



Revista Colombiana de Química

ISSN: 0120-2804

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Universidad Nacional de Colombia  
Colombia

Delgado, Daniel R.; Peña, María Á.; Martínez, Fleming  
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Revista Colombiana de Química, vol. 45, núm. 1, 2016, pp. 34-43  
Universidad Nacional de Colombia  
Bogotá, Colombia

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Recibido: 15 de Febrero de 2016. Aceptado: 29 de Marzo de 2016.

## Extended Hildebrand solubility approach applied to some structurally related sulfonamides in ethanol + water mixtures

### Abstract

Extended Hildebrand Solubility Approach (EHSA) was applied to evaluate the solubility of sulfadiazine, sulfamerazine, and sulfamethazine in some ethanol + water mixtures at 298.15 K. Reported experimental equilibrium solubilities and some fusion properties of these drugs were used for the calculations. In particular, a good predictive character of EHSA (with mean deviations lower than 3.0%) were found by using regular polynomials in order four correlating the interaction parameter  $W$  with the Hildebrand solubility parameter of solvent mixtures without drug. The predictive character of EHSA was the same as that obtained by direct correlation of drug solubilities with the same descriptor of polarity of the cosolvent mixtures.

**Keywords:** sulfonamides, ethanol, binary mixtures, extended Hildebrand solubility approach, Hildebrand solubility parameter.

## Método extendido de Hildebrand en la estimación de la solubilidad de algunas sulfonamidas estructuralmente relacionadas en mezclas etanol + agua

### Resumen

Se aplicó el Método Extendido de Solubilidad de Hildebrand (MESH) al estudio de la solubilidad de sulfadiazina, sulfamerazina y sulfametazina en mezclas binarias etanol + agua a 298,15 K. Se utilizaron valores reportados de solubilidad en equilibrio y algunas propiedades fisicoquímicas de fusión de estos compuestos. Se obtuvo una adecuada capacidad predictiva del MESH (con desviaciones promedio menores del 3,0%) al utilizar modelos polinómicos regulares de cuarto orden relacionando el parámetro de interacción  $W$  con el parámetro de solubilidad de Hildebrand de las mezclas solventes. El carácter predictivo del MESH fue de magnitud semejante al que se obtuvo calculando esta propiedad directamente, donde se utilizó una regresión empírica regular de cuarto orden de la solubilidad experimental logarítmica de los fármacos en función del parámetro de solubilidad de las mezclas disolventes.

**Palabras clave:** sulfonamidas, etanol, mezclas binarias, método extendido de solubilidad de Hildebrand, parámetro de solubilidad de Hildebrand.

## Método ampliado de Hildebrand na estimação da solubilidade de algumas sulfamidas estruturalmente relacionadas em misturas do etanol + água

### Resumo

Na presente investigação, aplicou-se o Método Estendido de Solubilidade do Hildebrand (MESH) ao estudo da solubilidade da sulfadiazina, sulfamerazina e sulfametazina em misturas binárias etanol + água a 298,15 K. Obteve-se uma adequada capacidade preditiva (com menor desvio padrão de 3,0%) do MESH ao utilizar modelos polinomiais regulares de quarta ordem relacionando o parâmetro de interação  $W$  com o parâmetro de solubilidade do Hildebrand das misturas de solventes. O caráter preditivo do MESH foi semelhante ao obtido pelo cálculo utilizando uma regressão empírica regular da quarta ordem, da solubilidade experimental logarítmica dos fármacos em função do parâmetro de solubilidade das misturas dissolventes.

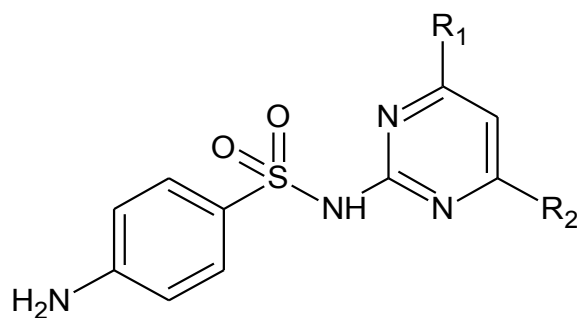
**Palavras-Chave:** sulfamidas, etanol, misturas binárias, método estendido de solubilidade do Hildebrand, parâmetro de solubilidade do Hildebrand.

## Introduction

Sulfonamides are synthetic drugs used to treat certain infections caused by a wide group of microorganisms in human and veterinary medicine practice (1-3). Nevertheless, the physicochemical properties of these drugs in aqueous solutions have not yet been studied completely (4). Regarding their aqueous solubilities, it is well known that they are very low, being considered as very slightly soluble or even practically insoluble (5). In this way, it has been reported that the cosolvency is the best technique used in pharmacy for increasing the drugs equilibrium solubility (6-8).

Moreover, it is clear that predictive methods of physicochemical properties of drugs, in particular those intended to estimate their solubilities, are very important for pharmaceutical and chemical industry. This is because these methods allow the optimization of several design and development processes (4). In this regard, some recent examples of these developments about the solubility prediction of drugs are described in the literature as follows: in neat water (9), in simulated gastrointestinal fluids (10), in organic solvents (11) and in mixed solvents (12-14). In addition, some attempts to estimate the solubility of sulfonamides in different aqueous or organic media have been reported in the literature (15-17).

For this reason, this research presents a physicochemical study about the solubility prediction of three structurally related sulfonamides, namely, sulfadiazine (SDZ, Fig. 1), sulfamerazine (SMR, Fig. 1) and sulfamethazine (SMT, Fig. 1), in binary mixtures conformed by ethanol (EtOH) and water at 298.15 K. The study was performed based on the Extended Hildebrand Solubility Approach (EHSA) (8, 18) by using reported experimental equilibrium solubility values and some thermal properties relative to the fusion of these drugs (19-21). Thus, this communication is similar to those developed previously for other drugs in the same cosolvent mixtures (22-26), and also to that developed about the behavior of other sulfonamides in propylene glycol + water mixtures (27).



**Figure 1.** Molecular structure of the sulfonamides considered. Sulfadiazine:  $R_1$  and  $R_2$  = H. Sulfamerazine:  $R_1$  = H,  $R_2$  =  $\text{CH}_3$ . Sulfamethazine:  $R_1$  and  $R_2$  =  $\text{CH}_3$ .

It is crucial to note that EHSA method has been widely used to study the solubility of many pharmaceutical compounds as has been exposed previously (28). Furthermore, it is still employed to analyze the behavior of several drugs in different cosolvent mixtures (29-32). On the other hand, it is remarkable that EtOH and its aqueous mixtures are the most employed solvent systems to develop liquid pharmaceutical dosage forms owing its solubilizing and antimicrobial properties (33, 34).

## Theoretical background

In a first approach, based on the Henry's law, the ideal solubility ( $X_2^{id}$ ) of a solid solute could be calculated by means of the following expression:

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

where  $\Delta H_{fus}$  is the molar enthalpy of fusion of the pure solute (at the melting point),  $T_{fus}$  is the absolute melting point,  $T$  is the absolute solution temperature,  $R$  is the constant gas (8.314 J/mol·K) and  $\Delta C_p$  is the difference between the molar heat capacity of the crystalline form and the molar heat capacity of the hypothetical supercooled liquid form, both at the solution temperature. Since  $\Delta C_p$  values are not commonly reported, they may be approximated to the entropy of fusion,  $\Delta S_{fus}$  calculated as follows:

$$\Delta C_p \approx \Delta S_{fus} = \frac{\Delta H_{fus}}{T_{fus}} \quad [2]$$

Ideal solubility depends on the physicochemical properties of the solid compound without considering the properties of the solvent. In this way, the ideal solubility would be higher if the solute-solute interactions are lower (35). Accordingly, compounds with high values of melting point and enthalpy of fusion have lower ideal solubilities.

On the other hand, the real solubility ( $X_2$ ) of a solid solute in a liquid solution is analyzed by means of the following expression (25-27):

$$-\log X_2 = -\log X_2^{id} + \log \gamma_2 \quad [3]$$

Here  $\log \gamma_2$  is the non-ideality term with  $\gamma_2$  as the solute activity coefficient defined on asymmetric basis. This property is determined experimentally from real and ideal solubilities. Nevertheless, a classical method of  $\gamma_2$  calculations is based on the regular solutions model as:

$$-\log X_2 = -\log X_2^{id} + \frac{V_2 \phi_1^2}{2.303RT} (\delta_1 - \delta_2)^2 \quad [4]$$

where,  $V_2$  is the partial molar volume of the solute,  $\phi_1$  is the volume fraction of the solvent in the saturated solution and  $\delta_1$  and  $\delta_2$  are the Hildebrand solubility parameters of solvent and solute, respectively.  $\phi_1$  is calculated as:

$$\phi_1 = \frac{V_1(1-X_2)}{V_1(1-X_2) + V_2X_2} \quad [5]$$

where  $V_1$  is the molar volume of the solvent.

However, all the pharmaceutical aqueous dissolutions deviate significantly from that predicted by the regular solutions theory. For this reason, Martin *et al.* (36-42) developed the EHSA method. Thereby, if the  $A$  term (defined as  $V_2 \phi_1^2 / (2.303RT)$ ) is introduced in the equation [4], the real solubility of drugs can be calculated from the expression:

$$-\log X_2 = -\log X_2^{id} + A(\delta_1^2 + \delta_2^2 - 2W) \quad [6]$$

Here, the  $W$  term is equal to  $2K\delta_1\delta_2$  (where,  $K$  is the Walker parameter (18)). The  $W$  factor can be calculated from experimental data by means of:

$$W = 0.5 (\delta_1^2 + \delta_2^2 - \frac{\log \gamma_2}{A}) \quad [7]$$

where,  $\gamma_2$  is the activity coefficient of the solute in the saturated solution and it is calculated as:  $X_2^{\text{id}} / X_2$ . The experimental values of the  $W$  parameter can be correlated by means of regression analysis by using regular polynomials as a function of  $\delta_1$  as follows:

$$W = C_0 + C_1\delta_1 + C_2\delta_1^2 + C_3\delta_1^3 \dots + C_n\delta_1^n \quad [8]$$

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 (25, 26).

## Results and discussion

The required properties about the sulfonamides studied such as ideal solubility, molar volume, and Hildebrand solubility parameter are presented in Table 1 (5, 21, 22). The volumetric behavior and polarity of EtOH + water mixtures, as a function of the composition, is shown in Table 2. Volume fractions and Hildebrand solubility parameters were calculated assuming additive behavior (8, 43). Table 2 also summarizes the experimental solubility of the sulfonamides expressed in molarity and mole fraction reported in the literature (20, 21).

In all cases the relative standard deviations in reported solubilities were lower than 2.0% (20, 21). It is important to note that by using the inverse Kirkwood-Buff integrals (44-46) these drugs are preferentially solvated by water in water-rich and EtOH-rich mixtures but preferentially solvated by EtOH in mixtures with similar proportions of both solvent components (47). These results were interpreted as a consequence of hydrophobic hydration around the non-polar moieties of these sulfonamides in aqueous-rich mixtures and by polarity effects in those mixtures of similar proportions.

Similar considerations about the aqueous behavior have been reported from the temperature-dependence of their octanol-water partition coefficients (48). Moreover, these sulfonamides are acting as Lewis acids with ethanol molecules, because this cosolvent is more basic than water based on their Kamlet-Taft hydrogen bond acceptor parameters reported (as  $\beta = 0.75$  for ethanol and 0.47 for water) (49). Furthermore, in EtOH-rich mixtures, where these drugs are preferentially solvated by water again, these results were analyzed by considering that the sulfonamides are acting mainly as Lewis bases with water based on the Kamlet-Taft hydrogen bond donor parameters of the solvents, i.e.  $\alpha = 1.17$  for water and 0.86 for EtOH, respectively (50, 51).

Figure 2 shows the ideal and experimental solubility, as well as those calculated by using the regular solution model (equation [4]), as a function of the Hildebrand solubility parameter of the solvent mixtures, i.e. from 26.5 to 47.8 MPa<sup>1/2</sup>. In order to use equation [4] the molar volume and Hildebrand solubility parameter of the sulfonamides were taken from the literature as shown in Table 1 (20, 21). These values were calculated by using the groups' contribution method proposed by Fedors (52).

**Table 1.** Some properties of the sulfonamides considered

Sulfonamide	Abbreviation	Molar mass (g/mol <sup>a</sup> )	CAS number <sup>a</sup>	$X_2^{\text{id}}$	$V_2$ (cm <sup>3</sup> /mol)	$\delta_2$ (MPa <sup>1/2</sup> )
Sulfadiazine	SDZ	250.28	68-35-9	$3.01 \times 10^{-3}{}^b$	$150.0{}^b$	$28.9{}^b$
Sulfamerazine	SMR	264.10	127-79-7	$5.45 \times 10^{-3}{}^c$	$164.5{}^c$	$28.1{}^c$
Sulfamethazine	SMT	278.33	57-68-1	$1.05 \times 10^{-2}{}^c$	$179.0{}^c$	$27.4{}^c$

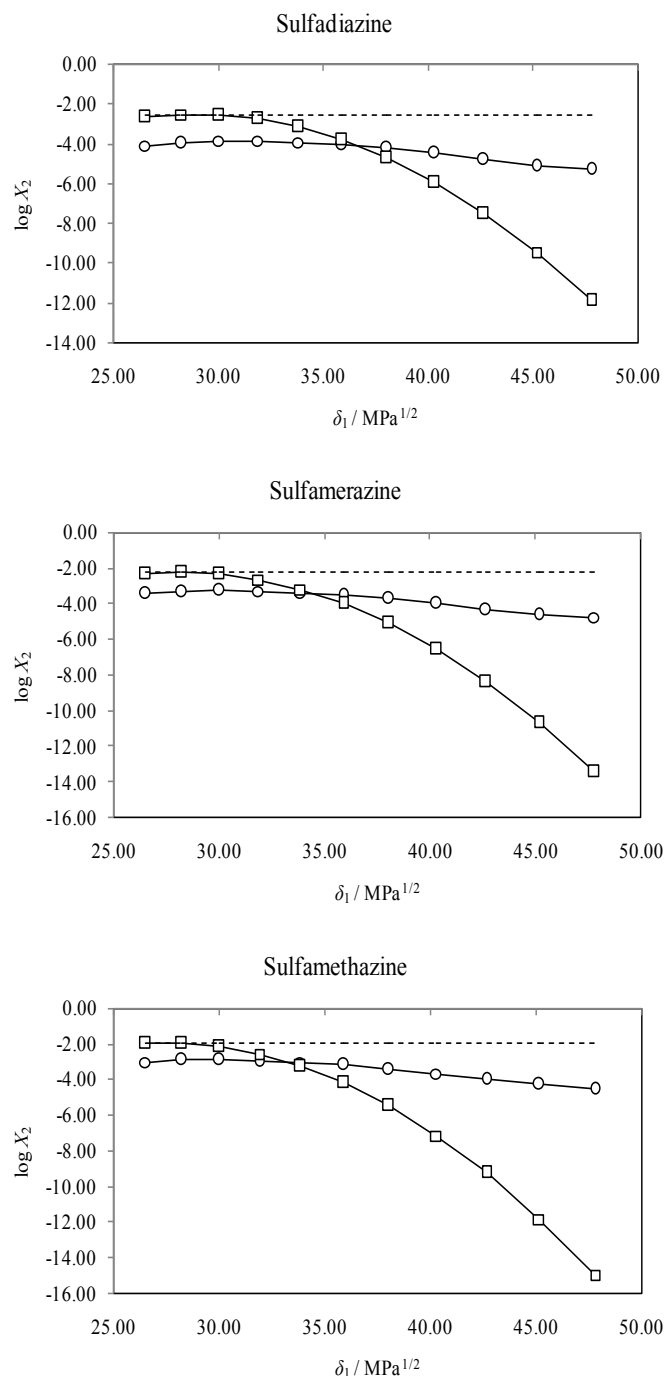
<sup>a</sup>From Ref. (4). <sup>b</sup>From Ref. (20). <sup>c</sup>From Ref. (21).

**Table 2.** Ethanol + water solvent mixtures composition, Hildebrand solubility parameter of mixtures and solubility of sulfonamides expressed in molarity and mole fraction at 298.15 K.

Mixtures composition <sup>a</sup>		$\delta_1$ (MPa <sup>1/2</sup> )	Sulfadiazine <sup>b</sup>		Sulfamerazine <sup>c</sup>		Sulfamethazine <sup>c</sup>	
$w_1$	$f_1$		(mol/L)	$X_2$	(mol/L)	$X_2$	(mol/L)	$X_2$
0.0000	0.0000	47.80	$2.66 \times 10^{-4}$	$4.81 \times 10^{-6}$	$9.47 \times 10^{-4}$	$1.71 \times 10^{-5}$	$1.56 \times 10^{-3}$	$2.81 \times 10^{-5}$
0.1000	0.1236	45.17	$4.03 \times 10^{-4}$	$7.88 \times 10^{-6}$	$1.19 \times 10^{-3}$	$2.32 \times 10^{-5}$	$2.53 \times 10^{-3}$	$4.95 \times 10^{-5}$
0.2000	0.2409	42.67	$7.08 \times 10^{-4}$	$1.50 \times 10^{-5}$	$2.09 \times 10^{-3}$	$4.43 \times 10^{-5}$	$4.68 \times 10^{-3}$	$9.94 \times 10^{-5}$
0.3000	0.3524	40.29	$1.39 \times 10^{-3}$	$3.22 \times 10^{-5}$	$4.08 \times 10^{-3}$	$9.45 \times 10^{-5}$	$8.62 \times 10^{-3}$	$2.00 \times 10^{-4}$
0.4000	0.4584	38.04	$2.25 \times 10^{-3}$	$5.75 \times 10^{-5}$	$7.03 \times 10^{-3}$	$1.80 \times 10^{-4}$	$1.43 \times 10^{-2}$	$3.66 \times 10^{-4}$
0.5000	0.5594	35.89	$3.12 \times 10^{-3}$	$8.88 \times 10^{-5}$	$1.03 \times 10^{-2}$	$2.94 \times 10^{-4}$	$2.21 \times 10^{-2}$	$6.31 \times 10^{-4}$
0.6000	0.6557	33.83	$3.55 \times 10^{-3}$	$1.14 \times 10^{-4}$	$1.27 \times 10^{-2}$	$4.08 \times 10^{-4}$	$2.76 \times 10^{-2}$	$8.88 \times 10^{-4}$
0.7000	0.7476	31.88	$3.81 \times 10^{-3}$	$1.39 \times 10^{-4}$	$1.37 \times 10^{-2}$	$4.99 \times 10^{-4}$	$3.07 \times 10^{-2}$	$1.12 \times 10^{-3}$
0.8000	0.8355	30.00	$3.40 \times 10^{-3}$	$1.42 \times 10^{-4}$	$1.32 \times 10^{-2}$	$5.55 \times 10^{-4}$	$3.05 \times 10^{-2}$	$1.28 \times 10^{-3}$
0.9000	0.9195	28.21	$2.27 \times 10^{-3}$	$1.11 \times 10^{-4}$	$9.49 \times 10^{-3}$	$4.66 \times 10^{-4}$	$2.38 \times 10^{-2}$	$1.17 \times 10^{-3}$
1.0000	1.0000	26.50	$1.32 \times 10^{-3}$	$7.74 \times 10^{-5}$	$5.81 \times 10^{-3}$	$3.41 \times 10^{-4}$	$1.57 \times 10^{-2}$	$9.18 \times 10^{-4}$

<sup>a</sup> $w_1$  and  $f_1$  are the mass and volume fraction of ethanol in the cosolvent mixtures free of sulfonamide. <sup>b</sup>Data from Ref. (20). <sup>c</sup>Data from Ref. (21).

Regarding Fig. 2, it is noteworthy that the regular solutions model predicts that the maximum solubility value corresponds to the ideal solubility and this is obtained when both the Hildebrand solubility parameters of drug and solvent mixture are coincident. In a similar way, according to the literature the maximum experimental solubility values are found when the Hildebrand solubility parameters of both solute and solvent are also coincident (8, 18), despite they can be very different regarding the ideal solubility.



**Figure 2.** Ideal solubility (---), experimental solubility (O), and calculated solubility according to the regular solutions model of Hildebrand (□) of sulfonamides as a function of the Hildebrand solubility parameter in ethanol + water mixtures at 298.15 K.

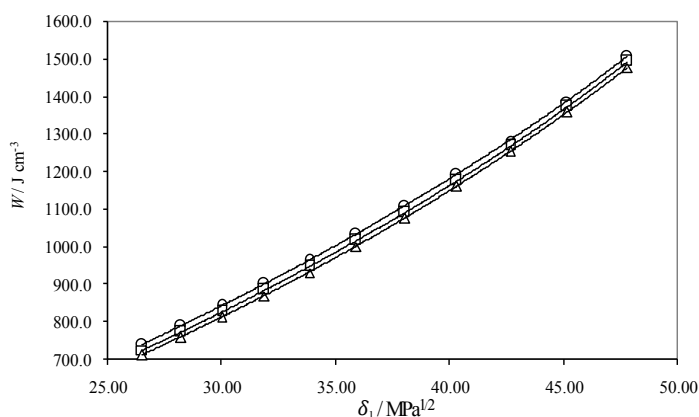
The  $\phi_1$  values for all these sulfonamides, calculated according to equation [5], are almost equal to 1.000 because the solubility of these sulfonamides is very low in all the solvent system considered (Table 3). The activity coefficients of these sulfonamides expressed as decimal logarithms are also shown in Table 3. Analysis of these activity coefficients has been reported previously in the literature (20, 21). Briefly, based on the activity coefficients magnitudes it follows that the solvent-solvent interactions are higher in neat water (with Hildebrand solubility parameter  $\delta = 47.8 \text{ MPa}^{1/2}$ ) and they are smaller in ethanol (with  $\delta = 26.5 \text{ MPa}^{1/2}$ ) (50).

Pure water and water-rich mixtures exhibiting larger  $\log \gamma_2$  values (even higher than 2.80) would imply high solvent-solvent interactions and low solvent-solute interactions. On the other hand, in ethanol-rich mixtures (exhibiting  $\log \gamma_2$  values between 0.90 and 1.30), the solvent-solvent interactions are comparatively low and the solvent-solute interactions would relatively be high. Accordingly, the solvation of these sulfonamides would be just higher in ethanol-rich mixtures. Table 3 also summarizes the calculated parameters  $A$ ,  $K$ , and  $W$  of the sulfonamides in EtOH + water mixtures.

Figure 3 shows that the  $W$  parameter of all sulfonamides exhibits some deviation from the linear behavior with respect to the Hildebrand solubility parameter of the solvent mixtures. This behavior is expectable because the  $W$  term implies the summation of two quadratic ( $\delta_1^2$  and  $\delta_2^2$ ) and one non-constant-quotient ( $-\log \gamma_2/A$ ) terms (equation [7]).

$W$  values were adjusted to regular polynomials in orders from 2 to 5 (equation [8]) (53). As comparison the linear equation was also considered. Table 4 summarizes the coefficients obtained in all the regular polynomials for these sulfonamides.

Searching for the best adjust, the first criterion used to define the best polynomial order of  $W$  term as function of  $\delta_1$  was the fitting standard error (Table 4). As another comparison criterion, the difference percentages between the experimental solubilities and those calculated by using EHSA were also calculated as shown in Table 5.



**Figure 3.**  $W$  parameter of sulfonamides in ethanol + water mixtures as a function of the Hildebrand solubility parameter of the solvent mixtures at 298.15 K. (O): Sulfadiazine; (□): sulfamerazine; (Δ): sulfamethazine.

It is observed that as more complex is the polynomial used, there is a better correlation between experimental and calculated solubility. Accordingly, the most important increment, in concordance, is obtained by passing from linear equation to polynomial in order 2. The concordances also increase significantly from orders 2 to 3 and 3 to 4.

Nevertheless, from order 4 to 5 the concordance increment is not so much relevant, because in the last case the mean uncertainties obtained are in the same order or lower than those reported experimentally (20, 21). It is important to know that uncertainties lower than 5% are useful for pharmaceutical purposes, but better agreements are required for academic and theoretical purposes.

As it has already been described, regarding the practical usefulness of the EHSA, a very important consideration is about the complex calculations involving other experimental variables of solute and solvents, instead of the simple empirical regression of the experimental solubility values as a function of the Hildebrand solubility parameters of solvent mixtures as shown in Fig. 4 (18). For this reason, Table 6 shows the coefficients of regular polynomials in order 4 of  $\log X_2$  vs.  $\delta_1$  values (equation [9]) (18), whereas Table 7 shows the calculated values of solubility by using equation [9] and also the respective deviation percentages in front of the experimental ones.

It is noteworthy that empirical regular polynomials, as shown in equation [9], are commonly referred as Bustamante's Equation and are widely used in pharmaceutical sciences owing its simplicity, as has been described in the literature (4).

$$\log X_2 = C_0^* + C_1^* \delta_1 + C_2^* \delta_1^2 + C_3^* \delta_1^3 + C_4^* \delta_1^4 \quad [9]$$

By using both calculation methods, the same mean deviation percentages were obtained as shown in Tables 5 and 7, i.e. 2.65%, 2.82% and 1.41% for sulfadiazine, sulfamerazine, and sulfamethazine, respectively. This behavior is similar to those described earlier for other drugs in different cosolvent mixtures (22-28). Thereby, the results for these sulfonamides could indicate a non-significant usefulness of EHSA method for practical and academic purposes. Nevertheless, it is necessary to know that this correlative method considers the drug solubility from a complete thermodynamic viewpoint.

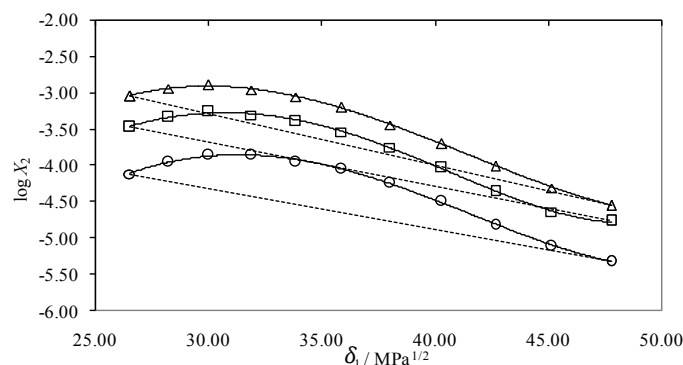
**Table 3.** Volume fraction of solvent, sulfonamide activity coefficients, and  $A$ ,  $K$ , and  $W$  experimental parameters of sulfonamides in ethanol + water mixtures at 298.15 K.

Sulfadiazine					
$\delta_1$ (MPa <sup>1/2</sup> )	$\phi_1$	$\log \gamma_2$	100 $A$ (cm <sup>3</sup> /J)	$K$ (J/cm <sup>3</sup> ) <sup>a</sup>	$W$ (J/cm <sup>3</sup> ) <sup>a</sup>
47.80	1.0000	2.797	2.62735	0.545379	1506.795
45.17	0.9999	2.583	2.62729	0.531852	1388.475
42.67	0.9999	2.302	2.62713	0.520668	1284.085
40.29	0.9999	1.971	2.62677	0.511765	1191.909
38.04	0.9998	1.719	2.62632	0.504095	1108.245
35.89	0.9997	1.531	2.62584	0.497710	1032.326
33.83	0.9996	1.424	2.62556	0.492356	962.847
31.88	0.9996	1.337	2.62530	0.488577	900.159
30.00	0.9996	1.325	2.62540	0.485796	842.490
28.21	0.9997	1.432	2.62597	0.483421	788.351
26.50	0.9998	1.590	2.62652	0.482116	738.457
Sulfamerazine					
$\delta_1$ (MPa <sup>1/2</sup> )	$\phi_1$	$\log \gamma_2$	100 $A$ (cm <sup>3</sup> /J)	$K$ (J/cm <sup>3</sup> ) <sup>a</sup>	$W$ (J/cm <sup>3</sup> ) <sup>a</sup>
47.80	0.9998	2.503	2.88066	0.556059	1493.776
45.17	0.9998	2.371	2.88060	0.541164	1373.677
42.67	0.9997	2.091	2.88005	0.529118	1268.802
40.29	0.9995	1.761	2.87879	0.519326	1176.038
38.04	0.9992	1.482	2.87691	0.511047	1092.427
35.89	0.9988	1.268	2.87473	0.504088	1016.612
33.83	0.9985	1.126	2.87293	0.498335	947.564
31.88	0.9983	1.039	2.87181	0.493882	884.744
30.00	0.9982	0.992	2.87145	0.490830	827.657
28.21	0.9986	1.069	2.87360	0.488277	774.229
26.50	0.9990	1.204	2.87605	0.486804	724.998
Sulfamethazine					
$\delta_1$ (MPa <sup>1/2</sup> )	$\phi_1$	$\log \gamma_2$	100 $A$ (cm <sup>3</sup> /J)	$K$ (J/cm <sup>3</sup> ) <sup>a</sup>	$W$ (J/cm <sup>3</sup> ) <sup>a</sup>
47.80	0.9997	2.572	3.13381	0.563569	1477.313
45.17	0.9996	2.327	3.13315	0.548583	1358.812
42.67	0.9994	2.024	3.13155	0.535872	1253.903
40.29	0.9989	1.720	3.12863	0.525063	1160.256
38.04	0.9982	1.458	3.12438	0.515830	1075.968
35.89	0.9972	1.221	3.11823	0.508258	1000.218
33.83	0.9965	1.073	3.11334	0.501800	931.063
31.88	0.9959	0.972	3.10972	0.496739	868.328
30.00	0.9956	0.913	3.10800	0.493103	811.368
28.21	0.9962	0.953	3.11196	0.490306	758.631
26.50	0.9972	1.058	3.11804	0.488615	710.085

<sup>a</sup> 1 J/cm<sup>3</sup> = 1 MPa



In this way, the main point about these calculations is about to find an effective method for the Walker  $K$  parameter estimation to calculate the  $W$  term as  $2K\delta_1\delta_2$ . Because the  $\delta_1$  and  $\delta_2$  terms would be known, the drug experimental solubility could be calculated in any mixture (18).



**Figure 4.** Logarithmic solubility of sulfonamides in ethanol + water mixtures as a function of the Hildebrand solubility parameter of the solvent mixtures at 298.15 K. Dotted lines are the additive log-solubility behavior. (O): Sulfadiazine; (□): sulfamerazine; (Δ): sulfamethazine.

## Conclusion

In this research, the extended Hildebrand solubility approach was adequately used to analyze the solubility of sulfadiazine, sulfamerazine, and sulfamethazine in EtOH + water mixtures at 298.15 K. A good predictive character within 3.0% were observed by using regular polynomials in orders four by correlating the interaction parameter  $W$  with the Hildebrand solubility parameter of the solvent mixtures without drugs. Nevertheless, the predictive character of EHSA method is the same as the one obtained by direct correlation of the sulfonamides solubility and the same descriptor of polarity of the cosolvent mixtures. Ultimately, it is noteworthy that this research expands the analyses developed previously based on classical dissolution thermodynamic properties as well as the preferential solvation of the drugs by the solvent components (20, 21, 47).

**Table 4.** Coefficients and statistical parameters of regular polynomials in several orders of  $W$  as a function of solubility parameters of cosolvent mixtures free of sulfonamide (Eq. (7)) in ethanol + water mixtures at 298.15 K.

Sulfadiazine					
Coefficient or Parameter	Polynomial order				
	1	2	3	4	5
$C_0$	$-2.319 \times 10^2$	$3.056 \times 10^2$	$-1.580 \times 10^1$	$2.438 \times 10^2$	$-1.584 \times 10^3$
$C_1$	$3.571 \times 10^1$	$5.644 \times 10^0$	$3.272 \times 10^1$	$3.505 \times 10^0$	$2.609 \times 10^2$
$C_2$		$4.065 \times 10^{-1}$	$-3.379 \times 10^{-1}$	$8.767 \times 10^{-1}$	$-1.346 \times 10^1$
$C_3$			$6.690 \times 10^{-3}$	$-1.544 \times 10^{-2}$	$3.797 \times 10^{-1}$
$C_4$				$1.491 \times 10^{-4}$	$-5.236 \times 10^{-3}$
$C_5$					$2.905 \times 10^{-5}$
Adj. $R^2$	0.995	1.000	1.000	1.000	1.000
Fit. Err.	18.09	1.838	0.424	0.382	0.310
Sulfamerazine					
Coefficient or Parameter	Polynomial order				
	1	2	3	4	5
$C_0$	$-2.466 \times 10^2$	$3.204 \times 10^2$	$-2.599 \times 10^1$	$3.970 \times 10^2$	$-1.544 \times 10^3$
$C_1$	$3.571 \times 10^1$	$3.992 \times 10^0$	$3.317 \times 10^1$	$-1.443 \times 10^1$	$2.589 \times 10^2$
$C_2$		$4.288 \times 10^{-1}$	$-3.735 \times 10^{-1}$	$1.606 \times 10^{+00}$	$-1.362 \times 10^1$
$C_3$			$7.209 \times 10^{-3}$	$-2.884 \times 10^{-2}$	$3.908 \times 10^{-1}$
$C_4$				$2.429 \times 10^{-4}$	$-5.476 \times 10^{-3}$
$C_5$					$3.085 \times 10^{-5}$
Adj. $R^2$	0.994	1.000	1.000	1.000	1.000
Fit. Err.	19.08	1.986	0.484	0.322	0.189
Sulfamethazine					
Coefficient or Parameter	Polynomial order				
	1	2	3	4	5
$C_0$	$-2.627 \times 10^2$	$3.129 \times 10^2$	$7.816 \times 10^1$	$1.698 \times 10^2$	$-5.142 \times 10^2$
$C_1$	$3.571 \times 10^1$	$3.518 \times 10^0$	$2.329 \times 10^1$	$1.298 \times 10^1$	$1.093 \times 10^2$
$C_2$		$4.353 \times 10^{-1}$	$-1.084 \times 10^{-1}$	$3.203 \times 10^{-01}$	$-5.048 \times 10^0$
$C_3$			$4.885 \times 10^{-3}$	$-2.923 \times 10^{-3}$	$1.450 \times 10^{-1}$
$C_4$				$5.261 \times 10^{-5}$	$-1.963 \times 10^{-3}$
$C_5$					$1.087 \times 10^{-5}$
Adj. $R^2$	0.994	1.000	1.000	1.000	1.000
Fit. Err.	19.32	1.320	0.165	0.155	0.133

**Table 5.** Calculated solubility of sulfonamides in ethanol + water mixtures by using the  $W$  parameters obtained from regression models in orders 1, 2, 3, 4 and 5, and standard deviations with respect to the experimental values, at 298.15 K.

Sulfadiazine										
$\delta_1$ (MPa <sup>1/2</sup> )	$X_2$ calculated					% dev. <sup>a</sup>				
	1	2	3	4	5	1	2	3	4	5
47.80	1.05 x 10 <sup>-7</sup>	3.52 x 10 <sup>-6</sup>	4.65 x 10 <sup>-6</sup>	4.76 x 10 <sup>-6</sup>	4.83 x 10 <sup>-6</sup>	98	26.9	3.4	1.02	0.43
45.17	3.24 x 10 <sup>-6</sup>	9.29 x 10 <sup>-6</sup>	8.27 x 10 <sup>-6</sup>	8.00 x 10 <sup>-6</sup>	7.70 x 10 <sup>-6</sup>	59	17.9	4.9	1.49	2.34
42.67	3.87 x 10 <sup>-5</sup>	2.02 x 10 <sup>-5</sup>	1.59 x 10 <sup>-5</sup>	1.56 x 10 <sup>-5</sup>	1.57 x 10 <sup>-5</sup>	157	34.3	5.8	3.58	4.29
40.29	2.03 x 10 <sup>-4</sup>	3.71 x 10 <sup>-5</sup>	3.05 x 10 <sup>-5</sup>	3.07 x 10 <sup>-5</sup>	3.16 x 10 <sup>-5</sup>	530	15.0	5.5	4.85	1.99
38.04	5.22 x 10 <sup>-4</sup>	5.87 x 10 <sup>-5</sup>	5.45 x 10 <sup>-5</sup>	5.59 x 10 <sup>-5</sup>	5.67 x 10 <sup>-5</sup>	807	1.9	5.3	2.91	1.47
35.89	7.22 x 10 <sup>-4</sup>	8.16 x 10 <sup>-5</sup>	8.71 x 10 <sup>-5</sup>	8.93 x 10 <sup>-5</sup>	8.81 x 10 <sup>-5</sup>	713	8.1	1.9	0.51	0.85
33.83	5.84 x 10 <sup>-4</sup>	1.01 x 10 <sup>-4</sup>	1.21 x 10 <sup>-4</sup>	1.22 x 10 <sup>-4</sup>	1.18 x 10 <sup>-4</sup>	415	10.7	6.3	7.12	4.20
31.88	2.97 x 10 <sup>-4</sup>	1.14 x 10 <sup>-4</sup>	1.42 x 10 <sup>-4</sup>	1.40 x 10 <sup>-4</sup>	1.38 x 10 <sup>-4</sup>	114	17.6	2.1	0.74	0.70
30.00	1.01 x 10 <sup>-4</sup>	1.18 x 10 <sup>-4</sup>	1.39 x 10 <sup>-4</sup>	1.35 x 10 <sup>-4</sup>	1.37 x 10 <sup>-4</sup>	29	17.3	2.5	5.18	3.60
28.21	2.41 x 10 <sup>-5</sup>	1.13 x 10 <sup>-4</sup>	1.13 x 10 <sup>-4</sup>	1.11 x 10 <sup>-4</sup>	1.15 x 10 <sup>-4</sup>	78	1.2	1.6	0.32	2.94
26.50	4.26 x 10 <sup>-6</sup>	1.01 x 10 <sup>-4</sup>	7.64 x 10 <sup>-5</sup>	7.86 x 10 <sup>-5</sup>	7.69 x 10 <sup>-5</sup>	94	30.4	1.4	1.47	0.67
Mean value <sup>b</sup>						281	16.5	3.7	2.65	2.14
Standard Deviation <sup>b</sup>						284	10.8	1.9	2.26	1.45
Sulfamerazine										
$\delta_1$ (MPa <sup>1/2</sup> )	$X_2$ calculated					% dev. <sup>a</sup>				
	1	2	3	4	5	1	2	3	4	5
47.80	2.00 x 10 <sup>-7</sup>	1.16 x 10 <sup>-5</sup>	1.62 x 10 <sup>-5</sup>	1.69 x 10 <sup>-5</sup>	1.72 x 10 <sup>-5</sup>	99	32.0	5.6	1.40	0.21
45.17	8.63 x 10 <sup>-6</sup>	2.92 x 10 <sup>-5</sup>	2.54 x 10 <sup>-5</sup>	2.39 x 10 <sup>-5</sup>	2.29 x 10 <sup>-5</sup>	63	25.5	9.4	3.05	1.53
42.67	1.31 x 10 <sup>-4</sup>	6.18 x 10 <sup>-5</sup>	4.67 x 10 <sup>-5</sup>	4.49 x 10 <sup>-5</sup>	4.52 x 10 <sup>-5</sup>	196	39.6	5.4	1.43	2.18
40.29	8.09 x 10 <sup>-4</sup>	1.13 x 10 <sup>-4</sup>	8.98 x 10 <sup>-5</sup>	9.09 x 10 <sup>-5</sup>	9.40 x 10 <sup>-5</sup>	755	19.7	5.0	3.86	0.53
38.04	2.28 x 10 <sup>-3</sup>	1.82 x 10 <sup>-4</sup>	1.67 x 10 <sup>-4</sup>	1.75 x 10 <sup>-4</sup>	1.78 x 10 <sup>-4</sup>	1166	1.4	7.0	2.83	1.20
35.89	3.26 x 10 <sup>-3</sup>	2.63 x 10 <sup>-4</sup>	2.84 x 10 <sup>-4</sup>	2.97 x 10 <sup>-4</sup>	2.92 x 10 <sup>-4</sup>	1008	10.6	3.4	0.88	0.75
33.83	2.59 x 10 <sup>-3</sup>	3.43 x 10 <sup>-4</sup>	4.21 x 10 <sup>-4</sup>	4.27 x 10 <sup>-4</sup>	4.13 x 10 <sup>-4</sup>	535	15.8	3.3	4.78	1.44
31.88	1.24 x 10 <sup>-3</sup>	4.10 x 10 <sup>-4</sup>	5.29 x 10 <sup>-4</sup>	5.16 x 10 <sup>-4</sup>	5.07 x 10 <sup>-4</sup>	148	17.7	6.1	3.48	1.73
30.00	3.80 x 10 <sup>-4</sup>	4.55 x 10 <sup>-4</sup>	5.52 x 10 <sup>-4</sup>	5.25 x 10 <sup>-4</sup>	5.35 x 10 <sup>-4</sup>	32	18.1	0.5	5.37	3.57
28.21	7.95 x 10 <sup>-5</sup>	4.71 x 10 <sup>-4</sup>	4.73 x 10 <sup>-4</sup>	4.57 x 10 <sup>-4</sup>	4.75 x 10 <sup>-4</sup>	83	1.2	1.7	1.76	1.96
26.50	1.19 x 10 <sup>-5</sup>	4.60 x 10 <sup>-4</sup>	3.31 x 10 <sup>-4</sup>	3.48 x 10 <sup>-4</sup>	3.40 x 10 <sup>-4</sup>	97	34.9	2.9	2.15	0.38
Mean value <sup>b</sup>						380	19.7	4.6	2.82	1.41
Standard Deviation <sup>b</sup>						417	12.6	2.5	1.46	0.97
Sulfamethazine										
$\delta_1$ (MPa <sup>1/2</sup> )	$X_2$ calculated					% dev. <sup>a</sup>				
	1	2	3	4	5	1	2	3	4	5
47.80	2.44 x 10 <sup>-7</sup>	2.17 x 10 <sup>-5</sup>	2.77 x 10 <sup>-5</sup>	2.80 x 10 <sup>-5</sup>	2.82 x 10 <sup>-5</sup>	99	22.8	1.6	0.56	0.11
45.17	1.47 x 10 <sup>-5</sup>	5.63 x 10 <sup>-5</sup>	5.09 x 10 <sup>-5</sup>	5.01 x 10 <sup>-5</sup>	4.93 x 10 <sup>-5</sup>	70	13.8	2.8	1.40	0.30
42.67	2.83 x 10 <sup>-4</sup>	1.23 x 10 <sup>-4</sup>	1.00 x 10 <sup>-4</sup>	9.93 x 10 <sup>-5</sup>	9.96 x 10 <sup>-5</sup>	185	24.0	0.8	0.07	0.26
40.29	2.04 x 10 <sup>-3</sup>	2.33 x 10 <sup>-4</sup>	1.97 x 10 <sup>-4</sup>	1.97 x 10 <sup>-4</sup>	2.00 x 10 <sup>-4</sup>	921	16.6	1.6	1.36	0.02
38.04	6.28 x 10 <sup>-3</sup>	3.88 x 10 <sup>-4</sup>	3.64 x 10 <sup>-4</sup>	3.68 x 10 <sup>-4</sup>	3.71 x 10 <sup>-4</sup>	1617	6.1	0.4	0.62	1.30
35.89	9.24 x 10 <sup>-3</sup>	5.78 x 10 <sup>-4</sup>	6.12 x 10 <sup>-4</sup>	6.18 x 10 <sup>-4</sup>	6.15 x 10 <sup>-4</sup>	1364	8.4	3.1	2.07	2.64
33.83	7.19 x 10 <sup>-3</sup>	7.78 x 10 <sup>-4</sup>	9.05 x 10 <sup>-4</sup>	9.08 x 10 <sup>-4</sup>	8.97 x 10 <sup>-4</sup>	710	12.4	1.9	2.21	0.98
31.88	3.23 x 10 <sup>-3</sup>	9.60 x 10 <sup>-4</sup>	1.16 x 10 <sup>-3</sup>	1.15 x 10 <sup>-3</sup>	1.14 x 10 <sup>-3</sup>	188	14.3	3.2	2.61	1.98
30.00	9.00 x 10 <sup>-4</sup>	1.10 x 10 <sup>-3</sup>	1.26 x 10 <sup>-3</sup>	1.25 x 10 <sup>-3</sup>	1.26 x 10 <sup>-3</sup>	30	14.6	1.6	2.71	1.98
28.21	1.65 x 10 <sup>-4</sup>	1.16 x 10 <sup>-3</sup>	1.17 x 10 <sup>-3</sup>	1.16 x 10 <sup>-3</sup>	1.18 x 10 <sup>-3</sup>	86	0.4	0.0	0.85	0.59
26.50	2.09 x 10 <sup>-5</sup>	1.17 x 10 <sup>-3</sup>	9.16 x 10 <sup>-4</sup>	9.27 x 10 <sup>-4</sup>	9.19 x 10 <sup>-4</sup>	98	27.0	0.2	0.95	0.01
Mean value <sup>b</sup>						488	14.6	1.6	1.40	0.93
Standard Deviation <sup>b</sup>						575	7.9	1.1	0.89	0.93

<sup>a</sup> Calculated as  $\%Dev = 100 \left( \frac{|X_{2\text{exp}} - X_{2\text{calc}}|}{X_{2\text{exp}}} \right)$

<sup>b</sup> Calculated considering the obtained values in the neat solvents and the nine binary mixtures.



**Table 6.** Coefficients and statistical parameters of regular polynomials in fourth degree of  $\log X_2$  as a function of solubility parameters of cosolvent mixtures free of sulfonamide (Eq. [9]) in ethanol + water mixtures.

Coefficient or Parameter	Sulfadiazine	Sulfamerazine	Sulfamethazine
$C_0^*$	$-1.168 \times 10^1$	$-2.223 \times 10^0$	$-1.515 \times 10^1$
$C_1^*$	$1.868 \times 10^{-1}$	$-8.244 \times 10^{-1}$	$8.361 \times 10^{-1}$
$C_2^*$	$1.973 \times 10^{-2}$	$6.354 \times 10^{-2}$	$-1.196 \times 10^{-2}$
$C_3^*$	$-8.107 \times 10^{-4}$	$-1.661 \times 10^{-3}$	$-1.748 \times 10^{-4}$
$C_4^*$	$7.834 \times 10^{-6}$	$1.400 \times 10^{-5}$	$3.266 \times 10^{-6}$
Adj. $R^2$	0.999	0.999	1.000
Fit. Err.	0.020	0.019	0.010

**Table 7.** Calculated solubility of sulfonamides in ethanol + water mixtures by using the equations of  $\log X_2$  vs.  $\delta_1$  as regression models in order 4, and standard deviations with respect to the experimental values, at 298.15 K.

$\delta_1$ (MPa <sup>1/2</sup> )	$X_2$ calculated			% dev. <sup>a</sup>		
	Sulfadiazine	Sulfamerazine	Sulfamethazine	Sulfadiazine	Sulfamerazine	Sulfamethazine
47.80	$4.76 \times 10^{-6}$	$1.69 \times 10^{-5}$	$2.80 \times 10^{-5}$	1.02	1.41	0.56
45.17	$8.00 \times 10^{-6}$	$2.39 \times 10^{-5}$	$5.01 \times 10^{-5}$	1.49	3.03	1.37
42.67	$1.56 \times 10^{-5}$	$4.49 \times 10^{-5}$	$9.93 \times 10^{-5}$	3.59	1.43	0.08
40.29	$3.07 \times 10^{-5}$	$9.09 \times 10^{-5}$	$1.97 \times 10^{-4}$	4.85	3.86	1.34
38.04	$5.59 \times 10^{-5}$	$1.75 \times 10^{-4}$	$3.68 \times 10^{-4}$	2.91	2.84	0.65
35.89	$8.93 \times 10^{-5}$	$2.97 \times 10^{-4}$	$6.18 \times 10^{-4}$	0.51	0.87	2.12
33.83	$1.22 \times 10^{-4}$	$4.27 \times 10^{-4}$	$9.08 \times 10^{-4}$	7.13	4.79	2.21
31.88	$1.40 \times 10^{-4}$	$5.16 \times 10^{-4}$	$1.15 \times 10^{-3}$	0.74	3.50	2.64
30.00	$1.35 \times 10^{-4}$	$5.25 \times 10^{-4}$	$1.25 \times 10^{-3}$	5.19	5.40	2.74
28.21	$1.11 \times 10^{-4}$	$4.57 \times 10^{-4}$	$1.16 \times 10^{-3}$	0.31	1.75	0.83
26.50	$7.86 \times 10^{-5}$	$3.48 \times 10^{-4}$	$9.27 \times 10^{-4}$	1.47	2.14	0.94
		Mean value <sup>b</sup>		2.65	2.82	1.41
		Standard deviation <sup>b</sup>		2.27	1.47	0.90

<sup>a</sup> Calculated as  $\%Dev = 100 \left( \frac{|X_{2\text{exp}} - X_{2\text{calc}}|}{X_{2\text{exp}}} \right)$

<sup>b</sup> Calculated considering the obtained values in the neat solvents and the nine binary mixtures.

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**Article citation:**

Delgado, D. R.; Peña, M. Á; Martínez, F. Extended Hildebrand solubility approach applied to some structurally related sulfonamides in ethanol + water mixtures. *Rev. Colomb. Quim.* **2016**, *45*(1), 34-43. DOI: <http://dx.doi.org/10.15446/rev.colomb.quim.v45n1.57201>