

1 Performance of local composition models to correlate the aqueous 2 solubility of naproxen in some choline based deep eutectic solvents at T 3 = (298.15-313.15) K

4 Masumeh Mokhtarpour¹, Hemayat Shekaari¹, Fleming Martinez², Mohammed Taghi Zafarani-Moattar¹

5 ¹Department of Physical Chemistry, University of Tabriz, Tabriz, Iran

6 ²Grupo de Investigaciones Farmacéutico-Fisicoquímicas, Departamento de Farmacia, Facultad de Ciencias, Universidad
7 Nacional de Colombia, Bogotá, Colombia

8 ABSTRACT

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

12 *Methods:* DESs were prepared by mixing of the two components with the molar ratios: ChCl/glycerol
13 (1:2) and ChCl/oxalic acid (1:1). The solubility of NAP in the aqueous DESs solutions was measured
14 at different temperatures with shake flask method.

15 *Results:* The solubility in these solvents enhanced with increasing the weight fraction of DESs,
16 especially in ChCl/OA. The solubility data were correlated by e-NRTL, Wilson and UNIQUAC
17 models. Also, the thermodynamic functions, Gibbs energy, enthalpy, and entropy of dissolution were
18 obtained.

19 *Conclusion:* Oxalic acid based DES reveals higher solubility than DES containing glycerol. The
20 thermodynamic models were successfully used to correlate solubility data. In addition, the results
21 show that, the main contribution for NAP solubility in the aqueous DES solutions is the enthalpy.

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

26 Introduction

27
28 It is well-known that the solubility data play an important role in optimizing the crystallization
29 procedure and improving the purity and yield of drugs manufacturing. Therefore, it is necessary to

* Corresponding author. Tel.: +98-41-33393094. Fax: +98-41-33340191.
E-mail address: hemayatt@yahoo.com (H. Shekaari).

30 know the solubility of drugs in different solvents at various temperatures. On the other hand, the low
31 solubility of drugs in water is one of the main challenges in pharmaceutical fields.

32 Naproxen or (+)-6-methoxy- α -methyl-2-naphthaleneacetic acid (NAP, Figure 1) is
33 a nonsteroidal anti-inflammatory drug (NSAID) that relieves pain, fever, swelling, and stiffness but it
34 is slightly soluble in water ($15.9 \text{ mg}\cdot\text{L}^{-1}$)¹, and poor aqueous solubility of a drug is the factor that
35 limits its development into desired formulation². In this respect, the low solubility of NAP should be
36 increased for the widespread uses and production process of liquid pharmaceutical dosage forms
37 (LPDF)^{3,4}. The most effective and inexpensive method for increasing the solubility is co-solvency
38 method. Conventionally, organic solvents⁵⁻⁸ and ionic liquids (ILs)⁹⁻¹¹ have been used as co-solvents
39 to improve the low solubility of drugs. However, these types of solvents are highly flammable,
40 expensive and toxic for human health^{12,13}. Therefore, it is necessary to develop new solvents with
41 lower costs and toxicity and wider availability. Newly, to overcome the limitations of organic solvents
42 and ILs, deep eutectic solvents (DESs) have been introduced and some of them are used to increase
43 solubility and bioavailability of poorly soluble drugs^{14,15}. These novel solvents can be prepared using
44 biodegradable, non-toxic and natural materials¹⁶. They are liquid at room temperature and are
45 considered safer and more environmentally benign and are made of cheap compounds such as a
46 quaternary ammonium salt as hydrogen bond acceptor (HBA) (e.g. choline chloride (ChCl)) and a
47 hydrogen bond donor (HBD) (e.g. urea or a carboxylic acid) at their eutectic composition with melting
48 point much lower than that of the individual components¹⁴. DESs properties could be tuned by
49 altering the HBA/HBD weight ratio.

50 In continuation of our systematic investigation of drug solubility in DESs systems¹⁷⁻¹⁹, the
51 solubility of NAP was measured in the aqueous DESs solutions (ChCl/glycerol (G) and ChCl/ oxalic
52 acid (OA) and **the activity coefficient models** such as Wilson²⁰, e-NRTL^{21,22}, and UNIQUAC²³ have
53 been used to correlate the aqueous solubility data, at various experimental temperatures. **In addition, to**
54 **describe the thermodynamic behavior of NAP in the aqueous DES solutions, the van't Hoff and Gibbs**

55 equations were used to calculate some thermodynamic functions such as, Gibbs energy, enthalpy, and
56 entropy of dissolution at $T = (298.15 \text{ K to } 313.15) \text{ K}$ ²⁴⁻²⁶.

57 **Experimental**

58 *Chemical*

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

63 *DES preparation*

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

69 *Solubility measurement*

70 There are different methods of testing and measuring the solubility reported in the literature ²⁸.
71 In this work, the shake flask method has been used (Fig. 2). Firstly, excess amounts of NAP were
72 added to sealed vials containing appropriate amount of solvent mixtures (DES + water) using an
73 analytical balance with precision $1 \times 10^{-4} \text{ g}$ (AW 220, GR220, Shimadzu, Japan). Then the vials with
74 the mixture (solid + liquid) and a magnet were stirred in a system with thermostat (ED, Julabo Co.,
75 Germany $T = \pm 0.1 \text{ K}$). Then the vials were placed in water bath thermostat that was equipped with a
76 temperature-controlling system for 3 days to reach equilibrium. When a saturated solution was
77 attained, the solid phase was removed by centrifugation (D-7200 Tuttlingen, Hettich Co., U.S.A.)
78 followed by filtration (Durapore® membrane filters, type HV, $0.45 \mu\text{m}$, Millipore, MA). The clear
79 solutions were diluted with (ethanol + water) and assayed by a double beam spectrophotometer (T80
80 UV-vis spectrometer PG instruments, U.K.) at 262 nm (Fig. 3). The concentrations of the diluted

81 solutions were determined using the calibration curve. Each experimental data point represented the
82 average of at least three repetitive experiments. Also, we recorded the UV-vis spectra (Figure 2) of
83 DESs and NAP in the aqueous DESs solutions which show no interference between them.

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

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

86 where M_i and w_i are the molecular weight and mass fractions of i component in the saturated solution,
87 respectively.

88 Theory

89 Modeling

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

$$-\ln x_1 = \frac{\Delta_{fus}H}{R} \left(\frac{1}{T} - \frac{1}{T_{fus}} \right) + \ln \gamma_1 \quad \text{Eq. (2)}$$

94 where T_{fus} , $\Delta_{fus}H$, T , x_1 and γ_1 refer to: melting temperature for the pure NAP (427.6 K),
95 enthalpy of fusion for the pure NAP (31.5 kJ.mol⁻¹), (solid + liquid) equilibrium temperature,
96 equilibrium mole fraction, and the activity coefficient of the NAP in the saturated solution,
97 respectively. The enthalpy of melting is considered to be temperature independent. To correlate the
98 solubility data of the present drug in the aqueous DES solutions, experimental activity coefficients
99 were obtained through Eq. (2) for the solutions.

100 The Pitzer–Debye–Hückel (PDH) equation

101 The PDH equation for excess Gibbs energy, G^{ex*LR} , can be written as ³⁰:

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

102 where M_s and ρ are the molar mass of the solvent and the closest distance parameter,
 103 respectively. I_x is the ionic strength in mole fraction scale ($I_x = \frac{1}{2} \sum x_i Z_i^2$) and

104 A_ϕ denotes the Debye–Hückel constant for the osmotic coefficient and is expressed by:

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

105 where N_A , k , ϵ , e , V_s and D_s are Avogadro's number, Boltzmann constant, permittivity of vacuum,
 106 electronic charge, molar volume and dielectric constant of pure solvent, respectively. The parameter ρ
 107 in Eq. (3) is related to the hard-core collision diameter, or distance of closest approach of ions in
 108 solution. The value of $\rho = 14.9$ has been regularly used for aqueous electrolyte solutions ³¹.

109 *Electrolyte-NRTL model*

110 One of the most commonly used activity coefficient based thermodynamic model for industrial
 111 systems is the electrolyte-NRTL model (e-NRTL) by Chen (1982) ³² and Chen and Evans (1986) ³³.
 112 For each species, the activity coefficient is the sum of the Pitzer–Debye–Hückel contribution and the
 113 NRTL contribution ³².

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

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

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

115 *Wilson model*

116 **Wilson (1964) presented the following expression for the component i activity coefficients ²⁰:**

$$\ln \gamma_i = 1 - \ln \left[\sum_{j=1}^n x_j \Lambda_{ij} \right] - \sum_{k=1}^n \left[\frac{x_k \Lambda_{ki}}{\sum_{j=1}^n x_j \Lambda_{kj}} \right] \quad \text{Eq. (6)}$$

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

$$\Lambda_{ij} = \frac{v_j}{v_i} \exp \left(- \frac{\lambda_{ij} - \lambda_{ii}}{RT} \right) \quad \text{Eq. (7)}$$

119 *UNIQUAC model*

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

$$\ln \gamma_i = \ln \gamma_i^C + \ln \gamma_i^R \quad \text{Eq. (8)}$$

$$\ln \gamma_i^C = \ln \left(\frac{\Phi_i}{x_i} \right) + \frac{z}{2} q_i \ln \left(\frac{\theta_i}{\Phi_i} \right) + l_i - \frac{\Phi_i}{x_i} \sum_{j=1}^m x_j l_j \quad \text{Eq. (9)}$$

$$l_j = \frac{z}{2} (r_i - q_i) - (r_i - 1) \quad \text{Eq. (10)}$$

$$\ln \gamma_i^R = -q_i \left(1 + \ln \left(\frac{\sum_{j=1}^m \theta_j \tau_{ji}}{\sum_{k=1}^m \theta_k \tau_{kj}} \right) \right) \quad \text{Eq. (11)}$$

$$\theta_i = \frac{q_i x_i}{\sum_{j=1}^m q_j x_j}; \quad \Phi_i = \frac{r_i x_i}{\sum_{j=1}^m r_j x_j} \quad \text{Eq. (12)}$$

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

128 parameter which is related to an energy parameter characteristic of the i - j interaction, Δu_{ij} , for this
129 model is:

$$\ln(\tau_{ij}) = \left(-\frac{\Delta u_{ij}}{RT}\right) \quad \text{Eq. (13)}$$

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

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

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

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

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

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

139 *Thermodynamic properties of dissolution*

140 **Thermodynamic properties of solute dissolved in solvent mixtures can present important**
141 **information** ³⁴. In this study, the thermodynamic functions in the process of NAP dissolution are
142 calculated based on the solubility of NAP in water and aqueous DES solutions as a function of
143 temperature. The standard molar enthalpy of dissolution, ΔH_{sol}^o , is calculated from van't Hoff equation
144 and defined as ³⁴⁻³⁶:

$$\Delta H_{sol}^o = -R \left(\frac{\partial \ln x_1}{\partial (1/T)} \right)_P \quad \text{Eq. (16)}$$

145 where x_1 is the mole fraction of NAP solubility, R represents the universal gas constant (8.314
 146 $\text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$) and T is the absolute temperature. The standard molar enthalpy change of solution, ΔH_{sol}^o ,
 147 is generally obtained from the slope of the solubility curve in a so-called van't Hoff plot where $\ln x_1$ is
 148 plotted against T^{-1} . Over a limited temperature interval, the heat capacity change of a solution may be
 149 assumed to be constant, hence the derived values of ΔH_{sol}^o will also be valid

150 for the mean temperature, $T_m = \frac{N}{\sum_{i=1}^N \frac{1}{T_i}} = 305.41 \text{ K}$ and Eq. (16) can also be written as ³⁷:

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

151 The standard molar Gibbs energy of the dissolution process, ΔG_{sol}^o can be calculated
 152 according to ³⁸:

$$\Delta G_{sol}^o = -RT_m \times \text{intercept} \quad \text{Eq. (18)}$$

153 where the intercept used is that obtained in plots of $\ln x_1$ versus $(1/T - 1/T_m)$. The
 154 standard molar entropy of dissolution is also obtained from the following equation ³⁴:

$$\Delta S_{sol}^o = \frac{\Delta H_{sol}^o - \Delta G_{sol}^o}{T_m} \quad \text{Eq. (19)}$$

155 The ξ_H and ξ_{TS} identify as the comparison of the relative contributions to the standard molar
 156 Gibbs energy by enthalpy and entropy in the dissolution process, respectively are expressed as follows
 157 ³⁹:

$$\% \xi_H = \frac{|\Delta H_{sol}^o|}{|\Delta H_{sol}^o| + |T\Delta S_{sol}^o|} \times 100 \quad \text{Eq. (20)}$$

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

158 Results and discussion

159 *Solubility results*

160 The experimental NAP solubility data in mixed solvents (DES + water) with different DESs
161 weight fractions at various temperatures (298.15 to 313.15 K) are listed in Table 4. The relationship
162 between solubility of NAP, x_1 , versus absolute temperature in the aqueous DES solutions with
163 different weight fractions of DESs has been revealed in Figure 3. It can be seen from these figure, the
164 solubility of the drug was increased in the aqueous DES solutions at higher concentration of DES and
165 temperatures. The comparison of experimental mole fraction solubility in this study and those values
166 in the literature in systems containing ethanol + water and poly ethylene glycol 200 (PEG 200) + water
167 are summarized in Table 5. The results in this table indicate that the mole fraction solubility of NAP in
168 ethanol + water mixture at each temperature and the same co-solvent weight fraction ($w_3= 0.9$)⁴⁰ is
169 slightly higher than its value compared to ChCl/OA. The solubility values of NAP in aqueous PEG
170 200 solutions however are higher than our obtained values and $w_3= 0.9$ ⁴¹. But the advantage of using
171 DESs is that they are more sustainable and environmentally friendly solvents for pharmaceutical
172 industry.

173 *Modeling results*

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

180 *Thermodynamic properties of dissolution results*

181 The results of ΔG_{sol}^o , ΔH_{sol}^o , and $T_m \Delta S_{sol}^o$ are collected in Table 8. The standard molar Gibbs
182 energy and enthalpy of dissolution are positive in the systems indicate that the process of NAP
183 dissolution in the studied DES solutions is always endothermic. The ΔG_{sol}^o values decrease with

184 increasing the weight fraction of DES, which show that the solubility of NAP in these types of the
185 solvents increases with the decrease of the ΔG_{sol}^o values. On the other hand, ΔS_{sol}^o is positive in most
186 studied systems.

187 The calculated ξ_H and ξ_{TS} values are given in Table 8. From this table it follows that the main
188 contribution to standard molar Gibbs energy of dissolution process of NAP is the enthalpy (greater
189 than 54% in all cases).

190 **Conclusion**

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

201 **Acknowledgements**

202 The authors wish to thank financial support from the graduate council of the University of
203 Tabriz.

204

205

206

207

208

209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224

References

225 1. Yalkowsky SH, Dannenfelser RM 1992. Aquasol database of aqueous solubility. College of
226 Pharmacy, University of Arizona, Tucson, AZ.

227 2. Rossi S. 2013. Australian Medicines Handbook (2013 ed.). Adelaide: The Australian Medicines
228 Handbook Unit Trust. ed.: ISBN 978-0-9805790-9-3.

229 3. Jouyban A. 2009. Handbook of solubility data for pharmaceuticals. ed.: CRC Press.

230 4. Pacheco DP, Manrique YJ, Martínez F 2007. Thermodynamic study of the solubility of ibuprofen
231 and naproxen in some ethanol+ propylene glycol mixtures. 262(1):23-31. doi:
232 10.1016/j.fluid.2007.07.076

233 5. Ahumada EA, Delgado DR, Martínez F 2012. Solubility of acetaminophen in polyethylene
234 glycol400+ water mixtures according to the extended Hildebrand. 41(3):433-477.

- 235 6. Jouyban A, Soltanpour S, Acree Jr WE 2010. Solubility of acetaminophen and ibuprofen in the
236 mixtures of polyethylene glycol 200 or 400 with ethanol and water and the density of solute-free
237 mixed solvents at 298.2 K. 55(11):5252-5257. doi: 10.1021/je100829d.
- 238 7. Romero S, Reillo A, Escalera B, Bustamante P 1996. The behavior of paracetamol in mixtures of
239 amphiprotic and amphiprotic-aprotic solvents. Relationship of solubility curves to specific and
240 nonspecific interactions. 44(5):1061-1064. doi: 10.1248/cpb.44.1061.
- 241 8. Subrahmanyam C, Reddy MS, Rao JV, Rao PG 1992. Irregular solution behaviour of paracetamol
242 in binary solvents. 78(1-3):17-24. doi: 10.1016/0378-5173(92)90350-B.
- 243 9. Smith K, Bridson R, Leeke G 2011. Solubilities of pharmaceutical compounds in ionic liquids.
244 56(5):2039-2043. doi: 10.1021/je101040p.
- 245 10. Mehrdad A, Miri AH 2016. Influence of 1-butyl-3-methyl imidazolium bromide, ionic liquid as
246 co-solvent on aqueous solubility of acetaminophen. 221:1162-1167. doi:
247 10.1016/j.molliq.2016.07.002.
- 248 11. Mehrdad A, Taeb S, Ehsani-Tabar S 2016. Solubility and thermodynamic properties of
249 acetaminophen in 1-hexyl-4-methylpyridinium bromide and water mixtures.1-14. doi:
250 10.1080/00319104.2016.1263631.
- 251 12. Habibi E, Ghanemi K, Fallah-Mehrjardi M, Dadolahi-Sohrab A 2013. A novel digestion method
252 based on a choline chloride–oxalic acid deep eutectic solvent for determining Cu, Fe, and Zn in fish
253 samples. 762:61-67. doi: 10.1016/j.aca.2012.11.054.
- 254 13. Abbott AP, Capper G, Davies DL, McKenzie KJ, Obi SU 2006. Solubility of metal oxides in deep
255 eutectic solvents based on choline chloride. 51(4):1280-1282. doi: 10.1021/je060038c.
- 256 14. Abbott AP, Capper G, Davies DL, Rasheed RK, Tambyrajah V 2003. Novel solvent properties of
257 choline chloride/urea mixtures. (1):70-71. doi: 10.1039/B210714G.
- 258 15. Abbott AP, Capper G, Davies DL, Munro HL, Rasheed RK, Tambyrajah V 2001. Preparation of
259 novel, moisture-stable, Lewis-acidic ionic liquids containing quaternary ammonium salts with
260 functional side chains. (19):2010-2011. doi:

261 10.1039/B106357J.

262 16. Hayyan M, Hashim MA, Hayyan A, Al-Saadi MA, AlNashef IM, Mirghani ME, Saheed OK 2013.

263 Are deep eutectic solvents benign or toxic? 90(7):2193-2195. doi:

264 10.1016/j.chemosphere.2012.11.004.

265 17. Shekaari H, Zafarani-Moattar MT, Mokhtarpour M 2017. Solubility, volumetric and

266 compressibility properties of acetaminophen in some aqueous solutions of choline based deep eutectic

267 solvents at T=(288.15 to 318.15) K. 109:121-130. doi: 10.1016/j.ejps.2017.07.021.

268 18. Shekaari H, Zafarani-Moattar MT, Shayanfar A, Mokhtarpour M 2017. Effect of choline

269 chloride/ethylene glycol or glycerol as deep eutectic solvents on the solubility and thermodynamic

270 properties of acetaminophen. 249: 1222-1235. doi: 10.1016/j.molliq.2017.11.057.

271 19. Shekaari H, Zafarani-Moattar MT, Mokhtarpour M 2018. Experimental determination and

272 correlation of acetaminophen solubility in aqueous solutions of choline chloride based deep eutectic

273 solvents at various temperatures. 462:100-110. doi: 10.1016/j.fluid.2018.01.017.

274 20. Wilson GM 1964. Vapor-liquid equilibrium. XI. A new expression for the excess free energy of

275 mixing. 86(2):127-130. doi: 10.1021/ja01056a002.

276 21. Renon H, Prausnitz JM 1968. Local compositions in thermodynamic excess functions for liquid

277 mixtures. 14(1):135-144. doi: 10.1002/aic.690140124.

278 22. Prausnitz JM, Lichtenthaler RN, de Azevedo EG. 1998. Molecular thermodynamics of fluid-phase

279 equilibria. ed.: Pearson Education.

280 23. Abrams DS, Prausnitz JM 1975. Statistical thermodynamics of liquid mixtures: a new expression

281 for the excess Gibbs energy of partly or completely miscible systems. 21(1):116-128. doi:

282 10.1002/aic.690210115.

283 24. Ren S, Mu H, Alchaer F, Chtatou A, Müllertz A 2013. Optimization of self nanoemulsifying drug

284 delivery system for poorly water-soluble drug using response surface methodology. 39(5):799-806.

285 doi: 10.3109/03639045.2012.710634.

- 286 25. Dixit RP, Nagarsenker M 2008. Formulation and in vivo evaluation of self-nanoemulsifying
287 granules for oral delivery of a combination of ezetimibe and simvastatin. 34(12):1285-1296. doi:
288 10.1080/03639040802071570.
- 289 26. Bandyopadhyay S, Katare O, Singh B 2012. Optimized self nano-emulsifying systems of
290 ezetimibe with enhanced bioavailability potential using long chain and medium chain triglycerides.
291 100:50-61. doi: 10.1016/j.colsurfb.2012.05.019.
- 292 27. Zhang Q, Vigier KDO, Royer S, Jérôme F 2012. Deep eutectic solvents: syntheses, properties and
293 applications. 41(21):7108-7146. doi:
294 10.1039/C2CS35178A.
- 295 28. Jouyban V, Khoubnasabjafari M, Martinez F, Peña A, Jouyban A 2012. Solubility of drugs in ethyl
296 acetate-ethanol mixtures at various temperatures. 22(6):545-547. doi: 10.1016/S1773-2247(12)50094-
297 8.
- 298 29. Forte A, Melo CI, Bogel-Lukasik R, Bogel-Lukasik E 2012. A favourable solubility of isoniazid,
299 an antitubercular antibiotic drug, in alternative solvents. 318:89-95. doi: 10.1016/j.fluid.2012.01.022.
- 300 30. Pitzer KS 1980. Electrolytes. From dilute solutions to fused salts. 102(9):2902-2906. doi:
301 10.1021/ja00529a006.
- 302 31. Simonson JM, Pitzer KS 1986. Thermodynamics of multicomponent, miscible ionic systems: the
303 system lithium nitrate-potassium nitrate-water. 90(13):3009-3013. doi: 10.1021/j100404a043.
- 304 32. Chen CC, Britt HI, Boston J, Evans L 1982. Local composition model for excess Gibbs energy of
305 electrolyte systems. Part I: Single solvent, single completely dissociated electrolyte systems.
306 28(4):588-596. doi: 10.1002/aic.690280410.
- 307 33. Chen CC, Evans LB 1986. A local composition model for the excess Gibbs energy of aqueous
308 electrolyte systems. 32(3):444-454. doi: 10.1002/aic.690320311.
- 309 34. Wang S, Qin L, Zhou Z, Wang J 2012. Solubility and solution thermodynamics of betaine in
310 different pure solvents and binary mixtures. 57(8):2128-2135. doi: 10.1021/je2011659.

- 311 35. Wei D, Li H, Li Y-N, Zhu J 2012. Effect of temperature on the solubility of 3-aminopyridine in
312 binary ethanol+ toluene solvent mixtures. 316:132-134. doi: 10.1016/j.fluid.2011.11.023.
- 313 36. Maher A, Croker D, Rasmuson ÅC, Hodnett BK 2010. Solubility of form III piracetam in a range
314 of solvents. 55(11):5314-5318. doi: 10.1021/je1003934.
- 315 37. Ruidiaz MA, Delgado DR, Martínez F, Marcus Y 2010. Solubility and preferential solvation of
316 indomethacin in 1, 4-dioxane+ water solvent mixtures. 299(2):259-265. doi:
317 10.1016/j.fluid.2010.09.027.
- 318 38. Zhou X, Fan J, Li N, Du Z, Ying H, Wu J, Xiong J, Bai J 2012. Solubility of l-phenylalanine in
319 water and different binary mixtures from 288.15 to 318.15 K. 316:26-33. doi:
320 10.1016/j.fluid.2011.08.029.
- 321 39. Panahi-Azar V, Ahmadian S, Martínez F, Acree WE, Jouyban A 2012. Thermodynamic studies of
322 fluphenazine decanoate solubility in PEG 200+ water mixtures. 330:36-43. doi:
323 10.1016/j.fluid.2011.06.008.
- 324 40. Pacheco DP, Martínez F 2007. Thermodynamic analysis of the solubility of naproxen in ethanol+
325 water cosolvent mixtures. 45(5):581-595. doi: 10.1080/00319100701313862.
- 326 41. Panahi-Azar V, Soltanpour S, Martinez F, Jouyban A 2015. Solubility of naproxen in polyethylene
327 glycol 200+ water mixtures at various temperatures. 14(4):1041.
- 328 42. García G, Aparicio S, Ullah R, Atilhan M 2015. Deep eutectic solvents: physicochemical
329 properties and gas separation applications. 29(4):2616-2644. doi: 10.1021/ef5028873.
- 330 43. Abbott AP, Harris RC, Ryder KS, D'Agostino C, Gladden LF, Mantle MD 2011. Glycerol
331 eutectics as sustainable solvent systems. 13(1):82-90. doi:
332 10.1039/C0GC00395F.
- 333 44. Leron RB, Soriano AN, Li M-H 2012. Densities and refractive indices of the deep eutectic solvents
334 (choline chloride+ ethylene glycol or glycerol) and their aqueous mixtures at the temperature ranging
335 from 298.15 to 333.15 K. 43(4):551-557. doi: 10.1016/j.jtice.2012.01.007.

336 45. Raatikainen T, Laaksonen A 2005. Application of several activity coefficient models to water-
337 organic-electrolyte aerosols of atmospheric interest. 5(9):2475-2495. doi: 10.5194/acp-5-2475-2005.

338

339

340

341

342

343

344

345

346

347

348

349

350

351

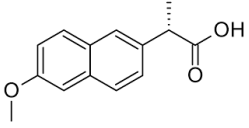
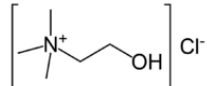
352

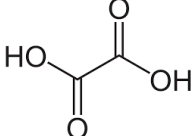
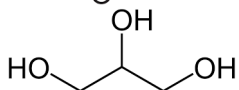
353

354

355 **Table1**

356 Descriptions of the used materials.

Chemical name	Provenance	CAS No.	Mass fraction (purity)	Structure
Naproxen	Merck	26159-31-9	>0.98	
Choline Chloride	Merck	67-48-1	>0.99	

DES	Salt – HBD (molar ratio)	Melting Point (K)	$10^{-3} d / (\text{kg}\cdot\text{m}^{-3})$		$u(\text{m}\cdot\text{s}^{-1})$	n_D		Water content (wt%)
			Exp	Lit		Exp	Lit	
ChCl /oxalic acid	1:1	307.15 ¹⁵	1.210926	1.2200 ²⁷	1925.00	1.4809	1.4868 ⁴²	0.26
ChCl / glycerol	1:2	233.15 ⁴³	1.176963	1.1800 ¹⁵	2012.59	1.4865	1.4867 ⁴⁴	0.33
	Oxalic acid	Merck	144-62-7		>0.99			
	Glycerol	Merck	56-81-5		>0.99			

357

358

359

360

361

362

363

364

365

366

367

368

369

370

371

372 **Table 2**

373 Common properties of DESs used in the article at 298.15 K

374

375

376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402

Table 3

UNIQUAC r and q parameters for the used components.

component	r	q
Water ⁴⁵	0.9200	1.4000
NAP	8.4429	6.2680
ChCl	5.6006	5.0560
OA	2.6026	2.4480
G	3.8399	3.6800

403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418

419 **Table 4**

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

T/K	$10^5 x_1^{\text{exp}}$	e-NRTL model		Wilson model		UNIQUAC model	
		$10^5 x_1^{\text{cal}}$	$100 \frac{x_1^{\text{exp}} - x_1^{\text{cal}}}{x_1^{\text{exp}}}$	$10^5 x_1^{\text{cal}}$	$100 \frac{x_1^{\text{exp}} - x_1^{\text{cal}}}{x_1^{\text{exp}}}$	$10^5 x_1^{\text{cal}}$	$100 \frac{x_1^{\text{exp}} - x_1^{\text{cal}}}{x_1^{\text{exp}}}$
NAP + water + ChCl / oxalic acid							
$w_3=0.0000$							
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
$w_3=0.6000$							
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 / glycerol

$w_3=0.0000$							
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

422 ^a Standard uncertainty $u(x_j^{exp}) = 0.5\%$, ^b Standard uncertainty $u(T) = 0.01$ K, ^c Standard uncertainty $u(w_3) = 0.0002$.

423

424

425
 426
 427
 428
 429
 430
 431
 432
 433
 434
 435
 436
 437 **Table 5**
 438 Comparison of NAP Solubility in this study and literature.
 439

NAP mole fraction solubility			
Experimental data in this study		Literature	
$w_3 = 0.9$ $T = 298.15$		$w_3 = 0.9$ $T = 298.15$	
ChCl/OA + water	7.40×10^{-3}	Ethanol + water	1.10×10^{-2} ⁴⁰
ChCl/G + water	2.10×10^{-3}	PEG 200 + water	1.23×10^{-2} ⁴¹
$w_3 = 0.9$ $T = 303.15$		$w_3 = 0.9$ $T = 303.15$	
ChCl/OA + water	9.37×10^{-3}	Ethanol + water	1.36×10^{-2} ⁴⁰
ChCl/G + water	2.38×10^{-3}	PEG 200 + water	1.79×10^{-2} ⁴¹
$w_3 = 0.9$ $T = 308.15$		$w_3 = 0.9$ $T = 308.15$	
ChCl/OA + water	11.22×10^{-3}	Ethanol + water	1.70×10^{-2} ⁴⁰
ChCl/G + water	2.97×10^{-3}	PEG 200 + water	2.45×10^{-2} ⁴¹
$w_3 = 0.9$ $T = 313.15$		$w_3 = 0.9$ $T = 313.15$	
ChCl/OA + water	13.37×10^{-3}	Ethanol + water	1.99×10^{-2} ⁴⁰
ChCl/G + water	3.33×10^{-3}	PEG 200 + water	3.22×10^{-2} ⁴¹

440
 441
 442
 443
 444

445

446

447

1) T / K	$10^{-4} \Delta g_{wd}^b$	$10^{-5} \Delta g_{dw}$	Δg_{Gd}^b	$10^{-4} \Delta g_{dG}$	$10^{-4} \Delta g_{caw}$	$10^{-4} \Delta g_{wca}$	$10^{-4} \Delta g_{cad}$	$10^{-4} \Delta g_{dca}$	$10^{-4} \Delta g_{Gca}$	Δg_{caG}	Δg_{Gw}	Δg_{wG}
NAP + water + ChCl / G												
298.15	2.069	-14.677	3.353	1.850	-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	2.180	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	2.830	4.146	-1.833	2.091	0.124	0.247	0.565
NAP + water + ChCl / OA												
298.15	1.653	7.710	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	1.320	-1.285	-7.212	-5.551	-1.237	-1.311	0.124	0.247	0.565

448

449

450

451

452

453

454

455

456

457

458

459 **Table 6**

3) T / K	$10^{-4} \Delta u_{wd}^b$	$10^{-3} \Delta u_{dw}$	$10^{-4} \Delta u_{Gd}^b$	$10^{-3} \Delta u_{dG}$	Δu_{caw}	Δu_{wca}	$10^{-3} \Delta u_{cad}$	Δu_{dca}	Δu_{EGca}	$10^{-3} \Delta u_{caG}$	$10^{-3} \Delta u_{Gw}$	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	-4.890	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	1.440	-4.545	1.509	-6.292	-6.057	420.460	2.075	-38.059	35.670	-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	-6.910	-7.516	329.091
313.15	1.402	-4.540	1.333	-6.163	-6.057	421.441	1.314	-38.332	36.137	-6.562	-7.337	181.278

460 The parameters of 1) e-NRTL 2) Wilson 3) UNIQUAC activity coefficient models for the NAP in the different solvents at

461 various temperatures.

462

463

464

465

466

2) T / K	$10^6 A_{wd}$	Λ_{dw}	$10^3 A_{Gd}$	A_{dG}	$10^3 A_{caw}$	A_{wca}	$10^3 A_{cad}$	A_{dca}	$10^3 A_{Gca}$	$10^5 A_{caG}$	A_{Gw}	A_{wG}
------------	---------------	----------------	---------------	----------	----------------	-----------	----------------	-----------	----------------	----------------	----------	----------

NAP + water + ChCl / G

twenty-two

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	0.010	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	-1.920	0.038	-0.03
308.15	7.008	3.225	-0.016	1.876	0.016	0.200	0.120	1.448	0.015	-1.704	0.040	-0.029
313.15	1.057	3.228	0.017	1.019	-0.016	0.051	0.078	0.536	0.080	1.562	-0.030	-0.245

467
468
469 d=drug, w=water, G= glycerol or oxalic acid, Ca=cation or anion.

470
471
472
473 **Table 7**

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

<i>T</i> / K	<i>ARD%</i>		
	e-NRTL	Wilson	UNIQUAC
NAP + water + ChCl / oxalic acid			
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 / glycerol			
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

476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493

494
495
496
497
498
499
500
501
502
503
504

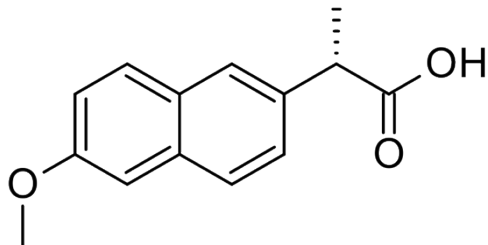
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521

Table 8

Thermodynamic functions for dissolution process at different weight fractions of DES (w_3) ^a at mean temperature ^b.

w_3	$\Delta H_{soln}^\circ / \text{kJ}\cdot\text{mol}^{-1}$	$T_m\Delta S_{soln}^\circ / \text{kJ}\cdot\text{mol}^{-1}$	$\Delta G_{soln}^\circ / \text{kJ}\cdot\text{mol}^{-1}$	ξ_H	ξ_{TS}
NAP + water + ChCl / oxalic acid					
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 / glycerol					
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

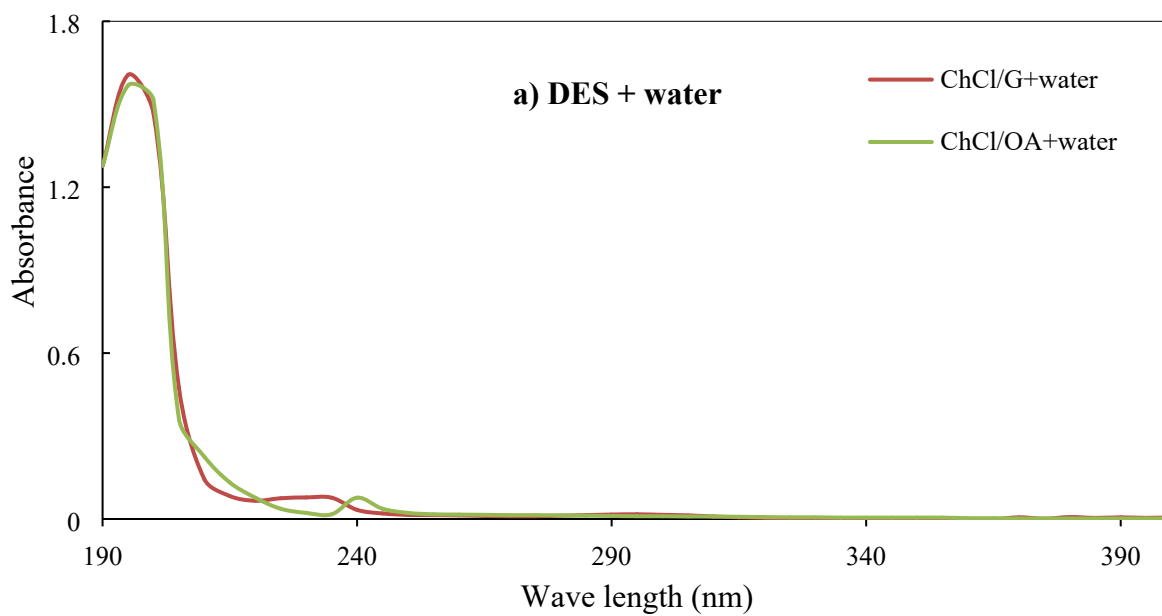
522
523
524
525
526
527



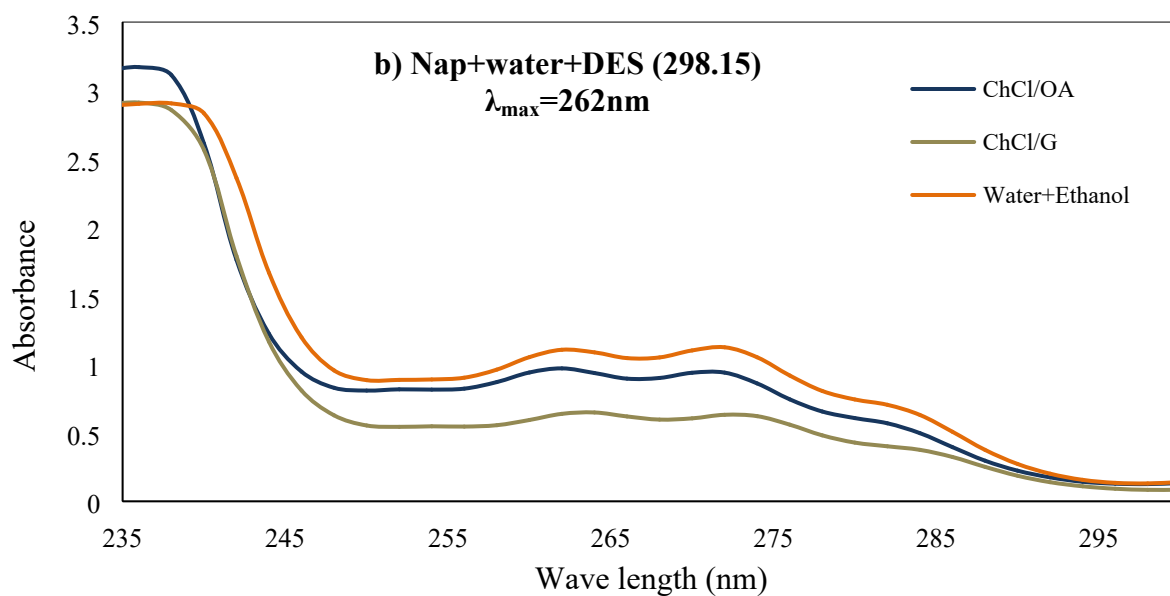
528
529

530 **Figure 1.** Chemical structure of naproxen.

531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547



548



549

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

551

552

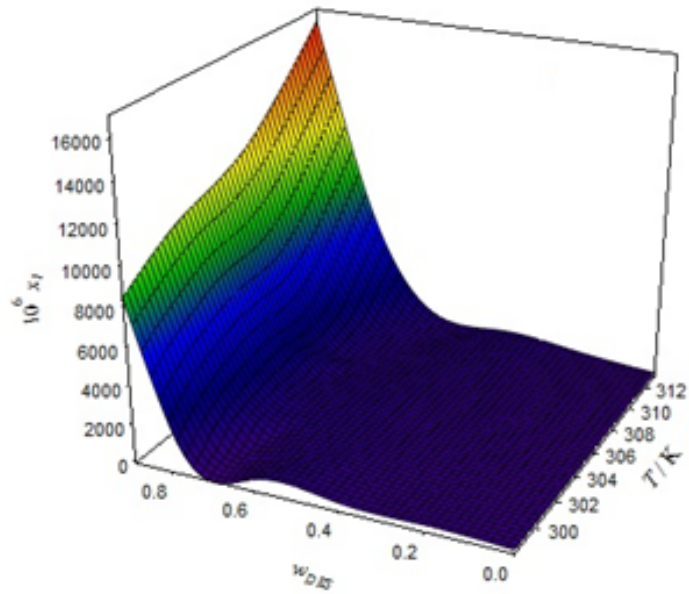
553

554

555

556

557



558

559 **Figure 3.** The relationship between the solubility of NAP, mole fraction x_f , versus mass fraction of DES, w_{DES} , in aqueous
560 ChCl/OA solutions at various temperatures.

561

562

563

564

565

566

567

568

569

570

571

572

573

574

575

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

Masumeh Mokhtarpour¹, Hemayat Shekaari^{*1}, Fleming Martinez², Mohammed Taghi Zafarani-Moattar¹

¹Department of Physical Chemistry, University of Tabriz, Tabriz, Iran

²Grupo de Investigaciones Farmacéutico-Fisicoquímicas, Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, Bogotá, Colombia

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.

* Corresponding author. Tel.: +98-41-33393094. Fax: +98-41-33340191.
E-mail address: hemayatt@yahoo.com (H. Shekaari).