Iranian Journal of Pharmaceutical Sciences
2023: 19 (2): 156- 165
https://journals.sbmu.ac.ir/IJPS

Original Article

Solubility Measurement and Thermodynamic Study of Clotrimazole in Aqueous Mixtures of *N*-Methyl-2-Pyrrolidone at Various Temperatures

Homa Rezaei[a,b], Hongkun Zhao[c], Elaheh Rahimpour[b,d,*] , Abolghasem Jouyban[b,e]

[a] *Student Research Committee, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.* [b]*Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.* [c]*College of Chemistry and Chemical Engineering, YangZhou University, YangZhou, Jiangsu, Republic of China.* [d]*Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.* [e]*Pharmaceutical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

Abstract

Clotrimazole is a broad-spectrum antifungal drug within the imidazole group that can potentially disrupt fungal cell ergosterol synthesis. It is a lipophilic molecule with a slow dissolution rate in water and poor aqueous solubility. Many efforts have been made in the literature to enhance clotrimazole's solubility. Herein, with the aim of solubility enhancement, the solubility profile of clotrimazole in the aqueous binary mixtures of *N*-methyl-2-pyrrolidone at temperatures ranging from 293.2 to 313.2 K was investigated. The experimental solubility values were enhanced by increasing cosolvent composition and temperature. Furthermore, four mathematical cosolvency models were applied to correlate the solid-liquid equilibrium data, and the model accuracy results were shown as the mean relative deviation. Additionally, density values of saturated clotrimazole solution in the studied binary system were determined and reported. Gibbs and van't Hoff equations were also employed to compute dissolution thermodynamic parameters at T_{hm}=303 K.

Keywords: Clotrimazole; Binary mixtures; Thermodynamic parameters; Solubility; Mathematical modeling; Cosolvency.

1. Introduction

Clotrimazole (CTZ) [1-[(2-chlorophenyl) (diphenyl)methyl]-1H-imidazole, **Figure 1** is known as a broad-spectrum antifungal drug within the imidazole group with the potential to disrupt fungal cell ergosterol synthesis. Its efficacy has been proven against several fungal strains, such as *Torulopsis glabrate* and *Candida topicalis*, and in a nutshell, against human infections caused by pathogenic dermatophytes and yeasts. Furthermore, it is used for prophylaxis and treatment, particularly

Corresponding Author: Elaheh Rahimpour. Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran. E-mail: rahimpour_e@yahoo.com
Cite this article as: Rezaei H, Zhao H, Rahimpour E, Jouyban A, *Solubility Measurement and Thermodynamic Study of Clotrimazole in Aqueous Mixtures of N-Methyl-2-Pyrrolidone at Various Temperatures*, Iran. J. Pharm. Sci., 2023, 19 (2): 156- 165.
DOI: https://doi.org/ 10.22037/ijps.v19i2.42241

after transplantation [1-4]. There is also promising research on using CTZ against tineapedis, malaria, Chagas disease, sickle cell anemia, and cancer [5-10]. CTZ is a crystalline powder and a lipophilic molecule (log $K_{O/W}$= 4.1) with a slow dissolution rate in water and poor aqueous solubility of 0.49 $\mu g.mL^{-1}$ at 25 °C [11, 12], resulting in low solubility in the biological fluids. It leads to attainable efficient drug concentration impairment and unsatisfactory bioavailability. In the literature, many efforts have been taken to enhance CTZ's solubility through suspension with hydroxyl propyl methyl cellulose and nano-sphere [13], micro-capsulation [14], solid dispersion technique using mannitol as a carrier [15], using liposome [16] or cyclodextrin inclusion complex [12, 17- 20], self-nano emulsifying drug delivery systems [21], surfactants [22- 24], nano-emulsion [25], micro-emulsion [26, 27], amorphous drug formulations [28], film formation [29] and cosolvency [30-32]. Since for *in vitro* availability, the water solubility of drugs was found to be of utmost importance and influential factor affecting the release rate and extent [33] and according to the need of the pharmaceutical market to develop novel formulations and/or upgrade previous formulations, efforts to increase the CTZ' aqueous solubility to achieve more favorable results are ongoing. For pharmaceutical specialists, solubilization of poorly-water soluble drugs is a challenge in formulation design and development and screening studies for new pharmaceuticals [34]. Among these techniques, cosolvency is considered one of the most convenient and popular strategies to enhance the apparent solubility of chemicals in the pharmaceutical industry [35].

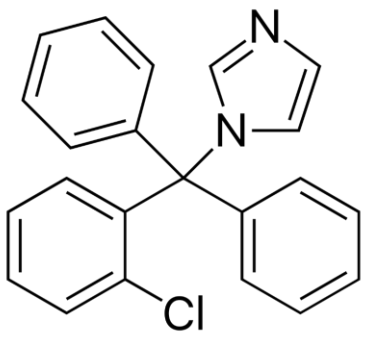

Figure 1. Chemical structure of CTZ.

In this work to be presented here, *N*-methyl-2-pyrrolidone (NMP) was used as a cosolvent to improve the aqueous solubility of CTZ. NMP is a remarkable solvent in the crystallization, purification, and extraction of drugs and is a commonly used cosolvent in the pharmaceutical industry that represents strong solubilization power [36]. Nevertheless, in the previous literature, there is no report on using NMP as a cosolvent to enhance the aqueous solubility of CTZ. Apart from experimental determinations of drug solubility in water-cosolvent systems, many computational models have been introduced to describe drug solubility in mixed solvents. These mathematical models enable researchers to predict the solubility of drugs in cosolvency systems and avoid a laborious, time and cost-consuming procedure leading to some limitations during the drug discovery and development procedure [37]. Briefly, the aims of the present study are to 1) investigate the effect of NMP as a pharmaceutically accepted cosolvent on the aqueous solubility of CTZ; 2) fit the recorded solubility data with the developed cosolvency models; 3) compute the thermodynamic parameters for CTZ dissolution and 4) measure density values of saturated CTZ solutions and

represent the experimental data with Jouyban-Acree model.

2. Materials and Methods

2.1. Materials

CTZ (99.3%) was from Behnavazan Pharmaceutical Co. (Tehran, Iran). NMP (99.5%, Scharlau Chemie, Spain), deionized water (Shahid Ghazi Pharmaceutical Co., Tabriz, Iran), and ethanol (93.5%, Jahan Alcohol Teb, Arak, Iran) were used as materials.

2.2. Quantification of CTZ

Estimation of CTZ was made at λmax of 260 nm by UV-Vis spectrophotometry method employing a UV-Vis spectrophotometer (Cecil BioAquarius CE 7250, UK). CTZ content was estimated using a calibration curve constructed between 5×10^{-4} to 2×10^{-3} mol·L^{-1} and depicted the regression equation of $A = 741.4\,C + 0.0265$ with $R^2 = 0.9941$.

2.3. Solubility studies of CTZ

Deionized water and NMP were mixed by weight and poured into volumetric flasks to form mixtures containing NMP as a cosolvent with mass fractions of 0.0-1.0. Excess amount of CTZ was added directly into the mono- and mixed-solvents and after tight sealing, they were placed on a shaker (Behdad, Tehran, Iran) that was located in the incubator (Kimia Idea Pardaz Azerbaijan, Tabriz, Iran) at temperatures ranged from 293.2 to 313.2 K. After 48 hours of shaking, aliquots were withdrawn, centrifuged and diluted with 30:70 v/v ethanol: water. These samples were analyzed using a UV-Vis spectrophotometer (Cecil BioAquarius CE 7250, UK) at 260 nm wavelength. Then, the drug content in each sample was measured using the obtained calibration curve.

2.4. Computational Models

Four different computational models, including the Jouyban-Acree, Jouyban-Acree-van't Hoff, Yalkowsky, and van't Hoff models, were applied to fit CTZ experimental solubility values. In the following, model parameters and *MRD%* of each model will be presented in detail.

van't Hoff equation

As a linear model which relates solubility values to temperature, the van't Hoff model is presented as [38]:

$$ln\,x = A + \frac{B}{T} \quad (1)$$

A and B are defined as the model's parameters.

Yalkowsky model

Yalkowsky's model depicts a straightforward relationship between a drug's solubility in several solvent mixtures and its solubility in mono-solvents [39].

$$\ln x = w_1 \ln x_1 + w_2 \ln x_2 \quad (2)$$

In this equation, x_1 and x_2 display the drug's solubility in mono-solvents 1 and 2 in mole fraction, while w_1 and w_2 denote the mass fraction of mono-solvents 1 and 2 when the solute is not present.

Jouyban-Acree model

Jouyban-Acree model not only has the potential to reflect the effect of temperature on solubility

but also the outcome of various components of the binary mixed solution can be reflected by this model [40].

$$ln\, x_{m,T} = w_1 . ln\, x_{1,T} + w_2 . ln\, x_{2,T} + \frac{w_1 . w_2}{T} \sum_{i=0}^{2} J_i . (w_1 - w_2)^i \quad (3)$$

here, J_i and T are model parameters and temperature, respectively, and $x_{m,T}$, $x_{1,T}$ and $x_{2,T}$ are the drug's mole fraction solubilities in mixed solvents and mono-solvents at temperatures of T.

Jouyban-Acree-van't Hoff

As an accurate model resulting from the combination of Jouyban-Acree and van't Hoff models, Jouyban-Acree-van't Hoff model predicts/correlates drug solubility data in binary mixed solvents and is expressed as follows [41]:

$$ln\, x_{m,T} = w_1 (A_1 + \frac{B_1}{T}) + w_2 (A_2 + \frac{B_2}{T}) + \frac{w_1 . w_2}{T} \sum_{i=0}^{2} J_i . (w_1 - w_2)^i \quad (4)$$

All letters here are defined as the same as formulas (1) and (3).

2.5. Thermodynamic study

Studying the thermodynamic profile of drugs provides a wealth of critical information for drug design and development studies [42], and thermodynamic parameters, including $\Delta H°$, $\Delta S°$, and $\Delta G°$, are considered key elements in this aspect. The modified van't Hoff equation is applied for thermodynamic parameters studies in the study ahead. This equation can be written as:

$$\frac{\partial \ln x}{\partial \left(\frac{1}{T} - \frac{1}{T_m}\right)_p} = -\frac{\Delta H^\circ}{R} \quad (5)$$

x, T, R, and T_{hm} are mole fraction solubility of CTZ in solvent mixtures, temperature, ideal gas constant ($J \cdot mol^{-1} \cdot K^{-1}$), and mean harmonic temperature, respectively [43]. $\Delta H°$ and $\Delta G°$ for the dissolution process of CTZ in binary mixtures of NMP and water are obtained by calculating the intercept and slope of the equation, while $\Delta S°$ values for the studied system are generated by applying the Gibbs equation.

The relative contributions of entropy (ζ_{TS}) and enthalpy (ζ_H) towards $\Delta G°$ of the studied dissolution procedure are obtained using the following equations [44]:

$$\zeta_H = \frac{|\Delta H^\circ|}{(|\Delta H^\circ| + |T\Delta S^\circ|)} \quad (6)$$

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

3. Results and Discussion

The experimental solubility values of CTZ in binary mixtures of NMP and water in mole fraction at temperatures ranging from 293.2 to 313.2 K were listed in **Table 1** and illustrated in **Figure 2**.

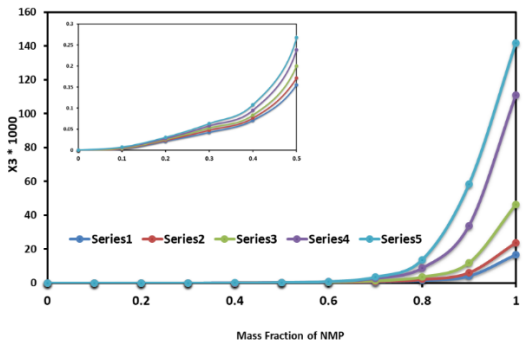

Figure 2. Experimental mole fraction solubility profile of CTZ in binary aqueous mixtures of NMP at different temperatures.

Experimental results of CTZ in the mentioned binary system indicate that solubility depended on solvent composition and temperature. The solubility of CTZ in a given temperature increased with the rise in the cosolvent mass ratio, and the curve witnessed an increase in solubility values as temperature increased. **Table 2** also displays the density values of saturated CTZ solutions measured using a pycnometer with the uncertainty of 0.001 g·cm^{-3}. Over the temperature ranged from 293.2 to 313.2 K, the maximum amount of CTZ solubility in mole fraction was obtained in neat NMP at 313.2 K (1.42×10^{-1}), whereas the lowest one was determined in neat deionized water at 293.2 K (2.42×10^{-8}).

Table 1: Experimental mole fraction solubility ($x_{m,T}$) values as the mean of three experiments (± standard deviation) measured for CTZ in the aqueous binary mixtures of NMP at different temperatures.

w_1[a]	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00 [b]	2.42 (±0.03) × 10^{-8}	2.92 (±0.25) × 10^{-8}	3.38 (±0.72) × 10^{-8}	3.77 (±0.45) × 10^{-8}	4.15 (±0.58) × 10^{-8}
0.10	2.58 (±0.20) × 10^{-6}	3.45 (±0.13) × 10^{-6}	4.45 (±0.36) × 10^{-6}	6.25 (±0.33) × 10^{-6}	7.30 (±0.13) × 10^{-6}
0.20	2.13 (±0.07) × 10^{-5}	2.32 (±0.10) × 10^{-5}	2.51 (±0.02) × 10^{-5}	2.74 (±0.05) × 10^{-5}	3.06 (±0.30) × 10^{-5}
0.30	4.24 (±0.15) × 10^{-5}	4.75 (±0.31) × 10^{-5}	5.25 (±0.10) × 10^{-5}	5.78 (±0.08) × 10^{-5}	6.33 (±0.33) × 10^{-5}
0.40	7.09 (±0.40) × 10^{-5}	7.63 (±0.23) × 10^{-5}	8.37 (±0.12) × 10^{-5}	9.52 (±0.50) × 10^{-5}	1.08 (±0.41) × 10^{-4}
0.50	1.55 (±0.81) × 10^{-4}	1.72 (±0.09) × 10^{-4}	2.00 (±0.13) × 10^{-4}	2.39 (±0.07) × 10^{-4}	2.68 (±0.24) × 10^{-4}
0.60	3.69 (±0.15) × 10^{-4}	3.99 (±0.21) × 10^{-4}	5.62 (±0.33) × 10^{-4}	7.62 (±0.40) × 10^{-4}	8.93 (±0.11) × 10^{-4}
0.70	6.61 (±0.29) × 10^{-4}	8.53 (±0.77) × 10^{-4}	1.33 (±0.04) × 10^{-3}	2.74 (±0.27) × 10^{-3}	3.51 (±0.42) × 10^{-3}
0.80	1.51 (±0.35) × 10^{-3}	2.08 (±0.12) × 10^{-3}	3.59 (±0.24) × 10^{-3}	8.83 (±0.17) × 10^{-3}	1.38 (±0.50) × 10^{-2}
0.90	4.08 (±0.31) × 10^{-3}	6.10 (±0.32) × 10^{-3}	1.20 (±0.07) × 10^{-2}	3.39 (±0.03) × 10^{-2}	5.85 (±0.08) × 10^{-2}
1.00	1.67 (±0.00) × 10^{-2}	2.38 (±0.16) × 10^{-2}	4.65 (±0.08) × 10^{-2}	1.11 (±0.00) × 10^{-1}	1.42 (±0.13) × 10^{-1}

[a] w_1 is the mass fraction of NMP in the NMP and water mixtures in the absence of CTZ. [b] Values are taken from reference (31).

Table 2: Measured density (g.cm^{-3}) of CTZ saturated solutions in the aqueous binary mixtures of NMP at different temperatures.

w_1	**293.2 K**	**298.2 K**	**303.2 K**	**308.2 K**	**313.2 K**
0.00	1.000 ± 0.001	1.000 ± 0.001	1.000 ± 0.001	0.990 ± 0.001	1.000 ± 0.001
0.10	1.003 ±0.001	1.001 ± 0.001	1.001 ± 0.001	1.000 ± 0.001	0.998 ± 0.001
0.20	1.011 ± 0.001	1.010 ± 0.001	1.008 ± 0.001	1.007 ± 0.001	1.005 ± 0.001
0.30	1.023 ± 0.001	1.022 ± 0.001	1.019 ± 0.001	1.016 ± 0.001	1.015 ± 0.001
0.40	1.029 ± 0.001	1.029 ± 0.001	1.029 ± 0.001	1.028 ± 0.001	1.028 ± 0.001
0.50	1.040 ± 0.001	1.039 ± 0.001	1.039 ± 0.001	1.038 ± 0.001	1.037 ± 0.001
0.60	1.049 ± 0.001	1.047 ± 0.001	1.047 ± 0.001	1.045 ± 0.001	1.044 ± 0.001
0.70	1.054 ± 0.001	1.052 ± 0.001	1.052 ± 0.001	1.051 ± 0.001	1.050 ± 0.001
0.80	1.055 ± 0.001	1.055 ± 0.001	1.055 ± 0.001	1.055 ± 0.001	1.055 ± 0.001
0.90	1.061 ± 0.001	1.061 ± 0.001	1.061 ± 0.001	1.060± 0.001	1.060 ± 0.001
1.00	1.067 ± 0.001	1.066 ± 0.001	1.065± 0.001	1.065 ± 0.001	1.064 ± 0.001

Some mathematical cosolvency equations like the Jouyban-Acree, Jouyban-Acree-van't Hoff, Yalkowsky, and van't Hoff models were employed to correlate experimental data for CTZ solubility. Each cosolvency model's constants, along with *MRDs%* of back-calculated data, were elucidated in **Tables 3-5**. The Jouyban-Acree and Jouyban-Acree-van't Hoff models were capable of predicting CTZ solubility at different solvent compositions as well as different temperatures, while van't Hoff model predicts CTZ solubility at different temperatures but at the same solvent mixture. These differences in the model's abilities make the $MRD_S\%$ calculated by each model to be different.

Table 3: The van't Hoff model parameters and the corresponding *MRD*% for CTZ in the aqueous binary mixtures of NMP.

w_1	*A*	*B*	*MRD*%
0.00	-9.130	-2456.515	2.1
0.10	3.905	-4915.318	2.4
0.20	-5.207	-1629.302970	0.9
0.30	-3.788	-1840.202	0.3
0.40	-2.913	-1954.483	1.9
0.50	0.091	-2604.618	1.7
0.60	7.111	-4422.372	5.1
0.70	20.770	-8267.515	10.3
0.80	30.070	-10767.595	13.0
0.90	38.346	-1954.547	14.4
1.00	32.212	-10673.454	12.7
Overall			5.9

Table 4: ln *x* values of CTZ obtained by the Yalkowsky model in the aqueous binary mixtures of NMP at different temperatures.

	ln *x*				
w_1	**293.2 K**	**298.2 K**	**303.2 K**	**308.2 K**	**313.2 K**
0.00	-17.54	-17.35	-17.20	-17.09	-17.00
0.10	-16.19	-15.99	-15.79	-15.60	-15.49
0.20	-14.85	-14.63	-14.38	-14.11	-13.99
0.30	-13.50	-13.27	-12.96	-12.63	-12.48
0.40	-12.16	-11.90	-11.55	-11.14	-10.98
0.50	-10.81	-10.54	-10.14	-9.65	-9.48
0.60	-9.47	-9.18	-8.72	-8.16	-7.97
0.70	-8.12	-7.82	-7.31	-6.67	-6.47
0.80	-6.78	-6.46	-5.90	-5.18	-4.96
0.90	-5.43	-5.10	-4.48	-3.69	-3.46
1.00	-4.09	-3.74	-3.07	-2.20	-1.95
MRD%	57.9	56.3	55.3	56.8	59.7
Overall *MRD*%			**57.2**		

Table 5: Parameters calculated for the Jouyban-Acree and Jouyban-Acree-van't Hoff model for CTZ solubility in the aqueous binary mixtures of NMP.

		Jouyban-Acree		Jouyban-Acree-van't Hoff
NMP + water	J_0	1881.570	A_1	32.212
	J_1	-5169.335	B_1	-10673.454
	J_2	6192.678	A_2	-9.130
			B_2	-2456.515
			J_0	1881.989
			J_1	-5169.326
			J_2	6193.725
MRD%		24.8		25.9

[a] Not statistically significant (*p*-value >0.05)

3.1. Thermodynamic analysis

Table 6 represents thermodynamic parameters (*i.e.,* $\Delta H°$, $\Delta S°$, and $\Delta G°$) of the CTZ dissolution process in the binary mixtures of NMP and water computed based on Gibbs and van't Hoff equations at T_{hm}=303.0 K. The values of $\Delta H°$ and $\Delta G°$ were positive in all solvent compositions, demonstrating that the CTZ dissolution process in the mentioned binary system was endothermic. When a solid drug is added to a solvent, the drug molecules are attracted to the solvent molecules.

However, the drug molecules are also attracted to each other through intermolecular forces such as hydrogen bonding, van der Waals forces, and dipole-dipole interactions. The solvent molecules must overcome the intermolecular forces holding the drug together to dissolve the drug in a solvent. It requires energy, called the lattice enthalpy or lattice energy, to break the bonds between the drug molecules. In addition to breaking the bonds between the drug molecules, the solvent molecules must also overcome the intermolecular forces holding the solvent molecules together. It requires energy as well, called the solvation energy or hydration energy. The solvent molecules surround the drug molecules and form new bonds, which release energy. The overall energy change involved in dissolving a drug in a solvent is the sum of the lattice enthalpy and the solvation energy. Whether the enthalpy of solution is positive or negative depends on the relative magnitudes of these two energies. In the case of a drug that is highly soluble in a solvent, the solvation energy is much greater than the lattice enthalpy, resulting in a negative enthalpy of the solution. However, if the drug is not very soluble in the solvent, the lattice enthalpy is larger than the solvation energy, resulting in a positive enthalpy of the solution. The maximum values of $\Delta H°$ and $\Delta G°$ were reported in w_1=0.9 (107.32 kJ·mol^{-1}) and w_1=0.0 (43.42 kJ·mol^{-1}), respectively, and the lowest values for these two parameters were observed in w_1=0.2 (13.55 kJ·mol^{-1}) and w_1=1.0 (7.59 kJ·mol^{-1}), respectively.

Table 6: Apparent thermodynamic parameters for dissolution behavior of CTZ in the aqueous binary mixtures of NMP 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	43.42	20.42	-75.90	-23.00	0.470	0.530
0.10	31.03	40.87	32.47	9.84	0.806	0.194
0.20	26.67	13.55	-43.30	-13.12	0.508	0.492
0.30	24.84	15.30	-31.5	-9.54	0.616	0.384
0.40	23.59	16.25	-24.22	-7.34	0.689	0.311
0.50	21.43	21.65	0.76	0.23	0.990	0.010
0.60	18.85	36.77	59.12	17.91	0.672	0.328
0.70	16.41	68.74	172.68	52.32	0.568	0.432
0.80	13.77	89.53	250.01	75.75	0.542	0.458
0.90	10.70	107.32	318.86	96.61	0.526	0.474
1.00	7.59	88.74	267.80	81.14	0.522	0.478

$\Delta S°$ values were also positive except for w_1= 0, 0.2, 0.3, and 0.4, with the highest value seen in w_1=0.9 (318.86 J· $mol^{-1}·K^{-1}$) and the lowest one obtained in w_1=0.0 (-75.90 J· $mol^{-1}·K^{-1}$).

Furthermore, a $\Delta H°$ vs. $\Delta G°$ plot was applied to study the cosolvency mechanism of CTZ in the aqueous binary mixtures of NMP. A non-linear trend with two negative slopes in mass fractions in the range of $0.2 \leq w_1 \leq 0.9$ and $0.0 \leq w_1 \leq 0.1$ demonstrates an entropy-driven mechanism, and two positive slopes in the ranges of $0.9 \leq w_1 \leq 1.0$ and $0.1 \leq w_1 \leq 0.2$ depicting an enthalpy-driven mechanism were shown in **Figure 3**.

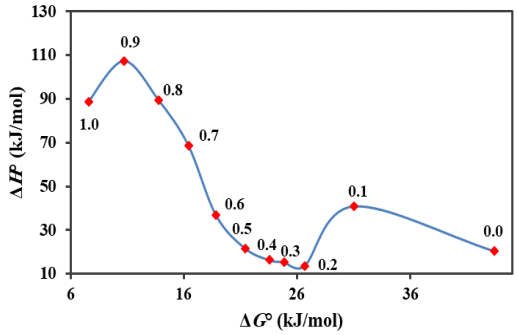

Figure 3. Enthalpy- entropy compensation curve for CTZ solubility in aqueous binary mixtures of NMP. Points depict the mass fraction of NMP as a cosolvent.

4. Conclusion

In the study, the CTZ solubility in the binary mixtures of NMP and water at five different temperatures from 293.2 to 313.2 K with five-degree intervals was carried out using a simple shake-flask method. The solubility curve reaches its maximum point when the mass fraction of NMP is reported as w_1=1 at 313.2 K. The obtained experimental data were fitted to some linear cosolvency equations, and most of the studied models could predict desired solubility values with an acceptable error, demonstrating the desired accuracy of these models for predicting solubility values.

Acknowledgments

The Student Research Committee, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran, supported this work under grant number 66892.

Conflict of interest

The authors declare to have no conflict of interest.

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