



Research Article

Solubility, Correlation, Dissolution Thermodynamics and Preferential Solvation of Meloxicam in Aqueous Mixtures of 2-Propanol

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Abstract

Background: Meloxicam is an analgesic drug widely used in current therapeutics. Because the very low equilibrium solubility of meloxicam in neat water, this property has been studied in {2-propanol + water} mixtures from (293.15 to 313.15) K to expand the solubility database of pharmaceuticals in mixed solvents useful for liquid dosage forms design.

Methods: Flask shaken method and UV-vis spectrophotometry were used for solubility determinations. Jouyban-Acree model was used for solubility correlation. By using the van't Hoff and Gibbs equations the respective apparent thermodynamic quantities for the dissolution and mixing processes, namely Gibbs energy, enthalpy, and entropy, were calculated. Further, based on the inverse Kirkwood-Buff integrals the preferential solvation parameters of meloxicam by 2-propanol were calculated.

Results: Meloxicam solubility increases with temperature arising and maximum value is observed in the mixture $x_1 = 0.70$ at all temperatures. Jouyban-Acree model correlates the meloxicam solubility very well. Dissolution processes were endothermic in all cases and entropy-driven in the interval $0.20 \leq x_1 \leq 1.00$. Non-linear enthalpy-entropy relationship was observed in the plot of enthalpy vs. Gibbs energy exhibiting negative but variant slopes in the composition region $0.00 < x_1 < 0.40$ and variant negative and positive slopes in the other mixtures. Meloxicam is preferentially solvated by water in water-rich mixtures, apparently solvated by water in 2-propanol-rich mixtures, but preferentially solvated by 2-propanol in the interval $0.19 < x_1 < 0.78$.

Conclusion: Solid-liquid equilibrium of meloxicam in {2-propanol + water} mixtures has been studied at several as contribution to preformulation studies of homogeneous liquid pharmaceutical dosage forms.

Introduction

Meloxicam (molecular structure shown in Figure 1, IUPAC name: 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide, molar mass $351.40 \text{ g}\cdot\text{mol}^{-1}$, CAS number: 71125-38-7, PubChem CID: 54677470) is a non-steroidal anti-inflammatory drug commonly employed in current therapeutics for pain and inflammatory treatments.¹⁻⁵ Meloxicam exhibits a very low solubility in pure water, which influences *in vitro* and *in vivo* dissolution rates, affecting negatively its biological activity. In addition, the very low aqueous solubility makes very hard the research and development of homogeneous liquid medicines at industrial level, like oral or injectable

products based on this drug. For all these reasons, some investigations have been published in the literature, which were intended to increase the meloxicam aqueous equilibrium solubility. These investigations were mainly based in the use of different common pharmaceutical cosolvents, as has recently been summarized.⁶ Moreover, recently aqueous mixtures with some other cosolvents including choline-based deep eutectic solvents have also been studied.⁷⁻¹⁰ Very good increasing in the meloxicam solubility has been reported reaching more than 1000-fold in some cases.

2-propanol (also known as isopropyl alcohol, molar mass: $60.10 \text{ g}\cdot\text{mol}^{-1}$, CAS number: 67-63-0, PubChem CID

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procedure mentioned above to determine meloxicam concentrations. All these procedures were performed successively until solid-liquid equilibrium was achieved at 293.15 K. All the solubility experiments mentioned were performed at least three times and the respective results were averaged. The density of the saturated solutions was measured by using a digital density meter (DMA 45 Anton Paar, Austria) that was connected to a recirculating thermostatic bath (Neslab RTE 10 Digital One Thermo Electron Company, USA) in order to transform the obtained solubility values into different concentration scales. Density meter was calibrated at every temperature by using air and water as standards as indicated in the respective instructions manual.³¹

Solid phase analyses

Differential Scanning Calorimetry (DSC) analysis

To identify the solid nature of the original meloxicam sample a DSC analysis was performed (TA Instruments DSC 2920, USA). Nearly 7.0 mg of meloxicam was used. The equipment was calibrated using Indium as standard. An empty sealed pan was used as reference sample. The sample and reference pans were both heated to preserve the programmed temperature following a precise heating rate of 10 K·min⁻¹ from (300 to 560) K in a dynamic atmosphere of nitrogen (10 cm³·min⁻¹).

X-Ray Diffraction (XRD) analysis

To determine the crystal nature of the solid meloxicam samples, both before and after the saturation in neat water, in the mixture of $x_1 = 0.50$, and in neat 2-propanol, the respective X-ray powder diffraction analyses were performed by using a PANalytical Xpert Pro X-ray diffractometer. The equipment is provided with CuK α radiation $\lambda = 1.5418$ Å. Generator setting: 40 kV and 40 mA and Bragg-Brentano geometry. Data were collected at 2θ from 5° to 70° and angle variation of 0.02° with detector data acquisition time of 9.46 min operating under room temperature.

Fourier Transform Infrared (FTIR) analysis

Additionally to XRD analyses, in order to confirm the nature of the solid meloxicam samples, both before and after the saturation in neat water, in the mixture of $x_1 = 0.50$, and in neat 2-propanol, FTIR analyses were also performed. The meloxicam solid samples were ground with quantities from 10 to 100 times its bulk of pure potassium bromide and the resulting mixtures were pressed into discs by using an especial mold and a manual hydraulic press (Specac®, USA). The respective spectra were obtained in a FTIR spectrophotometer (IRAffinity-1, Shimadzu, Japan).

Results and Discussion

Experimental mole fraction and molarity solubility

Tables 2 and 3 summarize the experimental equilibrium solubilities of meloxicam in {2-propanol (1) + water (2)} mixtures, as expressed in mole fraction and molarity

(mol·dm⁻³), respectively. Solubility values in neat water were taken from the published literature.²⁹ If mole fraction scale is considered, at 298.15 K Table 2 shows that the meloxicam solubility in {2-propanol (1) + water (2)} mixtures increased 45.7 times from $x_3 = 1.137 \times 10^{-6}$ in neat water to $x_3 = 5.199 \times 10^{-5}$ in the mixture of $x_1 = 0.70$, where maximum solubility is obtained. It is noteworthy that maximum solubility peak is observed in the mixture of $x_1 = 0.70$ at all temperatures studied. Moreover, mole fraction solubility of meloxicam in the mixed solvents at various temperatures is shown in Figure 2 (top). Comparison of meloxicam solubility in water has been reported and discussed earlier in our previous communication.⁶ Regarding the meloxicam mole fraction solubility in neat 2-propanol Sathesh-Babu *et al.*³² reported the value $x_3 = 3.93 \times 10^{-5}$ at 298.15 K,³² which is in good agreement with the one obtained in this research ($x_3 = 4.106 \times 10^{-5}$, Table 2). Moreover, by considering the molarity scale a value of $C = 6.10 \times 10^{-4}$ mol·dm⁻³ was reported by Castro *et al.* at 298.15 K,³³ which is also similar compared with our value ($C = 5.341 \times 10^{-3}$ mol·dm⁻³, Table 3). Observed solubility differences could be attributed to several reasons like different polymorphic states, different saturation times, or different analytical procedures, as described earlier.

Figure 2 (bottom) depicts the meloxicam solubility profiles as function of the Hildebrand solubility parameters (δ_{1+2}) of {2-propanol (1) + water (2)} mixtures at five temperatures. As widely described, δ_{1+2} is a very important polarity descriptor of cosolvent mixtures.²⁴⁻²⁷ It was calculated considering the Hildebrand solubility parameter

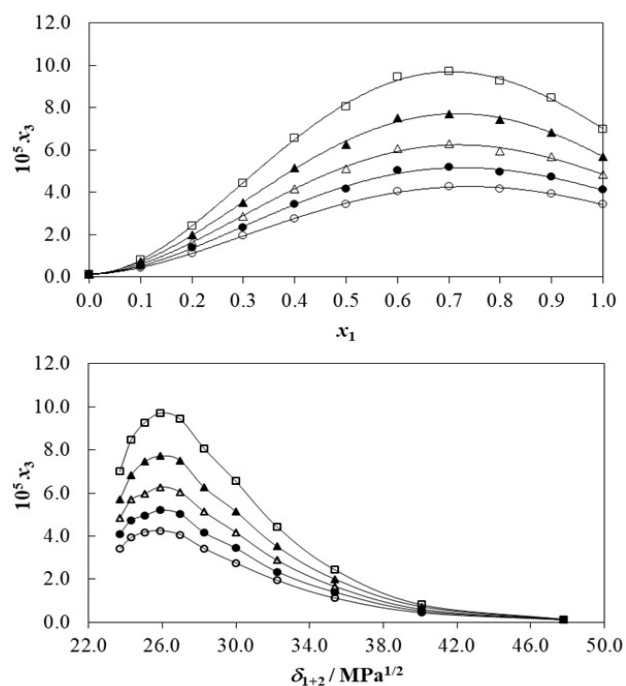


Figure 2. Mole fraction solubility of meloxicam (x_3) as function of the of the mole fraction of 2-propanol (top) and the Hildebrand solubility parameter (bottom) in {2-propanol (1) + water (2)} mixtures at different temperatures. ○: 293.15 K, ●: 298.15 K, △: 303.15 K, ▲: 308.15 K, □: 313.15 K.

Table 2. Experimental mole fraction solubility (x_3) of meloxicam in {2-propanol (1) + water (2)} mixtures at several temperatures and $p = 96$ kPa. ^{a,b}

x_1 ^{a,b}	T/K ^b				
	293.15	298.15	303.15	308.15	313.15
0.000 ^c	1.088×10^{-6}	1.137×10^{-6}	1.187×10^{-6}	1.262×10^{-6}	1.329×10^{-6}
0.100	4.418×10^{-6}	5.181×10^{-6}	6.020×10^{-6}	7.239×10^{-6}	8.126×10^{-6}
0.200	1.121×10^{-5}	1.397×10^{-5}	1.662×10^{-5}	1.997×10^{-5}	2.428×10^{-5}
0.300	1.946×10^{-5}	2.344×10^{-5}	2.877×10^{-5}	3.513×10^{-5}	4.429×10^{-5}
0.400	2.757×10^{-5}	3.444×10^{-5}	4.181×10^{-5}	5.152×10^{-5}	6.555×10^{-5}
0.500	3.424×10^{-5}	4.153×10^{-5}	5.127×10^{-5}	6.253×10^{-5}	8.055×10^{-5}
0.600	4.067×10^{-5}	5.036×10^{-5}	6.052×10^{-5}	7.518×10^{-5}	9.440×10^{-5}
0.700	4.258×10^{-5}	5.199×10^{-5}	6.280×10^{-5}	7.717×10^{-5}	9.710×10^{-5}
0.800	4.180×10^{-5}	4.946×10^{-5}	5.958×10^{-5}	7.450×10^{-5}	9.254×10^{-5}
0.900	3.933×10^{-5}	4.739×10^{-5}	5.690×10^{-5}	6.817×10^{-5}	8.470×10^{-5}
1.000	3.421×10^{-5}	4.106×10^{-5}	4.835×10^{-5}	5.695×10^{-5}	6.995×10^{-5}
Ideal ^c	2.607×10^{-3}	3.079×10^{-3}	3.627×10^{-3}	4.260×10^{-3}	4.991×10^{-3}

^a p is the atmospheric pressure in Bogotá, Colombia. x_1 is the mole fraction of 2-propanol (1) in the {2-propanol (1) + water (2)} mixtures free of meloxicam (3). Mean uncertainty in x_1 , $u(x_1) = 0.0005$. ^b Standard uncertainty in p is $u(p) = 3.0$ kPa. Average relative uncertainty in x_3 , $u_r(x_3) = 0.030$. Standard uncertainty in T is $u(T) = 0.10$ K. ^c Data taken from Delgado *et al.*²⁹

Table 3. Experimental molar solubility (C , mol·dm⁻³) of meloxicam in {2-propanol (1) + water (2)} mixtures at several temperatures and $p = 96$ kPa. ^{a,b}

x_1 ^{a,b}	T/K ^b				
	293.15	298.15	303.15	308.15	313.15
0.000 ^c	6.027×10^{-5}	6.292×10^{-5}	6.559×10^{-5}	6.964×10^{-5}	7.321×10^{-5}
0.100	1.904×10^{-4}	2.225×10^{-4}	2.577×10^{-4}	3.087×10^{-4}	3.451×10^{-4}
0.200	3.895×10^{-4}	4.831×10^{-4}	5.723×10^{-4}	6.841×10^{-4}	8.277×10^{-4}
0.300	5.638×10^{-4}	6.755×10^{-4}	8.244×10^{-4}	1.002×10^{-3}	1.256×10^{-3}
0.400	6.822×10^{-4}	8.483×10^{-4}	1.024×10^{-3}	1.255×10^{-3}	1.588×10^{-3}
0.500	7.394×10^{-4}	8.923×10^{-4}	1.095×10^{-3}	1.329×10^{-3}	1.702×10^{-3}
0.600	7.786×10^{-4}	9.583×10^{-4}	1.145×10^{-3}	1.415×10^{-3}	1.767×10^{-3}
0.700	7.308×10^{-4}	8.875×10^{-4}	1.066×10^{-3}	1.303×10^{-3}	1.630×10^{-3}
0.800	6.502×10^{-4}	7.652×10^{-4}	9.164×10^{-4}	1.140×10^{-3}	1.407×10^{-3}
0.900	5.592×10^{-4}	6.699×10^{-4}	7.997×10^{-4}	9.569×10^{-4}	1.177×10^{-3}
1.000	4.473×10^{-4}	5.341×10^{-4}	6.251×10^{-4}	7.324×10^{-4}	8.943×10^{-4}

^a p is the atmospheric pressure in Bogotá, Colombia. x_1 is the mole fraction of 2-propanol (1) in the {2-propanol (1) + water (2)} mixtures free of meloxicam (3). Mean uncertainty in x_1 , $u(x_1) = 0.0005$. ^b Standard uncertainty in p is $u(p) = 3.0$ kPa. Average relative uncertainty in C , $u_r(C) = 0.030$. Standard uncertainty in T is $u(T) = 0.10$ K. ^c Data taken from Delgado *et al.*²⁹

of both pure solvents ($\delta_1 = 23.7$ MPa^{1/2} for 2-propanol and $\delta_2 = 47.8$ MPa^{1/2} for water,^{34,35} and the volume fraction (f_i) of each solvent, assuming additive behavior, as follows:^{25,36}

$$\delta_{1+2} = \sum_{i=1}^2 f_i \delta_i \quad \text{Eq. (1)}$$

As observed the five solubility curves exhibited meloxicam solubility peaks in the mixture of $x_1 = 0.70$, where δ_{1+2} is 25.9 MPa^{1/2}. Because solutes normally reach their maximum solubilities in solvent systems exhibiting similar polarity,^{24,25} it would be expected that the meloxicam δ_3 value is 25.9 MPa^{1/2} at 298.15 K. However, this δ_3 value is lower compared with that reported earlier ($\delta_3 = 32.1$ MPa^{1/2}).^{6,29,30} This last δ_3 value was calculated by means of the Fedors' method.³⁷ This high discrepancy could be mainly attributed to specific drug solvation processes by 2-propanol or water, which are not considered in Fedors' calculations.³⁷ Otherwise, Figure 3 compares the logarithmic solubility of meloxicam as function of the

Hildebrand solubility parameter in {2-propanol (1) + water (2)},^{this work} {methanol (1) + water (2)},⁷ {ethanol (1) + water (2)},²⁹ and {Carbitol® (1) + water (2)} mixtures at 298.15 K.⁸ It is noteworthy that meloxicam solubilities are higher in mixtures {2-propanol (1) + water (2)} of $\delta_{1+2} > 36.0$ MPa^{1/2} than in the other aqueous-cosolvent mixtures under consideration. Moreover, in mixtures of 30.0 MPa^{1/2} < \delta_{1+2} < 36.0 MPa^{1/2} the meloxicam solubility is different regarding the cosolvent under study, following the order: Carbitol®-aqueous mixtures > methanol-aqueous mixtures > 2-propanol-aqueous mixtures \cong ethanol-aqueous mixtures. Finally, in mixtures of $\delta_{1+2} < 30.0$ MPa^{1/2} the meloxicam solubility follows the order: Carbitol®-aqueous mixtures > 2-propanol-aqueous mixtures > ethanol-aqueous mixtures. This result shows that meloxicam solubility depends not only on polarity but also on some other physicochemical properties of both, solutes and solvent systems.}

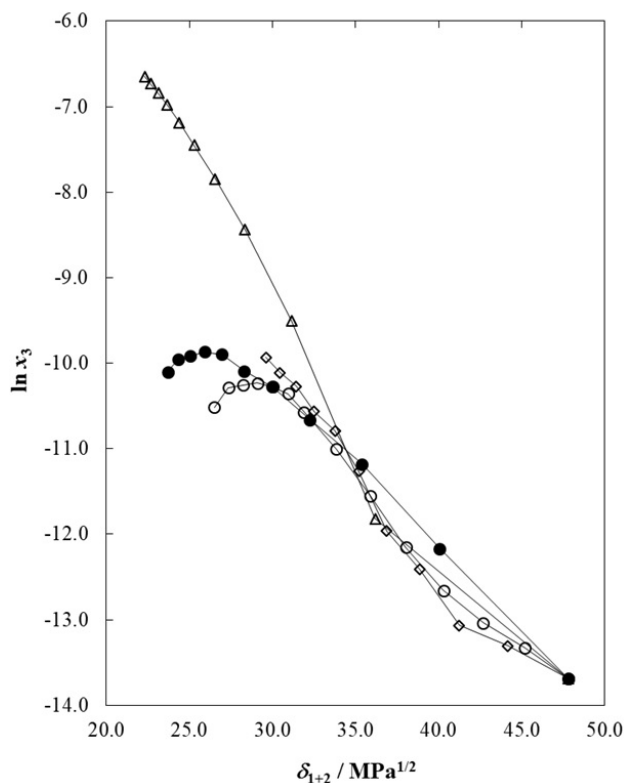


Figure 3. Logarithmic mole fraction solubility of meloxicam ($\ln x_3$) as function of the Hildebrand solubility parameter in some {alcohol (1) + water (2)} mixtures at 298.15 K. ●: 2-propanol (1) + water (2),^{this work} ○: ethanol (1) + water (2),²⁹ ◇: methanol (1) + water (2),⁷ △: Carbitol[®] (1) + water (2).⁸

Solid phases' analyses

DSC thermogram (Figure 4) exhibits an endothermic peak corresponding to the meloxicam melting as original sample with on-set temperature of 524.0 K and peak temperature of 535.4 K. This last value is similar regarding some other values reported in the literature, i.e. 535.0 K,³⁸ 535.2 K,³⁹ 535.7 K,⁴⁰ 536.1 K,⁴¹ and 536.7 K.²⁹ However, some significant differences are observed regarding the values reported by Sathesh-Babu *et al.* (530.0 K),³² Todoran *et al.* (531.2 K),⁴² and Weyna *et al.* (538.5 K).⁴³ Moreover, Freitas *et al.*⁴⁴ reported six different temperature values for seven different commercial samples of meloxicam available in the Brazilian market for pharmaceutical industrial production, i.e. 528.2 K, 532.2 K, 533.2 K, 534.2 K, 537.2 K and 539.2 K,⁴⁴ which also differ significantly regarding our peak value. X-ray diffraction spectra for meloxicam as original sample and after saturation in neat water, neat 2-propanol and the aqueous mixture of $x_1 = 0.50$ are shown in Figure 5. Because the high similarity among all spectra it could be concluded that no changes of the crystalline form of meloxicam are observed after its dissolution and saturation in these solvent systems. Moreover, all the observed XRD spectra in this research are very similar to the one reported earlier for polymorph I of meloxicam.^{29,44-47} FTIR spectra of solid meloxicam samples shown in Figure 6 are also coincident with those reported in the literature allowing to indicate that all bottom-solid phases after saturation

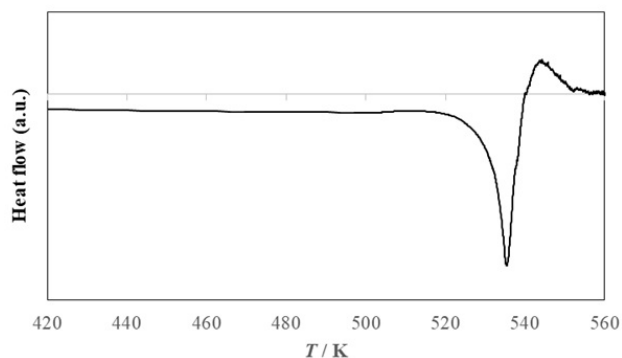


Figure 4. DSC thermogram of meloxicam as original sample.

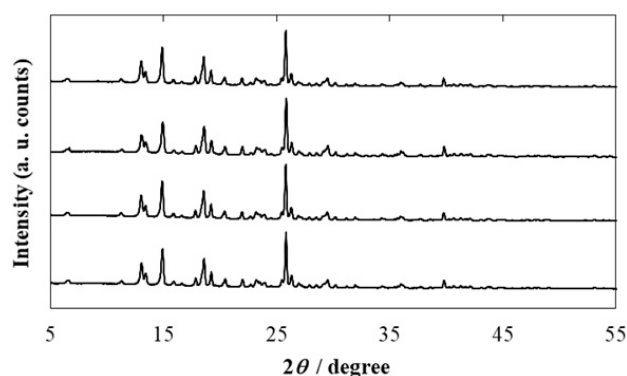


Figure 5. X-ray diffraction spectra of meloxicam. From top to bottom: original sample, crystallized in 2-propanol, crystallized in {2-propanol (1) + water (2)} ($x_1 = 0.50$) mixture, crystallized in water.

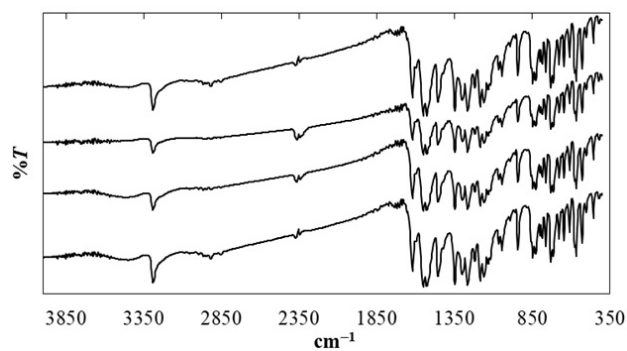


Figure 6. FTIR spectra of meloxicam. From top to bottom: original sample, crystallized in 2-propanol, crystallized in {2-propanol (1) + water (2)} ($x_1 = 0.50$) mixture, crystallized in water.

have the same nature as the original sample.⁴⁸⁻⁵⁰ Therefore, as observed meloxicam did not suffer crystal polymorphic transitions or solvates formation after saturation in these experiments.

Activity coefficients in mixed solvents

Table 4 summarizes the meloxicam activity coefficients (γ_3) in {2-propanol (1) + water (2)} mixtures. These values were calculated as the quotient x_3^{id}/x_3 from the experimental and ideal solubilities shown in Table 2. As observed, γ_3 values vary from 2708 in neat water (where the lower drug

solubility is observed) to 59.2 in the mixture of $x_1 = 0.70$ at 298.15 K, where the maximum drug solubility is observed at this temperature. In all the solvent systems the activity coefficients are higher than the unity at all temperatures because the experimental solubilities are lower than the ideal ones. Moreover, in neat water and the mixture of $x_1 = 0.10$ the γ_3 values increase with the temperature-arising. This implies some distancing from ideal dissolution behavior with temperature-increasing. On the contrary, in mixtures of $x_1 \geq 0.20$ the γ_3 values decrease with the temperature-arising, which in time implies some approaching to ideal drug dissolution behavior with temperature-increasing. Moreover, a rough estimate of the magnitudes of solute-solvent intermolecular interactions can be proposed from g_3 values by considering the following equation:⁵¹

$$\ln \gamma_3 = (e_{11} + e_{33} - 2e_{13}) \frac{V_3 \phi_1^2}{RT} \quad \text{Eq. (2)}$$

Subscript 1 stands for the solvent system (here, it corresponds to neat solvents or aqueous 2-propanol binary mixtures), e_{11} , e_{33} and e_{13} represent the solvent-solvent, solute-solute and solvent-solute interaction energies, respectively. However, it is important to keep in mind that in absolute ternary systems, like 2-propanol-water-meloxicam, some water-cosolvent interactions are present and could also play an important role in drugs dissolution. V_3 is the molar volume of the super-cooled liquid meloxicam, whereas, ϕ_1 is the volume fraction of the solvent system. For low solubility values, $V_3 \phi_1^2 / RT$ may be considered as constant despite of the solvent system under consideration. Thus, γ_3 values would depend mainly on e_{11} , e_{33} and e_{13} .⁵¹ As well-known, e_{11} and e_{33} are unfavorable for drug solubility and dissolution; whereas, e_{13} favors the respective drug dissolution process and the solubility increasing. The contribution of e_{33} could be considered as constant in the different solvent systems studied.

As indicated above, from a qualitative viewpoint the following analysis could be considered based on the energetic quantities described in Eq. (2). e_{11} is highest in neat water ($\delta_2 = 47.8 \text{ MPa}^{1/2}$) and lowest in neat 2-propanol ($\delta_1 = 23.7 \text{ MPa}^{1/2}$).^{34,35} Neat water and water-rich mixtures (exhibiting γ_3 values higher than 1000) would imply high e_{11} and low e_{13} values. However, in 2-propanol-rich mixtures (exhibiting γ_3 values lower than 76) the e_{11} values are relatively low (including the mixture of maximum meloxicam solubility, with $\delta_{1+2} = 25.9 \text{ MPa}^{1/2}$) and thus, the e_{13} values would be high. Therefore, it is expected a higher solvation of meloxicam by 2-propanol in 2-propanol-rich mixtures.

Solubility modelling

Numerous mathematical models were published to represent the solubility of drugs in cosolvent + water mixtures at a constant and/or different temperatures. These models have been reviewed previously.⁵²⁻⁵⁴ Basically, the Jouyban-Acree model was found as the most accurate model. It is presented as:⁵⁵

$$\ln X_{m,T} = x_1 \ln X_{1,T} + x_2 \ln X_{2,T} + \left(\frac{x_1 x_2}{T} \right) \left[\sum_{i=0}^n J_i (x_1 - x_2)^i \right] \quad \text{Eq. (3)}$$

where $X_{m,T}$, $X_{1,T}$ and $X_{2,T}$ are the mole fraction solubility of meloxicam in solvent mixtures, solvents 1 and 2 at temperature (T , K), x_1 and x_2 are the solute free mole fractions of solvents 1 (2-propanol in this work) and 2 (water in this work), and J_i are the model constants computed using a no-intercept least square analysis.⁵⁵ The individual percentage deviation (IPD) and its mean value (MPD) were computed as accuracy criteria of the computed values using:

$$IPD = \frac{100(X_m^{Calculated} - X_m^{Observed})}{X_m^{Observed}} \quad \text{Eq. (4)}$$

Table 4. Activity coefficients of meloxicam in {2-propanol (1) + water (2)} mixtures at several temperatures and $p = 96 \text{ kPa}$.^{a,b}

x_1 ^{a,b}	T/K ^b				
	293.15	298.15	303.15	308.15	313.15
0.000 ^c	2396	2708	3055	3376	3755
0.100	590	594	602	588	614
0.200	233	220	218	213	206
0.300	134	131	126	121	113
0.400	94.6	89.4	86.7	82.7	76.1
0.500	76.1	74.1	70.7	68.1	62.0
0.600	64.1	61.1	59.9	56.7	52.9
0.700	61.2	59.2	57.7	55.2	51.4
0.800	62.4	62.3	60.9	57.2	53.9
0.900	66.3	65.0	63.7	62.5	58.9
1.000	76.2	75.0	75.0	74.8	71.3

^a p is the atmospheric pressure in Bogotá, Colombia. x_1 is the mole fraction of 2-propanol (1) in the {2-propanol (1) + water (2)} mixtures free of meloxicam (3). Mean uncertainty in x_1 , $u(x_1) = 0.0005$. ^b Standard uncertainty in p is $u(p) = 3.0 \text{ kPa}$. Average relative uncertainty in V_3 is $u_r(V_3) = 0.034$. Standard uncertainty in T is $u(T) = 0.10 \text{ K}$. ^c Data taken from Delgado et al.²⁹

$$MPD = \frac{\sum_{i=1}^N |IPD|}{N} \quad \text{Eq. (5)}$$

where N is the number of experimental solubility data points.

The trained model for representing the equilibrium solubility of meloxicam in {2-propanol (1) + water (2)} mixtures at various temperatures is:

$$\ln X_{m,T} = x_1 \ln X_{1,T} + x_2 \ln X_{2,T} + \left(\frac{x_1 x_2}{T} \right) \left[2333.406 - 1370.722(x_1 - x_2) + 1020.359(x_1 - x_2)^2 \right] \quad \text{Eq. (6)}$$

From fitting the experimental data to Eq. (3). Equation (6) back-calculates the meloxicam solubility data with the MPD of $11.3 \pm 10.4\%$ ($N=55$). The experimental solubility data of the drug in the mono-solvents is required for predicting the solubility data at other temperatures which is a restriction for Eq. (6), and this could be covered by the combined version of the model with the van't Hoff equation as:⁵⁵

$$\ln X_{m,T} = x_1 \left(1.499 - \frac{3407.179}{T} \right) + x_2 \left(-10.582 - \frac{924.993}{T} \right) + \left(\frac{x_1 x_2}{T} \right) \left[2333.406 - 1370.722(x_1 - x_2) + 1020.359(x_1 - x_2)^2 \right] \quad \text{Eq. (7)}$$

which back-calculates the meloxicam solubility data with the MPD of $11.4 \pm 10.2\%$ ($N=55$). Solubility prediction based on those models trained using a minimum number of experimental data points provided the most accurate predictions, among other predictive models.⁵⁶ When Eqs. (6) and (7) were trained using a minimum number of 7 data points, the $MPDs$ for the predicted meloxicam solubility data points were obtained as $13.6 \pm 11.1\%$ and $13.5 \pm 10.7\%$ ($N=48$), respectively.

Apparent thermodynamic functions of dissolution

All apparent standard thermodynamic quantities of meloxicam dissolution were calculated at the mean harmonic temperature, $T_{hm} = 303.0$ K, which was obtained by using Eq. (8).⁵⁷

$$T_{hm} = \frac{n}{\sum_{i=1}^n \left(\frac{1}{T} \right)} \quad \text{Eq. (8)}$$

where $n = 5$ is the number of temperatures under study. Hence, the apparent standard enthalpy changes of dissolution ($\Delta_{soln} H^\circ$) were obtained by the modified van't Hoff equation as shown in Eq. (9).⁵⁸

$$\left(\frac{\partial \ln x_3}{\partial (1/T - 1/T_{hm})} \right)_p = -\frac{\Delta_{soln} H^\circ}{R} \quad \text{Eq. (9)}$$

The apparent standard Gibbs energy changes for the

meloxicam dissolution processes ($\Delta_{soln} G^\circ$) were calculated by means of:^{58,59}

$$\Delta_{soln} G^\circ = -RT \cdot \text{intercept} \quad \text{Eq. (10)}$$

Used intercepts of Eq. (10) were those obtained in the linear regressions of $\ln x_3$ as function of $(1/T - 1/T_{hm})$. In this way, Figure 7 depicts the meloxicam solubility behavior in all the {2-propanol (1) + water (2)} mixtures as well as in the neat solvents. Linear regressions with $r^2 > 0.993$ were observed in all the solvent systems.^{60,61} Finally, the apparent standard entropy changes for all the meloxicam dissolution processes ($\Delta_{soln} S^\circ$) were calculated from the respective $\Delta_{soln} H^\circ$ and $\Delta_{soln} G^\circ$ values by using:⁵⁹

$$\Delta_{soln} S^\circ = \frac{(\Delta_{soln} H^\circ - \Delta_{soln} G^\circ)}{T_{hm}} \quad \text{Eq. (11)}$$

Table 5 shows the apparent standard thermodynamic quantities for the dissolution of meloxicam in all the {2-propanol (1) + water (2)} mixtures at $T_{hm} = 303.0$ K, including those for dissolution processes in neat water and 2-propanol. Apparent standard dissolution thermodynamic quantities in neat water were taken from the literature.²⁹

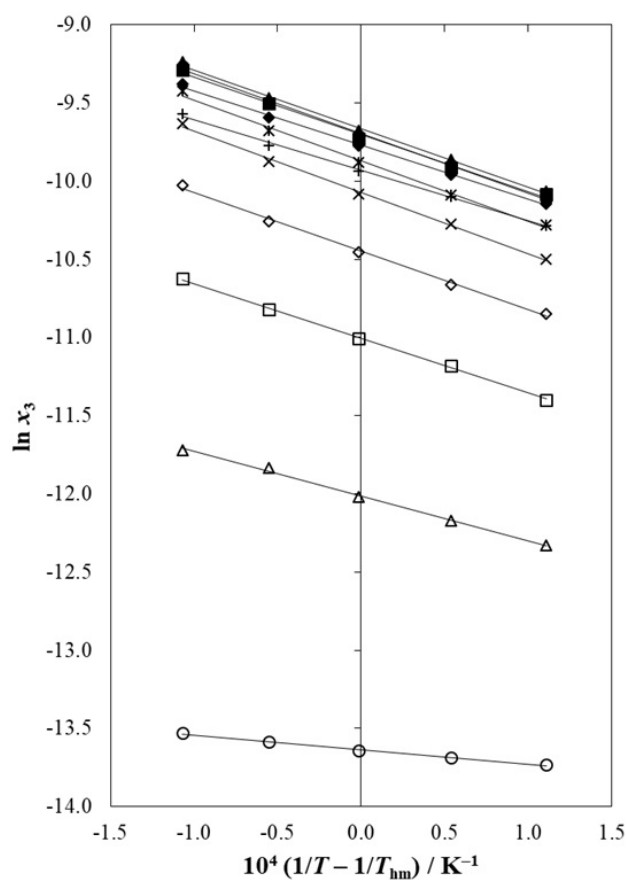


Figure 7. van't Hoff plot of the solubility of meloxicam (3) in {2-propanol (1) + water (2)} solvent systems. \circ : $x_1 = 0.00$ (neat water), Δ : $x_1 = 0.10$, \square : $x_1 = 0.20$, \diamond : $x_1 = 0.30$, \ast : $x_1 = 0.40$, \ast : $x_1 = 0.50$, \bullet : $x_1 = 0.60$, \blacktriangle : $x_1 = 0.70$, \blacksquare : $x_1 = 0.80$, \blacklozenge : $x_1 = 0.90$, $+$: $x_1 = 0.10$ (neat 2-propanol).*

As expected, the apparent standard Gibbs energies of dissolution of meloxicam in all these 2-propanol-aqueous systems are positive in every case as also are the respective apparent enthalpies of dissolution. Otherwise, apparent standard dissolution entropies were negative in neat water and the mixture of $x_1 = 0.10$ but positive from the mixture of $x_1 = 0.20$ to neat 2-propanol. Thus, the global dissolution processes of meloxicam are always endothermic and entropy-driven in the composition interval of $0.20 \leq x_1 \leq 1.00$; whereas, in neat water and the mixture of $x_1 = 0.10$ neither entropy nor enthalpy-driving are observed. $\Delta_{\text{soln}} G^\circ$ values decrease continuously from neat water to reach the lowest value in the mixture of $x_1 = 0.70$. $\Delta_{\text{soln}} H^\circ$ values increase from neat water to reach the highest in the mixture of $x_1 = 0.40$ and later they decrease continuously with the 2-propanol proportion. $\Delta_{\text{soln}} S^\circ$ values increase from negative values in neat water to reach the maximum positive value in the mixture of $x_1 = 0.50$ and later they decrease continuously with the 2-propanol proportion. As observed, the lowest $\Delta_{\text{soln}} H^\circ$ and $\Delta_{\text{soln}} S^\circ$ values are observed in neat water. Negative apparent dissolution entropies observed in neat water and the mixture of $x_1 = 0.10$ could be a consequence of the hydrophobic hydration around the methyl and phenylene groups of meloxicam (Figure 1). On the other hand, the relative contributions by enthalpy (ζ_H) and entropy (ζ_{TS}) toward the dissolution processes are given by the following equations:⁶²

$$\zeta_H = \frac{|\Delta_{\text{soln}} H^\circ|}{|\Delta_{\text{soln}} H^\circ| + |T \Delta_{\text{soln}} S^\circ|} \quad \text{Eq. (12)}$$

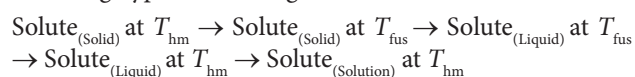
$$\zeta_{TS} = \frac{|T \Delta_{\text{soln}} S^\circ|}{|\Delta_{\text{soln}} H^\circ| + |T \Delta_{\text{soln}} S^\circ|} \quad \text{Eq. (13)}$$

As observed in Table 5 the main contributing function to the positive apparent standard molar Gibbs energies of

meloxicam dissolution is the positive enthalpy because $\zeta_H > 0.784$, which demonstrates the energetic predominance in almost all these dissolution processes, except in neat water, where $\zeta_H = 0.224$ and thus, the entropy is the dominant function.

Apparent thermodynamic quantities of mixing

The overall dissolution process of meloxicam in {2-propanol (1) + water (2)} solvent systems may be represented by the following hypothetical stages:



Here the hypothetical stages are as follows, i) the heating and fusion of meloxicam, ii) the cooling of the liquid drug to the considered temperature ($T_{\text{hm}} = 303.0$ K), and iii) the subsequent mixing of both the hypothetical super-cooled liquid meloxicam and the liquid solvent system at harmonic mean temperature.⁶³ This treatment allowed us the calculation of the individual thermodynamic contributions toward the overall drug dissolution process by means of the following equations:

$$\Delta_{\text{soln}} H^\circ = \Delta_{\text{fus}} H^{T_{\text{hm}}} + \Delta_{\text{mix}} H^\circ \quad \text{Eq. (14)}$$

$$\Delta_{\text{soln}} S^\circ = \Delta_{\text{fus}} S^{T_{\text{hm}}} + \Delta_{\text{mix}} S^\circ \quad \text{Eq. (15)}$$

where $\Delta_{\text{fus}} S^{T_{\text{hm}}}$ and $\Delta_{\text{fus}} H^{T_{\text{hm}}}$ represent the thermodynamic quantities relative to meloxicam melting and its cooling at $T_{\text{hm}} = 303.0$ K, which in turn, are calculated by means of:⁶⁴

$$\Delta_{\text{fus}} H^{T_{\text{hm}}} = \Delta_{\text{fus}} H^{T_{\text{fus}}} - \Delta C_p (T_{\text{fus}} - T_{\text{hm}}) \quad \text{Eq. (16)}$$

$$\Delta_{\text{fus}} S^{T_{\text{hm}}} = \Delta_{\text{fus}} S^{T_{\text{fus}}} - \Delta C_p \ln \left(\frac{T_{\text{fus}}}{T_{\text{hm}}} \right) \quad \text{Eq. (17)}$$

Table 5. Apparent thermodynamic functions relative to dissolution processes of meloxicam (3) in {2-propanol (1) + water (2)} mixtures at $T_{\text{hm}} = 303.0$ K and $p = 96$ kPa.^{a,b}

x_1 ^{a,b}	$\Delta_{\text{soln}} G^\circ / \text{kJ}\cdot\text{mol}^{-1}$ ^b	$\Delta_{\text{soln}} H^\circ / \text{kJ}\cdot\text{mol}^{-1}$ ^b	$\Delta_{\text{soln}} S^\circ / \text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$ ^b	$T\Delta_{\text{soln}} S^\circ / \text{kJ}\cdot\text{mol}^{-1}$ ^b	ζ_H ^c	ζ_{TS} ^c
0.000 ^d	34.35	7.69	-87.99	-26.66	0.224	0.776
0.100	30.27	23.72	-21.62	-6.55	0.784	0.216
0.200	27.73	29.05	4.38	1.33	0.956	0.044
0.300	26.32	31.26	16.28	4.93	0.864	0.136
0.400	25.37	32.57	23.75	7.20	0.819	0.181
0.500	24.87	32.33	24.64	7.46	0.812	0.188
0.600	24.43	31.80	24.34	7.38	0.812	0.188
0.700	24.34	31.17	22.54	6.83	0.820	0.180
0.800	24.44	30.48	19.91	6.03	0.835	0.165
0.900	24.61	28.95	14.33	4.34	0.870	0.130
1.000	25.02	26.81	5.92	1.79	0.937	0.063
Ideal ^d	14.16	24.78	35.03	10.61	0.700	0.300

^a p is the atmospheric pressure in Bogotá, Colombia. x_1 is the mole fraction of 2-propanol (1) in the {2-propanol (1) + water (2)} mixtures free of meloxicam (3). Mean uncertainty in x_1 , $u(x_1) = 0.0005$.^b Standard uncertainty in T_{hm} is $u(T_{\text{hm}}) = 0.13$ K. Standard uncertainty in p is $u(p) = 3.0$ kPa. Average relative standard uncertainty in apparent thermodynamic quantities of real dissolution processes are $u_r(\Delta_{\text{soln}} G^\circ) = 0.031$, $u_r(\Delta_{\text{soln}} H^\circ) = 0.041$, $u_r(\Delta_{\text{soln}} S^\circ) = 0.051$, $u_r(T\Delta_{\text{soln}} S^\circ) = 0.051$.^c ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward apparent Gibbs energy of dissolution. ^d Data taken from Delgado *et al.*²⁹

Table 6 summarizes the apparent standard thermodynamic quantities of mixing of the hypothetical super-cooled liquid meloxicam with all the aqueous-2-propanol mixtures and the neat solvents, water and 2-propanol, at $T_{\text{hm}} = 303.0$ K. Gibbs energies of mixing are positive in all cases because the experimental drug solubilities are lower than ideal solubilities, as indicated above. The contributions by the mixing process thermodynamic quantities to the overall dissolution processes of meloxicam are variable depending on the mixtures composition. Thus, $\Delta_{\text{mix}}H^\circ$ are negative in water and the mixture of $x_1 = 0.10$ but positive in the solvent systems $0.20 \leq x_1 \leq 1.00$. Moreover, $\Delta_{\text{mix}}S^\circ$ values are negative in all cases. Thus, the mixing processes in neat water and the mixture of $x_1 = 0.10$ are enthalpy-driven because of the exothermic character exhibited. In the mixtures $0.20 \leq x_1 \leq 1.00$ neither enthalpy nor entropy-driving is observed for mixing. Furthermore, to compare the relative contributions by enthalpy (ζ_H) and entropy (ζ_{TS}) to the mixing processes, two equations analogous to Eqs. (12) and (13) were employed. As observed, in water-rich and 2-propanol-rich mixtures the main contributor to Gibbs energies of mixing is the entropy, but in the mixtures of $0.30 \leq x_1 \leq 0.70$ is the enthalpy.

Net variation in $\Delta_{\text{mix}}H^\circ$ values with the change of mixtures composition depends on the contribution of different intermolecular interactions. Hence, the cavity formation in the solvent system is endothermic because some energy must be supplied against the respective cohesive forces. This diminishes the drug solubility. Oppositely, the solvent-solute interactions, resulting mainly from van der Waals and Lewis acid-base interactions, are exothermic. This effect increases the drug solubility. Even more, the structuring of water molecules around the phenylene ring and the methyl group of meloxicam (Figure 1) contributes to lowering the net $\Delta_{\text{mix}}H^\circ$ to small or even negative values in water-rich mixtures.⁶⁵ This is clearly observed with meloxicam in aqueous 2-propanol mixtures as shown in Table 6.

Enthalpy-entropy compensation analysis

An extra-thermodynamic study, in particular the enthalpy-entropy compensation analysis, provides a powerful tool to identify similar mechanisms associated with physical and chemical processes of organic compounds.^{66,67} Previous literature reports indicated non-linear-enthalpy-entropy compensation effects in the dissolution processes of many drugs in aqueous cosolvent mixtures. These studies have usually been performed to identify the main mechanisms associated to the cosolvent action on dissolution regarding the mixture's composition.^{68,69} As shown in Figure 8, meloxicam exhibits a non-linear $\Delta_{\text{soln}}H^\circ$ vs. $\Delta_{\text{soln}}G^\circ$ trend with variable but negative slope from neat water to the mixture of $x_1 = 0.40$, whereas, in the interval of $0.40 \leq x_1 \leq 0.70$ a positive slope is observed, and finally, a negative slope is observed again from the mixture of $x_1 = 0.70$ to neat 2-propanol. In the first case, the driving mechanism for transferring meloxicam from the most polar solvent system (neat water) to a less polar solvent mixture ($x_1 = 0.40$) is the entropy-increasing, probably owing the hydrophobic hydration effects. For the mixtures of positive slope, the

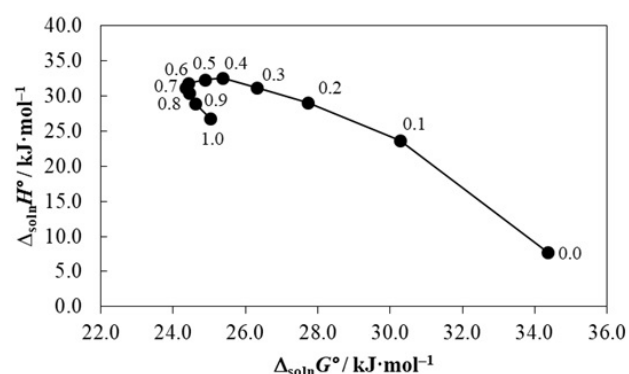


Figure 8. Enthalpy-entropy compensation plot for the solubility of meloxicam (3) in {2-propanol (1) + water (2)} mixtures at $T_{\text{hm}} = 303.0$ K. The points represent the mole fraction of 2-propanol (1) in the {2-propanol (1) + water (2)} mixtures in the absence of meloxicam (3).

Table 6. Apparent thermodynamic functions relative to mixing processes of meloxicam (3) in {2-propanol (1) + water (2)} mixtures at $T_{\text{hm}} = 303.0$ K and $p = 96$ kPa. ^{a,b}

x_1 ^{a,b}	$\Delta_{\text{mix}}G^\circ / \text{kJ}\cdot\text{mol}^{-1}$ ^b	$\Delta_{\text{mix}}H^\circ / \text{kJ}\cdot\text{mol}^{-1}$ ^b	$\Delta_{\text{mix}}S^\circ / \text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$ ^b	$T\Delta_{\text{mix}}S^\circ / \text{kJ}\cdot\text{mol}^{-1}$ ^b	ζ_H ^c	ζ_{TS} ^c
0.000	20.19	-17.09	-123.02	-37.27	0.314	0.686
0.100	16.11	-1.06	-56.65	-17.16	0.058	0.942
0.200	13.56	4.28	-30.64	-9.29	0.315	0.685
0.300	12.16	6.48	-18.75	-5.68	0.533	0.467
0.400	11.21	7.79	-11.28	-3.42	0.695	0.305
0.500	10.70	7.56	-10.39	-3.15	0.706	0.294
0.600	10.26	7.03	-10.69	-3.24	0.685	0.315
0.700	10.18	6.39	-12.49	-3.78	0.628	0.372
0.800	10.28	5.70	-15.12	-4.58	0.554	0.446
0.900	10.45	4.17	-20.70	-6.27	0.400	0.600
1.000	10.86	2.04	-29.11	-8.82	0.188	0.812

^a p is the atmospheric pressure in Bogotá, Colombia. x_1 is the mole fraction of 2-propanol (1) in the {2-propanol (1) + water (2)} mixtures free of meloxicam (3). Mean uncertainty in x_1 , $u(x_1) = 0.0005$. ^bStandard uncertainty in T_{hm} is $u(T_{\text{hm}}) = 0.13$ K. Standard uncertainty in p is $u(p) = 3.0$ kPa. Average relative standard uncertainty in apparent thermodynamic quantities of mixing processes are $u_r(\Delta_{\text{mix}}G^\circ) = 0.035$, $u_r(\Delta_{\text{mix}}H^\circ) = 0.045$, $u_r(\Delta_{\text{mix}}S^\circ) = 0.057$, $u_r(T\Delta_{\text{mix}}S^\circ) = 0.057$. ^c ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward apparent Gibbs energy of mixing.

drug transfer is driven by the enthalpy-decreasing, which is probably associated with a better solvation of meloxicam by 2-propanol molecules.

Preferential solvation analysis

The preferential solvation parameter of meloxicam (component 3) by 2-propanol (component 1) in the {2-propanol (1) + water (2)} mixtures at saturation is defined as:

$$\delta x_{1,3} = x_{1,3}^L - x_1 = -\delta x_{2,3} \quad \text{Eq. (18)}$$

where $x_{1,3}^L$ is the local mole fraction of 2-propanol in the molecular environment of meloxicam and x_1 is the bulk mole fraction of 2-propanol in the initial aqueous-cosolvent mixture free of meloxicam. If $\delta x_{1,3}$ values are positive meloxicam is preferentially solvated by 2-propanol, but if this parameter is negative, meloxicam is preferentially solvated by water. $\delta x_{1,3}$ values were obtained from the inverse Kirkwood-Buff integrals (IKBI) for the solvent components based on the following classical thermodynamic definitions:⁷⁰⁻⁷³

$$\delta x_{1,3} = \frac{x_1 x_2 (G_{1,3} - G_{2,3})}{x_1 G_{1,3} + x_2 G_{2,3} + V_{\text{cor}}} \quad \text{Eq. (19)}$$

with,

$$G_{1,3} = RT \kappa_T \bar{V}_3 + x_2 \bar{V}_2 \left(\frac{D}{Q} \right) \quad \text{Eq. (20)}$$

$$G_{2,3} = RT \kappa_T \bar{V}_3 + x_1 \bar{V}_1 \left(\frac{D}{Q} \right) \quad \text{Eq. (21)}$$

$$V_{\text{cor}} = 2522.5 \cdot \left\{ r_3 + 0.1363 \cdot (x_{1,3}^L \bar{V}_1 + x_{2,3}^L \bar{V}_2) \right\}^3 - 0.085 \quad \text{Eq. (22)}$$

As has been previously described,⁷⁰⁻⁷³ κ_T is the isothermal compressibility of the {2-propanol (1) + water (2)} mixtures. \bar{V}_1 and \bar{V}_2 are the partial molar volumes of 2-propanol and water in the mixtures. \bar{V}_3 is the partial molar volume of meloxicam in these mixtures. The function D is the first derivative of the standard molar Gibbs energies of transfer of meloxicam from neat water to {2-propanol (1) + water (2)} mixtures with respect to the 2-propanol-proportion in the mixtures, as shown in Eq. (23). The function Q involves the second derivative of the excess molar Gibbs energy of mixing of 2-propanol and water (G_{1+2}^{Exc}) with respect to the water-proportion in the mixtures, as shown in Eq. (24). V_{cor} is the correlation volume and r_3 is the molecular radius of meloxicam, which is commonly calculated from Eq. (25), where N_{Av} is the Avogadro's number.

$$D = \left(\frac{\partial \Delta_{\text{tr}} G_{3,2 \rightarrow 1+2}^{\circ}}{\partial x_1} \right)_{T,p} \quad \text{Eq. (23)}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G_{1+2}^{Exc}}{\partial x_2^2} \right)_{T,p} \quad \text{Eq. (24)}$$

$$r_3 = \left(\frac{3 \cdot 10^{21} V_3}{4\pi N_{\text{Av}}} \right)^{1/3} \quad \text{Eq. (25)}$$

Definitive V_{cor} value requires iteration because it depends on the local mole fractions of 2-propanol and water around the meloxicam molecules. Hence, this iteration is performed by substituting $\delta x_{1,3}$ and V_{cor} values in Eqs. (18), (19) and (22) to recalculate $x_{1,3}^L$ until an invariant value of V_{cor} is obtained.

Figure 9 shows the apparent Gibbs energies of transfer of meloxicam from neat water to {2-propanol (1) + water (2)} mixtures at 298.15 K. These values were calculated from the mole fraction solubility data shown Table 2 by using Eq. (26):

$$\Delta_{\text{tr}} G_{3,2 \rightarrow 1+2}^{\circ} = RT \ln \left(\frac{x_{3,2}}{x_{3,1+2}} \right) \quad \text{Eq. (26)}$$

$\Delta_{\text{tr}} G_{3,2 \rightarrow 1+2}^{\circ}$ values were correlated according to the regular fourth degree polynomial presented as Eq. (25), with adjusted $r^2 = 0.9986$, typical error = 0.1021, and F value = 2170.3.

$$\Delta_{\text{tr}} G_{3,2 \rightarrow 1+2}^{\circ} = -0.03 - 44.72x_1 + 86.16x_1^2 - 79.89x_1^3 + 29.63x_1^4 \quad \text{Eq. (27)}$$

The D values shown in Table 7 were calculated from the first derivative of Eq. (25) by considering the mixture's composition variation in incremental $x_1 = 0.05$ steps. Q , $RT \kappa_T$, \bar{V}_2 and \bar{V}_3 values of {2-propanol (1) + water (2)} mixtures were taken from the literature.⁷⁴ Because \bar{V}_3 is not available for meloxicam in {2-propanol (1) + water (2)} mixtures, it was considered as the one calculated based on the Fedors' method, $183.3 \text{ cm}^3 \cdot \text{mol}^{-1}$.⁶⁻⁹ $G_{1,3}$ and $G_{2,3}$ shown in Table 7 are negative in all cases, except $G_{2,3}$ in neat

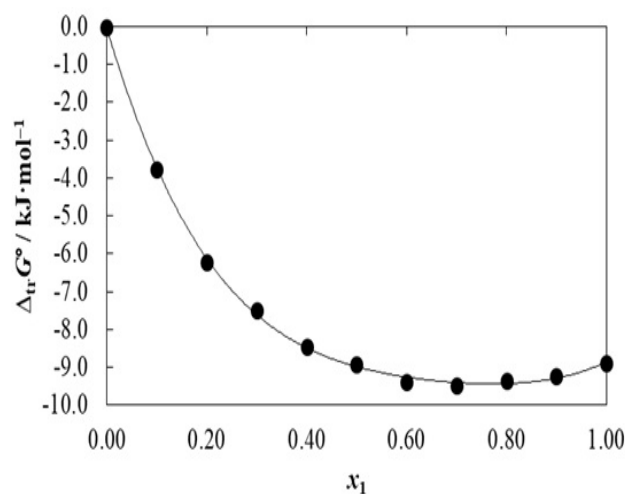


Figure 9. Gibbs energy of transfer of meloxicam (3) from neat water (2) to {2-propanol (1) + water (2)} mixtures at 298.15 K.

Table 7. Some properties associated to preferential solvation of meloxicam (3) in {2-propanol (1) + water (2)} mixtures at 298.15 K.

x_1^a	$D / \text{kJ}\cdot\text{mol}^{-1}$	$G_{1,3} / \text{cm}^3\cdot\text{mol}^{-1}$	$G_{2,3} / \text{cm}^3\cdot\text{mol}^{-1}$	$V_{\text{cor}} / \text{cm}^3\cdot\text{mol}^{-1}$	$100 \delta x_{1,3}$
0.00	-44.72	-507.0	-182.2	827	0.00
0.05	-36.69	-443.0	-237.1	870	-1.57
0.10	-29.76	-394.1	-277.9	931	-1.63
0.15	-23.86	-356.0	-308.9	1000	-0.88
0.20	-18.89	-326.0	-333.3	1071	0.16
0.25	-14.77	-302.2	-353.2	1140	1.20
0.30	-11.39	-283.3	-370.8	1207	2.13
0.35	-8.68	-268.5	-388.1	1272	2.94
0.40	-6.55	-256.9	-407.1	1335	3.65
0.45	-4.91	-248.1	-429.9	1396	4.30
0.50	-3.66	-240.8	-456.5	1456	4.87
0.55	-2.73	-233.3	-479.4	1512	5.21
0.60	-2.01	-222.3	-474.5	1561	4.89
0.65	-1.43	-207.0	-412.8	1599	3.55
0.70	-0.89	-192.2	-310.4	1632	1.77
0.75	-0.30	-182.9	-214.8	1670	0.40
0.80	0.42	-178.6	-144.2	1713	-0.36
0.85	1.37	-177.1	-92.7	1759	-0.67
0.90	2.63	-177.2	-51.5	1809	-0.69
0.95	4.28	-178.3	-15.2	1860	-0.46
1.00	6.43	-180.0	19.6	1913	0.00

^a x_1 is the mole fraction of 2-propanol (1) in the {2-propanol (1) + water (2)} mixtures free of meloxicam (3).

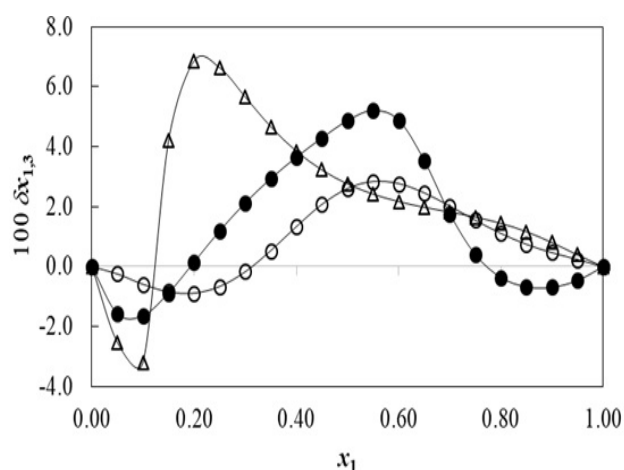


Figure 10. Preferential solvation parameters of meloxicam (3) in some {cosolvent (1) + water (2)} mixtures at 298.15 K. ●: 2-propanol (1) + water (2),^{this work} ○: methanol (1) + water (2),⁷ △: Carbitol[®] (1) + water (2).⁸

2-propanol, indicating that meloxicam exhibits affinity for 2-propanol and water. Meloxicam radius value (r_3) was calculated as 0.417 nm. Preferential solvation parameters of meloxicam by 2-propanol are also shown in Table 7. Figure 10 shows that $\delta x_{1,3}$ vary non-linearly with the 2-propanol proportion. Initially, the addition of 2-propanol to water makes negative the $\delta x_{1,3}$ values of meloxicam from neat water to the mixture of $x_1 = 0.19$. Maximum negative value of this parameter is obtained in the mixture of $x_1 = 0.10$, with $\delta x_{1,3} = -1.63 \times 10^{-2}$, which is higher than $|1.00 \times 10^{-2}|$, and therefore, it is a consequence of real preferential solvation effects by water, rather than a consequence of uncertainties propagation in the IKBI calculations.^{75,76}

The cosolvent action of 2-propanol for increasing the meloxicam solubility in these water-rich mixtures could be associated to the breaking of the ordered structure of water, like “icebergs”, around the non-polar moieties of meloxicam, which in turn, increases the meloxicam solubility and solvation, as described above. In mixtures of $0.19 < x_1 < 0.78$ the $\delta x_{1,3}$ values are positive indicating preferential solvation of meloxicam by 2-propanol. Maximum $\delta x_{1,3}$ value was obtained in the mixture of $x_1 = 0.55$ ($\delta x_{1,3} = 5.21 \times 10^{-2}$). It is worthy to note that this maximum positive $\delta x_{1,3}$ value is clearly higher than $|1.00 \times 10^{-2}|$, and therefore, it is a consequence of real preferential solvation effects by 2-propanol.^{75,76} From a mechanistic viewpoint, in the mixtures composition region of $0.19 < x_1 < 0.78$, it is conjecturable that meloxicam is acting as a Lewis acid with the 2-propanol molecules owing the unshared electrons of the hydroxyl oxygen atom of this alcohol. This cosolvent is more basic than water, as remarkable by comparing their Kamlet-Taft hydrogen bond acceptor parameters, namely $\beta = 0.84$ for 2-propanol and 0.47 for water.^{35,77} Finally, in 2-propanol-rich mixtures ($0.78 < x_1 < 1.00$), apparently meloxicam is preferentially solvated by water again. Maximum negative $\delta x_{1,3}$ value in this region is obtained in the mixture of $x_1 = 0.90$ being -6.9×10^{-3} , which is slightly lower than 1.00×10^{-2} . Nevertheless, from a qualitative viewpoint, these values could be analyzed as a possible consequence of preferential solvation of meloxicam by water molecules. Here meloxicam could be acting mainly as a Lewis base in favor of the water molecules because water is more acidic compared with 2-propanol, as described by the respective Kamlet-Taft hydrogen bond donor parameters, namely $\alpha = 1.17$ for

water and 0.76 for 2-propanol, respectively.^{35,78} Moreover, Figure 10 also compares the preferential solvation of meloxicam by methanol and Carbitol® in their respective aqueous mixtures.^{7,8} As observed, only two regions are observed with these other two alcohols, owing the fact that maximum meloxicam solubilities are observed in those neat cosolvents, whereas with 2-propanol, it is observed in the mixture of $x_1 = 0.70$. Otherwise, the magnitudes of preferential solvation by water and alcohol decrease in the order: Carbitol®-aqueous mixtures > 2-propanol-aqueous mixtures > methanol-aqueous mixtures, which is just the contrary order regarding the polarity of every cosolvent as described by the respective Hildebrand solubility parameters, *i.e.* 22.3 MPa^{1/2} for Carbitol® < 23.7 MPa^{1/2} for 2-propanol < 29.6 MPa^{1/2} for methanol. A similar behavior was observed with meloxicam in aqueous mixtures of *N*-methyl substituted formamides.⁶ Moreover, a similar trend was reported for ketoprofen in aqueous mixtures of ethanol and propylene glycol.⁷⁹ These behaviors could be a consequence of higher water-association effects around non-polar groups of drugs favored by the more hydrophobic moieties present in the cosolvents as they are less polar. In turn, these hydrophobic groups of cosolvents are also acting as water-association promoters depending on their respective sizes. Finally, from all the physicochemical analyses described, it is noteworthy to indicate that this research expands the equilibrium solubility database of non-steroidal anti-inflammatory drugs in aqueous cosolvent mixtures.⁸⁰

Conclusion

Equilibrium solubility values of meloxicam in {2-propanol (1) + water (2)} mixtures at five temperatures from 293.15 to 313.15 K were determined, reported and analyzed. Meloxicam solubility in these mixtures has adequately been correlated with the Jouyban-Acree model. Apparent standard thermodynamic quantities of dissolution and mixing processes, as well as the respective preferential solvation parameters of meloxicam by water and 2-propanol in these aqueous mixtures, have also been calculated and reported.

Author Contributions

DAT: Conceptualization; Methodology; Formal analysis; Investigation; Writing - Original Draft; Writing - Review & Editing. FM: Conceptualization; Methodology; Formal analysis; Investigation; Writing - Original Draft; Writing - Review & Editing; Funding acquisition. OAA: Conceptualization; Methodology; Investigation; Writing - Review & Editing; Funding acquisition. AJ: Conceptualization; Investigation; Writing - Review & Editing. WEA: Conceptualization; Investigation; Writing - Review & Editing. All authors have read and agreed to the published version of the manuscript.

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