Preferential solvation of acetaminophen in ethanol + water solvent mixtures according to the inverse Kirkwood-Buff integrals method

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Summary

The preferential solvation parameters, *i.e.*, the differences between the local mole fraction of solvents around the solute and those for the bulk co-solvent mixtures in solutions of acetaminophen in ethanol + water binary mixtures were derived from their thermodynamic properties by means of the inverse Kirkwood-Buff integrals (IKBI) method. It is found that acetaminophen is sensitive to solvation effects, so the preferential solvation parameter $\delta x_{E,A}$, is negative in water-rich and ethanol-rich mixtures but positive in co-solvent compositions from 0.24 to 0.73 in mole fraction of ethanol. It is conjecturable that in water-rich mixtures the hydrophobic hydration around the aromatic ring and methyl group present in the drug plays a relevant role in the solvation. The more solvation by ethanol in mixtures of similar co-solvent compositions could be due mainly to polarity effects. Finally, the preference of this drug for water in ethanol-rich mixtures could be explained in terms of the bigger acidic behavior of water molecules interacting with the hydrogen-acceptor groups present in acetaminophen such as the carbonyl group.

Key words: acetaminophen, ethanol, solubility, inverse Kirkwood-Buff integrals, IKBI, preferential solvation.

Resumen

Solvatación preferencial del acetaminofeno en mezclas cosolventes etanol + agua según el método de las integrales inversas de Kirkwood-Buff

Con base en algunas propiedades termodinámicas clásicas de solución en este trabajo, se calcularon los parámetros de solvatación preferencial del acetaminofeno ($\delta x_{E,A}$) en mezclas etanol + agua mediante las integrales inversas de Kirkwood-Buff. Los parámetros $\delta x_{E,A}$ corresponden a las diferencias entre las fracciones molares locales de los solventes alrededor del soluto y en el grueso de la solución. Con base en estos valores, se puede observar que este fármaco es altamente sensible a efectos específicos de solvatación que varían según la composición cosolvente. Así, los valores de $\delta x_{E,A}$ son negativos en mezclas ricas en agua y en mezclas ricas en etanol, pero positivos en composiciones desde 0,24 hasta 0,73 en fracción molar de etanol. Es probable que la hidratación hidrofóbica alrededor del anillo aromático y el grupo metilo del acetaminofeno pueda tener un papel relevante en la solvatación del fármaco en mezclas ricas de agua. En mezclas de composición intermedia, la mayor solvatación por las moléculas de etanol podría deberse principalmente a efectos de polaridad. Finalmente, la preferencia que este fármaco manifiesta por el agua en mezclas ricas en etanol podría explicarse en términos del mayor comportamiento ácido de las moléculas del agua, que estarían interactuando con los grupos aceptores de hidrógeno presentes en el acetaminofeno, tales como el carbonilo.

Palabras clave: acetaminofeno, etanol, solubilidad, integrales inversas de Kirkwood-Buff, IKBI, solvatación preferencial.

Introduction

Acetaminophen (A or ACP, N-(4-hydroxyphenyl)ethenamide, CAS 103-90-2, Figure 1), also known as paracetamol, is a classical drug commonly used in therapeutics because of its analgesic and antipyretic effects. This drug is specially indicated in the treatment of several minor diseases presented by pediatric patients [1, 2].

Solubility of drugs in co-solvent mixtures knowledge is very important for pharmaceutical scientists involved in several development stages such as drug purification and design of liquid medicines [3]. Although co-solvency has been employed in pharmacy for centuries it is recently that the mechanisms involved to increase or decrease drugs

solubility have been approached from a physicochemical point of view [4]. In this way, several thermodynamic works have been published based on the enthalpic and entropic contributions to the Gibbs energy of solution, and in some specific cases, the solvation of analgesic drugs in aqueous alcoholic mixtures has been analyzed from thermodynamic quantities of the drug sublimation [2, 5-7]. Nevertheless, the drug preferential solvation, *i.e.* the co-solvent specific composition around the drug molecules has not been completely studied for analgesic drugs [8]. Therefore, the main goal of this paper is to evaluate the preferential solvation of acetaminophen in ethanol + water co-solvent mixtures, based on thermodynamic definitions. Thus this work is a continuation of the ones presented previously in the literature for some analgesic drugs in co-solvent mixtures [9-11].
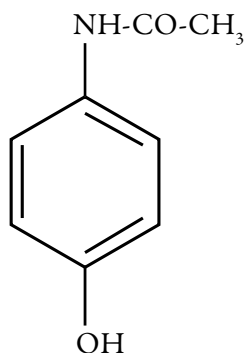
$$NH\text{-}CO\text{-}CH_3$$

Figure 1. Molecular structure of acetaminophen

The inverse Kirkwood-Buff integral (IKBI) is a powerful tool for evaluating the preferential solvation of nonelectrolytes in solvent mixtures, describing the local compositions around a solute with respect to the different components present in the solvent mixture [12-14].

In the present case, this treatment depends on the values of the standard molar Gibbs energies of transfer of the solute acetaminophen from neat water to the ethanol + water solvent mixtures and the excess molar Gibbs energy of mixing for the co-solvent binary mixtures. As has been indicated previously, this treatment is very important in pharmaceutical sciences to understand the molecular interactions solute-solvent because most of the solubility studies developed have been directed towards correlating or modeling the solubilities and possibly predicting them from the solubilities in the neat solvents, but not to analyze the local environment around the drug molecules describing the local fraction of the solvent components (E or W) in the surrounding of solute (A) [15, 16].

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In this paper the IKBI approach is applied to evaluate the preferential solvation of the acetaminophen in the binary mixtures conformed by ethanol (E or EtOH) and water (W). The results are expressed in terms of the preferential solvation parameter $\delta x_{E,A}$ of the solute by the two solvent components. Another well-known thermodynamic method used to calculate $\delta x_{E,A}$ is the one proposed by Marcus so-called Quasi-lattice quasi-chemical (QLQC) approach [15, 16]. This method is simpler to use than IKBI method but it is useful when the maximum solubility is found in the co-solvent under consideration. This is not the case with acetaminophen in ethanol + water mixtures where the maximum drug solubility is found in mixtures with 0.90 in mass fraction of ethanol [5].

Theoretical

The KBIs (Kirkwood-Buff integrals, $G_{i,A}$) are given by the following expression:

$$G_{i,A} = \int_0^{r_{cor}} (g_{i,A} - 1)4\pi r^2 dr \tag{1}$$

Here $g_{i,A}$ is the pair correlation function for the molecules of the solvent i in the ethanol + water mixtures around the solute acetaminophen, r the distance between the centers of the molecules of acetaminophen and ethanol or water, and r_{cor} is a correlation distance for which $g_{i,A}(r > r_{cor}) \approx 1$. Thus, for all distances $r > r_{cor}$ up to infinite, the value of the integral is essentially zero. Therefore, the results are expressed in terms of the preferential solvation parameter $\delta x_{i,A}$ for the solute in solution by the component solvents ethanol and water [17]. For ethanol (E) this parameter is defined as:

$$\delta x_{E,A} = x_{E,A}^L - x_E = -\delta x_{W,A} \tag{2}$$

Where x_E is the mole fraction of ethanol in the bulk solvent mixture and $x_{E,A}^L$ is the local mole fraction of ethanol in the environment near to the drug. If $\delta x_{E,A} > 0$ then the solute acetaminophen is preferentially solvated by ethanol; on the contrary, if it is < 0 the drug is preferentially solvated by water, within the correlation volume, $V_{cor} = (4\pi/3)r_{cor}^3$, and the bulk mole fraction of ethanol, x_E. Values of $\delta x_{E,A}$ are obtainable from those of $G_{E,A}$, and these in turn, from thermodynamic data of the co-solvent mixtures with the solute dissolved on it, as shown below [15].

Algebraic manipulation of the basic expressions presented by Newman [17] leads to expressions for the Kirkwood-Buff integrals (in cm³ mol⁻¹) for the individual solvent

components in terms of some thermodynamic quantities as shown in equations (3) and (4) [12, 15, 16]:

$$G_{E,A} = RT\kappa_T - V_A + x_W V_W D / Q \tag{3}$$

$$G_{W,A} = RT\kappa_T - V_A + x_E V_E D / Q \tag{4}$$

Where κ_T is the isothermal compressibility of the ethanol + water solvent mixtures (in GPa^{-1}), V_E and V_W are the partial molar volumes of the solvents in the mixtures (in cm^3 mol^{-1}), similarly, V_A is the partial molar volume of solute in these mixtures (in cm^3 mol^{-1}). The function D is the derivative of the standard molar Gibbs energies of transfer of the drug (from neat water to ethanol + water mixtures) with respect to the solvent composition (in kJ mol^{-1}, as also is RT) and the function Q involves the second derivative of the excess molar Gibbs energy of mixing of the two solvents (G_{E+W}^{Exc}) with respect to the water proportion in the mixtures (also in kJ mol^{-1}) [15, 16, 18]:

$$D = \left(\frac{\partial \Delta_{tr} G_{(A, W \to E+W)}^0}{\partial x_E} \right)_{T,p} \tag{5}$$

$$Q = RT - x_E x_W \left(\frac{\partial^2 G_{E,W}^{Exc}}{\partial x_W^2} \right)_{T,p} \tag{6}$$

Because the dependence of κ_T on composition is not known for a lot of the systems investigated and because of the small contribution of $RT\kappa_T$ to the IKBI the dependence of κ_T on composition could be approximated by considering additive behavior according to the equation (7) [19]:

$$\kappa_{T,\text{mix}} = \sum_{i=1}^{n} x_i \kappa_{T,i}^0 \tag{7}$$

Where x_i is the mole fraction of component i in the mixture and $\kappa_{T,i}^0$ is the isothermal compressibility of the pure component i.

Ben-Naim [12] showed that the preferential solvation parameter can be calculated from the Kirkwood-Buff integrals as follows:

$$\delta x_{E,A} = \frac{x_E x_W \left(G_{E,A} - G_{W,A} \right)}{x_E G_{E,A} + x_W G_{W,A} + V_{cor}} \tag{8}$$

The correlation volume, V_{cor}, is obtained by means of the following expression proposed by Marcus [8, 16]:

$$V_{cor} = 2522.5\left(r_A + 0.1363\left(x_{E,A}^L V_E + x_{W,A}^L V_W\right)^{1/3} - 0.085\right)^3 \tag{9}$$

Where r_A is the radius of the solute (in nm), calculated as:

$$r_A = \left(\frac{3 \cdot 10^{21} V_A}{4\pi N_{Av}}\right)^{1/3} \tag{10}$$

Where N_{Av} is the Avogadro number. However, the definitive correlation volume requires iteration, because it depends on the local mole fractions. This iteration is done by replacing $\delta x_{E,A}$ in the equation (2) to calculate $x_{E,A}^L$ until a non-variant value of V_{cor} is obtained.

Results and discussion

The solubility of acetaminophen in ethanol + water mixtures (Table 1) was taken from Jiménez and Martínez [5]. Standard molar Gibbs energy of transfer of this drug from neat water to ethanol + water mixtures is calculated and correlated to regular quartic polynomials from the drug solubility data by using equation (11). This degree of polynomials was chosen based on some significant statistical parameters as the respective determination coefficients and residual analyses (values not shown here). In this way, decimal places in the quantities reported in almost all the tables along the document were defined as has usually been done in some previous researches [9-11]. Otherwise, Figure 2 shows the Gibbs energy of transfer behavior at 298.15 K whereas Table 2 show the behavior at all the temperatures studied. Polynomials coefficients are shown in Table 3.

$$\Delta_{tr}G_{A,W \to E+W}^0 = RT\ln\left(\frac{x_{A,W}}{x_{A,E+W}}\right) = a + bx_E + cx_E^2 + dx_E^3 + ex_E^4 \tag{11}$$

Table 1. Mole fraction solubility $(x_A)^a$ of acetaminophen at several temperatures.

$x_{EtOH}{}^b$	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.0000	1.52 E-03	1.85 E-03	2.09 E-03	2.56 E-03	3.15 E-03
0.0417	2.43 E-03	3.27 E-03	3.82 E-03	4.42 E-03	5.70 E-03
0.0891	4.70 E-03	6.87 E-03	7.51 E-03	8.70 E-03	1.07 E-02

Table 1. Mole fraction solubility $(x_A)^a$ of acetaminophen at several temperatures (continuation).

$x_{EtOH}{}^b$	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.1436	1.05 E-02	1.32 E-02	1.54 E-02	1.81 E-02	2.18 E-02
0.2068	1.87 E-02	2.22 E-02	2.54 E-02	2.91 E-02	3.42 E-02
0.2812	3.02 E-02	3.47 E-02	3.94 E-02	4.45 E-02	5.21 E-02
0.3698	4.19 E-02	4.55 E-02	5.20 E-02	5.75 E-02	6.74 E-02
0.4772	5.24 E-02	5.72 E-02	6.25 E-02	6.88 E-02	7.91 E-02
0.6101	6.00 E-02	6.58 E-02	7.10 E-02	7.81 E-02	8.88 E-02
0.7788	6.25 E-02	6.61 E-02	7.41 E-02	8.09 E-02	9.13 E-02
1.0000	5.04 E-02	5.46 E-02	6.20 E-02	6.68 E-02	7.05 E-02

^{a} Data from Ref. [5].

$^b x_{EtOH}$ is the mole fraction of ethanol in the ethanol + water co-solvent mixtures free of acetaminophen.
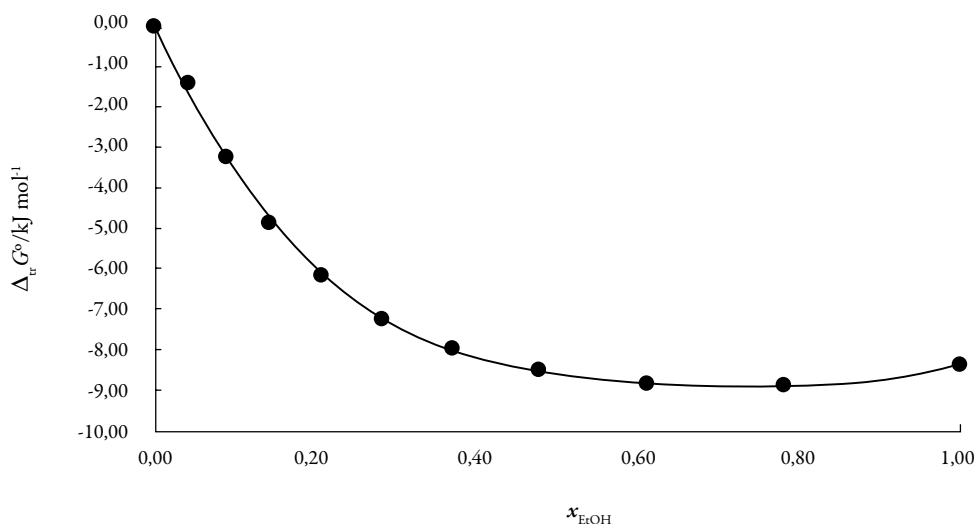
Figure 2. Gibbs energy of transfer of acetaminophen from neat water to ethanol + water co-solvent mixtures at 298.15 K

Thus D values are calculated from the first derivative of polynomial models (Equation 12) solved according to the co-solvent mixtures composition. This procedure was done varying by 0.05 in mole fraction of ethanol but in the following tables the respective values are reported varying only by 0.10. D values are reported in Table 4.

$$D = b + 2cx_E + 3dx_E^2 + 4ex_E^3 \tag{12}$$

Table 2. Gibbs energy of transfer (kJ mol⁻¹) of acetaminophen from neat water to ethanol + water co-solvent mixtures at several temperatures.

x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.0000	0.00	0.00	0.00	0.00	0.00
0.0417	−1.13	−1.40	−1.52	−1.40	−1.55
0.0891	−2.74	−3.25	−3.22	−3.14	−3.17
0.1436	−4.70	−4.87	−5.03	−5.01	−5.04
0.2068	−6.11	−6.15	−6.29	−6.23	−6.21
0.2812	−7.28	−7.26	−7.40	−7.32	−7.31
0.3698	−8.08	−7.93	−8.10	−7.98	−7.98
0.4772	−8.62	−8.50	−8.56	−8.43	−8.39
0.6101	−8.95	−8.85	−8.89	−8.76	−8.70
0.7788	−9.05	−8.86	−8.99	−8.85	−8.77
1.0000	−8.53	−8.38	−8.54	−8.36	−8.10

Table 3. Coefficients of the Equation (11) (kJ mol⁻¹) applied to Gibbs energy of transfer of acetaminophen from neat water to ethanol + water co-solvent mixtures at several temperatures.

Coefficient	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
a	0.28	0.13	0.14	0.18	0.13
b	−43.38	−45.62	−47.22	−47.16	−47.22
c	75.38	90.62	96.29	96.95	98.73
d	−58.96	−83.72	−90.86	−92.14	−95.78
e	18.14	30.21	33.10	33.80	36.04

Table 4. D values (kJ mol⁻¹) of acetaminophen in ethanol + water co-solvent mixtures at several temperatures.

x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	−43.38	−45.62	−47.22	−47.16	−47.22
0.10	−30.00	−29.89	−30.55	−30.40	−30.20
0.20	−19.72	−18.45	−18.55	−18.36	−18.07
0.30	−12.11	−10.59	−10.40	−10.22	−9.95
0.40	−6.73	−5.58	−5.32	−5.18	−4.98
0.50	−3.15	−2.69	−2.52	−2.42	−2.30
0.60	−0.93	−1.20	−1.20	−1.13	−1.05
0.70	0.37	−0.38	−0.56	−0.50	−0.35
0.80	1.17	0.49	0.19	0.27	0.65
0.90	1.93	2.13	1.84	2.01	2.83
1.00	3.06	5.28	5.19	5.52	7.05

In order to calculate the Q values the excess molar Gibbs energies of mixing $G_{E,W}^{Exc}$ at all the temperatures considered are required. Nevertheless, normally these values are reported only at one temperature, *i.e.* 298.15 K. For this reason, it is necessary to calculate it at other temperatures. In this way, $G_{E,W}^{Exc}$ values were calculated at 298.15 K by using the equation (13) as reported by Marcus [15]. On the other hand, the $G_{E,W}^{Exc}$ values at the other temperatures were calculated by using the equation (14), where, $H_{E,W}^{Exc}$ is the excess molar enthalpy of the co-solvent mixtures, T_1 is 298.15 K and T_2 is one of the other temperatures under consideration [15]. In turn, $H_{E,W}^{Exc}$ values were calculated by using the equation (15) at 298.15 K as also reported by Marcus [15].

$$G_{E,W}^{Exc} = x_E x_W \left(2907 - 777\left(1 - 2x_E\right) + 494\left(1 - 2x_E\right)^2\right) \tag{13}$$

$$G_{E,W}^{Exc}(T_2) = G_{E,W}^{Exc}(T_1) - T\int_{T_1}^{T_2} H_{E,W}^{Exc} d\left(\frac{1}{T}\right) \approx \frac{T_2}{T_1} G_{E,W}^{Exc}(T_1) + H_{E,W}^{Exc}\left(1 - \frac{T_2}{T_1}\right) \tag{14}$$

$$H_{E,W}^{Exc} = x_E x_W \left(-1300 - 3567\left(1 - 2x_E\right) - 4971\left(1 - 2x_E\right)^2\right) \tag{15}$$

It is important to note that quartic regular polynomials of $G_{E,W}^{Exc}$ as a function of the mole fraction of water were obtained. Q values at all temperatures are shown in Table 5. On the other hand, Table 6 shows the $RT\kappa_T$ values calculated by assuming additive behavior of κ_T (Equation 7) with the values 1.153 and 0.457 GPa^{-1}, for ethanol and water, respectively [19].

Table 5. Q values (kJ mol^{-1}) of ethanol + water co-solvent mixtures at several temperatures.

x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	2.437	2.479	2.520	2.562	2.604
0.10	2.077	2.039	2.000	1.962	1.924
0.20	1.855	1.813	1.771	1.729	1.687
0.30	1.668	1.658	1.648	1.638	1.627
0.40	1.460	1.487	1.515	1.543	1.570
0.50	1.220	1.272	1.324	1.377	1.429
0.60	0.985	1.040	1.095	1.149	1.204
0.70	0.838	0.875	0.912	0.949	0.986
0.80	0.906	0.918	0.930	0.942	0.953
0.90	1.365	1.367	1.370	1.372	1.374
1.00	2.437	2.479	2.520	2.562	2.604

Table 6. $RT\kappa_T$ values (cm³ mol⁻¹) of ethanol + water co-solvent mixtures at several temperatures.

x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	1.114	1.133	1.152	1.171	1.190
0.10	1.283	1.305	1.327	1.349	1.371
0.20	1.453	1.478	1.503	1.527	1.552
0.30	1.623	1.650	1.678	1.706	1.733
0.40	1.792	1.823	1.853	1.884	1.915
0.50	1.962	1.995	2.029	2.062	2.096
0.60	2.132	2.168	2.204	2.241	2.277
0.70	2.301	2.341	2.380	2.419	2.458
0.80	2.471	2.513	2.555	2.597	2.639
0.90	2.641	2.686	2.731	2.776	2.821
1.00	2.810	2.858	2.906	2.954	3.002

The partial molar volumes of ethanol (Table 7) and water (Table 8) were calculated by means of equations (16) and (17) from the density (ρ) values of ethanol + water mixtures reported by Jiménez *et al.* at all the temperatures under study [20]. V is the molar volume of the mixtures and it is calculated as $V = (x_E M_E + x_W M_W)/\rho$. M_E and M_W are 46.06 and 18.02 g mol⁻¹, respectively.

$$\overline{V}_E = V + x_W \frac{dV}{dx_E} \tag{16}$$

$$\overline{V}_W = V - x_E \frac{dV}{dx_E} \tag{17}$$

Partial molar volumes of non-electrolyte drugs are not frequently reported in the literature. This is because of the big uncertainty obtained in its determination due to the low solubilities exhibited in particular in aqueous media. For this reason, in a first approach the molar volume of acetaminophen is considered here as independent of co-solvent composition and temperature, just as it is calculated according to the groups contribution method proposed by Fedors [21, 22]. Thus, this value has been considered as reported by Ahumada *et al.* as V_A = 111.2 cm³ mol⁻¹ [23]. Additionally, from this volume value the radius of the drug molecule (required for equation 9) was calculated by using the equation (10) as r_A = 0.353 nm.

Table 7. Partial molar volume (cm³ mol⁻¹) of ethanol in ethanol + water co-solvent mixtures at several temperatures.

x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	52.49	52.77	53.38	53.95	54.30
0.10	54.05	54.37	54.86	55.30	55.68
0.20	55.31	55.65	56.06	56.40	56.79
0.30	56.29	56.65	56.99	57.28	57.68
0.40	57.03	57.40	57.70	57.96	58.37
0.50	57.57	57.93	58.22	58.47	58.87
0.60	57.94	58.28	58.57	58.83	59.23
0.70	58.16	58.50	58.79	59.07	59.45
0.80	58.28	58.61	58.91	59.21	59.58
0.90	58.33	58.65	58.95	59.28	59.64
1.00	58.34	58.65	58.96	59.29	59.66

Table 8. Partial molar volume (cm³ mol⁻¹) of water in ethanol + water co-solvent mixtures at several temperatures.

x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	18.05	18.07	18.09	18.11	18.14
0.10	17.97	17.99	18.01	18.04	18.07
0.20	17.75	17.77	17.80	17.85	17.88
0.30	17.42	17.44	17.49	17.55	17.58
0.40	17.03	17.04	17.11	17.19	17.21
0.50	16.59	16.60	16.69	16.77	16.80
0.60	16.15	16.17	16.27	16.34	16.37
0.70	15.73	15.78	15.86	15.90	15.95
0.80	15.38	15.46	15.52	15.48	15.56
0.90	15.12	15.25	15.25	15.12	15.24
1.00	14.99	15.18	15.11	14.83	15.00

Tables 9 and 10 show that the $G_{E,A}$ and $G_{W,A}$ values are negative with the exception of $G_{W,A}$ at 313.15 K in the mixture of 0.90 in mole fraction of ethanol. It is important to note that the same values for neat ethanol are also positive from 298.15 to 313.15 K but these values are not relevant in the general treatment because it correspond to a pure component.

Table 9. $G_{E,A}$ values ($cm^3 mol^{-1}$) for acetaminophen in ethanol + water co-solvent mixtures at several temperatures.

x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	−431.4	−442.7	−448.9	−443.4	−439.1
0.10	−343.5	−347.3	−357.4	−361.4	−365.1
0.20	−260.7	−254.4	−258.9	−261.3	−262.8
0.30	−198.2	−187.5	−186.8	−186.2	−184.7
0.40	−156.5	−147.7	−145.4	−143.9	−142.1
0.50	−130.7	−126.8	−125.1	−123.9	−122.7
0.60	−115.2	−116.5	−116.1	−115.4	−114.6
0.70	−106.8	−110.9	−111.7	−111.3	−110.4
0.80	−104.7	−107.0	−108.0	−107.7	−106.4
0.90	−106.4	−106.1	−106.4	−106.2	−105.2
1.00	−108.4	−108.3	−108.3	−108.2	−108.2

Table 10. $G_{W,A}$ values ($cm^3 mol^{-1}$) for acetaminophen in ethanol + water co-solvent mixtures at several temperatures.

x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	−110.1	−110.1	−110.0	−110.0	−110.0
0.10	−188.0	−189.6	−193.7	−195.5	−197.2
0.20	−227.4	−223.0	−227.1	−229.4	−231.3
0.30	−232.2	−218.1	−217.5	−216.7	−215.2
0.40	−214.6	−195.5	−190.5	−187.1	−183.4
0.50	−183.6	−170.4	−164.6	−160.4	−156.6
0.60	−141.8	−149.4	−147.5	−143.6	−139.9
0.70	−91.0	−126.8	−134.1	−130.7	−123.6
0.80	−48.3	−83.9	−99.1	−94.8	−75.9
0.90	−34.5	−26.3	−37.2	−30.2	2.2
1.00	−35.2	16.5	13.1	19.6	53.2

In order to use the IKBI method, the correlation volume was iterated three times by using the equations (2), (8) and (9) to obtain the values reported in Table 11. It is interesting to note that this value is almost independent on temperature in water-rich mixtures but increases in some extent in ethanol-rich mixtures.

Table 11. Correlation volume $(cm^3\ mol^{-1})$ for acetaminophen in ethanol + water co-solvent mixtures at several temperatures after three iterations.

x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	618	619	619	619	620
0.10	665	665	665	666	667
0.20	746	747	749	751	753
0.30	827	828	831	833	835
0.40	899	899	901	903	906
0.50	963	964	967	969	971
0.60	1023	1028	1031	1033	1036
0.70	1082	1090	1094	1097	1101
0.80	1143	1151	1156	1159	1162
0.90	1209	1213	1218	1222	1225
1.00	1276	1281	1286	1290	1296

The values of $\delta x_{E,A}$ vary non-linearly with the ethanol concentration in the aqueous mixtures at 298.15 K (Figure 3). Addition of ethanol to water tends to make negative the $\delta x_{E,A}$ values of acetaminophen from the pure water up to the mixture 0.24 in mole fraction of ethanol reaching a minimum of –0.031. Possibly the structuring of water molecules around the non-polar groups of this drug (aromatic ring and methyl group), *i.e.* hydrophobic hydration, contributes to lowering of the net $\delta x_{E,A}$ to negative values in these water-rich mixtures. This minimum is almost invariant with temperature (Table 12).

Table 12. $\delta x_{E,A}$ values of acetaminophen in ethanol + water co-solvent mixtures at several temperatures.

| x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	0.0000	0.0000	0.0000	0.0000	0.0000
0.10	–0.0303	–0.0308	–0.0324	–0.0329	–0.0334
0.20	–0.0104	–0.0097	–0.0098	–0.0099	–0.0098
0.30	0.0118	0.0104	0.0103	0.0103	0.0102
0.40	0.0197	0.0159	0.0148	0.0141	0.0134
0.50	0.0164	0.0134	0.0120	0.0111	0.0102
0.60	0.0071	0.0088	0.0083	0.0075	0.0066
0.70	–0.0034	0.0034	0.0048	0.0041	0.0028
0.80	–0.0086	–0.0035	–0.0014	–0.0020	–0.0046
0.90	–0.0058	–0.0064	–0.0056	–0.0061	–0.0086
1.00	0.0000	0.0000	0.0000	0.0000	0.0000
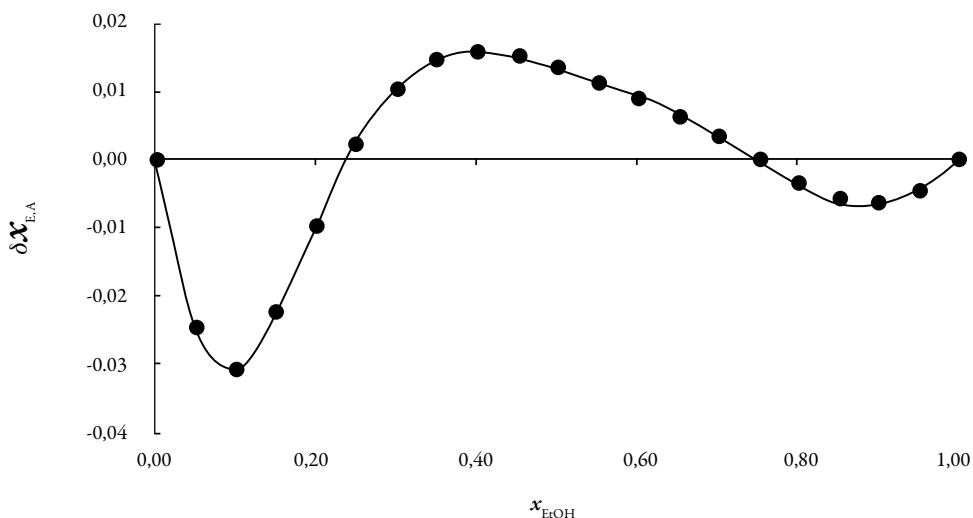
Figure 3. $\delta x_{E,A}$ values for acetaminophen in ethanol + water co-solvent mixtures at 298.15 K

In the mixtures with composition $0.25 < x_{EtOH} < 0.75$, the local mole fraction of ethanol is greater than the one for water and it decreases with the temperature increasing. In this way, the co-solvent action may be related to the breaking of the ordered structure of water (hydrogen bonds) around the non-polar moieties of the drug which increases the solvation of the acetaminophen and have a maximum value near to $x_{EtOH} = 0.40$, *i.e.* $\delta x_{E,A} = 0.0197$. Ultimately, from this ethanol proportion up to neat ethanol, the local mole fraction of the ethanol decreases, being the $\delta x_{E,A}$ values negative, as they also are in water-rich mixtures.

Acetaminophen acts in solution as a Lewis acid due to the hydrogen atoms in its –OH and –NH groups (Figure 1) in order to establish hydrogen bonds with proton-acceptor functional groups in the solvents (oxygen atoms in –OH). In addition, this drug could act as a Lewis base due to free electron pairs in oxygen atoms of hydroxyl and carbonyl groups (Figure 1) to interact with hydrogen in both solvents. In this context, acetaminophen has two hydrogen-bonding donor and two hydrogen-bonding acceptor groups.

According to the preferential solvation results, it is conjecturable that in intermediate composition mixtures, the acetaminophen is acting as Lewis acid with ethanol molecules because this co-solvent is more basic than water, *i.e.* the Kamlet-Taft hydrogen bond acceptor parameters are $\beta = 0.75$ for ethanol and 0.47 for water [24]. On the other hand, in ethanol-rich mixtures, where the drug is preferentially solvated by

water, the drug is acting mainly as a Lewis base in front to water because the Kamlet-Taft hydrogen bond donor parameters are, $\alpha = 1.17$ for water and 0.86 for ethanol, respectively [25]. Thus, water is more acidic than ethanol. In this way, the specific and nonspecific interactions between acetaminophen and the co-solvent decrease in these mixtures [9, 26].

Conclusions

Explicit expressions for local mole fraction of ethanol and water around of acetaminophen were derived on the basis of the IKBI method applied to equilibrium solubility values of this drug in ethanol + water mixtures. Thus, this drug is preferentially solvated by water in water-rich and ethanol-rich mixtures but preferentially solvated by ethanol in mixtures with intermediate composition at all temperatures considered. These results are in agreement with that described previously and based on more classical thermodynamic treatments.

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