Solubility of Lamotrigine in Polyethylene Glycol 400 + 2-Propanol Mixtures at Different Temperatures

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   In this study, the shake-flask method was used to determine the solubility of lamotrigine (LTG) in non-aqueous mixtures of polyethylene glycol 400 (PEG 400) and 2-propanol at temperatures of 293.15 to 313.15 K. Five main mathematical models were used to correlate the experimental data. The overall mean relative deviations for these models were less than 18.7%. In addition, the apparent thermodynamic properties of LTG dissolution were computed. It was found that the LTG dissolution in PEG 400-rich mixtures was more favorable and entropically driven. Both experimental and mathematical methods were used to determine the density of LTG-saturated solutions. The results showed that the Jouyban-Acree model could be used to predict the density of LTG-saturated solutions in mixtures with a very good approximation (back-calculated *MRD*% of 0.4).

INTRODUCTION

   The solubility of pharmaceuticals plays a critical role in drug development [1], preparation of poorly water-soluble drugs [2], development of suitable pharmaceutical drug delivery systems [3-4], and drug crystallization [5]. In addition, the solubility data are beneficial in studying the absorption, distribution, and solubilization mechanisms of drugs [6-7]. Various approaches have been reported to enhance the solubility of pharmaceuticals, such as pH adjustment, complexation, cosolvency, and micronization [8-9]. Due to the simplicity and low cost of the cosolvency models, these models are frequently used in drug dissolution studies. In the cosolvency model, the dissolution rate is dependent on experimental conditions, namely, the composition of solvent mixtures and temperature [10]. In the

present work, the solubility and thermodynamics of lamotrigine (LTG) were studied experimentally using a cosolvency model.

   The molecular structure of LTG is shown in Fig. 1. LTG is an antiepileptic drug prescribed to treat epilepsy and bipolar disorder [11]. Due to its poor solubility and good permeability, LTG falls into BCS class II drugs [12]. To
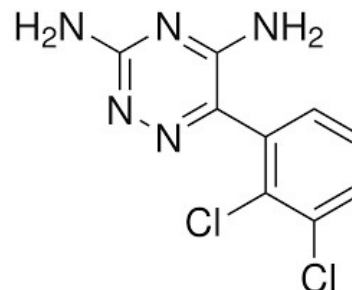

Fig. 1. Chemical structure of LTG.

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understand the dissolution trend and solution chemistry of LTG in aqueous and organic solvents and model its solubility, several mathematical models were used in mixed solvents.

To date, the solubility of LTG has been described in various binary mixtures of aqueous and organic solvents. Based on our best knowledge, LTG solubility in PEG 400 + 2-propanol system has not been reported yet.

The objectives of the present study were to investigate (1) the trend of the solubility of LTG and its dissolution mechanism in the binary mixture of PEG 400 and 2-propanol at temperatures of 293.2 to 313.2 K (2) the performance of the cosolvency model in data prediction, and (3) thermodynamic properties of LTG dissolution in the above system.

MATERIALS AND METHOD

Materials

LTG (99.9 wt.%) was supplied by Arasto Pharmaceutical Chemicals Inc. (Tehran, Iran), 2-Propanol (99.9 wt.%) by Scharlau Chemie (Spain), and PEG 400 (99.5 wt.%) by Merck (Germany). Ethanol (93.5 wt.%, Jahan Alcohol Teb, Arak, Iran) and laboratory-made deionized water were used to dilute the saturated solutions of LTG before spectrophotometric determination.

Measurement of LTG Solubility

A solid-liquid equilibrium model was utilized to study the solubility of LTG in the mixture of PEG 400 + 2-propanol (prepared by mass ratio) using the shake-flask method [13]. An excess amount of LTG was poured into 5-ml microcentrifuge tubes containing premixed solvents at different mass ratios (total mass of 3.0 g). Then, the sealed tubes were shaken on a shaker (Behdad, Tehran, Iran) at a constant temperature under incubation (Kimia Idea Pardaz Azerbaijan, Tabriz, Iran) for durations suggested by preliminary studies of dissolution rates. Solid-liquid equilibrium for LTG was achieved after 72 h, after which the saturated mixtures were centrifuged. An aliquot of clear upper solutions was diluted with ethanol: water (30:70, v/v). Then, their UV-Vis absorbance was recorded at 308 nm using a UV-Vis spectrophotometer (Cecil BioAquarius 7250 CE, UK) to calculate the concentrations of diluted solutions using

a plotted calibration curve of the standard solutions of LTG. All experiments were performed in triplicate. The density of the equilibrated solutions was measured using a 1.5-ml pycnometer.

X-Ray Powder Diffraction (XRD) Analysis

The crystallinity of LTG (raw and processed in PEG 400 and 2-propanol) was investigated using XRD analysis performed using a Philips PW 1730. The XRD data were recorded from 10° to 80° (2θ) at 30 mA and 40 kV at atmospheric pressure.

Mathematical Models

In this study, solubility data were regressed against solvent compositions and/or temperature using the main mathematical models, namely, the van't Hoff, the Jouyban-Acree, MRS, the Jouyban-Acree-van't Hoff, and the modified Wilson models. The van't Hoff equation (Eq. (1)) relates the dissolution process of the solute to the temperature in a given solvent mixture. The solubility of the solute was accurately determined using the Jouyban-Acree (Eq. (2)) and Jouyban-Acree-van't Hoff (Eq. (3)) models, which correlate the empirical solubility data based on both temperature and composition of solvents. The MRS model (Eq. (4)) was used to correlate the solubility of the solute at various solvent compositions at an individually examined temperature. The modified Wilson model (Eq. (5)) fitted the solubility data against mixture composition at a given temperature in a non-linear manner.

$$\ln x = A + \frac{B}{T} \tag{1}$$

$$\ln x_m = \beta_1 w_1' + \beta_2 w_2' + \beta_3 \left(\frac{1}{w_1'}\right) + \beta_4 \left(\frac{1}{w_2'}\right) + \beta_5 w_1' \cdot w_2' \tag{2}$$

$$\ln x_{m,T} = w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + \frac{w_1 \cdot w_2}{T} \sum_{i=0}^{2} J_i \cdot (w_1 - w_2)^i \tag{3}$$

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

$$-\ln x_m = 1 - \frac{w_1[1 + \ln x_1]}{w_1 + w_2\,\lambda_{12}} - \frac{w_2[1 + \ln x_2]}{w_1\,\lambda_{21} + w_2} \qquad (5)$$

where x_m, x_1, and x_2 indicate the solubilities of the drug in the mixed solvents and mono-solvents 1 and 2, respectively. The mass fraction of solvents 1 and 2 are shown by w_1 and w_2. The accuracy of the models prediction is expressed as the mean relative deviation (MRD%) (Eq. (6)):

$$MRD\% = \frac{100}{N}\sum\left(\frac{|Calculated\ Value - Observed\ Value|}{Observed\ Value}\right) \qquad (6)$$

where N denotes the number of experimental points.

Calculation of Thermodynamic Parameters

An apparent thermodynamic analysis was performed based on the van't Hoff equation to calculate thermodynamic parameters, namely, Gibbs free energy change $(\Delta G°)$, standard dissolution entropy $(\Delta S°)$, and standard dissolution enthalpy $(\Delta H°)$, of LTG in binary solvent mixtures. The $\Delta H°$ value of binary solvent mixtures was obtained using Eq. (7):

$$\frac{\partial \ln x}{\partial\left(\frac{1}{T} - \frac{1}{T_m}\right)_p} = -\frac{\Delta H°}{R} \qquad (7)$$

The value of $\Delta H°$ was calculated from the slope of the plots of $\ln x$ against $\frac{1}{T} - \frac{1}{T_m}$ (Eq. (7)) [14]. For a narrow range of temperature (293.15-313.15 K), it can be assumed that the change in the heat capacity of the solution remains constant. Consequently, it was expected that $\Delta H°$ be valid for the mean value of the investigated temperature range ($T_{mean} = 303.15$ K). The slope and intercept of the plot of Eq. (7) were used to calculate $\Delta H°$ and $\Delta G°$ involved in the dissolution of an LTG in mixed solvents at equilibrium, respectively. When the values of $\Delta H°$ and $\Delta G°$ were calculated, the value of $\Delta S°$ was obtained using the Gibbs equation as follows:

$$\Delta S° = \frac{\Delta H° - \Delta G°}{T_{hm}} \qquad (8)$$

Given that both enthalpy and entropy contribute to dissolution, the contribution of each (ζ_H and ζ_{TS}) can be expressed by Eqs. (9) and (10), respectively [15]:

$$\zeta_H = \frac{|\Delta H°|}{(|\Delta H°| + |T\Delta S°|)} \qquad (9)$$

$$\zeta_{TS} = \frac{|T\Delta S°|}{(|\Delta H°| + |T\Delta S°|)} \qquad (10)$$

RESULTS AND DISCUSSION

XRD Analysis

Using powder XRD at ambient temperature and pressure, the XRD data of LTG in mono-solvents were obtained and their patterns are presented in Fig. 2. This analysis was performed to determine whether the solid forms of LTG in the saturated solutions formed solvated compounds or polymorphs. As can be seen in Fig. 2, no new characteristic peaks appeared, indicating that the crystallinity of LTG remained unchanged and that it did not undergo a polymorphic transformation during the dissolution procedure.

The Solubility of LTG in Non-Aqueous Binary Mixture

The experimental data for the solubility (as mole fraction) of LTG are summarized in Table 1. The mean of three replicate measurements is reported for each experimental data point with relative standard deviations (RSD%) less than 10. Based on Table 1, it can be observed that LTG tended to be dissolved more in PEG 400; this trend continued up to the point where the mass fraction of PEG 400 was 0.7. At higher concentrations of PEG 400, the solubility of LTG decreased. Furthermore, the results showed that the solubility of the LTG linearly increased with an increase in temperature. This trend illustrates that the solvation of LTG molecules needed more energy than that of the intermolecular interactions between solvent molecules. In other words, the dissolution of LTG was an endothermic process in the studied solvent mixture. The maximum and minimum solubility for LTG was found in the mass fraction of 0.7 of PEG 400 at 313.2 K and in the neat 2-propanol at 293.2 K, respectively. The obtained solubility data for LTG in neat PEG 400 (1.13×10^{-1}) and 2-propanol (3.66×10^{-3}) had adequate consistency with that (*i.e.*, 1.12×10^{-1} for PEG 400 and 3.68×10^{-3} for 2-propanol)
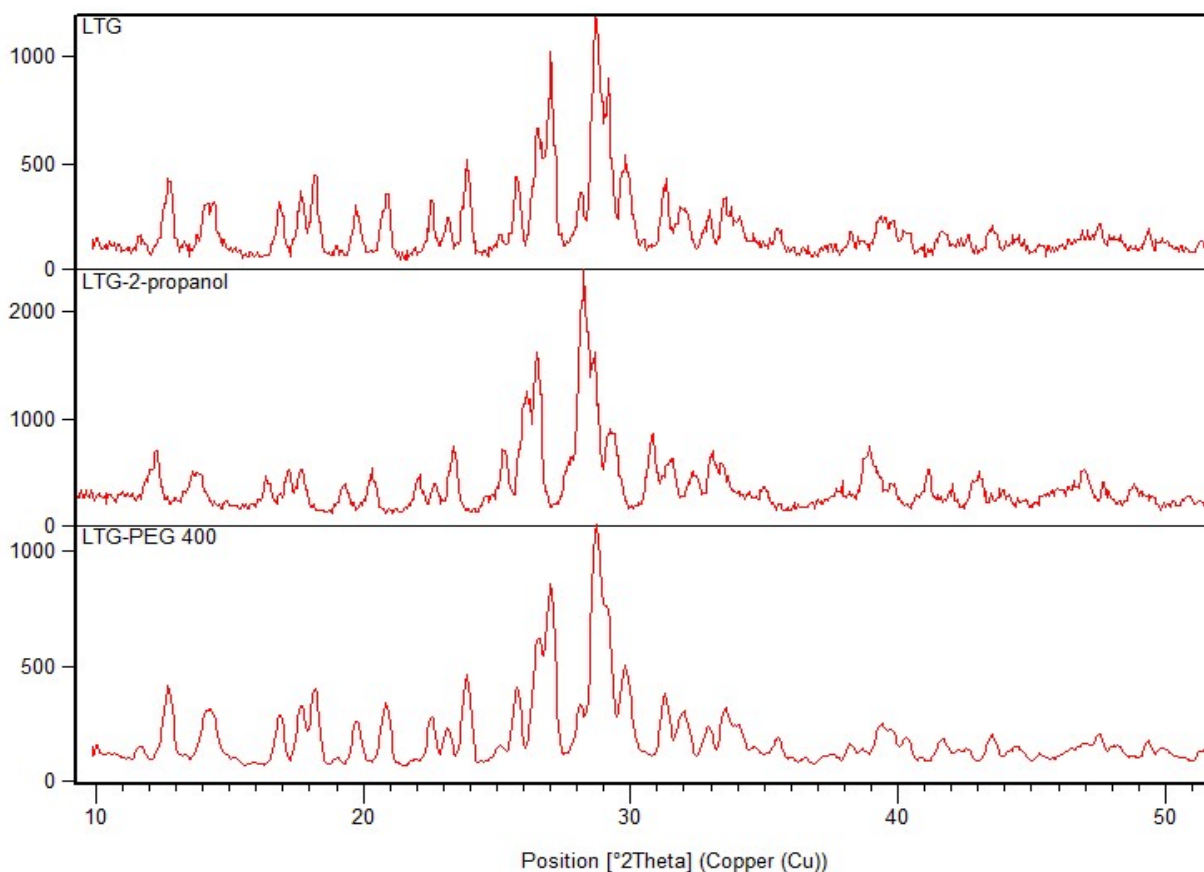
Fig. 2. The XRD pattern of LTG and equilibrated LTG in PEG 400 and 2-propanol.

Table 1. Measured Solubility ($x_{m,T}$) Values for LTG in PEG 400 + 2-Propanol (Mean ± SD, n = 3)

w_1[a]	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00	3.00 (±0.03) × 10^{-3}	3.66 (±0.06) × 10^{-3}	4.63 (±0.10) × 10^{-3}	4.97 (±0.05) × 10^{-3}	6.13 (±0.05) × 10^{-3}
0.10	3.66 (±0.11) × 10^{-3}	4.74 (±0.27) × 10^{-3}	5.56 (±0.11) × 10^{-3}	6.33 (±0.15) × 10^{-3}	7.43 (±0.18) × 10^{-3}
0.20	4.80 (±0.12) × 10^{-3}	5.73 (±0.23) × 10^{-3}	6.88 (±0.20) × 10^{-3}	8.20 (±0.21) × 10^{-3}	9.59 (±0.15) × 10^{-3}
0.30	9.00 (±0.34) × 10^{-3}	1.06 (±0.04) × 10^{-2}	1.26 (±0.05) × 10^{-2}	1.53 (±0.08) × 10^{-2}	1.89 (±0.03) × 10^{-2}
0.40	1.60 (±0.03) × 10^{-2}	1.83 (±0.03) × 10^{-2}	2.08 (±0.07) × 10^{-2}	2.65 (±0.07) × 10^{-2}	3.00 (±0.09) × 10^{-2}
0.50	2.78 (±0.03) × 10^{-2}	3.09 (±0.04) × 10^{-2}	3.36 (±0.12) × 10^{-2}	3.57 (±0.08) × 10^{-2}	4.12 (±0.11) × 10^{-2}
0.60	4.34 (±0.12) × 10^{-2}	4.97 (±0.15) × 10^{-2}	5.87 (±0.15) × 10^{-2}	6.82 (±0.24) × 10^{-2}	8.18 (±0.12) × 10^{-2}
0.70	1.13 (±0.06) × 10^{-1}	1.39 (±0.02) × 10^{-1}	1.61 (±0.03) × 10^{-1}	1.88 (±0.03) × 10^{-1}	2.15 (±0.09) × 10^{-1}
0.80	1.10 (±0.02) × 10^{-1}	1.37 (±0.03) × 10^{-1}	1.57 (±0.06) × 10^{-1}	1.73 (±0.02) × 10^{-1}	1.98 (±0.04) × 10^{-1}
0.90	1.06 (±0.03) × 10^{-1}	1.25 (±0.03) × 10^{-1}	1.40 (±0.03) × 10^{-1}	1.54 (±0.03) × 10^{-1}	1.83 (±0.03) × 10^{-1}
1.00	9.30 (±0.43) × 10^{-2}	1.13 (±0.08) × 10^{-1}	1.27 (±0.04) × 10^{-1}	1.51 (±0.06) × 10^{-1}	1.81 (±0.02) × 10^{-1}

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

Table 2. Calculated Parameters for the van't Hoff Model

w_1	A	B	$MRD\%$
0.00	5.097	-3192.879	2.3
0.10	5.137	-3139.784	2.6
0.20	5.565	-3197.289	0.3
0.30	6.852	-3397.205	1.9
0.40	6.011	-2982.287	2.4
0.50	2.251	-1710.865	1.3
0.60	6.759	-2906.515	1.4
0.70	7.804	-2921.485	1.3
0.80	6.691	-2598.210	2.4
0.90	5.966	-2405.948	1.6
1.00	7.781	-2976.846	1.4
	Overall		1.7

Table 3. Calculated Constants for the MRS Model

T (K)	β_1	β_2	β_3	β_4	β_5	$MRD\%$
293.2	-1.054	-6.107	0[a]	-0.025	0[a]	15.9
298.2	-0.904	-5.915	0[a]	-0.024	0[a]	16.5
303.2	-0.806	-5.719	0[a]	-0.024	0[a]	17.8
308.2	-0.686	-5.570	0[a]	-0.023	0[a]	16.8
313.2	-0.555	-5.388	0[a]	-0.023	0[a]	17.1
Overall $MRD\%$						16.8

[a]Not significant (p-value > 0.05).

reported in previous studies. The slight differences in data can be attributed to experimental imprecision and the methodology used by the researchers.

The above-described models were applied to fit the experimentally determined solubility data. The computed parameters of investigated models, along with calculated $MRDs\%$ values, are presented in Tables 2-5. The $MRD\%$ indicates the difference between the x_m and the values obtained from the mathematical models. Overall, the $MRDs\%$ for the back-calculated LTG solubility data were less than 18.7 for all models. As can be seen in Tables 2-5, the models that used Eqs. (2) and (3) to relate the solubility data to solvent composition and temperature showed good reliability for data correlation. To evaluate the predictive ability of Eq. (3), a seven-point fitting scheme was used to develop a model and the remainder of the data was predicted by the obtained model. The obtained $MRDs\%$ for the predicted solubility data were 15.3, 15.9, 18.2, 20.2, and 18.9 at five temperatures, respectively, and the overall $MRD\%$ of 17.7.

In the next step, the adopted version of Eq. (2) was used to calculate the density of the saturated solutions (Table 6). In this case, the density of neat and mixed solvents can be replaced with the solubility values in Eq. (3). The trained model can be written as follows:

Table 4. Calculated Parameters for the Jouyban-Acree and Jouyban-Acree-van't Hoff Models

	Jouyban-Acree		Jouyban-Acree-van't Hoff	
PEG 400 + 2-propanol	J_0	615.768	A_1	7.781
	J_1	1618.655	B_1	-29766.846
	J_2	0[a]	A_2	5.097
			B_2	-3192.879
			J_0	615.717
			J_1	1617.779
			J_2	0[a]
$MRD\%$	10.0		10.3	

[a]Not significant (p-value > 0.05).

Table 5. Calculated Parameters for the Modified Wilson Model

T (K)	λ_{12}	λ_{21}	$MRD\%$
293.2	18.961	0.883	17.0
298.2	27.627	0.901	17.5
303.2	40.080	0.898	20.0
308.2	41.688	1.003	18.9
313.2	139.563	1.023	20.1
Overall			18.7

$$\ln\rho_{m,T} = w_1\ln\rho_{1,T} + w_2\ln\rho_{2,T} - 9.066\frac{w_1 \cdot w_2}{T} + 62.665\frac{w_1 \cdot w_2(w_1 - w_2)}{T} \tag{11}$$

Table 6. The Measured Density (g cm^{-3}) of the Saturated Solutions of LTG

w_1	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00	0.798 ± 0.001	0.789 ± 0.001	0.786 ± 0.001	0.783 ± 0.001	0.780 ± 0.001
0.10	0.818 ±0.001	0.807 ± 0.001	0.798 ± 0.001	0.795 ± 0.001	0.792 ± 0.001
0.20	0.835 ± 0.001	0.829 ± 0.001	0.825 ± 0.002	0.822 ± 0.001	0.813 ± 0.001
0.30	0.882 ± 0.002	0.870 ± 0.001	0.862 ± 0.001	0.849 ± 0.001	0.847 ± 0.001
0.40	0.917 ± 0.001	0.909 ± 0.001	0.907 ± 0.001	0.880 ± 0.001	0.879 ± 0.001
0.50	0.962 ± 0.003	0.944 ± 0.001	0.940 ± 0.001	0.929 ± 0.001	0.921 ± 0.001
0.60	1.004 ± 0.001	0.997 ± 0.001	0.985 ± 0.001	0.979 ± 0.001	0.969 ± 0.002
0.70	1.050 ± 0.001	1.042 ± 0.001	1.033 ± 0.001	1.023 ± 0.001	1.005 ± 0.001
0.80	1.091 ± 0.002	1.085 ± 0.002	1.071 ± 0.001	1.067 ± 0.001	1.057 ± 0.001
0.90	1.131 ± 0.001	1.123 ± 0.001	1.117 ± 0.001	1.109 ± 0.001	1.096 ± 0.001

Table 7. Calculated Apparent Thermodynamic Parameters for LTG Dissolution in PEG 400 + 2-Propanol Mixtures at T_{hm} = 303.0 K

w_1	$\Delta G°$ (kJ mol^{-1})	$\Delta H°$ (kJ mol^{-1})	$\Delta S°$ (J K^{-1} mol^{-1})	$T\Delta S°$ (kJ mol^{-1})	ζ_H	ζ_{TS}
0.00	13.70	26.55	42.38	12.84	0.674	0.326
0.10	13.16	26.10	42.71	12.94	0.669	0.331
0.20	12.56	26.58	46.27	14.02	0.655	0.345
0.30	10.98	28.24	56.97	17.26	0.621	0.379
0.40	9.65	24.79	49.97	15.14	0.621	0.379
0.50	8.55	14.22	18.71	5.67	0.715	0.285
0.60	7.14	24.16	56.19	17.03	0.587	0.413
0.70	4.63	24.29	64.89	19.66	0.553	0.447
0.80	4.75	21.60	55.63	16.85	0.562	0.438
0.90	4.97	20.00	49.61	15.03	0.571	0.429
1.00	5.15	24.75	64.69	19.60	0.558	0.442

where $\rho_{m,T}$, $\rho_{1,T}$, and $\rho_{2,T}$ were the density of LTG saturated mixtures and mono-solvents 1 and 2, respectively. The back-calculated *MRD*% was 0.4, showing that the model provided an accurate estimation of density.

Apparent Thermodynamic Studies for LTG Dissolution

Table 7 presents the computed thermodynamic parameters of LTG dissolution in the mixture of PEG 400 and 2-propanol. Both $\Delta G°$ and $\Delta H°$ values were positive, indicating that LTG dissolution in all fractions of the studied solvents was an endothermic process and did not proceed spontaneously. $\Delta S°$ values were also positive in all solvent fractions, indicating an entropy-driven dissolution process. It was observed that with an increase in the amount of PEG 400 (up to $w_{PEG\ 400}$ = 0.7), the positive values of $\Delta G°$ decreased, which suggests that the PEG 400-rich solution was suitable for the dissolution process. Moreover, the plot of $\Delta G°$ versus $\Delta H°$ at the T_{hm} (Fig. 3) was employed to study the dissolution mechanism of LTG. A non-linear curve for $\Delta G°$ *versus* $\Delta H°$ was observed for LTG solubility in PEG 400 + 2-propanol systems. Regarding the dissolution process of LTG, the positive slopes in Fig. 3 reveal an enthalpy-driven mechanism while the negative slopes indicate an entropy-driven mechanism. The calculated values of ζ_H and ζ_{TS} (Table 7) suggest that the enthalpy $(\zeta_H > 0.5$ and $\zeta_H > \zeta_{TS})$
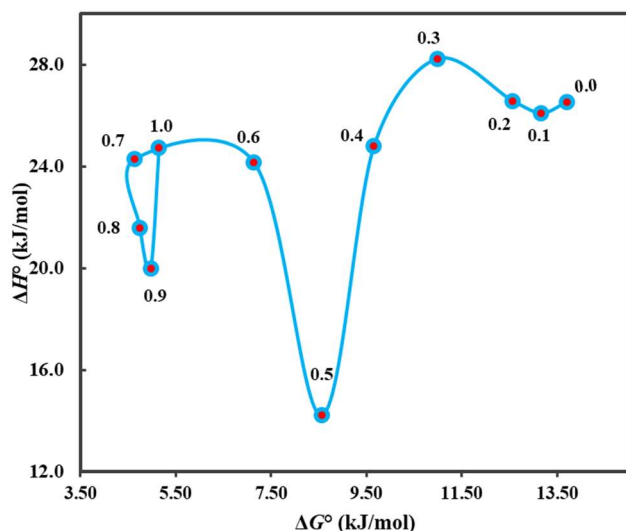
Fig. 3. The enthalpy-entropy compensation plot for the dissolution of LTG at 303.0 K.

made the main contribution to ΔG° in LTG dissolution.

CONCLUSIONS

The solid-liquid equilibrium model was performed to determine LTG solubility in non-aqueous binary mixtures of PEG 400 and 2-propanol at 293.2 to 313.2 K temperatures. The results showed that by increasing the concentration of PEG 400, the LTG solubility increased and attained a maximum value in the mass fraction of 0.70 of PEG 400 at 313.2 K. The low *MRD*% for back-calculated data showed that all investigated models were suitable to correlate and predicate the solubility data. Furthermore, the calculated thermodynamic parameters of the LTG dissolution reflected an endothermic and entropy-driven process.

ACKNOWLEDGEMENTS

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