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Thermodynamic studies of fluphenazine decanoate solubility in propylene glycol + water mixtures and correlation with the Jouyban–Acree model

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ABSTRACT

Solubilities of fluphenazine decanoate (FD) in binary mixtures of propylene glycol + water (PG + W) at 293.2, 298.2, 303.2, 308.2, and 313.2 K are reported. The combination of Jouyban–Acree model and van't Hoff equation is used to predict the solubility of FD in a given solvent mixture at different temperatures. The thermodynamic properties (enthalpy, entropy and Gibbs energy standard changes of solutions) for FD in PG + W mixtures are calculated from solubility data using the modified version of van't Hoff and Gibbs equations. The results show that Jouyban–Acree model can predict the solubility of FD in PG + W mixtures as a function of temperature over the studied temperature range. The study represents the first time that thermodynamic properties of solutes dissolved in binary solvent mixtures have been described by the Jouyban–Acree model. The calculated values are in good agreement with the measured experimental data.

1. Introduction

Solubility alteration of chemicals is required in many chemical and pharmaceutical applications, including crystallization, separation, decontamination, liquid extraction, and drug formulation. Solvent mixing or cosolvency is one of the most frequent and feasible methods used in the chemical industry. Temperature alteration and solvent mixing are common methods to modify solubility in crystallization studies. For many solutes there is insufficient solubility data. To address this concern considerable effort has been devoted to developing models that enable one to make solubility predictions from a minimum number of experimental input values [1–4].

Fluphenazine decanoate (FD) is an ester prodrug of fluphenazine that is used to treatment of schizophrenia [5]. FD is practically insoluble in water, and very soluble in alcohol, chloroform, cyclohexane and ether [6]. In this study the solubility of FD in binary propylene glycol + water (PG + W) mixtures was determined. PG is a stable, low toxic pharmaceutical cosolvent used in many commercially available oral and parenteral pharmaceutical formulations of poorly soluble drugs [7].

Experimental solubility determination is a time-consuming and costly process [8]. Several mathematical models have been proposed in the published literature to predict the solubility of drugs in cosolvent + water mixtures. The Jouyban–Acree model is one of the models developed by our group. The model provides an accurate mathematical description for how the solute solubility varies with both temperature and solvent composition. The model for representing the solubility of a solute in binary mixture at various temperatures is [9]:

$$\log x_{m,T}^{sat} = m_1 \log x_{1,T}^{sat} + m_2 \log x_{2,T}^{sat} + \frac{m_1 m_2}{T} \sum_{i=0}^{2} J_i (m_1 - m_2)^i \qquad (1)$$

where $x_{m,T}^{sat}$ is the solute solubility in the solvent mixtures at temperature T, m_1 and m_2 are the fractions of the PG and W in the absence of the solute, $x_{1,T}^{Sat}$ and $x_{2,T}^{Sat}$ denote the solubility of the solute in the mono-solvents 1 and 2, respectively, and J_i are the constants of the model computed by regression analysis. A predictive limitation of the Jouyban–Acree model is that the model constants must be known for the given solute dissolved in the binary solvent mixture under consideration in order to compute the J_i constants in Eq. (1). This limitation severely restricts the application of the Jouyban–Acree model in the early drug discovery and development stages as the drug candidate's solubility may not have been measured yet. Predictions, not measurements, are used in early drug

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discovery and development studies to select the more promising drug candidates for future studies.

Quantitative structure–property relationship (QSPR) models have been proposed to predict the numerical values of the model constants. The QSPR model that was recommended for predicting the solubility of drug molecules in binary PG + W mixtures is [9]:

$$\log x_{m,T}^{sat} = m_1 \log x_{1,T}^{sat} + m_2 \log x_{2,T}^{sat} + \left[\frac{37.030 m_1 m_2}{T} + \frac{319.490 m_1 m_2 (m_1 - m_2)}{T}\right]. \quad (2)$$

The required input values for the solubility at different temperatures in mono-solvent can be calculated using van't Hoff:

$$\log x_T^{Sat} = A + \frac{B}{T} \quad (3)$$

with the A and B model constants determined from a linear least square analysis of the measured solute solubility as a function of temperature, ($\log X_T^{Sat}$) [10], or from solubility data measured at two temperatures (e.g. at the lowest and at the highest temperatures studied for each mono-solvent). The Jouyban–Acree and van't Hoff models were combined to enable one to make solubility predictions for drug molecules in mixed solvents as a function of temperature using measured solubility data for the drug dissolved in each solvent at two temperatures [11].

Solubility measurements often employ spectroscopic methods that give the experimental concentration of the solute in the saturated solution as a molar solubility value. The density of the saturated solution is required to convert the measured molar solubility (mole per liter) value to a mole fraction solubility (or vice versa), which is required in many industrial applications, The Jouyban–Acree model also describes the variation of the density of liquid mixtures as a function of both temperature and composition [12]. In recent papers [13,14] we have used trained versions of the Jouyban–Acree model to calculate densities of saturated drug solutions. The model was trained using measured density data for the solute-free binary solvent mixture. The advantage of this latter application of the Jouyban–Acree model is the large reduction in the number of experimental measurements that must be made to just two measurements. One must measure the densities of saturated drug solutions for the two mono-solvents, $\rho_{1,T}^{sat}$ and $\rho_{2,T}^{sat}$. To apply the density version of the Jouyban–Acree model to FD dissolved in binary PG + W mixtures, we first trained the model for binary PG + W mixtures at various temperatures:

$$\log \rho_{m,T} = m_1 \log \rho_{1,T} + m_2 \log \rho_{2,T} + 17.543\left(\frac{m_1 m_2}{T}\right) + 4.755\left(\frac{m_1 m_2 (m_1 - m_2)}{T}\right) - 1.032\left(\frac{m_1 m_2 (m_1 - m_2)}{T}\right)^2 \quad (4)$$

in which $\rho_{m,T}$, $\rho_{1,T}$ and ρ_{2T} are the density of solute free mixtures and solvents 1 and 2 at temperatures T. The experimental density data were collected from the published literature [15]. The calculated interaction terms in Eq. (4) can be used to predict the density of saturated solutions of FD dissolved in binary PG + W mixtures by:

$$\log \rho_{m,T}^{sat} = m_1 \log \rho_{1,T}^{sat} + m_2 \log \rho_{2,T}^{sat} + 17.543\left(\frac{m_1 m_2}{T}\right) + 4.755\left(\frac{m_1 m_2 (m_1 - m_2)}{T}\right) - 1.032\left(\frac{m_1 m_2 (m_1 - m_2)}{T}\right)^2 \quad (5)$$

in which $\rho_{m,T}^{Sat}$ is the density of the saturated solution of the drug in the mixed solvent system, $\rho_{1,T}^{Sat}$ and $\rho_{2,T}^{Sat}$ are the densities of the saturated solutions of the drug in mono-solvents 1 and 2 at temperature of T.

Standard enthalpy (ΔH°), entropy (ΔS°), and Gibbs energy (ΔG°) changes can be calculated using modified version of van't Hoff equation [16–19]. The mean harmonic temperature (T_{hm}) that is used in van't Hoff analysis, is calculated as

$$T_{hm} = \frac{n}{\sum_{i=1}^{n}(1/T)} \quad (6)$$

where n is the number of temperatures studied. Expressed in terms of the mean harmonic temperature, the modified version of van't Hoff equation becomes [16–19]:

$$\log x_T^{Sat} = -\frac{\Delta H^\circ}{R}\left(\frac{1}{T} - \frac{1}{T_{hm}}\right) \quad (7)$$

R is the universal gas constant ($R = 8.314\ \mathrm{J\ K^{-1}\ mol^{-1}}$). The ΔG° and ΔS° values are calculated:

$$\Delta G^\circ = -RT_{hm} \cdot \text{intercept} \quad (8)$$

$$\Delta S^\circ = \frac{\Delta H^\circ - \Delta G^\circ}{T_{hm}} \quad (9)$$

from Eqs. (8) and (9), respectively. The relative enthalpic, ($\%\xi_H$), and entropic ($\%\xi_{TS}$), contributions of the solubility of FD in PG + W mixtures is given by Eqs. (10) and (11), respectively [16,18]:

$$\%\xi_H = 100\frac{\left|\Delta H^\circ\right|}{\left|\Delta H^\circ\right| + \left|T\Delta S^\circ\right|} \quad (10)$$

$$\%\xi_{TS} = 100\frac{\left|T\Delta S^\circ\right|}{\left|\Delta H^\circ\right| + \left|T\Delta S^\circ\right|} \quad (11)$$

To date, the Jouyban–Acree model has been applied to properties such as electrophoretic mobility, instability rate constants, acid dissociation constants, retention factor of analytes in HPLC, solvatochromic parameter, dielectric constant, surface tension, refractive index, ultrasound velocity and viscosity of solvent mixtures [9]. However, there is no report on prediction of thermodynamic properties (ΔH°, ΔS°, ΔG°) for solutes dissolved in binary solvent mixtures.

The objectives of the present study are: (1) to measure the experimental solubility data of FD in PG + W mixtures at different temperatures; (2) to determine the feasibility of predicting the solubility of FD in PG + W mixtures using a combination of Jouyban–Acree model and van't Hoff equation, (3) to further assess the applicability of our proposed method for predicting the density of saturated solutions based on the density of solute free solvent mixtures; (4) to compute the thermodynamic characteristic of FD dissolved in binary PG + W mixtures calculated by van't Hoff equation; and (5) to determine whether the calculated thermodynamic properties for FD dissolved in binary PG + W could be described by the Jouyban–Acree model.

2. Experimental

2.1. Materials

FD (99.4% in mass fraction) was a gift from Chemidaru, PG (99.5% in mass fraction) was purchased from Scharlau Chemie (Spain), ethanol (96% volume fraction) from Jahan Alcohol Teb (Arak, Iran) and used for dilution of the concentrated solutions before spectroscopic analysis, and double-distilled water was used for the preparation of the solutions. All chemicals were used as received from the company without further purifications.

Table 1
Details of different numerical methods in this study.

Method	Basic Eq.	Solubilities in mono-solvent
I	Eq. (1)	Experimental
II	Eq. (2)	Experimental
III	Eq. (1)	Calculated from van't Hoff equation employing the highest and lowest temperatures
IV	Eq. (2)	Calculated from van't Hoff equation employing the highest and lowest temperatures

2.2. Solubility determination in PG + W mixtures at different temperatures

Binary PG + W cosolvent mixtures were prepared by mass. The solubility of FD was determined by equilibrating an excess amount of FD with the solvent using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system having an uncertainty of 0.2 K (Nabziran, Tabriz, Iran). The saturated solutions were equilibrated for three days at 293.2 K prior to analysis. After solubility determination and density measurement at 293.2 K, the remaining solutions containing excess solid were then equilibrated at 298.2 K for 2 additional days and the measurements were performed. The procedure was repeated until all of the temperatures had been studied. The saturated solutions were filtered using hydrophilic Durapore filters (0.45 μm, Millipore, Ireland) and then diluted with ethanol. Absorbance of the diluted solutions were recorded at 317 nm using a UV–vis spectrophotometer (Beckman DU-650, Fullerton, USA) and the concentrations were calculated using the calibration graph. Each experimental data point is an average of at least three experimental measurements with the measured mol L^{-1} solubilities reproducible to within the mean relative standard deviations (RSDs) of 2.5%. Calculated standard deviations ranged from $\sigma_{n-1} = 2.4 \times 10^{-8}$ to $\sigma_{n-1} = 2.7 \times 10^{-5}$ mol L^{-1}. Densities of the saturated solutions were determined using a 5 mL pycnometer with the uncertainty of 0.001 g mL^{-1} as a single determination.

2.3. Computational methods

Solubilities of FD in binary PG + W solvent mixtures at different temperatures were predicted by four methods: (I) data fitting of the measured experimental data to the Jouyban–Acree model (i.e. Eq. (1)); (II) a previously trained version of Jouyban–Acree model (i.e. Eq. (2)) [9]; (III) calculated curve-fit coefficients for Eq. (1) with the solubility of FD in each mono-solvent calculated from Eq. (3); and (IV) a previously trained version of the Jouyban–Acree model with the solubility of FD in the each mono-solvent calculated with Eq. (3). In the latter two methods, the solubility calculations for FD in each mono-solvent employed solubility data at only two temperatures (e.g. the lowest and highest temperatures). Table 1 lists details of various numerical methods employed in this study.

Thermodynamic properties of solutions of FD in PG + W mixtures were calculated according to the Eqs. (6)–(10) and the calculated values were fitted to Eq. (1).

The mean deviation (MD) was computed as:

$$\mathrm{MD} = \frac{1}{N}\left[\frac{\text{Calculated} - \text{Experimental}}{\text{Experimental}}\right] \quad (12)$$

and was used to evaluate the predictive accuracy of the different numerical methods. In Eq. (12) N is the number of data points in each set.

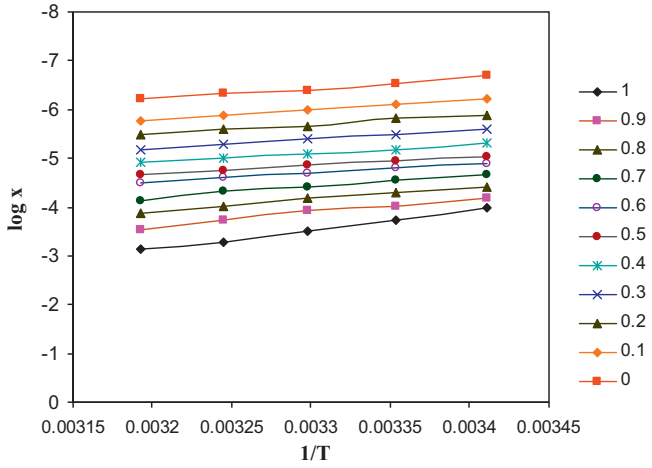

Fig. 1. Solubility of FD in PG + W mixtures at different temperatures.

3. Results and discussion

3.1. Solubility of FD in PG + W mixtures at different temperatures and prediction using different numerical methods

The calibration graph prepared from standard solutions of known concentrations gave molar absorptivities of FD ranging from 25446.11 ε/(L mol^{-1} cm^{-1}) to 27418.67 ε/(L mol^{-1} cm^{-1}). Mass fraction compositions of the binary solvent mixtures, densities of the saturated solutions, experimental and calculated FD solubilities at different temperatures using numerical methods 1 and 2 are tabulated in Table 2. Each experimental solubility value represents the average of at least three experimental measurements and were reproducible to within the mean relative standard deviations (RSDs) of 2.5%. Examination of the numerical values indicates that the minimum solubility of FD is observed in aqueous solution, and that the solubility increases both with temperature and with addition of the PG to the aqueous solution. Fig. 1 depicts the logarithm of FD solubility in binary solvent mixtures vs. $1/T$ according to the van't Hoff equation. The numerical values of the A and B coefficients of Eq. (3) are listed in Table 3.

Table 4 gives MD values of the four different numerical methods to predict solubility of FD at different temperatures. The results of our computations indicate that the combination of Jouyban–Acree model and van't Hoff equation can be used to predict the solubility of FD in binary PG + W solvent mixtures at different temperatures by employing four experimental data points.

3.2. Predicting the density of saturated solution at various temperatures using Jouyban–Acree model

Eq. (5) was used to predict densities of saturated solutions at various temperatures, and the predicted values were compared with the corresponding experimental data. The MD value between the predicted and experimental densities is 2.0 (±1.2) suggesting that the trained version of Jouyban–Acree model using density of liquid mixtures in the absence of solute can predict density of saturated solutions at different temperatures. Also, the mole fraction solubilities of FD in binary PG + W solvent mixtures calculated with the predicted saturated solution densities differed only slightly (MD = 1.9 (±1.2)) from the experimental mole fraction solubilities based on the measured saturated solution densities. There is no significant difference between the mole fraction solubilities obtained from experimental densities and those from predicted densities.

Table 2
Experimental and predicted values using different numerical methods for FD solubility (mole fraction) and density of saturated FD in PG + W mixtures at different temperatures along with the predicted densities using Eq. (5).

PG (mass fraction)	T (K)	$x_{m,T}^{Exp}$	$x_{m,T}^{Cal}$				ρ (g cm^{-3})$_{exp}$	ρ (g cm^{-3})$_{cal}$
		Mole fraction	I	II	III	IV		
1.00	293.2	1.00×10^{-4}	1.00×10^{-4}	1.00×10^{-4}	1.00×10^{-4}	1.00×10^{-4}	1.052	1.052
0.90	293.2	6.76×10^{-5}	4.75×10^{-5}	5.38×10^{-5}	4.97×10^{-5}	5.39×10^{-5}	1.046	1.063
0.80	293.2	3.87×10^{-5}	2.55×10^{-5}	2.89×10^{-5}	2.71×10^{-5}	2.89×10^{-5}	1.044	1.069
0.70	293.2	2.15×10^{-5}	1.49×10^{-5}	1.55×10^{-5}	1.59×10^{-5}	1.55×10^{-5}	1.040	1.072
0.60	293.2	1.30×10^{-5}	9.19×10^{-6}	8.33×10^{-6}	9.61×10^{-6}	8.33×10^{-6}	1.038	1.070
0.50	293.2	9.50×10^{-6}	5.75×10^{-6}	4.48×10^{-6}	$5.93 \times \times 10^{-6}$	4.48×10^{-6}	1.032	1.065
0.40	293.2	4.67×10^{-6}	3.52×10^{-6}	2.41×10^{-6}	3.60×10^{-6}	2.41×10^{-6}	1.028	1.057
0.30	293.2	2.61×10^{-6}	2.04×10^{-6}	1.29×10^{-6}	2.07×10^{-6}	1.29×10^{-6}	1.022	1.046
0.20	293.2	1.27×10^{-6}	1.08×10^{-6}	6.90×10^{-7}	1.09×10^{-6}	6.90×10^{-7}	1.016	1.033
0.10	293.2	5.91×10^{-7}	5.00×10^{-7}	3.70×10^{-7}	5.10×10^{-7}	3.70×10^{-7}	1.012	1.020
0.00	293.2	2.19×10^{-7}	2.00×10^{-7}	2.00×10^{-7}	2.00×10^{-7}	2.00×10^{-7}	1.006	1.006
1.00	298.2	1.88×10^{-4}	1.88×10^{-4}	1.88×10^{-4}	1.69×10^{-4}	1.69×10^{-4}	1.046	1.046
0.90	298.2	9.48×10^{-5}	8.71×10^{-5}	9.85×10^{-5}	8.28×10^{-5}	8.94×10^{-5}	1.040	1.056
0.80	298.2	5.10×10^{-5}	4.57×10^{-5}	5.17×10^{-5}	4.45×10^{-5}	4.75×10^{-5}	1.034	1.063
0.70	298.2	2.81×10^{-5}	2.62×10^{-5}	2.72×10^{-5}	2.56×10^{-5}	2.52×10^{-5}	1.030	1.065
0.60	298.2	1.57×10^{-5}	1.57×10^{-5}	1.43×10^{-5}	1.54×10^{-5}	1.34×10^{-5}	1.026	1.063
0.50	298.2	1.14×10^{-5}	9.59×10^{-6}	7.50×10^{-6}	9.38×10^{-6}	7.11×10^{-6}	1.022	1.058
0.40	298.2	6.93×10^{-6}	5.73×10^{-6}	3.94×10^{-6}	5.61×10^{-6}	3.78×10^{-6}	1.018	1.050
0.30	298.2	3.25×10^{-6}	3.24×10^{-6}	2.07×10^{-6}	3.19×10^{-6}	2.01×10^{-6}	1.012	1.039
0.20	298.2	1.47×10^{-6}	1.68×10^{-6}	1.09×10^{-6}	1.67×10^{-6}	1.07×10^{-6}	1.010	1.027
0.10	298.2	7.94×10^{-7}	7.70×10^{-7}	5.70×10^{-7}	7.70×10^{-7}	5.70×10^{-7}	1.006	1.014
0.00	298.2	2.62×10^{-7}	3.00×10^{-7}	3.00×10^{-7}	3.00×10^{-7}	3.00×10^{-7}	1.000	1.000
1.00	303.2	3.10×10^{-4}	3.10×10^{-4}	3.10×10^{-4}	2.79×10^{-4}	2.79×10^{-4}	1.042	1.042
0.90	303.2	1.19×10^{-4}	1.41×10^{-4}	1.59×10^{-4}	1.34×10^{-4}	1.45×10^{-4}	1.036	1.052
0.80	303.2	6.43×10^{-5}	7.25×10^{-5}	8.19×10^{-5}	7.06×10^{-5}	7.52×10^{-5}	1.030	1.058
0.70	303.2	3.81×10^{-5}	4.05×10^{-5}	4.21×10^{-5}	3.97×10^{-5}	3.91×10^{-5}	1.026	1.060
0.60	303.2	2.09×10^{-5}	2.38×10^{-5}	2.17×10^{-5}	2.33×10^{-5}	2.03×10^{-5}	1.020	1.058
0.50	303.2	1.40×10^{-5}	$1.42 \times \times 10^{-5}$	1.11×10^{-5}	1.39×10^{-5}	1.06×10^{-5}	1.016	1.053
0.40	303.2	8.33×10^{-6}	8.28×10^{-6}	5.73×10^{-6}	8.10×10^{-6}	5.49×10^{-6}	1.012	1.045
0.30	303.2	4.03×10^{-6}	4.58×10^{-6}	2.95×10^{-6}	4.51×10^{-6}	2.85×10^{-6}	1.008	1.035
0.20	303.2	2.20×10^{-6}	2.32×10^{-6}	1.51×10^{-6}	2.30×10^{-6}	1.48×10^{-6}	1.004	1.023
0.10	303.2	1.02×10^{-6}	1.04×10^{-6}	7.80×10^{-7}	1.04×10^{-6}	7.70×10^{-7}	1.002	1.009
0.00	303.2	3.65×10^{-7}	4.00×10^{-7}	4.00×10^{-7}	4.00×10^{-7}	4.00×10^{-7}	0.996	0.996
1.00	308.2	5.12×10^{-4}	5.12×10^{-4}	5.12×10^{-4}	4.53×10^{-4}	4.53×10^{-4}	1.038	1.038
0.90	308.2	1.87×10^{-4}	2.27×10^{-4}	2.56×10^{-4}	2.13×10^{-4}	2.29×10^{-4}	1.036	1.048
0.80	308.2	9.64×10^{-5}	1.14×10^{-4}	1.28×10^{-4}	1.09×10^{-4}	1.16×10^{-4}	1.032	1.053
0.70	308.2	4.86×10^{-5}	6.16×10^{-5}	6.39×10^{-5}	5.97×10^{-5}	5.87×10^{-5}	1.028	1.055
0.60	308.2	2.53×10^{-5}	3.51×10^{-5}	3.20×10^{-5}	3.41×10^{-5}	2.97×10^{-5}	1.022	1.053
0.50	308.2	1.81×10^{-5}	2.03×10^{-5}	1.60×10^{-5}	1.97×10^{-5}	1.51×10^{-5}	1.016	1.047
0.40	308.2	9.33×10^{-6}	1.15×10^{-5}	8.00×10^{-6}	1.12×10^{-5}	7.62×10^{-6}	1.012	1.039
0.30	308.2	5.57×10^{-6}	6.17×10^{-6}	4.00×10^{-6}	6.05×10^{-6}	3.86×10^{-6}	1.006	1.029
0.20	308.2	2.83×10^{-6}	3.04×10^{-6}	2.00×10^{-6}	3.01×10^{-6}	1.95×10^{-6}	1.002	1.017
0.10	308.2	1.30×10^{-6}	1.33×10^{-6}	1.00×10^{-6}	1.33×10^{-6}	9.90×10^{-7}	0.996	1.003
0.00	308.2	4.69×10^{-7}	5.00×10^{-7}	5.00×10^{-7}	5.00×10^{-7}	5.00×10^{-7}	0.990	0.990
1.00	313.2	7.26×10^{-4}	7.26×10^{-4}	7.26×10^{-4}	7.26×10^{-4}	7.26×10^{-4}	1.032	1.032
0.90	313.2	2.85×10^{-4}	3.17×10^{-4}	3.57×10^{-4}	3.31×10^{-4}	3.57×10^{-4}	1.026	1.041
0.80	313.2	1.33×10^{-4}	1.56×10^{-4}	1.75×10^{-4}	1.65×10^{-4}	1.75×10^{-4}	1.020	1.047
0.70	313.2	7.40×10^{-5}	8.32×10^{-5}	8.63×10^{-5}	8.77×10^{-5}	8.63×10^{-5}	1.016	1.048
0.60	313.2	3.20×10^{-5}	4.65×10^{-5}	4.24×10^{-5}	4.85×10^{-5}	4.24×10^{-5}	1.010	1.046
0.50	313.2	2.16×10^{-5}	2.64×10^{-5}	2.09×10^{-5}	2.72×10^{-5}	2.09×10^{-5}	1.006	1.041
0.40	313.2	1.25×10^{-5}	1.47×10^{-5}	1.03×10^{-5}	1.50×10^{-5}	1.03×10^{-5}	1.002	1.033
0.30	313.2	6.53x 10^{-6}	7.74×10^{-6}	5.05×10^{-6}	7.86×10^{-6}	5.05×10^{-6}	0.998	1.022
0.20	313.2	3.16×10^{-6}	3.75×10^{-6}	2.48×10^{-6}	3.81×10^{-6}	2.48×10^{-6}	0.994	1.010
0.10	313.2	1.75×10^{-6}	1.62×10^{-6}	1.22×10^{-6}	1.63×10^{-6}	1.22×10^{-6}	0.988	0.997
0.00	313.2	5.89×10^{-7}	6.00×10^{-7}	6.00×10^{-7}	6.00×10^{-7}	6.00×10^{-7}	0.984	0.984

3.3. Thermodynamic parameters of FD solutions in PG + W mixtures

Table 5 shows the thermodynamic parameters including ΔH°, ΔS°, and ΔG° of FD dissolved in PG + W mixtures at 303.2 K (harmonic temperature). The ΔH°, ΔS°, and ΔG° values positive at all binary solvent fractions indicating that the dissolution process is endothermic, entropically favorable, and solution process is not spontaneous. Relative contributions of enthalpy and entropy reveal that in all cases the main contributor to standard free energy of solution process of FD is the enthalpy (greater than 57%).

3.4. Enthalpy–entropy compensation of solution

Enthalpy–entropy compensation of drugs solubility was used to investigate the mechanism of cosolvency at different temperatures [17]. Fig. 2 shows enthalpy–entropy compensation plot for FD solubility in PG + W mixtures at 303.2 K. This profile is a non-linear ΔG° vs. ΔH° compensation with negative slope up to 50% of PG that in this case driving function for drug solubility is the entropy. After increasing solvent fraction of PG from 50% the slope is positive that revealing enthalpy is important for dissolution.

Table 3
Coefficient (*A*,*B*) of van't Hoff equation in each fraction of PG + W, calculated using solubility data at different temperatures using a least square method.

PG (mass fraction)	*A*	*B*
1.00	24.3	−9016.5
0.90	15.0	−6430.7
0.80	11.7	−5600.1
0.70	10.7	−5439.9
0.60	5.6	−4069.2
0.50	4.3	−3762.0
0.40	4.8	−4048.5
0.30	5.0	−4245.9
0.20	5.1	−4457.3
0.10	5.7	−4778.3
0.00	4.4	−4603.3

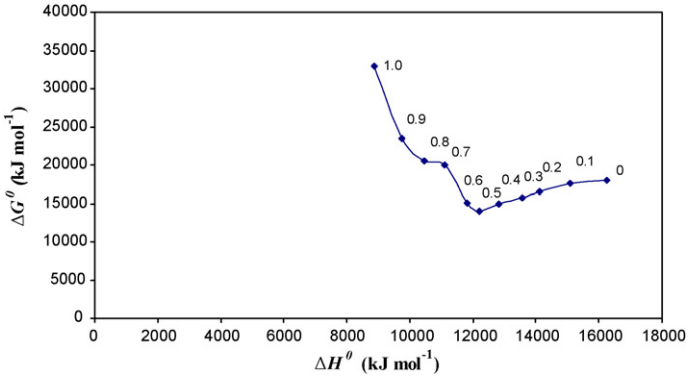

Fig. 2. Enthalpy–entropy compensation for solubility of FD in PG + W mixtures at 303.2 K (The values on the curve are mass fractions of PG).

3.5. Fitting of thermodynamic data of FD solutions in PG + W mixtures at different temperatures to Jouyban–Acree model

The Jouyban–Acree model was used to fit the thermodynamic properties (TP) of the FD solutions. The values of ΔH°, ΔS°, and ΔG° were fitted to the Jouyban–Acree model and the corresponding MD values calculated. For the TP data, the model was written as:

$$\log TP_m = m_1 \log TP_1 + m_2 \log TP_2 + m_1 m_2 \sum_{i=0}^{2} A_i (m_1 - m_2)^i \quad (13)$$

in which A_i is the model constants. In order to evaluate predictive accuracy of Eq. (13) we compared the predicted values to the experimental thermodynamic data, and to the calculated values based on just the two first terms, ($m_1 \log TP_1 + m_2 \log TP_2$). According to the results shown in Fig. 3 and Table 6, Jouyban–Acree model accurately described the ΔH°, ΔG°, and ΔS° values of solvent mixtures better than simple mass fraction logarithmic average. It reveals that the third term of Jouyban–Acree model $\left(m_1 m_2 \sum_{i=0}^{2} A_i (m_1 - m_2)^i\right)$ that indicates interaction between solute-solvent and solvent–solvent [20] is a useful term for prediction of thermodynamic properties in solvent mixtures.

Table 4
Mean deviations of solubility prediction of FD in PG + W mixtures at different temperatures.

Method	100·MD
I	13.2
II	21.3
III	13.4
IV	21.5

Table 5
Thermodynamic properties of FD solutions in PG + W mixtures and calculated values using mass fraction average and Jouyban–Acree model.

PG/mass fraction	ΔG° (kJ mol^{-1})	ΔH° (kJ mol^{-1})	ΔS° (J mol^{-1} K^{-1})	$T\Delta S^\circ$ (kJ mol^{-1})	$\%\xi_H$	$\%\xi_{TS}$	ΔG°_{cal} using mass fraction average (kJ mol^{-1})	ΔG°_{cal} using Jouyban–Acree model (kJ mol^{-1})	ΔH°_{cal} using mass fraction average (kJ mol^{-1})	ΔH°_{cal} using Jouyban–Acree model (kJ mol^{-1})	ΔS°_{cal} using mass fraction average (J mol^{-1} K^{-1})	ΔS°_{cal} using Jouyban–Acree model (J mol^{-1} K^{-1})
1.00	8.88	32.93	79.36	24.05	57.79	42.21	8.88	8.88	32.93	32.93	79.4	79.4
0.90	9.78	23.52	45.44	13.77	63.08	36.92	9.43	9.75	31.00	25.47	61.3	57.5
0.80	10.46	20.55	33.31	10.09	67.07	32.93	10.01	10.49	29.18	20.61	47.3	34.3
0.70	11.11	19.97	29.22	8.85	69.28	30.72	10.63	11.13	27.47	17.56	36.5	19.4
0.60	11.81	15.09	10.81	3.28	82.16	17.84	11.29	11.71	25.85	15.77	28.2	11.7
0.50	12.20	13.93	5.73	1.734	88.93	11.07	11.99	12.28	24.34	14.92	21.7	8.0
0.40	12.84	14.96	6.98	2.116	87.61	12.39	12.73	12.87	22.91	14.79	16.8	6.4
0.30	13.55	15.64	6.91	2.093	88.20	11.80	13.52	13.52	21.56	15.22	12.9	6.0
0.20	14.31	16.08	5.84	1.771	90.08	9.92	14.35	14.26	20.30	16.05	10.0	6.1
0.10	15.09	17.01	6.32	1.914	89.89	10.11	15.24	15.14	19.11	17.09	7.7	6.4
0.00	16.18	17.99	5.95	1.802	90.89	9.11	16.18	16.18	17.99	17.99	6.0	6.0

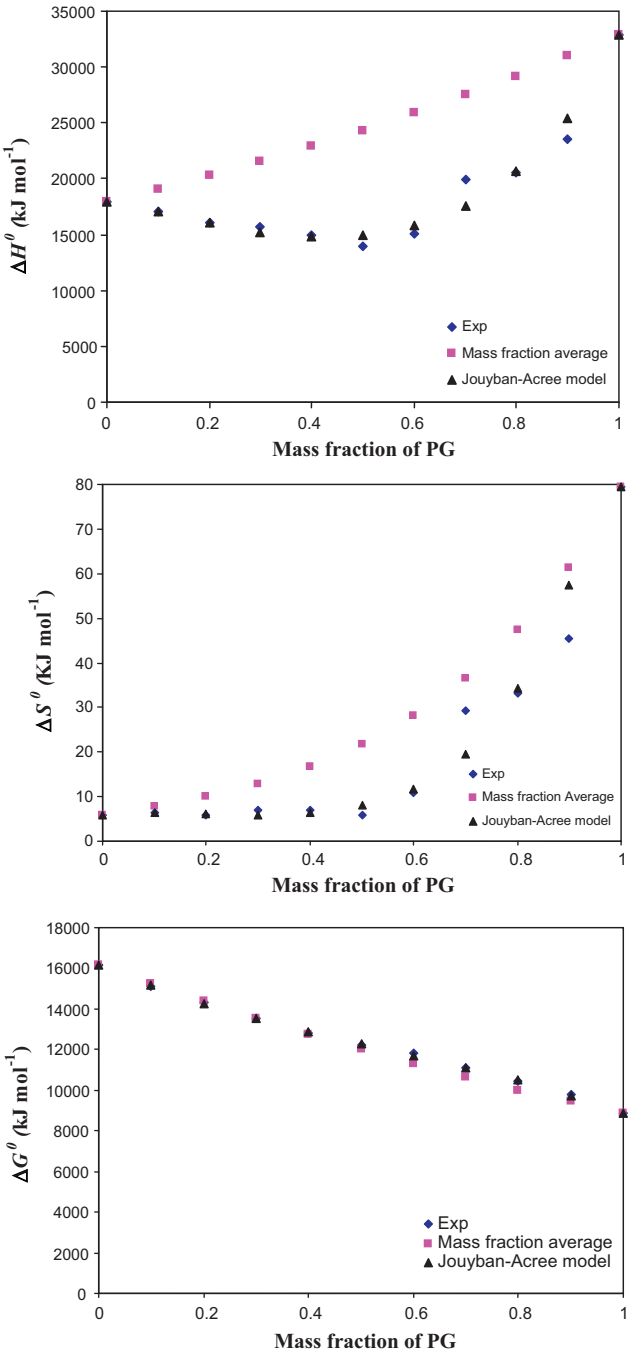

Fig. 3. Prediction of thermodynamic properties (ΔH°, ΔS°, and ΔG°) of FD in PG + W mixtures using mass fraction logarithmic average and Jouyban–Acree models.

Table 6
Mean deviations of thermodynamic properties of FD in PG + W mixtures.

Thermodynamic properties	Mass fraction average	Jouyban–Acree model
ΔG° (kJ mol^{-1})	1.9	0.3
ΔH° (kJ mol^{-1})	35.2	3.3
ΔS° (J mol^{-1} K^{-1})	78.4	12.6

4. Conclusion

Solubility prediction of drugs and chemical compounds such as FD in solvent mixtures at different temperatures is very important in chemical and pharmaceutical sciences. Combination of Jouyban–Acree model with van't Hoff equation can be used to predict solubility in PG + W mixtures with only four solubility data in mono-solvents. It is also concluded that the solution process of FD in PG + W mixtures is very complex and dependent on the cosolvent composition. Non-linear enthalpy–entropy compensation was found for this drug in this cosolvent system. The Jouyban–Acree model provides a reasonably accurate mathematical description of the thermodynamic data of FD dissolved in the PG + W binary solvent systems.

List of symbol

ΔH°	standard enthalpy changes (kJ mol^{-1})
ΔS°	standard entropy changes (J mol^{-1} K^{-1})
ΔG°	standard Gibbs free energy changes (kJ mol^{-1})
ρ_T^{Sat}	density of saturated solution (g cm^{-3})
$\%\xi_H$	relative contributions by entropy
$\%\xi_{TS}$	relative contributions by enthalpy
A, B	coefficients (Eq. (3))
m	fraction of solvents
J_i	Jouyban–Acree model constants
FD	fluphenazine decanote
MD	mean deviation
PG	propylene glycol
R	gas constant
T	temperature (K)
T_{hm}	the mean harmonic temperature
W	water
x_T^{Sat}	drug solubility (mole fraction)

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