Daniel R. Delgado [1], Edgar F. Vargas [2], Fleming Martínez [1*]

1 Grupo de Investigaciones Farmacéutico Fisicoquímicas, Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, A.A. 14490, Bogotá D.C., Colombia.
2 Grupo de Termodinámica de Soluciones, Departamento de Química, Facultad de Ciencias, Universidad de los Andes, Bogotá D.C., Colombia.
* Autor para correspondencia: fmartinezr@unal.edu.co.

Recibido: 15 de febrero de 2013 • Aceptado: 29 de abril de 2013

Solvatación preferencial del xilitol en mezclas cosolventes etanol + agua según los métodos IKBI y QLQC

Resumen

Partiendo de algunas propiedades termodinámicas clásicas se calcularon los parámetros de solvatación preferencial del xilitol ($\delta x_{E,S}$) en mezclas etanol + agua mediante el método de las integrales inversas de Kirkwood-Buff (IKBI) y el método cuasi-reticular-cuasi-químico (QLQC). Los parámetros $\delta x_{E,S}$ corresponden a las diferencias entre las fracciones molares locales alrededor del soluto y en el grueso de la solución. Con base en estos valores, se encuentra que este compuesto es altamente sensible a los efectos específicos de solvatación según la composición cosolvente. Así, según el método IKBI, los valores de $\delta x_{E,S}$ son positivos en mezclas ricas en agua pero negativos en composiciones desde 0.25 en fracción molar de etanol hasta el etanol puro. Sin embargo, según el método QLQC, los valores de $\delta x_{E,S}$ son negativos en todas las composiciones co-solventes analizadas. En mezclas ricas en agua la mayor solvatación por las moléculas de etanol podría deberse principalmente a efectos de polaridad. De otro lado, la preferencia que manifiesta este compuesto por el agua en mezclas ricas en etanol podría explicarse en términos del mayor comportamiento ácido del agua que estaría interactuando con los grupos aceptores de hidrógeno presentes en el soluto.

Palabras clave: xilitol, etanol, solubilidad, IKBI, QLQC, solvatación preferencial.

Preferential solvation of xylitol in ethanol + water co-solvent mixtures according to the IKBI and QLQC methods

Abstract

The preferential solvation parameters, i.e., the differences between the local around the solute and bulk mole fractions of the solvents in solutions of xylitol in ethanol + water binary mixtures are derived from their thermodynamic properties by means of the inverse Kirkwood-Buff integrals (IKBI) and quasi-lattice quasi-chemical (QLQC) methods. According to IKBI method it is found that xylitol is sensitive to solvation effects, so the preferential solvation parameter $\delta x_{E,S}$, is slightly positive in water-rich and negative in mixtures beyond 0.25 in mole fraction of ethanol. In different way, according to QLQC method, negative values of $\delta x_{E,S}$ are found in all the compositions evaluated. The more solvation by ethanol observed in water-rich mixtures could be due mainly to polarity effects. Otherwise, the preference of this compound for water in ethanol-rich mixtures could be explained in terms of the bigger acidic behavior of water interacting with hydrogen-acceptor hydroxyl groups in xylitol.

Keywords: Xylitol, ethanol, solubility, IKBI, QLQC, preferential solvation.

Solvatação preferencial do xilitol no misturas cosolventes etanol + água acordo o métodos IKBI e QLQC

Resumo

Começando a partir de algumas propriedades termodinâmicas clássicos neste trabalho, foram calculados os parâmetros de solvatação preferenciais de xilitol ($\delta x_{E,S}$) em misturas etanol + água pelo método de integrais inversas de Kirkwood-Buff (IKBI) e o método quase-reticulado quase-químicas (QLQC). Parâmetros $\delta x_{E,S}$ correspondem às diferenças entre as fracções molares locais ao redor do soluto na solução e a granel. Com base nestes valores se verifique que este composto é extremamente sensível aos efeitos específicos de solvatação por composição de cosolvente. Assim, de acordo com o método IKBI, valores $\delta x_{E,S}$ são positivas em misturas ricas em água, mas negativas em composições 0,25 de fracção mole de etanol a etanol puro. No entanto, de acordo com o método QLQC, os valores de $\delta x_{E,S}$ são negativas em todas as composições testadas. Solvatação de xilitol por moléculas de etanol em misturas ricas em água pode ser devido por polaridade. Por outro lado, a preferência de este composto por água em misturas em etanol pode ser explicada em termos de comportamento ácido de água com os grupos aceitadores de hidrogénio presentes no soluto.

Palavras-chave: xilitol, etanol, a solubilidade, IKBI, QLQC, solvatação preferencial.

REV. COLOMB. QUIM. Vol 42 No. 1 – 2013.indb 59 24/11/14 7:34 p.m.

Introduction

Xylitol ((2*R*,4*S*)-Pentane-1,2,3,4,5-pentol, CAS RN 87-99-0) is an alditol commonly used as additive in several cosmetic and nutraceutical formulations and products (Figure 1). As nutrient agent it is given as oral and intravenous way (1). This compound has been used as a sweetener for diabetic patients and it is actively beneficial for dental health by reducing caries to a third when used regularly. Thus, this sweetening agent is finding increasing application in chewing gum, mouth-rinses, and toothpastes. Unlike sucrose, xylitol is not fermented into cariogenic acid end products (2). According to the US Pharmacopeia it is classified as an official pharmaceutical aid (3).

Normally xylitol is obtained from xylose by following several biotechnological procedures (4-6). In its industrial manufacture, xylitol is purified through crystallization from solution as the final step and dilution crystallization generally is preferable. Aqueous alcoholic mixtures are widely used for this purpose. Because the knowledge about solubility is crucial for crystallization processes, Wang *et al.* (7) studied the xylitol solubility in several ethanol + water mixtures at several temperatures.

Solubility of drugs and other pharmaceutical ingredients, as well as cosmetically and food ingredients, in co-solvent mixtures knowledge is very important for scientists involved in several development stages such as drug and excipients purification and design of liquid medicines (8). Although co-solvency has been employed in pharmacy for several decades it is recently that the mechanisms involved to increase or decrease organic compounds solubility have been approached from a physicochemical point of view (9). In this way, a recent thermodynamic work has been published based on the enthalpic and entropic contributions to the Gibbs energy of solution of this sweetener agent (7). Nevertheless, the preferential solvation, i.e., the co-solvent specific composition in the environment near to the xylitol molecules has not been studied. Therefore, the main goal of this paper is to evaluate the preferential solvation of xylitol in ethanol + water co-solvent mixtures, based on some classical thermodynamic definitions, by using the experimental solubility values reported by Wang et al. (7). Thus, this work is similar to the ones presented previously in the literature for some analgesic drugs in similar co-solvent mixtures (10-13).

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 (14-16). In similar way, quasi-lattice quasi-chemical (QLQC) approach is also useful to do this although is not too much exact as IKBI is (17).

The first treatment depends on the values of the standard molar Gibbs energies of transfer of the solute xylitol from neat water to the ethanol + water co-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 solute molecules describing the local fraction of the solvent components (E or W) in the surrounding of solute (S) (18, 19).

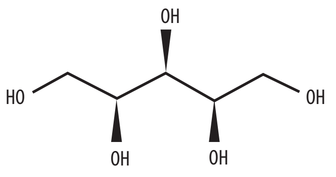

Figure 1. Molecular structure of xylitol.

In the second case, the QLQC method, proposed by Marcus (17), supposes that the number of nearest neighbors a molecule has (the lattice parameter *Z*) is the weighted mean of the lattice parameter of the pure components. It also presumes that the interaction energy of a molecule of any component with others is independent of the nature of the other neighbors. The model also assumes that ideal volumes and entropies of mixing take place ($V^{Exc} = 0$; $S^{Exc} = 0$). The main advantage of this method is that non-derivative functions are required as they are in the case of IKBI method (17).

In this work the IKBI and QLQC approaches are applied to evaluate the preferential solvation of xylitol in the binary mixtures conformed by ethanol (E or EtOH) and water (W). The results are expressed in terms of the preferential solvation parameter $\delta x_{\mathrm{E,S}}$ of the solute by the ethanol molecules according to the mixtures composition. Up to the best of our knowledge this is the first systematic research about preferential solvation considering polyhydroxyalcoholic-compounds as solutes in ethanol + water mixtures developed by using only classical thermodynamic tools.

Theoretical background and calculations

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

$$G_{i,\mathrm{S}} = \int_0^{r_{\mathrm{cor}}} (g_{i,\mathrm{S}} - 1) 4\pi r^2 dr \qquad \text{[equation 1]}$$

Here $g_{i,\mathrm{S}}$ is the pair correlation function for the molecules of the solvent *i* in the ethanol + water mixtures around the solute xylitol, *r* the distance between the centers of the molecules of xylitol and ethanol or water, and r_{cor} is a correlation distance for which $g_{i,\mathrm{S}}\ (r > r_{\mathrm{cor}}) \approx 1$. Thus, for all distances $r > r_{\mathrm{cor}}$ up to infinite, the value of the integral is essentially zero. Therefore, the results are expressed in terms of the preferential solvation parameter $\delta x_{i,\mathrm{S}}$ for the solute in solution by the component solvents ethanol and water (20). For ethanol (E) this parameter is defined as:

$$\delta x_{\mathrm{E,S}} = x_{\mathrm{E,S}}^{L} - x_{\mathrm{E}} = -\delta x_{\mathrm{W,S}} \qquad \text{[equation 2]}$$

Where x_{E} is the mole fraction of ethanol in the bulk solvent mixture and $x^{\mathrm{L}}_{\mathrm{E,S}}$ is the local mole fraction of ethanol in the environment near to the solute. If $\delta x_{\mathrm{E,S}} > 0$ then the solute xylitol is preferentially solvated by ethanol; on the contrary, if $\delta x_{\mathrm{E,}} < 0$ the solute is preferentially solvated by water, within the correlation volume, $V_{\mathrm{cor}} = (4\pi/3)r^3_{\mathrm{cor}}$, and the bulk mole fraction of ethanol, x_{E}. Values of $\delta x_{\mathrm{E,S}}$ are obtainable from those of $G_{\mathrm{E,S}}$, and these in turn, from thermodynamic data of the co-solvent mixtures with the solute dissolved on it, as shown below (18).

Algebraic manipulation of the basic expressions presented by Newman (20) leads to expressions for the Kirkwood-Buff integrals (in cm^3 mol^{-1}) for the individual solvent components in terms of some thermodynamic quantities as shown in equations [3] and [4] (15, 18, 19):

$$G_{\mathrm{E,S}} = RT\kappa_T - V_{\mathrm{S}} + x_{\mathrm{W}} V_{\mathrm{W}} D/Q \qquad \text{[equation 3]}$$

$$G_{\mathrm{W,S}} = RT\kappa_T - V_{\mathrm{S}} + x_{\mathrm{E}} V_{\mathrm{E}} D/Q \qquad \text{[equation 4]}$$

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_{S} is the partial molar volume of xylitol in these mixtures (in cm^3 mol^{-1}). The function *D* is the derivative of the standard molar Gibbs energies of transfer of the solute (from neat water to ethanol + water mixtures) with respect to the solvent composition (in kJ mol^{-1}, as also is *RT*) and the function

REV. COLOMB. QUIM. Vol 42 No. 1 – 2013.indb 60 24/11/14 7:34 p.m.

Q involves the second derivative of the excess molar Gibbs energy of mixing of the two solvents (G^{Exc}_{E+W}) with respect to the water proportion in the mixtures (also in kJ mol^{-1}) (18-21):

$$D = \left(\frac{\partial \Delta_{tr} G^0_{(S,W \to E+W)}}{\partial x_E} \right)_{T,p} \qquad \text{[equation 5]}$$

$$Q = RT + x_E x_W \left(\frac{\partial^2 G^{Exc}_{E,W}}{\partial x^2_W} \right)_{T,p} \qquad \text{[equation 6]}$$

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] (22):

$$\kappa_{T,\text{mix}} = \sum_{i=1}^{n} x_i \kappa^0_{T,i} \qquad \text{[equation 7]}$$

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

Ben-Naim (15) showed that the preferential solvation parameter could be calculated from the Kirkwood-Buff integrals as follows:

$$\delta x_{E,S} = \frac{x_E x_W \left(G_{E,S} - G_{W,S} \right)}{x_E G_{E,S} + x_W G_{W,S} + V_{cor}} \qquad \text{[equation 8]}$$

The correlation volume, V_{cor}, is obtained by means of the following expression proposed by Marcus (10, 19):

$$V_{cor} = 2522.5 \left(r_S + 0.1363 \left(x^L_{E,S} V_E + x^L_{W,S} V_W \right)^{1/3} - 0.085 \right)^3 \qquad \text{[equation 9]}$$

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

$$r_S = \left(\frac{3 \cdot 10^{21} V_S}{4\pi N_{Av}} \right)^{1/3} \qquad \text{[equation 10]}$$

Here, 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 $\delta x_{E,S}$ in the equation [2] to calculate $x^L_{E,S}$ until a non-variant value of V_{cor} is obtained.

For the QLQC method, the local mole fraction of solvent component ethanol around the xylitol molecules is defined as (17, 19):

$$x^L_S = 1 / \left[1 + \left(N_{EE} / N_{WW} \right)^{0.5} \exp\left(\Delta E_{EW,S} / 2RT \right) \right] \qquad \text{[equation 11]}$$

$$N_{EE} / N_{WW} = \left[x_E - N_{EW} / Z \left(N_E + N_W \right) \right] / \left[x_W - N_{EW} / Z \left(N_E + N_W \right) \right] \qquad \text{[equation 12]}$$

$$\frac{N_{EW}}{Z \left(N_E + N_W \right)} = \frac{1 - \left[1 - 4 x_E x_W \left(1 - \exp\left\{ -\Delta E_{EW} / RT \right\} \right) \right]^{0.5}}{2 \left[1 - \exp\left(-\Delta E_{EW} / RT \right) \right]} \qquad \text{[equation 13]}$$

$$\Delta E_{EW,S} = \Delta_{tr} G^0_{(S,W \to E)} / Z \qquad \text{[equation 14]}$$

$$\exp\left(\Delta E_{EW} / RT \right) = \left[\left(2 \exp\left\{ -G^{Exc}_{EW(x=0.5)} / ZRT \right\} \right) - 1 \right]^2 \qquad \text{[equation 15]}$$

In these equations, the lattice parameter Z is usually assumed as 10. N_E and N_W are the number of molecules of both components in the bulk, whereas, N_{EE}, N_{WW}, and N_{EW} are the number of neighboring pairs of these molecules in the quasi lattice. Equation [14] expresses the difference in the molar neighbor interaction energies of xylitol with the solvents ethanol and water, $\Delta E_{EW,S}$, by the molar Gibbs energy of transfer from water to ethanol per neighboring lattice. ΔE_{EW} denotes the molar energy of interaction of solvent on neighboring quasi-lattice sites. It is important to note that only the Gibbs energy of the xylitol transfer between the neat solvents and the excess Gibbs energy of mixing at equimolar composition of both solvents are required for this method.

Results and discussion

The experimental solubility values of xylitol in ethanol + water mixtures (Table 1) was taken from Wang *et al*. (7). Xylitol solubility diminishes with the increasing the proportion of ethanol in the mixtures at all the temperatures studied. It is for this reason that this compound is purified by precipitation after adding ethanol to its aqueous solutions.

Table 1. Mole fraction solubility (1000 x_S) of xylitol at several temperatures [a].

x_{EtOH} [b]	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.0000	162.5	180.6	204.2	234.4	265.5
0.0706	121.5	138.0	172.9	198.7	226.2
0.1741	97.0	108.5	136.8	167.8	202.3
0.2821	80.1	97.2	119.8	145.9	173.2
0.3654	60.0	73.6	90.9	114.8	141.8
0.4777	38.2	48.5	61.7	77.6	101.8
0.6101	16.2	24.0	31.0	40.9	53.4
0.7000	10.1	12.4	15.9	20.7	25.1
0.7827	6.7	8.8	11.0	14.7	19.4
1.0000	2.1	2.5	3.1	4.2	5.7

[a] Data from Wang et al. (7).

[b] x_{EtOH} is the mole fraction of ethanol in the ethanol + water co-solvent mixtures free of xylitol.

Table 2. Gibbs energy of transfer (kJ mol^{-1}) of xylitol 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
0.0706	0.71	0.67	0.42	0.42	0.42
0.1741	1.26	1.26	1.01	0.86	0.71
0.2821	1.72	1.54	1.34	1.21	1.11
0.3654	2.43	2.23	2.04	1.83	1.63
0.4777	3.53	3.26	3.02	2.83	2.50
0.6101	5.62	5.00	4.75	4.47	4.18
0.7000	6.77	6.64	6.43	6.22	6.14
0.7827	7.77	7.49	7.36	7.09	6.81
1.0000	10.60	10.61	10.55	10.30	10.00

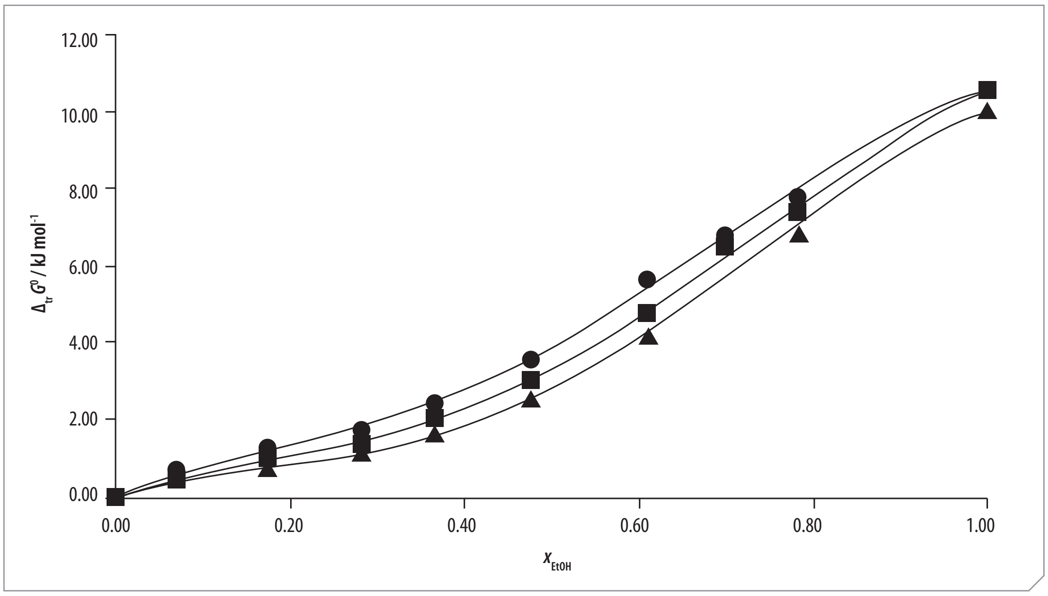

Figure 2. Gibbs energy of transfer of xylitol from neat water to ethanol + water co-solvent mixtures at several temperatures.
Triangles: 293.15 K;
squares: 303.15 K;
circles: 313.15 K.

Standard molar Gibbs energy of transfer of this sweetening agent from neat water to ethanol + water mixtures is calculated and correlated to regular quartic polynomials from the drug solubility data by using equation [16]. x_E is the mole fraction of ethanol in the ethanol + water co-solvent mixtures free of xylitol, and a, b, c, d and e are the coefficients. Polynomials in fourth degree were chosen based on some significant statistical parameters as the determination coefficients and residual analyses (values not shown here). In this way, the number of decimal places in the quantities reported in almost all the tables presented along the document was defined just as it has usually been done in some similar researches (11-13). Figure 2 shows the Gibbs energy of transfer behavior at several temperatures whereas Table 2 shows the behavior at all the temperatures studied. Otherwise, the respective polynomials coefficients are shown in Table 3.

$$\Delta_{\mathrm{tr}} G^0_{\mathrm{S,W \to E+W}} = RT \ln\left(\frac{x_{\mathrm{S,W}}}{x_{\mathrm{S,E+W}}}\right) = a + bx_{\mathrm{E}} + cx^2_{\mathrm{E}} + dx^3_{\mathrm{E}} + ex^4_{\mathrm{E}} \quad \text{[equation 16]}$$

Thus D values are calculated from the first derivative of the polynomial models (equation [17]) 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 in mole fraction. D values are reported in Table 4.

$$D = b + 2cx_{\mathrm{E}} + 3dx^2_{\mathrm{E}} + 4ex^3_{\mathrm{E}} \qquad \text{[equation 17]}$$

Table 3. Coefficients of the equation [16] (kJ mol^{-1}) applied to Gibbs energy of transfer of xylitol 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	0.09	0.06	0.01	0.03	0.03
b	7.87	9.22	7.15	6.25	6.25
c	–16.49	–26.61	–19.41	–18.19	–22.44
d	44.71	60.28	50.63	49.72	58.59
e	–25.61	–32.36	–27.85	–27.52	–32.46

In order to calculate the Q values the excess molar Gibbs energies of mixing $G^{Exc}_{\mathrm{E,W}}$ 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, $G^{Exc}_{\mathrm{E,W}}$ values were calculated at 298.15 K by using the equation [18] as reported by Marcus (18). On the other hand, the $G^{Exc}_{\mathrm{E,W}}$ values at the other temperatures were calculated by using the equation [19], where, $H^{Exc}_{\mathrm{E,W}}$ 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 (18). In turn, $H^{Exc}_{\mathrm{E,W}}$ values were calculated by using the equation [20] at 298.15 K as also reported by Marcus (18).

$$G^{Exc}_{\mathrm{E,W}} = x_{\mathrm{E}} x_{\mathrm{W}} \left(2907 - 777(1 - 2x_{\mathrm{E}}) + 494(1 - 2x_{\mathrm{E}})^2\right) \quad \text{[equation 18]}$$

$$G^{Exc}_{\mathrm{E,W}}(T_2) = G^{Exc}_{\mathrm{E,W}}(T_1) - T\int_{T_1}^{T_2} H^{Exc}_{\mathrm{E,W}}\, d\left(\frac{1}{T}\right) \approx \frac{T_2}{T_1} G^{Exc}_{\mathrm{E,W}}(T_1) + H^{Exc}_{\mathrm{E,W}}\left(1 - \frac{T_2}{T_1}\right) \quad \text{[equation 19]}$$

Table 4. *D* values (kJ mol^{-1}) of xylitol 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	7.87	9.22	7.15	6.25	6.25
0.10	5.81	5.57	4.68	4.00	3.39
0.20	5.82	4.77	4.57	4.06	3.27
0.30	7.28	6.03	6.17	5.79	5.11
0.40	9.58	8.58	8.80	8.52	8.12
0.50	12.10	11.63	11.79	11.59	11.53
0.60	14.24	14.42	14.48	14.34	14.57
0.70	15.37	16.17	16.20	16.11	16.44
0.80	14.88	16.09	16.28	16.24	16.38
0.90	12.15	13.42	14.05	14.07	13.60
1.00	6.58	7.38	8.84	8.93	7.33

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

$$H^{Exc}_{\mathrm{E,W}} = x_{\mathrm{E}} x_{\mathrm{W}} \left(-1300 - 3567(1-2x_{\mathrm{E}}) - 4971(1-2x_{\mathrm{E}})^2\right) \quad \text{[equation 20]}$$

It is important to note that quartic regular polynomials of $G^{Exc}_{\mathrm{E,W}}$ 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 (22).

The partial molar volumes of ethanol (Table 7) and water (Table 8) were calculated by means of equations [21] and [22] from the density (ρ) values of ethanol + water mixtures reported by Jiménez *et al.* at all the temperatures under study (23). In these equations V is the molar volume of the mixtures and it is calculated as $V = (x_{\mathrm{E}} \cdot M_{\mathrm{E}} + x_{\mathrm{W}} \cdot M_{\mathrm{W}})/\rho$. M_{E} and M_{W} are 46.06 and 18.02 g mol^{-1}, respectively (1).

Table 7. Partial molar volume (cm^3 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 6. RT k_{T} values (cm^3 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

$$\overline{V}_{\mathrm{E}} = V + x_{\mathrm{W}} \frac{dV}{dx_{\mathrm{E}}} \quad \text{[equation 21]}$$

$$\overline{V}_{\mathrm{W}} = V - x_{\mathrm{E}} \frac{dV}{dx_{\mathrm{E}}} \quad \text{[equation 22]}$$

Partial molar volumes of non-electrolyte drugs are not frequently reported in the literature. This is because this property is dependent on temperature and composition and therefore it requires a lot of experiments. Moreover, these experiments could be very complicated when the solubilities are too low, just as it happens with a lot of pharmaceutical ingredients. In this way, no values of partial molar volume of xylitol are available. For this reason, in a first approach the molar volume of xylitol is considered here as independent of co-solvent composition and tem-

Table 8. Partial molar volume (cm^3 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

REV. COLOMB. QUIM. Vol 42 No. 1 – 2013.indb 63 24/11/14 7:34 p.m.

Table 9. $G_{E,S}$ values (cm^3 mol^{-1}) for xylitol 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	−40.7	−31.8	−47.6	−54.7	−55.3
0.10	−53.6	−54.6	−60.9	−65.7	−70.1
0.20	−54.3	−61.3	−61.9	−65.1	−70.9
0.30	−45.2	−54.0	−52.6	−54.9	−59.8
0.40	−31.1	−39.2	−38.5	−41.1	−44.7
0.50	−15.7	−22.0	−23.6	−27.2	−30.0
0.60	−4.6	−8.2	−11.7	−16.3	−18.5
0.70	−11.4	−10.5	−13.3	−16.9	−18.0
0.80	−47.4	−43.5	−43.5	−44.4	−44.2
0.90	−84.1	−82.5	−81.8	−81.9	−82.3
1.00	−97.3	−97.2	−97.2	−97.1	−97.1

Table 10. $G_{W,S}$ values (cm^3 mol^{-1}) for xylitol 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	−99.0	−99.0	−98.9	−98.9	−98.9
0.10	−83.7	−83.9	−85.9	−87.5	−88.9
0.20	−64.0	−69.4	−69.7	−72.1	−76.5
0.30	−24.8	−36.6	−34.4	−37.6	−44.1
0.40	51.4	34.2	35.9	29.9	22.6
0.50	187.5	166.8	161.2	148.4	139.7
0.60	404.2	386.9	367.1	342.7	332.1
0.70	648.5	658.5	632.9	603.6	595.8
0.80	667.0	723.7	726.4	718.2	720.2
0.90	369.2	420.2	446.1	449.2	433.4
1.00	60.2	77.3	109.6	109.6	70.9

perature, and equal to that presented in solid state, just as it is calculated by considering the density value reported in the literature (1.52 g cm^{-3}) (2) obtaining the value 100.10 cm^3 mol^{-1}. Similar assumptions have been applied previously in other studies (11-13). It is important to note that no significant uncertainty is introduced in the following calculations by using the calculated volume values instead of the partial ones. Additionally, from this volume value the radius of the drug molecule (required for equation [9]) was calculated by using the equation [10] as r_S = 0.341 nm.

Table 9 shows that all the $G_{E,S}$ values are negative with the maximum in x_{EtOH} = 0.60. In different way, Table 10 shows that $G_{W,S}$ values are negative in water-rich mixtures but positive beyond the mixture with x_{EtOH} = 0.40 reaching maximum value in the mixture with x_{EtOH} = 0.80. This could be interpreted as the preference of xylitol by water in ethanol-rich mixtures.

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. This could be a consequence of the greater molar expansibility of ethanol in comparison with water (23).

The values of $\delta x_{E,S}$ vary non-linearly with the ethanol concentration in the aqueous mixtures at all the temperatures studied (Table 12 and Figure 3). In the beginning, the addition of ethanol to water tends to make positive the $\delta x_{E,S}$ values of xylitol from the pure water up to the mixture 0.25 in mole fraction of ethanol reaching a maximum of 4.8 x 10^{-3}. This maximum diminishes with the temperature increasing.

Table 11. Correlation volume (cm^3 mol^{-1}) for xylitol 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	583	583	584	584	585
0.10	650	651	652	653	654
0.20	713	714	716	717	719
0.30	773	775	778	780	782
0.40	826	830	833	836	839
0.50	872	876	880	884	888
0.60	910	914	920	925	930
0.70	954	957	962	967	972
0.80	1030	1030	1033	1037	1041
0.90	1133	1136	1138	1142	1147
1.00	1219	1223	1228	1232	1238

Table 12. 100 $\delta x_{E,S}$ values of xylitol in ethanol + water co-solvent mixtures at several temperatures according to IKBI method.

x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	0.00	0.00	0.00	0.00	0.00
0.10	0.48	0.46	0.40	0.35	0.30
0.20	0.24	0.20	0.19	0.17	0.14
0.30	−0.58	−0.50	−0.52	−0.49	−0.45
0.40	−2.35	−2.11	−2.13	−2.03	−1.93
0.50	−5.30	−4.98	−4.87	−4.65	−4.50
0.60	−9.18	−8.91	−8.58	−8.18	−8.00
0.70	−12.15	−12.25	−11.87	−11.46	−11.32
0.80	−10.16	−10.77	−10.77	−10.66	−10.64
0.90	−3.73	−4.10	−4.28	−4.29	−4.16
1.00	0.00	0.00	0.00	0.00	0.00

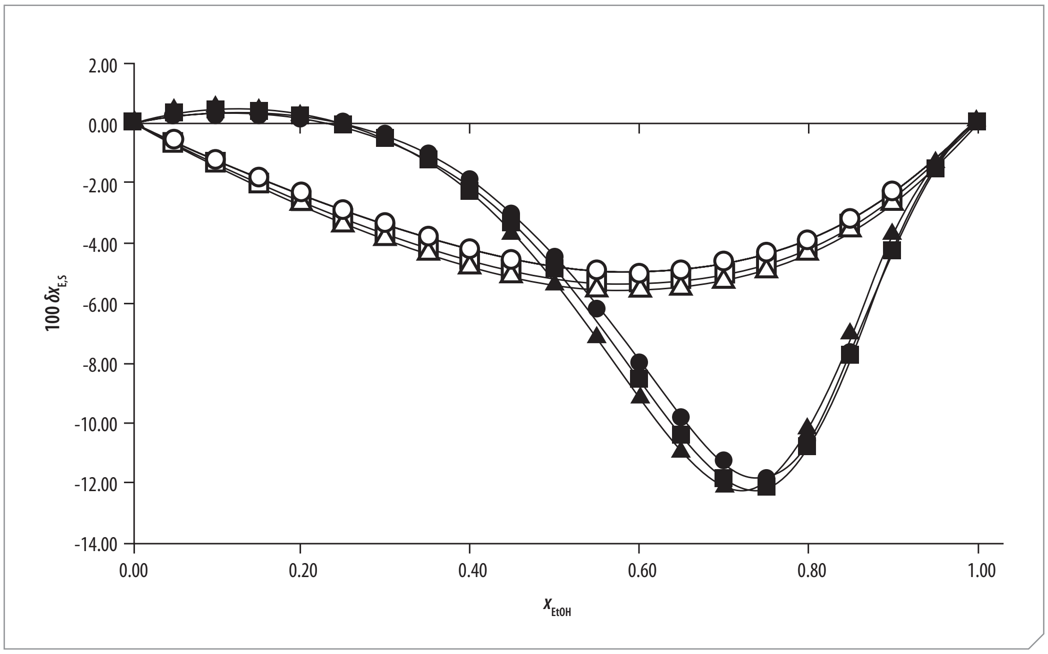

Figure 3. $\delta x_{E,S}$ values (x 100) for xylitol in ethanol + water co-solvent mixtures at several temperatures according to the IKBI (filled symbols) and QLQC (empty symbols) methods at several temperatures. Triangles: 293.15 K; squares: 303.15 K; circles: 313.15 K.

From this ethanol proportion up to neat ethanol, the local mole fraction of the ethanol around the solute decreases, being the $\delta x_{E,S}$ values negative, and therefore, xylitol is preferentially solvated by water.

Xylitol acts in solution as a Lewis acid due to the hydrogen atoms in its –OH groups (see 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 groups to interact with acidic hydrogen atoms in both solvents.

According to the preferential solvation results, it is conjecturable that in water-rich mixtures, the xylitol 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 solute is preferentially solvated by water, this compound 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 xylitol and the co-solvent decrease in these mixtures (12, 26).

Table 13. $100\,\delta x_{E,S}$ values of xylitol in ethanol + water co-solvent mixtures at several temperatures according to QLQC method.

x_{EtOH}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	0.00	0.00	0.00	0.00	0.00
0.10	−1.43	−1.40	−1.37	−1.30	−1.22
0.20	−2.76	−2.71	−2.64	−2.52	−2.38
0.30	−3.92	−3.85	−3.75	−3.59	−3.41
0.40	−4.83	−4.75	−4.64	−4.45	−4.24
0.50	−5.41	−5.33	−5.21	−5.01	−4.79
0.60	−5.60	−5.51	−5.40	−5.20	−4.98
0.70	−5.28	−5.20	−5.10	−4.92	−4.72
0.80	−4.34	−4.28	−4.20	−4.05	−3.89
0.90	−2.64	−2.61	−2.56	−2.47	−2.38
1.00	0.00	0.00	0.00	0.00	0.00

On the other hand, in order to use the QLQC method, the excess Gibbs energy of mixing of equimolar mixture of both solvents was used as follows: 0.709, 0.727, 0.744, 0.762, and 0.780 kJ mol^{-1}, at temperatures from 293.15 to 313.15 K, respectively (12). According to QLQC method (Table 13 and Figure 3) xylitol is preferentially solvated by water in all the mixtures and the $\delta x_{E,S}$ values are bigger (as negative magnitude) than the ones obtained by using the IKBI method in mixtures with composition $0.25 < x_{EtOH} < 0.50$ but they are lower in the other mixtures ($0.50 < x_{EtOH} < 1.00$). Therefore, as has been indicated in the literature the IKBI method is more indicate than QLQC to discriminate the effect of co-solvent composition on the local mole fraction around the drugs molecules (12, 13). Nevertheless, it is important to keep in mind that QLQC requires only two specific experimental values, i.e. the Gibbs energy of transfer of xylitol from water to ethanol and the excess Gibbs energy of mixing in the co-solvent mixture with composition $x_{EtOH} = 0.50$, and therefore, it is more easy to use.

Conclusions

Explicit expressions for local mole faction of ethanol and water around of xylitol were derived on the basis of the IKBI and QLQC methods applied to equilibrium solubility values of this sweetening agent in ethanol + water mixtures. As expectable IKBI method exhibited more realistic result in comparison with QLQC method. In this way, this compound is preferentially solvated by ethanol in water-rich mixtures but preferentially solvated by water in mixtures beyond 0.25 in mole fraction of ethanol at all temperatures considered. These results expand widely the analysis described previously in the literature for this compound based only in classical thermodynamic quantities of solution like Gibbs energy, enthalpy and entropy. Thus, the present treatment allowed the evaluation of the local environment around the solute molecules according to the co-solvent mixtures composition (7).

References

1. Budavari, S.; O'Neil, M. J.; Smith, A.; Heckelman, P. E.; Obenchain Jr., J. R.; Gallipeau, J. A. R.; D'Arecea, M. A. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th edition. Whitehouse Station, NJ: Merck & Co. 2001.
2. Rowe, R. C.; Sheskey, P. J.; Owen, S. C. Handbook of Pharamaceutical Excipients. 5th. edition London: Pharmaceutical Press. 2006.
3. US Pharmacopeia. 23 ed. Rockville, MD: United States Pharmacopeial Convention. 1994.
4. Converti, A.; Perego, P.; Dominguez, J. M. Xylitol production from hardwood hemicellulose hydrolysates by *Pachysolen tannophilus*, *Debaryomyces hansenii*, and *Candida guilliermondii*. *Appl. Biochem. Biotechnol.* 1999. **82**: 141-151.
5. Sreenivas Rao, R.; Pavana Jyothi, Ch.; Prakasham, R. S.; Sarma, P. N.; Venkateswar Rao, L. Xylitol production from corn fiber and sugarcane bagasse hydrolysates by *Candida tropicalis*. *Bioresource Technol.* 2006. **97**: 1974-1978.
6. Rambo, M. K. D.; Bevilaqua, D. B.; Brenner, C. G. B.; Martins, A. F.; Mario, D. N.; Alves, S. H.; Mallmann, C. A. Xylitol from rice husks by acid hydrolysis and *Candida* yeast fermentation. *Quim. Nova* 2013. **36**: 634-639.
7. Wang, Zh.; Wang, Q.; Liu, X.; Fang, W.; Li, Y.; Xiao, H. Measurement and correlation of solubility of xylitol in binary water+ethanol solvent mixtures between 278.00 K and 323.00 K. *Korean J. Chem. Eng.* 2013. **30**: 931-936.
8. Jouyban, A. Handbook of Solubility Data for Pharmaceuticals. Boca Raton, FL: CRC Press, 2010.
9. Rubino, J. T. Cosolvents and cosolvency. In: Encyclopedia of Pharmaceutical Technology. Vol 3. Swarbrick, J.; Boylan, J. C. (eds). New York: Marcel Dekker, Inc. 1988. pp. 375-398.
10. Marcus, Y. Preferential solvation of ibuprofen and naproxen in aqueous 1,2-propanediol. *Acta Chim. Slov.* 2009. **56**. 40-44.
11. Ruidiaz, M. A.; Delgado, D. R.; Martínez, F.; Marcus, Y. Solubility and preferential solvation of indomethacin in 1,4-dioxane + water solvent mixtures. *Fluid Phase Equilib.* 2010. **299**: 259-265.
12. Delgado, D. R.; Holguín, A. R.; Almanza, O.A.; Martínez, F.; Marcus, Y. Solubility and preferential solvation of meloxicam in ethanol + water mixtures. *Fluid Phase Equilib.* 2011. **305**: 88-95.
13. Holguín, A. R.; Delgado, D. R.; Martínez, F.; Marcus, Y. Solution thermodynamics and preferential solvation of meloxicam in propylene glycol + water mixtures. *J. Solution Chem.* 2011. **40**: 1987-1999.
14. Ben-Naim, A. Theory of preferential solvation of nonelectrolytes. *Cell Biophysics* 1988. **12**: 255-269.
15. Ben-Naim, A. Preferential solvation in two- and in three-component systems. *Pure Appl. Chem.* 1990. **62**: 25-34.
16. Marcus, Y. Solubility and solvation in mixed solvent systems. *Pure Appl. Chem*. 1990. **62**: 2069-2076.
17. Marcus, Y. Preferential solvation in mixed solvents. In: Fluctuation Theory of Solutions: Applications in Chemistry, Chemical Engineering, and Biophysics. Smith, P. E.; Matteoli, E.; O'Connell, J. P. (eds). Boca Raton: CRC Press, Taylor & Francis Group, 2013.
18. Marcus, Y. Solvent Mixtures: Properties and Selective Solvation. New York: Marcel Dekker, Inc., 2002.
19. Marcus, Y. On the preferential solvation of drugs and PAHs in binary solvent mixtures. *J. Mol. Liq.* 2008. **140**: 61-67.
20. Newman, K. E. Kirkwood-Buff solution theory: Derivation and applications. *Chem. Soc. Rev.* 1994. **23**: 31-40.
21. Cortez-Nunez, N.G. Caracterização das Interacções Soluto (Ou Substrato)-Solvente-Solvente em Misturas Ternárias. Ph.D. thesis, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Lisboa, 2010.
22. Marcus, Y. The Properties of Solvents. Chichester (UK): John Wiley & Sons, 1998.
23. Jiménez, J.; Manrique, J.; Martínez, F. Effect of temperature on some volumetric properties for ethanol + water mixtures. *Rev. Colomb. Cienc. Quím. Farm.* 2004. **33**: 145-155.
24. Kamlet, M. J.; Taft, R. W. The solvatochromic comparison method. I. The beta-scale of solvent hydrogen-bond acceptor (HBA) basicities. *J. Am. Chem. Soc.* 1976. **98**: 377-383.
25. Taft, R. W.; Kamlet, M. J. The solvatochromic comparison method. II. The alpha-scale of solvent hydrogen-bond donor (HBD) acidities. *J. Am. Chem. Soc.* 1976. **98**, 2886-2894.
26. Ruckenstein, E.; Shulgin, I. Effect of a third component on the interactions in a binary mixture determined from the fluctuation theory of solutions. *Fluid Phase Equilib.* 2001. **180**: 281-297.

Article citation:
Delgado, D. R.; Vargas, E. F.; Martínez, F. Preferential solvation of xylitol in ethanol + water co-solvent mixtures according to the IKBI and QLQC methods. *Rev Colomb Quim*. 2013. **42**(1): 59-66.