Solubility Prediction of Paracetamol in N-Methyl-2-pyrrolidone + Ethanol + Water Mixtures at 25 °C

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Abstract: The solubility of paracetamol in N-Methyl-2-pyrrolidone (NMP) + ethanol and NMP + ethanol + water solvent mixtures at 25 °C was determined using the shake flask method. The generated data extended the solubility database of pharmaceuticals and also was used to assess the solubility prediction capability of the Jouyban-Acree model in NMP + ethanol + water mixtures. The accuracy of the predicted solubilities was evaluated by the mean percentage deviation (MPD) between the predicted and experimental solubilities. The MPD of the Jouyban-Acree model for predicting the solubility of paracetamol in NMP + ethanol + water mixtures at 25 °C was 14.6 %.

Keywords: Paracetamol, binary solvents, ternary solvents, solubility prediction, pharmaceutical cosolvents.

INTRODUCTION

Solubility of drugs could be increased using cosolvency, complexation, addition of surface active and hydrotrop agents. Among these methods, cosolvency is more reliable and feasible method for industrial applications. In addition to the experimental efforts to determine the solubility of drugs in solvent + cosolvent mixtures, a number of cosolvency models were proposed to calculate the solubility values. The proposed models include the simplest log-linear model of Yalkowsky [1] and the most accurate model developed in our research group [2, 3]. The Jouyban-Acree model was used to calculate many physico-chemical properties in mixed solvent systems including the electrophoretic mobility of analytes in mixed solvent electrolyte systems [4], the instability rate constants in binary solvent systems [5], the acid dissociation constants in water-organic solvent mixtures at a fixed [6] and various temperatures [7], the capacity factor of analytes in HPLC [8], the dielectric constant [9], surface tension [10], viscosity [11], density [12], solvatochromic parameter [13], refractive index [14] and ultrasound velocity [15] in the solvent mixtures. The trained model provided reasonable predictions for the solubility of drugs in the aqueous mixtures of dioxane [16], ethanol [17], propylene glycol [18], polyethylene glycol (PEG) 400 [19], glycerol [20], and N-methyl-2-pyrrolidone (NMP) [21] mixtures and also for the solubility of drugs in non-aqueous solvent mixtures of ethanol + ethyl acetate [22] and ethanol + propylene glycol [23].

Solubility of paracetamol was reported in a number of solvent mixtures compiled in a database [24]. In recent works, the solubility of paracetamol in binary and ternary solvent mixtures of PEG 600 + ethanol + water [25] and PEG 600 + NMP + water [21] at 25 °C was reported. In this work, the solubility of paracetamol in NMP + ethanol and NMP + ethanol + water mixtures at 25 °C is determined. The generated solubility data is used to check the prediction capability of previously trained models to provide a predictive tool using minimum number of experimental efforts which is highly in demand in the pharmaceutical industries.

EXPERIMENTAL

Chemicals

Paracetamol was purchased from Zahravi pharmaceutical company (Tabriz, Iran), NMP (0.99 m/m) and ethanol (0.99 m/m) were purchased from

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Scharlau Chemie (Spain). Ethanol with purity of 96 % v/v (or 0.935 m/m) was supplied by Jahan Teb Alcohol (Arak, Iran) and used for dilution of paracetamol solutions prior to spectrophotometric analyses of the samples. Double distilled water was used throughout this study.

Solubility Measurements

Various solubility mesaurement methods could be found from the literature. For a comprehensive review of these methods, readers could be refered to a recent book chapter [26]. In this work the shake flask method has been employed. Briefly, the sealed flasks containing an excess amount of paracetamol powder in the mono-solvents and/or solvent mixtures were mixed using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system at 25 with the uncertainty of 0.2 ^{o}C (Kimia Idea Pardaz Azarbayjan (KIPA) Co., Tabriz, Iran) for 3 days to reach the equilibrium. The dissolution profile of the drug was monitored with time. When saturated solution was attained, the solid phase was removed by centrifugation followed by filtration (Durapore® membrane filters, type HV, 0.45 µm, Millipore, MA). No significant adsorption of the drug was found on the filtration membranes. The clear solutions were diluted with ethanol (96 %) + water (1:1) and assayed by a double beam spectrophotometer (Shimadzo, Japan) at 245 nm. All the experimental results were averages of at least triplicates.

Computational Methods

The Jouyban-Acree model was proposed to calculate the solubility of drugs in solvent mixtures and provided good correlation capabilities [24, 27]. Its basic form to compute the solubility of a drug in a binary solvent mixture at various temperatures is:

$$\log S_{m,T} = \varphi_1 \log S_{1,T} + \varphi_2 \log S_{2,T} + \frac{\varphi_1\varphi_2}{T}\sum_{i=0}^{2} A_i\left(\varphi_1 - \varphi_2\right)^i \quad (1)$$

where $S_{m,T}$ is the solubility of drug in solvent mixture at temperature T (K), φ_1 and φ_2 the volume fractions of solvents 1 and 2 in the absence of the solute, $S_{1,T}$ and $S_{2,T}$ the solubilities at temperature T in neat solvents 1 and 2, respectively, and A_i the solvent-solvent and solute-solvent interaction terms [3].

The model could be extended to Eq. (2) for computing drug solubility in ternary solvent mixtures at various temperatures [28] as:

$$\log S_{m,T} = \varphi_1 \log S_{1,T} + \varphi_2 \log S_{2,T} + \varphi_3 \log S_{3,T} + \frac{\varphi_1\varphi_2}{T}\sum_{i=0}^{2} A_i\left(\varphi_1 - \varphi_2\right)^i + \frac{\varphi_1\varphi_3}{T}\sum_{i=0}^{2} A_i^{'}\left(\varphi_1 - \varphi_3\right)^i + \frac{\varphi_2\varphi_3}{T}\sum_{i=0}^{2} A_i^{''}\left(\varphi_2 - \varphi_3\right)^i \quad (2)$$

where φ_3 and $S_{3,T}$ are the volume fraction of the third solvent in the solvent mixture and drug's solubility in the neat solvent 3, respectively, $A_i^{'}$ and $A_i^{''}$ are the interaction parameters of the sub-binary systems.

The experimental solubility of paracetamol in NMP + ethanol mixtures at 25 °C were employed to compute the constants of the model. The trained versions of the Jouyban-Acree model for calculating the solubility of drugs in ethanol + water [17] and NMP + water [21] mixtures at various temperatures taken from previous works, were used for solubility prediction of paracetamol in NMP + ethanol + water mixtures at 25 ºC. The required data for predicting the solubility of paracetamol at various temperatures are the solubility in the mono-solvents.

The mean percentage deviations (MPD) were used to check the accuracy of the predicted data and was calculated using Eq. (3).

$$MPD = \frac{100}{N}\sum \frac{|Calculated - Observed|}{Observed} \quad (3)$$

in which N is the number of experimental solubility data. All computations were carried out using SPSS software.

RESULTS AND DISCUSSIONS

Figure **1** shows the molar solubility of paracetamol in NMP + ethanol mixtures at 25 °C. The paracetamol solubility in NMP + ethanol mixtures was increased with the increasing NMP concentration and the maximum solubility of paracetamol is observed in 90 % of NMP. The generated solubility data in NMP + ethanol mixtures is mathematically represented by Eq. (1) and the obtained model is:

$$\log S_{m,T} = \varphi_1 \log S_{1,T} + \varphi_2 \log S_{2,T} + 256.99\left(\frac{\varphi_1\varphi_2}{T}\right) - 143.95\left(\frac{\varphi_1\varphi_2\left(\varphi_1 - \varphi_2\right)}{T}\right) + 168.86\left(\frac{\varphi_1\varphi_2\left(\varphi_1 - \varphi_2\right)^2}{T}\right) \quad (4)$$

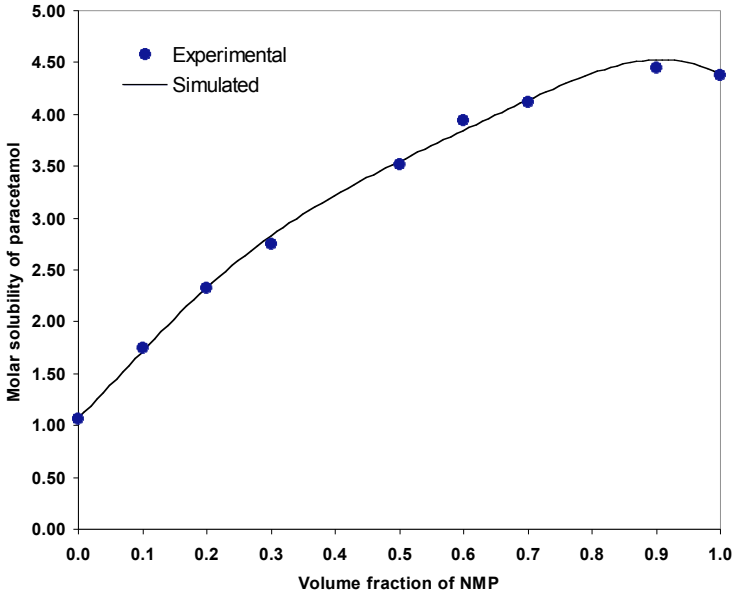

Figure 1: The experimental molar solubility of paracetamol in N-Methyl-2-pyrrolidone + ethanol and the simulated Curve by Eq. (4) employing the experimental solubilities in N-Methyl-2-pyrrolidone and ethanol.

which back-calculates the solubility data with the correlation coefficient of 0.999 and the MPD of 14.9 %. Figure **1** also depicts the reproduced solubility curve of paracetamol in NMP + ethanol at 25 °C by using Eq. (4) employing the experimental solubilities in neat NMP and ethanol as input values. Excellent agreement could be observed for simulated and experimental solubilities as shown in Figure **1**.

Table **1** lists the numerical values of molar solubility of paracetamol in ternary solvent mixtures of NMP + ethanol + water mixtures at 25 ºC. The solubility of paracetamol is increased by addition of NMP and ethanol to water and the maximum solubility (4.76 M) among measured solubility data points is observed in the volume fractions of 0.57, 0.07 and 0.36 of NMP, ethanol and water. The maximum solubility of 4.76 M was not obtained using binary aqueous mixtures of NMP and/or ethanol at their higher concentrations in the binary solvent mixtures. This is an important point from liquid drug formulation viewpoint where we should keep the concentration of the added cosolvents to water at the lowest possible concentrations to minimize their side effects.

To predict the solubility of paracetamol in NMP + ethanol + water mixtures using Eq. (2), the model constants for ethanol + water and NMP + water are also required. These constants were provided using earlier trained models for solubility of drugs in ethanol + water [17] and NMP + water [21] mixtures as:

$$\log S_{m,T} = \varphi_1 \log S_{1,T} + \varphi_2 \log S_{2,T} + 724.21\left(\frac{\varphi_1\varphi_2}{T}\right) + 485.17\left(\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)}{T}\right) + 194.41\left(\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)^2}{T}\right) \quad (5)$$

Table 1: The Experimental Molar Solubility of Paracetamol in Various Volume Fractions of N-Methyl-2-pyrrolidone (φ_1) + Ethanol (φ_2) + Water (φ_3) Mixtures at 25 °C

φ_1	φ_2	φ_3	$S_{m,T}$
0.06	0.39	0.56	1.4971
0.17	0.28	0.56	1.6280
0.11	0.33	0.56	1.6620
0.23	0.09	0.68	2.1195
0.07	0.57	0.36	2.3054
0.27	0.05	0.68	2.3588
0.14	0.50	0.36	2.7581
0.21	0.43	0.36	3.0426
0.28	0.17	0.56	3.1235
0.22	0.22	0.56	3.1364
0.36	0.29	0.36	3.1639
0.29	0.36	0.36	3.1930
0.33	0.11	0.56	3.4759
0.50	0.14	0.36	3.8995
0.43	0.21	0.36	3.9027
0.57	0.07	0.36	4.7612

and

$$\log S_{m,T} = \varphi_1 \log S_{1,T} + \varphi_2 \log S_{2,T} + 668.67\left(\frac{\varphi_1\varphi_2}{T}\right) - 678.59\left(\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)}{T}\right) + 1220.50\left(\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)^2}{T}\right) \quad (6)$$

By combining Eqs. (4)-(6):

$$\log S_{m,T} = \varphi_1 \log S_{1,T} + \varphi_2 \log S_{2,T} + \varphi_3 \log S_{3,T} + 256.99\left(\frac{\varphi_1\varphi_2}{T}\right) - 143.95\left(\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)}{T}\right) + 168.86\left(\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)^2}{T}\right) + 668.67\left(\frac{\varphi_1\varphi_3}{T}\right) - 678.59\left(\frac{\varphi_1\varphi_3(\varphi_1-\varphi_3)}{T}\right) + 1220.50\left(\frac{\varphi_1\varphi_3(\varphi_1-\varphi_3)^2}{T}\right) + 724.21\left(\frac{\varphi_2\varphi_3}{T}\right) + 485.17\left(\frac{\varphi_2\varphi_3(\varphi_2-\varphi_3)}{T}\right) + 194.41\left(\frac{\varphi_1\varphi_2(\varphi_2-\varphi_3)^2}{T}\right) \quad (7)$$

Equation (7) predicts the solubility of paracetamol in NMP + ethanol + water mixtures at various temperatures using experimental solubility data of paracetamol in the mono-solvents at temperatures of interest. The obtained MPD was 14.6 % which is an acceptable in the pharmaceutical area. Figure **2** shows the simulated solubility data of paracetamol in NMP + ethanol + water mixtures at 25 ºC using the model developed based on the solubility data in the corresponding binary solvents i.e. Eq. (7). As expected the lowest solubility was obtained in aqueous solutions and the maximum solubility (~ 5.65 M) is expected in NMP fractions of 0.80-0.90 and ethanol fractions of ~ 0.03. The solubility of 5.65 M is even more than the measured maximum solubility of 4.76 M in the ternary solvents. This means that using predictive equations like Eq. (7), it is possible to find out the best solvent composition for solubilizing the maximum amount of paracetamol using the minimum experimental efforts.

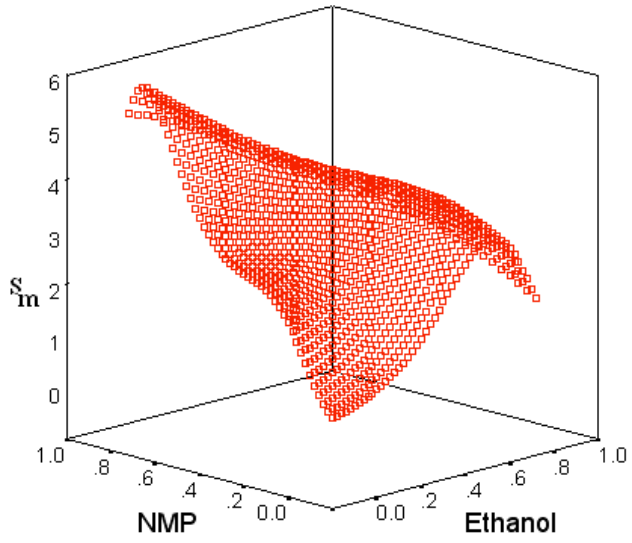

Figure 2: The predicted molar solubility of paracetamol in N-Methyl-2-pyrrolidone + ethanol + water mixtures at 25 °C by using Eq. (7).

In conclusion, it has been shown that a trained version of the Jouyban-Acree model is able to predict the solubility of paracetamol in binary and ternary solvents and the prediction error lies within an acceptable range and these trained models could be recommended to the pharmaceutical industry for practical applications where solubilization or crystallization of paracetamol is required.

REFERENCES

[1] Yalkowsky SH, Ed., Solubilization of drugs by cosolvents. New York, Marcel Dekker, 1981.

[2] Acree Jr WE. 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 1992; 198: 71-9. http://dx.doi.org/10.1016/0040-6031(92)85059-5

[3] Jouyban-Gharamaleki A, Acree Jr WE. Comparison of models for describing multiple peaks in solubility profiles. Int J Pharm 1998; 167: 177-82. http://dx.doi.org/10.1016/S0378-5173(98)00073-8

[4] Jouyban-Gharamaleki A, Khaledi MG, Clark BJ. Calculation of electrophoretic mobilities in water-organic modifier mixtures in capillary electrophoresis. J Chromatogr A 2000; 868: 277-84. http://dx.doi.org/10.1016/S0021-9673(99)01258-3

[5] Jouyban A, Chan HK, Barzegar-Jalali M, Acree Jr WE. A model to represent solvent effects on chemical stability of solutes in mixed solvent systems. Int J Pharm 2002; 243 167-72. http://dx.doi.org/10.1016/S0378-5173(02)00276-4

[6] Jouyban A, Chan HK, Clark BJ, Acree Jr WE. Mathematical representation of apparent acid dissociation constants in aqueous-organic solvent mixtures. Int J Pharm 2002; 246: 135-42. http://dx.doi.org/10.1016/S0378-5173(02)00355-1

[7] Jouyban A, Soltani S, Chan HK, Acree Jr WE. Modeling acid dissociation constant of analytes in binary solvents at various temperatures using Jouyban-Acree model. Thermochim Acta 2005; 428: 119-23. http://dx.doi.org/10.1016/j.tca.2004.11.002

[8] Jouyban A, Rashidi MR, Vaez-Gharamaleki Z, Matin AA, Djozan Dj. Mathematical representation of analyte's capacity factor in binary solvent mobile phases using Jouyban-Acree model. Pharmazie 2005; 60: 827-9.

[9] Jouyban A, Soltanpour Sh, Chan HK. A simple relationship between dielectric constant of mixed solvents with solvent composition and temperature. Int J Pharm 2004; 269: 353-60. http://dx.doi.org/10.1016/j.ijpharm.2003.09.010

[10] Jouyban A, Fathi-Azarbayjani A, Acree Jr WE. Surface tension calculation of mixed solvents with respect to solvent

composition and temperature by using Jouyban-Acree model. Chem Pharm Bull 2004; 52: 1219-22. http://dx.doi.org/10.1248/cpb.52.1219

[11] Jouyban A, Khoubnasabjafari M, Vaez-Gharamaleki Z, Fekari Z, Acree Jr WE. Calculation of the viscosity of binary liquids at various temperatures using Jouyban-Acree model. Chem Pharm Bull 2005; 53: 519-23. http://dx.doi.org/10.1248/cpb.53.519

[12] Jouyban A, Fathi-Azarbayjani A, Khoubnasabjafari M, Acree Jr WE. Mathematical representation of the density of liquid mixtures at various temperatures using Jouyban-Acree model. Indian J Chem A 2005; 44: 1553-560.

[13] Jouyban A, Khoubnasabjafari M, Acree Jr WE. Modeling the solvatochromic parameter (E_T^N) of mixed solvents with respect to solvent composition and temperature using Jouyban-Acree model. Daru 2006; 14: 22-5.

[14] Jouyban A, Soltani S, Khoubnasabjafari M, Acree Jr WE. Refractive index correlation of solvent mixtures at various temperatures. Asian J Chem 2006; 18: 2037-40.

[15] Hasan M, Shirude DF, Hiray AP, Sawant AB, Kadam UB. Densities, viscosities and ultrasonic velocities of binary mixtures of methylbenzene with hexan-2-ol, heptan-2-ol and octan-2-ol at T = 298.15 and 308.15 K. Fluid Phase Equilib 2006; 252: 88-95. http://dx.doi.org/10.1016/j.fluid.2007.01.001

[16] Jouyban A. In silico prediction of drug solubility in water-dioxane mixtures using Jouyban-Acree model. Pharmazie 2007; 62: 46-50.

[17] Jouyban A, Acree Jr WE. In silico prediction of drug solubility in water-ethanol mixtures using Jouyban-Acree model. J Pharm Pharmaceut Sci 2006; 9: 262-9.

[18] Jouyban A. Prediction of drug solubility in water-propylene glycol mixtures using Jouyban-Acree model. Pharmazie 2007; 62: 365-7.

[19] Jouyban A. Solubility prediction of drugs in water-PEG 400 mixtures. Chem Pharm Bull 2006; 54: 1561-6. http://dx.doi.org/10.1248/cpb.54.1561

[20] Jouyban A, Fakhree MAA, Mirzaei Sh, Ghafourian T, Soltanpour Sh, Nokhodchi A. Solubility prediction of paracetamol in water-glycerol mixtures at 25 and 30 °C using Jouyban-Acree model. Asian J Chem 2009; 21: 7249-53.

[21] Soltanpour Sh, Jouyban A. Solubility of acetaminophen and ibuprofen in polyethylene glycol 600, N-methyl pyrrolidone and water mixtures. J Solution Chem 2011; 40: 2032-45. http://dx.doi.org/10.1007/s10953-011-9767-2

[22] Jouyban A, Acree Jr WE. Prediction of drug solubility in ethanol-ethyl acetate mixtures at various temperatures using the Jouyban-Acree model. J Drug Del Sci Technol 2007; 17: 159-60.

[23] Jouyban A, Khoubnasabjafari M, Martinez F. A model to predict the solubility of drugs in ethanol + propylene glycol mixtures at various temperatures. Submitted.

[24] Jouyban A. Handbook of Solubility Data for Pharmaceuticals. CRC Press, Boca Raton, 2010.

[25] Soltanpour Sh, Jouyban A. Solubility of acetaminophen and ibuprofen in binary and ternary mixtures of polyethylene glycol 600, ethanol and water. Chem Pharm Bull 2010; 58: 219-24. http://dx.doi.org/10.1248/cpb.58.219

[26] Jouyban A, Fakhree MAA. Experimental and computational methods pertaining to drug solubility. In: Acree Jr WE. Editor. Toxicity and Drug Testing. InTech Co., New York, 2012.

[27] Jouyban-Gharamaleki A, Valaee L, Barzegar-Jalali M, Clark BJ, Acree Jr WE. Comparison of various cosolvency models for calculating solute solubility in water-cosolvent mixtures. Int J Pharm 1999; 177: 93-101. http://dx.doi.org/10.1016/S0378-5173(98)00333-0

[28] Jouyban-Gharamaleki A, Clark BJ, Acree Jr WE. Models to predict solubility in ternary solvents based on sub-binary experimental data. Chem Pharm Bull 2000, 48: 1866-71. http://dx.doi.org/10.1248/cpb.48.1866

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