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Solubility of acetaminophen in polyethylene glycol 400 + water mixtures according to the extended Hildebrand solubility approach

Estimación de la solubilidad del acetaminofeno en mezclas polietilenglicol 400 + agua según el método extendido de Hildebrand

Solubilidade estimada do paracetamol em misturas polietileno glicol 400 + água de acordo com o método estendido de Hildebrand

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ABSTRACT

The Extended Hildebrand Solubility Approach (EHSA) was applied in the present work to evaluate the solubility of the analgesic drug acetaminophen (paracetamol) in polyethylene glycol 400 + water mixtures at 298.15 K. An acceptable correlative capacity of EHSA was found using a regular polynomial model in order four (overall deviation below 0.7%), when the *W* interaction parameter is related to the solubility parameter of the mixtures. Thus, the deviations obtained in the estimated solubility with respect to experimental solubility were lower than those obtained directly by means of an empiric regression of the experimental solubility as a function of the mixtures' solubility parameters (close to 1.5%).

Key words: acetaminophen, binary mixtures, extended Hildebrand solubility approach, solubility parameter.

RESUMEN

En el presente trabajo se aplicó el Método Extendido de Solubilidad de Hildebrand (MESH) al estudio de la solubilidad del acetaminofeno en mezclas binarias polietilenglicol 400 + agua a 298,15 K. Se obtuvo una capacidad predictiva aceptable del MESH (desviación general inferior al 0,7%) al utilizar un modelo polinómico regular de cuar-

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to orden que relaciona el parámetro de interacción *W* con el parámetro de solubilidad de las mezclas solventes. Las desviaciones obtenidas en la solubilidad estimada fueron de menor magnitud que 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 (cerca del 1.5%).

Palabras clave: acetaminofeno, Método Extendido de Solubilidad de Hildebrand, mezclas binarias, parámetro de solubilidad.

RESUMO

O método estendido de solubilidade de Hildebrand (MESH) foi aplicado nesta pesquisa para avaliar a solubilidade do paracetamol em água de misturas binárias + polietileno glicol 400 em 298,15 K. Obteve-se boa capacidade preditiva com o MESH (desvio inferior a 0,7%) quando se utiliza um polinômio regular de quarta ordem do parâmetro de interação *W* com o parâmetro de solubilidade das misturas de solventes. Os desvios obtidos na solubilidade estimada foram inferiores do que os obtidos através do cálculo desta propriedade diretamente, utilizando uma regressão normal empírica da mesma ordem da solubilidade experimental da droga em função do parâmetro de solubilidade das misturas solventes (cerca de 1,5 %).

Palavras-chave: acetaminofeno, Método estendido de solubilidade de Hildebrand, misturas binárias, parâmetro de solubilidade.

INTRODUCTION

Acetaminophen (ACP, Figure 1) is a drug widely used as analgesic and antipyretic which physicochemical properties have not yet been studied throroughly (1). In particular, its solubility in aqueous media is very important in several processes associated to research and development during the design of homogeneous liquid dosage forms intended mainly for pediatric patients (2). It is important to note that cosolvency is the best technique used in pharmacy to increase drug solubility (3). On the other hand, it is clear that predictive methods of physicochemical properties of drugs, in particular its solubility, are very important for industrial pharmacists because they allow the optimization of design processes (4).

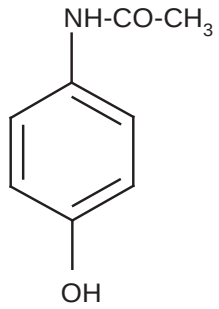

Figure 1. Molecular structure of acetaminophen.

For this reason, the present work presents a physicochemical study about the solubility prediction of ACP in binary mixtures conformed by polyethylene glycol 400 (PEG) and water. The study was made based on the Extended Hildebrand Solubility Approach (EHSA) (5). Thus, this work is a continuation of previous research on acetaminophen in ethanol + water (6), propylene glycol + water (7), and ethanol + propylene glycol

(8) mixtures. It is important to take into consideration that the EHSA method has been widely used to study the solubility of a lot of pharmaceutical compounds (9-27). On the other hand, PEG is after ethanol and propylene glycol the most used cosolvent to develop liquid pharmaceutical dosage forms (28). Moreover, PEG is also employed to regulate product evaporation (29).

THEORETICAL

The real solubility (X_2) of a solid solute in a liquid solution is calculated adequately by means of the expression:

$$-\log X_2 = \frac{\Delta H_{fus}\left(T_{fus} - T\right)}{2.303RT_{fus}T} + \log \gamma_2 \qquad [1]$$

where, ΔH_{fus} is the fusion enthalpy of the solute, R is the gas constant, T_{fus} is the melting point of the solute, T is the absolute temperature of the solution, $\log \gamma_2$ is the non-ideality term. The γ_2 term is the activity coefficient of the solute and it is determined experimentally. One method of calculating γ_2 is the referent to regular solutions obtained from

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

where V_2 is the partial molar volume of the solute, 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. Pharmaceutical dissolutions deviate from predicted by the regular solutions theory. In this respect, Martin *et al*. developed the EHSA method (9-15). If the A term (defined as $V_2\phi_1^2/(2.303RT)$) is introduced in the Eq. [2], the real solubility of drugs can be calculated from the expression

$$-\log X_2 = -\log X_2^{id} + A\left(\delta_1^2 + \delta_2^2 - 2W\right) \qquad [3]$$

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

$$W = 0.5 \times \left(\delta_1^2 + \delta_2^2 - \frac{\log \gamma_2}{A}\right) \qquad [4]$$

where γ_2 is the activity coefficient of the solute in the saturated solution, and it is calculated as X_2^{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 δ_1, as follows

$$W = C_0 + C_1\delta_1 + C_2\delta_1^2 + C_3\delta_1^3 ..... + C_n\delta_1^n \qquad [5]$$

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 and materials

Acetaminophen (Paracetamol, N-Acetyl-p-aminophenol, CAS RN: 103-90-2) was in agreement with the quality requirements of the American Pharmacopeia, USP (30). Polyethylene glycol 400 from DOW Chemicals (PEG), distilled water with conductivity < 2 mS cm^{-1}, and filter units from Millipore Corp. Swinnex®-13 were also used.

Solvent mixtures preparation

The PEG employed was maintained over molecular sieve (Merck Number 3, 0.3 nm in pore diameter) to obtain a dry solvent prior to preparing the solvent mixtures. All PEG + water solvent mixtures were prepared in quantities of 50.00 g by mass using an Ohaus Pioneer TM PA214 analytical balance, in mass fractions from 0.10 to 0.90 varying by 0.10.

Solubility determination

An excess of ACP was added to each mixed solvent 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 K for at least 7 days to reach the saturation equilibrium. Once at equilibrium, supernatant solutions were filtered before analysis. ACP concentrations were determined by measuring UV-absorbance after appropriate gravimetric dilutions with water and interpolation from a previously constructed UV spectrophotometric calibration curve (UV/VIS BioMate 3 Thermo Electron Company spectrophotometer). Density of the saturated solutions was determined with a digital density meter (DMA 45 Anton Paar) according to the procedure described in the literature (31).

Estimation of the volumetric contributions

Apparent specific volumes (ϕ_V^{spc}) of the drug were calculated according to Eq. [6], 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 (2).

$$\phi_V^{spc} = \frac{m_2 + m_1(1 - VE_1\rho_{soln})}{m_2\rho_{soln}} \qquad [6]$$

The ACP apparent molar volume is calculated by multiplying the ϕ_V^{spc}value and the molar mass of the solute.

RESULTS AND DISCUSSION

The information about polarity and volumetric behavior of PEG + water mixtures, as a function of the composition, is shown in Table 1. On the other hand, the reported ideal solubility for this drug is 2.602×10^{-2} in mole fraction (32). Table 1 also summarizes the ACP solubility expressed in molarity and mole fraction, the density of the solvent and saturated mixtures, the apparent molar volume of ACP, 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 as a function of the solubility parameter of solvent mixtures.

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

Ultimately, the activity coefficients of ACP as decimal logarithms are also presented in Table 1. These values were calculated from experimental solubility val-

Table 1. Solvent composition, Hildebrand solubility parameter of mixtures, ACP solubility expressed in molarity and in mole fraction, density of the solvent and the saturated mixtures, apparent molar volume of ACP, solvent volume fraction in the saturated solutions, and activity coefficient of ACP as decimal logarithm, at 298.15 K.

φ **PEG**	δ_1 / **MPa**$^{1/2}$	**ACP**			$\rho_{solvent}$ / **g cm**$^{-3}$	$\rho_{satd\ soln}$ / **g cm**$^{-3}$ *a*	ϕ_V^{mol} / **cm**^{3} **mol**$^{-1}$	ϕ_1	**log** γ_2
		Mol L^{-1}	X_2	**%CV**					
0.0000	47.80	0.103	1.88 E-3	0.18	0.9970	0.9997	125.6	0.9871	1.142
0.0898	45.58	0.167	3.35 E-3	0.79	1.0131	1.0173	124.6	0.9791	0.891
0.1817	43.31	0.266	5.91 E-3	0.87	1.0298	1.0361	123.9	0.9671	0.644
0.2757	40.99	0.425	1.07 E-2	0.45	1.0471	1.0563	123.7	0.9474	0.386
0.3719	38.61	0.640	1.87 E-2	0.42	1.0650	1.0762	125.5	0.9197	0.144
0.4704	36.18	0.956	3.35 E-2	0.58	1.0821	1.0963	126.0	0.8795	-0.109
0.5713	33.69	1.319	5.73 E-2	0.53	1.0971	1.1145	125.8	0.8341	-0.343
0.6745	31.14	1.613	9.01 E-2	0.72	1.1090	1.1296	124.8	0.7987	-0.539
0.7804	28.52	1.834	0.141	0.35	1.1164	1.1407	123.5	0.7734	-0.733
0.8888	25.85	1.907	0.221	0.20	1.1204	1.1477	122.2	0.7670	-0.930
1.0000	23.10	1.616	0.417	0.18	1.1224	1.1465	121.4	0.8039	-1.205

[a] From Rodríguez *et al*. (33).

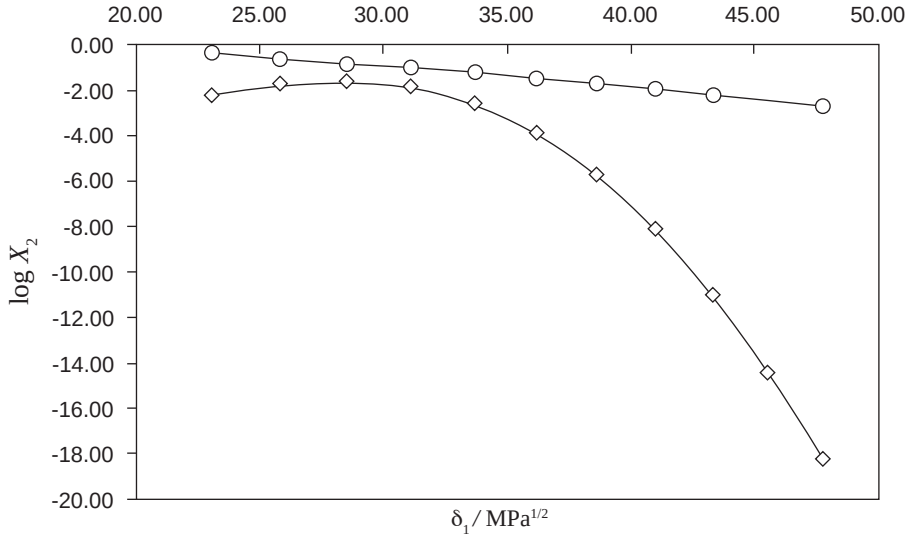

Figure 2. Experimental solubility (○) and calculated solubility according to the regular solutions model of Hildebrand (◊) of ACP as a function of the solubility parameter of the solvent mixtures at 298.15 K.

ues and ideal solubility at 298.15 K (X_2 = 2.602 x 10^{-2}). In water rich mixtures, γ_2 values were greater than unit because the experimental solubilities are lower than the ideal value but in PEG rich mixtures these values were below one.

In order to calculate the *W* parameter, the solubility parameter of ACP (δ_2) is required and for this reason it was calculated by using Fedors and Van Krevelen methods as showed in Table 2 (34) obtaining the value 27.3 $MPa^{1/2}$ which is similar to that obtained experimentally in ethanol + water and ethanol (6) + propylene glycol mixtures (8), i.e. 28.0 $MPa^{1/2}$. In the next calculations the experimental value was used. It is interesting that PEG, where the maximum drug solubility is obtained, has a lower δ value (23.1 $MPa^{1/2}$) compared to ACP. This result demonstrates that the maximum solubility is not always obtained in mixtures where the solubility parameters of drug and solvent are coincident.

Table 3 summarizes the parameters *A*, *K*, and *W* for ACP in PEG + water mixtures. 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 (Eq. 5). Table 4 summarizes the coefficients obtained in all the regular polynomials from degrees one to five, whereas the *W* values back-calculated by using the respective 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 this drug and for several other compounds in different solvent mixtures (6-27).

Table 6 summarizes the solubility values obtained by using the *W* values obtained by back-calculation from the polynomial models (Table 4) which are presented in Table 5. In the same way it was made previously (6-27) and because the best adjustment is being searched, the first criterion used to define the polynomial order of *W* term as function of δ_1 was the fitting standard uncertainties obtained, which values were as follows, 30.4, 0.420, 0.282, 0.074, and 0.066 (Table 4), for orders one to five, respectively. As another comparison criterion, Table 6 also summarizes the percentages of difference between ACP experimental solubility and those calculated by using EHSA.

It was found that the more complex the polynomial used, the better the agreement found between experimental and calculated solubility. The most important increment in concordance is obtained when going from order 1 to order 2 (From 2925 to 4.13%). It is important to note that for pharmaceutical purposes an uncertainty below 5% is useful for practical purposes but for academic purposes a better agreement is required. In this way, the best improvement is obtained going from 3rd to 4th degree, i.e. from 3.27 to 0.69%. Thereby, in the following calculations the model in order 4 was used, just as has been made earlier on (26, 27). Nevertheless, it is interesting that the mean deviation using a polynomial of order 5 (0.49%, Table 6) is almost the same obtained as mean in the experimental uncertainties obtained (0.50%, Table 1)

Table 2. Application of group contribution method to estimate the molar volume, partial solubility parameters, and total Hildebrand solubility parameter of ACP.

Group	Quantity	Fedors [a]	Van Krevelen [a]		
		V / cm^3 mol^{-1}	F_d / J$^{1/2}$ cm$^{3/2}$ mol^{-1}	F_p^2 / J cm^3 mol^{-2}	U_h / J mol^{-1}
–OH	1	10.0	210	5002	20000
>C=O	1	10.8	290	7702	2000
–NH–	1	4.5	160	2102	3100
Phenylene	1	52.4	1270	1102	0
–CH_3	1	33.5	420	02	0
		111.2 [b]	2350	899100	25100
		δ_d [c]	δ_p [d]	δ_h [e]	
			(2350/111.2) = 21.13 MPa$^{1/2}$	((899100)$^{1/2}$/111.2) = 8.53 MPa$^{1/2}$	(25100/111.2)$^{1/2}$ = 15.02 MPa$^{1/2}$
			δ_T [f]		
			(21,13^2 + 8.53^2 + 15.02^2)$^{1/2}$ = **27.3 MPa$^{1/2}$**		

[a] Calculated according to values and procedures presented by Barton (34). [b] Molar volume. [c] Partial solubility parameter by dispersion forces. [d] Partial solubility parameter by dipolar forces. [e] Partial solubility parameter by hydrogen bonding. [f] Total solubility parameter.

Table 3. A, K, and W experimental parameters for ACP in PEG + water mixtures at 298.15 K.

δ_1 / MPa$^{1/2}$	100 A / cm^3 J^{-1}	K / J cm^{-3} [a]	W_{expt} / J cm^{-3} [a]
47.80	4.25994	0.568223	1521.021
45.58	4.15917	0.556353	1420.116
43.31	4.03337	0.545040	1321.969
40.99	3.86480	0.534579	1227.081
38.61	3.69406	0.525147	1135.548
36.18	3.39298	0.517311	1048.134
33.69	3.04575	0.511563	965.133
31.14	2.77110	0.508406	886.542
28.52	2.57233	0.509009	813.088
25.85	2.50179	0.514442	744.595
23.10	2.73008	0.526342	680.877

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

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 ACP (equation [6]). Values in parentheses are the respective uncertainties.

Coefficient or Parameter	Polynomial order				
	1	**2**	**3**	**4**	**5**
C_0	-154 (43)	460.4 (2.9)	429 (10)	295 (14)	184 (70)
C_1	34.1 (1.2)	-2.22 (0.17)	0.6 (0.9)	16.7 (1.7)	33 (10)
C_2	-	0.5105 (0.0024)	0.427 (0.025)	-0.28 (0.07)	-1.3 (0.6)
C_3	-	-	7.8 (2.4) E-4	1.44 (0.14) E-2	4.3 (1.8) E-2
C_4	-	-	-	-9.6 (1.0) E-5	-5.1 (2.5) E-4
C_5	-	-	-	-	2.3 (1.4) E-6
Adj. r^2	0.9868	1.0000	1.0000	1.0000	1.0000
Fit. Err.	30.412	0.4200	0.2820	0.0737	0.0656

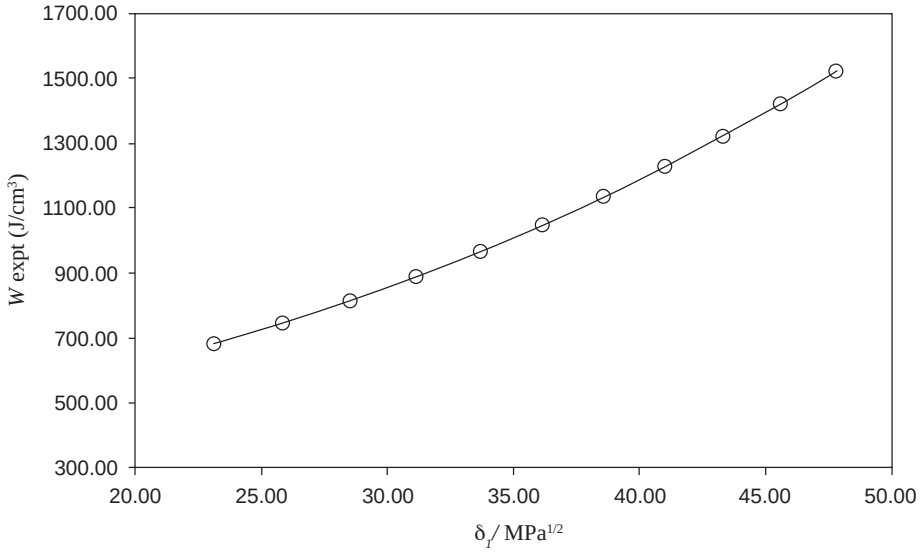

Figure 3. *W* parameter as a function of the solubility parameter of the solvent mixtures at 298.15 K.

Table 5. *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	1475.361	1520.838	1521.260	1520.995	1521.021
45.58	1399.751	1419.981	1419.937	1420.159	1420.110
43.31	1322.412	1322.019	1321.738	1322.006	1321.989
40.99	1243.285	1227.234	1226.907	1226.998	1227.024
38.61	1162.308	1135.933	1135.701	1135.573	1135.610
36.18	1079.414	1048.443	1048.393	1048.142	1048.151
33.69	994.535	965.118	965.274	965.066	965.037
31.14	907.598	886.339	886.653	886.644	886.605
28.52	818.528	812.520	812.857	813.094	813.093
25.85	727.245	744.104	744.233	744.523	744.576
23.10	633.666	681.573	681.151	680.905	680.882

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

Table 6. Calculated solubility of ACP 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	2.42 E-7	1.81 E-3	1.97 E-3	1.87 E-3	1.88 E-3	100	3.52	4.82	0.51	0.01
45.58	6.77 E-5	3.26 E-3	3.23 E-3	3.38 E-3	3.34 E-3	98	2.56	3.38	0.82	0.12
43.31	6.42 E-3	5.97 E-3	5.66 E-3	5.95 E-3	5.93 E-3	9	0.93	4.20	0.70	0.38
40.99	0.191	1.10 E-2	1.04 E-2	1.05 E-2	1.06 E-2	1689	2.76	3.06	1.48	1.01
38.61	1.773	2.00 E-2	1.92 E-2	1.88 E-2	1.89 E-2	9386	6.77	2.63	0.43	1.06
36.18	4.439	3.51 E-2	3.49 E-2	3.35 E-2	3.36 E-2	13164	4.95	4.13	0.13	0.27
33.69	3.542	5.72 E-2	5.84 E-2	5.68 E-2	5.65 E-2	6081	0.21	2.01	0.94	1.33
31.14	1.323	8.78 E-2	9.14 E-2	9.13 E-2	9.08 E-2	1369	2.55	1.43	1.31	0.81
28.52	0.268	0.132	0.137	0.141	0.141	90	6.50	2.70	0.07	0.06
25.85	3.00 E-2	0.209	0.212	0.220	0.221	86	5.50	4.09	0.83	0.23
23.10	1.10 E-3	0.455	0.432	0.419	0.418	100	9.15	3.51	0.36	0.07
Standard Deviation [b]				Mean value [b]		2925	4.13	3.27	0.69	0.49
						4572	2.70	1.02	0.45	0.48

[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.

As it has been described previously, an important consideration about the usefulness of the EHSA method is that which refers to justifying the complex calculations involving any other variables, instead of the simple empiric regression of the experimental solubility as a function of the solvent mixtures' solubility parameters (Table 1, Figure 4). For this reason, in the Table 7 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 [7], with adjusted determination coefficient $r^2 = 0.9998$ and fitting standard uncertainty = 0.0111) and also to those calculated involving the *W* parameters obtained from Eq. [5] adjusted to order 4 (Tables 4 and 5). The respective difference percentages are also presented in Table 7.

$$\log X_2 = 11.8(2.1) - 1.34(0.25)\delta_1 + 5.5(1.1)\times 10^{-2}\delta_1^2 - 1.06(0.21)\times 10^{-3}\delta_1^3 + 7.3(1.5)\times 10^{-6}\delta_1^4 \qquad [7]$$

Table 7. Comparison of the ACP solubility values calculated directly and by using the EHSA at 298.15 K.

δ_1 / MPa$^{1/2}$	X_2			% dev. [a]	
	Exptl.	Calc. direct. [b]	Calc. *W* [c]	Calc. direct.	Calc. *W*
47.80	1.878 E-3	1.91 E-3	1.87 E-3	1.49	0.51
45.58	3.348 E-3	3.26 E-3	3.38 E-3	2.54	0.82
43.31	5.910 E-3	5.88 E-3	5.95 E-3	0.57	0.70
40.99	1.070 E-2	1.07 E-2	1.05 E-2	0.36	1.48
38.61	1.869 E-2	1.93 E-2	1.88 E-2	3.45	0.43
36.18	3.347 E-2	3.36 E-2	3.35 E-2	0.37	0.13
33.69	5.730 E-2	5.58 E-2	5.68 E-2	2.60	0.94
31.14	9.010 E-2	8.92 E-2	9.13 E-2	1.05	1.31
28.52	0.141	0.140	0.141	0.37	0.07
25.85	0.221	0.228	0.220	2.92	0.83
23.10	0.417	0.412	0.419	1.23	0.36
		Mean value [d]		1.54	0.69
		Standard Deviation [d]		1.14	0.45

[a] Calculated as $100 \times |X_2 \text{ expt} - X_2 \text{ calc}| / X_2$ expt. [b] Calculated using Eq [5] adjusted to order 4 (Table 3). [c] Calculated using Eq. [7]. [d] Calculated considering the obtained values in the neat solvents and the nine binary mixtures.

Based on mean deviation percentages presented in Table 6 (1.54% and 0.69% for direct calculation and EHSA method, respectively) it follows that a slight difference is found between the values obtained by using both methods. As it has happened for several drugs, the present results show a significant usefulness of the EHSA method for practical and academic purposes, in particular, if differences below 1% are required.

On the other hand, it is very interesting that this drug mainly exhibits posi-

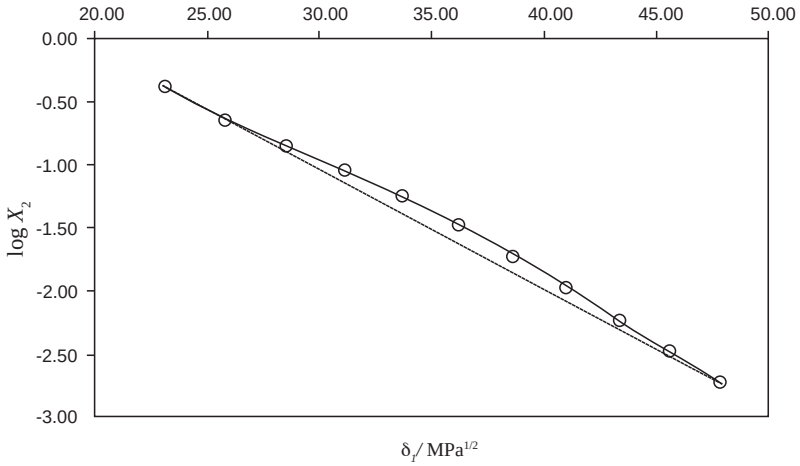

Figure 4. Logarithmic solubility of ACP as a function of the solubility parameter of the solvent mixtures at 298.15 K. Dotted line is the additive solubility behavior.

tive deviations with respect to the ideal log-linear additive model proposed by Yalkowsky and Roseman (dotted line in Figure 4) (3). This behavior is different compared to those observed by Rubino and Obeng (35) who found negative deviations in water-rich mixtures and positive deviations in propylene glycol-rich mixtures by studying the solubility of homologous series of some alkyl *p*-hydroxybenzoates and *p*-aminobenzoates. It is also different compared to those reported for ibuprofen, naproxen, ketoprofen, and indomethacin in the similar cosolvent mixtures (36-40) where negative and positive deviations were also found in water-rich and cosolvent-rich mixtures, respectively. The results for ACP in PEG mixtures could be attributed to a better solvation of the drug by the cosolvent molecules by means of hydrogen bonding where the phenolic hydroxyl group of ACP would be interacting with the ether groups of PEG.

CONCLUSION

The EHSA method has been adequately used in the present work to study the solubility of acetaminophen in PEG + 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. In this way, the predictive character of EHSA is better than that obtained by direct correlation between solubility and mixtures composition.

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