Solubility Prediction of Etodolac, Lamotrigine, Diazepam and Clonazepamin in Cosolvent Mixtures Using UNIQUAC Model

***Hashemi, Seyed Hossein*•**
Faculty of Chemical Engineering, University of Mohaghegh Ardabili, Ardabil, I.R. IRAN

Khodadadi, Abdolhamid
Nanotechnology Engineering, Sapienza University of Rome, Rome, ITALY

Dinmohammad, Mahmoud*+
Research Institute of Petroleum Industry, Tehran, I.R. IRAN

ABSTRACT: *Etodolac, Lamotrigine, diazepam, and clonazepamine are four important drugs in the pharmaceutical industry that optimizing the solvent concentration in the least amount can reduce the cost and toxicity of these drugs. Due to the lack of thermodynamic modeling based on the activity coefficient equation in previous studies for solubility of Etodolac, Lamotrigine, diazepam, and clonazepamine in aqueous solution, in this study, based on thermodynamic equations and UNIQUAC model, their solubility is optimized with the presence of water and ethanol. Based on the objective function defined, the error rate of the model optimization value was acceptable for each system. The results of this study can be used to better understand the intermolecular reaction of Etodolac, Lamotrigine diazepam, and clonazepamine in the presence of ethanol and water solvents. Also, the importance of the optimization results of this study in order to design a computer program to predict the solubility of these drugs is significant.*

KEYWORDS: *Solubility; UNIQUAC model; Lamotrigine, Diazepam; Clonazepamine; Etodolac.*

INTRODUCTION

In the field of pharmaceutical sciences, proper solvents for drugs (for extraction, separation, and many other things) are very important. In other words, changes in the solubility of drugs due to ionic liquids affect the production of many different drugs .Numerous studies have been performed on the solubility of drugs in various solvents, including lamotrigine in binary and ternary mixtures of N-methyl pyrrolidone and water with polyethyleneglycols 200, 400, and 600 [1], benzene polycarboxylic acids in water [2], Imidacloprid in Different Solvents [3], o-acetylsalicylic, 4-aminosalicylic, 3,5-dinitrosalicylic, andp-toluic acid, and magnesium-DL-aspartate in water from T = (278 to 348) K [4], benzoic acid in binary (benzyl alcohol+benzaldehyde) solvent

* *To whom correspondence should be addressed.*
+ *E-mail: dinmohammadm@ripi.ir*
• *Other Address: Young Researchers and Elite Club, Shiraz Branch, Uslamic Azad University, Shiraz, I.R. IRAN*
1021-9986/2022/6/2013-2024 12/$/6.02

mixtures [5], Benzoic Acid in Mixed Solvents [6], GLZ in 12 different neat solvents, namely, water, methanol, ethanol, isopropanol (IPA), 1-butanol, 2-butanol, ethylene glycol (EG), propylene glycol (PG), poly(ethylene glycol)-400 (PEG-400), ethyl acetate (EA), dimethyl sulfoxide (DMSO), and Transcutol-HP (THP) [7] and nisoldipine in ethyl acetate, toluene, 1-butanol, 1-propanol, ethanol, acetonitrile, water, 2-propanol, cyclohexane, and two binary solvents mixtures (2-propanol/ethanol + water) [8].

Using new carriers to create some SD-based formulations for their clinical use will be very useful. For this reason, *Alshehri et al.*, in experimental work, analyzed and evaluated novel methodologies for SD preparation to enhance the dissolution rate, solubility, therapeutic efficacy, and bioavailability of poorly water-soluble drugs [9].

In an experiment, *Zarmpi et al.* [10] investigated the impact of super disintegrants (sodium starch glycolate, croscarmellose sodium, crospovidone) on the apparent solubility of drugs with different physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility). Based on the results of their work, the variety of excipients has no effect on the effect of excipients on the apparent solubility of the drug.

Jacob et al. [11] investigated the role of nanosuspensions in drug delivery systems in experimental work. Based on the results of their work, nano-suspension has the potential to solve many problems of drug formulation issues in the field of poorly water and lipid-soluble drugs.

Senjoti et al. [12] studied poorly soluble drugs to incorporate in situ gelling systems due to the importance of drug solubility. According to the results of their study, poorly soluble drugs be complexed with cyclodextrin and loaded into an in situ gelling system without interfering with the gelation.

The importance of application of ionic liquids in the pharmaceutical industry in the preparation of optimal drug formulation, by studying the thermodynamic model for systems involving drugs and ionic liquids, can be a good approach. In other words, the study of drug solubility with thermodynamic models can help to identify the interactions and determine the thermodynamic properties of drug production equilibrium systems in the presence of an ionic liquid. Also, some drugs in the aqueous solution have low solubility, so thermodynamic study of some water-soluble drugs in the presence of some ionic liquids can help the pharmaceutical products to achieve optimum composition. For this reason, the prediction study of the solubility of Etodolac, Lamotrigine, Diazepam, and Clonazepam in water and cosolvent based on the thermodynamic model has not been considered by previous researchers. Therefore, in this study, the UNIQUAC model due to optimization with Genetic Algorithm) is used for the prediction of solubility of Etodolac, Lamotrigine, Diazepam, and Clonazepam (at 298.15 K). However, for these four cases, the correlational method has been studied by previous researchers.

THEORETICAL SECTION

The thermodynamic prediction equation for the solubility of the solute in the presence of organic and inorganic solvents can be defined as the following [6]:

$$\ln x_i = -\frac{\Delta H_{fus,i}}{RT}\left(1-\frac{T}{T_{fus,i}}\right)-\ln\gamma_i \qquad (1)$$

In Equation (1), x_i and γ_i represent the molar fraction and the activity coefficient of solid solute in the desired solution, respectively. Also, $T_{fus,i}$, $\Delta H_{fus,i}$, T, and R represent the melting temperature, melting enthalpy for the solid solute, temperature system, and gas constant, respectively. UNIQUAC thermodynamic model is studied for the activity coefficient of solute in presence of Water and Ethanol, and can be defined as the following [13-16]:

$$G^E = G^E_{combinatorrial} + G^E_{Residual} \qquad (2)$$

For two terms of Combinatorial and Residual based on Eqs (3) and (4) (respectively) we can write:

$$\frac{G^E_{combinatorrial}}{RT} = \sum x_i \ln\left(\frac{\phi_i}{x_i}\right)-\frac{z}{2}\sum q_i x_i \ln\left(\frac{\phi_i}{\theta_i}\right) \qquad (3)$$

$$\frac{G^E_{Residual}}{RT} = \sum_i q_i x_i \ln\left(\sum_k \theta_k \varphi_{ki}\right) \qquad (4)$$

Finally, we have:

$$\ln\gamma_i = \ln\left(\frac{\phi_i}{x_i}\right)+1-\ln\frac{\phi_i}{x_i}-\frac{z}{2}q_i\left[\ln\left(\frac{\phi_i}{\theta_i}\right)+1-\frac{\phi_i}{\theta_i}\right]- \qquad (5)$$

$$l\ln\left(\frac{r_i}{r_w}\right)+1-\frac{r_i}{r_w}-\frac{z}{2}q_i\left[\ln\left(\frac{r_i q_w}{r_w q_i}\right)+1-\frac{r_i q_w}{r_w q_i}\right]+$$

$$q_i\left[1-\ln\left(\sum_k \theta_k\varphi_{lk}\right)-\sum_k\frac{\theta_k\varphi_{ik}}{\theta_l\varphi_{lk}}\right]-q_i\left[1-\ln\left(\varphi_{wi}\right)-\varphi_{iw}\right]$$

In equation 5, φ_{ij} is given by

$$\varphi_{ij} = \exp\left(-\frac{u_{ij} - u_{ii}}{RT}\right) \quad (6)$$

Where R is the gas constant (8.314 J/(K.mol)), T is the temperature in Kelvin, u_{ii} is the interaction energy between similar ions in an equilibrium system of solid-liquid and also u_{ij} is the interaction energy between different ions. The interaction energy is defined as:

$$u_{ij} = u_{ij}^{\circ} + u_{ij}^{t}\left(T - 298.15\right) \quad (7)$$

In Equation (5), z is the coordination number with a value of 10 and also $\emptyset_i$ and θi are the volume fraction and the surface tension, respectively, and can be defined as the following:

$$\varnothing_i = \frac{x_i r_i}{\sum_l x_l r_l} \quad (8)$$

$$\theta_i = \frac{x_i q_i}{\sum_l x_l q_l} \quad (9)$$

In Equations (8) and (9), for the solute and solvents in a solid-liquid equilibrium system, *q* and *r* indicate the surface tension and volume parameters respectively, and also x_i is the mole fraction of species *i*. The three parameters *r*, *q*, and *u* are adjustable parameters in the optimization of this model. The subscript of w in Equation (5) is for water.

for optimization of solubility of Etodolac, Lamotrigine, Diazepam, and Clonazepam in water and cosolvents in Equation (5), based on experimental results, the equation of the objective function is defined as the following:

$$F_{obj} = \left(1/N \sum_{k=1}^{N} \left|x_{exp} - x_{calc}\right|\right)^{0.5} \quad (10)$$

The subscripts of exp and calc in Equation (10) are for solubility based on experimental and theoretical results respectively.

Thermodynamic modeling background

Solid-liquid equilibrium systems have non-ideal behavior in chemical systems [17]. Therefore, to better understand intermolecular interaction, thermodynamic models can be more important to study Solid-liquid equilibrium systems (Such as drugs in different solvents in order to study of thermodynamic properties of the drug such as solubility).

Two methods of correlation [18-19] and a thermodynamic model (based on the activity coefficient model) [20] are used to predict drug solubility.

In a theoretical work based on the Wilson model, *Matsuda et al.* [21] studied the solubility of drug compounds such as salicylic acid, acetaminophen, benzocaine, stabilize and phenacetine. In their work, the solvents used were water and ethanol, methanol, and 1,4-dioxane.

Yu et al. [22] investigated the solubilities of nimodipine in pure solvents (i.e., methanol, ethanol, n-propanol, i-propanol, n-butanol, i-butanol, s-butanol, n-pentanol, i-pentanol, acetone, cyclohexanone, acetonitrile, tetrahydrofuran, ethyl formate, methyl acetate, and ethyl acetate) and binary solvent mixtures (methanol + water) at the temperature range from 278.15 K to 318.15 K at atmospheric pressure in theoretical work. In their work, The solubility data in the single solvents were fitted by the modified Apelblat equation, kh equation, NRTL equation, and Wilson equation. Also, the solubility data in binary solvent mixtures were correlated by the CNIBS/R-K equation, modified Jouyban-Acree equation, NRTL equation, and Wilson equation.

In an experimental-theoretical work, *Delgado et al.* [23] investigated The equilibrium solubility of sulfadiazine (SD, 3) in {acetonitrile (MeCN, 1) + methanol (MeOH, 2)} mixtures at nine temperatures from 278.15 K to 318.15 K. In their study, Five models including van't Hoff, the mixture response surface (MRS), Jouyban-Acree, Jouyban-Acree-van't Hoff and the modified Wilson models were applied to thermodynamic modeling.

Jafari et al. [24] Studied the prediction of drug solubility in binary mixtures of ethylene glycol + water at different temperatures due to the Yalkowsky and Jouyban-Acree models. In their study, the Abraham solvation solute parameters are combined with the Jouyban-Acree and Jouyban-Acree-van't Hoff models. Based on the results of their study, the overall mean relative deviation generally has an acceptable performance in predicting solubility and can be useful in the pharmaceutical industry.

Wei et al. [25] Studied the solubility of Atorvastatin calcium (ATV) in 11 kinds of mono-solvents and binary solvent mixtures (acetone + water) of different ratios in an experimental-theoretical work. In their study, The solubility data were correlated by the modified Apelblat equation, van't Hoff equation, CNIBS/R-K equation,

Sun model and NRTL model. In the case study in their work, the experimental data and calculated data of the five models have a good correlation.

Borra et al. [26] examined the solubility of Furan 2-carboxylic acid in seven mono solvents toluene, hexane, diisopropylether, 1, 2–dichloroethane, acetonitrile, methylisobutylketone, methanol at temperatures ranging from 283.15 K – 333.15 K and five binary systems toluene + hexane, diisopropylether + hexane, 1, 2–dichloroethane + hexane, methylisobutylketone + hexane, ethanol + hexane at 293.15 K – 333.15 K in experimental and theoretical work. In their work, Van't Hoff, Modified Apelblat, Buchowski, CNIBS/R-K, Jouyban – Acree, modified Van't Hoff–Jouyban–Acree, modified Apelblat–Jouyban–Acree thermodynamic models have been used to theoretical section. Based on the results obtained from their study, the data is in good harmony with the Modified Apelblat equation for most of the solvent systems. Also the models CNIBS/R-K method showed the least deviation for diisopropylether + hexane system.

Due to the better description of the ionic interactions in the equation of thermodynamic equilibrium than the correlation method, in this study, the prediction of solubility of Etodolac, Lamotrigine, Diazepam, and Clonazepam based on UNIQUAC thermodynamic model was performed in the presence of suitable solvents. The UNIQUAC activity coefficient model considering the effect of the enthalpy and entropy term can be significant for better investigating the solubility behavior of drugs with aqueous and organic solvents.

Optimization procedure

In this study, the genetic algorithm is considered an optimization method for the thermodynamic prediction of the solubility of Etodolac, Lamotrigine, Diazepam, and Clonazepam based on UNIQUAC thermodynamic model. Many researchers have used genetic algorithms to solve engineering and chemical problems, including *Agrawal et al.* [27], *Cao et al*. [28], *Elliot et al.* [29], *Jezowski et al.* [30], and *Hashemi et al*. [31].

Agrawal et al. for the optimization of PE reactor, *Cao et al.* for the optimization of freshwater consumption, *Elliot et al.* for the optimization of aviation fuel combustion, *Jezowski et al.* for the optimization of heat exchanger retrofit, *Hashemi et al.* for the optimization of inorganic ions activity coefficient in aqueous solution electrolyte systems Genetic algorithms were used. The results of their research indicate the optimal performance of the genetic algorithm in optimizing problems. An important feature of the Genetic Algorithm is the ability to optimize with many variables, and the ability to obtain multiple solutions simultaneously and without dependence on the derivation of functions.

In this study, changes in temperature and initial concentration of the system components (based on mole fraction) are input to the algorithm. In the UNIQUAC model, three important parameters *r, q, u* are the main part of the model, all of which can be optimized and adjusted. Also in the algorithm, the activity coefficients of inorganic ions are calculated based on the mole fraction and applied to Eq. (1). According to the defined objective function (Eq. (8)), if the error is accepted, the optimization process stops and the results are printed; otherwise, the calculation process continues until the appropriate error criterion is reached.

RESULTS AND DISCUSSION

In this study, prediction of Etodolac solubility in the presence of water and α - CD, β - CD, γ - CD, 2 - HP - β - CD, 2 - HE - β - CD, and M - β - CD based on the model of UNIQUAC has been discussed. For this reason, the genetic algorithm was used to optimize the model. In Table 1, the results of the objective function optimization for six equilibrium systems based on the experimental results (at 298 K) are presented.

According to the results of Table 1, the genetic algorithm performed optimally in order to optimize the objective function in 6 equilibrium systems and the highest optimization objective function was 0.0029.

In Table 2, the results of the comparison of Etodolac solubility predictions in the presence of α - CD + Water and β - CD + Water with experimental results (at 298 K) are presented. According to the results of Table 2, the solubility of Etodolac in the presence of an aqueous solution is 0.9e-05.

However, by adding two α-CD and β-CD solvents to the aqueous solution, a significant increase in the solubility of Etodolac is observed.

Based on the results of Table 2, the solubility of Etodolac in water increased by 85.56% compared to the solubility of Etodolac in water + α-CD system. However, the increase in solubility of Etodolac in the water and β-CD system compared to the aqueous solution was 46.6%.

Table 1: The values of the optimization objective function for equilibrium systems in this study.

Equilibrium Systems	N	F_{obj}
Etodolac (1) + α – CD (2) +Water(3)	11	6.49e-06
Etodolac (1) + β – CD (2) +Water(3)	29	1.61e-05
Etodolac (1) + γ– CD (2) +Water(3)	12	2.11e-05
Etodolac (1) + 2-HP-β – CD (2) +Water(3)	21	2.38e-03
Etodolac (1) + 2-HE-β – CD (2) +Water(3)	21	3.09e-04
Etodolac (1) + M-β – CD (2) +Water(3)	21	0.0029

Table 2: Comparison of etodolac solubility prediction results in α - CD + Water and β - CD + Water systems with experimental results [32].

X_2	X_1^{Exp}	X_1^{Calc}	X_2	X_1^{Exp}	X_1^{Calc}
		Etodolac (1) + α – CD (2) +Water(3)			
0	0.65e-5	0.9e-05	0.006	1.41e-5	1.35e-05
0.001	0.93e-5	1.02e-05	0.007	1.44e-5	1.43e-05
0.002	1.08e-5	1.08e-05	0.008	1.52e-5	1.51e-05
0.003	1.18e-5	1.14e-05	0.009	1.6e-5	1.59e-05
0.004	1.26e-5	1.21e-05	0.0099	1.67e-5	1.67e-05
0.005	1.36e-5	1.28e-05			
		Etodolac (1) + β – CD (2) +Water(3)			
0	0.65e-5	9 e-06	0.002	1.02e-5	1.02e-05
0.0001	0.7e-5	8.97e-06	0.0023	1.03e-5	1.04e-05
0.0002	0.73e-5	9.03e-06	0.0025	1.05e-5	1.05e-05
0.0003	0.75e-5	9.09e-06	0.0028	1.07e-5	1.07e-05
0.0004	0.79e-5	9.15e-06	0.003	1.1e-5	1.09e-05
0.0005	0.81e-5	9.21e-06	0.0033	1.11e-5	1.11e-05
0.0006	0.83e-5	9.28e-06	0.0035	1.12e-5	1.12e-05
0.0007	0.85e-5	9.34e-06	0.0038	1.16e-5	1.15e-05
0.0008	0.88e-5	9.40e-06	0.004	1.18e-5	1.16e-05
0.0009	0.91e-5	9.47e-06	0.0045	1.22e-5	1.20e-05
0.001	0.93e-5	9.53e-06	0.0048	1.26e-5	1.22e-05
0.0012	0.94e-5	9.66e-06	0.0053	1.3e-5	1.26e-05
0.0013	0.95e-5	9.73e-06	0.0055	1.32e-5	1.28e-05
0.0016	0.97e-5	9.93e-06	0.006	1.36e-5	1.32e-05
0.00018	0.99e-5	1.006e-05			

Table 3: Comparison of etodolac solubility prediction results in 2-HP-β-CD + Water and 2-HE-β- CD + Water systems with experimental results [32].

X_2	X_1^{Exp}	X_1^{Calc}	X_2	X_1^{Exp}	X_1^{Calc}
		Etodolac (1) + 2-HP-β – CD (2) +Water(3)			
0	0.65e-5	0.9e-05	0.011	30.53e-5	4.12e-04
0.001	2.33e-5	1.96e-04	0.012	35.92e-5	4.42e-04
0.002	4.18e-5	2.12e-04	0.013	41.73e-5	4.73e-04
0.003	6.34e-5	2.29e-04	0.014	48.12e-5	5.06e-04
0.004	8.76e-5	2.47e-04	0.015	54.26e-5	5.41e-04
0.005	11.26e-5	2.67e-04	0.016	60.35e-5	5.78e-04
0.006	13.12e-5	2.88e-04	0.017	66.46e-5	6.17e-04
0.007	15.7e-5	3.10e-04	0.018	73.88e-5	6.58e-04
0.008	18.6e-5	3.33e-04	0.19	81.09e-5	7.01e-04
0.009	21.9e-5	3.58e-04	0.02	87.34e-5	7.46e-04
0.01	26.2e-5	3.84e-04			
		Etodolac (1) + 2-HE-β – CD (2) +Water(3)			
0	0.65e-5	0.9e-05	0.011	23.63E-5	2.26e-04
0.001	2.16e-5	6.38e-05	0.012	26.41E-5	2.53e-04
0.002	3.67e-5	7.33e-05	0.013	29E-5	2.82e-04
0.003	5.58e-5	8.41e-05	0.014	32.11E-5	3.14e-04
0.004	7.29e-5	9.62e-05	0.015	35.26E-5	3.48e-04
0.005	9.08e-5	1.09e-04	0.016	38.88E-5	3.85e-04
0.006	11e-5	1.24e-04	0.017	42.58E-5	4.25e-04
0.007	13.42e-5	1.41e-04	0.018	46.76E-5	4.68e-04
0.008	15.65e-5	1.59e-04	0.19	50.54E-5	5.15e-04
0.009	17.9e-5	1.80e-04	0.02	53.65E-5	5.65e-04
0.01	20.42e-5	2.02e-04			

The concentration range for α-CD solvent is 0.001 to 0.0099 and for β-CD solvent is 0.0001 to 0.006.

In Table 3, the results of the comparison of Etodolac solubility predictions in the presence of α - CD + Water and β - CD + Water with experimental results (at 298 K) are presented. According to the results of Table 3, Etodolac significantly increased with increasing concentration (from 0.001 to 0.2) of 2-HP-β-CD and 2-HE-β-CD solvents in the equilibrium system (in the presence of water). In other words, in the 2-HP-β-CD + Water equilibrium system, the solubility of Etodolac was 1.96e-04 with a mole fraction of 0.001 from 2-HP-β-CD (0.999 water fraction). However, with a molar fraction of 0.02 of 2-HP-β-CD (0.98 water fraction), the Etodolac solubility is about 7.46e-04.

Based on the results in Table 3, the percentage of increase in solubility of Etodolac in 2-HP-β-CD + Water and 2-HE-β-CD + Water systems in the presence of pure water (solvent-free), 81.89% and 61.78%, respectively.

In Fig. 1, the results of the comparison of Etodolac solubility predictions with the presence of M-β - CD + Water with experimental results (at 298 K) are presented.

According to the results of Fig. 1, an increase in Etodolac solubility was observed with increasing

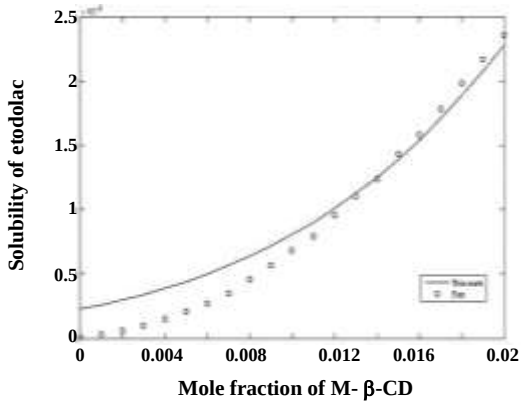

Fig. 1: Comparison of Etodolac solubility prediction results in M-β - CD + Water system with experimental results [32].

the concentration of M-β-CD solvent in an aqueous solution. The solubility of Etodolac at 0.001 M-β-CD concentration (0.999 of water) was 0.00026 and the Etodolac solubility of 0.00228 increased by 0.02 M-β-CD concentration. According to Fig. 1, at low concentrations of M-β-CD in the equilibrium system, the difference between the model value and the experimental results is greater, and with increasing concentration, the difference is smaller. This may be related to the characteristic of the UNIQUAC thermodynamic activity coefficient model, which performs better in Thick solution than in dilute solution.

In Fig. 2, the results of the comparison of Etodolac solubility predictions in the presence of γ - CD + Water with experimental results (at 298 K) are presented.

According to the results of Fig. 2, due to the non-polar structure of Etodolac and the high polarity of water, the solubility of Etodolac in an aqueous solution is very low. Therefore, in the presence of γ-CD solvent due to lower polarity than water, Etodolac solubility was associated with an increase. This is also true for other solvents studied. In other words, in the presence of solvents α - CD, β - CD, γ - CD, 2-HP-β - CD, 2-HE-β - CD, and M-β - CD due to polar and nonpolar segments In their molecular structure, a greater amount of Etodolac dissolves in the sediment.

Based on the results in Tables 2 and 3 and Figs. 1 and 2, the combination of aqueous solvents in the presence of Etodolac can reduce solvent interactions and reduce the surface tension and dielectric constant of the aqueous solvent.

Table 4 presents the results of comparing the prediction of solubility of Lamotrigine, Diazepam, and Clonazepam

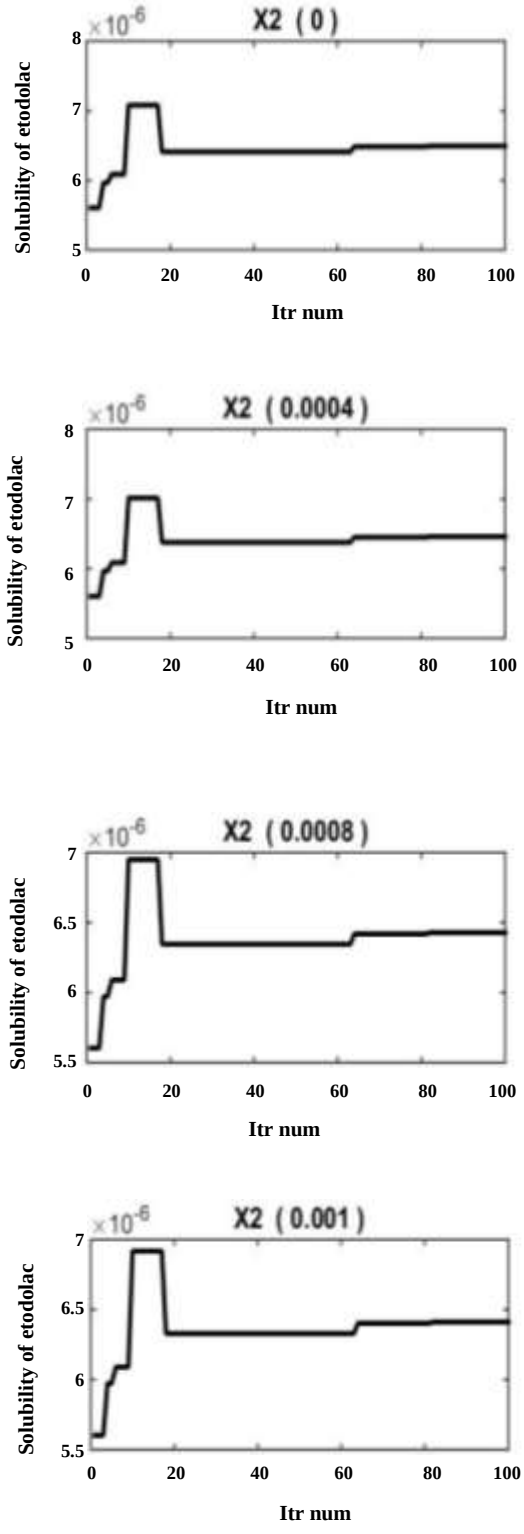

Fig. 2: Comparison of Etodolac solubility prediction results in γ-CD + Water system with experimental results [32] according to the genetic algorithm at different concentrations of γ-CD solvent.

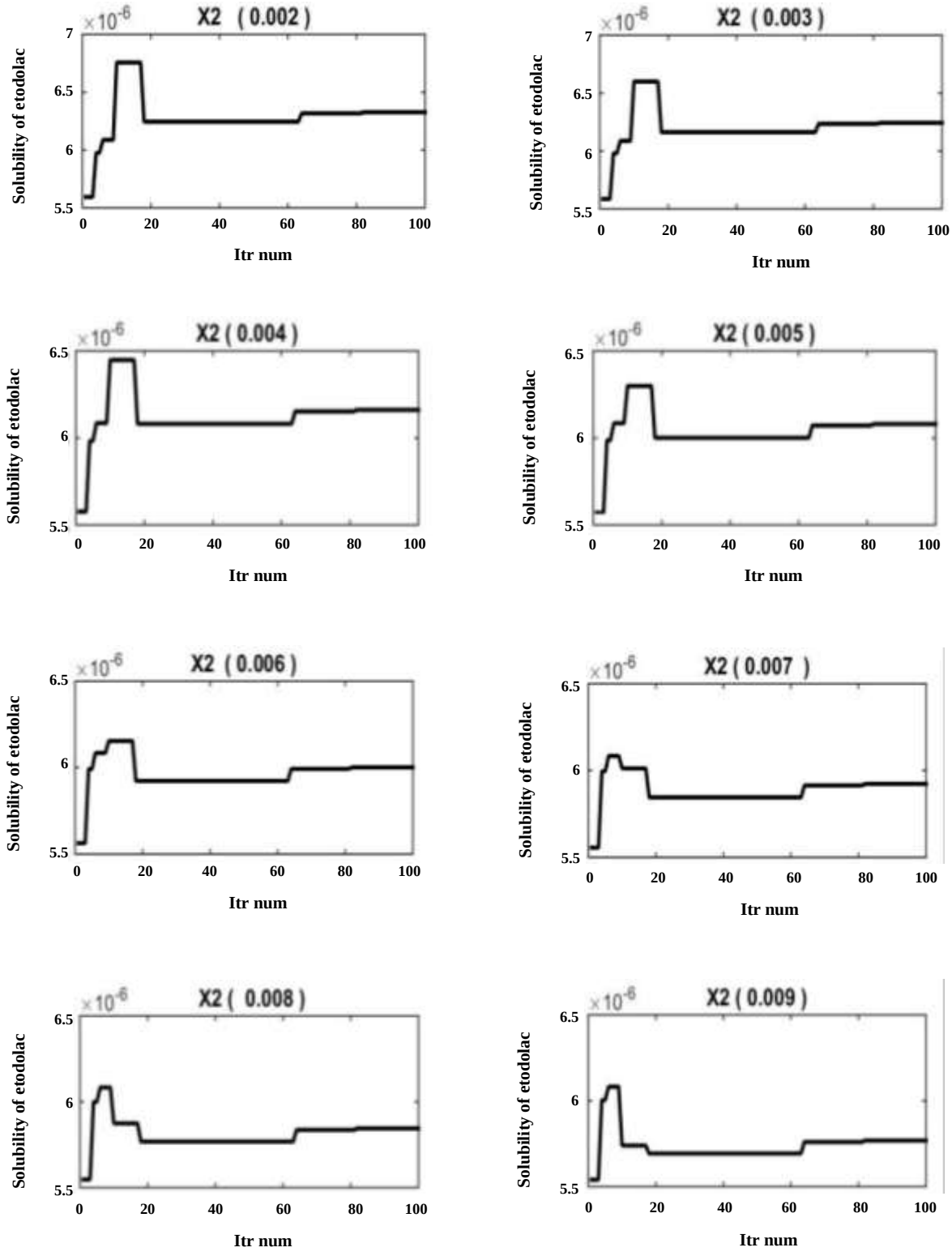

Fig. 2: Comparison of Etodolac solubility prediction results in γ-CD + Water system with experimental results [32] according to the genetic algorithm at different concentrations of γ-CD solvent. (Continued).

Table 4: Comparison between solubility values (mole fraction) predicted by UNIQUAC model and experimental data [19].

The volume fraction of Ethanol	Exp	Calc
Lamotrigine + Ethanol +Water		
0	0.0131	0.0509
0.1	0.0368	0.0648
0.2	0.0493	0.0814
0.3	0.1013	0.1223
0.4	0.2420	0.2416
0.5	0.5478	0.5733
0.6	1.0381	1.0519
0.7	1.3392	1.3119
0.8	1.4939	1.4320
0.9	1.3934	1.4607
1	0.5698	0.5576
Diazepam + Ethanol +Water		
0	0.0027	0.0061
0.1	0.0077	0.0093
0.2	0.0157	0.0151
0.3	0.0460	0.0281
0.4	0.1660	0.0691
0.5	0.4510	0.2277
0.6	1.1376	0.9120
0.7	2.3580	2.4916
0.8	3.4104	3.9122
0.9	4.9369	3.9211
1	3.6496	3.5990
Clonazepam + Ethanol +Water		
0	0.0018	0.0007
0.1	0.0026	0.0013
0.2	0.0053	0.0029
0.3	0.0145	0.0073
0.4	0.0475	0.0222
0.5	0.1211	0.0757
0.6	0.2436	0.2248
0.7	0.4227	0.4479
0.8	0.6090	0.6133
0.9	0.7301	0.7126
1	0.6566	0.6395

in the presence of water and ethanol with the experimental results (at 298 K). Based on Equations 1 and 2, the thermodynamic model was optimized based on the experimental results that the error value of the optimization of the objective function after performing the calculations for Lamotrigine, Diazepam, and Clonazepam were 0.17, 0.45, and 0.12, respectively.

According to the results of Table 4, the solubility of Lamotrigine, Diazepam, and Clonazepam in water was 0.0509 , 0.0061and 0.0007 respectively. The low solubility of these three materials in water is related to the non-polar structure of the solubility of Lamotrigine, Diazepam, and Clonazepam and the high polarity of water. However, the solubility of Lamotrigine, Diazepam, and Clonazepam is higher in inorganic ethanol solvent, which has less polarity than water.

Therefore, the presence of a suitable organic solvent can be a suitable solution for the solubility of Lamotrigine, Diazepam, and Clonazepam in an aqueous solvent In other words, according to the results in Table 4, the solubility of Lamotrigine, Diazepam and Clonazepam is associated with an increasing trend with increasing ethanol content. Also, according to the results of Table 4, the highest solubility is observed for Lamotrigine, Diazepam, and Clonazepam with a volume fraction of ethanol of 0.9 (water volume fraction of 0.1).

CONCLUSIONS

Solubility is one of the important thermodynamic properties of drug production and development. In other words, drug dissolution is an important prerequisite for drug absorption. For this reason, in this study, the solubility of Etodolac, Lamotrigine, Diazepam, and Clonazepam was studied according to the thermodynamic model. In this study, the solubility of Lamotrigine, Diazepam, and Clonazepam in the presence of solvents of Ethanol and Water based on UNIQUAC model was considered. According to the results of this study, the solubility of Lamotrigine, Diazepam, and Clonazepam in the presence of pure water was lower than that of pure ethanol. Therefore, the best solution to improve the solubility of these three drugs in water (to reduce the polarity of water structure) is the presence of Ethanol. Also in this study, the prediction of solubility of Etodolac in the presence of aqueous solution and co-solvents of α - CD, β - CD, γ - CD, 2-HP-β - CD, 2-HE-β - CD and M-β - CD According to the UNIQUAC model has been studied. The optimization method of the thermodynamic model was based on a genetic algorithm that based on the objective function results, the maximum optimization error for 6 equilibrium systems was 0.0029. According to the results of this study, to improve the solubility of Etodolac in an aqueous solution, the use of α-CD, β-CD, γ-CD 2-HP-β-CD, 2-HE-β - CD, and M-β - CD can be a good solution.

Received : May 3, 2021 ; Accepted : Aug. 2, 2021

REFERENCES

[1] Soltanpour S., Jouyban A., Solubility of Lamotrigine in Binary Andternary Mixtures of N-methyl Pyrrolidone and Water with Polyethyleneglycols 200, 400, and 600 at 298.2 K, *J. Mol. Liq.*, **180**:1-6 (2013).

[2] Pelblat A., Manzurola E., Abo Balal N., The Solubilities of Benzene Polycarboxylic Acids in Water, *J. Chem. Thermodyn.*, **38**: 565-571 (2006).

[3] Kong M.Z., Shi X.H., Cao Y.C., Zhou C.R., Solubility of Imidacloprid in Different Solvents, *J. Chem. Eng. Data*, **53**: 615−618 (2008).

[4] pelblat A., Manzurola E., Solubilities of o-acetylsalicylic, 4-aminosalicylic, 3,5-dinitrosalicylic, Andp-Toluic Acid, and Magnesium-DL-Aspartate in Water from T = (278 to 348) K, *J. Chem. Thermodyn*, **31**: 85-91 (1999).

[5] Wang H., Wang Q., Xiong Z., Chen C., Shen B., Solubilities of Benzoic Acid in Binary (Benzyl Alcohol+Benzaldehyde) Solvent Mixtures, *J. Chem. Thermodyn*, **83**: 61-66 (2015).

[6] Oliveira A.C., Coelho M.G., Pires R.F., Franco M.R., Solubility of Benzoic Acid in Mixed Solvents, *J. Chem. Eng. Data*, **52**: 298-300 (2007).

[7] Mohd Abul K., Aws A., Musaed A., Ibrahim A.A., Raisuddin A., Nazrul H., Md Khalid A., Faiyaz Sh., Solubility Measurement and Various Solubility Parameters of Glipizide in Different Neat Solvents, *ACS Omega*, **5(3):** 1708-1716 (2020).

[8] Xia Ch., Qianqian X., Zhiying L., Xianling Zh., Huilin Zh., Jia Zh., Rongrong L., Deman H., Solubility Determination, Model Correlation, and Solvent Effect Analysis of Nisoldipine in Different Solvent Systems at a Series of Temperature, *Journal of Chemical & Engineering Data*, **65(4):** 1627-1635 (2020).

[9] Alshehri S., Imam S.S., Hussain A., Altamimi M.A., Alruwaili N.K., Alotaibi F., Alanazi A., Shakeel F., Potential of Soliddispersions to Enhance Solubility, Bioavailability, and Therapeutic Efficacy of Poorly Water-Solubledrugs: Newer Formulation Techniques, Current Marketed Scenario and Patents, *Drug Delivery*, **27(1)**: 1625-1643(2020).

[10] Zarmpi P., Flanagan T., Meehan E., Mann J., Fotaki N., Biopharmaceutical Understanding of Excipient Variability on Drug Apparent Solubility Based on Drug Physicochemical Properties. Case Study: Superdisintegrants, *AAPS J*., **22(46)**: (2020).

[11] Jacob S., Nair A.B., Shah J., Emerging Role of Nanosuspensions in Drug Delivery Systems, *Biomater Res*., **24(3)**: (2020).

[12] Senjoti F.G., Timmins P., Conway B.R., Smith A.M., Optimizing Ophthalmic Delivery of a Poorly Water Soluble Drug from an Aqueous In Situ Gelling System, *European Journal of Pharmaceutics and Biopharmaceutics* (2020).

[13] Denis A.S., Prausnitz J.M., Statistical Thermodynamics of Liquid Mixtures. New Expression for the Excess Gibbs Energy of Partly or Completely Miscible Systems, *AIChE Journal*, **21(1):** 116-128 (1975).

[14] Anderson T.F., Prausnitz J.M., Application of the UNIQUAC Equation to Calculation of Multicomponent Phase Equilibriums. 2. Liquid-Liquid Equilibriums, *Industrial & Engineering Chemistry Process Design and Development*, **17(4)**: 561-567 (1978).

[15] Prausnitz J.M., Lichtenthaler R.N., de Azevedo E.G., "Molecular Thermodynamics of Fluid-Phase Equilibria" (3rd ed.), Prentice Hall PTR; New Jersey (1999).

[16] Thomsen K., Rasmussen P., Modeling of Vapor–Liquid–Solid Equilibrium in Gas–Aqueous Electrolyte Systems, *Chem. Eng. Sci*., **54**: 1787–1802 (1999).

[17] Jaime W.M., Hector R.G., Felipe H.L., Raquel R.R., Activity Coefficients of NaClO4 in (PEG 4000 + H2O) Mixtures at (288.15, 298.15 and 308.15) K. *Iranian Journal of Chemistry and Chemical Engineering (IJCCE)*, **39(2)**: 145-157 (2020).

[18] Shayanfar A., Acree W.E., Jouyban A., Solubility of Lamotrigine, Diazepam, Clonazepam, and Phenobarbital in Propylene Glycol+WaterMixtures at 298.15 K, *J. Chem. Eng. Data*, **54**:1153−1157. (2009).

[19] Shayanfar A., Fakhree M.A.A., Acree W.E., Jouyban A., Solubility of Lamotrigine, Diazepam, and Clonazepam in Ethanol+Water Mixtures at 298.15 K, *J. Chem. Eng. Data*, **54**: 1107−1109 (2009).

[20] Chen C., Crafts P.A., Correlation and Prediction of Drug Molecule Solubility in Mixed Solvent Systems with the Nonrandom Two-Liquid Segment Activity Coefficient (NRTL-SAC) Model, *Ind. Eng. Chem. Res*., **45**: 4816-4824 (2006).

[21] Matsuda H., Kaburagi K., Matsumoto S., Kurihara K., Tochigi K., Tomono K., Prediction of Solubilities of Pharmaceutical Compounds in Water + Co-Solvent Systems Using an Activity Coefficient Model, *Chem. Eng. Data*., **54**: 480 (2009).

[22] Shuai Yu., Wenguo X., Fumin X., Yan Ch., Bing L., Solubility and Thermodynamic Properties of Nimodipine in Pure and Binary Solvents at a Series of Temperatures, *The Journal of Chemical Thermodynamics*,**152**: 106259 (2020).

[23] Delgado D., Bahamón-Hernandez O., Cerquera N., Ortiz C., Martínez F., Rahimpour E., Jouyban A., Acree W., Solubility of Sulfadiazine in (Acetonitrile + Methanol) Mixtures: Determination, Correlation, Dissolution Thermodynamics and Preferential Solvation, *Journal of Molecular Liquids*, **322**: 114979 (2021).

[24] Jafari P., Rahimpour E., Acee W.E., Jouyban A., Prediction of Drug Solubility in Ethylene Glycol + Water Mixtures Using Generally Trained Cosolvency Models, *Journal of Molecular Liquids*, **328**: 115325 (2021).

[25] Wei J., Chen Sh., Fu H.L., Wang X., Li H., Lin J., Xu F., He Ch., Liang X., Tang H., Shu G., Zhang W., Measurement and Correlation of Solubility Data for Atorvastatin Calcium in Pure and Binary Solvent Systems from 293.15 K to 328.15 K, *Journal of Molecular Liquids*, **324**: 115124 (2021).

[26] Borra A., Kosuru R.K., Bharadwaj R., Satyavathi B., Measurement and Modeling of Solubility of Furan 2-Carboxylic Acid in Mono and Binary Systems, *Journal of Molecular Liquids*, **326**: 115271 (2021)

[27] Agrawal N., Rangaiah G., Ray A.K., Gupta S.K., Multi-Objective Optimization of the Operation of an Industrial Low-Density Polyethylene Tubular Reactor Using Genetic Algorithm and Its Jumping Gene Adaptations, *Industrial and Engineering Chemistry Research*, **45(9)**: 3182 -3199 (2006).

[28] Cao K., Feng X., Ma H., Pinch Multi-Agent Genetic Algorithm for Optimizing Water-Using Networks, *Computers and Chemical Engineering*, **31(12)**: 1565-1575 (2007).

[29]Elliott L., Ingham D., Kyne A., Mera N., Pourkashanian M., Wilson C., A Novel Approach to Mechanism Reduction Optimization for an Aviation Fuel/Air Reaction Mechanism Using a Genetic Algorithm, *Journal of Engineering for Gas Turbines and Power*, **128(2)**: 255- 263 (2006).

[30] Jezowski J., Bochenek R., Poplewski G., On Application of Stochastic Optimization Techniques to Designing Heat Exchanger- and Water Networks, *Chemical Engineering and Processing: Process Intensi cation*, **46(11)**:1160- 1174 (2007).

[31] Hashemi S.H, Mousavi Dehghani S.A., Khodadadi H., Dinmohammad M., Hosseini S.M, Hashemi S.H., Optimization of Extended UNIQUAC Parameter for Activity Coefficients of Ions of an Electrolyte System Using Genetic Algorithms, *Korean Chemical Engineering Research*, **55(5)**: 652-659 (2017).

[32] Naito Y., Matsuda H., Shimomura K., Kurihara K., Tochigi K., Tomono K., Measurement and Correlation of Solubilities of the Poorly Water-Soluble Pharmaceutical Compound Etodolac by Addition of Co-Solvents, *Fluid Phase Equilibria*, **357(2)**: 43-49 (2013).