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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ABSTRACT

Background: To increase the low solubility of naproxen (NAP), deep eutectic solvents (DESs) based on choline chloride (ChCl) with glycerol (G) and oxalic acid (OA) as new class of solvents have been used up to 0.9 mole fraction of DES at $T = (298.15$ to 313.15) K.

Methods: DESs were prepared by mixing of the two components with the molar ratios: ChCl/glycerol (1:2) and ChCl/oxalic acid (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 enhanced 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: Oxalic acid based DES reveals higher solubility than DES containing glycerol. 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.

Keywords: Deep eutectic solvents; Solubility; Naproxen; Activity coefficient models; Thermodynamic properties.

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.

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 $T = (298.15 \text{ K to } 313.15) \text{ K}$.

**Experimental**

**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. 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. In this work, the shake flask method has been used (Fig. 2). Firstly, excess amounts of NAP were added to sealed vials containing appropriate amount of solvent mixtures (DES + water) using an analytical balance with precision $1 \times 10^{-4} \text{ g}$ (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 $T = \pm 0.1 \text{ K}$). 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 (Fig. 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, \( x_i \), in \{NAP (1) + water (2) + DESs (3)\} system was obtained by flowing formula 29:

\[
x_i = \frac{w_i}{M_i} \frac{1}{w_1 + w_2 + w_3}
\]

Eq. (1)

where \( M_i \) and \( w_i \) are the molecular weight and mass fractions of \( i \) component in the saturated solution, respectively.

Theory

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:

\[
-\ln x_i = \frac{\Delta_{fus}H}{R} \left( \frac{1}{T} - \frac{1}{T_{fus}} \right) + \ln \gamma_i
\]

Eq. (2)

where \( T_{fus} \), \( \Delta_{fus}H \), \( T \), \( x_i \) and \( \gamma_i \) refer to: melting temperature for the pure NAP (427.6 K), enthalpy of fusion for the pure NAP (31.5 kJ.mol\(^{-1}\)), (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, $G^{ex,LR}_{PDH}$, can be written as:

$$
\frac{G^{ex,PDH}}{RT} = -\sum_j x_j \left( \frac{1000}{M_j} \right)^{1/2} \frac{4A^e_x}{\rho} \ln(1 + \rho^{0.5})
$$

Eq. (3)

where $M_S$ and $\rho$ 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 $A^e_x$ denotes the Debye–Hückel constant for the osmotic coefficient and is expressed by:

$$
A^e_x = \frac{1}{3} \left( \frac{2\pi N_A}{V_s} \right)^{1/2} \frac{e^2}{4\pi \varepsilon D_s kT}^{1/2}
$$

Eq. (4)

where $N_A$, $k$, $\varepsilon$, $e$, $V_s$ 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 $\rho$ 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.

**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) and Chen and Evans (1986).

For each species, the activity coefficient is the sum of the Pitzer–Debye–Hückel contribution and the NRTL contribution:

$$
\ln(\gamma^*_i) = \ln(\gamma^*_{i,PDH}) + \ln(\gamma^*_{i,NRTL})
$$

Eq. (5)

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

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

**Wilson model**

Wilson (1964) presented the following expression for the component $i$ activity coefficients:

$$
\ln \gamma^*_{i} = \ln \left( \frac{\gamma^*_{i,PDH}}{\gamma^*_{i,NRTL}} \right) + \ln(\gamma^*_{i})
$$
\[ \ln y_i = 1 - \ln \left[ \sum_{j=1}^{n} x_j A_{ij} \right] - \sum_{k=1}^{n} \left[ \frac{x_k A_{ki}}{\sum_{j=1}^{n} x_j A_{kj}} \right] \]  

Eq. (6)

where \( \Lambda_y \) is the binary interaction parameter which are related to the pure-component molar volumes, \( \nu \), and to characteristic energy, \( \lambda \), differences by:

\[ \Lambda_y = \frac{\nu}{\nu_i} \exp \left( \frac{-\lambda_y - \lambda_{ii}}{RT} \right) \]  

Eq. (7)

**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:

\[ \ln \gamma^C_i = \ln \frac{\Phi_i}{x_i} + \frac{z}{2} q_i \ln \left( \frac{\theta_i}{\phi_i} \right) + \frac{r_i}{x_i} \sum_{j=1}^{n} x_j f_j \]  

Eq. (8)

\[ \ln \gamma^R_i = -q_i \left[ 1 + \ln(\sum_{j=1}^{m} x_j \tau_{ji}) - \sum_{j=1}^{m} x_j \tau_{ji} \sum_{k=1}^{m} \frac{\theta_k \tau_{ki}}{\phi_k \tau_{kj}} \right] \]  

Eq. (9)

\[ l_j = \frac{z}{2} \left( r_i - q_i \right) - \left( r_i - 1 \right) \]  

Eq. (10)

\[ \ln \gamma^R_i = -q_i \left[ 1 + \ln(\sum_{j=1}^{m} x_j \tau_{ji}) - \sum_{j=1}^{m} x_j \tau_{ji} \sum_{k=1}^{m} \frac{\theta_k \tau_{ki}}{\phi_k \tau_{kj}} \right] \]  

Eq. (11)

\[ \theta = \frac{q_i x_j}{\sum_{j=1}^{m} q_j x_j}; \quad \Phi = \frac{r_i x_j}{\sum_{j=1}^{m} r_j x_j} \]  

Eq. (12)

The variables \( \Phi_i, \theta_i, \) and \( \tau_{ji} \) 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 six
parameter which is related to an energy parameter characteristic of the $i$–$j$ interaction, $\Delta u_{ij}$, for this model is:

$$\ln(\tau_{ij}) = (-\frac{\Delta u_{ij}}{RT})$$ \hspace{1cm} \text{Eq. (13)}

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

$$OF = \sum_{i=1}^{n} (\ln \gamma_{i}^{\exp} - \ln \gamma_{i}^{\text{cal}})^2$$ \hspace{1cm} \text{Eq. (14)}

where $n$ is the experimental points, also $\ln \gamma_{i}^{\exp}$ and $\ln \gamma_{i}^{\text{cal}}$ 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 ($\text{ARD\%}$) and it is calculated for all activity coefficient models using the following equation:

$$\% \text{ARD} = 100 \left( \frac{\sum_{i=1}^{N} |x_{i}^{\exp} - x_{i}^{\text{cal}}|}{N} \right)$$ \hspace{1cm} \text{Eq. (15)}

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

**Thermodynamic properties of dissolution**

Thermodynamic properties of solute dissolved in solvent mixtures can present important information. 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, $\Delta H_{\text{sol}}^\circ$, is calculated from van’t Hoff equation and defined as:

$$\Delta H_{\text{sol}}^\circ = -R \left( \frac{\partial \ln x_i}{\partial (1/T)} \right)_p$$ \hspace{1cm} \text{Eq. (16)}
where $x_i$ 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, $\Delta H_{\text{sol}}^o$, is generally obtained from the slope of the solubility curve in a so-called van’t Hoff plot where $\ln x_i$ 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 $\Delta H_{\text{sol}}^o$ will also be valid for the mean temperature, $T_m = \frac{N}{\sum_{i=1}^{N} \frac{1}{T_i}} = 305.41$ K and Eq. (16) can also be written as:

$$\Delta H_{\text{sol}}^o = -R \left( \frac{\partial \ln x_i}{\partial \left( \frac{1}{T} - \frac{1}{T_m} \right) \rho} \right)_p$$

Eq. (17)

The standard molar Gibbs energy of the dissolution process, $\Delta G_{\text{sol}}^o$, can be calculated according to:

$$\Delta G_{\text{sol}}^o = -RT_m \times \text{intercept}$$

Eq. (18)

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

$$\Delta S_{\text{sol}}^o = \frac{\Delta H_{\text{sol}}^o - \Delta G_{\text{sol}}^o}{T_m}$$

Eq. (19)

The $\xi_H$ and $\xi_{TS}$ 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:

$$\%\xi_H = \left( \frac{\Delta H_{\text{sol}}^o}{\Delta H_{\text{sol}}^o + T \Delta S_{\text{sol}}^o} \right) \times 100$$

Eq. (20)

$$\%\xi_{TS} = \left( \frac{T \Delta S_{\text{sol}}^o}{\Delta H_{\text{sol}}^o + T \Delta S_{\text{sol}}^o} \right) \times 100$$

Eq. (21)

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 these 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 ($w_3 = 0.9$) 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 $w_3 = 0.9$. But the advantage of using DESs is that they are more sustainable and environmentally friendly solvents for pharmaceutical industry.

Modeling results

In the next step, the solubility data of NAP in the aqueous solutions were correlated with the activity coefficient models including Wilson, 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 > NRTL for systems.

Thermodynamic properties of dissolution results

The results of $\Delta G_{sol}^\circ$, $\Delta H_{sol}^\circ$, and $T_m \Delta S_{sol}^\circ$ 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 $\Delta G_{sol}^\circ$ values decrease with nine
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 $\Delta G_{sol}^{\alpha}$ values. On the other hand, $\Delta S_{sol}^{\alpha}$ is positive in most studied systems.

The calculated $\xi_H$ and $\xi_{TS}$ 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 $\Delta H_{sol}^{\alpha}$ and $\Delta G_{sol}^{\alpha}$ 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.

**Acknowledgements**

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References


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44. Leron RB, Soriano AN, Li M-H 2012. 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. 43(4):551-557. doi: 10.1016/j.jtice.2012.01.007.

**Table 1**

Descriptions of the used materials.

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<th>Chemical name</th>
<th>Provenance</th>
<th>CAS No.</th>
<th>Mass fraction (purity)</th>
<th>Structure</th>
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<td>Salt – HBD (molar ratio)</td>
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</table>

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

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<thead>
<tr>
<th>component</th>
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<th>$q$</th>
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The experimental ($x_1^{exp}$) and calculated ($x_1^{cal}$) solubility of NAP in the aqueous DES solutions at different temperatures ($T$) and weight fractions of DES ($w_3$) from e-NRTL, Wilson and UNIQUAC models.

<table>
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<tr>
<th>$T$ / K</th>
<th>$10^3 x_1^{exp}$</th>
<th>e-NRTL model</th>
<th>Wilson model</th>
<th>UNIQUAC model</th>
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<td></td>
<td>$10^5 x_1^{cal}$</td>
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NAP + water + ChCl / glycerol

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<tr>
<td>313.15</td>
<td>333</td>
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</tbody>
</table>

a Standard uncertainty u(x_i) = 0.5%, b Standard uncertainty u(T) = 0.01 K. c Standard uncertainty u(w_i) = 0.0002.
### Table 5

Comparison of NAP Solubility in this study and literature.

<table>
<thead>
<tr>
<th>Experimental data in this study</th>
<th>Literature</th>
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<tr>
<td><strong>w_3 = 0.9</strong>&lt;br&gt;<strong>T = 298.15</strong>&lt;br&gt;ChCl/OA + water</td>
<td>7.40 x 10^{-3}</td>
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<tr>
<td><strong>w_3 = 0.9</strong>&lt;br&gt;<strong>T = 298.15</strong>&lt;br&gt;ChCl/G + water</td>
<td>2.10 x 10^{-3}</td>
</tr>
<tr>
<td><strong>w_3 = 0.9</strong>&lt;br&gt;<strong>T = 303.15</strong>&lt;br&gt;ChCl/OA + water</td>
<td>9.37 x 10^{-3}</td>
</tr>
<tr>
<td><strong>w_3 = 0.9</strong>&lt;br&gt;<strong>T = 303.15</strong>&lt;br&gt;ChCl/G + water</td>
<td>2.38 x 10^{-3}</td>
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<td>11.22 x 10^{-3}</td>
</tr>
<tr>
<td><strong>w_3 = 0.9</strong>&lt;br&gt;<strong>T = 308.15</strong>&lt;br&gt;ChCl/G + water</td>
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<td><strong>w_3 = 0.9</strong>&lt;br&gt;<strong>T = 313.15</strong>&lt;br&gt;ChCl/OA + water</td>
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<td><strong>w_3 = 0.9</strong>&lt;br&gt;<strong>T = 313.15</strong>&lt;br&gt;ChCl/G + water</td>
<td>3.33 x 10^{-3}</td>
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</table>
The parameters of 1) e-NRTL 2) Wilson 3) UNIQUAC activity coefficient models for the NAP in the different solvents at various temperatures.

<table>
<thead>
<tr>
<th>1) T / K</th>
<th>10^4 \Delta G_{\text{vdw}}</th>
<th>10^3 \Delta G_{\text{w}}</th>
<th>10^4 \Delta G_{\text{vdw}}</th>
<th>10^3 \Delta G_{\text{w}}</th>
<th>10^4 \Delta G_{\text{vdw}}</th>
<th>10^3 \Delta G_{\text{w}}</th>
<th>10^4 \Delta G_{\text{vdw}}</th>
<th>10^3 \Delta G_{\text{w}}</th>
<th>10^4 \Delta G_{\text{vdw}}</th>
<th>10^3 \Delta G_{\text{w}}</th>
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<th>10^3 \Delta G_{\text{w}}</th>
<th>10^4 \Delta G_{\text{vdw}}</th>
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<td>0.247</td>
<td>0.565</td>
<td>1.124</td>
</tr>
<tr>
<td>303.15</td>
<td>4.065</td>
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<td>-8.395</td>
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<td>-4.279</td>
<td>2.642</td>
<td>-2.1407</td>
<td>-123.566</td>
<td>-2.445</td>
<td>0.124</td>
<td>0.247</td>
<td>0.565</td>
<td>0.124</td>
</tr>
<tr>
<td>308.15</td>
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<td>1.802</td>
<td>2.122</td>
<td>2.042</td>
<td>-6.763</td>
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<td>-1.078</td>
<td>2.162</td>
<td>2.177</td>
<td>0.124</td>
<td>0.247</td>
<td>0.565</td>
<td>0.124</td>
</tr>
<tr>
<td>313.15</td>
<td>3.175</td>
<td>-6.007</td>
<td>1.025</td>
<td>1.304</td>
<td>-1.269</td>
<td>2.830</td>
<td>-1.833</td>
<td>2.091</td>
<td>0.124</td>
<td>0.247</td>
<td>0.565</td>
<td>0.124</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NAP + water + ChCl / G</th>
</tr>
</thead>
</table>

| 308.15 | 2.223          | 2.718          | -5.551         | 1.320          | -1.285         | -7.212         | -5.551         | -1.237         | -1.311         | 0.124          | 0.247          | 0.565          |

<table>
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<tr>
<th>3) T / K</th>
<th>10^4 \Delta u_{\text{vdw}}</th>
<th>10^3 \Delta u_{\text{w}}</th>
<th>10^4 \Delta u_{\text{vdw}}</th>
<th>10^3 \Delta u_{\text{w}}</th>
<th>10^4 \Delta u_{\text{vdw}}</th>
<th>10^3 \Delta u_{\text{w}}</th>
<th>10^4 \Delta u_{\text{vdw}}</th>
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<th>10^3 \Delta u_{\text{w}}</th>
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<td>10.01</td>
<td>-42.521</td>
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<table>
<thead>
<tr>
<th>NAP + water + ChCl / OA</th>
</tr>
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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.

twenty-two
Table 7

The calculated average relative deviation percent \((\text{ARD}\%)\) for the solubility of the NAP in the aqueous DES solutions at several temperatures from different models.

<table>
<thead>
<tr>
<th>(T^\circ\ K)</th>
<th>e-NRTL</th>
<th>Wilson</th>
<th>UNIQUAC</th>
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</thead>
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<td>NAP + water + ChCl / oxalic acid</td>
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<td>3.08</td>
<td>0.14</td>
<td>0.63</td>
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<tr>
<td>308.15</td>
<td>4.56</td>
<td>0.50</td>
<td>4.44</td>
</tr>
<tr>
<td>313.15</td>
<td>7.84</td>
<td>0.68</td>
<td>0.74</td>
</tr>
<tr>
<td>Average</td>
<td>4.05</td>
<td>0.47</td>
<td>1.71</td>
</tr>
<tr>
<td>NAP + water + ChCl / glycerol</td>
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<td></td>
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<tr>
<td>298.15</td>
<td>1.51</td>
<td>0.78</td>
<td>3.47</td>
</tr>
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<td>303.15</td>
<td>2.01</td>
<td>0.56</td>
<td>2.64</td>
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<td>308.15</td>
<td>7.88</td>
<td>0.51</td>
<td>7.09</td>
</tr>
<tr>
<td>313.15</td>
<td>8.71</td>
<td>2.14</td>
<td>3.57</td>
</tr>
<tr>
<td>Average</td>
<td>5.03</td>
<td>0.99</td>
<td>4.19</td>
</tr>
</tbody>
</table>

d=drug, w=water, G=glycerol or oxalic acid, Ca=cation or anion.
Table 8

Thermodynamic functions for dissolution process at different weight fractions of DES (w₃) at mean temperature.

| w₃    | ΔHₛₒₙₙ / kJ·mol⁻¹ | TₛΔSₛₒₙₙ / kJ·mol⁻¹ | ΔGₛₒₙₙ / kJ·mol⁻¹ | θₛ | θₛₛ
|-------|------------------|---------------------|------------------|----|----
| 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 / oxalic acid

<table>
<thead>
<tr>
<th>w₃</th>
<th>ΔHₛₒₙₙ / kJ·mol⁻¹</th>
<th>TₛΔSₛₒₙₙ / kJ·mol⁻¹</th>
<th>ΔGₛₒₙₙ / kJ·mol⁻¹</th>
<th>θₛ</th>
<th>θₛₛ</th>
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<td>30.44</td>
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<td>31.70</td>
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<td>0.0200</td>
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<td>9.82</td>
<td>15.07</td>
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</table>

NAP + water + ChCl / glycerol

NAP + water + ChCl / oxalic acid
Figure 1. Chemical structure of naproxen.
Figure 2. UV–vis absorption spectra of a) studied DESs in water b) naproxen in aqueous DES solutions.
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.
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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ABSTRACT

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 mole 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/glycerol (1:2) and ChCl/oxalic acid (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: Oxalic acid based DES exhibits higher solubility than glycerol 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.

Keywords: Deep eutectic solvents; Solubility; Naproxen; Activity coefficient models; Thermodynamic properties.

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