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Solubility Prediction of Paracetamol in Water-Glycerol Mixtures at 25 and 30 ºC using the Jouyban-Acree Model

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The solubility of paracetamol in water-glycerol mixtures at 25 and 30 ºC was determined using flask shake method. The generated data extended the solubility database for further computational investigations and was also used to assess the prediction capability of a trained version of the Jouyban-Acree model for solubility prediction in water-glycerol mixtures at various temperatures. The accuracy of the predicted solubilities was evaluated by the mean percentage deviation between the predicted and experimental solubilities. The overall mean percentage deviation of the Jouyban-Acree model for the back-calculated solubility data from the literature was 37.9 ± 21.9 %. The corresponding value for the predicted solubilities of paracetamol in binary mixtures using experimental values of paracetamol solubilities in water and glycerol was 15.6 ± 11.1 %.

Key Words: Paracetamol, Binary solvents, Jouyban-Acree model, Solubility prediction.

INTRODUCTION

Aqueous solubility is one of the most important properties involved in the extraction and re-crystallization of solutes and also preparation of the liquid pharmaceutical formulations. For poorly water soluble compounds, there are various methods for the enhancement of the solubility including the addition of a cosolvent to the aqueous solution (cosolvency). In practice, searching of a suitable solvent system with experimental trial and error to dissolve a desired amount of the solute is not cost efficient. A number of models were presented for prediction of aqueous solubility[1-3]. The Jouyban-Acree model is one of the cosolvency models which has proved successful for the prediction purposes[4]. It requires solubility data of the solute in the neat cosolvent and water as input values and its trained versions for four commonly

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investigated cosolvents have been provided so far[4-7]. The main limitation of these models is that they are trained for a specific water-cosolvent system and the model should be trained for each cosolvent system separately. In continuation our previous works[4-9] for providing the trained versions of the developed model, the trained model for predicting drug solubilities in water-glycerol at various temperatures is presented in this communication. We also report the experimental solubilities of paracetamol in water-glycerol at 25 and 30 °C. The measured solubility values will be used in the trained version of the Jouyban-Acree model for water-glycerol system.

Our previous investigations[4-9] showed that the Jouyban-Acree model is the most accurate model among other cosolvency models. The basic form of the Jouyban-Acree model for calculating the solubility in binary solvent mixtures is:

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

where X is the solubility of the solute, f denotes the fractions of the solvents 1 (cosolvent) and 2 (water) in the solvent mixture, subscripts m, 1 and 2 are the mixed solvent and solvents 1 and 2, respectively, T is the absolute temperature, A_j is the model constant which represent various solute-solute, solvent-solvent and solute-solvent interactions. The trained versions of the Jouyban-Acree model were provided for predicting the solubility of drugs in four common water-cosolvent systems, *i.e.* aqueous mixtures of ethanol[4], dioxane[5], propylene glycol[6] and polyethylene glycol 400 at various temperatures. It also predicts accurate solubilities in non-aqueous binary mixtures at different temperatures[8]. The model provided good predictions employing two solubility data points, *i.e.* $X_{1,T}$ and $X_{2,T}$ for the solubility of drugs in a given cosolvent. The main limitation of the published models is that they were trained for a specific water-cosolvent system using experimental solubility data for several solutes in hopes of obtaining a predictive expression that would be applicable to a large number of diverse solute molecules. In combining solubility data for several solutes, we assumed that the equation coefficients in eqn. 1, (the A_j values), were independent of the solute's structure. While the assumption may be good for structurally similar solute molecules, it is certainly not true in general. In order to provide a more accurate predictive model and to incorporate more structural information about the drug molecule into the basic model, we added an additional term:

$$\ln X_{m,T} = f_1 \ln X_{1,T} + f_2 \ln X_{2,T} + \frac{f_1 f_2}{T} \sum_{j=0}^{2} A_j (f_1 - f_2)^j + B f_1 f_2 \log P \quad (2)$$

containing the logarithm of the water-to-glycerol partition coefficients, log P, of the drugs and a model constant, B. The log P values of the drugs should contain information about the drug characteristics and the numerical values used in the computations were calculated using ACD software.

The mean percentage deviations (MPD) between observed and predicted X_m were used to access the accuracy of the predicted data and was calculated using eqn. 3:

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

In eqn. 3, N is the number of experimental solubility data. All computations were carried out using SPSS software (version 11.5).

EXPERIMENTAL

Paracetamol was a gift from Zahravi pharmaceutical company (Tabriz, Iran), glycerol was purchased from Merck (Germany). Double distilled water was used throughout this study.

Solubility measurements: Sealed flasks containing an excess of paracetamol in the pure solvent and solvent mixtures were agitated at 25 and/or 30 ± 0.1 °C in a temperature controlled shaker bath (Clifton, UK). The solubility profile of the drug was monitored with time. When saturated solution was attained, the solid phase was removed by centrifugation followed by filtration (Durapore® membrane filters, type HV, 0.45 μm, Millipore, MA). No significant adsorption of the drug was found on the filtration membranes. The clear solutions were diluted with ethanol and assayed by a double beam spectrophotometer (Shimadzu, Japan) at 245 nm. The reported experimental values represent the averages of at least three replicates.

RESULTS AND DISCUSSION

All data points of the five collected solubility data sets in water-glycerol mixtures (Table-1) were used to train eqn. 2 and the obtained model was:

$$\ln X_{m,T} = f_1 \ln X_{1,T} + f_2 \ln X_{2,T} + 2413.947\left(\frac{f_1 f_2}{T}\right) - 2.837 f_1 f_2 \log P \quad (4)$$

in which all model constants were statistically significant at the probability level of < 0.05. The back-calculated solubility data from eqn. 4 was used to compute mean percentage deviation (MPD) values where the overall MPD (± SD) was 40.7 ± 35.8 % (N = 52).

TABLE-1
LOGARITHMS OF SOLUBILITIES OF DRUGS IN GLYCEROL ($\ln X_1$) AND WATER ($\ln X_2$) AT TEMPERATURE (T), NUMBER OF DATA POINTS IN EACH SET (N), LOGARITHMS OF PARTITION COEFFICIENTS (log P) CALCULATED USING ACD SOFTWARE, THE MEAN PERCENTAGE DEVIATION (MPD) OF THE PREDICTED SOLUBILITIES OF PARACETAMOL IN WATER-GLYCEROL MIXTURES BY EQUATION 4 AND THE REFERENCES OF DATA

Solute	$\ln X_{1,T}$	$\ln X_{2,T}$	t (ºC)	N	log P	MPD	Reference
Furosemide	-8.73	-12.98	25	12	3.10	68.7	9
Ketoprofen	1.26	-2.23	25	11	2.81	31.9	10
Ketoprofen	1.30	-2.03	37	11	2.81	31.7	10
Phenytoin	6.92	3.01	25	11	2.52	47.7	11
Valdecoxib	4.11	2.42	37	7	1.71	9.6	12

TABLE-2
LOGARITHMS OF EXPERIMENTAL mol/L SOLUBILITY OF PARACETAMOL IN DIFFERENT COMPOSITIONS OF WATER-GLYCEROL MIXTURES AT 25 AND 30 ºC AND THE PREDICTED VALUES USING EQUATION 4

Volume fraction of glycerol	Experimental	Predicted	Volume fraction of glycerol	Experimental	Predicted
25 ºC			30 ºC		
0.00	-2.40	-2.40	0.00	-2.28	-2.28
0.10	-2.20	-2.43	0.10	-2.06	-2.28
0.20	-2.21	-2.44	0.20	-2.00	-2.26
0.30	-2.16	-2.44	0.30	-1.96	-2.23
0.40	-2.14	-2.43	0.40	-1.92	-2.18
0.50	-2.08	-2.40	0.50	-1.85	-2.11
0.60	-1.92	-2.36	0.60	-1.74	-2.03
0.70	-2.20	-2.30	0.70	-1.73	-1.93
0.80	-2.17	-2.24	0.80	-1.65	-1.81
0.90	-2.15	-2.15	0.90	-1.64	-1.68
1.00	-2.05	-2.05	1.00	-1.53	-1.53

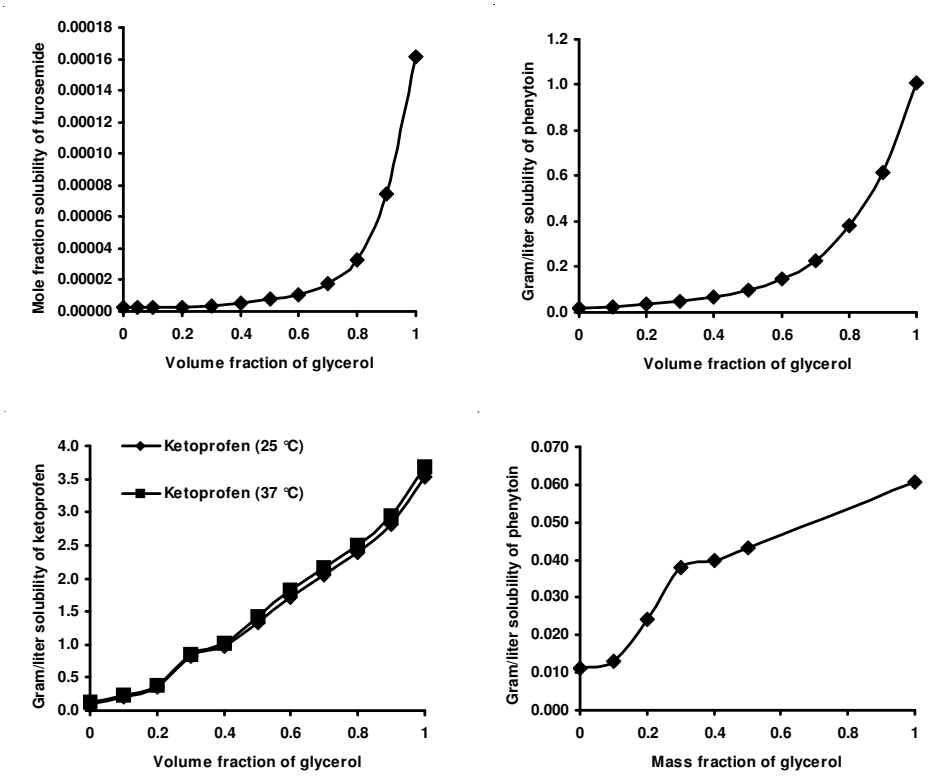

Fig. 1. Solubility profiles of various drugs in water-glycerol mixtures

Table-2 shows the molar solubility of paracetamol in water-glycerol mixtures at 25 and 30 °C. The paracetamol solubility in water-glycerol was increased with the increasing glycerol and the maximum solubility is reached at neat glycerol. This pattern is also confirmed for solubility profiles of other solutes in water-glycerol mixtures in other data sets (Fig. 1). Solubility data in $f_1 = 0.5$ and 0.6 possess the largest deviations from the predicted values by eqn. 4. This is an example of the application of cosolvency modelling for the observation of precision of the experimentally determined solubility data where the outlier points could be identified.

In conclusion, this work provided a trained version of the Jouyban-Acree model for one of the important cosolvents in the field of liquid formulations of drugs. It has been shown that the trained version of the model is able to predict the solubility of paracetamol (as a model drug) in water-glycerol mixtures at various temperatures and the prediction errors lies within an acceptable range. The trained model could be recommended to the pharmaceutical industry for practical applications.

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