# Aplicación del Método Extendido de Hildebrand a la solubilidad de la mitomicina C en mezclas etanol + agua

# Application of the Extended Hildebrand solubility approach applied to mitomycin C in ethanol + water mixtures

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**Resumen**

En este trabajo se aplicó el método extendido de solubilidad de Hildebrand (MESH) para evaluar la solubilidad de mitomicina C en mezclas etanol + agua a 293,15 K. Se reporta la solubilidad experimental y algunas propiedades de fusión de éste fármaco que fueron utilizados para los cálculos del método extendido de Hildebrand. En particular, EHSA presenta un buen carácter predictivo mediante el uso de un polinomio regular de orden cinco para el parámetro de interacción *W* en una función del parámetro de solubilidad de mezclas cosolvente libre de fármaco.

***Palabras clave***: Mitomicina; Etanol; Mezclas binarias; Método extendido Hildebrand; parámetros de solubilidad.

**Abstract**

In this work, we applied the extended Hilderband solubility approach (EHSA) to evaluate the solubility of mitomycin C in ethanol-water mixtures at 293.15 K. We report the experimental solubility and some of the drug's fusion properties that were used for the calculations in the extended Hilderband approach. In particular, EHSA presents good predicative properties by means of a regular fifth-degree polynomial for interaction parameter *W* in a function of the solubility parameter of solvent mixtures without the drug.

***Key words****:* Mitomycin, etanol; binary mixtures, extended Hildebrand solubility approach; solubility parameters.

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## 1. Introduction

Mitomycin C Fig 1. ($C_{15}H_{18}N_4O_5$, molecular weight 334.33, IUPAC [6-Amino-8a-methoxy-5-methyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazireno[2',3':3,4] pyrrolo[1,2-a]indol-8-yl]methyl carbamate, CAS Registry No.: 50-07-7) (Gandhi and Murthy, 2012) is an antibiotic and anti-neoplastic material isolated from the broth of Streptomyces caespitosus and is one of the naturally occurring antibiotics that was first discovered in 1956 (Hata, *et al*., 1956). This drug has been demonstrated to have antifibroblastic activity in vitro and in vivo (Unal, 2004). It is an antineoplastic antibiotic that acts as an alkylating agent by inhibiting DNA and protein synthesis. It can inhibit cell division, protein synthesis, and fibroblast proliferation (Rahbar, *et al*., 2000). Despite the usefulness of these drugs, their physicochemical properties in aqueous solution have not yet studied completely (Budavari, *et al.*, 2001; Gandhi and Murthy, 2012). In particular, it is well known that their solubilities in neat aqueous media are very low (Jouyban, 2010). It is noteworthy that cosolvency is the best technique used in pharmacy for increasing drugs solubility (Rubino, 1988; Yalkowsky, 1999). On the other hand, it is clear that predictive methods of physicochemical properties of drugs, in particular the ones intended to estimate solubilities, are very important for industrial pharmacists because they allow optimizing several design processes (Budavari, 2001; Martin, *et al*., 1993; Regosz, *et al*., 1992; Martínez and Gómez, 2002; Hanaee, *et al*., 2005).

For this reason, this work presents a physicochemical study about the solubility prediction of the mitomycin C, in binary mixtures conformed by ethanol (EtOH) and water at 293.15 K. The study was done based on the Extended Hildebrand Solubility Approach (EHSA) (Martin, *et al.*, 1993; Martin and Bustamante, 1989; Martínez, 2005) by using experimental solubility values and some properties relative to the fusion of these drugs taken from the literature (Gandhi and Murthy, 2012). It is important to keep in mind that EHSA method has been widely used to study the solubility of a lot of pharmaceutical compounds as has been recently exposed in the literature (Holguín, *et al*., 2012). Furthermore, it is still employed to evaluate the behavior of drugs in several co-solvent mixtures (Sotomayor, *et al.*, 2013; Cristancho, *et al.*, 2013; Gómez, *et al.*, 2013; Rathi, 2011; Dehpande, *et al.*, 2014). On the other hand, it is remarkable that EtOH is one of the more employed co-solvent to develop liquid pharmaceutical dosage forms because of its solubilizing and antimicrobial properties (Smolinske, 1992; Aulton, 2002).

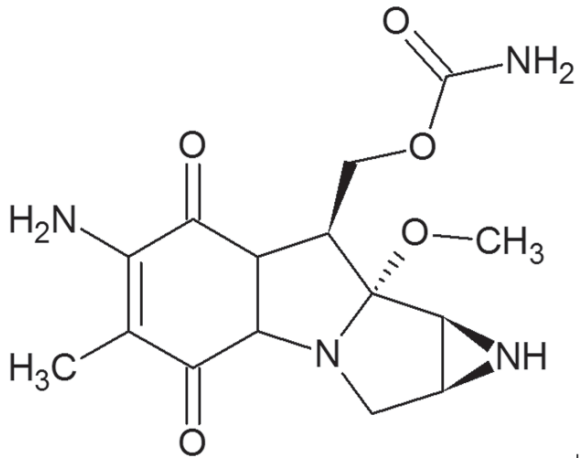


**Figura 1.** Molecular structure of Mitomycin C.

## 2. Theoretical

The ideal solubility ($X_3^{id}$) of a solid solute is calculated by means of the expression,

$$\log X_3^{id} = -\frac{\Delta H_{fus}\left(T_{fus}-T\right)}{2.303RT_{fus}T}+\left(\frac{\Delta C_p}{2.303R}\right)\left[\left(\frac{T_{fus}-T}{T}\right)+\ln\left(\frac{T}{T_{fus}}\right)\right] \quad (1)$$

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 gas constant (8.314 J $mol^{-1}$ $K^{-1}$), 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 $\Delta C_p$ cannot be easy experimentally determined, this property may be approximated to the entropy of fusion, $\Delta S_{fus}$. Ideal solubility depends only on the physicochemical properties of the solid compound without considering the properties of the solvent. For this reason the ideal solubility would be higher as the solute-solute interactions are lower (Gandhi and Murthy, 2012). Accordingly, compounds with high values of melting point and enthalpy of fusion have lower ideal solubilities.

On the other hand, the real solubility ($X_3$) of a solid solute in a liquid solution is calculated by means of the expression,

$$-\log X_3 = -\log X_3^{id} + \log \gamma_3 \quad (2)$$

where, $\log \gamma_3$ is the non-ideality term, being $\gamma_3$ the solute activity coefficient, which is determined experimentally.

Nevertheless, one method of calculating $\gamma_3$ is the referent to regular solutions obtained from,

$$-\log X_3 = -\log X_3^{id} + \frac{V_3\phi_1^2}{2.303RT}(\delta_1 - \delta_3)^2 \qquad (3)$$

where, $V_3$ 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 $\delta_3$ are the solubility parameters of solvent and solute, respectively. $\phi_1$ is calculated as,

$$\phi_1 = \frac{V_1(1 - X_3)}{V_1(1 - X_3) + V_3X_3} \qquad (4)$$

where $V_1$ is the molar volume of solvent.

Nevertheless, all the pharmaceutical dissolutions deviate of predicted by the regular solutions theory. For this reason, Martin et al. developed the EHSA method (Martin and Carstense, 1980; Martin and Wu, 1981; Martin and Miralles, 1982; Martin, *et al.*, 1981, 1982, 1985). Thus, if the *A* term (defined as $V_3\phi_1^2/(2.303RT)$) is introduced in the Eq. (3), the real solubility of drugs can be calculated from the expression, $X_3$

$$-\log X_3 = -\log X_3^{id} + A\left(\delta_1^2 + \delta_3^2 - 2W\right) \quad (5)$$

where, the *W* term is equal to $2K\delta_1\delta_3$ (where, *K* is the Walker parameter (Martínez and Gómez, 2002). The *W* factor can be calculated from experimental data by means of,

$$W = 0.5 \times \left(\delta_1^2 + \delta_3^2 - \frac{\log \gamma_3}{A}\right) \qquad (6)$$

where, $\gamma_3$ is the activity coefficient of the solute in the saturated solution, and it is calculated as, $X_3^{id} / X_3$. The experimental values of the *W* parameter can be correlated by means of regression analysis by using regular polynomials as a function of $d_1$, as follows,

$$W = C_0 + C_1\delta_1 + C_2\delta_1^2 + C_3\delta_1^3 ..... + C_n\delta_1^n \quad (7)$$

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.

## 3. Results and discussion

The required properties about the mitomycin C studied, like ideal solubility, molar volume and Hildebrand solubility parameter (Table 1), was calculated from the drug thermodynamic data reported previously in the literature (Gandhi and Murthy, 2012); whereas, the volumetric behavior and polarity of EtOH + water mixtures, as a function of the composition, is shown in Table 2 (Gandhi and Murthy, 2012). Volume fractions and Hildebrand solubility parameters were calculated assuming additive behavior (Martin, *et al*., 1993; Connors, 2002). Table 2 also summarizes the experimental solubility of the mitomycin expressed in mole fraction reported in the literature (Gandhi and Murthy, 2012), including ideal solubility.

Figure 2 shows the ideal and experimental solubility, as well as the calculated solubility by using the regular

**Table 1.** Interne energy, molar volume and Hildebrand solubility parameter of mitomycin C according to the Fedors method.

| Group | Number | $\Delta U°$ / kJ mol$^{-1}$ | $V°$ / cm$^3$ mol$^{-1}$ |
|---|---|---|---|
| -$NH_2$ | 2 | 2x12.6=25.2 | 2x19.2=38.4 |
| -NH- | 1 | 8.4 | 4.5 |
| >N- | 1 | 4.2 | -9.0 |
| –O– | 2 | 2x3.35=6.7 | 2x3.8=7.6 |
| –$CH_3$ | 2 | 2 x 4.71=9.42 | 2 x 33.5=67.0 |
| >C=O | 3 | 3x17.4=52.2 | 3x18.8=56.4 |
| >C= | 4 | 4x4.31=17.24 | 4x-5.5=-22.2 |
| >C< | 1 | 1.47 | -19.2 |
| -$CH_2$- | 2 | 2x4.94=9.88 | 2x16.1=32.2 |
| –CH< | 3 | 3x3.43=10.29 | 3x-1.0=-3 |
| Ring closure | 4 | 4x1.05=4.20 | 4x16.0=64.00 |
| Conjugated bond | 2 | 2x1.67=3.34 | 2x–2.20=-4.40 |
| | Σ | 152.54 | 212.50 |
| | | $\delta = (152{,}540/212.5)^{1/2} = 26.79$ MPa$^{1/2}$ | |

**Table 2.** Ethanol + water solvent mixtures composition, Hildebrand solubility parameter of mixtures and solubility of mitomycin expressed in mole fraction, including ideal solubility at 293.15 K.

| Mitomycin C | | |
|---|---|---|
| $x_1$ [a] | $\delta_1$ / MPa$^{1/2}$ | $x_3$ [b] |
| 0.0000 | 47.86 | $2.46\times10^{-5}$ |
| 0.1000 | 43.59 | $4.65\times10^{-5}$ |
| 0.2000 | 40.18 | $4.62\times10^{-5}$ |
| 0.3000 | 37.39 | $1.59\times10^{-4}$ |
| 0.4000 | 35.06 | $4.33\times10^{-4}$ |
| 0.5000 | 33.09 | $9.63\times10^{-4}$ |
| 0.6000 | 31.40 | $1.43\times10^{-3}$ |
| 0.7000 | 29.93 | $2.47\times10^{-3}$ |
| 0.8000 | 28.65 | $1.13\times10^{-3}$ |
| 0.9000 | 27.52 | $9.23\times10^{-4}$ |
| 1.0000 | 26.51 | $7.53\times10^{-4}$ |
| Ideal Ideal solubility | | $3.819\times10^{-2}$ |

[a] $x_1$ is the mass and volume fraction of ethanol in the co-solvent mixtures free of mitomycin C.
[b] Data from Ref. (Gandhi and Murthy, 2012)

solution model, i.e. Eq. (3), as a function of the solubility parameter of solvent mixtures, from 26.5 to 47.8 MPa$^{1/2}$. In order to use Eq. (3) the molar volume and Hildebrand solubility parameter of the mitomycin C, estimated according to the groups contribution method proposed by Fedors, is 26.70 MPa$^{1/2}$ Table 1 (Fedors, 1974). It is important to keep in mind that according to regular solutions model the maximum solubility value corresponds to the ideal solubility and it is obtained just when both solubility parameters of drug and solvent mixture are coincident, like it is shown in Fig. 2. On the other hand, according to the literature the maximum experimental solubility values are found when the solubility parameters of both solute and solvent are also coincident (Martin and Bustamante, 1993, 1989). Nevertheless, in the present case the experimental drug solubilities are lower than the calculated according to Eq. (3) in all the compositions for the mitomycin C.

The $\phi_1$ values calculated according to Eq. (4) are almost equal to 1.000 because the solubility of mitomycin C is very low in all the solvent system considered, varies form 0.9997 and 0.9888 in EtOH-rich mixtures due to its high solubility (Table 3). Otherwise, the activity coefficients of mitomycin C expressed as decimal

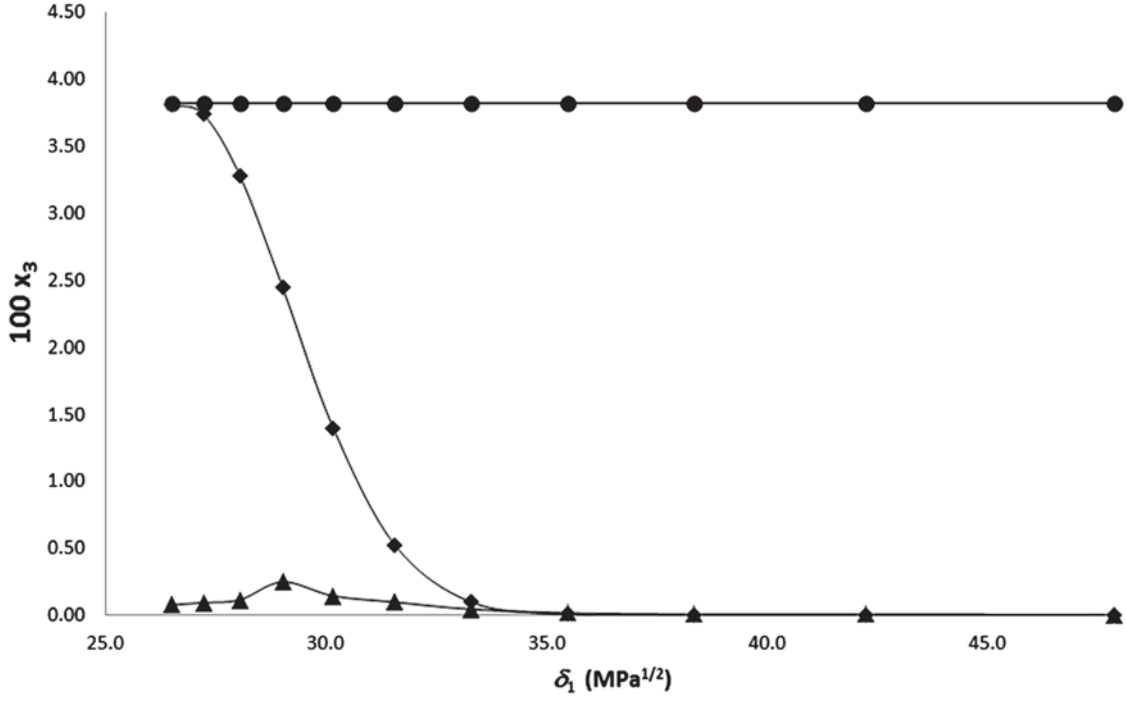


**Figure 2.** Ideal solubility (●), experimental solubility (▲) and calculated solubility according to the regular solutions model of Hildebrand (◆) of mitomycin C as a function of the solubility parameter in ethanol + water mixtures at 293.15 K.

logarithms are also presented in Table 3. This table also summarizes the parameters *A*, *K*, and *W* for the mitomycin C in EtOH + water mixtures; whereas, Figure 3 shows that the variation of the *W* parameter with respect to the solubility parameter of solvent mixtures, presents deviation from linear behavior, just as it is expectable because the *W* term implies the summation of two quadratic ($\delta_2^2$ and $\delta_2^2$) and one non-constant-quotient (–log $\delta\gamma_2$ / *A*) terms, as Eq. (6) shows.

*W* values were adjusted to regular polynomials in orders from 2 to 5 (Eq. 7). Linear equation was also considered just as comparison. Table 4 summarizes the coefficients obtained in all the regular polynomials

**Table 3.** Volume fraction of solvent, mitomicyn C activity coefficients, *A*, *K*, and *W* experimental parameters of mitomycin C in ethanol + water mixtures at 293.15 K.

| Mitomycin C | | | | | |
|---|---|---|---|---|---|
| $\delta_1$ / MPa$^{1/2}$ | $\phi_1$ | log $\gamma_3$ | 100 *A* / cm$^3$ J$^{-1}$ | *K* / J cm$^{-3}$ [a] | *W* / J cm$^{-3}$ [a] |
| 47.86 | 0.9997 | 3.191 | 3.698 | 0.57072 | 1458.6 |
| 43.59 | 0.9996 | 2.915 | 3.697 | 0.53595 | 1208.3 |
| 40.18 | 0.9996 | 2.917 | 3.697 | 0.51372 | 1051.2 |
| 37.39 | 0.9989 | 2.381 | 3.692 | 0.50325 | 953.0 |
| 35.06 | 0.9973 | 1.946 | 3.680 | 0.49731 | 883.8 |
| 33.09 | 0.9946 | 1.599 | 3.661 | 0.49404 | 832.5 |
| 31.40 | 0.9929 | 1.428 | 3.647 | 0.49157 | 791.7 |
| 29.93 | 0.9888 | 1.189 | 3.618 | 0.49112 | 760.8 |
| 28.65 | 0.9953 | 1.530 | 3.665 | 0.48667 | 728.8 |
| 27.52 | 0.9965 | 1.617 | 3.674 | 0.48495 | 704.9 |
| 26.51 | 0.9973 | 1.705 | 3.680 | 0.48365 | 684.7 |

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

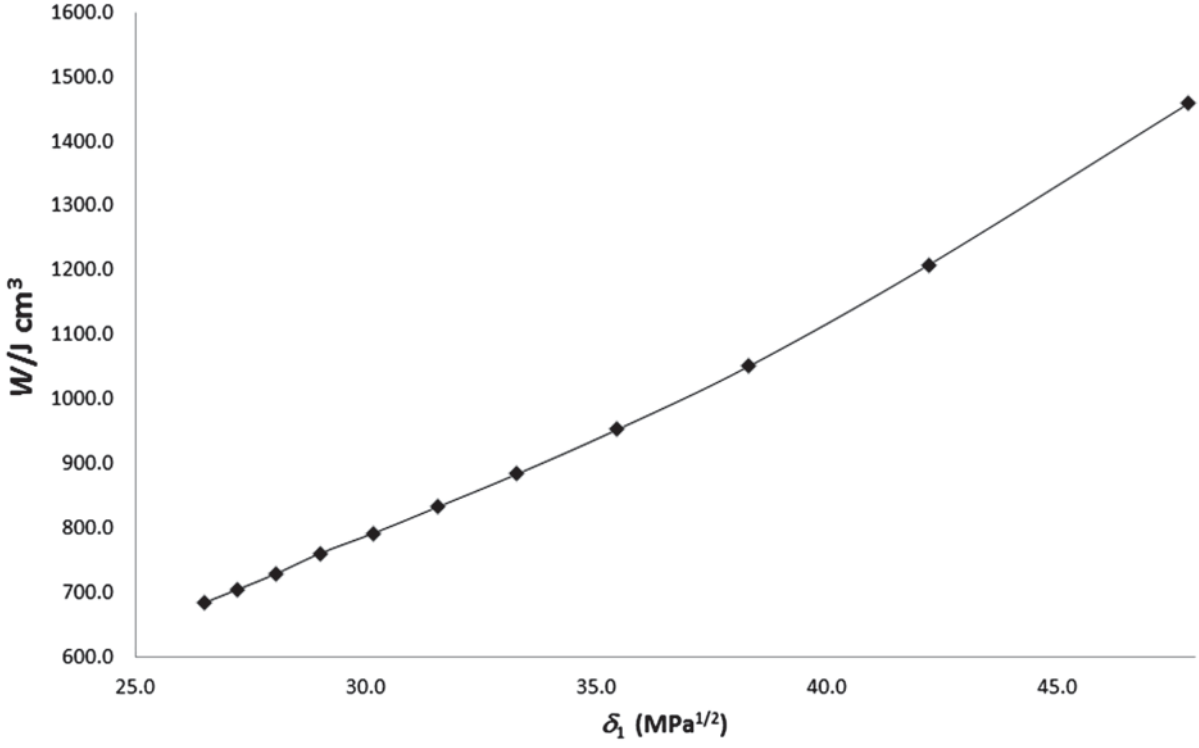


**Figure 3.** *W* parameter of mitomycin C in ethanol + water mixtures as a function of the solubility parameter of the solvent mixtures at 293.15 K.

for the mitomycin. The significant figures in the coefficients and uncertainties were defined according to the criterion 3-30, when that was possible (Shoemaker and Garland, 1968). Briefly, this criterion establishes that the numeric quantity in uncertainty should be placed between 3 and 29, without consider decimal positions, except if they integers greater than 30. In this way the number of decimal places for the coefficients is defined according to the decimal places of the respective uncertainties.

It is found that as more complex the polynomial used is, better the agreement found between experimental and calculated solubility also is. Accordingly, the most important increment in concordance is obtained

**Table 4.** Coefficients and statistical parameters of regular polynomials in several orders of *W* as a function of solubility parameters of co-solvent mixtures free of mitomycin C (Eq. 7) in ethanol + water mixtures at 293.15 K. Values in parentheses are the respective uncertainties.

| Mitomycin C | | | | | |
|---|---|---|---|---|---|
| Coefficient or Parameter | Polynomial order | | | | |
| | 1 | 2 | 3 | 4 | 5 |
| $C_0$ | -271 (36) | 383 (39) | -162 (184) | -3426 (644) | 2443 (5394) |
| $C_1$ | 35.3 (1.1) | -1.9 (2.2) | 44 (16) | 415 (73) | -425 (771) |
| $C_2$ | - | 0.509 (0.030) | -0.8 (0.4) | -16 (3) | 31 (44) |
| $C_3$ | - | - | 0.012 (0.004) | 0.30 (0.06) | -1.0 (1.2) |
| $C_4$ | - | - | - | -0.0019 (0.0004) | 0.017 (0.017) |
| $C_5$ | - | - | - | - | 10 (9)x$10^{-5}$ |
| Adj. $r^2$ | 0.989 | 0.9997 | 0,9998 | 1.0000 | 1.0000 |
| Fit. Err. | 22.90 | 3.953 | 2.795 | 1.304 | 1.283 |

In the same way as was previously made (Sotomayor, *et al*., 2013; Gómez, *et al*., 2013; Tathi and deshpande, 2014), since we are 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 uncertainties obtained (Table 4). As another comparison criterion, beside the calculated solubility values, Table 5 also summarizes the difference percentages between the experimental solubilities and those calculated by using EHSA.

**Table 5.** Calculated solubility of mitomicyn C 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 293.15 K.

| **Mitomycin C** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\delta_1$ / | $X_3$ **calculated** | | | | | **% dev.** [a] | | | | |
| **MPa$^{1/2}$** | **1** | **2** | **3** | **4** | **5** | **1** | **2** | **3** | **4** | **5** |
| 47,8600 | 2.16E-08 | 1.80E-05 | 2.90E-05 | 2.48E-05 | 2.46E-05 | 99.91 | 26.70 | 17.74 | 0.99 | 0.01 |
| 42,2210 | 2.56E-04 | 5.22E-05 | 2.32E-05 | 4.31E-05 | 4.63E-05 | 450.75 | 12.36 | 50.16 | 7.42 | 0.39 |
| 38,3214 | 7.06E-03 | 1.15E-04 | 7.63E-05 | 5.48E-05 | 4.77E-05 | 15181.39 | 149.56 | 65.18 | 18.62 | 3.30 |
| 35,4640 | 1.55E-02 | 2.14E-04 | 2.32E-04 | 1.44E-04 | 1.45E-04 | 9686.42 | 34.89 | 45.97 | 9.07 | 8.65 |
| 33,2802 | 1.12E-02 | 3.52E-04 | 5.11E-04 | 4.20E-04 | 4.60E-04 | 2475.86 | 18.61 | 18.12 | 3.06 | 6.21 |
| 31,5569 | 4.90E-03 | 5.33E-04 | 8.47E-04 | 9.59E-04 | 1.03E-03 | 408.50 | 44.65 | 12.03 | 0.41 | 6.67 |
| 30,1624 | 1.75E-03 | 7.45E-04 | 1.12E-03 | 1.54E-03 | 1.54E-03 | 22.93 | 47.74 | 21.80 | 8.15 | 7.81 |
| 29,0108 | 6.04E-04 | 1.00E-03 | 1.28E-03 | 1.82E-03 | 1.70E-03 | 75.57 | 59.34 | 48.38 | 26.52 | 31.09 |
| 28,0436 | 1.90E-04 | 1.21E-03 | 1.22E-03 | 1.52E-03 | 1.41E-03 | 83.15 | 6.96 | 8.04 | 35.10 | 24.77 |
| 27,2199 | 6.46E-05 | 1.46E-03 | 1.12E-03 | 1.06E-03 | 1.03E-03 | 92.99 | 58.11 | 21.40 | 15.06 | 11.65 |
| 26,5100 | 2.32E-05 | 1.73E-03 | 9.82E-04 | 6.28E-04 | 6.86E-04 | 96.91 | 129.05 | 30.40 | 16.58 | 8.90 |
| | | | | Mean value [a] | | 2606.8 | 53.5 | 30.8 | 12.8 | 9.9 |
| | | | | Standard Deviation [b] | | 4825.1 | 43.9 | 17.8 | 10.4 | 9.2 |

[a] Calculated as $100 \times |X_3 \text{ expt} - X_3 \text{ calc}| / X_3 \text{ expt}$.

passing from order 1 to order 2. The concordances also increase in good way from order 2 to 3 and from order 3 to 4. In the last case the mean uncertainties obtained are in the same order or lower than those reported experimentally (Gandhi and Murthy, 2012). It is important to keep in mind that for pharmaceutical purposes uncertainties lower than 5% are useful for practical purposes but for academic purposes best agreements are required. In this way, although an additional improves is obtained by passing from order 4 to 5 this result is not relevant because the mean uncertainties are lower in comparison with those reported for experimental values (Gandhi and Murthy, 2012).

As has been previously described, a very important consideration about the usefulness of the EHSA method is the one referent to justify the complex calculations involving any other experimental variables of solute and solvents, instead of the simple empiric regression of the experimental solubility as a function of the solubility parameters of solvent mixtures as shown in Fig. 3. For this reason, Table 6 shows the coefficients of regular polynomials in order 4 of $\log X_3$ as a function of $d_1$ values (Eq. 8). The significant figures in the coefficients and uncertainties were also defined according to the criterion 3-30 (Shoemaker and Garland, 1968).

**Table 6.** Coefficients and statistical parameters of regular polynomials in fourth degree of $\log X_3$ as a function of solubility parameters of cosolvent mixtures free of Mitomycin C (Eq. 8) in ethanol + water mixtures. Values in parentheses are the respective uncertainties.

| Coefficient or Parameter | Data |
|---|---|
| $C_0^*$ | -287 (49) |
| $C_1^*$ | 31 (5) |
| $C_2^*$ | -1.28 (0.23) |
| $C_3^*$ | 0.022 (0.004) |
| $C_4^*$ | -14.7 (2.9) x $10^{-5}$ |
| Adj. $r^2$ | 0.9756 |
| Fit. Err. | 0.0990 |

$$\log X_2 = C_0^* + C_1^*\delta_1 + C_2^*\delta_1^2 + C_3^*\delta_1^3 + C_4^*\delta_1^4 \quad (8)$$

On the other hand, Table 7 shows the calculated values of solubility by using Eq. (8) in and also the respective difference percentages in front the experimental ones.

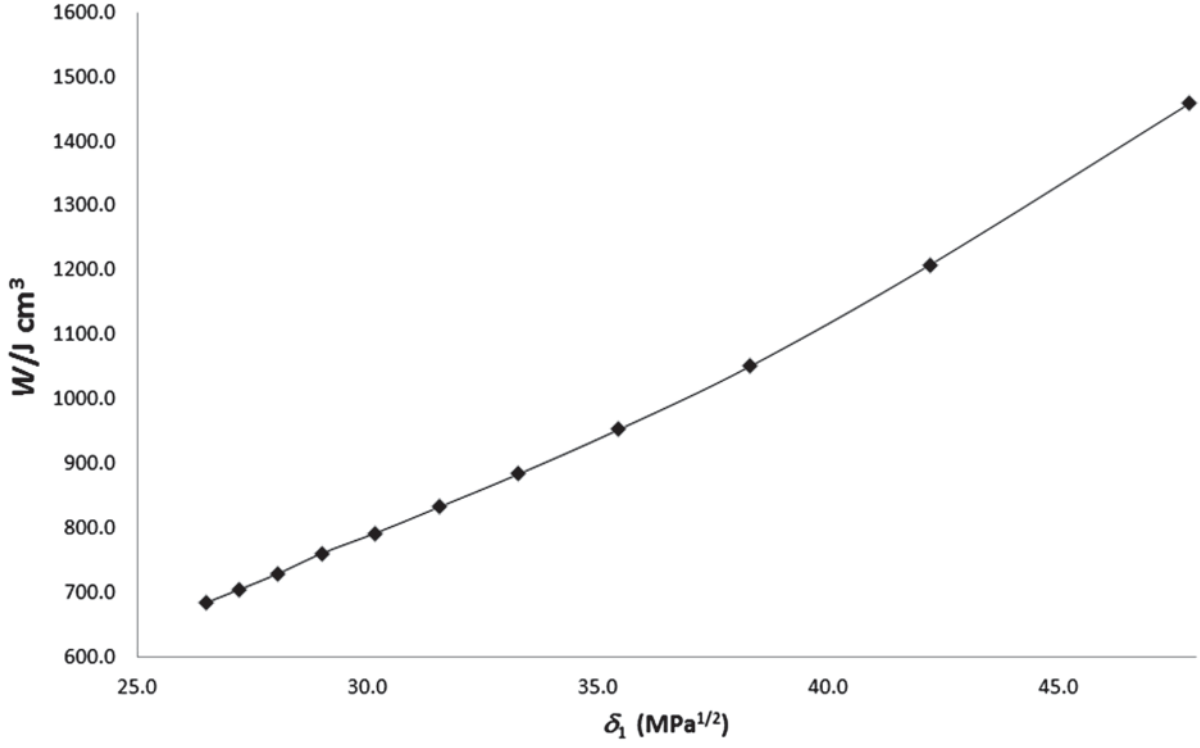


**Figure 3.** Logarithmic solubility of mitomycin C in etanol + water mixtures as a function of the solubility parameter of the solvent mixtures at 293.15 K. Dotted lines are the additive solubility behavior.

**Table 7.** Calculated solubility of Mitomycin C in ethanol + water mixtures by using the equations of log $X_3$ vs. $?_1$ as regression models in order 4, and standard deviations with respect to the experimental values, at 293.15 K.

| $\delta_1$ / MPa$^{1/2}$ | $X_3$ | % dev. [a] |
|---|---|---|
| 47.86 | $2.48x10^{-5}$ | 0.81 |
| 42.22 | $4.32x10^{-5}$ | 7.17 |
| 38.32 | $5.46x10^{-5}$ | 18.12 |
| 35.46 | $1.44x10^{-4}$ | 9.21 |
| 33.28 | $4.19x10^{-4}$ | 3.13 |
| 31.56 | $9.54x10^{-4}$ | 0.92 |
| 30.16 | $1.54x10^{-3}$ | 7.89 |
| 29.01 | $1.77x10^{-3}$ | 28.28 |
| 28.04 | $1.54x10^{-3}$ | 36.55 |
| 27.22 | $1.07x10^{-3}$ | 16.20 |
| 26.51 | $6.30x10^{-4}$ | 16.29 |
| Mean value[a] | | 13.09 |
| Standard deviation[b] | | 10.97 |

[a] Calculated as $100 \times | x \text{ expt} - x_3 \text{ calc} | / x_3 \text{ expt.}$

[b] Calculated considering the obtained values in the neat solvents and the nine binary mixtures

Based on mean deviation percentages presented in Tables 5 and 7 it follows that no difference is found between the values obtained by using both methods. These results would show a non-significant usefulness of EHSA method for practical and academic purposes in the case of the mitomycin C studied. Nevertheless, it is necessary keep in mind that this correlative method considers the drug solubility from a systematic physicochemical point of view. Moreover, it would just be necessary to find an effective method to calculate the Walker *K* parameter in order to calculate the *W* term according to the expression $W = 2Kd_1d_3$, because the $d_1$ and $d_3$ terms would be known, and thus, the drug experimental solubility could be calculated in any mixture (Martin and Bustamante, 1989).

## 4. Conclusions

In this investigation the extended Hildebrand solubility approach has been adequately used to study the solubility of mitomycin C in ethanol + water mixtures at 293.15 K. In particular, a good predictive character has been found by using a regular polynomial in order five of the interaction parameter *W* as a function of the solubility parameter of solvent mixtures free of drug. Nevertheless, the predictive character of EHSA is the same as the one obtained by direct correlation between mitomycin C solubility and the same descriptor of polarity of the co-solvent mixtures.

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