Pharmaceutical Sciences, 2020, 26(4), 423-433
doi:10.34172/PS.2020.48
https://ps.tbzmed.ac.ir/

Research Article

Significant Increase in the Solubility of Celecoxib in Presence of Some Deep Eutectic Solvents as Novel Sustainable Solvents and the Thermodynamic Analysis of These Systems

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Article Info

Article History:
Received: 30 January 2020
Accepted: 9 June 2020
ePublished: 25 December 2020

Keywords:
-Deep eutectic solvent
-Solubility
-Celecoxib
-Jouyban–Acree model
-Dissolution thermodynamics

Abstract

Background: Deep eutectic solvents (DESs) exist a wide variety of potential and existing applications. Based on the fact that the choline chloride (ChCl) is a complex B vitamin and widely used as food additive, the choline-based DESs are generically regarded as being harmless and non-toxic. In this regard, the low aqueous solubility of celecoxib (CLX) have been increased by use of DESs as neoteric class of solvents at T = (298.15 to 313.15) K.

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

Results: The solubility of the CLX increased with increasing the weight fraction of DESs. The observed solubility data was subjected to evaluate the relative performance of a number of models including Apelblat, Yalkowsky and Jouyban–Acree models for their correlation efficacy. Moreover, the apparent dissolution enthalpy, entropy and Gibbs free energy were obtained from the experimental solubility values.

Conclusion: It was found that the solubility data was satisfactorily fitted using the mentioned models at different temperatures. The dissolution process of CLX in the studied solvent mixtures within investigated temperature range was endothermic, and the driving mechanism is the positive entropy.

Introduction

Celecoxib (CLX) (Figure 1) or 4-[5-(4-Methylphenyl)-3-(trifluoromethyl) pyrazol-1- yl] benzene sulfonamide is a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID) and it is used clinically to treat pain and inflammation, and rheumatoid arthritis.[1,2]

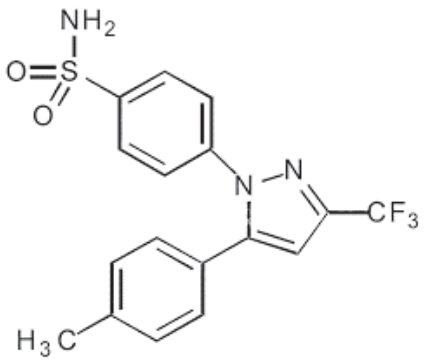

Figure 1. Chemical structure of CLX.

However, CLX is a lipophilic drug with a slow dissolution rate and very poor water solubility (about 3 µg/mL), which could limit the efficacy of its formulation in dry powder for inhalation. It should be mentioned that water solubility of CLX should be increased because poor solubility is a persistent challenge in drug discovery which represents the most frequent causes of limited bioavailability.[3,4]

The solubilization of drugs in co-solvents is employed for enhancing the solubility of low intrinsic water soluble drugs. Additionally, it is well-known that an organic co-solvent or ionic liquids (ILs) as co-solvent can improve the solubility of drugs.[5-8] But ILs are expensive, sometimes highly toxic, poor biodegradable and barely biocompatible, whereas, volatile organic solvents are a class of chemical solvents in the environment that can cause severe health problems.[9] By contrast, deep eutectic solvents (DESs) have lower costs and environmental impacts. Secondly, the synthesis methods of IL and DES are different. While DES

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are prepared by simply mixing the components, without waste and no purification step of the solvent is required, Preparation of ILs is difficult and costly. Finally, ILs are organic salts that are wholly composed of ions; DES are the result of complexation between a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD), whose interactions involve mostly hydrogen bonds.[10,11]

The current work represents a continuation of our systematic study on drugs solubility and related properties[12-18] and to develop the application of DESs as novel co-solvents in pharmaceutical science, the CLX was used for investigation of its solubility in four DESs (ChCl/urea, malonic acid, ethylene glycol and glycerol) using UV spectrophotometry and shake flask method for drug quantification at T = (298.15 to 313.15) K. For correlation of the experimental solubility data of CLX in these solvents, the Apelblat,[19] Yalkowsky[20] and Jouyban–Acree[21,22] models were used. Comparison and discussion of the solubility and used equations were carried out. Additionally, we evaluated the apparent thermodynamic properties of the systems by using the experimental solubility data and Van't Hoff equation.[23]

Materials and Methods

Materials

Celecoxib (0.99 mass fraction purity) was obtained from Zahravi pharmaceutical company (Tabriz, Iran). Urea, malonic acid, ethylene glycol, glycerol and choline chloride extra pure and absolute ethanol (was used for dilution of the samples prior to spectrophotometric analysis) were purchased from Merck (Germany). All chemicals were used as received without further purification. The description of the materials has been comprehensively collected in Table 1.

Preparation of DESs

The DESs were prepared by weighing choline chloride (ChCl) as hydrogen bonding acceptor (HBA) with urea, malonic acid, ethylene glycol and glycerol as hydrogen bonding donors, with mole ratios of 1:2, 1:1, 1:2 and 1:2, respectively,[10] using an electronic balance with a precision of $\pm 10^{-4}$ g (AW 220, GR220, Shimadzu, Japan). After continuous stirring for about 1 h at 353.15 K, a homogeneous colorless liquid was obtained. Finally, the mixture was allowed to cool down to room temperature naturally. Water content was analyzed by applying the Karl–Fisher titration technique (method TitroLine KF) for the prepared DESs and it has been used for calculation of concentrations. Some of the thermophysical properties of these solvents as measured in this study and these findings are similar to those reported by other researchers, they are listed in Table 2.

Apparatus and procedure

Density measurement

Density and speed of sound measurements of neat DESs were made with an accuracy of $\pm 4\times10^{-3}$ kg·m^{-3} and ± 1 m·s^{-1}, using a vibrating-tube densimeter (Anton Paar, DSA 5000 densimeter and speed of sound analyzer, Austria). The densimeter is calibrated with dry air and water as reference fluid. Furthermore, the speed of sound of samples is measured using a propagation time method.

Solubility determination

There are various methodological approaches for solubilization studies reported in the literature.[24] In this study, for solubility measurement, the shake flask method was chosen. In order to measure the solubility of drug in the aqueous solutions of DESs, an excess amount of drug with 5 g of solvent was poured to a glass tube. The electrical heating plates with magnetic stirring and thermostat control (ED, Julabo Co., Germany, temperature variation ± 0.1 K) were used to heat the mixtures (solid + liquid). Then the samples were placed in water bath thermostat until equilibrium is reached (for 3 days). Samples were centrifuged for 15 min to remove the solid phase (D-7200 Tuttlingen, Hettich Co., U.S.A.) in addition, the undissolved crystals was removed by filtration at isothermal condition through a membrane filters (Durapore® membrane filters, type HV, 0.45 µm, Millipore, MA, U.S.A.). A certain

Table 1. The sources and some properties of the materials.

Chemical name	Provenance	Molar mass (g.mol^{-1})	CAS No.	Mass fraction (purity)
Celecoxib	Zahravi Pharmaceutical Co. (Tabriz, Iran)	381.37	-	>0.99
Choline Chloride	Merck	139.62	67-48-1	>0.99
Urea	Merck	60.06	57-13-6	>0.99
Malonic Acid	Merck	104.06	141-82-2	>0.99
Ethylene glycol	Merck	62.09	107-21-1	>0.99
Glycerol	Merck	92.09	56-81-5	>0.99

Table 2. Some properties of DESs used in the article at 298.15 K 863 hPa.

DES designation	Molar ratio	Water content	ρ / g·cm^{-3}(exp)	ρ / g·cm^{-3}(Lit)	u / m·s^{-1}(exp)
ChCl / U	1.00:2.00	<0.03%	1.193926	1.1979[25]	2062.27
ChCl / MA	1.00:1.00	<0.01%	1.251470	1.2500[10]	1962.69
ChCl / EG	1.00:2.00	<0.01%	1.115551	1.116072[10]	1909.20
ChCl / G	1.00:2.00	<0.06 %	1.186358	1.176963[10]	2012.42

Standard uncertainties (u) for each variables are u (ρ) = 0.004 g·cm^{-3}; u (u) = 1 m·s^{-1}; u (T) = 10^{-2} K; u (p) = 10 hPa
Standard uncertainty (u) for DESs composition was estimated to be less than 0.05 molar ratio.

amount of solution depending on temperature and composition was taken and diluted with a certain amount of ethanol/water mixtures. The concentration of the drug was measured using double beam spectrophotometers model T80 UV-vis spectrometer PG instruments, U.K. The λ_{max} (wavelength of maximum absorption) for CLX was at 254 nm. A calibration curve was required to calculate the drug concentration in the samples. Data points represent the average of triplicate samples each from triplicate independent experimental tissues. The aqueous solubility of CLX in terms of mole fraction, x_1, in {CLX (1) + water (2) + DESs (3)} systems are calculated by using of Eq. (1):

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

where M_i and w_i denote the molar mass and mass fractions of i component in the saturated solution, respectively.[25-28]

Modeling of the solubility data

To correlate the obtained solubility data, the Apelblat and Yalkowsky equations at dilute region, while Jouyban-Acree model for full concentration range, were used respectively.

The modified Apelblat equation

The modified Apelblat equation corresponds to the following expression and the assumption of this equation is that the enthalpy of a solution is directly proportional to the temperature:[19,29]

$$\ln x_1 = A + \frac{B}{T} + C \ln T \quad \text{Eq. (2)}$$

where T is the absolute temperature, and A, B and C are three parameters obtained by fitting the experimental solubility data. Eq. (2) is used to correlate the solubility of CLX in every aqueous solutions. The parameters A, B and C were evaluated by using a non-linear optimization method.

Yalkowsky equation

The simplest model to predict and correlate drug solubility in co-solvent mixtures is the one based on the algebraic rule of mixing, in binary mixtures takes the following form: where $x_{1\text{-mix}}$ and $x_{1\text{-water}}$ are the total solute solubilities

$$\ln x_{1-mix} = \ln x_{1-water} + \sigma w_3 \quad \text{Eq. (3)}$$

in the (co-solvent + water) mixture and in pure water, respectively, σ is the co-solvent solubilization power for the particular co-solvent-solute system, and w_3 is the weight fraction of the co-solvent in the aqueous mixture.

Jouyban-Acree model

The Jouyban-Acree model, as a precise mathematical model can be used to correlate the solubility with respect to temperature and co-solvent composition.[30,31] Its basic form to calculate the solubility of a solute in a binary solvent mixture is:[32]

$$\log X_{m,T} = w_1 \log X_{1,T} + w_2 \log X_{2,T} + \frac{w_1 w_2}{T} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \quad \text{Eq. (4)}$$

where X_m is the mole fraction solubility of the solute in solvent mixture, w_1 and w_2 the weight fractions of solvents 1 and 2 in the absence of the solute, X_1 and X_2 the mole fraction solubilities in neat solvents 1 and 2, respectively, and J_i the solvent–solvent and solute–solvent interaction parameters for each binary solvent system. Two data points of solubilities in mono-solvent systems at every temperature should have measured in order to obtain the model parameters.

The evaluation of the accuracy and applicability of the mentioned models are studied by the average relative deviation percent (*ARD%*). This calculation can be done using the following equation:[33]

$$ARD = 100\left(\frac{\sum_{i=1}^{N} \frac{\left|x_i^{exp} - x_i^{cal}\right|}{\left|x_i^{exp}\right|}}{N}\right) \quad \text{Eq. (5)}$$

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

Thermodynamic properties of the drug dissolution

The experimental solubility data of the investigated drug was plotted versus the temperature to calculate the thermodynamic properties of dissolution. This process gives us a deep insight into the microscopic mechanisms in the solution processes by thermodynamic properties of solvation. In this regard, the modified Van't Hoff equation was applied to calculate the ΔH^{o}_{soln} of CLX in the studied mixtures. The mean harmonic temperature (T_{hm}) is considered as:

$$T_{hm} = \frac{N}{\sum_{i=1}^{N} \frac{1}{T_i}} \quad \text{Eq. (6)}$$

where N is the number of experimental temperatures. The calculated T_{hm} value was 305.55 K within the temperature range (from 298.15 K to 313.15 K) in this work. In the present case by plotting ln x versus ($1/T - 1/T_{hm}$), the values

ΔH^{o}_{soln} of and Gibbs free energy change (ΔG^{o}_{soln}) of dissolution can be obtained from the slope and the intercept.[34] Moreover, the values of entropy (ΔH^{o}_{soln}-ΔG^{o}_{soln}/ T_{hm}) are calculated as ΔS^{o}_{soln} . Furthermore, the following equations can be used to compare the relative contributions to the dissolution Gibbs energy by enthalpy (ζ_H) and entropy (ζ_{TS}) toward the processes of CLX dissolution:

$$\%\xi_H = \frac{\left|\Delta H^{o}_{so\,ln}\right|}{\left|\Delta H^{o}_{so\,ln}\right| + \left|T\Delta S^{o}_{so\,ln}\right|} \times 100 \qquad \text{Eq. (7)}$$

$$\%\xi_{TS} = \frac{\left|T\Delta S^{o}_{soln}\right|}{\left|\Delta H^{o}_{soln}\right| + \left|T\Delta S^{o}_{soln}\right|} \times 100 \qquad \text{Eq. (8)}$$

Results and Discussion

Solubility of CLX in aqueous solutions of DESs

The results of the CLX solubility in terms of mole fraction, x_1, at different weight fraction of co-solvent and temperature ranges from 298.15 to 313.15 K is presented in Tables 3 and 4 and shown graphically in Figure 2. The results show that the solubility of CLX in aqueous DESs solutions enhanced with the rising of DESs weight fraction and temperature. However, the increasing extent of solubility differs in the studied co-solvents. At same temperature, the mole fraction solubility is highest in the presence of ChCl / malonic acid, and lowest in neat water. The solubility of the drug in the presence of co-solvent containing ChCl / malonic acid has increased 62,700-fold than its solubility in pure water. In general, the solubility of CLX in different co-solvents decreases according to the order: ChCl / malonic acid > ChCl / ethylene glycol > ChCl / urea > ChCl / glycerol. The solubility is determined by the competition of the interaction between the solute-solvent and solvent-solvent. Figure 1 shows that the CLX molecule contains both hydrogen donor and hydrogen acceptor groups, then hydrogen bonds can be formed between the solute and solvents molecules.[35] Thus in these systems, both van der Waals interactions (represented by polarity) and hydrogen bonding (represented by hydrogen bond donor/acceptor propensity) solvation were favorable driving forces for solute–solvent interactions. In addition, According to Jouyban et al [4] the solubility of CLX in water at 298.15 K is 8.02×10^{-8}, this value is in good agreement with the obtained value in this work (8.01×10^{-8}). Also, it is well adapted for other investigated temperatures.

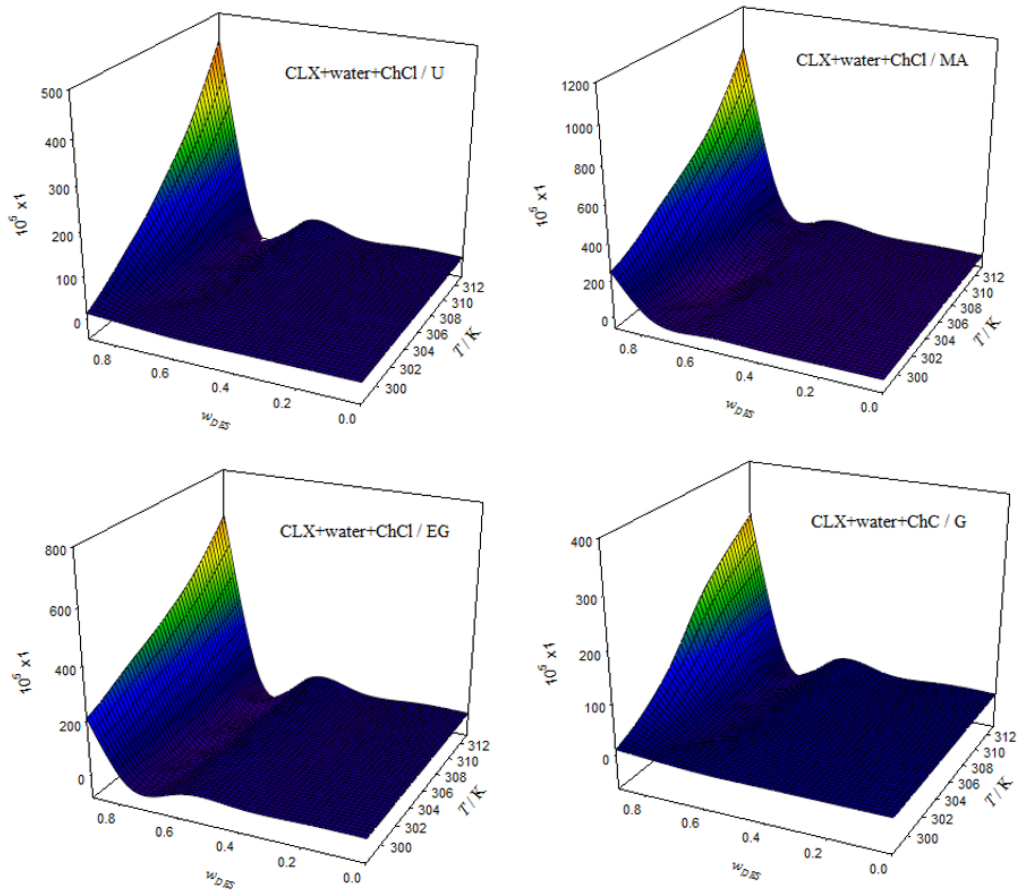

Figure 2. The relationship between mole fraction solubility of CLX (x_1) in the aqueous DESs mixtures versus temperature (T) and weight fractions (w_{DES}).

Table 3. The experimental CLX solubilities in aqueous mixtures of DESs (x_1^{exp})[a] and calculated values (x_1^{cal}) from Apelblat and Yalkowsky models at T = (298.15–313.15)[b] K and P = 863 hPa.

T / K	$10^5 x_1^{exp}$	Apelblat equation		Yalkowsky model	
		$10^5 x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$	$10^5 x_1^{cal}$	$100\frac{x_1^{exp}-x_1^{cal}}{x_1^{exp}}$
CLX + water + ChCl / U					
w_3=0.0200					
298.15	0.0239	0.0245	-2.79	0.0249	-4.19
303.15	0.0702	0.0645	8.11	0.0670	4.49
308.15	0.0913	0.0995	-9.02	0.0909	0.44
313.15	0.0960	0.0932	2.90	0.0937	2.38
w_3=0.0500					
298.15	0.0299	0.0302	-1.11	0.0298	0.29
303.15	0.0885	0.0856	3.33	0.0967	-9.19
308.15	0.1384	0.1433	-3.52	0.1472	-6.38
313.15	0.1483	0.1465	1.17	0.1542	-3.96
w_3=0.0700					
298.15	0.0344	0.0346	-0.53	0.0336	2.42
303.15	0.1227	0.1207	1.62	0.1234	-0.55
308.15	0.2144	0.2180	-1.68	0.2031	5.25
313.15	0.2136	0.2124	0.57	0.2148	-0.54
w_3=0.1000					
298.15	0.0428	0.0436	-1.72	0.0403	6.03
303.15	0.1899	0.1802	5.10	0.1780	6.29
308.15	0.3382	0.3568	-5.49	0.3292	2.68
313.15	0.3606	0.3541	1.80	0.3533	2.02
w_3=0.1500					
298.15	0.0518	0.0525	-1.36	0.0544	-4.94
303.15	0.3220	0.3090	4.06	0.3277	-1.77
308.15	0.7193	0.7504	-4.33	0.7359	-2.30
313.15	0.8076	0.7960	1.43	0.8096	-0.25
CLX + water + ChCl / MA					
w_3=0.0200					
298.15	0.0252	0.0256	-1.48	0.0239	5.36
303.15	0.0980	0.0937	4.41	0.0962	1.88
308.15	0.1673	0.1752	-4.72	0.1726	-3.14
313.15	0.1772	0.1744	1.56	0.1772	-0.70
w_3=0.0500					
298.15	0.0369	0.0373	-1.21	0.0364	1.13
303.15	0.1514	0.1459	3.63	0.1525	-0.73
308.15	0.2700	0.2804	-3.85	0.2852	-5.63
313.15	0.2804	0.2768	1.28	0.2994	-6.78
w_3=0.0700					
298.15	0.0458	0.0460	-0.46	0.0483	-5.59
303.15	0.2100	0.2071	1.39	0.2074	1.24
308.15	0.4295	0.4357	-1.44	0.3987	7.17
313.15	0.4511	0.4489	0.49	0.4248	5.84
w_3=0.1000					
298.15	0.0682	0.0678	0.57	0.0738	-8.27
303.15	0.3118	0.3173	-1.76	0.3289	-5.50

Table 3 Continued.

308.15	0.7082	0.6957	1.77	0.6590	6.94
313.15	0.7447	0.7492	-0.61	0.7177	3.62
w_3=0.1500					
298.15	0.1598	0.1620	-1.37	0.1495	6.48
303.15	0.7312	0.7014	4.08	0.7094	2.97
308.15	1.4342	1.4965	-4.34	1.5228	-6.18
313.15	1.6693	1.6453	1.44	1.7203	-3.06
CLX + water + ChCl / EG					
w_3=0.0200					
298.15	0.0293	0.0296	-1.11	0.0304	-3.77
303.15	0.0818	0.0791	3.34	0.0865	-5.72
308.15	0.1323	0.1370	-3.53	0.1374	-3.88
313.15	0.1599	0.1581	1.17	0.1576	1.44
w_3=0.0500					
298.15	0.0388	0.0392	-1.07	0.0382	1.48
303.15	0.1323	0.1280	3.21	0.1264	4.45
308.15	0.2199	0.2274	-3.4	0.2121	3.54
313.15	0.2310	0.2284	1.13	0.2359	-2.10
w_3=0.0700					
298.15	0.0445	0.0452	-1.42	0.0445	0.05
303.15	0.1680	0.1609	4.23	0.1627	3.16
308.15	0.2854	0.2983	-4.51	0.2833	0.73
313.15	0.3044	0.2999	1.49	0.3086	-1.37
w_3=0.1000					
298.15	0.0596	0.0601	-0.86	0.0559	6.17
303.15	0.2387	0.2325	2.60	0.2376	0.44
308.15	0.4431	0.4552	-2.73	0.4374	1.30
313.15	0.4754	0.4711	0.91	0.4617	2.88
w_3=0.1500					
298.15	0.0783	0.0793	-1.27	0.0818	-4.44
303.15	0.4359	0.4193	3.81	0.4469	-2.52
308.15	0.8841	0.9199	-4.05	0.9017	-1.99
313.15	0.8977	0.8856	1.34	0.9038	-0.68
CLX + water + ChCl / G					
w_3=0.0200					
298.15	0.0135	0.0138	-1.79	0.0137	-0.88
303.15	0.0447	0.0423	5.30	0.0438	2.03
308.15	0.0724	0.0766	-5.72	0.0689	4.83
313.15	0.0862	0.0846	1.88	0.0878	-1.93
w_3=0.0500					
298.15	0.0189	0.0191	-1.05	0.0184	2.52
303.15	0.0551	0.0533	3.16	0.0582	-5.75
308.15	0.0972	0.1005	-3.34	0.1004	-3.28
313.15	0.1324	0.1309	1.11	0.1327	-0.24
w_3=0.0700					
298.15	0.0225	0.0229	-2.02	0.0224	0.20
303.15	0.0711	0.0668	5.94	0.0704	0.88
308.15	0.1233	0.1313	-6.46	0.1290	-4.63
313.15	0.1821	0.1783	2.11	0.1746	4.12
w_3=0.1000					
298.15	0.0292	0.0295	-0.83	0.0302	-3.43

Table 3 Continued.

303.15	0.0982	0.0957	2.50	0.0937	4.55
308.15	0.1902	0.1952	-2.62	0.1879	1.19
313.15	0.2596	0.2573	0.88	0.2637	-1.61
w_3=0.1500					
298.15	0.0503	0.0495	1.62	0.0496	1.33
303.15	0.1480	0.1556	-5.14	0.1508	-1.87
308.15	0.3583	0.3404	4.99	0.3516	1.85
313.15	0.5208	0.5300	-1.76	0.5243	-0.67

[a] Standard uncertainty u(x_1^{exp}) = 1%, [b] Standard uncertainty u(T)= 0.1 K, [c] Standard uncertainty u(w_3)=0.0005.

Table 4. The calculated solubilities values of CLX (x_1^{cal}) from Jouyban-Acree model at T = (298.15–313.15) K and P = 863 hPa.

	$10^5 x_1^{cal}$	**Jouban-Acree model**		
w_3	**T = 298.15 K**	**T = 303.15 K**	**T = 308.15 K**	**T = 313.15 K**
		CLX + water + ChCl / EG		
0.0000	0.0080	0.0094	0.0139	0.0157
0.0200	0.0123	0.0175	0.0355	0.0379
0.0500	0.0215	0.0447	0.1134	0.1157
0.0700	0.0293	0.0705	0.2184	0.2147
0.1000	0.0439	0.1389	0.4813	0.4695
0.1500	0.0713	0.7684	1.0216	1.1200
0.2000	0.0997	0.8154	1.5238	1.8957
0.4000	0.2326	4.1091	1.3438	2.8780
0.6000	1.1816	6.7170	2.8655	3.2937
0.8000	27.249	29.3848	86.869	114.0738
0.9000	146.909	287.8234	477.8924	529.6825
		CLX + water + ChCl / G		
0.0000	0.0080	0.0094	0.0138	0.0156
0.0200	0.0110	0.0180	0.0286	0.0325
0.0500	0.0167	0.0408	0.0712	0.0826
0.0700	0.0211	0.0641	0.1170	0.1390
0.1000	0.0284	0.1131	0.2130	0.2653
0.1500	0.0424	0.2049	0.4207	0.5810
0.2000	0.0557	0.3020	0.5954	0.9214
0.4000	0.1336	0.3622	0.6425	1.1570
0.6000	0.4842	0.7718	1.4762	1.5313
0.8000	5.2674	9.4479	25.2816	35.2905
0.9000	11.1981	53.8913	136.0013	172.1680
		CLX + water + ChCl / MA		
0.0000	0.0080	0.0094	0.0139	0.0157
0.0200	0.0127	0.0254	0.0378	0.0434
0.0500	0.0228	0.0888	0.1353	0.1579
0.0700	0.0321	0.1763	0.2752	0.3236
0.1000	0.0476	0.4050	0.6811	0.7848
0.1500	0.0785	1.0561	1.8637	2.2771
0.2000	0.1112	1.7571	3.7023	4.2973
0.4000	0.2784	1.9671	6.6644	7.6434
0.6000	2.1683	4.1275	16.5374	21.1613
0.8000	58.2723	73.7275	200.2261	272.4577
0.9000	279.9740	395.0926	803.6523	1208.5182
		CLX + water + ChCl / U		
0.0000	0.0080	0.0094	0.0138	0.0155
0.0200	0.0121	0.0213	0.0417	0.0960
0.0500	0.0206	0.0598	0.0972	0.1033
0.0700	0.0277	0.1048	0.1705	0.1847
0.1000	0.0406	0.2063	0.3556	0.3751
0.1500	0.0641	0.4446	0.8081	0.8593
0.2000	0.0873	0.6564	1.1891	1.3610

Table 4 Continued.

0.4000	0.1705	0.5798	1.1936	1.8614
0.6000	0.5758	1.0922	2.6389	4.7934
0.8000	5.5472	19.3841	52.6669	81.6271
0.9000	20.4181	132.2978	293.4671	353.9852

Modeling results

In the next step, the generated solubility data points were correlated with the Apelblat , Yalkowsky equations and Jouyban-Acree model. The modeling results are summarized in Tables 3 and 4. The calculated parameters of Jouyban-Acree model are given in Table S1 (Supplementary Data) respectively. The calculated *ARD%* values are given in Table 5 for the used models in this work. As shown in these tables, the overall %*ARD* results for these three models are Apelblat (2.63), Yalkowsky (2.64) and Jouyban-Acree (1.08). As one can see the Jouyban-Acree model presents better results in respect to the other models, even this model is more accurate than the modified Apelblat and Yalkowsky correlations. Thus, the performance of these models in correlation of the experimental solubility data can be ordered as Jouyban-Acree > modified Apelblat > Yalkowsky.

Apparent thermodynamic quantities of dissolution

Thermodynamic properties of a solute dissolved in a particular solvent may provide essential information about the dissolution procedure. Table 6 reports the apparent standard molar thermodynamic functions for dissolution of CLX (1) in all the {water (2) + DES (3)} solvent mixtures. As expected, the standard Gibbs energies of dissolution of this drug are positive in every case, as also are the standard enthalpies and entropies of dissolution (except ΔS^{o}_{soln} in neat water).

Table 5. The calculated average relative deviation percent (*ARD*%) for the solubility of the CLX in the aqueous DES solutions at several temperatures from different models.

		Apelblat **CLX + water + DES**		
w_3	ChCl / U	ChCl / MA	ChCl / EG	ChCl / G
0.0200	5.71	3.04	2.29	3.67
0.0500	2.28	2.49	2.20	2.17
0.0700	1.10	0.94	2.91	4.13
0.1000	3.53	1.18	1.78	1.71
0.1500	2.79	2.81	2.62	3.40
Average	3.08	2.09	2.36	3.02
		Yalkowsky **CLX + water +DES**		
T / K	ChCl / U	ChCl / MA	ChCl / EG	ChCl / G
298.15	2.98	4.47	2.65	1.39
303.15	3.72	2.05	2.71	2.51
308.15	2.84	4.84	1.91	2.63
313.15	1.53	3.22	1.41	1.43
Average	2.77	3.64	2.17	1.99

Table 6. Thermodynamic functions of dissolution of CLX for different weight fractions of DESs (w_3) at mean harmonic temperature (T_{hm}) and P = 863 hPa.

w_3	ΔH^{o}_{soln} / kJ·mol^{-1}	$T_M\Delta S^{o}_{soln}$ / kJ·mol^{-1}	ΔG^{o}_{soln} / kJ·mol^{-1}	ζ_H	ζ_{TS}
		CLX + water + ChCl / MA			
0.0000	33.87	-6.84	40.72	83.19	16.81
0.0200	104.27	68.94	35.33	60.20	39.80
0.0500	113.48	79.22	34.26	58.89	35.78
0.0700	125.08	91.85	33.23	57.66	42.34
0.1000	137.64	105.48	32.17	56.62	43.38
0.1500	158.99	128.51	30.48	55.30	44.70
0.2000	167.69	137.70	29.99	54.91	45.09
0.4000	177.06	150.13	26.94	54.12	45.88
0.6000	133.38	109.91	23.47	54.82	45.18
0.8000	88.66	71.38	17.28	55.40	44.60
0.9000	70.25	56.75	13.50	55.32	44.68

Table 6 Continued.

CLX + water + ChCl / U					
0.0000	33.87	-6.84	40.72	83.19	16.81
0.0200	69.44	33.13	36.31	67.70	32.30
0.0500	82.07	46.59	35.48	63.79	25.75
0.0700	94.31	59.63	34.68	61.26	38.74
0.1000	108.88	75.25	33.64	59.13	40.87
0.1500	141.21	109.02	32.19	56.43	43.57
0.2000	141.09	109.54	31.55	56.29	43.71
0.4000	108.40	78.27	30.12	58.07	41.93
0.6000	139.51	111.99	27.52	55.47	44.53
0.8000	99.80	78.84	20.96	55.87	44.13
0.9000	179.79	162.44	17.36	52.54	47.46
CLX + water + ChCl / EG					
0.0000	33.87	-6.84	40.72	83.19	16.81
0.0200	105.04	69.32	35.72	60.24	39.76
0.0500	104.73	70.15	34.58	59.89	39.64
0.0700	110.22	76.29	33.93	59.09	40.91
0.1000	117.10	84.20	32.90	58.17	41.83
0.1500	128.80	97.45	31.34	56.93	43.07
0.2000	124.03	92.96	31.07	57.16	42.84
0.4000	71.97	42.32	29.65	62.97	37.03
0.6000	103.4	77.57	25.83	57.14	42.86
0.8000	69.90	50.18	19.72	58.21	41.79
0.9000	55.81	41.56	14.25	57.32	42.68
CLX + water + ChCl / G					
0.0000	33.87	-6.84	40.72	83.19	16.81
0.0200	101.57	64.35	37.23	61.22	38.78
0.0500	107.59	71.24	36.35	60.16	35.98
0.0700	110.91	75.19	35.72	59.60	40.40
0.1000	113.41	78.52	34.89	59.09	40.91
0.1500	125.23	91.70	33.52	57.73	42.27
0.2000	128.72	95.96	32.76	57.29	42.71
0.4000	97.98	66.73	31.25	59.49	40.51
0.6000	86.32	57.22	29.10	60.14	39.86
0.8000	75.92	53.24	22.68	58.78	41.22
0.9000	153.06	134.2	18.86	53.28	46.72

Thus, the dissolution processes are endothermic. The relative contributions by enthalpy (ζ_H) and entropy (ζ_{TS}) toward all the dissolution processes are given. In addition, it can be found that the values of apparent molar enthalpy of dissolution are all positive, which illustrates that the dissolution process of CLX in (DESs + water) systems is always endothermic and the entropy is the driving force for the dissolution process.

Conclusion

The solubility of the celecoxib in four aqueous DESs solutions, namely, ChCl / urea, ChCl / ethylene glycol, ChCl / glycerol and ChCl / malonic acid, were determined experimentally by spectrophotometric absorbance measurements at different temperatures. The celecoxib solubility has increased 35000-fold in the presence of co-solvent containing ChCl / malonic acid regarding its solubility in pure water. Some correlations have been made using the modified Apelblat, Yalkowsky and Jouyban-Acree models. It turned out that the Jouyban-Acree model gave a satisfactory correlation results compared with those obtained by using the Apelblat and Yalkowsky models. Moreover, according to the thermodynamic properties of the drug dissolution, the apparent dissolution enthalpies were positive and the celecoxib has an endothermic dissolution process in every case, and the driving force of this process is entropy. On the basis of the experimental solubility values and the thermodynamic results of this drug in the presence of deep eutectic solvents, it is remarkable that this information can be useful in the aspects of the co-crystals preparation and the synthesis and improvement of celecoxib derivatives.

Acknowledgments

The authors wish to acknowledge the financial support received from the graduate council of the University of Tabriz.

Conflict of Interest

The authors declare they have no conflict of interest.

Supplementary Data

Supplementary file contains Table S1 which is available on the journal's web site along with the published article.

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