Thermodynamic Study of Deferiprone Dissolution in Polyethylene Glycol 400 and 2-Propanol Mixture

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ABSTRACT: *In the current study, the solubility and density of deferiprone were determined in the polyethylene glycol (PEG) 400 and 2-propanol mixtures at 293.2 – 313.2 K using a shake-flask method before a spectrophotometric method. The results showed that the solubility increases with both PEG 400 mass fraction and temperature increase. The measured data were fitted to some mathematical models including van't Hoff, MRS, Jouyban-Acree, Jouyban-Acree–van't Hoff, and the modified Wilson models. The results from the investigation of model accuracy showed that there were only tiny differences between measured data and back-calculated data from solubility values (MRD% <3.5%). Moreover, thermodynamic studies showed that the deferiprone dissolution process was endothermic and entropy-driven, and the main contributor of ΔG° was the enthalpy.*

KEYWORDS: *Solubility; Deferiprone; Binary mixtures; Cosolvency models; Dissolution thermodynamics.*

INTRODUCTION

Deferiprone (Fig. 1) as a membrane-permeant bidentate iron chelator [1] is employed for the treatment of disorders related to iron overload *e.g.* Friedreich's ataxia [2] and hemosiderosis [3]. Deferiprone with a high

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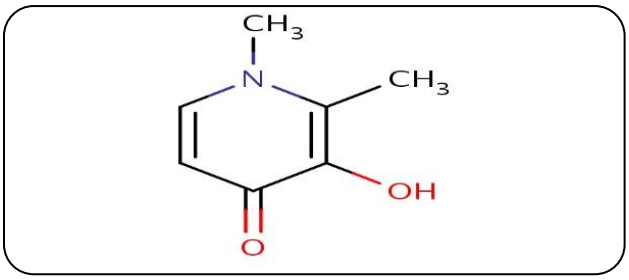

Fig. 1: Molecular structure of deferiprone.

affinity toward iron possesses the capability to eliminate iron from various parts of the body [4]. Furthermore, it decreases tau hyperphosphorylation and downregulates the tau kinase glycogen synthase kinase 3-beta (GSK3β) in animal models showing that it can be one of the main culprits in the development of tauopathies [5, 6].

In the steps of discovery and development of a drug, the numerical value of solubility and related properties in different solvents are the critical features for various purposes such as pre-formulation studies, design of liquid forms, purification, and extraction procedures [7, 8]. Various techniques were employed for the solubilization of deferiprone including complex formation [9], micro-emulsion formation [10, 11], crystal engineering [12, 13], and cosolvency [14]. Cosolvency is a commonly used and reliable method for drug solubilization. Some published cosolvency research for deferiprone solubility including in mono-solvents of ethyl acetate, chloroform, acetonitrile, 1,4-dioxane and dichloromethane [15], aqueous mixtures of ethylene glycol, propylene glycol and polyethylene glycol (PEG) 400 [16], non-aqueous mixtures of ethanol and acetonitrile and ethanol and ethyl acetate [17], and ethanol and N-methyl-2-pyrrolidone [18, 19]. However, there is no report on the solubility study of deferiprone in the mixtures of PEG 400 and 2-propanol which are both important solvents and cosolvents in the pharmaceutical industries. In continuation of our previous works, our aims in this work were the determination of the deferiprone solubility and density in the non-aqueous mixtures of PEG 400 and 2-propanol at different temperatures and the representation of the measured data with some thermodynamic models. Moreover, the thermodynamic behavior of its dissolution process was studied.

EXPERIMENTAL SECTION

Materials

Deferiprone (0.997 purchased from Arastoo Pharmaceutical Company, Iran), PEG 400 (0.980, Merck, Germany), 2-propanol (>0.995 %, Merck, Germany), ethanol (0.935, Jahan Alcohol Tab, Iran) and distilled water (Lab made) were the used solvents in this study.

Study of solubility and density of deferiprone mixtures

A classic method of shake-flask [20] followed by the spectrophotometric method was employed for deferiprone solubility determination in the mixtures of PEG 400 and 2-propanol. For this regard, the drug powder was dispersed into the vials containing 5.0 g of solvents or mixed solvents and placed on a shaker (Behdad, Tehran, Iran) in an incubator (Kimia Idea Pardaz Azerbaijan (KIPA.co)), at a temperature range of 293.2 – 313.2 (with temperature intervals of 5.0 K). After 48 h, their supernatants were centrifuged and diluted with 30:70 % v/v ethanol: water mixture. Then their absorbance intensity was measured at 273 nm in a spectrophotometer (Cecil BioAquarius CE 7250, UK).

Furthermore, the density of the prepared mixtures was measured utilizing a 1.5 mL pycnometer (±0.001 g/cm^3).

Computational section

For the mathematical representation of solubility data, the solubility data were usually fitted to some mathematical models [21-23] including; 1) the van't Hoff equation [24] with capability for data at a given solvent mixture at different temperatures; 2) the modified Wilson model [25] with capability for data fitting at different mixtures at the isothermal temperature; and 3) the Jouyban-Acree and the Jouyban-Acree-van't Hoff models [26] with capability for data fitting in different mixtures and temperatures. The models were reported in the following equations and the details of each model were given in our previous publications.

$$lnx = A + \frac{B}{T} \quad (1)$$

$$-\ln x_m = 1 - \frac{w_1[1+\ln x_1]}{w_1+w_2\lambda_{12}} - \frac{w_2[1+\ln x_2]}{w_1\lambda_{21}+w_2} \quad (2)$$

$$lnx_{m,T} = w_1 lnx_{1,T} + w_2 lnx_{2,T} + \frac{w_1.w_2}{T}\sum_{i=0}^{2} J_i.(w_1 - w_2)^i \quad (3)$$

$$\ln x_{m,T} = w_1\left(A_1 + \frac{B_1}{T}\right) + w_2\left(A_2 + \frac{B_2}{T}\right) + \frac{w_1.w_2}{T}\sum_{i=0}^{2} J_i.(w_1 - w_2)^i \quad (4)$$

Table 1: Experimental mole fraction solubility ($x_{m,T}$) data measured for deferiprone in PEG 400 and 2-propanol at different temperatures

w_1[a]	*T* (K)				
	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00	5.95 (±0.11) × 10^{-4}	7.65 (±0.31) × 10^{-4}	9.21 (±0.05) × 10^{-4}	1.07 (±0.00) × 10^{-3}	1.22 (±0.04) × 10^{-3}
0.10	8.07 (±0.02) × 10^{-4}	9.31(±0.17) × 10^{-4}	1.09 (±0. 11) × 10^{-3}	1.26 (±0.06) × 10^{-3}	1.41 (±0.06) × 10^{-3}
0.20	1.02 (±0.07) × 10^{-3}	1.17 (±0.04) × 10^{-3}	1.34(±0.06) × 10^{-3}	1.52 (±0.05) × 10^{-3}	1.72 (±0.05) × 10^{-3}
0.30	1.27 (±0.04) × 10^{-3}	1.42 (±0.04) × 10^{-3}	1.62 (±0.08) × 10^{-3}	1.83 (±0.10) × 10^{-3}	2.03(±0.10) × 10^{-3}
0.40	1.55 (±0.04) × 10^{-3}	1.74(±0.16) × 10^{-3}	1.97 (±0.09) × 10^{-3}	2.21(±0.09) × 10^{-3}	2.43(±0.13) × 10^{-3}
0.50	1.89 (±0.06) × 10^{-3}	2.11 (±0.15) × 10^{-3}	2.37(±0.18) × 10^{-3}	2.66 (±0.03) × 10^{-3}	2.92 (±0.02) × 10^{-3}
0.60	2.35 (±0.02) × 10^{-3}	2.62 (±0.11) × 10^{-3}	2.93 (±0.03) × 10^{-3}	3.21 (±0.09) × 10^{-3}	3.50 (±0.02) × 10^{-3}
0.70	2.96 (±0.12) × 10^{-3}	3.29 (±0.08) × 10^{-3}	3.61 (±0.24) × 10^{-3}	3.97 (±0.02) × 10^{-3}	4.29 (±0.16) × 10^{-3}
0.80	3.90 (±0.19) × 10^{-3}	4.24 (±0.43) × 10^{-3}	4.67(±0.28) × 10^{-3}	5.10 (±0.12) × 10^{-3}	5.53 (±0.25) × 10^{-3}
0.85	4.51 (±0.28) × 10^{-3}	4.95(±0.20) × 10^{-3}	5.41 (±0.04) × 10^{-3}	5.89 (±0.10) × 10^{-3}	6.37 (±0.13) × 10^{-3}
0.90	4.84 (±0.09) × 10^{-3}	5.38 (±0.16) × 10^{-3}	5.88(±0.13) × 10^{-3}	6.39 (±0.11) × 10^{-3}	6.98(±0.28) × 10^{-3}
1.00	6.30 (±0.10) × 10^{-3}	6.92(±0.09) × 10^{-3}	7.61 (±0.26) × 10^{-3}	8.31 (±0.76) × 10^{-3}	9.23 (±0.58) × 10^{-3}

[a] w_1 is mass fraction of PEG 400 in the PEG 400 and 2-propanol mixtures in the absence of deferiprone.

x_m, x_1 and x_2 are considered as the solubility in the mixed solvents, and mono solvents 1 and 2 and w_1 and w_2 are the mass ratios of solvents 1 (herein is PEG 400) and 2 (herein is 2-propanol) in the absence of solute, respectively. *T* is the absolute temperature (K).

After data fitting, the Mean Relative Deviation (MRD%) was computed for back-calculated data as a measure of the model's accuracy according to Eq. (5).

$$MRD\% = \frac{100}{N}\sum\left(\frac{\left|Calculated\ Value - Observed\ Value\right|}{Observed\ Value}\right) \quad (5)$$

where *N* is the number of data points.

Thermodynamic study

The thermodynamic parameters such as enthalpy (Δ*H*°), entropy (Δ*S*°) and Gibbs free energy change (Δ*G*°) for the deferiprone dissolution in the PEG 400 + 2-propanol mixtures are reported based on the van't Hoff and Gibbs equations. The modified van't Hoff equation is as:

$$\frac{\partial \ln x}{\partial\left(\frac{1}{T}-\frac{1}{T_{hm}}\right)_p} = -\frac{\Delta H^\circ}{R} \quad (7)$$

R is the ideal gas constant [27] and T_{hm} is the mean harmonic temperature and calculated according to the equation of $T_{hm} = n/\sum_{i=1}^{n}(1/T)$, where *n* is the number of studied temperatures. The intercept and slope of the modified van't Hoff are employed for computing Δ*G*° and Δ*H*°, and Gibbs equation is used to obtain Δ*S*°.

The relative contributions of entropy (ζ_{TS}) and enthalpy (ζ_H) to Δ*G*° are obtained from the following equations [28].

$$\zeta_H = \frac{\left|\Delta H^\circ\right|}{\left(\left|\Delta H^\circ\right| + \left|T\Delta S^\circ\right|\right)} \quad (8)$$

$$\zeta_{TS} = \frac{\left|T\Delta S^\circ\right|}{\left(\left|\Delta H^\circ\right| + \left|T\Delta S^\circ\right|\right)} \quad (9)$$

RESULTS AND DISCUSSIONS

Solubility measurement and data modeling

The solubility data for deferiprone in mole fraction units at different temperatures along with the standard deviation of replicated measurements were given in Table 1. As can be seen, the solubility of deferiprone in the investigated mixture and different temperatures positively depends on both PEG 400 mass fraction and temperature so that the lowest solubility was reported for neat 2-propanol at 293.2 K, and the highest one was observed for neat PEG 400 at 313.2 K. This profile may be due to the high solubilization feature of PEG 400 and providing a suitable medium for solubility improving by this solvent.

The solubility data in PEG 400 (6.92×10^{-3}) at 298.2 K measured in this study have relatively consistency with those given in the literature (9.77×10^{-3}) [16] and the observed deviation may be ascribed to the person to person, the material source and/or the methodology error. The literature investigation proved that variations of the solubility among reports are sometimes very large. The potential reasons for this discrepancy are listed here: (1) variations in the experimental period for equilibration may become a reason for the discrepancy in the solubility data [29] also show that the dispensed solid amount may significantly affect the observed solubility values due to the competition between the dissolution and crystallization rates. *Baka et al*. [30] show that the observed differences could be attributed to the effect of particle size, crystallinity and other molecular features of the sample. For investigation of these variations between reported solubility data in various laboratories, *Kishi* and *Hashimoto* [31] studied solubility data of anthracene and fluoranthene reported by 17 different laboratories using a standard method by the environmental agency of Japan. The results showed that even when all variables were kept constant, the inter-laboratory differences can still be very significant. They showed that the mean solubilities of anthracene and fluoranthene span 0.17 and 0.36 log unit and MPD value is 51 %.

The main parameters affecting the solute solubility as a physico-chemical property are temperature and solvent composition. Changing in both temperature and composition can change the solvent capacity for a solute dissolving. For many solid solutes, the solubility increases with temperature. The increase in kinetic energy that comes with higher temperatures allows the solvent molecules to more effectively break apart the solute molecules that are held together by intermolecular attractions. Solvent composition as another parameter must be considered in the solubility studies due to the fact that strong solute-solvent attractions equate to greater solubility while weak solute-solvent attractions equate to lesser solubility. Interactions between solute and solvent can be based on polarity, acidity- basicity, hydrogen bonding properties, etc. [32]. In the current work, considering the presence of Hydrogen Bond Donor (HBD) and Acceptor (HBA) counts on the structures of deferiprone (one HBD and three HBA), ethanol (one HBA and one HBD) and PEG 400 (two HBD and eight HBA), the possible reason for increasing of deferiprone solubility with an increasing mass fraction of PEG 400 can be more intense hydrogen bonding between deferiprone and PEG 400 in comparison of deferiprone-ethanol. Both temperature and solvent composition were investigated in the current work. The effect of temperature was studied in the temperature ranges of 293.2 – 313.2 K with a temperature interval of 5.0 K and the effect of the solvent composition was studied with variation in the ratios of selected solvents from 0.0 to 1.0 with a mass fraction interval of 0.1. Another reported parameter which affects the solubility is the amount of excess solid [33]. However, this is mostly true for the ionizable compound. On the other hand, due to the high cost of the raw material, we tried to keep the minimum excess amount of the solid at the bottom of the container. So, this effect can be ignored in the current work. In addition to solubility, another concept is defined as dissolution rate. Most of the proposed parameters such as time, type of stirring and sedimentation time affect this feature which can be mistaken for solubility [33]. However, in the current work, the dissolution rate for reaching an equilibration time was determined by finding a constant value for deferiprone solubility. As solubility, as a main reported data herein, is measured after finding the dissolution rate for deferiprone in the investigated solvent mixture, other parameters (*i.e.* time, type of stirring and sedimentation time) couldn't be considered.

The generated data measured by the shake-flask method were correlated with some cosolvency models such as the van't Hoff, Jouyban-Acree, Jouyban-Acree–van't Hoff and the modified Wilson models. The details of models including model' parameters and *MRD%* of the back-calculated data were summarized in Tables 2-4. The overall *MRDs%* for the back-calculated data were 0.6 for the van't Hoff model, 2.9 for the Jouyban–Acree model, 3.1 for the Jouyban-Acree-van't Hoff model, and 1.5 for the modified Wilson model. Considering the low MRD% values (< 3.5) for all models can be said that these models have good accuracy for data fitting. For the investigation of the prediction capability of the Jouyban-Acree-van't Hoff model as a general model that was dependent on both temperature and solvent composition, the model was trained with the minimum number of data, *i.e.* solubility data in neat solvents at low and high temperature and mixed solutions with w_1 of 0.7, 0.5 and 0.3 at 298.2 K. The *MRDs%* of predicted data were 3.7, 2.0, 2.1, 3.6 and 6.0 for 293.2, 298.2, 303.2, 308.2 and 313.2 K, respectively (overall *MRD* was 3.5%).

Table 2: The van't Hoff model coefficients and the MRD% for deferiprone in PEG 400 and 2-propanol mixture

w_1	A	B	MRD%
0.00	3.734	-3261.455	2.7
0.10	1.771	-2607.135	0.7
0.20	1.300	-2400.575	0.1
0.30	0.793	-2188.956	0.5
0.40	0.665	-2091.816	0.4
0.50	0.630	-2023.886	0.3
0.60	0.219	-1837.790	0.5
0.70	0.012	-1709.442	0.4
0.80	-0.018	-1621.958	0.3
0.85	0.018	-1588.358	0.2
0.90	0.342	-1661.750	0.3
1.00	0.857	-1738.182	0.5
Overall MRD%			0.6

Table 3: The Jouyban-Acree and Jouyban-Acree-van't Hoff models model coefficients and the MRD% for deferiprone in PEG 400 and 2-propanol mixture

Jouyban-Acree		Jouyban-Acree-van't Hoff	
J_0	-101.138	A_1	0.857
J_1	-58.285	B_1	-1738.182
J_2	0[a]	A_2	3.734
		B_2	-3261.455
		J_0	-100.885
		J_1	-58.548
		J_2	0[a]
MRD%	2.9		3.1

Table 4: The modified Wilson model coefficients and the MRD% for deferiprone in PEG 400 and 2-propanol mixture

T (K)	λ_{12}	λ_{21}	MRD%
293.2	0.996	1.004	3.0
298.2	1.139	0.878	1.2
303.2	1.212	0.825	1.1
308.2	1.252	0.798	1.0
313.2	1.338	0.748	1.3
Overall MRD%			1.5

Furthermore, the reported data for mono-solvents in the literature were fitted to a new modified van't Hoff model combined with the solubility parameters (*i.e.* Abraham solvation parameters, Hansen solubility and Catalan parameters) reported in a reference [34] and used for solubility prediction in the investigated mono-solvents. It should be said that none of the measured data was used for model training. The general model is as:

$$\ln x_T = \left(\begin{array}{c} 28.004\ (\pm 14.40) - 1.688\ (\pm 0.108)s - 1.699\ (\pm 0.679)\delta_d + \\ 0.216\ (\pm 0.011)\delta_h + 28.654\ (\pm 2.226)SP - 20.176\ (\pm 6.614)SdP \end{array}\right) + \left(\frac{\begin{array}{c} -16190.841(\pm 356.041) + 462.448\ (\pm 204.659)\delta_d + 6651.045\ (\pm 1999.289)SdP \\ -480.440\ (\pm 72.436)SB \end{array}}{T}\right)$$

The molar unit for the solubility data was used for the training and prediction procedures. As solubility parameters for PEG 400 are not available, the above equation was only used for the solubility prediction of deferiprone in neat 2-propanol at different temperatures. The overall *MRD*% was obtained 18.1 which shows the high accuracy of this model for the solubility prediction with a requirement to only solubility parameters (*i.e.* Abraham solvation parameters, Hansen solubility and Catalan parameters) for the investigated solvent.

In the next step, the measured density data for the investigated mixtures (Table 5) were correlated to the Jouyban-Acree model by replacing the solubility parameters with density parameters in Eq. (3) and the obtained model was:

$$\ln\rho_{m,T} = w_1 ln\rho_{1,T} + w_2 ln\rho_{2,T} - 10.259\frac{w_1.w_2}{T} + 2.601\ \frac{w_1.w_2(w_1 - w_2)}{T} \qquad (11)$$

herein, $\rho_{m,T}$ is the density value in the mixtures and $\rho_{1,T}$, and $\rho_{2,T}$ are the density values in neat solvents. The overall back-calculated *MRD*% was 0.1 showing the reliability of the Jouyban-Acree model for density prediction in the binary systems.

Calculation of the thermodynamic parameters

Thermodynamic property of the deferiprone dissolution process was investigated by calculation of thermodynamic parameters. Table 6 summarizes these parameters that were obtained by the van't Hoff and Gibbs equations. Intercept of $\ln x$ *vs* $1/T - 1/T_{hm}$ plot is employed to compute ΔH° and ΔG° and ΔS° values are obtained by Gibbs equation. In these equations, it is assumed that the thermodynamic solute activity is equal to the mole fraction solubility, which implies that the symmetrical activity coefficient of the solute (related to solvent) is the unit. However, the asymmetrical coefficient of the solute (related to solvent) could be very different regarding the unit,

Table 5: Measured density (g/cm^3) for deferiprone in the binary mixtures of PEG 400 and 2-propanol

w_1	T (K)				
	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00	0.780 ± 0.001	0.779± 0.000	0.777 ± 0.000	0.775 ± 0.000	0.775 ± 0.003
0.10	0.808 ±0.002	0.805 ± 0.001	0.802 ± 0.001	0.802 ± 0.000	0.798 ± 0.000
0.20	0.835 ± 0.002	0.832 ± 0.002	0.829 ± 0.001	0.829 ± 0.000	0.826 ± 0.000
0.30	0.864 ± 0.001	0.861 ± 0.000	0.860 ± 0.000	0.860 ± 0.001	0.858 ± 0.001
0.40	0.895 ± 0.001	0.891 ± 0.001	0.890 ± 0.000	0.888 ± 0.000	0.886 ± 0.001
0.50	0.926 ± 0.001	0.925 ± 0.000	0.925 ± 0.000	0.924 ± 0.001	0.919 ± 0.002
0.60	0.962 ± 0.002	0.958 ± 0.000	0.958± 0.003	0.957 ± 0.000	0.955 ± 0.000
0.70	0.998 ± 0.001	0.995 ± 0.000	0.994 ± 0.000	0.994 ± 0.000	0.991 ± 0.002
0.80	1.037 ± 0.002	1.035 ± 0.000	1.034 ± 0.000	1.033 ± 0.000	1.029 ± 0.001
0.85	1.060 ± 0.001	1.059 ± 0.001	1.054 ± 0.001	1.052 ± 0.003	1.050 ± 0.000
0.90	1.078 ± 0.001	1.075 ± 0.002	1.075 ± 0.001	1.074 ± 0.001	1.070 ± 0.001
1.00	1.119 ± 0.000	1.118 ± 0.001	1.118± 0.000	1.117 ± 0.000ΔS°	1.111 ± 0.002

Table 6 :Apparent thermodynamic parameters for dissolution of deferiprone in PEG 400 and 2-propanol mixture

w_1	ΔG° (kJ/mol)	ΔH° (kJ/mol)	ΔS° (J/mol.K)	TΔS° (kJ/mol)	ζ_H	ζ_{TS}
0.00	17.71	27.13	31.085	9.42	0.742	0.258
0.10	17.22	21.62	14.531	4.40	0.831	0.169
0.20	16.68	19.99	10.913	3.31	0.858	0.142
0.30	16.20	18.31	6.9608	2.11	0.897	0.103
0.40	15.72	17.26	5.1038	1.55	0.918	0.082
0.50	15.24	16.89	5.4384	1.65	0.911	0.089
0.60	14.73	15.35	2.0601	0.62	0.961	0.039
0.70	14.18	14.21	0.1112	0.03	0.998	0.002
0.80	13.53	13.46	-0.227	-0.07	0.995	0.005
0.85	13.16	13.24	0.2411	0.07	0.995	0.005
0.90	12.95	13.80	2.7923	0.85	0.942	0.058
1.00	12.29	14.45	7.126	2.16	0.870	0.130

being high as 1000 or even higher depending on the experimental and ideal solubilities. It is important to note that these thermodynamic quantities are just apparent because no dissolution calorimetric measurements of enthalpy were performed and the drug activities at saturation are considered the same as the respective mole fraction concentrations. As can be seen, $\Delta H°$ values were positive in all studied mixtures with the highest (27.13 kJ/mol) and lowest (13.24 kJ/mol) values in $w_1 = 0.0$ and $w_1 = 0.85$, respectively. The $\Delta S°$ values were also positive in all investigated solvents except for the mixture with w_1=0.8 and the lowest and highest values were 31.09 and -0.23 J/mol.K in $w_1 = 0.0$ and $w_1 = 0.8$, respectively. Positive values for both of these parameters show that deferiprone dissolution process in the investigated mixtures was endothermic and entropically favorable. Moreover, $\Delta G°$ values decreased with an increase PEG 400 mass fraction and show a minimum value in the mixture with the highest solubility (*i.e.* $w_1 = 1.0$). However, the positive value for $\Delta G°$ showed that the deferiprone dissolution process was a non-spontaneous procedure. Although the dissolution process is spontaneous until the drug saturation is reached in every solvent system, in saturated solutions trend is different and apparent properties are observed. So, the apparent thermodynamic parameters suggested that deferiprone dissolution is mainly favored in PEG 400 -rich mixtures, where the maximal drug solubilities are observed. ζ_H and ζ_{TS} were also shown in Table 6. In all mixtures, $\zeta_H > \zeta_{TS}$ demonstrated that the enthalpy was the main contributor to $\Delta G°$.

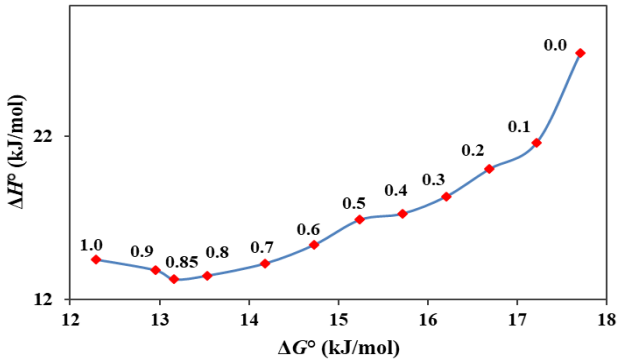

Fig. 2: Enthalpy-entropy compensation plot for deferiprone dissolution in PEG 400 + 2-propanol mixture. The points represent the mass fraction of PEG 400 in the mixtures in the absence of deferiprone.

Enthalpy-entropy compensation analysis was also performed to show the main mechanism involved in the cosolvent action according to the solvent composition. As can be seen from Fig. 2, deferiprone thermodynamic profile exhibits a non-linear trend with a positive slope in the range of w_1 = 0.0 to w_1 =0.85 indicating an enthalpy-driven mechanism and a negative slope in the range of w_1 =0.9 to w_1 =1.0 indicating an entropy-driven mechanism.

CONCLUSIONS

In the current study, the solubility and density of deferiprone were determined in the PEG 400 and 2-propanol mixtures at 293.2 – 313.2 K. The results showed that the solubility increases with both PEG 400 mass fraction and temperature increase. The measured data were fitted to some mathematical models. The results from the investigation of model accuracy showed that there were only tiny differences between measured data and back-calculated data from models (*MRD*% <3.5). Moreover, thermodynamic studies showed that the deferiprone dissolution process was endothermic and entropy-driven, and the main contributor of $\Delta G°$ was the enthalpy.

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