Journal of Molecular Liquids 323 (2021) 114617

Contents lists available at ScienceDirect

Journal of Molecular Liquids

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

Solid-liquid equilibrium of paracetamol in water-ethanol and water-propylene glycol mixtures

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ARTICLE INFO

Article history:
Received 9 August 2020
Received in revised form 13 October 2020
Accepted 17 October 2020
Available online 27 October 2020

Keywords:
Paracetamol
Solubility
Ethanol
Propylene glycol
X-rays diffraction

ABSTRACT

Solubility is one of most important property to produce active pharmaceutical ingredients (APIs), beyond of being related to its bioavailability. In this context, it was determined paracetamol solid-liquid equilibrium in temperatures from 20 to 50 °C for two solvent systems: water - ethanol and water - propylene glycol (PG), by refractometry method. The experimental results were compared with five thermodynamic models (Apelblat, Wilson, UNIQUAC, NRTL and λh) and data from the literature, showing good correlations for Apelblat and the best predictive fit for the NRTL model in both solvent mixtures. Maximum solubility values were observed in a 75% ethanol composition, this result being unusual and not the same with PG. the results of this work were compared with the literature and some references point to similar behavior. Optical microscopy and X-ray diffraction measurements of the solids in equilibrium with the liquid indicate that maximum solubility is not associated with a change in the crystalline structure of the solid

1. Introduction

Solubility is probably the most important property that must be known for the production and purification of active pharmaceutical ingredients (APIs) by crystallization, which is crucial for the pharmaceutical industry both in the separation of intermediate products such as in the final stage of their production [1,2].

The most APIs have size from 10 to 100 Da with high structural diversity, having ionizable and hydrophobic parts. Thus, their interaction with each other, solvents or antisolvents, and cossolutes and impurities in the solution are very diverse. Furthermore, their solid phases, including polymorphs (the same chemical species with more than one possible crystalline type) and several solvates (formation of crystals with the presence of solvents physically similar) formed by such molecules are still very poorly understood [3–5].

Study of polymorphs by the solubility technique consists in determining the solubility in the pre-formulation, obtaining the solubility curve as a function of temperature, and transition evaluation of the phases mediated by solvents [6], becoming experimental challenges for low solubilities which are limited, mainly due to the difficulty of reaching the thermodynamic balance between the solid and liquid phases, among other factors [4].

For the study of possible polymorphs formed in the solid portion, may be used the techniques of differential scanning calorimetry (DSC), thermogravimetry, X-ray powder diffraction (XRD), Raman and NMR spectroscopy [6].

The paracetamol or acetaminophen (CAS 103–90-2), with a molecular mass of 151.16 g/mol, is one of the API's most widely used in the world and can be associated with other's substances. It is a derivative of p-aminophenol used as analgesic and antipyretic [7,8]. Some references show a maximum solubility value of paracetamol in ternary mixtures of ethanol-water [9–12], while the same does not occur with water-propylene glycol (PG) mixture [12,13]. However, reported values show significant differences, on top of an unusual behavior for the water-ethanol system, with a maximum solubility value close to 80% (m/m) of ethanol. Articles written by Jouyban et al. (2006) and Romero et al. (1996) indicate a possible change of the crystalline form at this concentration, but do not report a deep investigation of solid phase.

Haisa et al. [14] report success on obtaining paracetamol orthorhombic form (II) by evaporating the ethanol solution, and in 1976, a monoclinic form (I) obtained from the aqueous solutions [15]. Nichols and Frampton [16] observed that, depending on used solution and temperature conditions, form II can converge to form I of paracetamol while Espeau et al. [17] report that form I can converge into form II when under pressure.

According to Hojjati and Rohani [18], it is preferable to use thermodynamic models to predict pharmaceuticals solubility due to the large amount of solute and time required to obtain experimental solubility.

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https://doi.org/10.1016/j.molliq.2020.114617
0167-7322/

Many thermodynamic models were tested to predict the solubility of Paracetamol in different solvents and solvent mixtures. Among them, there are the Apelblat, λh, Wilson, UNIQUAC and NRTL models.

Apelblat and λh models are simple and adjust solubility in relation to temperature [19]. Hojjati and Rohani applied the Apelblat model in a water-paracetamol system, which showed a good correlation for the data in reported article [18]. Both models were also applied by Baluja and Talaviya for di-hydropyridine, with adequate convergence to the reported data [20].

Wilson, NRTL and UNIQUAC models are non-correlative models of activity coefficient, for non-ideal binary mixtures, it may be preferable to use robust models such as NRTL, or UNIQUAC [21]. For binary and ternary systems, and systems with high structural complexity molecules shown good relation for UNIQUAC model [18,22–24].

Thus, the determination of experimental solubility data for the paracetamol in water-ethanol and water-PG systems to evaluate the fit with five thermodynamic models (Apelblat, Wilson, UNIQUAC, NRTL, λh) and the effect of the solvent mixture in behavior and crystal structure of the solid in equilibrium with the solution by optical microscopy and XRD techniques.

2. Experimental section

2.1. Chemicals

For the experiments were used demineralized water, 99,81% mass purity ethanol (NEON, Brazil) and 99,5% mass purity propylene-glycol (LABSYNTH, Brazil). 99,3% mass purity paracetamol was commercially obtained (Anqiu Lu'an Pharma, China).

2.2. Solubility measurements

Solubility was measured experimentally by isothermal method [4]. Solvent-system concentration conditions were evaluated using an aqueous mixture with 0%, 25%, 50%, 75% and 100% ethanol or propylene glycol, at temperatures of 20, 25, 30, 35, 40, 45 and 50 °C. All proposed conditions were evaluated in triplicate.

Desired quantities of each solvent were measured in analytical balance from QUIMIS with an accuracy of 0,1 mg and mixture for the preparation of the solvent system. Into the solution were added exceeding quantities of Paracetamol, in a such way that solid presence remains in suspension in the system. The suspensions were kept in Erlenmeyer with constant temperature under agitation in a SOLAB thermostatic shaker for at least 48 h. Required stirring time to reach the balance was experimentally determined by dissolution specific test. Then, the suspensions were kept at rest at that constant temperature for 4 h to decant the solid. Samples of the supernatant liquid were collected in triplicate to measure the concentration, and samples of the solid were collected by filtration for characterization (optical microscopy and X-ray diffraction) [25].

Concentration analyzes of solutions were made by refractometry method, used by Crestani et al. [26]. Previously, a correlation was obtained between the refractive index (RI) and the solution composition of each solute in the different used solvents at a fixed temperature of 55 °C. All liquid samples were withdrawn using a preheated syringe, to avoid solid formation in the syringe during sampling. Samples were added to Eppendorfs vials heated up to 55 °C. The RI was then measured by the ABBE refractometer type from Analytikjena and the concentration determined from the obtained correlations from the same refractometer.

2.3. Solid characterization

To characterize the crystalline phases, present in the material, X-ray powder diffraction analyzes were performed on the Bruker D8 equipment, equipped with a scintillation detector and graphite monochromator. The analyzes were performed with 0,025° path, 10 s per step, with 1080 W of Cu-Kα. Divergence slits and spreading of 2,0 mm (approximately 1°), reception slit of 0,4 mm, and the goniometer radius of 250 mm, with variation of 2Theta from 8° to 60°. To carry out the analysis, the samples were previously ground in a mortar and agate mill.

3. Thermodynamic models

3.1. Modified Apelblat model

The Apelblat model uses 3 empirical constants obtained from experimental data, expressed by Eq. 1 [27,28].

$$ln\,x_1 = A + \frac{B}{T} + C\,lnT \qquad \text{Eq 1}$$

Where A and B are constants that represent the variation of the activity coefficient in solution and C represents the effect of temperature over fusion enthalpy.

3.2. λh model

The λh equation, or Buchowski model, uses two parameters obtained from the experimental data, adjusted for multicomponent mixtures by a mixing rule [29,30]. The λh equation is expressed by Eq. 2.

$$\ln\left(1+\frac{\lambda(1-x_A)}{x_A}\right)_{sat} = \lambda h\left(\frac{1}{T}-\frac{1}{T_m}\right) \qquad \text{Eq 2}$$

Where, for multicomponent mixtures, the values of λ and h are:

$$h = h_1\left(x_1^0\right)^2 + 2(1-k_{12})\left(x_1^0\right)\left(x_2^0\right)\sqrt{h_1 h_2} + h_2\left(x_2^0\right)^2 \qquad \text{Eq 3}$$

$$\lambda = \lambda_1\left(x_1^0\right)^2 + 2(1-k_{12})\left(x_1^0\right)\left(x_2^0\right)\sqrt{\lambda_1 \lambda_2} + \lambda_2\left(x_2^0\right)^2 \qquad \text{Eq 4}$$

3.3. Modified Van't Hoff equation

To minimize the activity coefficients of the Wilson, UNIQUAC and NRTL, was used the modified Van't Hoff equation [18], by ΔCp ≅ ΔS, Eq. 5.

$$ln\,\gamma_2 x_2 = \frac{-\Delta H_m^{fus}}{RT_m}\,ln\,(T_r) \qquad \text{Eq 5}$$

3.4. Wilson model

Wilson model uses two interaction parameters and for multicomponent systems it is expressed in Eq. 6 [31,32].

$$ln\,\gamma_k = -ln\left(\sum_{j=1}^{N} x_j \Lambda_{kj}\right) + 1 - \sum_{i=1}^{N}\left(\frac{x_i \Lambda_{ik}}{\sum_{j=1}^{N} x_j \Lambda_{ij}}\right) \qquad \text{Eq 6}$$

Where, $\Lambda_{ij} = \frac{\nu_j}{\nu_i}\exp\left(-\frac{\lambda_{ij}-\lambda_{ii}}{RT}\right)$; $\Lambda_{ji} = \frac{\nu_i}{\nu_j}\exp\left(-\frac{\lambda_{ji}-\lambda_{jj}}{RT}\right)$.

3.5. UNIQUAC model

For the UNIQUAC model, the activity coefficient equation for multicomponent systems is expressed as a combination of the combinatorial part and the residual part, expressed by eqs. 7 and 8 [33].

Table 1
Experimental solubility (molar fraction) of paracetamol in water-ethanol and water-propylene glycol system.

Ethanol/Propylene glycol (%, w/w)	Molar Fraction				
	0%	25%	50%	75%	100%
Water-Ethanol[a]					
20(°C)	0.0011	0.0059	0.0219	0.0450	0.0435
25(°C)	0.0016	0.0091	0.0295	0.0562	0.0546
30(°C)	0.0020	0.0106	0.0353	0.0610	0.0590
35(°C)	0.0021	0.0126	0.0410	0.0668	0.0634
40(°C)	0.0027	0.0152	0.0489	0.0729	0.0676
45(°C)	0.0032	0.0203	0.0597	0.0823	0.0778
50(°C)	0.0034	0.0230	0.0655	0.0947	0.0921
Water-Propylene glycol[b]					
20(°C)	0.0011	0.0029	0.0102	0.0298	0.0451
25(°C)	0.0016	0.0034	0.0123	0.0305	0.0536
30(°C)	0.0020	0.0044	0.0164	0.0369	0.0576
35(°C)	0.0021	0.0050	0.0192	0.0422	0.0636
40(°C)	0.0027	0.0055	0.0262	0.0473	0.0690
45(°C)	0.0032	0.0082	0.0304	0.0595	0.0767
50(°C)	0.0034	0.0095	0.0350	0.0655	0.0881

[a] Standard uncertainty for water-ethanol concentration curve: 2.95E-4.
[b] Standard uncertainty for water-propylene glycol concentration curve: 6.78E-4.

Table 2
Literature interaction parameters - Water (1) - Ethanol (2) - PG (2).

Solvent	WILSON		UNIQUAC		NRTL		
	λ12	λ21	a12	a21	g12	g21	α
Ethanol	1.36	3.99	30.48	155.60	3.55	0.14	0.47
PG	−1678.13	−3118.64	−297.00	297.00	2.8113	−1.82	0.29

$$ln\left(\gamma_i^c\right) = ln\left(\frac{\phi_i}{x_i}\right) + \frac{z}{2} q_i \ln\frac{\theta_i}{\phi_i} + l_i - \frac{\phi_i}{x_i}\sum_j x_j l_j \quad \text{Eq 7}$$

$$ln\left(\gamma_i^R\right) = q_i\left[1 - ln\left(\sum_j \theta_j \tau_{ji}\right) - \sum_j \frac{\theta_j \tau_{ij}}{\sum_k \theta_k \tau_{kj}}\right] \quad \text{Eq 8}$$

Where, $\phi_i = \frac{x_i r_i}{\sum_j x_j r_j}$; $\theta_i = \frac{x_i q_i}{\sum_j x_j q_j}$; $l_i = \frac{z}{2}(r_i - q_i) + 1 - r_i$ e $\tau_i = \exp\left(\frac{a_{ij}}{T}\right)$.

3.6. NRTL model

The NRTL model is derived from Wilson model with 3 interaction parameters. NRTL equation is expressed in Eq. 9 [21,34].

Table 4
Specific molar volume, volume (r_i) and surface area (q_i) parameters, coordination number (z_i), molecular mass (MM), melting point enthalpy and melting temperature (Tm) data.

Components	Wilson	UNIQUAC			MM	ΔH_m	T_m
	v_i	r_i	q_i	z_i			
Paracetamol	119.97	5.76	4.56	10.00	151.16	27.6	443.2
Water	18.06	0.92	1.40	10.00	18.01	–	–
Ethanol	58.39	2.58	2.59	10.00	46.07	–	–
PG	73.16	4.25	4.33	10.00	76.09	–	–

$$\ln(\gamma_i) = \frac{\sum_j G_{ji} x_j}{\sum_k G_{ki} x_k} + \sum_j \frac{x_j G_{ij}}{\sum_k G_{kj} x_k}\left(\tau_{ij} - \frac{\sum_k x_k \tau_{kj} G_{kj}}{\sum_k G_{kj} x_k}\right) \quad \text{Eq 9}$$

Where, $G_{ij} = exp\left(-\alpha_{ij}\tau_{ij}\right)$ e $\tau_{ij} = \frac{\Delta g_{ij}}{RT}$.

4. Results and discussion

4.1. Experimental solubility

From average values of experimental data of RI from paracetamol at different temperatures and concentrations and the curves obtained for each concentration of solvent-solvent system, the solubilities were obtained and expressed in Table 1.

From Table 1, it is possible to confirm the increase in Paracetamol solubility with the increase in the temperature of the solvents. Compared to pure solvents, the order of solubility in molar fraction of paracetamol, within the temperatures employed, was as follows: ethanol > propylene glycol > water. Comparing the results of the

Table 5
Parameters of Apelblat at different concentrations in ethanol-water systems and water-PG.

Solvent (%, m/m)	A	B	C	10^2 RAD	10^3 RMSD
Ethanol					
0%	744.20	−37,240.35	−109.83	4.90	0.13
25%	347.31	−19,563.37	−50.28	5.89	0.96
50%	395.44	−21,133.10	−57.59	2.80	1.64
75%	57.06	−4559.36	−7.85	4.23	3.45
100%	−73.60	1457.60	11.54	4.54	3.57
PG					
0%	744.20	−37,240.35	−109.83	4.90	0.13
25%	−542.97	21,413.38	81.70	5.76	0.44
50%	187.21	−12,184.79	−26.45	3.82	0.96
75%	−441.67	17,782.16	66.45	3.11	1.78
100%	−50.89	527.44	8.10	2.02	1.08

Table 3
Parameters estimated with the experimental data of this work for pure solvents, Paracetamol (1)-solvent (2).

Parameters	Water	Ethanol	PG	Water	Ethanol	PG
	Wilson			UNIQUAC		
λ12 (kJ/mol)	3.2695	−3.3608	−3.5277	−9.6582	−319.7255	242.5473
λ21(kJ/mol)	5.8950	4.1112	7.2673	64.8779	694.9511	−211.4090
10^2 RAD	7.1780	5.2250	2.0150	8.5449	7.4014	1.9995
10^3 RMSD	0.1930	4.0470	1.4790	0.1925	6.002	1.4523
	NRTL			λh		
g12(kJ/mol)	25.5271	−6.1555	60.6860	0.5000	0.5000	0.5000
g21(kJ/mol)	8.6659	10.9699	−0.5147	10,805.8676	4268.5160	4280.1870
α	0.4700	0.2000	0.2000	–	–	–
10^2 RAD	6.9790	4.9830	2.0340	22.831	4.765	3.552
10^3 RMSD	0.181	3.998	1.523	0.888	3.831	2.727

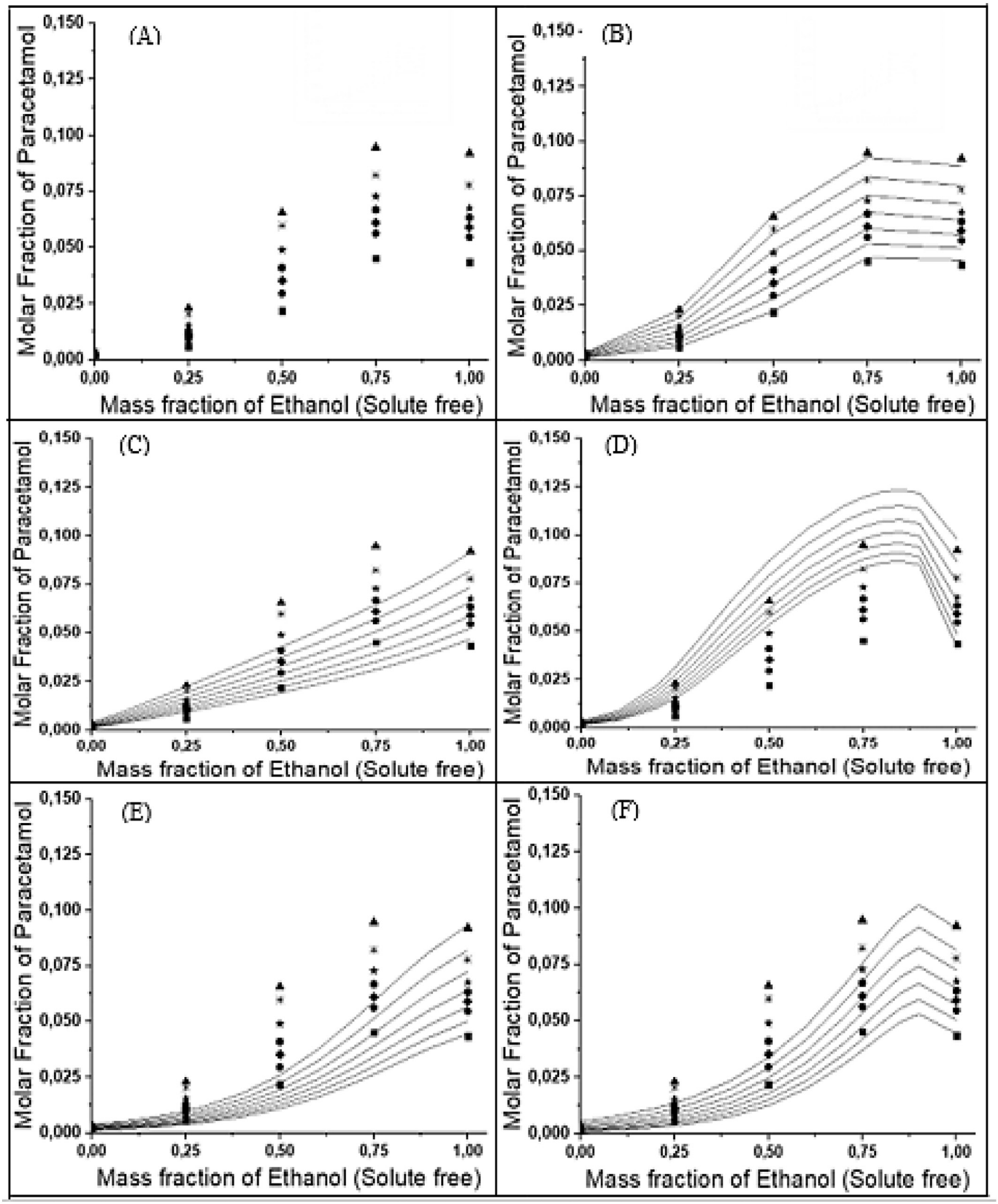

Fig. 1. Solubility curve water-ethanol-paracetamol in different temperatures, ■ to 20 °C, ● to 25 °C,♦ to 30 °C, ⬟ to 35 °C, ⋆ to 40 °C, * to 45 °C e ▲ to 50 °C. (A) Experimental, (B) Apelblat, (C) Wilson, (D) UNIQUAC, (E) NRTL, (F) λh.

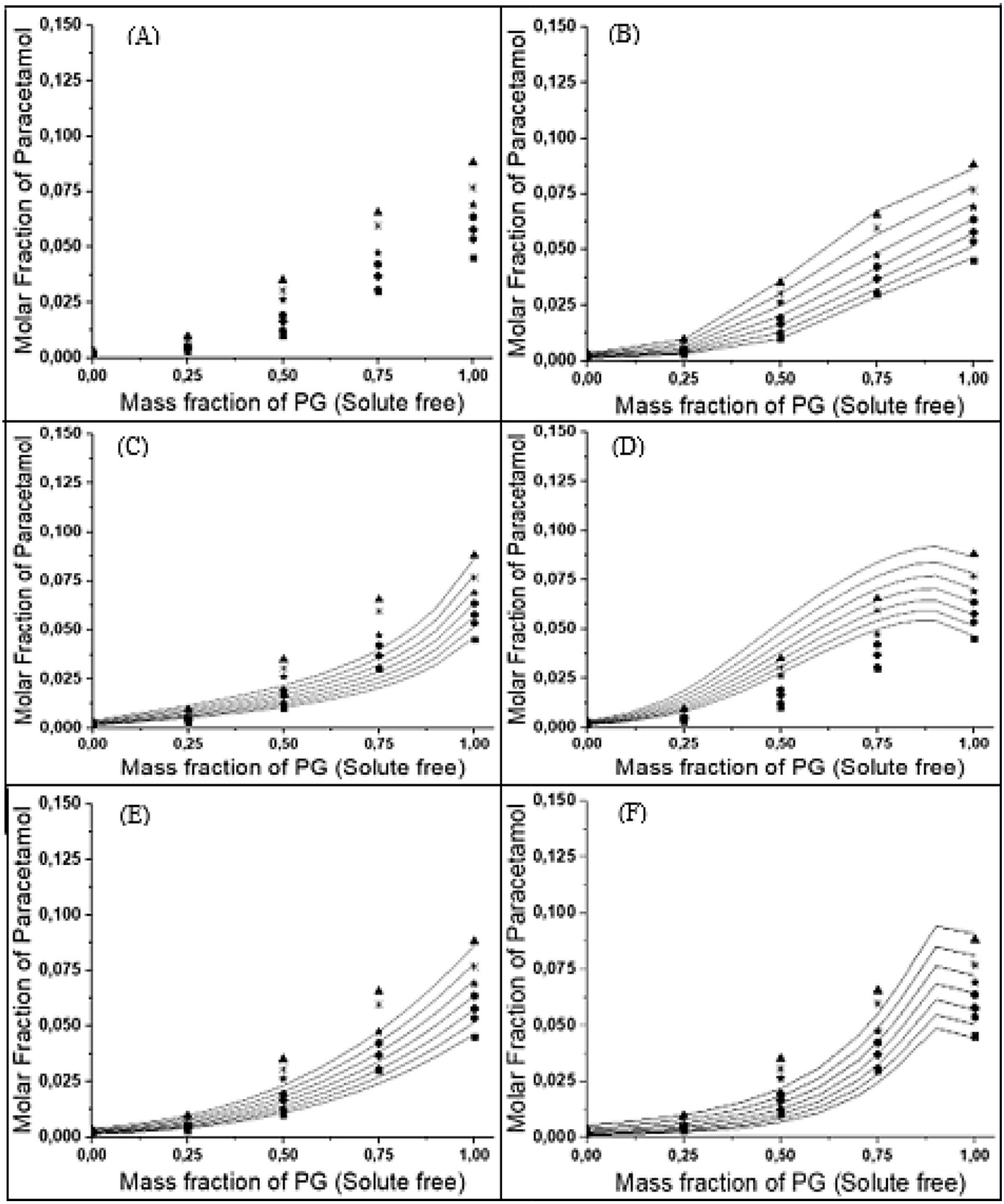

Fig. 2. Solubility curve water-PG-paracetamol in different temperatures, ■ to 20 °C, ● to 25 °C, ♦ to 30 °C, ⬟ to 35 °C, ⋆ to 40 °C, * to 45 °C e ▲ to 50 °C. (A) Experimental, (B) Apelblat, (C) Wilson, (D) UNIQUAC, (E) NRTL, (F) λh.

Table 6
AAD medium and maximum of the models using the parameters 1 in relation to the experimental data.

AAD Models	Ethanol					PG				
	0%	25%	50%	75%	100%	0%	25%	50%	75%	100%
Apelblat										
AADmedium	0.0001	0.0008	0.0012	0.0029	0.0030	0.0001	0.0003	0.0008	0.0014	0.0013
AADmaximum	0.0002	0.0013	0.0023	0.0044	0.0052	0.0002	0.0006	0.0015	0.0028	0.0020
Wilson										
AADmedium	0.0002	0.0019	0.0133	0.0220	0.0034	0.0002	0.0024	0.0059	0.0151	0.0013
AADmaximum	0.0004	0.0035	0.0228	0.0302	0.0059	0.0004	0.0033	0.0134	0.0255	0.0020
UNIQUAC										
AADmedium	0.0001	0.0082	0.0240	0.0301	0.0054	0.0002	0.0071	0.0180	0.0209	0.0012
AADmaximum	0.0003	0.0088	0.0279	0.0320	0.0082	0.0003	0.0091	0.0192	0.0237	0.0020
NRTL										
AADmedium	0.0001	0.0074	0.0257	0.0275	0.0033	0.0001	0.0010	0.0053	0.0097	0.0013
AADmaximum	0.0003	0.0131	0.0396	0.0356	0.0049	0.0003	0.0018	0.0119	0.0178	0.0020
λh										
AADmedium	0.0006	0.0061	0.0212	0.0134	0.0032	0.0020	0.0024	0.0058	0.0070	0.0145
AADmaximum	0.0020	0.0094	0.0318	0.0190	0.0050	0.0067	0.0073	0.0082	0.0135	0.0355

multicomponent mixtures, a different solubility behavior is observed for the water-ethanol system, presenting a maximum solubility in the concentration of 75% w/w of water-ethanol.

4.2. Thermodynamic models 1

Parameters found in the literature. Solvent - solvent interaction parameters for predictive models were obtained in the literature and shown in Table 2 [24,35–38]. To λh model was used the default value for K12 alcohol solutions equal to 0.453, also was considered the λ value for nonideal solution between 0.5 and 10 [30].

The parameters used for solute-solvent in the predictive models were determined by minimizing the relative least squares of the activity coefficients, as proposed by Englezos [39] and expressed in Eq. 10, where the experimental activity coefficient (γ^{exp}) was obtained through Eq. 2 and the calculated activity coefficient (γ^{calc}) was obtained by the respective equation for each model.

$$S(k) = \sum_{i=1}^{N}\sum_{j=1}^{2}\left[\left(\gamma_j^{calc} - \gamma_j^{exp}\right)/\gamma_j^{exp}\right]_i^2 \quad \text{Eq 10}$$

The parameters are shown in Table 3.

Solubility experimental values in pure solvent were correlated with Apelblat, Wilson UNIQUAC, NRTL and λh models. The relative average deviation (RAD), Eq. 11, and the root mean square deviation (RMSD), Eq. 12, were used to assess the applicability and accuracy of the models.

$$RAD = \frac{1}{N}\sum_{I=1}^{N}\left|\frac{\left(X_{1,i}^{exp} - X_{1,i}^{calc}\right)}{X_{1,i}^{exp}}\right| \quad \text{Eq 11}$$

$$\mathrm{RMSD} = \left(\frac{\sum_{I=1}^{N}\left(X_{1,i}^{exp} - X_{1,i}^{calc}\right)^2}{N}\right)^{\frac{1}{2}} \quad \text{Eq 12}$$

Where, x^{exp} is the experimental solubility, x^{calc} is the calculated solubility and N is the number of experimental points.

The solute-solvent parameters presented were determined from the experimental solubility data in pure solvent for all cases. Literature that presents these parameters is scarce. Matsuda [23] determined the interaction parameters in ethanol-paracetamol for NRTL models (g12 = −12.85 kJ.mol^{-1}; g21 = 20.75 kJ.mol^{-1} and α = 0.1) and UNIQUAC (a12 = −2.21 kJ.mol^{-1} and a21 = 3.85 kJ.mol^{-1}). Both models showed distinction in relation to the parameters calculated in this work, NRTL model showed a slight difference from data presented which can be justified by the value of "α" that did not follow the condition of $0.2 < \alpha < 0.47$, it should be noted that the work did not present a graph, or the relative deviation, for comparison with its experimental data.

In comparison to the parameters of water-paracetamol, Hojjati and Rohani [40] presented 4 pairs of distinct interaction parameters for the UNIQUAC model calculated from the non-linear regression of paracetamol solubility in relation to temperature, the best parameter pair presented was a12 = −4.319 and the a21 = 47.69. The parameters are not far from those presented in this work and the existing difference can be justified by the difference in relation to the experimental data.

For the models, values of specific molar volume, UNIQUAC molecular parameters, ΔH_m and T_m are expressed on Table 4.

Only data of ΔH_m and T_m for paracetamol are shown since there is no point on presenting for the other substances. All the parameters of volume and surface area for UNIQUAC model were calculated with UNIFAC group parameters presented on [21], for the coordination number all values were considered equal to 10 [41].

The parameters for the adjustment of Apelblat were made for each of the solvent-solvent concentrations proposed in this work, as performed by Hojjati and Rohani [18] and Zhang et al. [42]. The results are shown in Table 5.

Shakeel [27] and Hojjati and Rohani [18] also reported Apelblat parameters for the water-paracetamol system. The parameters reported by Shakel (A = −62.23; B = 57.60; C = 10.970) and by Hojjati (A = −298.59288; B = 10,495.9; C = 45.11344) have no apparent correlation between themselves and among the results reported in this work, so there is no way to compare the model parameters.

From the parameters presented in Tables 2 to 5, all models were calculated and presented in Figs. 1 and 2.

The absolute average deviation (AAD), medium and maximum, for direct comparison of experimental data with calculated thermodynamic

Table 7
Water Parameters (1) – Solvent (2) determined in this article.

Solvent	WILSON		UNIQUAC		NRTL		
	λ12	λ21	a12	a21	g12	g21	α
Ethanol	774.29	2177.71	−226.48	1000.00	5.65	−1347.06	0.47
PG	3.33	−3.05	9986.48	−424.41	−1266.64	−1524.98	0.2

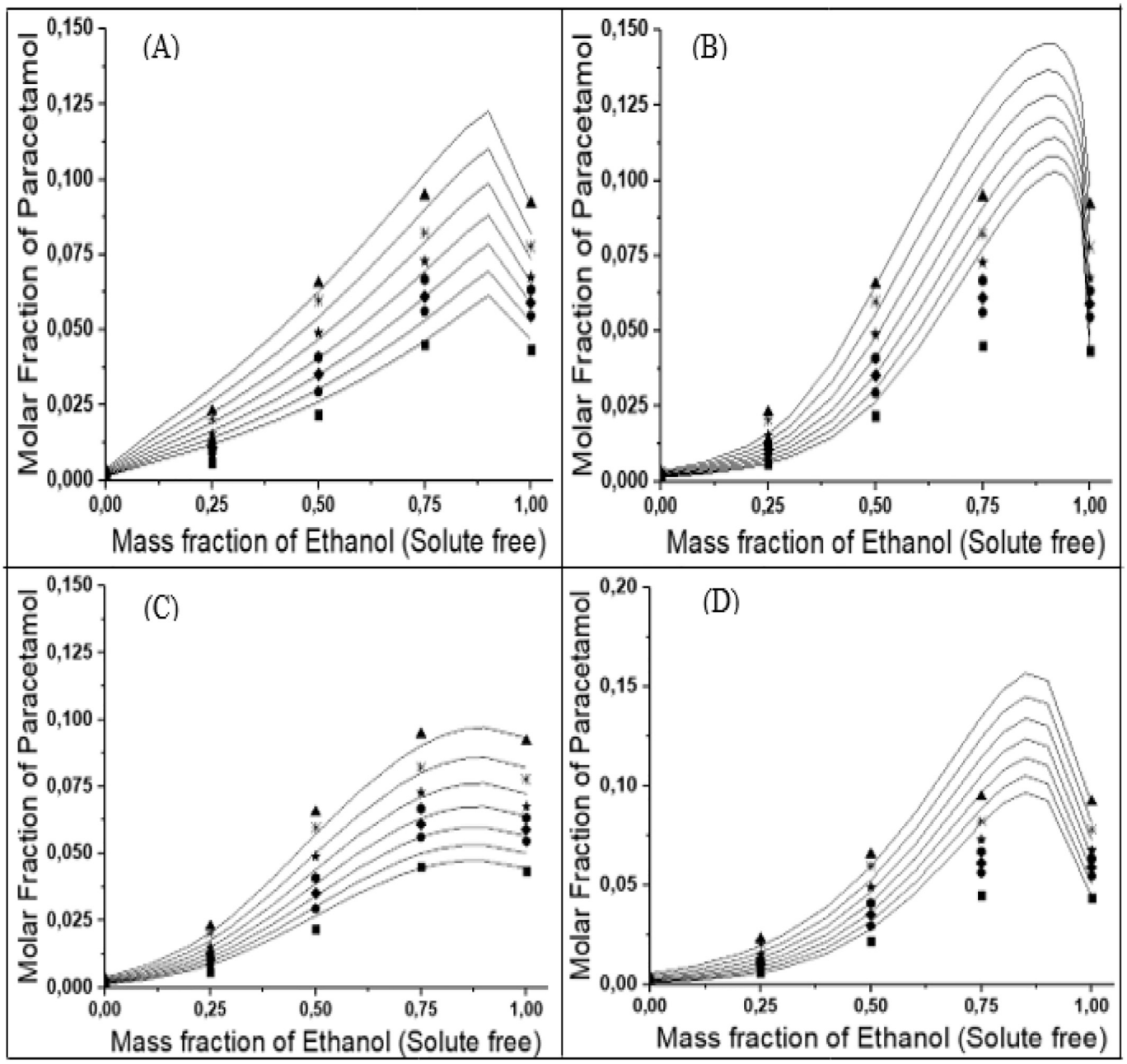

Fig. 3. – Solubility curve 2 for water–ethanol–paracetamol in different temperatures, ■ to 20 °C, ● to 25 °C,♦ to 30 °C,⬟ to 35 °C, ★ to 40 °C, * to 45 °C e ▲ to 50 °C. (A) Wilson, (B) UNIQUAC, (C) NRTL, (D) λh.

data for each model are shown in Table 6. The equation of the AAD is shown in Eq. 13.

$$AAD = \sum_{i=1}^{N} \left(X_i^{exp} - X_i^{calc} \right) / N \qquad \text{Eq 13}$$

Analyzing the adjustments of the thermodynamic models to the experimental data presented in Fig. 1, the UNIQUAC and λh model were the only predictive models capable of qualitatively representing the behavior of the water-ethanol system curve, using the parameters presented in Tables 2 and 3. The UNIQUAC and λh models presents a peak solubility, respectively, in 85% w/w and 93% w/w of ethanol in water.

By comparing the values of 10^2 RAD and 10^3 RMSD of the parameters, for pure solvents, by the models presented, it is possible to define the Apelblat model as the model capable of presenting a better correlation with the experimental results, which is repeated in Table 5. In the other hand, evaluating the parameters of the predictive models, NRTL model showed to be the best model for the pure solvents water and ethanol, while UNIQUAC model showed to be the best model for the pure solvent polypropylene glycol.

Comparing the values of AAD medium and AAD maximum, the predictive model that presented results closer to the experimental data for the water-ethanol system was the Wilson model, and for the water-PG system was the NRTL model.

4.3. Thermodynamic models 2

Once observed that, with the exception of the UNIQUAC and Apelblat models, the interaction parameters of the water-ethanol system for the thermodynamic models obtained from liquid-vapor balance

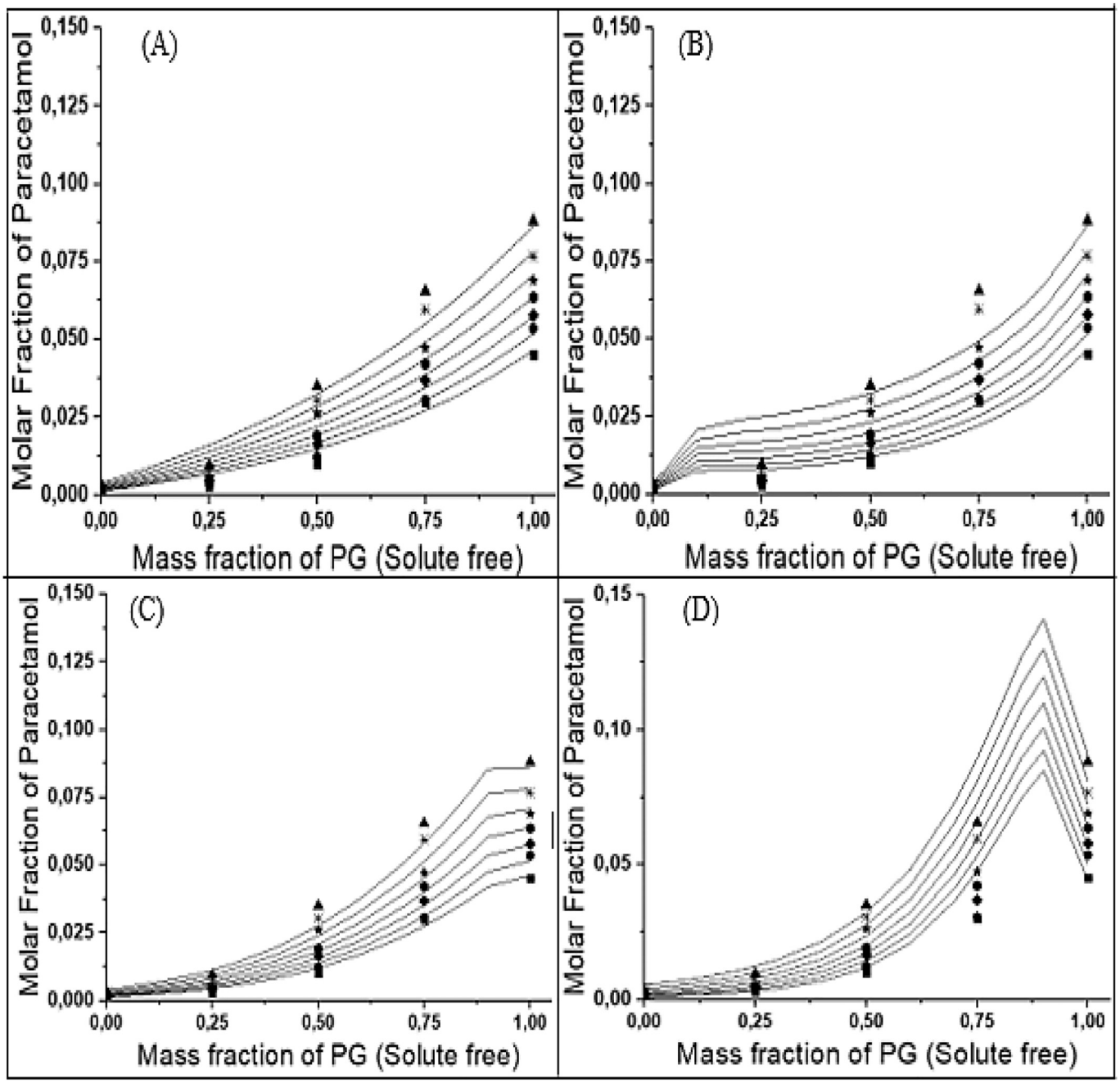

Fig. 4. - Solubility curve 2 for water–PG–paracetamol in different temperatures, ■ to 20 °C, ● to 25 °C, ♦ to 30 °C, ⬟ to 35 °C, ★ to 40 °C, * to 45 °C e ▲ to 50 °C. (A) Wilson, (B) UNIQUAC, (C) NRTL, (D) λh.

Table 8
AAD medium and maximum of the models using the parameters 2 in relation to the experimental data.

AAD Models	Ethanol					PG				
	0%	25%	50%	75%	100%	0%	25%	50%	75%	100%
Wilson										
AADmedium	0.0002	0.0063	0.0024	0.0045	0.0034	0.0002	0.0054	0.0030	0.0048	0.0013
AADmaximum	0.0004	0.0078	0.0055	0.0094	0.0059	0.0004	0.0066	0.0047	0.0105	0.0020
UNIQUAC										
AADmedium	0.0001	0.0042	0.0015	0.0321	0.0054	0.0002	0.0096	0.0019	0.0104	0.0012
AADmaximum	0.0003	0.0071	0.0041	0.0355	0.0082	0.0003	0.0154	0.0031	0.0165	0.0020
NRTL										
AADmedium	0.0001	0.0015	0.0045	0.0038	0.0033	0.0001	0.0018	0.0035	0.0035	0.0013
AADmaximum	0.0003	0.0027	0.0095	0.0062	0.0049	0.0003	0.0027	0.0076	0.0082	0.0020
λh										
AADmedium	0.0006	0.0021	0.0037	0.0383	0.0032	0.0006	0.0014	0.0019	0.0225	0.0023
AADmaximum	0.0020	0.0041	0.0071	0.0431	0.0049	0.0020	0.0028	0.0030	0.0258	0.0043

studies in the literature were not able to describe the maximum observed solubility for paracetamol in the water-ethanol solvent system, the solvent-solvent interaction parameters for the predictive models were calculated by minimizing Eq. 6 from the experimental data with a concentration of 50% w/w water-ethanol and water-PG, maintaining constant the parameters solvent-solute from Table 3. The new solvent-solvent parameters are shown in Table 7. The values for K12 for systems water-ethanol and water-PG were calculated for values lower them 1 [30]. They are, respectively, equal to 0.7886 and 0.7189.

From the parameters presented in Table 3 and Table 7, the models were calculated and presented in Figs. 3 and 4. The values of AAD medium and maximum are presented in Table 8.

Except for UNIQUAC model for the system water-propylene glycol, all systems had significant improvement with the use of parameters solvent-solvent determined from the experimental data from 50% w/w.

All the models used were able to present a maximum solubility in the water-ethanol system, as shown in Fig. 3. Also, in Fig. 4, the UNIQUAC and λh models did not show the solubility peak for the water-PG. For both studied systems the predictive NRTL model was the best representative data of this article, using the new parameters of water-solvent interaction as it is possible to evaluate by Figs. 3 and 4 and from Table 8.

4.4. Thermodynamic functions of solutions

From the Apelblat model and experimental solubility values we may infer to respect of apparent enthalpy solution (ΔH^*_{sol}) and the apparent entropy of solution (ΔS^*_{sol}) of paracetamol from eqs. 14 and 15 [18,27].

$$\Delta H^*_{sol} = bT - a \quad \text{Eq 14}$$

Table 9
Thermodynamic functions related to the mixing process of paracetamol (1) - water (2) - ethanol (3)/PG (3) using the Apelblat equation.

Pure solvent	ΔH^*_{sol} (kJ/mol*K)	ΔS^*_{sol} (J/mol*K)
Water	28.52	92.65
Ethanol	17.41	56.55
PG	16.35	53.11

Table 10
Thermodynamic functions related to the mixing process of Paracetamol (1) - water (2) - Ethanol (3) / PG (3) by the experimental data.

Solvent (%, w/w)	ΔHsol (kJ/mol*K)	ΔGsol (kJ/mol*K)	ΔS_{sol} (J/mol*K)	$\%\zeta_H$	$\%\zeta_{TS}$
Water	30.12	15.68	46.9268	67.589	13.809
Ethanol	17.39	7.04	33.620	62.694	11.084
PG	16.34	7.06	30.141	63.777	11.738

$$\Delta S_{sol} = b - \frac{a}{T} \quad \text{Eq 15}$$

Where, a = B*R and b = C*R. The results obtained by eqs. 14 and 15 are shown for the pure solvents in Table 9.

From the experimental data, the variation of ΔH_{sol} can be calculated by Eq. 16, obtained by modified Van't Hoff equation with the introduction of harmonic average temperature to minimize errors (Eq. 17) [43].

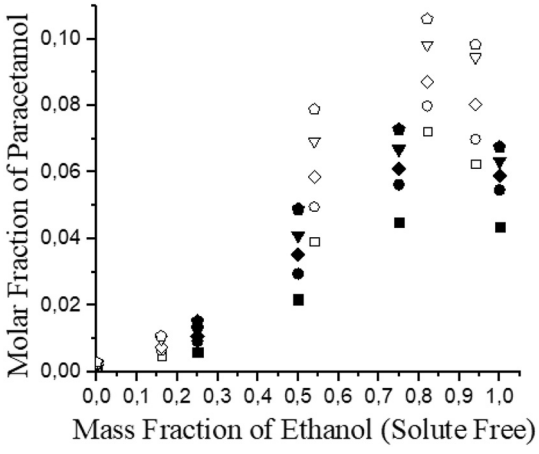

Fig. 6. Solubility data of paracetamol in water-ethanol obtained in this work (filled symbols) compared to BUSTAMANTE (1995) (open symbols). ■ to 20 °C, ● to 25 °C, ♦ to 30 °C, ▾ to 35 °C, ⬟ to 40 °C.

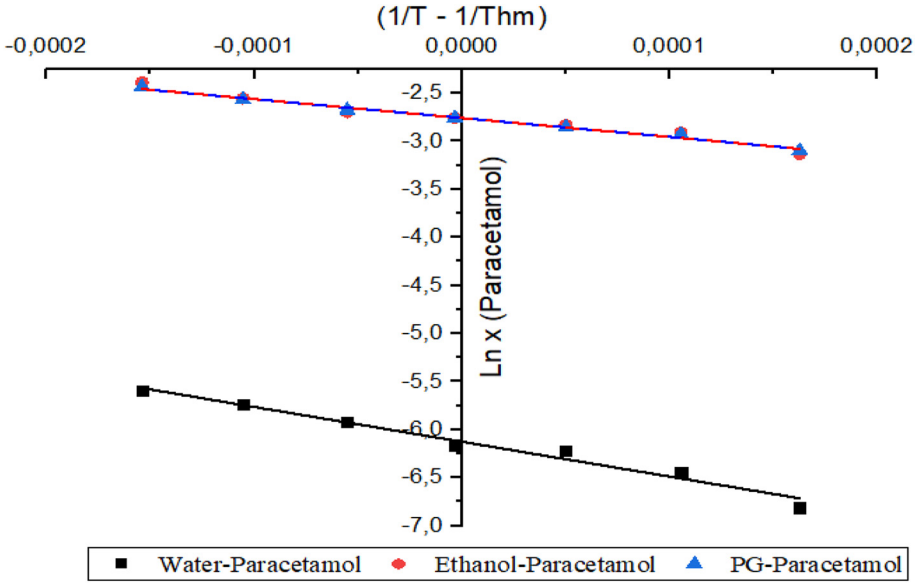

Fig. 5. Ln *x* vs $(1/T - 1/T_{hm})$.

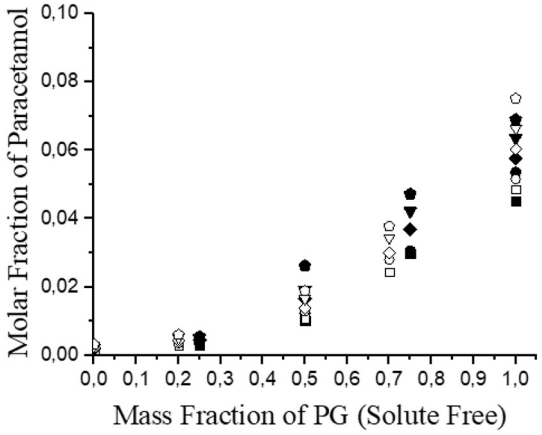

Fig. 7. Solubility data of Paracetamol in water -propylene glycol obtained in this study (filled symbols) in comparison with JIMENEZ (2006) (open symbols). ■ to 20 °C, ● to 25 °C, ♦ to 30 °C, ▾ to 35 °C, ⬟ to 40 °C.

$$\Delta^{*}_{sol}H = -R\left(\frac{\partial \ln X}{\partial(1/T - 1/T_{hm})}\right)_p \quad \text{Eq 16}$$

$$T_{hm} = \frac{n}{\sum_{i}^{n}(1/T)} \quad \text{Eq 17}$$

In practice, the ΔH_{sol} is obtained by the inclination of the graph curve ln x vs (1/T-1/Thm), Fig. 5. Considering an approximation present in Jiménez and Martinez [13], the value of ΔG_{sol} can be obtained by $\Delta G_{sol} = -RT^{*}$Intersection. The ΔS_{sol} is then calculated by Eq. 18.

$$\Delta S_{sol} = \frac{(\Delta H_{sol} - \Delta G_{sol})}{T_{hm}} \quad \text{Eq 18}$$

The relative contribution of enthalpy ($\%\zeta_H$) and entropy ($\%\zeta_{TS}$) in the solution is given by Eqs. 19 and 20 [43].

$$\%\zeta H = \frac{|\Delta H_{sol}|}{|\Delta H_{sol}| + |T\Delta S_{sol}|} \quad \text{Eq 19}$$

$$\%\zeta H = \frac{|T\Delta S_{sol}|}{|\Delta H_{sol}| + |T\Delta S_{sol}|} \quad \text{Eq 20}$$

The results obtained are shown in Table 10.

The values of ΔH_{sol} from Apelblat (Table 9) are close to the values obtained by the experimental data (Table 10), except for water, which presents a relative error of 5.31%.

All values ΔG_{sol} are positive, indicating that the solubility does not occur spontaneously, as such ΔH_{sol} values are also positive, and indicate that systems solubility occurs by an endothermic process. The enthalpy values are lower for PG, which indicates that less energy is needed for solubility. ΔS_{sol} values are positive in all cases, indicating that entropy is leading solubility process.

For all cases, the relative contribution to enthalpy ($\%\zeta_H$) was above 60%. Thus, the main contributor to the standard Gibbs molar energy (positive) for paracetamol solution is enthalpy, in line with Jiménez and Martinez [13].

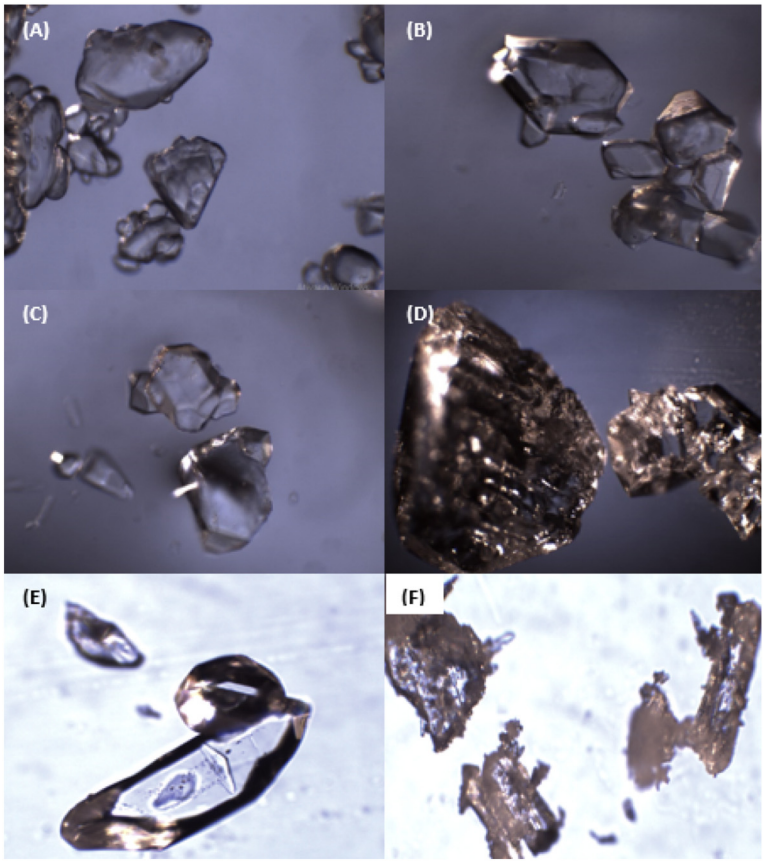

Fig. 8. OM with 100× magnification of paracetamol crystals in water-ethanol system. (A) water, (B) water- ethanol 25%, (C) water-ethanol 50%, (D) water-ethanol 75%, (E) ethanol, (F) pure paracetamol.

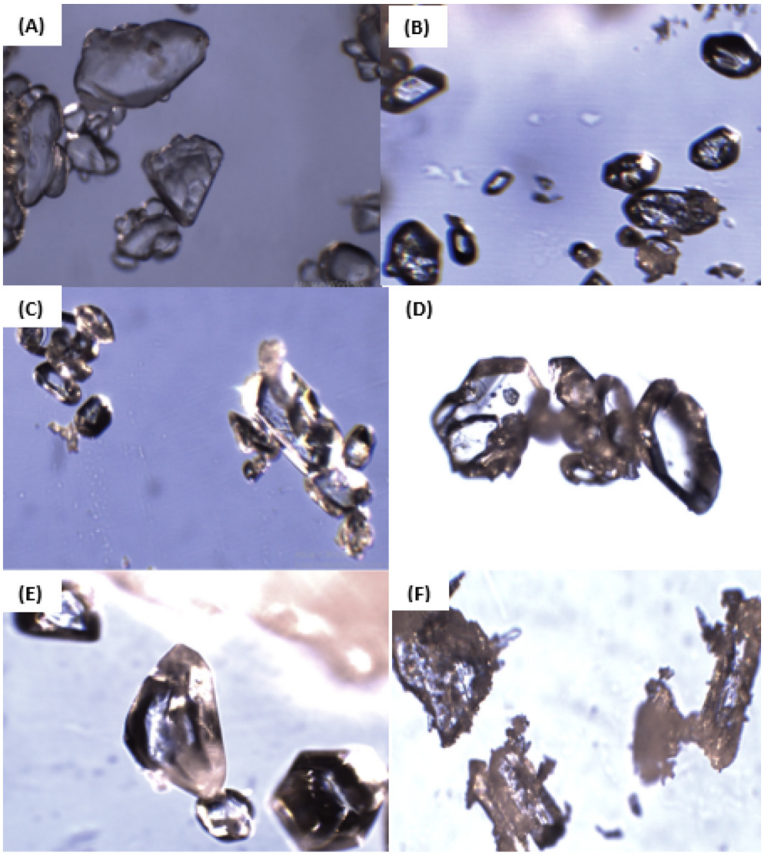

Fig. 9. OM with 100× magnification of the paracetamol crystals in the water-propylene glycol system. (A) water, (B) water-PG 25%, (C) water-PG 50%, (D) water-PG 75%, (E) propylene glycol, (F) pure paracetamol.

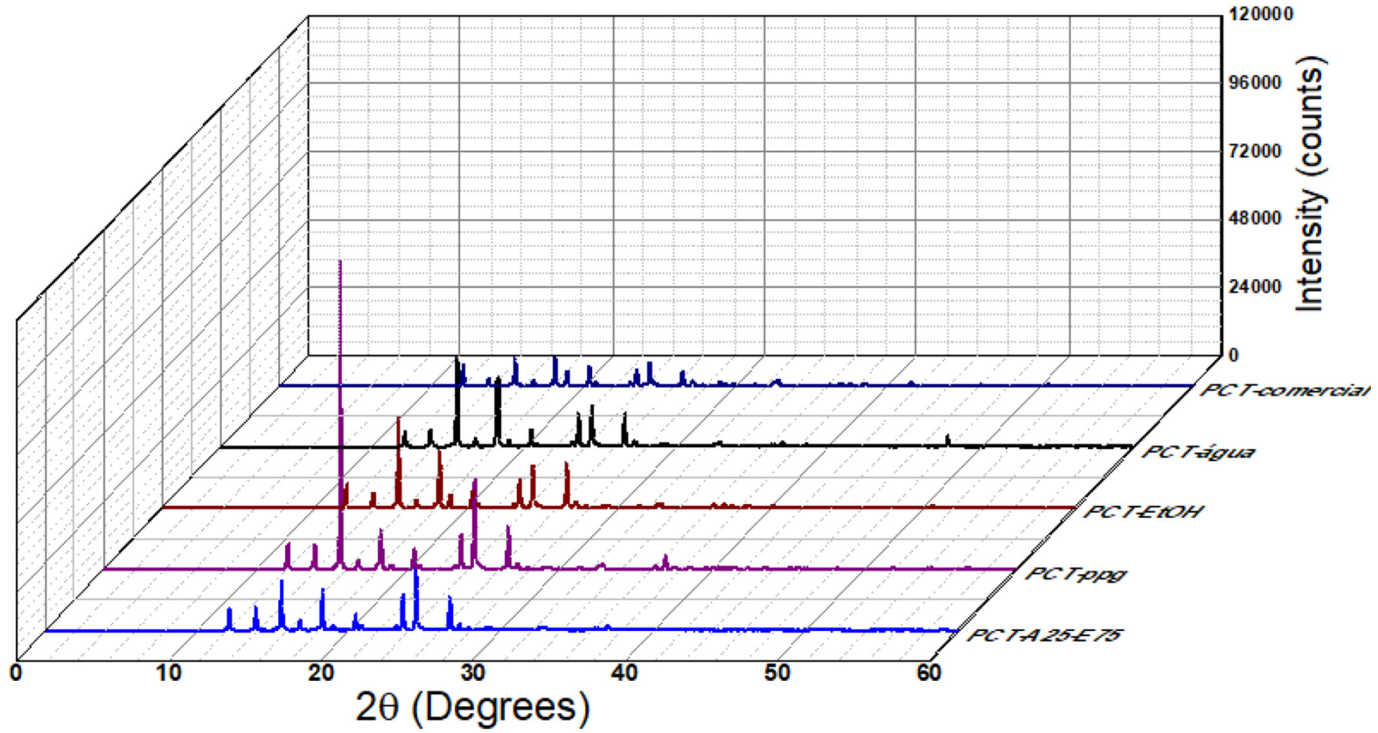

Fig. 10. X-ray diffraction analysis of the crystals of commercial paracetamol, suspended in water, in ethanol, in propylene glycol and in the mixture of 25% water and 75% ethanol by mass.

4.5. Literature reference

The experimental results of this article were compared to available literature [11,13]. Since the data were not obtained at the same solvent concentrations, the comparison was made by graph interpolation. Comparisons are shown in Figs. 6 and 7.

Comparing the experimental results of this article with the literature data for the water-ethanol system, shown in Fig. 6, even with a dispersion between the reported values, which are systematically higher than those presented in this work, the trend of the solubility curve shows a peak of solubility between 75% w/w (this work) and 80% w/w [10].

Obtained data compared with water-propylene glycol system (Fig. 7) show high similarity, identifying a fidelity of methodology applied in this work, which does not use a series of dilutions in analyzed samples to reduce the propagation of experimental errors.

4.6. Characterization of solids formed

Optical microscopy (OM) were performed with magnification of 100× of crystals in equilibrium with the solution at environment temperature for different solvent compositions (Figs. 8 and 9) to evaluate the effect of solvent composition in paracetamol crystals habit.

In Fig. 8 it is possible to notice a similarity in the habits of the crystals presented in figures (A), (B), (C), coming from the water-ethanol system with up to 50% ethanol. However, a difference can be seen in crystal habit of the figure (D), obtained from the system with 75% ethanol, and (E) from the solution with pure ethanol.

From the images shown are in Fig. 9, there are no significant changes in the crystal habit with change of composition from solvent system to water-PG.

Fig. 10 shows the results of X-ray powder diffraction of paracetamol crystals. Original paracetamol crystals, acquired for the experiments, were analyzed, as well as the crystals suspended in pure water, in propylene glycol, in pure ethanol, and in the mixture of 25% water and 75% mass ethanol.

From the results of the analysis of X-ray powder diffraction all the paracetamol samples analyzed have the same crystalline structure. Therefore, any polymorphic transition did not occur during the solubility tests. The peak solubility observed in the water-ethanol system is not the result of a change in the crystalline structure of the crystals in equilibrium with the solution.

5. Conclusion

From presented and discussed data in this work, it is possible to verify the complexity of paracetamol in solution and a huge dependence on the solvents and solvent mixtures used. The solubility data in water-ethanol and water-propylene glycol systems obtained by refractometry were reported and have a good correlation with the models used when determining the solvent-solvent interaction parameters from the experimental data.

The system ethanol-water-paracetamol achieved a maximum solubility value for a mixture of 25% water and 75% ethanol, while the system water-propylene glycol- paracetamol showed a higher solubility with pure propylene glycol. Optical microscopy data indicate a possible slight change in the crystalline habit of paracetamol crystals, which suggests the occurrence of recrystallization or maturation of the crystals during the solubility tests. Furthermore, the results of the X-ray analyze indicate that there is no change in the crystalline structure of the crystals in any solvent system studied. Being so, the change in habit seems to be linked more to the surface energy of the solute-solvent interaction.

Thermodynamic models were adjusted using interaction water-solvent systems obtained from literature from the vapor-liquid and liquid-liquid balance. For this set of parameters, only the UNIQUAC and λh model were able to describe the maximum solubility point of the water-ethanol-paracetamol system. Considering water-solvent interaction parameters adjust with experimental water-solvent data of this work, NRTL model is the one that come closer to the experimental solubility data.

In all the pure solvents used, the values of ΔG, ΔH and ΔS indicated a non-spontaneous endothermic process, conducted by entropy.

Funding

We acknowledge the financial support from Coordination of Improvement of Higher Education Personnel (CAPES, Finance Code 001), and National Council for Scientific and Technological Development (CNPq).

CRediT authorship contribution statement

Gabriel Pereira Assis: Investigation, Validation, Writing - original draft. **Rafael Henrique Lazzari Garcia:** Data curation, Writing - review & editing. **Silas Derenzo:** Writing - review & editing. **André Bernardo:** X-ray diffraction analysis of the crystals of commercial paracetamol, suspended in water, in ethanol, in propylene glycol and in the mixture of 25% water and 75% ethanol by mass. Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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