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Natural deep eutectic solvents for enhancing the solubility of two B vitamins in aqueous solutions: Experimental study and thermodynamic aspects

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Abstract−Natural deep eutectic solvents (NADESs) as green solvents have substantial potential for enhancing the solubility of pharmaceuticals in aqueous solutions. In this work, the solubility of two B vitamins (nicotinic acid and 4aminobenzoic acid) in aqueous solutions of two NADESs was measured at temperatures between 298.15 K and 313.15 K and different concentrations of NADESs. The studied NADESs were prepared by mixing dried choline chloride with urea or malonic acid with molar ratios of 1 : 2 and 1 : 1, respectively. Based on the results, chloride+malonic acid was more effective on the solubility of the pharmaceuticals in aqueous solutions. Furthermore, the DESs increased the aqueous solubility of 4aminobenzoic acid more than that of nicotinic acid. The experimental solubility data were modeled with the van Laar activity model as well as the modified Apelblat equation to correlate the solubility of the pharmaceuticals to the temperature and NADESs concentration. The molar enthalpy of dissolution (Δh_d) and the molar enthalpy of mixing (Δh_{mix}) of the pharmaceuticals in the aqueous solutions of the NADESs were calculated. These parameters showed that all the dissolution processes were endothermic, while the mixing process as a part of the dissolution process was exothermic.

Keywords: Nicotinic Acid, 4aminobenzoic Acid, Deep Eutectic Solvent, Solubility, Van Laar, Modified Apelblat

INTRODUCTION

According to the Biopharmaceutics Classification System (BCS) [1], pharmaceuticals are categorized into four classes: (1) highly soluble and highly permeable, (2) highly permeable but poorly soluble, (3) highly soluble but poorly permeable, and (4) poorly soluble and poorly permeable**.** Thus, solubility is an important property of pharmaceuticals [2], because this parameter is critical in many processes such as separation and formulation of pharmaceuticals [3]. The low solubility of most pharmaceuticals in water causes fundamental challenges to the pharmaceutical industry [4]. To overcome this problem, several methods have been proposed for enhancing the solubility of poorly soluble pharmaceuticals, such as particle size reduction, adding a surfactant, salt formation, solid dispersions, and cosolvency [5,6]. Cosolvency refers to the process of adding a cosolvent to the primary solvent for enhancing the solubility of the low-soluble solute [7].

In recent years, the role of ionic liquids, as green solvents, on the enhancing of the solubility of pharmaceutical in water, has been investigated by some studies [8-10]. Based on the literature, several issues make it challenging to use of ionic liquids in the pharmaceutical industry, such as toxicity, high price, and corrosivity [11,12].

Another type of green solvent is the deep eutectic solvent (DESs) that has many physical properties similar to ionic liquids, such as high viscosity and low vapor pressure [13]. However, DESs compared to ionic liquids are more environmentally friendly, easier to prepare and have lower toxicity [14-16]. DESs are formed by combining a hydrogen bond donor (amides, carboxylic acids, alcohols, …) and a hydrogen bond acceptor (usually halide salts) in a certain ratio [17,18]. The deep eutectic solvent first introduced by Abbott et al. in 2003 was a mixture of choline chloride and urea with an eutectic point of 12 °C and 66.7% urea by mole [19].

A group of DESs is the natural deep eutectic solvents (NADESs), which have recently been reported by Dai et al. [20], are formed by the natural components and consequently are less harmful to humans and the environment; thus they can be used in green industries [20-22]. Aqueous NADESs have been applied to different processes such as catalytic reactions [23,24], pharmaceutical solubilization [25,26], gas absorption [27-29], distillation [30,31], extraction [32-34], electrochemistry [35-37], sulfur removal [38-40], and enhancing enzyme activity [41].

According to the literature, NADESs with low concentration in water are promising cosolvents that do not harm the viability of plants, animals, and microorganisms. Thus they are potential solvents for the pharmaceuticals and foods [14,15,42-46].

In this study, the cosolvency effect of two NADESs (choline chloride-urea and choline chloride-malonic acid) on the solubility of 4-aminobenzoic acid and nicotinic acid in aqueous solution was investigated at different temperatures and NADESs concentrations.

MATERIALS

The chemicals include 4-aminobenzoic acid, nicotinic acid, choline chloride, urea, and malonic acid, which were of analytical grade. Choline chloride was purchased from Solarbio with a purity of more than 0.98, urea and malonic acid were purchased from Samchun

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with purity of more than 0.99. 4-aminobenzoic acid and nicotinic acid were provided from Sigma-Aldrich with purity of more than 0.98. Double deionized water was also used in this work. Furthermore, choline chloride was dried before use because of its high hygroscopicity.

The shake-flask method is a typical method to determine the solubility of pharmaceuticals in solvents. In this process, a surplus amount of the pharmaceutical is added to a given volume of the solvent and the sample is shaken at a constant temperature for sufficient time to achieve the equilibrium. After equilibration, the undissolved solid is separated from the solution and the concentration of the solute is measured with an appropriate method [2].

In this work, the solubility of two B vitamins, including nicotinic acid and 4aminobenzoic acid in aqueous solutions of two NADES, including choline chloride+malonic acid (with a molar ratio of 1 : 1) and choline chloride+urea (with a molar ratio of 1 : 2) was investigated at temperatures between 298.15 K and 313.15 K 3. The chemical structures of the two NADESs and two B vitamins are illustrated in Fig. 1. To prepare a NADES, choline chloride and the hydrogen bond donor component (urea or malonic acid) were dried separately at 100 °C for 5 hours. Then, choline chloride and the hydrogen bond donor component were weighed by an analytical balance (HR200, A&D with a precision of 0.0001 g) and were mixed to make a mixture with a certain ratio (choline chloride and malonic acid with a molar ratio of 1 : 1, choline chloride and urea with molar ratio of 1 : 2). The mixture was heated and mixed using a heater-stirrer at 70 °C and a mixing speed of 150 rpm until a homogeneous colorless liquid was formed. Afterward, the NADES and deionized water were weighed by an analytical balance and were mixed to prepare an aqueous solution of the NADES with a given mole fraction of the NADES. About 7 cm^3 of the aqueous solution was added to a 15 cm^3 falcon tube, and a surplus amount of the pharmaceutical was added to the solution. Aqueous solutions with different concentrations of the NADESs were prepared to study the effect of NADES concentration on the pharmaceuticals' solubility.

In the next step, the falcon tubes were placed in a Shaker Incubator (BS631, Fater Iran) for 24 hours at a mixing speed of 100 rpm and a constant temperature. Then, the tubes were put in insulated boxes and were centrifuged (TL320, Selecta Lab) with a speed of 1,000 rpm for two minutes to separate the undissolved pharmaceutical (B vitamin) from the solution. Then, the equilibrium concentration of the pharmaceutical was measured by a using spectrophotometer (7315, Jenway).

To measure the concentration of nicotinic acid and 4aminobenzoic acid, two spectrophotometric methods were proposed in this work. At first, a survey scan for the aqueous solution of the pharmaceutical was carried out to obtain the peak of the optical density (OD) for both the pharmaceuticals, which found to be 305 nm for nicotinic acid and 285 nm for 4aminobenzoic acid. Then, the calibration curves for nicotinic acid and 4aminobenzoic acid were prepared against the blank solution at the corresponding wavelength. To eliminate the effect of the NADESs individual components on the measurement methods, the pharmaceutical-free aqueous solution of the NADES was selected as the blank solution. The calibration curves fit the experimental data well as seen in Fig. 2.

MODEL

Two models were employed to correlate the solubility data to the temperature and concentration of DESs. A thermodynamic model based on the fugacity equality combined with the van Laar activity coefficient model and the modified Apelblat equation were used in this study.

1. Thermodynamic Model

The fugacity equality for the solute component in a solid-liquid equilibrium can be expressed as Eq. (1) [47]:

$$\frac{1}{x_i\gamma_i} = \exp\left(\frac{\Delta h_{fus}}{RT_t}\left(\frac{T_t}{T}-1\right) - \frac{\Delta C_p}{R}\left(\frac{T_t}{T}-1\right) + \frac{\Delta C_p}{R}\ln\frac{T_t}{T}\right) \quad (1)$$

where x_i and γ_i are the mole fraction and activity coefficient of the

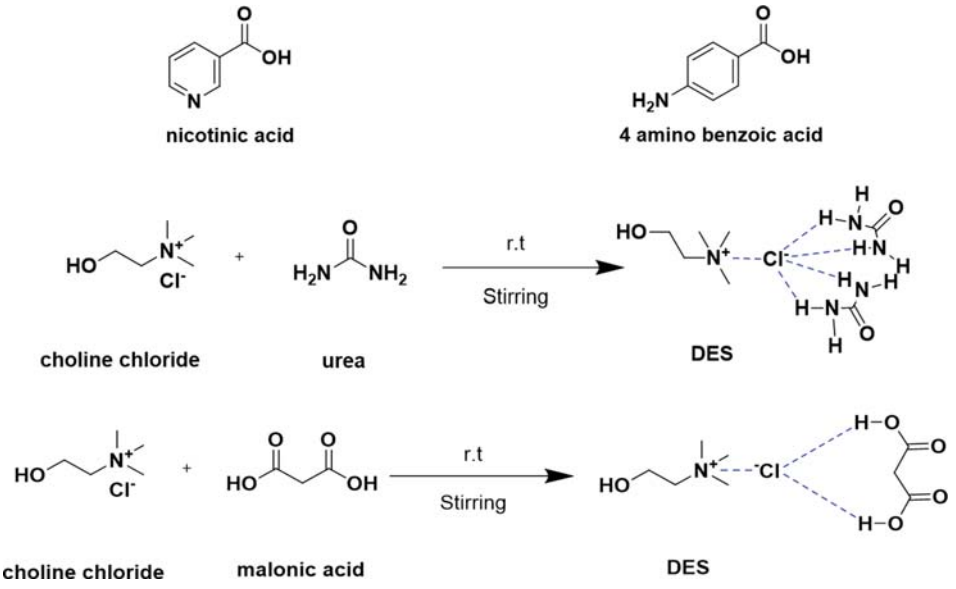

Fig. 1. The chemical structures of the B vitamins and DESs.

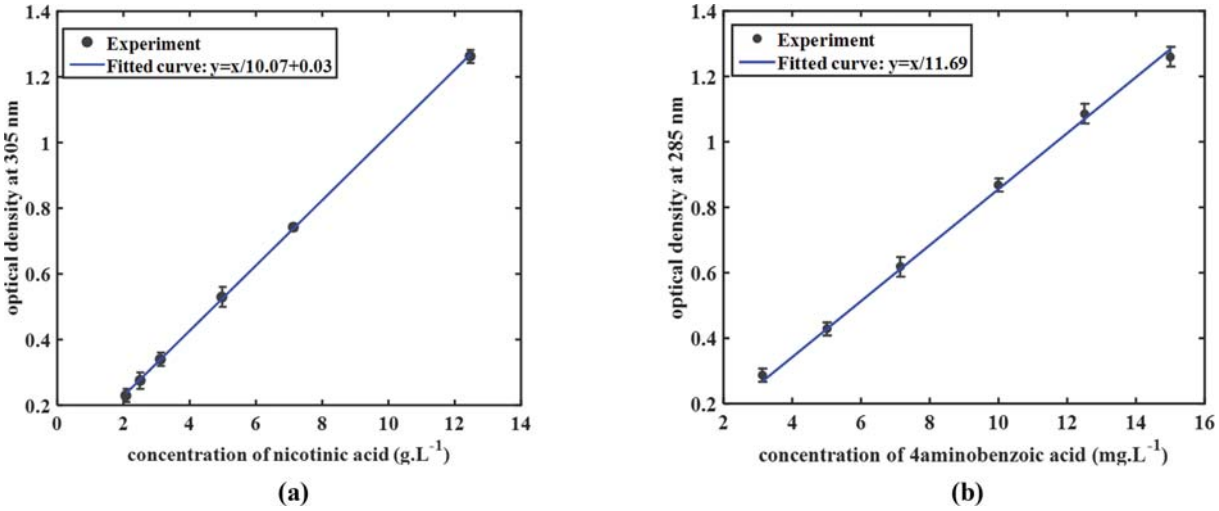

Fig. 2. The calibration curves for measurement of pharmaceuticals: (a) nicotinic acid, (b) 4aminobenzoic acid.

solute in the liquid phase. Δh_{fus}, T_t, and ΔC_p are the enthalpy of fusion of the solute, the triple temperature of the solute, and the difference between the specific heat capacity of the solute in the liquid and solid states. Furthermore, T and R denote for the temperature and the gas constant. In this study, ΔC_p was assumed to be zero due to the lack of data for nicotinic acid and 4aminobenzoic acid in the literature. The values of Δh_{fus} and T_t of nicotinic acid were collected from the literature (504 K and 24.6 kJ·mol^{-1}) [48,49], and these values are 460 K and 24.0 kJ·mol^{-1} for 4aminobenzoic acid based on the literature [50]. The activity coefficient of the solute in binary and ternary mixtures was obtained using the van Laar model as shown by Eq. (2) [47]:

$$\ln\gamma_1 = \frac{\lambda_{12}}{\left(1+\frac{\lambda_{12}x_1}{\lambda_{21}x_2}\right)^2}, \quad \lambda_{ij} = \frac{\Lambda_{ij}}{RT} \tag{2a}$$

$$\ln\gamma_1 = \frac{x_2^2\lambda_{12}\left(\frac{\lambda_{21}}{\lambda_{12}}\right)^2 + x_3^2\lambda_{13}\left(\frac{\lambda_{31}}{\lambda_{13}}\right)^2 + x_2x_3\frac{\lambda_{21}\lambda_{31}}{\lambda_{12}\lambda_{13}}\left(\lambda_{12}+\lambda_{13}-\frac{\lambda_{32}\lambda_{13}}{\lambda_{31}}\right)}{\left(x_1+x_2\frac{\lambda_{21}}{\lambda_{12}}+x_3\frac{\lambda_{31}}{\lambda_{13}}\right)^2}, \quad \lambda_{ij} = \frac{\Lambda_{ij}}{RT} \tag{2b}$$

The binary interaction parameters of the van Laar equation were correlated to the temperature with a linear equation as shown in Eq. (3)

$$\Lambda_{ij} = \alpha_{ij} + \beta_{ij}T \tag{3}$$

To estimate the parameters of Eq. (3), the binary interaction parameters were classified into three parts, including the parameters between the pharmaceutical and water, the parameters between the DES and water, and the parameters between the pharmaceutical and the DES.

The binary parameters between the pharmaceutical and water were estimated by using the solubility of the pharmaceutical in deionized water. To estimate these parameters, Eq. (3) was substituted in Eq. (2a), and then Eq. (2a) was substituted into Eq. (1), and the genetic algorithm (GA), as a global optimization method, was employed for minimizing the deviation between the solubility estimated by Eq. (1) and the experimental data.

The binary interaction parameters between the DESs and water were estimated by using the experimental bubble pressure of DES-water mixtures at different temperatures and different DES concentrations [51]. In this regard, the activity coefficient of water was calculated by substituting experimental data [51] data into Eq. (4) [47], and then the GA was used to minimize the deviation between the calculated activity coefficient and the activity coefficient estimated by Eqs. (2a) and (3).

$$\gamma_{water} = \frac{y_{water}\varphi_{water}P}{x_{water}P^{sat,\,water}} \tag{4}$$

where P and $P^{sat,\,water}$ denote for the bubble pressure of the system and the vapor pressure of water. Besides, y and φ are the mole fraction and the fugacity coefficient of water vapor, respectively; y was expected to be unity because the vapor phase was pure, and φ was assumed to be unity because the bubble pressure was low.

The binary interaction parameters of pharmaceutical-DES were estimated by using the solubility of the pharmaceutical in the aqueous solution of the DES. In this regard, the binary parameters of pharmaceutical-water and DES-water were substituted into Eq. (2b), and then Eq. (2b) was substituted into Eq. (1) and the GA method was employed for minimizing the deviation between the experimental solubility and the solubility estimated by Eq. (1).

2. Modified Apelblat Equation

The modified Apeblat equation is an equation for correlating the solubility of a solid solute in a liquid phase to the temperature, as shown in Eq. (5), and has been derived from the Clausius-Clapeyron equation [52].

$$\ln(x) = A + \frac{B}{T} + C\ln(T) \tag{5}$$

where x is the solubility of solute, T is the temperature of the system in K, and A, B, and C are the empirical parameters that can be estimated by the experimental solubility. In this study, the solubil-

ity of nicotinic acid and 4aminobenzoic acid in the aqueous solutions of the DESs were correlated to the temperature by using the modified Apelblat equation. Furthermore, in this study, to investigate the effect of DES concentration on the pharmaceutical solubility, the parameters of the modified Apelblat equation (A, B, and C) were correlated to the DES concentration by using quadratic equations, as shown by Eq. (6):

$$A, B, \text{ or } C = \psi_0 + \psi_1 x_{DES} + \psi_2 (x_{DES})^2 \quad (6)$$

3. Enthalpy of Dissolution

In the next part, the equation of Williamson [53] was used to exact calculation of the dissolution enthalpy (Δh_{sol}) as shown by Eq. (7).

$$\Delta h_{sol} = RT^2 \left(\frac{dm}{dT}\right)_{sat} \left(\left(\frac{1}{m}\right)_{sat} + \left(\frac{\partial \ln \gamma^*}{\partial m}\right)_T\right) \quad (7)$$

where T and R are the temperature and the gas constant, respectively. m is the molality of pharmaceutical and γ^* is the molal ionic activity coefficient of pharmaceutical and is calculated by Eq. (8).

$$\gamma^* = \frac{x\gamma}{m} \quad (8)$$

The derivative part of the right-hand side of Eq. (7) was calculated by combining Eq. (8) and the van Laar model (Eq. (2)). Then, the enthalpy of dissolution and the enthalpy of fusion of the pharmaceutical were used to calculate the enthalpy of mixing as shown by Eq. (9) [54,55]:

$$\Delta h_{sol} = \Delta h_{fus} + \Delta h_{mix} \quad (9)$$

RESULTS AND DISCUSSION

Experimental data corresponding to the solubility of nicotinic acid in pure water and the aqueous solution of DESs (choline chloride+urea and choline chloride+malonic acid) at temperature ranges of 298.15 K to 313.15 K are listed in Tables 1 and 2. In addition, the uncertainty of the solubility data is provided in the footnotes to these tables. The uncertainty consists of the instruments, sample preparation, and the possible deviation from the equilibrium. The results showed that the solubility of nicotinic acid increases with both the concentration of DES and temperature. However, the effect of malonic acid+choline chloride DES on the nicotinic acid solubility is more pronounced. The solubility of nicotinic acid in a solution of 8.9% DES (malonic acid+choline chloride) by mole is

Table 1. Experimental solubility of nicotinic acid in the mixture of (malonic acid+choline chloride with a molar ratio of 1 : 1) DES and water at temperature T and pressure P=0.1 MPa[a]

	298.15 K	303.15 K	308.15 K	313.15 K
x_1	$10^3 x_2$			
0.000	2.21	2.60	3.53	3.94
0.008	2.63	3.32	3.69	4.29
0.016	3.33	3.93	4.40	5.07
0.025	3.73	4.30	4.93	5.62
0.035	4.14	4.80	5.48	6.12
0.059	5.06	5.74	6.49	7.08
0.089	5.90	6.56	7.33	8.20

[a]Standard uncertainty for temperature is u(T)=0.5 K. Relative standard uncertainty for mole fraction, $u_r(x)=0.04$, and $u_r(P)=0.1$.
x_1: mole fraction of DES, x_2: mole fraction of nicotinic acid.

Table 2. Experimental solubility of nicotinic acid in the mixture of (urea+choline chloride with a molar ratio of 2 : 1) DES and water at temperature T and pressure P=0.1 MPa[a]

	298.15 K	303.15 K	308.15 K	313.15 K
x_1	$10^3 x_2$			
0.000	2.21	2.60	3.53	3.94
0.007	2.53	3.21	3.64	3.96
0.023	2.94	3.55	4.15	4.67
0.045	3.30	3.89	4.51	4.92
0.057	3.40	3.98	4.56	4.99

[a]Standard uncertainty for temperature is u(T)=0.5 K. Relative standard uncertainty for mole fraction, $u_r(x)=0.04$, and $u_r(P)=0.1$.
x_1: mole fraction of DES, x_2: mole fraction of nicotinic acid.

Table 3. Experimental solubility of 4aminobenzoic acid in the mixture of (malonic acid+choline chloride with a molar ratio of 1 : 1) DES and water at temperature T and pressure P= 0.1 MPa[a]

	298.15 K	303.15 K	308.15 K	313.15 K
x_1	$10^3 x_2$			
0.000	0.69	0.81	0.94	1.11
0.008	2.14	2.50	2.76	3.10
0.017	3.38	3.90	4.41	5.07
0.025	4.79	5.37	6.27	6.76
0.035	6.51	7.27	7.80	8.79
0.060	9.98	11.18	12.38	13.83

[a]Standard uncertainty for temperature is u(T)=0.5 K. Relative standard uncertainty for mole fraction, $u_r(x)=0.04$, and $u_r(P)=0.1$.
x_1: mole fraction of DES, x_2: mole fraction of 4aminobenzoic acid.

Table 4. Experimental solubility of 4aminobenzoic acid in the mixture of (urea+choline chloride with a molar ratio of 2 : 1) DES and water at temperature T and pressure P=0.1 MPa[a]

	298.15 K	303.15 K	308.15 K	313.15 K
x_1	$10^3 x_2$			
0.000	0.69	0.81	0.94	1.11
0.008	0.87	1.05	1.17	1.48
0.016	1.06	1.20	1.47	1.74
0.024	1.29	1.62	1.75	2.06
0.035	1.68	1.90	2.15	2.44
0.057	2.26	2.72	3.14	3.57
0.089	3.19	3.89	4.21	4.93

[a]Standard uncertainty for temperature is u(T)=0.5 K. Relative standard uncertainty for mole fraction, $u_r(x)=0.04$, and $u_r(P)=0.1$.
x_1: mole fraction of DES, x_2: mole fraction of 4aminobenzoic acid.

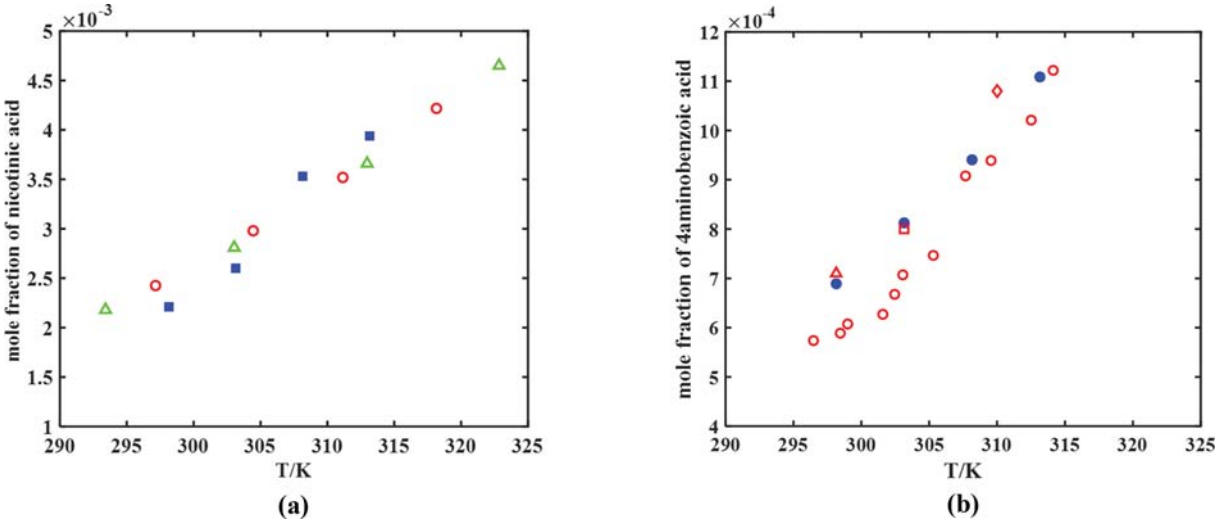

Fig. 3. A comparison between the solubility of pharmaceuticals in deionized water and literature data. (a) nicotinic acid, ■: this work, △: [49], ○: [56]; (b) 4aminobenzoic acid, ●: this work, ○: [60], △: [57], □: [58], ◇: [59].

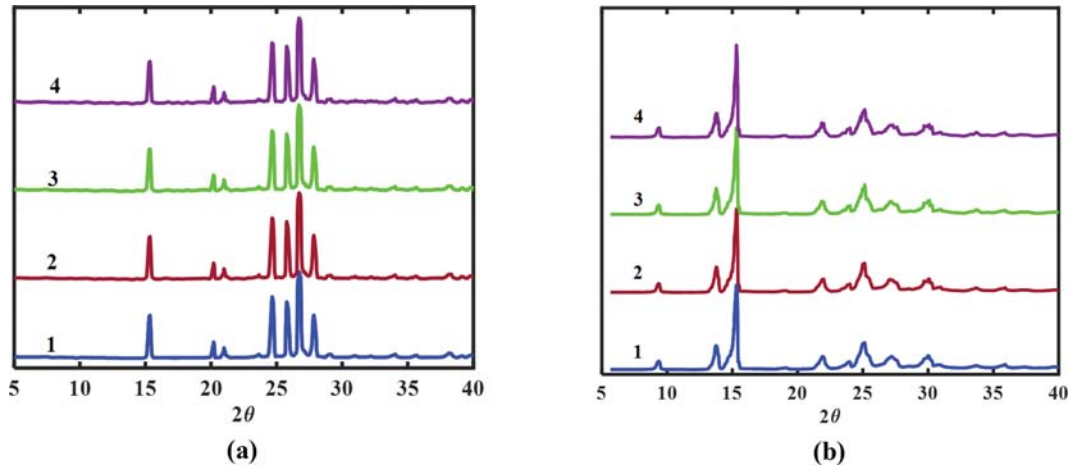

Fig. 4. XRD pattern graph for pharmaceuticals: (a) nicotinic acid, (b) 4-aminobenzoic acid. (1) raw pharmaceutical, (2) pharmaceutical equilibrated with water, (3) pharmaceutical equilibrated with DES (malonic acid+choline chloride) solution, (4) pharmaceutical equilibrated with DES (urea+choline chloride) solution.

more than two-times the solubility of nicotinic acid in deionized water. Furthermore, the effect of DES concentration on the solubility of nicotinic acid is more significant at lower temperatures.

The experimental solubility of 4aminobenzoic acid in pure water and the aqueous solution of DESs (choline chloride+urea and choline chloride+malonic acid) at temperature ranges of 298.15 K to 313.15 K are reported in Tables 3 and 4. A comparison between the results of Tables 3 and 4 shows that the solution of choline chloride+malonic acid DES is more effective on the solubility of 4aminobenzoic acid. The solubility of 4aminobenzoic acid in a solution of 6% DES (choline chloride+malonic acid) by mole is more than 12 times the solubility of 4aminobenzoic acid in deionized water.

By comparing the results of Tables 1 to 4, it becomes clear that both the DESs increased the solubility of 4aminobenzoic acid more than the nicotinic acid solubility.

To evaluate the experiments, the solubility of nicotinic acid and 4aminobenzoic acid in deionized water are compared with literature data [49,56-59]. The comparison is illustrated in Fig. 3. As seen in this figure, the current data are in agreement with literature data.

An X-Ray diffractometer (D8-ADVANCE, Bruker) was used to study the possibility of polymorphisms of the B vitamins in the DESs solutions. The X-ray diffraction (XRD) of the pharmaceuticals equilibrated with the DESs and equilibrated with water, and raw pharmaceuticals are illustrated in Fig. 4. All XRD patterns of a vitamin are the same, which showed that the polymorphisms did not occur in the dissolving processes.

As discussed previously, the van Laar activity coefficient model was used to correlate experimental data. In this regard, the binary parameters between the pharmaceuticals (nicotinic acid or 4aminobenzoic acid) and water were calculated using the solubility of pharmaceuticals in deionized water and were reported in Table 5. The binary parameters between DESs and water were calculated by using the vapor-liquid equilibria available in the literature [51]. These parameters are also reported in Table 5. Finally, the binary

Table 5. Estimated parameters of Eq. (3) for the van Laar model

Component i	Component j	α_{ij} (J·mol^{-1})	β_{ij} (J·mol^{-1}·K^{-1})	α_{ji} (J·mol^{-1})	β_{ji} (J·mol^{-1}·K^{-1})	*AARD*%
Nicotinic acid	Water	0	16.80	0	13.61	1.02
4aminobenzoic acid	Water	0	32.35	0	9.40	0.30
DES (malonic acid+choline chloride)	Water	0	−17.34	0	−4.17	1.85
DES (urea+choline chloride)	Water	0	−8.16	0	−4.86	0.66
DES (malonic acid+choline chloride)	Nicotinic acid	−9,068.79	154.100	−6428.64	27.21	1.32
DES (urea+choline chloride)	Nicotinic acid	1,087.16	524.94	−2790.35	21.54	1.89
DES (malonic acid+choline chloride)	4aminobenzoic acid	−564.47	65.50	−2890.03	13.71	3.54
DES (urea+choline chloride)	4aminobenzoic acid	1,242.72	26.97	−1151.95	12.33	1.96

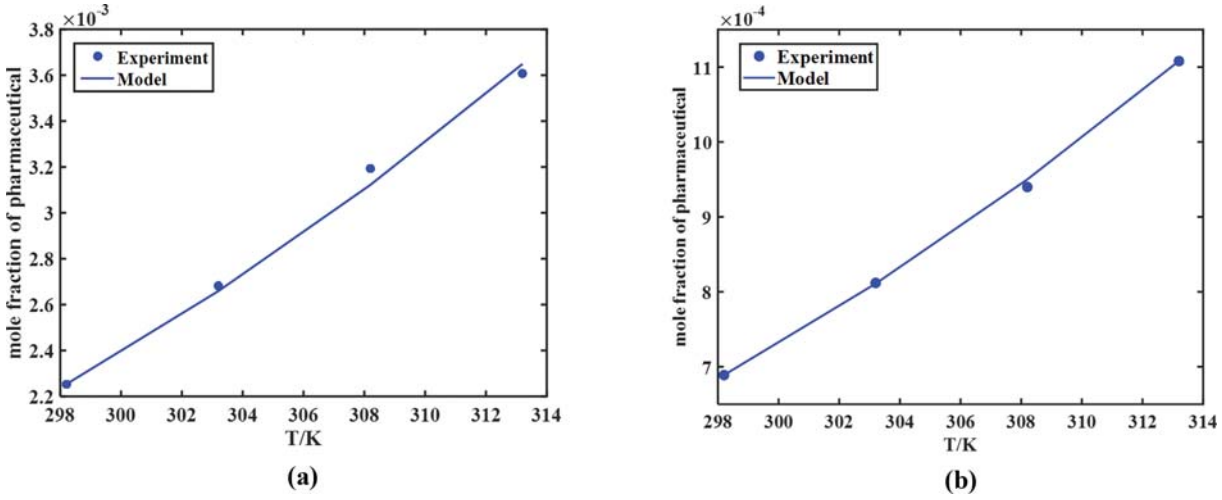

Fig. 5. Comparison between the van Laar model and experimental solubility of pharmaceutical in deionized water: (a) nicotinic acid, (b) 4aminobenzoic acid.

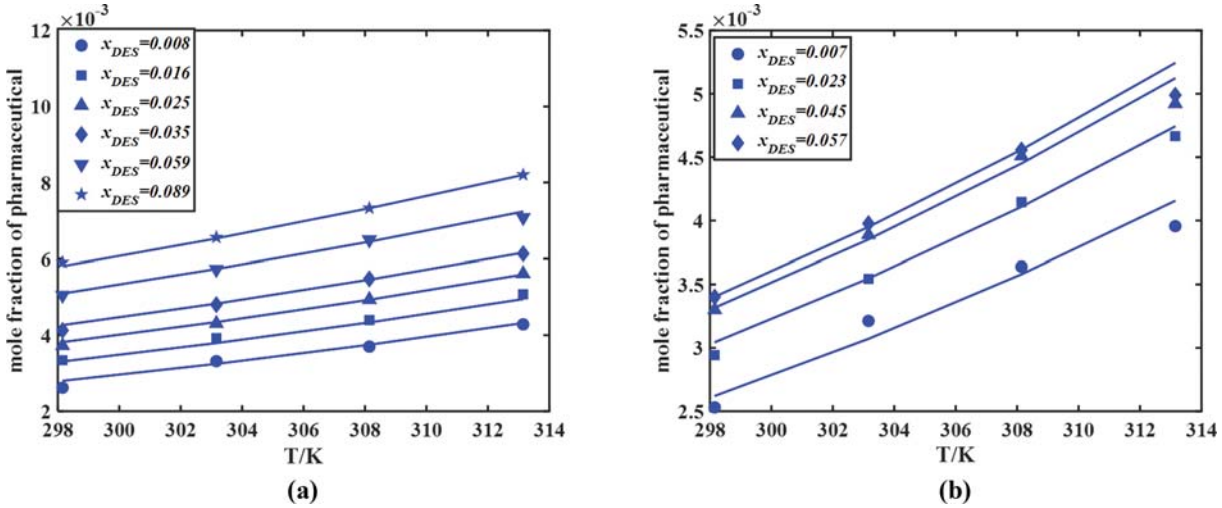

Fig. 6. Comparison between the van Laar model and experimental solubility of nicotinic acid in DES+water system; (a): DES of malonic acid+choline chloride, (b): DES of urea+choline chloride.

parameters between DESs and pharmaceuticals were calculated by using the solubility of pharmaceuticals in solutions of DESs and having the binary interaction parameters of pharmaceuticals-water and DESs-water. Beside the binary parameters, the *AARD* of the model is listed in Table 5. The *AARD* values indicate that the model can accurately estimate the effect of temperature and DES concentration on the solubility of nicotinic acid and 4aminobenzoic acid. Moreover, the results of the van Laar model are compared with the experiments in Figs. 5-7. Fig. 5 illustrates the dependence of the solubility of nicotinic acid and 4aminobenzoic acid in deion-

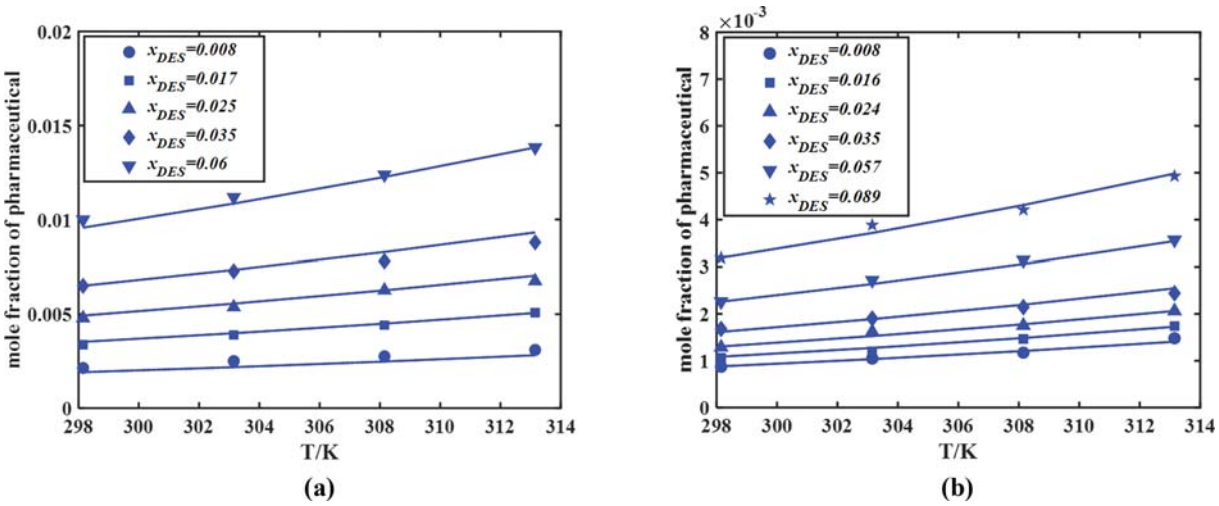

Fig. 7. Comparison between the van Laar model and experimental solubility of 4aminobenzoic acid in DES+water system; (a): DES of malonic acid+choline chloride, (b): DES of urea+choline chloride.

ized water on the temperature. As seen in this figure, the van Laar model is appropriate in estimating the temperature effect on the pharmaceuticals' solubility in deionized water. Fig. 6 compares the results of the van Laar model with experimental solubility of nicotinic acid at different temperatures and DESs concentrations. In addition, the results of the van Laar model are compared with experimental solubility of 4aminobenzoic acid at different temperatures and DESs concentrations in Fig. 7.

The modified Apelblat equation was applied to the experimental solubility of nicotinic acid and 4aminobenzoic acid in the solutions of choline chloride+urea and choline chloride+malonic acid DESs to estimate the effect of temperature on the solubility of the pharmaceuticals. The estimated parameters of the modified Apelblat and the *AARD* between the model results and the experimental data are listed in Tables 6-9. Furthermore, to estimate the effect of the concentration of the DESs on the pharmaceuticals' solubility, the parameters of the modified Apelblat were correlated to a quadratic equation as reported in Table 10. Also, to show the accuracy of the modified Apelblat equation, the model results are compared with the experimental solubility in Figs. 8 and 9.

Table 6. Parameters of modified Apelblat model (Eq. (5)) for nicotinic acid - DES (malonic acid+choline chloride) - water system

x_1 (mole fraction of DES)	Parameters of Apelblat model			*AARD*%
	A	B	C	
0.000	−3.21	−3305.73	1.43	
0.008	−3.81	−2615.65	1.17	
0.016	−4.96	−2298.41	1.22	
0.025	−5.03	−2358.47	1.29	1.69
0.035	−5.68	−2123.22	1.28	
0.059	−9.45	−1490.92	1.61	
0.089	−14.43	−729.77	2.07	

Table 7. Parameters of modified Apelblat model (Eq. (5)) for nicotinic acid - DES (urea+choline chloride) - water system

x_1 (mole fraction of DES)	Parameters of Apelblat model			*AARD*%
	A	B	C	
0.000	−3.21	−3,305.73	1.43	
0.007	−3.94	−2,915.60	1.36	
0.023	−5.02	−2,665.25	1.43	2.31
0.045	−7.77	−2,053.72	1.57	
0.057	−8.67	−1,735.22	1.55	

Table 8. Parameters of modified Apelblat model (Eq. (5)) for 4aminobenzoic acid - DES (malonic acid+choline chloride) - water system

x_1 (mole fraction of DES)	Parameters of Apelblat model			*AARD*%
	A	B	C	
0.000	19.27	−3,713.15	−2.47	
0.008	19.27	−3,377.18	−2.48	
0.017	19.20	−3,145.18	−2.52	1.22
0.025	19.07	−2,978.61	−2.53	
0.035	18.60	−2,699.45	−2.56	
0.060	18.15	−2,429.89	−2.56	

Table 9. Parameters of modified Apelblat model (Eq. (5)) for 4aminobenzoic acid - DES (urea+choline chloride) - water system

x_1 (mole fraction of DES)	Parameters of Apelblat model			*AARD*%
	A	B	C	
0.000	19.27	−3,713.15	−2.47	
0.008	18.79	−3,496.55	−2.48	
0.016	18.44	−3,274.74	−2.51	
0.024	18.15	−3,030.06	−2.56	3.44
0.035	18.02	−2,842.14	−2.61	
0.057	17.93	−2,666.61	−2.63	
0.089	17.78	−2,484.56	−2.65	

Table 10. Parameters of modified Apelblat model as a function of DES mole fraction (Eq. (6))

Pharmaceutical	DES	Parameter A			Parameter B			Parameter C		
		ψ_0	ψ_1	ψ_2	ψ_0	ψ_1	ψ_2	ψ_0	ψ_1	ψ_2
Nicotinic acid	Malonic acid-choline chloride	−3.38	−49.07	−848.63	−3,053.56	32,033.27	−72,132.32	−3,053.56	32,033.27	−72,132.32
Nicotinic acid	Urea-choline chloride	−3.23	−82.59	−268.43	−3,228.77	27,179.34	−20,397.60	−3,228.77	27,179.34	−20,397.60
4aminobenzoic acid	Malonic acid-choline chloride	19.33	−9.87	−174.4	−3,695.0	36,940	−263,800	−2.46	−3.79	35.73
4aminobenzoic acid	Urea-choline chloride	19.13	−42.7	317.1	−3,703	301,500	−187,600	−2.45	−4.97	31.30

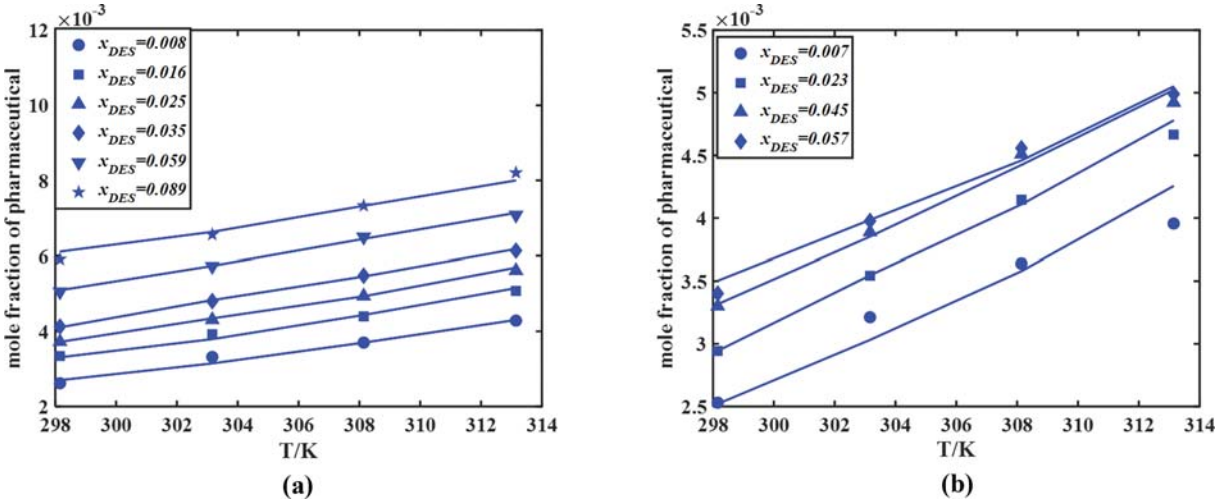

Fig. 8. Comparison between the modified Apelblat model and experimental solubility of nicotinic acid in DES+water system; (a): DES of malonic acid+choline chloride, (b): DES of urea+choline chloride.

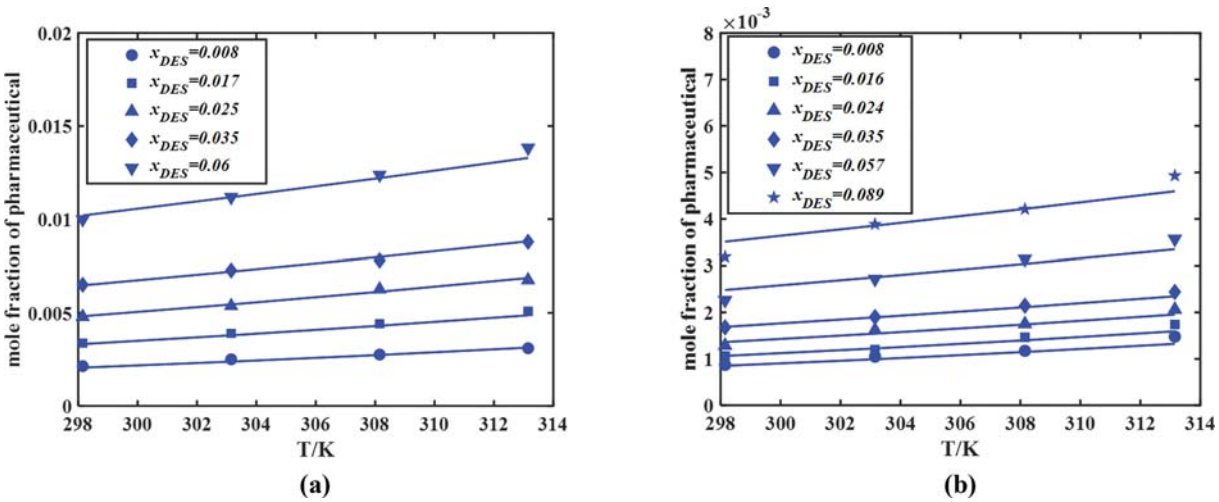

Fig. 9. Comparison between the modified Apelblat model and experimental solubility of 4aminobenzoic acid in DES+water system; (a): DES of malonic acid+choline chloride, (b): DES of urea+choline chloride.

A comparison between the *AARD*s of the van Laar model (reported in Table 5) and the *AARD* of modified Apelblat equation (reported in Tables 6-9) shows that both models have good accuracy in estimating the dependence of the solubility of the pharmaceuticals on the temperature and DESs concentration.

The average enthalpy of dissolution (Δh_d) and enthalpy of mixing (Δh_{mix}) are listed in Table 11. As can be seen in this table, the enthalpies of dissolution are positive and, consequently, the disso-

Table 11. Average molar enthalpy of dissolution (Δh_d) and the mixing enthalpy (Δh_{mix})

Pharmaceutical	DES	Δh_d ($kJ \cdot mol^{-1}$)	Δh_{mix} ($kJ \cdot mol^{-1}$)
Nicotinic acid	Malonic acid-choline chloride	21.4	−3.2
Nicotinic acid	Urea-choline chloride	24.0	−0.6
4aminobenzoic acid	Malonic acid-choline chloride	21.7	−2.3
4aminobenzoic acid	Urea-choline chloride	23.2	−0.8

lution processes are endothermic. In addition, the dissolution of the pharmaceuticals in the aqueous solutions of urea+choline chloride DES is more endothermic due to larger enthalpies of dissolution. However, as can be seen in Table 11, the calculated enthalpies of dissolution are less than the enthalpy of fusion of the pharmaceuticals. Thus, the enthalpies of mixing are obtained to be negative according to Eq. (11). The negative and small values of the mixing enthalpies show that the mixing process as a part of the dissolution process is a low exothermic process.

CONCLUSIONS

The importance of the solubility of pharmaceuticals in water persuaded us to study the effect of NADESs as green cosolvents on the solubility of low-water-soluble pharmaceuticals. In this work, the effect of two NADESs, including choline chloride+urea and choline chloride+malonic acid on the aqueous solubility of nicotinic acid and 4aminobenzoic acid was investigated. Based on the results, DESs can enhance the solubility of the studied pharmaceuticals in water. However, the effect of NADESs on the solubility of 4aminobenzoic acid was more significant. Another finding was that adding NADES is more effective at lower temperatures. Therefore, NADESs are efficient cosolvents for enhancing the solubility of low-water-soluble pharmaceuticals. The solubility data was correlated to two models, including a thermodynamic model combined with the van Laar activity coefficient model and the modified Apelblat equation. Based on the results, both the models can well estimate the effect of temperature and NADES concentration on the aqueous solubility of pharmaceuticals. Furthermore, the results showed that all the dissolution processes were endothermic while the dissolutions in the aqueous solutions of urea+choline chloride DES were more endothermic.

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