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Nicotinamide Solubility in Ethanol + Acetonitrile at Different Temperatures

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In the current study, the solubility of nicotinamide in all fractions (with 0.1 intervals) of the acetonitrile and ethanol mixture was gravimetrically determined. The results showed that maximum solubility was obtained in the ethanol mass fraction of 0.8 ($x_m = 8.52 \times 10^{-2}$) at 313.2 K and the minimum solubility in the pure acetonitrile ($x_m = 7.33 \times 10^{-3}$) at 293.2 K. In the next step, all data were fitted and back-calculated by several cosolvency models. The deviation of the back-calculated values from experimental values (<5.0%) confirmed the applicability of the models for the solubility prediction. Also, density data for saturated systems were determined and fitted to the adopted version of the Jouyban-Acree model, resulting in a mean relative deviation MRD% of 0.7% of the back-calculated data. Furthermore, the thermodynamic behavior of nicotinamide in the studied mixtures was investigated using Gibbs free energy, enthalpy, and entropy at T_{hm}. The inverse Kirkwood-Buff integrals method was used to evaluate the preferential solvation of nicotinamide by acetonitrile in acetonitrile-rich solutions.

Keywords: Nicotinamide, Solubility, Binary systems, Thermodynamic

INTRODUCTION

As an amide derivative of nicotinic acid, Nicotinamide has high aqueous solubility due to its structure (Fig. 1). In the human body, nicotinamide is a basic substrate for many enzymes and one of the precursors in the biosynthesis of nicotinamide adenine dinucleotide, which plays a crucial role in human homeostasis [1]. Nicotinamide, as a systemic therapeutic agent, can be used in the treatment of various diseases, such as diabetes mellitus, stroke, bullous pemphigoid, and psoriasis vulgaris [2]. In pharmaceutical research, nicotinamide has been used in cocrystal studies as a component of several cocrystals synthesized recently [3-4]. The solubility of nicotinamide in various solvents and solvent mixtures is considered an important physicochemical property. As reported in the literature, solubility is an important property in pharmaceutical agents since it has a direct effect on bioavailability [5]. Several methods, including cosolvency, have been developed and introduced for the solubilization of poorly soluble pharmaceuticals [6]. While Mixing organic and inorganic solvents is a reliable method to improve solubility, non-aqueous solvent systems

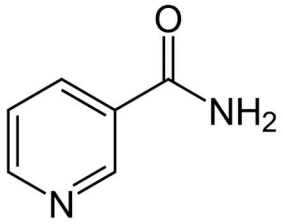

Fig. 1. The chemical structure of nicotinamide.

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are applied in drug crystallization [7]. Experimental solubility measurements, despite being accurate, are time-consuming and costly; as a result, there has been considerable interest in theoretical models. However, using both computational and theoretical models is the ideal choice for predicting drug solubility, yet it requires a large set of different drug solubility data in various solvent mixtures [8]. Thus, it needs a complete database for drug solubility in the mono or binary system.

The solubility of nicotinamide has been previously determined in various solvent systems as in mono-solvents, such as water, methanol, ethanol, 2-propanol, n-butanol, and ethyl acetate at temperatures of 288.15 K to 318.15 K [9], in methanol, 1,4-dioxane, acetonitrile, dimethyl sulfoxide, dimethylformamide, and their aqueous-organic binary mixtures [10], in binary mixtures of methanol + ethanol and methanol + 2-propanol [11], in 1-propanol, isopropanol, ethanol, ethyl acetate, methanol, 1-butanol, methyl acetate, isobutanol, acetone, and butyl acetate [12], in ethanol-water mixtures [13], and in methanol + 2-propanol and methanol + ethanol mixtures [14]. However, determining and expanding the solubility data in other pure and mixed solvents could be helpful and informative in various stages of drug discovery and development, including solvent preparation, purification, extraction, formulation, etc. The solubility of nicotinamide in ethanol + acetonitrile has not been investigated yet; therefore, in the present study, an attempt was made to gravimetrically determine the solubility of nicotinamide in all fractions of acetonitrile (with 0.1 intervals) and ethanol mixtures. Both mentioned solvents are very popular in extractions and high-pressure liquid chromatography [15-16]; thus, measuring solubility in such systems provides valuable information because these solvents are used in crystallization procedures.

The solubility of nicotinamide in ethanol + acetonitrile was determined at 5 different temperatures (293.15-313.15 K), which helped us to detect the impact of temperature on solubility and calculate the thermodynamic properties of dissolution (ΔH°, ΔS°, and ΔG°). Moreover, the data were correlated using cosolvency models. The comparison of experimental and calculated data was used to determine the accuracy of the solubility models. Finally, the preferential solvation of nicotinamide by solvent components was also determined.

EXPERIMENTAL

Materials

Nicotinamide (0.998, Dana Pharmaceutical Company, Iran), ethanol (>0.999, Merck, Germany), and acetonitrile (>0.999, Merck, Germany) were used for the preparation of the mixture.

Solubility Measurement

The equilibrium solubility of nicotinamide in a neat mixture of solvents acetonitrile-ethanol was measured at five temperatures using a shake-flask method [8] as well as a gravimetric method. Solvent systems with mass fractions of acetonitrile in ethanol 0.1 to 0.9 were prepared by weighing the pure solvents using a balance (Model AB204-S, Mettler Toledo, Switzerland) and eventually mixed. Excess nicotinamide was added to solvent systems; then, the solvent systems were shaken in a shaker (Heidolph, Germany) and incubated in an incubator (Nabziran, Iran) for 72 h to achieve the desired temperature until solid-liquid phase equilibrium was obtained and the solutions were saturated. To measure solubility, exactly 1 ml of the solution was taken using a calibrated micropipette and left in a microtube for about 24 h until the complete evaporation of the solvents occurred. The weight of the solid residue was determined by the amount of dissolved nicotinamide in 1 ml of solution. The process was repeated at least three times for each fraction, and the mean data are presented in this article.

X-Ray Powder Diffraction (XRD)

To study the changes in the crystallinity of nicotinamide during equilibration in the studied mixtures, XRD analysis was performed on a PHILIPS PW1730 (Holland) diffractometer. XRD data were obtained using the range of 2θ from 10° to 70° at 30 mA and 40 kV.

Thermodynamic Studies

Gibbs and van't Hoff equations were employed to investigate nicotinamide dissolution in ethanol and acetonitrile. The modified van't Hoff equation used is presented below [17]:

$$\frac{\partial(\ln x)}{\partial(\frac{1}{T}-\frac{1}{T_{hm}})_p} = -\frac{\Delta H}{R}$$ (C: solubility, R: ideal gas constant, and T: temperature) (1)

In the above equation, T_{hm} is the harmonic mean temperature and was computed from Eq. (2).

$$T_{hm} = {n}\Big/{\sum_{i=1}^{n}(\frac{1}{T})} \quad (n\text{: number of studied temperatures}) \tag{2}$$

After plotting ln x against $1/T - 1/T_{hm}$, the slope and the intercept of the curve were used to calculate ΔG° and ΔH°, respectively. In addition, the Gibbs equation was employed to calculate ΔS°calulating.

$$\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ} \tag{3}$$

As free Gibbs energy is dependent on enthalpy and entropy, to calculate the relative enthalpy (ζH) and entropy (ζTS), Eqs. (4) and (5) were used [18].

$$\varsigma_H = (\frac{|\Delta H^{\circ}|}{|\Delta H^{\circ}| + |T\Delta S^{\circ}|}) \tag{4}$$

$$\varsigma_{TS} = \frac{|T\Delta S^{\circ}|}{|\Delta H^{\circ}| + |T\Delta S^{\circ}|} \tag{5}$$

Computational Section

Aside from the experimental solubility measurements for nicotinamide in ethanol + acetonitrile, the generated data were also correlated with some mathematical models to obtain an equation that can be used for the prediction of solubility. The models used included the combined nearly ideal binary solvent (CNIBS)/Redlich-Kister model (Eq. (6)), Jouyban-Acree model (Eq. (7)), Jouyban-Acree-van't Hoff model (Eq. (8)), as linear equations, and the modified Wilson equation (Eq. (9)), as a non-linear equation. Eqs. ((6)-(9)) are shown below:

$$\ln x_m = w_1 \ln x_1 + w_2 \ln x_2 + w_1 w_2 \sum_{i=0}^{2} S_i (w_1 - w_2)^i \tag{6}$$

$$\ln x_{m,T} = w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + \frac{w_1 w_2}{T} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \tag{7}$$

$$\ln x_{m,T} = w_1 \left(A_1 + \frac{B_1}{T}\right) + w_2 \left(A_2 + \frac{B_2}{T}\right) + \frac{w_1 w_2}{T} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \tag{8}$$

$$-\ln x_m = 1 - \frac{w_1(1 + \ln x_1)}{w_1 + w_2 \lambda_{12}} - \frac{w_2(1 + \ln x_2)}{w_1 \lambda_{21} + w_2} \tag{9}$$

where $x_1$and x_2 are solubilities in mono-solvents 1 and 2, respectively, x_m is solubility in mixtures, and w_1 and w_2 are mass fractions of mono-solvents without solute.

In order to check the ability of the investigated models to predict solubility, the deviation of each set of back-calculated data obtained by the trained models was calculated from the data obtained in the present study. Equation (10) represents the percentage of this deviation, *i.e.* mean relative deviation (*MRD*).

$$\%MRD = \frac{100}{N} \sum (\frac{|Calculated\ value - Observed\ value|}{Observed\ value}) \quad (N\text{: number of data points}) \tag{10}$$

RESULTS AND DISCUSSION

XRD Analysis

Using powder XRD data at ambient temperature and pressure, XRD data of nicotinamide residues in neat solvents were obtained and their patterns are shown in Fig. 2. Data analysis showed that no new peaks appeared, meaning that crystalline nicotinamide did not undergo a polymorphic transformation in the dissolution process. Nicotinamide possess several polymorphic forms, including: α, β, γ, δ, ε, ζ, η, θ, and ι forms [19]. Form α is the most stable polymorph, and we used this polymorph to investigate the solubility of nicotinamide in ethanol + acetonitrile mixtures.

Solubility for Nicotinamide and Data Modeling

The data related to the solubility of nicotinamide in ethanol + acetonitrile in the defined temperatures as well as the standard deviation of measurements are summarized in Table 1. The solubility of nicotinamide was found to be dependent on the temperature and increased with the increase of nicotinamide in the range of the investigated temperatures (293.2-313.2 K). Furthermore, the results showed that the solubility of nicotinamide depended on mixture composition and increased with the increase in the ethanol mass fraction in ethanol + acetonitrile mixtures. Moreover, maximum solubility was observed in the ethanol mass fraction of 0.8.

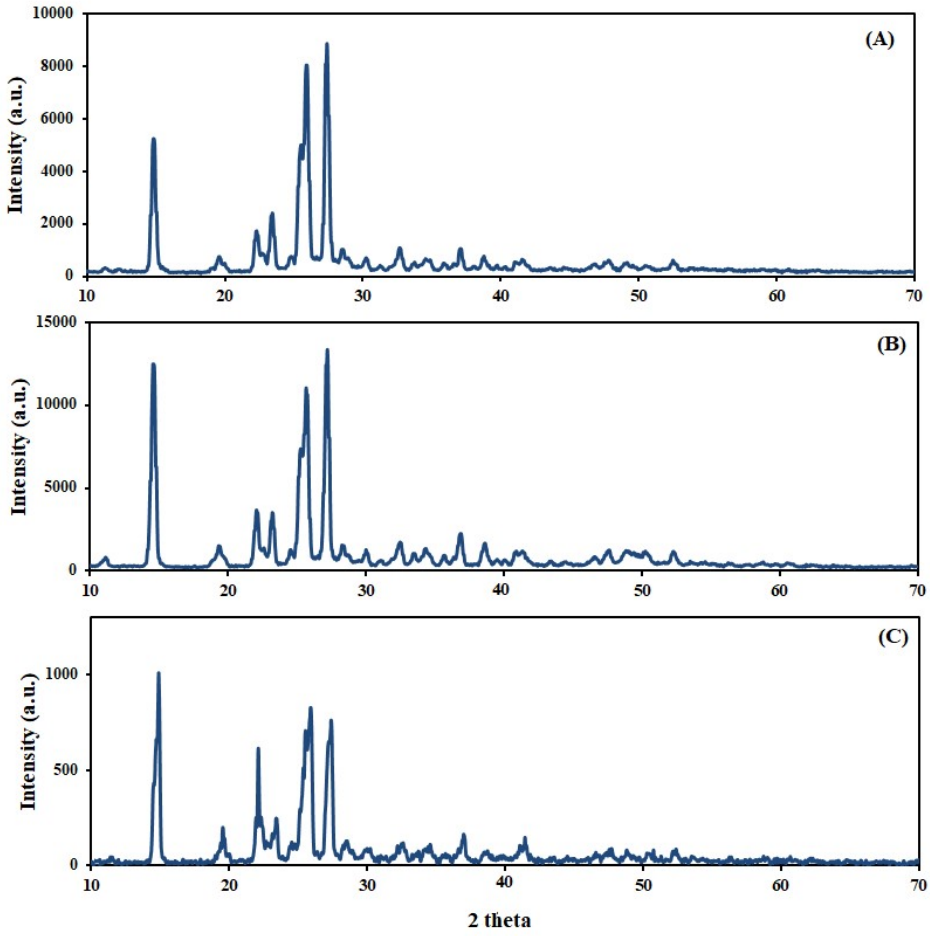

Fig. 2. XRD patterns of the unprocessed nicotinamide (A) and equilibrated nicotinamide in ethanol (B), and acetonitrile (C).

Table 1. Experimental Results (x_m) Related to the Solubility of Nicotinamide in the Mixtures of Ethanol + Acetonitrile

w_1[a]	T (K)				
	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00	$7.33 (\pm0.09) \times 10^{-3}$	$9.62 (\pm0.35) \times 10^{-3}$	$1.12 (\pm0.08) \times 10^{-2}$	$1.27 (\pm0.07) \times 10^{-2}$	$1.39 (\pm0.04) \times 10^{-2}$
0.10	$1.18 (\pm0.03) \times 10^{-2}$	$1.52 (\pm0.03) \times 10^{-2}$	$1.67 (\pm0.12) \times 10^{-2}$	$1.84 (\pm0.05) \times 10^{-2}$	$2.21 (\pm0.02) \times 10^{-2}$
0.20	$1.87 (\pm0.05) \times 10^{-2}$	$2.07 (\pm0.07) \times 10^{-2}$	$2.34 (\pm0.13) \times 10^{-2}$	$2.81 (\pm0.19) \times 10^{-2}$	$3.09 (\pm0.13) \times 10^{-2}$
0.30	$2.59 (\pm0.01) \times 10^{-2}$	$2.92 (\pm0.34) \times 10^{-2}$	$3.27 (\pm0.09) \times 10^{-2}$	$3.69 (\pm0.04) \times 10^{-2}$	$4.31 (\pm0.17) \times 10^{-2}$
0.40	$3.45 (\pm0.06) \times 10^{-2}$	$3.87 (\pm0.14) \times 10^{-2}$	$4.02 (\pm0.26) \times 10^{-2}$	$4.76 (\pm0.07) \times 10^{-2}$	$5.27 (\pm0.22) \times 10^{-2}$
0.50	$3.94 (\pm0.04) \times 10^{-2}$	$4.57 (\pm0.19) \times 10^{-2}$	$4.84 (\pm0.14) \times 10^{-2}$	$5.75 (\pm0.23) \times 10^{-2}$	$5.93 (\pm0.08) \times 10^{-2}$
0.60	$4.69 (\pm0.17) \times 10^{-2}$	$5.05 (\pm0.34) \times 10^{-2}$	$5.51 (\pm0.12) \times 10^{-2}$	$6.44 (\pm0.13) \times 10^{-2}$	$7.62 (\pm0.17) \times 10^{-2}$
0.70	$4.95 (\pm0.32) \times 10^{-2}$	$5.52 (\pm0.38) \times 10^{-2}$	$5.84 (\pm0.20) \times 10^{-2}$	$6.96 (\pm0.19) \times 10^{-2}$	$8.19 (\pm0.31) \times 10^{-2}$
0.80	$5.05 (\pm0.16) \times 10^{-2}$	$5.58 (\pm0.37) \times 10^{-2}$	$6.24 (\pm0.22) \times 10^{-2}$	$7.19 (\pm0.19) \times 10^{-2}$	$8.52 (\pm0.08) \times 10^{-2}$
0.90	$5.09 (\pm0.04) \times 10^{-2}$	$5.57 (\pm0.08) \times 10^{-2}$	$5.97 (\pm0.25) \times 10^{-2}$	$7.05 (\pm0.07) \times 10^{-2}$	$8.08 (\pm0.15) \times 10^{-2}$
1.00	$4.02 (\pm0.04) \times 10^{-2}$	$4.62 (\pm0.05) \times 10^{-2}$	$5.70 (\pm0.04) \times 10^{-2}$	$6.06 (\pm0.04) \times 10^{-2}$	$7.01 (\pm0.05) \times 10^{-2}$

Note. [a]w_1 = The mass fraction of ethanol in ethanol + acetonitrile binary mixtures.

Nicotinamide showed minimum solubility in the minimum studied temperature in pure acetonitrile, compared to pure ethanol and its mixtures with acetonitrile, which can be attributed to the high polarity of ethanol for a relatively polar drug with a log of P = -0.45 [20]. Furthermore, the solubility of nicotinamide in neat ethanol (x = 4.62 × 10^{-3}) and acetonitrile (x = 9.62 × 10^{-3}) measured at 298.2 K showed relatively good consistency with the values reported in the literature (x = 4.44 × 10^{-3} for ethanol [9,21] and x = 8.6 × 10^{-3} for acetonitrile [10]). Figure 3 shows a comparison of the results of this study with those reported in the literature. The solubility of nicotinamide in neat ethanol seemed to be consistent with the values reported in previous studies. However, in the case of acetonitrile, a slight difference was noticed regarding the effect of temperature when the results were compared to those in the literature. The variations in the solubility as reported in the literature were considerably higher than that obtained in the present study. Possible reasons for this discrepancy include the following: (i) variations in the equilibration time of experiments, (ii) the weight of the dispersed solid investigated by Kawakami *et al.* [22], and (iii) the impact of particle size, crystallinity, and other molecular properties of the solute investigated by Baka *et al.* [23]. In an attempt to explain these variations, Kishi and Hashimoto [24] investigated the solubility data for anthracene and fluoranthene recorded by 17 different laboratories employing a standard technique provided by the Japanese Ministry of the Environment. The results showed that even when all variables were kept constant, inter-laboratory differences could still have a significant effect on the results. Furthermore, they reported that the mean solubility values of anthracene and fluoranthene varied between 0.17 and 0.36 log units and that the mean percentage deviation was 51%.

No data have been reported in the literature regarding the mixture of ethanol and acetonitrile to compare the solubility data. In fact, the contribution of the present study is to provide experimental data concerning the solubility of nicotinamide in the mixtures of ethanol and acetonitrile.

To obtain experimental solubility data, several models, including CNIBS/Redlich-Kister model, Jouyban-Acree model, Jouyban-Acree-van't Hoff model, and the modified Wilson model were employed. The obtained data were incorporated into equations. Then, after model training, the

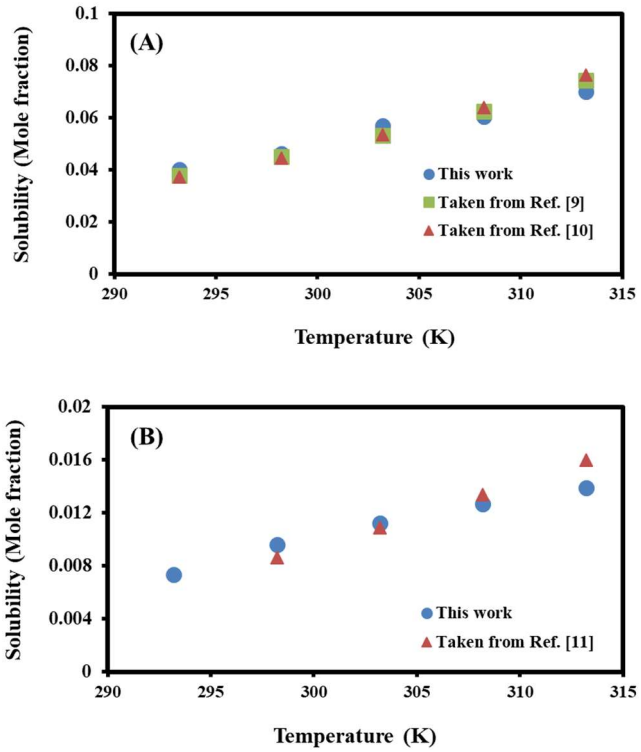

Fig. 3. A comparison of the results of this study versus those reported in the literature regarding the solubility of nicotinamide in neat ethanol (A) and acetonitrile (B).

error percentage of the back-calculated values compared to the main values was calculated and used as a scale for the investigation of the ability of the model to predict solubility. The trained equations for each model are reported in Tables 2-4, and the back-calculated values for nicotinamide in each fraction are given in Table 1S. CNIBS/Redlich-Kister is the first version of the Jouyban-Acree model, and, as can be seen in Eq. (6), in this model, solubility is defined as a function of the composition of the mixtures. Thus, it needs one model for each temperature. The model coefficients, along with the MRD%, are presented in Table 2.

The CNIBS/Redlich-Kister model is a linear model that correlates/predicts data in isothermal conditions. The modified Wilson model is a non-linear model for solubility prediction with the same properties as those of the CNIBS/Redlich-Kister model. Similar to the CNIBS/Redlich-Kister model, the modified Wilson model needs five individual models for the five investigated

temperatures. The model coefficients, along with the MRD%, are given in Table 3.

Unlike the above models, Jouyban-Acree and Jouyban-Acree-van't Hoff models are dependent on solvent composition and temperature. Therefore, it performs data regression in one step and presents one equation for all temperatures and mixtures. The model coefficients, along with the MRD%, are shown in Table 4.

The models utilized in the present study had significant features, including the regression of all data in one step and the use of one equation for the prediction of solubility, which, in turn, allow them to be considered useful cosolvency models. Furthermore, another advantage of the above-mentioned models is that they offer the possibility of data training with the minimum data and the use of the treated data for prediction. To examine the predictive ability of Eq. (8), solubility data in neat solvents at the minimum and maximum investigated temperatures as well as solutions with w_1 of 0.7, 0.5, and 0.3 at 298.2 K were employed to train the model. Then, the MRD% for the predicted values were obtained as 5.6%, 4.9%, 5.0%, 2.8%, and 3.2% at 293.2, 298.2, 303.2, 308.2, and 313.2 K, respectively. The overall MRD% was 4.3%.

In addition to the solubility, the density measured for the saturated mixtures (Table 5) was fitted to the adopted version of the Jouyban-Acree equation. The obtained equation after training the model with the data from Table 5 is presented below:

$$\ln\rho_{m,T} = w_1\ln\rho_{1,T} + w_2\ln\rho_{2,T} + 20.236\frac{w_1.w_2}{T} + 27.707\frac{w_1.w_2(w_1-w_2)}{T} + 23.232\frac{w_1.w_2(w_1-w_2)^2}{T} \quad (11)$$

where $\rho_{m,T}$, $\rho_{1,T}$, and $\rho_{2,T}$ are the density of nicotinamide in saturated mixed and mono solvents at the desired T. The MRD% for the back-calculated data was 0.7%, showing the ability of the Jouyban-Acree model to predict density at various temperatures.

Table 2. Parameters Related to the CNIBS/Redlich-Kister Model for Nicotinamide in Ethanol + Acetonitrile

T (K)	S_0	S_1	S_2	MRD%
293.2	3.525	0[a]	0[a]	2.2
298.2	3.094	0[a]	0[a]	1.8
303.2	2.584	-0.154	0[a]	1.0
308.2	3.128	-0.298	0.772	0.8
313.2	2.953	0[a]	0[a]	2.8
Overall				1.7

Note. [a] = Not statistically significant ($p > 0.05$).

Table 3. Parameters of the Modified Wilson Model at Different Temperatures and the MRD% for the solubility of Nicotinamide in Ethanol + Acetonitrile

T (K)	λ_{12}	λ_{21}	MRD%
293.2	2.038	1.672	2.2
298.2	2.045	1.578	1.8
303.2	1.662	1.612	1.2
308.2	1.885	1.853	1.2
313.2	2.316	1.645	2.1
Overall			1.7

Table 4. Parameters of the Jouyban-Acree and Jouyban-Acree-van't Hoff Models for the Solubility of Nicotinamide in Ethanol + Acetonitrile

	Jouyban-Acree		Jouyban-Acree-van't Hoff	
Ethanol + acetonitrile	J_0	933.439	A_1	5.472
	J_1	0[a]	B_1	-2543.937
	J_2	0[a]	A_2	4.088
			B_2	2622.064
			J_0	933.105
			J_1	0[a]
			J_2	0[a]
MRD%	4.3		3.2	

Note. [a] = Not statistically significant ($p > 0.05$).

Table 5. The Density (g cm^{-3}) of Nicotinamide Saturated Solutions in Ethanol + Acetonitrile

w_1	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00	0.746 ± 0.007	0.739 ± 0.000	0.737 ± 0.004	0.737 ± 0.008	0.737 ± 0.017
0.10	0.753 ± 0.004	0.748 ± 0.020	0.740 ± 0.009	0.740 ± 0.010	0.740 ± 0.010
0.20	0.765 ± 0.006	0.758 ± 0.019	0.744 ± 0.002	0.744 ± 0.016	0.751 ± 0.012
0.30	0.775 ± 0.005	0.762 ± 0.007	0.759 ± 0.001	0.748 ± 0.008	0.741 ± 0.005
0.40	0.779 ± 0.004	0.777 ± 0.006	0.760 ± 0.010	0.749 ± 0.012	0.748 ± 0.007
0.50	0.790 ± 0.009	0.779 ± 0.024	0.774 ± 0.012	0.774 ± 0.011	0.772 ± 0.019
0.60	0.800 ± 0.014	0.773 ± 0.015	0.773 ± 0.006	0.766 ± 0.016	0.763 ± 0.010
0.70	0.806 ± 0.002	0.776 ± 0.012	0.775 ± 0.019	0.771 ± 0.019	0.772 ± 0.018
0.80	0.801 ± 0.005	0.802 ± 0.010	0.803 ± 0.060	0.785 ± 0.017	0.778 ± 0.036
0.90	0.792 ± 0.009	0.789 ± 0.025	0.789 ± 0.012	0.785 ± 0.010	0.785 ± 0.006
1.00	0.786 ± 0.003	0.786 ± 0.007	0.774 ± 0.018	0.774 ± 0.071	0.772 ± 0.055

Furthermore, the density plot as a function of temperature in the solute-free [25] and -saturated solvent mixture is shown in Fig. 1S. As can be seen, the density-temperature plot for saturated solutions is irregular. This can be attributed to the fact that in solute-free solutions, volume increases as temperature increases, leading to a decreasing plot. However, in solute-saturated solutions, there are two conflicting phenomena: An increase in the mass and volume of the solution after solute dissolution and an increase in the volume following a rise in the temperature. These two phenomena can disrupt the gradual reduction in the density following the decrease in temperature. It is critical to note that nicotinamide, compared to a poorly soluble drug, has good solubility in solute-saturated mixtures, which, in turn, can significantly affect the variation in the mass and volume (density) of mixtures.

Thermodynamic Properties

ΔG°, ΔH°, and ΔS°, which are referred to as the apparent thermodynamic parameters, were calculated by plotting the ln$x$ *vs*. the $1/T$ - $1/T_m$ for each mixture and using their slopes and intercepts. The resultant plot is illustrated in Fig. 4. As can be seen in Fig. 4, all mixtures showed a linear trend with a negative slope, showing that solubility increased with the increase in temperature. The calculated thermodynamic parameters are given in Table 6. The parameters for all solutions were positive, which shows that the solubility of nicotinamide was an endothermic and entropy-driven procedure in ethanol + acetonitrile. ΔG° values ranged from 6.93 to 11.50 J K^{-1} mol^{-1}, with the lowest value being observed in w_1 = 0.8, which indicates the feasibility of dissolution in the mixture with high solubility. To investigate enthalpy/entropy compensation, the relative contributions of enthalpy (ζ_H) and entropy (ζ_{TS}) were calculated and are summarized in Table 6, which presents the results of enthalpy in the dissolution process of nicotinamide.

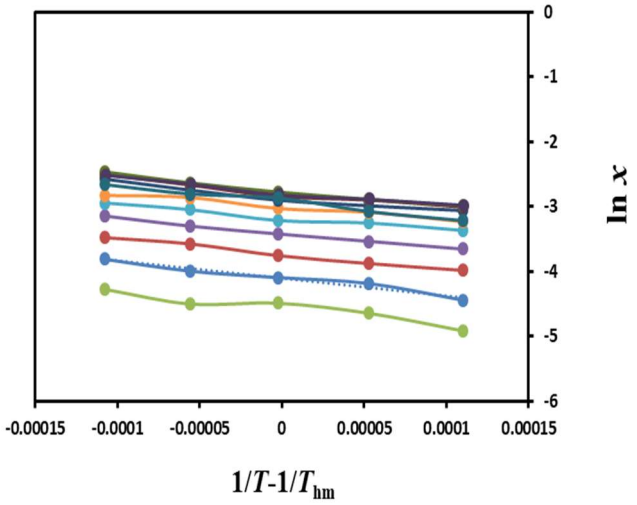

Fig. 4. Van't Hoff plot of the solubility of nicotinamide in the investigated mixed solutions.

Table 6. Thermodynamic Properties of Nicotinamide Dissolution in Ethanol and Acetonitrile at T_{hm}

w_1	$\Delta G°$ (kJ mol^{-1})	$\Delta H°$ (kJ mol^{-1})	$\Delta S°$ (J K^{-1} mol^{-1})	$T\Delta S°$ (kJ mol^{-1})	ζ_H	ζ_{TS}
0.00	11.50	21.80	33.98	10.30	0.679	0.321
0.10	10.34	22.20	39.13	11.86	0.652	0.348
0.20	9.41	20.01	35.01	10.61	0.654	0.346
0.30	8.59	19.14	34.81	10.55	0.645	0.355
0.40	7.97	16.06	26.69	8.089	0.665	0.335
0.50	7.57	15.96	27.68	8.387	0.656	0.344
0.60	7.19	18.46	37.20	11.27	0.621	0.379
0.70	7.01	18.86	39.11	11.85	0.614	0.386
0.80	6.93	19.85	42.65	12.92	0.606	0.394
0.90	6.98	17.70	35.37	10.72	0.623	0.377
1.00	7.37	21.15	45.49	13.78	0.605	0.395

To investigate the enthalpy- or entropy-driven process responsible for the solubility of nicotinamide, ΔH° *vs*. ΔG° was plotted and the result is shown in Fig. 5. These data are provided with and without the polygonal line. As can be seen, a polygonal line with two segments can fit the data, which indicates that enthalpy- and entropy-driven processes were responsible for mixtures of $0 \leq w_1 \leq 0.5$ (positive slope) and mixtures of $0.5 \leq w_1 \leq 1.0$ (negative slope), responsibly.

Preferential Solvation Parameters

Moreover, the preferential solvation parameters of nicotinamide (component 3) by ethanol (component 1) in ethanol (1) + acetonitrile (2) were calculated using Eq. (12) [26-28]:

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \qquad (12)$$

where $x_{1,3}^{L}$ is the local mole fraction of ethanol (1) in a molecular medium of nicotinamide (3) and x_1 is the bulk mole fraction of ethanol (1) in the initial non-aqueous co-solvent mixture without nicotinamide (3). If $\delta x_{1,3} > 0$, nicotinamide was preferentially solvated using ethanol (1), and if $\delta x_{1,3} < 0$, nicotinamide was preferentially solvated using acetonitrile (2). Values of $\delta x_{1,3}$ were derived using the inverse Kirkwood-Buff integrals (IKBI) for each mixture and the following classical thermodynamic properties:

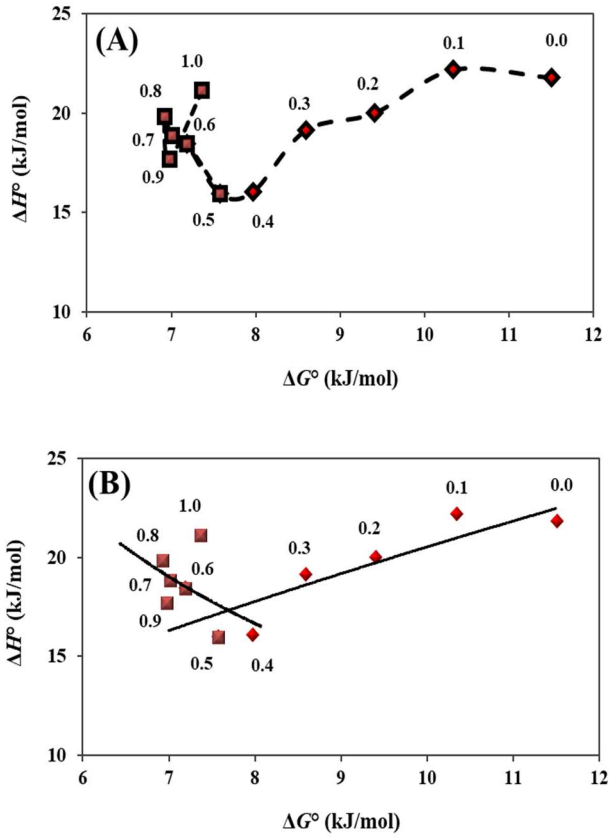

Fig. 5. Enthalpy-entropy compensation for nicotinamide in ethanol + acetonitrile at T_{hm}. The points in the figure show the mass fraction of nicotinamide in binary systems in the absence of nicotinamide.

$$\delta x_{1,3} = \frac{x_1 x_2 \left(G_{1,3} - G_{2,3}\right)}{x_1 G_{1,3} + x_2 G_{2,3} + V_{\text{cor}}} \tag{13}$$

and

$$G_{1,3} = RT\kappa_T - \overline{V}_3 + x_2 \overline{V}_2 D / Q \tag{14}$$

$$G_{2,3} = RT\kappa_T - \overline{V}_3 + x_1 \overline{V}_1 D / Q \tag{15}$$

$$V_{\text{cor}} = 2522.5 \cdot \left\{ r_3 + 0.1363 \cdot \left(x_{1,3}^L \overline{V}_1 + x_{2,3}^L \overline{V}_2 \right)^{1/3} - 0.085 \right\}^3 \tag{16}$$

In the above equations, κ_T is the isothermal compressibility of ethanol (1) + acetonitrile (2), calculated with the assumption that it was an additional feature from the solvent composition derived from κ_T for mono-solvents). $\overline{V}_1$ and $\overline{V}_2$ are partial molar volumes of ethanol and acetonitrile, respectively. $\overline{V}_3$ is a partial molar volume of nicotinamide in solutions. Parameter D is the first derivative of standard molar Gibbs energies of nicotinamide transfer (3) from pure acetonitrile (2) to ethanol (1) + acetonitrile (2) regarding ethanol fraction in mixtures (Eq. (17)). The Q entered the second derivative of excess molar Gibbs energy of ethanol + acetonitrile (G_{1+2}^{Exc}) mixture regarding the acetonitrile fraction in mixtures (Eq. (18)). V_{cor} is the correlation volume, and r_3 is the molecular radius of nicotinamide, which is commonly obtained by Eq. (19), in which N_{Av} is Avogadro's number.

$$D = \left(\frac{\partial \Delta_{\text{tr}} G^{\text{o}}_{3,2\to 1+2}}{\partial x_1} \right)_{T,p} \tag{17}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G_{1+2}^{Exc}}{\partial x_2^2} \right)_{T,p} \tag{18}$$

$$r_3 = \left(\frac{3 \cdot 10^{21} \overline{V}_3}{4\pi N_{\text{Av}}} \right)^{1/3} \tag{19}$$

Definitive V_{cor} required iteration owing to its dependency on local mole fractions of ethanol and acetonitrile surrounding nicotinamide molecules. The iteration was performed by replacing $\delta x_{1,3}$ and V_{cor} values in Eqs. (12), (13), and (16) to recalculate $x_{1,3}^L$ until an invariant value of V_{cor} was obtained.

Figure 6 demonstrates the Gibbs energy of transfer of nicotinamide (3) from pure acetonitrile (2) to ethanol (1) + acetonitrile (2) at 293.2 K. The values were calculated using the mole fraction solubility data presented in Table 1 and the following equations:

$$\Delta_{\text{tr}} G^{\text{o}}_{3,2\to 1+2} = RT \ln \left(\frac{x_{3,2}}{x_{3,1+2}} \right) \tag{20}$$

$\Delta_{\text{tr}} G^{\text{o}}_{3,2\to 1+2}$ values were fitted to the polynomial shown in Eq. (21), with $r^2 = 0.9984$.

$$\Delta_{\text{tr}} G^{\text{o}}_{3,2\to 1+2} = 0.04 - 16.20 x_1 + 22.36 x_1^2 - 18.42 x_1^3 + 8.03 x_1^4 \tag{21}$$

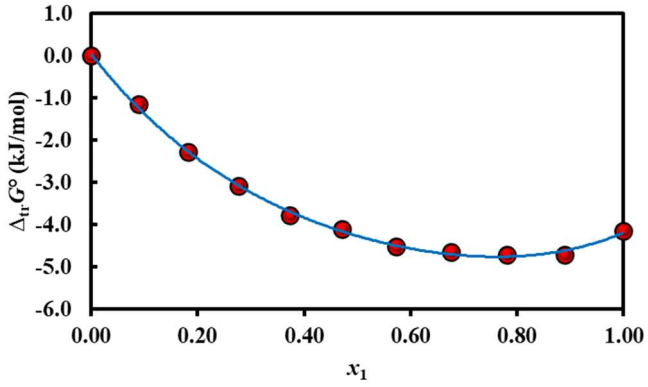

Fig. 6. The Gibbs energy of transfer of nicotinamide (3) from neat acetonitrile (2) to ethanol (1) + acetonitrile (2) mixtures at T = 293.2 K.

The D values reported in Table 7 were calculated using the first derivative of Eq. (21) based on the co-solvent mixture varying in $x_1 = 0.05$. Since this is the first time that the IKBI method is used to calculate the preferential solvation in ethanol (1) + acetonitrile (2) at 293.2 K, the respective Q, $RT\kappa_T$, $\overline{V}_1$, and $\overline{V}_2$ were calculated as shown below.

Table 7. Some Properties Associated with the Preferential Solvation of Nicotinamide (3) in Ethanol (1) + Acetonitrile (2) Mixtures at T = 293.2 K

x_1 [a]	D (kJ mol^{-1})	Q (kJ mol^{-1})	$RT\cdot\kappa_T$ (kJ mol^{-1})	$\overline{V}_1$ (cm^3 mol^{-1})	$\overline{V}_2$ (cm^3 mol^{-1})	$G_{1,3}$ (cm^3 mol^{-1})	$G_{2,3}$ (cm^3 mol^{-1})	V_{cor} (cm^3 mol^{-1})	100 $\delta x_{1,3}$
0.00	-16.20	2.437	2.608	58.90	52.75	-435.2	-84.6	1073	0.00
0.05	-14.10	2.020	2.618	58.78	52.75	-434.4	-105.1	1075	-1.64
0.10	-12.25	1.701	2.628	58.69	52.76	-426.5	-126.9	1078	-2.93
0.15	-10.63	1.463	2.638	58.61	52.77	-410.5	-148.5	1082	-3.74
0.20	-9.21	1.287	2.648	58.54	52.78	-386.8	-168.4	1086	-4.00
0.25	-7.97	1.159	2.659	58.49	52.80	-356.9	-185.1	1090	-3.74
0.30	-6.89	1.068	2.669	58.46	52.81	-323.0	-197.7	1094	-3.06
0.35	-5.94	1.003	2.679	58.43	52.82	-287.8	-205.6	1099	-2.16
0.40	-5.10	0.958	2.689	58.42	52.83	-253.3	-208.9	1104	-1.21
0.45	-4.34	0.926	2.699	58.42	52.83	-220.7	-207.7	1108	-0.36
0.50	-3.64	0.906	2.709	58.42	52.83	-190.7	-201.9	1112	0.31
0.55	-2.98	0.896	2.719	58.43	52.82	-163.4	-191.2	1116	0.73
0.60	-2.32	0.900	2.729	58.45	52.80	-139.0	-175.0	1120	0.89
0.65	-1.66	0.922	2.740	58.46	52.77	-117.7	-152.9	1124	0.80
0.70	-0.96	0.968	2.750	58.48	52.72	-100.1	-125.0	1128	0.51
0.75	-0.19	1.047	2.760	58.51	52.67	-86.9	-92.6	1132	0.10
0.80	0.65	1.172	2.770	58.53	52.60	-78.6	-58.3	1135	-0.31
0.85	1.61	1.356	2.780	58.54	52.51	-75.1	-25.3	1139	-0.59
0.90	2.70	1.615	2.790	58.56	52.41	-75.7	3.7	1143	-0.66
0.95	3.95	1.969	2.800	58.57	52.28	-79.2	27.2	1147	-0.47
1.00	5.38	2.437	2.810	58.57	52.14	-84.4	44.8	1152	0.00

Note. [a]x_1 = The mole fraction of ethanol (1) in the ethanol (1) + acetonitrile (2) mixtures without nicotinamide (3).

As mentioned above, molar excess Gibbs energies (G_{1+2}^{Exc}/J mol^{-1}) of the mixture were needed to calculate the Q. Marcus [29] reported the equation of these amounts at 293.2 K, which was fitted to Eq. (22).

$$G_{1+2}^{Exc} = 3820x_2 - 5338x_2^2 + 2834x_2^3 - 1317x_2^4 \quad (22)$$

ethanol and acetonitrile, respectively [30].

$$\kappa_{T,1+2} = \sum_{i=1}^{2} x_i \kappa_{T,i}^{o} \quad (23)$$

Moreover, partial molar volumes of ethanol and acetonitrile (Table 7) were calculated using Eqs. (24) and (25) from the density (ρ) of the non-aqueous solutions reported by Tahery *et al.* at 293.2 K [31]. In the models, V is the molar volume of the mixed solvents and was obtained as $V = (x_1M_1 + x_2M_2)/\rho$, where M_1 and M_2 are 46.07 and 41.05 g mol^{-1} for ethanol and acetonitrile, respectively [23].

$$\overline{V}_1 = V + x_2 \frac{dV}{dx_1} \quad (24)$$

$$\overline{V}_2 = V - x_1 \frac{dV}{dx_1} \quad (25)$$

Since $\overline{V}_3$ values were not accessible for nicotinamide in the above-mentioned non-aqueous systems, nicotinamide was considered a pure compound, and the $\overline{V}_3$ values were

calculated using a density (81.40 g cm^{-3}) and molar mass (122.13 g mol^{-1}), *i.e.* 87.23 cm^3 mol^{-1} [32]. $G_{1,3}$ and $G_{2,3}$ values reported in Table 7 were negative in all cases, except for $G_{2,3}$ in $0.90 \leq x_1 \leq 1.00$, suggesting that nicotinamide had a tendency to ethanol and acetonitrile. The molecular radius (r_3) of nicotinamide was obtained as 0.326 nm. In addition, the preferential solvation parameters for nicotinamide (3) by ethanol (1), $\delta x_{1,3}$, are reported in Table 7. Figure 7 shows that $\delta x_{1,3}$ values varied non-linearly with ethanol (1) mole fraction. Thus, adding ethanol (1) to acetonitrile (2) resulted in negative $\delta x_{1,3}$ values for nicotinamide (3) from pure acetonitrile to the mixed solvent with x_1 = 0.48. The maximum negative value was observed in the mixed solvent with x_1 = 0.20 and $\delta x_{1,3}$ = -4.00 × 10^{-2}, showing the preferential solvation of nicotinamide by acetonitrile in this composition interval, probably due to some polarizability effects.

In mixtures within the range of $0.48 < x_1 < 0.76$, $\delta x_{1,3}$ values were positive, showing the preferential solvation of nicotinamide using ethanol. On other hand, in mixed solvents of $0.76 < x_1 < 1.00$, $\delta x_{1,3}$ values were negative again, showing the preferential solvation of nicotinamide using acetonitrile. However, in mixed intervals of $0.48 < x_1 < 1.00$, the magnitudes of $\delta x_{1,3}$ were lower than 1.00 × 10^{-2}, which could be the result of uncertainty propagation in IKBI calculations rather than the effects of preferential solvation [33-34].

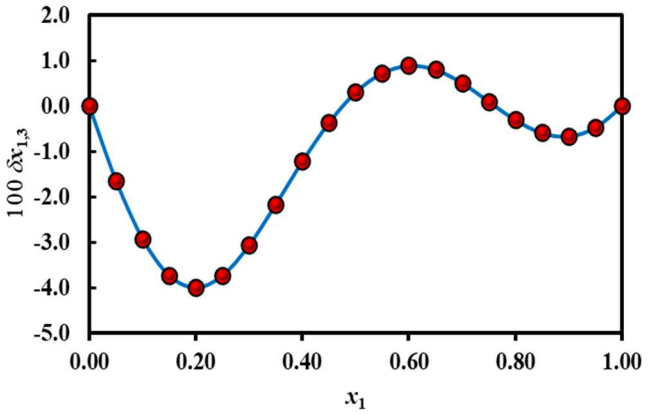

Fig. 7. Preferential solvation parameters ($\delta x_{1,3}$) of nicotinamide by ethanol in ethanol (1) + acetonitrile (2) mixtures at T = 293.2 K.

CONCLUSIONS

Solubility measurements for nicotinamide in non-aqueous systems of ethanol + acetonitrile showed that the solubility profile of nicotinamide was dependent on solvent composition and temperature. The generated data not only expanded the solubility database for nicotinamide in cosolvency systems but also can be used for solvent preparation, extraction, purification, and formation. To find a reasonable relationship between solubility, solvent mass fraction, and temperature, data were fitted to some cosolvency models and the solubility data were back-calculated. The low deviation of models (< 5.0) for the back-calculated data confirmed the ability of the studied equations to determine solubility. Finally, the thermodynamic calculations and preferential solvation were performed for the dissolution of nicotinamide.

Limitations of the Study

The main limitation in solubility studies, including the present study, is temperature fluctuations during the experiment that can diminish the reproducibility of data. Another limitation was the volatility of the used solvents which can also be another source of error in experimental studies.

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