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Influence of choline-based ionic liquids as neoteric green solvents on aqueous solubility of lamotrigine and piroxicam drugs

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Abstract

Background: New compounds called choline-based ionic liquids (ILs) that are environmentally friendly have become more attractive. In this study, some choline-based ILs (choline lactate (ChLa) and choline propionate (ChPro) have been used to increase the aqueous solubility of lamotrigine (LTG) and piroxicam (PXM) at T = 298.15 to 313.15 K.

Methods: ILs were prepared and purified. The solubility of drugs in the aqueous ILs solutions was measured at different temperatures with shake flask method.

Results: The solubility of the investigated drugs increased with increasing the weight fraction of ILs. The solubility data were correlated by e-NRTL, Wilson, Apelblat and λh (Buchowski) models.

Conclusion: The aqueous solubility of drugs depends on both the weight fraction of co-solvents and the solution temperature. These two essential parameters were analyzed through some semi-empirical and activity coefficient models getting the average relative deviation percent as e-NRTL (3.09%) < Wilson (3.92%) (for full range concentration of co-solvent) and Apelblat (3.52%) < λh (Buchowski) (5.11%) (for the dilute region of co-solvent). In addition, the results show that the aqueous solubility increases with rising temperature and there are strong interactions between the drug and the ILs.

.*Keywords*: Choline-based ionic liquids; Solubility; Lamotrigine; Piroxicam; Activity coefficient models.

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1. Introduction

Piroxicam (PXM, 4-hydroxy-2-methyl-N-(pyridine-2-yl)-2H-1, 2-benzo-thiazine-3-carboxamide-1, 2-dioxide) is a chemically different potent drug with a long half-life which makes it suitable to use once a day. In addition, it is a member of oxicams that can treat rheumatoid arthritis and osteoarthritis. So, it can be concluded that the application of PXM is in musculoskeletal and joint disorders [1,2]. The mentioned drug is a sub-branch of non-steroidal anti-inflammatory drugs (NSAIDs) [3]. Moreover, this poorly soluble, highly permeable drug be a suitable alternative to aspirin, indomethacin, naproxen, ibuprofen, ketoprofen, sulindac, phenylbutazone, and diclofenac in the treatment of rheumatic diseases. The solubility of a drug is significant in the pharmaceutical industry because the amount of medicine absorbed by the body depends on its solubility in water [4]. The second drug used in this research is lamotrigine (LTG). The LTG, 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, is an antiepileptic agent for monotherapy and as an adjunct in treatment with other antiepileptic agents for partial seizures [5]. To enhance the usage of these compounds, it is necessary to examine the procedure for increasing the aqueous solubility of the mentioned drugs. The co-solvency method, addition of surface-active agents, salt formation, complexation, hydrotropism, crystal engineering, preparation of soluble pro-drug, and more recently, the addition of ionic liquids (ILs) are the methods that can increase the solubility of drugs in water, consequently the usage of them [6,7]. Paul Walden performed the first IL study in 1914 on the physical properties of ethyl ammonium nitrate [$EtNH_3^+$] [NO_3^-]. In recent years, ILs have been emerged as novel solvents in a wide range of areas due to their specific properties. In other words, ILs are organic salts and can be

categorized in green solvents because they are near non-volatile. They also have a low melting point and dissolve a wide range of components [8]. These novel and green solvents are also named designer solvents. Their physicochemical properties which can be changed by choosing suitable cation and anion. The choline 2-hydroxy-N, N, N-trimethylethanaminium (or 2-hydroxyethyl-trimethyl-ammonium) quaternary ammonium cations that couple with lots of onions like chloride, iodide, acetate, hydroxide, tartrate, etc. [9]. The ILs that contain choline are considered choline-based ILs. These classes of ILs are non-toxic, environmental, low-cost, and water-soluble, so they are famous among the various kinds of ILs [10]. The ILs can be used as solubility enhancers, permeability enhancers, drug-ILs, protein stabilizers, etc. [11].

In this work, we measured the solubility of LTG and PXM in choline-based ILs at different weight fractions at temperatures T = (298.15 to 313.15) K. For correlation between LTG and PXM experimental data in the dilute region of the ILs mass fraction from the semi-experimental models of Apelblat and λh and in the concentrated area of the co-solvent, the local composition models Wilson and e- NRTL were used. Finally, to minimize the cost of the measurement process, the used ILs were recovered.

2. Experimental

2. 1. Chemicals

Lamotrigine and piroxicam were employed by the Zahravi pharmaceutical company (Tabriz, Iran). The detailed information about all materials is listed in Table 1.

2. 2. Synthesis of ILs

The ILs were prepared as follows: the reaction was conducted by slow addition of an aqueous solution of choline hydroxide to aqueous lactic acid or propionic acid solutions with

stirring. From ChLa and ChPro, water was removed using a rotational evaporator (Heidolph Labrorota 4003 control, Germany) under the temperature of 343.15 K to minimize moisture [12]. Fig. 1 shows the steps for the synthesis of the IL ChLa.

2. 3. ILs recovery method

Due to the high cost of the ILs and the need to spend a lot of money to provide them, the process of purification and recovery of the ILs and their reuse in later processes were used without losing their original quality. For this purpose, because drugs have very low solubility in water, the solution containing IL + drug is diluted with water to separate and dissolve the drug dissolved in ILs from the mixtures. The residue is removed with a filter paper, and the solution containing IL + water is placed by rotary (Heidolph Labrorota 4003 control, Germany) at 70 ° C to evaporate the excess water; the remaining IL is washed with solvents such as ethyl acetate or acetonitrile to purify. The drug separated by the filter paper is rinsed with water. Then the precipitated drug is separated again by the filter paper and dried at room temperature.

3. Solubility measurement

Solubility is an important topic that has been the subject of much research for several years [13,14]. In this research work, the saturation shake-flask method [15] has been used to measure the solubility of drugs in the solvent mixtures. For this purpose, solutions with a known weight fraction of 0.00 to 0.15 ILs were prepared. The mixtures with specific amounts of pure solvents (water, IL) were made. Then, a large amount of drug was added to the solvents in glass vials under permanent stirring in a system with a thermostat (ED, Julabo Co., Germany T = ±0.1 K). Preliminary tests show that to measure the solubility of the drug, the time required to balance in the system is 72h. Then the supernatant solutions were filtered through a 0.45 μm membrane

(Durapore® membrane filters, type HV, 0.45 μm, Millipore, MA). Drug uptake in diluted samples (using water/ethanol solutions with 20/80 volume fraction) was measured by UV–Vis spectrophotometer (BiotechUltraspec 2000, England) for LTG at 309 nm and PXM at 251 nm. As shown in Fig. 3, the drugs studied (LTG and PXM) in the presence of choline lactate and choline propionate did not change much in their λ_{Max}.

3. Thermodynamic modeling

Recently, models for the solubility of drugs in water + co-solvent mixtures have been proposed to correlate or predict experimental studies. This research aims to increase the solubility of LTG and PXM in pharmaceutical and industrial studies. The co-solvency models include three types of models, theoretical [16], semi-empirical [17], and empirical [18]. A series of the proper models for the correlation of experimental solubility in solvent mixtures at different temperatures are presented: Apelblat [19], λh [20], Wilson [21], and e-NRTL [22] models, which provide excellent and suitable correlations for LTG and PXM in aqueous ILs solutions. The general characteristics of the applied models are described as follows:

3.1. Modified Apelblat equation

The modified Apelblat equation is, known as a semi-empirical model, has three parameters. This study used this model to fit the experimental solubility data [29]. According to this model, the solubility of the drug can potentially change by variations in temperature, and Eq. (1) shows this [27]:

$$\ln x_1 = A + \frac{B}{T} + C \ln T \quad (1)$$

where *A*, *B*, and *C* are empirical constants. The values of *A* and *B* represent the variation of the activity coefficient of the solution components, and the *C* value reveals the temperature impact on fusion enthalpy.

3.2. λh (Buchowski) equation

Buchowski *et al.* [28] expressed the solubility behavior of a solid components in liquid solvents as the Buchowski equation. This equation provided a reasonable explanation for many solid–liquid systems using two adjustable parameters, λ, and h, as reported in previous studies [30, 31]. This equation can be written as:

$$\ln(1+\lambda\frac{1-x_1}{x_1}) = \lambda h(\frac{1}{T}-\frac{1}{T_{m1}}) \quad (2)$$

where λ and h are two parameters and T_{m1} is the melting temperature of drugs. The value of λ is recognized as the approximate mean association number of solute molecules, which shows the non-ideality of the solution system, and h estimates the excess mixing enthalpy of solution [28].

3. 3. Local composition models

The following equation is used to express a solid-liquid equilibrium (SLE) framework [23]:

$$-\ln x_1 = \frac{\Delta_{fus}H}{R}(\frac{1}{T}-\frac{1}{T_{fus}}) + \ln\gamma_1 \quad (4)$$

where T_{fus}, $\Delta_{fus}H$, T, x_1 and γ_1 are: fusion temperature and enthalpy for the pure drug, the experimental temperature, equilibrium mole fraction, and the activity coefficient of the drug in the saturated solutions, respectively. Moreover, the fusion enthalpy appears to be temperature independent. To correlate the solubility data of the present drug, the molar excess Gibbs energy, G^{ex}, is identified as the sum of two contributions to generalize the e-NRTL and Wilson for a multi-component aqueous solution containing electrolytes,

$$\frac{G^{ex*}}{RT} = \frac{G^{ex*,LR}}{RT} + \frac{G^{ex*,SR}}{RT} \quad (5)$$

where superscript *, *LR*, and *SR*, represent the asymmetric convention, long-range and short-range interactions, respectively. The extended version of the Pitzer–Debye–Hückel model, $G^{ex*,\,PDH}$, proposed by Pitzer [24] can be used for the long-range contribution term. Also, in this study, the activity coefficient models e-NRTL [25] and Wilson [21] were applied for representing short-range interactions, G^{ex*SR}.

3. 3. 1. The Pitzer–Debye–Hückel (PDH) equation

The PDH equation for excess Gibbs energy, G^{ex*LR}, can be written as [24]:

$$\frac{G^{ex*,PDH}}{RT} = -\sum_j x_j \left(\frac{1000}{M_s}\right)^{1/2} \frac{4A_\varphi I_x}{\rho} \ln(1+\rho I_x^{0.5}) \quad (6)$$

where M_S is the molar mass of the solvent. The parameter ρ in Eq. (6) is related to the closest approach parameter of ions in solution. The value of ρ = 14.9 has been commonly applied for aqueous electrolyte solutions [26]. I_x is the ionic strength on a mole fraction basis ($I_x = \frac{1}{2}\sum x_i Z_i^2$), Z is the charge number of ions in the solution, x is the mole fraction of ions, and A_φ signifies the usual Debye-Huckel parameter for the osmotic coefficient, which is stated by:

$$A_\varphi = \frac{1}{3}\left(\frac{2\pi N_A}{V_S}\right)^{1/2}\left(\frac{e^2}{4\pi\varepsilon D_S kT}\right)^{3/2} \quad (7)$$

V_S is the molar volume, N_A is Avogadro's number, e is the charge of an electron, ε is the average dielectric constant of the solvent, k is the Boltzmann constant, and T is the temperature in Kelvin.

3. 3. 2. Electrolyte-NRTL model

In thermodynamics, commonly considered models are based on activity coefficient for industrial systems such as the electrolyte-NRTL model (e-NRTL) introduced by Chen (1982) [25]

and Chen and Evans (1986) [27]. For each component, the activity coefficient is defined as the sum of the NRTL and the PDH contributions [25].

$$\ln(\gamma_i^*) = \ln(\gamma_i^{*PDH}) + \ln(\gamma_i^{*NRTL}) \quad (8)$$

3. 3. 3. Wilson model

A non-linear model, known as the Wilson model, represents the solubility values of drugs in the binary solvents at experimental temperatures. The equation for this model in a solution with *n*-component was shown in terms of the activity coefficient as [21]:

$$\ln\gamma_i = 1 - \ln\left[\sum_{j=1}^{n} x_j \Lambda_{ij}\right] - \sum_{k=1}^{n}\left[\frac{x_k \Lambda_{ki}}{\sum_{j=1}^{n} x_j \Lambda_{kj}}\right] \quad (9)$$

where Λ_{ij} is the interaction parameters between two components, which is related to the molar volumes of the pure components, υ and characteristic energy, λ differences by:

$$\Lambda_{ij} = \frac{\upsilon_j}{\upsilon_i} \exp\left(-\frac{\lambda_{ij} - \lambda_{ii}}{RT}\right) \quad (10)$$

Interaction parameters were determined by minimizing the value of the objective function as:

$$OF = \sum_{i=1}^{n} (\ln \gamma_i^{\exp} - \ln \gamma_i^{cal})^2 \quad (11)$$

where n is the experimental points and expresses the experimental and calculated activity coefficients.

To evaluate the goodness of fit between the experimental and correlated solubility data, the average relative deviation percent (*ARD%*) is used. This parameter for comparison of the models can be calculated using the following equation:

$$\%ARD = 100\left(\frac{\sum_{i=1}^{N}\frac{\left|x_i^{\exp} - x_i^{cal}\right|}{\left|x_i^{\exp}\right|}}{N}\right) \quad (12)$$

where $x_i^{\exp}$, x_i^{cal} and N are experimental and calculated solubility mole fraction and the total number of experimental measurements, respectively.

4. Results and discussion

4.1. Results obtained from solubility

The mole fraction solubility of LTG or PXM (x_1) in the two solvent mixtures (IL (2) + water (3)) are obtained with Eq. (13):

$$x_1 = \frac{\frac{w_1}{M_1}}{\frac{w_1}{M_1} + \frac{w_2}{M_2} + \frac{w_3}{M_3}} \quad (13)$$

where M_i and w_i are the molar mass and weight fractions of i component in the saturated solution, respectively [28]. Tables 2 and 3 show the experimental data obtained from the LTG and PXM solubility in the (water + ILs) mixtures with different concentrations of ILs at various temperatures (T=298.15 to 313.15) K. According to the results, it was found that with increasing ILs concentration and with increasing temperature, the solubility of both drugs increases. The results showed that because the heat dissolution process according to the principle of Le Chatelier's equilibrium proceeds towards dissolution and with increasing temperature the dissolution rate increases and because there are strong interactions between the drug and co-solvent help with increasing IL concentration the solubility of drugs increases significantly.

The solubility of LTG and PXM in the aqueous solutions of ILs at different temperatures is given in Figs. 2 and 3. The solubility of LTG and PXM in the presence of ChPro increased

more than in ChLa because it was observed that with an increased molecular mass of anion, the solubility in that IL decreased. The molar mass of ChLa is larger than the molar mass of ChPr,o and ChLa has a lower pH than ChPro, i.e. it is more acidic. As a result, ChLa exhibits fewer tendencies than ChPro to take LTG and PXM. Therefore, the solubility of LTG and PXM in ChPro increased more than ChLa, [ChLa] < [ChPrO]. On the other hand, due to the acidic nature of these ILs, certain interactions that could be van der Waal's type or hydrogen bonding can appear. It also appears that such interactions increase as concentrations of ILs in solution increase, which is evident from the greater solubilization of the drugs [29]. The solubility improvement in the presence of applied ILs could be due to solute−solvent interactions. The interactions can be divided into H-bonds, van der Waals forces, ion-dipole and dipole-dipole between solute−solvent. They can cause the solubilization of hydrophobic drugs in a solvent [30,31]. At the atomic scale, drugs (LTG and PXM) molecules and ILs can interact with each other generally through H-bonds and strong ion-dipole interactions. In addition, the more benzene rings in the drugs cause polarity to decrease as a result the higher the solubility, and these results are well consistent with the experimental results. The LTG has less benzene ring rather than PXM; this is why LTG is more soluble in water than PXM. The solvating power of ILs is much higher than that of pure water, because, there are H-bonds and dipole-dipole interactions in the water + drug system. Finally, to demonstrate the high accuracy of the LTG and PXM experimental data which have been measured in this study, the LTG mole fraction solubility in neat water (Tables 2 and 3) was compared with data of literature which is 1.30×10^{-5} and 7.26×10^{-5} at 298.15 K and 313.15 K, respectively. Also, the experimental data were reported in Table 2, which is 1.315×10^{-5} and 7.340×10^{-5} at 298.15 K and 313.15 K, respectively [32]. In addition, for PXM solubility in water, the obtained value was 4.499×10^{-7} and 4.1×10^{-7} at

298.15 K in our study and the literature, respectively [33]. The obtained experimental data and the literature values compression demonstrate that the achieved data has a good agreement with some previously reported values (Table 4). On the other hand, there are some reports on the solubility of LTG in systems containing ILs and deep eutectic solvents. In ILs (choline alaninate, choline bitartrate and choline glycinate) + water co-solvent with a weight fraction of 0.15 for ILs at 298.15 K, the values of 2.987×10^{-5}, 2.629×10^{-5} and 4.750×10^{-5} (mole fraction) has been reported by Shekaari et al. [34]. The value of 3.29×10^{-5} and 4.65×10^{-5}wase achieved at the same temperature and weight fraction for LTG solubility in ChLA and ChPro, respectively. These outcomes show an enhancement in the solubility of this drug using these ILs. According to Barzegar-Jalali et al. [6],the solubility of LTG in (1-hexyl-3-methylimidazolium bromide + water) mixtures at 298.15 K and weight fraction of 0.1 for the IL is 4.4×10^{-5}; this value is higher than the solubility we measured in the systems containing the investigated ILs.

4. 2. Data modeling

Tables 2-6 show the fitting results of four models for the solubility of the investigated drugs in neat and binary water + ILs solvent systems. In many studies on the solubility of drugs in different solvents, quasi-experimental models have been used to fit the experimental rsolubility results. The most important of these models, as mentioned earlier, are the Apelblat, Yalkowsky, and λh equations. In this study, Apelblat and λh models were used to model the solubility of the drugs in aqueous IL solutions and the dilute region. According to the results, it is observed that the efficiency of the Apelblat (R^2=0.998) model is better in systems containing LTG and PXM. It can be seen from Tables 5, 6, and Fig. 4 that the Wilson and e-NRTL models correlate the solubility of the drug in a solvent mixture (water + IL) with an acceptable deviation. The experimental data are almost consistent with the computational data.

From Tables 7 and 8, according to the results of modeling in the dilute and concentrated regions of ILs mass fraction, it is clear that Apelblat, λh, Wilson and e- NRTL models for LTG and PXM in the presence of two ILs, ChLa and ChPro, are in good agreement with the experimental results.

The results show that the %*ARD* values of the modified Apelblat and e-NRTL models are relatively low, which indicates that they can be used to correlate the solubility data drugs in solvent mixtures. For the solubility data in binary solvent system in full range concentration of the co-solvent, the e-NRTL model is more suitable for data fitting. It can be seen from Figs. 3 and 4 that the solubility of LTG and PXM in the binary solvent system increases.

5. Conclusions

The chief idea in this research was the aqueous lamotrigine, and piroxicam solubility determination in the presence of two choline-based ionic liquids (ChPro and ChLa) in water under ambient pressure and at temperatures 298.15 K to 313.15 K. The obtained results demonstrated that by increasing the co-solvent mass fractions and temperatures, the higher solubility of the LTG and PXM is reached. In addition, some activity coefficient and semi-empirical models were used to fit the experimental solubility data. Their performance was classified as e-NRTL (3.09%) < Wilson (3.92%) (for full range concentration of co-solvent) and Apelblat (3.52%) < λh (Buchowski) (5.11%) (for the dilute concentration of co-solvent).

The analyses showed that ChPro is an efficient co-solvent to enhance the solubility of these two poorly water-soluble drugs. These procedure collections can be used efficiently for the separation and crystallization of drugs in various fields of pharmaceutical sciences.

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Contributions

Negar Basteholia, Masumeh Mokhtarpour; investigation, Hemayat Shekaari, Mohammed Taghi Zafarani-Moattar; project administration, Negar Basteholia, Masumeh Mokhtarpour; data curation, Negar Basteholia, Masumeh Mokhtarpour; analysis, Hemayat Shekaari, Mohammed Taghi Zafarani-Moattar; writing—original draft, Negar Basteholia, Masumeh Mokhtarpour; investigation, Hemayat Shekaari, Mohammed Taghi Zafarani-Moattar; writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no competing interests.

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Table 1

Explanation of the materials used in this research work.

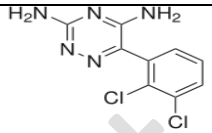
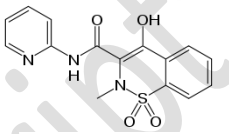
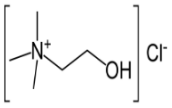
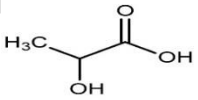
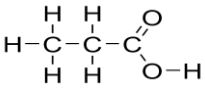
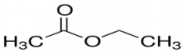
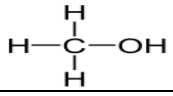
Chemical name	Source	Mass fraction (purity)	chemical formula	Structure
Lamotrigine	Zahravi	>0.98	$C_9H_7Cl_2N_5$	
Piroxicam	Zahravi	>0.98	$C_{15}H_{13}N_3O_4S_1$	
Choline Chloride	Dae Jung	>0.98	$C_5H_{14}ClNO$	
Lactic acid	Merck	>0.99	$C_3H_6O_3$	
Propionic acid	Merck	>0.99	$CH_3CH_2CO_2H$	
Potassium hydroxide	Merck	>0.98	KOH	K^+OH^-
Ethyl acetate	Merck	>0.995	$C_4H_8O_2$	
Methanol	Merck	≥0.98	CH_4O	

Table 2

Experimental (x_1 ^{exp})[a] and calculated (x_1 ^{cal}) solubility of LTG in the aqueous IL solutions at different temperatures (T)[b] and weight fractions of IL (w_3)[c] from Apelblat and λh models.

T / K	$10^5\ x_1^{exp}$	Apelblat equation		λh equation	
		$10^5\ x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$	$10^5\ x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$
		LTG (1) + ChLa (2) + water (3)			
w_2=0.000					
298.15	1.06	1.07	-1.28	1.03	2.71
303.15	1.47	1.41	3.83	1.33	9.62
308.15	1.67	1.74	-4.08	1.70	-1.61
313.15	2.04	2.01	1.35	2.15	-5.61
w_2=0.020					
298.15	1.38	1.39	-0.28	1.12	18.86
303.15	1.75	1.74	0.85	1.60	8.85
308.15	2.15	2.17	-0.88	2.25	-4.57
313.15	2.70	2.70	0.29	3.13	-15.77
w_2=0.050					
298.15	1.54	1.59	-3.38	1.80	-16.91
303.15	2.63	2.38	9.70	2.34	10.95
308.15	3.04	3.38	-10.99	3.03	0.33
313.15	4.72	4.56	3.49	3.89	17.57
w_2=0.070					
298.15	1.85	1.91	-2.86	2.07	-11.61
303.15	2.90	2.66	8.29	2.68	7.26
308.15	3.40	3.72	-9.25	3.45	-1.48
313.15	5.40	5.24	2.96	4.41	18.43
w_2=0.100					
298.15	2.08	2.09	-0.16	2.80	-34.71
303.15	3.56	3.54	0.49	3.58	-0.70
308.15	5.04	5.06	-0.50	4.54	9.86
313.15	6.18	6.17	0.17	5.71	7.67
w_2=0.150					
298.15	3.29	3.24	1.75	3.30	-0.08
303.15	4.04	4.26	-5.59	4.18	-3.34
308.15	6.03	5.70	5.41	5.25	12.97
313.15	7.59	7.74	-1.91	6.55	13.73
		LTG (1) + ChPro(2) + water (3)			
w_2=0.000					
298.15	1.06	1.07	-1.28	1.03	2.71
303.15	1.48	1.41	3.83	1.33	9.62
308.15	1.67	1.74	-4.08	1.70	-1.61
313.15	2.04	2.01	1.35	2.15	-5.61
w_2=0.020					
298.15	1.61	1.61	-0.24	1.49	7.43
303.15	2.00	1.99	0.75	1.92	4.18
308.15	2.43	2.45	-0.77	2.46	-1.13
313.15	3.03	3.02	0.26	3.13	-3.32
w_2=0.050					
298.15	1.71	1.77	-3.32	2.29	-33.77
303.15	3.03	2.74	9.54	2.89	4.55
308.15	3.49	3.87	-10.79	3.63	-3.86
313.15	5.18	5.00	3.43	4.52	12.81
w_2=0.070					
298.15	2.20	2.26	-2.92	2.42	-10.14

303.15	3.39	3.11	8.47	3.12	8.14
308.15	3.88	4.24	-9.47	3.98	-2.64
313.15	5.95	5.77	3.03	5.04	15.31
w_2=0.100					
298.15	2.96	2.22	-0.79	3.26	-10.14
303.15	4.08	3.98	2.39	4.13	-1.27
308.15	5.61	5.75	-2.50	5.20	7.32
313.15	6.83	6.78	0.84	6.49	5.01
w_2=0.150					
298.15	4.65	4.73	-1.80	5.18	-11.45
303.15	6.36	6.02	5.35	6.41	-0.81
308.15	8.14	8.60	-5.78	7.88	3.18
313.15	13.99	13.72	1.89	16.15	-15.44

Table 3

Experimental (x_1 ^{exp}) [a] and calculated (x_1 ^{cal}) solubility of PXM in the aqueous IL solutions at different temperatures (T) [b] and weight fractions of IL (w_2) [c] from Apelblat and λh models.

T / K	$10^7\ x_1^{exp}$	Apelblat equation		λh equation	
		$10^7\ x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$	$10^7\ x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$
		PXM (1) + ChLa (2) + water (3)			
w_2=0.000					
298.15	4.50	4.29	4.76	4.53	-0.65
303.15	7.15	8.30	-16.15	7.10	0.66
308.15	17.73	15.21	14.19	10.98	38.05
313.15	25.80	26.42	-5.35	16.75	33.23
w_2=0.020					
298.15	31.25	31.76	-1.62	42.87	-37.18
303.15	53.99	51.40	4.82	53.78	0.38
308.15	67.71	71.21	-5.18	66.93	1.16
313.15	86.75	85.28	1.71	82.64	4.74
w_2=0.050					
298.15	43.22	43.74	-1.23	49.57	-14.68
303.15	66.40	63.99	3.67	61.99	6.64
308.15	80.63	83.79	-3.90	76.97	4.54
313.15	100.23	98.90	1.29	94.92	5.30
w_2=0.070					
298.15	64.52	64.05	0.74	62.51	3.12
303.15	75.23	76.93	-2.31	77.37	-2.85
308.15	97.53	95.27	2.31	95.11	2.48
313.15	120.39	121.39	-0.80	116.15	3.52
w_2=0.100					
298.15	71.37	71.49	-0.15	75.25	-5.44
303.15	96.07	95.64	0.45	92.38	3.84
308.15	118.08	118.59	-0.46	112.66	4.59
313.15	137.13	136.94	0.16	136.52	0.45
w_2=0.150					
298.15	98.11	98.78	-0.68	105.09	-7.12
303.15	124.82	122.25	2.08	127.10	-1.83
308.15	148.90	152.10	-2.17	152.79	-2.60
313.15	191.63	190.15	0.73	182.58	4.72
		PXM (1) + ChPro(2) + water (3)			
w_2=0.000					
298.15	4.50	4.29	4.76	4.53	-0.65
303.15	7.15	8.30	-16.15	7.10	0.66
308.15	17.73	15.21	14.19	10.98	38.05
313.15	25.08	26.42	-5.35	16.75	33.23
w_2=0.020					
298.15	50.86	51.47	-1.19	58.73	-15.47
303.15	75.85	73.17	3.57	72.58	4.3
308.15	89.39	92.78	-3.78	89.00	0.43
313.15	106.98	105.68	1.26	108.32	-1.26
w_2=0.050					
298.15	82.58	84.07	-1.77	104.12	-26.09
303.15	131.07	124.24	5.25	125.98	3.88
308.15	148.90	157.30	-5.66	151.50	-1.74
313.15	175.56	172.32	1.86	181.11	-3.16
w_2=0.070					
298.15	118.50	120.73	-1.86	117.47	0.87
303.15	147.83	139.71	5.50	141.37	4.37
308.15	155.16	164.33	-5.95	169.12	-8.99

313.15	200.25	196.25	1.95	201.16	-0.45
w_2=0.100					
298.15	135.85	136.64	-0.63	141.42	-4.10
303.15	163.83	160.76	1.90	168.79	-3.03
308.15	192.05	195.92	-1.98	200.31	-4.30
313.15	248.50	246.76	0.67	236.42	4.86
w_2=0.150					
298.15	175.60	176.36	-0.46	186.80	-6.38
303.15	212.49	209.54	1.41	220.21	-3.63
308.15	247.71	251.29	-1.46	258.22	-4.24
313.15	305.56	304.04	0.49	301.24	1.41

Table 4

Comparison between experimental and literature solubility data of the drugs in water

LTG solubility in water	*T*=298.15 K	*T*=303.15 K	*T*=308.15 K	*T*=313.15 K
This work	1.315×10^{-5}	3.133×10^{-5}	4.153×10^{-5}	7.340×10^{-5}
Rezaei, H.; Jouyban, A [32]	$1.38 (\pm 0.05) \times 10^{-5}$	$2.52 (\pm 0.06) \times 10^{-5}$	$4.40 (\pm 0.37) \times 10^{-5}$	$8.16 (\pm 0.49) \times 10^{-5}$
Shekaari, H.; Zafarani-Moattar, M. T [35]	1.33×10^{-5}	3.14×10^{-5}	4.16×10^{-5}	7.31×10^{-5}
PXM solubility in water	*T*=298.15 K	*T*=303.15 K	*T*=308.15 K	*T*=313.15 K
This work	4.499×10^{-7}	7.151×10^{-7}	17.730×10^{-7}	25.799×10^{-7}
Sotomayor et al. [36]	4.1×10^{-7}	-	-	-

Table 5

Experimental (x_1 ^{exp})[a] and calculated (x_1 ^{cal}) solubility of LTG in the aqueous ChLa and ChPro solutions at different temperatures (T)[b] and weight fractions of IL (w_2)[c] from e-NRTL and Wilson models.

T / K	$10^5 x_1^{exp}$	e-NRTL model		Wilson model	
		$10^5 x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$	$10^5 x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$
		LTG (1) + ChLa (2) + water (3)			
w_2=0.000					
298.15	1.06	1.05	0.31	1.06	1.44
303.15	1.47	1.46	0.48	1.47	0.14
308.15	1.67	1.67	-0.10	1.67	0.05
313.15	2.04	2.05	-0.55	2.04	-0.34
w_2=0.200					
298.15	4.36	4.25	2.47	4.15	4.78
303.15	6.66	6.46	2.94	6.40	3.83
308.15	8.60	8.79	-2.16	8.40	2.34
313.15	10.98	10.28	6.33	10.52	4.17
w_2=0.400					
298.15	7.71	7.84	-1.65	7.28	5.65
303.15	10.59	10.90	-2.89	10.32	2.60
308.15	13.20	12.77	3.29	12.92	2.12
313.15	18.92	20.33	-7.44	18.25	3.55
w_2=0.600					
298.15	11.94	12.10	-1.33	11.22	5.98
303.15	18.89	19.14	-1.34	18.62	1.40
308.15	23.82	24.03	-0.86	23.44	1.58
313.15	27.34	26.73	2.24	26.95	1.44
w_2=0.800					
298.15	70.03	70.23	-0.27	65.07	7.08
303.15	95.08	95.99	-0.95	92.80	2.40
308.15	113.07	112.15	0.81	112.19	0.78
313.15	160.28	160.05	0.14	157.96	1.44
w_2=0.900					
298.15	471.00	466.06	1.04	448.48	4.78
303.15	636.43	626.55	1.55	612.67	0.31
308.15	907.52	887.83	2.16	864.17	4.77
313.15	1420.00	1403.00	1.22	1344.70	5.30
w_2=1.000					
298.15	2110.01	2114.71	-0.22	2503.80	-18.66
303.15	2780.02	2790.30	-0.37	2675.51	-0.27
308.15	3650.04	3651.50	-0.04	3443.11	5.66
313.15	4730.02	4739.00	-0.18	4774.00	-0.93
		LTG (1) + ChPro (2) + water (3)			
w_2=0.000					
298.15	1.057	1.06	-0.08	1.05	0.18
303.15	1.47	1.46	0.31	1.46	0.33
308.15	1.67	1.67	0.14	1.66	0.57
313.15	2.04	2.02	0.93	2.04	0.03
w_2=0.200					
298.15	6.05	5.76	4.92	5.80	4.16
303.15	9.63	9.07	5.84	9.18	4.72
308.15	13.88	13.83	0.32	12.91	6.96
313.15	16.86	17.00	-0.84	16.27	3.48
w_2=0.400					
298.15	9.97	10.47	-4.96	9.61	3.58

303.15	13.44	14.18	-5.51	13.04	2.98
308.15	16.27	16.30	-0.20	16.05	1.31
313.15	23.06	22.90	0.69	22.49	2.44
w_2=0.600					
298.15	16.45	17.13	-4.14	16.11	2.02
303.15	22.44	22.92	-2.10	22.36	0.39
308.15	36.51	37.24	-2.01	36.75	-0.64
313.15	46.23	46.58	-0.75	45.70	1.14
w_2=0.800					
298.15	155.22	142.20	8.39	156.03	-0.52
303.15	220.85	213.95	3.12	220.87	-0.01
308.15	242.87	233.61	3.81	246.66	-1.56
313.15	262.77	263.86	-0.41	267.22	-1.69
w_2=0.900					
298.15	817.80	904.16	-10.55	838.23	-2.49
303.15	1050.01	1099.30	-4.69	1076.10	-2.48
308.15	1430.05	1461.90	-2.23	1475.02	-3.14
313.15	1970.00	1993.01	-1.16	1935.10	1.77
w_2=1.000					
298.15	5420.00	5442.50	-0.24	4671.20	13.96
303.15	6100.01	6101.70	-0.02	5651.40	7.35
308.15	7310.01	7290.10	0.27	6777.01	7.29
313.15	8230.01	8226.12	0.04	7589.10	7.78

Table 6

Experimental (x_1 ^{exp})[a] and calculated (x_1 ^{cal}) solubility of PXM in the aqueous ChLa and ChPro solutions at different temperatures (T)[b] and weight fractions of IL (w_2)[c] from e-NRTL and Wilson models.

T / K	$10^7 x_1^{Exp}$	e-NRTL model		Wilson model	
		$10^7 x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$	$10^7 x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$
		PXM (1)+ ChLa(2) + water (3)			
w_2=0.000					
298.15	4.45	4.55	-1.15	4.51	-0.14
303.15	7.15	7.27	-1.63	7.15	-0.05
308.15	17.73	17.69	0.20	17.82	-0.48
313.15	25.08	25.05	0.11	25.12	-0.14
w_2=0.200					
298.15	147.12	149.22	-1.42	137.19	6.74
303.15	174.40	182.46	-4.62	168.42	3.43
308.15	195.84	191.40	2.26	182.45	6.83
313.15	234.32	224.85	4.04	224.29	4.28
w_2=0.400					
298.15	267.67	271.72	-1.51	270.32	-0.98
303.15	302.77	305.84	-1.01	290.11	4.18
308.15	351.72	351.72	-5.44	376.41	-7.01
313.15	428.77	456.21	-6.40	409.82	4.42
w_2=0.600					
298.15	412.45	431.61	-4.64	395.04	4.22
303.15	675.65	599.59	11.25	641.71	5.02
308.15	854.76	815.37	4.60	841.53	1.54
313.15	980.77	950.60	3.07	937.57	4.40
w_2=0.800					
298.15	2515.20	2123.80	15.56	2544.90	-1.18
303.15	3423.90	3623.01	-5.80	3274.01	4.37
308.15	4117.70	4180.10	-1.51	4587.50	-11.41
313.15	5450.30	5469.20	-0.34	5366.02	1.54
w_2=0.900					
298.15	9239.40	10330.01	-11.80	9193.90	0.49
303.15	32445.01	32530.02	-0.27	29662.01	8.57
308.15	49514.00	49304.01	0.42	41770.12	15.64
313.15	63935.00	63317.90	0.96	56524.06	11.59
w_2=1.000					
298.15	92005.01	91127.01	0.95	70348.01	23.53
303.15	10999.90	11087.00	0.11	102140.25	7.98
308.15	137001.01	136819.99	0.13	108740.03	20.62
313.15	154000.02	153740.02	0.17	142579.99	7.41
		PXM (1) + ChPro (2) + water (3)			
w_2=0.000					
298.15	4.50	4.53	-0.71	4.56	-1.30
303.15	7.15	7.16	-0.13	7.15	0.03
308.15	17.73	17.72	0.05	17.56	0.97
313.15	25.08	25.05	0.13	25.26	-0.71
w_2=0.200					
298.15	375.85	392.08	-4.31	374.76	0.28
303.15	491.91	490.49	0.28	480.59	2.30
308.15	541.74	535.89	1.07	522.07	3.63
313.15	749.64	743.51	0.18	730.81	2.51
w_2=0.400					
298.15	932.70	864.63	7.29	844.14	9.49

303.15	1470.00	1489.90	-1.37	1395.60	5.04
308.15	1583.00	1599.40	-0.47	1513.90	4.25
313.15	1803.01	1836.01	-1.81	17220.21	4.60
w_2=0.600					
298.15	3141.62	3048.20	2.97	3243.60	-3.24
303.15	3932.00	3833.09	2.51	3722.10	5.33
308.15	4500.06	4463.81	0.80	4294.00	4.55
313.15	5663.00	5757.00	-1.66	53404.01	5.69
w_2=0.800					
298.15	27196.99	31291.00	-15.05	25622.02	5.78
303.15	37740.01	39201.10	-3.85	34550.99	8.46
308.15	46661.02	46377.03	0.59	43357.01	7.07
313.15	67749.99	64282.11	5.11	60449.10	10.77
w_2=0.900					
298.15	121501.02	111009.99	9.00	110089.66	9.76
303.15	128098.30	125009.94	2.34	121571.01	5.02
308.15	137301.07	137410.01	-0.29	128478.96	6.21
313.15	148399.99	153529.89	-3.73	144661.01	2.25
w_2=1.000					
298.15	514501.03	521421.01	-1.24	484251.12	5.97
303.15	576598.99	578439.86	-0.25	526469.98	8.75
308.15	607701.01	607209.12	0.12	566609.10	6.80
313.15	645989.99	644120.32	0.29	585201.35	9.41

Table 7

The calculated average relative deviation percent (*ARD*%) for the solubility of the LTG and PXM in the aqueous IL solutions at several temperatures from Apelblat and λh models.

w_2	ChLa	ChPro	ChLa	ChPro
	Apelblat *ARD%*		*λh ARD%*	
LTG (1) + IL (2)+ water (3)				
0.0200	0.57	0.51	9.60	3.20
0.0500	6.90	6.80	9.20	11.00
0.0700	5.80	6.00	7.80	7.20
0.1000	0.33	1.60	10.60	4.80
0.1500	3.70	3.70	6.00	9.30
Average	3.46	3.72	8.64	7.10
PXM (1) + IL (2)+ water (3)				
0.0200	8.70	2.40	8.70	4.30
0.0500	6.20	3.60	6.20	7.00
0.0700	2.40	3.80	2.40	2.90
0.1000	2.90	1.30	2.90	3.30
0.1500	3.30	0.95	3.30	3.10
Average	4.47	2.41	4.70	4.12

Table 8

The calculated average relative deviation percent (*ARD*%) for the solubility of the LTG and PXM in the aqueous IL solutions at several temperatures from e-NRTL and Wilson models.

T / K	ChLa	ChPro	ChLa	ChPro
	e-NRTL *ARD%*		Wilson *ARD%*	
LTG (1) + IL (2)+ water (3)				
298.15	1.00	4.80	2.80	3.80
303.15	1.50	3.10	0.78	2.61
308.15	1.40	1.30	1.06	3.07
313.15	2.60	0.69	1.90	2.62
Average	1.62	2.47	1.63	3.02
PXM (1) + IL (2)+ water (3)				
298.15	5.30	8.10	5.30	5.10
303.15	3.50	9.50	4.80	4.99
308.15	2.10	0.57	9.08	4.80
313.15	2.20	1.90	4.83	5.14
Average	3.27	5.01	6.00	5.01

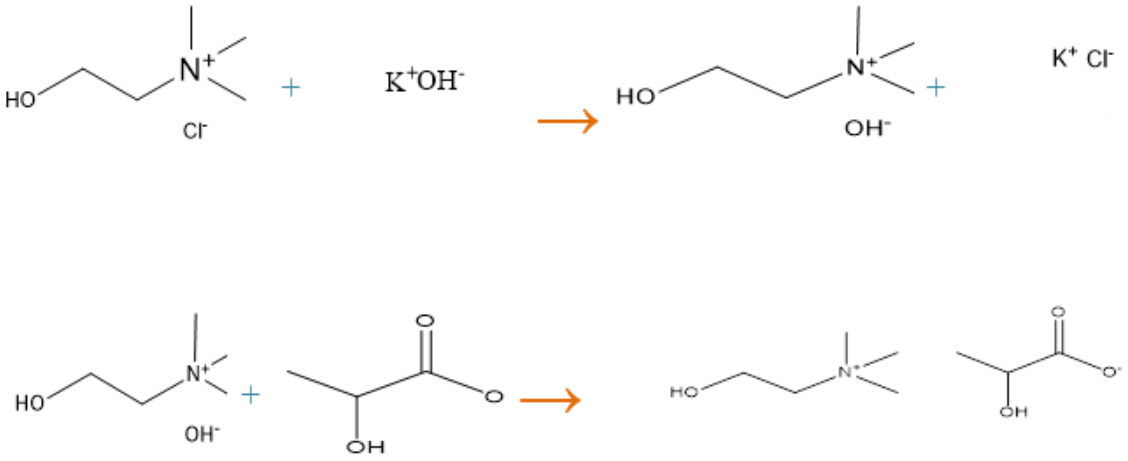


Fig. 1. Stages of ChLa synthesis.

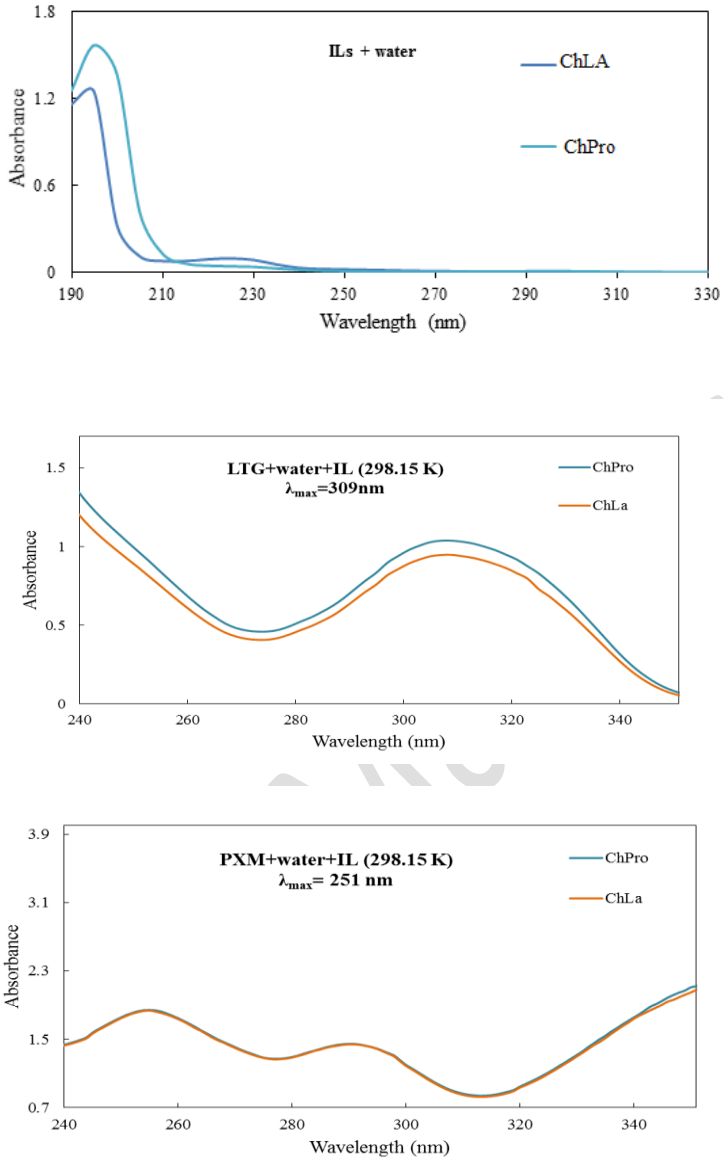


Fig. 2. UV-Vis spectra of (ILs + water) and samples (PXM and LTG + water + ILs).

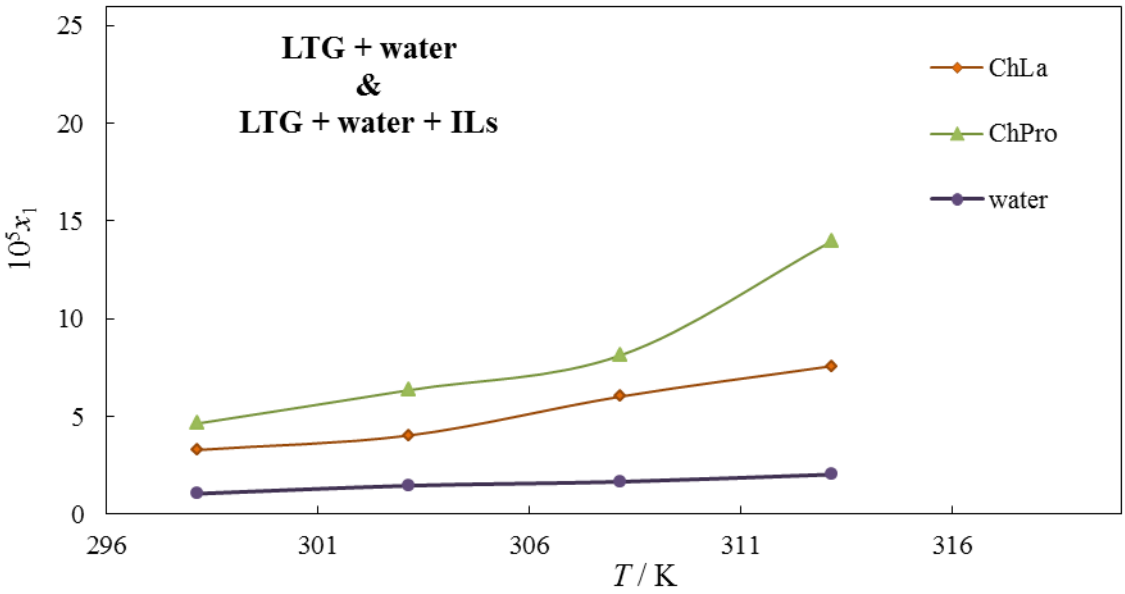


Fig. 3. Solubility of LTG, x_1, at a mass fraction of 0.15 of IL at different temperatures.

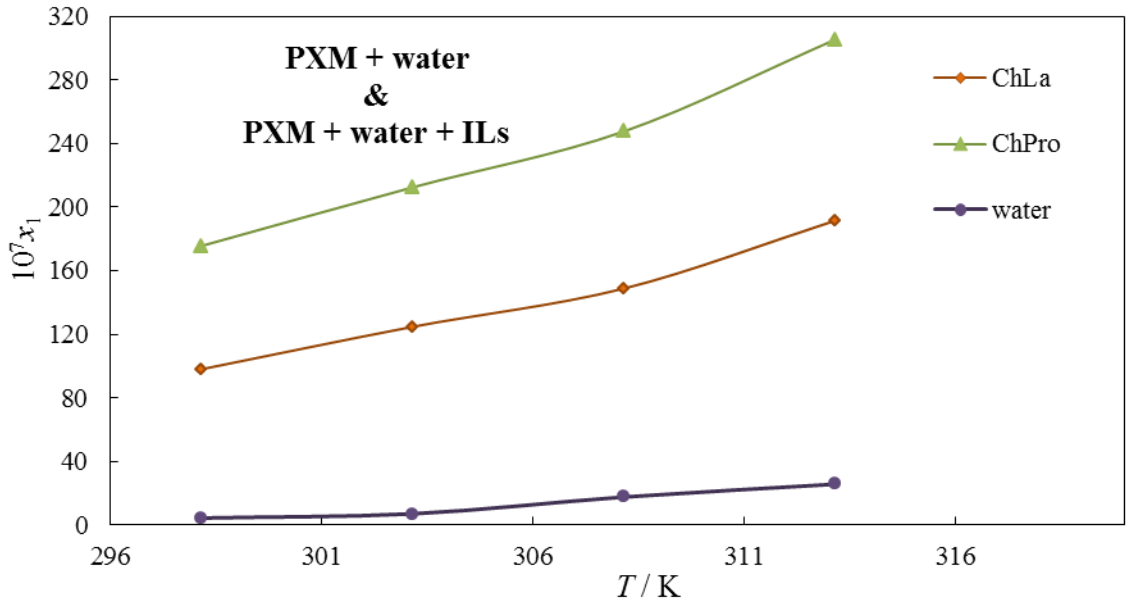


Fig. 4. Solubility of PXM, x_1, at a mass fraction of 0.15 of IL at different temperatures.