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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

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A B S T R A C T

Background: To overcome low solubility of naproxen (NAP), deep eutectic solvents (DESs) based on choline chloride (ChCl) with glycerol (G) and oxalic acid (OA) as green solvents have been used up to 0.9 weight fraction of DES at T = (298.15 to 313.15) K.
Methods: DESs were prepared by combination of the two components with the molar ratios: ChCl/G (1:2) and ChCl/OA (1:1). The solubility of NAP in the aqueous DESs solutions was measured at different temperatures with shake flask method.
Results: The solubility in these solvents increased with increasing the weight fraction of DESs, especially in ChCl/OA. The solubility data were correlated by e-NRTL, Wilson and UNIQUAC models. Also, the thermodynamic functions, Gibbs energy, enthalpy, and entropy of dissolution were obtained.
Conclusion: OA based DES exhibits higher solubility than G based DES. The thermodynamic models were successfully used to correlate solubility data. In addition, the results show that, the main contribution for NAP solubility in the aqueous DES solutions is the enthalpy.

Introduction

It is well-known that the solubility data play an important role in optimizing the crystallization procedure and improving the purity and yield of drugs manufacturing. Therefore, it is necessary to know the solubility of drugs in different solvents at various temperatures. On the other hand, the low solubility of drugs in water is one of the main challenges in pharmaceutical fields.
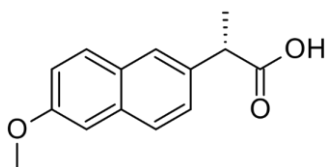

Figure 1. Chemical structure of naproxen.

Naproxen or (+)-6-methoxy-α-methyl-2-naphthaleneacetic acid (NAP, Figure 1) is a nonsteroidal anti-inflammatory drug (NSAID) that relieves pain, fever, swelling, and stiffness but it is slightly soluble in water (15.9 mg.L^{-1}),[1] and poor aqueous solubility of a drug is the factor that limits its development into desired formulation.[2] In this respect, the low solubility of NAP should be increased for the widespread uses and production process of liquid pharmaceutical dosage forms (LPDF).[3,4] The most

effective and inexpensive method for increasing the solubility is co-solvency method. Conventionally, organic solvents[5-8] and ionic liquids (ILs)[9-11] have been used as co-solvents to improve the low solubility of drugs. However, these types of solvents are highly flammable, expensive and toxic for human health.[12,13] Therefore, it is necessary to develop new solvents with lower costs and toxicity and wider availability. Newly, to overcome the limitations of organic solvents and ILs, deep eutectic solvents (DESs) have been introduced and some of them are used to increase solubility and bioavailability of poorly soluble drugs.[14,15] These novel solvents can be prepared using biodegradable, non-toxic and natural materials.[16] They are liquid at room temperature and are considered safer and more environmentally benign and are made of cheap compounds such as a quaternary ammonium salt as hydrogen bond acceptor (HBA) (e.g. choline chloride (ChCl)) and a hydrogen bond donor (HBD) (e.g. urea or a carboxylic acid) at their eutectic composition with melting point much lower than that of the individual components.[14] DESs properties could be tuned by altering the HBA/HBD weight ratio.

In continuation of our systematic investigation of drug solubility in DESs systems,[17-19] the solubility of NAP was measured in the aqueous DESs solutions (ChCl/glycerol (G) and ChCl/ oxalic acid (OA) and the activity

coefficient models such as Wilson,[20] e-NRTL,[21,22] and UNIQUAC[23] have been used to correlate the aqueous solubility data, at various experimental temperatures. In addition, to describe the thermodynamic behavior of NAP in the aqueous DES solutions, the van't Hoff and Gibbs equations were used to calculate some thermodynamic functions such as, Gibbs energy, enthalpy, and entropy of dissolution at $T = (298.15 \text{ K to } 313.15) \text{ K}$.[24-26]

Materials and methods
Chemical
Naproxen was procured from Zahravi pharmaceutical company (Tabriz, Iran), choline chloride, oxalic acid and glycerol extra pure and absolute ethanol were purchased from Merck (Germany). All materials were used as received without other purification. The complete description of the materials has been reported in Table 1.

DES preparation
Two DESs were synthesized in this work. Firstly, choline chloride (ChCl) was selected as hydrogen bonding acceptor (HBA), which was mixed with glycerol and oxalic acid with a mole ratio of 1:2 and 1:1 respectively.[27] Briefly, the corresponding mixtures were stirred and heated at 353.15 K for 1 h until homogeneous and transparent liquid was obtained. Some of the thermophysical properties of these solvents measured in this study and reported by others researchers are summarized in Table 2.

Solubility measurement
There are different methods of testing and measuring the solubility reported in the literature.[28] In this work, the shake flask method has been used for the solubility measurement. Firstly, excess amounts of NAP were added to sealed vials containing appropriate amount of solvent mixtures (DES + water) using an analytical balance with precision 1×10^{-4} g (AW 220, GR220, Shimadzu, Japan). Then the vials with the mixture (solid + liquid) and a magnet were stirred in a system with thermostat (ED, Julabo Co., Germany $T = \pm 0.1$ K). Then the vials were placed in water bath thermostat that was equipped with a temperature-controlling system for 3 days to reach equilibrium. When a saturated solution was attained, the solid phase was removed by centrifugation (D-7200 Tuttlingen, Hettich Co., U.S.A.) followed by filtration (Durapore® membrane filters, type HV, 0.45 µm, Millipore, MA). The clear solutions were diluted with (ethanol + water) and assayed by a double beam spectrophotometer (T80 UV-vis spectrometer PG instruments, U.K.) at 262 nm (Figure 3). The concentrations of the diluted solutions were determined using the calibration curve. Each experimental data point represented the average of at least three repetitive experiments. Also, we recorded the UV-vis spectra (Figure 2) of DESs and NAP in the aqueous DESs solutions which show no interference between them.

The aqueous solubility of NAP in term of drug mole fraction, x_1, in {NAP (1) + water (2) + DESs (3)} system was obtained by flowing formula:[29]

$$x_1 = \frac{\frac{w_1}{M_1}}{\frac{w_1}{M_1} + \frac{w_2}{M_2} + \frac{w_3}{M_3}} \qquad \text{Eq. (1)}$$

where M_i and w_i are the molar mass and mass fractions of i component in the saturated solution, respectively.

Table 1. Descriptions of the used materials.
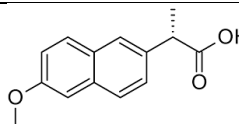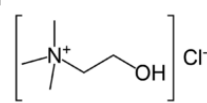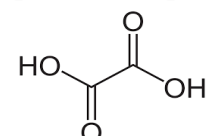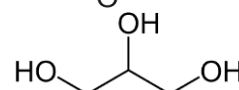
Chemical name	Provenance	CAS No.	Mass fraction (purity)	Structure
Naproxen	Zahravi Pharmaceutical company	26159-31-9	>0.98	
Choline Chloride	Merck	67-48-1	>0.99	
Oxalic acid	Merck	144-62-7	>0.99	
Glycerol	Merck	56-81-5	>0.99	

Table 2. Common properties of DESs used in the article at 298.15 K.

DES	Salt – HBD	Melting Point (K)	$10^{-3} d$ / (kg·m⁻³)		u(m·s⁻¹)	n_D		Water content
	(molar ratio)		Exp	Lit		Exp	Lit	(wt %)
ChCl/OA	1:1	307.15[15]	1.210926	1.2200 [27]	1925.00	1.4809	1.4868 [31]	0.26
ChCl/G	1:2	233.15[30]	1.176963	1.1800 [15]	2012.59	1.4865	1.4867 [32]	0.33

Figure 2. UV–Vis absorption spectra of a) studied DESs in water b) naproxen in aqueous DES solutions.

Modeling

One of the most important issue in the pharmaceutical science is knowledge of the drugs solubility, because it allows scientists and engineers to select appropriate solvents for drug manufacturing processes. In this regard, through a solid-liquid equilibrium (SLE) framework, the following equation is obtained:[22]

$$-lnx_1 = \frac{\Delta_{fus}H}{R}\left(\frac{1}{T} - \frac{1}{T_{fus}}\right) + ln\gamma_1 \qquad \text{Eq. (2)}$$

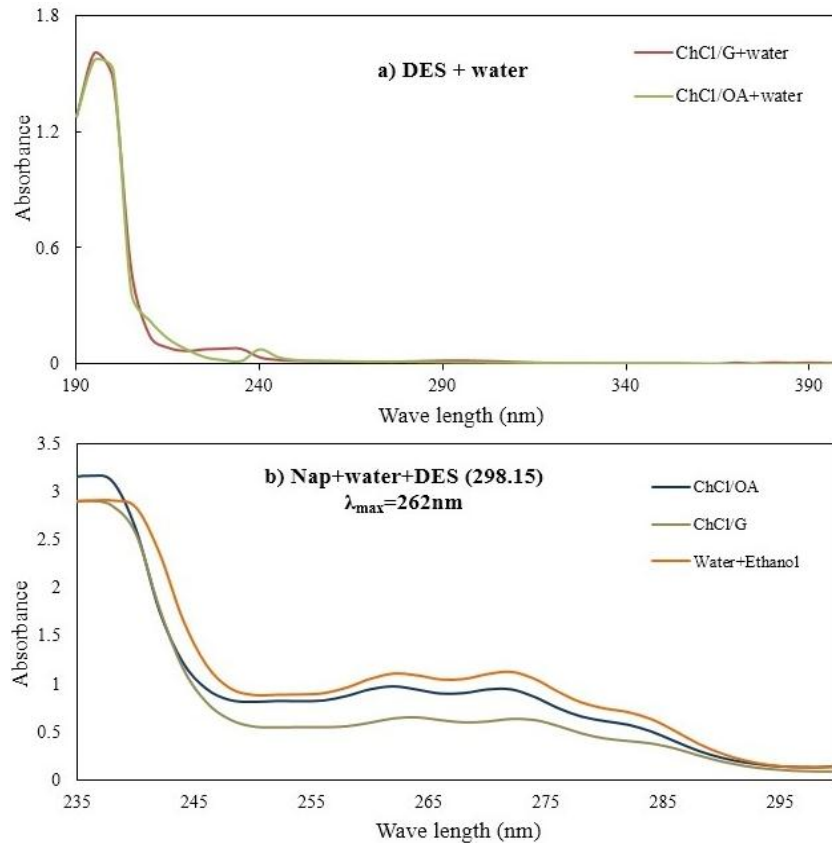where T_{fus}, $\Delta_{fus}H$, T, x_1 and γ_1 refer to: melting temperature for the pure NAP, enthalpy of fusion for the pure NAP, (solid + liquid) equilibrium temperature, equilibrium mole fraction, and the activity coefficient of the NAP in the saturated solution, respectively. The enthalpy of melting is considered to be temperature independent. To correlate the solubility data of the present drug in the aqueous DES solutions, experimental activity coefficients were obtained through Eq. (2) for the solutions.

The Pitzer–Debye–Hückel (PDH) equation

The PDH equation for excess Gibbs energy, G^{ex*LR}, can be written as:[33]

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

$$\text{Eq. (3)}$$

where M_S and ρ are 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 expressed by:

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

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.[34]

Electrolyte-NRTL model

One of the most commonly used activity coefficient based thermodynamic model for industrial systems is the electrolyte-NRTL model (e-NRTL) by Chen (1982) [35] and Chen and Evans (1986).[36] For each species, the activity coefficient is the sum of the Pitzer–Debye–Hückel contribution and the NRTL contribution.[35]

$$\ln(\gamma_i^*) = \ln(\gamma_i^{*PDH}) + \ln(\gamma_i^{*NRTL}) \qquad \text{Eq. (5)}$$

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

$$\text{Eq. (6)}$$

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

Wilson model
Wilson (1964) presented the following expression for the component i activity coefficients:[20]

$$\ln \gamma_i = 1 - \ln \left[\sum_{j=1}^{n} x_j \Lambda_{ij} \right] - \sum_{k=1}^{n} \left[\frac{x_k \Lambda_{ki}}{\sum_{j=1}^{n} x_j \Lambda_{kj}} \right]$$

$$\text{Eq. (7)}$$

where Λ_{ij} is the binary interaction parameter which are related to the pure-component molar volumes, υ, and to characteristic energy, λ, differences by:

$$\Lambda_{ij} = \frac{\upsilon_j}{\upsilon_i} exp \left(-\frac{\lambda_{ij} - \lambda_{ii}}{RT} \right) \qquad \text{Eq. (8)}$$

UNIQUAC model
The Universal Quasi-Chemical theory, from which the UNIQUAC model is derived, can be expressed in terms of the activity coefficients as. The UNIQUAC equation[23] contains adjustable interaction parameters and is written as:

$$\ln(\gamma_i) = \ln(\gamma_i^C) + \ln(\gamma_i^R) \qquad \text{Eq. (9)}$$

$$\ln(\gamma_i^C) = \ln \left(\frac{\Phi_i}{x_i} \right) + \frac{z}{2} q_i \ln \left(\frac{\theta_i}{\Phi_i} \right) + l_i - \frac{\Phi_i}{x_i} \sum_{j=1}^{m} x_j l_j$$

$$\text{Eq. (10)}$$

$$l_i = \frac{z}{2}(r_i - q_i) - (r_i - 1) \qquad \text{Eq. (11)}$$

$$\ln(\gamma_i^{CR}) = -q_i \left(1 + \ln \left(\sum_{j=1}^{m} \theta_i \tau_{ji} \right) - \sum_{j=1}^{m} \frac{\theta_i \tau_{ji}}{\sum_{k=1}^{m} \theta_k \tau_{ki}} \right) \qquad \text{Eq. (12)}$$

$$\theta_i = \frac{q_i x_i}{\sum_{j=1}^{m} q_j x_j}, \qquad \Phi_i = \frac{r_i x_i}{\sum_{j=1}^{m} r_j x_j} \quad \text{Eq. (13)}$$

The variables Φ_i, θ_i, and τ_{ji} are the volume fraction, area fraction, and interaction parameter between molecule i and j, respectively. The coordination number, z, the number of molecules surrounding the central molecule, is set to 10. Parameters r and q are pure component molecular-structure constants depending on molecular size and external surface areas. The r and q are the model parameters that their values for used materials have been listed in Table 3. The adjustable interaction parameter which is related to an energy parameter characteristic of the i–j interaction, Δu_{ij}, for this model is:

$$\ln(\tau_{ij}) = \left(-\frac{\Delta u_{ij}}{RT} \right) \qquad \text{Eq. (14)}$$

The interaction parameters of the Wilson, e-NRTL and UNIQUAC models were determined by minimizing the objective function Eq. (14).

$$OF = \sum_{j=1}^{n} (ln\gamma_i{}^{exp} - ln\gamma_i{}^{cal})^2 \qquad \text{Eq. (15)}$$

where n is the experimental points, also $\ln \gamma_i^{\exp}$ and $\ln \gamma_i^{cal}$ are representing the experimental and calculated activity coefficients.

The difference between the experimental and the calculated solubility's results is defined by average relative deviation percent (*ARD%*) and it is calculated for all activity coefficient models using the following equation:

$$\%ARD = 100 \left(\frac{\sum_{i=1}^{N} \frac{|x_i^{exp} - x_i^{cal}|}{|x_i^{exp}|}}{N} \right) \qquad \text{Eq. (16)}$$

where $x_i^{\exp}$, x_i^{cal} and N are experimental and calculated solubility and number of experimental points, respectively.

Table 3. UNIQUAC *r* and *q* parameters for the used components.

component	r	q
Water[37]	0.9200	1.4000
NAP	8.4429	6.2680
ChCl	5.6006	5.0560
OA	2.6026	2.4480
G	3.8399	3.6800

Thermodynamic properties of dissolution
Thermodynamic properties of solute dissolved in solvent mixtures can present important information.[38] In this study, the thermodynamic functions in the process of NAP dissolution are calculated based on the solubility of NAP in water and aqueous DES solutions as a function of temperature. The standard molar enthalpy of dissolution, ΔH_{sol}^o, is calculated from van't Hoff equation and defined as:[39-41]

$$\Delta H_{sol}^o = -R \left(\frac{\partial \ln x_1}{\partial (1/T)} \right)_P \qquad \text{Eq. (17)}$$

where x_1 is the mole fraction of NAP solubility, R represents the universal gas constant (8.314 J·K^{-1}·mol^{-1}) and T is the absolute temperature. The standard molar enthalpy change of solution, ΔH_{sol}^o, is generally obtained from the slope of the solubility curve in a so-called van't Hoff plot where *lnx₁* is plotted against T^{-1}. Over a limited temperature interval, the heat capacity change of a solution may be assumed to be constant, hence the derived values of ΔH_{sol}^o will also be valid for the mean temperature, $T_m = \dfrac{N}{\sum_{i=1}^{N} \dfrac{1}{T_i}} = 305.41$ K and

Eq. (16) can also be written as:[41]

$$\Delta H_{sol}^o = -R\left(\frac{\partial \ln x_1}{\partial (1/T - 1/T_m)}\right)_P \qquad \text{Eq. (18)}$$

The standard molar Gibbs energy of the dissolution process, ΔG_{sol}^o can be calculated according to:[42]

$$\Delta G_{sol}^o = -RT_m \times intercept \qquad \text{Eq. (19)}$$

where the intercept used is that obtained in plots of lnx_1 versus $(1/T - 1/T_m)$. The standard molar entropy of dissolution is also obtained from the following equation:[38]

$$\Delta S_{sol}^o = \frac{\Delta H_{sol}^o - \Delta G_{sol}^o}{T_m} \qquad \text{Eq. (20)}$$

The ξ_H and ξ_{TS} identify as the comparison of the relative contributions to the standard molar Gibbs energy by enthalpy and entropy in the dissolution process, respectively are expressed as follows:[43]

$$\%\xi_H = \frac{|\Delta H_{sol}^o|}{|\Delta H_{sol}^o| + |T\Delta S_{sol}^o|} \times 100 \qquad \text{Eq. (21)}$$

$$\%\xi_{TS} = \frac{|T\Delta S_{sol}^o|}{|\Delta H_{sol}^o| + |T\Delta S_{sol}^o|} \times 100 \qquad \text{Eq. (22)}$$

Results and Discussion
Solubility results
The experimental NAP solubility data in mixed solvents (DES + water) with different DESs weight fractions at various temperatures (298.15 to 313.15 K) are listed in Table 4. The relationship between solubility of NAP, x_1, versus absolute temperature in the aqueous DES solutions with different weight fractions of DESs has been revealed in Figure 3. It can be seen from this figure, the solubility of the drug was increased in the aqueous DES solutions at higher concentration of DES and temperatures. The

comparison of experimental mole fraction solubility in this study and those values in the literature in systems containing ethanol + water and poly ethylene glycol 200 (PEG 200) + water are summarized in Table 5. The results in this table indicate that the mole fraction solubility of NAP in ethanol + water mixture at each temperature and the same co-solvent weight fraction ($w_3= 0.9$)[44] is slightly higher than its value compared to ChCl/OA. The solubility values of NAP in aqueous PEG 200 solutions however are higher than our obtained values and $w_3= 0.9$.[45] But the advantage of using DESs is that they are more sustainable and environmentally friendly solvents for pharmaceutical industry.
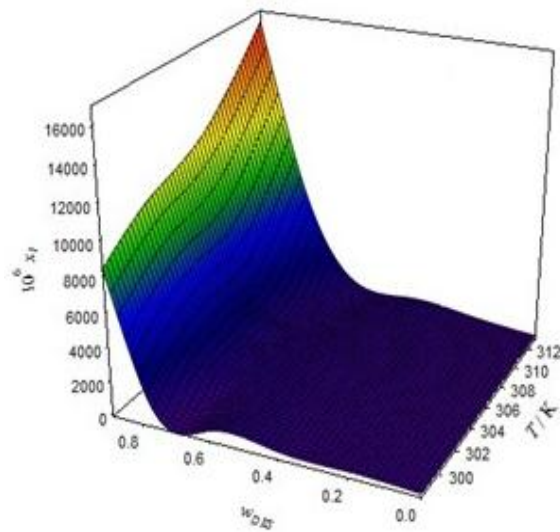
Figure 3. The relationship between the solubility of NAP, mole fraction x_1, versus mass fraction of DES, w_{DES}, in aqueous ChCl/OA solutions at various temperatures.

Table 4. The experimental (x_1^{exp})[a] and calculated (x_1^{cal}) solubility of NAP in the aqueous DES solutions at different temperatures (T)[b] and weight fractions of DES (w_3)[c] from e-NRTL, Wilson and UNIQUAC models.

T/K	$10^5 x_1^{exp}$	e-NRTL model		Wilson model		UNIQUAC model	
		$10^5 x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$	$10^5 x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$	$10^5 x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$
NAP + water + ChCl/ OA							
w_3=0.0000							
298.15	0.510	0.510	-0.09	0.510	0.01	0.505	0.96
303.15	0.596	0.594	0.18	0.595	0.02	0.600	-0.76
308.15	0.656	0.657	-0.18	0.656	-0.04	0.655	0.11
313.15	0.772	0.768	0.48	0.770	0.25	0.772	-0.05
w_3=0.2000							
298.15	16.9	16.9	0.28	17.1	-0.75	16.9	0.28
303.15	19.1	19.1	0.13	19.1	0.13	19.1	0.18
308.15	26.4	26.2	0.70	26.2	0.64	25.6	3.08
313.15	37.3	36.4	2.55	36.9	1.16	36.9	0.98
w_3=0.4000							
298.15	25.9	25.8	0.41	26.1	-0.44	25.5	1.68
303.15	40.5	38.9	4.00	40.3	0.55	40.8	-0.62
308.15	58.2	26.0	7.87	28.3	-0.03	31.1	-9.97
313.15	83.8	82.8	1.19	83.8	0.02	84.5	-0.85

Table 4. Continued

w_3=0.6000							
298.15	44.5	44.3	0.47	45.1	-1.49	45.0	-1.18
303.15	86.3	89.9	-4.26	86.3	-0.01	86.2	0.05
308.15	95.5	101.6	-6.35	96.7	-1.23	86.1	9.87
313.15	183	189	-3.48	187	-2.17	180	1.61
w_3=0.8000							
298.15	170	168	1.13	171	-0.60	167	1.83
303.15	454	416	8.39	453	0.08	448	1.18
308.15	696	618	11.25	690	0.86	705	-1.29
313.15	1006	776	22.84	1004	0.17	999	0.68
w_3=0.9000							
298.15	740	724	2.08	739	0.02	741	-0.18
303.15	937	951	-1.53	937	0.03	947	-1.03
308.15	1122	1110	1.06	1124	-0.18	1148	-2.32
313.15	1337	1558	-16.52	1332	0.34	1340	-0.25
NAP + water + ChCl / G							
w_3=0.0000							
298.15	0.510	0.509	0.16	0.511	-0.14	0.510	0.01
303.15	0.596	0.593	0.37	0.596	-0.15	0.592	0.51
308.15	0.656	0.650	0.94	0.656	-0.02	0.643	2.03
313.15	0.772	0.771	0.13	0.772	-0.06	0.781	-1.16
w_3=0.2000							
298.15	3.48	3.50	-0.69	3.48	-0.17	3.58	-2.99
303.15	3.85	3.83	0.55	3.84	0.25	3.91	-1.65
308.15	4.17	4.44	-6.39	4.18	-0.05	4.35	-4.33
313.15	4.57	4.85	-6.06	4.50	1.57	4.56	0.21
w_3=0.4000							
298.15	4.68	4.56	2.54	4.61	1.53	4.39	6.21
303.15	5.12	5.10	0.35	5.04	1.47	4.87	4.80
308.15	7.42	6.25	15.83	7.36	0.79	6.47	12.77
313.15	9.38	7.64	18.50	9.35	0.31	9.57	-2.03
w_3=0.6000							
298.15	5.60	5.74	-2.42	5.51	1.68	5.99	-7.07
303.15	6.44	6.34	1.62	6.35	1.42	6.75	-4.75
308.15	7.72	8.99	-16.56	7.73	-0.15	8.74	-13.31
313.15	12.2	14.4	-17.60	12.5	-1.86	12.3	-0.82
w_3=0.8000							
298.15	30.2	29.4	2.52	29.9	0.83	29.1	3.54
303.15	46.2	48.5	-4.95	46.2	0.01	44.9	3.00
308.15	49.8	48.6	2.22	50.4	-1.41	46.0	7.51
313.15	50.6	49.1	8.98	52.5	-3.58	49.6	1.98
w_3=0.9000							
298.15	210	209	0.75	211	-0.37	212	-1.02
303.15	238	228	4.23	238	0.09	241	-1.11
308.15	297	281	5.38	295	0.68	305	-2.60
313.15	333	330	0.61	315	5.47	336	-0.76

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

Table 5. Comparison of NAP Solubility (model fraction) in this study and literature.

NAP mole fraction solubility			
Experimental data in this study		Literature[44,45]	
w_3= 0.9 T=298.15			
ChCl/OA + water	7.40×10^{-3}	Ethanol + water	1.10×10^{-2}
ChCl/G + water	2.10×10^{-3}	PEG 200 + water	1.23×10^{-2}
w_3= 0.9, T=303.15			
ChCl/OA + water	9.37×10^{-3}	Ethanol + water	1.36×10^{-2}
ChCl/G + water	2.38×10^{-3}	PEG 200 + water	1.79×10^{-2}
w_3= 0.9, T=308.15			
ChCl/OA + water	11.22×10^{-3}	Ethanol + water	1.70×10^{-2}
ChCl/G + water	2.97×10^{-3}	PEG 200 + water	2.45×10^{-2}
w_3= 0.9, T= 313.15			
ChCl/OA + water	13.37×10^{-3}	Ethanol + water	1.99×10^{-2}
ChCl/G + water	3.33×10^{-3}	PEG 200 + water	3.22×10^{-2}

Modeling results

In the next step, the solubility data of NAP in the aqueous solutions were correlated with the activity coefficient models including Wilson, e-NRTL and UNIQUAC models. The modeling results are summarized in Table 4. The corresponding parameters for used models are given in Table 6 and the calculated *ARD%* values are given in Table 7 for used models in this work. Thus, the proficiency of these models in correlation of the experimental solubility data can be ordered as Wilson> UNIQUAC > e-NRTL for systems.

Table 6. The parameters of 1) e-NRTL 2) Wilson 3) UNIQUAC activity coefficient models for the NAP in the different solvents at various temperatures.

1) T / K	10^{-4} $\Delta g_{wd}{}^{b}$	10^{-5} Δg_{dw}	$\Delta g_{Gd}{}^{b}$	10^{-4} Δg_{dG}	10^{-4} Δg_{caw}	10^{-4} Δg_{wca}	10^{-4} Δg_{cad}	10^{-4} Δg_{dca}	10^{-4} Δg_{Gca}	Δg_{caG}	Δg_{Gw}	Δg_{wG}
					NAP + water + ChCl / G							
298.15	2.069	-14.677	3.353	1.85	-4.525	5.346	2.792	339.069	1.368	0.124	0.247	0.565
303.15	4.065	-9.309	-8.395	1.861	-4.279	2.642	-214.07	-123.566	-2.445	0.124	0.247	0.565
308.15	2.18	1.802	2.122	2.042	-6.763	7.067	-1.078	2.162	2.177	0.124	0.247	0.565
313.15	3.175	-6.007	1.025	1.304	-1.269	2.83	4.146	-1.833	2.091	0.124	0.247	0.565
					NAP + water + ChCl / OA							
298.15	1.653	7.71	4.9796	2.026	-3.949	4.921	-2.744	-1.112	3.367	0.124	0.247	0.565
303.15	2.116	2.718	-1.795	1.284	-1.285	4.957	-5.762	-1.862	-4.924	0.124	0.247	0.565
308.15	3.002	-5.408	-1.479	1.288	5.291	1.023	-1.646	3.233	2.112	0.124	0.247	0.565
313.15	2.223	2.718	-5.551	1.32	-1.285	-7.212	-5.551	-1.237	-1.311	0.124	0.247	0.565

2) T / K	10^{6} Λ_{wd}	Λ_{dw}	10^{3} Λ_{Gd}	Λ_{dG}	$10^{3}\Lambda_{caw}$	Λ_{wca}	10^{3} Λ_{cad}	Λ_{dca}	$10^{3}\Lambda_{Gca}$	$10^{5}\Lambda_{caG}$	Λ_{Gw}	Λ_{wG}
					NAP + water + ChCl / G							
298.15	8.019	3.515	-0.013	4.165	0.026	0.288	0.154	4.794	0.015	-2.017	0.038	-0.029
303.15	8.139	3.355	-0.013	4.205	0.026	0.244	0.153	4.754	0.015	-1.746	0.038	-0.028
308.15	6.187	3.256	-3.271	0.321	6.708	0.157	0.056	0.413	3.757	-2.554	0.001	-0.015
313.15	1.925	3.216	0.01	0.711	-0.019	-0.984	0.127	0.279	0.186	1.147	-0.028	-0.274
					NAP + water + ChCl / OA							
298.15	3.332	2.695	-0.015	8.584	0.017	1.096	0.272	6.634	0.015	-2.042	0.036	-0.031
303.15	1.152	3.22	-0.016	4.958	0.017	0.401	0.149	4.487	0.015	-1.92	0.038	-0.03
308.15	7.008	3.225	-0.016	1.876	0.016	0.2	0.12	1.448	0.015	-1.704	0.04	-0.029
313.15	1.057	3.228	0.017	1.019	-0.016	0.051	0.078	0.536	0.08	1.562	-0.03	-0.245

3) T / K	10^{-4} $\Delta u_{wd}{}^{b}$	10^{-3} Δu_{dw}	10^{-4} $\Delta u_{Gd}{}^{b}$	10^{-3} Δu_{dG}	Δu_{caw}	Δu_{wca}	10^{-3} Δu_{cad}	Δu_{dca}	$\Delta u EG_{ca}$	10^{-3} Δu_{caG}	10^{-3} Δu_{Gw}	Δu_{wG}
					NAP + water + ChCl / G							
298.15	1.433	-4.501	1.562	-4.768	-6.056	181.285	5.616	-38.767	36.97	0.005	-3.148	161.215
303.15	0.889	-3.427	-0.006	-1.269	-1381	3875.01	10.01	-42.521	58.201	-0.241	-3.495	-3.007
308.15	1.455	-4.596	1.567	-4.906	-6.056	164.827	5.879	-38.575	36.94	4.635	-3.065	159.006
313.15	1.621	-4.89	1.665	-5.187	-6.058	1.74	7.761	-38.413	35.832	4.544	-3.63	206.581
					NAP + water + ChCl / OA							
298.15	1.326	-4.322	1.131	-3.905	-6.057	336.288	1.069	-38.484	36.423	-2.741	-6.027	175.932
303.15	1.44	-4.545	1.509	-6.292	-6.057	420.46	2.075	-38.059	35.67	-6.409	-7.152	190.121
308.15	1.477	-4.633	1.616	-6.687	-6.057	434.649	2.153	-26.827	23.122	-6.91	-7.516	329.091
313.15	1.402	-4.54	1.333	-6.163	-6.057	421.441	1.314	-38.332	36.137	-6.562	-7.337	181.278

d=drug, w=water, G= glycerol or oxalic acid, Ca=cation or anion.

Table 7. The calculated average relative deviation percent (*ARD%*) for the solubility of the NAP in the aqueous DES solutions at several temperatures from different models.

	ARD%		
T / K	e-NRTL	Wilson	UNIQUAC
	NAP + water + ChCl / OA		
298.15	0.74	0.55	1.02
303.15	3.08	0.14	0.63
308.15	4.56	0.50	4.44
313.15	7.84	0.68	0.74
Average	4.05	0.47	1.71
	NAP + water + ChCl / G		
298.15	1.51	0.78	3.47
303.15	2.01	0.56	2.64
308.15	7.88	0.51	7.09
313.15	8.71	2.14	3.57
Average	5.03	0.99	4.19

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

w_3	ΔH°_{soln} / kJ·mol^{-1}	$T_m\Delta S^{\circ}_{soln}$ / kJ·mol^{-1}	ΔG°_{soln} / kJ·mol^{-1}	ξ_H	ξ_{TS}
		NAP + water + ChCl / OA			
0.0000	20.79	-9.65	30.44	68.30	31.70
0.0200	21.00	-4.63	25.63	81.95	18.05
0.0500	39.95	15.15	24.81	72.51	27.49
0.0700	52.95	28.76	24.19	64.80	35.20
0.1000	51.40	28.03	23.37	64.71	35.29
0.1500	39.13	16.79	22.34	69.98	30.02
0.2000	41.67	20.48	21.20	67.05	32.95
0.4000	51.72	32.14	19.58	61.67	38.33
0.6000	45.42	27.13	18.29	62.61	37.39
0.8000	72.46	58.72	13.74	55.24	44.76
0.9000	33.56	22.25	11.31	60.14	39.86
		NAP + water + ChCl / G			
0.0000	20.79	-9.65	30.44	68.30	31.70
0.0200	48.05	20.13	27.92	70.47	29.53
0.0500	34.50	7.06	27.43	83.01	48.44
0.0700	27.14	0.04	27.10	99.86	0.14
0.1000	22.05	-4.62	26.67	82.68	17.32
0.1500	10.84	-15.05	25.89	41.88	58.12
0.2000	14.05	-11.67	25.73	54.62	45.38
0.4000	38.05	13.51	24.53	73.79	26.21
0.6000	39.01	14.93	24.08	72.33	27.67
0.8000	25.48	5.80	19.67	81.45	18.55
0.9000	24.89	9.82	15.07	71.70	28.30

Thermodynamic properties of dissolution results

The results of ΔG^{o}_{sol}, ΔH^{o}_{sol}, and $T_m\Delta S^{o}_{sol}$ are collected in Table 8. The standard molar Gibbs energy and enthalpy of dissolution are positive in the systems indicate that the process of NAP dissolution in the studied DES solutions is always endothermic. The ΔG^{o}_{sol} values decrease with increasing the weight fraction of DES, which show that the solubility of NAP in these types of the solvents increases with the decrease of the ΔG^{o}_{sol} values.

On the other hand, ΔS^{o}_{sol} is positive in most studied systems. The calculated ξ_H and ξ_{TS} values are given in Table 8. From this table it follows that the main contribution to standard molar Gibbs energy of dissolution process of NAP is the enthalpy (greater than 54% in all cases)

Conclusion

The aqueous solubility of naproxen in the presence of some deep eutectic solvents (ChCl/oxalic acid and ChCl/glycerol), as co-solvents was determined experimentally within the temperatures ranging from 298.15 to 313.15 K. The naproxen solubility mole fraction in the studied solvents was increased with increasing deep eutectic solvents concentration and temperature. The solubility data was correlated with some activity coefficient models and their performance was Wilson > UNIQUAC > e-NRTL. Also, dissolution thermodynamic functions were calculated for these systems and the positive ΔH^{o}_{sol} and ΔG^{o}_{sol} indicate that the dissolution process of naproxen to be endothermic and nonspontaneous which this trend decreases with addition of DES in aqueous media. Also, the main contribution to standard molar Gibbs energy in dissolution process of naproxen in the aqueous DES solutions is enthalpic.

Conflict of interests

The authors claim that there is no conflict of interest.

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