Artículo de investigación científica

Estimation of the indomethacin solubility in ethanol + water mixtures by the extended Hildebrand solubility approach

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Summary

Indomethacin (IMC) is an analgesic drug whose physicochemical properties have not been thoroughly studied. In this work the Extended Hildebrand Solubility Approach (EHSA) was applied to evaluate the solubility of IMC in ethanol + water mixtures at 298.15 K. An acceptable correlative capacity of EHSA was found using a regular polynomial model in order four (overall deviation lower than 4.1%), when the *W* interaction parameter is related to the solubility parameter of the mixtures. Besides, the deviations obtained in the estimated solubility with respect to experimental solubility were lower compared with those obtained directly by means of an empiric regression of the experimental solubility as a function of the mixtures' solubility parameters.

Key words: Binary mixtures, Extended Hildebrand Solubility Approach, Indomethacin, Solubility parameter.

Resumen

Método extendido de Hildebrand en la estimación de la solubilidad de la indometacina en mezclas etanol + agua

La indometacina (IMC) es un analgésico cuyas propiedades fisicoquímicas aún no han sido totalmente estudiadas. En la presente investigación, se aplicó el Método Extendido de Solubilidad de Hildebrand (MESH) al estudio de la solubilidad de la IMC en mezclas binarias etanol + agua a 298,15 K. Se obtuvo una capacidad predictiva aceptable del MESH (desviación general inferior al 4,1%) al utilizar un modelo polinómico regular de cuarto orden relacionando el parámetro de interacción *W* con el parámetro de solubilidad de las mezclas solventes. De esta forma, las desviaciones obtenidas en la solubilidad estimada, fueron de magnitud inferior a las obtenidas al calcular esta propiedad directamente, utilizando una regresión empírica regular del mismo orden, de la solubilidad experimental del fármaco en función del parámetro de solubilidad de las mezclas disolventes.

Palabras clave: Indometacina, Método Extendido de Solubilidad de Hildebrand, Mezclas binarias, Parámetro de solubilidad.

Introduction

Indomethacin (IMC, Fig. 1) is a non-steroidal anti-inflammatory drug used as analgesic and antipyretic, among other indications (1, 2). In the Colombian market this drug is available as capsules, oil ophthalmic drops, and injectable powder for reconstitution intended to intramuscular administration, but it is not available as any homogeneous liquid dosage form (3). Although IMC is used in therapeutics, the physicochemical information about its solubility is not abundant. On this way, it is well known that several physicochemical properties such as, the solubility of active ingredients and excipients close to the respective occupied volumes in useful solutions, are very important for the pharmaceutical scientist, because they facilitate the processes associate to design and development of new products in the pharmaceutical industries (4). In view of the facts, there is considerable scope for the study the behavior of IMC in hydroalcoholic solutions. Taking into account that IMC is practically insoluble in water by the low polarity in comparison with that, the hydroalcoholic solution reduces the polarity of the medium and is expected then an increase of IMC solubility.

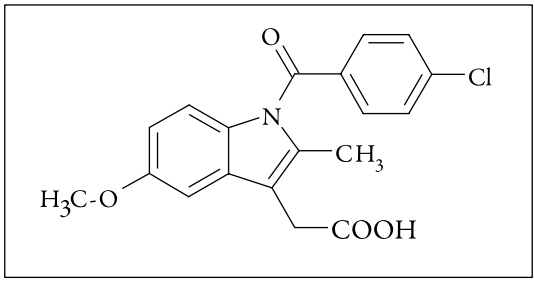

Figure 1. Molecular structure of indomethacin.

For these reasons, this report presents a physicochemical study about the solubility prediction of IMC in binary mixtures conformed by ethanol 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 (5-7). 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 (8, 9). This report expands the information presented about the solubility prediction of other analgesic drugs by means of EHSA method (10-14) including the one developed recently for this drug in ethyl acetate + ethanol mixtures (15).

Theoretical

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

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

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. On the other hand, the real solubility (X_2) is calculated by adding the non-ideality term, ($\log \gamma_2$), to equation 1 (16, 17), in order to obtain the following expression,

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

The γ_2 term is the activity coefficient of the solute and it must be determined experimentally in the case of 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 (18). The solubility in regular solutions is obtained from,

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

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 $\left((\Delta H_v - RT)/V_l\right)^{1/2}$, 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 solutions theory (because of the strong interactions present, such as hydrogen bonding, in addition to the differences in molar volumes among solutes and solvents). On this way, 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 (5-7). 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,

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

where, the W term is equal to $2K\delta_1\delta_2$ (where, K is the Walker parameter, Ref. 16). 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,

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

where, γ_2 is the activity coefficient of the solute in the saturated solution, and it is calculated as the quotient, 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,

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

These empiric models can be used to estimate the drug solubility by means of back-calculation resolving this property from the specific *W* value obtained in the respective polynomial regression.

Experimental

Reagents

Indomethacin [1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid, CAS: 53-86-1] used was in agreement with the quality requirements indicated in the British Pharmacopoeia, BP (19). In similar way, absolute ethanol A.R. Merck (EtOH), distilled water with conductivity < 2 μS cm^{-1}, and Millipore Corp. Swinnex®-13 filter units, were also used.

Solvent mixtures preparation

The dehydrated ethanol employed was maintained over molecular sieve (Merck Number 3, 0.3 nm in pore diameter) to obtain a dry solvent previously to prepare the solvent mixtures. The ethanol dryness was demonstrated by the respective density value obtained (0.7854 g cm^{-3} at 298.15 K), which was thus coincident with those reported in the literature (20, 21). All EtOH + water solvent mixtures were prepared in quantities of 50.00 g by mass using an Ohaus Pioneer TM PA214 analytical balance with sensitivity ± 0.1 mg, in mass fractions from 0.10 to 0.90 varying by 0.10, in order to study nine mixtures and both pure solvents.

Solubility determination

An excess of IMC was added to each cosolvent mixture evaluated in stoppered dark glass flasks. Solid-liquid mixtures were placed on a thermostatic bath (Neslab RTE 10 Digital One Thermo Electron Company) kept at 298.15 ± 0.05 K with sporadic stirring for at least seven days to reach the saturation equilibrium (this equilibrium time was established by quantifying the IMC concentration up to obtain a constant value). In the case of neat water or water-rich mixtures the equilibration time was 14 days. Once at equilibrium, supernatant solutions were filtered (at isothermal condi-

tions) to remove insoluble particles before composition analysis. IMC concentrations in neat EtOH and the EtOH + W mixtures up to 0.40 in mass fraction of water were determined by mass balance by weighing a specified quantity of the respective saturated solutions and allowing the solvent evaporation up to constant masses. In the other hand, IMC concentrations in all the other systems studied (from 0.50 in mass fraction of water to pure water) were determined by measuring UV-absorbance after appropriate gravimetric dilutions with ethanol and interpolation from a previously constructed UV spectrophotometric calibration curve (UV/VIS BioMate 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.

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 (22),

$$\phi_V^{spc} = \frac{m_2 + m_1\left(1 - VE_1\rho_{soln}\right)}{m_2\rho_{soln}} \qquad \text{(Equation 7)}$$

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}, Ref. 1). Otherwise, the calculated molar volume value obtained by means of the Fedors method was used in the later calculations and it was taken from the literature (230.0 cm^3 mol^{-1}, Ref. 15).

Results and Discussion

The information about polarity and volumetric behavior of EtOH + water mixtures as a function of the composition is shown in Table 1 and it was taken from the literature (13, 14, 23). It is important to note that the solubility parameter values of the solvent medium are in good agreement with those obtained from experimental permittivity data (24), which were thus calculated by using the Paruta equation (25). 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} (26). From these values the calculated ideal solubility for this drug was 7.123 × 10^{-3} in mole fraction (15).

Table 1 also summarizes the 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 the saturated solutions at 298.15 K. 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.

The IMC solubility is greater in EtOH but this value is lower than the obtained in the mixture of 0.6720 in volume fraction of ethyl acetate in mixtures conformed by ethyl acetate + EtOH (whose mixture has $\delta_1 = 20.86$ MPa$^{1/2}$)(15).

Table 1. Solvent composition in volume fraction (without considering the solute), Hildebrand solubility parameter of mixtures, IMC solubility expressed in mass percent and in mole fraction, density of the saturated mixtures, apparent molar volume of IMC, solvent volume fraction in the saturated solutions, and activity coefficient of IMC as decimal logarithm, at 298.15 K.

φ EtOH	δ_1 / MPa$^{1/2}$	IMC		$\rho_{\text{satd soln}}$ / g cm^{-3}	ϕ_V^{mol} / cm^3 mol^{-1}	ϕ_1	$\log\gamma_2$
		Mol L^{-1}	X_2				
0.0000	47.80	5.16×10^{-5}	9.32×10^{-7}	0.9970	358.9	1.0000	3.883
0.1236	45.17	7.67×10^{-5}	1.50×10^{-6}	0.9806	−5395.6	1.0000	3.676
0.2409	42.67	1.44×10^{-4}	3.06×10^{-6}	0.9665	848.5	1.0000	3.367
0.3524	40.29	4.95×10^{-4}	1.15×10^{-5}	0.9516	−1111.8	0.9999	2.793
0.4584	38.04	1.77×10^{-3}	4.53×10^{-5}	0.9323	242.6	0.9996	2.197
0.5594	35.89	5.61×10^{-3}	1.60×10^{-4}	0.9121	−11.5	0.9987	1.649
0.6557	33.83	1.44×10^{-2}	4.63×10^{-4}	0.8892	246.9	0.9967	1.187
0.7476	31.88	2.89×10^{-2}	1.06×10^{-3}	0.8682	232.5	0.9934	0.829
0.8355	30.00	5.16×10^{-2}	2.18×10^{-3}	0.8469	248.5	0.9881	0.514
0.9195	28.21	6.86×10^{-2}	3.40×10^{-3}	0.8259	212.2	0.9842	0.322
1.0000	26.50	7.01×10^{-2}	4.17×10^{-3}	0.7966	249.8	0.9839	0.233

From density values of cosolvent mixtures (23) and saturated solutions (Table 1), in addition to IMC solubility (Table 1), the solvent volume fraction (ϕ_1) and apparent molar volume of the solute $\left(\phi_V^{\text{mol}}\right)$ in the saturated mixtures, were calculated. These values are also presented in Table 1.

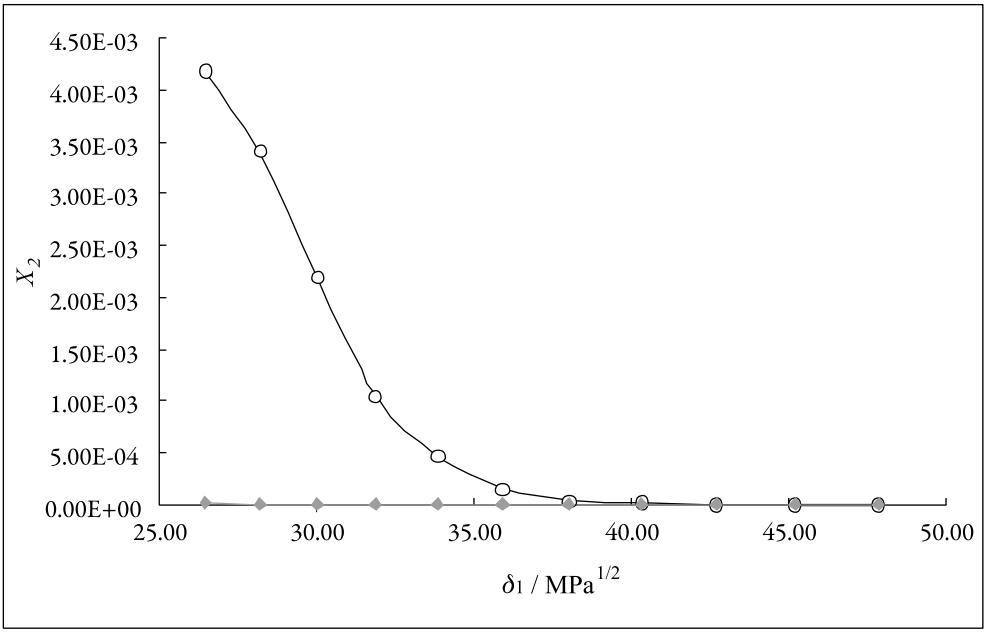

Figure 2. Experimental solubility (o) and calculated solubility according to the regular solutions model of Hildebrand (◊) of IMC as a function of the solubility parameter of the solvent mixtures at 298.15 K.

In the literature (16, 17), the solute molar volume in the saturated solution has been considered as a constant value when EHSA method is used. On this way, for solid compounds this property is generally calculated by means of groups' contribution methods such as developed by Fedors (27). Nevertheless, this property is not independent on the solvent composition as can be see in Table 1 for apparent molar volume of IMC. This fact would be due to the different intermolecular interactions, depending on the respective solvent proportions. Nevertheless, the experimental values are variable and unclear, in particular for water-rich mixtures, where negative values were obtained. For this reason, in this investigation the calculated molar volume (230.0 cm^3 mol^{-1}, Ref. 15) was employed in the following calculations.

On the other hand, according to the literature (16, 17), the volume fraction of the solvent mixture in the saturated solution has been calculated by means of the expression,

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

where, V_1 is the molar volume of the solvent (calculated for solvent mixtures as $V_{1mix} = \sum_{i=1}^{n} V_{1i}\varphi_i$, assuming additive volumes). 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 among their components. For this reason, the experimental volume fractions were used in this investigation for all the calculations involved (Table 1).

Ultimately, the activity coefficients of IMC as decimal logarithms are also presented in Table 1. These values were calculated from experimental solubility values (Table 1) and ideal solubility at 298.15 K ($X_2 = 7.123 \times 10^{-3}$). In all cases, γ_2 values 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 2. In order to calculate the *W* parameter the experimental solubility parameter of IMC obtained in ethyl acetate + ethanol mixtures (20.86 $MPa^{1/2}$) was used. This δ_2 value is the same of the solvent mixture where the greatest drug solubility was found (15).

Table 2. *A*, *K*, and *W* experimental parameters for IMC in EtOH + 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]
47.80	8.00566	0.669805	1335.736
45.17	8.00557	0.644585	1214.629
42.67	8.00532	0.621774	1106.832
40.29	8.00403	0.601957	1011.939
38.04	7.99933	0.584304	927.211
35.89	7.98519	0.568497	851.109
33.83	7.95285	0.554333	782.467
31.88	7.89986	0.541677	720.349
30.00	7.81695	0.530775	664.412
28.21	7.75536	0.521212	613.515
26.50	7.74964	0.513028	567.193

[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 (Fig. 1) and both solvents stu-

died can establish these interactions, as hydrogen donors or acceptors because of their polar moieties, in particular due to –OH groups.

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 3 (the empirical regressions were obtained by using MS Excel® and TableCurve 2D v5.01). The *W* values calculated by using the respective regular polynomials are presented in Table 4. It is well 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 (5-7, 10-17).

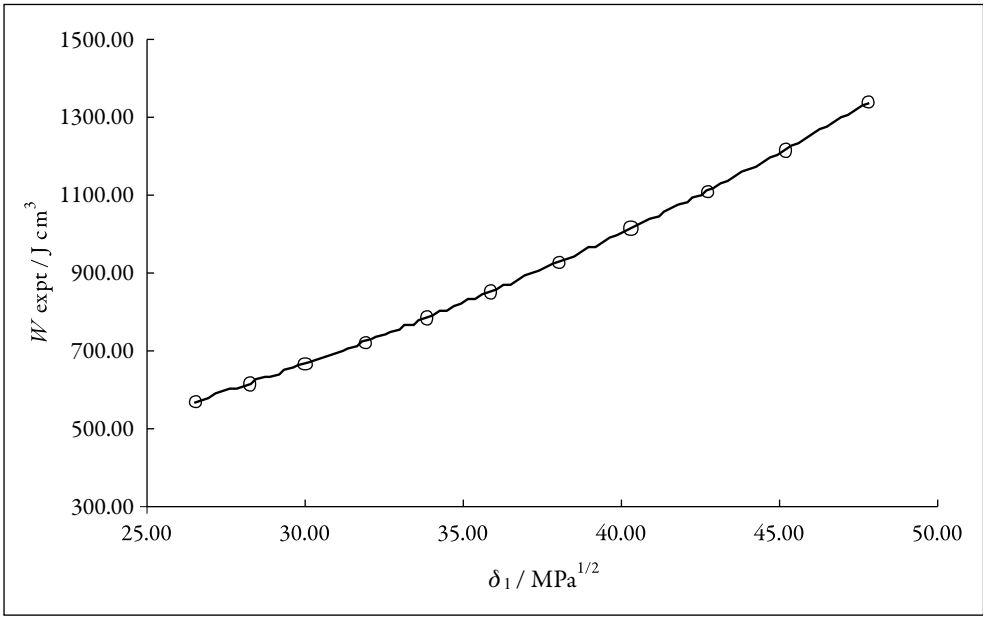

Figure 3. Variation of the *W* parameter as a function of the solubility parameter of the solvent mixtures at 298.15 K.

Table 3. Coefficients and statistical parameters of regular polynomials in several orders of W as a function of solubility parameters of cosolvent mixtures free of indomethacin (equation 6). Values in parentheses are the respective uncertainties.

Coefficient or Parameter	Polynomial order				
	1	2	3	4	5
C_0	–411 (36)	244 (12)	27 (16)	199 (88)	805 (611)
C_1	35.8 (1.0)	–0.9 (0.7)	17.4 (1.3)	–2 (10)	–87 (86)
C_2	-	0.496 (0.009)	–0.01 (0.04)	0.8 (0.4)	6 (5)
C_3	-	-	4.5 (0.3) $\times 10^{-3}$	–0.010 (0.007)	–0.14 (0.13)
C_4	-	-	-	1.0 (0.5) $\times 10^{-4}$	1.9 (1.8) $\times 10^{-3}$
C_5	-	-	-	-	–1.0 (1.0) $\times 10^{-5}$
r^2	0.992	1.000	1.000	1.000	1.000
Fit. Err.	22.0	1.23	0.247	0.208	0.208

Table 4. W parameters (J cm^{-3} [a]) calculated by using several polynomial models at 298.15 K.

δ_1 / MPa$^{1/2}$	Polynomial order				
	1	2	3	4	5
47.80	1298.735	1334.139	1335.694	1335.826	1335.780
45.17	1204.528	1215.139	1214.490	1214.308	1214.408
42.67	1115.141	1108.580	1107.252	1107.135	1107.112
40.29	1030.213	1013.069	1011.976	1012.013	1011.928
38.04	949.418	927.391	926.981	927.116	927.073
35.89	872.461	850.484	850.850	850.983	851.018
33.83	799.076	781.418	782.388	782.432	782.506
31.88	729.020	719.376	720.578	720.502	720.540
30.00	662.071	663.637	664.557	664.403	664.357
28.21	598.026	613.564	613.587	613.482	613.393
26.50	536.701	568.596	567.039	567.194	567.251

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

Table 5 summarizes the solubility values obtained by using the W values obtained by back-calculation from the polynomial models presented in Table 4. 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, 22.0, 1.23, 0.247, 0.208, and 0.208 (Table 3), for orders one to five, respectively. As another comparison criterion, Table 5 also summarizes the percentages of difference between IMC experimental solubility and those calculated by using EHSA.

Table 5. Calculated solubility of IMC 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 values at 298.15 K.

δ_1 / MPa$^{1/2}$	X_2 calculated					% dev.[a]				
	1	2	3	4	5	1	2	3	4	5
47.80	1.11×10^{-11}	5.17×10^{-7}	9.17×10^{-7}	9.63×10^{-7}	9.47×10^{-7}	100	44.5	1.6	3.4	1.6
45.17	3.62×10^{-8}	1.81×10^{-6}	1.43×10^{-6}	1.33×10^{-6}	1.38×10^{-6}	98	20.7	5.0	11.2	7.8
42.67	6.55×10^{-5}	5.83×10^{-6}	3.57×10^{-6}	3.42×10^{-6}	3.39×10^{-6}	2039	90.5	16.7	11.8	10.8
40.29	9.65×10^{-3}	1.74×10^{-5}	1.16×10^{-5}	1.18×10^{-5}	1.14×10^{-5}	84091	51.7	1.4	2.7	0.4
38.04	0.162	4.84×10^{-5}	4.16×10^{-5}	4.37×10^{-5}	4.31×10^{-5}	357051	6.9	8.1	3.4	4.9
35.89	0.411	1.27×10^{-4}	1.45×10^{-4}	1.52×10^{-4}	1.54×10^{-4}	256954	20.5	9.1	4.5	3.3
33.83	0.203	3.15×10^{-4}	4.49×10^{-4}	4.57×10^{-4}	4.69×10^{-4}	43742	31.9	2.8	1.2	1.5
31.88	2.47×10^{-2}	7.41×10^{-4}	1.15×10^{-3}	1.12×10^{-3}	1.13×10^{-3}	2244	29.8	8.7	5.7	7.2
30.00	9.40×10^{-4}	1.65×10^{-3}	2.30×10^{-3}	2.18×10^{-3}	2.14×10^{-3}	57	24.4	5.3	0.3	2.0
28.21	1.34×10^{-5}	3.46×10^{-3}	3.49×10^{-3}	3.36×10^{-3}	3.25×10^{-3}	100	1.8	2.6	1.2	4.3
26.50	7.83×10^{-8}	6.88×10^{-3}	3.94×10^{-3}	4.17×10^{-3}	4.26×10^{-3}	100	65.0	5.4	0.0	2.1
				Mean value[b]		67871	35.2	6.1	4.1	4.2
				Standard Deviation[b]		123221	26.1	4.5	4.0	3.2

[a] Calculated as $100\times|X_2\ \text{expt} - X_2\ \text{calc}|/X_2\ \text{expt}$. [(b)] Calculated considering the obtained values in the neat solvents and the nine binary mixtures.

According to Table 5 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 (4.1 % and 4.2 %, for orders 4 and 5, respectively). In similar way to that found in other similar investigations (4-11), in this case, the most important increment in concordance is obtained passing from order 1 to order 2 (from 67871 to 35.2 % as mean value), although significant increment is also obtained form order 2 to order 3 (from 35.2 to 6.1% as mean value). Thereby, in

the following calculations the model with lowest general deviation was used (order 4, Table 3).

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 1 to 4), instead of the simple empiric regression of the experimental solubility as a function of the solvent mixtures' solubility parameters (Table 1, Fig. 2). For this reason, in the Table 6 the experimental solubilities are confronted to those calculated directly by using a regular polynomial in order 4 of $\log X_2$ as a function of δ_1 values (Equation 9, with determination coefficient $r^2 = 0.999$ and fitting standard uncertainty = 0.033) and also to those calculated involving the W parameters obtained from equation 6 adjusted to order 4 (Table 3). The respective difference percentages are also presented in Table 6.

$$\log X_2 = -7(14) - 0.1(1.6)\delta_1 + 4(6)\times 10^{-2}\delta_1^2 - 1.5(1.2)\times 10^{-3}\delta_1^3 + 1.0(0.8)\times 10^{-5}\delta_1^4 \qquad \text{(Equation 9)}$$

Table 6. Comparison of the IMC solubility values 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
47.80	9.32×10^{-7}	9.63×10^{-7}	9.63×10^{-7}	3.3	3.4
45.17	1.50×10^{-6}	1.33×10^{-6}	1.33×10^{-6}	11.1	11.2
42.67	3.06×10^{-6}	3.42×10^{-6}	3.42×10^{-6}	11.7	11.8
40.29	1.15×10^{-5}	1.18×10^{-5}	1.18×10^{-5}	2.7	2.7
38.04	4.53×10^{-5}	4.38×10^{-5}	4.37×10^{-5}	3.4	3.4
35.89	1.60×10^{-4}	1.53×10^{-4}	1.52×10^{-4}	4.4	4.5
33.83	4.63×10^{-4}	4.57×10^{-4}	4.57×10^{-4}	1.3	1.2
31.88	1.06×10^{-3}	1.12×10^{-3}	1.12×10^{-3}	5.7	5.7
30.00	2.18×10^{-3}	2.17×10^{-3}	2.18×10^{-3}	0.4	0.3
28.21	3.40×10^{-3}	3.36×10^{-3}	3.36×10^{-3}	1.0	1.2
26.50	4.17×10^{-3}	4.17×10^{-3}	4.17×10^{-3}	0.1	0.0
		Mean value[b]		4.1	4.1
		Standard Deviation[b]		4.0	4.0

[a] Calculated as $100 \times |X_2 \text{ expt} - X_2 \text{ calc}| / X_2 \text{ expt}$. [b] Calculated using the equation 6 adjusted to order 4 (Table 3). [c] Calculated using the equation 9. [d] Calculated considering the obtained values in the neat solvents and the nine binary mixtures.

Based on mean deviation percentages presented in Table 6 (4.1% and 4.1% 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 naproxen and ketoprofen (other analgesic drugs) in the same cosolvent system (13, 14), and for IMC in ethyl acetate + ethanol mixtures (15), the present results would be showing non-significant usefulness of EHSA method for practical purposes. The last point exposed would be a big controversial subject 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 is 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.

Conclusion

In this investigation the EHSA method has been adequately used to study the solubility of IMC in EtOH + water mixtures by using experimental values of molar volume and Hildebrand solubility parameter of this analgesic drug. In particular, a good predictive character has been found by using a regular polynomial in order four of the interaction parameter *W* as a function of the solubility parameter of solvent mixtures free of solute. Form a practical viewpoint EtOH + water binary mixtures were thus constituted in good cosolvent systems for IMC, especially at higher fractions of alcohol, by generate a decrease on polarity of the medium.

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