Fluid Phase Equilibria 535 (2021) 112970

Contents lists available at ScienceDirect

Fluid Phase Equilibria

journal homepage: www.elsevier.com/locate/fluid

Modeling and parameters estimation for the solubility calculations of nicotinamide using UNIFAC and COSMO-based models

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ARTICLE INFO

Article history:
Received 15 September 2020
Revised 26 January 2021
Accepted 28 January 2021
Available online 31 January 2021

Keywords:
solubility
solid-liquid equilibrium
UNIFAC
UNIFAC Dortmund
COSMO-SAC
nicotinamide

ABSTRACT

Nicotinamide is an organic acid belonging to the vitamin B3 family. This material holds high nutritional importance especially related to different aspects of health and tissue recovery. The development of alternative strategies for its production depends on studies concerning experiments and modeling. Solubility experiments provide data about the distribution of a target material under solid-liquid equilibrium. This information coupled with mathematical models allows the determination of interaction parameters that can be used both for scientific and industrial improvements. In this work, the solubility of nicotinamide was experimentally studied in binary liquid mixtures formed by methanol + ethanol and methanol + 2-propanol covering the entire molar fraction of the binary liquid solution. The solubility was gravimetrically determined in the temperature range from 293.2 K to 323.2 K. The experimental results were used to perform the parameters optimization for the UNIFAC and UNIFAC-DO models. Furthermore, the COSMO-SAC and COSMO-UNIFAC models (and variants) were used to predict the solid-liquid equilibrium. The model UNIFAC-DO has presented the most reliable results, providing the sum of the absolute errors (SAE) and the sum of the relative errors (SRE) of 0.2448 and 11.4634, respectively, while the original UNIFAC presented 1.5636 and 28.2620, and the COSMO-SAC-based methods presented, as best result, 4.7228 and 75.0050.

1. Introduction

Solubility has a major role in drug discovery and manufacturing, since solvents are used as a medium for the synthesis reaction and to separate the desired components from a mixture [1,2]. It is estimated that about 2000 new compounds are synthesized daily [3], assuring the importance of reliable models to predict the behavior of pharmaceuticals and other compounds of interest. Since compounds with low solubility can cause problems for assays in drug discovery, solubility becomes an important physicochemical property for the pharmaceutical industry, as reported by Shayanfar and coworkers. The authors report, besides, that compounds with insufficient solubility have higher costs in drug development [4].

Amongst the several compounds of interest found in the industry, there is the Nicotinamide molecule, which belongs to the vitamin B3 family. This compound can act as a precursor of nicotinamide adenine dinucleotide (NAD), which works as a coenzyme in several cellular processes, such as energy metabolism and DNA repair [5]. Although nicotinamide can be found in several foods, such as meats, nuts, and mushrooms, it has been frequently added to cereals, protein bars, and more frequently, multivitamins as an option to decrease its deficiency [6,7].

Recent studies have been developed concerning the use of nicotinamide. Meng et al. [5] described the effects of nicotinamide use in improving stem cell survival and differentiation, and in suppressing actomyosin contraction. Li and coworkers [8] reported a very promising application of topical nicotinamide in enhancing the healing of wounds in corneal endothelium. The use of nicotinamide was also found to play an important role in traumatic brain injury recovery [9], in protecting the liver against fibrosis [10], and its derivatives were found to be effective in inhibiting the Aurora kinases, which are enzymes that play a major role in cells proliferation and are overexpressed in various solid tumors, hence, reducing the tumor progression [11].

The production of drugs based on nicotinamide depends on diverse molecular interactions especially those that take place in a liquid mixture. The knowledge about how different groups interact, especially under different conditions of temperature

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https://doi.org/10.1016/j.fluid.2021.112970
0378-3812/

Table 1
Source and purity of the chemicals used in this work.

Component	Source	Mass fraction*	Analysis method	Purification
water	Our lab.	–	refractive index	doubly distilled
methanol	Biotec - Brazil	0.999	refractive index	none
ethanol	Biotec - Brazil	0.995	refractive index	none
2-propanol	Biotec - Brazil	0.995	refractive index	none
nicotinamide	Sigma-Aldrich - China	≥0.995	none	drying
adipic acid	Sigma-Aldrich - Germany	≥0.995	none	drying

*purity informed by supplier.

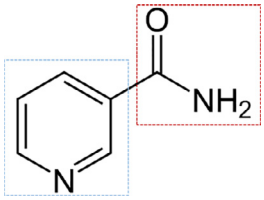

Fig. 1. Nicotinamide molecule structure (functional groups highlighted).

and composition, is essential for scientific purposes and industrial applications. The interactions, generally described by binary parameters, are determined by the application of mathematical models. The nicotinamide molecule is composed of two functional groups, as depicted in Fig. 1. The interaction parameters for the functional groups C_5H_5N and $CONH_2$ present in the nicotinamide molecule can be estimated from solid-liquid equilibrium data applied to a suitable model.

In this work, we measure the solubility of the nicotinamide in different solvent mixtures involving methanol + ethanol and methanol + 2-propanol. For each binary solvent mixture, the experiments covered the entire range of molar fractions and different temperatures. A total of 252 experimental points was obtained (2 different solvent mixtures, 4 temperatures, 11 experimental points in each temperature, and all the experiments performed in triplicate).

Besides, it is presented the modeling and parameter estimation for the solubility calculations of the nicotinamide in the referred experimental conditions. The excess Gibbs energy models chosen to be used in this work were the UNIFAC (original version) [12], the UNIFAC-DO (Dortmund version) [13], and the COSMO-SAC (2002) [14], the COSMO-SAC (2010) [15], the COSMO-SAC (2013) [16], and the recently proposed COSMO-UNIFAC [17] also extended to the, here called, COSMO-UNIFAC-DO. The prediction accuracy of these models was then compared.

Since the binary interaction parameters between the functional groups C_5H_5N- and $CONH_2$- for both UNIFAC and UNIFAC-DO were not available, there were 2 parameters to be obtained for the UNIFAC model and 6 parameters for the UNIFAC-DO. The parameters were obtained by two different methods, which will be described in Sections 2.3 and 2.4. No parameters were needed to be estimated for any of the COSMO-SAC models.

2. Material and methods

2.1. Experimental methods

For the experimental procedure, the alcohol and doubly distilled water were used without any further purification. Prior to the study, nicotinamide and adipic acid (testing material) were dried in an electrical furnace for at least 2 h under the temperature of 353.2 K and kept in a desiccator until the beginning of the experiment. The source and purity of the materials used are presented in Table 1.

Table 2
Comparison of experimental refractive index (n_D^{Exp}) and literature values (n_D^{Lit}) at 298.2 K.

Component (i)	n_D^{Exp}	n_D^{Lit}
Water	1.33251	1.33255 [18], 1.33248 [19]
Methanol	1.32655	1.32629 [18], 1.32645 [20], 1.32661 [21]
Ethanol	1.35947	1.35922 [19], 1.3591 [22], 1.35972 [23]
2-propanol	1.37503	1.37496 [24], 1.37507 [25], 1.37515 [26]

A digital refractometer (Atago, model RX-5000i, accuracy ± 0.00004) was used to analyze the refractive index of the solvents at 298.2 K and the results were compared with values published as shown in Table 2. The results confirm the quality of the liquid reagents used in this work.

The experiments were conducted in a jacketed glass cell coupled with a thermostatic bath Tecnal (model TE-2005, precision of ± 0.1 K). Solid and liquid compounds were added inside the equilibrium cells. The mixture was agitated for 3 h to achieve saturation of the solvent. After the stirring period, the mixture remained without agitation for 5 h, so the phase equilibrium could occur. The equilibrium time was previously determined by measuring the refractive index of the liquid mixture over time.

Three samples were removed for each cell in equilibrium. The aliquots were evaluated through a gravimetric method, similar to those previously published [27]. The assays were conducted under atmospheric pressure for the isotherms of 293.2 K, 303.2 K, 313.2 K, and 323.2 K. The values of solubility were expressed as a molar fraction.

2.2. Modeling and simulation

For a solid-liquid equilibrium, a mixture under the same temperature and pressure follows the isofugacity condition described by Eq. (1) [28] wherein x_1 is the mole fraction of the solute in the liquid phase, γ_1 represents the activity coefficient of the solute in the mixture, $\Delta_{fus}\bar{H}(T_m)$ is the enthalpy of fusion at the solute melting temperature (T_m), R is the universal gas constant, and T represents the equilibrium temperature.

$$\ln x_1\gamma_1 = -\frac{\Delta_{fus}\bar{H}(T_m)}{RT}\left(1-\frac{T}{T_m}\right) - \frac{1}{RT}\int_{T_m}^{T}\Delta C_P dT + \frac{1}{R}\int_{T_m}^{T}\frac{\Delta C_P}{T}dT \quad (1)$$

Neglecting the difference between the molar heat capacity of the melting and solid states of the solute (ΔC_P), although introducing a certain degree of inaccuracy, the simplified Eq. (2) [28] allows the calculation of solid solubility.

$$\ln x_1\gamma_1 = -\frac{\Delta_{fus}\bar{H}(T_m)}{RT}\left(1-\frac{T}{T_m}\right) \quad (2)$$

The values of $\Delta_{fus}\bar{H}$ and T_m applied in Eq. (2), 20,490 J·mol^{-1} and 401.6 K respectively, were taken from the literature [29].

Due to the dependence on the mole fractions of the activity coefficients, to solve Eq. (2) to the solute mole fraction, a numerical method must be used. In this work, we have used a Trust-Region-Dogleg algorithm embedded in MATLAB under the function *fsolve* [30] for both UNIFAC and UNIFAC-DO, and the *fsolve* of the SciPy library for Python language [31] for the other COSMO-based models.

The activity coefficients γ_i of the mixture were obtained using UNIFAC (implemented by the authors), UNIFAC-DO (implemented by the authors), COSMO-SAC (2002) [32], COSMO-SAC (2010) [32], COSMO-SAC (2013) [16], COSMO-UNIFAC [17] models. It is very important to notice that the UNIFAC and UNIFAC-DO binary interaction parameters for the functional groups C_5H_5N- and $CONH_2$- are missing. To obtain these parameters we have used the methods described in Section 2.3 (parameters estimation) and Section 2.4 (COSMO-UNIFAC model).

2.3. Parameters estimation

Since 2 binary interaction parameters were missing for the UNIFAC model (a_{ij} and a_{ji}) and 6 for the UNIFAC-DO model (a_{ij}, a_{ji}, b_{ij}, b_{ji}, c_{ij} and c_{ji}), a parameters estimation procedure was performed using the same experimental data used to validate the models. No parameters were estimated for any of the COSMO-SAC models in this work, thus it is important to notice that, although this manuscript compares both type of models (group-contribution methods and solvation energy models) performance, the estimation of parameters with the same data used to validate will heavily impact on the model's results.

The parameters were estimated by using all the data available for both solvent mixtures, thus a total of 264 experimental points were available for the estimation procedure of two parameters for the UNIFAC model and 6 parameters for the UNIFAC-DO model.

Since the UNIFAC parameters may range from values between −2000 and 5000, or even broader ranges, it was opted to use an unconstrained method to obtain these parameters. Also, since the initial estimation can greatly affect the convergence of numerical methods, the parameters optimization procedure was performed by using a MATLAB hybrid function that combines the Genetic Algorithm (GA) algorithm (*ga* function) [33,34] with a Nelder-Mead derivative-free method (*fminsearch* function) [35] for enhancing the results.

The objective function (OF) to be minimized during the parameters optimization procedure was a SSE (Sum of Squared Errors) function, presented by Eq. (3), wherein NP and NC represent the numbers of experimental points and components, respectively, and the superscripts exp and calc denote the experimental and calculated results.

$$OF = \sum_{i}^{NP}\sum_{j}^{NC}\sqrt{\left(x_{i,j}^{exp} - x_{i,j}^{calc}\right)^2} \tag{3}$$

2.4. COSMO-UNIFAC model

Recently, an alternative method for using the UNIFAC model when the interaction parameters are missing was proposed [17,36]. The authors have used the infinite-dilution activity coefficients (IDAC) obtained from COSMO-SAC (2002) [14] to obtain the UNIFAC missing parameters through the minimization of the Average Relative Deviation (ARD) Objective Function (OF), as presented by Eq. (4).

$$ARD_{\gamma^\infty} = \frac{1}{N}\sum_{1}^{N}\frac{\left|\gamma_{i,calc}^{\infty} - \gamma_{i,COSMO-SAC}^{\infty}\right|}{\gamma_{i,COSMO-SAC}^{\infty}} \tag{4}$$

Thus, the method seeks to minimize the differences between the IDAC obtained by the COSMO-SAC model and the IDAC obtained by the UNIFAC model by changing the interaction parameters $a_{C_5H_5N,CONH_2}$ and a_{CONH_2,C_5H_5N}. Hence, no experimental data is needed.

In this work, using the same method, we also extended the use of the UNIFAC-DO model alongside COSMO-SAC, obtaining 6 parameters from the minimization of Eq. (4) - $a_{C_5H_5N,CONH_2}$ and a_{CONH_2,C_5H_5N}, $b_{C_5H_5N,CONH_2}$ and b_{CONH_2,C_5H_5N}, $c_{C_5H_5N,CONH_2}$ and c_{CONH_2,C_5H_5N}.

It is worth noting that the COSMO-UNIFAC method is useful when there is no information regarding the interaction parameters available nor experimental data to be used, as the results suggest.

The minimization was carried out by a MATLAB hybrid function using a Particle Swarm algorithm [37,38] for global optimization alongside a deterministic unconstrained method (*particleswarm* with *fminunc*). The resulting parameters were then used as an initial guess for a least-squares nonlinear routine (*lsqnonlin*) in order to refine the results.

3. Results and discussions

3.1. Experimental results

To test the methodology of this work it was used adipic acid as a testing material and its solubility in pure water is presented in Table 3. It is observed that the experimental procedure applied in this work is adequate. For each temperature, the deviation between experimental data and the average of the published values is lower than 7.7%.

Standard uncertainties u [44] are $u(T) = 0.1$ K; $u(p) = 0.0003$ MPa; $u_r(x_s) = 0.015$; $u_r(x_s) = \frac{u(x_s)}{|x_s|}$

The solubility of nicotinamide in pure solvents was reported by Wu et al. [29] and Ouyang et al. [45]. Table 4 shows the comparison of some chosen data with the published values. Considering the literature results as a reference, it is observed that the solubility of nicotinamide in methanol presents a deviation between 2.3% and 9.6%. For the solubility in ethanol, the deviation ranges from 1.9% to 15.6% and regarding the solubility of nicotinamide in 2-propanol the data shows a deviation between 0.3% to 21.3%. It is important to notice that from the 9 results compared, 5 of them show values between the published results.

As expected, it can be seen from the data of this work presented in Table 5 that the nicotinamide solubility increases with temperature. Also, the greater content of methanol favored the nicotinamide solubility in the solvent mixtures. Considering the interval of temperature under investigation, a plot of $\ln(x_s)$ versus $^1/_T$ shows a linear trend ($R^2 \geq 0.9982$) for each binary composition. For the mixtures of methanol + ethanol it is observed a mean slope of −3240 (standard deviation of 126) and for the mixtures of methanol + 2-propanol the mean value is −3339 (standard deviation of 151). The similar behavior of linearity indicates that nicotinamide does not present polymorphism or pseudo polymorphism in the alcohol mixtures and temperature range investigated. This indicative is supported by the work of Hino et al. [46]. The work reports at least four polymorphs of nicotinamide although, for temperatures below 80 °C, it is suggested that Form I is the stable form and predominant.

When no methanol is present in the mixture, it becomes evident that the nicotinamide is more soluble in ethanol than in 2-propanol. To better understand this difference in solubility, we investigated the sigma-profiles of the mixture components (Fig. 2) in order to evaluate the charge density profile role in the solubility. It was also investigated the combinatorial (entropic) and residual (enthalpic) contributions to the activity coefficients to obtain more information on the solubility mechanism.

It can be seen from Fig. 2 that there are no significant differences between the sigma-profile of the ethanol and 2-propanol,

Table 3
Solubility (x_s) of adipic acid in water as a function of temperature (T) at 0.1 MPa.

T/K	x_s	$x_s^{Literature}$
293.2	0.0023	0.0024 [39], 0.0023 [40], 0.0023 [41]
303.2	0.0039	0.0038 [39], 0.0038 [40], 0.0038 [41], 0.0041 [42], 0.0043 [43]
313.2	0.0065	0.0062 [39], 0.0063 [40], 0.0063 [41], 0.0069 [42], 0.0061 [43]
323.2	0.0112	0.0108 [39], 0.0110 [40], 0.0106 [42], 0.0092 [43]

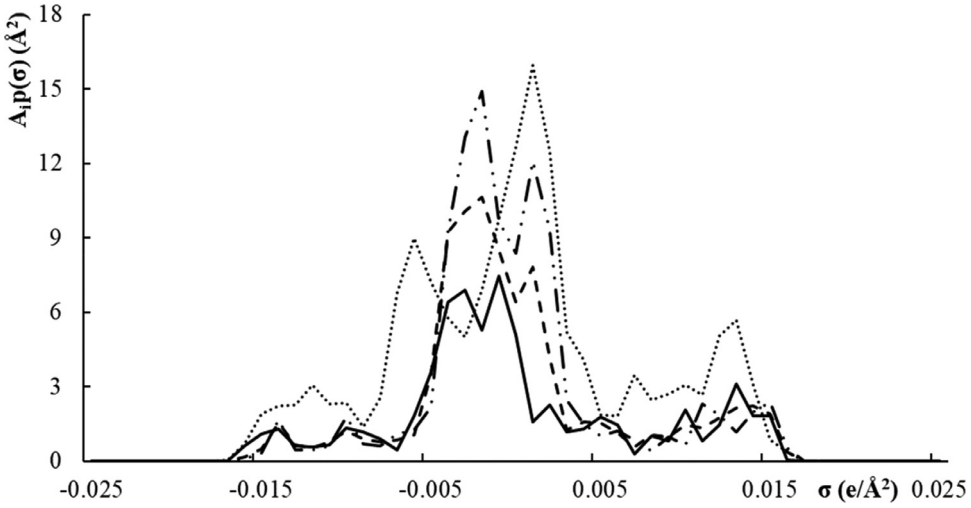

Fig. 2. Sigma-profile (VT-2005 Sigma Profile Database [47]) of the components studied in this work: – methanol, ——ethanol, ··–·· 2-propanol, ····· nicotinamide.

Table 4
Solubility (x_s) of nicotinamide in methanol, ethanol and 2-propanol as a function of temperature (T) at 0.1 MPa.

Component	T/K	x_s	$x_s^{Literature}$
methanol	293.2	0.0687	0.0671 [29]; 0.0748 [45]
	303.2	0.0961	0.0892 [29]; 0.1019 [45]
	313.2	0.1320	0.1205 [29]; 0.1413 [45]
Ethanol	293.2	0.0394	0.0387 [29]; 0.0374 [45]
	303.2	0.0569	0.0582 [29]; 0.0537 [45]
	313.2	0.0811	0.0960 [29]; 0.0766 [45]
2-propanol	293.2	0.0281	0.0269 [29]; 0.0281 [45]
	303.2	0.0413	0.0362 [29]; 0.0396 [45]
	313.2	0.0591	0.0487 [29]; 0.0573 [45]

Standard uncertainties u [44] are $u(T) = 0.1$ K; $u(p) = 0.0003$ MPa; $u_r(x_s) = 0.015$; $u_r(x_s) = \frac{u(x_s)}{|x_s|}$.

Table 5
Solubility (x_s) as a function of temperature and molar fraction of methanol (x_1) in the binary liquid mixture at 0.1 MPa.

	x_s			
	293.2 K	**303.2 K**	**313.2 K**	**323.2 K**
nicotinamide + methanol + ethanol				
0.0000	0.0394	0.0569	0.0811	0.1161
0.1000	0.0414	0.0598	0.0853	0.1218
0.2006	0.0432	0.0628	0.0892	0.1247
0.3000	0.0458	0.0659	0.0935	0.1319
0.4001	0.0486	0.0693	0.0964	0.1395
0.5000	0.0513	0.0726	0.1023	0.1451
0.5999	0.0545	0.0770	0.1062	0.1499
0.7000	0.0577	0.0818	0.1130	0.1594
0.8000	0.0613	0.0866	0.1183	0.1645
0.8999	0.0651	0.0915	0.1245	0.1730
1.0000	0.0687	0.0961	0.1320	0.1796
nicotinamide + methanol + 2-propanol				
0.0000	0.0281	0.0413	0.0591	0.0830
0.1004	0.0289	0.0419	0.0601	0.0877
0.1997	0.0301	0.0436	0.0620	0.0913
0.3000	0.0318	0.0457	0.0653	0.0956
0.4000	0.0338	0.0485	0.0702	0.1001
0.5003	0.0369	0.0527	0.0760	0.1091
0.6003	0.0409	0.0582	0.0836	0.1198
0.7002	0.0464	0.0660	0.0925	0.1306
0.7999	0.0526	0.0745	0.1036	0.1457
0.8995	0.0600	0.0845	0.1157	0.1620
1.0000	0.0687	0.0961	0.1320	0.1796

Standard uncertainties u [44] are $u(T) = 0.1$ K; $u(p) = 0.0003$ MPa; $u_r(x_1) = 0.002$; $u_r(x_s) = 0.015$;.
$u_r(x_1) = \frac{u(x_1)}{|x_1|}$; $u_r(x_s) = \frac{u(x_s)}{|x_s|}$.

meaning that both alcohols may exert similar attractive and repulsive forces over the nicotinamide molecule. Thus, the differences in the solubilities of both solvents may be regarded due to two main factors: the lower number of neutral segments of the ethanol when compared to 2-propanol, which may allow a more stable system with nicotinamide; and the molecular configuration, the linear structure of the ethanol may favor the contact and interaction between the nicotinamide and the solvent, allowing greater solubility when compared to the 2-propanol molecule. In fact, the calculations of the combinatorial and residual terms of the activity coefficients suggest that the combinatorial contribution of the nicotinamide is greater for the methanol + ethanol mixture of solvents than for the methanol + 2-propanol association, revealing that the entropic effect of the sizes and shapes of the molecules plays an important role in the solubility.

Moreover, mixtures formed by methanol + ethanol and methanol + 2-propanol present the ability to dissolve nicotinamide depending on the amount of ethanol or 2-propanol in the solution. For both cases, the addition of ethyl or isopropyl alcohol leads to a reduction of nicotinamide solubility. This decrease, due to the addition of an antisolvent, is related to the change of the dielectric constant of the binary liquid solution. The dissolution of a solid depends on the dielectric constant of the mixture. Methanol has a dielectric constant larger than ethanol, and ethanol presents a

Table 6
Statistical results of the UNIFAC and UNIFAC-DO models.

Model	SAE	SRE	SSE
UNIFAC	1.5636	28.2620	0.0412
UNIFAC-DO	0.2448	11.4634	0.0009

dielectric constant larger than 2-propanol. Therefore, a mixture of two of these three alcohols will form a solution with an intermediate dielectric constant reflecting in intermediate values of solubility.

3.2. Modeling and simulation results

To describe the solubility of the nicotinamide in both solvents mixture (methanol + ethanol and methanol + 2-propanol), different excess Gibbs energy models (UNIFAC, UNIFAC-DO, COSMO-SAC versions, COSMO-UNIFAC, and COSMO-UNIFAC-DO) were applied to represent the activity coefficient of the solute in the ternary mixtures.

Since the UNIFAC and UNIFAC-DO binary parameters for the functional groups C_5H_5N- and $CONH_2$- interaction were not available, we have correlated these models to the experimental data through the estimation of the parameters. This correlation will impact heavily on the model's performance, especially when compared to those models whose parameters were not calibrated for this specific data set. Hence, we will present the modeling and simulation results in two parts: i) correlative models performance (which will comprise the UNIFAC and the UNIFAC-DO models); and ii) predictive models performance (which will comprise the COSMO-SAC-based, the COSMO-UNIFAC, and the COSMO-UNIFAC-DO models).

3.2.1. Correlative models performance

In this section, the UNIFAC and UNIFAC-DO models, which had their binary interaction parameters optimized for the data set obtained in this work, were compared. The performance of the implemented models was evaluated by the sum of the absolute errors (SAE) denoted by Eq. (5), the sum of the relative errors (SRE) denoted by Eq. (6), and by the sum of the squared errors (SSE) denoted by Eq. (7). The performance of both models is presented in Table 6.

$$\mathrm{SAE} = \sum_{i=1}^{\mathrm{NP}} \left| x_{\mathrm{exp,i}} - x_{\mathrm{calc,i}} \right| \tag{5}$$

$$\mathrm{SRE} = \sum_{i=1}^{\mathrm{NP}} \frac{\left| x_{\mathrm{exp,i}} - x_{\mathrm{calc,i}} \right|}{x_{\mathrm{exp,i}}} \tag{6}$$

$$\mathrm{SSE} = \sum_{i=1}^{\mathrm{NP}} \left(x_{\mathrm{exp,i}} - x_{\mathrm{calc,i}} \right)^2 \tag{7}$$

As expected, since the UNIFAC-DO model has 6 parameters to adjust the model to the experimental data, while the UNIFAC model has only 2, it presented smaller values for all the statistical results. Fig. 3 illustrates the behavior of the models for the chosen temperatures of 293.2 K and 323.2 K.

Ratifying the quantitative results presented in Table 6, the qualitative results reveal that, although the UNIFAC model presents a solubility curve close to the experimental data (predictive models will reveal a very different performance), it also presents a difficulty in following the experimental data trend, even with its parameters optimized for this experimental data set. The UNIFAC-DO model, however, presented a very good agreement with the experimental solubility tendency to decrease when the ethanol/isopropanol content increases, including the temperature effect on the solubility.

Possibly, the only reason why UNIFAC-DO was more accurate than the other models was that it has 6 parameters to be adjusted. The COSMO-SAC models (not including the COSMO-UNIFAC and COSMO-UNIFAC-DO models) had no parameters optimized for this data, and the UNIFAC model had 2 parameters optimized for this data set. Thus, because of its number of parameters, it is expected that the UNIFAC-DO model describes the data with more accuracy. Also, besides the larger number of parameters to be estimated, the UNIFAC-DO model has greater temperature dependence than the UNIFAC model, allowing it to better describe the data in all temperatures in which it was optimized.

The optimized UNIFAC and UNIFAC-DO parameters will be presented in the next section (Table 8), and the complete numerical results can be seen in the Supplementary Data File (Table S1).

Table 7
Statistical results of the COSMO-SAC and COSMO-UNIFAC models.

Model	SAE	SRE	SSE
COSMO-SAC (2002)	10.6096	163.9887	1.4624
COSMO-SAC (2010)	22.5772	303.8280	5.8337
COSMO-SAC (2013)	20.0142	292.2024	4.5880
COSMO-UNIFAC	4.7228	75.0050	0.3078
COSMO-UNIFAC-DO	13.5739	199.0638	2.1242

3.2.2. Predictive models performance

Since experimental data is not always available, the use of *a priori* methods (COSMO-based models) or hybrid methods (COSMO-UNIFAC) may become useful. The performance of the COSMO-SAC models (2002, 2010, and 2013), and the COSMO-UNIFAC and the COSMO-UNIFAC-DO approaches were compared and the results are presented in Table 7.

Table 7 shows the statistical results for all the predictive methods used in this work. The COSMO-UNIFAC approach presented the smallest errors, with its sum of squared errors being 21.04% of the COSMO-SAC (2002) SSE, which was the second-best predictive model, and only 5.27% of the SSE of the COSMO-SAC (2010), which provided the least accurate results.

Although the errors obtained by the use of the COSMO-UNIFAC, presented in Table 7, are small and promising, the model still does not provide very accurate qualitative predictions. Fig. 4 illustrates the behavior of the models for the chosen temperatures of 303.2 K and 313.2 K.

It also can be seen from Fig. 4 that the COSMO-UNIFAC model was the only predictive approach that was able to get close results to the experimental data, the other models offered results that were not qualitative neither quantitative satisfactory. Even the COSMO-UNIFAC-DO approach, which had more parameters obtained from correlation with the COSMO-SAC model, did not present results as good as those obtained from COSMO-UNIFAC, revealing that the most reliable predictive model was the combination of the COSMO-SAC (2002) with the UNIFAC model. This fact supports the results presented for vapor-liquid equilibria by Dong and coworkers [17] when using the COSMO-UNIFAC model.

The good results presented by the COSMO-UNIFAC model show that this approach can be used as an alternative for when the UNIFAC energetic binary interaction parameters are missing and no experimental data is available to perform a parameter optimization procedure.

The UNIFAC and UNIFAC-DO parameters obtained by both parameters optimization and COSMO-UNIFAC methods are presented in Table 8. It is interesting to notice that, while the COSMO-UNIFAC parameters were close to those obtained directly by parameters

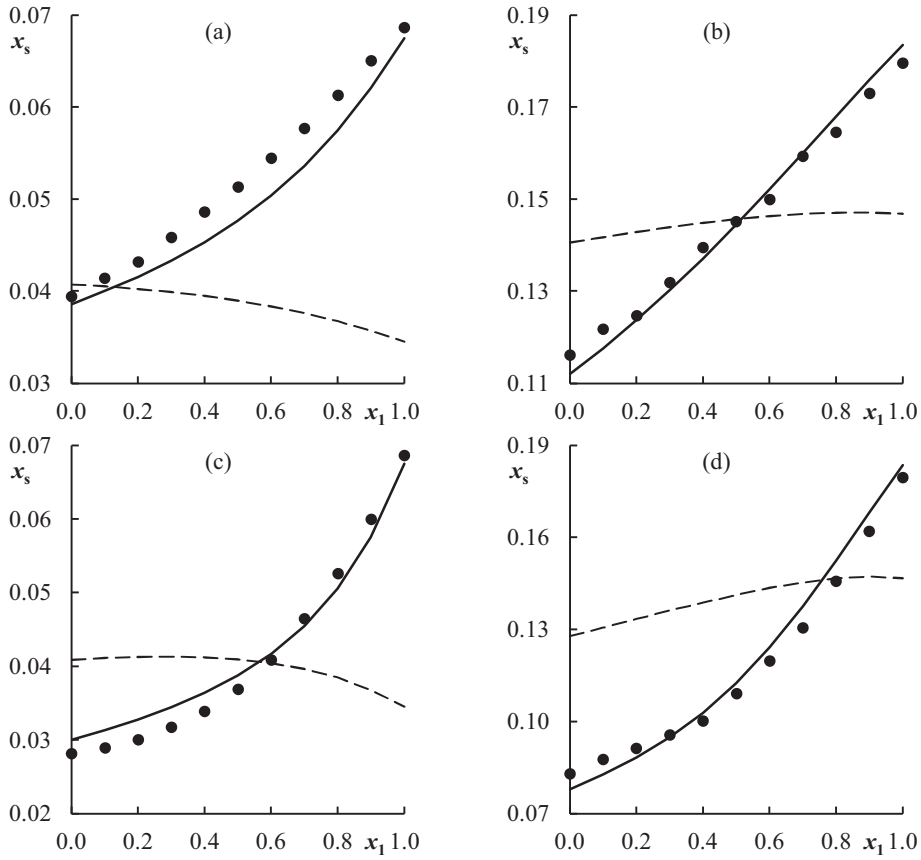

Fig. 3. Solubility of nicotinamide (x_s) in methanol (1) + ethanol (2) at (a) 293.2 K, and (b) 323.2 K; and in methanol (1) + 2-propanol (2) at (c) 293.2 K, and (d) 323.2 K: • experiment; continuous line represents UNIFAC-DO model, and dashed line represents UNIFAC model.

Table 8
C_5H_5N- and $CONH_2$- functional groups interaction parameters for UNIFAC, UNIFAC-DO, COSMO-UNIFAC, and COSMO-UNIFAC-DO.

C_5H_4N - $CONH_2$			$CONH_2$ - C_5H_4N		
a_{ij}	b_{ij}	c_{ij}	a_{ij}	b_{ij}	c_{ij}
UNIFAC					
−224 ± 31	–	–	−462 ± 47	–	–
UNIFAC-DO					
3620 ± 241	−1.81 ± 1.27	−0.032 ± 0.003	−1482 ± 315	5.38 ± 1.82	−0.076 ± 0.028
COSMO-UNIFAC					
−152 ± 21	–	–	−508 ± 33	–	–
COSMO-UNIFAC-DO					
7905 ± 923	2096 ± 412	−0.417 ± 0.083	1490 ± 854	−5.8 ± 2520	−0.004 ± 41.645

optimization, the COSMO-UNIFAC-DO parameters were very different than those obtained for UNIFAC-DO solely. In fact, the confidence intervals of the parameters $b_{CONH_2-C_5H_4N}$ and $c_{CONH_2-C_5H_4N}$ suggests that these parameters could assume the value 0 (zero) at some point, meaning that there would be no difference in the energy interaction between C_5H_5N–$CONH_2$ functional group pair and C_5H_5N–C_5H_5N, which is unexpected and shifts the residual contribution to the activity coefficient.

Further, the COSMO-UNIFAC approach (including the COSMO-UNIFAC-DO) used the IDAC obtained from the COSMO-SAC (2002) model. Even though the results presented in Table 7 suggest that the COSMO-SAC (2002) described more accurately the experimental data than its other two versions (2010 and 2013), the use of the other COSMO-SAC versions to obtain the UNIFAC parameters is also an alternative for obtaining UNIFAC energetic binary interaction parameters.

Lastly, it is important to note the poor results obtained with the use of the COSMO-SAC models, especially the 2010 and 2013 versions. Mullins et al. [2] report high errors in solubility calculations using COSMO-SAC alone, with no calibration with experimental data, which was the case in this work. The authors also evaluate the COSMO-SAC performance in predicting the solubility in binary and mixed solvents, reporting poor results obtained by the model.

Shu and Lin [48] report the accuracy of the COSMO-SAC model in predicting solubility of mixed solvents as semiquantitative. To improve the COSMO-SAC performance in drug solubility calculations, the authors proposed the use of a Margules-type activity equation as a correction term. More recently, Kang et al. [49] also proposed modifications to the COSMO-SAC model in order to improve its accuracy in carboxylic acid solubility calculations, since the improvements of the newer versions of the model mainly focus on vapor-liquid and liquid-liquid data [49].

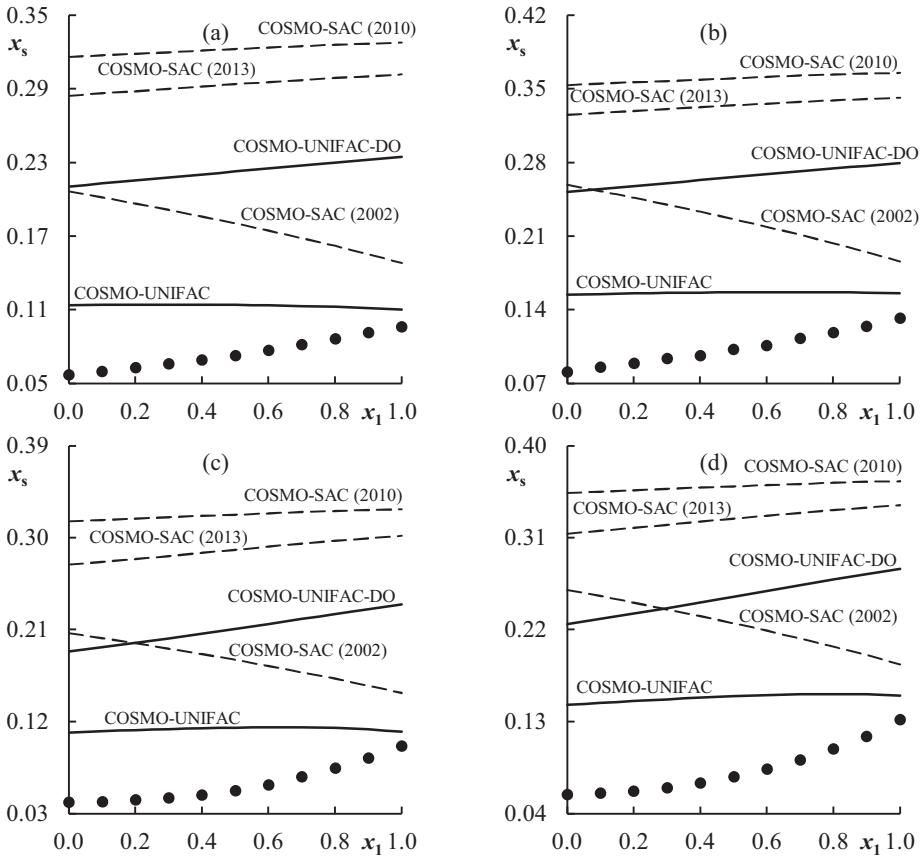

Fig. 4. Solubility of nicotinamide (x_s) in methanol (1) + ethanol (2) at (a) 303.2 K, and (b) 313.2 K; and in methanol (1) + 2-propanol (2) at (c) 303.2 K, and (d) 313.2 K: • experiment; continuous lines represent versions of COSMO-UNIFAC model, and dashed lines represent versions of COSMO-SAC model.

Table 9
SSE and SRE for the studied models at different temperatures.

Model	293.2 K SSE	303.2 K	313.2 K	323.2 K	293.2 K SRE	303.2 K	313.2 K	323.2 K
nicotinamide + methanol + ethanol								
(a)	0.00357	0.00466	0.00411	0.00372	2.67104	2.09888	1.47964	1.19571
(b)	0.00009	0.00002	0.00018	0.00009	0.55824	0.16445	0.43127	0.19141
(c)	0.09151	0.13115	0.17769	0.21608	19.96617	16.65693	13.75341	10.63258
(d)	0.60732	0.67618	0.72344	0.71695	51.06388	37.80218	27.97213	19.75670
(e)	0.45451	0.52820	0.58456	0.59288	44.13125	33.39524	25.14166	17.96833
(f)	0.00982	0.01851	0.03271	0.04728	6.40693	6.20462	5.91926	5.03580
(g)	0.18188	0.24183	0.29011	0.30470	27.94386	22.59797	17.70626	12.87974
nicotinamide + methanol + 2-propanol								
(a)	0.00255	0.00416	0.00662	0.01189	3.18749	3.21676	3.22148	3.19021
(b)	0.00005	0.00025	0.00002	0.00024	0.58453	0.95213	0.17193	0.40885
(c)	0.11563	0.17238	0.24265	0.31538	30.54651	25.89470	21.51607	17.02196
(d)	0.66502	0.76305	0.84427	0.88365	71.38889	53.43049	39.65037	28.43672
(e)	0.47930	0.57621	0.66139	0.71098	60.32586	46.27698	35.01430	25.47218
(f)	0.01923	0.03475	0.05847	0.08709	12.35387	11.56591	10.54535	8.97287
(g)	0.18633	0.25417	0.31431	0.35091	37.50236	30.59649	24.01764	17.81889

(a) UNIFAC, (b) UNIFAC-DO, (c) COSMO-SAC (2002), (d) COSMO-SAC (2010), (e) COSMO-SAC (2013), (f) COSMO-UNIFAC, (g) COSMO-UNIFAC-DO.

The results obtained in this work, alongside the results reported in the literature for the COSMO-SAC predictions in solubility calculations, suggest that the model should be extended and optimized in order to be used as a reliable model for solubility calculations.

3.2.3. Temperature and molar fraction dependence

Useful analysis to better understand each model's behavior is to analyze their performance for each simulated temperature. Table 9 shows the SSE and the SRE for the studied models at different temperatures. It can be seen that, except for the UNIFAC and UNIFAC-DO models (it is worth remembering that the parameters of both models were estimated using this work's data set), every other approach resulted in a growing error pattern, i.e., the greater the temperature the larger the errors (SSE). Meanwhile, different behavior is observed when the SRE is used. It can be seen that each model (except for both correlative models, UNIFAC and UNIFAC-DO) presents a decreasing SRE with increasing temperature, the opposite of what was shown by the SSE values.

This different behavior can be explained with the support of Fig. 4, which shows that as the temperature increases, the solubil-

ity of nicotinamide also increases. The predictive models, however, do not increase as much as the experimental data, diminishing the relative gap between the experimental and simulated data as the temperature increases. So, although the errors are still large (cf., Fig. 4), they are relatively closer to the experimental data.

Also, no trends were found for the prediction behavior as we change the system's composition. For example, the UNIFAC model errors slightly increase with the amount of nicotinamide in solution while the opposite is observed for the COSMO-SAC (2002) and COSMO-UNIFAC. The COSMO-SAC (2010) and the COSMO-SAC (2013) presents a very small change in the SSE as we increase the amount of nicotinamide, remaining almost at the same magnitude. So, no general rule for a composition dependence could be found.

Conclusions

The solubility of nicotinamide was measured and evaluated using two different solvent mixtures, methanol + ethanol, and methanol + 2-propanol, at 4 different temperatures. 11 experimental points were measured at each temperature for each solvent mixture.

The nicotinamide solubility is greatly favored by the temperature increase. Also, the addition of methanol to the solvent mixture increased the nicotinamide solubility. When no methanol was present, the nicotinamide molecule was more soluble in ethanol than in 2-propanol, probably due to its molecular configuration.

The parameters for the UNIFAC and UNIFAC-DO models were optimized using the experimental data. The results suggest that the UNIFAC-DO model can provide very accurate predictions of the solubility using the estimated parameters. The UNIFAC model has also presented results close to the experimental data, however with less quantitative accuracy and poor qualitative behavior.

In the predictive part (considering only the models that used no experimental data), we have found that the UNIFAC model with parameters obtained through IDAC data from COSMO-SAC (2002), the so-called COSMO-UNIFAC, provided the best results, with higher accuracy than the pure COSMO-SAC models and even than the COSMO-UNIFAC-DO model, which used 4 extra parameters than the COSMO-UNIFAC. These results show that the COSMO-UNIFAC approach is a relevant model which be considered when the UNIFAC parameters are missing.

Finally, the model UNIFAC Dortmund, which comprises the temperature effects on its parameters, presented very reliable results, with great quantitative and qualitative accuracy. Thus, the UNIFAC Dortmund is the most advisable one, amongst the 7 tested models, to be used in predicting the solubility of nicotinamide in both methanol + ethanol and methanol + 2-propanol solvent mixtures.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Christian L. Silveira: Formal analysis, Writing - original draft, Writing - review & editing. **Alessandro C. Galvão:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Weber S. Robazza:** Formal analysis, Writing - review & editing. **João Victor T. Feyh:** Investigation.

Acknowledgements

The authors wish to thank FAPESC (*Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina*, grant number 2019TR583) and CAPES (*Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*) for the financial support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.fluid.2021.112970.

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