of solubility data points. The individual percentage deviations (IPD) was also computed using:

$$\mathrm{IPD} = 100 \left(\frac{|\mathrm{Calculated} - \mathrm{Observed}|}{\mathrm{Observed}} \right).$$

2.2. Results and discussion

Available experimental solubility data of drugs in water-dioxane mixtures at a constant and/or various temperatures were collected from the literature (for details see Table) and regressed using Eq. (2). The obtained equation is:

$$\ln X_{m,T} = f_c \ln X_{c,T} + f_w \ln X_{w,T} + f_c f_w \times \left[\frac{2206.9}{T} + \frac{1173.1(f_c - f_w)}{T} + \frac{1997.4(f_c - f_w)^2}{T} \right] \quad (4)$$

$$R = 0.972, \quad N = 504, \quad F = 2870.7, \quad p < 0.0005$$

Statistical parameters shown above indicate that the model is a significant model with high F value. The significance of the model constants was checked using t-test and the constants were statistically significant with $p < 0.0005$.

As discussed above, the model constants of the Jouyban-Acree model are functions of solute and solvents of a solution. Using these constants it is possible to predict the solubility of a solute in water-dioxane mixtures at various temperatures and the required experimental data are the

Table: Details of experimental solubility data of solutes in water-dioxane mixtures at various temperatures (T, °K), the number of data points in each set (N), logarithms of the mole fraction solubilities in mono-solvent systems ($\ln X_{c,T}$ and $\ln X_{w,T}$), mean percentage deviation (MPD) and the model constants (J_0, J_1 and J_2) computed using leave one out

No.	Solute	Ref.	T	$\ln X_{c,T}$	$\ln X_{w,T}$	N	MPD	MPD	J_0	J_1	J_2
1	Acetanilide	[1]	293	−2.37	−7.26	11	33.3	–	2216.4	1193.3	1979.5
2	Acetanilide	[1]	298	−2.12	−7.13	11	36.9	–	2217.1	1195.7	1978.2
3	Acetanilide	[1]	303	−2.01	−7.01	11	33.0	–	2214.1	1195.9	1979.8
4	Acetanilide	[1]	308	−1.81	−7.01	11	32.5	–	2210.3	1201.2	1982.4
5	Acetanilide	[1]	313	−1.55	−6.81	11	36.9	–	2212.2	1201.8	1984.4
6	Caffeine	[2]	298	−4.77	−6.08	16	34.8	–	2226.8	1188.3	1991.4
7	Nalidixic acid	[1]	283	−6.91	−13.23	12	62.2	–	2228.2	1170.1	2012.5
8	Nalidixic acid	[1]	293	−6.76	−13.07	12	53.5	–	2224.8	1168.8	2013.3
9	Nalidixic acid	[1]	298	−6.62	−12.94	12	44.3	–	2222.2	1168.6	2010.0
10	Nalidixic acid	[1]	303	−6.50	−12.75	12	34.7	–	2218.7	1166.8	2011.2
11	Nalidixic acid	[1]	308	−6.50	−12.53	12	24.8	–	2215.6	1165.8	2008.3
12	Nalidixic acid	[1]	313	−6.40	−12.21	12	19.9	–	2211.6	1161.2	2017.9
13	p-Hydroxybenzoic acid	[3]	298	−2.47	−7.42	13	33.4	–	2211.8	1205.5	2019.0
14	Paracetamol	[1]	293	−3.70	−6.38	12	12.2	–	2201.3	1174.2	1997.6
15	Paracetamol	[1]	298	−3.62	−6.27	12	15.7	–	2198.7	1174.7	1995.5
16	Paracetamol	[1]	303	−3.53	−6.07	12	16.9	–	2196.1	1175.3	2003.0
17	Paracetamol	[1]	308	−3.45	−5.95	12	21.3	–	2192.7	1177.0	2006.3
18	Paracetamol	[1]	313	−3.34	−5.81	12	22.7	–	2192.0	1177.0	2006.8
19	Paracetamol	[4]	298	−3.03	−6.27	17	9.4	18.1	2200.1	1178.7	2013.2
20	Phenacetin	[5]	293	−4.26	−9.61	13	13.0	17.8	2208.0	1152.8	2016.6
21	Phenacetin	[5]	298	−4.07	−9.41	13	11.4	17.1	2205.2	1156.3	2019.7
22	Phenacetin	[5]	303	−3.84	−9.18	13	11.3	17.3	2204.3	1157.1	2020.9
23	Phenacetin	[5]	308	−3.63	−9.04	13	8.1	15.1	2202.5	1166.5	2012.0
24	Phenacetin	[5]	313	−3.48	−8.84	13	10.4	17.0	2200.3	1167.6	2014.6
25	Salmeterol xinafoate	[6]	292	−5.45	−12.79	12	45.0	47.9	2180.5	1116.4	1984.6
26	Sulfadiazine	[7]	298	−7.61	−12.33	17	24.7	32.8	2195.1	1167.0	1964.2
27	Sulfadimidine	[7]	298	−6.51	−12.71	19	16.2	23.9	2208.8	1153.0	2000.1
28	Sulfamethizole	[8]	298	−6.94	−10.25	19	41.6	47.3	2201.9	1103.4	1840.9
29	Sulfamethoxazol	[7]	298	−3.51	−10.67	15	15.1	24.5	2196.1	1184.8	1995.4
30	Sulfanilamide	[9]	298	−2.52	−7.35	16	14.1	15.7	2202.4	1180.3	2014.5
31	Sulfapyridine	[10]	298	−10.29	−13.24	17	38.8	29.1	2229.7	1177.6	1969.8
32	Sulfisomidine	[11]	298	−5.99	−9.21	21	24.7	33.4	2189.6	1158.3	1973.3
33	Sulphamethoxypyridazine	[7]	298	−3.74	−10.20	18	27.7	36.1	2183.1	1148.2	2008.2
34	Theobromine	[12]	298	−7.72	−10.32	11	51.1	32.1	2216.9	1194.6	2020.8
35	Theophylline	[13]	298	−5.95	−7.21	21	7.8	16.6	2203.5	1162.4	2016.1
36	Trimethoprim	[14]	298	−5.80	−10.77	20	39.6	25.4	2209.7	1240.5	2018.3
						Mean:	27.2	26.0	2206.9	1173.0	1997.2

[1] Bustamante et al. (1998); [2] Adjei et al. (1980); [3] Wu et al. (1983); [4] Romero et al. (1996); [5] Bustamante and Bustamante (1996); [6] Jouyban-Gh et al. (2001b); [7] Bustamate et al. (1993); [8] Reillo et al. (1995a); [9] Reillo et al. (1993); [10] Reillo et al. (1995b); [11] Martin et al. (1985); [12] Martin et al. (1981); [13] Martin et al. (1980); [14] Subrahmanyam et al. (1996)

numerical values of $X_{c,T}$ and $X_{w,T}$. The predicted solubility is compared with the corresponding experimental value, the MPD values were computed and the results were listed in the Table. The minimum MPD (7.8%) was obtained for solubility prediction of theophylline at 25 °C and the maximum MPD (62.2 %) was observed for solubility prediction of nalidixic acid at 10 °C. The average (± SD) of MPD for the studied data sets was 27.2 (±14.3). The produced error is relatively high, however it could be considered as an acceptable error in pharmaceutical applications where $< 30\%$ was accepted (Beerbower et al. 1984; Reillo et al. 1995a).

The IPDs of predicted solubilities were sorted in three subgroups, i.e. IPD $\leq 4\%$ (comparable with experimental uncertainity), 4–30 (acceptable error range in pharmaceutical applications) and $> 30\%$ (unacceptable error range). The relative frequency of IPDs were illustrated in Fig. 1. The probability of solubility prediction in water-dioxane at various temperatures within acceptable error range is 0.66. There are good agreements between experimental ($-\ln X_m$) and predicted solubilities as shown in Fig. 2.

To show the applicability of the proposed prediction method on unmeasured solubility data of solutes, the data set numbers of 1–18 from the Table, were used to train Eq. (2) and the solubility data of set numbers 19–36 were predicted using the trained model. The average MPD (± SD) was 26.0 (± 10.5)%. There was no significant difference between 27.2 and 26.0% obtained using trained models employing 36 and 18 data sets, respectively, and this confirms that the model is capable of predicting unmeasured

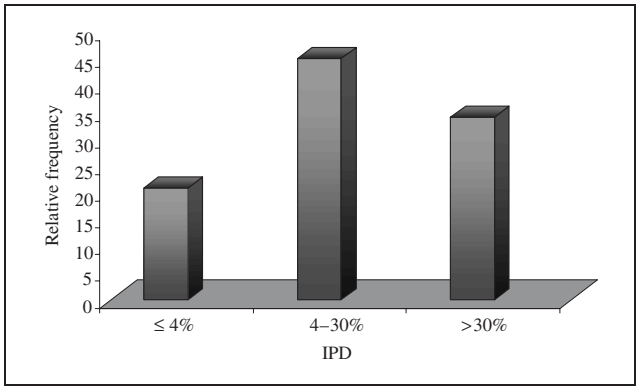

Fig. 1: Relative frequency of individual percentage deviation (IPD) for predicted solubilities (N = 504)

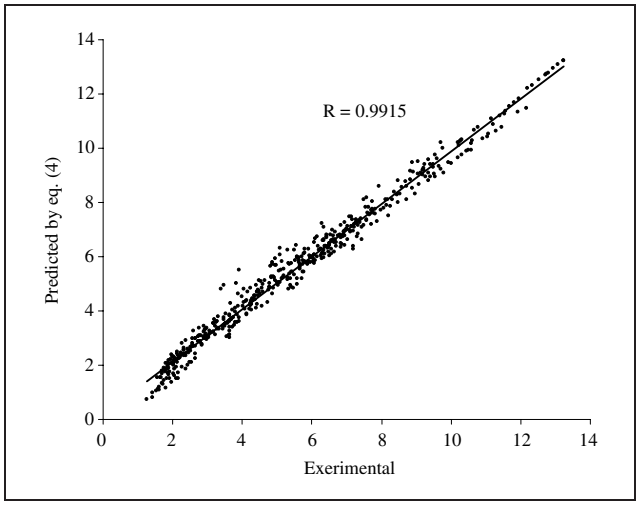

Fig. 2: Experimental $-\ln X_m$ versus predicted values using Eq. (4)

solubilities with the overall prediction error of ~27%. In order to further check on the stability of the model constants, leave one out method was used. In each run of computing the model constants, one data set was excluded from the calculations. The results shown in the Table and the means of J_i values from this analysis which are exactly the same as appeared in Eq. (4) reveal that the model constants are robust and Eq. (4) could be used to predict the solubility of drugs in water-dioxane mixtures at various temperatures.

While using the proposed prediction method, one should consider that:

- Solubility of the solute of interest in water and dioxane should be determined experimentally and used as input variable of the model. Although, there is a number of models to estimate the solubility of solutes in mono-solvent systems (as an example see Abraham and Lee 1999), their prediction capability is questionable because of a large prediction error.
- The solvent composition of the mixed solvent system should be expressed as volume fraction (f_c for volume fraction of dioxane and f_w for volume fraction of water).
- Natural logarithm of the mole fraction solubilities of the solutes was predicted using Eq. (4).
- Temperature should be expressed as absolute temperature (°K).

In conclusion, the proposed trained model is capable of estimating the solubility of drugs in water-dioxane mixtures at various temperatures and mean of the expected prediction error is ~27% which is an acceptable error range in pharmaceutical applications. The proposed numerical method reduced the number of required experimental data from five to two points and could also be extended to predict solubility at various temperatures.

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