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Measurement and correlation of deferiprone solubility: Investigation of solubility parameter and application of van't Hoff equation and Jouyban–Acree model

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ABSTRACT

The available solubility of deferiprone (DFP) in mono and mixed solvent systems is limited. The aim of this work is to find solvation of DFP with respect to the composition of the solvent mixture. Solubility of DFP in water, ethanol (EtOH) and N-methyl-2-pyrrolidone (NMP) was experimentally determined at 293.2, 298.2, 303.2, 308.2 and 313.2 K. Its solubility in aqueous binary mixtures of EtOH and NMP was also investigated. Solubility of DFP in aqueous binary solvent mixtures of ethylene glycol (EG), propylene glycol (PG) and polyethylene glycol 400 (PEG 400) and non-aqueous binary solvent mixtures of EG + EtOH, EG + NMP, EG + PG and EG + PEG 400 is investigated and solubility profile shape of each system is explained in terms of solubility parameter. Total solubility parameter of DFP is calculated by Fedor's group contribution method and compared to solubility parameter of various solvent mixtures in order to estimate maximum solubility in specific co-solvent ratio.
Based on the generated experimental solubility data, trained versions of the van't Hoff and Jouyban–Acree models were used to simulate DFP solubility in the binary mixture compositions. The applicability of the thermodynamic model to predict the solubility of DFP was studied. The experimental data was used to provide accurate estimations of solubility in the investigated solvent systems using van't Hoff and Jouyban–Acree equations.

1. Introduction

Deferiprone (DFP), 1,2-dimethyl-3-hydroxypyridin-4-one (Fig. 1), is a white crystalline solid with very bitter taste that is sparingly soluble in water at neutral pH DFP (molar mass of 139 g/mol) is very stable in solid-state form at room temperature. It has a pKa of approximately 3.6 and, therefore it is highly soluble in acidic solutions and its affinity to iron element is more than any other biological trace elements such as Cu, Al and Zn [1,2].

Solubility of drugs and drug-like molecules is one of the important and crucial parameters in drug absorption [3,4]. Co-solvency is a widely used approach employed for solubility enhancement. One of the biggest challenges facing solubility is the estimation of preferential solvent composition for enhanced drug solubility [5,6].

Solubility parameter is an intrinsic physicochemical parameter used to characterize different behaviors of regular solutions. This parameter directly reflects the degree of cohesive forces that hold the molecules together. It can also indicate the strength of interactions between drug and solvent molecules to help in selecting the right cosolvent composition for optimum level of solubility. This concept has received considerable interest by the pharmaceutical scientists in many fields to explain different phenomena of regular solutions such as adsorption, dissolution, compatibility and miscibility. Suitable mixture of solvent composition is a great step in drug solubility prediction. Efforts are continuously made to apply this parameter in selecting the right solvent ratio for optimum level of solubility [5,7–9]. It is known that the solubility parameter of a solute is assumed to be similar to the solubility parameter of the solvent composition with maximum drug solubility. Solubility parameter can also help to estimate a suitable ratio of solvent for maximum drug solubility and help to explain the solubility profile shape [5–7]. Solubility parameters have been determined to study the effect of solute solubility parameter on solvent polarity. Solute–solvent interaction was investigated to determine co-solvency profile shape on the solubility of drug molecules [3,9,10].

Solubility measurements in all possible cosolvent + water compositions are time consuming and not feasible. In this instance investigators

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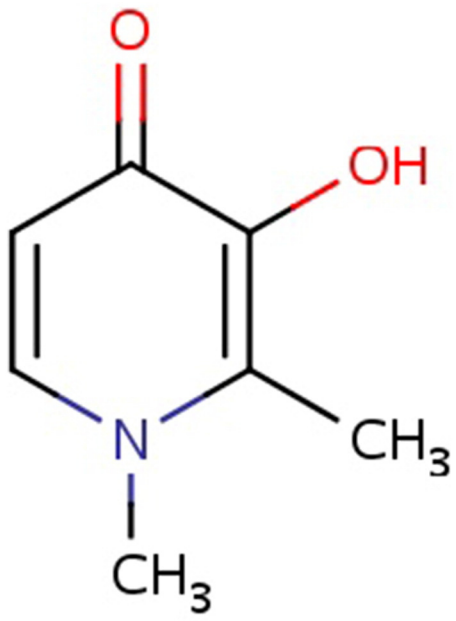

Fig. 1. Chemical structure of DFP.

may rely on cosolvency models to estimate solubility. Predictive cosolvency models have been developed and trained on a limited number of properly controlled experimental data values. The solubility of the drug in a solvent at any temperatures could be predicted using an interpolation technique. The model requires two solubility data points as a function of temperature (preferably solubility at the highest and lowest temperatures of interest) to regress parameters A and B. These parameters can then be applied to predict solubility in a multi-solvent system. van't Hoff equation and the enthalpy and enthropy of solution and Gibb's free energy help to better understand the solubility behavior of solute in solvent mixture [11].

The two previous papers of this series were focused on the solubility of DFP in aqueous binary solvent mixtures of ethylene glycol (EG), propylene glycol (PG) and polyethylene glycol 400 (PEG 400) [12] and non-aqueous binary solvent mixtures of EG + ethanol (EtOH), EG + N-methyl-2-pyrrolidone (NMP), EG + PG and EG + PEG 400 [13]. The present paper extends the method suggested in the above publications as well as the solubility parameter approach to understand drug solubilization pattern. In this work experimental solubility of DFP in water, EtOH and NMP and in aqueous solvent mixtures (EtOH and NMP) at 298.2 K is reported. We also attempt to calculate DFP solubility parameter in various solvent blends and to compare it with solubility parameter of solvent mixture in order to estimate maximum solubility in a specific cosolvent ratio. Finally van't Hoff equation and Jouyban–Acree model are used to predict the experimental data.

2. Materials and methods

DFP with the mass fraction purity of 99.7% was purchased from Arastoo Pharmaceutical Co. (Tehran, Iran). EtOH and NMP were of analytical grade and were purchased from Scharlau Chemie (Spain). All chemicals were used as received from the companies without further purifications.

2.1. Experimental solubility

Various experimental methods have been reported to determine drug solubility [11]. In this work the solubility of DFP in solvent mixtures was measured using Higuchi and Connors shake-flask method [14]. Briefly, an excess amount of drug is introduced into screw-capped bottles containing solvent. The bottles were placed on a shaker-incubator at 25 ± 0.1 °C or specified temperatures and allowed to equilibrate for 48 h. Pure solvents and binary solvent mixtures of water (solvent 2) and cosolvent (solvent 1) from $w_1 = 0.0$ to $w_1 = 1.0$ were prepared by mixing EtOH and NMP with water. The ratio of the co-solvents was prepared in the desired combination and was kept to measure the equilibrium solubility of DFP. After equilibrium samples were filtered and aliquots were analyzed spectrophotometrically (Cecil, Cambridge, UK) at 273.5 nm for drug contents. All experiments were repeated in triplicates, average values were calculated and the results were being reproducible to within ±3.5%.

2.2. Determination of solubility parameter

Various methods are available to calculate solubility parameter of drug substances. DFP solubility parameter was experimentally determined using Fedor's group contribution method with well established accuracy [15]. This method examines the atomic and functional groups that comprise the compound. DFP solubility parameter is calculated by opening its ring structure to treat the resultant structure as a linear chain compound and to calculate the contribution of each functional group as well as a correction for ring closure. Solubility parameter is then calculated by summing the individual contributions of its atomic and functional groups [3,16].

Hildebrand solubility parameter is proportional to the cohesive energy of materials. It is used to define solubility parameter as the square root of its energy of vaporization per unit volume using the original Hidlebrand equation 1970 [17]:

$$\delta_1 = \left[\sum_i \Delta_{ei} \Big/ \sum_i \Delta_{vi}\right]^{1/2} \tag{1}$$

where Δ_{ei} denotes the substituent energy of vaporization and Δ_{vi} is the fragmental molar volume which is the measure of the solute–solvent attraction strength [3].

Solubility parameter of pure solvents "δ" was taken from literature. Solubility parameter for binary solvent mixtures (δ_m) is calculated by [18]:

$$\delta_m = \frac{w_1\delta_1 + w_2\delta_2}{w_1 + w_2} \tag{2}$$

where w is the fraction of each solvent and subscripts 1 and 2 denote cosolvent and water, respectively.

Solubility profile curves vary with different co-solvent systems. From the shape of the solubility curve the appropriate composition of the solvent mixture can then be selected [9].

2.3. Solubility prediction using van't Hoff equation

The relationship between temperature and mole fraction solubility in different solvents is described by the ideal solution equation. The van't Hoff equation relates the logarithm of the mole fraction of a solute as a linear function of the reciprocal of the absolute temperature T [19], assuming that the ideal solution is given by:

$$\log C_T^{Sat} = A + \frac{B}{T} \tag{3}$$

where $C_{m,T}^{Sat}$ is the mole fraction solubility of solute ($mol \cdot L^{-1}$), A and B are the model constants calculated using a least square analysis.