Pharmaceutical Sciences, 2021, 27(1), 86-101
doi:10.34172/PS.2020.58
https://ps.tbzmed.ac.ir/

TUOMS PRESS

Research Article

Solubility Enhancement of Betamethasone, Meloxicam and Piroxicam by Use of Choline-Based Deep Eutectic Solvents

Salva Golgoun[1], Masumeh Mokhtarpour[1], Hemayat Shekaari[1*]

[1]*Department of Physical Chemistry, University of Tabriz, Tabriz, Iran.*

Article Info

Article History:
Received: 1 March 2020
Accepted: 18 July 2020
ePublished: 26 September 2020

Keywords:
-Drug solubility
-Deep eutectic solvent
-Betamethasone
-Meloxicam
-Piroxicam
-Activity coefficient model
-Dissolution thermodynamic

Abstract

Background: The low aqueous solubility of three important drugs (betamethasone (BETA), meloxicam (MEL) and piroxicam (PIR)) have been increased by use of deep eutectic solvents (DESs) based choline chloride/urea (ChCl/U), choline chloride/ethylene glycol (ChCl/EG) and choline chloride/glycerol (ChCl/G) as new class of solvents at T = (298.15 to 313.15) K.

Methods: DESs were prepared by combination of the ChCl/EG, U and G with the molar ratios: 1:2. The solubility of drugs in the aqueous DESs solutions was measured at different temperatures with shake flask method.

Results: The solubility of the investigated drugs increased with increasing the weight fraction of DESs. The solubility data were correlated by e-NRTL and Wilson models. Also, the thermodynamic functions, Gibbs energy, enthalpy, and entropy of dissolution were calculated.

Conclusion: At the same composition of co-solvents and temperature, the BETA, PIR and MEL solubility was highest in (ChCl/U + water), (ChCl/U + water) and (ChCl/EG + water) respectively. The calculated solubility based on these models was in good agreement with the experimental values. In addition, the results show that, the main contribution for drugs solubility in the aqueous DES solutions is the enthalpy.

Introduction

One of the most important issues in drug manufacturing and development is to increase the permeability and bioavailability by enhancement of the solubility of poorly water-soluble drugs.[1] Since the water solubility of drugs is an important factor in drug absorption, low solubility should be increased. In order to overcome this problem, different methods have been tested by researchers including use of cyclodextrins and surface-active agents, pH adjustment, and co-solvency. It is well-known that the co-solvency method is an efficient method to improve the solubility of a low water-soluble drug and addition of a co-solvent to water can considerably alter the drugs solubility.[2] In recent years organic solvents and ionic liquids (ILs) have been applied as co-solvents to enhance the solubility of drugs but these kinds of solvents suffer from toxicity, high prices and flammability.[3-7] ILs have obtained a great scientific attention through their unique physical and chemical properties (thermal stability, low flammability, negligible vapor pressure) as solvents and co-solvents in various fields. However there are some limitations to the use of ILs, such as the high price of synthesis, their toxicity, and poor biodegradability and biocompatibility.[8] A new class of solvents has discovered namely deep eutectic solvents (DESs) as an alternative for ILs and organic solvents.[9,10] These solvents obtain by the combination of biodegradable and natural components including one hydrogen bond acceptor (HBA) such as quaternary ammonium salt (e.g. choline chloride (ChCl)) and at least one hydrogen bond donor (HBD) (e.g. urea or a carboxylic acid).[9,11] These types of solvents are liquid at ambient temperature and it was established that they are less toxic compared with organic solvents and ILs. The DESs properties can be simply changed by varying the mixing ratio of the applied HBDs and salts.

Betamethasone (BETA), piroxicam (PIR) and meloxicam (MEL) are low soluble-drugs in water that their aqueous solubility is studied in this work in the presence of some green DESs based on ChCl. Studies reporting drugs solubility in aqueous DESs solutions are rare which show significant enhancement in the solubility at higher DESs concentrations.[12-14]

In continuation of our previous works,[15-21] the purpose of this attempt is to overcome the problems associated with aqueous solubility of BETA, PIR and MEL using DESs based on ChCl as HBA and urea (U), ethylene glycol (EG) and glycerol (G) as HBDs at T = (298.15 to 313.15) K and atmospheric pressure. Additionally, in the phase equilibrium calculations, the activity coefficient models including Wilson[22] and electrolyte-NRTL[23] have been widely applied. In this work, Wilson and e-NRTL

---

*Corresponding Author: Hemayat Shekaari, E-mail: hemayatt@yahoo.com

models were used to evaluate fitness of experimental solubility data. Also, apparent dissolution thermodynamic properties of drugs were obtained using Gibbs and van't Hoff equations.[24-26]

Theoretical consideration

Two activity coefficient models (Wilson and e-NRTL) are used to express the drug solubility in the water + co-solvent solutions of ChCl/U, ChCl/EG and, ChCl/G in this paper. One of the most key subjects in medicinal science is information about the solubility of drugs. This important parameter allows engineers and scientists to choose the suitable solvents for formulation processes of drugs. In this respect, using a solid-liquid equilibrium (SLE) framework, the next relation can be employed:[27]

$$-\ln x_1 = \frac{\Delta_{fus}H}{R}\left(\frac{1}{T}-\frac{1}{T_{fus}}\right)+\ln\gamma_1 \qquad \text{Eq. (1)}$$

where T_{fus} and T are melting temperature for the pure drugs and equilibrium temperature, $\Delta_{fus}H$ is fusion enthalpy, x_1 and γ_1 are equilibrium mole fraction and the activity coefficient of the drug in the saturated solutions. The melting enthalpy is assumed to be temperature independent. To fit the experimental solubility data of the investigated drugs in the aqueous DES solutions, experimental activity coefficients were calculated using Eq. (1) for the solutions.

Electrolyte-NRTL model

The e-NRTL activity coefficient model is one of the most frequently employed models for various systems in different fields. This model is introduced by Chen *et al.*[23] and Chen and Evans[28]. The activity coefficient for each species is the sum of the NRTL and the PDH contributions.[23]

$$\ln(\gamma_i^{*}) = \ln(\gamma_i^{*PDH}) + \ln(\gamma_i^{*NRTL}) \qquad \text{Eq. (2)}$$

$$\ln\gamma_I^{NRTL} = \sum_i r_{i,I}\left[\frac{\sum_j X_j G_{ji}\tau_{ji}}{\sum_k X_k G_{ki}} + \sum_j \frac{\sum_j X_j G_{ij}}{\sum_k X_k G_{kj}}\left(\tau_{ij}-\frac{\sum_k X_k G_{kj}\tau_{kj}}{\sum_k X_k G_{kj}}\right)\right]$$

with interaction parameters as $\tau_{ji} = \frac{g_{ji}-g_{ii}}{RT}$.

The Pitzer–Debye–Hückel (PDH) equation

excess Gibbs energy, G^{ex*LR}, in the PDH equation can be written as:[29]

$$\frac{G^{ex*,PDH}}{RT} = -\sum_j x_j\left(\frac{1000}{M_s}\right)^{1/2}\frac{4A_\phi I_x}{\rho}\ln(1+\rho I_x^{0.5}) \qquad \text{Eq. (3)}$$

where M_S and ρ represent the molar mass of the solvent and the closest distance parameter, respectively. I_x is the ionic strength in mole fraction scale ($I_x = \frac{1}{2}\sum x_i Z_i^2$) and A_φ denotes the Debye–Hückel constant for the osmotic coefficient and is stated as:

$$A_\phi = \frac{1}{3}\left(\frac{2\pi N_A}{V_S}\right)^{1/2}\left(\frac{e^2}{4\pi\varepsilon D_S kT}\right)^{3/2} \qquad \text{Eq. (4)}$$

where N_A, k, ε, e, V_S and D_S are Avogadro's number, Boltzmann constant, permittivity of vacuum, electronic charge, molar volume and dielectric constant of pure solvent, respectively. The parameter ρ in Eq. (3) is related to the hard-core collision diameter, or distance of closest approach of ions in solution. The value of $\rho = 14.9$ has been regularly used for aqueous electrolyte solutions.[30]

Wilson model

The expressions of Wilson (1964) model for each component i activity coefficients are presented as:[22]

$$ln\gamma_i = 1 - ln\left[\sum_{j=1}^{n} x_j\Lambda_{ij}\right] - \sum_{k=1}^{n}\left[\frac{(x_k\Lambda_{ki})}{\sum_{j=1}^{n} x_{j=1}\, x_j\,\Lambda_{kj}}\right] \qquad \text{Eq. (5)}$$

where Λ_{ij} is the interaction parameter between i and j which are associated to molar volumes of the pure-component, υ, and differences of characteristic energy, λ, using the next relation:

$$\Lambda_{ij} = \frac{\upsilon_j}{\upsilon_i}\exp\left(-\frac{\lambda_{ij}-\lambda_{ii}}{RT}\right) \qquad \text{Eq. (6)}$$

Finally, to present the error and evaluate the different models, the relative average deviation (RAD) is employed, which is described as Eq. (7).

$$\%ARD = 100\left(\frac{\sum_{i=1}^{N}\frac{\left|x_i^{\exp}-x_i^{cal}\right|}{\left|x_i^{\exp}\right|}}{N}\right) \qquad \text{Eq. (7)}$$

where $x_i^{\exp}$, x_i^{cal} and N refer to determined solubility in the present work and calculated solubility and the number of solubility data points, respectively.

Thermodynamic properties of the drugs dissolution

The experimental solubility data of the investigated drugs was plotted versus the temperature to calculate the thermodynamic properties of dissolution. This process gives us a deep insight into the microscopic mechanisms in the solution processes by thermodynamic properties of solvation.[31] The solution standard molar enthalpy, ΔH_{soln}^{o}, is obtained using van't Hoff equation and expressed as follows:[31-33]

$$\Delta H^{o}_{soln} = -R\left(\frac{\partial \ln x_1}{\partial(1/T)}\right) \quad \text{Eq. (8)}$$

where x_1 is the solute mole fraction solubility and T is the studied temperature. The standard molar enthalpy change of solution, ΔH_{soln}^{o}, is mostly achieved from the slope of the solubility curve in a so-called van't Hoff plot where $\ln x_1$ is plotted versus T^{-1}. The heat capacity change of a solution may be supposed to be constant over a limited temperature interval, therefore the derived values of ΔH_{soln}^{o} will also be valid for the mean temperature, $T_m = 305.55$ K.[34]
Eq. (8) can also be written as:

$$\Delta H^{o}_{soln} = -R\left(\frac{\partial \ln x_1}{\partial(1/T - 1/T_m)}\right) \quad \text{Eq. (9)}$$

The next relation is used to calculate the standard molar Gibbs energy of solution, ΔG_{soln}^{o}:[35]

$$\Delta G^{o}_{soln} = -RT_m \times \text{intercept} \quad \text{Eq. (10)}$$

where the intercept can be obtained from plots of $\ln x_1$ versus $(1/T - 1/T_m)$. The entropic change for the dissolution process is calculated from Eq. (11):[31]

$$\Delta S^{o}_{soln} = \frac{\Delta H^{o}_{soln} - \Delta G^{o}_{soln}}{T_m} \quad \text{Eq. (11)}$$

To compare the relative contributions of entropy ($\%\xi_{TS}$) and enthalpy ($\%\xi_{H}$) to the dissolution process, Eqs. (12) and (13) were used, respectively:[36]

$$\%\xi_{H} = \frac{\left|\Delta H^{o}_{soln}\right|}{\left|\Delta H^{o}_{soln}\right| + \left|T\Delta S^{o}_{soln}\right|} \times 100 \quad \text{Eq. (12)}$$

$$\%\xi_{TS} = \frac{\left|T\Delta S^{o}_{soln}\right|}{\left|\Delta H^{o}_{soln}\right| + \left|T\Delta S^{o}_{soln}\right|} \times 100 \quad \text{Eq. (13)}$$

Materials and Methods

Materials

The detailed aspects (origin, purity and CAS number) of the compounds employed here are presented in Table 1. The fresh distilled deionized water was used to prepare all the solutions used in the experiment.

Preparation of the ChCl-based DESs

The purified and dried compounds of ChCl as HBA and U, EG and G as HBDs were combined with the molar ratios 1:2. The ChCl and HBDs were stirred at 353.15 K for 2 hours until a uniform liquid was reached.[11] A number of measured physical properties of the studied DESs are also collected in Table 2.

Solubility measurements

During the experiment, the mixtures of solvent (DES + water) were prepared by mixing the proper amounts of solvents (in grams) using an analytical balance (AW 220, GR220, Shimadzu, Japan) with precision 10^{-4} g. The weight fractions of DES in the binary mixtures varied from 0.00 to 0.90. There are many various methods of measuring and testing the solubility in the literature.[37] The solubility of drugs in the binary solvent mixtures of (ChCl/U + water), (ChCl/EG + water) and (ChCl/G + water) was measured using a saturation shake-flask method.[38,39] The solubility measurements experiment was performed at temperatures from $T = 298.15$ K to 313.15 K at intervals of 5 K and pressure $p = 86.6$ kPa. The excess drugs were introduced to a certain amount of each solvent mixture. Each drug solution was mixed properly and then moved to a thermostatically controlled shaker obtained from Behdad, Tehran, Iran. The solution was shaken at a speed of 150 rpm. Three days are enough to reach equilibrium for any drug. After equilibrium, the solid and liquid were separated using a centrifuge (D-7200 Tuttlingen, Hettich Co., America) and filters (Durapore® membrane filters, 0.45 μm, type HV, Millipore, MA). The lucid solutions were diluted with the proper ratio of ethanol/water for BETA and PIR and NaOH/water for MEL, assayed by a double beam spectrophotometer (Specord 250, Analytik Jena) at 271 nm for MEL,[40] 254 nm for PIR and 245 nm for BETA. The concentrations of the final solutions were determined according to the calibration curve. Each point in the solubility data is the average of at least three repetitions.

Results and Discussion

Solubility data and modeling results

The equilibrium mole fraction solubility of drugs (x_1) in the three solvent mixtures (water + DES) are obtained with:

$$x_1 = \frac{\dfrac{w_1}{M_1}}{\dfrac{w_1}{M_1} + \dfrac{w_2}{M_2} + \dfrac{w_3}{M_3}} \quad \text{Eq. (14)}$$

where w_i and M_i are the weight fractions of i component in the saturated solution and the molar mass, respectively.[41] Tables 3, 4 and 5 show the experimental solubility data of investigated drugs in binary solvent (water + co-solvent) mixtures with different DESs weight fractions at temperature range (298.15 to 313.15) K.

Table 1. Detailed information of drugs and the used chemicals.

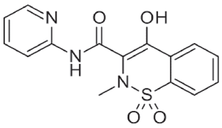
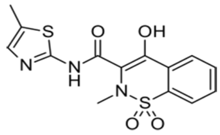
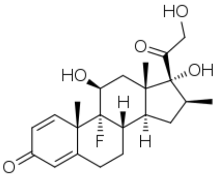
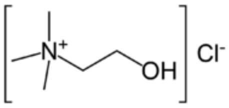
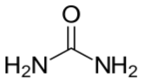
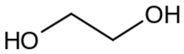
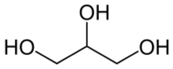
Chemical name	Source	Molar mass (g·mol^{-1})	CAS No.	Mass fraction (purity)	Structure
Piroxicam	Zahravi	331.348	36322-90-4	>0.98	
Meloxicam	Zahravi	351.403	71125-38-7	>0.98	
Betamethasone	Zahravi	392.461	378-44-9	>0.98	
Choline Choloride	Merck	139.623	67-48-1	>0.99	
Urea	Merck	60.060	57-13-6	>0.98	
Ethylene glycol	Merck	62.070	107-21-1	>0.99	
Glycerol	Merck	92.094	56-81-5	>0.99	

Table 2. Common properties of DESs used in this work at 298.15 K and 0.0866 MPa[a].

DES	Salt – HBD (molar ratio)	Water content	10^{-3} d / (kg·m^{-3}) Exp	Lit	u (m·s^{-1})	n$_D$ Exp	Lit
ChCl/U	1:2	0.09%	1.1939	1.1979[42]	2062.27	1.5041	1.5044[43]
ChCl/EG	1:2	0.02%	1.1160	1.1200[11]	1911.04	1.4685	1.4682[44]
ChCl/G	1:2	0.05%	1.1769	1.1800[11]	2012.59	1.4865	1.4867[44]

[a] Standard uncertainties for u(*d*) = 0.006 kg·m^{-3}, u(*u*) = 0.50 m·s^{-1}, u(n_D) = 0.0002, u(*T*) = 0.1K and u(*P*) = 0.0001 MPa.

Table 3. The experimental ($x_1^{\exp}$)[a] and calculated (x_1^{cal}) solubility of BETA in the aqueous DES solutions with various weight fractions (w_3)[c] within the temperature range *T*[b]/ K=298.15 to 313.15 from e-NRTL and Wilson models.

T / K	$10^6 x_1^{\exp}$	e-NRTL model $10^6 x_1^{cal}$	$100\frac{x_1^{\exp}-x_1^{cal}}{x_1^{\exp}}$	Wilson model $10^6 x_1^{cal}$	$100\frac{x_1^{\exp}-x_1^{cal}}{x_1^{\exp}}$
BETA (1) + water (2) + ChCl/G (3)					
w_3=0.0000					
298.15	2.232	2.252	-0.89	2.104	5.73
303.15	3.182	3.111	2.23	3.029	4.80
308.15	4.022	3.766	6.36	4.145	-3.05
313.15	5.609	6.565	-17.08	5.745	2.42
w_3=0.2000					
298.15	3.149	3.574	-13.51	3.653	-15.99
303.15	5.275	4.947	6.21	4.861	7.85

Table 3. Continued

308.15	9.007	8.589	4.64	8.970	0.41
313.15	13.55	10.581	21.90	13.52	0.21
w_3=0.4000					
298.15	6.909	6.363	7.90	6.239	9.69
303.15	7.144	8.917	-24.82	8.064	-12.88
308.15	9.675	9.987	-3.22	10.430	-7.80
313.15	15.860	19.801	-24.84	15.880	-0.12
w_3=0.6000					
298.15	12.080	12.551	-3.87	10.323	14.54
303.15	14.720	14.443	1.88	14.640	0.54
308.15	14.880	14.874	0.04	15.140	-1.74
313.15	37.960	43.766	-15.29	37.940	0.05
w_3=0.8000					
298.15	17.240	20.060	-16.35	20.486	-18.82
303.15	29.640	36.573	-23.33	32.007	-7.99
308.15	47.520	52.525	-10.53	44.127	7.14
313.15	123.900	123.958	-0.04	123.772	0.10
w_3=0.9000					
298.15	42.070	49.086	-16.67	40.286	4.24
303.15	51.980	65.666	-26.32	58.533	-12.61
308.15	87.170	78.551	9.88	92.923	-6.59
313.15	224.200	251.239	-12.06	224.729	-0.23
BETA (1) + water (2) + ChCl/EG (3)					
w_3=0.0000					
298.15	2.232	2.261	-1.28	2.106	4.68
303.15	3.182	3.073	7.91	3.644	-14.53
308.15	4.022	5.181	-28.81	4.113	-2.26
313.15	5.609	6.567	-17.08	5.608	0.02
w_3=0.2000					
298.15	3.330	3.765	-13.06	3.968	-17.70
303.15	6.160	5.274	14.38	6.137	0.37
308.15	14.350	10.146	29.29	14.178	1.19
313.15	16.050	14.216	11.43	15.925	0.78
w_3=0.4000					
298.15	7.417	6.928	6.58	7.296	1.35
303.15	8.142	9.655	-18.58	8.180	-0.47
308.15	27.420	21.073	23.14	29.904	-9.05
313.15	33.380	35.061	-5.03	33.560	-0.54
w_3=0.6000					
298.15	15.388	14.215	7.62	12.799	16.82
303.15	103.010	27.029	73.76	34.239	66.71
308.15	144.620	34.482	76.16	42.254	70.78
313.15	173.301	57.688	66.71	45.721	73.62
w_3=0.8000					
298.15	18.321	32.682	-78.32	20.183	-10.12
303.15	104.010	95.570	8.11	105.461	-2.41
308.15	152.002	161.674	-6.36	154.561	-1.68
313.15	173.485	223.192	-28.65	174.936	-0.83
w_3=0.9000					

Table 3. **Continued**

298.15	47.261	46.693	-1.20	39.342	16.75
303.15	202.301	198.303	1.98	203.358	-.52
308.15	290.090	405.747	-39.86	290.114	-0.01
313.15	318.610	419.619	-31.70	319.655	-0.33
		BETA (1) + water (2) + ChCl/U (3)			
w_3=0.0000					
298.15	2.242	1.824	18.64	2.250	-0.36
303.15	3.153	4.741	-50.33	3.420	-8.49
308.15	4.171	5.749	-37.86	4.001	4.08
313.15	5.612	5.830	-3.88	5.629	-0.29
w_3=0.2000					
298.15	10.390	9.417	9.36	11.311	-8.86
303.15	10.940	11.755	-7.44	12.091	-10.52
308.15	15.090	15.678	-3.95	17.155	-13.68
313.15	34.701	25.299	27.09	34.850	-0.43
w_3=0.4000					
298.15	37.550	34.440	8.28	31.583	15.89
303.15	39.830	35.084	11.91	35.117	11.83
308.15	41.602	42.063	-1.11	40.566	2.49
313.15	66.690	71.251	-6.83	66.746	-0.08
w_3=0.6000					
298.15	57.150	58.696	-2.71	62.801	-9.88
303.15	64.480	77.933	-20.70	75.678	-17.37
308.15	71.860	87.563	-21.85	79.321	-10.38
313.15	114.011	123.636	-8.44	113.799	0.17
w_3=0.8000					
298.15	144.202	111.725	22.52	153.731	-6.60
303.15	227.201	242.178	-6.59	185.733	18.25
308.15	251.998	334.465	-32.72	241.490	4.17
313.15	373.201	476.526	-27.68	370.784	0.64
w_3=0.9000					
298.15	173.702	130.258	25.01	181.346	-4.40
303.15	265.303	315.570	-18.94	293.666	-10.69
308.15	319.811	440.863	-37.85	323.189	-1.06
313.15	404.404	557.135	-37.76	406.256	-0.45

[a] Standard uncertainty u(x_1^{exp}) = 0.5%, [b] Standard uncertainty u(T) = 0.01 K and [c] Standard uncertainty u(w_3) = 0.0002

Table 4. The experimental ($x_1^{\exp}$)and calculated (x_1^{cal}) solubility of MEL in the aqueous DES solutions with various weight fractions (w_3) within the temperature range T/ K=298.15 to 313.15 from e-NRTL and Wilson models.

T / K	$10^5 x_1^{cal}$	**e-NRTL model**		**Wilson model**	
		$10^5 x_1^{cal}$	$100\frac{x_1^{\exp}-x_1^{cal}}{x_1^{\exp}}$	$10^5 x_1^{cal}$	$100\frac{x_1^{\exp}-x_1^{cal}}{x_1^{\exp}}$
		MEL (1) + water (2) + ChCl/G (3)			
w_3=0.0000					
298.15	1.125	1.094	2.77	1.113	1.07
303.15	1.220	1.222	-0.14	1.122	8.03
308.15	1.299	1.292	0.55	1.130	13.01
313.15	1.382	1.389	-0.50	1.138	17.65

Table 4. Continued

w_3=0.2000					
298.15	1.491	1.485	0.40	1.481	0.69
303.15	1.553	1.565	-0.77	1.528	1.62
308.15	1.805	1.722	4.59	1.811	-0.33
313.15	1.823	1.843	-1.10	1.826	-0.16
w_3=0.4000					
298.15	2.103	1.953	7.13	2.131	-1.35
303.15	2.217	2.378	-7.26	2.213	0.17
308.15	2.556	2.425	5.12	2.463	3.65
313.15	2.713	2.951	-8.79	2.746	-1.22
w_3=0.6000					
298.15	2.211	2.171	1.88	2.213	-0.09
303.15	2.763	2.525	8.61	2.716	1.70
308.15	2.816	2.710	3.76	2.926	-3.91
313.15	3.579	3.338	6.73	3.465	3.17
w_3=0.8000					
298.15	2.304	2.411	-4.63	2.301	0.19
303.15	3.302	3.109	5.84	3.173	3.90
308.15	3.351	3.248	3.07	3.186	4.93
313.15	4.005	4.155	-3.74	4.319	-7.84
w_3=0.9000					
298.15	2.914	2.793	4.16	2.934	-0.69
303.15	3.629	4.210	-16.01	3.749	-3.30
308.15	3.706	4.351	-17.40	3.766	-1.63
313.15	4.753	4.383	7.78	4.459	6.19
MEL (1) + water (2) + ChCl/EG (3)					
w_3=0.0000					
298.15	1.125	1.126	-0.05	1.130	-0.55
303.15	1.220	1.217	0.25	1.221	-0.03
308.15	1.299	1.297	0.16	1.302	-3.60
313.15	1.382	1.378	0.27	1.380	7.20
w_3=0.2000					
298.15	2.808	2.696	3.98	2.795	0.44
303.15	3.148	3.077	2.24	3.122	0.84
308.15	3.474	3.398	2.19	3.447	0.77
313.15	5.076	4.833	4.78	5.079	-0.06
w_3=0.4000					
298.15	3.706	3.723	-0.45	3.804	-2.65
303.15	3.947	3.956	-0.24	3.966	-0.48
308.15	4.495	4.591	-2.14	4.563	-1.51
313.15	8.410	8.135	3.27	8.433	-0.28
w_3=0.6000					
298.15	3.869	3.894	-0.65	3.854	0.39
303.15	4.081	4.134	-1.31	4.099	-0.44
308.15	5.256	5.242	0.27	5.178	1.49
313.15	10.48	9.598	8.42	10.399	0.77
w_3=0.8000					
298.15	4.014	4.287	-6.78	4.052	-0.94
303.15	4.624	4.985	-7.81	4.507	2.53
308.15	6.588	7.155	-8.61	6.620	-0.48
313.15	12.320	12.37	-0.44	12.416	-0.78

Table 4. Continued

w_3=0.9000					
298.15	7.147	6.913	3.28	7.067	1.12
303.15	7.159	8.188	-14.38	7.168	-0.13
308.15	9.712	10.02	-3.21	9.680	0.33
313.15	25.441	25.38	0.25	25.409	0.12
		MEL (1) + water (2) + ChCl/U (3)			
w_3=0.0000					
298.15	1.125	1.144	-1.67	1.130	-0.18
303.15	1.220	1.227	-0.54	1.218	0.51
308.15	1.299	1.302	-0.23	1.301	0.01
313.15	1.382	1.381	0.11	1.381	0.05
w_3=0.2000					
298.15	1.297	1.218	6.09	1.318	-1.62
303.15	1.342	1.391	-3.65	1.403	-4.54
308.15	1.573	1.531	2.70	1.562	0.73
313.15	1.664	1.651	0.77	1.671	-0.44
w_3=0.4000					
298.15	1.375	1.673	-21.64	1.586	-15.31
303.15	1.476	1.701	-15.26	1.596	-8.13
308.15	1.875	2.097	-11.86	1.960	-4.53
313.15	2.055	2.182	-6.19	2.071	-0.79
w_3=0.6000					
298.15	2.135	1.958	8.27	2.031	4.87
303.15	2.282	2.026	11.20	2.114	7.36
308.15	2.504	2.354	5.982	2.374	5.21
313.15	2.669	2.722	-1.99	2.670	-0.04
w_3=0.8000					
298.15	2.395	2.235	6.67	2.373	0.90
303.15	2.564	2.676	-4.38	2.587	-0.91
308.15	2.940	3.004	-2.18	2.884	1.90
313.15	3.407	3.653	-7.23	3.422	-0.43
w_3=0.9000					
298.15	2.623	2.947	-12.33	2.721	-3.72
303.15	2.805	3.176	-13.23	2.961	-5.57
308.15	3.085	3.660	-18.63	3.358	-8.84
313.15	4.773	5.469	-14.59	4.797	-0.51

Table 5. The experimental ($x_1^{\exp}$) and calculated (x_1^{cal}) solubility of PIR in the aqueous DES solutions with various weight fractions (w_3) within the temperature range *T*/ K=298.15 to 313.15 from e-NRTL and Wilson models.

T / K	$10^5 x_1^{cal}$	**e-NRTL model**		**Wilson model**	
		$10^5 x_1^{cal}$	$100\frac{x_1^{\exp}-x_1^{cal}}{x_1^{\exp}}$	$10^5 x_1^{cal}$	$100\frac{x_1^{\exp}-x_1^{cal}}{x_1^{\exp}}$
		PIR (1) + water (2) + ChCl/G (3)			
w_3=0.0000					
298.15	0.0401	0.0401	-0.18	0.0405	-0.99
303.15	0.0434	0.0434	-0.03	0.0433	0.23
308.15	0.0478	0.0476	0.36	0.0477	0.21
313.15	0.0506	0.0505	0.17	0.0510	-0.79

Table 5. Continued

w_3=0.2000					
298.15	1.147	1.148	-0.06	1.181	-2.95
303.15	1.252	1.264	-0.93	1.251	0.06
308.15	1.497	1.503	-0.40	1.416	5.41
313.15	1.529	1.544	-0.98	1.575	-2.99
w_3=0.4000					
298.15	1.908	2.038	-6.80	1.849	3.10
303.15	2.265	2.375	-4.84	2.220	1.98
308.15	2.502	2.482	0.79	2.526	-0.96
313.15	2.672	2.797	-4.67	2.612	2.24
w_3=0.6000					
298.15	2.525	2.481	1.73	2.418	4.22
303.15	2.983	2.939	1.48	2.980	0.09
308.15	3.054	3.136	-2.68	3.103	-1.59
313.15	3.326	3.275	1.54	3.227	2.98
w_3=0.8000					
298.15	2.772	3.382	-22.01	3.001	-8.218
303.15	3.053	3.853	-26.21	3.044	0.30
308.15	3.432	4.185	-21.93	3.962	-15.45
313.15	3.614	4.401	-21.78	4.175	-15.51
w_3=0.9000					
298.15	4.142	4.118	0.59	4.213	-1.72
303.15	4.380	4.579	-4.54	4.387	-0.16
308.15	5.974	5.615	6.01	4.991	16.45
313.15	6.790	6.661	1.90	5.866	13.61
			PIR (1) + water (2) + ChCl/EG (3)		
w_3=0.0000					
298.15	0.0401	0.0400	0.13	0.0400	0.04
303.15	0.0434	0.0434	-0.05	0.0431	0.50
308.15	0.0478	0.0477	0.12	0.0480	-0.01
313.15	0.0506	0.0504	0.29	0.0505	0.09
w_3=0.2000					
298.15	1.806	1.796	0.53	1.796	0.55
303.15	1.839	1.819	1.08	1.836	0.16
308.15	1.856	1.897	-2.20	1.850	0.32
313.15	1.925	1.963	-1.95	2.079	-7.99
w_3=0.4000					
298.15	2.233	2.299	-2.97	2.228	0.22
303.15	2.868	2.406	16.10	2.751	4.08
308.15	3.027	3.012	0.49	3.204	-5.84
313.15	3.674	3.694	-0.54	3.270	10.99
w_3=0.6000					
298.15	2.908	2.805	3.55	2.891	0.62
303.15	2.983	2.892	3.05	3.261	-9.32
308.15	3.863	3.779	2.17	3.800	1.64
313.15	4.058	4.149	-2.23	4.327	-6.63
w_3=0.8000					
298.15	3.053	3.414	-11.82	3.160	-3.50
303.15	4.161	4.186	-0.60	4.791	-15.14
308.15	4.806	5.967	-24.17	5.133	-6.80
313.15	6.196	6.896	-11.29	7.156	-15.49

Table 5. Continued

w_3=0.9000					
298.15	4.380	4.458	-1.78	5.316	-21.36
303.15	5.313	5.751	-8.24	6.309	-18.74
308.15	12.601	9.960	20.94	12.684	-0.66
313.15	14.131	12.19	13.73	13.873	1.82
			PIR (1) + water (2) + ChCl/U (3)		
w_3=0.0000					
298.15	0.0401	0.0417	-4.06	0.0402	-0.03
303.15	0.0434	0.0433	0.29	0.0433	0.31
308.15	0.0478	0.0477	0.14	0.0478	0.01
313.15	0.0506	0.0507	-0.16	0.0507	-0.32
w_3=0.2000					
298.15	5.284	5.128	2.95	5.255	0.54
303.15	6.148	6.217	-1.11	6.309	-2.62
308.15	39.120	38.830	0.74	39.099	0.06
313.15	42.360	41.320	2.47	42.387	-0.06
w_3=0.4000					
298.15	17.921	17.856	0.36	17.807	0.63
303.15	31.229	30.226	3.28	27.719	11.24
308.15	48.331	50.160	-3.79	48.587	-0.53
313.15	55.842	60.461	-8.28	55.703	0.25
w_3=0.6000					
298.15	38.710	37.950	1.97	38.807	-0.25
303.15	42.649	49.531	-16.12	49.725	-16.59
308.15	61.351	58.849	4.07	60.158	1.94
313.15	81.138	70.920	12.60	80.699	0.54
w_3=0.8000					
298.15	65.020	65.651	-0.97	64.230	1.21
303.15	82.990	72.091	13.13	74.542	10.18
308.15	83.469	91.202	-9.26	88.828	-6.42
313.15	97.001	103.602	-6.82	97.464	-0.48
w_3=0.9000					
298.15	88.871	90.624	-1.97	89.307	-0.49
303.15	100.099	104.701	-4.55	105.013	-4.91
308.15	119.699	115.099	3.84	111.375	6.95
313.15	128.801	133.902	-3.95	128.392	0.32

The relationship between the solubility of drugs, x_1, versus temperature and weight fractions in aqueous DESs solutions has been graphically plotted in Figures 1-3. These figures show that the solubility of drugs was raised in the presence of DESs at higher temperatures and concentration of DES. Also, the order for the performance of the co-solvents in drugs solubility enhancement is as follows:

MEL: ChCl/EG> ChCl/G> ChCl/U

MEL: ChCl/U> ChCl/EG> ChCl/G

BETA: ChCl/U> ChCl/EG> ChCl/G

The high solubility of drugs in the presence of DESs reinforces their ability as powerful solubilizing agents. The levels of solubility observed for drugs in the studied systems could be due to solute–solvent interactions. The hydrophobic drugs can be solved in a solvent-based on interactions such as H-bonds, van der Waals forces, ion-dipole and dipole-dipole between solute–solvent.[45,46] At the atomic level, the used drugs and DESs can interact with each other mainly via H-bonds interactions.

The studied drugs have the ability to act as HBDs or HBAs, forming H-bonds with DESs. The H-bond is formed between the carboxyl and hydroxyl groups of used drugs and the hydroxyl or carboxyl and Cl group of DESs. The solvating power of DESs is remarkable rather than water, because, there are H-bonds and dipole-dipole interactions between drug and water. But in drug + water + DESs systems, there are strong ion-dipole interactions in addition to H-bonds and dipole-dipole interactions. In order of these interactions, significant increase in the solubility of

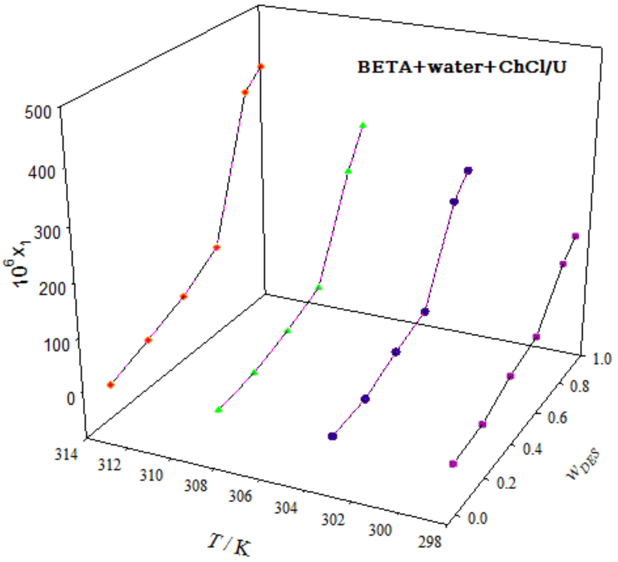


Figure 1. The relationship between mole fraction solubility of BETA, x_1, versus w_{DES} and T in aqueous ChCl/U solutions and solid lines obtained from Wilson model.

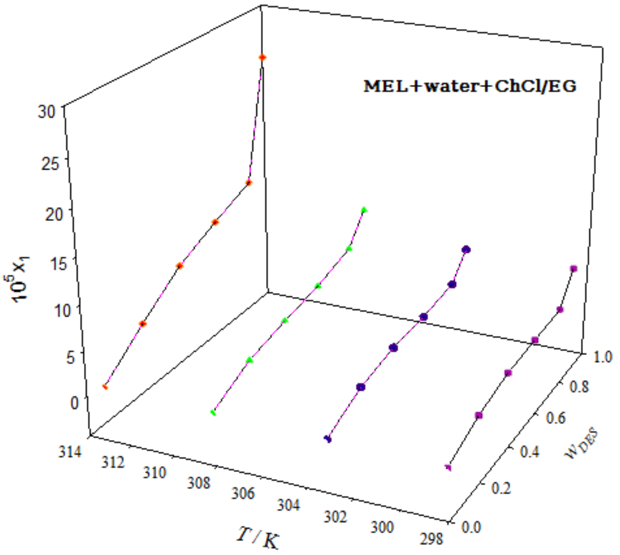


Figure 2. The relationship between mole fraction solubility of MEL, x_1, versus w_{DES} and T in aqueous ChCl/EG solutions and solid lines obtained from Wilson model.

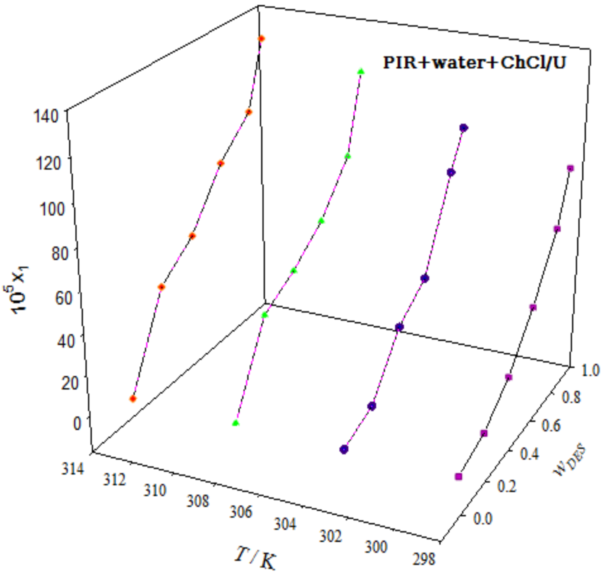


Figure 3. The relationship between mole fraction solubility of PIR, x_1, versus w_{DES} and T in aqueous ChCl/U solutions and solid lines obtained from Wilson model.

drugs in the presence of DESs yielded. Moreover, it should also be noted that the performance of and DES as a co-solvent for a drug is different. Some DESs have stronger intermolecular interactions, thus their interactions with the drugs are weak. Also, H-bonds interactions between HBA and HBD in DESs were increased with the increased H-bonds group (hydroxyl and carboxyl groups) and H-bonds interaction of ChCl with second component is weakened.[45,47] Otherwise, it is noteworthy that the monohydrated solid form of PIR has been reported in neat water after saturation of anhydrate form.[48]

The results of the applied models are given in Tables 3, 4 and 5. Figures 1, 2 and 3 present the calculated and experimental solubility of drugs in aqueous DES solutions using Wilson model. The obtained results for %*ARD* are collected in Table 6. It can be understood the Wilson model presents better outcomes with respect to the e-NRTL, even this model is more accurate. Thus, the efficiency of the models employed in the solubility values correlation can be written as Wilson > e-NRTL.

Thermodynamic properties of dissolution

The values of apparent standard Gibbs free energy, enthalpy, entropy for solution process, $\%\xi_H$ and $\%\xi_{TS}$ in investigated co-solvent systems at studied temperatures are given in Tables 7, 8 and 9. The apparent standard dissolution enthalpy in all the systems is positive, which denotes that the crystal lattice energy is more than the essential energy for the process of solute solvation as a favorable parameter.

Accordingly, the dissolution process of the studied drugs in co-solvent systems is endothermic. Also, apparent standard dissolution entropy of BETA is positive in the three DESs systems, which specifies that the apparent standard dissolution entropy is favorable parameter for the solvation of this drug in the investigated systems. But in the case of MEL in the presence of studied DESs ΔS^0_{Soln} is negative in water and aqueous solutions of ChCl/U and ChC/G at a weigh fraction of 0.20 to 0.80 and its value is positive for 0.90. In addition, ΔS^0_{Soln} is positive for solutions containing ChCl/EG. The ΔS^0_{Soln} for PIR in water is negative and in ChCl/G and ChCl/EG at 0.20 to 0.80 and 0.2 to 0.6 weight fractions are negative respectively (positive for w_{DES}=0.9), however it is positive in systems (PIR + water + ChCl/U). The apparent standard dissolution Gibbs free energy have positive values in all studied systems, consequently the solution process is non-spontaneous (Figure 4). ΔG^0_{Soln} values for drug dissolution were in good agreement with for solubilities of them in the investigated systems.

Table 6. The calculated average relative deviation percent (*ARD%*) for the solubility of the drugs in the aqueous DES solutions at different temperatures from two models.

T / K	e-NRTL	Wilson	e-NRTL	Wilson	e-NRTL	Wilson
	BETA (1) + water (2) + ChCl/U (3)		**MEL (1) + water (2) + ChCl/U (3)**		**PIR (1) + water (2) + ChCl/U (3)**	
298.15	16.56	4.20	9.13	4.60	3.89	0.51
303.15	9.51	10.09	7.37	4.70	5.81	6.88
308.15	9.44	0.45	6.70	3.80	3.30	2.59
313.15	10.56	0.35	4.58	0.35	5.18	0.18
Average	11.51	3.77	6.94	3.36	4.54	2.54
	BETA (1) + water (2) + ChCl/G (3)		**MEL (1) + water (2) + ChCl/G (3)**		**PIR(1) + water (2) + ChCl/G (3)**	
298.15	9.46	7.80	3.66	0.47	4.58	3.29
303.15	7.49	3.67	5.51	1.70	5.40	0.09
308.15	7.06	3.20	6.00	2.30	5.28	8.37
313.15	7.41	0.14	5.33	2.70	4.81	6.61
Average	7.85	3.68	5.12	1.79	5.02	4.59
	BETA (1) + water (2) + ChCl/EG (3)		**MEL (1) + water (2) + ChCl/EG (3)**		**PIR (1) + water (2) + ChCl/EG (3)**	
298.15	8.11	5.29	9.13	1.30	1.60	1.33
303.15	13.72	8.92	7.37	0.65	6.27	0.68
308.15	5.73	5.13	6.70	0.67	8.58	0.67
313.15	6.13	0.39	4.58	0.29	5.51	0.29
Average	8.09	4.73	6.94	0.73	5.49	0.73

Table 7. Thermodynamic functions for solution process of BETA at different weight fractions of DES (w_3) at mean temperature (T_m).

w_3	ΔH^0_{Soln}/ kJ·mol^{-1}	$T_M\Delta S^0_{Soln}$/ kJ·mol^{-1}	ΔG^0_{Soln}/ kJ·mol^{-1}	$\xi_{\mathcal{B}}$	$\xi_{\mathcal{B}}$
		BETA (1) + water (2) + ChCl/U (3)			
0.0000	47.09	15.24	31.85	75.55	24.45
0.2000	60.75	32.64	28.11	65.05	34.95
0.4000	27.30	1.89	25.41	93.53	6.47
0.6000	33.67	9.51	24.16	77.98	22.02
0.8000	45.92	24.7	21.22	65.02	34.98
0.9000	42.35	21.55	20.80	66.28	33.72
		BETA (1) + water (2) + ChCl/G (3)			
0.0000	47.09	15.21	31.88	75.58	24.42
0.2000	76.31	46.05	30.26	62.36	37.64
0.4000	43.17	13.75	29.42	75.85	24.15
0.6000	53.11	25.33	27.78	67.71	32.29
0.8000	98.96	73.34	25.62	57.44	42.56
0.9000	85.57	61.63	23.94	58.13	41.87
		BETA (1) + water (2) + ChCl/EG (3)			
0.0000	46.54	14.67	31.87	76.03	23.97
0.2000	85.36	55.62	29.74	60.55	39.45
0.4000	88.83	60.67	28.16	59.42	40.58
0.6000	61.59	34.91	26.69	63.83	36.17
0.8000	103.78	80.20	23.58	56.41	43.59
0.9000	95.15	73.13	22.01	56.54	43.46

Furthermore, the order of Gibbs free energy change values is the reverse of the solubility values as MEL was lower in (water + ChCl/EG), PIR in (water + ChCl/U) and BETA in (water + ChCl/U).

For most of theinvestigated systems, $\%\xi_H$ are greater than $\%\xi_{\mathcal{B}}$, which means that the main contributing force to the apparent standard dissolution Gibbs free energy are the enthalpy. It means that the dissolution process contains some effects such as the interactions between solute-solvent, hydrogen bonds, electrostatic forces and hydrophobic interaction. Consequently, the energy new bond made between solvent and solute molecules is not adequate to provide the energy needed for breaking the original bond in various solvents, the enthalpy change contributing force is larger in dissolving process.

Table 8. Thermodynamic functions for solution process of MEL at different weight fractions of DES (w_3) at mean temperature (T_m).

w_3	ΔH^0_{Soln}/ kJ·mol^{-1}	$T_M\Delta S^0_{Soln}$/ kJ·mol^{-1}	ΔG^0_{Soln}/ kJ·mol^{-1}	ξ_H	ξ_{TS}
		MEL (1) + water (2) + ChCl/U (3)			
0.0000	10.56	-23.96	34.52	30.60	69.40
0.2000	24.36	-4.13	28.49	85.51	14.49
0.4000	22.41	-5.53	27.94	80.22	14.78
0.6000	11.84	-15.20	27.03	43.79	56.21
0.8000	18.50	-8.13	26.63	69.45	30.54
0.9000	29.17	2.90	26.27	90.97	9.03
		MEL (1) + water (2) + ChCl/G (3)			
0.0000	10.56	-23.96	34.52	30.60	69.40
0.2000	10.79	-16.38	27.17	39.70	60.30
0.4000	18.22	-8.59	26.81	67.96	32.04
0.6000	26.07	-0.24	26.31	99.09	0.91
0.8000	23.09	-2.83	25.93	89.08	10.92
0.9000	44.04	18.79	25.25	70.10	29.90
		MEL (1) + water (2) + ChCl/EG (3)			
0.0000	10.56	-23.96	34.52	30.60	69.40
0.2000	28.97	2.93	26.04	90.53	9.17
0.4000	39.89	14.66	25.24	73.13	26.87
0.6000	50.01	25.06	24.95	66.62	33.38
0.8000	57.47	32.87	24.60	63.62	36.38
0.9000	63.37	40.12	23.25	61.23	38.77

Table 9. Thermodynamic functions for solution process of PIR at different weight fractions of DES (w_3) at mean temperature (T_m).

w_3	ΔH^0_{Soln}/ kJ·mol^{-1}	$T_M\Delta S^0_{Soln}$/ kJ·mol^{-1}	ΔG^0_{Soln}/ kJ·mol^{-1}	ξ_{TS}	ξ_{TS}
		PIR (1) + water (2) + ChCl/U (3)			
0.0000	12.34	-24.76	37.11	33.26	66.74
0.2000	125.68	103.35	22.33	54.87	45.13
0.4000	59.91	39.70	20.21	60.14	39.86
0.6000	40.01	20.88	19.13	65.71	34.29
0.8000	18.58	0.51	18.07	97.32	2.68
0.9000	20.08	2.73	17.35	88.02	11.97
		PIR (1) + water (2) + ChCl/G (3)			
0.0000	12.34	-24.77	37.11	33.26	66.74
0.2000	16.19	-12.30	28.49	56.84	43.16
0.4000	17.28	-9.83	27.11	63.74	45.36
0.6000	13.24	-13.25	26.29	49.97	50.03
0.8000	14.19	-12.10	25.05	53.98	46.02
0.9000	27.80	2.74	24.73	91.02	8.98
		PIR (1) + water (2) + ChCl/EG (3)			
0.0000	12.34	-24.77	37.11	33.26	66.74
0.2000	3.11	-24.57	27.68	11.22	88.78
0.4000	24.05	-2.48	26.54	90.64	9.36
0.6000	17.67	-8.38	26.05	67.85	32.15
0.8000	35.23	9.75	25.48	78.32	21.68
0.9000	50.21	26.75	23.47	65.25	34.75

Conclusion

The equilibrium solubilities of three drugs (betamethasone, meloxicam, piroxicam) in co-solvent mixtures of {water + ChCl/U}, {water + ChCl/EG} and {water + ChCl/G} were measured experimentally by the saturation shake-flask method within the temperature range from 298.15 K to 313.15 K at atmospheric pressure. At the same temperature

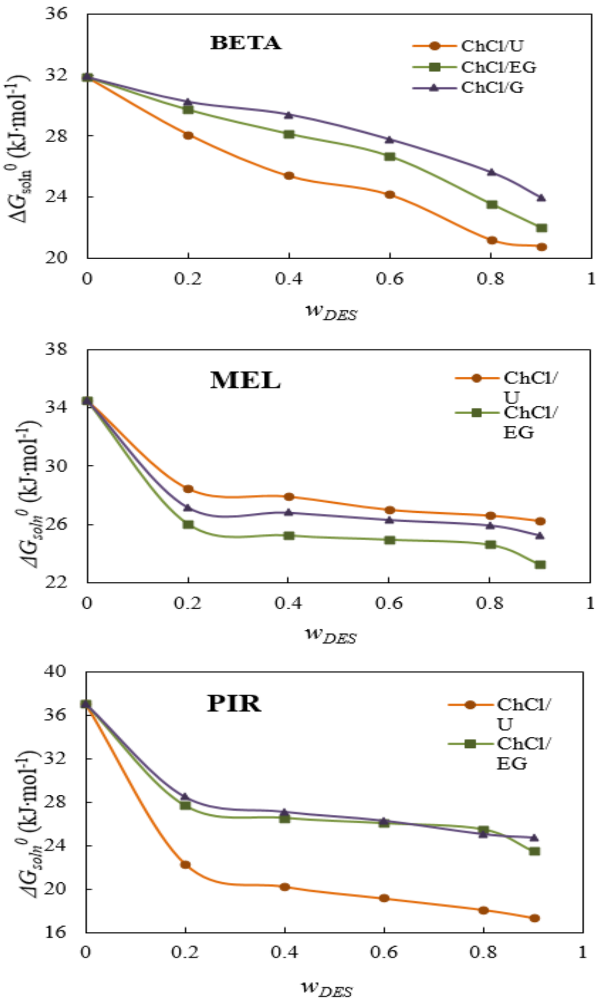


Figure 4. ΔG_{soln}^{0}, relative to dissolution process of drugs in DES + water co-solvent mixtures at 305.5 K.

and weight fraction of DESs the mole fraction solubility of MEL was higher in (water + ChCl/EG), PIR in (water + ChCl/U) and BETA in (water + ChCl/U) than in the other studied mixtures.

Furthermore, the drugs' solubilities were mathematically correlated through the Wilson and e-NRTL activity coefficient models obtaining %*ARD* lower than 3.30% for Wilson model. It turned out that the Wilson model could provide a better acceptable fitting result than those obtained by the e-NRTL. Finally, thermodynamic functions of the dissolution were obtained using Gibbs free energy and van't Hoff equations. The apparent standard dissolution Gibbs free energy and enthalpy change are positive in all the binary solvents investigated in this paper. These results indicate that the dissolution process is more favorable as the concentration of DES increases in the mixtures and it is endothermic. In addition, in most of the studied systems, the main contributor to the apparent standard dissolution Gibbs free energy in the dissolution process is the enthalpy during the dissolution, consequently, this procedure is enthalpy-dominated.

Acknowledgments

We are most grateful for the continuing financial support of this work by the University of Tabriz.

Conflict of Interest

The authors claim that there is no conflict of interest.

Reference

1. Pate JN, Rathod DM, Patel NA, Modasiya MK. Techniques to improve the solubility of poorly soluble drugs. Int J Pharm Life Sci. 2012;3(2):1459-69.
2. Yalkowsky SH, Roseman TJ. Solubilization of drugs by cosolvents. In: Yalkowsky SH, editor. Techniques of solubilization of drugs. New York: Marcel Dekker; 1981.
3. Ahumada EA, Delgado DR, Martínez F. Solubility of acetaminophen in polyethylene glycol400+ water mixtures according to the extended hildebrand. Rev Colomb de Quimica. 2012;41(3):433-77.
4. Jouyban A, Soltanpour S, Acree Jr WE. Solubility of acetaminophen and ibuprofen in the mixtures of polyethylene glycol 200 or 400 with ethanol and water and the density of solute-free mixed solvents at 298.2 k. J Chem Eng Data. 2010;55(11):5252-7. doi:10.1021/je100829d
5. Smith K, Bridson R, Leeke G. Solubilities of pharmaceutical compounds in ionic liquids. J Chem Eng Data 2011;56(5):2039-43. doi:10.1021/je101040p
6. Mehrdad A, Miri AH. Influence of 1-butyl-3-methyl imidazolium bromide, ionic liquid as co-solvent on aqueous solubility of acetaminophen. J Mol Liq. 2016;221:1162-7. doi:10.1016/j.molliq.2016.07.002
7. Mehrdad A, Taeb S, Ehsani-Tabar S. Solubility and thermodynamic properties of acetaminophen in 1-hexyl-4-methylpyridinium bromide and water mixtures. Phys and Chem Liq. 2016:1-14. doi:10.1080/00319104.2016.126363
8. Hayyan M, Abo-Hamad A, AlSaadi MA, Hashim MA. Functionalization of graphene using deep eutectic solvents. Nanoscale Res Lett 2015;10(1):324. doi:10.1186/s11671-015-1004-2
9. Abbott AP, Capper G, Davies DL, Rasheed RK, Tambyrajah V. Novel solvent properties of choline chloride/urea mixtures. Chem Comm. 2003(1):70-1. doi:10.1039/B210714G
10. 10. Smith EL, Abbott AP, Ryder KS. Deep eutectic solvents (dess) and their applications. Chem Rev. 2014;114(21):11060-82. doi:10.1021/cr300162p
11. Abbott AP, Capper G, Davies DL, Munro HL, Rasheed RK, Tambyrajah V. Preparation of novel, moisture-stable, lewis-acidic ionic liquids containing quaternary ammonium salts with functional side chainselectronic supplementary information (esi) available: Plot of conductivity vs. Temperature for the ionic liquid formed from zinc chloride and choline chloride (2: 1). Chem Comm. 2001(19):2010-1. doi:10.1039/B106357J
12. Zhang Q, Vigier KDO, Royer S, Jérôme F. Deep eutectic

solvents: Syntheses, properties and applications. Chem Soc Rev. 2012;41(21):7108-46. doi:10.1039/c2cs35178a
13. Liu P, Hao J-W, Mo L-P, Zhang Z-H. Recent advances in the application of deep eutectic solvents as sustainable media as well as catalysts in organic reactions. RSC Adv. 2015;5(60):48675-704. doi:10.1039/C5RA05746A
14. Lu C, Cao J, Wang N, Su E. Significantly improving the solubility of non-steroidal anti-inflammatory drugs in deep eutectic solvents for potential non-aqueous liquid administration. Med Chem Comm. 2016;7(5):955-9. doi:10.1039/C5MD00551E
15. Shekaari H, Zafarani-Moattar MT, Mokhtarpour M, Faraji S. Exploring cytotoxicity of some choline-based deep eutectic solvents and their effect on the solubility of lamotrigine in aqueous media. J Mol Liq. 2019;1(283):834-42. doi:10.1016/j.molliq.2019.03.079
16. Shekaari H, Zafarani-Moattar MT, Mokhtarpour M. Solubility, volumetric and compressibility properties of acetaminophen in some aqueous solutions of choline based deep eutectic solvents at T=(288.15 to 318.15) K. Eur J Pharm Sci. 2017;15(109):121-30. doi:10.1016/j.ejps.2017.07.021
17. Shekaari H, Zafarani-Moattar MT, Mokhtarpour M. Experimental determination and correlation of acetaminophen solubility in aqueous solutions of choline chloride based deep eutectic solvents at various temperatures. Fluid Phase Equilib. 2018;25(462):100-10. doi:10.1016/j.fluid.2018.01.017
18. Shekaari H, Zafarani-Moattar MT, Shayanfar A, Mokhtarpour M. Effect of choline chloride/ethylene glycol or glycerol as deep eutectic solvents on the solubility and thermodynamic properties of acetaminophen. J Mol Liq. 2018;1(249):1222-35. doi:10.1016/j.molliq.2017.11.057
19. Mokhtarpour M, Shekaari H, Martinez F, Zafarani-Moattar MT. Effect of tetrabutylammonium bromide-based deep eutectic solvents on the aqueous solubility of indomethacin at various temperatures: Measurement, modeling, and prediction with three-dimensional hansen solubility parameters. AAPS PharmSciTech. 2019;20(5):204. doi:10.1208/s12249-019-1373-4
20. Mokhtarpour M, Shekaari H, Martinez F, Zafarani-Moattar MT. Study of naproxen in some aqueous solutions of choline-based deep eutectic solvents: Solubility measurements, volumetric and compressibility properties. Int J Pharm. 2019;564:197-206. doi:10.1016/j.ijpharm.2019.04.029
21. Mokhtarpour M, Shekaari H, Martinez F, Zafarani-Moattar MT. Performance of local composition models to correlate the aqueous solubility of naproxen in some choline based deep eutectic solvents at t=(298.15-313.15) k. Pharm Sci. 2019;25(3):244-53. doi:10.15171/PS.2019.31
22. Wilson GM. Vapor-liquid equilibrium. Xi. A new expression for the excess free energy of mixing. J Am Chem Soc. 1964;86(2):127-30. doi:10.1021/ja01056a002
23. Chen CC, Britt HI, Boston J, Evans L. Local composition model for excess gibbs energy of electrolyte systems. Part i: Single solvent, single completely dissociated electrolyte systems. AIChE J. 1982;28(4):588-96. doi:10.1002/aic.690280410
24. Ren S, Mu H, Alchaer F, Chtatou A, Müllertz A. Optimization of self nanoemulsifying drug delivery system for poorly water-soluble drug using response surface methodology. Drug dev Ind Pharm. 2013;39(5):799-806. doi:10.1002/aic.690280410
25. Dixit RP, Nagarsenker M. Formulation and in vivo evaluation of self-nanoemulsifying granules for oral delivery of a combination of ezetimibe and simvastatin. Drug Dev Ind Pharm. 2008;34(12):1285-96. doi:10.1080/03639040802071570
26. Bandyopadhyay S, Katare O, Singh B. Optimized self nano-emulsifying systems of ezetimibe with enhanced bioavailability potential using long chain and medium chain triglycerides. Colloids Surf B. 2012;100:50-61. doi:10.1016/j.colsurfb.2012.05.019
27. Prausnitz JM, Lichtenthaler RN, de Azevedo EG. Molecular thermodynamics of fluid-phase equilibria. London:Pearson Education; 1998.
28. Chen CC, Evans LB. A local composition model for the excess gibbs energy of aqueous electrolyte systems. AIChE J. 1986;32(3):444-54. doi:10.1002/aic.690320311
29. Pitzer KS. Electrolytes; From dilute solutions to fused salts. J Am Chem Soc. 1980;102(9):2902-6. doi:10.1021/ja00529a006
30. Simonson JM, Pitzer KS. Thermodynamics of multicomponent, miscible ionic systems: The system lithium nitrate-potassium nitrate-water. J Phys Chem. 1986;90(13):3009-13. doi:10.1021/j100404a043
31. Wang S, Qin L, Zhou Z, Wang J. Solubility and solution thermodynamics of betaine in different pure solvents and binary mixtures. J Chem Eng Data. 2012;57(8):2128-35. doi:10.1021/je2011659
32. Wei D, Li H, Li Y-N, Zhu J. Effect of temperature on the solubility of 3-aminopyridine in binary ethanol+ toluene solvent mixtures. Fluid Phase Equilib. 2012;316:132-4. doi:10.1016/j.fluid.2011.11.023
33. Maher A, Croker D, Rasmuson ÅC, Hodnett BK. Solubility of form III piracetam in a range of solvents. J Chem Eng Data. 2010;55(11):5314-8. doi:10.1021/je1003934
34. Ruidiaz MA, Delgado DR, Martínez F, Marcus Y. Solubility and preferential solvation of indomethacin in 1,4-dioxane+ water solvent mixtures. Fluid Phase Equilib. 2010;299(2):259-65. doi:10.1016/j.fluid.2010.09.027
35. Zhou X, Fan J, Li N, Du Z, Ying H, Wu J, et al. Solubility of l-phenylalanine in water and different binary mixtures from 288.15 to 318.15 k. Fluid Phase Equilib. 2012;316:26-33. doi:10.1016/j.fluid.2011.08.029
36. Panahi-Azar V, Ahmadian S, Martínez F, Acree WE, Jouyban A. Thermodynamic studies of fluphenazine decanoate solubility in PEG 200+ water mixtures.

Fluid Phase Equilib. 2012;330:36-43. doi:10.1016/j.fluid.2011.06.008

37. Jouyban V, Khoubnasabjafari M, Martinez F, Peña A, Jouyban A. Solubility of drugs in ethyl acetate-ethanol mixtures at various temperatures. J Drug Del Sci and Tech. 2012;22(6):545-7. doi:10.1016/S1773-2247(12)50094-8
38. Ma J, Liang J, Han J, Zheng M, Zhao H. Solubility modeling and solvent effect for flubendazole in 12 neat solvents. J Chem Eng Data. 2019;64(3):1237-43. doi:10.1021/acs.jced.8b01126
39. Ha E-S, Ha D-H, Kuk D-H, Sim W-Y, Baek I-h, Kim J-S, et al. Solubility of cilostazol in the presence of polyethylene glycol 4000, polyethylene glycol 6000, polyvinylpyrrolidone K30, and poly (1-vinylpyrrolidone-co-vinyl acetate) at different temperatures. J Chem Thermodyn. 2017;113:6-10. doi:10.1016/j.jct.2017.05.040
40. Esteghamat-Panah R, Hadadzadeh H, Farrokhpour H, Mortazavi M, Amirghofran Z. A mononuclear Ru(II) complex with meloxicam: DNA-and bsa-binding, molecular modeling and anticancer activity against human carcinoma cell lines. Inorg Chim Acta. 2017;454:184-96. doi:10.1016/j.ica.2016.04.037
41. Forte A, Melo CI, Bogel-Łukasik R, Bogel-Łukasik E. A favourable solubility of isoniazid, an antitubercular antibiotic drug, in alternative solvents. Fluid Phase Equilib. 2012;318:89-95. doi:10.1016/j.fluid.2012.01.022
42. Xie Y, Dong H, Zhang S, Lu X, Ji X. Effect of water on the density, viscosity, and co2 solubility in choline chloride/urea. J Chem Eng Data. 2014;59(11):3344-52. doi:10.1021/je500320c
43. García G, Aparicio S, Ullah R, Atilhan M. Deep eutectic solvents: Physicochemical properties and gas separation applications. Energ Fuel. 2015;29(4):2616-44. doi:10.1021/ef5028873
44. Leron RB, Soriano AN, Li M-H. Densities and refractive indices of the deep eutectic solvents (choline chloride+ ethylene glycol or glycerol) and their aqueous mixtures at the temperature ranging from 298.15 to 333.15 k. J Taiwan Inst Chem Eng. 2012;43(4):551-7. doi:10.1016/j.jtice.2012.01.007
45. Wang H, Liu S, Zhao Y, Wang J, Yu Z. Insights into the hydrogen bond interactions in deep eutectic solvents composed of choline chloride and polyols. ACS Sustainable Chem Eng. 2019;7(8):7760-7. doi:10.1021/acssuschemeng.8b06676
46. Shah D, Mansurov U, Mjalli FS. Intermolecular interactions and solvation effects of dimethylsulfoxide on type III deep eutectic solvents. Phys Chem Chem Phys. 2019;21(31):17200-8. doi:10.1039/C9CP02368B
47. Higashi K, Yamamoto K, Pandey MK, Mroue KH, Moribe K, Yamamoto K, et al. Insights into atomic-level interaction between mefenamic acid and eudragit epo in a supersaturated solution by high-resolution magic-angle spinning nmr spectroscopy. Mol. Pharm. 2013;11(1):351-7. doi:10.1021/mp4005723
48. Paaver U, Lust A, Mirza S, Rantanen J, Veski P, Heinämäki J, Kogermann K. Insight into the solubility and dissolution behavior of piroxicam anhydrate and monohydrate forms. Int J Pharm. 2012;431(1-2):111-9. doi:10.1016/j.ijpharm.2012.04.042