International Pharmacy Acta. 2020;3(1):e11
Original Research Article
OPEN ACCESS
ISSN: 2645-3266

Measurement solubility of Acetylsalicylic Acid in water and alcohols

Amir Hosein Ostadhashem, Kiana Peyvandi *

Faculty of Chemical, Petroleum and Gas Engineering, Semnan University, Semnan, Iran.

Article Info:
Received: September 2020
Accepted: December 2020
Published online:
December 2020

Author:
Amir Hosein Ostadhashem
Email:
amirostadhashem@yahoo.com

*** Corresponding Author:**
Kiana Peyvandi
Email:k_peyvandy@semnan.ac.ir

Abstract:

Low aqueous solubility of drugs is one of the problems in pharmaceutical industry and the enhancement of the solubility of these poorly soluble drugs has recently attracted the consideration of researchers. In this way, one of the essential methods to overcome this challenge is to use co-solvents. In this study, a set of experiments was conducted to measure the solubility and density of Acetylsalicylic Acid as a painkiller drug in water, 1-octanol, ethanol, methanol, and ethylene glycol as solvents in the temperature range of 298 to 330 K. Furthermore, the experiments are carried out at 298 K in the binary mixture of solvents to investigate the interaction effect of another solvent or anti-solvent in different percentages of mixtures. The results of this investigation revealed that using binary solution of water and ethanol, as a solvent aid, increased the solubility especially in high percentage of ethanol. Moreover, to indicate the applicability of simple empirical model, the experimental data was used to optimize two adjustable parameters of the selected model. In future research, a successful thermodynamic models will be offered based on gathered data for prediction of solubility in the different temperature with high accuracy.

Keywords: Solubility; Acetylsalicylic Acid; co-solvent; antisolvent; Pharmaceutical Research

Please Cite this article as: Ostadhashem, A.H., Peyvandi, K. Measurement solubility of Acetylsalicylic Acid in water and alcohols. Int. Pharm. Acta. 2020;3(1):e11
DOI: https://doi.org/10.22037/ipa.v3i1.32231

1. Introduction

Understanding drug solubility is a key factor for the modern drug discovery process. Over the years, understanding drug dissolution has been a subject of pharmaceutical research. Despite many mathematical models and well-established experimental methods, it is often not clear for researchers how a drug molecule detaches itself from the solid phase and enters into solution stage. One possible reason is that the dissolution mechanism at a molecular level is difficult to deduce even with highly sophisticated experimental approaches. Pharmaceuticals (Phs) are substances with very different structure especially based on media in the body. The Phs substance that had been studied in this research was Acetylsalicylic Acid (ASA), also known as aspirin, which is a commonly used drug for the treatment of pain and fever due to various causes. Acetylsalicylic acid has both anti-inflammatory and antipyretic effects. This drug also inhibits platelet aggregation and is used for the prevention of blood clots stroke and myocardial infarction [1]. Many researchers have investigated the solubility of the drug and the effect of different parameters such as temperature. For example, according to Aneta Pobudkowska et al. the solubility of aminophylline, indomethacin, and perphenazine in solvents has been predicted by thermodynamic models [2]. Gustavo D. Maia has measured the solubility of the Acetylsalicylic Acid in acetone, propylene glycol, 2-propanol and then the effect of anti-solvent on these solvents has been investigated [3]. The solubility of other antibiotics, such as Amoxicillin were measured in isopropanol, water, ethylene glycol and N,N-Dimethylformamide. In a study by Wanxin Li et al., The effect of solubility was increased using these solvents [4]. For another drug called Risperidone, the solubility of this drug has been measured with water as a solvent. The data obtained from this study were measured for drug + solvent and the solubility of solute could be increased by the addition of co-solvent. This experimental data is also predicted by the Apelbelat equation [5]. To measure the solubility of 4-Nitrobenzaldehyde by the isothermal saturation method at atmospheric pressure and temperature range between 273 to 313 K, Chao Cheng et al. Performed experiments to achieve the goal of optimizing the purification process and other parameters [6].

Jackson A. Jiménez and Fleming Martínez evaluated the solubility of Acetaminophen in aqueous solution of propylene glycol as co-solvent. The results have been used to estimate the enthalpy and entropy of solution by Van't Hoff and Gibbs equations. These facts can be explained in terms of water-structure loss, and a diminishing in the energy required for cavity formation in the solvent [7]. This research team was able to calculate the van't Hoff and Gibbs equations, the thermodynamic function free energy, the entropy, and the enthalpy of Ibuprofen in the mixture of water and ethanol solvents. They concluded that the solubility of this drug in pure ethanol was much greater than water [8]. Samir D. Roy and Gordon L. Fillnn used organic solvents to calculate the solubility and other parameters such as heats of fusion, and the melting point of Morphine and Fentanyl [9]. In another research related to drug at 35 ° C, the effect of high and low pH media has been investigated on solubility and pKa parameters and then a brief description of the parameter dependency in different media has been reported [10]. In another experiment by Chao Cheng et al., the solubility of Dehydroepiandrosterone in solvents such as cyclohexane, acetone, methanol, etc. was measured and compared the amount of solubility for each solvent and concluded that when the temperature was increased, the solubility of the solute would be increased. They also calculated and compared this parameter using the modified Apelblat equation, NRTL model, Wilson model, and λh equation [11]. The main purpose of this experiment is to extend the database on experimental solubility of Acetylsalicylic acid and solubility measuring of drug in different solvents has been conducted. In this study, we used five solvents: water, 1-octanol, ethanol, methanol, and ethylene glycol. Solubility in these solvents were measured in a wide temperature range between 298 up to 330 K.

2. Materials & Methods

2.1. Materials

Temad Co. Ltd, Iran, supplied a pale white crystalline powder of Acetylsalicylic Acid. The solvents, including; Ethanol,1-octanol, and water, were all prepared respectively by Iran, Golriz Co. Ltd, Iran, 1-octanol was purchased from Merck Co, and water that we used to all experiment was deionized water. The details of the materials are given in Table 1 and Table 2.

Table 1. Details of solvents.

Materials	Source	Molar mass g.mol^{-1}	Density (293 K)/ KJ. mol^{-1}	Mass Fraction purity
water	Semnan University	18.0152	0.9880	-
Ethanol	Golriz Co.	46.07	0.8057	≥ 0.96
1-Octanol	Merck Co.	130.23	0.8240	≥ 0.99
Methanol	Merck Co.	32.04	0.7918	≥ 0.99
Ethylene Glycol	Merck Co.	62.07	1.1132	≥ 0.99

2.2. Apparatus

The experimental apparatus designed to measure the solubility of drug is displayed in Fig 1. The equipment used in this study consists of a three-neck round-bottom flask that is inserted into the water bath to provide desired temperature uniformity during the experiments. A mercury thermometer is used to measure the bath temperature and another temperature sensor is employed to monitor the soluble temperature. Furthermore, the heater Stirrer is used as heat generator with ability of mixing the drug solution by magnetic stirrer. [12,13,14].

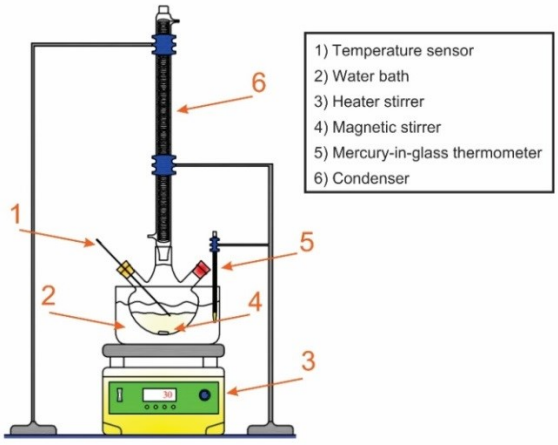
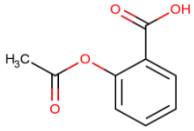


Figure 1. The experimental apparatus.

Table 2. Name abbreviation, molecular formula, structure, and molar mass of Acetylsalicylic Acid.

Name of drug	Molecular formula	Structural formula	Molar mass (g.mol$^{-1)}$	Source	Mass Fraction purity
Acetylsalicylic Acid	$C_9H_8O_4$		180.158	Temad Co.	≥ 0.9967

2.3. Solubility determination

To measure the solubility of Acetylsalicylic Acid in the desired solvents, the water bath and flask containing 100 cc of the solvent which was firstly reached to equilibrium temperature. The temperature inside the flask is measured by a temperature sensor and the bath temperature is controlled by a mercury thermometer. After inserting drug to the cell and placing the magnetic stirrer, the solution has been mixed at 1800 rpm. The drug has been added and shaken at a predetermined time until the solution reach to saturation point which is confirmed by observing of un-dissolved solid at the bottom of the solution. After that the sample is removed to measure the amount of residual sediment. In fact, after confirmation of saturation point, the weight of solid particles precipitated in the mixture can be measured by filtering the slurry solution at the same temperature. By separation of precipitated solid from sample, the solubility of the drug can be measured at the desired temperature and the residual solution should be analyzed to measure the viscosity and density of the solution. These data are required for thermodynamic modeling of solubility in the future research. Furthermore, measurements are taken in the binary mixtures of solvent. According to mentioned method, by addition of drug into solvent mixture, the solubility can be measured at ambient temperature. Note that to achieve equilibrium solubility, before adding the solute, a centrifuge with speed of 3500 rpm was applied to make homogeneous mixture and finally, the solubility of the drug at 298.15 K was investigated [12- 14]. The mole fraction solubility (x^e) of Acetylsalicylic Acid in a pure solvent and binary mixture of solvents can be obtained by Eq. (1) and Eq. (2) respectively [15- 21]

$$x^e = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

$$x^e = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (2)$$

where m_1 and M_1 denote the mass and molar mass of Acetylsalicylic Acid, respectively; and (m_2, m_3) and (M_2, M_3), the mass and molar mass of solvents.

2.4. Experimental Modeling

Measurements show that Acetylsalicylic Acid is very insoluble in water. The results for the solubility of the solvent as water, ethanol, 1-octanol, Methanol, and Ethylene Glycol are presented in Table 3.

Table 3

Experimental solubility for {Acetylsalicylic Acid (1) + solvent (2)} binary system in mole fraction, $\mathbf{x_1}$ vs. equilibrium temperature *T* at saturated solution at *p* = 101.3 kPa (1bar) and density $\boldsymbol{\rho_1}$

x_1	T/(K)	ρ_1	x_1	T/(K)	ρ_1
Water					
0.00042	298.15	0.99795	0.00082	318.15	0.99113
0.00048	303.15	0.99686	0.00093	323.15	0.98754
0.00056	308.15	0.99523	0.00120	328.15	0.98650
0.00068	313.15	0.99345	0.00130	333.15	0.98431
Ethanol					
0.0486	298.15	0.86894	0.0ʏ08	313.15	0.88890
0.0542	303.15	0.87177	0.0862	318.15	0.89051
0.0634	308.15	0.88064	0.0938	323.15	0.89087
1-Octanol					
0.0257	298.15	0.83297	0.0498	318.15	0.83547
0.0320	303.15	0.83401	0.0613	323.15	0.83619
0.0342	308.15	0.83445	0.0716	328.15	0.83790
0.0445	313.15	0.83501	0.0858	333.15	0.84418
Methanol					
0.0694	298.15	0.89312	0.1044	313.15	0.91632
0.0772	303.15	0.90231	0.1208	318.15	0.94227
0.0889	308.15	0.90832			
Ethylene Glycol					
0.0150	298.15	1.11439	0.0301	313.15	1.11191
0.0212	303.15	1.11346	0.0382	318.15	1.10822
0.0264	308.15	1.11215	0.0466	323.15	1.10763

Measures were taken to investigate the impact of cosolvent into the solubility point and the anti-solvent effect of other solvent are shown in Table 4, Table 5, Table 6, and Table 7.

According to the results mentioned in the tables and presented empirical models, it was found that the model capable to predict the extent of drug solubility the extent of solubility of Aspirin in the specific solvents can be presented as Equation 3. This model can be used to correlate experimental data with the least error. This experimental model has two adjustable parameters, which are given in Table 8. This experimental model is expressed as the following Eq. (3).

$$Ln\ x = a + b\sqrt{T} \quad (3)$$

which x as the solubility parameter, temperature T, a, and b are adjustable parameters.

Table 4

Experimental solubility for {Acetylsalicylic Acid (1) + Ethanol & Water (2)} in mole fraction, $\mathbf{x_1}$ vs. equilibrium temperature T=298.15 K at saturated solution at p = 101.3 kPa (1bar) and calculated density $\boldsymbol{\rho_1}$.

Component	x_1	ρ_1	Component	x_1	ρ_1
Water + Ethanol					
W (90%) + Eth (10%)	0.00064	0.98394	W (40%) + Eth (60%)	0.0018	0.91234
W (80%) + Eth (20%)	0.00092	0.97319	W (30%) + Eth (70%)	0.0019	0.89408
W (70%) + Eth (30%)	0.0011	0.95843	W (20%) + Eth (80%)	0.0031	0.86705
W (60%) + Eth (40%)	0.0011	0.94367	W (10%) + Eth (90%)	0.0044	0.84794
W (50%) + Eth (50%)	0.0015	0.93205			

Table 5

Experimental solubility for {Acetylsalicylic Acid (1) + Ethanol & 1-Octanol (2)} in mole fraction, $\mathbf{x_1}$ vs. equilibrium temperature T=298.15 K at saturated solution at p = 101.3 kPa (1bar) and calculated density $\boldsymbol{\rho_1}$.

Component	x_1	ρ_1	Component	x_1	ρ_1
1-Octanol + Ethanol					
1-Oct (90%) + Eth (10%)	0.0058	0.82247	1-Oct (30%) + Eth (70%)	0.0079	0.81401
1-Oct (70%) + Eth (30%)	0.0066	0.82079	1-Oct (10%) + Eth (90%)	0.0080	0.81192
1-Oct (50%) + Eth (50%)	0.0074	0.81874			

Table 6

Experimental solubility for {Acetylsalicylic Acid (1) + Methanol & Water (2)} in mole fraction, $\mathbf{x_1}$ vs. equilibrium temperature T=298.15 K at saturated solution at p = 101.3 kPa (1bar) and calculated density $\boldsymbol{\rho_1}$.

Component	x_1	ρ_1	Component	x_1	ρ_1
Water + Methanol					
W (90%) + Meth (10%)	0.0017	0.98156	W (40%) + Meth (60%)	0.0112	0.91181
W (80%) + Meth (20%)	0.0023	0.96555	W (30%) + Meth (70%)	0.0132	0.90306
W (70%) + Meth (30%)	0.0043	0.94365	W (20%) + Meth (80%)	0.0164	0.87888
W (50%) + Meth (50%)	0.0102	0.92938	W (10%) + Meth (90%)	0.0271	0.86572

Table 7
Experimental solubility for {Acetylsalicylic Acid (1) + Ethanol & Methanol (2)} in mole fraction, $\mathbf{x_1}$ vs. equilibrium temperature T=298.15 K at saturated solution at p = 101.3 kPa (1bar) and calculated density $\boldsymbol{\rho_1}$.

Component	x_1	ρ_1	Component	x_1	ρ_1
Methanol + Ethanol					
Meth (90%) + Eth (10%)	0.0510	0.88416	Meth (40%) + Eth (60%)	0.0372	0.84805
Meth (80%) + Eth (20%)	0.0561	0.88216	Meth (30%) + Eth (70%)	0.0342	0.84041
Meth (70%) + Eth (30%)	0.0434	0.87445	Meth (20%) + Eth (80%)	0.0241	0.83121
Meth (60%) + Eth (40%)	0.0394	0.86239	Meth (10%) + Eth (90%)	0.0171	0.82846
Meth (50%) + Eth (50%)	0.0393	0.85137			

Table 8
Adjustable parameters for experimental modeling.

Component	a	b	R^2
Water	-10.104463	0.44841384	0.98894143
Ethanol	-4.3848435	0.31560590	0.99131709
Methanol	-4.3848435	0.31560590	0.99131709
1-Octanol	-5.7825980	0.44988337	0.99257114
Ethylene Glycol	-6.7243700	0.51633574	0.99330288

Parameters a and b are the adjustable parameters of experimental modeling obtained from the laboratory data of Table 3.

3. Results and discussion

According to measurements, the solubility of Acetylsalicylic Acid in water was very low. Furthermore, the results showed that the solubility of the drug in ethanol was higher than octanol Fig. 2. Also the experiment was done to measure the solubility of Acetylsalicylic Acid in the combined solvents and the solubility measurement was performed for the binary solvents Fig. 4-9. The results obtained from the experimental data of combined solvents have shown that by adding ethanol to water as a solvent aid, the solubility of Acetylsalicylic Acid has been increased, and this value increased in higher percentages than ethanol. From another point of view, it can be concluded that if the main solvent was ethanol, by increasing the amount of water, it reduces the solubility of the drug, so water can be introduced as an anti-solvent. The results obtained from experimental data are shown in Fig. 2 and Fig. 3. According to the experiments performed to investigate the effect of drug solubility in water and 1-octanol solvents, we encountered a lack of homogeneity of solvents. As a result, the solubility of Acetylsalicylic Acid in these solvents has not been investigated.

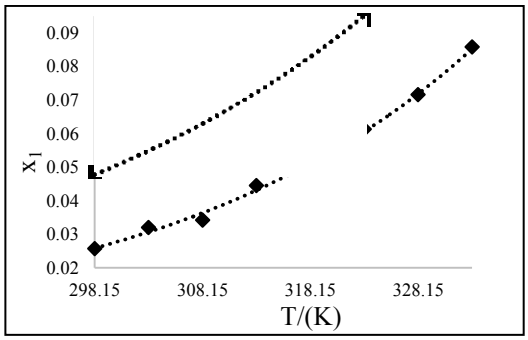


Figure 2. Experimental solubility for {Acetylsalicylic Acid (1) + solvent (2)} binary system: (■) Ethanol; (◆)1-octanol

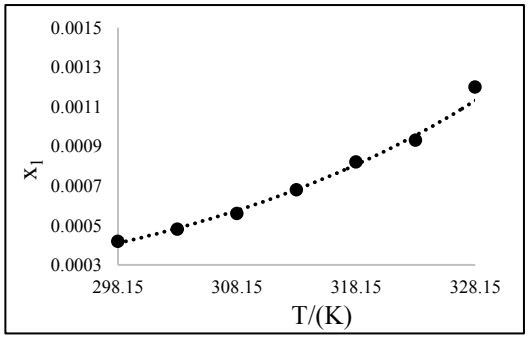


Figure 3. Experimental solubility for {Acetylsalicylic Acid (1) + solvent (2)} binary system: (•) water

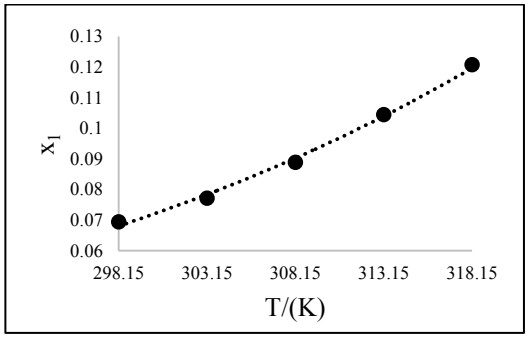


Figure 4. Experimental solubility for {Acetylsalicylic Acid (1) + solvent (2)} binary system: (•) Methanol

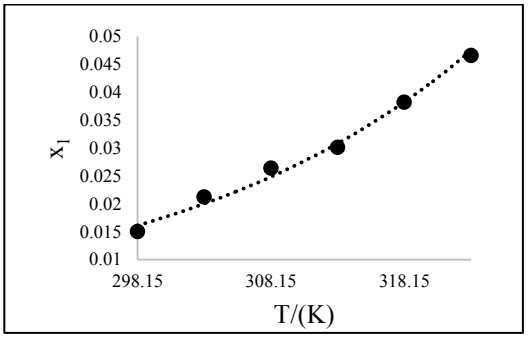


Figure 5. Experimental solubility for {Acetylsalicylic Acid (1) + solvent (2)} binary system: (•) Ethylene Glycol

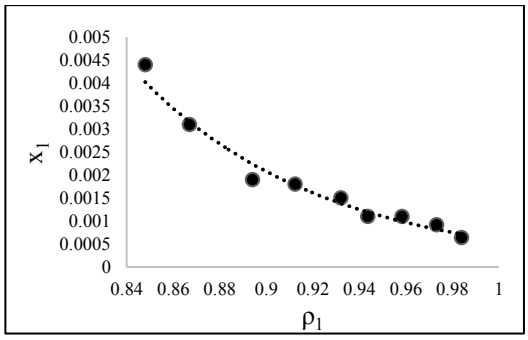


Figure 6. Experimental solubility for {Acetylsalicylic Acid (1) + Ethanol & Water (2)} in mole fraction, $\mathbf{x_1}$ vs. density $\boldsymbol{\rho_1}$ at T=298.15 K

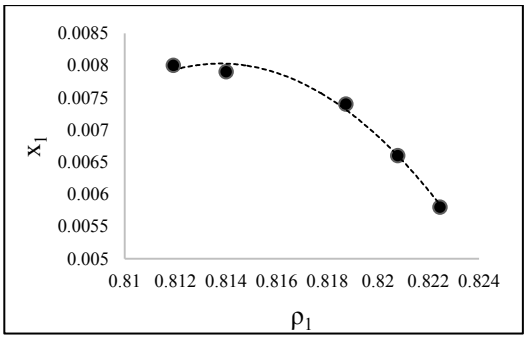


Figure 7. Experimental solubility for {Acetylsalicylic Acid (1) + Ethanol & 1-octanol (2)} in mole fraction, $\mathbf{x_1}$ vs. density $\boldsymbol{\rho_1}$ at T=298.15 K

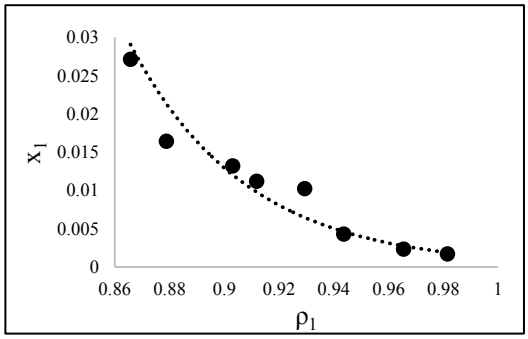


Figure 8. Experimental solubility for {Acetylsalicylic Acid (1) + Methanol & Water (2)} in mole fraction,x_1 vs. density ρ_1 at T=298.15 K

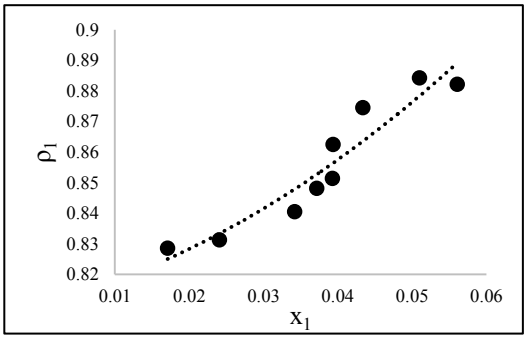


Figure 9. Experimental solubility for {Acetylsalicylic Acid (1) + Methanol & Ethanol (2)} in mole fraction,x_1 vs. density ρ_1 at T=298.15 K

4. Conclusions

Poor drug solubility is one of the main problems in drug discovery. According to this fact that water is the main component of human body, it is selected as a common solvent to investigate drug solubility. Also many parameters which are effective on solubility are investigated. The results of this work showed that the solubility of aspirin increases with increasing temperature while the density of solution decreases. Specific co solvent can be used to increase the solubility. Although water can be expressed as a special solvent to check the solubility of drug, it can be introduced as a very good anti-solvent. To prove this fact, the second stage of the experiment was carried out by mixture of solvents in the different percentage of water. As these experiments continued and ethanol was added as the main solvent, and 10% of water was added as the solvent, the solubility of aspirin decreased. Also the results could be regressed by very simple empirical model with high accuracy.

References

1. https://www.drugbank.ca/drugs/DB00945.
2. Aneta Pobudkowska, Urszula Domanska, Barbara A. Jurkowski, Katarzyna Dymczuk, Fluid Phase Equilibria 392 (2015) 56–64.
3. Gustavo D. Maia, Marco Giulietti, J. Chem. Eng. Data 2008, 53, 256–258.
4. Wanxin Li, Ali Farajtabar, Rong Xing, Yiting Zhu, Hongkun Zhao, J. Chem. Thermodynamics 142 (2020) 106010.
5. Faiyaz Shakeel, Fars K. Alanazi, Ibrahim A. Alsarra, NazrulHaq, Journal of Molecular Liquids 191 (2014) 68–72.
6. Chao Cheng, Yang Cong, Cunbin Du, Jian Wang, Hongkun Zhao, J. Chem. Thermodynamics 104 (2017) 50–60.
7. Jackson A. Jiménez and Fleming Martínez, J. Braz. Chem. Soc., Vol. 17, No. 1, 125-134, 2006.
8. Juliana MANRIQUE and Fleming MARTÍNEZ, J. Pharm. 26 (3): 344-354 (2007).
9. Samir D.Roy and Gordon L.Flynn, Pharmaceutical Research, Vol.5, No.9, 1988.
10. Samir D.Roy and Gordon L.Flynn, Pharmaceutical Research, Vol.6, No.2, 1989.
11. Chao Cheng, Yang Cong, Long Meng, Jian wang, GanBing Yao, Hongkun Zhao, J. Chem. Thermodynamics 97 (2016) 158–166.
12. Juliana MANRIQUE and Fleming MARTÍNEZ, J. Pharm. 26 (3): 344-354 (2007).
13. Xinbao Li, Chao Cheng, Yang Cong, Cunbin Du, Hongkun Zhao, J. Chem. Thermodynamics 105 (2017) 362–374.
14. G.B. Yao, Z.X. Xia, Z.H. Li, C. Shao, Fluid Phase Equilibria. 417 (2016) 242–247.
15. G.B. Yao, Z.H. Li, Z.X. Xia, Q.C. Yao, J. Chem. Thermodyn. 103 (2016) 218–227.
16. C. Held, L.F. Cameretti, G. Sadowski, Ind. Eng. Chem. Res. 50 (2011) 131–141.
17. M. Sajadian, K. Peyvandi, Fluid Phase Equilibria 425 (2016) 152–157.
18. Florey, K. Acetylsalicylic Acid. Analytical Profiles of Drug Substances 8; Academic Press Inc.: London, 1979.
19. Hamer, W. E.; Philips, G. V. Aspirin Crystallization, United States Patent Office 2,890,240, Monsanto Chemicals Limited: London, 1959.
20. Prausnitz, J. M.; Lichtenthaler, R. N.; Gomes de Azevedo, E. Molecular Thermodynamics of Fluid-Phase Equilibria, 2nd ed.; Prentice-Hall Inc.: Englewood, USA, 1986.
21. Smith, J. M.; Van Ness, H. C. Introdução à Termodinâmica da Engenharia Química. Terceira Edição, trad. Macedo, H., Ed.; Guanabara Koogan: Rio de Janeiro, Brazil, 1980.