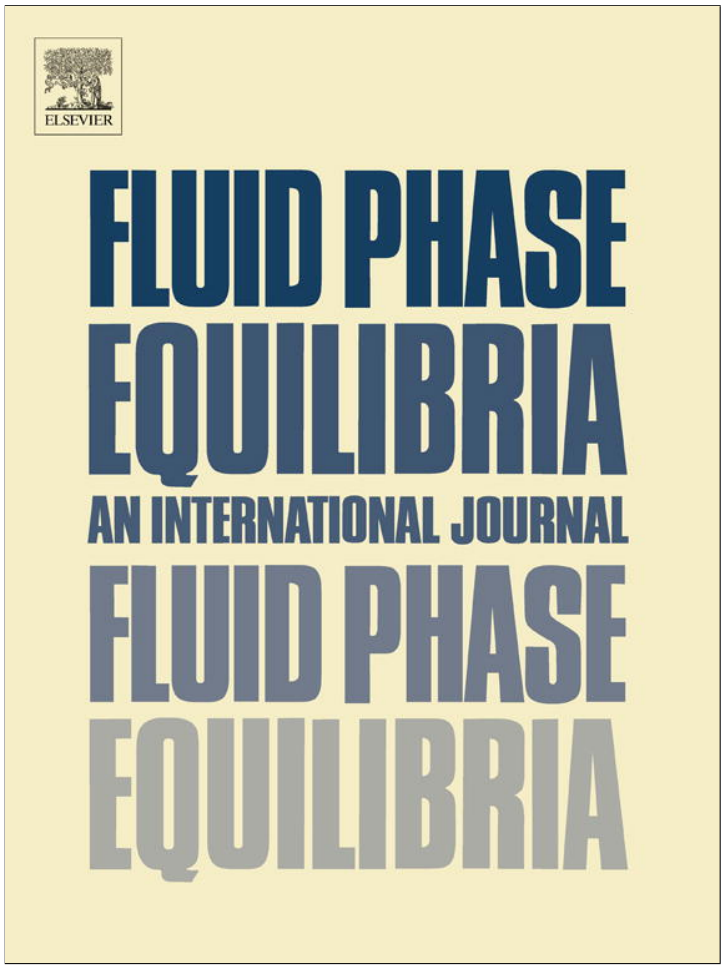

(This is a sample cover image for this issue. The actual cover is not yet available at this time.)

Fluid Phase Equilibria 330 (2012) 36–43

Contents lists available at SciVerse ScienceDirect

Fluid Phase Equilibria

journal homepage: www.elsevier.com/locate/fluid

Thermodynamic studies of fluphenazine decanoate solubility in PEG 200 + water mixtures

Vahid Panahi-Azar[a], Somaieh Ahmadian[b], Fleming Martínez[c], William E. Acree Jr.[d], Abolghasem Jouyban[e,*]

[a] Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran
[b] Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran
[c] Grupo de Investigaciones Farmacéutico-Fisicoquímicas, Departamento de Farmacia, Universidad Nacional de Colombia, A.A. 14490, Bogotá D.C., Colombia
[d] Department of Chemistry, University of North Texas, Denton, TX 76203-5070, USA
[e] Drug Applied Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran

ARTICLE INFO

Article history:
Received 1 April 2012
Received in revised form 2 June 2012
Accepted 6 June 2012

Keywords:
Fluphenazine decanoate
Solubility
Thermodynamic
Prediction

ABSTRACT

The solubility of fluphenazine decanoate (FD) in binary mixtures of polyethylene glycol 200 (PEG 200) + water at the temperature range from 298.0 K to 318.0 K is reported. The previously trained version of the Jouyban–Acree model for PEG 200 + water, a recently proposed general cosolvency model employing partial solubility parameters, and a combination of the model with van't Hoff equation were used to predict the solubility of FD in PEG 200 + water at different temperatures. The results show that the Jouyban–Acree model can be used for solubility prediction of FD in PEG 200 + water mixtures at different temperatures. The solubility data as a function of temperature were used to determine the thermodynamic properties of the dissolution process including Gibbs energy, enthalpy and entropy of the solution. An adapted version of the model is used to represent the thermodynamic properties of the solutions in the solvent mixtures and the obtained results were satisfactory. Densities of solute free PEG 200 + water and FD-saturated solutions are also reported.

1. Introduction

The knowledge of the solubility of drugs is required in different chemical, pharmaceutical and industrial applications, such as crystallization, separation, decontamination, liquid–liquid extraction, and drug formulation design. Cosolvency or solvent mixing is a common method for solubilization of drugs in the pharmaceutical industry to prepare liquid dosage forms. Another method for changing the solubility of compounds is temperature alteration. Due to the significant lack of solubility data for many solute–solvent combinations, efforts have been made to present mathematical models for estimating drug solubilities from a minimum number of required experimental input values [1–4].

Polyethylene glycols (PEGs) are prepared by polymerization of ethylene oxide and are linear or branched polyethers with the approximate molecular weight of 200–36,000 g mol^{-1}. Liquid PEGs (200–800 g mol^{-1}) are commonly used as pharmaceutical cosolvents. Because of strong H-bonding between PEGs and water, they are readily soluble in both water and many organic solvents. These liquids are used frequently in the pharmaceutical, chemical, cosmetic, and food industries [5]. Their low toxicity and high water solubility enable their use in purification of biological materials.

Fluphenazine decanoate (FD), CAS number of 5002-47-1, is an ester prodrug of an antipsychotic drug (fluphenazine) which is a long acting phenothiazine drug used to treat schizophrenia. FD is a low soluble drug in water, and is soluble in alcohol, acetone, benzene and ether [6]. In a recent study, the solubility of FD in propylene glycol + water mixtures at various temperatures was reported along with the data of Gibbs energy, enthalpy and entropy [7].

Solubility determination is time-consuming and costly, and sometimes impossible for newly synthesized or virtual compounds and drug candidates. For these reasons, and as noted above, mathematical models have been developed to predict the solubility of pharmaceutical compounds in cosolvent + water mixtures. The log-linear model of Yalkowsky, the extended Hildebrand solubility approach of Martin, the excess free energy of Amidon, mixture response surface method of Sokolosky, the phenomenological model of Connors, the double log–log of Barzegar–Jalali, the Margules equations, and the modified Wilson models are well known cosolvency models in the published literature [8]. In addition to the fore-mentioned models, the Jouyban–Acree model is one of the well-established models developed in recent years. The latter model has been shown to provide reasonably accurate

* Corresponding author.
E-mail address: ajouyban@hotmail.com (A. Jouyban).

0378-3812/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.fluid.2012.06.005

mathematical descriptions for the variation of solute solubility versus both temperature and solvent composition.

The goals of the present study are to report:

(1) The experimental solubility data of FD in PEG 200 + water mixtures at different temperatures.
(2) The feasibility of predicting the solubility of FD in PEG 200 + water mixtures using a combination of the Jouyban–Acree + van't Hoff equations and the Jouyban–Acree model + partial solubility parameters.
(3) The density of solute free mixtures of PEG 200 + water mixtures at various temperatures.
(4) The applicability of the proposed model to predict the density of saturated solutions using the density of solute free solvent mixtures.
(5) The thermodynamic characteristic of FD in the investigated binary solvent mixture by the Jouyban–Acree model.

2. Experimental

2.1. Materials

FD (0.994 in mass fraction) was a gift from Chimidaru, PEG 200 (0.995 in mass fraction) was purchased from Scharlau Chemie (Spain) and ethanol (0.935 in mass fraction), used for dilution of the solutions for spectrophotometric analysis, was purchased from Jahan Alcohol Teb (Arak, Iran). Double-distilled water was used in the preparation of solvent mixtures.

2.2. Solubility determination in PEG 200 + water at different temperatures

PEG 200 + water mixtures were prepared by mixing appropriate masses of the solvents with the uncertainty of 0.1 g. The solubility of FD was determined by equilibrating an excess amount of the solid with the binary solvent mixtures 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) for 3 days. After the attainment of equilibrium at 298 K the solubility and density measurements were performed, and the unused samples containing excess solid were then equilibrated at the next higher temperature (i.e. 303 K) for 2 days. The procedure was repeated until all five temperatures had been studied. The solutions were filtered using hydrophilic Durapore filters (0.45 μm, Millipore, Ireland) and the filtrate was diluted with ethanol. The absorbance of the diluted solutions were recorded at 317 nm using a UV–vis spectrophotometer (Beckman DU-650, Fullerton, USA) and the concentrations of FD were calculated based on the Beer–Lambert law calibration curve constructed from the measured absorbances of standard solutions of known FD concentration. Calibration graph was constructed using the molar absorptivities (ranging from 25,446.11ε/(L mol^{-1} cm^{-1}) to 27,418.67ε/(L mol^{-1} cm^{-1})) of FD standard solutions. The mean relative standard deviations (RSDs) of three repetitive solubility experiments were 2.5% for all data points. Each experimental data point is an average of at least three experimental measurements. Densities of the saturated solutions were determined using a 5 mL pycnometer as a single determination. Densities of the solute free PEG 200 + water mixtures at various temperatures were measured in triplicates. Details of the relative standard deviations (RSDs) for repeated measurements are reported in Table 1.

2.3. Computational method

The Jouyban–Acree model for representing the solubility of a solute in binary solvent mixture at various temperatures [8] is:

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

in which $x_{m,T}^{sat}$ is the solute's mole fraction solubility in the binary solvent mixtures at temperature T, m_1 and m_2 are the initial mass fractions of the solvent 1 (PEG 200) and solvent 2 (water) in the absence of the solute, $x_{1,T}^{sat}$ and $x_{2,T}^{sat}$ denote the mole fraction solubility of the solute in the mono-solvents 1 and 2, respectively, and J_i represent the constants of the model computed by regression analysis. A predictive limitation of the Jouyban–Acree model is that model constants are required input parameters, and their determination requires measured experimental solubility data in binary solvent system at several different mixture compositions. A trained version of the Jouyban–Acree model for prediction of drug solubility in PEG 400 + water mixtures at different temperatures was proposed as [9]:

$$\log x_{m,T}^{sat} = m_1 \log x_{1,T}^{sat} + m_2 \log x_{2,T}^{sat} + \left(\frac{m_1 m_2}{T}\right)[394.82 - 355.28(m_1 - m_2) + 388.89(m_1 - m_2)^2]. \quad (2)$$

Eq. (2) is applicable to the solubility prediction of drugs in other PEGs + water mixtures at various temperatures [10]. Recently, a general model which is a combination of the Jouyban–Acree model and partial solubility parameters was proposed for prediction solubility of drugs in cosolvent + water mixture as [11]:

$$\log x_{m,T} = m_1 \log x_{1,T} + m_2 \log x_{2,T} + \left(\frac{m_1 m_2}{T}\right)\{0.606\delta_{ps}(\delta_{p1} - \delta_{p2})^2 + 0.013\delta_{hs}(\delta_{h1} - \delta_{h2})^2\} + \left(\frac{m_1 m_2 (m_1 - m_2)}{T}\right) \times \{-8.696\delta_{ds}(\delta_{d1} - \delta_{d2})^2 + 0.376\delta_{ps}(\delta_{p1} - \delta_{p2})^2 + 0.013\delta_{hs}(\delta_{h1} - \delta_{h2})^2\} + \left(\frac{m_1 m_2 (m_1 - m_2)^2}{T}\right) \times \{9.277\delta_{ds}(\delta_{d1} - \delta_{d2})^2 - 0.461\delta_{ps}(\delta_{p1} - \delta_{p2})^2 + 0.017\delta_{hs}(\delta_{h1} - \delta_{h2})^2\} \quad (3)$$

in which δ_{ds}, δ_{ps} and δ_{hs} are the partial solubility parameters of the solutes, δ_d, δ_h and δ_p are the partial solubility parameters of solvents and subscripts 1 and 2 denote cosolvent (PEG 200 in this work) and water, respectively. Solubility in mono-solvent at different temperatures could be calculated using van't Hoff equation (Eq. (4)). The required experimental data for training the model are the solubility at the lowest and highest temperatures of interest ($\log x_T^{sat}$), which are needed to compute the A and B model constants in Eq. (4).

$$\log x_T^{sat} = A + \frac{B}{T} \quad (4)$$

Combination of the Jouyban–Acree and van't Hoff models could be used for solubility prediction of pharmaceutical compounds in mono-solvents and binary mixed solvents at different temperatures using a minimum number of experimental solubility data (i.e. the solubility in the lowest and highest temperatures and a number of solubility data in binary mixtures) [12]. The combined version of

Table 1
Experimental and predicted values of fluphenazine decanoate solubility (mole fraction) using different numerical methods and density of solute free ($\rho_{m,T}$) PEG 200 + water mixtures at different temperatures along with the experimental and calculated densities ($\rho^{sat}_{m,T}$) of FD saturated solutions.

PEG 200 (mass fraction)	T (K)	$X^{sat}_{m,T}$ [a]	$X^{sat}_{m,T}$						$\rho_{m,T}$ (g cm^{-3})[a]	$(\rho^{sat}_{m,T})_{exp}$ (g cm^{-3})	$(\rho^{sat}_{m,T})_{calc}$ (g cm^{-3})
			I	II	III	IV	V	VI			
1.00	298.2	8.75E−05 (2.7)	8.75E−05	8.75E−05	8.75E−05	7.33E−05	7.33E−05	7.33E−05	1.136 (0.2)	1.138	1.138
0.90	298.2	4.29E−05 (2.7)	4.65E−05	4.86E−05	4.88E−05	3.90E−05	4.13E−05	4.14E−05	1.124 (0.2)	1.131	1.128
0.80	298.2	1.90E−05 (1.8)	2.57E−05	2.70E−05	3.03E−05	2.17E−05	2.32E−05	2.60E−05	1.116 (0.2)	1.128	1.120
0.70	298.2	1.37E−05 (3.0)	1.50E−05	1.50E−05	1.96E−05	1.29E−05	1.30E−05	1.71E−05	1.100 (0.7)	1.118	1.110
0.60	298.2	7.49E−06 (2.7)	9.35E−06	8.30E−06	1.26E−05	8.14E−06	7.31E−06	1.11E−05	1.094 (0.7)	1.099	1.098
0.50	298.2	5.11E−06 (2.6)	6.09E−06	4.60E−06	7.66E−06	5.37E−06	4.11E−06	6.83E−06	1.076 (0.2)	1.084	1.083
0.40	298.2	3.00E−06 (2.4)	4.01E−06	2.55E−06	4.35E−06	3.58E−06	2.30E−06	3.93E−06	1.064 (0.1)	1.053	1.065
0.30	298.2	2.15E−06 (1.8)	2.55E−06	1.42E−06	2.29E−06	2.30E−06	1.29E−06	2.09E−06	1.040 (0.1)	1.043	1.046
0.20	298.2	1.23E−06 (3.3)	1.45E−06	7.80E−07	1.12E−06	1.33E−06	7.30E−07	1.04E−06	1.028 (0.2)	1.031	1.027
0.10	298.2	6.80E−07 (2.2)	6.90E−07	4.30E−07	5.20E−07	6.40E−07	4.10E−07	4.90E−07	1.008 (0.2)	1.015	1.011
0.00	298.2	2.40E−07 (4.5)	2.40E−07	2.40E−07	2.40E−07	2.30E−07	2.30E−07	2.30E−07	1.000 (0.1)	1.000	1.000
1.00	303.2	1.13E−04 (2.1)	1.13E−04	1.13E−04	1.13E−04	1.01E−04	1.01E−04	1.01E−04	1.128 (0.2)	1.132	1.132
0.90	303.2	5.67E−05 (4.1)	6.01E−05	6.28E−05	6.30E−05	5.40E−05	5.70E−05	5.72E−05	1.118 (0.1)	1.124	1.123
0.80	303.2	2.73E−05 (2.9)	3.32E−05	3.49E−05	3.90E−05	3.01E−05	3.21E−05	3.59E−05	1.112 (0.1)	1.120	1.115
0.70	303.2	1.77E−05 (2.2)	1.94E−05	1.93E−05	2.52E−05	1.78E−05	1.80E−05	2.35E−05	1.106 (0.1)	1.114	1.106
0.60	303.2	9.56E−06 (4.5)	1.21E−05	1.07E−05	1.61E−05	1.12E−05	1.01E−05	1.52E−05	1.090 (0.9)	1.093	1.094
0.50	303.2	6.32E−06 (2.2)	7.82E−06	5.94E−06	9.80E−06	7.40E−06	5.68E−06	9.37E−06	1.072 (0.4)	1.074	1.080
0.40	303.2	4.69E−06 (2.2)	5.14E−06	3.29E−06	5.57E−06	4.93E−06	3.19E−06	5.40E−06	1.060 (0.5)	1.047	1.062
0.30	303.2	3.46E−06 (1.5)	3.25E−06	1.83E−06	2.93E−06	3.16E−06	1.79E−06	2.88E−06	1.038 (0.2)	1.035	1.044
0.20	303.2	1.98E−06 (2.2)	1.86E−06	1.01E−06	1.44E−06	1.82E−06	1.01E−06	1.43E−06	1.024 (0.1)	1.030	1.025
0.10	303.2	1.01E−06 (4.1)	8.80E−07	5.60E−07	6.70E−07	8.80E−07	5.70E−07	6.80E−07	1.004 (0.1)	1.010	1.009
0.00	303.2	3.10E−07 (5.0)	3.10E−07	3.10E−07	3.10E−07	3.20E−07	3.20E−07	3.20E−07	0.996 (0.1)	0.999	0.999
1.00	308.2	1.36E−04 (2.1)	1.36E−04	1.36E−04	1.36E−04	1.38E−04	1.38E−04	1.38E−04	1.116 (0.1)	1.128	1.128
0.90	308.2	7.77E−05 (3.3)	7.39E−05	7.72E−05	7.74E−05	7.39E−05	7.80E−05	7.82E−05	1.104 (0.1)	1.121	1.119
0.80	308.2	3.91E−05 (2.4)	4.17E−05	4.38E−05	4.89E−05	4.12E−05	4.39E−05	4.90E−05	1.098 (0.1)	1.109	1.111
0.70	308.2	2.39E−05 (2.1)	2.49E−05	2.48E−05	3.22E−05	2.44E−05	2.47E−05	3.20E−05	1.090 (0.3)	1.088	1.101
0.60	308.2	1.55E−05 (1.7)	1.57E−05	1.40E−05	2.09E−05	1.54E−05	1.39E−05	2.07E−05	1.078 (0.1)	1.063	1.090
0.50	308.2	1.01E−05 (1.8)	1.04E−05	7.95E−06	1.30E−05	1.01E−05	7.78E−06	1.27E−05	1.068 (0.2)	1.049	1.076
0.40	308.2	7.63E−06 (0.9)	6.97E−06	4.50E−06	7.54E−06	6.70E−06	4.37E−06	7.33E−06	1.050 (0.5)	1.040	1.059
0.30	308.2	4.46E−06 (0.9)	4.50E−06	2.55E−06	4.06E−06	4.29E−06	2.46E−06	3.92E−06	1.034 (0.1)	1.028	1.040
0.20	308.2	2.55E−06 (1.7)	2.62E−06	1.44E−06	2.04E−06	2.48E−06	1.38E−06	1.95E−06	1.020 (0.1)	1.018	1.022
0.10	308.2	1.30E−06 (2.6)	1.27E−06	8.20E−07	9.80E−07	1.19E−06	7.80E−07	9.30E−07	1.000 (0.8)	1.009	1.007
0.00	308.2	4.60E−07 (1.0)	4.60E−07	4.60E−07	4.60E−07	4.40E−07	4.40E−07	4.40E−07	0.992 (0.2)	0.997	0.997
1.00	313.2	1.74E−04 (2.2)	1.74E−04	1.74E−04	1.74E−04	1.87E−04	1.87E−04	1.87E−04	1.108 (0.2)	1.121	1.121
0.90	313.2	1.13E−04 (2.0)	9.45E−05	9.87E−05	9.90E−05	1.00E−04	1.06E−04	1.06E−04	1.100 (0.5)	1.115	1.112

the model can be written as:

$$\log x_{m,T}^{sat} = m_1\left(A_1 + \frac{B_1}{T}\right) + m_2\left(A_2 + \frac{B_2}{T}\right) + \frac{m_1 m_2}{T}\sum_{i=0}^{2} J_i (m_1 - m_2)^i \quad (5)$$

in which A_1, B_1, A_2 and B_2 are the coefficients of the van't Hoff equation for solutions of the monosolvents 1 and 2 [7,13–15]. The J terms of Eqs. (1) and (5) depend on the nature of solute and solvents.

The standard enthalpy (ΔH), entropy (ΔS) and Gibbs free energy (ΔG) variations of the solutions can be calculated using the modified version of van't Hoff equation [16,17]. For this purpose, the mean harmonic temperature (T_{hm}) is calculated as:

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

where n is the number of temperatures studied. The enthalpy change (ΔH) during the solubility process was evaluated from:

$$\left(\frac{\partial \ln x_T^{sat}}{\partial(1/T - 1/T_{hm})}\right)_P = -\frac{\Delta H}{R} \quad (7)$$

The slope of the plot of $\ln x_T^{sat}$ vs. $(1/T - 1/T_{hm})$ for the modified version of the van't Hoff equation. Similarly the respective (ΔG) variation is calculated:

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

where the intercept is the one obtained in the same $\ln x_T^{sat}$ vs. $(1/T - 1/T_{hm})$ plot. The entropy (ΔS) of solution is determined by substituting the computed numerical values of ΔH and ΔG into Eq. (9):

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

The relative enthalpic (% ξ_H) and entropic (% ξ_{TS}) contributions to the dissolution process are calculated using Eqs. (10) and (11) [17]:

$$\%\ \xi_H = 100 \times \frac{|\Delta H|}{|\Delta H| + |T\Delta S|} \quad (10)$$

$$\%\ \xi_{TS} = 100 \times \frac{|T\Delta S|}{|\Delta H| + |T\Delta S|}. \quad (11)$$

Solubility of FD in PEG 200 + water mixtures at different temperatures (298, 303, 308, 313 and 318 K) was calculated using six numerical methods. In method I, the measured solubility data were fitted to Eq. (1) and the model constants were computed along with the mean deviation (MD) values. In methods II and III, the experimental solubility of FD in both mono-solvents were employed and the solubility in the mixed solvents were predicted using Eqs. (2) and (3), respectively. Only two experimental data points were needed for each temperature of interest as the numerical values of the equation coefficients had been previously computed. In method IV, ten experimental data points (i.e. m_1 = 0.00, 0.30, 0.50, 0.70 and 1.00 at both 298.2 and 318.2 K) were used to compute the model constants of Eq. (5) and the rest of data points were predicted using the trained model. In methods V and VI, the equivalent terms of $\log x_{1,T}^{sat}$ and $\log x_{2,T}^{sat}$ terms derived from Eq. (4) were replaced in Eqs. (2) and (3) and the solubilities of FD in PEG 200 + water at various temperatures were predicted. The partial solubility parameters of FD, δ_{ds} = 17.00 $MPa^{1/2}$, δ_{ps} = 9.57 $MPa^{1/2}$, and δ_{hs} = 2.11 $MPa^{1/2}$, used in Eq. (3) were computed using a commercial software package [18]. The partial solubility parameters of PEG 200 are δ_{d1} = 13.67 $MPa^{1/2}$, δ_{p1} = 11.66 $MPa^{1/2}$, and δ_{h1} = 16.77 $MPa^{1/2}$ and those of water are δ_{d2} = 13.56 $MPa^{1/2}$, δ_{p2} = 18.41 $MPa^{1/2}$, and δ_{h2} = 20.45 $MPa^{1/2}$ [11].

Table 1 (*Continued*)

PEG 200 (mass fraction)	T (K)	$X_{m,T}^{sat}$ [a]	$X_{m,T}^{sat}$						$\rho_{m,T}$ (g cm^{-3}) [a]	$(\rho_{m,T}^{sat})_{exp}$ (g cm^{-3})	$(\rho_{m,T}^{sat})_{calc}$ (g cm^{-3})
			I	II	III	IV	V	VI			
0.80	313.2	4.81E−05 (1.4)	5.33E−05	5.59E−05	6.24E−05	5.59E−05	5.94E−05	6.63E−05	1.096 (0.2)	1.097	1.104
0.70	313.2	3.26E−05 (7.1)	3.17E−05	3.16E−05	4.09E−05	3.31E−05	3.34E−05	4.32E−05	1.087 (0.1)	1.072	1.094
0.60	313.2	2.11E−05 (1.9)	2.00E−05	1.79E−05	2.65E−05	2.08E−05	1.88E−05	2.78E−05	1.076 (0.1)	1.057	1.083
0.50	313.2	1.53E−05 (0.9)	1.32E−05	1.01E−05	1.64E−05	1.36E−05	1.06E−05	1.71E−05	1.064 (0.1)	1.047	1.069
0.40	313.2	1.05E−05 (3.3)	8.81E−06	5.73E−06	9.52E−06	9.03E−06	5.93E−06	9.87E−06	1.047 (0.2)	1.033	1.052
0.30	313.2	5.55E−06 (2.9)	5.67E−06	3.24E−06	5.12E−06	5.77E−06	3.33E−06	5.28E−06	1.032 (0.2)	1.011	1.034
0.20	313.2	2.98E−06 (1.5)	3.30E−06	1.83E−06	2.58E−06	3.33E−06	1.87E−06	2.64E−06	1.012 (0.1)	1.005	1.016
0.10	313.2	1.62E−06 (2.1)	1.60E−06	1.04E−06	1.24E−06	1.61E−06	1.05E−06	1.26E−06	0.997 (0.1)	0.998	1.000
0.00	313.2	5.90E−07 (1.4)	5.90E−07	5.90E−07	5.90E−07	5.90E−07	5.90E−07	5.90E−07	0.989 (0.2)	0.990	0.990
1.00	318.2	1.91E−04 (1.5)	1.91E−04	1.91E−04	1.91E−04	2.51E−04	2.51E−04	2.51E−04	1.102 (0.2)	1.115	1.115
0.90	318.2	1.27E−04 (1.7)	1.05E−04	1.09E−04	1.09E−04	1.34E−04	1.42E−04	1.42E−04	1.098 (0.1)	1.105	1.106
0.80	318.2	7.63E−05 (1.4)	5.94E−05	6.23E−05	6.94E−05	7.50E−05	7.97E−05	8.88E−05	1.094 (0.1)	1.085	1.098
0.70	318.2	5.89E−05 (1.7)	3.56E−05	3.55E−05	4.57E−05	4.44E−05	4.48E−05	5.77E−05	1.084 (0.1)	1.065	1.088
0.60	318.2	3.18E−05 (3.0)	2.26E−05	2.02E−05	2.98E−05	2.79E−05	2.52E−05	3.71E−05	1.074 (0.2)	1.047	1.077
0.50	318.2	2.02E−05 (3.1)	1.50E−05	1.15E−05	1.86E−05	1.82E−05	1.42E−05	2.28E−05	1.060 (0.3)	1.037	1.062
0.40	318.2	1.29E−05 (1.8)	1.00E−05	6.57E−06	1.08E−05	1.21E−05	7.97E−06	1.32E−05	1.044 (0.1)	1.017	1.046
0.30	318.2	7.25E−06 (2.0)	6.50E−06	3.75E−06	5.88E−06	7.69E−06	4.48E−06	7.04E−06	1.030 (0.5)	1.002	1.028
0.20	318.2	3.91E−06 (1.0)	3.81E−06	2.13E−06	2.99E−06	4.44E−06	2.52E−06	3.53E−06	1.006 (0.1)	0.994	1.010
0.10	318.2	1.94E−06 (1.0)	1.86E−06	1.22E−06	1.45E−06	2.15E−06	1.42E−06	1.69E−06	0.994 (0.1)	0.990	0.994
0.00	318.2	6.90E−07 (1.7)	6.90E−07	6.90E−07	6.90E−07	8.00E−07	8.00E−07	8.00E−07	0.984 (0.1)	0.984	0.984

[a] Values in parentheses are relative standard deviations.

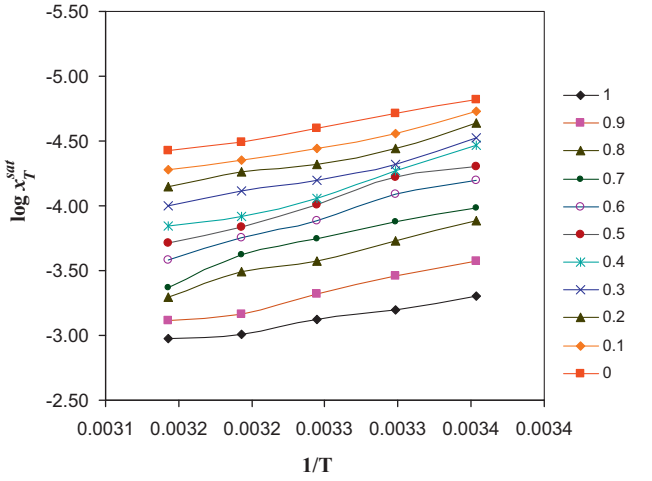

Fig. 1. The van't Hoff plots of fluphenazine decanoate solutions in PEG 200 + water at different mass fractions of PEG 200.

In the density analysis, the experimental densities of the solute free PEG 200 + water mixtures at various temperatures were fitted to the adopted version of the Jouyban–Acree model [19]. The computed interaction terms were then used to predict the density of FD saturated solutions.

The mean deviation (MD) between experimental (exp) and calculated (calc) solubility (or densities) was computed to evaluate the accuracy of different numerical methods using:

$$\mathrm{MD} = \frac{100}{N}\sum\left[\frac{\left|(x_{m,T}^{sat})_{\mathrm{calc}} - (x_{m,T}^{sat})_{\mathrm{exp}}\right|}{(x_{m,T}^{sat})_{\mathrm{exp}}}\right] \quad (12)$$

To evaluate the accuracy of the different numerical methods studied, the summation in Eq. (12) extends over the number of data points, N, in each data set.

3. Results and discussion

3.1. Solubility of fluphenazine decanoate in PEG 200 + water at different temperatures and prediction using different numerical methods

Mass fraction compositions of the binary solvent mixtures, densities of the solute free and saturated solutions, experimental and calculated solubilities of FD at different temperatures (298–318 K) using numerical methods I–VI are reported in Table 1. Examination of the numerical in the first three columns of Table 1 reveals that the solubility of FD increases with both increasing PEG concentration and increasing solution temperature. Fig. 1 depicts the logarithm of measured FD mole fraction solubility in the 9 different solvent mixtures and in both mono-solvents vs. $1/T$ (the van't Hoff plots). A linear correlation is observed in the investigated temperature range.

The experimental solubility data was analyzed according to method I and the obtained mathematical expression is:

$$\log x_{m,T}^{sat} = m_1 \log x_{1,T}^{sat} + m_2 \log x_{2,T}^{sat} + \left(\frac{m_1 m_2}{T}\right)[145.910 + 449.116(m_1 - m_2) + 235.902(m_1 - m_2)^2]. \quad (13)$$

The correlation is significant ($p < 0.0005$) with the correlation coefficient of 0.906 and F value of 79. Eq. (13) was used to back-calculate the solubility of FD. The maximum individual deviation (ID) between experimental and back-calculated FD solubility was 39.5% for PEG 200 + water mixture of (0.30 + 0.70) at 318.2 K and the MD was 10.5 ± 10.5%. Eq. (1) could be trained using a minimum number of experimental data points ($N = 10$) as described in Section 2.3. The obtained MD of predicted solubilities is 15.5 ± 16.4%.

Table 2
Mean deviations (MDs) of solubility prediction of fluphenazine decanoate in PEG 200 + water mixtures at different temperatures.

Method	MD	
	Fitted data	Predicted data using trained models with the minimum number of data points
I	10.5	15.5
II	22.3	–
III	20.2	–
IV	8.5	13.2
V	21.5	22.4
VI	18.6	13.4

The J terms of the Jouyban–Acree model reflect solvent–solvent and solute–solvent interactions in the solution [20]. These interactions should be similar for PEG 400 + water and PEG 200 + water mixtures, so the trained model for PEG 400 + water (i.e. Eq. (2)) could be used to predict the solubility in PEG 200 + water mixtures as it was evident from a previous work [10]. The solubility of FD in PEG 200 + water was predicted using the experimental solubility in the mono-solvents (method II) and the obtained MD was 22.4 ± 17.6%. In deriving Eq. (2), the effects of the solute structure on the solubility of drugs in PEG + water mixtures were ignored which is not necessarily true for real mixtures. This simplifying approximation may increase the prediction error levels. In method III, structural effects are taken into account by including terms containing the partial solubility parameters of the solute. In addition, method III is not specific for PEG + water mixtures and the solubility of drugs in other cosolvent + water mixtures could also be predicted. The obtained MD of FD data using method III was 20.2 ± 18.2%.

In numerical method IV, the experimental solubility data were analyzed in accordance to Eq. (5) to yield the following mathematical expression:

$$\log x_{m,T}^{sat} = m_1\left(1.981 - \frac{2570.559}{T}\right) + m_2\left(4.373 - \frac{2536.612}{T}\right) + \frac{m_1 m_2}{T}[140.134 + 449.292(m_1 - m_2) + 221.460(m_1 - m_2)^2]. \quad (14)$$

The main advantage of Eq. (14) is that it does not require any further experimental data to predict the solubility of FD in the mixed solvents at any temperature of interest. The maximum ID of Eq. (14) was 31.5% for aqueous solubility of FD at 318.2 K and the obtained MD was 8.5 ± 6.3%. As noted above, Eq. (5) could be trained using a minimum number of experimental data points ($N = 10$) and employed to predict the solubility of FD at the remaining mixture compositions and temperatures. The obtained MD for this analysis was 13.2 ± 10.5%. In numerical methods V and VI, the first two terms of Eqs. (2) and (3), i.e. $[m_1 \log x_{1,T}^{sat} + m_2 \log x_{2,T}^{sat}]$, are replaced with the corresponding values from van't Hoff equation, i.e. $[m_1(1.981 - (2570.559/T)) + m_2(4.373 - (2536.612/T))]$, and the solubility of FD in PEG 200 + water mixtures was predicted to within MD values of 21.5 ± 16.0% and 18.6 ± 14.2%, respectively. When the van't Hoff model constants were computed using the minimum number of solubility data in the monosolvents at the lowest and the highest temperatures ($N = 4$), MD values of 22.4 ± 18.0% and 18.6 ± 13.4% were obtained for methods V and VI, respectively. Table 2 summarizes the MD values of different numerical

Table 3
Thermodynamic properties of fluphenazine decanoate solutions in PEG 200 + water mixtures.

PEG 200 (mass fraction)	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})	$T\Delta S$ (kJ mol^{-1})	$\%\xi_H$	$\%\xi_{TS}$
1.00	22.8 (0.6)	31.5 (0.9)	28.2 (1.1)	8.7 (0.3)	78.40	21.60
0.90	24.3 (0.6)	45.2 (1.4)	67.9 (2.6)	20.9 (0.8)	68.35	31.65
0.80	26.1 (0.7)	52.8 (1.6)	86.6 (3.4)	26.7 (1.0)	66.42	33.58
0.70	27.1 (0.7)	55.5 (1.7)	92.2 (3.6)	28.4 (1.1)	66.14	33.86
0.60	28.4 (0.7)	58.0 (1.7)	96.1 (3.7)	29.6 (1.2)	66.23	33.77
0.50	29.5 (0.7)	57.3 (1.7)	90.2 (3.5)	27.8 (1.1)	67.32	32.68
0.40	30.5 (0.8)	58.9 (1.8)	92.2 (3.6)	28.4 (1.1)	67.45	32.55
0.30	31.7 (0.8)	45.9 (1.4)	46.2 (1.8)	14.2 (0.6)	76.35	23.65
0.20	33.2 (0.8)	43.1 (1.3)	32.0 (1.2)	9.9 (0.4)	81.35	18.65
0.10	34.8 (0.9)	40.6 (1.2)	18.8 (0.7)	5.8 (0.2)	87.54	12.46
0.00	37.6 (0.9)	43.5 (1.3)	19.4 (0.8)	6.0 (0.2)	87.93	12.07

methods revealing that these six numerical methods could be employed in the practical applications involving solubility data in the pharmaceutical industry. The computational error of each method fell within an acceptable range. Our computations also revealed that more accurate predictions were obtained whenever more experimental solubility data were employed in the model training process.

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

Densities of the solute-free mixtures of PEG 200 + water are reported in Table 1 for 298.2, 303.2, 308.2, 313.2 and 318.2 K. To our knowledge there is no published density data for PEG 200 + water mixtures in the literature. As noted in Section 2.3, the solute-free data were fitted to the Jouyban–Acree model and the trained model for correlating the density of PEG 200 + water mixtures is:

$$\log \rho_{m,T} = m_1 \log \rho_{1,T} + m_2 \log \rho_{2,T} + \frac{m_1 m_2}{T}[7.850 + 6.032(m_1 - m_2) - 9.797(m_1 - m_2)^2] \quad (15)$$

in which $\rho_{m,T}$, $\rho_{1,T}$ and $\rho_{2,T}$ are the densities of the solute-free mixed solvent and the solute-free mono-solvents 1 and 2 at the different temperatures, respectively. Because of the very low drug solubilities, the effect of the dissolved drug on the numerical values of the interaction terms of the Jouyban–Acree model is not significant. The terms can be employed to predict the density of FD saturated solutions as [19]:

$$\log \rho^{sat}_{m,T} = m_1 \log \rho^{sat}_{1,T} + m_2 \log \rho^{sat}_{2,T} + \frac{m_1 m_2}{T}[7.850 + 6.032(m_1 - m_2) - 9.797(m_1 - m_2)^2] \quad (16)$$

in which $\rho^{sat}_{m,T}$ is the density of the drug saturated solution of mixed solvent system, and $\rho^{sat}_{1,T}$ and $\rho^{sat}_{2,T}$ are the density of drug saturated solutions of mono-solvents 1 and 2 at different temperatures. Eq. (16) predicted the density of saturated solutions at various temperatures to within a MD value of 0.9 ± 0.9%.

3.3. Thermodynamic parameters of fluphenazine decanoate solutions in PEG 200 + W

The thermodynamic parameters (i.e. ΔH, ΔS and ΔG) of FD in PEG 200 + water at the mean harmonic temperature of T_{hm} = 308 K are reported in Table 3. The positive values of ΔH, ΔS and ΔG at all solvent compositions showed that the dissolution process is endothermic, entropically favorable and solution process is apparently not spontaneous. The last two columns in Table 3 give the relative enthalpic and entropic contributions of the dissolution process. In all cases the main contributor to standard Gibbs energy of solubility process of FD is the enthalpy (greater than 66%).

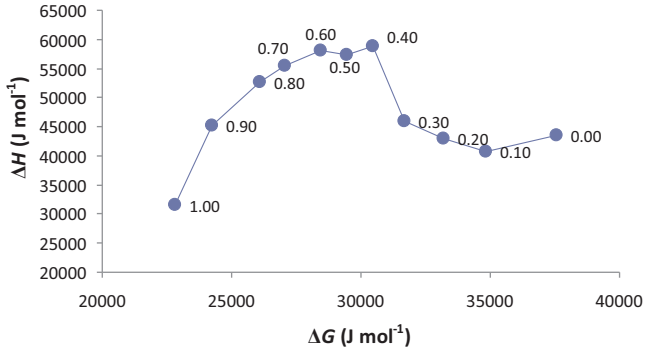

Fig. 2. ΔH vs. ΔG enthalpy–entropy compensation plot for the solubility of fluphenazine decanoate in PEG 200 + water solvent mixtures at 308 K (the numerical values in figure refer to the mass fraction of PEG 200).

3.4. Enthalpy–entropy compensation of solution

An enthalpy–entropy compensation analysis of drug solubility was used to identify the mechanism of cosolvent action [16]. Fig. 2 depicts the graph of ΔH vs. ΔG for the solubility of FD in PEG 200 + water mixtures at 308 K. This profile is non-linear over the entire composition range. A positive slope is observed up to 0.10 mass fraction of PEG 200 which shows that enthalpy is the driving factor for drug solubility when the concentration PEG 200 is small. In the PEG 200 solvent concentration region from 0.10 to 0.40 mass fraction the slope is negative, indicating the importance of the entropic contribution in the overall solubility process. The slope becomes positive again at PEG 200 mass fractions greater than 0.60. According to the published literature negative slopes are attributed

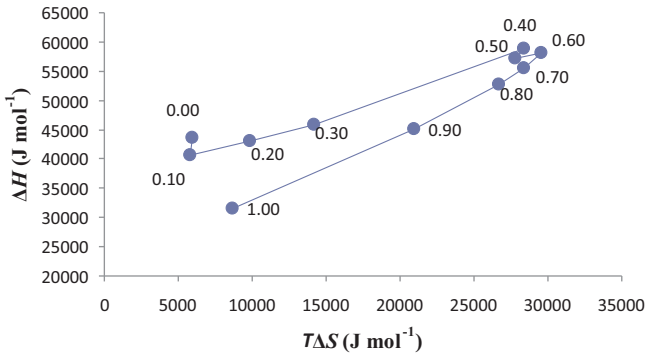

Fig. 3. ΔH vs. $T\Delta S$ enthalpy–entropy compensation plot for the solubility of fluphenazine decanoate in PEG 200 + water solvent mixtures at 308 K (the numerical values in the figure denote the mass fraction of PEG 200).

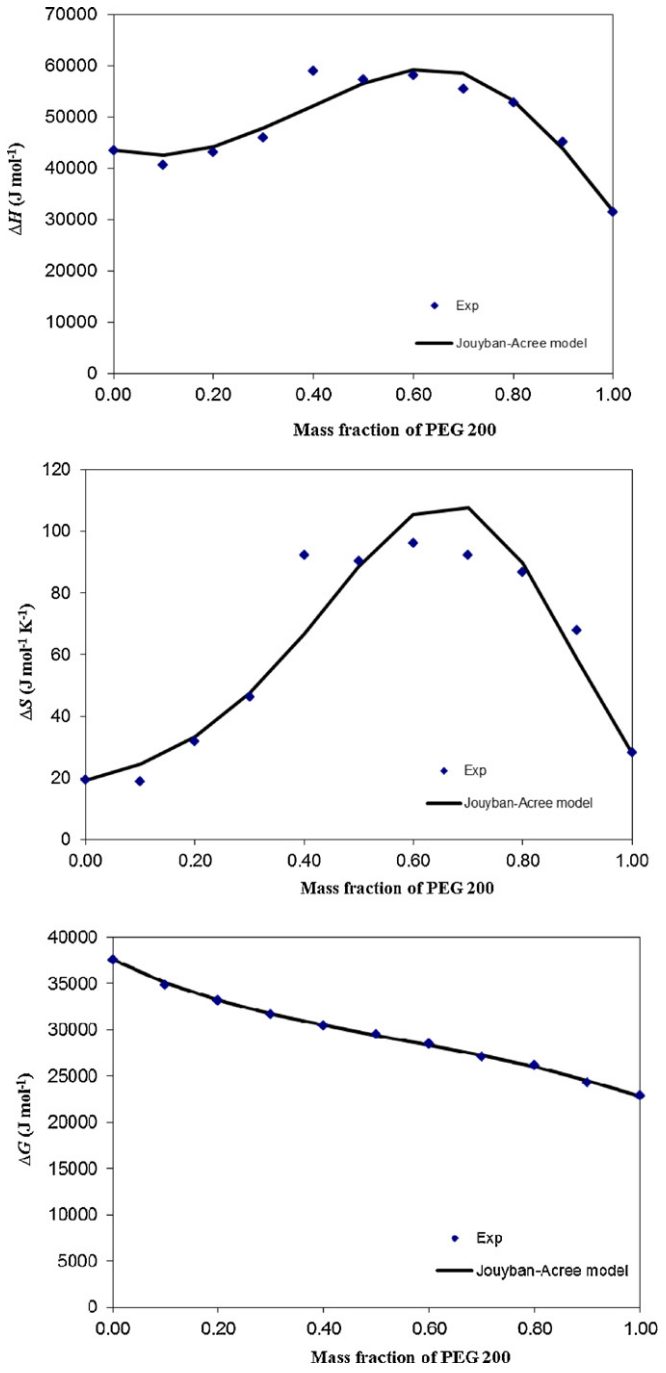

Fig. 4. Experimental and calculated thermodynamic properties (ΔH, ΔS and ΔG) of fluphenazine decanoate solutions in PEG 200 + water using the Jouyban–Acree model.

to regions where the "like iceberg" water aggregates around the non-polar portions of the solute are broken by effect of co-solvents, whereas, positive slopes are attributed to regions where the solute is more solvated by the organic co-solvent molecules [16,17].

A second compensation graph is obtained by plotting ΔH as a function of $T\Delta S$ [17] for each of the different solvent compositions as shown in Fig. 3. For this type of graph the slopes of the straight lines are important – slopes of less than 1.0 indicate an entropy-driven solution processes, whereas slopes greater than 1.0 correspond to an enthalpy-driven process. Analysis of the experimental ΔH and $T\Delta S$ values in this fashion gives the linear equation ΔH (J mol^{-1}) = 0.731 $T\Delta S$ + 36,913 (with adjusted r^2 of 0.974) from water up to 0.60 mass fraction of PEG 200. A second linear equation, ΔH (J mol^{-1}) = 1.241 $T\Delta S$ + 20,222 and adjusted r^2 of 0.994, is obtained at PEG 200 mass fractions ranging from 0.60 to 1.00.

Table 4
The model constants and the mean deviations (MDs) of thermodynamic properties of fluphenazine decanoate solutions in PEG 200 + water mixtures.

Thermodynamic property	J_0	J_1	MD
ΔG	0.006	−0.121	0.3
ΔH	0.736	−0.856	3.3
ΔS	2.310	−1.726	10.1

3.5. Fitting thermodynamic data of fluphenazine decanoate solutions in PEG 200 + water to the Jouyban–Acree model

The ΔH, ΔS and ΔG were analyzed in accordance to an adapted version of the Jouyban–Acree model [7] and the MD values were calculated. The Jouyban–Acree model was found to mathematically describe the variations of ΔH, ΔG and ΔS in solvent mixtures with acceptable accuracy [7] and could be employed to predict the thermodynamic properties of the solubility process in the different PEG 200 + water solvent mixtures (Fig. 4). Table 4 lists the numerical values of the model constants along with the MD values. It should be noted that the J_2 terms were not statistically significant ($p > 0.05$) and are thus excluded from the models. The MD values are in good agreement with those of FD solutions in propylene glycol + water mixtures [7].

4. Conclusion

Solubility data of FD in PEG 200 + water mixtures are reported which extends the available solubility database of pharmaceuticals. The database could provide very crucial information for a pharmaceutical technologist in formulating liquid drug formulations. The data could be used in designing separation and/or extraction processes and also developing computational software to predict the solubility. The results of this work show that the Jouyban–Acree model and its previously trained versions could be used to predict the solubility of FD at different temperatures in PEG 200 + water. Non-linear enthalpy–entropy compensation was found for solubility process of FD in PEG 200 + water mixtures and depends on the cosolvent composition. Using the Jouyban–Acree model the thermodynamic properties were calculated for FD in PEG 200 + water mixtures at different temperatures.

List of symbols

FD	fluphenazine decanoate
J	Jouyban–Acree coefficients
m_1	mass fraction of polyethylene glycol 200 in the solvent binary mixture free of fluphenazine decanoate
m_2	mass fraction of water in the solvent binary mixture free of fluphenazine decanoate
MD	mean deviation
PEG	polyethylene glycol
R	gas constant
T	absolute temperature
T_{hm}	mean harmonic temperature
$x^{sat}_{m,T}$	solute mole fraction solubility in mixed solvents at T
$x^{sat}_{1,T}$	solute mole fraction solubility in solvent 1 at T
$x^{sat}_{2,T}$	solute mole fraction solubility in solvent 2 at T

Greek letters

$\rho^{sat}_{m,T}$	density of solvent mixtures saturated of solute
$\rho_{m,T}$	density of solvent mixtures without solute

ζ_H partial enthalpy contribution
ζ_{TS} partial entropy contribution
δ_{ds}, δ_{ps} and δ_{hs} the partial solubility parameters of the solute
δ_{d1}, δ_{p1} and δ_{h1} the partial solubility parameters of solvent 1 (PEG 200)
δ_{d2}, δ_{p2} and δ_{h2} the partial solubility parameters of solvent 2 (water)
ΔG Gibbs energy of solution
ΔH enthalpy of solution
ΔS entropy of solution

References

[1] A. Jouyban, Handbook of Solubility for Pharmaceuticals, CRC Press, Boca Raton, FL, 2009.
[2] H. Matsuda, K. Kaburagi, K. Kurihara, K. Tochigi, K. Tomono, Fluid Phase Equilib. 290 (2010) 153–157.
[3] J.T. Rubino, Cosolvents and cosolvency, in: Encyclopedia of Pharmaceutical Technology, third edition, Marcel Dekker, New York, 2006, pp. 806–819.
[4] R. Mohan, H. Lorenz, A.S. Myerson, Ind. Eng. Chem. Res. 41 (2002) 4854–4862.
[5] J.M. Harris, Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, Plenum Press, New York, 1992.
[6] A.C. Moffat, M.D. Osselton, B. Widdop, L.Y. Galichet, Clarke's Analysis of Drug and Poisons, third edition, Pharmaceutical Press, London, 2004.
[7] V. Panahi-Azar, A. Shayanfar, F. Martinez, W.E. Acree Jr., A. Jouyban, Fluid Phase Equilib. 308 (2011) 72–77.
[8] A. Jouyban, J. Pharm. Pharmaceut. Sci. 11 (2008) 32–58.
[9] A. Jouyban, Chem. Pharm. Bull. 54 (2006) 1261–1266.
[10] A. Jouyban, Sh. Soltanpour, E. Tamizi, Pharmazie 63 (2008) 548–550.
[11] A. Jouyban, A. Shayanfar, V. Panahi-Azar, J. Soleymani, B. Yousefi, W.E. Acree Jr., J. Pharm. Sci. 100 (2011) 4368–4382.
[12] D.J.W. Grant, M. Mehdizadeh, A.H.L. Chow, J.E. Fairbrother, Int. J. Pharm. 18 (1984) 25–38.
[13] A. Jouyban, M.A.A. Fakhree, W.E. Acree Jr., J. Chem. Eng. Data 57 (2012) 1344–1346.
[14] A. Jouyban, A. Shayanfar, W.E. Acree Jr., Fluid Phase Equilib. 293 (2010) 47–58.
[15] A. Shayanfar, Sh. Eghrary, F. Sardari, W.E. Acree Jr., A. Jouyban, J. Chem. Eng. Data 56 (2011) 2290–2294.
[16] P. Bustamante, S. Romero, A. Peña, B. Escalera, A. Reillo, J. Pharm. Sci. 87 (1998) 1590–1596.
[17] M. Gantiva, F. Martínez, Fluid Phase Equilib. 293 (2010) 242–250.
[18] J. Aerts, The Hoy Solubility Parameter Calculation Software, Computer Chemistry Consultancy, Germany, 2005.
[19] A. Jouyban, A. Fathi-Azarbayjani, M. Khoubnasabjafari, W.E. Acree Jr., Indian J. Chem. A 44 (2005) 1553–1560.
[20] W.E. Acree Jr., Thermochim. Acta 198 (1992) 71–79.