

# Solvatación preferencial de 4-hidroxi-2,5-dimetil-3(2H)-furanona (HDMF) en mezclas etanol + agua de acuerdo a los métodos IKBI y QLQC

## Preferential solvation of 4-hydroxy-2,5-dimethyl-3(2H)-furanone (DMHF) in ethanol + water mixtures according to IKBI and QLQC methods

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### Resumen

Los parámetros de solvatación preferencial por etanol (EtOH) de 4-hidroxi-2,5-dimetil-3 (2H) -furanona (HDMF) fueron derivados de sus propiedades termodinámicas de solución por medio de los métodos de las integrales inversas de Kirkwood-Buff y cuasi-reticular -cuasi-químico (QLQC). Según el método IKBI, el parámetro de solvatación preferencial  $\delta x_{1,3}$  del EtOH es negativo en mezclas ricas en agua pero positivo en mezclas de ricas en etanol. Posiblemente la hidratación hidrofóbica alrededor de los grupos metilo de la HDMF juega un papel relevante en la solvatación en mezclas ricas en agua. La mayor solvatación por parte del EtOH en mezclas ricas en etanol puede ser debido principalmente a los efectos de polaridad y comportamiento ácido de los grupos hidroxilo del compuesto frente a los disolventes más básicos presentes en las mezclas. De otro lado, según el método QLQC, este compuesto es solvatado preferentemente por el cosolvente en la mayoría de las mezclas de sistema de agua etanol.

**Palabras clave:** HDMF; etanol; solvatación preferencial; integrales inversas de Kirkwood-Buff ; cuasi-reticular-cuasi-químico.

### Abstract

The parameters of preferential solvation of 4-hydroxy-2,5-dimethyl-3 (2H)-furanone (HDMF) in ethanol (EtOH) were derived from its thermodynamic properties of solution by means of inverse Kirkwood-Buff integrals

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and quasi-lattice-quasi-chemical (QLQC) methods. According to the IKBI method, the preferential solvation parameter  $\delta x_{1,3}$  of EtOH is negative in water-rich mixtures but positive in ethanol-rich mixtures. It is possible that the hydrophobic hydration around the methyl groups of the HDMF plays a role in the solvation in water-rich mixtures. The greatest EtOH solvation in ethanol-rich mixtures may have been due, mainly, to the effects of polarity and acid-base behavior of the hydroxyl groups in the compound against the most basic solvents in the solution. On the other hand, using the QLQC method, this compound is preferably solvated by the cosolvent in most of the water-ethanol system mixtures.

**Key words:** HDMF, ethanol; preferential solvation, inverse Kirkwood-Buff integrals, quasi-lattice-quasi-chemical

## 1. Introduction

DMHF, is an important aroma compound which has been identified in many fruits, e.g. pineapples (Rodin *et al.*, 1965), strawberries (Ohloff, 1969), arctic bramble (in trace) (Kallio, 1976), raspberries (Honkanen *et al.*, 1980), as an off-flavour in aged orange juice (Tatum *et al.*, 1975), and in experimental hybrids of German wine (Rapp *et al.*, 1980). It occurs in cooked, roasted and fermented food materials, e.g. beef broth (Tonsbeek *et al.*, 1968), roasted filberts, d roasted almond (Sheldon *et al.*, 1972), coffee and soy sauce (Tressl *et al.*, 1978). DMHF (Fig. 1, IUPAC 4-hydroxy-2,5-dimethyl-3(2H)-furanone, DMHF, C<sub>6</sub>H<sub>8</sub>O<sub>3</sub>, CAS Registry No. 3658-77-3).

Solubility determination of drugs and similar compounds in all possible co-solvent mixtures is very important for pharmaceutical and chemical scientists involved in several development stages such as substances purification and design of liquid medicines (Jouyban, 2010). Co-solvency has been employed in pharmacy to increase solubility of drugs to develop homogeneous pharmaceutical liquid dosage forms long time ago (Rubino, 1988; Yalkowsky, 1999; Jouyban, 2010). In this way, an investigation have been carried out to evaluate the effect of composition and temperature on the solubility of DMHF in ethanol + water (Wang *et al.*, 2015). Nevertheless, the drug preferential solvation by the solvents, i.e. the co-solvent specific composition around the DMHF molecules has not been studied. It is important to note that ethanol is the most widely used co-solvents to develop liquid medicines (Aulton, 2002); moreover, they are also used as additives in several kinds of industrial foods (Smolinske, 1992).

The inverse Kirkwood-Buff integrals (IKBI) are a powerful tool for evaluating the preferential solvation

of non-electrolyte compounds in co-solvent mixtures, describing the local compositions around the solute with respect to the different components present in the solvent mixture (Marcus, 2002, 2009, 2013). Applied to the present research, this treatment depends on the values of the standard molar Gibbs energies of transfer of DMHF from neat water to the co-solvent + water mixtures and the excess molar Gibbs energy of mixing for the binary mixtures free of drug. In similar way, quasi-lattice quasi-chemical (QLQC) approach is also useful to do evaluate preferential solvation although is not too much exact as IKBI approach is. This method 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 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, 2002, 2009, 2013).

In this paper the IKBI and QLQC approaches are applied to evaluate the preferential solvation of DMHF in the binary mixtures conformed by ethanol (EtOH) and water (W). QLQC is applicable in both systems because the maximum solubility is obtained in the neat co-solvent (Wang *et al.*, 2015). The results are expressed in terms of the preferential solvation parameter ( $\delta x_{1,3}$ ) of the solute by the co-solvent, ethanol according to the mixtures composition. Thus, this study is similar to that developed by analyzing the behavior of the different drugs in some co-solvent + water mixtures (Jiménez *et al.*, 2015; Muñoz *et al.*, 2015; Cárdenas *et al.*, 2014; Delgado and Martínez, 2015, 2014a; Peña *et al.*, 2014; Delgado *et al.*, 2014a, 2014b, 2013a, 2013b, 2011; Cristancho *et al.*, 2013; Ruidiaz *et al.*, 2010).

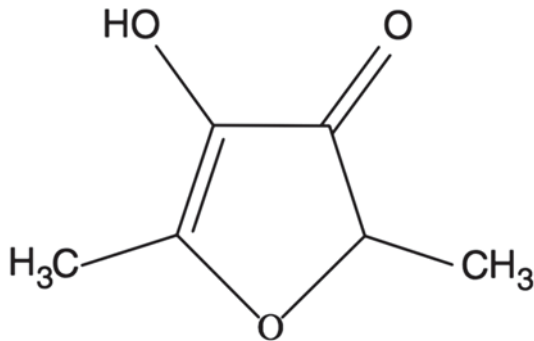


Figure 1. Molecular structure of DMHF.

## 2. Theoretical background

According to IKBI method, the solvation results are expressed in terms of the preferential solvation parameter  $\delta x_{1,3}$  of the solute by the co-solvent (compound 1) according to the following expression:

$$\delta x_{1,3} = x_{1,3}^L - x_1 = -\delta x_{2,3} \quad (1)$$

Where  $x_1$  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 the drug. If  $\delta x_{1,3} > 0$  then DMHF is preferentially solvated by co-solvent; on the contrary, if it is  $< 0$  the drug is preferentially solvated by water. Values of  $\delta x_{1,3}$  are obtainable from of the Kirkwood-Buff integrals,  $G_{1,3}$ , and these, in turn, from thermodynamic data of the co-solvent mixtures with the solute dissolved on it, as shown in equations 2 and 3 (Marcus, 2008, 2009):

$$G_{1,3} = RT\kappa_T - \bar{V}_3 + x_2\bar{V}_2D/Q \quad (2)$$

$$G_{2,3} = RT\kappa_T - \bar{V}_3 + x_1\bar{V}_1D/Q \quad (3)$$

Where  $\kappa_T$  is the isothermal compressibility of the co-solvent + water solvent mixtures (in  $\text{GPa}^{-1}$ ),  $\bar{V}_1$  and  $\bar{V}_2$  are the partial molar volumes of the solvents in the mixtures (in  $\text{cm}^3 \text{mol}^{-1}$ ), similarly,  $\bar{V}_3$  is the partial molar volume of solute in these mixtures (in  $\text{cm}^3 \text{mol}^{-1}$ ). The function  $D$  is the derivative of the standard molar Gibbs energies of transfer of the drug (from neat water to co-solvent + water mixtures) with respect to the solvent composition (in  $\text{kJ mol}^{-1}$ , as also is  $RT$ ) and the function  $Q$  involves the second derivative of the excess molar Gibbs energy of mixing of the two solvents ( $G_{1+2}^{Exc}$ ) with respect to the water proportion in the mixtures (also in  $\text{kJ mol}^{-1}$ ) (Marcus, 1998, 2008, 2009). These quantities are calculated according to equations (4) and (5).

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

$$Q = RT + x_1x_2 \left( \frac{\partial^2 G_{1,2}^{Exc}}{\partial x_2^2} \right)_{T,p} \quad (5)$$

The preferential solvation parameter of DMHF by the co-solvent can be calculated from the Kirkwood-Buff integrals as follows (Marcus, 2008, 2009):

$$\delta x_{1,3} = \frac{x_1x_2(G_{1,3} - G_{2,3})}{x_1G_{1,2} + x_2G_{2,3} + V_{cor}} \quad (6)$$

Here  $V_{cor}$  is the correlation volume which is obtained by using (Marcus, 2008, 2009):

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

where  $r_3$  is the radius of DMHF (expressed in nm). However, the definitive correlation volume requires iteration, because it depends on the local mole fractions around the solute. This iteration is done by replacing  $\delta x_{1,3}$  in the equation (1) to calculate  $x_{1,3}^L$  until a non-variant value of  $V_{cor}$  is obtained.

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

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

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

$$\frac{N_{12}}{Z(N_1 + N_2)} = \frac{1 - [1 - 4x_1x_2(1 - \exp\{-\Delta E_{12} / RT\})]^{0.5}}{2[1 - \exp\{-\Delta E_{12} / RT\}]} \quad (10)$$

$$\Delta E_{12,3} = \Delta_{tr} G_{3,2 \rightarrow 1}^{\circ} / Z \quad (11)$$

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

In these equations, the lattice parameter  $Z$  is usually assumed as 10.  $N_1$  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 (10) expresses the difference in the molar neighbor interaction energies of DMHF with the co-solvent and water,  $\Delta E_{12,3}$ , by the

molar Gibbs energy of transfer from water to co-solvent per neighboring lattice.  $DE_{12}$  denotes the molar energy of interaction of solvent on neighboring quasi-lattice sites. It is important to keep in mind that just the Gibbs energy of the solute transfer between the neat solvents and the excess Gibbs energy of mixing at equimolar composition of both solvents are required for this method.

### 3. Results and discussion

Standard molar Gibbs energy of transfer of DMHF from neat water to co-solvent + water mixtures (Table 1) was calculated and correlated to non-regular polynomials by using the equation 13 from the drug solubility data reported previously in the literature (Wang *et al.*, 2015). Thus, the coefficients of the polynomials are shown in Table 2.

$$\Delta_{tr} G_{3,2 \rightarrow 1+2}^{\circ} = RT \ln \left( \frac{x_{3,2}}{x_{3,1+2}} \right) = \frac{(a + cx^2 + ex^4 + gx^6)}{(1 + bx^2 + dx^4 + fx^6 + hx^8)} \quad (13)$$

$D$  values are calculated from the first derivative of the polynomial models solved according to the co-solvent mixtures composition. This procedure was done varying by 0.05 in mole fraction of co-solvent.

$Q$  and  $RT k_T$  values, as well as the partial molar volumes of co-solvents and water in these binary mixtures were taken from the literature (Delgado and Martínez, 2014b; Jiménez, *et al.*, 2014). Otherwise, as it is well known, the partial molar volumes of non-electrolyte drugs are not frequently reported in the literature. For this reason, as was made previously with other drugs in similar studies (Delgado *et al.*, 2014c), the molar volume of DMHF is considered

**Table 1.** Gibbs energy of transfer ( $\text{kJ mol}^{-1}$ )<sup>a</sup> of DMHF from neat water to ethanol + water mixtures at both temperatures.

$x_1^b$	Ethanol + water mixtures <sup>a</sup>				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15
0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
0.0447	-1.7232	-1.4043	-1.0547	-0.7191	-0.3683
0.0932	-2.5945	-2.2439	-1.8280	-1.3401	-0.8268
0.1509	-2.8749	-2.4399	-1.9689	-1.4831	-0.9487
0.2084	-3.1862	-2.6840	-2.1399	-1.5853	-0.9809
0.2737	-3.5503	-2.9565	-2.3243	-1.6848	-1.0198
0.3540	-3.7015	-3.0717	-2.5073	-1.8279	-1.1929
0.4662	-3.7994	-3.2678	-2.5832	-1.9655	-1.2991
0.6224	-4.1059	-3.5107	-2.9705	-2.2593	-1.5900
0.7724	-4.5446	-3.9659	-3.3276	-2.6750	-2.0190
1.0000	-4.9072	-4.3303	-3.6819	-3.0363	-2.3515

<sup>a</sup> Values calculated from the solubility values reported by Wang *et al.* (2015).

<sup>b</sup>  $x_1$  are the mole fractions of co-solvent in the co-solvent + water mixtures free of DMHF.

**Table 2.** Coefficients ( $\text{kJ mol}^{-1}$ ) of the equation 13 applied to Gibbs energy of transfer of DMHF from neat water to ethanol + water mixtures.

Coefficient	Ethanol + water mixtures				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15
$a$	0.002	0.003	0.002	0.001	$8.249 \times 10^{-5}$
$b$	1006.442	773.754	594.581	467.803	213.140
$c$	-2480.106	-1712.508	-1025.284	-580.443	-171.621
$d$	33828.751	31574.003	61639.997	69976.484	79487.892
$e$	-125782.246	-93104.793	-135072.174	-112225.846	-76052.119
$f$	18779.906	12442.128	-5044.967	-60057.558	-89366.295
$g$	-126568.388	-106680.205	-134338.520	-18888.077	-24537.296
$h$	-1889.026	1621.004	16252.148	32916.896	52526.192

here as independent of co-solvent composition and temperature. Thus, the  $V_3$  value presented in Table 3 was calculated according to the groups contribution method proposed by Fedors (1974). Furthermore, the molecular radius was also calculated from the respective molar volume by using the equation (14), where  $N_{Av}$  is the Avogadro number, as 0.3483 nm.

$$r_3 = \left( \frac{3 \cdot 10^{21} V_3}{4\pi N_{Av}} \right)^{1/3} \quad (14)$$

On the other hand, Table 4 shows that the  $G_{1,3}$  and  $G_{2,3}$  are negative in all compositions at all temperatures considered indicating that this compound has affinity for both organic and aqueous media.

In order to use the IKBI method, the correlation volume was iterated by using the equations 1, 6 and 7 to obtain the values.  $V_{cor}$  is almost independent on temperature in water-rich mixtures but it increases in some extent in co-solvent-rich mixtures. This behavior is proportional to the increase in molar

**Table 3.** Interne energy, molar volume and Hildebrand solubility parameter of DMHF according to the Fedors method.

Group	Number	$\Delta U^\circ / \text{kJ mol}^{-1}$	$V^\circ / \text{cm}^3 \text{mol}^{-1}$
-OH	1	29.80	10.00
-CH <sub>3</sub>	2	2 x 4.71=9.42	2 x 33.50=67.00
-O-	1	3.35	3.80
-CH<	1	3.43	-1.00
>C=O	1	17.40	10.80
Ring closure	1	1.05	16.00
Conjugated bond	1	1.67	-2.20
	$\Sigma$	65.47	104.40
$\delta = (65,470/104.40)^{1/2} = 25.04 \text{ MPa}^{1/2}$			

**Table 4.**  $G_{1,3}$  and  $G_{2,3}$  values ( $\text{cm}^3 \text{mol}^{-1}$ ) of DMHF in co-solvent + water mixtures at both temperatures.

$x_1^a$	Ethanol + water mixtures					
	$G_{1,3}$			$G_{2,3}$		
	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.00	-103.29	-103.25	-103.21	-103.29	-103.25	-103.21
0.05	-290.03	-274.07	-212.01	-132.27	-130.12	-120.52
0.10	-173.72	-157.24	-132.20	-126.71	-121.40	-113.01
0.15	-147.83	-126.86	-112.64	-127.23	-116.03	-108.29
0.20	-134.73	-118.41	-109.67	-127.70	-115.11	-108.27
0.25	-126.68	-115.86	-109.55	-128.05	-116.74	-110.07
0.30	-121.75	-115.18	-110.04	-129.04	-120.12	-113.03
0.35	-118.76	-115.15	-110.68	-131.16	-124.97	-117.13
0.40	-116.98	-115.33	-111.39	-134.71	-131.29	-122.62
0.45	-115.94	-115.57	-112.18	-139.96	-139.25	-129.98
0.50	-115.34	-115.77	-113.04	-147.21	-149.12	-139.91
0.55	-114.96	-115.86	-113.95	-156.77	-161.11	-153.28
0.60	-114.61	-115.71	-114.80	-168.72	-175.18	-170.90
0.65	-114.03	-115.11	-115.33	-182.38	-190.36	-192.75
0.70	-112.93	-113.79	-115.07	-195.52	-203.81	-216.14
0.75	-111.09	-111.56	-113.42	-204.01	-210.31	-233.06
0.80	-108.66	-108.61	-110.20	-203.89	-204.56	-231.05
0.85	-106.13	-105.66	-106.31	-194.83	-186.49	-203.56
0.90	-104.03	-103.42	-103.24	-180.63	-162.68	-160.17
0.95	-102.54	-102.11	-101.71	-165.70	-140.49	-118.28
1.00	-101.59	-101.49	-101.40	-152.63	-123.41	-88.56

<sup>a</sup>  $x_1$  is the mole fraction of co-solvent in the co-solvent + water free of DMHF.

volume of the respective co-solvent mixtures with the temperature (Jiménez *et al.*, 2004; Jiménez and Martínez, 2005).

DMHF could act in solution as a Lewis acid due to the hydrogen atoms in its –OH groups (Fig. 1) in order to establish hydrogen bonds with proton-acceptor functional groups in the solvents (oxygen atoms in –OH groups). In addition, this compound could act as a Lewis base due to free electron pairs in oxygen atoms of –O–, >C=O, or –OH groups (Fig. 1), to interact with acidic hydrogen atoms in water and EtOH.

According to IKBI method the values of  $\delta x_{1,3}$  vary non-linearly with the co-solvent proportion in the aqueous mixtures (Table 5, Figs. 2). Addition of co-solvent to water tends to make negative the  $\delta x_{1,3}$  values of DMHF from the pure water up to the mixture  $x_1 = 0.25$  in both systems reaching minimum values near to  $x_1 = 0.05$ . Possibly the structuring of water molecules around the non-polar groups of this drug (Fig. 1) contributes to lowering of the net  $\delta x_{1,3}$  to negative values in these water-rich mixtures. IKBI  $\delta x_{1,3}$  values are higher again in EtOH + water.

In the mixtures with composition  $0.25 < x_1 < 1.00$ , the local mole fractions of co-solvent 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 (aggregates stabilized by hydrogen bonding) around the non-polar moieties of DMHF, which could increase the solvation, exhibiting maximum values near to  $x_1 = 0.70$ .

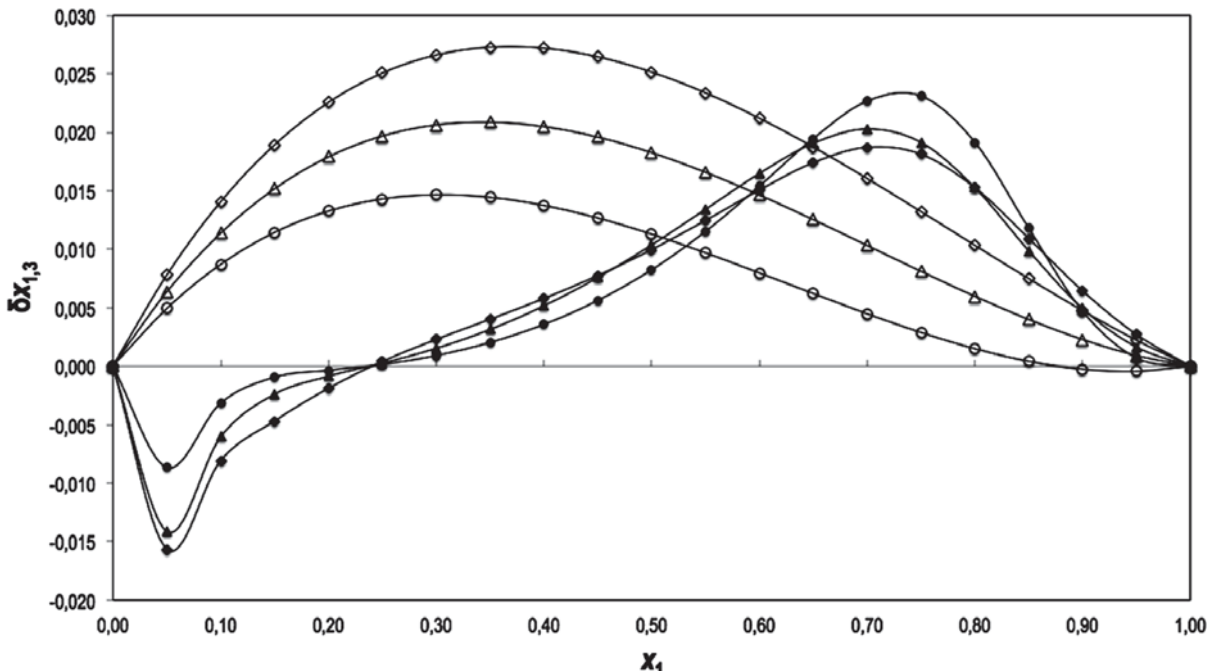
According to the preferential solvation results, it is conjecturable that in intermediate composition and in co-solvent-rich mixtures, DMHF is acting as Lewis acid, because these co-solvents are more basic than water, i.e. the Kamlet-Taft hydrogen bond acceptor parameters are  $\beta = 0.75$  for EtOH, and 0.47 for water (Kamlet and Taft, 1976; Marcus, 1998).

On the other hand, in order to use the QLQC method, the excess Gibbs energy of mixing values of the equimolar mixture of EtOH + water mixtures was calculated according to some equations reported in the literature (Marcus, 1998; Delgado and Martínez, 2014a). According to the QLQC method (Table 5 and Fig. 2), DMHF is preferentially solvated by the co-solvent in all the mixtures between 293.95 and 308,15 K, the other

**Table 5.** IKBI and QLQC  $\delta x_{1,3}$  values (x 1000) of DMHF in ethanol + water.

$x_1^a$	IKBI			QLQC		
	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
0.05	-15.64	-14.12	-8.66	7.82	6.37	4.95
0.10	-8.05	-6.02	-3.14	14.07	11.38	8.71
0.15	-4.67	-2.39	-0.94	18.93	15.17	11.44
0.20	-1.88	-0.86	-0.36	22.55	17.90	13.26
0.25	0.41	0.26	0.15	25.07	19.68	14.30
0.30	2.29	1.52	0.91	26.60	20.63	14.66
0.35	4.02	3.14	2.03	27.28	20.87	14.44
0.40	5.79	5.16	3.58	27.19	20.49	13.75
0.45	7.75	7.58	5.62	26.45	19.59	12.67
0.50	9.97	10.37	8.25	25.15	18.25	11.29
0.55	12.46	13.42	11.53	23.37	16.57	9.70
0.60	15.07	16.48	15.40	21.20	14.64	7.98
0.65	17.40	19.06	19.47	18.73	12.53	6.21
0.70	18.71	20.28	22.66	16.04	10.32	4.48
0.75	18.12	19.13	23.09	13.22	8.11	2.88
0.80	15.27	15.26	19.14	10.34	5.97	1.50
0.85	10.92	9.87	11.80	7.48	4.00	0.41
0.90	6.43	4.93	4.70	4.75	2.28	-0.27
0.95	2.71	1.63	0.70	2.22	0.91	-0.44
1.00	0.00	0.00	0.00	0.00	0.00	0.00

<sup>a</sup>  $x_1$  is the mole fraction of co-solvent in the co-solvent + water mixtures free of DMHF.



**Figure 2.** IKBI (filled symbols) and QLQC (open symbols)  $\delta x_{1,3}$  values of DMHF in ethanol + water mixtures at both temperatures. Circles: 298.2 K; triangles: 313.2 K.

hand at 313,15 K DMHF is preferentially solvated by the EtOH from near water at 0.85 in molar fraction of EtOH and solvated by the water from 0.85 in molar fraction of EtOH at near EtOH.

The QLQC method show higher  $\delta x_{1,3}$  values in water-rich mixtures unlike the method the IKBI method which reports greater values in ethanol rich mixtures. Maximum values are found in the mixture with  $x_1 = 0.70$  EtOH + water mixtures. It is important to note that, as has been indicated in the literature, the IKBI method is more adequate than QLQC method in order to discriminate the effect of the co-solvent composition on the local mole fraction of the solvents around the drug molecules, in particular in the water-rich mixtures (Delgado *et al.*, 2014a; Peña *et al.*, 2014). Nevertheless, it is important to keep in mind that QLQC only requires the Gibbs energy of transfer of DMHF from water to co-solvent and the excess Gibbs energy of mixing in the co-solvent mixture with composition  $x_1 = 0.50$ , and therefore, it is more easy to use.

#### 4. Conclusions

According to IKBI method DMHF is preferentially solvated by water in water-rich mixtures but preferentially solvated by co-solvent in mixtures with

compositions from  $x_1 = 0.25$  to neat co-solvent in EtOH + water at all temperatures considered. It is possible that the hydrophobic hydration around methyl groups of DMHF plays a relevant role in the solvation in water-rich mixtures. The more solvation by co-solvents in mixtures of similar composition and co-solvent-rich mixtures could be due to basic behavior of DMHF in front to water, which is the more acidic solvent. On the other hand, according to the QLQC method, this compound would be preferentially solvated by the co-solvents in all the possible mixtures. Nevertheless, it is important to consider that the IKBI method is more rigorous than QLQC and more reliable results are thus obtained with the former method. Finally, it is noteworthy that these treatments contribute to the understanding of the chemical behavior of pharmaceutical and food components in complex solutions.

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