Journal of Applied Solution Chemistry and Modeling, 2018, 7, 1-8

Solution Thermodynamics and Preferential Solvation of Atenolol in {Ethanol (1) + Water (2)} Cosolvent Mixtures

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Abstract: The solubility of atenolol (ATN) in some {ethanol (1) + water (2)} mixtures expressed in mole fraction at temperatures from 298.2 to 313.2 K was calculated from reported solubility values expressed in molarity scale. The van't Hoff and Gibbs equations were used to calculate the respective apparent thermodynamic functions: Gibbs energy, enthalpy, and entropy of the dissolution processes. Non-linear enthalpy–entropy relationship was observed for this drug ATN in the plot of enthalpy vs. Gibbs energy of solution with negative slope in the composition region $0.00 \le w_1 \le 0.20$ but positive slope in the region $0.20 \le w_1 \le 0.40$. Beyond this composition, the behavior is more complex. Hence, the driving mechanism for ATN dissolution process is the entropy in water-rich mixtures and the enthalpy in mixtures $0.20 \le w_1 \le 0.40$. Furthermore, the preferential solvation of ATN by both solvents was analyzed by using the inverse Kirkwood-Buff integrals observing that this drug is preferentially solvated by water molecules in water-rich and also in ethanol-rich mixtures but preferentially solvated by ethanol molecules in mixtures $0.24 \le x_1 \le 0.51$.

Keywords: Atenolol, (ethanol + water) mixtures, solubility, solution thermodynamics, preferential solvation.

INTRODUCTION

Cosolvency as a very useful solubilizing technique has been widely employed in the design of several kinds of pharmaceutical dosage forms [1]. Nevertheless, it was recently that the main mechanisms involved in the modification of the drug solubility started to be approached from a deep thermodynamic point of view that includes the analysis of the preferential solvation of the solute by all the solvents in the mixtures [2, 3]. Moreover, the physicochemical behavior of drugs in cosolvent mixtures is frequently evaluated, regarding both composition and temperature, for purification of raw materials, preformulation studies, and/or the understanding of the molecular mechanisms involved in physical and chemical stability of pharmaceutical dissolutions [4]. Furthermore, the equilibrium solubility of active pharmaceutical ingredients is a crucial property to be considered because this property affects several biopharmaceutical and pharmacokinetic properties [5]. On the other hand, the preferential solvation of the solute by the solvent components in the mixtures provides a powerful tool for the understanding of the main molecular interactions involved in the drug dissolution processes [2, 3].

Atenolol (ATN, molar mass: 266.34 g mol^{-1}, IUPAC name: (*RS*)-2-{4-[2-Hydroxy-3-(propan-2-ylamino) propoxy]phenyl}acetamide, CAS number: 29122-68-7, Figure **1**) is a drug belonging to the beta blockers group used primarily in treatment of some cardiovascular diseases [6, 7]. Despite the therapeutically use of ATN its solubility data in cosolvent mixtures and the respective thermodynamic treatments are not abundant [4].

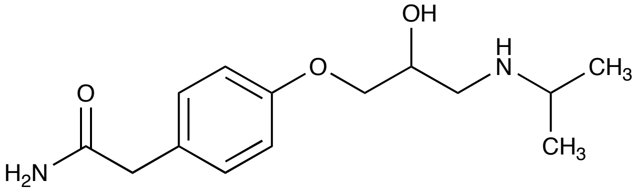

Figure 1: Molecular structure of atenolol.

For this reason, the main purposes of this communication are i) to calculate the mole fraction solubility of ATN from experimental molar solubility values reported previously [8], ii) to analyze the effect of the mixtures composition on the solubility and solution thermodynamics, and iii) to evaluate the preferential solvation of ATN in binary mixtures conformed by ethanol and water.

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E-ISSN: 1929-5030/18

RESULTS AND DISCUSSION

Mole Fraction Solubility

As indicated above, the ATN solubility expressed in molarity (C, mol dm^{-3}) in {ethanol (1) + water (2)} mixtures at four temperatures from 298.2 K to 313.2 K was reported previously in the literature [8]. As reported by the authors, the equilibrium solubility of ATN was determined using the saturation shake-flask method proposed by Higuchi and Connors [9]. Nevertheless, no density values of the saturated solutions were reported in this research and thus, no direct calculation of the solubility expressed in mole fraction was possible. It is important to note that no individual nor global experimental uncertainties are reported for the ATN molar solubility values in this reference [8].

Because the ATN solubility in these mixtures was not high in that research [8], it was assumed that the molar volume of the drug in all the saturated solutions is equivalent to that reported for the pure compound as calculated from its molar mass (266.34 g mol^{-1}) and density (1.125 g cm^{-3}) values, i.e. 236.7 cm^3 mol^{-1} [10]. In this way, the mole fraction solubility of ATN (x_3) is easily calculated from the reported solubility values expressed in molarity by means of the following expression:

$$x_3 = \frac{C_{3,1+2}}{C_{3,1+2} + \dfrac{1000\rho - C_{3,1+2}M_3}{M_{1+2}}} \tag{1}$$

Here, $C_{3,1+2}$ is the molarity of ATN at saturation (identified as compound 3) in the mixtures of ethanol (identified as compound 1) and water (identified as compound 2), ρ is the density of the saturated solution (expressed in g cm^{-3}), and M_3 and M_{1+2} are the molar masses of ATN and the {ethanol (1) + water (2)} mixtures, respectively [11].

ATN solubility values in {ethanol (1) + water (2)} mixtures, expressed as mole fraction at various temperatures, are shown in Table **1**. No uncertainties are reported for these values because no uncertainties were reported in the original molarity values [8]. As observed maximum solubility is observed in the mixture w_1 = 0.70 at all temperatures. As normally expected, the drug solubility increases with temperature arising in all cases indicating that the dissolution processes are endothermic.

On the other hand, Figure **2** shows the solubility profiles as a function of the polarity of the mixtures, expressed by their Hildebrand solubility parameters (δ_{1+2}). For dissolvent mixtures, δ_{1+2} can be calculated from the Hildebrand solubility parameter of the pure solvents (δ_1 = 26.5 MPa$^{1/2}$ for ethanol and δ_2 = 47.8 MPa$^{1/2}$ for water) and the volume fraction f_i of each component in the mixture, by assuming volume fraction additivity as follows [11-13]:

$$\delta_{1+2} = \sum_{i=1}^{n} f_i \delta_i \tag{2}$$

Table 1: Calculated Mole Fraction Solubility of Atenolol (3) in {Ethanol (1) + Water (2)} Mixtures at Several Temperatures

w_1 [a]	x_1 [a]	$10^3 x_3$			
		T = 298.2 K	T = 303.2 K	T = 308.2 K	T = 313.2 K
0.000	0.0000	1.33	1.38	1.44	1.82
0.100	0.0417	2.00	2.66	3.01	3.69
0.200	0.0891	3.06	4.24	5.02	6.74
0.300	0.1436	6.57	8.00	8.91	11.89
0.400	0.2068	12.69	13.05	14.77	16.90
0.500	0.2812	19.45	20.09	22.81	27.69
0.600	0.3698	23.57	25.42	28.69	38.33
0.700	0.4772	28.81	33.88	36.18	46.91
0.800	0.6101	26.57	27.47	33.20	41.63
0.900	0.7788	20.11	24.01	28.44	33.71
1.000	1.0000	11.43	12.70	14.42	18.09

[a] w_1 and x_1 are the mass and mole fractions of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of atenolol (3), respectively.

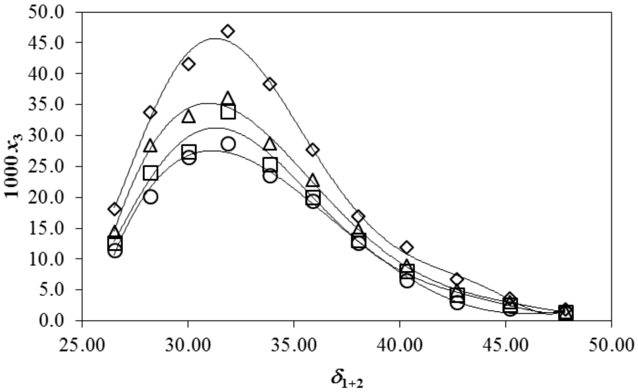

Figure 2: Calculated mole fraction solubility of atenolol (x_3) as function of the Hildebrand solubility parameter of the {ethanol (1) + water (2)} mixtures at different temperatures. ○: 298.2 K; □: 303.2 K; Δ: 308.2 K; ◊: 313.2 K.

By considering the entire polarity range in this binary system all the curves show maximum solubility values in the mixture with δ_{1+2} = 31.9 MPa$^{1/2}$ (w_1 = 0.70, f_1 = 0.7476). According to the literature, solutes reach their maximum solubilities in solvents with the same Hildebrand solubility parameter [11]. Therefore, the δ_3 value of ATN in this cosolvent system would be 31.9 MPa$^{1/2}$. Nevertheless, this value is different regarding that calculated by using the Fedors' method [14], as shown in Table **2** (26.96 MPa$^{1/2}$). This difference could be attributed to specific solvation processes that are not normally considered in Fedors' calculations as has been described for other drugs [15, 16].

Apparent Thermodynamic Functions of Dissolution

All apparent thermodynamic quantities of solution were estimated at 298.2 K. In this way, apparent standard enthalpy change of solution ($\Delta_{\mathrm{soln}}H°$) was obtained by the van't Hoff method as:

$$\left(\frac{\partial \ln x_3}{\partial\left(1/T - 1/298.2\ \mathrm{K}\right)}\right)_P = -\frac{\Delta_{\mathrm{soln}}H^\circ}{R} \qquad (3)$$

The apparent standard Gibbs energy change for the solution process ($\Delta_{\mathrm{soln}}G°$) was is calculated by means of:

$$\Delta_{soln}G^\circ = -RT \cdot \mathrm{intercept} \qquad (4)$$

in which, the intercept used is the one obtained in the analysis of ln x_3 as a function of (1/T – 1/298.2K). Finally, the standard apparent entropic change for solution process ($\Delta_{\mathrm{soln}}S°$) is obtained from the respective $\Delta_{\mathrm{soln}}H°$ and $\Delta_{\mathrm{soln}}G°$ values by using:

$$\Delta_{\mathrm{soln}}S^\circ = \frac{\left(\Delta_{\mathrm{soln}}H^\circ - \Delta_{\mathrm{soln}}G^\circ\right)}{298.2\mathrm{K}} \qquad (5)$$

Table **3** shows the standard molar thermodynamic functions for dissolution of ATN (3) in all the {ethanol (1) + water (2)} solvent mixtures, including those for the neat solvents.

The apparent standard Gibbs energy of solution of ATN (3) is positive in every case as also are the enthalpy and entropy of solution (except in neat water, where negative value is observed for $\Delta_{\mathrm{soln}}S°$). Therefore, the global dissolution process is always endothermic and entropy-driven (except in neat water). In general way, the $\Delta_{\mathrm{soln}}H°$ and $\Delta_{\mathrm{soln}}S°$ values increase from pure water (2) to the mixture w_1 = 0.20 and later they decrease with the ethanol (1) proportion to reach a minimum in the mixture w_1 = 0.40. After that these values increase in irregular way with the ethanol (1) proportion in the mixtures. This behavior is similar to those exhibited by some other drugs in the same

Table 2: **Internal Energy, Molar Volume, and Hildebrand Solubility Parameter of Atenolol (Compound 3), According to the Fedors' Method**

Group	Number	$\Delta U°$ / kJ mol^{-1}	$V°$ / cm^3 mol^{-1}
$-CH_3$	2	2 x 4.71 = 9.42	2 x 33.5 = 67.0
$-CH_2-$	3	3 x 4.94 = 14.82	3 x 16.1 = 48.3
>CH–	2	2 x 3.43 = 6.86	2 x –1.0 = –2.0
Disubstituted phenyl ring	1	31.9	52.4
–OH	1	29.8	10.0
–O–	1	3.35	3.8
–NH–	1	8.4	4.5
$-CONH_2$	1	41.9	17.5
	Σ	146.45	201.5
	δ_3 = (146,450/201.5)$^{1/2}$ = 26.96 MPa$^{1/2}$		

Table 3: Apparent Thermodynamic Functions Relative to Solution Process of Atenolol (3) in {Ethanol (1) + Water (2)} Mixtures at 298.2 K

w_1 [a]	x_1 [a]	$\Delta_{soln}G°$ / kJ mol^{-1}	$\Delta_{soln}H°$ / kJ mol^{-1}	$\Delta_{soln}S°$ / J mol^{-1} K^{-1}	$T\Delta_{soln}S°$ / kJ mol^{-1}	ζ_H [b]	ζ_{TS} [b]
0.000	0.0000	16.51	15.03	–4.96	–1.48	0.910	0.090
0.100	0.0417	15.33	30.45	50.71	15.12	0.668	0.332
0.200	0.0891	14.30	39.37	84.06	25.06	0.611	0.389
0.300	0.1436	12.49	29.23	56.17	16.75	0.636	0.364
0.400	0.2068	10.90	15.21	14.46	4.31	0.779	0.221
0.500	0.2812	9.87	18.36	28.47	8.49	0.684	0.316
0.600	0.3698	9.41	24.43	50.36	15.01	0.619	0.381
0.700	0.4772	8.82	23.68	49.85	14.86	0.614	0.386
0.800	0.6101	9.13	23.76	49.08	14.63	0.619	0.381
0.900	0.7788	9.68	26.69	57.04	17.01	0.611	0.389
1.000	1.0000	11.15	23.29	40.69	12.13	0.657	0.343

[a] w_1 and x_1 are the mass and mole fractions of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of atenolol (3), respectively.
[b] ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward apparent Gibbs energy of solution.

cosolvent mixtures [15-18]. Negative entropy observed in neat water could be explained in terms of the possible hydrophobic hydration around the non-polar groups of the drug, in particular the methyl and disubstituted phenyl ring groups (Figure **1**). Moreover, as has been described in the literature, in water-rich mixtures the cosolvent action of ethanol increasing the drug solubility may be related to the breaking of the ordered structure of water (stabilized by hydrogen bonds) around the same non-polar moieties of the drug, which increases both the enthalpy and the entropy of the system [19].

Furthermore, the relative contributions by enthalpy (ζ_H) and entropy (ζ_{TS}) toward the solution process are given by the following equations [20]:

$$\zeta_H = \frac{|\Delta_{soln}H°|}{|\Delta_{soln}H°| + |T\Delta_{soln}S°|} \tag{6}$$

$$\zeta_{TS} = \frac{|T\Delta_{soln}S°|}{|\Delta_{soln}H°| + |T\Delta_{soln}S°|} \tag{7}$$

In all cases the main contributor to the positive standard molar Gibbs energy of solution of ATN is the positive enthalpy ($\zeta_H > 0.61$), which indicates the energetic predominance on all the dissolution processes.

Enthalpy-Entropy Compensation Analysis

Several reports are present in the literature demonstrating non-enthalpy-entropy compensation in the dissolution process of drugs in different aqueous cosolvent mixtures. These analyses have been performed to identify the main mechanisms of the cosolvent action. Thus, weighted graphs of $\Delta_{soln}H°$ as a function of $\Delta_{soln}G°$ could permit such an analysis [21, 22]. Figure **3** shows that ATN (3) in the water-rich mixtures of the {ethanol (1) + water (2)} system presents a non-linear $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$ curve with negative slope in the interval from pure water to the mixture $w_1 = 0.20$ and positive slope in the composition interval from $w_1 = 0.20$ to $w_1 = 0.40$. Accordingly, in the first case the driving mechanism for the transfer of ATN (3) from more polar to less polar solvents is the positive entropy, possibly due to hydrophobic effects; whereas, in the second case, the transfer is driven by the enthalpy, which is owing probably to better solvation of the drug by ethanol molecules.

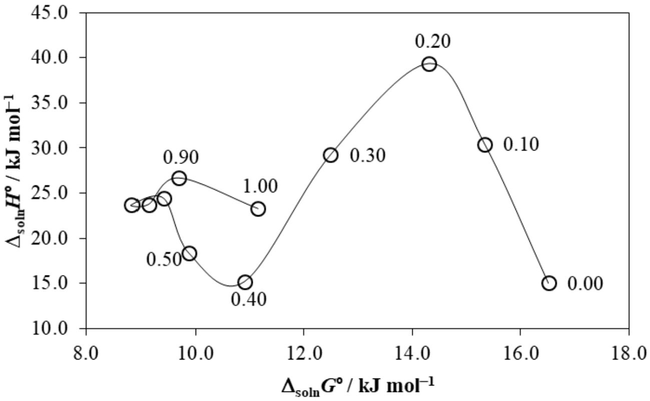

Figure 3: $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$ enthalpy-entropy compensation plot for dissolution process of atenolol (3) in {ethanol (1) + water (2)} mixtures at 298.2 K.

Preferential Solvation

The preferential solvation parameter of ATN (compound 3) by ethanol (compound 1) in the {ethanol (1) + water (2)} mixtures is defined as [2, 3, 23]:

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \tag{8}$$

Here $x_{1,3}^{L}$ is the local mole fraction of ethanol in the environment near to ATN (3) and x_1 is the bulk mole fraction composition of ethanol in the initial binary solvent. If $\delta x_{1,3} > 0$ then the solute is preferentially solvated by ethanol. On the contrary, ATN is preferentially solvated by water if this parameter is negative. The values of $\delta x_{1,3}$ are obtainable for the individual solvent components analyzed from the inverse Kirkwood-Buff integrals in terms of some thermodynamic quantities as shown as follows [2, 3, 23]:

$$\delta x_{1,3} = \frac{x_1 x_2 \left(G_{1,3} - G_{2,3}\right)}{x_1 G_{1,3} + x_2 G_{2,3} + V_{\mathrm{cor}}} \tag{9}$$

With,

$$G_{1,3} = RT\kappa_T - V_3 + x_2 V_2 D / Q \tag{10}$$

$$G_{2,3} = RT\kappa_T - V_3 + x_1 V_1 D / Q \tag{11}$$

$$V_{\mathrm{cor}} = 2522.5\left(r_3 + 0.1363\left(x_{1,3}^{L} V_1 + x_{2,3}^{L} V_2\right)^{1/3} - 0.085\right)^3 \tag{12}$$

As has been described in the literature [2, 3, 23], in these equations κ_T is the isothermal compressibility of the {ethanol (1) + water (2)} mixtures, calculated as an additive property by using the mixtures compositions and the reported values for neat solvents, V_1 and V_2 are the partial molar volumes of the solvents in the mixtures, and similarly, V_3 is the partial molar volume of ATN in all these mixtures. The function D {Eqn. (13)} is the derivative of the standard molar Gibbs energies of transfer of ATN from neat water (2) to {ethanol (1) + water (2)} mixtures with respect to the solvent mixtures composition free of drug. The function Q {Eqn. (14)} involves the second derivative of the excess molar Gibbs energy of mixing of the two solvents (G_{1+2}^{Exc}) with respect to the water proportion in the mixtures. V_{cor} is the correlation volume and r_3 is the molecular radius of ATN calculated by means of Eqn. (15) with N_{Av} as the Avogadro's number.

$$D = \left(\frac{\partial \Delta_{\mathrm{tr}} G_{3,2\to 1+2}^{\mathrm{o}}}{\partial x_1}\right)_{T,p} \tag{13}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G_{1+2}^{Exc}}{\partial x_2^2}\right)_{T,p} \tag{14}$$

$$r_3 = \left(\frac{3 \cdot 10^{21} V_3}{4\pi N_{\mathrm{Av}}}\right)^{1/3} \tag{15}$$

As it is well known, the definitive correlation volume requires iteration because it depends on the local mole fractions of the solvents around the solute. This iteration is performed by replacing $\delta x_{1,3}$ and V_{cor} in the Eqns. (8), (9) and (12) to recalculate $x_{1,3}^{L}$ until a non-variant value of V_{cor} is obtained.

Figure **4** shows the Gibbs energy of transfer behavior of ATN (3) from neat water (2) to {ethanol (1) + water (2)} mixtures at 298.2 K. These values were calculated from the mole fraction drug solubility data reported in Table **1** by using the following expression:

$$\Delta_{\mathrm{tr}} G_{3,2\to 1+2}^{\mathrm{o}} = RT \ln\left(\frac{x_{3,2}}{x_{3,1+2}}\right) \tag{16}$$

$\Delta_{\mathrm{tr}} G_{3,2\to 1+2}^{\mathrm{o}}$ values were correlated according to the regular polynomial in order four presented as Eqn. (17). The obtained coefficients are as follows: a = 0.28, b = –36.03, c = 47.67, d = –13.25 and e = –4.02, with r^2 = 0.992.

$$\Delta_{\mathrm{tr}} G_{3,2\to 1+2}^{\mathrm{o}} = a + b x_1 + c x_1^2 + d x_1^3 + e x_1^4 \tag{17}$$

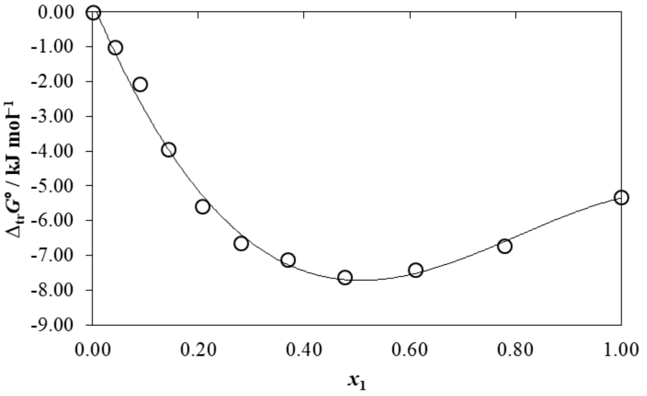

Figure 4: Gibbs energy of transfer of atenolol (3) from neat water (2) to {ethanol (1) + water (2)} mixtures at 298.2 K.

Thus, D values reported in Table **4** were calculated from the first derivative of the respective polynomial model and solved according to the cosolvent mixtures composition. For the studied {ethanol (1) + water (2)} mixtures the Q, $RT\kappa_T$, V_1 and V_2 values were taken from the literature [14, 24, 25]. On the other hand, the molar volume of ATN was also considered as 236.7 cm^3 mol^{-1} despite the mixtures composition. $G_{1,3}$ and $G_{2,3}$ values shown in Table **4** are negative in almost all cases indicating that ATN exhibits affinity for both solvents in the mixtures. Solute radius value (r_3) was

Table 4: Some Properties Associated to Preferential Solvation of Atenolol (3) in {Ethanol (1) + Water (2)} Mixtures at 298.2 K

x_1 [a]	D	$G_{1,3}$ / cm^3 mol^{-1}	$G_{2,3}$ / cm^3 mol^{-1}	V_{cor} / cm^3 mol^{-1}	100 $\delta x_{1,3}$
0.00	–36.03	–498.3	–235.6	970	0.00
0.05	–31.36	–477.7	–273.4	1003	–1.35
0.10	–26.91	–449.2	–307.2	1045	–1.77
0.15	–22.68	–416.0	–333.4	1093	–1.41
0.20	–18.68	–381.7	–350.0	1145	–0.64
0.25	–14.93	–349.0	–356.2	1197	0.16
0.30	–11.44	–319.3	–352.4	1247	0.77
0.35	–8.22	–293.4	–339.1	1293	1.07
0.40	–5.29	–271.2	–316.5	1337	1.05
0.45	–2.64	–252.5	–284.4	1378	0.71
0.50	–0.31	–236.8	–241.8	1416	0.11
0.55	1.70	–223.8	–187.5	1452	–0.72
0.60	3.38	–213.5	–120.7	1486	–1.70
0.65	4.72	–206.4	–44.0	1521	–2.70
0.70	5.71	–203.5	32.8	1556	–3.49
0.75	6.32	–205.6	89.0	1596	–3.77
0.80	6.56	–212.1	100.9	1642	–3.36
0.85	6.40	–220.5	62.1	1691	–2.38
0.90	5.84	–227.5	–8.5	1742	–1.28
0.95	4.87	–231.9	–85.1	1789	–0.45
1.00	3.46	–233.9	–151.9	1833	0.00

[a] x_1 is the mole fraction of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of atenolol (3).

calculated as 0.454 nm by using Eqn. (14). The correlation volume was iterated three times by means of Eqns. (8), (9) and (12) to obtain the values reported in Table **4**. This table also shows the preferential solvation parameters of ATN (3) by ethanol (1), $\delta x_{1,3}$.

Figure **5** shows that the values of $\delta x_{1,3}$ vary non-linearly with the ethanol (1) proportion in these aqueous mixtures. Addition of ethanol (1) to water (2) makes negative the $\delta x_{1,3}$ values of ATN (3) in the composition interval $0.00 < x_1 < 0.24$. Maximum negative value is obtained in the mixture $x_1 = 0.10$ (with $\delta x_{1,3} = -1.77 \times 10^{-2}$). Possibly the structuring of water molecules around the non-polar groups of ATN (methyl groups and aromatic ring, Figure **1**) by hydrophobic hydration, contributes to lowering of the net $\delta x_{1,3}$ to negative values in these water-rich mixtures, as was already exposed.

In the mixtures with composition $0.24 < x_1 < 0.51$, the local mole fractions of ethanol (1) around ATN (3) molecules are greater than the ones of water (2) compared with those of the bulk mixtures. Probably, the cosolvent action may be related to the breaking of the ordered structure of water by hydrogen bonding around the non-polar moieties of ATN, as was appointed previously. The higher preferential solvation by ethanol (1) reach a maximum value in $x_1 = 0.35$ ($\delta x_{1,3} = 1.07 \times 10^{-2}$).

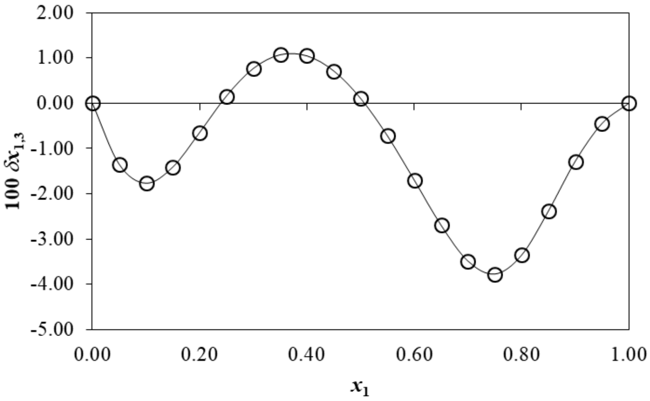

Figure 5: $\delta x_{1,3}$ values of atenolol (3) in {ethanol (1) + water (2)} mixtures at 298.2 K.

Regarding the preferential solvation results, in these intermediate-composition mixtures, ATN could be acting as Lewis acid with ethanol molecules in some extent because this cosolvent exhibits higher Lewis basicity as compared with water, i.e. the Kamlet-Taft hydrogen bond acceptor parameters β are 0.75 for ethanol and 0.47 for water [26, 27].

On the other hand, in ethanol-rich mixtures, where ATN is preferentially solvated by water again, it would be acting mainly as a Lewis base in front to water because this solvent is more acidic than ethanol as described by their Kamlet-Taft hydrogen bond donor parameters α, i.e. 1.17 for water and 0.86 for ethanol, respectively [27, 28].

CONCLUSIONS

From all previously exposed it can be concluded that the dissolution process of ATN (3) in {ethanol (1) + water (2)} mixtures depends strongly on the solvent composition. Non-linear enthalpy-entropy compensation was found for this drug in this aqueous cosolvent system. In this context, entropy and enthalpy-driving was observed for transfer processes in the water-rich mixtures. Moreover, ATN is preferentially solvated by water in water-rich and ethanol-rich mixtures. Furthermore, it can also be stated that the data presented in this report expands the physicochemical information about drugs in binary aqueous-cosolvent mixtures.

CONFLICT OF INTEREST

The authors report no conflict of interest related with this manuscript.

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Received on 08-10-2017 Accepted on 16-04-2018 Published on 10-05-2018

DOI: https://doi.org/10.6000/1929-5030.2018.07.01