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Thermodynamic solubility of piroxicam in propylene glycol + water mixtures at 298.2–323.2 K – data report and modeling

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Abstract: The solubility of piroxicam (66 data points) in binary mixtures of propylene glycol (PG) + water at six different temperatures ranging from 298.2 to 323.2 K are reported. Three different cosolvency models, *i.e.*, the Yalkowsky, the Jouyban–Acree and a combined version of the Jouyban–Acree model with the van't Hoff approach, were used for correlating the reported data. All the results of the analyses showed an acceptable range of the error percentages.

Keywords: thermodynamic; solubility; piroxicam; propylene glycol.

INTRODUCTION

The solubility of drugs is an important field in the pharmaceutical area, because it permits the scientist to choose the best solvent or solvent mixture for dissolving a drug or a combination of drugs. Solutions of drugs could be used to measure the purity of the bulk drug, prepare a liquid formulation and/or extract an ingredient from a synthetic mixture or a natural source. Hence, it is important to determine systematically the solubility of pharmaceutical compounds. The dependence of the solubility enhancement at higher temperatures to the molecular mechanisms enables respective thermodynamic analyses.

Piroxicam is a nonsteroidal anti-inflammatory drug, which is used for pain relieving and anti-inflammatory effects. The anhydrate form of piroxicam can be hydrated to dihydrate species by crystallization with water or exposure to a relative humidity over 43 %. The drug is described as a poorly water soluble and highly permeable drug (class II of the Biopharmaceutics Classification System (BCS)).[1,2]

To achieve an optimized solvent composition of a mixture for dissolving a certain amount of a drug in a given volume of the solvent, the trial and error approach is employed in practice, which is time consuming and expensive.

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Therefore, using cosolvency models could be an appropriate solution. Numerous models have been presented for correlation/prediction of the solubility of drugs in mixed solvents.[3] The final goal of developing cosolvency equations is to predict the solute solubility in mixed solvents using a minimum number of experimental data points or even without them.

COMPUTATIONAL METHOD END EXPERIMENTAL

One of the main cosolvency models is the log–linear model of Yalkowsky, which has a linear relationship between the solute solubility and the solvent fraction and is very simple and suitable for mixtures. It can be written as:[4]

$$\log X_{\mathrm{m}}^{\mathrm{Sat}} = w_1 \log X_1^{\mathrm{Sat}} + w_2 \log X_2^{\mathrm{Sat}} \quad (1)$$

where $X_{\mathrm{m}}^{\mathrm{Sat}}$ is the solubility of the solute in the solvent mixture; X_1^{Sat} and X_2^{Sat} denote the solubility in neat solvents 1 and 2, respectively; and w_1 and w_2 represent the mass fraction of solvents 1 (cosolvent) and 2 (water) in the absence of the solute. Equation (1) can be rearranged as Eq. (2) by considering w_2=1–w_1:

$$\log X_{\mathrm{m}}^{\mathrm{Sat}} = \log X_2^{\mathrm{Sat}} + K_1 w_1 \quad (2)$$

or

$$\log X_{\mathrm{m}}^{\mathrm{Sat}} = K_0 + K_1 w_1 \quad (3)$$

By further investigations, $K_1 = A + B \log P$ was obtained in which $\log P$ is the partition coefficient of the drug:[5]

$$\log X_{\mathrm{m}}^{\mathrm{Sat}} = \log X_2^{\mathrm{Sat}} + (A + B \log P) w_1 \quad (4)$$

where A and B are model constants and w_1 is the mass fraction of the cosolvent.

If there is no interaction between solvent–solvent or solvent–solute, the model of Yalkowsky can predict the solubility well. However, most solvent mixtures are not ideal and interactions occur; therefore, other terms need to be added to the basic log–linear model in order to illustrate the roles of these interactions in the solute solubility.

For showing the variation of the solubility with both temperature and solvent composition, the Jouyban–Acree model, which can compute the mathematical descriptors for the probable interactions in the mixture, can be used. The general form of the model for the solubility in binary solvent mixture at various temperatures can be written as:[3]

$$\log X_{\mathrm{m},T}^{\mathrm{Sat}} = w_1 \log X_{1,T}^{\mathrm{Sat}} + w_2 \log X_{2,T}^{\mathrm{Sat}} + \frac{w_1 w_2}{T} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \quad (5)$$

in which $X_{\mathrm{m},T}^{\mathrm{Sat}}$ is the molar solubility of the solute in the solvent mixture at temperature T, w_1 and w_2 are the mass fractions of solvents 1 and 2, respectively. $X_{1,T}^{\mathrm{Sat}}$ and $X_{2,T}^{\mathrm{Sat}}$ are the solubility of the solute in the neat solvents 1 and 2, respectively, and J_i are the constants of the model computed by regression analysis. A limitation for the Jouyban–Acree model is computing the model constants that require a number of experimental solubility data of the solute in the binary solvent mixtures.

Solubility of the drugs in mono-solvents at different temperatures can be predicted using the van't Hoff approach (Eq. (6)).[6] The required experimental data are the solubilities in the solvents mixture ($\log X_T^{\mathrm{Sat}}$).

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$$\log X_T^{\text{Sat}} = A + \frac{B}{T} \tag{6}$$

where A and B are the model constants calculated by regression method.

A combination of the Jouyban–Acree and van't Hoff models enables the prediction of drug solubility in mixed solvents at different temperatures after a training process using solubility data points; e.g. at the lowest and highest temperatures.[7,8] The combined version could be represented as:

$$\log X_{\text{m},T}^{\text{Sat}} = w_1\left(A_1 + \frac{B_1}{T}\right) + w_2\left(A_2 + \frac{B_2}{T}\right) + \frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i \tag{7}$$

where A_1, B_1, A_2, B_2 and J_i terms are the model constants. With this combination, the experimental solubility data are replaced with the calculated ones, which in this case, Eq. (7) is a valuable model for fitting the solubility data because the input includes no experimental data.

In a previous study,[9] a generally trained version of the Jouyban–Acree model was reported for propylene glycol (PG)–water binary mixtures:

$$\log X_{\text{m},T}^{\text{Sat}} = w_1 \log X_{1,T}^{\text{Sat}} + w_2 \log X_{2,T}^{\text{Sat}} + \frac{w_1 w_2}{T}\left[37.030 + 319.490(w_1 - w_2)\right] \tag{8}$$

In this step, this equation was used for predicting the solubilities of piroxicam at 6 different temperatures.

To evaluate the accuracy of the computational parts, the mean relative deviation (*MRD*) between the calculated and observed solubilities was used. The *MRD* value is calculated using:

$$MRD = \frac{100}{N}\left(\frac{\left|X_{\text{m},T}^{\text{Calculated}} - X_{m,T}^{\text{Observed}}\right|}{X_{\text{m},T}^{\text{Observed}}}\right) \tag{9}$$

where N is the number of data points in each set.

Materials

Piroxicam (0.999 mass fraction) was purchased from Alborz–Daru (Qazvin, Iran). The purity of piroxicam was checked by measuring the melting point range (471–473 K) and by comparing the measured solubilities in monosolvents with the corresponding data from the literature.[10] PG (0.995 mass fraction) was purchased from Merck (Germany). Double distilled water was used for the preparation of the solutions.

Drug solution preparation

All binary mixtures were prepared with an accuracy of 0.001 mass fractions.

Solubility determination

The solubility of piroxicam was determined by equilibrating an excess amount of the solid in the prepared binary solvent mixtures using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system at different temperatures with an uncertainty of 0.2 K (Hoorteb, Tehran, Iran) for 3 days to reach the equilibrium at 298.2 K. After solubility determination and density measurement at 298.2 K, the remaining solutions containing the excess solid were placed at 303.2 K for 2 day and the measurements were performed. The same procedure was repeated for the other temperatures. The solutions were

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filtered using hydrophilic Durapore filters (0.45 μm, Millipore, Ireland) and after diluting with methanol, the absorbance of these solutions were recorded at 360 nm using a UV–Vis spectrophotometer (Beckman DU-650, Fullerton, USA). The reported concentrations of the dilute solutions are an average of at least three experimental measurements, and the mean relative standard deviation (*RSD*) of three repetitive experiments was 2.6 %. The densities of the saturated solutions were determined using a 5 mL pycnometer.

RESULTS AND DISCUSSION

The minimum solubility of piroxicam was observed in aqueous solution (2.8×10^{-5} M or 1.3×10^{-7} mole fraction), which is in agreement with the literature value,[11] and the maximum solubility of piroxicam was observed in neat PG at 323.2 K (1.95×10^{-4} M). As a clear result for the experimental solubility data, the addition of the cosolvent to the aqueous solutions and increasing the temperature led to solubility enhancement. Table S-I of the Supplementary material to this paper presents the mass fractions of the binary solvent mixtures, the densities of the saturated solutions, the experimental and calculated solubilities of piroxicam at different temperatures using three analyses, which are described as follow.

Numerical analysis I includes fitting the binary solubility data to Eq. (4) (Yalkowsky). The highest and lowest *MRD*s belong to the solubility set at 298.2 and 318.2 K with 16.6 and 1.4 %, respectively, and the overall mean relative deviation (*OMRD*) was 9.6 %. As it is clear from the equation, the aqueous solubility is the only input data that was used for the fitting process, and the purpose of the modeling was to use a model with less input data and the simplest view. Thus, the *OMRD* value of 9.6 % for Eq. (4) is very good and acceptable.

In numerical analysis II, the solubility data were fitted to the Eq. (5) (the Jouyban–Acree model) and the highest *MRD* was 6.6 % for the solubilities at 323.2 K, and the lowest one was 0.7 % for the solubilities at 318.2 K. In this model, the solubilities of piroxicam in the neat solvents were the input data, and some terms were also added to the model to cover the interactions between solvent–solvent and solvent–solute molecules. Overall, these additions in this model resulted in a very low *OMRD* (2.5 %) for fitting process, which was completely good and acceptable. The produced model is:

$$\log X_{\mathrm{m},T}^{\mathrm{Sat}} = f_1 \log X_{1,T}^{\mathrm{Sat}} + f_2 \log X_{2,T}^{\mathrm{Sat}} + \\ + \frac{f_1 f_2}{T}\left(1.244 - 20.174\left(f_1 - f\right) - 39.030\left(f_1 - f\right)^2\right) \tag{10}$$

In numerical analysis III, the reported solubility data were fitted to Eq. (7), the Jouyban–Acree model combined with the van't Hoff equation. The highest and lowest *MRD*s were for the solubilities at 298.2 and 318.2 K with 29.9 and 4.5 %, respectively. In this analysis, the input data contained no experimental values, and the solubilities in the neat solvents were replaced by the constants from the van't Hoff approach. Hence, despite its complicated view compared with that of

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the Yalkowsky model, this model is very valuable for cases for which there is no experimental data available. The *OMRD* for the fitting process was 13.8 %, which is acceptable.

The back-calculated *MRD* values of piroxicam solubility calculated by the different numerical analyses at different temperatures are presented in Table I. The results show that the highest and lowest *OMRD* values were achieved in analysis III and II, with 13.8 and 2.5 %, respectively.

TABLE I. *MRD*s and *OMRD*s of the three fitting analyses of piroxicam solubility in binary aqueous mixtures of PG at six different temperatures

T / K	Analysis		
	I, Eq. (4)	II, Eq. (5)	III, Eq. (7)
298.2	16.6	2.1	29.9
303.2	15.8	2.0	19.1
308.2	9.7	1.8	12.3
313.2	6.0	1.9	5.1
318.2	1.4	0.7	4.5
323.2	8.1	6.6	12.2
OMRD	9.6	2.5	13.8

In numerical analysis IV, Eq. (8) was used for predicting the solubility of piroxicam in the reported mixtures at 6 different temperatures. The highest and lowest prediction *MRD*s were for the solubility sets at 323.2 and 318.2 K with 19.1 and 14.2 %, respectively, and the *OMRD* value was 15.4 % for all 66 data points. The predicted solubilities and the *MRD* values are listed in Table II.

TABLE II. Predicted solubilities ($X_{\mathrm{m}}^{\mathrm{predicted}} \times 10^5$) of piroxicam in PG (1) + water (2) mixtures at different temperatures (*T*), prediction *MRD*s and *OMRD* obtained by the trained version (Eq. (9))

w_1	*T* / K					
	298.2	303.2	308.2	313.2	318.2	323.2
0.00	2.8	7.6	8.1	8.7	9.1	9.7
0.10	2.7	6.9	7.4	7.9	8.3	9.0
0.20	3.0	6.9	7.4	7.9	8.4	9.3
0.30	3.5	7.6	8.1	8.6	9.2	10.4
0.40	4.4	8.7	9.4	9.9	10.6	12.2
0.50	5.6	10.3	11.0	11.5	12.5	14.7
0.60	7.2	12.1	12.9	13.5	14.6	17.5
0.70	8.9	13.7	14.6	15.2	16.6	20.3
0.80	10.2	14.5	15.6	16.1	17.7	22.0
0.90	10.7	14.1	15.1	15.6	17.2	22.0
1.00	9.9	12.1	13.0	13.4	15.0	19.5
MRD	15.4	14.9	14.6	14.3	14.2	19.1
OMRD						15.4

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CONCLUSIONS

Experimental solubilities of piroxicam are reported in aqueous binary mixtures of PG at six different temperatures ranging from 298.2 to 323.2 K, which extended the available solubility database of pharmaceuticals in mixed solvents.[12]

The main goal of this research was to improve the aqueous solubility of piroxicam by adding a cosolvent and increasing the temperature. The additions of PG and temperature enhancement increased the solubility of piroxicam dramatically. PG is a safe pharmaceutical cosolvent and could be used for formulating piroxicam in liquid forms (oral or parenteral) after performance of the appropriate toxicity tests.

The linear model of Yalkowsky, the Jouyban−Acree model and the version of the Jouyban–Acree model combined with the van't Hoff approach fitted the experimental solubility data for piroxicam well at almost all compositions of the solvent mixtures. These findings were supported by the acceptable *MRD* values of the back-calculated and experimental solubility data.

In modeling, the simplest model is the best unless its error percentage is high. The results of this study showed that the Jouyban–Acree model has the lowest fitting *MRD* values in comparison with the other two models. The noticeable point is that in the Jouyban–Acree model, the solubilities of piroxicam in the neat solvents at each temperature were added to the model; hence, for modeling the solubility data, these experimental values were required. Also in the Yalkowsky linear model, one must know the aqueous solubility of the drug at each temperature. However, when the van't Hoff approach was used in conjunction with the Jouyban–Acree model, in fact, the experimental data were replaced with calculated values.

SUPPLEMENTARY MATERIAL

Mass fractions of PG, experimental molar solubility of piroxicam in PG (1) + water (2) mixtures at various temperatures, the predicted solubilities by numerical analyses I, II and III, the densities of the saturated solutions and the fitting *OMRD*s are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

РАСТВОРЉИВОСТ ПИРОКСИКАМА У СМЕШИ ПРОПИЛЕН-ГЛИКОЛ (1,2-ПРОПАНДИОЛ)–ВОДА НА ТЕМПЕРАТУРАМА ОД 298,2 ДО 323,2 K

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Одређена је растворљивост пироксикама у бинарним смешама 1,2-пропандиол–вода на шест температура у интервалу од 298,2 до 323,2 K (66 експерименталних

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тачака). Коришћена су три модела за корелацију експерименталних резултата: модел Yalkowsky, Jouyban–Acree модел и облик последњег модела модификован приступом van't Hoff-a. Анализа резултата обраде моделима је показала прихватљив опсег грешке.

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