Review

Thermodynamic analysis of the solubility of triclocarban in ethylene glycol + water mixtures

Ana María Cruz-González [a,b], Martha Sofía Vargas-Santana [a,b], Sebastian de Jesus Polania-Orozco [a],
Claudia Patricia Ortiz [c], Nestor Enrique Cerquera [d], Fleming Martínez [e], Daniel Ricardo Delgado [f,*],
Abolghasem Jouyban [g,h], William E. Acree Jr [i]

[a] Research Group of Science, Ciencia, Ingeniería e Innovación, Sifati Group Ingeniería S.A.S, Palermo, Huila, Colombia
[b] Estudiante de Maestría en Ingeniería y Gestión Ambiental, Universidad Surcolombiana, Avenida Pastrana Borrero - Carrera 1, Neiva, Huila, Colombia
[c] Corporación Universitaria Minuto de Dios-UNIMINUTO, Programa de Administración en Salud Ocupacional, Grupo de Investigación en Seguridad y Salud en el Trabajo, Neiva, Huila, Colombia
[d] Universidad Surcolombiana, Faculty of Engineering, Agricultural Engineering Program, Hydro Engineering and Agricultural Development Research Group (GHIDA), Avenida Pastrana Borrero - Carrera 1, Neiva, Huila, Colombia
[e] Universidad Nacional de Colombia, Sede Bogotá, Facultad de Ciencias, Departamento de Farmacia, Grupo de Investigaciones Farmacéutico-Fisicoquímicas, Cra. 30 No. 45-03, Bogotá D.C., Colombia
[f] Universidad Cooperativa de Colombia, Facultad de Ingeniería, Programa de Ingeniería Civil, Grupo de Investigaciones GRIAUCC, Calle 11 No. 1-51, Neiva, Huila, Colombia
[g] Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[h] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[i] Department of Chemistry, University of North Texas, Denton, TX 76203-5070, USA

ARTICLE INFO

ABSTRACT

The solubility of triclocarban (TCC) was determined in {ethylene glycol (EG) + water} cosolvent mixtures at 7 temperatures (288.15–318.15 K). The solubility of TCC increases with increasing temperature and the polarity of the cosolvent system decreases with increasing EG concentration. In that case, TCC reaches its minimum solubility in pure water at 288.15 K and maximum solubility in EG at 318 K. The thermodynamic functions were calculated using the van Hoff equation, and it was determined that the process is endothermic and, according to entropy enthalpy compensation analysis, is driven by entropy in water-rich mixtures, and by enthalpy in intermediate and EG-rich mixtures. According to transfer functions, TCC tends to transfer from polar to less polar media. Regarding preferential solvation analysis, carried out using the IKBI model, TCC is preferentially solvated by water in water-rich mixtures and by EG in intermediate and EG-rich mixtures.

© 2020 Elsevier B.V. All rights reserved.

Contents

* Corresponding author.
  E-mail address: danielr.delgado@ucc.edu.co (D.R. Delgado).

A.M. Cruz-González, M.S. Vargas-Santana, S. de Jesus Polania-Orozco et al.

Journal of Molecular Liquids 325 (2021) 115222

1. Introduction

Triclocarban (TCC, $C_{13}H_9Cl_3N_2O$, Figs. 1, 1-(4-chlorophenyl)-3-(3,4-dichlorophenyl)-urea, CAS number: 101–20-2, molar mass: 315.58 g.mol^{-1}) is a powerful antimicrobial, which affects plants, fungi and bacteria, because it inhibits the activity of the enzyme enoyl - (acyl-carrier protein) (ACP) reductase [1]. This is essential for the production of fatty acids necessary for the development of cell membranes and therefore for the survival of these organisms [2].

However, the increase in the development of pharmaceutical and cosmetic products containing TCC [3], have generated an environmental problem due to the excessive dumping of these products into wastewater, increasing the presence of this drug in natural systems [4–7], to the point that organizations such as the NORMAN Network has classified it as a "highly toxic emerging pollutant".

From an industrial point of view, one of the best strategies for reducing the volume of TCC dumping is the optimization of processes and/or the development of clean methodologies for development of products containing TCC [8,9]. These alternatives are viable as long as there is information on properties directly related to the development of pharmaceutical products, such as solubility in different media, product stability, partition coefficient, among other physicochemical properties, which will allow elucidating production strategies with low environmental impact [10,11]. This is due to the fact that data as important as the solubility of in different solvents and co-solvent mixtures, allows to develop more efficient processes in terms of crystallization, purification, analysis and quality control, processes typical of the pharmaceutical industry that involve a significant amount of technical resources [12].

The environmental problem generated by the presence of TCC in aquatic, benthic, sludge, sediment and biota environments has been recorded by many researchers [13–16], however the study of its physicochemical properties is limited, therefore, the objective of this research work is to present the solubility of TCC in a cosolvent system of great importance for the pharmaceutical industry, especially in analysis and quality control processes where the use of these reagents is constant [17,18].

2. Experimental methods

2.1. Reagents

In this research, triclocarban (Sigma-Aldrich, USA; compound 3; with purity of at least 0.990 in mass fraction), ethylene glycol (Merck A.R., Germany; the solvent component 1, purity at least 0.998 in mass fraction), ethanol (Sigma-Aldrich, USA; with purity of at least 0.990 in mass fraction), and distilled water with conductivity 2 μS.cm^{-1} (the solvent component 2) were used.

2.2. Preparation of solvent mixtures

The solubility study was carried out in {ethylene glycol (EG) + water} cosolvents mixtures. Between 10 and 100 g of each mixture was prepared, using an analytical balance with a sensitivity of ± 0.1 mg. The EG mass fractions were prepared varying in 0.05 from 0.05 to 0.95, for a total of 19 cosolvent mixtures.

2.3. Solubility determinations

The solubility of TCC was determined using the shake flask method followed by UV/Vis spectrophotometry (EMC-11-UV spectrophotometer, Germany). According to this, it was used amber type I glass flasks with a capacity of 10 cm^3, an amount of solvent or cosolvent mixture was added to each flask that would fill 2/3 of the capacity of each flask, then TCC was added, stirring constantly until the mixture was saturated, checking that a quantity of solid TCC was always present at the bottom of the flask. Subsequently, the samples were taken to a water recirculation bath with thermostat (Medingen K-22/T100, Germany) remaining there for 72 h at each study temperature (288.15 K - 318.5 K; varying from 5 to 5 degrees).

In the case of co-solvent mixtures with low EG mass fractions (between 0.05 and 0.035), 50 cm^3 bottles were used, due to the low solubility of TCC and the need for a large quantity of sample to quantify the drug.

To determine solubility, an aliquot was taken from each sample, filtering it isothermally through a membrane with a pore size of 0.45 μm (Millipore Corp. Swinnex®-13, USA), diluting it with pure ethanol (EtOH), to guarantee a homogeneous solution avoiding the precipitation of the drug. This is due to the high solubility of TCC in EtOH at room temperature [19].

In cosolvent mixtures with mass concentrations of EG less than 0.3, the standard addition technique had to be used due to the low solubility of TCC. This method was described in a work published by Delgado et al. [4]. Each procedure was performed in triplicate, presenting the results as an average of the three experimental data ± their standard deviation.

2.4. Calorimetric study

It was determined the temperature and enthalpy of fusion of 4 samples of TCC: a sample of the standard and three samples obtained from solid phase in equilibrium with the W, the EG and the mixture 1: 1 {EG (1) + water (2)}, by means of differential colorimetric scanning or DCS (DSC 204 F1 Phoenix, Germany). The heating ramp used in the study was 10 K.min^{-1} from 303.15 K to 580 K with a nitrogen stream of 10 cm^3.min^{-1}. The equipment was calibrated using 99.99% pure indium. The procedure was developed in a similar way to other published procedures [20].
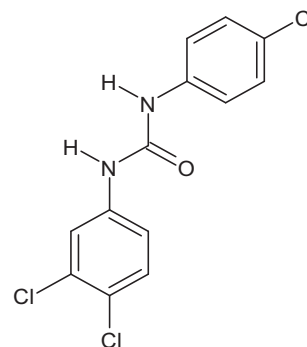

Fig. 1. Molecular structure of triclocarban.

A.M. Cruz-González, M.S. Vargas-Santana, S. de Jesus Polania-Orozco et al.

Journal of Molecular Liquids 325 (2021) 115222

3. Results and discussion

3.1. Solubility of TCC in {EG (1) + water (2)} cosolvent mixtures

Table 1 shows the solubility data of TCC in two pure solvents (EG and water) and 19 {EG (1) + water (2)} cosolvent mixtures at 7 different temperatures (288.15 K, 293.15 K, 298.15 K, 303.15 K, 308.15 K, 313.15 K and 318.15 K), expressed in mole fraction in addition to the ideal solubility calculated from Eq. (1).

$$x_3^{id} = e^{\left\{-[\Delta_{fus}H(T_{fus}-T)]RT_{fus}^{-1}T + \Delta C_p R^{-1}\left[(T_{fus}-T)T^{-1} + \ln\left(TT_{fus}^{-1}\right)\right]\right\}} \tag{1}$$

where $\Delta_{fus}H$ is the enthalpy of fusion, T_{fus} is the melting temperature, T is the solution temperature, ΔC_p is the change in heat capacity when going from its crystalline state to a hypothetical supercooled liquid. Since ΔC_p is difficult to calculate experimentally, a good approximation is to replace ΔC_p by the entropy of fusion ($\Delta_{fus}S$) [21,22]. The solubility data are also presented graphically in Fig. 2. The data on solubility in water between 293.15 K and 313.15 K were taken from the literature [4,23].

According to the behavior of the solubility of TCC, in all cases it increases as the study temperature increases, indicating an endothermic process. On the other hand, in relation to the cosolvent composition, the solubility of the drug increases as the concentration of EG increases, indicating a greater affinity for the solvent of lower polarity. Thus, the lowest solubility is obtained in pure water, $x_3 = 1.96 \ (0.12) \times 10^{-9}$ ($\delta_2 = 47.8$ MPa$^{1/2}$ [24]) at 288.15 K and the highest solubility in pure EG, $x_3 = 2.639 \ (0.027) \times 10^{-5}$ ($\delta_1 = 34.9$ MPa$^{1/2}$ [24]) at 318.15 K. This behavior is reasonable, since the calculated polarity of the TCC is 27.9 MPa$^{1/2}$ (Table 2), therefore it would be expected that the maximum solubility would be reached. in the middle of the lowest polarity.

In order to determine any polymorphic change of the TCC when interacting with the study solvents, it was performed a differential calorimetric scanning analysis on both the original sample and 3 solid

phases in equilibrium with their respective saturated solution (W, $w_1 = 0.50$, EG). The thermograms present two peaks, where the second represents a phrase transition, which had already been reported by Delgado et al. [4]. As can be seen in Fig. 3, the 5 samples have melting points similar to the original sample (Original sample = 527.8 K, W = 527.2 K, $w_{0.50-EG}$ = 527.6 K, EG = 529.1 K), indicating that possible polymorphic changes are not present. The melting temperature data coincide with some data published by different authors, 528.2 K [25], 528.15–528.15 K [26,27], 525 K [4].

In general terms, triclocarban presents a very low solubility in systems rich in water, which could be due to differences in polarities among other factors. However, in the present work (and in another already published), it is shown that the solubility in less polar media as organic solvents, such as acetone, ethyl acetate, acetonitrile [25] and dioxane [4], the solubility of TCC can reach up to molar fractions of 0.5, extremely high concentrations compared to that of water.

3.2. Activity coefficients

In Table 3, the activity coefficients (γ_3) of the TCC in {EG (1) + water (2)} cosolvent mixtures are presented at the 7 calculated study temperatures, considered from Eq. (2) [28].

$$\gamma_3 = x_3^{id} x_3^{-1} \tag{2}$$

In all cases, the activity coefficients are greater than unity, indicating a wide deviation from ideality [29].

Although the ideal solubility depends exclusively on the physicochemical properties of the drug, regardless of the solvent or mixture of solvents [30,31], the calculation of the activity coefficients makes it possible to elucidate the possible molecular interactions from the analysis of Eq. (3) [19].

$$\ln \gamma_3 = (e_{11} + e_{33} - 2e_{13})V_3\phi_1^2 R^{-1}T^{-1} \tag{3}$$

where e_{11} and e_{33} represent the solvent-solvent and solute-solute molecular interactions respectively, and e_{13} represents the solute-solvent interactions (V_3: Molar volume of the solute; φ_1: volumetric fraction of the solvent, R: Ideal gas constant, T: Solution temperature), because $V_3\phi_1^2 R^{-1}T^{-1}$ can be considered a constant, $\ln \gamma_3$ dependent only on e_{11}, e_{33} and e_{12}; therefore, a global analysis of the behavior of the activity coefficient can be carried out as a function of possible molecular interactions.

According to Eq. (3), the solute-solute and solvent-solvent molecular interactions are possibly greater than the solute-solvent internments, which increases as the EG concentration increases. In water and in water-rich mixtures, hydrophobic hydration can lead to an increase in e_{11} by increasing the concentration of EG, the energy of solute-solvent interaction (e_{33}) could increase.

3.3. Solubility correlation

Mathematical models to calculate the solubility of drugs in mixed solvent systems at isothermal condition and/or various temperatures are highly in demand in the industry and several methods were published in the literature [32]. Most of these methods were compared regarding their correlation capability for the equilibrium solubility of several drugs [33–35].

The most commonly applied model in the pharmaceutical applications, because of its simplicity, is the log-linear model of Yalkowsky [36] which was represented as:

$$\ln x_{3(1+2)} = w_1 \ln x_{3(1)} + w_2 \ln x_{3(2)} \tag{4}$$

where $x_{3(1+2)}$ is the mole fraction solubility in the binary solvent mixture, w_1 denotes the mass fraction of EG (solvent 1) in the absence

Table 1
Triclocarban solubility in {ethylene glycol (1) + water (2)} mixtures expressed in mole fraction ($10^7 \times _3$) at different temperatures and $p = .096$ MPa.[a]

w_1[b]	T / K[c, d]						
	288.15	293.15	298.15	303.15	308.15	313.15	318.15
0.00	0.0196	0.0238[e]	0.0285[e]	0.0378[e]	0.0572[e]	0.0748[e]	0.0928
0.05	0.0331	0.0424	0.0506	0.0675	0.101	0.126	0.146
0.10	0.0651	0.0771	0.0971	0.134	0.184	0.237	0.280
0.15	0.112	0.140	0.178	0.238	0.314	0.394	0.487
0.20	0.198	0.244	0.296	0.362	0.529	0.649	0.819
0.25	0.289	0.335	0.466	0.622	0.741	0.815	1.05
0.30	0.535	0.611	0.892	1.13	1.41	1.52	1.95
0.35	0.955	1.14	1.58	2.10	2.53	2.89	3.93
0.40	1.36	1.82	2.10	2.93	3.63	4.71	5.95
0.45	1.92	2.50	3.18	4.33	5.16	6.58	8.80
0.50	2.56	3.14	4.51	5.84	6.99	8.77	11.99
0.55	3.22	4.38	5.27	7.27	8.75	12.03	15.59
0.60	3.83	5.64	6.57	8.71	11.27	15.96	19.23
0.65	5.48	7.30	9.93	11.90	16.22	20.32	28.64
0.70	7.48	11.26	13.16	20.16	22.42	32.76	39.59
0.75	9.92	13.71	18.48	25.00	31.05	42.12	54.09
0.80	12.83	17.24	25.37	31.58	42.04	53.30	71.79
0.85	18.60	26.40	33.53	48.20	64.24	76.91	104.18
0.90	24.69	36.71	44.92	66.61	88.07	103.64	145.77
0.95	32.37	45.75	62.12	82.53	110.06	152.03	197.69
1.00	42.49	58.86	82.95	102.18	137.61	213.59	263.86
Ideal	30,665	36,140[f]	42,475[f]	49,786[f]	58,205[f]	67,876[f]	78,961

[a] Standard uncertainty in pressure $u(p) = 0.001$ MPa.
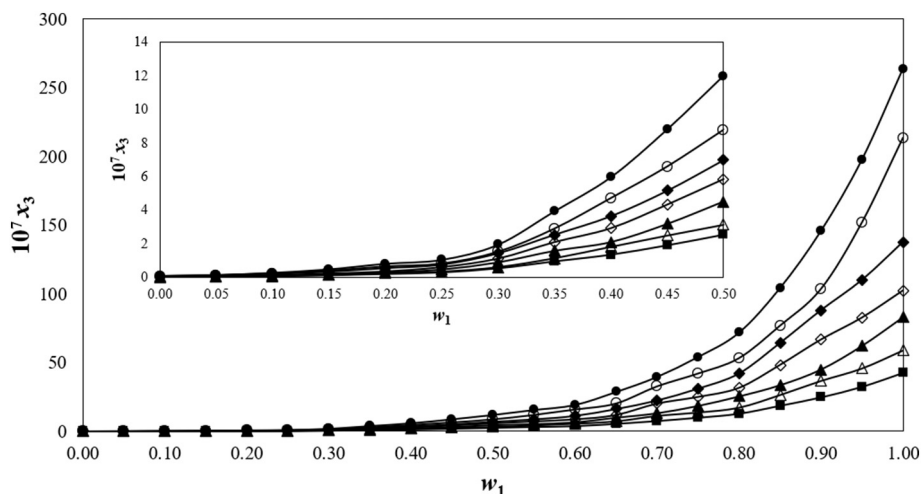[b] w_1 is the mass fraction of ethylene glycol (1) in the {ethylene glycol (1) + water (2)} mixtures free of triclocarban (3).
[c] T is the absolute temperature. Standard uncertainty in temperature is $u(T) = 0.05$ K.
[d] Average relative uncertainty in mole fraction solubility is $u(x_3) = 0.025$.
[e] Values taken from a reference [4].
[f] Values taken from a reference [25].

A.M. Cruz-González, M.S. Vargas-Santana, S. de Jesus Polania-Orozco et al.

Journal of Molecular Liquids 325 (2021) 115222

Fig. 2. Triclocarban solubility in {ethylene glycol (1) + water (2)} mixtures at different temperatures. ■ = 288.15 K, △ = 293.15 K, ▲ = 298.15 K, ◇ = 303.15 K, ♦ = 308.15 K, ○ = 313.15 K, ● = 318.15 K.

of the solute, $x_{3(2)}$ is the mole fraction solubility in the neat water [36]. Yalkowsky model represent the ideal mixing behavior of mixture and no non-ideality parameter is included in the model. Eq. (4) was used to predict the solubility in the various compositions of the binary mixture employing the corresponding experimental data at the temperature of interest and the mean percentage deviations (MPDs ± standard deviation, SD) of 39.1 (± 21.0) % was obtained. The MPD values were computed using:

$$\text{MPD} = \frac{100}{N} \sum \frac{\left| x_{3(1+2)}^{cal} - x_{3(1+2)} \right|}{x_{3(1+2)}} \quad (5)$$

in which N is the number of experimental data points. Although the log-linear model is produced relatively large MPD values, however, it is preferred in practical applications due to its simplicity and requiring very small number of data points in training process. For this model, one only needs the experimental solubility data in the mono-solvents at each temperature of interest and no solubility data in mixed solvents is required. To calculate the solute's solubility in binary solvents at various temperatures with better interpolation capability (i.e. no need for the solubility data in the mono-solvents at all temperatures), the model was modified as [37]:

$$\ln x_{3(1+2)} = w_1 \left(A_1 + \frac{B_1}{T} \right) + w_2 \left(A_2 + \frac{B_2}{T} \right) \quad (6)$$

where A and B terms are the intercept and slope of van't Hoff model, which could be simply computed from linear regression of $\ln x_{3\,(1)}$ or $\ln$

Table 2
Application of Fedors' method to estimate the internal energy, molar volume, and Hildebrand solubility parameter of triclocarban.

Group	Group number	$U°$ / kJ mol^{-1}	$V°$ / cm^3 mol^{-1}
–NH–	1	8.4·1 = 8.4	4.5·1 = 4.5
–CONH–	1	33.5·1 = 33.5	9.5·1 = 9.5
–Cl	3	11.55·3 = 34.65	24·3 = 72
Halogen attached to C atom with double bond	3	−11.55·0.2·3 = 6.93	
Trisubst phenyl	1	31.9·1 = 31.9	33.4·1 = 33.4
Phenylene	1	31.9·1 = 31.9	52.4·1 = 52.4
		$U°_{\text{total}}$ = 133.42	$V°_{\text{total}}$ = 171.8

$\delta 3 = \left(\frac{U°_{\text{Total}} \left(\frac{J}{\text{mol}} \right)}{V°_{\text{Total}} \left(\frac{\text{cm}^3}{\text{mol}} \right)} \right)^{\frac{1}{2}} = \left(\frac{133420}{171.8} \right)^{\frac{1}{2}} = 27.87$ MPa$^{\frac{1}{2}}$

$x_{3\,(2)}$ against $1/T$. The numerical values of these constants for the investigated system are presented as:

$$\ln x_{3(1+2)} = w_1 \left(7.078 + \frac{5608.059}{T} \right) + w_2 \left(-2.797 + \frac{5000.035}{T} \right) \quad (7)$$

The obtained MPD was 39.6 (± 19.9) %. Although 39.6% is relatively large deviation from observed solubilities, however, this prediction tool does not require any more measurement in the mono-solvents or binary solvent mixtures.

The Jouyban-Acree model [38] describes the solubility of a drug in binary solvent mixtures at various temperatures and expressed as:

$$\ln x_{3(1+2)} = w_1 \ln x_{3(1)} + w_2 \ln x_{3(2)} + \left(\frac{w_1 w_2}{T} \right) \sum_{i=0}^{2} J_i (w_1 - w_2)^i \quad (8)$$

where J_i terms are the model constants computed using a no intercept least square analysis [39]. The J_i terms represent non-ideal mixing behavior of the solution. When no significant non-ideal interactions occur in the solution, i.e. J_i terms are not statistically significant, the Jouyban-Acree model reduces to the log-linear model of Yalkowsky. It is an extended version of the combined nearly ideal binary solvent/ Redlich-Kister model [40] and provided the most accurate computations for the solubility of drugs in mixed solvents at various temperatures [34]. The generated solubility of TCC in {EG (1) + water (2)} mixtures was fitted to Eq. (7) and the trained model is:

$$\begin{aligned} \ln x_{3(1+2)} = w_1 \, \ln x_{3(1)} + w_2 \, \ln x_{3(2)} + 1127.964 \left(\frac{w_1 w_2}{T} \right) \\ - 546.633 \left(\frac{w_1 w_2 (w_1 - w_2)}{T} \right) - 336.855 \left(\frac{w_1 w_2 (w_1 - w_2)^2}{T} \right) \end{aligned} \quad (9)$$

The F value of Eq. (9) was 1632, and the correlation and the model constants were significant with $p < .001$. The obtained MPD for the back-calculated solubility data of TCC using Eq. (9) was 8.3 (± 7.8) % (N=147). Eq. (9) is valid for calculating the solubility of TCC in {EG (1) + water (2)} mixtures at various temperatures by employing the solubility data of TCC in mono solvents, EG (1) and water (2) at a specific temperature. Using a combined version of the model with van't Hoff equation, i.e. the Jouyban-Acree-van't Hoff model, one could calculate the solubility in the binary mixtures at each temperature of interest using an interpolation technique. The trained model is:
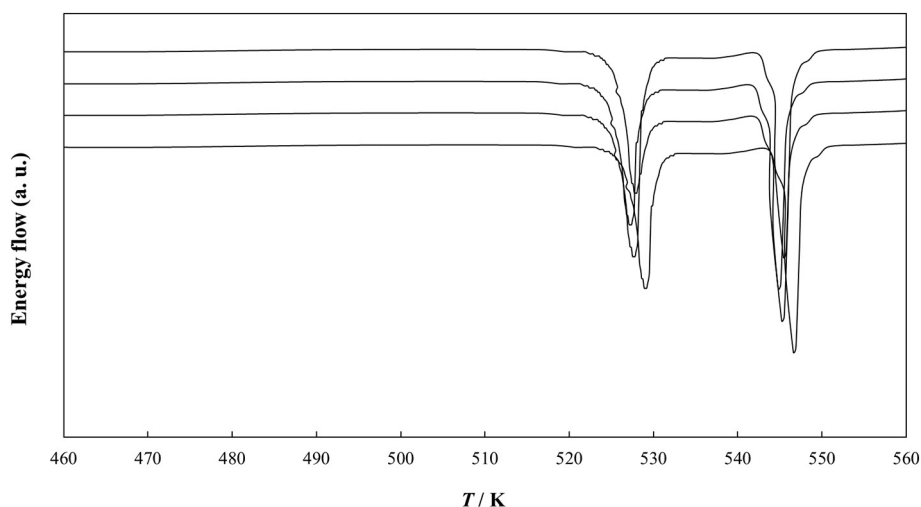
Fig. 3. DSC thermograms of the solid phases in equilibrium with the saturated solutions. From top to bottom: original sample, neat water, mixture $w_1 = 0.50$ and neat ethylene glycol.

$$\ln x_{3(1+2)} = w_1\left(7.078 + \frac{5608.059}{T}\right) + w_2\left(-2.797 + \frac{5000.035}{T}\right)$$
$$+ 1127.964\left(\frac{w_1 w_2}{T}\right) - 546.633\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right)$$
$$- 336.855\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right) \quad (10)$$

which back-calculates the solubility data with the MPD of 8.1 (± 6.7) % ($N = 147$).

To evaluate the prediction capability of the models, the solubility of TCC in all mass fractions of EG at various temperatures, the models were trained by the minimum number of experimental data points. In this respect, seven experimental solubility data, i.e. the solubility data in the mono-solvents at the highest and lowest temperatures and in three data points ($w_1 = 0.25$, $w_1 = 0.50$ and $w_1 = 0.75$ at 298.15 K) were used as training set [54,55]. The following equations were generated to predict the solubility data of TCC:

$$\ln x_{3(1+2)} = w_1\left(7.001 + \frac{5581.307}{T}\right) + w_2\left(-3.560 + \frac{4751.563}{T}\right) \quad (11)$$

$$\ln x_{3(1+2)} = w_1 \ln x_{3(1)} + w_2 \ln x_{3(2)} + 1183.002\left(\frac{w_1 w_2}{T}\right)$$
$$- 488.180\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right) - 1019.250\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right) \quad (12)$$

$$\ln x_{3(1+2)} = w_1\left(7.001 - \frac{5581.307}{T}\right) + w_2\left(-3.560 - \frac{4751.563}{T}\right)$$
$$+ 1187.841\left(\frac{w_1 w_2}{T}\right) - 330.226\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right)$$
$$- 1146.132\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right) \quad (13)$$

Table 3
Coefficient activity of triclocarban in {ethylene glycol (1) + water (2)} mixtures at different temperatures and pressure $p = .096$ MPa.

w_1[a]	T / K						
	288.15	293.15	298.15	303.15	308.15	313.15	318.15
0.00	1,563,539	1,516,747	1,490,509	1,318,631	1,017,314	907,885	850,576
0.05	927,531	852,598	839,145	737,617	578,053	538,614	539,332
0.10	471,230	468,664	437,429	370,348	316,794	286,129	281,547
0.15	273,905	257,408	238,818	208,816	185,134	172,166	162,254
0.20	155,157	148,103	143,560	137,551	110,117	104,618	96,457
0.25	106,139	107,887	91,193	80,020	78,521	83,269	75,344
0.30	57,306	59,183	47,613	44,234	41,174	44,650	40,522
0.35	32,102	31,693	26,932	23,678	23,033	23,455	20,079
0.40	22,625	19,820	20,265	17,003	16,023	14,426	13,261
0.45	15,978	14,467	13,373	11,502	11,286	10,314	8972
0.50	11,998	11,499	9424	8524	8329	7744	6589
0.55	9511	8249	8056	6849	6651	5645	5064
0.60	8012	6412	6465	5718	5163	4253	4106
0.65	5601	4949	4279	4185	3589	3341	2757
0.70	4098	3211	3229	2470	2596	2072	1995
0.75	3090	2637	2299	1991	1875	1612	1460
0.80	2391	2097	1675	1577	1385	1274	1100
0.85	1649	1369	1267	1033	906	883	758
0.90	1242	985	946	747	661	655	542
0.95	947	790	684	603	529	447	399
1.00	722	614	512	487	423	318	299

[a] w_1 is the mass fraction of ethylene glycol (1) in the ethylene glycol (1) + water (2) mixtures free of triclocarban (3).

A.M. Cruz-González, M.S. Vargas-Santana, S. de Jesus Polania-Orozco et al.

Journal of Molecular Liquids 325 (2021) 115222

Eqs. [11–13] were applied to predict the remaining solubility data points (N=182) and the obtained MPDs were 38.8 ($\pm$ 19.2) % (N= 143), 11.1 ($\pm$ 9.4) % (N=130) and 10.9 ($\pm$ 7.3) % (N=140), respectively. No significant difference between MPD values for models trained by whole data points and those of models trained using seven data points revealed that one may determine the solubility of TCC in EG + water after only seven measurements. One may also employ a previously trained model [41] for drugs' solubility prediction in EG + water mixtures presented as:

$$\ln x_{3(1+2)} = w_1 \ln x_{3(1)} + w_2 \ln x_{3(2)}$$
$$+ 2.303 \left[394.82 \left(\frac{w_1 w_2}{T} \right) - 355.28 \left(\frac{w_1 w_2 (w_1 - w_2)}{T} \right) + 388.89 \left(\frac{w_1 w_2 (w_1 - w_2)^2}{T} \right) \right]$$

(14)

which predicted TCC solubility employing the solubility data in the mono-solvents with the MPD of 14.2 ($\pm$12.5) % (N=143). For this prediction method, no solubility determination in the binary solvents is required.

3.4. Thermodynamic functions of solution

Having into consideration the experimental solubility data (Table 1), using the van't Hoff-Krug model, the enthalpy and Gibbs energy of the solution are determined according to Eqs. [15,16], respectively [42,43]:

$$\Delta_{soln} H^o = -R \left\{ \partial \ln x_3 / \partial \left[\left(\frac{1}{T} \right) - \left(\frac{1}{T_{hm}} \right) \right] \right\}_P$$

(15)

$$\Delta_{soln} G^o = -RT_{hm} \cdot \text{intercept}$$

(16)

Where T is the experimental temperature from each test and T_{hm} is the harmonic average of the study temperatures, which for the present case corresponds to 302.82 K. As example, Fig. 4 depicts the van't Hoff plots for the mixtures w_1 = 0.20, 0.40, 0.60 and 0.80.

Finally, from the data of Gibbs energy and solution enthalpy, the solution entropy is calculated according to Eq. (17) [44].

$$\Delta_{soln} S^o = (\Delta_{soln} H^o - \Delta_{soln} G^o) T_{hm}^{-1}$$

(17)

Table 4 presents the calculated values of dissolution thermodynamic functions of TCC in {EG (1) + water (2)} cosolvent mixtures at 302.82 K, including that of the ideal process.

Gibbs energy is positive in all cases. It decreases from pure water, where the highest value is found, to pure EG. The high Gibbs energy values in water and in water-rich mixtures are due to the low solubility of TCC in these media. As for the enthalpy of solution, this is positive in all cases, indicating once again that the process is endothermic; Its

Fig. 4. van't Hoff plot of the solubility of triclocarban (3) in some {ethylene glycol (1) + water (2)} mixtures. ●: w_1 = 0.20; ▲: w_1 = 0.40; ■: w_1 = 0.60; ◆: w_1 = 0.80.

Table 4
Thermodynamic functions relative to the triclocarban dissolution in {ethylene glycol (1) + water (2)} mixtures, including the ideal process at T_{hm} = 302.82 K.

w_1[a]	$\Delta_{soln} G^o$ /kJ. mol^{-1}	$\Delta_{soln} H^o$ /kJ. mol^{-1}	$\Delta_{soln} S^o$ /J. mol^{-1}.K^{-1}	$T\Delta_{soln} S^o$ /kJ. mol^{-1}	ζ_H	ζ_{TS}
0.00	48.62	41.55	−23.33	−7.06	0.855	0.145
0.05	47.25	39.90	−24.26	−7.35	0.845	0.155
0.10	45.63	39.55	−20.09	−6.08	0.867	0.133
0.15	44.22	38.35	−19.40	−5.87	0.867	0.133
0.20	42.93	36.96	−19.72	−5.97	0.861	0.139
0.25	42.03	33.33	−28.74	−8.70	0.793	0.207
0.30	40.47	33.62	−22.60	−6.84	0.831	0.169
0.35	38.91	35.86	−10.09	−3.06	0.921	0.079
0.40	37.94	37.48	−1.54	−0.47	0.988	0.012
0.45	37.03	38.06	3.42	1.04	0.973	0.027
0.50	36.28	38.81	8.35	2.53	0.939	0.061
0.55	35.66	39.47	12.60	3.82	0.912	0.088
0.60	35.09	40.64	18.32	5.55	0.880	0.120
0.65	34.25	40.82	21.70	6.57	0.861	0.139
0.70	33.28	41.79	28.09	8.51	0.831	0.169
0.75	32.59	42.78	33.64	10.19	0.808	0.192
0.80	31.92	43.21	37.29	11.29	0.793	0.207
0.85	30.97	43.37	40.97	12.41	0.778	0.222
0.90	30.18	44.02	45.70	13.84	0.761	0.239
0.95	29.48	45.76	53.75	16.28	0.738	0.262
1.00	28.81	46.60	58.75	17.79	0.724	0.276
Ideal	13.36	24.03	35.22	10.67	0.693	0.307

[a] w_1 is the mass fraction of ethylene glycol (1) in the {ethylene glycol (1) + water (2)} mixtures free of triclocarban (3).

behavior tends to decrease from pure water to w_1 = 0.25, a different behavior than that usually occurs in aqueous mixtures, where the formation of water-water bonds due to the hydrophobic hydration of solute in its non-polar groups tends to a initial increase in enthalpy of solution. However, in this case, the enthalpy decreases, indicating a possible bond break and then increases, from w_1 = 0.1 to pure EG, this same behavior occurs in the dioxane + water system [4].

Regarding the solution entropy, it presents a trend analogous to enthalpy, presenting negative values from pure water to w_1 = 0.4, and positive values from w_1 = 0.4 to pure EG. These negative values of the solution entropy agree with the theory of the structuring of the water molecules around the nonpolar groups of the solute (hydrophobic hydration) [45,46]. However, the increase in entropy, from w_1 = 0.4 to obtained positive values, clearly favors the solubility of TCC.

In general, it can be analyzed that the TCC low solubilities are possibly measured by both a tendency of the system to organize itself that the probability of solute-solvent bond formation will decrease. The energetic (solution enthalpy) and organizational (solution entropy) contributions are calculated using Eqs. [18,19] [22].
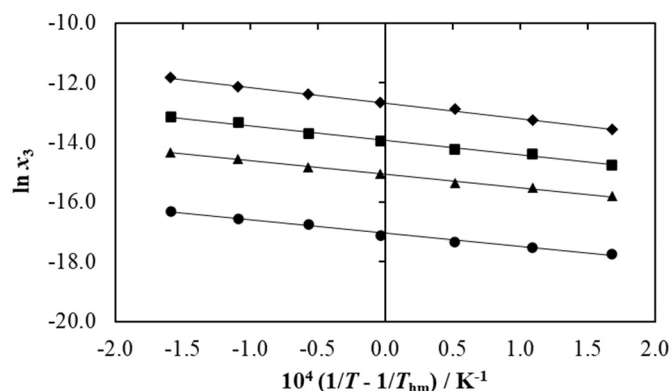
$$\zeta_H = |\Delta_{soln} H^o| (|\Delta_{soln} H^o| + |T\Delta_{soln} S^o|)^{-1}$$

(18)

$$\zeta_{TS} = |T\Delta_{soln} S^o| (|\Delta_{soln} H^o| + |T\Delta_{soln} S^o|)^{-1}$$

(19)

In all cases, the enthalpy of solution is the largest contributor to the Gibbs energy of solution. In contract extreme values such as w_1 = 0.4, where the enthalpy contributes 99% to the Gibbs energy value of the solution.

3.5. Thermodynamic functions of TCC transfer

Thermodynamic transfer functions are one of the most important indicators for in pharmacological terms and today it can also be so in environmental sciences [47,48]. The innumerable flow of bioactive substances into bodies of water (for different reasons ranging from industrial and hospital discharges to small and continuous domestic discharges resulting from the incorrect disposal of prescription or

A.M. Cruz-González, M.S. Vargas-Santana, S. de Jesus Polania-Orozco et al.

Journal of Molecular Liquids 325 (2021) 115222

self-medicated drugs [49,50]) show the importance of studies that allow making rational decisions based on reducing the environmental impact generated by processes typical of the chemical and pharmaceutical industry [51].

The analysis of the hypothetical transfer process of the TCC from the medium with the highest polarity, to the medium with the lowest polarity, allows identifying the cosolvent action of EG. This information may become important in studies of stability, environmental distribution, bioaccumulation analysis, analysis of toxic effects, bioavailability, among others [47].

In this case, the thermodynamic transfer functions are calculated as the difference between the function of the least polar medium and the function of the more polar medium, according to Eq. (20).

$$\Delta_{tr}F^{o} = \Delta_{soln}F^{o}_{less\ polar} - \Delta_{soln}F^{o}_{more\ polar} \tag{20}$$

Where F represents the thermodynamic functions Gibbs energy, enthalpy and entropy [52].

A practical way to perform an analysis of thermodynamic transfer functions is through Perlovich graphical analysis (Fig. 5) [53–55]. In this order of ideas, the TCC transfer process from the pure water to the cosolvent mixture $w_1 = 0.10$ ($[\Delta_{tr}H^{\circ} < 0; T\Delta_{tr}S^{\circ} < 0; |\Delta_{tr}H^{\circ}| > |T\Delta_{tr}S^{\circ}|]$ = sector V) is determined by the enthalpy. From this cosolvent mixture to $w_1 = 0.10$ ($[\Delta_{tr}H^{\circ} < 0; T\Delta_{tr}S^{\circ} > 0; |\Delta_{tr}H^{\circ}| < |T\Delta_{tr}S^{\circ}|]$ = sector III) the process is determined by the entropy, from $w_1 = 0.10$ to $w_1 = 0.20$ ($[\Delta_{tr}H^{\circ} < 0; T\Delta_{tr}S^{\circ} > 0; |\Delta_{tr}H^{\circ}| > |T\Delta_{tr}S^{\circ}|]$ = sector IV) the process is determined by the enthalpy, from $w_1 = 0.20$ to $w_1 = 0.25$ ($[\Delta_{tr}H^{\circ} < 0; T\Delta_{tr}S^{\circ} < 0; |\Delta_{tr}H^{\circ}| > |T\Delta_{tr}S^{\circ}|]$ = sector V) the process is determined by the enthalpy too. Finally, from $w_1 = 0.25$ to pure EG ($[(T\Delta_{tr}S^{\circ} > \Delta_{tr}H^{\circ} > 0)]$ = sector II) the process is determined by the entropy, which is positive in all the cases [56,57].

In general terms, TCC tends to transfer from polar environments such as water to less polar environments, such as biological tissues, which makes it a dangerous emerging pollutant.

3.6. Thermodynamic functions of mixing

The solution process can be hypothetically divided into two phases: the first, consisting of the change of state of the solute from solid to liquid (fusion) and the second, a mixing process between the two liquids (solute in liquid state and the solvent or mixture of solvents). A clearly described scheme is the following:

Table 5
Thermodynamic functions related to the mixing process of triclocarban in {ethylene glycol (1) + water (2)} mixtures, including the ideal process at $T_{hm} = 302.82$ K.

$w_1{}^{a}$	$\Delta_{mix}G^{\circ}$ / kJ.mol^{-1}	$\Delta_{mix}H^{\circ}$ / kJ.mol^{-1}	$\Delta_{mix}S^{\circ}$ / J.mol^{-1}.K^{-1}	$T\Delta_{mix}S^{\circ}$ / kJ.mol^{-1}
0.00	35.25	17.52	−58.55	−17.73
0.05	33.89	15.87	−59.48	−18.01
0.10	32.27	15.52	−55.31	−16.75
0.15	30.86	14.32	−54.62	−16.54
0.20	29.57	12.93	−54.94	−16.64
0.25	28.67	9.30	−63.96	−19.37
0.30	27.10	9.59	−57.83	−17.51
0.35	25.55	11.83	−45.31	−13.72
0.40	24.58	13.45	−36.76	−11.13
0.45	23.66	14.03	−31.80	−9.63
0.50	22.92	14.78	−26.88	−8.14
0.55	22.29	15.44	−22.62	−6.85
0.60	21.73	16.61	−16.91	−5.12
0.65	20.88	16.79	−13.53	−4.10
0.70	19.92	17.76	−7.14	−2.16
0.75	19.23	18.75	−1.59	−0.48
0.80	18.56	19.18	2.06	0.62
0.85	17.60	19.34	5.75	1.74
0.90	16.82	19.99	10.48	3.17
0.95	16.12	21.73	18.53	5.61
1.00	15.44	22.57	23.53	7.12

^{a} w_1 is the mass fraction of ethylene glycol (1) in the {ethylene glycol (1) + water (2)} mixtures free of triclocarban (3).

Solute$_{(solid)}$ at $T \rightarrow$ Solute$_{(solid)}$ at $T_{fus} \rightarrow$ Solute$_{(liquid)}$ at T_{fus}
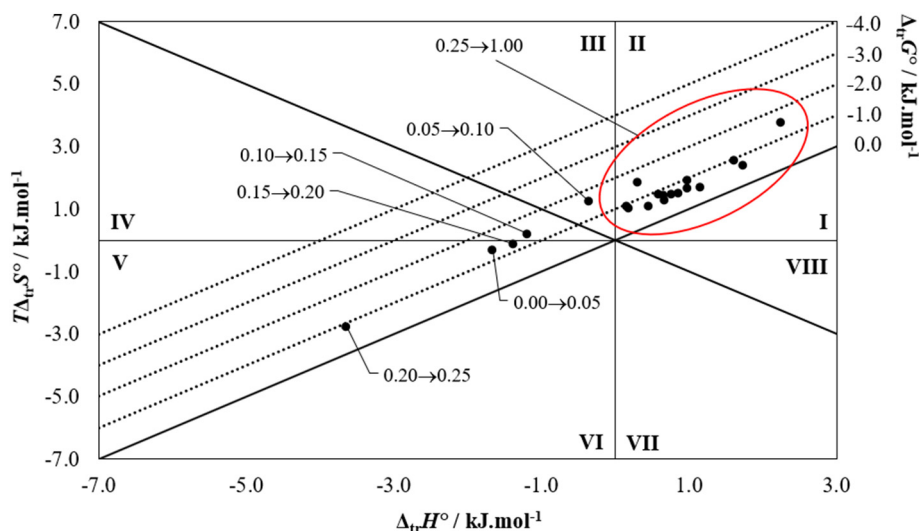$\rightarrow$ Solute$_{(liquid)}$ at $T \rightarrow$ Solute$_{(solution)}$ at T

Thus, the thermodynamic mixing functions are calculated according to Eqs. [20–23].

$$\Delta_{mix}G^{o} = \Delta_{soln}G^{o} - \Delta_{soln}G^{o-id} \tag{21}$$

$$\Delta_{mix}H^{o} = \Delta_{soln}H^{o} - \Delta_{soln}H^{o-id} \tag{22}$$

$$\Delta_{mix}S^{o} = \Delta_{soln}S^{o} - \Delta_{soln}S^{o-id} \tag{23}$$

Table 5 and Fig. 6 show the thermodynamic transfer functions of TCC in {EG (1) + water (2)} cosolvent mixtures.

Fig. 5. Relationship between the enthalpy and entropic terms of transfer functions of TCC from more polar solvents to less polar solvents at $T_{hm} = 302.82$ K. The isoenergetic curves of $\Delta_{tr}G^{\circ}$ function are marked by dotted lines.
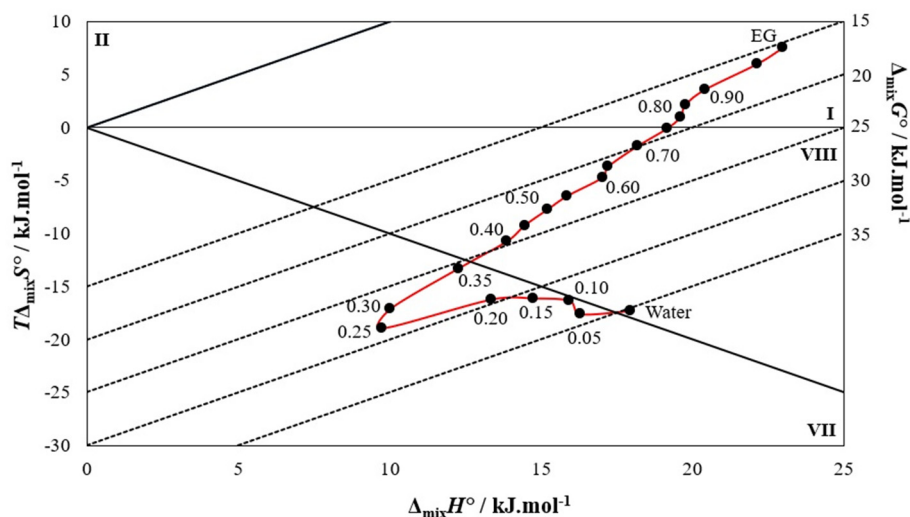
Fig. 6. Relationship between the enthalpy and entropic terms of transfer mixing of TCC at $T_{hm} = 302.82$ K. The isoenergetic curves of $\Delta_{mix}G°$ function are marked by dotted lines.

The Gibbs energy of mixing is positive in all cases and decreases as the EG concentration increases from the pure water to the pure EG. Therefore, in general terms, the mixing process does not favor the solution process. As for the mixing enthalpy, related to the formation of the cavity between the solvent molecules to accommodate the solute, it is also positive, which in the first instance would disadvantage the solution process, contrary to what usually occurs with aqueous systems in where initially there is an increase, usually attributed to two factors, the formation of the cavity and the hydration of the nonpolar groups of the solute, in this study, from pure water to $w_1 = 0.1$, the enthalpy of the mixture decreases. Finally, as regards the entropy of the mixture, it is negative from pure water up to $w_1 = 0.75$, indicating an entropy disadvantage to the mixing process and therefore to the solution process, at $w_1 = 0.75$ up to pure EG, the mixing entropy is positive favoring the mixing process.

According with Fig. 5, between $w_1 = 0.05$ and $w_1 = 0.35$ ($[(\Delta_{mix}H° > 0; T\Delta_{mix}S° < 0; |\Delta_{mix}H°| < |T\Delta_{mix}S°|)] = $ sector VII), the mixing process is determined by the mixing entropy, and between $w_1 = 0.35$ and the EG ($[(\Delta_{mix}H° > 0; T\Delta_{mix}S° < 0; |\Delta_{mix}H°| > |T\Delta_{mix}S°|)] = $ sector VIII) and ($[(\Delta_{mix}H° > T\Delta_{mix}S° > 0) = $ sector I]) the process is driven by enthalpy.

3.7. Enthalpy-entropy compensation analysis

The $\Delta_{soln}H°$ vs $\Delta_{soln}G°$ graphs allow to identify the cosolvent action mechanisms [58,59], this is because $\Delta_{soln}H°$ can be considered as an indicator of solute-solvent molecular interactions [60]. Furthermore, when plotting $\Delta_{soln}H°$ vs $T\Delta_{soln}S°$, the analysis in the first graph can be corroborated, so, in the graph $\Delta_{soln}H°$ vs $\Delta_{soln}G°$, trends with negative slope indicate entropic conduction, and trends with positive slope indicate that the process it is driven by enthalpy. On the other hand, when plotting $\Delta_{soln}H°$ vs $T\Delta_{soln}S°$, linear functions are usually observed, where slopes higher than 1.0 indicate that the process is driven by enthalpy, while slopes less than 1.0 indicate processes driven by entropy [4,61]. According to Fig. 7, from pure water to the cosolvent mixture $w_1 = 0.25$, the process is driven by the enthalpy of solution and from $w_1 = 0.25$ to neat EG the process is driven by entropy.

Fig. 8 corroborates the analysis obtained in Fig. 7, from $w_1 = 0.25$ to pure EG, where a defined linear function is observed, with a slope less than one (0.454) indicating entropic conduction. From pure water to $w_1 = 0.25$ to, the data shows a dispersion, so with this method (Fig. 8), it is not possible to clearly define which thermodynamic
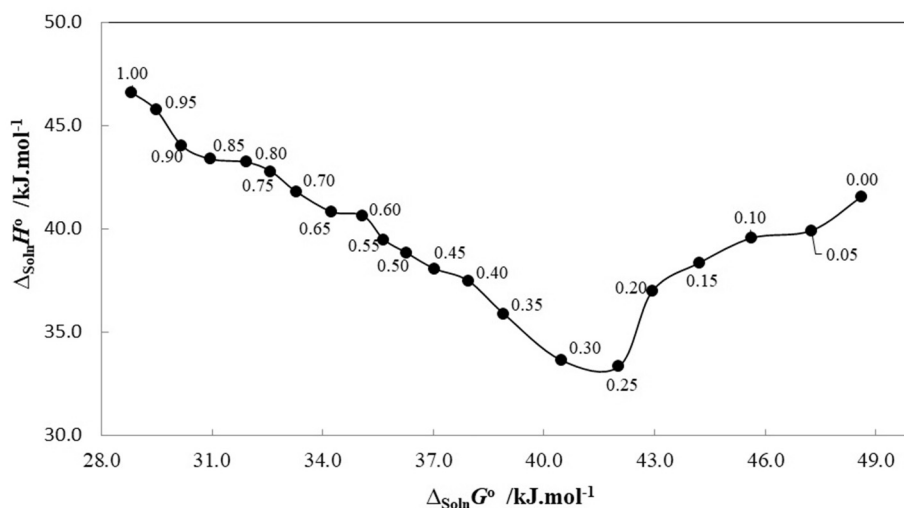

Fig. 7. $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$ enthalpy–entropy compensation plot for dissolution process of TCC in EG+W mixtures at $T_{hm} = 302.82$ K.
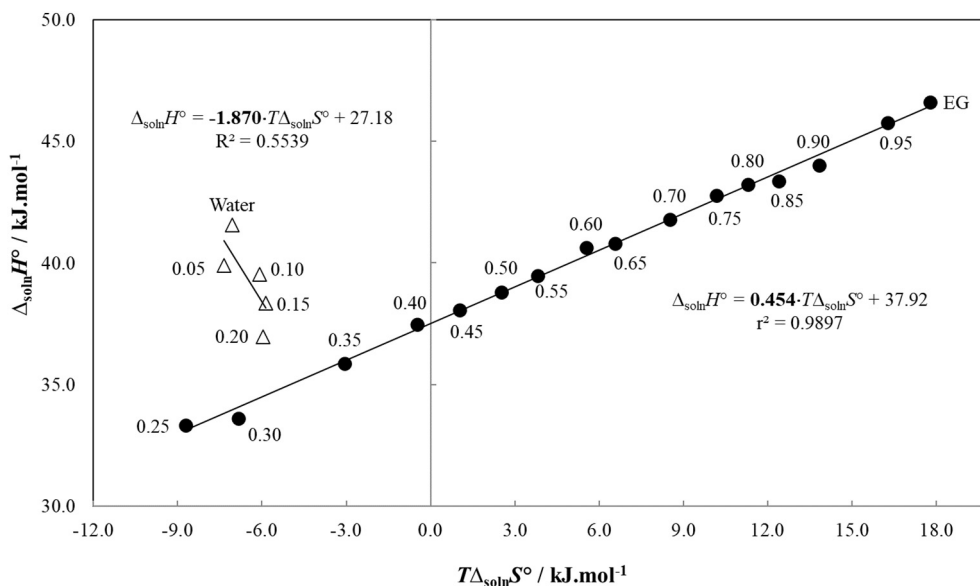
Fig. 8. $\Delta_{soln}H°$ vs. $T\Delta_{soln}S°$ enthalpy–entropy compensation plot for dissolution process of triclocarban in {ethylene glycol (1) + water (2)} mixtures at $T_{hm} = 302.82$ K.

function drives the process, although the observed slope is higher than 1.0 as absolute value what allows to propose enthalpy driving in this region.

3.8. Preferential solvation

An analysis that better elucidates possible interactions at the molecular level is the preferential solvation analysis [62]. Although mathematical modeling aimed at predicting solubility has proven to be an excellent tool for the pharmaceutical industry when optimizing processes [63–66], in most cases it falls short of understanding the possible molecular interactions that the solution process entails.

One of the most widely used models in preferential solvation studies are the Kirkwood-Buff Inverse Integrals (IKBI). Thus, the mathematical expressions for the development of IKBI are the following [67–69]:

$$\delta x_{1,3} = x_1 x_2 (G_{1,3} - G_{2,3})[x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}]^{-1} \tag{24}$$

$$G_{1,3} = RT\kappa_T - V_3 + x_2 \overline{V}_2 DQ^{-1} \tag{25}$$

$$G_{2,3} = RT\kappa_T - V_3 + x_1 \overline{V}_1 DQ^{-1} \tag{26}$$

$$\kappa_{T(1+2)} = x_1 \kappa_1 + x_2 \kappa_2 \tag{27}$$

$$\overline{V}_1 = V + x_2(\partial V/\partial x_1) \tag{28}$$

$$\overline{V}_2 = V - x_1(\partial V/\partial x_1) \tag{29}$$

$$V_{cor} = 2522.5\left[r_3 + 0.1363\sqrt[3]{x_1^L V_1 + x_2^L V_2} - 0.085\right]^3 \tag{30}$$

$$x_1^L = \delta x_{1,3} + x_1 \tag{31}$$

$$Q = RT + x_1 x_2 \left(\partial^2 G_{1+2}^E / \partial x_2^2\right) \tag{32}$$

$$G^E = x_1 x_2 \left[-558 + 164(1 - 2x_1) - 189(1 - 2x_1)^2\right] \tag{33}$$

$$D = \partial \Delta_{tr} G_{3,2 \to 1+2}^o / \partial x_1 \tag{34}$$
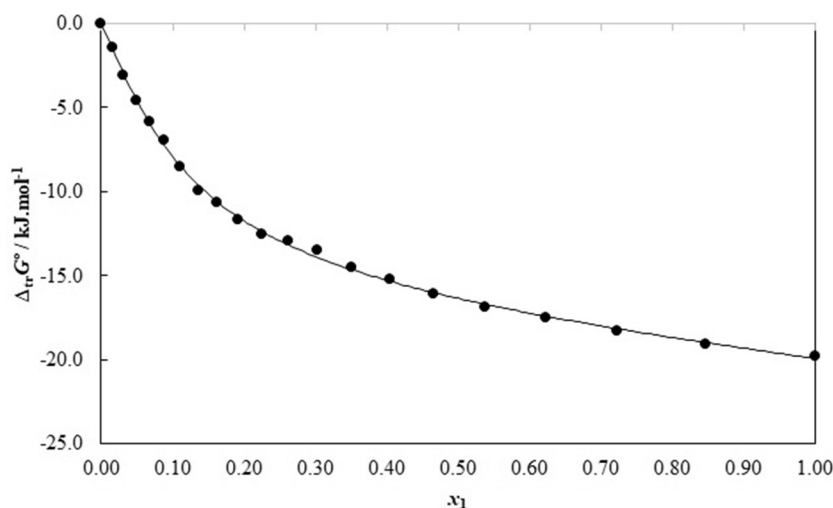

Fig. 9. Gibbs energy of transfer of triclocarban (3) from neat water (2) to {ethylene glycol (1) + water (2)} mixtures at 298.15 K.

Table 6
Some properties associated to preferential solvation of triclocarban (3) in {ethylene glycol (1) + methanol (2)} mixtures at 298.15 K.

x_1[a]	D /kJ.mol^{-1}	Q /kJ.mol^{-1}	$RT\kappa_T$ /kJ.mol^{-1}	V_1 /cm^3.mol^{-1}	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	−84.09	2.479	1.133	53.97	18.08	−784.0	−170.7	797	0.00
0.05	−81.25	2.559	1.125	54.26	18.07	−715.8	−256.8	804	−4.16
0.10	−53.57	2.605	1.117	54.53	18.05	−504.7	−282.8	849	−3.67
0.15	−36.91	2.627	1.109	54.76	18.02	−385.9	−286.1	901	−2.12
0.20	−27.06	2.633	1.101	54.97	17.97	−318.5	−283.7	950	−0.84
0.25	−20.91	2.631	1.093	55.15	17.92	−277.5	−280.3	996	0.07
0.30	−16.87	2.627	1.085	55.31	17.86	−251.0	−277.3	1038	0.72
0.35	−14.09	2.626	1.076	55.44	17.80	−232.8	−274.9	1079	1.17
0.40	−12.11	2.631	1.068	55.56	17.73	−219.7	−273.1	1118	1.48
0.45	−10.66	2.643	1.060	55.65	17.66	−209.9	−271.7	1156	1.68
0.50	−9.57	2.663	1.052	55.73	17.59	−202.3	−270.9	1192	1.79
0.55	−8.74	2.692	1.044	55.79	17.52	−196.4	−270.4	1228	1.83
0.60	−8.09	2.725	1.036	55.84	17.46	−191.5	−270.2	1263	1.82
0.65	−7.58	2.760	1.028	55.87	17.40	−187.5	−270.5	1297	1.75
0.70	−7.18	2.793	1.020	55.90	17.35	−184.2	−271.4	1331	1.63
0.75	−6.86	2.816	1.012	55.91	17.31	−181.3	−273.0	1364	1.48
0.80	−6.61	2.822	1.004	55.92	17.28	−178.9	−275.6	1396	1.29
0.85	−6.41	2.803	0.996	55.92	17.26	−176.7	−279.5	1428	1.06
0.90	−6.25	2.747	0.988	55.93	17.26	−174.7	−285.4	1460	0.78
0.95	−6.13	2.643	0.980	55.92	17.27	−172.8	−294.0	1490	0.44
1.00	−6.04	2.479	0.972	55.92	17.30	−170.8	−307.0	1520	0.00

[a] x_1 is the mole fraction of ethylene glycol (1) in the {ethylene glycol (1) + methanol (2)} mixtures free of triclocarban (3).

Where $G_{1,3}$, $G_{2,3}$, are the inverse Kirkwood-Buff integrals (cm^3 mol^{-1}); V_{cor} is the correlation volume around the TCC (3) where the preferential solvation occurs; κ_T is the isothermal compressibility of the mixture (GPa^{-1}), V_1, V_2 and V_3 are the partial molar volumes of EG, water and TCC respectively (cm^3.mol^{-1}) and D and Q (kJ mol^{-1}) are given in Eqs. [32,34] [70,71]. Fig. 9 shows the Gibbs energy of transfer behavior of TCC (3) from neat water (2) to {EG (1) + water (2)} mixtures at 298.15 K. These values were calculated from the mole fraction drug solubility data shown in Table 1, by using the following expression:

$$\Delta_{tr}G^o_{3,2\to1+2} = RT\,\ln\left(\frac{x_{3,2}}{x_{3,2}}\right) = (-0.01 - 84.37x_1 - 2863.95x_1^2)$$
$$/(1 + 22.06x_1 + 149.88x_1^2 - 24.99x_1^3) \qquad (35)$$

To calculate the preferential solvation parameters (Eq. (13)), some data necessary for the development of the model were taken from the literature; the isothermal compressibilities of the mixtures were calculated from the compressibilities of the pure solvents using EQ. (27), by using κ_T of EG 0.392 GPa^{-1} and κ_T of water 0.457 GPa^{-1} [72];

$V_3 = 171.8$ cm^3.mol^{-1}, the partial molar volumes of both solvents, water and EG necessary for the calculation of the inverse integrals of Kirkwood-Buff (Eqs. [25,26]) were calculated from the experimental data of the density of the {EG (1) + water (2)} mixtures at 298.15 K published by Fogg et al. [73] through Eqs. [28,29] [74]; r_3, necessary for the calculation of the correlation volume (Eq. (30)) was taken as 0.408 nm; the excess Gibbs energy for the {EG (1) + water (2)} mixtures free of TCC, necessary for the calculation of Q (Eq. (32)), was calculated from the equation and coefficients presented by Marcus (Eq. (33)). Other values, such as D, were calculated from the experimental solubility data according to Eq. (35).

Table 6 presents the data of the solvation parameters and some other parameters necessary for the development of the IKBI model. From the analysis of $\delta x_{1,3}$ (Fig. 10), from pure water to $x_1 = 0.20$, the TCC is preferentially solvated by water, and between $x_1 = 0.55$ and $x_1 = 1.00$, the TCC is preferentially solvated by the EG. This behavior is very similar to that exhibited by other drugs that, such as TCC in EG + W cosolvent mixtures, reach their maximum solubility in a pure solvent [71].
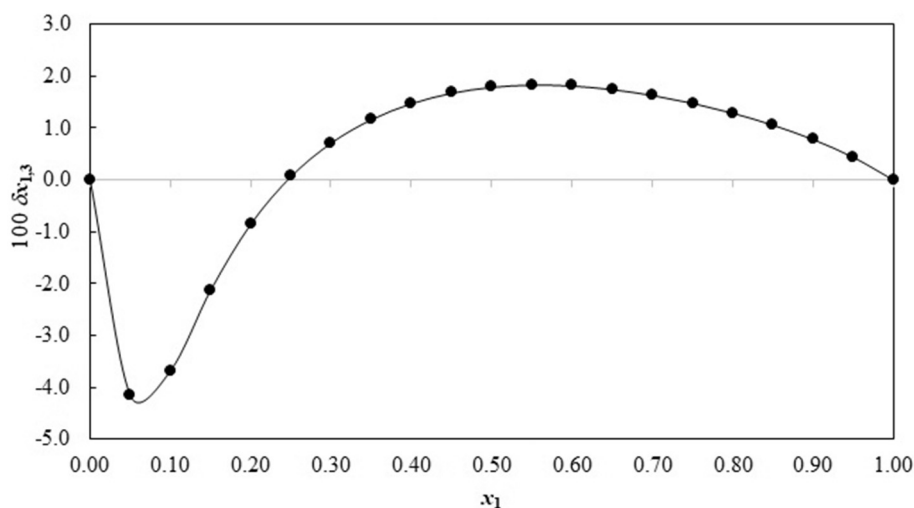
Fig. 10. Preferential solvation parameters of triclocarban in {ethylene glycol (1) + water (2)} mixtures at 298.15 K.

A.M. Cruz-González, M.S. Vargas-Santana, S. de Jesus Polania-Orozco et al.

Journal of Molecular Liquids 325 (2021) 115222

In water-rich mixtures, TCC acts as a Lewis' base against water, since the Kamlet-Taft parameter α for water is 1.017 ± 0.023 and that of EG is 0.792 ± 0.004 [75]. In mixtures intermediate and rich in EG, where the TCC is preferentially solvated by EG, the TCC would behave like a Lewis acid owing the hydrogen acid of the -NH- groups.

4. Conclusions

The solubility of TCC in {EG (1) + water (2)} cosolvent mixtures is an endothermic process, where EG has a positive co-solvent effect. According to thermodynamic analysis, the Gibbs energy of solution is positive in all cases and decreases as the EG concentration increases, because of the increase in solubility. According to the transfer functions, TCC has to be transferred to polar media, which could be interpreted as a risk indicator for aquatic organisms found in media contaminated with TCC.

Regarding the entropy-enthalpy compensation analysis, the solution process is driven by entropy in systems rich in water and by enthalpy in intermediate and EG-rich mixtures. Considering preferential solvation, TCC tends to be preferentially solvated by water in water-rich mixtures, possibly because its nonpolar groups present hydrophobic hydration, in intermediate and EG-rich mixtures it is preferentially solvated by EG. Finally, it can be concluded that the information presented in this research will lead to a better understanding of processes related to the solubility of TCC.

Declaration of Competing Interest

None.

Acknowledgments

References

[1] R. Khan, A. Zeb, N. Roy, R.T. Magar, H.J. Kim, K.W. Lee, S.W. Lee, Biochemical and structural basis of triclosan resistance in a novel enoyl-acyl carrier protein reductase, Antimicrob. Agents Chemother. 62 (2018) (e00648-18).

[2] L. Zhu, H. Bi, J. Ma, Z. Hu, W. Zhang, J.E. Cronan, H. Wang, The two functional enoyl-acyl carrier protein reductases of enterococcus faecalis do not mediate triclosan resistance, MBio 4 (2013) (e00613-13).

[3] T.E.A. Chalew, R.U. Halden, Environmental exposure of aquatic and terrestrial biota to triclosan and triclocarban, J. Am. Water Resour. Assoc. 45 (2009) 4–13.

[4] D.R. Delgado, E.M. Mogollon-Waltero, C.P. Ortiz, M. Peña, O.A. Almanza, F. Martínez, A. Jouyban, Enthalpy-entropy compensation analysis of the triclocarban dissolution process in some {1,4-dioxane (1) + water (2)} mixtures, J. Mol. Liq. 271 (2018) 522–529.

[5] T.M. Tran, H.T. Trinh, H.Q. Anh, T. Van Le, S.N. Le, T.B. Minh, Characterization of triclosan and triclocarban in indoor dust from home micro-environments in Vietnam and relevance of non-dietary exposure, Sci. Total Environ. 732 (2020) 139326.

[6] Z.F. Chen, H.B. Wen, X. Dai, S.C. Yan, H. Zhang, Y.Y. Chen, Z. Du, G. Liu, Z. Cai, Contamination and risk profiles of triclosan and triclocarban in sediments from a less urbanized region in China, J. Hazard. Mater. 357 (2018) 376–383.

[7] Z.F. Chen, G.G. Ying, Y.S. Liu, Q.Q. Zhang, J.L. Zhao, S.S. Liu, J. Chen, F.J. Peng, H.J. Lai, C.G. Pan, Triclosan as a surrogate for household biocides: an investigation into biocides in aquatic environments of a highly urbanized region, Water Res. 58 (2014) 269–279.

[8] C.M. Marques, S. Moniz, J.P. de Sousa, A.P. Barbosa-Povoa, G. Reklaitis, Decision-support challenges in the chemical-pharmaceutical industry: Findings and future research directions, Comput. Chem. Eng. 134 (2020) 106672.

[9] E. Strade, D. Kalnina, J. Kulczycka, Water efficiency and safe re-use of different grades of water - Topical issues for the pharmaceutical industry, Water Resour. Ind. 24 (2020) 100132.

[10] A. Fàbregas-Fernández, E. García-Montoya, P. Pérez-Lozano, J.M. Suñé-Negre, J.R. Ticó, M. Miñarro, Quality assurance in research: incorporating ISO9001:2000 into a GMP quality management system in a pharmaceutical R+D+I center, Accred. Qual. Assur. 15 (2010) 297–304.

[11] H.C. Poynton, W.E. Robinson, Contaminants of emerging concern, with an emphasis on nanomaterials and pharmaceuticals, Green Chemistry: An Inclusion Approach, Elsevier Inc. 2018, pp. 291–315.

[12] A.M. Romero-Nieto, N.E. Cerquera, F. Martínez, D.R. Delgado, Thermodynamic study of the solubility of ethylparaben in acetonitrile + water cosolvent mixtures at different temperatures, J. Mol. Liq. 287 (2019) 110894.

[13] J.M. Brausch, G.M. Rand, A review of personal care products in the aquatic environment: environmental concentrations and toxicity, Chemosphere 82 (2011) 1518–1532.

[14] Q. Bu, B. Wang, J. Huang, S. Deng, G. Yu, Pharmaceuticals and personal care products in the aquatic environment in China: a review, J. Hazard. Mater. 262 (2013) 189–211.

[15] H. Montaseri, P.B.C. Forbes, A review of monitoring methods for triclosan and its occurrence in aquatic environments, TrAC—Trends, Anal. Chem. 85 (2016) 221–231.

[16] M. Kajta, J. Rzemieniec, A. Wnuk, W. Lasoń, Triclocarban impairs autophagy in neuronal cells and disrupts estrogen receptor signaling via hypermethylation of specific genes, Sci. Total Environ. 701 (2020) 134818.

[17] J.K. Neelima, V.A. Loyd, Studies on microemulsions using Brij 96 as surfactant and glycerin, ethylene glycol and propylene glycol as cosurfactants, Int. J. Pharm. 57 (1998) 87–93.

[18] M. Hussain, J. Liu, Practical synthesis of 4H-pyrido[1, 2-a]pyrimidin-4-ones using ethylene glycol as a promoting solvent, Tetrahedron Lett. 61 (2020) 152269.

[19] A.R. Holguín, D.R. Delgado, F. Martínez, Thermodynamic study of the solubility of triclocarban in ethanol + propylene glycol mixtures, Quim Nova 35 (2012) 280–285.

[20] J.H. Blanco-Márquez, C.P. Ortiz, N.E. Cerquera, F. Martínez, A. Jouyban, D.R. Delgado, Thermodynamic analysis of the solubility and preferential solvation of sulfamerazine in (acetonitrile + water) cosolvent mixtures at different temperatures, J. Mol. Liq. 293 (2019) 111507.

[21] S. Abbott, Solubility Science: Principles and Practice, University of Leeds, Ipswich (UK, 2017.

[22] S.H. Yalkowsky, M. Wu, Estimation of the ideal solubility (crystal–liquid fugacity ratio) of organic compounds, J. Pharm. Sci. 99 (2010) 1100–1106.

[23] J.H. Blanco-Márquez, Y.A. Quigua-Medina, J.D. García-Murillo, J.K. Castro-Camacho, C.P. Ortiz, N.E. Cerquera, D.R. Delgado, Thermodynamic analysis and applications of the Abraham solvation parameter model in the study of the solubility of some sulfonamides, Rev. Colomb. Cienc. Quím. Farm. 49 (2020) 234–255.

[24] A. Barton, CRC Handbook of Solubility Parameters and Other Cohesion Parameters, 2nd ed. CRC Press LLC, Boca Raton (FL, 1991.

[25] D.R. Delgado, A. Holguin, F. Martínez, Solution thermodynamics of triclosan and triclocarban in some volatile organic solvents, Vitae 19 (2012) 79–92.

[26] H. Yun, B. Liang, D. Kong, X. Li, A. Wang, Fate, risk and removal of triclocarban: A critical review, J. Hazard. Mater. 387 (2020) 121944.

[27] G. Kor-Bicakci, T. Abbott, E. Ubay-Cokgor, C. Eskicioglu, Occurrence and fate of antimicrobial triclocarban and its transformation products in municipal sludge during advanced anaerobic digestion using microwave pretreatment, Sci. Total Environ. 705 (2020) 135862.

[28] A.M. Romero-Nieto, D.I. Caviedes-Rubio, J. Polania-Orozco, N.E. Cerquera, D.R. Delgado, Temperature and cosolvent composition effects in the solubility of methylparaben in acetonitrile + water mixtures, Phys. Chem. Liq. Forthcoming (2020), https://doi.org/10.1080/00319104.2019.1636379.

[29] D.R. Delgado, D.I. Caviedes-Rubio, C.P. Ortiz, Y.L. Parra-Pava, M.Á. Peña, A. Jouyban, S.N. Mirheydari, F. Martínez, W.E. Acree, Solubility of sulphadiazine in (acetonitrile + water) mixtures: measurement, correlation, thermodynamics and preferential solvation, Phys. Chem. Liq. 58 (2020) 381–396.

[30] J.H. Hildebrand, J.M. Prausnitz, R.L. Scott, Regular and Related Solutions, Van Nostrand Reinhold Co., New York, 1970.

[31] A.M. Romero Nieto, N.E. Cerquera, D.R. Delgado, Measurement and correlation of solubility of ethylparaben in pure and binary solvents and thermodynamic properties of solution, Rev. Colomb. Cienc. Quím. Farm. 48 (2019) 332–347.

[32] A. Jouyban, Handbook of Solubility Data for Pharmaceuticals, CRC Press, Boca Raton (FL), 2010.

[33] A. Jouyban, Review of the cosolvency models for predicting solubility of drugs in water-cosolvent mixtures, J. Pharm. Pharmaceut. Sci. 11 (2008) 32–58.

[34] A. Jouyban, Review of the cosolvency models for predicting drug solubility in solvent mixtures: an update, J. Pharm. Pharmaceut. Sci. 22 (2019) 466–485.

[35] A. Jouyban-Gharamaleki, L. Valaee, M. Barzegar-Jalali, B.J. Clark, W.E. Acree Jr., Comparison of various cosolvency models for calculating solute solubility in water-cosolvent mixtures, Int. J. Pharm. 177 (1999) 93–101.

[36] S.H. Yalkowsky, T. Roseman, in: S.H. Yalkowsky (Ed.), Solubilization of Drugs by Cosolvents, Marcel Dekker, New York 1981, pp. 91–134.

[37] A. Jouyban, S. Romero, H.K. Chan, B.J. Clark, P. Bustamante, A cosolvency model to predict solubility of drugs at several temperatures from a limited number of solubility measurements, Chem. Pharm. Bull. 50 (2002) 594–599.

[38] A. Jouyban, W.E. Acree Jr., Mathematical derivation of the Jouyban-Acree model to represent solute solubility data in mixed solvents at various temperatures, J. Mol. Liq. 256 (2018) 541–547.

[39] A. Jouyban, M. Khoubnasabjafari, H.K. Chan, W.E. Acree Jr., Mathematical representation of solubility of amino acids in binary aqueous-organic solvent mixtures at various temperatures using the Jouyban-Acree model, Pharmazie 61 (2006) 789–792.

[40] W.E. Acree Jr., Mathematical representation of thermodynamic properties: part 2. Derivation of the combined nearly ideal binary solvent (NIBS)/Redlich-Kister

A.M. Cruz-González, M.S. Vargas-Santana, S. de Jesus Polania-Orozco et al.

Journal of Molecular Liquids 325 (2021) 115222

mathematical representation from a two-body and three-body interactional mixing model, Thermochim. Acta 198 (1992) 71–79.

[41] A. Jouyban, Sh. Soltanpour, E. Tamizi, Solubility prediction of solutes in aqueous mixtures of ethylene glycols, Pharmazie 63 (2008) 548–550.

[42] R.R. Krug, W.G. Hunter, R.A. Grieger, Enthalpy-entropy compensation. 1. Some fundamental statistical problems associated with the analysis of van't Hoff and Arrhenius data, J. Phys. Chem. 80 (1976) 2335–2341.

[43] R.R. Krug, W.G. Hunter, R.A. Grieger, Enthalpy-entropy compensation. 2. Separation of the chemical from the statistical effect, J. Phys. Chem. 80 (1976) 2341–2351.

[44] D.R. Delgado, M.A. Ruidiaz, S.M. Gómez, M. Gantiva, F. Martínez, Thermodynamic study of the solubility of sodium naproxen in some ethanol + water mixtures, Quim. Nova 33 (2010) 1923–1927.

[45] S.H. Yalkowsky, Solubility and Solubilization in Aqueous Media, American Chemical Society and Oxford University Press, New York, 1999.

[46] C.J. van Oss, Interfacial Forces in Aqueous Media, 2nd ed. CRC Press, Boca Raton, 2006.

[47] S. Endo, K.U. Goss, Applications of polyparameter linear free energy relationships in environmental chemistry, Environ. Sci. Technol. 48 (2014) 12477–12491.

[48] M. Brumfield, W.E. Acree, M.H. Abraham, Abraham model correlations for describing solute transfer into diisopropyl ether, Phys. Chem. Liq. 53 (2015) 25–37.

[49] P.S. Dourado Arrais, A.D. Bertoldi, Prevalence of self-medication in Brazil and associated factors, Rev. Saúde Pública. 50 (2016) 11–22.

[50] D.I. Caviedes Rubio, D.R. Delgado, A. Olaya Amaya, Normatividad ambiental dirigida a regular la presencia de los productos farmacéuticos residuales en ambientes acuáticos, Rev. Jurídica Piélagus 16 (2017) 121–130.

[51] A. Benazzouz, L. Moity, C. Pierlot, M. Sergent, V. Molinier, J.M. Aubry, Selection of a greener set of solvents evenly spread in the Hansen space by space-filling design, Ind. Eng. Chem. Res. 52 (2013) 16585–16597.

[52] J.L. Gómez, G.A. Rodríguez, D.M. Cristancho, D.R. Delgado, F. Martínez, Solution thermodynamics of nimodipine in some PEG 400 + ethanol mixtures, Phys. Chem. Liq. 51 (2013) 651–662.

[53] G.L. Perlovich, N.N. Strakhova, V.P. Kazachenko, T.V. Volkova, V.V. Tkachev, K.-J. Schaper, O.A. Raevsky, Sulfonamides as a subject to study molecular interactions in crystals and solutions: sublimation, solubility, solvation, distribution and crystal structure, Int. J. Pharm. 349 (2008) 300–313.

[54] G.L. Perlovich, A.M. Ryzhakov, N.N. Strakhova, V.P. Kazachenko, K.-J. Schaper, O.A. Raevsky, Thermodynamic aspects of solubility and partitioning processes of some sulfonamides in the solvents modeling biological media, J. Chem. Thermodyn. 69 (2014) 56–65.

[55] G.L. Perlovich, V.V. Tkachev, N.N. Strakhova, V.P. Kazachenko, T.V. Volkova, O.V. Surov, K.J. Schaper, O.A. Raevsky, Thermodynamic and structural aspects of sulfonamide crystals and solutions, J. Pharm. Sci. 98 (2009) 4738–4755.

[56] T.V. Volkova, G.L. Perlovich, Comparative analysis of solubilization and complexation characteristics for new antifungal compound with cyclodextrins. Impact of cyclodextrins on distribution process, Eur J Pharm Sci. 54 (2020) 105531.

[57] J.H. Blanco-Márquez, D.I. Caviedes Rubio, C.P. Ortiz, N.E. Cerquera, F. Martínez, D.R. Delgado, Thermodynamic analysis and preferential solvation of sulfamethazine in acetonitrile + water cosolvent mixtures, Fluid Phase Equilib. 505 (2020) 112361.

[58] P. Bustamante, S. Romero, A. Peña, B. Escalera, A. Reillo, Enthalpy–entropy compensation for the solubility of drugs in solvent mixtures: paracetamol, acetanilide, and nalidixic acid in dioxane–water, J. Pharm. Sci. 87 (1998) 1590–1596.

[59] E. Tomlinson, Enthalpy-entropy compensation analysis of pharmaceutical, biochemical and biological systems, Int. J. Pharm. 13 (1983) 115–144.

[60] F. Martínez, M.Á. Peña, P. Bustamante, Thermodynamic analysis and enthalpy-entropy compensation for the solubility of indomethacin in aqueous and non-aqueous mixtures, Fluid Phase Equilib. 308 (2011) 98–106.

[61] D.R. Delgado, A. Romdhani, F. Martínez, Thermodynamics of sulfanilamide solubility in propylene glycol + water mixtures, Lat. Am. J. Pharm. 30 (2011) 2024–2054.

[62] Y. Marcus, On the preferential solvation of drugs and PAHs in binary solvent mixtures, J. Mol. Liq. 140 (2008) 61–67.

[63] B. Churchill, W.E. Acree Jr., M.H. Abraham, Abraham model correlation for direct water-to-2,2,5,5-tetramethyloxolane solute transfer partitioning process revisited, Phys. Chem. Liq. (2020), https://doi.org/10.1080/00319104.2019.1675161 Forthcoming.

[64] S. Maghami, A. Mehrabani-Zeinabad, M. Sadeghi, J. Sánchez-Laínez, B. Zornoza, C. Téllez, J. Coronas, Mathematical modeling of temperature and pressure effects on permeability, diffusivity and solubility in polymeric and mixed matrix membranes, Chem. Eng. Sci. 205 (2019) 58–73.

[65] D.R. Delgado, M.Á. Peña, F. Martínez, Extended Hildebrand solubility approach applied to sulphadiazine, sulphamerazine and sulphamethazine in some {1-propanol (1) + water (2)} mixtures at 298.15 K, Phys, Chem. Liq. 57 (2019) 388–400.

[66] D.R. Delgado, M. Peña, F. Martínez, Extended Hildebrand solubility approach applied to some sulphapyrimidines in some {methanol (1) + water (2)} mixtures, Phys. Chem. Liq. 56 (2018) 176–188.

[67] Y. Marcus, Solvent Mixtures: Properties and Selective Solvation, Marcel Dekker, Inc, New York, 2002.

[68] A. Ben-Naim, Theory of preferential solvation of nonelectrolytes, Cell Biophys. 12 (1988) 255–269.

[69] A. Ben-Naim, Preferential solvation in two- and in three-component systems, Pure Appl. Chem. 62 (1990) 25–34.

[70] J.J. Sandoval-Castro, C.P. Ortiz, J. Diego Rodríguez-Rubiano, G. Andrés Rodríguez-Rodríguez, D.R. Delgado, Preferential solvation of tricin in {ethanol (1) + water (2)} mixtures at several temperatures, Rev. Colomb. Cienc. Quím. Farm. 47 (2018) 135–148.

[71] A. Farajtabar, H. Zhao, Equilibrium solubility of 7-amino-4-methylcoumarin in several aqueous co-solvent mixtures revisited: Transfer property, solute-solvent and solvent-solvent interactions and preferential solvation, J. Mol. Liq. 320 (2020) 114407.

[72] Y. Marcus, The Properties of Solvents, John Wiley & Sons Ltd, New York, 1999.

[73] E.T. Fogg, A.N. Hixson, A.R. Thompson, Densities and refractive indexes for ethylene glycol-water solutions, Anal. Chem. 27 (1955) 1609–1611.

[74] J.M. Corkill, J.F. Goodman, T. Walker, Partial molar volumes of surface-active agents in aqueous solution, Trans. Faraday Soc. 63 (1967) 768–772.

[75] R.W. Taft, M.J. Kamlet, The solvatochromic comparison method. 2. The .Alpha.-scale of solvent hydrogen-bond donor (HBD) acidities, J. Am. Chem. Soc. 98 (1976) 2886–2894.