

Solubility Data of Diazepam in Binary and Ternary Mixtures of PEGs 200 and 400 with *N*-Methyl Pyrrolidone and Water at 298.2 K: Experimental Data and Modeling

Shahla Soltanpour · Vahid Panahi-Azar · Azade Taheri · Zahra Bastami · Abolghasem Jouyban

Received: 10 April 2013 / Accepted: 15 August 2013 / Published online: 19 November 2013
© Springer Science+Business Media New York 2013

Abstract Experimental solubilities of diazepam in binary and ternary solvents of polyethylene glycols 200 and 400 with *N*-methyl pyrrolidone and water at $T = 298.2$ K are reported. The Jouyban–Acree model was used to fit solubility data of diazepam in the binary and ternary solvent mixtures (106 data points) in which the overall mean relative deviations (OMRD %) is 13.1 % and the prediction OMRD % is 31.7 %. The combined version of the Jouyban–Acree model with Hansen solubility parameters was used for fitting and predicting the solubility data and the OMRDs % are 10.0 and 20.8 %, respectively. Also, the previously proposed trained versions of the Jouyban–Acree model were used for predicting the reported data in this work and all results are listed in the tables. The density of the solute-free solvent mixtures were measured and employed to calculate the constants of the Jouyban–Acree model and then the densities of the saturated solutions were predicted.

Keywords Diazepam · Solubility · PEG 200 and 400 · NMP · Modeling

S. Soltanpour (✉) · A. Taheri · Z. Bastami
Faculty of Pharmacy, Zanjan University of Medical Sciences, 45139 Zanjan, Iran
e-mail: Shahla.soltanpour@gmail.com

V. Panahi-Azar
Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

A. Jouyban
Drug Applied Research Center, Faculty of Pharmacy, Tabriz University of Medical Sciences, 51664 Tabriz, Iran

A. Jouyban
Pharmaceutical Engineering Laboratory School of Chemical Engineering, College of Engineering, University of Tehran, P.O. Box 11155/4563, Tehran, Iran

1 Introduction

In the pharmaceutical industry and in developing liquid dosage forms, the solubility of drugs has a very important role because modifying the drug solubility sometimes affects the bioavailability and may result in its improvement.

Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one) is a sedative–hypnotic drug which is classified in the benzodiazepine group. The main clinical usages of diazepam are for treating seizures, anxiety, insomnia and depression. From the physical properties point of view, diazepam is a white or yellow solid crystalline powder with melting point in the range 131.5–134.5 °C and it is odorless and with a slightly bitter taste. According to the British Pharmacopeia (BP) [1], diazepam is very slightly soluble in water, soluble in alcohol and freely soluble in chloroform, and from the United States Pharmacopeia (USP) [2], diazepam is described as practically insoluble in water, soluble 1 in 16 parts of ethyl alcohol, 1 in 2 parts of chloroform, and 1 in 39 parts of ether. In the biopharmaceutics classification system (BCS) diazepam has been placed in class II, which includes the poorly water-soluble drugs. The aqueous solubility is one of the most important properties of the drugs in the pharmaceutical industry. When considering the use of drugs dissolution of the drugs in the gastrointestinal fluid or in blood is an essential role in the distribution and absorption of the drug throughout the body. So, the solubilities of poorly water-soluble drugs such as diazepam are very important in the pharmaceutical industry, especially when the formulation is as a liquid dosage (oral or parenteral). In addition to the insufficient aqueous solubility of some drugs, their bioavailability is low too, so these types of drugs are excluded from clinical research. Many solubilization studies have been carried out to modify the solubility of poorly water-soluble drugs, and each of several different methods such as cosolvency, complexation, surface-active agents, and prodrugs and salt formation [3–5] have been used for increasing the solubility. In this study our intent is to increase the solubility of diazepam by the cosolvency method.

Polyethylene glycols (PEGs) are nontoxic, odorless, neutral, lubricating, nonvolatile, nonirritating polymers. Because of their low toxicity and high water solubility, they have a variety of applications in pharmaceutical and medicinal fields as a cosolvent, dispensing agent, ointment and suppository bases, vehicle, and tablet excipient [6–8]. PEGs are variable in molecular weight; the range of their molecular weight is from 200 to 36,000 g·mol^{−1}. PEGs with molecular weights of 200–800 g·mol^{−1} are liquids freely miscible with water, and PEGs with molecular weights higher than 1,000 g·mol^{−1} are solids which are commonly used for preparing nano-particles, which is another technique for increasing the solubility of drugs.

N-Methyl pyrrolidone (NMP) is a polar and stable solvent; it is a powerful solubilizing agent that is used in some pharmaceutical products [9]. In the pharmaceutical and medicinal fields, NMP has various applications such as a solubilizing agent for poorly soluble drugs [10], entrapment of poorly water-soluble drugs in hybrid nanoparticles [11], increasing the skin permeation of drugs [12], and is used in dental barrier membranes [13] and subcutaneous drug delivery systems [14–16].

These solvents are safe pharmaceutical solvents, so for formulating diazepam in the liquid form (oral or parenteral), the investigated solvent mixtures could be used after passing the toxicity tests. Doing systematic solubility measurements and suggesting applicable trained models for predicting the solubilities are necessary and important because it is clear that the experimental measurement of the drug's solubility is very time consuming.

Recently prediction of the solubilities of drugs in the mixed solvents has been considered, which could avoid doing the time-consuming experimental work. With this aim, several

mathematical models have been presented for both correlating and predicting the solubilities in solvent mixtures. One of these algorithms is the Jouyban–Acree model that provides very accurate descriptions of the solute's solubility dependence on temperature and solvent composition. The general form of the Jouyban–Acree model can be written as [17]:

$$\log_{10} C_{m,T}^{Sat} = w_1 \log_{10} C_{1,T}^{Sat} + w_2 \log_{10} C_{2,T}^{Sat} + \left[\frac{w_1 w_2}{T} \sum_{i=0}^2 J_i (w_1 - w_2)^i \right], \quad (1)$$

where $C_{m,T}^{Sat}$ is the solute molar solubility in the binary solvent mixtures at temperature T (K), w_1 and w_2 are the mass fractions of the solvents 1 and 2 in the absence of the solute, and $C_{1,T}^{Sat}$ and $C_{2,T}^{Sat}$ denote the molar solubility of the solute in the neat solvents 1 and 2, respectively. The J_i terms are constants of the model and are computed by regressing values of $\left(\log_{10} C_{m,T}^{Sat} - w_1 \log_{10} C_{1,T}^{Sat} - w_2 \log_{10} C_{2,T}^{Sat} \right)$ against $\frac{w_1 w_2}{T}$, $\frac{w_1 w_2 (w_1 - w_2)}{T}$, and $\frac{w_1 w_2 (w_1 - w_2)^2}{T}$. The Jouyban–Acree model has a theoretical basis [18], and it shows more accurate correlations than other cosolvency models [19]. The only limitation of this model is the necessity of knowing the solubility of the drug in single solvents for predicting the solubility in the mixed solvents at various temperatures [20–22].

In practical applications of Eq. 1 at isothermal conditions, the equation can be written as:

$$\log_{10} C_m^{Sat} = w_1 \log_{10} C_1^{Sat} + w_2 \log_{10} C_2^{Sat} + w_1 w_2 \left[A_0 + A_1 (w_1 - w_2) + A_2 (w_1 - w_2)^2 \right] \quad (2)$$

in which $A_0 = \frac{J_0}{T}$, $A_1 = \frac{J_1}{T}$ and $A_2 = \frac{J_2}{T}$. A theoretical justification for this derivation has been provided in an earlier work [23]. The incorporation of T within the A terms makes the appearance of the model slightly simpler; however, we recommend the use of Eq. 1. By using Eq. 1, it is possible to calculate the J terms at one temperature and predict the solubility of a drug at other temperatures by employing its experimental solubilities in the single solvents, i.e. C_1^{Sat} and C_2^{Sat} , at the temperature of interest. This hypothesis has been successfully examined in earlier work [24–27] and provides a practical method to predict the solubility in mixed solvents at various temperatures using minimal experimental information.

In addition to binary solvent mixtures, the extended versions of the model for predicting the solubility data of drugs in ternary solvent mixtures are:

$$\begin{aligned} \log_{10} C_{m,T}^{Sat} = & w_1 \log_{10} C_{1,T}^{Sat} + w_2 \log_{10} C_{2,T}^{Sat} + w_3 \log_{10} C_{3,T}^{Sat} + \left[\frac{w_1 w_2}{T} \sum_{i=0}^2 J_i (w_1 - w_2)^i \right] \\ & + \left[\frac{w_1 w_3}{T} \sum_{i=0}^2 J'_i (w_1 - w_3)^i \right] + \left[\frac{w_2 w_3}{T} \sum_{i=0}^2 J''_i (w_2 - w_3)^i \right] \end{aligned} \quad (3)$$

$$\begin{aligned} \log_{10} C_{m,T}^{Sat} = & w_1 \log_{10} C_{1,T}^{Sat} + w_2 \log_{10} C_{2,T}^{Sat} + w_3 \log_{10} C_{3,T}^{Sat} + \left[\frac{w_1 w_2}{T} \sum_{i=0}^2 J_i (w_1 - w_2)^i \right] \\ & + \left[\frac{w_1 w_3}{T} \sum_{i=0}^2 J'_i (w_1 - w_3)^i \right] + \left[\frac{w_2 w_3}{T} \sum_{i=0}^2 J''_i (w_2 - w_3)^i \right] \\ & + \left[\frac{w_1 w_2 w_3}{T} \sum_{i=0}^2 J'''_i (w_1 - w_2 - w_3)^i \right], \end{aligned} \quad (4)$$

where $C_{3,T}^{Sat}$ is the solute molar solubility in solvent 3 at temperature T , and w_3 is the mass fraction of the solvent 3 in the absence of the solute. The J'_i and J''_i terms are computed using the same procedure as for the J_i terms. The J'''_i terms are the ternary solvent interaction terms and are computed by regressing $\left\{ \log_{10} C_{m,T}^{Sat} - w_1 \log_{10} C_{1,T}^{Sat} - w_2 \log_{10} C_{2,T}^{Sat} - w_3 \log_{10} C_{3,T}^{Sat} - \left[\frac{w_1 w_2}{T} \sum_{i=0}^2 J_i (w_1 - w_2)^i \right] - \left[\frac{w_1 w_3}{T} \sum_{i=0}^2 J'_i (w_1 - w_3)^i \right] - \left[\frac{w_2 w_3}{T} \sum_{i=0}^2 J''_i (w_2 - w_3)^i \right] \right\}$ against $\frac{w_1 w_2 w_3}{T}$, $\frac{w_1 w_2 w_3 (w_1 - w_2 - w_3)}{T}$, and $\frac{w_1 w_2 w_3 (w_1 - w_2 - w_3)^2}{T}$. The existence of these model constants that require a number of solubility data in solvent mixtures, for the training process, is a limitation for the model when the solubility predictions are the goal of the computations in early drug discovery studies.

For covering the physicochemical properties of the solute or solvents, we can combine the Jouyban–Acree model with the parameters that are used for determining the properties of the substances. By combining the Jouyban–Acree model and the Hansen solubility parameters, Eq. 1 can be written as:

$$\begin{aligned} \log_{10} C_{m,T}^{Sat} = & w_1 \log_{10} C_{1,T}^{Sat} + w_2 \log_{10} C_{2,T}^{Sat} \\ & + \frac{w_1 w_2}{T} \left[W_0 + W_1 \delta_{ds} (\delta_{d1} - \delta_{d2})^2 + W_2 \delta_{ps} (\delta_{p1} - \delta_{p2})^2 + W_3 \delta_{hs} (\delta_{h1} - \delta_{h2})^2 \right] \\ & + \frac{w_1 w_2 (w_1 - w_2)}{T} \left[W'_0 + W'_1 \delta_{ds} (\delta_{d1} - \delta_{d2})^2 + W'_2 \delta_{ps} (\delta_{p1} - \delta_{p2})^2 + W'_3 \delta_{hs} (\delta_{h1} - \delta_{h2})^2 \right] \\ & + \frac{w_1 w_2 (w_1 - w_2)^2}{T} \left[W''_0 + W''_1 \delta_{ds} (\delta_{d1} - \delta_{d2})^2 + W''_2 \delta_{ps} (\delta_{p1} - \delta_{p2})^2 + W''_3 \delta_{hs} (\delta_{h1} - \delta_{h2})^2 \right], \end{aligned} \quad (5)$$

where δ_{ds} , δ_{ps} , and δ_{hs} are the Hansen solubility parameters that represent dispersion, polarity and hydrogen bonding of the solute, respectively. The δ_{d1} , δ_{p1} , δ_{h1} and δ_{d2} , δ_{p2} , and δ_{h2} are the Hansen parameters for solvent 1 and 2, respectively, and the W terms are the model constants.

For ternary solvent mixtures, Eq. 5 can be modified as:

$$\begin{aligned} \log_{10} C_{m,T}^{Sat} = & w_1 \log_{10} C_{1,T}^{Sat} + w_2 \log_{10} C_{2,T}^{Sat} + w_3 \log_{10} C_{3,T}^{Sat} \\ & + \frac{w_1 w_2}{T} \left[W_0 + W_1 \delta_{ds} (\delta_{d1} - \delta_{d2})^2 + W_2 \delta_{ps} (\delta_{p1} - \delta_{p2})^2 + W_3 \delta_{hs} (\delta_{h1} - \delta_{h2})^2 \right] \\ & + \frac{w_1 w_2 (w_1 - w_2)}{T} \left[W'_0 + W'_1 \delta_{ds} (\delta_{d1} - \delta_{d2})^2 + W'_2 \delta_{ps} (\delta_{p1} - \delta_{p2})^2 \right. \\ & \left. + W'_3 \delta_{hs} (\delta_{h1} - \delta_{h2})^2 \right] + \frac{w_1 w_2 (w_1 - w_2)^2}{T} \\ & \times \left[W''_0 + W''_1 \delta_{ds} (\delta_{d1} - \delta_{d2})^2 + W''_2 \delta_{ps} (\delta_{p1} - \delta_{p2})^2 + W''_3 \delta_{hs} (\delta_{h1} - \delta_{h2})^2 \right] \\ & + \frac{w_1 w_2 w_3 (w_1 - w_2 - w_3)^2}{T} \left[\begin{aligned} & W'''_0 + W'''_1 \delta_{ds} (\delta_{d1} - \delta_{d2} - \delta_{d3})^2 \\ & + W'''_2 \delta_{ps} (\delta_{p1} - \delta_{p2} - \delta_{p3})^2 \\ & + W'''_3 \delta_{hs} (\delta_{h1} - \delta_{h2} - \delta_{h3})^2 \end{aligned} \right], \end{aligned} \quad (6)$$

where δ_{d3} , δ_{p3} , and δ_{h3} are the Hansen solubility parameters for solvent 3.

2 Experimental

2.1 Chemical

Diazepam (99.9 %) was purchased from Sobhan Pharmaceutical Company (Iran). The purity of the drug was checked by determining its melting point and comparing its measured solubilities in single solvents with the corresponding data from the literature [28]. NMP (99.5 w/w %) was purchased from Merck (Germany), and PEGs 200 (95.0 w/w %) and 400 (95.0 w/w %) were purchased from Merck (Germany). Double distilled water was used for preparation of the solutions.

2.2 Apparatus and Procedures

The binary and ternary solvent mixtures were prepared by mixing the appropriate number of grams of the solvents, with uncertainty of 0.1 g, to make a total quantity of 100 g of binary and ternary solvent mixtures. Different methods have been presented for determining the solubility of drugs [29]. The solubility of diazepam was determined using the classical saturating shake-flask method of Higuchi and Connors, by equilibrating excess amounts of diazepam at 298.2 K using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature controlling system maintained constant within ± 0.2 K (Nabziran, Tabriz, Iran). The solutions were placed in the incubator for 72 h, then the saturated solutions of diazepam were centrifuged at 13,000 rpm for 15 min, diluted with methanol, and then assayed at 250 nm using a UV–Vis spectrophotometer (Beckman DU-650, Fullerton, USA). Concentrations of the diluted solutions were determined from the calibration curve. Each experimental data point represents the average of at least three repeat experiments with the measured molar solubilities being reproducible to within ± 3.7 %. Densities of the saturated solutions and the solute free solvent mixtures were measured using a 5 mL pycnometer and the results reported are those from a single measurement.

3 Theory and Calculations

In the numerical analysis method I, the experimental solubility data of diazepam in binary solvents were fitted with Eq. 1, the model constants were computed and the back-calculated solubilities were used to compute the mean relative deviation percent (MRD %) values. In the next step, the obtained model constants were included in Eq. 3, and then it was used to calculate the solubility of diazepam in ternary solvent mixtures. In order to provide better calculations, the ternary interaction terms of Eq. 4 were calculated using a linear regression analysis.

In the numerical analysis method II, the combined forms of the Jouyban–Acree model were used for fitting and predicting the solubility data in binary and ternary mixtures. At the first step the experimental solubility data of diazepam in binary mixtures were fitted with Eq. 5, and the sub-binary model constants were calculated. Then, the experimental solubility data in ternary mixtures were fitted with Eq. 6 by employing the calculated sub-binary model constants. At this step the ternary model constants were also calculated. Then, by employing the calculated sub-binary and ternary model constants and the solubility data in single solvents, the solubility data in binary and ternary mixtures were predicted.

In the numerical analysis method III, to demonstrate the ability of the Jouyban–Acree model to predict solubility data, the minimum number of data points of both binary and ternary mixtures were used for fitting the model. The constants of Eq. 3 were computed by fitting the minimum number of the experimental data (five data points with the mass fraction compositions of 0.00 + 1.00, 0.30 + 0.70, 0.50 + 0.50, 0.70 + 0.30 and 1.00 + 0.00) for NMP (1)—PEGs 200 or 400 (2), PEGs 200 or 400 (2)—water (3) and NMP (1)—water (3) mixtures and then the ternary interaction terms, i.e. J_i''' , were calculated by fitting a minimum number of experimental solubility data (six data points with the mass fraction compositions of NMP + PEGs 200 or 400 + water: 0.10 + 0.80 + 0.10, 0.80 + 0.10 + 0.10, 0.10 + 0.10 + 0.80, 0.50 + 0.30 + 0.20, 0.50 + 0.20 + 0.30, 0.30 + 0.20 + 0.50) in ternary solvents. These trained versions were then used for predicting the solubility of diazepam in binary and ternary solvent mixtures, and the results are compared with the results of the numerical analyses I and II and the applicability of the Jouyban–Acree model is discussed.

In a previous study [30], a trained version of the Jouyban–Acree model was proposed for modeling the solubility of drugs in PEG 400 (1)—water (2) mixtures as:

$$\log_{10} C_{m,T}^{Sat} = w_1 \log_{10} C_{1,T}^{Sat} + w_2 \log_{10} C_{2,T}^{Sat} + \frac{w_1 w_2}{T} [394.82 - 355.28(w_1 - w_2) + 388.89(w_1 - w_2)^2]. \quad (7)$$

So, in numerical analysis method IV, this trained version was used to predict the solubility data of diazepam in binary mixtures of PEGs 200 or 400 with water.

Previously, two generally trained models for PEG 600–water and NMP–water mixtures have been proposed for Jouyban–Acree model [31]. The trained version for PEG 600 (1)—water (2) mixtures is:

$$\log_{10} C_{m,T}^{Sat} = w_1 \log_{10} C_{1,T}^{Sat} + w_2 \log_{10} C_{2,T}^{Sat} + 213.21 \frac{w_1 w_2}{T} \quad (8)$$

and the trained version for NMP (1)—water (2) mixtures is:

$$\log_{10} C_{m,T}^{Sat} = w_1 \log_{10} C_{1,T}^{Sat} + w_2 \log_{10} C_{2,T}^{Sat} + \frac{w_1 w_2}{T} [668.67 - 678.59(w_1 - w_2) + 1220.13(w_1 - w_2)^2]. \quad (9)$$

In the numerical analyses methods V and VI, Eqs. 8 and 9 were used for predicting diazepam solubilities in aqueous binary mixtures with PEGs 200 or 400 and NMP, respectively.

In addition to those trained versions of the Jouyban–Acree model, one generally trained model for PEG 200 (1)—water (2) mixtures, using data sets taken from previous works [22, 32, 33], is presented in this work; it is written as:

$$\log_{10} C_{m,T}^{Sat} = w_1 \log_{10} C_{1,T}^{Sat} + w_2 \log_{10} C_{2,T}^{Sat} + \frac{w_1 w_2}{T} [164.74 + 552.654(w_1 - w_2)]. \quad (10)$$

In the numerical analysis method VII, Eq. 10 was used for predicting the solubility of diazepam in the aqueous mixtures of PEG 200. In the next step of this analysis, the leave-one-out cross-validation method was applied; one drug was excluded from the training sets and Eq. 10 was trained with the rest of the data sets, and then by using the trained version, the solubility of the excluded drug was predicted.

In addition to solubility data, the applicability of the Jouyban–Acree model for predicting the density of solvent mixtures at various temperatures was shown in previous

Table 1 Experimental molar solubilities ($C_{m,T}^{Sat}$) of diazepam in NMP (1)—PEG 200 or 400 (2)—water (3) mixtures (mass fractions), at 298.2 K and their standard deviations ($N = 3$), along with the density ($\text{g}\cdot\text{cm}^{-3}$) of the saturated and solute free solutions

NMP	PEG 200	PEG 400	Water	$C_{m,T}^{Sat}$ ($\pm$ SD)	Density of the saturated solution	Density of the solute free solutions
0.10	–	0.80	0.10	0.0527 (0.015)	1.120	–
0.20	–	0.70	0.10	0.0802 (0.015)	1.100	1.059
0.30	–	0.60	0.10	0.1382 (0.010)	1.100	–
0.40	–	0.50	0.10	0.1965 (0.015)	1.090	1.082
0.50	–	0.40	0.10	0.2417 (0.021)	1.090	–
0.60	–	0.30	0.10	0.2673 (0.015)	1.080	1.076
0.70	–	0.20	0.10	0.3249 (0.015)	1.080	–
0.80	–	0.10	0.10	0.4088 (0.015)	1.070	1.065
0.10	–	0.70	0.20	0.0456 (0.015)	1.100	–
0.20	–	0.60	0.20	0.0679 (0.015)	1.100	1.067
0.30	–	0.50	0.20	0.0888 (0.020)	1.850	–
0.40	–	0.40	0.20	0.1106 (0.031)	1.080	1.064
0.50	–	0.30	0.20	0.1515 (0.020)	1.080	–
0.60	–	0.20	0.20	0.1997 (0.020)	1.070	1.056
0.70	–	0.10	0.20	0.2241 (0.015)	1.055	–
0.10	–	0.60	0.30	0.0273 (0.011)	1.098	1.063
0.20	–	0.50	0.30	0.0348 (0.011)	1.090	–
0.30	–	0.40	0.30	0.0410 (0.015)	1.080	1.079
0.40	–	0.30	0.30	0.0575 (0.010)	1.070	–
0.50	–	0.20	0.30	0.0655 (0.023)	1.060	1.052
0.60	–	0.10	0.30	0.0744 (0.010)	1.050	–
0.10	–	0.50	0.40	0.0111 (0.001)	1.085	1.073
0.20	–	0.40	0.40	0.0145 (0.002)	1.070	–
0.30	–	0.30	0.40	0.0344 (0.005)	1.070	1.063
0.40	–	0.20	0.40	0.0415 (0.015)	1.060	–
0.50	–	0.10	0.40	0.0605 (0.015)	1.050	1.046
0.10	–	0.40	0.50	0.0075 (0.005)	1.070	–
0.20	–	0.30	0.50	0.0105 (0.005)	1.060	1.057
0.30	–	0.20	0.50	0.0135 (0.005)	1.050	–
0.40	–	0.10	0.50	0.0166 (0.000)	1.040	1.035
0.10	–	0.30	0.60	0.0020 (0.000)	1.060	–
0.20	–	0.20	0.60	0.0030 (0.005)	1.050	1.049
0.30	–	0.10	0.60	0.0052 (0.001)	1.040	–
0.10	–	0.20	0.70	0.0018 (0.000)	1.050	1.039
0.20	–	0.10	0.70	0.0033 (0.001)	1.050	–
0.10	–	0.10	0.80	0.0007 (0.000)	1.035	1.027
–	–	0.00	1.00	0.0002 (0.000)	1.003	0.997
–	–	0.10	0.90	0.0003 (0.000)	1.025	–
–	–	0.20	0.80	0.0003 (0.000)	1.040	1.017
–	–	0.30	0.70	0.0005 (0.000)	1.057	–

Table 1 continued

NMP	PEG 200	PEG 400	Water	$C_{m,T}^{Sat}$ ($\pm$ SD)	Density of the saturated solution	Density of the solute free solutions
–	–	0.40	0.60	0.0008 (0.000)	1.073	1.035
–	–	0.50	0.50	0.0021 (0.000)	1.088	–
–	–	0.60	0.40	0.0041 (0.000)	1.100	1.067
–	–	0.70	0.30	0.0137 (0.000)	1.120	–
–	–	0.80	0.20	0.0704 (0.001)	1.130	1.098
–	–	0.90	0.10	0.0804 (0.001)	1.140	1.114
–	–	1.00	0.00	0.0879 (0.002)	1.145	1.124
0.00	–	1.00	–	0.0879 (0.002)	1.145	1.123
0.20	–	0.80	–	0.2355 (0.002)	1.114	1.108
0.40	–	0.60	–	0.3787 (0.005)	1.129	1.084
0.60	–	0.40	–	1.2608 (0.025)	1.102	1.075
0.80	–	0.20	–	2.3571 (0.036)	1.106	1.059
1.00	–	0.00	–	0.6320 (0.017)	1.117	1.051
0.00	1.00	–	–	0.0588 (0.005)	1.127	1.112
0.20	0.80	–	–	0.1261 (0.005)	1.114	1.104
0.40	0.60	–	–	0.2126 (0.003)	1.129	1.080
0.60	0.40	–	–	0.4449 (0.065)	1.102	1.073
0.80	0.20	–	–	0.5934 (0.030)	1.106	1.057
1.00	0.00	–	–	0.6320 (0.017)	1.117	1.051
–	0.00	–	1.00	0.0002 (0.000)	1.002	0.997
–	0.10	–	0.90	0.0002 (0.000)	1.010	–
–	0.20	–	0.80	0.0004 (0.000)	1.030	1.015
–	0.30	–	0.70	0.0006 (0.000)	1.035	–
–	0.40	–	0.60	0.0012 (0.000)	1.060	1.033
–	0.50	–	0.50	0.0024 (0.000)	1.074	–
–	0.60	–	0.40	0.0054 (0.001)	1.087	1.065
–	0.70	–	0.30	0.0167 (0.001)	1.100	–
–	0.80	–	0.20	0.0319 (0.001)	1.108	1.076
–	0.90	–	0.10	0.0463 (0.001)	1.116	1.098
–	1.00	–	0.00	0.0588 (0.002)	1.127	1.112
0.10	0.80	–	0.10	0.0261 (0.010)	1.090	–
0.20	0.70	–	0.10	0.0398 (0.015)	1.080	1.055
0.30	0.60	–	0.10	0.0539 (0.010)	1.080	–
0.40	0.50	–	0.10	0.0802 (0.010)	1.070	1.060
0.50	0.40	–	0.10	0.0934 (0.010)	1.070	–
0.60	0.30	–	0.10	0.1463 (0.025)	1.060	1.052
0.70	0.20	–	0.10	0.1908 (0.025)	1.060	–
0.80	0.10	–	0.10	0.2097 (0.020)	1.050	1.042
0.10	0.70	–	0.20	0.0176 (0.000)	1.085	–
0.20	0.60	–	0.20	0.0330 (0.005)	1.085	1.065
0.30	0.50	–	0.20	0.0687 (0.010)	1.070	–
0.40	0.40	–	0.20	0.0810 (0.010)	1.060	1.050

Table 1 continued

NMP	PEG 200	PEG 400	Water	$C_{m,T}^{Sat}$ ($\pm$ SD)	Density of the saturated solution	Density of the solute free solutions
0.50	0.30	–	0.20	0.0930 (0.015)	1.060	–
0.60	0.20	–	0.20	0.1494 (0.015)	1.050	1.044
0.70	0.10	–	0.20	0.1968 (0.025)	1.040	–
0.10	0.60	–	0.30	0.0080 (0.005)	1.080	1.061
0.20	0.50	–	0.30	0.0131 (0.000)	1.075	–
0.30	0.40	–	0.30	0.0335 (0.005)	1.060	1.056
0.40	0.30	–	0.30	0.0587 (0.015)	1.050	–
0.50	0.20	–	0.30	0.0869 (0.015)	1.045	1.038
0.60	0.10	–	0.30	0.1009 (0.015)	1.035	–
0.10	0.50	–	0.40	0.0037 (0.001)	1.070	1.061
0.20	0.40	–	0.40	0.0065 (0.005)	1.055	–
0.30	0.30	–	0.40	0.0096 (0.005)	1.050	1.041
0.40	0.20	–	0.40	0.0264 (0.010)	1.040	–
0.50	0.10	–	0.40	0.0368 (0.015)	1.030	1.022
0.10	0.40	–	0.50	0.0030 (0.001)	1.050	–
0.20	0.30	–	0.50	0.0049 (0.000)	1.040	1.034
0.30	0.20	–	0.50	0.0068 (0.000)	1.030	–
0.40	0.10	–	0.50	0.0097 (0.000)	1.025	1.013
0.10	0.30	–	0.60	0.0028 (0.000)	1.040	–
0.20	0.20	–	0.60	0.0066 (0.000)	1.030	1.025
0.30	0.10	–	0.60	0.0096 (0.000)	1.020	–
0.10	0.20	–	0.70	0.0018 (0.001)	1.030	1.027
0.20	0.10	–	0.70	0.0030 (0.001)	1.030	–
0.10	0.10	–	0.80	0.0008 (0.000)	1.020	1.015

papers [31, 34]. For showing the model's applicability in predicting the density of the saturated solvent mixtures, in the numerical analysis method VIII, the Jouyban–Acree model was fitted to the measured densities of the solute-free solvent mixtures (with the uncertainty of 0.1 g) and a trained version was produced for each binary and ternary solvent of PEGs 200 or 400 with NMP and water. Then, the densities of the saturated solutions were predicted using these trained versions. Finally, the experimental and calculated densities were used to convert the molar solubilities to the corresponding mole fractions.

The MRD % between the calculated and observed (solubility/density) values are used to evaluate the accuracy of the model. The MRD % values were calculated using

$$MRD \% = \frac{100}{N} \sum \left\{ \frac{|C_{Cal}^{Sat} - C_{Exp}^{Sat}|}{C_{Exp}^{Sat}} \right\}, \quad (11)$$

where N is the number of data points in each set.

Table 2 The constants of the Eq. 1 and the MRDs % of back-calculation for solubility of diazepam in binary and ternary solvent mixtures of PEGs 200 or 400, NMP and water mixtures

Solvent system	<i>N</i>	<i>J</i> ₀	<i>J</i> ₁	<i>J</i> ₂	MRD %
PEG 400—water	11	−449.475	869.046	1,202.800	12.8
PEG 400—NMP	6	260.051	179.054	^b	3.2
PEG 200—water	11	−116.596	755.193	^b	7.4
PEG 200—NMP	6	261.246	138.201	^b	4.0
NMP—water ^a	11	−186.345	−1,448.733	266.121	3.0
				OMRD %	6.1
NMP—PEG 400—water	36	5,388.563	9,346.591	6,965.564	29.7
NMP—PEG 200—water	36	3,776.716	8,144.600	^b	41.9
				OMRD %	35.8

^a Experimental data are taken from a previous paper [39], and the solvent compositions were converted to mass fractions

^b Parameter not significant

4 Results and Discussions

Table 1 lists the experimental solubilities of diazepam in the binary and ternary solvent mixtures along with the measured density of the saturated solution and solute free solvent mixtures, respectively, at 298.2 K. The minimum solubility of diazepam ($0.0002 \text{ mol}\cdot\text{L}^{-1}$) among the investigated solvent systems is observed for water and the maximum solubility of diazepam ($2.3571 \text{ mol}\cdot\text{L}^{-1}$) in the studied solvent mixtures is observed for the NMP + PEG 400 (0.8 + 0.2) mixture.

With using the Hildebrand solubility parameter (δ) as a polarity index, it has become clear that the maximum solubility of a solute (δ_2) is observed in a solvent with the same solubility parameter (δ_1) or $[(\delta_2 - \delta_1)^2 = 0]$ [35, 36]. So, the very low solubility of diazepam in water can be explained by considering its lesser polarity in comparison with water. The addition of organic co-solvents to water can break the strong hydrogen bond interactions among the water molecules and reduce the polarity of water; therefore, the solubility of less polar solutes can be increased.

In the numerical analysis method I, Eqs. 1 and 4 were used to fit the data sets of diazepam, and the constants and MRD % values are shown in Table 2. Using these constants, it is possible to predict the solubility of diazepam in all composition ranges of the solvents at various temperatures just by employing the experimental solubility in the pure solvents, i.e. $C_{1,T}^{\text{Sat}}$, $C_{2,T}^{\text{Sat}}$ and $C_{3,T}^{\text{Sat}}$. In the binary mixtures of diazepam the lowest MRD % value belong to PEG 200 or 400—water mixtures with 3.0 % and the highest MRD % value is observed for NMP—PEG 400 mixtures with 12.8 %. The overall MRD % (OMRD %) values are 5.6 and 35.8 %, respectively, for the binary and ternary mixtures. All the MRD % values along with the data set detail are listed in Table 2. The MRD % values for ternary solvent mixtures are higher than those of the binary solvent mixtures. More complex solute–solvent interactions in the ternary mixtures could be a possible reason for higher MRD % values.

In the numerical analysis method II, the combined versions of the Jouyban–Acree model and the Hansen solubility parameters for binary and ternary mixtures (Eqs. 5 and 6) were used for correlating the whole solubility data set for diazepam at once. The observed

prediction MRD % for all data points of binary and ternary mixtures of PEG 200, NMP and water is 22.5 % and for PEG 400, NMP and water mixtures is 14.6 %. In the next step all the data points, including PEGs 200 or 400, NMP and water, were used to train the model at once and the prediction MRD % is 20.8 %.

In numerical analysis method III, the sub-binary model constants were calculated by employing a minimum number of experimental data and then these were included in Eq. 4, and the ternary interaction terms were calculated. The obtained equation for diazepam in NMP (1)—PEG 200 (2)—water (3) mixtures is then:

$$\begin{aligned} \log_{10} C_{m,T}^{Sat} = & w_1 \log_{10} C_{1,T}^{Sat} + w_2 \log_{10} C_{2,T}^{Sat} + w_3 \log_{10} C_{3,T}^{Sat} + \frac{w_1 w_2}{T} [300.15 + 113.07(w_1 - w_2)] \\ & + \frac{w_1 w_3}{T} [374.99 - 881.69(w_1 - w_3) + 1247.27(w_1 - w_3)^2] \\ & - \frac{w_2 w_3}{T} [184.20 - 828.43(w_2 - w_3) - 808.42(w_2 - w_3)^2]. \end{aligned} \quad (12)$$

Equation 12 was used to predict the solubility data of diazepam, and the prediction OMRD % is 42.3 %.

For NMP (1)—PEG 400 (2)—water (3) mixtures the trained model is:

$$\begin{aligned} \log_{10} C_{m,T}^{Sat} = & w_1 \log_{10} C_{1,T}^{Sat} + w_2 \log_{10} C_{2,T}^{Sat} + w_3 \log_{10} C_{3,T}^{Sat} + \frac{w_1 w_2}{T} [295.49 + 250.16(w_1 - w_2)] \\ & + \frac{w_1 w_3}{T} [374.99 - 881.69(w_1 - w_3) + 1247.27(w_1 - w_3)^2] \\ & - \frac{w_2 w_3}{T} [357.95 - 675.05(w_2 - w_3) - 421.98(w_2 - w_3)^2]. \end{aligned} \quad (13)$$

By using Eq. 13 the prediction OMRD % value for the solubility data of diazepam in binary and ternary solvents is 22.0 %.

In numerical analysis method IV, the trained version of the Jouyban–Acree model for aqueous solutions of PEG 400 (Eq. 7) has been used for predicting the solubility of diazepam in binary mixtures of water and PEGs 200 or 400, and the prediction MRD % are 28.0 and 32.4 %, respectively.

In numerical analysis method V, the trained version of the Jouyban–Acree model for aqueous solutions of PEG 600 (Eq. 8) has been used for predicting the solubility of diazepam in binary mixtures of water and PEGs 200 or 400, and the prediction MRD % are 22.0 and 42.1 %, respectively.

In numerical analysis method VI, the trained version of the Jouyban–Acree model for aqueous solutions of NMP (Eq. 9) has been used for predicting the solubility of diazepam in binary mixtures of water and NMP, and the prediction MRD % is 50.7 %.

In numerical analysis method VII, another trained version of the Jouyban–Acree model (Eq. 10), which is proposed in this work, was used to back-calculate the solubility of diazepam in PEG 200 and water binary solvent mixtures. The back-calculated MRD % value for diazepam solubility in this analysis is 42.0 %. The back-calculated MRDs % of Eq. 10, the references of the employing data sets, and the MRDs % for the leave-one-out method are shown in Table 3. In the back-calculated part, the lowest (6.2 %) and highest (42.0 %) MRDs % are observed for lamotrigine and diazepam, respectively. The back-calculated OMRD % value for Eq. 10 is 29.6 %. Comparing the MRD % values of Eq. 10 with those of Eq. 1 (listed in Table 2) reveals that the MRD %

values of Eq. 1 are less than those of Eq. 10. But the main advantage of Eq. 10 is the requirement of only needing experimental solubility data of drugs in single solvents, but for computing the constants of Eq. 1 at least three solubility data in mixed solvents are needed. Therefore, with these advantage and weakness of Eq. 10, the MRD % values of this equation are acceptable. In the leave-one-out method the lowest (6.3 %) and highest (72.0 %) MRDs % are observed for lamotrigine and diazepam and the OMRD % of the leave-one-out analysis is 35.2 %.

The most important advantage of the trained versions is that for predicting the solubility data with these trained versions there is no need for any more experimental data points for mixed solvents, only the solubilities in the single solvents. So, if we have two data points for each solute, i.e. the solubilities in the single solvents, we can predict the solubility in binary mixed solvents.

For predicting the densities of the saturated solutions ($\rho_{m,T}^{Sat}$), the densities of solute-free binary and ternary solvent mixtures ($\rho_{m,T}$) were measured and fitted to Eq. 14:

$$\log_{10} \rho_{m,T} = w_1 \log_{10} \rho_{1,T} + w_2 \log_{10} \rho_{2,T} + w_3 \log_{10} \rho_{3,T} = \left[\frac{w_1 w_2}{T} \sum_{i=0}^2 J_i (w_1 - w_2)^i \right] + \left[\frac{w_1 w_3}{T} \sum_{i=0}^2 J'_i (w_1 - w_3)^i \right] + \left[\frac{w_2 w_3}{T} \sum_{i=0}^2 J''_i (w_2 - w_3)^i \right], \quad (14)$$

where $\rho_{m,T}$, $\rho_{1,T}$, $\rho_{2,T}$, and $\rho_{3,T}$ are the densities of the solute-free mixed solvents and solvents 1–3, respectively, at temperature T [37]. Then, by using these sub-binary constants, the ternary constants of Eq. 15 were computed:

$$\log_{10} \rho_{m,T} = w_1 \log_{10} \rho_{1,T} + w_2 \log_{10} \rho_{2,T} + w_3 \log_{10} \rho_{3,T} + \left[\frac{w_1 w_2}{T} \sum_{i=0}^2 J_i (w_1 - w_2)^i \right] + \left[\frac{w_1 w_3}{T} \sum_{i=0}^2 J'_i (w_1 - w_3)^i \right] + \left[\frac{w_2 w_3}{T} \sum_{i=0}^2 J''_i (w_2 - w_3)^i \right] + \left[\frac{w_1 w_2 w_3}{T} \sum_{i=0}^2 J'''_i (w_1 - w_2 - w_3)^i \right]. \quad (15)$$

Table 3 The details of data sets and MRD % of the back-calculation and leave-one-out methods using Eq. 10

Drug	<i>N</i>	Solvent system	Reference	MRD % (Back-calculation)	MRD % (Leave-one-out)
Acetaminophen	6	PEG 200—water	[22]	14.1	16.4
Ibuprofen	7	PEG 200—water	[22]	40.4	44.6
Pioglitazone—HCl	6	PEG 200—water	[32]	33.2	36.9
Diazepam	6	PEG 200—water	This work	42.0	72.0
Lamotrigine	6	PEG 200—water	[33]	6.2	6.3
		OMRD		29.6	35.2

Table 4 The constants of the Eq. 15 and the back-calculated MRDs % for density of the solute free solutions

Solvent system	J_0	J_1	J_2	Back-calculated MRD %
PEG 400—water	−2.737	a	a	0.3
PEG 400—NMP	−2.771	a	a	0.1
PEG 200—water	−2.150	a	a	0.1
PEG 200—NMP	4.889	a	a	0.1
NMP—water	−0.401	a	a	0.1
			OMRD %	0.2
NMP—PEG 400—water	106.811	a	a	0.5
NMP—PEG 200—water	89.552	−78.639	a	0.4
			OMRD %	0.5

^a Parameter not significant

The model constants of the Jouyban–Acree model (after excluding the constants with $p > 0.10$) for all studied data sets are listed in Table 4. Employing these model constants and the densities of saturated solutions in single solvents, one can predict the densities of the saturated solvent mixtures [31, 34]. The experimental and calculated densities were used to convert the molar solubilities to the mole fraction solubilities separately. The OMRD % value for the difference of the two groups of calculated mole fraction solubilities is 4.5 %.

5 Conclusions

Experimental solubilities of diazepam are reported in aqueous and non-aqueous mixtures of PEGs 200 or 400 with NMP that extend the available solubility database of pharmaceuticals in mixed solvents [38].

In this investigation the main goal was to improve the solubility of diazepam which is a poorly water-soluble drug. As shown by the solubility data in Table 1, addition of NMP and PEGs 200 and 400 caused the solubility to increase dramatically.

The Jouyban–Acree model fits well to the experimental solubility data of drugs at all composition ranges of solvent mixtures. These findings are also supported by the small MRD % values of the back-calculated and experimental solubility data, and the produced MRDs % are very low, especially for sub-binary solvents. The trained versions of the Jouyban–Acree model also have acceptable predicted MRD % values. So we can say that generally the observed OMRDs % in these predictions show that the Jouyban–Acree model provides more accurate predictions in the presence of one or two cosolvents. The applicability of the Jouyban–Acree model in predicting the density of the saturated solutions by training with the density of the solute free solutions is very considerable, because the densities of the saturated solutions are necessary for converting the molar solubilities to their corresponding mole fractions, and this model can save time and cost over measuring the densities experimentally.

Acknowledgments The authors are grateful for financial support from Zanjan University of Medical Sciences, Iran (No. A-11-387-1).

References

1. BP. Office of the British Pharmacopoeia Commission, London (1998)
2. USP: 23rd Revision. US Pharmacopeial Convention, Rockville (1995)
3. Serajuddin, A.T.M., Pudipeddi, M.: Salt selection strategies. In: Stahl, P.H., Wermuth, C.G. (eds.) *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, pp. 135–160. Wiley-VCH, Weinheim (2002)
4. Dressman, J., Reppas, C.: Drug solubility: how to measure it, how to improve it. *Adv. Drug Deliv. Rev.* **59**, 531–532 (2007)
5. Blagden, N., de Matas, M., Gavan, P.T., York, P.: Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Adv. Drug Deliv. Rev.* **59**, 617–630 (2007)
6. Rahbari-Sisakht, M., Taghizadeh, M., Eliassi, A.: Densities and viscosities of binary mixtures of poly(ethylene glycol) and poly(propylene glycol) in water and ethanol in the 293.15–338.15 K temperature range. *J. Chem. Eng. Data* **48**, 1221–1224 (2003)
7. Harris, J.M.: *Poly(ethylene glycol) Chemistry, Biotechnical and Biomedical Applications*. Plenum, New York (1992)
8. Powell, G.M., Davidson, R.I. (eds.): *Handbook of Water Soluble Gums and Resins*. McGraw-Hill, New York (1980)
9. Strickley, A.: Solubilizing excipients in oral and injectable formulations. *Pharm. Res.* **21**, 201–229 (2004)
10. Uch, A.S., Hesse, U., Dressman, J.B.: Use of 1-methyl-pyrrolidone as a solubilizing agent for determining the uptake of poorly soluble drugs. *Pharm. Res.* **16**, 968–971 (1999)
11. Ishihara, T., Goto, M., Kanazawa, H., Higaki, M., Mizushima, Y.: Efficient entrapment of poorly water-soluble pharmaceuticals in hybrid nanoparticles. *J. Pharm. Sci.* **98**, 2357–2363 (2008)
12. Koizumi, A., Makiko, F., Kondoh, M., Watanabe, Y.: Effect of *N*-methyl pyrrolidone on skin permeation of estradiol. *Eur. J. Pharm. Biopharm.* **57**, 473–487 (2004)
13. Pirhonen, E., Nieuwenhuis, J., Kaikkonen, A., Nieminen, T., Weber, F.: Resorbable polymer compositions, implant and method of making implant. Patent No.: 6926903, 2005
14. Malook, S.U., Boon, P.F.G., Morgan, J.P.: Method of reducing the swelling or pain associated with antibiotics compositions. Patent No. 4772460, 1988
15. Komer, G.: Avermectin formulation. Patent No. 5773422, 1998
16. Dornhofer, W., Embrechts, E.: Injection solution for intramuscular and subcutaneous administration to animal. Patent No. 5753636, 1998
17. Jouyban, A.: Review of the cosolvency models for predicting solubility of drugs in water-cosolvent mixture. *J. Pharm. Pharm. Sci.* **11**, 32–58 (2008)
18. Acree Jr, W.E.: Mathematical representation of thermodynamic properties: part II. Derivation of the combined nearly ideal binary solvent (NIBS)/Redlich–Kister mathematical representation from a two-body and three-body interactional mixing model. *Thermochim. Acta* **198**, 71–79 (1992)
19. Jouyban-Gharamaleki, A., Valaee, L., Barzegar-Jalali, M., Clark, B.J., Acree Jr, W.E.: Comparison of various cosolvency models for calculating solute solubility in water–cosolvent mixtures. *Int. J. Pharm.* **171**, 93–101 (1999)
20. Jouyban, A., Acree Jr, W.E.: In silico prediction of drug solubility in water–ethanol mixtures using Jouyban–Acree model. *J. Pharm. Pharm. Sci.* **9**, 262–269 (2006)
21. Jouyban, A., Acree Jr, W.E.: Prediction of drug solubility in ethanol–ethyl acetate mixtures at various temperatures using the Jouyban–Acree model. *J. Drug Deliv. Sci. Technol.* **17**, 159–160 (2007)
22. Jouyban, A., Soltanpour, Sh., Acree Jr, W.E.: Solubility of acetaminophen and ibuprofen in the mixtures of polyethylene glycol 200 or 400 with ethanol, and water, and density of solute free mixed solvents at 298.2 K. *J. Chem. Eng. Data* **55**, 5252–5257 (2010)
23. Jouyban-Gharamaleki, A., Acree Jr, W.E.: Comparison of models for describing multiple peaks in solubility profiles. *Int. J. Pharm.* **167**, 177–182 (1998)
24. Jouyban, A., Shokri, J., Barzegar-Jalali, M., Hassanzadeh, D., Acree Jr, W.E., Ghafourian, T., Nokhodchi, A.: Solubility of chlorthalidoxepoxide, diazepam, and lorazepam in ethanol + water mixtures at 303.2 K. *J. Chem. Eng. Data* **54**, 2142–2145 (2009)
25. Jouyban, A., Fakhree, M.A.A., Mirzaei, Sh., Ghafourian, T., Soltanpour, Sh., Nokhodchi, A.: Solubility prediction of paracetamol in water–glycerol mixtures at 25 and 30 °C using the Jouyban–Acree model. *Asian J. Chem.* **21**, 7249–7253 (2009)

26. Sardari, F., Jouyban, A.: Solubility of 3-ethyl-5-methyl-(4RS)-2-((2-aminoethoxy)methyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate monobenzenesulfonate (amlodipine besylate) in ethanol + water and propane-1,2-diol + water mixtures at various temperatures. *J. Chem. Eng. Data* **57**, 2848–2854 (2012)
27. Eghrary, Sh., Zarghami, R., Martinez, F., Jouyban, A.: Solubility of 2-butyl-3-benzofuranyl 4-(2-(diethylamino)ethoxy)-3,5-diiodophenyl ketone hydrochloride (amiodarone HCl) in ethanol + water and *N*-methyl-2-pyrrolidone + water mixtures at various temperatures. *J. Chem. Eng. Data* **57**, 1544–1550 (2012)
28. Moffat, A.C.: *Clarke's Analysis of Drug and Poisons*. Pharmaceutical Press, London (2004)
29. Jouyban, A., Fakhree, M.A.A.: Experimental and computational methods pertaining to drug solubility. In: Acree Jr, W.E. (ed.) *Toxicity and Drug Testing*. InTech, New York (2012)
30. Jouyban, A.: Solubility prediction of drugs in water–polyethylene glycol 400 mixtures using Jouyban–Acree model. *Chem. Pharm. Bull.* **54**, 1561–1566 (2006)
31. Soltanpour, Sh., Jouyban, A.: Solubility of acetaminophen and ibuprofen in polyethylene glycol 600, *N*-methyl pyrrolidone and water mixtures. *J. Solution Chem.* **40**, 2032–2045 (2011)
32. Jouyban, A., Soltanpour, Sh.: Solubility of pioglitazone hydrochloride in binary and ternary mixtures of water, propylene glycol, and polyethylene glycols 200, 400 and 600 at 298.2 K. *AAPS PharmSciTech.* **11**, 1713–1717 (2010)
33. Soltanpour, Sh., Jouyban, A.: Solubility of lamotrigine in binary and ternary mixtures of *N*-methyl pyrrolidone and water with polyethylene glycols 200, 400 and 600 at 298.2 K. *J. Mol. Liq.* **180**, 1–6 (2013)
34. Soltanpour, Sh., Jouyban, A.: Solubility of acetaminophen and ibuprofen in binary and ternary mixtures of polyethylene glycol 600, ethanol and water. *Chem. Pharm. Bull.* **58**, 219–224 (2010)
35. Hill, L.W.: *Paint and coating testing manual*. In: Koleske, J.V. (ed.) *Gardner–Sward Handbook*, 14th edn. ASTM, Philadelphia, PA (1995)
36. Amiran, J., Nicolosi, V., Bergin, S.D., Khan, O., Lyons, P.E., Coleman, J.N.: High quality dispersions of functionalized single walled nanotubes at high concentration. *J. Phys. Chem. C* **112**, 3519–3524 (2008)
37. Jouyban, A., Fathi-Azarbayjani, A., Khoubnasabjafari, M., Acree Jr, W.E.: Mathematical representation of the density of liquid mixtures at various temperatures using Jouyban–Acree model. *Indian J. Chem.* **44**, 1553–1560 (2005)
38. Jouyban, A.: *Handbook of Solubility Data for Pharmaceuticals*. CRC Press, Boca Raton (2009)
39. Shayanfar, A., Acree Jr, W.E., Jouyban, A.: Solubility of clonazepam, diazepam, lamotrigine, and phenobarbital in *N*-methyl-2-pyrrolidone + water mixtures at 298.2 K. *J. Chem. Eng. Data* **54**, 2964–2966 (2009)