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Prediction of drug solubility in water-propylene glycol mixtures using Jouyban-Acree model

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A trained version of the Jouyban-Acree model was presented to predict drug solubility in water-propylene glycol mixtures at various temperatures. The model is able to predict the solubility in various solubility units and requires the experimental solubility of a solute in mono-solvent systems. The mean percentage deviation (MPD) of predicted solubilities was computed to show the accuracy of the predicted data and 24% was found as the average MPD for 27 data sets studied. The proposed model enables the researchers to predict solubiliy in water-propylene glycol mixtures at various temperatures and reduces the number of required experimental data from five to two points.

1. Introduction

Solubilization of a drug/drug candidate in water is one of the main problems in drug development studies and addition of a water miscible cosolvent is the most common method to increase aqueous solubility of drugs. Propylene glycol is one of the pharmaceutical cosolvents and has been used in many liquid formulations (Steetana and Akers 1996; Strickley 2004; Yalkowsky and Rubino 1985). The main limitation of the cosolvent is their toxicity and the next consideration is the cost of the formulation. To optimize the solvent composition of a liquid drug formulation, trial and error method often used in practice and the lowest concentration of a cosolvent dissolving the desired amount of a drug was chosen. In addition to experimental efforts to measure the solubility, a number of attempts have been made to predict solubility data in aqueous-cosolvent mixtures which most of them reviewed in a recent paper (Jouyban et al. 2006a). The most practical and the simplest model, is the log-linear model of Yalkowsky which requires aqueous solubility of the drug and its partition coefficient as input data (Millard et al. 2002). The log-linear model produces relatively high prediction error and a more accurate model is demanded in practice. To continue our systematic studies on solubility prediction methods, a trained version of the Jouyban-Acree model has been presented in this work for predicting the solubility of drugs in water-propylene glycol at various temperatures. The applicability of the model has been shown using 27 data sets collected from the literature.

2. Investigations, results and discussions

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 general form to calculate a solute solubility in water-cosolvent mixtures at various temperatures is:

$$\ln X_{m,T} = f_c \ln X_{c,T} + f_w \ln X_{w,T} + f_c f_w \sum_{i=0}^{2} \frac{J_i (f_c - f_w)^i}{T} \quad (1)$$

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 at temperature (T, K), f_c and f_w denote the volume fractions of cosolvent and water in the absence of the solute and J_i is the model constant computed using a no-intercept least square analysis (Jouyban-Gharamaleki and Hanaee 1997) for each binary solvent system. The J_i coefficients in Eq. (1) do have theoretical signficance in a way that each coefficient is a function of two-body and three-body interaction energies that describe the attractions between the various molecules in solution which is discussed in details in previous papers (Acree 1992; Jouyban et al. 2006b).

The mean percentage deviations (MPD) were used to check the accuracy of the prediction method and is calculated using Eq. (2).

$$\text{MPD} = \frac{100}{N} \sum \frac{|\text{Calculated} - \text{Observed}|}{\text{Observed}} \quad (2)$$

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

$$\text{IPD} = 100 \left(\frac{|\text{Calculated} - \text{Observed}|}{\text{Observed}} \right). \quad (3)$$

2.2 Results and discussions

Available experimental solubility data of drugs in water-propylene glycol mixtures at a constant and/or various temperatures were collected from the literature (for details

Table: Details of experimental solubility data of solutes in water-propylene glycol mixtures at various temperatures (t, °C) expressed in various solubility units, the number of data points in each set (N), logarithms of the mole fraction solubilities in mono-solvent systems ($\ln X_{c,T}$ and $\ln X_{w,T}$) and mean percentage deviation (MPD)

No.	Solute	t (°C)	$\ln X_{c,T}$	$\ln X_{w,T}$	MPD	N	Reference
1	Acetaminophen	20	−3.02	−6.49	6.8	12	Jiménez and Martínez, 2006
2	Acetaminophen	25	−2.96	−6.29	9.5	11	Jiménez and Martínez, 2006
3	Acetaminophen	30	−2.81	−6.17	8.4	11	Jiménez and Martínez, 2006
4	Acetaminophen	35	−2.71	−5.97	8.1	11	Jiménez and Martínez, 2006
5	Acetaminophen	40	−2.59	−5.76	6.2	11	Jiménez and Martínez, 2006
6	Amoxycillin trihydrate	25	−7.81	−8.98	8.0	5	Karanth and Josyula, 2005
7	Butyl p-aminobenzoate	27	−2.41	−11.02	37.0	11	Rubino and Obeng, 1991
8	Butyl p-aminobenzoate	37	−1.63	−10.36	12.8	6	Yalkowsky et al., 1975
9	Butyl p-hydroxybenzoate	27	−1.76	−10.45	43.5	11	Rubino and Obeng, 1991
10	Dodecyl p-aminobenzoate	37	−6.83	−21.97	45.2	6	Yalkowsky et al., 1975
11	Ethyl p-aminobenzoate	27	−2.87	−9.14	14.8	11	Rubino and Obeng, 1991
12	Ethyl p-aminobenzoate	37	−2.67	−8.60	27.1	6	Yalkowsky et al., 1975
13	Ethyl p-hydroxybenzoate	27	−2.55	−9.19	15.1	11	Rubino and Obeng, 1991
14	Furosemide	25	−5.59	−12.98	50.0	13	Jouyban-Gharamaleki et al., 2001
15	Hexyl p-aminobenzoate	37	−2.65	−13.16	61.8	6	Yalkowsky et al., 1975
16	Hydrocortisone	25	−5.69	−11.13	8.9	5	Hagen and Flynn, 1983
17	Ketoprofen	25	6.10	−2.23	36.1	11	Singhai et al., 1996
18	Ketoprofen	37	6.24	−2.03	38.6	11	Singhai et al., 1996
19	Methyl p-aminobenzoate	27	−3.44	−8.74	14.0	11	Rubino and Obeng, 1991
20	Methyl p-hydroxybenzoate	27	−2.36	−8.10	9.3	11	Rubino and Obeng, 1991
21	Octyl p-aminobenzoate	37	−3.89	−16.45	41.5	6	Yalkowsky et al., 1975
22	Paracetamol (Acetaminophen)	25	−3.03	−6.35	30.7	11	Jouyban et al., 2006c
23	Propyl p-aminobenzoate	27	−2.48	−9.95	30.4	11	Rubino and Obeng, 1991
24	Propyl p-hydroxybenzoate	27	−2.45	−10.04	27.1	11	Rubino and Obeng, 1991
25	Salicylic acid	25	−1.99	−8.34	6.8	11	Jouyban et al., 2006b
26	Theophylline anhydrate	30	2.53	2.15	26.6	8	Gould et al., 1989
27	Theophylline hydrate	30	2.56	2.16	25.9	8	Gould et al., 1989
					24.1		

see Table) and were regressed using Eq. (1). The obtained equation is:

$$\ln X_{m,T} = f_c \ln X_{c,T} + f_w \ln X_{w,T} + f_c f_w \left[\frac{85.254}{T} + \frac{735.662(f_c - f_w)}{T}\right] \quad (4)$$

The significance of the model constants was checked using t-test and the constants were statistically significant with $p < 0.05$. The model constant of $\frac{(f_c - f_w)^2}{T}$ term was not statistically significant ($p > 0.1$) and ignored from the equation. Using Eq. (4), it is possible to predict the solubility of a solute in water-propylene glycol mixtures at various temperatures and the required experimental data are the 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 (6.3%) was obtained for solubility prediction of acetaminophen at 40 °C and the maximum MPD (61.0%) was observed for the solubility of hexyl p-aminobenzoate at 37 °C. The average (±SD) of MPD for the studied data sets (total N = 257) was 24.1 (±15.9). The produced error is relatively high, however, it could be considered acceptable since the solubility range was very wide and the model covered the solubility prediction at the temperature range of 20–40 °C. To show the roubostness of the model constants and the applicability of the proposed prediction method on unmeasured solubility data, the data sets with even serial numbers from the Table, were used to train Eq. (1) and the solubility data with odd set numbers were predicted using the trained model. The average MPD (±SD) was 25.5 (±27.6) %. When even set numbers were predicted using the model trained using odd set numbers, the average MPD (±SD) was 23.3 (±31.3) %. There was no significant difference between 25.5 and 23.3 % obtained using two separate trained models and this reveals that the model is capable of predicting unmeasured solubilities with the overall prediction error of ∼24%.

The IPDs of predicted solubilities were sorted in three subgroups, i.e. IPD ≤ 4% (comparable with experimental uncertainity), 4–30 (acceptable error range in pharmaceutical applications) and >30% (unacceptable error range). The relative frequency of IPDs is illustrated in Fig. 1. The probability of solubility prediction in water-propylene glycol at various temperatures within acceptable error range is 0.72. There are good agreements between experimental (–lnXm) and predicted solubilities as shown in Fig. 2. High correlation coefficient (0.9974) of predicted and ex-

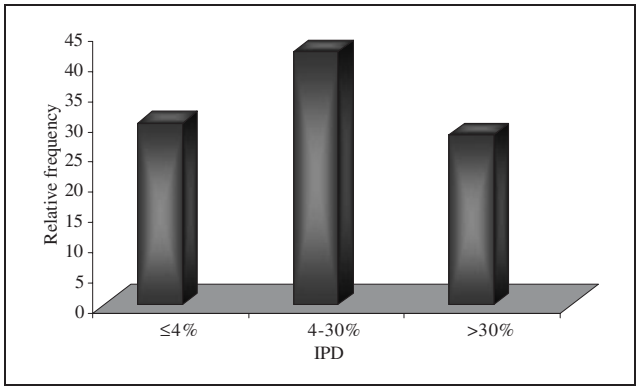

Fig. 1: Relative frequency of individual percentage deviation (IPD) for predicted solubilities (N = 257) in water-propylene glycol at various temperatures

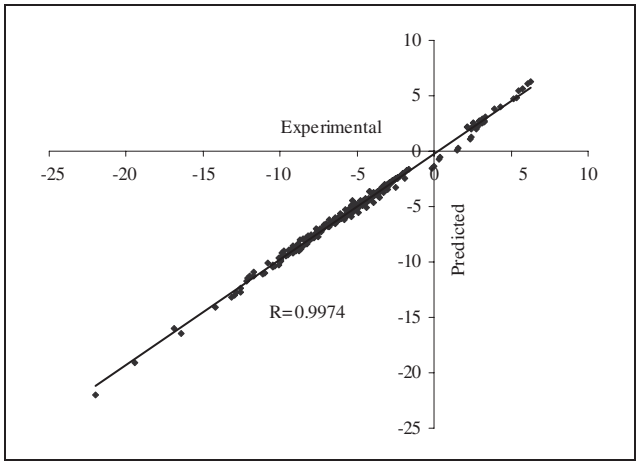

Fig. 2: Experimental $\ln X_{m,T}$ versus predicted values using Eq. (4)

perimental solubilities confirmed the accuracy of the proposed model.

An accurate mathematical model could also be used to screen the experimental data to detect possible outliers in order to re-determination. As shown in Fig. 3, there are discrepancies between experimental data reported from two different laboratories. As an example, solubility of ethyl p-aminobenzoate in propylene glycol : water (0.8 : 0.2) at 37 °C (Yalkowsky et al. 1975) was less than that of 27 °C (Rubino and Obeng 1991). However, the reproduced solubility profiles at 27 and 37 °C are quite acceptable and showed that the solubility of the solute in $f_c = 0.6$ and 0.8 at 37 °C could be considered for re-determination. To provide an accurate predictive model, the quality of training data sets is one of the most important criteria and any outlier data point could be resulted with a poor predictive model. In this work, in order to avoid any bias in data selection, all collected data sets were assumed as valid data sets and were used in the training process of the model.

In conclusion, the proposed trained model is capable of estimating the solubility of drugs in water-propylene glycol mixtures at various temperatures and mean of the expected prediction error is $\sim$ 24% which is an acceptable error range in pharmaceutical applications (Beerbower et al. 1984; Reillo et al. 1995). The proposed numerical method was reduced the number of required experimental data from five (Jouyban-Gharamaleki et al. 2001) to two points and it could also be extended to predict solubility at various temperatures which is demanded in pharmaceutical industry.

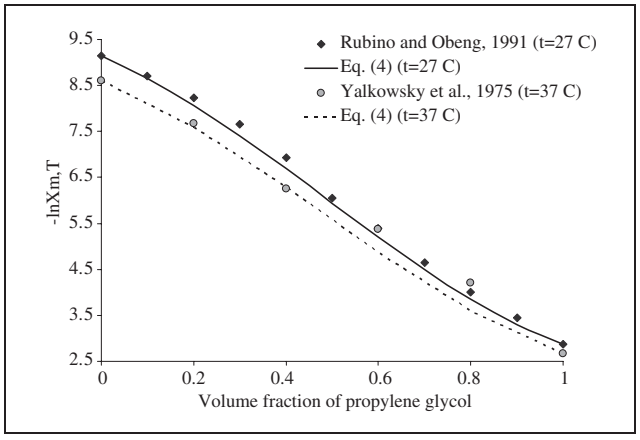

Fig. 3: Experimental solubility data of ethyl p-aminobenzoate at 27 and 37 °C collected from the literature and the reproduced solubility curves by Eq. (4)

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