Quim. Nova, Vol. 34, No. 9, 1569-1574, 2011

Artigo

INDOMETHACIN SOLUBILITY ESTIMATION IN 1,4-DIOXANE + WATER MIXTURES BY THE EXTENDED HILDEBRAND SOLUBILITY APPROACH

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Recebido em 19/1/11; aceito em 9/5/11; publicado na web em 29/6/11

Extended Hildebrand Solubility Approach (EHSA) was successfully applied to evaluate the solubility of Indomethacin in 1,4-dioxane + water mixtures at 298.15 K. An acceptable correlation-performance of EHSA was found by using a regular polynomial model in order four of the *W* interaction parameter vs. solubility parameter of the mixtures (overall deviation was 8.9%). Although the mean deviation obtained was similar to that obtained directly by means of an empiric regression of the experimental solubility vs. mixtures solubility parameters, the advantages of EHSA are evident because it requires physicochemical properties easily available for drugs.

Keywords: Extended Hildebrand Solubility Approach; indomethacin; solubility parameter.

INTRODUCTION

Indomethacin (IMC, Figure 1) is a non-steroidal anti-inflammatory drug used as analgesic and antipyretic, among other indications.[1] Although IMC is used in therapeutics, the physicochemical information about its solubility is scarce. It is well known that several physicochemical properties such as the solubility of active ingredients and their respective occupied volumes in useful solutions are very important for pharmaceutical scientists. This kind of information facilitates the drug design processes and the development of new products.[2]

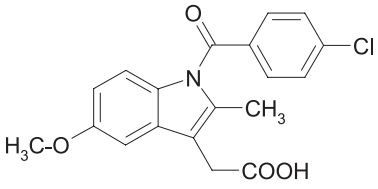

Figure 1. *Molecular structure of indomethacin*

This work presents a physicochemical study about the solubility prediction of IMC in binary mixtures of 1,4-dioxane and water. The study was done based on the Extended Hildebrand Solubility Approach (EHSA), developed by Martin *et al.* to use it in pharmaceutical systems.[3] As has been already described, the solubility behavior of drugs in cosolvent mixtures is very important because cosolvent blends are frequently used in purification methods, preformulation studies, and pharmaceutical dosage forms design, among other applications.[4]

It is known that 1,2-propanediol and ethanol are the cosolvents most widely used in drug formulation design, especially those intended for peroral and parenteral administration and several examples of pharmaceutical formulations using these cosolvents have been presented by Rubino.[4] 1,2-propanediol and ethanol can act both as hydrogen-donor and hydrogen-acceptor solvents and have relatively large dielectric constants (24 and 32 at 293.15 K, respectively).[5] Therefore, the behavior of solutes in cosolvent mixtures with low polarities could not be studied by using mixtures of these two solvents with water.

On the other hand, 1,4-dioxane is miscible with water in all possible compositions, although it has a low dielectric constant (2.2 at 293.15 K).[5] Mixtures of 1,4-dioxane + water can be varied from non-polar to polar since dielectric constant vary from 2 to 80. While 1,4-dioxane acts only as a Lewis base in aqueous solution, 1,2-propanediol and ethanol can act either as Lewis acid or Lewis base. Although 1,4-dioxane is a toxic solvent, it has been widely used as a model cosolvent for solubility studies of drugs by several authors.[3,6]

This report expands the information presented about the solubility prediction of other analgesic drugs by means of EHSA method,[7] including the ones developed recently for this drug in ethyl acetate + ethanol and ethanol + water mixtures.[8] It is remarkable that the solution thermodynamics of IMC in 1,4-dioxane + water mixtures has also been reported earlier.[9] Accordingly that work, the driving mechanism for IMC solubility in water-rich mixtures is the entropy, probably due to water-structure loss around the drug non-polar moieties by 1,4-dioxane, whereas, above 0.60 mass fraction of 1,4-dioxane the driving mechanism is the enthalpy, probably due to IMC solvation increase by the cosolvent molecules.[9]

THEORETICAL

The ideal solubility (X_2^{id}) of a solid solute in a liquid solution is calculated adequately by means of the expression,

$$\log X_2^{id} = -\frac{\Delta H_{fus}\left(T_{fus} - T\right)}{2.303RT_{fus}T} \quad (1)$$

where, ΔH_{fus} is the fusion enthalpy of the solute, R is the universal gas constant (8.314 J mol^{-1} K^{-1}), T_{fus} is the melting point of the solute, and T is the absolute temperature of the solution.[9] On the other hand, the real solubility (X_2) is calculated by adding the non-ideality term, ($\log \gamma_2$), to Equation 1 in order to obtain the following expression,[10]

$$-\log X_2 = \frac{\Delta H_{fus}\left(T_{fus} - T\right)}{2.303RT_{fus}T} + \log \gamma_2 \quad (2)$$

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The γ_2 term is the activity coefficient of the solute and it must be determined experimentally for real solutions. Nevertheless, several techniques have been developed in order to obtain reasonable estimates of this term. One of these methods is the referent to regular solutions, in which, opposite to ideal solutions, a little positive enthalpic change is allowed.[10] The solubility in regular solutions is obtained from,

$$-\log X_2 = \frac{\Delta H_{fus}\left(T_{fus}-T\right)}{2.303RT_{fus}T} + \frac{V_2\phi_1^{\,2}}{2.303RT}\left(\delta_1-\delta_2\right)^2 \quad (3)$$

where, V_2 is the partial molar volume of the solute ($cm^3\ mol^{-1}$), ϕ_1 is the volume fraction of the solvent in the saturated solution, and δ_1 and δ_2 are the solubility parameters of solvent and solute, respectively. The solubility parameter, δ, is calculated as $(\Delta H_v - RT)/V_l)^{1/2}$, where, ΔH_v is the vaporization enthalpy and V_l is the molar volume of the liquid.

The vast majority of pharmaceutical dissolutions deviate notoriously of that predicted by the regular solution-theory because strong interactions are present, such as hydrogen bonding, in addition to the differences in molar volumes among solutes and solvents. For these reasons, at the beginning of the 80s of the past century, Martin *et al*. developed the EHSA method, which has been useful to estimate the solubility of several drugs in binary and ternary cosolvent systems.[3] Accordingly, if the *A* term (defined as $V_2\phi_1^2/(2.303RT)$) is introduced in the Equation 3, the real solubility of drugs and other compounds in any solvent can be calculated from the expression,

$$-\log X_2 = -\log X_2^{id} + A\left(\delta_1^2+\delta_2^2-2W\right) \quad (4)$$

where W is equal to $2K\delta_1\delta_2$ and K is the Walker parameter.[11] The W factor compensates the deviations observed with respect to the behavior of regular solutions, and it can be calculated from experimental data by means of the following expression,

$$W = 0.5\times\left(\delta_1^2+\delta_2^2-\frac{\log\gamma_2}{A}\right) \quad (5)$$

where, γ_2 is the activity coefficient of the solute in the saturated solution, and is calculated as X_2^{id}/X_2.

The experimental values obtained for the W parameter can be correlated by means of regression analysis by using regular polynomials in superior order as a function of the solubility parameter of the solvent mixtures, as follows,

$$W = C_0 + C_1\delta_1 + C_2\delta_1^{\,2} + C_3\delta_1^{\,3} ..... + C_n\delta_1^{\,n} \quad (6)$$

These empiric models can be used to estimate the drug solubility by means of back-calculation to resolve this property from the specific W value obtained in the respective polynomial regression.[3,5,7]

EXPERIMENTAL

All reagents, materials, and procedures employed in this work have been reported earlier and were as follows.[9]

Reagents and materials

In this investigation the following reagents and materials were used: indomethacin (CAS: [53-86-1], 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid, purity at least 0.998 in mass fraction)[1] accomplishing the British Pharmacopoeia quality requirements,[12] 1,4-dioxane A.R. Scharlau, distilled water with conductivity < 2 μS cm^{-1}, molecular sieve Merck (numbers 3 and 4, pore size 0.3 and 0.4 nm, respectively), and Durapore® 0.45 μm filters from Millipore Corp.

Solvent mixtures preparation

All 1,4-dioxane + water solvent mixtures were prepared by mass, using an Ohaus Pioneer TM PA214 analytical balance with sensitivity ± 0.1 mg, in quantities of 50 g. The mass fractions of 1,4-dioxane of the twelve binary mixtures prepared varied by 0.10 from 0.10 to 0.70 and by 0.05 from 0.75 to 0.95.

Solubility determination

An excess of IMC was added to approximately 10 g of each solvent mixture or neat solvent, in stoppered dark glass flasks. Solid-liquid mixtures were placed in re-circulating thermostatic baths (Neslab RTE 10 Digital One Thermo Electron Company) kept at 298.15 (± 0.05) K for at least 7 days to reach the equilibrium. In the case of neat water or water-rich mixtures the equilibration time was 14 days. These equilibrium times were established by measuring the drug concentrations till they became constant. After this time the supernatant solutions were filtered (at isothermal conditions) to ensure that they were free of particulate matter before sampling. Drug concentrations were determined after appropriate dilution by measuring the light absorbance and interpolation from a previously constructed UV spectrophotometry calibration curve (UV/VIS Bio-Mate 3 Thermo Electron Company spectrophotometer). In order to make the equivalence between volumetric and gravimetric concentration scales, the density of the saturated solutions was determined with a digital density meter (DMA 45 Anton Paar) connected to the same recirculating thermostatic bath. All the solubility experiments were run in triplicate at least.

Estimation of the volumetric contributions

Because the Equations 3 to 5 require the volume contributions of each component to the saturated solution, in this investigation the IMC apparent specific volume (ϕ_V^{spc}) was used to calculate these contributions. The ϕ_V^{spc} values were calculated according to Equation 7,[13]

$$\phi_V^{spc} = \frac{m_2 + m_1(1-VE_1\rho_{soln})}{m_2\rho_{soln}} \quad (7)$$

where, m_2 and m_1 are the masses of solute and solvent in the saturated solution, respectively, VE_1 is the specific volume of the solvent, and ρ_{soln} is the solution density. The IMC apparent molar volume is calculated by multiplying the ϕ_V^{spc} value and the molar mass of the solute (357.8 g mol^{-1}).[1] Otherwise, the calculated molar volume value obtained by means of the Fedors method was used in all calculations and it was taken from the literature (230.0 $cm^3\ mol^{-1}$).[8]

RESULTS AND DISCUSSION

The information about polarity and volumetric behavior of 1,4-dioxane + water mixtures as a function of the composition is shown in Table 1.[14] On the other hand, the calorimetric values reported in the literature for IMC were as follows, T_{fus} = 432.6 K and ΔH_{fus} = 39.46 kJ mol^{-1}.[15] From these values the calculated ideal solubility for this drug was 7.123×10^{-3} in mole fraction at 298.15 K.[8] This value was calculated according to Equation 1.

Table 2 summarizes the experimental IMC solubility expressed in molarity and mole fraction, the density of the saturated mixtures, the apparent molar volume of IMC, and the solvent volume fraction in

Table 1. Solvent composition in mass and volume fraction of 1,4-dioxane (without considering IMC) in 1,4-dioxane + water mixtures, density, and Hildebrand solubility parameters at 298.15 K

1,4-dioxane mass fraction	1,4-dioxane volume fraction	ρ_1 / g cm^{-3}	δ_1 / MPa$^{1/2}$
0.0000	0.0000	0.9970	47.8
0.1000	0.0974	1.0052	45.1
0.2000	0.1953	1.0138	42.5
0.3000	0.2938	1.0216	39.8
0.4000	0.3929	1.0280	37.1
0.5000	0.4926	1.0328	34.4
0.6000	0.5928	1.0356	31.6
0.7000	0.6937	1.0361	28.9
0.7500	0.7444	1.0357	27.5
0.8000	0.7952	1.0348	26.1
0.8500	0.8462	1.0333	24.7
0.9000	0.8973	1.0315	23.3
0.9500	0.9486	1.0294	21.9
1.0000	1.0000	1.0271	20.5

the saturated solutions, at 298.15 K. The uncertainty in experimental solubility was lower than 1.2% from the mean. Figure 2 shows the experimental solubility and the calculated solubility by using the regular solution model (Equation 3) as a function of the solubility parameter of solvent mixtures. It is clear that experimental solubility is greater than calculated solubility probably due to strong hydrogen-bonding interactions between drug and solvents. This behavior is more evident in mixtures with δ_1 lower than 32 MPa$^{1/2}$.

The IMC solubility is greater in the mixture of 0.95 in mass fraction of 1,4-dioxane (X_2 = 3.99 x 10^{-2} with δ_1 = 21.9 MPa$^{1/2}$), but this value is slightly greater than the maximum obtained in the mixture of 0.70 in mass fraction of ethyl acetate in mixtures conformed by ethyl acetate + ethanol (X_2 = 3.00 x 10^{-2} with δ_1 = 20.86 MPa$^{1/2}$).[8] It is important to note that the maximum solubility is obtained at similar

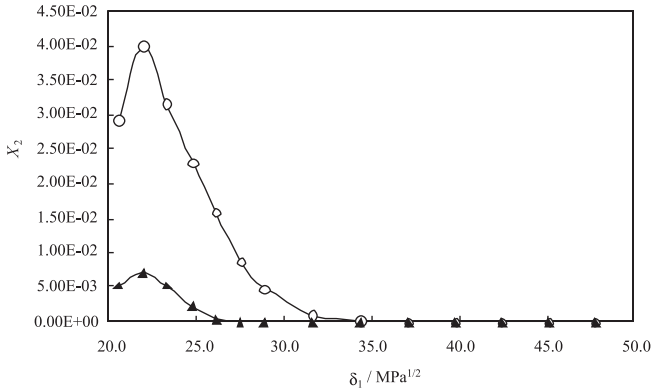

Figure 2. *Experimental solubility (○) and calculated solubility according to the regular solution model of Hildebrand (▲) of IMC as a function of the solubility parameter of the solvent mixtures at 298.15 K. IMC experimental solubilities were taken from Table 2, Column 3*

but slightly different mixtures-solubility parameters in both binary solvent systems. Otherwise, similar but slightly different solubility values were also found in both systems. This result could be interpreted in terms of different Lewis acid or base interactions. Besides, the main reason to obtain the maximum solubility of this drug in the mixture of 0.95 in mass fraction of 1,4-dioxane is referent to similar polarities between drug and solvent mixture in agreement with the expression "like dissolves like".[5]

From density values of cosolvent mixtures and saturated solutions (Tables 1 and 2), in addition to IMC solubility (Table 2), the solvent volume fraction (ϕ_1) and apparent molar volume of the solute (ϕ_V^{mol}) in the saturated mixtures, were calculated. These values are also presented in Table 2.

In the literature the solute molar volume in the saturated solution has been considered as a constant value when EHSA method is used.[5,11] On this way, for solid compounds this property is generally calculated by means of groups' contribution methods such as the one developed by Fedors.[16] Nevertheless, this property is not independent on the solvent composition as can be see in Table 2 for apparent molar volume of IMC. This fact would be due to the different intermole-

Table 2. Hildebrand solubility parameter of mixtures, IMC solubility expressed in molarity and mole fraction, density of the saturated mixtures, apparent molar volume of IMC, solvent volume fraction in the saturated solutions, and activity coefficient of IMC expressed as decimal logarithm, at 298.15 K

δ_1 / MPa$^{1/2}$	IMC		$\rho_{satd\ soln}$ / g cm^{-3}	ϕ_V^{mol} / cm^3 mol^{-1}	ϕ_1	log γ_2
	Mol L^{-1}	X_2				
47.8	5.16×10^{-5}	9.32×10^{-7}	0.9970	358.9	1.0000	3.883
45.1	1.19×10^{-4}	2.32×10^{-6}	1.0052	355.9	1.0000	3.487
42.5	2.17×10^{-4}	4.60×10^{-6}	1.0138	352.9	0.9999	3.190
39.8	4.28×10^{-4}	9.92×10^{-6}	1.0216	350.2	0.9999	2.856
37.1	1.72×10^{-3}	4.42×10^{-5}	1.0280	348.0	0.9996	2.207
34.4	7.23×10^{-3}	2.10×10^{-4}	1.0330	315.2	0.9983	1.531
31.6	3.17×10^{-2}	1.06×10^{-3}	1.0378	279.4	0.9927	0.826
28.9	0.122	4.93×10^{-3}	1.0467	261.3	0.9719	0.160
27.5	0.192	8.64×10^{-3}	1.0507	269.8	0.9559	–0.084
26.1	0.308	1.59×10^{-2}	1.0549	282.6	0.9291	–0.349
24.7	0.390	2.30×10^{-2}	1.0595	281.4	0.9103	–0.510
23.3	0.464	3.17×10^{-2}	1.0647	277.4	0.8933	–0.648
21.9	0.502	3.99×10^{-2}	1.0704	268.3	0.8846	–0.748
20.5	0.319	2.90×10^{-2}	1.0551	262.8	0.9266	–0.610

cular interactions, depending on the respective solvent proportions. Nevertheless, great variability is found in the experimental ϕ_V^{mol} values without a rational order. In particular, the great difference obtained in water-rich mixtures (greater than 315 $cm^3\ mol^{-1}$) and those obtained in 1,4-dioxane-rich mixtures (lower than 280 $cm^3\ mol^{-1}$) is anomalous. For these reasons, in this investigation the calculated molar volume of IMC (230.0 $cm^3\ mol^{-1}$) was employed in the following calculations as was made with this drug in ethanol + water mixtures.[8] Otherwise, no significant differences in the predictive character of EHSA were obtained in other investigations when experimental or calculated values of drug molar volumes were interchanged.[7]

On the other hand, according to the literature the volume fraction of the solvent mixture in the saturated solution has been calculated by means of the expression,[5,11]

$$\phi_1 = \frac{V_1(1-X_2)}{V_1(1-X_2)+V_2X_2} \quad (8)$$

where, V_1 is the molar volume of the solvent which is calculated for solvent mixtures assuming additive volumes as,[17]

$$V_{1mix} = \sum_{i=1}^{n} V_{1i}\varphi_i \quad (9)$$

Nevertheless, it is well known that the mixing volumes are not additives in those mixtures with strong presence of hydrogen bonding and great differences in molar volumes. For this reason, the experimental solvent volume fractions were used in this investigation for all the calculations (Table 2). Solvent volume fractions were calculated by subtracting the respective drug volume contributions. The last values were calculated from molar volumes and concentrations of the drug at saturation for each cosolvent mixture.

Ultimately, the activity coefficients of IMC as decimal logarithms are also presented in Table 2. These values were calculated from experimental solubility values (Table 2) and ideal solubility at 298.15 K ($X_2 = 7.123 \times 10^{-3}$).[8] γ_2 values in water-rich mixtures were greater than unit because the experimental solubilities are lower than the ideal one.

On the other hand, the parameters *A*, *K*, and *W* are presented in Table 3. In order to calculate the *W* parameter the experimental solubility parameter of IMC obtained in the mixture of 0.95 in mass fraction of 1,4-dioxane (with $\delta_1 = 21.9\ MPa^{1/2}$) was used. According with the literature, this δ_2 value is the same of the solvent mixture where the greatest drug solubility was found.[5,11]

Table 3. *A*, *K*, and *W* parameters for IMC in 1,4-dioxane + water mixtures at 298.15 K

δ_1 / $MPa^{1/2}$	10^2 *A* / $cm^3\ J^{-1}$	*K* / J cm^{-3} [a]	W_{expt} / J cm^{-3} [a]
47.8	8.00566	0.648617	1357.970
45.1	8.00541	0.625590	1236.934
42.5	8.00505	0.603009	1121.676
39.8	8.00427	0.581498	1013.169
37.1	7.99952	0.562403	913.261
34.4	7.97924	0.545157	820.277
31.6	7.88963	0.530300	734.336
28.9	7.56219	0.518332	655.241
27.5	7.31568	0.513404	617.909
26.1	6.91153	0.509893	582.700
24.7	6.63405	0.507175	548.683
23.3	6.38883	0.505937	516.416
21.9	6.26509	0.506222	485.669
20.5	6.87359	0.506033	454.367

[a] 1 J cm^{-3} = 1 MPa

As has been already indicated, the *W* parameter accounts for the deviations presented by real solutions with respect to regular solutions. These deviations are mainly due to specific interactions such as hydrogen bonding. IMC (Figure 1) and both solvents studied can establish these interactions, as hydrogen donors or acceptors because of their polar moieties, in particular due to –OH groups. 1,4-dioxane interacts just as hydrogen acceptor.

Figure 3 shows that the variation of the *W* parameter with respect to the solubility parameter of solvent mixtures, presents deviation from linear behavior. *W* values were adjusted to regular polynomials in orders from 1 to 5 (Equation 6) and their coefficients and statistical parameters are presented in the Table 4 (the empirical regressions were obtained by using MS Excel® and TableCurve 2D v5.01). The obtained *W* values by using the respective regular polynomials are presented in Table 5. It is clear that these values depend on the model used in the *W* back-calculation. Similar behaviors have been reported in the literature for several other compounds.[3,7,8]

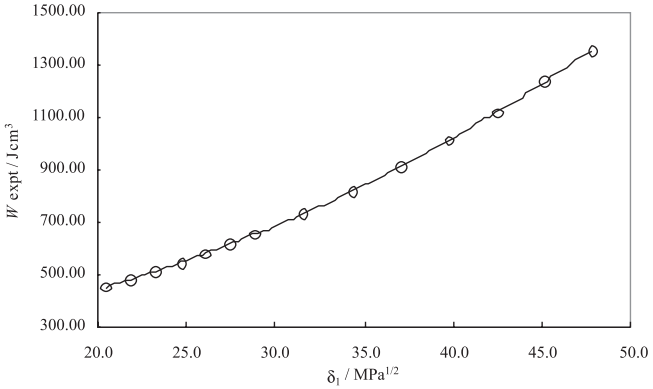

Figure 3. *Variation of the W parameter as a function of the solubility parameter of the solvent mixtures at 298.15 K*

Table 6 summarizes all the calculated drug solubility values. These solubilities were calculated employing the *W* values which were obtained by back-calculation from the polynomial models presented in Tables 4 and 5. Because we are searching the best adjust, the first criterion used to define the polynomial order of *W* as function of δ_1 was the fitting standard uncertainties obtained, whose values were as follows, 32.6, 1.61, 0.644, 0.403, and 0.427 (Table 4), for orders 1 to 5, respectively. As another comparison criterion, Table 6 also summarizes the percentages of difference between IMC experimental solubility and those calculated by using EHSA.

According to Table 6 it follows that, as more complex the polynomial used is, better the agreement found between experimental and calculated solubility is. This fact is confirmed based on the mean deviation percentages (8.9 and 8.8%, for orders 4 and 5, respectively). In similar way to that found in other similar investigations,[3,7,8] in this case, the most important increment in concordance is obtained passing from order 1 to order 2 (from 1.88 x 10^7 to 47.8% in mean deviation). It is remarkable that mole fractions greater than unit are found between 0.40 and 0.75 in mass fraction of 1,4-dioxane by using order 1, which of course is not logic. Otherwise, significant increment in concordance is also obtained by passing from order 2 to order 3 (from 47.8 to 15.7%). Therefore, in the following calculations the model with lowest fitting uncertainty was used (order 4, Table 4).

An important consideration about the usefulness of the EHSA method is the one referent to justify the complex calculations involving any other variables of the considered system (Equation 4, Tables

Table 4. Coefficients and statistical parameters for the regular polynomials of *W* vs. Solubility parameters of solvent mixtures free of IMC (Equation 6). Values in parentheses are the respective uncertainties

Coefficient or Parameter	Polynomial order				
	1	2	3	4	5
C_0	–260 (34)	271 (8)	172 (13)	20 (38)	57 (194)
C_1	32.6 (1.0)	–1.1 (0.5)	8.3 (1.2)	28 (5)	22 (31)
C_2	-	0.498 (0.007)	0.21 (0.04)	–0.70 (0.23)	–0.3 (1.9)
C_3	-	-	$2.8\ (0.4) \times 10^{-3}$	$2.1\ (0.5) \times 10^{-2}$	$1\ (6) \times 10^{-2}$
C_4	-	-	-	$1.4\ (0.3) \times 10^{-4}$	$3\ (9) \times 10^{-5}$
C_5	-	-	-	-	$-1\ (5) \times 10^{-6}$
r^2	0.988	1.000	1.000	1.000	1.000
Fit. Err.	32.6	1.61	0.644	0.403	0.427

Table 5. *W* parameters (J cm^{-3})[a] back-calculated by using several polynomial models at 298.15 K

δ_1 / MPa$^{1/2}$	Polynomial order				
	1	2	3	4	5
47.8	1297.730	1356.449	1358.718	1358.119	1358.100
45.1	1211.103	1236.318	1236.015	1236.565	1236.603
42.5	1123.965	1122.578	1121.036	1121.640	1121.650
39.8	1036.312	1015.348	1013.598	1013.760	1013.738
37.1	948.139	914.750	913.511	913.179	913.152
34.4	859.442	820.908	820.572	819.985	819.980
31.6	770.215	733.949	734.572	734.085	734.105
28.9	680.455	654.002	655.289	655.199	655.225
27.5	635.373	616.698	618.095	618.245	618.261
26.1	590.156	581.197	582.493	582.847	582.848
24.7	544.802	547.515	548.453	548.913	548.896
23.3	499.313	515.669	515.943	516.335	516.308
21.9	453.686	485.676	484.931	484.991	484.973
20.5	407.921	457.553	455.386	454.745	454.773

[a] 1 J cm^{-3} = 1 MPa

1 to 5), instead of the simple empiric regression of the experimental solubility as a function of the solvent mixtures' solubility parameters (Table 2, Figure 4). For this reason, in the Table 7 the experimental solubilities are confronted to those calculated directly by using a regular polynomial in grade 4 of log X_2 as a function of δ_1 values (Equation 10, with determination coefficient $r^2 = 0.999$ and fitting standard uncertainty = 0.054) and are also confronted to those calculated involving the *W* parameters obtained from Equation 6 adjusted to order 4 (Table 4). The respective difference percentages are also presented in Table 7.

$$\log X_2 = -34(5) + 3.9(0.7)\delta_1 - 0.16(0.03)\delta_1^2 + 2.8(0.6)\times10^{-3}\delta_1^3 - 1.7(0.4)\times10^{-5}\delta_1^4 \quad (10)$$

Based on mean deviation percentages presented in Table 7 (8.1 and 8.9% for direct calculation and EHSA method, respectively) it follows that non-significant differences are found between the values obtained by using both methods. In similar way with that found for IMC in ethyl acetate + ethanol and ethanol + water mixtures,[8] the present results would be showing non-significant usefulness of EHSA method for practical purposes. The last point apparently could be controversial

Table 6. Calculated solubility of IMC in 1,4-dioxane + water mixtures by using the *W* parameters obtained from regression models in orders 1, 2, 3, 4 and 5, and difference-percentages with respect to the experimental value at 298.15 K

δ_1 / MPa$^{1/2}$	X_2 calculated					% dev.[a]				
	1	2	3	4	5	1	2	3	4	5
47.8	2.11×10^{-16}	5.32×10^{-7}	1.23×10^{-6}	9.84×10^{-7}	9.77×10^{-7}	100.0	42.9	31.7	5.6	4.9
45.1	1.70×10^{-10}	1.85×10^{-6}	1.65×10^{-6}	2.02×10^{-6}	2.05×10^{-6}	100.0	20.3	28.8	12.7	11.5
42.5	1.07×10^{-5}	6.41×10^{-6}	3.63×10^{-6}	4.54×10^{-6}	4.55×10^{-6}	132.5	39.4	21.0	1.3	1.0
39.8	5.03×10^{-2}	2.22×10^{-5}	1.16×10^{-5}	1.23×10^{-5}	1.22×10^{-5}	$5.07\times10^{+5}$	123.2	17.1	24.3	23.3
37.1	16.8	7.65×10^{-5}	4.85×10^{-5}	4.29×10^{-5}	4.25×10^{-5}	$3.80\times10^{+7}$	73.1	9.6	2.9	3.9
34.4	373	2.65×10^{-4}	2.34×10^{-4}	1.88×10^{-4}	1.88×10^{-4}	$1.78\times10^{+8}$	26.1	11.5	10.2	10.3
31.6	487	9.23×10^{-4}	1.16×10^{-3}	9.70×10^{-4}	9.77×10^{-4}	$4.59\times10^{+7}$	13.1	8.9	8.7	8.0
28.9	32.1	3.20×10^{-3}	5.01×10^{-3}	4.86×10^{-3}	4.90×10^{-3}	$6.51\times10^{+5}$	35.1	1.7	1.4	0.6
27.5	3.10	5.75×10^{-3}	9.20×10^{-3}	9.68×10^{-3}	9.73×10^{-3}	$3.58\times10^{+4}$	33.5	6.5	12.0	12.6
26.1	0.171	9.86×10^{-3}	1.49×10^{-2}	1.67×10^{-2}	1.67×10^{-2}	972.9	38.0	6.4	4.8	4.8
24.7	7.04×10^{-3}	1.61×10^{-2}	2.15×10^{-2}	2.47×10^{-2}	2.46×10^{-2}	69.4	30.0	6.8	7.3	6.7
23.3	2.07×10^{-4}	2.54×10^{-2}	2.76×10^{-2}	3.09×10^{-2}	3.07×10^{-2}	99.3	19.7	13.0	2.4	3.1
21.9	3.92×10^{-6}	4.00×10^{-2}	3.22×10^{-2}	3.28×10^{-2}	3.26×10^{-2}	100.0	0.2	19.2	17.8	18.2
20.5	1.20×10^{-8}	7.95×10^{-2}	4.01×10^{-2}	3.27×10^{-2}	3.30×10^{-2}	100.0	174.1	38.0	12.7	13.7
				Mean value[b]		$1.88\times10^{+7}$	47.8	15.7	8.9	8.8
				Standard Deviation[b]		$5.38\times10^{+7}$	30.6	9.8	6.6	6.5

[a] Calculated as $100\times|X_2$ expt $- X_2$ calc$|/X_2$ expt. [b] Calculated considering the obtained values in the neat solvents and the twelve binary mixtures.

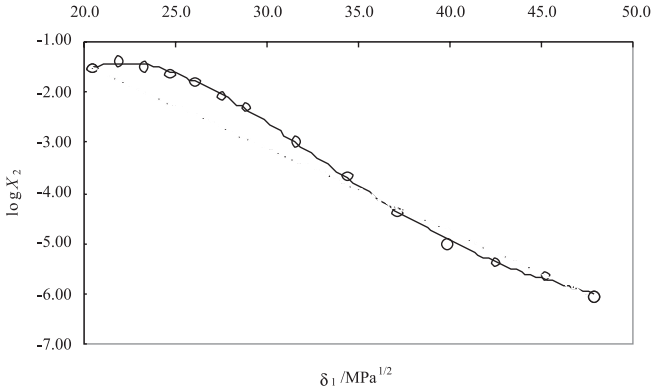

Figure 4. *Logarithmic experimental solubility of IMC as a function of the solubility parameter of the solvent mixtures at 298.15 K. Straight line corresponds to hypothetical logarithmic additive solubility in mixtures*

Table 7. Comparison of the IMC solubility values in 1,4-dioxane + water mixtures which were calculated directly and by using the EHSA

δ_1 / MPa$^{1/2}$	X_2			% dev. [a]	
	Exptl.	Calc. direct. [b]	Calc. W [c]	Calc. direct.	Calc. W
47.8	9.32×10^{-7}	1.02×10^{-6}	9.84×10^{-7}	9.1	5.6
45.1	2.32×10^{-6}	1.93×10^{-6}	2.02×10^{-6}	16.7	12.7
42.5	4.60×10^{-6}	4.38×10^{-6}	4.54×10^{-6}	4.8	1.3
39.8	9.92×10^{-6}	1.25×10^{-5}	1.23×10^{-5}	25.7	24.3
37.1	4.42×10^{-5}	4.52×10^{-5}	4.29×10^{-5}	2.2	2.9
34.4	2.10×10^{-4}	1.99×10^{-4}	1.88×10^{-4}	5.1	10.2
31.6	1.06×10^{-3}	9.73×10^{-4}	9.70×10^{-4}	8.4	8.7
28.9	4.93×10^{-3}	4.52×10^{-3}	4.86×10^{-3}	8.3	1.4
27.5	8.64×10^{-3}	8.97×10^{-3}	9.68×10^{-3}	3.8	12.0
26.1	1.59×10^{-2}	1.62×10^{-2}	1.67×10^{-2}	1.6	4.8
24.7	2.30×10^{-2}	2.55×10^{-2}	2.47×10^{-2}	10.5	7.3
23.3	3.17×10^{-2}	3.37×10^{-2}	3.09×10^{-2}	6.4	2.4
21.9	3.99×10^{-2}	3.59×10^{-2}	3.28×10^{-2}	10.0	17.8
20.5	2.90×10^{-2}	2.92×10^{-2}	3.27×10^{-2}	0.7	12.7
		Mean value [d]		8.1	8.9
		Standard Deviation [d]		7.1	6.6

[a] Calculated as $100\times|X_2$ expt $- X_2$ calc$|/X_2$ expt. [b] Calculated using the Equation 10. [c] Calculated using the Equation 6 in order 4. [d] Calculated considering the obtained values in the neat solvents and the twelve binary mixtures.

considering that EHSA method implies additional experimentation including density determinations and thermal characterization of the solid-liquid equilibrium for the solid compound. Nevertheless, it is necessary keep in mind that EHSA method considers the drug solubility from a systematic physicochemical point of view. Moreover, it would be just necessary to found an effective method to calculate the Walker K parameter in order to calculate the W term according to the expression $2K\delta_1\delta_2$, because the δ_1 and δ_2 terms would be known, and thus, the drug experimental solubility could be calculated in any mixture in particular. Otherwise, as it was already said EHSA method has been widely employed to estimate drugs solubilities since beginning 80s of the past century and it proved to be a powerful technique in pharmaceutical sciences because it uses physicochemical properties that are easily available for several kinds of drugs.

CONCLUSION

In this investigation the EHSA method has been adequately used to study the solubility of IMC in 1,4-dioxane + water mixtures by using calculated values of molar volume and estimated Hildebrand solubility parameter of this analgesic drug. In particular, a good predictive character has been found by using a regular polynomial in order 4 of the interaction parameter W vs. Solubility parameter of the solvent mixtures free of solute. Finally, this work expands the number of analgesic drugs successfully evaluated in front to EHSA method.

ACKNOWLEDGEMENTS

The authors thank to the DIB the Universidad Nacional de Colombia (UNC) for the financial support and the Department of Pharmacy of UNC for facilitating the equipments and installations used in the experimental solubility determinations.

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