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Prediction of deferiprone solubility in aqueous mixtures of ethylene glycol, propylene glycol and polyethylene glycol 400 at various temperatures

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ABSTRACT

Solubility of drugs is essential information and no data is available for deferiprone (DFP) in the literature. The solubility of DFP in water, ethylene glycol (EG), propylene glycol (PG) and polyethylene glycol 400 (PEG 400) at 293.2, 298.2, 303.2, 308.2 and 313.2 K is reported and mathematically represented by van't Hoff equation. The solubility of DFP in aqueous binary mixtures of EG, PG and PEG 400 at 298.2 K is determined using the shake flask method and the generated data is used to train the Jouyban–Acree model. The trained versions of the van't Hoff and Jouyban–Acree models are combined to provide predictive models for solubility of DFP in the investigated solvent systems. The mean percentage deviations of the back-calculated solubilities against the corresponding experimental values were 1.3 and 1.1%, respectively for the mono- and mixed solvent systems.
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1. Introduction

Deferiprone (DFP, molar mass of 139.15 g mol^{-1}, see Fig. 1 for chemical structure) with CAS number of 30652-11-0 is a white crystalline solid with very bitter taste which is sparingly soluble in water at neutral pH. It is more soluble in acidic solutions and rapidly absorbed from stomach [1]. DFP forms stable complexes with ferrous (1:2) and ferric (1:3) ions with the complex formation constants of 1.7×10^8 and 3.9×10^{12} for Fe^{2+} and Fe^{3+}, respectively [2]. It is metabolized by glucuronidation and the chelate and the free drug are excreted in urine [3].

β-Thalassemia is a blood disorder which is divided to main subtypes of thalassemia major and thalassemia intermedia. Patients with thalassemia major need chronic blood transfusions developing iron overload which lead to tissue damages [1]. Excess iron causes congestive heart failure, cirrhosis and endocrine disorders [4]. Iron chelation therapy eliminates the excess iron [5]. Deferoxamin, DFP and defersirox are the available oral iron chelators and Heli et al. [6] reviewed their clinical applications and readers could be referred to this review article for more information. DFP is also administered in renal dialysis patients for aluminum removal and in rheumatoid arthritis patients for reducing inflammation [1]. DFP and its derivatives possess potential anti-parasitic activities via inhibition of iron related enzymes of the parasites [7,8].

Solubility of drugs and drug-like molecules is one of the more important and crucial parameters in drug discovery and the measurement procedure is a time-consuming process. Therefore, any alternative methods such as predictive models could be valuable tools for pharmaceutical scientists.

Ethylene glycol (EG) is a pharmaceutical vehicle which is used in a limited amount as cosolvent because of its toxic metabolites. Propylene glycol (PG) or 1,2-propanediol is considered as a relatively safe cosolvent which is used in oral, intravenous and topical pharmaceutical formulations [9]. The half-life of PG, in adults with normal liver and kidney functions, is 1.4 to 3.3 h. The acceptable level of PG has not been defined and the clinical implication of PG level is unclear [10]. The exact amount of PG in most of pharmaceutical formulations is not reported, but in some of the formulations, the maximum amount of PG is up to 55% in oral solutions and elixirs [11]. Polyethylene glycols (PEGs) are non-toxic, odorless, neutral, lubricating, nonvolatile, nonirritating polymers. Because of their low toxicity and high water solubility, they have a variety of applications in pharmaceutical industry mainly as cosolvent, ointment and suppository bases, and tablets' excipient [12,13]. PEGs with the molecular weight of 200 to 800 are in liquid form and freely

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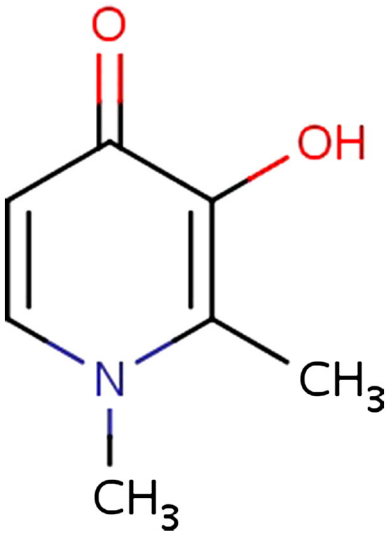

Fig. 1. Chemical structure of DFP.

miscible with water, and PEGs with the molecular weights higher than 1000 are in solid form.

The solubility of DFP in the mono- and mixed solvents is scarce in the literature; however, this information is required in many applications. This work is aimed to report the experimental solubility data of DFP in EG, PG, PEG 400 and water at various temperatures and also in aqueous binary solvent mixtures of EG, PG and PEG 400 at 298.2 K, in addition to the solution thermodynamic behavior of this drug in neat solvents. The generated data provides an accurate solubility prediction method for DFP in the investigated solvent systems at various temperatures using an interpolation technique.

2. Materials and methods

DFP with the mass fraction purity of 99.7% was purchased from Arastoo Pharmaceutical Co. (Tehran, Iran). EG, PG and PEG 400 with stated purity of more than 99.5% were purchased from Merck (Germany). All chemicals were used as received from the companies without further purifications.

Various experimental methods could be used for determination of drug's solubility [14] and the solubility of DFP in solvent mixtures was measured using the shake-flask method of Higuchi and Connors [15]. Briefly, excess amounts of DFP were equilibrated with the mono-solvents using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature controlling system at (293.2, 298.2, 303.2, 308.2 and 313.2) ± 0.2 K (Kimia Idea Pardaz Azarbayjan (KIPA) Co., Tabriz, Iran). For assurance of equilibrium, samples were incubated for three days at the investigated temperatures. The saturated solutions were filtered using regenerated cellulose membrane filters (0.45 μm, Albet Lab Science, Spain), diluted with water and then assayed spectrophotometrically (Cecil, Cambridge, UK) at 273.5 nm. Concentrations of the diluted solutions were determined from UV absorbance and each experimental data point is an average of at least three experimental measurements. The same procedure was employed for determination of DFP solubility in solvent mixtures at 298.2 K. Mean uncertainty in solubility determinations was 4.3%. The solvent mixtures are prepared by mixing appropriate masses of the solvents weighed by a balance with the uncertainty of 0.1 g.

The van't Hoff equation correlates the logarithm of solubility against the reciprocal of the absolute temperature T is presented as [16]:

$$\log C_T^{Sat} = A + \frac{B}{T} \tag{1}$$

where A and B are the model constants calculated using a least square analysis. The solubility of the drug in a solvent at other temperatures could be predicted using an interpolation technique. From a mathematical point of view, two solubility data points (preferably solubility at the highest and lowest temperatures of interest) could be used to compute A and B constants. It is obvious that more experimental data points for computing A and B constants will result in more accurate predictions. These predictions could be used in re-crystallization investigations in which changing the temperature of the solution results in solubilization and/or crystallization of the solutes. As a general rule, elevated temperatures increase the solubility of solids and concerning the B constant, one could justify the effects of temperature on the solubility of a target drug and the possible impurities in crystallization investigations. When purification using temperature alteration is not successful, solvent mixing or cosolvency is an alternative solution. Addition of a less polar solvent to water usually increases the solubility of hydrophobic drugs and decreases the solubility of hydrophilic and/or ionized drugs. Measurement of drug solubility in all cosolvent + water compositions is a too much time consuming and expensive process, and for these reasons, researchers usually use cosolvency models to compute the solubility values. However, there is no fully predictive cosolvency model to be used for this purpose and the available models require a number of experimental data points as input values.

Our previous investigations showed that the Jouyban–Acree model is the most accurate model among other cosolvency models and could be presented as Eq. (2) for calculating the solubility of drugs in binary solvent mixtures at various temperatures as [17]:

$$\log C_{m,T}^{Sat} = w_1 \log C_{1,T}^{Sat} + w_2 \log C_{2,T}^{Sat} + \left[\frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i\right] \tag{2}$$

where $C_{m,T}^{Sat}$ is the solute (mol·L^{-1}) solubility in the solvent mixtures at temperature T (K), w_1 and w_2 are the mass fractions of solvents 1 (cosolvent) and 2 (water) in the absence of the solute, $C_{1,T}^{Sat}$ and $C_{2,T}^{Sat}$ denote the (mol·L^{-1}) solubility of the solute in solvents 1 and 2, respectively. The J terms are the constants of the model and are computed by regressing $(\log C_{m,T}^{Sat} - w_1 \log C_{1,T}^{Sat} - w_2 \log C_{2,T}^{Sat})$ against $\frac{w_1 w_2}{T}$, $\frac{w_1 w_2 (w_1 - w_2)}{T}$, and $\frac{w_1 w_2 (w_1 - w_2)^2}{T}$ [18]. From a mathematical viewpoint, it is possible to compute J_i terms at one temperature, and employing these constants for prediction of a drug solubility in the binary mixtures at other temperatures by using the solubility data in the mono-solvents as input values as has been shown in earlier works [19–24]. This numerical method provided acceptable and accurate predictions however two data points are required at each temperature of interest. These experimental solubility data points could be replaced with the predicted values from Eq. (1) which provides more practical and predictive tool and reduces the required experimental data points. This hypothesis is investigated in this work.

Accuracies of the models were calculated by mean percentage deviation (MPD) which is defined as:

$$MPD = \frac{100}{N}\sum \left|\frac{C^{calculated} - C^{observed}}{C^{observed}}\right| \tag{3}$$

in which N is the number of data points.

Table 1
Experimental molar solubility of DFP (100 × mol·L^{-1}) in the investigated mono-solvents at various temperatures.

T (K)	Water	EG	PG	PEG 400
293.2	9.23	10.17	7.16	2.42
298.2	10.79	12.39	8.55	2.76
303.2	12.92	14.17	11.74	3.08
308.2	14.84	17.08	14.19	3.67
313.2	17.99	19.28	18.46	4.16

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