Chemical Engineering Communications

ISSN: 0098-6445 (Print) 1563-5201 (Online) Journal homepage: http://www.tandfonline.com/loi/gcec20

Preferential Solvation of Indomethacin in Some Aqueous Co-Solvent Mixtures

María Á Peña, Daniel R. Delgado & Fleming Martínez

To cite this article: María Á Peña, Daniel R. Delgado & Fleming Martínez (2016) Preferential Solvation of Indomethacin in Some Aqueous Co-Solvent Mixtures, Chemical Engineering Communications, 203:5, 619-627, DOI: 10.1080/00986445.2015.1074898

To link to this article: http://dx.doi.org/10.1080/00986445.2015.1074898

Accepted author version posted online: 04 Aug 2015.

Chemical Engineering Communications, 203:619–627, 2016

ISSN: 0098-6445 print/1563-5201 online
DOI: 10.1080/00986445.2015.1074898

Preferential Solvation of Indomethacin in Some Aqueous Co-Solvent Mixtures

MARÍA Á PEÑA[1], DANIEL R. DELGADO[2], and FLEMING MARTÍNEZ[3]

[1]*Departamento de Ciencias Biomédicas, Facultad de Farmacia, Universidad de Alcalá, Alcalá de Henares, Madrid, Spain*
[2]*Programa de Ingeniería Industrial, Facultad de Ingeniería, Universidad Cooperativa de Colombia, Neiva, Colombia*
[3]*Grupo de Investigaciones Farmacéutico Fisicoquímicas, Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, Bogotá D.C., Colombia*

The preferential solvation parameters for indomethacin (IMC) in ethanol (EtOH) + water and propylene glycol (PG) + water binary mixtures were obtained from their thermodynamic properties by means of the inverse Kirkwood–Buff integrals (IKBI) and the quasi-lattice quasi-chemical (QLQC) methods. According to IKBI method, the preferential solvation parameter by co-solvents, ($\delta x_{1,3}$), is negative in the water-rich mixtures of both binary systems but positive in the other compositions at temperatures of 293.15, 303.15, and 313.15 K. It is conjecturable that in water-rich mixtures the hydrophobic hydration around the aromatic rings and methyl groups of the drug plays a relevant role in the solvation. The higher drug solvation by co-solvent in mixtures of similar solvent proportion and in co-solvent-rich mixtures could be due mainly to polarity effects. Here IMC would be acting as a Lewis acid with the EtOH or PG molecules because these co-solvents are more basic than water.

Keywords: Ethanol; Indomethacin; Inverse Kirkwood–Buff integrals (IKBI); Preferential Solvation; Propylene glycol; Quasi-lattice quasi-chemical (QLQC)

Introduction

Indomethacin (IMC, 357.8 g mol^{-1}, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid, CAS RN 53-86-1, Figure 1) is a non-steroidal anti-inflammatory drug used sometimes as an analgesic, among other indications (Budavari et al., 2001). Although IMC is widely used in current therapeutics the information about its solubility in aqueous media is not abundant (Jouyban, 2010). In this way, some physicochemical studies about its solution thermodynamics in co-solvent mixtures have been reported but none has specifically been carried out to study the preferential solvation of this drug by the solvent components (Holguín et al., 2012, Martínez et al., 2011).

The inverse Kirkwood–Buff integrals (IKBI) method is a powerful tool for evaluating the preferential solvation of non-electrolytes and non-dissociated weak electrolytes in binary solvent mixtures, describing the local composition or proportion of both solvents around the solute molecules (Ben-Naim, 1990; Marcus, 1990, 2002). Accordingly, in the case of aqueous co-solvent solutions, this treatment depends on the values of the standard molar Gibbs energies of transfer of the solute from neat water to the co-solvent + water mixtures and also on the excess molar Gibbs energy of mixing of the co-solvent binary mixtures. In similar way, quasi-lattice quasi-chemical (QLQC) approach is also useful to evaluate the preferential solvation although it is not too much exact as IKBI is. This method supposes that the number of nearest neighbors of a molecule (i.e., 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 neighbors. The model also assumes that ideal volumes and entropies of mixing take place. The main advantage of this method is that non-derivative functions are required as they are in the case of the IKBI method (Marcus, 2008).

Thereby, the main goal of this paper is to evaluate the preferential solvation of IMC in ethanol (EtOH) + water and propylene glycol (PG) + water co-solvent mixtures. It is important to note that EtOH and PG are the most widely used co-solvents in the formulation of liquid pharmaceutical dosage products (Rubino, 1988). This physicochemical treatment is made based on some well-established thermodynamic definitions, as has been made previously for several drugs in aqueous co-solvent mixtures (Delgado and Martínez, 2014; Delgado et al., 2011, 2013, 2014; Holguín et al., 2011; Marcus, 2008, 2009; Ruidiaz et al., 2010). The results are expressed in terms of the preferential solvation parameter ($\delta x_{1,3}$) of the solute by the respective co-solvent in the mixtures. In this way, this research is similar to that

Address correspondence to Fleming Martínez, Grupo de Investigaciones Farmacéutico Fisicoquímicas, Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, Carrera 30 No. 45-03, Bogotá D.C., Colombia. E-mail: fmartinezr@unal.edu.co

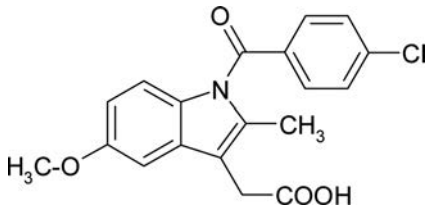

Fig. 1. Molecular structure of indomethacin.

developed with the analgesic ketoprofen in the same mixtures (Cárdenas et al., 2014).

Theoretical Background

In co-solvent + water mixtures the preferential solvation parameter by the co-solvent (component 1) ($\delta x_{1,3}$) is defined as

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

here x_1 is the mole fraction of co-solvent in the bulk solvent mixture and $x_{1,3}^{L}$ is the local mole fraction of co-solvent in the environment near to IMC (component 3). Otherwise, $\delta x_{2,3}$ is the preferential solvation parameter by water (component 2). If $\delta x_{1,3}$ has positive value (i.e., $\delta x_{1,3} > 0$) the drug is preferentially solvated by co-solvent; on the contrary, if this parameter is negative (i.e., $\delta x_{1,3} < 0$) the drug is preferentially solvated by water. Values of $\delta x_{1,3}$ are obtainable from the IKBI for the individual solvent components ($G_{1,3}$ and $G_{2,3}$) analyzed in terms of some thermodynamic quantities as shown in Equations (2) and (3) (Marcus, 2008, 2009):

$$G_{1,3} = RT\kappa_T - V_3 + x_2 V_2 D/Q \tag{2}$$

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

where κ_T is the isothermal compressibility of the co-solvent + water solvent mixtures (expressed in GPa^{-1}), x_2 is the mole fraction of water in the co-solvent mixtures free of drug, V_1 and V_2 are the partial molar volumes of the solvents 1 and 2 in the mixtures (expressed in $cm^3\,mol^{-1}$), similarly, V_3 is the partial molar volume of IMC in these mixtures (also expressed in $cm^3\,mol^{-1}$). The function D is the first derivative of the standard molar Gibbs energies of transfer of the drug from neat water to co-solvent + water mixtures ($\Delta_{tr}G^{o}_{3,2\rightarrow 1+2}$), with respect to the mole fraction of co-solvent free of drug (expressed in $kJ\,mol^{-1}$, as also is RT). Otherwise, the function Q involves the second derivative of the excess molar Gibbs energy of mixing of both solvents (G^{Exc}_{1+2}) with respect to the water mole fraction (x_2) in the mixtures free of drug (also expressed in kJ mol^{-1}), as defined in Equations (4) and (5) (Marcus, 2008, 2009):

$$D = \left(\frac{\partial \Delta_{tr}G^{o}_{3,2\rightarrow 1+2}}{\partial x_1}\right)_{T,p} \tag{4}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G^{Exc}_{1+2}}{\partial x_2^2}\right)_{T,p} \tag{5}$$

Because the dependence of κ_T on composition is not known for a lot of the systems commonly investigated as well as the small contribution of the term $RT\kappa_T$ to the IKBI calculations, the dependence of κ_T on the composition could be approximated by considering additive behavior. This is made according to: $\kappa_{T,mix} = \sum_{i=1}^{n} x_i \kappa^{o}_{T,i}$ (Marcus, 1998), where x_i is the mole fraction of component i in the mixture and $\kappa^{o}_{T,i}$ is the isothermal compressibility of the pure component i. Thus, the preferential solvation parameter can be calculated from the IKBI as follows:

$$\delta x_{1,3} = \frac{x_1 x_2 (G_{1,3} - G_{2,3})}{x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}} \tag{6}$$

here the correlation volume (V_{cor}) is obtained by means of the following expression (Marcus, 2008, 2009):

$$V_{cor} = 2522.5\left(r_3 + 0.1363\left(x_{1,3}^{L} V_1 + x_{2,3}^{L} V_2\right)^{1/3} - 0.085\right)^3 \tag{7}$$

where r_3 is the solute molecular radius (expressed in nm). However, the definitive correlation volume requires iteration, because it depends on the local mole fractions around the drug by co-solvent ($x_{1,3}^{L}$) and water ($x_{2,3}^{L}$). This iteration is done by replacing $\delta x_{1,3}$ in Equation (1) to calculate $x_{1,3}^{L}$ until a constant value of V_{cor} is obtained.

For the QLQC method (Marcus, 2008), the local mole fraction of the co-solvent around the IMC molecules is defined as

$$x_3^{L} = 1/\left[1 + (N_{11}/N_{22})^{0.5} \exp\left(\Delta E_{12,3}/2RT\right)\right] \tag{8}$$

$$N_{11}/N_{22} = [x_1 - N_{12}/Z(N_1 + N_2)]/[x_2 - N_{12}/Z(N_1 + N_2)] \tag{9}$$

$$\frac{N_{12}}{Z(N_1 + N_2)} = \frac{1 - [1 - 4x_1 x_2(1 - \exp\{-\Delta E_{12}/RT\})]^{0.5}}{2[1 - \exp(-\Delta E_{12}/RT)]} \tag{10}$$

$$\Delta E_{12,3} = \Delta_{tr}G^{o}_{3,2\rightarrow 1}/Z \tag{11}$$

$$\exp(\Delta E_{12}/RT) = \left[\left(2\exp\left\{-G^{Exc}_{12(x=0.5)}/ZRT\right\}\right) - 1\right]^2 \tag{12}$$

In these equations, the lattice parameter Z is usually assumed as 10 for this kind of compounds (Marcus, 2008). N_1 and N_2 are the number of molecules of both components in the bulk, whereas, N_{11}, N_{22}, and N_{12} are the number of neighboring pairs of these molecules in the quasi-lattice. Equation (11) expresses the difference in the molar neighbor interaction energies of IMC with the co-solvents and water, $\Delta E_{12,3}$, by the molar Gibbs energy of transfer from neat

water to neat co-solvent per neighboring lattice. ΔE_{12} 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 drug 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 equilibrium solubility of IMC in both co-solvent + water systems presented in Table I at temperatures of 293.15, 303.15, and 313.15 K was taken from the literature (Holguín et al., 2012; Martínez et al., 2011). This temperature interval covers the normal room conditions of medicines storage as well as the normal human body temperature. As was mentioned earlier, the solubility of this drug increases from neat water to neat co-solvents indicating more affinity for semipolar organic media. Standard molar Gibbs energy of transfer of IMC from neat water to co-solvent + water mixtures ($\Delta_{tr}G^{o}_{3,2\rightarrow1+2}$) is calculated and correlated to regular third order polynomials by using Equation (13) from the drug solubility data ($x_{3,2}$ is the drug solubility in water and $x_{3,1+2}$ is the drug solubility in co-solvent + water mixtures). Figure 2 shows the behavior of Gibbs energy of transfer at 303.15 K, whereas Table II shows the behavior at all the studied temperatures. On the other hand, the coefficients of the polynomials are shown in Table III. It is noteworthy that all the coefficients follow a logic sequence with the temperature-increasing, except for a in EtOH + water mixtures at 313.15 K; nevertheless, the reasons for this exception are not clear:

$$\Delta_{tr}G^{o}_{3,2\rightarrow1+2} = RT\ln\left(\frac{x_{3,2}}{x_{3,1+2}}\right) = a + bx_1 + cx_1^2 + dx_1^3 \quad (13)$$

Thus D values are calculated from the first derivative of polynomial models solved according to the solvent mixtures composition. This procedure was done varying by 0.05 in mole fraction of every co-solvent in both systems but in the following tables the respective values are summarized and reported varying only by 0.10. Table IV shows that the behavior of D with temperature at low x_1 values is inversed at higher x_1 values. This could be attributed to the different mechanisms of drug dissolution which vary with the mixtures composition as has been described earlier (Holguín et al., 2012; Martínez et al., 2011).

For both co-solvent + water binary systems, Q and $RT\kappa_T$ values, as well as the partial molar volumes of co-solvents and water, at the three temperatures considered here, were taken from the literature (Delgado and Martínez, 2014; Delgado et al., 2014; Peña et al., 2014).

Otherwise, partial molar volumes of non-dissociated weak 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 by them, in particular in aqueous media. For this reason, in a first approach the molar volume of IMC is considered here as independent of co-solvent composition and temperature, as it is calculated according to the groups contribution method proposed by Fedors (1974). Thus, this value was taken from the literature as $V_3 = 220.3\,cm^3\ mol^{-1}$ where the same calculated value was used to estimate the preferential solvation of this drug in ethyl acetate + EtOH mixtures (Rodríguez et al., 2014). In similar way, the radius of the drug molecule was also taken from the literature as $r_3 = 0.444$ nm (Rodríguez et al., 2014).

Tables V and VI show that the $G_{1,3}$ and $G_{2,3}$ values are negative in both co-solvent systems at all temperatures under study. Nevertheless, depending on co-solvent compositions, in some cases $G_{1,3}$ values are higher in magnitude compared

Table I. Mole fraction solubility of indomethacin in both co-solvent + water mixtures at several temperatures

Ethanol + water[a]				Propylene glycol + water[b]			
x_1^c	293.15 K	303.15 K	313.15 K	x_1^c	293.15 K	303.15 K	313.15 K
0.0000	7.81×10^{-7}	1.10×10^{-6}	1.52×10^{-6}	0.0000	7.80×10^{-7}	1.10×10^{-6}	1.52×10^{-6}
0.0417	1.22×10^{-6}	1.88×10^{-6}	2.81×10^{-6}	0.0256	1.12×10^{-6}	1.58×10^{-6}	2.27×10^{-6}
0.0891	2.41×10^{-6}	3.84×10^{-6}	6.57×10^{-6}	0.0559	1.60×10^{-6}	2.31×10^{-6}	3.37×10^{-6}
0.1436	8.50×10^{-6}	1.53×10^{-5}	2.73×10^{-5}	0.0921	2.69×10^{-6}	3.92×10^{-6}	5.83×10^{-6}
0.2068	3.42×10^{-5}	6.39×10^{-5}	1.13×10^{-4}	0.1364	5.06×10^{-6}	7.61×10^{-6}	1.14×10^{-5}
0.2812	1.20×10^{-4}	2.11×10^{-4}	4.04×10^{-4}	0.1915	1.13×10^{-5}	1.71×10^{-5}	2.85×10^{-5}
0.3698	3.34×10^{-4}	6.46×10^{-4}	1.06×10^{-3}	0.2621	2.46×10^{-5}	4.15×10^{-5}	7.43×10^{-5}
0.4772	7.96×10^{-4}	1.43×10^{-3}	2.24×10^{-3}	0.3559	6.77×10^{-5}	1.26×10^{-4}	2.34×10^{-4}
0.6101	1.69×10^{-3}	2.78×10^{-3}	4.28×10^{-3}	0.4154	1.06×10^{-4}	2.01×10^{-4}	3.98×10^{-4}
0.7788	2.70×10^{-3}	4.26×10^{-3}	6.21×10^{-3}	0.4865	1.55×10^{-4}	2.92×10^{-4}	6.17×10^{-4}
1.0000	3.32×10^{-3}	4.89×10^{-3}	7.41×10^{-3}	0.5730	2.60×10^{-4}	5.14×10^{-4}	9.81×10^{-4}
				0.6807	4.85×10^{-4}	8.41×10^{-4}	1.62×10^{-3}
				0.8182	8.32×10^{-4}	1.46×10^{-3}	2.52×10^{-3}
				1.0000	1.37×10^{-3}	2.27×10^{-3}	3.68×10^{-3}

[a]Values reported by Martínez et al. (2011).
[b]Values reported by Holguín et al. (2012).
[c]x_1 is the mole fraction of co-solvent in the co-solvent + water mixtures free of indomethacin.

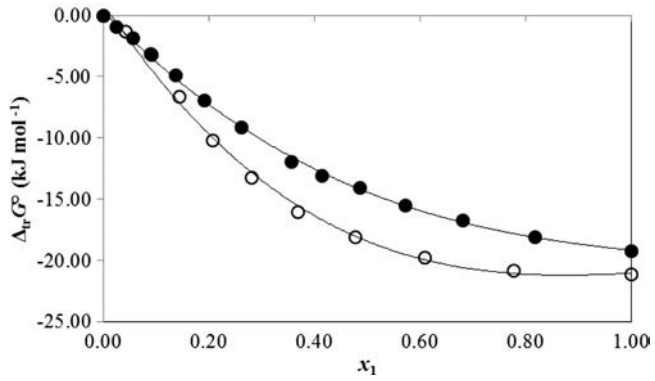

Fig. 2. Gibbs energy of transfer of indomethacin from neat water to co-solvent + water mixtures ($\Delta_{tr}G^{o}_{3,2\rightarrow1+2}$) vs. the mole fraction of co-solvent in the bulk solvent mixture (x_1) at 303.15 K. Ethanol + water mixtures (empty circles); propylene glycol + water mixtures (filled circles).

with $G_{2,3}$ values but in other cases the behavior is opposite. These differences are related with the relative affinity of IMC with co-solvent or water in the mixtures. Moreover, this affinity is variant with respect to the mixtures composition depending on the Lewis acid–base behavior and molar volumes of the components, among other reasons (Marcus, 2002).

In order to apply the IKBI method, the correlation volume was iterated three times by using the Equations (1), (6), and (7) to obtain the final values which are reported in Table VII. It is interesting to note that these V_{cor} values are almost independent on temperature in water-rich mixtures (i.e., at x_1 0.00 and 0.10) but they increase in some extent in co-solvent-rich mixtures as expectable according to the variation of the respective molar expansibilities with the mixtures composition (Jiménez et al., 2004; Jiménez and Martínez, 2005). Nevertheless, a very interesting behavior is observed in EtOH + water mixtures with composition $0.50 \leq x_1 \leq 0.70$ where no clear dependence of V_{cor} with temperature is observed; in particular, in the mixture $x_1 = 0.50$ with a constant value. This confusing behavior could be due to the iteration process which is involving no constant $x^L_{1,3}$ and $x^L_{2,3}$ values.

According to Figure 3 the values of $\delta x_{1,3}$ vary nonlinearly with the co-solvent proportion in the aqueous mixtures for both co-solvent systems at 303.15 K. Thus, the addition of co-solvent to water tends to make negative the $\delta x_{1,3}$ values

Table II. Gibbs energy of transfer (kJ mol^{-1}) of indomethacin from water to co-solvent + water mixtures at several temperatures

Ethanol + water[a]				Propylene glycol + water[a]			
x_1^b	293.15 K	303.15 K	313.15 K	x_1^b	293.15 K	303.15 K	313.15 K
0.0000	0.00	0.00	0.00	0.0000	0.00	0.00	0.00
0.0417	−1.08	−1.34	−1.59	0.0256	−0.88	−0.91	−1.04
0.0891	−2.75	−3.14	−3.81	0.0559	−1.75	−1.86	−2.08
0.1436	−5.82	−6.62	−7.52	0.0921	−3.02	−3.19	−3.50
0.2068	−9.21	−10.23	−11.22	0.1364	−4.55	−4.87	−5.24
0.2812	−12.27	−13.24	−14.53	0.1915	−6.51	−6.90	−7.63
0.3698	−14.77	−16.06	−17.05	0.2621	−8.41	−9.14	−10.13
0.4772	−16.89	−18.07	−19.00	0.3559	−10.88	−11.94	−13.11
0.6101	−18.73	−19.74	−20.68	0.4154	−11.97	−13.12	−14.49
0.7788	−18.73	−19.74	−20.68	0.4865	−12.89	−14.06	−15.64
1.0000	−20.36	−21.16	−22.11	0.5730	−14.16	−15.48	−16.85
				0.6807	−15.68	−16.72	−18.15
				0.8182	−16.99	−18.12	−19.30
				1.0000	−18.21	−19.22	−20.29

[a]Calculated from the solubility values reported in Table I.
[b]x_1 is the mole fraction of co-solvent in the co-solvent + water mixtures free of indomethacin.

Table III. Coefficients of Equation (13) applied to the Gibbs energy of transfer of indomethacin from neat water to co-solvent + water mixtures at several temperatures

	Ethanol + water			Propylene glycol + water		
Coefficient (kJ mol^{-1})	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
a	0.99	1.01	0.96	0.23	0.33	0.40
b	−58.20	−64.99	−72.37	−40.52	−44.61	−49.87
c	49.91	61.52	76.59	31.95	35.27	40.42
d	−12.93	−18.58	−27.20	−9.87	−10.17	−11.13

Table IV. D values (kJ mol^{-1}) for indomethacin in co-solvent + water mixtures at several temperatures

	Ethanol + water			Propylene glycol + water		
x_1^a	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	−58.20	−64.99	−72.37	−40.52	−44.61	−49.87
0.10	−48.61	−53.24	−57.87	−34.42	−37.86	−42.12
0.20	−39.79	−42.61	−45.00	−28.92	−31.72	−35.04
0.30	−31.74	−33.09	−33.76	−24.01	−26.20	−28.62
0.40	−24.47	−24.68	−24.15	−19.70	−21.28	−22.88
0.50	−17.98	−17.40	−16.18	−15.97	−16.97	−17.80
0.60	−12.26	−11.22	−9.84	−12.84	−13.27	−13.39
0.70	−7.32	−6.16	−5.13	−10.30	−10.18	−9.65
0.80	−3.16	−2.22	−2.05	−8.36	−7.70	−6.57
0.90	0.23	0.61	−0.60	−7.00	−5.83	−4.16
1.00	2.85	2.33	−0.79	−6.24	−4.57	−2.43

[a] x_1 is the mole fraction of co-solvent in the co-solvent + water mixtures free of indomethacin.

Table V. $G_{1,3}$ values (cm^3 mol^{-1}) for indomethacin in co-solvent + water mixtures at several temperatures

	Ethanol + water			Propylene glycol + water		
x_1[a]	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	−650.2	−685.5	−723.4	−519.5	−539.7	−567.2
0.10	−597.5	−650.4	−708.1	−442.9	−472.2	−509.2
0.20	−523.5	−561.5	−600.2	−383.4	−406.0	−434.1
0.30	−450.8	−464.5	−473.9	−336.6	−349.5	−365.1
0.40	−389.8	−385.7	−377.2	−300.1	−305.7	−312.3
0.50	−340.6	−327.9	−313.4	−272.5	−274.1	−275.7
0.60	−298.6	−284.8	−271.6	−252.6	−252.3	−251.6
0.70	−259.3	−250.1	−242.7	−238.9	−237.9	−236.4
0.80	−228.6	−225.2	−224.4	−229.8	−228.6	−227.0
0.90	−217.4	−216.9	−218.1	−223.7	−222.8	−221.7
1.00	−217.5	−217.4	−217.3	−219.1	−219.1	−219.0

[a] x_1 is the mole fraction of co-solvent in the co-solvent + water mixtures free of indomethacin.

of IMC in the composition-region from pure water to the mixtures with 0.24 in mole fraction of EtOH, or 0.20 in mole fraction of PG. In these cases, minimum values are obtained in $x_1 = 0.10$ ($\delta x_{1,3} = -4.395 \times 10^{-2}$ for EtOH + water and -1.856×10^{-2} for PG + water mixtures). As was indicated previously, probably the structuring of water molecules

Table VI. $G_{2,3}$ values (cm^3 mol^{-1}) for indomethacin in co-solvent + water mixtures at several temperatures

	Ethanol + water			Propylene glycol + water		
x_1^a	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	−219.2	−219.1	−219.1	−219.2	−219.1	−219.1
0.10	−345.5	−365.0	−386.4	−316.5	−330.1	−347.0
0.20	−456.1	−488.6	−521.8	−384.0	−407.7	−437.1
0.30	−540.1	−562.0	−577.5	−426.3	−450.0	−478.4
0.40	−601.0	−594.5	−577.5	−446.7	−463.2	−482.1
0.50	−642.5	−600.6	−551.6	−449.2	−456.2	−463.2
0.60	−650.9	−578.4	−508.5	−439.3	−437.2	−432.9
0.70	−574.0	−496.2	−434.4	−423.2	−412.7	−397.3
0.80	−380.3	−330.3	−320.2	−407.8	−387.6	−359.7
0.90	−208.7	−193.9	−241.1	−399.7	−366.3	−322.4
1.00	−149.3	−163.0	−235.4	−407.1	−353.2	−288.4

[a] x_1 is the mole fraction of co-solvent in the co-solvent + water mixtures free of indomethacin.

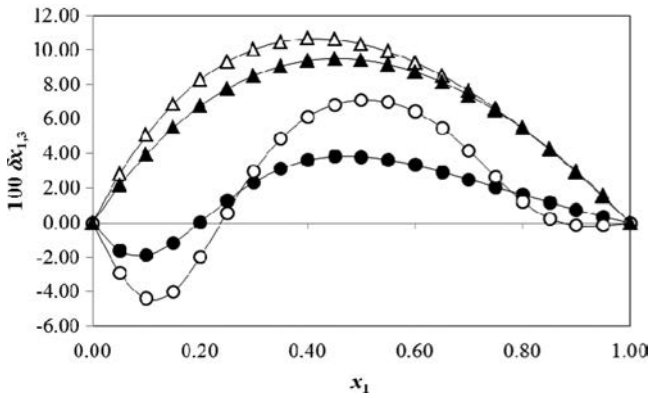

Fig. 3. IKBI (circles) and QLQC (triangles) $\delta x_{1,3}$ values for indomethacin in ethanol + water (empty symbols) and propylene glycol + water (filled symbols) mixtures vs. the mole fraction of co-solvent in the bulk solvent mixture (x_1) at 303.15 K.

around the non-polar groups of this drug, which leads to hydrophobic hydration of the aromatic rings and methyl groups (Figure 1), contributes to lowering of the net $\delta x_{1,3}$ to negative values in these water-rich mixtures. Similar behaviors are observed at the other temperatures as can be seen in Table VIII. The possibility of hydrophobic hydration of IMC in water-rich mixtures has been previously mentioned based on enthalpy-entropy compensation plots and some thermodynamic quantities of transfer (Martínez et al., 2011; Holguín et al., 2012). Additionally, in the case of IMC in EtOH + water mixtures, the negative deviations to the log-linear model proposed by Yalkowsky and Roseman (1981), exhibited in water-rich mixtures, have also been attributed to an increase in the water-structuring in these compositions (Ruidiaz et al., 2011).

In the mixtures with composition $0.20 < x_1 < 0.88$ for EtOH + water mixtures and $0.24 < x_1 < 1.00$ for PG + water water mixtures, the local mole fractions of the co-solvents are greater than those for water. In this way, the co-solvent action may be related to the breaking of the ordered structure of water around the non-polar moieties of the drug. This fact could increase the drug solvation exhibiting maximum values near to $x_1 = 0.50$ in both co-solvent systems, i.e., $\delta x_{1,3} = 7.109 \times 10^{-2}$ and 3.801×10^{-2} at 303.15 K for EtOH + water and PG + water mixtures, respectively. The higher preferential solvation parameters obtained in EtOH + water mixtures compared with those obtained in PG + water mixtures could be attributed to the differences in the co-solvent polarities in comparison with the polarity of the drug. Thus, if the Hildebrand solubility parameters (δ) are considered, i.e., 26.9, 26.5, and 30.2 $MPa^{1/2}$, for IMC, EtOH, and PG, respectively (Barton, 1991; Rodríguez et al., 2014), it follows that when the similarity in solvent-solute polarity is significant the solute-solvation by the co-solvent is also higher.

As has been indicated earlier, IMC could act in solution as a Lewis acid, due to the hydrogen atoms of its –OH group (Figure 1), in order to establish hydrogen bonds with proton-acceptor functional groups in the solvents (free electron pairs in oxygen atoms of –OH groups). In addition, this drug could act as a Lewis base due to free electron pairs in oxygen atoms of hydroxyl, methoxyl, and carbonyl groups (Figure 1) to interact with hydrogen atoms in both solvents. In this context, IMC has one hydrogen-bonding donor and three hydrogen-bonding acceptor groups (Holguín et al., 2012; Martínez et al., 2011).

According to these preferential solvation results, it is conjecturable that in intermediate composition mixtures and PG-rich mixtures for PG + water mixtures, and in intermediate composition mixtures for EtOH + water mixtures, IMC is acting as Lewis acid with the co-solvent molecules because these co-solvents are more basic than water, i.e., the Kamlet–Taft hydrogen bond acceptor parameters (β) are 0.78 for PG, 0.75 for EtOH, and 0.47 for water (Kamlet and Taft, 1976; Marcus, 1998). On the other hand, it is interesting to note what happens in EtOH-rich mixtures, where the drug is apparently solvated preferentially by water ($0.88 < x_1 < 1.00$, with $\delta x_{1,3} = -1.40 \times 10^{-3}$). In that case the drug could be acting mainly as a Lewis base in front to water because the Kamlet–Taft hydrogen bond donor parameters (α) are 1.17 for water and 0.86 for EtOH, respectively

Table VII. Correlation volume of indomethacin ($cm^3\ mol^{-1}$) in co-solvent + water mixtures at several temperatures

	Ethanol + water			Propylene glycol + water		
x_1^a	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	927	928	929	927	928	930
0.10	982	978	973	1034	1034	1032
0.20	1086	1088	1090	1175	1180	1184
0.30	1210	1218	1227	1316	1324	1333
0.40	1324	1331	1335	1442	1451	1460
0.50	1423	1423	1423	1555	1563	1571
0.60	1505	1501	1499	1658	1664	1671
0.70	1566	1565	1567	1754	1760	1766
0.80	1618	1623	1633	1847	1853	1858
0.90	1683	1693	1706	1937	1944	1951
1.00	1762	1773	1786	2025	2034	2043

[a] x_1 is the mole fraction of co-solvent in the co-solvent + water mixtures free of indomethacin.

Table VIII. IKBI $\delta x_{1,3}$ values ($\times 100$) of indomethacin in co-solvent + water mixtures at several temperatures

	Ethanol + water			Propylene glycol + water		
x_1^a	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	0.000	0.000	0.000	0.000	0.000	0.000
0.10	−3.711	−4.395	−5.223	−1.614	−1.856	−2.181
0.20	−1.747	−1.994	−2.272	0.011	0.036	0.064
0.30	2.691	2.985	3.201	2.057	2.335	2.679
0.40	6.274	6.114	5.738	3.338	3.596	3.895
0.50	8.104	7.109	6.015	3.699	3.801	3.903
0.60	7.939	6.412	5.020	3.366	3.316	3.230
0.70	5.450	4.162	3.176	2.652	2.497	2.281
0.80	1.787	1.221	1.103	1.801	1.597	1.323
0.90	−0.053	−0.140	0.139	0.934	0.756	0.528
1.00	0.000	0.000	0.000	0.000	0.000	0.000

[a] x_1 is the mole fraction of co-solvent in the co-solvent + water mixtures free of indomethacin.

Table IX. QLQC $\delta x_{1,3}$ values ($\times 100$) of indomethacin in co-solvent + water mixtures at several temperatures

	Ethanol + water			Propylene glycol + water		
x_1^a	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.10	5.02	5.06	5.13	3.84	3.96	4.08
0.20	8.21	8.27	8.37	6.58	6.75	6.95
0.30	9.97	10.03	10.15	8.32	8.52	8.74
0.40	10.59	10.65	10.77	9.17	9.38	9.60
0.50	10.29	10.34	10.46	9.23	9.42	9.62
0.60	9.25	9.29	9.38	8.57	8.73	8.90
0.70	7.59	7.62	7.70	7.26	7.38	7.51
0.80	5.44	5.46	5.51	5.36	5.44	5.53
0.90	2.88	2.89	2.91	2.93	2.97	3.01
1.00	0.00	0.00	0.00	0.00	0.00	0.00

[a] x_1 is the mole fraction of co-solvent in the co-solvent + water mixtures free of indomethacin.

(Marcus, 1998; Taft and Kamlet, 1976). Thus, water is more acidic than EtOH. Nevertheless, it is important to keep in mind that the minimum $\delta x_{1,3}$ value is low in comparison with those described for other drugs like some sulfonamides in EtOH + water mixtures, where $\delta x_{1,3}$ values near to 2.0×10^{-2} were reported in compositions x_1 near to 0.70 (Delgado and Martínez, 2014). Therefore, in the case of IMC is not well clear the presence of preferential solvation by water in EtOH-rich mixtures.

On the other hand, in order to use the QLQC method, the excess Gibbs energy of mixing values of the equimolar mixture of both solvents were used as follows: for EtOH + water: 0.709, 0.744, and 0.780 kJ mol^{-1}, at temperatures of 293.15, 303.15, and 313.15 K, respectively (Delgado et al., 2011), whereas for PG + water: -7.03×10^{-2}, -4.81×10^{-2}, and -1.35×10^{-2} kJ mol^{-1}, at the same temperatures (Holguín et al., 2011). According to the QLQC method (Figure 3 and Table IX), IMC is preferentially solvated by the co-solvents in all the mixtures, being the similar behavior in EtOH + water and PG + water systems. Clearly the QLQC $\delta x_{1,3}$ values are higher than those obtained by using the IKBI method in all the mixtures. Therefore, as has been indicated in the literature, the IKBI method is more adequate than QLQC method to discriminate the effect of the co-solvent composition on the local mole fraction of the solvents around the drug molecules (Delgado et al., 2011; Holguín et al., 2011; Cárdenas et al., 2014; Peña et al., 2014). Nevertheless, it is important to keep in mind that QLQC requires only two specific experimental values, namely, the Gibbs energy of transfer of IMC from water to co-solvent and the excess Gibbs energy of mixing in the co-solvent mixture with composition $x_1 = 0.50$, therefore, it is more easy to be used.

Conclusions

According to the points analyzed previously, some explicit expressions for the local mole fraction of co-solvents and water around IMC were derived on the basis of the IKBI and QLQC methods applied to the equilibrium solubility values reported for this drug in EtOH + water and PG + water water mixtures at several temperatures. Thereby, according to the IKBI method, this compound is preferentially solvated by water in water-rich mixtures but preferentially solvated by

co-solvent in those mixtures with intermediate composition for EtOH + water and PG + water systems and also in co-solvent-rich mixtures for the PG + water system at all temperatures considered. In the case of EtOH-rich mixtures the drug is apparently solvated preferentially by water but these results are not clear. Nevertheless, from a molecular point of view, it is important to note that these results are in good agreement with those described previously based in more classical thermodynamic treatments (Holguín et al., 2012; Martínez et al., 2011).

Nomenclature

E	pair-wise interactions energy
EtOH	ethanol
G	molar Gibbs energy; Kirkwood–Buff integral
IKBI	inverse Kirkwood–Buff integral
IMC	indomethacin
N	number of molecules or of neighboring molecule pairs
N_A	Avogadro's constant
QLQC	quasi-lattice quasi-chemical
R	gas constant
S	molar entropy
T	absolute temperature
U	internal energy
V	molar volume
x	mole fraction
Z	quasi-lattice parameter

Greek Letters

α	Kamlet–Taft hydrogen bond donor parameter
β	Kamlet–Taft hydrogen bond acceptor parameter
Δ	change on transformation
δx	preferential solvation parameter
κ_T	isothermal compressibility

Superscripts

$^\circ$	standard molar
Exc	excess thermodynamic function
L	local

Subscripts

0.5	equimolar composition
$\rightarrow$	transfer
cor	correlation, where preferential solvation occurs
i	component i
P	constant pressure
PG	propylene glycol
T	constant absolute temperature

References

Barton, A. F. M. (1991). *Handbook of Solubility Parameters and Other Cohesion Parameters*, 2nd ed., CRC Press LLC, Boca Raton, FL, pp. 101–103.

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

Budavari, S., O'Neil, M. J., Smith, A., Heckelman, P. E., Obenchain Jr., J. R., Gallipeau, J. A. R., and D'Arecea, M. A. (2001). *The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals*, 13th ed., Merck & Co., Inc., Whitehouse Station, NJ, p. 892.

Cárdenas, Z. J., Jiménez, D. M., and Martínez, F. (2014). Preferential solvation of ketoprofen in some co-solvent binary mixtures, *J. Solution Chem.*, **43**, 1904–1915.

Delgado, D. R., and Martínez, F. (2014). Preferential solvation of sulfadiazine, sulfamerazine and sulfamethazine in ethanol + water solvent mixtures according to the IKBI method, *J. Mol. Liq.*, **193**, 152–159.

Delgado, D. R., Holguín, A. R., Almanza, O. A., Martínez, F., and Marcus, Y. (2011). Solubility and preferential solvation of meloxicam in ethanol + water mixtures, *Fluid Phase Equilib.*, **305**, 88–95.

Delgado, D. R., Peña, M. Á., and Martínez, F. (2013). Preferential solvation of acetaminophen in ethanol + water solvent mixtures according to the inverse Kirkwood-Buff integrals method, *Rev. Colomb. Cienc. Quím. Farm.*, **42**, 298–314.

Delgado, D. R., Peña, M. Á., and Martínez, F. (2014). Preferential solvation of some sulfonamides in propylene glycol + water solvent mixtures according to the IKBI and QLQC methods, *J. Solution Chem.*, **43**, 360–374.

Fedors, R. F. (1974). A method for estimating both the solubility parameters and molar volumes of liquids, *Polym. Eng. Sci.*, **14**, 147–154.

Holguín, A. R., Delgado, D. R., Martínez, F., and Marcus, Y. (2011). Solution thermodynamics and preferential solvation of meloxicam in propylene glycol + water mixtures, *J. Solution Chem.*, **40**, 1987–1999.

Holguín, A. R., Rodríguez, G. A., Cristancho, D. M., Delgado, D. R., and Martínez, F. (2012). Solution thermodynamics of indomethacin in propylene glycol + water mixtures, *Fluid Phase Equilib.*, **314**, 134–139.

Jiménez, J., Manrique, J., and Martínez, F. (2004). Effect of temperature on some volumetric properties for ethanol + water mixtures, *Rev. Colomb. Cienc. Quím. Farm.*, **33**, 145–155.

Jiménez, J., and Martínez, F. (2005). Study of some volumetric properties of 1,2-propanediol + water mixtures at several temperatures, *Rev. Colomb. Cienc. Quím. Farm.*, **34**, 46–57.

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

Kamlet, M. J., and Taft, R. W. (1976). The solvatochromic comparison method. I. The beta-scale of solvent hydrogen-bond acceptor (HBA) basicities, *J. Am. Chem. Soc.*, **98**, 377–383.

Marcus, Y. (1990). Solubility and solvation in mixed solvent systems, *Pure Appl. Chem.*, **62**, 2069–2076.

Marcus, Y. (1998). *The Properties of Solvents*, John Wiley & Sons, Chichester, pp. 145–146.

Marcus, Y. (2002). *Solvent Mixtures: Properties and Selective Solvation*, Marcel Dekker, Inc., New York, NY, pp. 180–208.

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

Marcus, Y. (2009). Preferential solvation of ibuprofen and naproxen in aqueous 1,2-propanediol, *Acta Chim. Slov.*, **56**, 40–44.

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

Peña, M. Á., Delgado, D. R., and Martínez, F. (2014) Preferential solvation of acetaminophen in propylene glycol + water co-solvent mixtures, *J. Appl. Sol. Chem. Model.*, **3**, 65–73.

Rodríguez, G. A., Delgado, D. R., and Martínez, F. (2014). Preferential solvation of indomethacin and naproxen in ethyl acetate + ethanol mixtures according to the IKBI method, *Phys. Chem. Liq.*, **52**, 533–545.

Rubino, J. T. (1988). Cosolvents and cosolvency, in: Swarbrick, J., and Boylan, J. C. (Eds.), *Encyclopedia of Pharmaceutical Technology*, vol. 3, Marcel Dekker, Inc., New York, NY, pp. 375–398.

Ruidiaz, M. A., Delgado, D. R., and Martínez, F. (2011). Performance of the Jouyban-Acree and Yalkowsky-Roseman models for estimating the solubility of indomethacin in ethanol + water mixtures, *Rev. Acad. Colomb. Cienc.*, **35**, 329–336.

Ruidiaz, M. A., Delgado, D. R., Martínez, F., and Marcus, Y. (2010). Solubility and preferential solvation of indomethacin in 1,4-dioxane + water solvent mixtures, *Fluid Phase Equilib.*, **299**, 259–265.

Taft, R. W., and Kamlet, M. J. (1976). The solvatochromic comparison method. II. The alpha-scale of solvent hydrogen-bond donor (HBD) acidities, *J. Am. Chem. Soc.*, **98**, 2886–2894.

Yalkowsky, S. H., and Roseman, T. J. (1981). Solubilization of drugs by cosolvents, in: Yalkowsky, S. H. (Ed.), *Techniques of Solubilization of Drugs*, Marcel Dekker, Inc., New York, NY, pp. 91–134.