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Solubility of acetaminophen in the ethanol and glycerol mixtures at different temperatures

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Abstract. Acetaminophen solubility in the glycerol and ethanol mixture was determined by a simple shake-flask technique at different temperatures and fitted to some mathematical models and the models' accuracy was investigated by the computation of the mean relative deviations. The densities of acetaminophen saturated mixtures were also studied by the Jouyban-Acree model. Moreover, the Gibbs and van't Hoff equations were utilized to compute apparent thermodynamic parameters of the acetaminophen dissolving.

***Keywords*:** acetaminophen; solubility; glycerol; ethanol; binary mixture; cosolvency models.

1. Introduction

Acetaminophen (2,2,2-trideuterio-*N*-(4-hydroxyphenyl)acetamide, Fig. 1.) is an antipyretic and analgesic medication which is widely prescribed for alleviating acute and chronic pain. Its safety has been proven in patients who were diagnosed with bronchial asthma and gastric ulcers for which non-steroidal anti-inflammatory drugs are contraindicated [1].

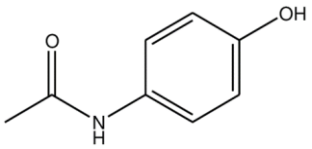

Figure 1. Molecular structure of acetaminophen.

Acetaminophen induces its analgesic effects by turning into *p*-aminophenol and crossing the blood-brain barrier. Therefore, in contrast with what has been assumed for many years, induces analgesia via direct action on the brain [2]. Acetaminophen is commercially available in more than 200 different formulations and over the counter medications either as a single drug or combined with other drugs such as tablets, syrups, suppositories, and injection [3]. Knowledge of solubility value and related physicochemical properties in a wide range of aqueous and non-aqueous solvents is vitally important because it facilitates taking the best decision in drug development and drug purification steps [4]. Moreover, determination of drug solubility in cosolvent blends is of great importance because mixed solvents are widely used in preformulation studies, pharmaceutical dosage forms design and purification techniques [5-7]. This information can be widely referenced by pharmacists associated with the research and development of new products in the pharmaceutical industry [8]. Among various techniques which have been utilized for decades, cosolvency is considered as the frequently used method for solubility investigation of a drug powder in a mixture of solvents or solubility enhancement of a drug by adding a certain proportion of a cosolvent [9].

Until now, the acetaminophen solubility has been investigated in aqueous binary mixtures of ethanol, 2-propanol, 1-propanol, polyethylene glycol 200 (PEG 200), PEG 400, PEG 600, propylene glycol (PG), N-methyl pyrrolidone (NMP), methanol, carbitol, and 1, 4-dioxane, acetonitrile and non-aqueous binary mixtures of NMP + PEG 600, PEG 600 + PG, PEG 200 + ethanol, PEG 400 + ethanol, PEG 600 + ethanol, PG + ethanol and ethyl acetate + ethanol which had been reviewed by our previous works [8, 10]. To the best of our knowledge, there is no report of the solubility profile of acetaminophen in the non-aqueous solvents of ethanol and glycerol.

The aims of this work were: (1) determination of the density and solubility of acetaminophen in ethanol and glycerol at 293.2-313.2 K; (2) data fitting to some mathematical equations; and (3) computation of the apparent thermodynamic factors for acetaminophen dissolving in the ethanol and glycerol mixture.

2. Experimental

2.1. Materials

Acetaminophen (99.90%, Daana Pharmaceutical Company, Tabriz, Iran), glycerol (98.00%, Merck, Germany), ethanol (99.90% Merck, Germany) and

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distilled water (lab made) were used in the current study. Ethanol with a purity of 93.50% (Jahan Alcohol Teb, Iran) was employed for diluting procedure before spectrophotometric measurements.

2.2. Measurement of the acetaminophen solubility

A simple shake-flask technique [11] was used for measuring the solubility behavior of acetaminophen in binary non-aqueous mixtures of ethanol and glycerol. Excess amounts of acetaminophen were dispersed into the glasses containing 10 g of each mentioned mono-solvents or mixed solvents with various mass fractions (w_1 = 0.1-0.9). In the following, it was completely sealed and incubated in an incubator (Kimia Idea Pardaz Azerbaijan, Tabriz, Iran) on a shaker (Behdad, Tehran, Iran) and was shaken at 293.2 to 313.2 K for 72 hours. Then, the prepared solutions were centrifuged, diluted with ethanol: water (30:70 v/v), and absorbance of diluted mixtures was measured at 248 nm using a UV-vis spectrophotometric method (Cecil BioAquarius CE 7250, UK). Concentrations of acetaminophen in mentioned mixtures were computed by a previously drawn calibration plot. The density values of solutions were determined by a 5.0 mL pycnometer with an uncertainty of 0.001 g·cm^{-3}. The given solubility and density data were the mean of three replicated data.

2.3. Data modeling

The solubility data for acetaminophen in ethanol and glycerol were correlated to some linear and non-linear equations including van't Hoff equation (Eq. 1 [12]), the Jouyban-Acree (Eq. 2 [13]), the Jouyban-Acree-van't Hoff (Eq. 3 [13]), and the modified Wilson model (Eq. 4 [14]), which were listed in Eq. 1-4 and their details were given in our previous works [12-14].

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

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

$$lnC_{m,T} = w_1\left(A_1 + \frac{B_1}{T}\right) + w_2\left(A_2 + \frac{B_2}{T}\right) + \frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i \quad (3)$$

$$lnC_m = 1 - \frac{w_1(1+lnC_1)}{w_1 + w_2\lambda_{12}} - \frac{w_2(1+lnC_2)}{w_1\lambda_{21} + w_2} \quad (4)$$

where C is the acetaminophen solubility expressed in molar unit and w is the mass ratio of the solvents in the absence of the solute. Subscriptions T, m, 1 and 2 refer to temperature, solvent mixture and mono-solvents 1 and 2, respectively. A, B, J, λ are the constants of the models.

The obtained solubility data were correlated to these models and the mean relative deviation (*MRD* %) (Eq. 5) for back-calculated values is utilized as a model accuracy parameter.

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

in which N is the data point's number.

2.4. Thermodynamic investigations

To investigate the dissolving procedure of acetaminophen in ethanol and glycerol, the Gibbs and van't Hoff equations are employed. The modified van't Hoff model is [15]:

$$\frac{\partial\, ln\, C}{\partial\left(\frac{1}{T} - \frac{1}{T_{hm}}\right)_p} = -\frac{\Delta H^\circ}{R} \quad (6)$$

where C is the solubility of solute, T is the temperature and R is the ideal gas constant [16]. T_{hm} is the mean harmonic temperature obtained from $T_m = n/\sum_{i=1}^{n}(\frac{1}{T})$ (n is the number of investigated temperatures). The intercept and slope the of ln x *vs* $1/T - 1/T_{hm}$ plot are employed for computation of ΔG^o and ΔH^o, and ΔS^o values are obtained from Gibbs equation.

To compute the relative contributions of entropy (ζ_{TS}) and enthalpy (ζ_H) to ΔG^o of acetaminophen dissolution profile in ethanol and glycerol mixtures, the following equations are used [16]:

$$\zeta_H = \frac{|\Delta H^\circ|}{(|\Delta H^\circ| + |T\Delta S^\circ|)} \quad (7)$$

$$\zeta_{TS} = \frac{|T\Delta S^\circ|}{(|\Delta H^\circ| + |T\Delta S^\circ|)} \quad (8)$$

3. Results and discussions

3.1. Solubility pattern of acetaminophen and mathematical modeling

The solubility values (S, in molar unit) for acetaminophen in ethanol and glycerol mixtures determined at different temperatures (293.2 - 313.2 K) and their standard deviation were given in Table 1.

Results depict that the acetaminophen solubility increased with the rising in both temperature and the mass fraction of ethanol; so that the lowest value in the acetaminophen solubility pattern was in neat glycerol at 293.2 K and the highest one was is in neat ethanol at 313.2 K. The measured data for the acetaminophen in neat glycerol (2.11×10^{-1} mol·L^{-1}) and neat ethanol (1.11 mol·L^{-1}) have a good consistency with reported ones in the literature for ethanol (0.886 mol·L^{-1} [17]) and glycerol (1.28×10^{-1} mol·L^{-1} [18]) and the observed deviation can be ascribed to within-person measurement error or some methodology differences.

Table 1. Experimental molar solubility ($C_{m,T}$ ± standard deviation) for acetaminophen in ethanol and glycerol mixtures.

w_1[a]	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00	1.32 (±0.03) × 10^{-1}	2.11 (±0.03) × 10^{-1}	3.25 (±0.03) × 10^{-1}	4.70 (±0.02) × 10^{-1}	6.17 (±0.04) × 10^{-1}
0.10	3.01 (±0.01) × 10^{-1}	3.50 (±0.04) × 10^{-1}	4.72 (±0.02) × 10^{-1}	5.92 (±0.05) × 10^{-1}	7.29 (±0.03) × 10^{-1}
0.20	4.28 (±0.02) × 10^{-1}	5.13 (±0.07) × 10^{-1}	6.21 (±0.09) × 10^{-1}	7.17 (±0.08) × 10^{-1}	8.27 (±0.05) × 10^{-1}
0.30	5.70 (±0.05) × 10^{-1}	6.31 (±0.08) × 10^{-1}	7.48 (±0.05) × 10^{-1}	8.23 (±0.04) × 10^{-1}	9.28 (±0.05) × 10^{-1}
0.40	6.41 (±0.10) × 10^{-1}	7.15 (±0.06) × 10^{-1}	8.38 (±0.05) × 10^{-1}	9.08 (±0.10) × 10^{-1}	1.01 (±0.09) × 10^{-1}
0.50	7.41 (±0.01) × 10^{-1}	8.03 (±0.07) × 10^{-1}	8.90 (±0.08) × 10^{-1}	9.67 (±0.10) × 10^{-1}	1.09 (±0.10) × 10^{0}

w_1[a]	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.60	7.92 (±0.03) × 10^{-1}	8.81 (±0.02) × 10^{-1}	9.71 (±0.10) × 10^{-1}	1.03 (±0.05) × 10^{0}	1.13 (±0.05) × 10^{0}
0.70	8.81 (±0.09) × 10^{-1}	9.51 (±0.05) × 10^{-1}	1.02 (±0.05) × 10^{0}	1.08 (±0.05) × 10^{0}	1.19 (±0.05) × 10^{0}
0.80	9.20 (±0.05) × 10^{-1}	9.82 (±0.05) × 10^{-1}	1.06 (±0.02) × 10^{0}	1.13 (±0.01) × 10^{0}	1.25 (±0.01) × 10^{0}
0.90	9.47 (±0.08) × 10^{-1}	1.03 (±0.01) × 10^{0}	1.14 (±0.07) × 10^{0}	1.20 (±0.07) × 10^{0}	1.32 (±0.01) × 10^{0}
1.00	9.75 (±0.01) × 10^{-1}	1.11 (±0.01) × 10^{0}	1.19 (±0.10) × 10^{0}	1.23 (±0.01) × 10^{0}	1.38 (±0.06) × 10^{0}

[a] w_1 is mass fraction of ethanol in the ethanol and glycerol mixtures in the absence of acetaminophen

The solubility of acetaminophen was correlated to some equations, *i.e.* the van't Hoff, Jouyban-Acree, the Jouyban-Acree-van't Hoff, the modified Wilson and Yalkowsky [4]. Each model parameter and the back-calculated data *MRDs*% were displayed in Tables 2-5. The mean *MRDs%* for acetaminophen in the studied systems were 11.4% and 12.1% for Jouyban–Acree and Jouyban-Acree-van't Hoff models (Table 2), 1.2 for modified Wilson model (Table 3), 1.4% for the van't Hoff model (Table 4), and 20.9% for Yalkowsky model (Table 5). Jouyban–Acree and Jouyban-Acree-van't Hoff models are two equations that correlate data at various temperatures and solvent mixtures. Whereas the modified Wilson and van't Hoff equations relate the solubility to solvent mass fraction and temperature, respectively. This reason leads to generation of five different trained models for the modified Wilson and eleven different trained models for van't Hoff which are time consuming and problematic for the solubility prediction. However, low *MRD*% values for all mentioned models (except for Yalkowsky) show the high acceptability of studied equations for prediction of the solubility. To investigate the prediction power of the Jouyban–Acree–van't Hoff equation, the minimum data, *i.e.* the experimental solubility of acetaminophen in w_1 = 0.0 and 1.0 at 293.2 and 313.2 K and w_1 = 0.3, 0.5 and 0.7 at 298.2 K, were used to train Eq. 3 and the solubility data in other mass fractions were predicted using the trained model. The *MRD*% values for back-calculated data were 11.4, 3.9, 8.0, 19.4 and 29.3% for 293.2, 298.2, 303.2, 308.2, 313.2 K, respectively with overall *MRD*% of 14.4%.

Table 2. Model parameters for the Jouyban-Acree, and Jouyban-Acree-van't Hoff model for acetaminophen solubility in the ethanol and glycerol mixtures.

	Jouyban-Acree		Jouyban-Acree-van't Hoff	
Ethanol + glycerol	J_0	518.629	A_1	5.146
	J_1	-389.788	B_1	-1510.475
	J_2	0[a]	A_2	22.370
			B_2	-7139.026
			J_0	518.865
			J_1	-389.569
			J_2	0[a]
MRD%	11.4		12.1	

[a] Not statistically significant (*p*-value >0.

Table 3. The model parameters for the modified Wilson and *MRD*% for back-calculated data for acetaminophen in the ethanol and glycerol mixtures.

T (K)	λ_{12}	λ_{21}	*MRD*%
293.2	0.138	5.149	1.5
298.2	0.205	3.331	1.4
303.2	0.216	0.635	1.2
308.2	0.354	2.282	1.3
313.2	0.438	2.285	0.8
Overall			1.2

Table 4. The van't Hoff model parameters and the corresponding *MRD*% for acetaminophen in the ethanol and glycerol mixtures.

w_1	A	B	*MRD*%
0.00	22.370	-7139.026	4.1
0.10	13.105	-4204.091	2.2
0.20	9.522	-3038.29	0.9
0.30	7.214	-2282.076	1.2
0.40	6.789	-2120.533	1.1
0.50	5.628	-1741.132	0.9
0.60	5.242	-1602.740	0.8
0.70	4.385	-1323.184	0.7
0.80	4.595	-1374.291	0.9
0.90	5.111	-1514.136	0.7
1.00	5.146	-1510.475	1.4
Overall			1.4

Table 5. ln x values of acetaminophen obtained by Yalkowsky model in ethanol and glycerol mixtures.

	ln x				
w_1	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00	-2.02	-1.56	-1.12	-0.76	-0.48
0.10	-1.82	-1.39	-0.99	-0.66	-0.4
0.20	-1.62	-1.22	-0.86	-0.56	-0.32
0.30	-1.42	-1.06	-0.73	-0.46	-0.24
0.40	-1.22	-0.89	-0.6	-0.36	-0.16
0.50	-1.02	-0.73	-0.47	-0.26	-0.08
0.60	-0.82	-0.56	-0.34	-0.16	0.01
0.70	-0.62	-0.39	-0.21	-0.06	0.08
0.80	-0.42	-0.23	-0.08	0.04	0.16
0.90	-0.22	-0.06	0.05	0.14	0.24
1.00	-0.02	0.1	0.18	0.23	0.32
MRD%	35.6	26.5	20.3	13.0	8.9
Overall					20.9

In the next step, a trained Jouyban–Acree model reported in the literature for acetaminophen [19] to predict its solubility in these mixed solvents of ethanol and glycerol. This model is:

$$lnC_{m,T} = w_1 lnC_{1,T} + w_2 lnC_{2,T} + 960.300\frac{w_1 w_2}{T} \quad (9)$$

It should be noted that Eq. (9) is a previously reported model and none of the measured solubility value for acetaminophen in this work is employed in the training of this equation, and the only used data are the solubility data in monosolvents. The *MRDs*% for prediction of the solubility values with Eq. 9 at 293.2,

298.2, 303.2, 308.2 and 313.2 K were 13.9%, 19.4%, 28.4%, 40.9% and 47.4% (overall *MRD*% 29.9), respectively (Table 6) which is considered as an acceptable error range for predictive models [4]. The relatively low value of MRD for the model prove its capability for solubility prediction.

3.2. Thermodynamic study of the acetaminophen dissolution process

The apparent thermodynamic properties (*i.e.* ΔH^o, ΔS^o, and ΔG^o) of acetaminophen solubility in the ethanol and glycerol were computed by the Gibbs and van't Hoff equations at T_{hm}. ΔH^o values were positive and the lowest value (11.00 kJ·mol^{-1}) and the highest one (59.35 kJ·mol^{-1}) were observed for acetaminophen saturated solutions with ethanol mass fraction w_1 = 0.7 and w_1 = 0.0, respectively. ΔS^o was positive showing that the acetaminophen dissolution was entropically-favorable in these mixtures. ΔG^o was in the range of -0.41 – 3.0 kJ·mol^{-1} with the lowest amount in neat ethanol which acetaminophen show the maximum solubility in this mixture. ζ_H and ζ_{TS} were also computed and displayed in Table 6. The results show that ΔH^o is the main contributor of $\Delta G°$ in acetaminophen dissolution procedure.

Table 6. Apparent thermodynamic factors for acetaminophen dissolution in the ethanol and glycerol at T_{hm}.

w_1	$\Delta G°$ (kJ·mol^{-1})	$\Delta H°$ (kJ·mol^{-1})	$\Delta S°$ (J·K^{-1}·mol^{-1})	$T\Delta S°$ (kJ·mol^{-1})	ζ_H	ζ_{TS}
0.00	3.00	59.35	185.98	56.35	0.513	0.487
0.10	1.94	34.95	108.96	33.01	0.514	0.486
0.20	1.27	25.26	79.16	23.99	0.513	0.487
0.30	0.80	18.97	59.98	18.17	0.511	0.489
0.40	0.53	17.63	56.44	17.10	0.508	0.492
0.50	0.30	14.48	46.79	14.18	0.505	0.495
0.60	0.12	13.32	43.58	13.21	0.502	0.498
0.70	-0.05	11.00	36.46	11.05	0.499	0.501
0.80	-0.15	11.43	38.20	11.57	0.497	0.503
0.90	-0.29	12.59	42.50	12.88	0.494	0.506
1.00	-0.41	12.56	42.79	12.96	0.492	0.508

The ΔH^o vs. ΔG^o was drawn to investigate the cosolvency mechanism of acetaminophen in non-aqueous binary mixtures of ethanol and glycerol. Fig. 2 elucidates a relatively linear profile with a positive slope demonstrating an enthalpy-driven mechanism for the acetaminophen solubility in the mentioned binary mixtures.

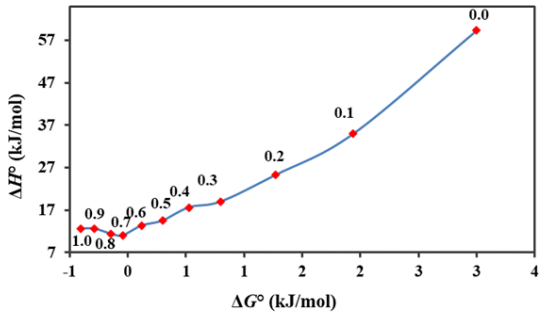

Figure 2. Enthalpy-entropy compensation plot for acetaminophen in the non-aqueous binary mixtures of ethanol and glycerol at 303.0 K. The points represent the mass fraction of ethanol in ethanol and glycerin mixtures in the absence of acetaminophen.

4. Conclusions

The solubility pattern of acetaminophen in ethanol and glycerol mixtures at different temperatures in the range of 293.2 to 313.2 K was determined by a simple shake-flask technique and fitted to some mathematical cosolvency equations. *MRDs*% for used models were reported to be 1.2% – 12.1% which were in the acceptable error range. Moreover, apparent thermodynamic factors demonstrate that acetaminophen dissolution procedure in the studied mixtures was an endothermic, entropically-favor process.

Conflict of interest

The authors declare that there is no conflict of interest regarding this research article.

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References

[1]. E. Roberts, V.D. Nunes, S. Buckner, S. Latchem, M. Constanti, P. Miller, M. Doherty, W. Zhang, F. Birrell, M. Porcheret, K. Dziedzic, Paracetamol: not as safe as we thought? A systematic literature review of observational studies, Annals of the Rheumatic Diseases 75 (2016) 552-559.

[2]. E.D. Högestätt, B.A. Jönsson, A. Ermund, D.A. Andersson, H. Björk, J.P. Alexander, B.F. Cravatt, A.I. Basbaum, P.M. Zygmunt, Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system, Journal of Biological Chemistry 280 (2005) 31405-31412.

[3]. P.J. Amar, E.R. Schiff, Acetaminophen safety and hepatotoxicity – where do we go from here?, Expert Opinion on Drug Safety 6 (2007) 341-355.

[4]. A. Jouyban, Review of the cosolvency models for predicting solubility of drugs in water-cosolvent mixtures, Journal of Pharmacy & Pharmaceutical Sciences 11 (2008) 32-58.
[5]. J.T. Rubino, J. Swarbrick, J. Boylan, Encyclopedia of pharmaceutical technology, Dekker, Inc. 3 (1988) 375-398.
[6]. S.H. Yalkowsky. Solubility and solubilization in aqueous media, American Chemical Society, New York 1999.
[7]. A. Jouyban, WE. Acree Jr. Pharmaceuticals solubility is still nowadays widely studied everywhere, Pharmaceutical Sciences 23 (2017) 1-2.
[8]. A. Romdhani, F. Martínez, O.A. Almanza, A. Jouyban, W.E. Acree Jr., Solubility of acetaminophen in (ethanol+ propylene glycol+ water) mixtures: Measurement, correlation, thermodynamics, and volumetric contribution at saturation, Journal of Molecular Liquids 318 (2020) 114065.
[9]. L. Di, P.V. Fish, T. Mano, Bridging solubility between drug discovery and development, Drug Discovery Today 17 (2012) 486-495.
[10]. A. Hatefi, A. Jouyban, E. Mohammadian, W.E. Acree Jr., E. Rahimpour, Prediction of paracetamol solubility in cosolvency systems at different temperatures, Journal of Molecular Liquids 273 (2019) 282-291.
[11]. A. Jouyban, M.A.A. Fakhree, Experimental, computational methods pertaining to drug solubility, Toxicity and Drug Testing, Intech Co., New York 2012.
[12]. D.J.W. Grant, M. Mehdizadeh, A.L. Chow, J.E. Fairbrother, Non-linear van't Hoff solubility-temperature plots and their pharmaceutical interpretation, International Journal of Pharmaceutics 18 (1984) 25-38.
[13]. A. Jouyban, W.E. Acree Jr., Mathematical derivation of the Jouyban-Acree model to represent solute solubility data in mixed solvents at various temperatures. Journal of Molecular Liquids 256 (2018) 541–547.
[14]. A. Jouyban, The modified Wilson model and predicting drug solubility in water-cosolvent mixtures, Chemical and Pharmaceutical Bulletin 46 (1998) 1058–1061.
[15]. D.J.W. Grant, M. Mehdizadeh, A.L. Chow, J.E. Fairbrother, Non-linear van't Hoff solubility-temperature plots and their pharmaceutical interpretation, International Journal of Pharmaceutics 18 (1984) 25-38.
[16]. G.L. Perlovich, S.V. Kurkov, A. Bauer-Brandl, Thermodynamics of solutions: II. Flurbiprofen and diflunisal as models for studying solvation of drug substances, European Journal of Pharmaceutical Sciences 19 (2003) 423-432.
[17]. J.A. Jiménez, F. Martínez, Thermodynamic magnitudes of mixing and solvation of acetaminophen in ethanol + water cosolvent mixtures, Revista Colombiana de Ciencias Pecuarias 30 (2006) 87-99.
[18]. A. Jouyban, M.A.A. Fakhree, S. Mirzaei, T. Ghafourian, S. Soltanpour, A. Nokhodchi, Solubility prediction of paracetamol in water-glycerol mixtures at 25 and 30 ºC using the Jouyban-Acree model, Asian Journal of Chemistry 21 (2009)7249-7253.
[19]. A. Hatefi, A. Jouyban, E. Mohammadian, W.E. Acree Jr., E. Rahimpour, Prediction of paracetamol solubility in cosolvency systems at different temperatures, Journal of Molecular Liquids 273 (2019) 282-291.

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