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

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Abstract

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

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

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

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

Introduction

One of the most important issues in drug manufacturing and development is to increase the permeability and bioavailability by enhancement of the solubility of poorly water-soluble drugs. Since the water solubility of drugs is an important factor in drug absorption, low solubility should be increased. In order to overcome this problem, different methods have been tested by researchers including use of cyclodextrins and surface-active agents, pH adjustment, and co-solvency. It is well-known that the co-solvency method is an efficient method to improve the solubility of a low water-soluble drug and addition of a co-solvent to water can considerably alter the drugs solubility.

In recent years organic solvents and ionic liquids (ILs) have been applied as co-solvents to enhance the solubility of drugs but these kinds of solvents suffer from toxicity, high prices and flammability. ILs have obtained a great scientific attention through their unique physical and chemical properties (thermal stability, low flammability, negligible vapor pressure) as solvents and co-solvents in various fields. However there are some limitations to the use of ILs, such as the high price of synthesis, their toxicity, and poor biodegradability and biocompatibility. A new class of solvents has discovered namely deep eutectic solvents (DESs) as an alternative for ILs and organic solvents. These solvents obtain by the combination of biodegradable and natural components including one hydrogen bond donor (HBD) such as quaternary ammonium salt (e.g. choline chloride (ChCl)) and at least one hydrogen bond acceptor (HBA) such as urea or a carboxylic acid. These types of solvents are liquid at ambient temperature and it was established that they are less toxic compared with organic solvents and ILs. The DESs properties can be simply changed by varying the mixing ratio of the applied HBDs and salts.

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

In continuation of our previous works, the purpose of this attempt is to overcome the problems associated with aqueous solubility of BETA, PIR and MEL using DESs based on ChCl as HBA and urea (U), ethylene glycol (EG) and glycerol (G) as HBDs at T = (298.15 to 313.15) K and atmospheric pressure. Additionally, in the phase equilibrium calculations, the activity coefficient models including Wilson and electrolyte-NRTL have been widely applied. In this work, Wilson and e-NRTL...
models were used to evaluate fitness of experimental solubility data. Also, apparent dissolution thermodynamic properties of drugs were obtained using Gibbs and van’t Hoff equations.\(^\text{24,26}\)

**Theoretical consideration**

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

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

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

**Electrolyte-NRTL model**

The e-NRTL activity coefficient model is one of the most frequently employed models for various systems in different fields. This model is introduced by Chen et al.\(^\text{23}\) and Chen and Evans\(^\text{24}\). The activity coefficient for each species is the sum of the NRTL and the PDH contributions.\(^\text{25}\)

\[
\ln(\gamma_i^*) = \ln(\gamma_i^{PDH}) + \ln(\gamma_i^{NRTL}) \tag{2}
\]

\[
\ln(\gamma_i^{NRTL}) = \sum r_i, I \left[ \frac{\sum_j x_j G_{ji} \tau_{ji}}{\sum_k x_k G_{ki}} + \frac{\sum_j x_j G_{ji}}{\sum_k x_k G_{ki}} \left( \tau_{ji} - \frac{\sum_k x_k G_{kj} \tau_{kj}}{\sum_k x_k G_{kj}} \right) \right]
\]

with interaction parameters \(\tau_{ji} = \frac{g_{ji} - g_{ii}}{RT}\).

**The Pitzer–Debye–Hückel (PDH) equation**

Excess Gibbs energy, \(G^{ex. PDH}\), in the PDH equation can be written as:\(^\text{29}\)

\[
G^{ex. PDH} = -\sum_{j} x_j \left( \frac{1000}{M_j} \right)^{1/2} \frac{4A_e P_x}{\rho} \frac{f_x}{I_x} \ln(1 + \rho f_x^{0.5}) \tag{3}
\]

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

\[
A_e = \frac{1}{3} \left( \frac{2\pi N e^2}{V_S} \right)^{1/2} \frac{e^2}{4\pi \epsilon D k T} \tag{4}
\]

where \(N, e, \epsilon, V_S\) 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.\(^\text{30}\)

**Wilson model**

The expressions of Wilson (1964) model for each component \(i\) activity coefficients are presented as:\(^\text{22}\)

\[
\ln(\gamma_i) = 1 - \ln \left( \sum_{j=1}^{n} x_j \Lambda_{ij} \right) - \sum_{k=1}^{n} \left[ \frac{(x_i^\Lambda_{ik})}{\sum_{j=1}^{n} x_j \Lambda_{kj}} - \frac{1}{\sum_{j=1}^{n} x_j \Lambda_{kj}} \right] \tag{5}
\]

where \(\Lambda_{ij}\) is the interaction parameter between \(i\) and \(j\) which are associated to molar volumes of the pure-component, \(\nu\), and differences of characteristic energy, \(\lambda\), using the next relation:

\[
\Lambda_{ij} = \frac{\nu_j \exp \left( -\frac{\lambda_{ij} - \lambda_{ji}}{RT} \right)}{\nu_j} \tag{6}
\]

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

\[
% \text{ARD} = 100 \left( \frac{\sum_{i=1}^{N} \left| x_i^\text{exp} - x_i^\text{cal} \right|}{x_i^\text{exp}} \right) \tag{7}
\]

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

**Thermodynamic properties of the drugs dissolution**

The experimental solubility data of the investigated drugs was plotted versus the temperature to calculate the thermodynamic properties of dissolution. This process gives us a deep insight into the microscopic mechanisms.
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drug solutions by thermodynamic properties of solvation. The solution standard molar enthalpy, $\Delta H_{soln}^o$, is obtained using van’t Hoff equation and expressed as follows:

$$\Delta H_{soln}^o = -R \left( \frac{\partial \ln x_1}{\partial (1/T)} \right)$$

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

$$\Delta H_{soln}^o = -R \left( \frac{\partial \ln x_1}{\partial (1/T)} \right)$$

The next relation is used to calculate the standard molar Gibbs energy of solution, $\Delta G_{soln}^o$:

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

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

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

To compare the relative contributions of entropy ($\% \Delta S_T$) and enthalpy ($\% \Delta H_H$) to the dissolution process, Eqs. (12) and (13) were used, respectively:

$$\% \Delta S_T = \left( \frac{\Delta S_{soln}^o}{\Delta H_{soln}^o} \right) \times 100$$

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

Preparation of the ChCl-based DESs

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

Solubility measurements

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

Results and Discussion

Solubility data and modeling results

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

$$x_1 = \frac{w_1}{M_1} + \frac{w_2}{M_2} + \frac{w_3}{M_3}$$

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

Materials and Methods

Materials

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

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

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

| DES         | Salt – HBD (molar ratio) | Water content | 10³ d / (kg·m⁻³) | u (m·s⁻¹) | nₑ | Exp | Lit |
|-------------|--------------------------|---------------|------------------|-----------|----|-----|-----|
| ChCl/U      | 1:2                      | 0.09%         | 1.1939           | 1.1979⁴⁴  | 2062.27 | 1.5041 | 1.5044⁴³ |
| ChCl/EG     | 1:2                      | 0.02%         | 1.1160           | 1.1200¹¹  | 1911.04 | 1.4685 | 1.4682⁴⁴ |
| ChCl/G      | 1:2                      | 0.05%         | 1.1769           | 1.1800¹¹  | 2012.59 | 1.4685 | 1.4687⁴⁴ |

*a Standard uncertainties for u(d) = 0.006 kg·m⁻³, u(u) = 0.50 m·s⁻¹, u(nₑ) = 0.0002, u(T) = 0.1K and u(P) = 0.0001 MPa.

### Table 3. The experimental (x₁⁾⁾ and calculated (x₁⁾⁾ solubility of BETA in the aqueous DES solutions with various weight fractions (w₃) within the temperature range T / K = 298.15 to 313.15 from e-NRTL and Wilson models.

| T / K | 10⁶ x₁ exp | 10⁶ x₁ e-NRTL model | 10⁶ x₁ Wilson model |
|-------|------------|---------------------|---------------------|
|       |            | 10⁶ x₁ col | 100 x₁ exp - x₁ col | 10⁶ x₁ col | 100 x₁ exp - x₁ col |
|       |            | e-NRTL model      | Wilson model        |
| w₃ = 0.0000 |          |           |         |           |           |         |         |
| 298.15 | 2.232      | 2.252     | -0.89   | 2.104     | 5.73      |
| 303.15 | 3.182      | 3.111     | 2.23    | 3.029     | 4.80      |
| 308.15 | 4.022      | 3.766     | 6.36    | 4.145     | -3.05     |
| 313.15 | 5.609      | 6.565     | -17.08  | 5.745     | 2.42      |
| w₃ = 0.2000 |          |           |         |           |           |         |         |
| 298.15 | 3.149      | 3.574     | -13.51  | 3.653     | -15.99    |
| 303.15 | 5.275      | 4.947     | 6.21    | 4.861     | 7.85      |
### Table 3. Continued

| Temperature (°C) | w_3 | Amount of Solvent (g) |
|-----------------|-----|-----------------------|
| 298.15          | 0.4000 | 6.909 6.363 7.90 6.239 |
| 303.15          | 0.4000 | 7.144 8.917 -24.82 8.064 |
| 308.15          | 0.4000 | 9.675 9.987 -3.22 10.430 |
| 313.15          | 0.4000 | 15.860 19.801 -24.84 15.880 |
| 298.15          | 0.6000 | 12.080 12.551 -3.87 10.323 |
| 303.15          | 0.6000 | 14.720 14.443 1.88 14.640 |
| 308.15          | 0.6000 | 14.880 14.874 0.04 15.140 |
| 313.15          | 0.6000 | 37.960 43.766 -15.29 37.940 |
| 298.15          | 0.8000 | 17.240 20.060 -16.35 20.486 |
| 303.15          | 0.8000 | 29.640 36.573 -23.33 32.007 |
| 308.15          | 0.8000 | 47.520 52.525 -10.53 44.127 |
| 313.15          | 0.8000 | 123.900 123.958 -0.04 123.772 |

**BETA (1) + water (2) + ChCl/EG (3)**

| Temperature (°C) | w_3 | Amount of Solvent (g) |
|-----------------|-----|-----------------------|
| 298.15          | 0.0000 | 2.232 2.261 -1.28 2.106 |
| 303.15          | 0.0000 | 3.182 3.073 7.91 3.644 |
| 308.15          | 0.0000 | 4.022 5.181 -28.81 4.113 |
| 313.15          | 0.0000 | 5.609 6.567 -17.08 5.608 |
| 298.15          | 0.2000 | 3.330 3.765 -13.06 3.968 |
| 303.15          | 0.2000 | 6.160 5.274 14.38 6.137 |
| 308.15          | 0.2000 | 14.350 10.146 29.29 14.178 |
| 313.15          | 0.2000 | 16.050 14.216 11.43 15.925 |
| 298.15          | 0.4000 | 7.417 6.928 6.58 7.296 |
| 303.15          | 0.4000 | 8.142 9.655 -18.58 8.180 |
| 308.15          | 0.4000 | 14.350 21.073 23.14 29.904 |
| 313.15          | 0.4000 | 16.050 14.216 11.43 15.925 |
| 298.15          | 0.6000 | 15.388 14.215 7.62 12.799 |
| 303.15          | 0.6000 | 144.620 34.482 76.16 42.254 |
| 308.15          | 0.6000 | 173.301 57.688 66.71 45.721 |
| 313.15          | 0.6000 | 173.301 223.192 -28.65 174.936 |

**BETA (1) + water (2) + ChCl/EG (3)**

| Temperature (°C) | w_3 | Amount of Solvent (g) |
|-----------------|-----|-----------------------|
| 298.15          | 0.8000 | 18.321 32.682 -78.32 20.183 |
| 303.15          | 0.8000 | 104.010 95.570 8.11 105.461 |
| 308.15          | 0.8000 | 152.002 161.674 -6.36 154.561 |
| 313.15          | 0.8000 | 173.485 223.192 -28.65 174.936 |
| 298.15          | 0.9000 | 18.321 32.682 -78.32 20.183 |
| 303.15          | 0.9000 | 104.010 95.570 8.11 105.461 |
| 308.15          | 0.9000 | 152.002 161.674 -6.36 154.561 |
| 313.15          | 0.9000 | 173.485 223.192 -28.65 174.936 |
### Table 3. Continued

| T / K  | 298.15 | 303.15 | 308.15 | 313.15 |
|-------|--------|--------|--------|--------|
|        | 47.261 | 202.301| 290.090| 316.610|
|        | 46.693 | 198.303| 405.747| 419.619|
|        | -1.20  | 1.98   | -39.86 | -31.70 |
|        | 39.342 | 203.358| 290.114| 319.655|
|        | 16.75  | -0.52  | -0.01  | -0.33  |

BETA (1) + water (2) + ChCl/U (3)

| T / K  | 298.15 | 303.15 | 308.15 | 313.15 |
|-------|--------|--------|--------|--------|
|        | 2.242  | 3.153  | 4.171  | 5.612  |
|        | 1.824  | 4.741  | 5.749  | 5.830  |
|        | 18.64  | -50.33 | -37.66 | -3.88  |
|        | 2.250  | 3.420  | 4.001  | 5.629  |
|        | -0.36  | -8.49  | -4.08  | -0.29  |

| T / K  | 298.15 | 303.15 | 308.15 | 313.15 |
|-------|--------|--------|--------|--------|
|        | 10.390 | 10.940 | 15.090 | 34.701 |
|        | 9.417  | 11.755 | 15.678 | 25.299 |
|        | 9.36   | -7.44  | -3.95  | -6.58  |
|        | 11.311 | 12.091 | 17.155 | 34.850 |
|        | -8.86  | -10.52 | -13.68 | -0.43  |

| T / K  | 298.15 | 303.15 | 308.15 | 313.15 |
|-------|--------|--------|--------|--------|
|        | 37.550 | 39.830 | 41.602 | 57.150 |
|        | 34.440 | 35.084 | 42.063 | 58.696 |
|        | 8.28   | 11.91  | -1.11  | -2.71  |
|        | 31.583 | 35.117 | 40.566 | 62.801 |
|        | 15.89  | 11.83  | 2.49   | -9.88  |

| T / K  | 298.15 | 303.15 | 308.15 | 313.15 |
|-------|--------|--------|--------|--------|
|        | 144.202| 227.201| 251.998| 373.201|
|        | 111.725| 242.178| 476.526| 123.636|
|        | 22.52  | -6.59  | -27.68 | -6.44  |
|        | 153.731| 185.733| 370.784| 113.799|
|        | -6.60  | -18.25 | 0.64   | -9.88  |

| T / K  | 298.15 | 303.15 | 308.15 | 313.15 |
|-------|--------|--------|--------|--------|
|        | 173.702| 265.303| 319.811| 404.404|
|        | 130.258| 315.570| 440.863| 557.135|
|        | 25.01  | -18.94 | -37.85 | -37.76 |
|        | 181.346| 293.666| 323.189| 406.256|
|        | -4.40  | -10.69 | -1.06  | -27.68 |

* Standard uncertainty $u(x_{1}^{\text{exp}}) = 0.5\%$, * Standard uncertainty $u(T) = 0.01$ K and * Standard uncertainty $u(w_{3}) = 0.0002$

### Table 4.
The experimental ($x_{1}^{\text{exp}}$) and calculated ($x_{1}^{\text{cal}}$) solubility of MEL in the aqueous DES solutions with various weight fractions ($w_{3}$) within the temperature range $T / K = 298.15$ to $313.15$ from e-NRTL and Wilson models.

| T / K  | 298.15 | 303.15 | 308.15 | 313.15 |
|-------|--------|--------|--------|--------|
|        | e-NRTL model | Wilson model |
| $10^3 x_{1}^{\text{cal}}$ | $x_{1}^{\text{cal}}$ | $100 \frac{x_{1}^{\text{cal}} - x_{1}^{\text{exp}}}{x_{1}^{\text{exp}}}$ | $10^3 x_{1}^{\text{cal}}$ | $100 \frac{x_{1}^{\text{cal}} - x_{1}^{\text{exp}}}{x_{1}^{\text{exp}}}$ |

MEL (1) + water (2) + ChCl/G (3)

| T / K  | 298.15 | 303.15 | 308.15 | 313.15 |
|-------|--------|--------|--------|--------|
|        | 1.125  | 1.222  | 1.299  | 1.382  |
|        | 1.094  | 1.222  | 1.292  | 1.389  |
|        | 2.77   | -0.14  | 0.55   | -0.50  |
|        | 1.113  | 1.122  | 1.130  | 1.138  |
|        | 1.07   | 8.03   | 13.01  | 17.65  |
| $w_{3}$=0.0000 | 298.15 | 303.15 | 308.15 | 313.15 |
| $w_{3}$=0.2000 | 298.15 | 303.15 | 308.15 | 313.15 |
| $w_{3}$=0.4000 | 298.15 | 303.15 | 308.15 | 313.15 |
| $w_{3}$=0.6000 | 298.15 | 303.15 | 308.15 | 313.15 |
| $w_{3}$=0.8000 | 298.15 | 303.15 | 308.15 | 313.15 |
| $w_{3}$=0.9000 | 298.15 | 303.15 | 308.15 | 313.15 |
| Temperature | \( w_3 = 0.2000 \) | \( w_3 = 0.4000 \) | \( w_3 = 0.6000 \) | \( w_3 = 0.8000 \) | \( w_3 = 0.9000 \) |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 298.15      | 1.491           | 2.103           | 2.211           | 2.304           | 2.914           |
|             | 1.485           | 1.953           | 2.171           | 2.411           | 2.793           |
|             | 0.40            | 7.13            | 1.88            | -4.63           | 4.16            |
|             |                 |                 |                 |                 |                 |
| 303.15      | 1.553           | 2.217           | 2.763           | 3.302           | 3.629           |
|             | 1.565           | 2.378           | 2.525           | 3.109           | 4.210           |
|             | -0.77           | -7.26           | 8.61            | 5.84            | -16.01          |
|             |                 |                 |                 |                 |                 |
| 308.15      | 1.805           | 2.556           | 2.816           | 3.351           | 3.706           |
|             | 1.722           | 2.425           | 2.710           | 3.248           | 4.351           |
|             | 4.59            | 5.12            | 3.76            | 3.07            | -17.40          |
|             |                 |                 |                 |                 |                 |
| 313.15      | 1.823           | 2.713           | 3.579           | 4.005           | 4.753           |
|             | 1.843           | 2.951           | 3.338           | 4.155           | 4.383           |
|             | -1.10           | -8.79           | 6.73            | -3.74           | 7.78            |

| Temperature | \( w_3 = 0.0000 \) | \( w_3 = 0.2000 \) | \( w_3 = 0.4000 \) | \( w_3 = 0.6000 \) | \( w_3 = 0.8000 \) |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 298.15      | 1.125           | 2.808           | 3.706           | 3.869           | 4.014           |
|             | 1.126           | 2.696           | 3.723           | 3.894           | 4.287           |
|             | -0.05           | 3.98            | -0.45           | -0.65           | -6.78           |
|             |                 |                 |                 |                 |                 |
| 303.15      | 1.220           | 3.148           | 3.947           | 4.081           | 4.624           |
|             | 1.217           | 3.077           | 3.956           | 4.134           | 4.985           |
|             | 0.25            | 2.24            | -0.24           | -1.31           | -7.81           |
|             |                 |                 |                 |                 |                 |
| 308.15      | 1.299           | 3.474           | 4.495           | 5.256           | 6.588           |
|             | 1.297           | 3.398           | 4.591           | 5.242           | 7.155           |
|             | 0.16            | 2.19            | -2.14           | 0.27            | -8.61           |
|             |                 |                 |                 |                 |                 |
| 313.15      | 1.382           | 5.076           | 8.410           | 10.48           | 12.320          |
|             | 1.378           | 4.833           | 8.135           | 9.598           | 12.37           |
|             | 0.27            | 4.78            | 3.27            | 8.42            | -0.44           |

| Temperature | \( w_3 = 0.6000 \) | \( w_3 = 0.8000 \) |
|-------------|-----------------|-----------------|
| 298.15      | 3.869           | 4.014           |
|             | 3.894           | 4.287           |
|             | -0.65           | -6.78           |
|             |                 |                 |
| 303.15      | 4.081           | 4.624           |
|             | 4.134           | 4.985           |
|             | -1.31           | -7.81           |
|             |                 |                 |
| 308.15      | 5.256           | 6.588           |
|             | 5.242           | 7.155           |
|             | 0.27            | -8.61           |
|             |                 |                 |
| 313.15      | 10.48           | 12.320          |
|             | 9.598           | 12.37           |
|             | 8.42            | -0.44           |

\[ MEL (1) + \text{water (2)} + \text{ChCl/EG (3)} \]
Table 4. Continued

| $w_3$ | $T / K$ | $X_{1\text{cal}}$ | $X_{1\text{exp}}$ | $\frac{X_{1\text{exp}} - X_{1\text{cal}}}{X_{1\text{exp}}}$ | $\frac{X_{1\text{exp}} - X_{1\text{cal}}}{X_{1\text{exp}}}$ |
|-------|---------|-----------------|----------------|---------------------------------|---------------------------------|
| 0.0000 | 298.15  | 0.0401          | 0.0401         | -0.18                           | 0.0405                          |
|       | 303.15  | 0.0434          | 0.0434         | -0.03                           | 0.0433                          |
|       | 308.15  | 0.0478          | 0.0476         | 0.36                            | 0.0477                          |
|       | 313.15  | 0.0506          | 0.0505         | 0.17                            | 0.0510                          |

MEL (1) + water (2) + ChCl/U (3)

| $w_3$ | $T / K$ | $X_{1\text{cal}}$ | $X_{1\text{exp}}$ | $\frac{X_{1\text{exp}} - X_{1\text{cal}}}{X_{1\text{exp}}}$ | $\frac{X_{1\text{exp}} - X_{1\text{cal}}}{X_{1\text{exp}}}$ |
|-------|---------|-----------------|----------------|---------------------------------|---------------------------------|
| 0.0000 | 298.15  | 0.0401          | 0.0401         | -0.18                           | 0.0405                          |
|       | 303.15  | 0.0434          | 0.0434         | -0.03                           | 0.0433                          |
|       | 308.15  | 0.0478          | 0.0476         | 0.36                            | 0.0477                          |
|       | 313.15  | 0.0506          | 0.0505         | 0.17                            | 0.0510                          |

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

| $T / K$ | $10^3 x_1^{\text{cal}}$ | $10^3 x_1^{\text{exp}}$ | $10^3 x_1^{\text{exp}} - x_1^{\text{cal}}$ | $x_1^{\text{exp}}$ | $10^3 x_1^{\text{exp}} - x_1^{\text{cal}}$ |
|---------|-----------------|----------------|---------------------------------|----------------|---------------------------------|
| 298.15  | 0.0401          | 0.0401         | -0.18                           | 0.0405                          |
| 303.15  | 0.0434          | 0.0434         | -0.03                           | 0.0433                          |
| 308.15  | 0.0478          | 0.0476         | 0.36                            | 0.0477                          |
| 313.15  | 0.0506          | 0.0505         | 0.17                            | 0.0510                          |
**Table 5. Continued**

| \( w_r \) = 0.2000 |        |        |        |        |        |
|-----------------|--------|--------|--------|--------|--------|
| 298.15          | 1.147  | 1.148  | -0.06  | 1.181  | -2.95  |
| 303.15          | 1.252  | 1.264  | -0.93  | 1.251  | 0.06   |
| 308.15          | 1.497  | 1.503  | -0.40  | 1.416  | 5.41   |
| 313.15          | 1.529  | 1.544  | -0.98  | 1.575  | -2.99  |

| \( w_r \) = 0.4000 |        |        |        |        |        |
|-----------------|--------|--------|--------|--------|--------|
| 298.15          | 1.908  | 2.038  | -6.80  | 1.849  | 3.10   |
| 303.15          | 2.265  | 2.375  | -4.84  | 2.220  | 1.98   |
| 308.15          | 2.502  | 2.482  | 0.79   | 2.526  | -0.96  |
| 313.15          | 2.672  | 2.797  | -4.67  | 2.612  | 2.24   |

| \( w_r \) = 0.6000 |        |        |        |        |        |
|-----------------|--------|--------|--------|--------|--------|
| 298.15          | 2.525  | 2.481  | 1.73   | 2.418  | 4.22   |
| 303.15          | 2.983  | 2.939  | 1.48   | 2.980  | 0.09   |
| 308.15          | 3.054  | 3.136  | -2.68  | 3.103  | -1.59  |
| 313.15          | 3.326  | 3.275  | 1.54   | 3.227  | 2.98   |

| \( w_r \) = 0.8000 |        |        |        |        |        |
|-----------------|--------|--------|--------|--------|--------|
| 298.15          | 2.772  | 3.382  | -22.01 | 3.001  | -8.218 |
| 303.15          | 3.053  | 3.853  | -26.21 | 3.044  | 0.30   |
| 308.15          | 3.432  | 4.185  | -21.93 | 3.962  | -15.45 |
| 313.15          | 3.614  | 4.401  | -21.78 | 4.175  | -15.51 |

| \( w_r \) = 0.9000 |        |        |        |        |        |
|-----------------|--------|--------|--------|--------|--------|
| 298.15          | 4.142  | 4.118  | 0.59   | 4.213  | -1.72  |
| 303.15          | 4.380  | 4.579  | -4.54  | 4.387  | -0.16  |
| 308.15          | 5.974  | 5.615  | 6.01   | 4.991  | 16.45  |
| 313.15          | 6.790  | 6.661  | 1.90   | 5.866  | 13.61  |

**PIR (1) + water (2) + ChCl/EG (3)**

| \( w_r \) = 0.0000 |        |        |        |        |        |
|-----------------|--------|--------|--------|--------|--------|
| 298.15          | 0.0401 | 0.0400 | 0.13   | 0.0400 | 0.04   |
| 303.15          | 0.0434 | 0.0434 | 0.05   | 0.0431 | 0.50   |
| 308.15          | 0.0478 | 0.0477 | 0.12   | 0.0480 | -0.01  |
| 313.15          | 0.0506 | 0.0504 | 0.29   | 0.0505 | 0.09   |

| \( w_r \) = 0.2000 |        |        |        |        |        |
|-----------------|--------|--------|--------|--------|--------|
| 298.15          | 1.806  | 1.796  | 0.53   | 1.796  | 0.55   |
| 303.15          | 1.839  | 1.819  | 1.08   | 1.836  | 0.16   |
| 308.15          | 1.856  | 1.897  | -2.20  | 1.850  | 0.32   |
| 313.15          | 1.925  | 1.963  | -1.95  | 2.079  | -7.99  |

| \( w_r \) = 0.4000 |        |        |        |        |        |
|-----------------|--------|--------|--------|--------|--------|
| 298.15          | 2.233  | 2.299  | -2.97  | 2.228  | 0.22   |
| 303.15          | 2.868  | 2.406  | 16.10  | 2.751  | 4.08   |
| 308.15          | 3.027  | 3.012  | 0.49   | 3.204  | -5.84  |
| 313.15          | 3.674  | 3.694  | -0.54  | 3.270  | 10.99  |

| \( w_r \) = 0.6000 |        |        |        |        |        |
|-----------------|--------|--------|--------|--------|--------|
| 298.15          | 2.908  | 2.805  | 3.55   | 2.891  | 0.62   |
| 303.15          | 2.983  | 2.892  | 3.05   | 3.261  | -9.32  |
| 308.15          | 3.863  | 3.779  | 2.17   | 3.800  | 1.64   |
| 313.15          | 4.058  | 4.149  | -2.23  | 4.327  | -6.63  |

| \( w_r \) = 0.8000 |        |        |        |        |        |
|-----------------|--------|--------|--------|--------|--------|
| 298.15          | 3.053  | 3.414  | -11.82 | 3.160  | -3.50  |
| 303.15          | 4.161  | 4.186  | -0.60  | 4.791  | -15.14 |
| 308.15          | 4.806  | 5.967  | -24.17 | 5.133  | -6.80  |
| 313.15          | 6.196  | 6.896  | -11.29 | 7.156  | -15.49 |
The relationship between the solubility of drugs, $x_j$, versus temperature and weight fractions in aqueous DESs solutions has been graphically plotted in Figures 1-3. These figures show that the solubility of drugs was raised in the presence of DESs at higher temperatures and concentration of DES. Also, the order for the performance of the co-solvents in drugs solubility enhancement is as follows:

- **MEL**: ChCl/EG > ChCl/G > ChCl/U
- **BETA**: ChCl/U > ChCl/EG > ChCl/G

The high solubility of drugs in the presence of DESs reinforces their ability as powerful solubilizing agents. The levels of solubility observed for drugs in the studied systems could be due to solute–solvent interactions. The hydrophobic drugs can be solved in a solvent-based on interactions such as H-bonds, van der Waals forces, ion-dipole and dipole-dipole between solute–solvent. At the atomic level, the used drugs and DESs can interact with each other mainly via H-bonds interactions. The studied drugs have the ability to act as HBDS or HBAs, forming H-bonds with DESs. The H-bond is formed between the carboxyl and hydroxyl groups of used drugs and the hydroxyl or carboxyl and Cl group of DESs. The solvating power of DESs is remarkable rather than water, because, there are H-bonds and dipole-dipole interactions between drug and water. But in drug + water + DESs systems, there are strong ion-dipole interactions in addition to H-bonds and dipole-dipole interactions. In order of these interactions, significant increase in the solubility of...
drugs in the presence of DESs yielded. Moreover, it should also be noted that the performance of and DES as a co-solvent for a drug is different. Some DESs have stronger intermolecular interactions, thus their interactions with the drugs are weak. Also, H-bonds interactions between HBA and HBD in DESs were increased with the increased H-bonds group (hydroxyl and carboxyl groups) and H-bonds interaction of ChCl with second component is weakened.\(^{45,47}\) Otherwise, it is noteworthy that the monohydrated solid form of PIR has been reported in neat water after saturation of anhydrate form.\(^{48}\) The results of the applied models are given in Tables 3, 4 and 5. Figures 1, 2 and 3 present the calculated and experimental solubility of drugs in aqueous DES solutions using Wilson model. The obtained results for %ARD are collected in Table 6. It can be understood the Wilson model presents better outcomes with respect to the e-NRTL, even this model is more accurate. Thus, the efficiency of the models employed in the solubility values correlation can be written as Wilson > e-NRTL.

**Thermodynamic properties of dissolution**

The values of apparent standard Gibbs free energy, enthalpy, entropy for solution process, \(\%\_H\) and \(\%\_S\) in investigated co-solvent systems at studied temperatures are given in Tables 7, 8 and 9. The apparent standard dissolution enthalpy in all the systems is positive, which denotes that the crystal lattice energy is more than the essential energy for the process of solute solvation as a favorable parameter. Accordingly, the dissolution process of the studied drugs in co-solvent systems is endothermic. Also, apparent standard dissolution entropy of BETA is positive in the three DESs systems, which specifies that the apparent standard dissolution entropy is favorable parameter for the solvation of this drug in the investigated systems. But in the case of MEL in the presence of studied DESs \(\Delta S^{0}_{\text{Soln}}\) is negative in water and aqueous solutions of ChCl/U and ChC/G at a weigh fraction of 0.20 to 0.80 and its value is positive for 0.90. In addition, \(\Delta G^{0}_{\text{Soln}}\) is positive for solutions containing ChCl/EG. The \(\Delta S^{0}_{\text{Soln}}\) for PIR in water is negative and in ChCl/G and ChCl/EG at 0.20 to 0.80 and 0.2 to 0.6 weight fractions are negative respectively (positive for \(w_{DES}=0.9\)), however it is positive in systems (PIR + water + ChCl/U). The apparent standard dissolution Gibbs free energy have positive values in all studied systems, consequently the solution process is non-spontaneous (Figure 4). \(\Delta G^{0}_{\text{Soln}}\) values for drug dissolution were in good agreement with for solubilities of them in the investigated systems.
Table 6. The calculated average relative deviation percent (ARD%) for the solubility of the drugs in the aqueous DES solutions at different temperatures from two models.

| T / K | e-NRTL | Wilson | e-NRTL | Wilson | e-NRTL | Wilson |
|-------|--------|--------|--------|--------|--------|--------|
|       | BETA (1) + water (2) + ChCl/U (3) | MEL (1) + water (2) + ChCl/U (3) | PIR (1) + water (2) + ChCl/U (3) |       |        |        |
| 298.15 | 16.56 | 4.20 | 9.13 | 4.60 | 3.89 | 0.51 |
| 303.15 | 9.51 | 10.09 | 7.37 | 4.70 | 5.81 | 6.88 |
| 308.15 | 9.44 | 0.45 | 6.70 | 3.80 | 3.30 | 2.59 |
| 313.15 | 10.56 | 0.35 | 4.58 | 0.35 | 5.18 | 0.18 |
| Average | 11.51 | 3.77 | 6.94 | 3.36 | 4.54 | 2.54 |

|       | BETA (1) + water (2) + ChCl/G (3) | MEL (1) + water (2) + ChCl/G (3) | PIR (1) + water (2) + ChCl/G (3) |       |        |        |
| 298.15 | 9.46 | 7.80 | 3.66 | 0.47 | 4.58 | 3.29 |
| 303.15 | 7.49 | 3.67 | 5.51 | 1.70 | 5.40 | 0.09 |
| 308.15 | 7.06 | 3.20 | 6.00 | 2.30 | 5.28 | 8.37 |
| 313.15 | 7.41 | 0.14 | 6.70 | 3.80 | 5.81 | 6.61 |
| Average | 7.85 | 3.68 | 5.12 | 1.79 | 5.02 | 4.59 |

|       | BETA (1) + water (2) + ChCl/EG (3) | MEL (1) + water (2) + ChCl/EG (3) | PIR (1) + water (2) + ChCl/EG (3) |       |        |        |
| 298.15 | 8.11 | 5.29 | 9.13 | 1.30 | 1.60 | 1.33 |
| 303.15 | 13.72 | 8.92 | 7.37 | 0.65 | 6.27 | 0.68 |
| 308.15 | 5.73 | 5.13 | 6.70 | 0.67 | 8.58 | 0.67 |
| 313.15 | 6.13 | 0.39 | 8.58 | 0.67 | 5.51 | 0.29 |
| Average | 8.09 | 4.73 | 6.94 | 0.73 | 5.49 | 0.73 |

Table 7. Thermodynamic functions for solution process of BETA at different weight fractions of DES (w₃) at mean temperature (Tₘ).

| w₃ | ΔHₛₑ₋ₑ / kJ∙mol⁻¹ | TₘΔSₛₑ₋ₑ / kJ∙mol⁻¹ | ΔGₛₑ₋ₑ / kJ∙mol⁻¹ | ¹ξ | ²ξ |
|----|-------------------|----------------------|-------------------|-----|-----|
|    | BETA (1) + water (2) + ChCl/U (3) |                     |                   |     |     |
| 0.0000 | 47.09 | 15.24 | 31.85 | 75.55 | 24.45 |
| 0.2000 | 60.75 | 32.64 | 28.11 | 65.05 | 34.95 |
| 0.4000 | 27.30 | 1.89 | 25.41 | 93.53 | 6.47 |
| 0.6000 | 33.67 | 9.51 | 24.16 | 77.98 | 22.02 |
| 0.8000 | 45.92 | 24.7 | 21.22 | 65.02 | 34.98 |
| 0.9000 | 42.35 | 21.55 | 20.80 | 66.28 | 33.72 |
|    | BETA (1) + water (2) + ChCl/G (3) |                     |                   |     |     |
| 0.0000 | 47.09 | 15.21 | 31.88 | 75.58 | 24.42 |
| 0.2000 | 76.31 | 46.05 | 30.26 | 62.36 | 37.64 |
| 0.4000 | 43.17 | 13.75 | 29.42 | 75.85 | 24.15 |
| 0.6000 | 53.11 | 25.33 | 27.78 | 67.71 | 32.29 |
| 0.8000 | 98.96 | 73.34 | 25.62 | 57.44 | 42.56 |
| 0.9000 | 85.57 | 61.63 | 23.94 | 58.13 | 41.87 |
|    | BETA (1) + water (2) + ChCl/EG (3) |                     |                   |     |     |
| 0.0000 | 46.54 | 14.67 | 31.87 | 76.03 | 23.97 |
| 0.2000 | 85.36 | 55.62 | 29.74 | 60.55 | 39.45 |
| 0.4000 | 88.83 | 60.67 | 28.16 | 59.42 | 40.58 |
| 0.6000 | 61.59 | 34.91 | 26.69 | 63.83 | 36.17 |
| 0.8000 | 103.78 | 80.20 | 23.58 | 56.41 | 43.59 |
| 0.9000 | 95.15 | 73.13 | 22.01 | 56.54 | 43.46 |

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

For most of the investigated systems, ¹ξ > ²ξ , which means that the main contributing force to the apparent standard dissolution Gibbs free energy are the enthalpy. It means that the dissolution process contains some effects such as the interactions between solute-solvent, hydrogen bonds, electrostatic forces and hydrophobic interaction. Consequently, the energy new bond made between solvent and solute molecules is not adequate to provide the energy needed for breaking the original bond in various solvents, the enthalpy change contributing force is larger in dissolving process.
Table 8. Thermodynamic functions for solution process of MEL at different weight fractions of DES (w₃) at mean temperature (Tₘ).

| w₃   | ΔHₛₑₐₜ / kJ·mol⁻¹ | TₛΔSₛₑₐₜ / kJ·mol⁻¹ | ΔGₛₑₐₜ / kJ·mol⁻¹ | ξ / I | ξ / G |
|------|--------------------|-----------------------|-------------------|-------|-------|
| MEL (1) + water (2) + ChCl/U (3) |
| 0.0000 | 10.56 | -23.96 | 34.52 | 30.60 | 69.40 |
| 0.2000 | 24.36 | -4.13 | 28.49 | 85.51 | 14.49 |
| 0.4000 | 22.41 | -5.53 | 27.94 | 80.22 | 14.78 |
| 0.6000 | 11.84 | -15.20 | 27.03 | 43.79 | 56.21 |
| 0.8000 | 18.50 | -8.13 | 26.63 | 69.45 | 30.54 |
| 0.9000 | 29.17 | 2.90 | 26.27 | 90.97 | 9.03 |
| MEL (1) + water (2) + ChCl/G (3) |
| 0.0000 | 10.56 | -23.96 | 34.52 | 30.60 | 69.40 |
| 0.2000 | 28.97 | 2.93 | 26.04 | 90.53 | 9.17 |
| 0.4000 | 39.89 | 14.66 | 25.24 | 73.13 | 26.87 |
| 0.6000 | 50.01 | 25.06 | 24.95 | 66.62 | 33.38 |
| 0.8000 | 57.47 | 32.87 | 24.60 | 63.62 | 36.38 |
| 0.9000 | 63.37 | 40.12 | 23.25 | 61.23 | 38.77 |
| MEL (1) + water (2) + ChCl/EG (3) |
| 0.0000 | 10.56 | -23.96 | 34.52 | 30.60 | 69.40 |
| 0.2000 | 3.11 | -24.57 | 27.68 | 11.22 | 88.78 |
| 0.4000 | 24.05 | -2.48 | 26.54 | 90.64 | 9.36 |
| 0.6000 | 17.67 | -8.38 | 26.05 | 67.85 | 32.15 |
| 0.8000 | 35.23 | 9.75 | 25.48 | 78.32 | 21.68 |
| 0.9000 | 50.21 | 26.75 | 23.47 | 65.25 | 34.75 |

Table 9. Thermodynamic functions for solution process of PIR at different weight fractions of DES (w₃) at mean temperature (Tₘ).

| w₃   | ΔHₛₑₐₜ / kJ·mol⁻¹ | TₛΔSₛₑₐₜ / kJ·mol⁻¹ | ΔGₛₑₐₜ / kJ·mol⁻¹ | ξ / I | ξ / G |
|------|--------------------|-----------------------|-------------------|-------|-------|
| PIR (1) + water (2) + ChCl/U (3) |
| 0.0000 | 12.34 | -24.76 | 37.11 | 33.26 | 66.74 |
| 0.2000 | 125.68 | 103.35 | 22.33 | 54.87 | 45.13 |
| 0.4000 | 59.91 | 39.70 | 20.21 | 60.14 | 39.86 |
| 0.6000 | 50.01 | 20.88 | 19.13 | 50.03 | 34.29 |
| 0.8000 | 18.58 | 0.51 | 18.07 | 97.32 | 2.68 |
| 0.9000 | 20.08 | 2.73 | 17.35 | 88.02 | 11.97 |
| PIR (1) + water (2) + ChCl/G (3) |
| 0.0000 | 12.34 | -24.77 | 37.11 | 33.26 | 66.74 |
| 0.2000 | 16.19 | -12.30 | 28.49 | 56.84 | 43.16 |
| 0.4000 | 17.28 | -9.83 | 27.11 | 63.74 | 45.36 |
| 0.6000 | 13.24 | -13.25 | 26.29 | 49.97 | 50.03 |
| 0.8000 | 14.19 | -12.10 | 25.05 | 53.98 | 46.02 |
| 0.9000 | 27.80 | 2.74 | 24.73 | 91.02 | 8.98 |
| PIR (1) + water (2) + ChCl/EG (3) |
| 0.0000 | 12.34 | -24.77 | 37.11 | 33.26 | 66.74 |
| 0.2000 | 3.11 | -24.57 | 27.68 | 11.22 | 88.78 |
| 0.4000 | 24.05 | -2.48 | 26.54 | 90.64 | 9.36 |
| 0.6000 | 17.67 | -8.38 | 26.05 | 67.85 | 32.15 |
| 0.8000 | 35.23 | 9.75 | 25.48 | 78.32 | 21.68 |
| 0.9000 | 50.21 | 26.75 | 23.47 | 65.25 | 34.75 |

Conclusion
The equilibrium solubilities of three drugs (betamethasone, meloxicam, piroxicam) in co-solvent mixtures of {water + ChCl/U}, {water + ChCl/EG} and {water + ChCl/G} were measured experimentally by the saturation shake-flask method within the temperature range from 298.15 K to 313.15 K at atmospheric pressure. At the same temperature...
and weight fraction of DESs the mole fraction solubility of MEL was higher in (water + ChCl/EG), PIR in (water + ChCl/U) and BETA in (water + ChCl/U) than in the other studied mixtures. Furthermore, the drugs’ solubilities were mathematically correlated through the Wilson and e-NRTL activity coefficient models obtaining $\%\text{ARD}$ lower than 3.30% for Wilson model. It turned out that the Wilson model could provide a better acceptable fitting result than those obtained by the e-NRTL. Finally, thermodynamic functions of the dissolution were obtained using Gibbs free energy and van’t Hoff equations. The apparent standard dissolution Gibbs free energy and enthalpy change are positive in all the binary solvents investigated in this paper. These results indicate that the dissolution process is more favorable as the concentration of DES increases in the mixtures and it is endothermic. In addition, in most of the studied systems, the main contributor to the apparent standard dissolution Gibbs free energy in the dissolution process is the enthalpy during the dissolution, consequently, this procedure is enthalpy-dominated.

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Conflict of Interest
The authors claim that there is no conflict of interest.

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