Journal of Molecular Liquids 203 (2015) 16–19

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Prediction of deferiprone solubility in some non-aqueous binary solvent mixtures at various temperatures

Masoumeh Abbasi [a], Jalil Vaez-Gharamaleki [a], Rana Fazeli-Bakhtiyari [b], Fleming Martinez [c], Abolghasem Jouyban [d,e,*]

[a] Hematology–Oncology Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran
[b] Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran
[c] Grupo de Investigaciones Farmacéutico-Fisicoquímicas, Departamento de Farmacia, Universidad Nacional de Colombia, Cra. 30 No. 45-03, Bogotá D.C., Colombia
[d] Drug Applied Research Center, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran
[e] Pharmaceutical Engineering Laboratory, School of Chemical Engineering, College of Engineering, University of Tehran, P.O. Box 11155/4563, Tehran, Iran

ARTICLE INFO

Article history:
Received 18 October 2014
Received in revised form 23 December 2014
Accepted 25 December 2014
Available online 31 December 2014

Keywords:
Deferiprone
Solubilization
Prediction
Jouyban–Acree model
van't Hoff equation
Cosolvency

ABSTRACT

Solubility of deferiprone (DFP) in binary mixtures of ethylene glycol (EG) with ethanol (EtOH), N-Methyl-2-pyrrolidone (NMP), propylene glycol (PG) and polyethylene glycol 400 (PEG 400) at 298.2 K was determined by using the shake flask method. A combination of the van't Hoff and the Jouyban–Acree models was used to predict the solubility of DFP in the investigated solvent mixtures. The overall mean percentage deviation (MPD) of the calculated solubilities against the corresponding experimental values was 2.7%.

1. Introduction

Deferiprone (DFP) is 3-hydroxy-1,2-dimethyl-1,4-dihydropyridin-4-one with molar mass of 139.15 g mol^{-1} (see Fig. 1 for chemical structure) and the CAS registry number of 30652-11-0. White solid crystalline DFP is very stable at room temperature and its solutions have a bitter taste. It is sparingly soluble in water at neutral pH and highly soluble in acidic solutions [1]. DFP forms stable complexes with ferrous (1:2) and ferric (1:3) ions [2] and prevents the progression of body iron load in transfusion-dependent thalassemia [1]. It is metabolized by glucuronidation and the complex and free drug are almost totally excreted in urine [3].

Excess iron catalyzes the oxidative breakdown of biomolecules such as lipids, sugars, amino acids, DNA, which lead to heart, pancreas and gonads damages [4]. Elimination of the excess iron can be done by iron chelation therapy [5]. Deferoxamin, DFP and deferasirox are the iron chelators and Heli et al. [6] have reviewed their clinical applications and readers could be referred to this review article for more information. Long term use of DFP can enhance the right and left ventricular ejection fraction in thalassemia major patients [7,8].

Solubility data are required in many industrial applications and solubility alteration is employed for solubilization and/or crystallization purposes. Various techniques are used to alter the solubility of drugs which include physical and chemical modifications of drug and other methods like cosolvency, particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant and complexation.

The experimental determination of solubility is tedious and time-consuming process. In order to provide a faster and easier tool, mathematical models have been developed to correlate/predict the solubility of drugs. Most of these models are compared [9] and reviewed [10] in earlier works.

Ethylene glycol (EG) has been widely used in polyol synthesize of metal nanoparticles due to its strong reducing power and relatively high boiling point. Other applications of EG include, as a cross-linker reagent in sol–gel processing of crack-free files, and as a reagent in fabricating mesostructures of some metals [11]. In some cases, EG is the best solvent for wood among tested solvents at a similar condition [12]. Propylene glycol (PG) is an odorless, colorless and viscous liquid. It is used in pharmaceutical preparations as a solvent and water-miscible cosolvent. Poly (ethylene glycol) (PEG) is a polymer consists of repeating units of the monomer ethylene oxide which is important industrial solvent because of its favorable properties, i.e. low toxicity, high chemical stability, and low melting point. Lower molecular-weight grades (PEG 200, PEG 400) are preferred as cosolvents in pharmaceutical

* Corresponding author at: Drug Applied Research Center, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran.
E-mail address: ajouyban@hotmail.com (A. Jouyban).

http://dx.doi.org/10.1016/j.molliq.2014.12.034
0167-7322/

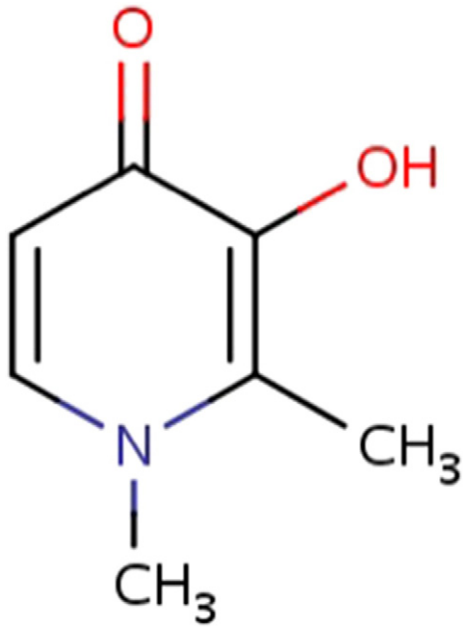

Fig. 1. Chemical structure of DFP.

solutions. N-methyl-2-pyrrolidone (NMP) is one of the main pharmaceutical cosolvents that has important applications in different fields of industry, especially in the pharmaceutical industries [13]. Ethanol (EtOH) is one of the most common cosolvent which is used in many applications of poorly water soluble compounds. The solubility data of DFP in the mono- and mixed solvents is insufficient in the literature; however, this information is required in many industrial applications. The solubility of DFP in EG, EtOH, NMP, PG and PEG 400 at 293.2, 298.2, 303.2, 308.2 and 313.2 K has been reported in previous works [14,15]. This work is aimed to report the experimental solubility data of DFP in EG binary solvent mixtures of PG, PEG 400, NMP, and EtOH at 298.2 K. 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). EtOH and NMP both with stated purity of more than 99.5% were purchased from Scharlau Chemie (Spain).

All chemicals were used as received from the companies without further purifications.

Various experimental methods could be used for determination of drug's solubility [16] and the solubility of DFP in solvent mixtures was measured using the shake-flask method of Higuchi and Connors [17]. Approximately excess amount of powder of the DFP was dissolved in mixed solvent fractions. This solution was shaken by shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system at (298.2 ± 0.2) K (Kimia Idea Pardaz Azarbayjan (KIPA) Co., Tabriz, Iran) for 3 days until equilibrium was reached. After separation of the solid by filtration using regenerated cellulose membrane filters (0.45 μm, Albet Lab Science, Spain), the concentration of the DFP in the filtrate after dilution by water was determined spectrophotometrically (Cecil, Cambridge, UK) at 273.5 nm. Concentrations of the diluted solutions were determined from UV absorbance and each experimental data point was an average of at least three experimental measurements. Mean uncertainty in solubility determinations was 4.3%. The solvent mixtures were prepared by mixing appropriate masses of the solvents weighed by a balance with the uncertainty of 0.1 g. Densities of the saturated solutions were determined using a 5 mL pycnometer with the uncertainty of 0.001 $g \cdot mL^{-1}$.

The van't Hoff equation that correlates the logarithm of solubility against the reciprocal of the absolute temperature T is presented as [18]:

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

where A and B are the model constants calculated using a least square analysis. In previous work, the solubility of DFP in mono-solvents at various temperatures was predicted by using an interpolation technique. When purification using temperature alteration is not successful, solvent mixing or cosolvency is an alternative solution. Addition of a less polar solvent to EG usually increases the solubility of hydrophobic drugs and decreases the solubility of hydrophilic and/or ionized drugs.

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 [19]:

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

where $C_{m,T}^{Sat}$ is the solute solubility ($mol \cdot L^{-1}$) in the binary solvent mixtures at temperature T (K), w_1 and w_2 are the mass fractions of the solvents 1 (EG) and 2 (cosolvent) in the absence of the solute, $C_{1,T}^{Sat}$ and $C_{2,T}^{Sat}$ denote the $mol \cdot L^{-1}$ solubility of the solute in the solvents 1 and 2, respectively. The J_i 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 $\frac{w_1 w_2 (w_1 - w_2)^2}{T}$ [20]. From a mathematical viewpoint, it is possible to compute J_i terms at one temperature, and employ these constants for solubility prediction of pharmaceutical compounds 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 [14,15,21–26]. 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. (2) 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.

3. Results and discussion

Table 1 reports the experimental molar solubility of DFP in various mass fractions of EG in EG + PG, EG + PEG 400, EG + NMP and EG + EtOH mixtures at 298.2 K. The solubility was decreased continuously by addition of the second solvent for PEG 400 and NMP and increased slightly by addition of PG and EtOH and reached the maximum values at $w_1 = 0.10$. The generated solubility data which extend the available databases [27] were fitted to Eq. (2) and the model constants for EG + PG, EG + PEG 400, EG + NMP and EG + EtOH mixtures along with their statistical parameters were computed and listed in Table 2. The overall MPD of 2.7% (N = 44) reveal that the model is an accurate model to correlate the molar solubility of DFP in binary solvent mixtures. It is also forecasted that the model possesses good prediction capability. To test this capability, it was trained using a minimum number of data points, i.e. $w_1 = 0.30$, 0.50, and 0.70, and