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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

Anahita Fathi-Azarbayjani [a,b], Masoumeh Abbasi [c], Jalil Vaez-Gharamaleki [d], Abolghasem Jouyban [e,f,*]

[a] Solid Tumor Research Center, Urmia University of Medical Sciences, Urmia, Iran
[b] Faculty of Pharmacy, Urmia University of Medical Sciences, Urmia, Iran
[c] Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Hematology & Oncology Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran
[e] Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran
[f] Kimia Idea Pardaz Azarbayjan (KIPA) Science Based Company, Tabriz University of Medical Sciences, Tabriz 51664, Iran

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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

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

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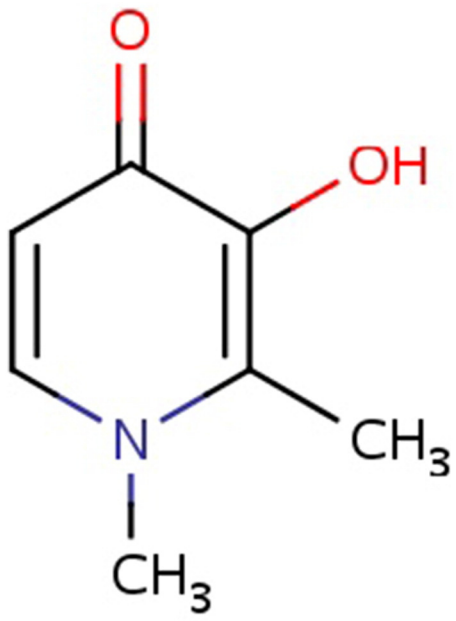

Fig. 1. Chemical structure of DFP.

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.

In practice most of the real solutions exhibit non-ideal behavior; therefore the enthalpy and entropy of mixing must be taken into consideration. The real solubility can be calculated from the expression:

$$\log C_T^{Sat} = \frac{\Delta H_d}{RT} + \frac{\Delta S_d}{R} \quad (4)$$

where ΔH_d and ΔS_d are enthalpy and entropy of solution respectively [20].

Temperature dependence of experimental solubility was correlated using Eq. (3). Correlation coefficients (R), F values and the mean percent deviation (MPDs) between the calculated and experimental values are computed. Accuracies of the models were calculated by MPD according to:

$$\mathrm{MPD} = \frac{100}{\mathrm{N}} \sum \left| \frac{C^{calculated} - C^{observed}}{C^{observed}} \right| \quad (5)$$

where N represents the number of experimental data points.

2.4. Solubility prediction using Jouyban–Acree model

There are various well-known co-solvency methods available for prediction of drug solubility in solvent mixtures. Computational methods are able to predict solubility of drug molecules and provide a unique and vivid approach to solubility calculation. Theoretical methods avoid time-consuming experiments. To date, considerable effort has been spent on the development of computational models to predict solubility of drug molecules in solvent mixtures. Our previous investigations showed the Jouyban–Acree model to be the most accurate model amongst the available cosolvency models in literature. This equation is applicable to binary solvent mixtures at various temperatures [21]:

$$\log\ C_{m,T}^{Sat} = w_1 \log\ C_{1,T}^{Sat} + w_2 \log\ C_{2,T}^{Sat} + \left[\frac{w_1 w_2}{T} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \right] \quad (6)$$

where $C_{m,T}^{Sat}$ is the solute ($\mathrm{mol \cdot L^{-1}}$) solubility in the solvent mixtures at temperature T (K), w_1 and w_2 are the mass fractions of solvents 1 and 2 in the absence of the solute, $C_{1,T}^{Sat}$ and $C_{2,T}^{Sat}$ denote the ($\mathrm{mol \cdot L^{-1}}$) 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 $\frac{w_1 w_2 (w_1 - w_2)^2}{T}$ [22]. From a mathematical viewpoint, it is possible to compute J_i terms at one temperature, and employs these constants for solubility prediction in binary mixtures at various temperatures. This is done by using experimental solubilities in the mono-solvents as input data to train the model. This approach provides acceptable and accurate predictions [23–28]. It is worth mentioning that two experimental data points are needed as input parameters at each temperature of interest in order to reliably predict solubility using this approach. The experimental solubility values could be replaced with the predicted values generated from Eq. (3). This approach provides a more practical and predictive tool for solubility prediction, thus reducing the number of required experimental data points needed. This particular approach was investigated in this work.

3. Results and discussion

3.1. Solubility study

Solubility data in selected mono-solvents at various temperatures are listed in Table 2. As expected the solubility value of DFP is increased with the increasing temperature.

Solubility values in pure solvent were in the following order: water > NMP > EtOH. Maximum solubility is found in neat water ($0.10026\ \mathrm{mol \cdot L^{-1}}$) where solubility is 5 times greater in comparison with that of EtOH ($0.01949\ \mathrm{mol \cdot L^{-1}}$) and nearly 4 times that of NMP ($0.02719\ \mathrm{mol \cdot L^{-1}}$). Lower solubility of DFP in ethanol was attributed to its polarity.

Table 3 reports solubility of DFP in various mass fractions of EtOH + water and NMP + water mixtures at 298.2 K. It can be seen that the solubility enhancement is similar in both solvent systems. Solubility increased by co-solvent addition and reached a maximum values at $w_2 = 0.50$ and $w_2 = 0.40$ for EtOH and NMP respectively. The solubility decreased with further addition of the cosolvents.

DFP has a hydroxyl and aldehyde group in the molecule which possesses strong polarity. Because of the proton on its hydroxyl group it may interact with the free electron pairs in the oxygen atoms present in all the solvents. Solubility parameter of solvents is in the following order: water > EG > PG > EtOH > NMP, PEG 400 (Table 1). It is expected that a solute will dissolve better in a solvent that has similar polarity or solubility parameter [8,20]. Similar drug solubility pattern in EtOH and NMP is attributed to their comparable solubility parameter ($\delta_{EtOH} = 13$, $\delta_{NMP} = 11.3\ (\mathrm{cal/cm^3})^{0.5}$).

3.2. Determination of solubility parameter

Factors governing drug solubility can be better understood by studying solubility parameter involved in various solvent mixtures. The principle of similarity matching states that, chemical structure and polarity can influence drug solubility. Similar solubility parameter of two materials leads to nearly identical energy of interaction and balance of mixing energy which facilitates the dissolution of solute. In solvent mixtures peak solubility closely represents the drug solubility parameter. It is universally acknowledged that solutes reach their maximum solubility value in solvents with the same solubility parameter. Probably the oldest rule of solubility is “like dissolves like” [8,20].

Solubility parameter of DFP was computed by summing the individual group contribution for the energy of vaporization and molar volume to the overall structure of the solute molecule (Table 4). DFP solubility parameter was calculated to be $13.6\ (\mathrm{cal/cm^3})^{0.5}$.

Solubility of DFP against the solubility parameter of solvent mixtures of this study and those taken from earlier works [12,13] are displayed in Figs. 2 and 3. The experimental values obtained were compared with the theoretical values obtained by Fedor's group contribution method. The curves were either concave downward at the high end in aqueous mixtures (Fig. 2) or sigmoid in shape in nonaqueous solutions (Fig. 3). It is seen that changing the cosolvent does not significantly alter the solubility trend seen in Fig. 2. It is assumed that the solubility parameter of DFP should resemble the solubility parameter of the solvent composition with maximum drug solubility.

Fig. 3 represents mole fraction solubility against solubility parameter of non-aqueous solvent mixture. A common feature is the linear relationship between mole fraction solubility and solubility parameter.

In aqueous mixtures, for most of the cosolvents the curves pass through a maximum at higher mole fraction values. While in nonaqueous mixtures the maximum value is near $w = 0.2$. According to the thermodynamic reports DFP could act mainly as a Lewis acid to form

Table 1
Solvent solubility parameter.

Solvent	$\delta\ (\mathrm{cal/cm^3})^{0.5}$[a]
Water	23.5
Ethanol	13.0
Ethylene glycol	16.0
Propylene glycol	15.0
PEG 400	11.3
NMP	11.3

[a] From Refs. [10,42].

Table 2
Experimental molar solubility (mol·L^{-1}) of DFP in the investigated mono-solvents at various temperatures.

T (K)	Water	EtOH	NMP
293.2	0.100258	0.019419	0.027188
298.2	0.107853	0.024507	0.029397
303.2	0.129207	0.032872	0.033268
308.2	0.148423	0.037472	0.035631
313.2	0.179911	0.049634	0.040044

hydrogen bonds with functional groups present in proton acceptor solvents [12].

In regular solutions, maximum solubility occurs when δ of the solvent closely represents δ of the solute. Therefore peak solubility represents solubility parameter. Due to solute–solvent interaction some solutions deviate from regular solutions. In non-regular solutions the peak solubility does not approximate the ideal solubility. The extended Hildebrand solubility approach may be employed to understand the non-regular behavior of solutions. This requires a Flory–Huggins size correction to be applied to the regression model [6,16].

In this work, the PEG 400 + water and EtOH + EG systems appear to be an ideal solvent system and the peak solubility technique was able to reasonably predict the solubility parameter of DFP. The other solvent systems used in the study showed large deviation compared to the abovementioned solvents. In some solvent mixtures, maximum DFP solubility is somewhat different than expected. In such solvent systems the ideal mole fraction solubility may not be predicted using the peak solubility method. This could be due to the solvent–solute interaction which is not taken into account using this method [6,16].

There are very few papers which tend to correlate solubility parameter of solute to solvent mixture. Peña and coworkers have investigated the solubility parameter as a tool to predict the shape of the solubility profile of a drug in dioxane–water mixtures [29].

Solubility parameter of trimethoprim was experimentally calculated. It was assumed that the peak solubility in solvent mixture closely represented the drug solubility parameter. Dioxane–water represents an ideal system whereas hexane–ethyl acetate mixture, showed deviation from experimental solubility parameter [6].

The use of Hildebrand model may not always be successful and this lack of success is due to the uncertainty in the calculation of cohesion strength and solute solvent interactions which is neglected in this model. The early definition of the model had limited applications and was modified by Hansen. Hansen's model employs intermolecular forces into dispersion, polar and hydrogen bonding interaction to allow better correlation of solubility parameter to solubilization by cosolvents. However, Hansen approach ignores Lewis acid–base behavior [30]. Abraham solvation parameter model has been employed to estimate solubility using molecular descriptors [31–33].

Table 3
Experimental molar solubility (mol·L^{-1}) of DFP in aqueous mixtures of EtOH and NMP at 298.2 K.

w_1	EtOH	NMP
0.00	0.10785	0.10785
0.10	0.12428	0.15618
0.20	0.14076	0.17906
0.30	0.15958	0.18663
0.40	0.16345	0.19457
0.50	0.16963	0.17881
0.60	0.15387	0.15635
0.70	0.12984	0.13166
0.80	0.10413	0.09063
0.90	0.05839	0.05821
1.00	0.02451	0.02858

Table 4
Calculation of solubility parameter of DFP by Fedor's group substitution method.*

Drug fragment	Drug fragments	Δ_{ei} (cal/mol)		Δ_{vi} (cm^3/mol)	
O═	1	800	800	3.8	3.8
OH	1	7122	7122	10	10
CH_3	2	1126	2252	33.5	67
N	1	1000	1000	−9.0	−9.0
>C═	3	1030	3090	−5.5	−16.5
–CH═	2	1030	2060	13.5	27
Conjugated bond	2	400	800	−2.2	−4.4
Ring closure	1	250	250	16.0	16.0
Total		17,374		93.9	
δ = 13.60 cal/cm^3					

* From Refs. [3,16,43].

3.3. Solubility prediction using van't Hoff equation and Jouyban–Acree model

The experimental data were correlated with the ideal solution equation of van't Hoff. The resulting equations for EtOH, NMP and water, the correlation coefficients (R), F values and the MPDs of the back-calculated solubilities are:

$$\log C_T^{Sat} = 4.551 - \frac{1835.594}{T} \quad (7)$$

R = 0.995, F = 324, MPD = 2.5%

$$\log C_T^{Sat} = 1.058 - \frac{770.366}{T} \quad (8)$$

R = 0.996, F = 380, MPD = 1.2%

$$\log C_T^{Sat} = 3.457 - \frac{1317.983}{T} \quad (9)$$

R = 0.999, F = 1016, MPD = 1.2%.

The high correlation coefficient (R) and F values for Eqs. (7)–(9) reveal that the models are statistically significant and could be used to predict solubility using interpolation technique.

The generated solubility data which extend the available databases [34,35] is fitted to Eq. (6) and the trained models for

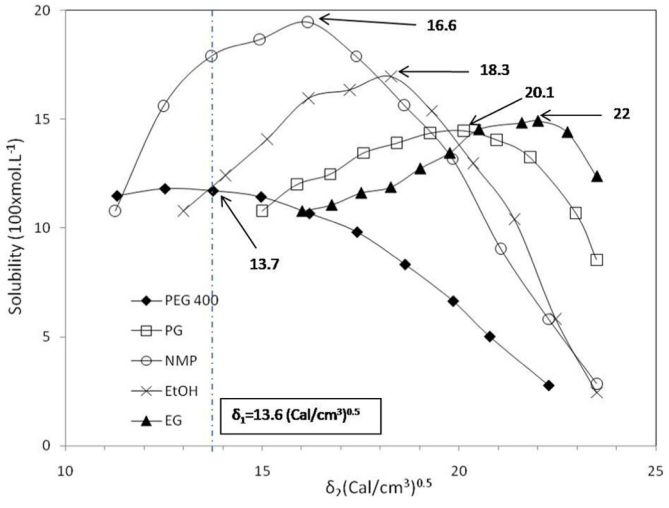

Fig. 2. Molar solubility of DFP against the solubility parameter of aqueous solvent mixture (The cosolvent ratios are given in Table 3).

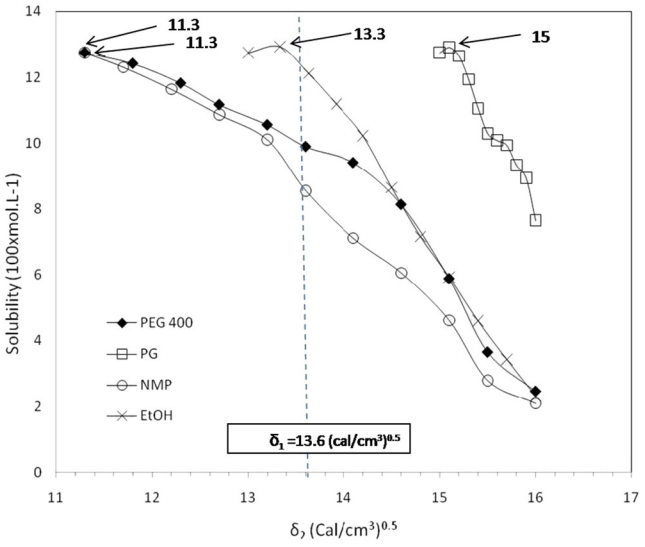

Fig. 3. Mole fraction solubility of DFP against the solubility parameter of solvent mixture (in ethylene glycol). The cosolvent ratios are given in Table 3.

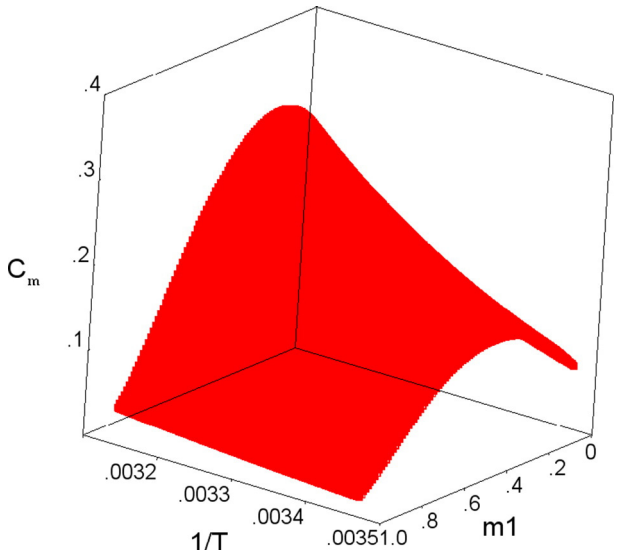

Fig. 4. Plot of predicted molar solubility of DFP in various solvent compositions of EtOH + water at different temperatures.

EtOH + water and NMP + water mixtures as well as their statistical parameters are:

$$\log C_{m,T}^{Sat} = w_1 \log C_{1,T}^{Sat} + w_2 \log C_{2,T}^{Sat} + 606.179\left(\frac{w_1 w_2}{T}\right) + 357.399\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right) + 207.577\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right) \quad (10)$$

R = 0.999, F = 3132, MPD = 2.0

$$\log C_{m,T}^{Sat} = w_1 \log C_{1,T}^{Sat} + w_2 \log C_{2,T}^{Sat} + 604.969\left(\frac{w_1 w_2}{T}\right) + 93.039\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right) + 228.253\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right) \quad (11)$$

R = 0.999, F = 5079, MPD = 1.5%.

As described earlier the J_i terms of Eq. (6) can be computed at 298.2 K. The obtained value can then be used to predict the solubility at other temperatures. The only required data for these predictions are the solute solubility in the mono-solvents at temperature of interest [28,36–38].

3.4. Validation of modeling approach

It is possible to combine the trained versions of the Jouyban–Acree model and the van't Hoff equation for solubility prediction of DFP in EtOH + water and NMP + water mixtures at various temperatures. Solubility data from van't Hoff equation are incorporated into Eq. (6) as:

$$\log C_{m,T}^{Sat} = w_1\left(4.551 - \frac{1835.594}{T}\right) + w_2\left(3.457 - \frac{1317.983}{T}\right) + 606.179\left(\frac{w_1 w_2}{T}\right) + 357.399\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right) + 207.577\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right) \quad (12)$$

$$\log C_{m,T}^{Sat} = w_1\left(1.058 - \frac{770.366}{T}\right) + w_2\left(3.457 - \frac{1317.983}{T}\right) + 604.969\left(\frac{w_1 w_2}{T}\right) + 93.039\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right) + 228.253\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right) \quad (13)$$

Eqs. (12) and (13) are able to predict the solubility of DFP in all solvent compositions of EtOH and NMP in their aqueous mixtures at any temperature of interest. Fig. 4 is a graphical representation of predicted molar solubility of DFP solubility in EtOH binary solvent mixtures at various temperatures.

Solubility prediction with trained models employing the least number of experimental data is another practical means which has been tested in a number of previous works [39–41]. With this approach it is possible to reduce the cost and time associated with experimental solubility measurements. It is also a valuable approach in early stages of drug discovery and requires a minimum amount of drug. The applicability of this procedure can be shown by combining the Jouyban–Acree and van't Hoff equations. The obtained Jouyban–Acree models for EtOH + water and NMP + water mixtures (using data points in w_1 = 0.00, 0.30, 0.50, 0.70 and 1.00 at 298.2 K) are:

$$\log C_{m,T}^{Sat} = w_1 \log C_{1,T}^{Sat} + w_2 \log C_{2,T}^{Sat} + 618.290\left(\frac{w_1 w_2}{T}\right) + 297.905\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right) + 103.323\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right) \quad (14)$$

$$\log C_{m,T}^{Sat} = w_1 \log C_{1,T}^{Sat} + w_2 \log C_{2,T}^{Sat} + 605.805\left(\frac{w_1 w_2}{T}\right) + 140.567\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right) + 213.876\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right) \quad (15)$$

and the trained models for EtOH, NMP and water (using solubility data points at 298.2 and 313.2 K) are:

$$\log C_T^{Sat} = 4.788 - \frac{1907.677}{T} \tag{16}$$

$$\log C_T^{Sat} = 1.271 - \frac{835.516}{T} \tag{17}$$

$$\log C_T^{Sat} = 3.672 - \frac{1383.223}{T} \tag{18}$$

Eqs. (14) and (15) could be combined with Eqs. (16)–(18) resulting in:

$$\begin{aligned}\log\ C_{m,T}^{Sat} = {} & w_1\left(4.788 - \frac{1907.677}{T}\right) + w_2\left(3.672 - \frac{1383.223}{T}\right) \\ & + 618.290\left(\frac{w_1 w_2}{T}\right) + 297.905\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right) \\ & + 103.323\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right)\end{aligned} \tag{19}$$

$$\begin{aligned}\log\ C_{m,T}^{Sat} = {} & w_1\left(1.271 - \frac{835.516}{T}\right) + w_2\left(3.672 - \frac{1383.223}{T}\right) \\ & + 605.805\left(\frac{w_1 w_2}{T}\right) + 140.567\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right) \\ & + 213.876\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right)\end{aligned} \tag{20}$$

The remaining data points (N = 6 in each data set) in the EtOH + water and NMP + water solvent mixtures at 298.2 K were predicted using Eqs. (19) and (20). The resulting MPD values are 4.8 and 4.7%, respectively. The MPD values for the predicted solubility in EtOH, NMP and water at other temperatures are 4.1, 2.2 and 4.5%, respectively. These predictions were carried out by employing seven experimental data points and the resulting prediction errors lie within the experimental uncertainty values. The van't Hoff equation and Jouyban–Acree model both provide reasonable prediction in selected solvents.

4. Conclusion

This paper was mainly focused on providing solubility data of DFP in aqueous solvent mixtures of EtOH and NMP. The objective of this study was to determine solubility of DFP in mono-solvent and various co-solvent mixtures at room temperature and to correlate solubility parameter of solute and solvent with respect to the solubility profile shape.

The solubility of DFP in EtOH, NMP and water binary aqueous mixtures was studied. A bell shaped curve was observed when mole fraction solubility was plotted against solubility parameter. The agreement between the experimental solubility parameter and the values calculated from the Fedor's group contribution method is low. It is suggested that this method can apply when no interaction between solute–solvent is estimated. In most solvent mixtures, solubility parameter is larger than expected. Solute–solvent interaction which is not taken into account can overestimate the calculated solubility parameters.

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 data was mathematically represented by van't Hoff equation and used to train the Jouyban–Acree model. The data presented in this work enhances the existing information related to the solubility of DFP in various solvent mixtures.

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