Original Research Article

Ketoprofen Solubility in Organic Solvents and Aqueous Co-solvent Systems: Interactions and Thermodynamic Parameters of Solvation

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ABSTRACT

Ketoprofen (KET) solubility was determined in fifteen pure solvents and aqueous-cosolvent mixtures systems. The results obtained and the parameterized values solvents allowed us to observe the influence of the latter on the solubility of KET. The experimental data obtained indicates that the $\pi*$ parameter, which accounts for the polarity/polarizability of the solvent, and the Hildebrand's solubility parameter, which depicts the cohesive forces of the solvent ,has the greatest influence on the solubility of KET. In all the analyzed cosolvent mixtures, the solute was preferentially solvated by the organic cosolvent. This indicates that with a decreasing polarity of the solvent, solvent-solvent interactions decrease, favoring the solute-solvent interactions. For aqueous binary mixtures of ethanol, ethylene glycol and propylene glycol, the apparent enthalpy, entropy and Gibbs free energy changes involved in the solvation process were determined.

Keyword: Ketoprofen; co-solvents; solubility; interactions; thermodynamic parameters

INTRODUCTION

The analysis of the physicochemical properties of drugs is of great interest in pharmacy. Ketoprofen (KET) (±) 2-(3-benzoylphenyl) propionic acid (Figure1) is a non-steroidal antiinflammatory drug (NSAIDs) nonselective COX propionic acid derivative [1]. The NSAIDs propionic acid derivatives have low water solubility. KET being used a non-steroidal analgesic and antipyretic in Argentina in different presentations [2]. Whereas KET has wide spread use as NSAIDs, it is important to know their physicochemical properties and how it interacts with pure solvents and water. Knowledge of these interactions is important in the design of new presentations of liquid dosage forms [3]. The availability of this information is often used for other applications

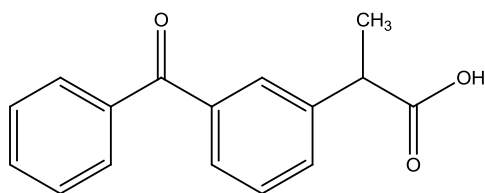such as purification methods and preformulation [4, 5].

Fig. 1: Scheme of Ketoprofen (KET)

On the other hand, in analysis of interactions at play between KET and solvents, it is possible to analyze it from the thermodynamic point of view by a thermal analysis of the dissolution process [6].

Through solubility studies in different conditions with different solvent sand water, using solvent properties as descriptors for KET solubilization process, we aim at finding characteristics that favor the process of solubilization of this drug. Furthermore, the study of thermodynamic parameters improves the interpretation of the results of the solubilization of KET.

EXPERIMENTAL
Solubility determinations
Pure solvents and/or binary water and organic cosolvent mixtures were prepared in a closed system which provides continuous and stirring thermally conditioned using a stirrer SI Lab Companion 300R. KET excess was added in a glass tube with a lid of 10 mL capacity containing the pure solvent or the prepared mixtures. A sufficient amount of KET was added to achieve system saturation. The same was held for at least 72 hours, with continuous agitation. The saturated system was then analyzed by a UV-Vis spectrophotometer extracting an aliquot of the system [7]. The concentrations were determined by the necessary dilutions to the wavelength of maximum absorption of KET (λ= 254.4 nm; ε =16853 L mol^{-1} cm^{-1}) using methanol as solvent during the dilution process. In order to ensure

the reproducibility and saturation of the solutions, all dilutions and solubility measurements were performed in triplicate and experimental results reported were the average of three measurements. Absorbance measurements were performed with a Shimadzu double beam UV 160 A with a fitted thermostatic cell holder. Furthermore, a thermodynamic study modifying the temperature systems for water-organic solvent mixtures (ethanol, ethylene glycol and propylene glycol) was carried out at a working temperature (291.15±0.3 - 307.15±0.3 K). The solvents used were spectroscopic grade and KET (CAS 22071-15-4;Molar mass 254.28 g mol^{-1} 99.7%, analytical quality).

Data analysis
Data processing and fitting of all equations were performed using the scientific program Origin v 8.0. To fit equations, linear regression was performed by minimum squares. Statistical analysis was performed using IBM SPSS Statistics 19 v program.

RESULTS AND DISCUSSION
Pure solvents
The analysis of the drug solubility at constant temperature in pure solvents or mixtures of cosolvents reveals chemical properties of both solute and solvent. Due to the fact that physicochemical properties of the solvents are generally well known, we carried out this study to analyze the interaction of the drug with its environment through knowledge of the solvents. To analyze the positive or negative influence of solvents on the solubility of KET, an analysis of multiple linear regression was used. To this end the description of linear free energy relationships (LSER) is proposed. The most widely used of these is the Kamlet-Taft expression [8, 9], in which XYZ is a property linearly related to Gibbs energy:

$$XYZ = XYZ_{\circ} + energy_{cf} + \sum energy_{sto-ste} \quad (1)$$

where, XYZ_o is a constant that depends only on the solute; $energy_{cf}$ is the energy of the formation of cavity, term related to the solvent, and the $energy_{sto\text{-}ste}$ term includes all modes of solute-solvent interaction.

Now we can write [10]:

$$XYZ = XYZ_{\circ} + m\delta_H^2 + p\pi^* + a\alpha + b\beta \quad (2)$$

In the above expression the descriptors used are. δ_H is the Hildebrand's solubility parameter of the solvent, that represents their self-cohesiveness; the solvatochromic parameter π^* describes a combination of properties, the polarity and the polarizability of the solvent. The α and β quantities are solvatochromic properties of the solvent, α is the hydrogen bond donation (HBD) ability and β is the hydrogen bond acceptance (HBA) ability or electron pair donation ability to form a coordinative bond.

These parameters are determined primarily by the energies of the longer wavelength absorption peaks of certain carefully selected probe solutes in the solvents in question, after subtraction of the effect that non-HBD and/or non-HBA solvents would have on the probe, determined in separate experiments [11]. They have been designed and given numerical values so that ideally they describe exclusively the HBD and HBA properties of the solvents, unaffected by their other properties, such as polarity, polarizability or tightness of cohesion. For some processes, any of the coefficients XYZ_0, m, p, a and/or b may be neglected, then the property that they represent does not play an important role in the solubilization process.

The solubility results obtained (Table 1) were adjusted with the following expression:

$$\log S = -1.469 - 3.133(\delta_H^2/1000) + 3.505\pi^* + 1.135\alpha + 0.855\beta \quad (3)$$

$$r = 0,961; \sigma = 0,00001$$

as may be seen, the positive values of coefficients π^*, α and β indicate that solubility increases with the increase in the value of these parameters. Therefore, both HBD and HBA interactions of the solvent with the carbonyl group of the solute have a positive effect on the solubility of the solute. On the same lines, the dipolar solute-solvent interaction results in an increase in solubility but with a very significant value showing the greatest positive effect on the solubility of KET. It may be observed that the magnitude of the coefficients α and β is is small compared with the value of π^*, which has a significant weight in the solubility of KET. Moreover, as can be observed, another coefficient which has a great effect on the solubility of KET is the Hildebrand's solubility. This parameter represents the square root of the cohesive energy density and it is an index of polarity, i.e. the greater value of δ_H is the most polar compound. The negative sign indicates that the solubility decreases as the cohesive forces of the solvent increase. This means that an increase in the solvent-solvent interaction inducing self-cohesiveness has an adverse effect on the solubility of the solute.

According to the data given in Table 1, at 300.15 K, KET showed very low solubility in water ($6.27.10^{-4}$ mol L^{-1}) and ciclohexane ($4.16.10^{-3}$ mol L^{-1}) solvents. As can be seen, the Hildebrand solubility parameter of water has a very significant value as compared to the terms which contribute favorably to the increase in solubility. The π^*, α and β parameters, and therefore the significant cohesive forces which manifest themselves in the water, determine the low solubility of KET in this solvent. Ciclohexane does not contribute as a donor or acceptor of hydrogen bridges, nor does it influence the polarity/polarizability.

On the other hand, the NSAID analyzed has a greater solubility in dimethyl sulfoxide (2.89 mol L^{-1}) and dimethylformamide (2.73 mol L^{-1}). KET solubility in these two solvents results from the predominant influence on the polarity/polarizability of the solvent, having a value slightly higher than that for β which also contributes to the high solubility of KET in these two solvents.

Table 1: Experimental Solubility of KET and parameters related to solvents

Solvent	log S	α	β	π^*	$\delta^2_H/1000$
Water	-3.203	1.17	0.47	1.09	2.294
Methanol	0.232	0.98	0.66	0.60	0.880
Ethanol	0.267	0.86	0.75	0.54	0.707
i-Propanol	0.109	0.76	0.84	0.48	0.552
n-Propanol	0.143	0.84	0.9	0.52	0.602
i-Butanol	-0.047	0.79	0.84	0.40	0.467
n-Butanol	0.052	0.84	0.84	0.47	0.533
Octanol	-0.424	0.77	0.81	0.40	0.444
Ethylene glycol	-0.591	0.90	0.52	0.92	1.084
Propylene glycol	-0.302	1.21	0.51	0.62	0.912
Dimethylformamide	0.437	0.00	0.69	0.88	0.613
Dimethyl sulfoxide	0,461	0.00	0.76	1.00	0.707
Ciclohexane	-2.381	0.00	0.00	0.00	0.281
Acetone	0.256	0.08	0.43	0.71	0.402
Acetonitrile	-0.123	0.19	0.40	0.75	0.581

α: HBD ability; β: HBA ability; $\pi*$: polarity/polarizability; dimensionless
$\delta^2_H/1000$: Hildebrand parameter, Jcm^{-3}; T=300.15 K

Table 2: Solubility and parameters for the cosolvent systems analyzed

Cosolvent	A	B	C	D	r	S	S $_{exp}$
Methanol	4.343	1.250	-6.711	1.882	0.998	2.203	1.706±0.026
Ethanol	4.308	-1.603	8.142	-10.48	0.999	2.032	1.849±0.028
i-Propanol	4.143	-2.158	8.720	-11.671	0.992	1.389	1.285±0.022
n-Propanol	4.185	-1.374	8.591	-10.813	0.997	1.531	1.390±0.025
Ethylene glycol	3.395	-0.838	-1.590	-0.189	0.999	0.248	0.256±0.005
Propylene glycol	3.732	-1.052	3.648	-5.862	0.998	0.539	0.499±0.011
Acetone	4.270	-0.683	5.143	-7.503	0.989	1.862	1.803±0.027
Acetonitrile	3.939	0.090	5.403	8.562	0.997	0.869	0.753±0.015

A, B, C, D: parameters; S: Solubility in pure organic solvents obtained from A: S=10$^{(A-4)}$ (mol L^{-1});
S$_{exp}$ (experimental solubility; mol L^{-1}); r=correlation coefficient. T=300.15 K.

When interpreting KET solubility data in the monoalcohols tested, it may be observed that the higher the amount of carbon atoms, the lower the solubility. KET presents the largest solubility in methanol (1.71 mol L^{-1}) and in ethanol (1.85 mol L^{-1}), a value close to that reported by Singhai et al. [12] to 298.15 K, while the lowest is in octanol (0.38 mol L^{-1}).

If we analyze the KET solubility in the polyalcohols studied, it is lower compared to then-alcohol with the same number of carbon atom and this is due to an increase in the value of the forces of cohesion of polyalcohols.

It can be seen that the solubility values determined by us were some what higher than those reported by other authors. For example, we obtained for solubility of KET in water $6.27 \cdot 10^{-4}$ mol L^{-1} to 300.15 K, while Gantiva et al. [13] reported $4.295 \cdot 10^{-4}$ mol L^{-1} to 298.15 K. The data provided by Epitalier et al. [14] to 303.15 K ($8.89 \cdot 10^{-4}$ mol L^{-1}) is close to what is reported in this study. According to the data available, the value of solubility in this solvent presented by Kommury et al [15] ($5.58 \cdot 10^{-3}$ mol L^{-1}) is significantly higher than those reported by other authors. In ethanol, the solubility of KET reported in this work (1.85 mol L^{-1} to 300.15 K) is close to what is reported by Jouyban et al. [16] (1.8 M at 298.15 K), whereas the data reported by Gantiva et al. [13] is substantially lower (0.67 M at 298.15 K).

The solubility value of KET in cyclohexane informed by Gantiva et al. [16] at 298.15 K was $5.50 \cdot 10^{-4}$ mol L^{-1}, far below the value reported in our study ($4.16 \cdot 10^{-3}$ mol L^{-1} to 300.15 K), which was ratified in additional experiences. Regarding the value of solubility of this NSAIDs in propylene glycol, Gantiva et al. [17] reported 0.1832 mol L^{-1} at 298.15 K, much lower than the value found by us (0.499 mol L^{-1} to 300.15K).

It is observed that the solubility values reported by Gantiva et al. [13, 17] are lower than those presented in this study. This enables us to claim that the contact time and the technique used to determine the solubility plays an important role in the results. In our determinations, the samples analyzed were left in contact for a period of at least 5 days after the saturation process, with continuous agitation of the entire bulk solution. These times were extended even more when KET was contacted with solvents of high viscosity such as propylene glycol or ethylene glycol and also in the case where saturation conditions created a situation of high viscosity in the solution.

Analysis in water-organic solvent mixtures

The solvent mixtures are widely used in industry and laboratories as a single solvent to satisfy multiple requirements: to increase the solubility of poorly water soluble drugs, to enhance the chemical and physical stability of a drug, among others. In the preformulation of pharmaceuticals, these mixtures are used extensively for vehiculization.

The solubility (log S) is related to the standard molar Gibbs energy of solvation. In an ideal solvation, the standard Gibbs energy in a mixture of cosolvents is given by the average of molar fraction, and the solubility in a mixture binary solvent, while log S$_{wo}$ is a linear function of molar fraction. The deviation from linearity expresses the existence of a non-ideal process of solvation. For all the mixtures analyzed, the data for log S$_{wo}$ (solubility in the cosolvent mixture) can be fitted satisfactorily with a polynomial cubic in X$_w$ (mole fraction of water) according to the following equation [18]:

$$\log S_{WO} = A + BX_W + CX_W^2 + DX_W^3 \qquad (4)$$

In this equation, A represents the value of log S in the pure organic solvent. The representation of the equation (4) allows the classification of the solubility profiles in two groups [19]: solubility profiles having a maximum peak and those which do not. For the former class of profiles, the nonlinear variation of log S$_{wo}$ with mole fraction might be attributed to the preferential solvation of the solute through one of the two components of the mixture [20].

The parameter used to observe the excess or deficiency of one of the components of the mixture in the local region of the solute is the δ$_w$ parameter calculated for water using the following equation:

$$\delta_W = \left[\log S_{WO} - \left(X_W \log S_W + X_O \log S_O\right)\right]/\left[\log S_W - \log S_O\right] (5)$$

δ_w is useful to compare the performance of different mixtures of cosolvents, and its variation with X_w responds to a cubic polynomial that can be expressed by:

$$\delta_W = Intercept + B_1 X_W + B_2 X_W^2 + B_3 X_W^3 \quad (6)$$

X^L expresses the local mole fraction of water or organic cosolvent in the surrounding of the solute and it is related to the solubility [20] as follows:

$$\log S_{WO} = X_W^L \log S_W + X_O^L \log S_O \quad (7)$$

Considering that:
$$X_W^L + X_O^L = 1 \quad (8), \text{ we obtain:}$$

$$X_W^L = \left[\log S_{WO} - \log S_O\right]/\left[\log S_W - \log S_O\right] \quad (9)$$

Combining (5) and (7) gives the expression for the δ_w parameter, which, according to [20, 21], represents an excess or deficit of solvent in the local region, as follows:

$$\delta_W = X_W^L - X_W = -\delta_O \quad (10)$$

When $\delta_W > 0$, the solute is preferentially solvated for water, otherwise it is solvated by the organic solvent. If $|\delta_W \leq 0,01|$, the preferential solvation is negligible, but when $X_W^L \approx 1$, there is a complete solvation of solute by water.

Some samples tested showed phase separation and because of this in some proportions it was not possible to determine solubility. This situation occurred for acetonitrile-water mixtures for X_W values between 0.5 and 0.8 as well as in mixtures of n-propanol for values

between 0.7 and 0.9 of X_W. The literature does not provide details regarding this situation, neither similar observation were reported. Because the scope of this research does not cover the study of these events in particular, we believe that it may be the subject of further studies.

The graphical representation of log S_{WO} versus X_W (eq.4) for KET is illustrated in Figure 2 for binary mixtures of water with methanol, ethanol, ethylene glycol, propylene glycol and acetonitrile. Table 2 shows the A, B, C and D parameters for all the cosolvent systems analyzed. As can be observed, the solubility values obtained from A (solubility in pure organic solvent) agree with the experimental values. In all the cosolvent mixtures analyzed, the solubility profile did not shows a maximum.

From equations 4 and/or 9 the δ_w values were calculated. The negative values obtained indicate that there is a deficit of water around the solute. In other words, the organic cosolvent is preferred over the water in this area. This can be attributed to the hydrogen bond linking the water molecules that the strongly hydrophobic solute cannot break, thus reducing the amount of water molecules participating in the solvation process.

Figure 3 shows the profile of variation of negative values of δ_w versus X_w at different compositions of binary mixtures for KET in methanol and acetonitrile as organic cosolvent. For all the cosolvent-water mixtures used, the curves pass through a maximum, which is about 0.5 for X_W values. Table 3 shows the values of coefficients obtained by representation of -δ_w versus X_w for different cosolvent systems.

Table 3: Coefficients obtained by representation of $-\delta_w$ versus X_w for cosolvent systems

Cosolvent	Intercept	B_1	B_2	B_3	r
Methanol	-0.012	1.349	1.876	0.526	0.977
Ethanol	0.011	0.587	2.097	-2.700	0.994
i-Propanol	0.011	0.614	2.411	-3.035	0.993
n-Propanol	0.108	0.978	1.096	-2.200	0.985
Ethylene glycol	-0.005	0.677	-0.612	-0.073	0.976
Propylene glycol	0.010	0.679	1.109	-1.782	0.991
Acetone	0.006	0.770	1.469	-1.976	0.988
Acetonitrile	0.020	1.029	1.763	-2.796	0.987

r=correlation coefficient. T=300.15K.

In Figure 4 we illustrate the variation of X_w^L versus X_w for ethanol and ethylene glycol aqueous binary mixtures. Evidently, the preferential salvation of the cosolvent is higher in ethanol than in ethylene glycol, and this may be attributed to the fact that the KET solution acts primarily as a Lewis acid by forming hydrogen bonds with the functional groups of the solvent proton acceptor (oxygen -OH). In addition, the KET compound can act as a proton accept or through its carbonyl, hydroxyl and ketone moieties [17].
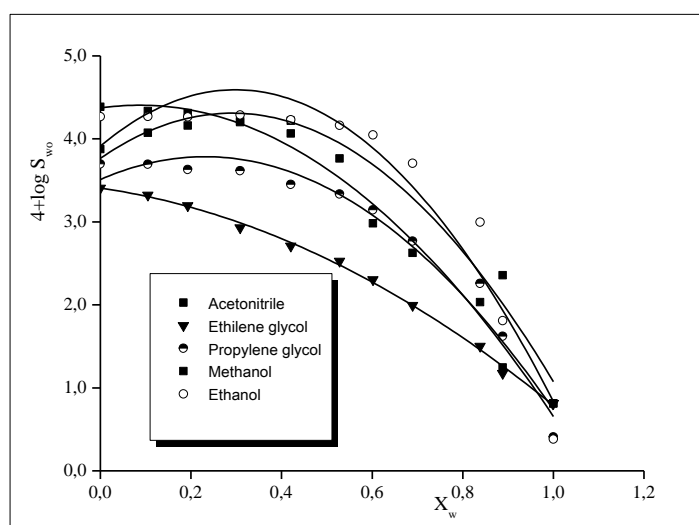

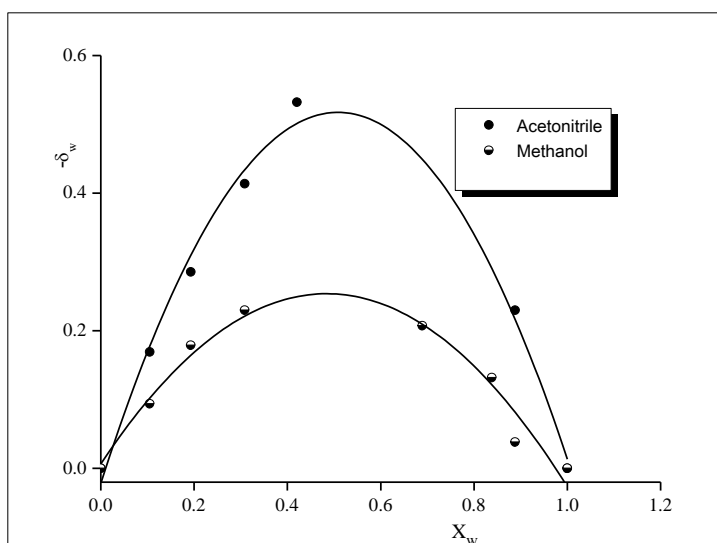**Fig. 2: Plot of 4+log S as function of X_W^L in water-organic cosolvent mixtures**

Fig. 3: Plot of -δ$_w$ as a function of solvent composition (X_W)
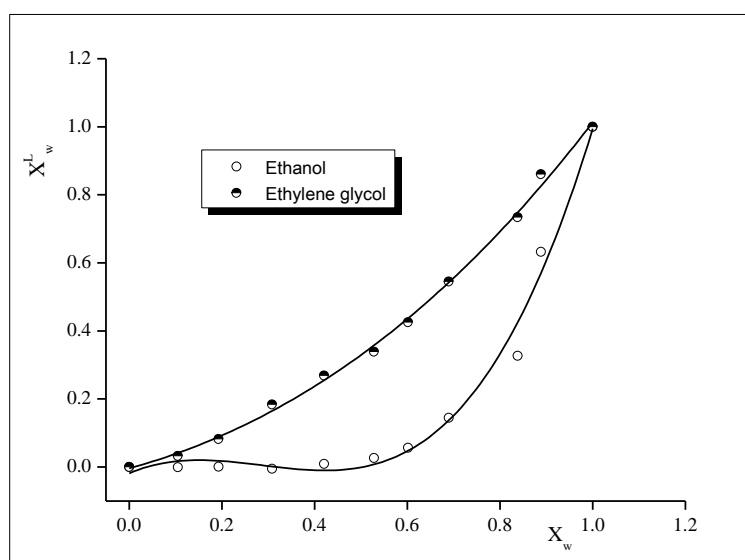

Fig. 4: Graphic representation of X_W^L calculated as function of X_W

It is reasonable to consider that the water surrounding the carboxyl group interacts with the ketone group as well, as is the case with the organic solvent. As seen in the solubility values, all pure cosolvents facilitate the solubility of KET. KET solubility in aqueous mixtures of ethanol increases to a maximum value corresponding to pure cosolvent. The same situation has been described in studies by Gantiva et al. [3, 17]. Alcohols which haves one or two hydroxyl groups (in the case of propylene glycol and ethylene glycol) may donate or accept hydrogen bonds of the carboxyl and ketone groups. Moreover, the hydrocarbon portion of the alcohol can interact with the aromatic portions of the drug via dispersion forces more effectively than water. As expressed above, the existence of preferential solvation for these drugs is then expected. Profiles such as those seen in Figure 4 shows solvation capabilities of the solvents relative to water. These capabilities have been found to be greater than those reported in

other studies on KET, in which only one solvent was used.

Analysis of temperature in water-organic solvent mixtures

In order to analyze the process of dissolution, it is possible to consider that it is carried out in a succession of stages: the first step involves the breaking of the existing bonds between adjacent molecules of solute; the second step is the creation of a hole in the solvent to accept the molecule solute. These two steps are produced with consumption of heat $(\Delta H^0 > 0)$ and are unfavorable enthalpically, because solute and solvent must beat the cohesive forces that are held together. In the third step, the solute molecule is finally placed in the cavity in the solvent. This stage occurs with heat release $(\Delta H^0 < 0)$, enthalpically favorable, due to solute-solvent interactions. The sign and magnitude of $\Delta H°$ for overall processes depend on the nature of these interactions. The entropy is an indicator of the disorder, the more positive the entropy change, the more favorable the process [22].

Standard enthalpy and entropy variation for solution process may be calculated using the van't Hoff thermodynamic relation [23, 24]:

$$\ln C_2 = \Delta S^0_{so\ln}/R - \Delta H^0_{so\ln}/RT \qquad (11)$$

where C_2 is the solubility of KET in the cosolvent system used, expressed as molar concentration; T is the absolute temperature (K); R represents the gas constant, and $\Delta H°$ and $\Delta S°$ the standard changes for enthalpy and entropy for the solubilization process. For a lineal relation of ln C_2 versus 1/T, the slope and intercept are -$\Delta H°/R$ and $\Delta S°/R$ respectively.

To minimize errors in the calculation of the thermodynamic parameters, some modifications were included. We used the so

called mean harmonic temperature, defined as [25-27]:

$$T_{hm} = n\left/\sum_{n=1}^{n}\left(1/T\right)\right. \qquad (12)$$

Where n is the number of temperatures analyzed. The van't Hoff modified expression can be written [28] as follows:

$$-\Delta H°_{so\ln}/R = \delta \ln C_2 \left/ \delta\left(\frac{1}{T} - \frac{1}{T_{hm}}\right)_p\right. \qquad (13)$$

The Gibbs free energy change ($\Delta G°$) that takes place during the solubilization process is calculated at T_{hm}, considering the approach proposed by Krug et al. using [25, 26]:

$$\Delta G°_{so\ln} = -RT_{hm} \times Intercept \qquad (14)$$

in which, the intercept used is the one obtained in the analysis by treatment of ln C_2 as a function of ($1/T - 1/T_{hm}$).

The enthalpy data obtained through the equation (13) are the same as those calculated using the equation of traditional equation of van't Hoff. But, nevertheless, the values of $\Delta G°$ obtained through the equation (14) are slightly different, because in the latter case, it all depends on the solubility data. The entropy change of the process at T_{hm} is obtained from:

$$\Delta S°_{so\ln} = \left[\Delta H°_{so\ln} - \Delta G°_{so\ln}\right]/T_{hm} \qquad (15)$$

Using equations (16) and (17), it is possible to calculate the relative contributions of enthalpy ($\zeta H\%$) and entropy ($\zeta S\%$) to Gibbs energy of solution process [29, 30]:

$$\varsigma\%H = \left[\left|\Delta H°_{so\ln}\right|\left/\left(\left|\Delta H°_{so\ln}\right| + \left|T\Delta S°_{so\ln}\right|\right)\right.\right]100 \quad (16)$$

$$\varsigma\%S = \left[T\left|\Delta S°_{so\ln}\right|\left/\left(\left|\Delta H°_{so\ln}\right| + \left|T\Delta S°_{so\ln}\right|\right)\right.\right]100 \quad (17)$$

The thermodynamic functions for solution processes obtained for the three systems

analyzed are shown in Table 4. The thermodynamic parameters for dissolving KET in pure water suggest that it is an exothermic and non-spontaneous process. The entropy of solution is negative, and considering the percentage contribution of enthalpy appears to be similar when compared to the contribution of the entropic term.

Table 4: Thermodynamic parameters for solution processes

	X	ΔH^o_{soln}	ΔS^o_{soln}	ΔG^o_{soln}	%ζH	r
Water	**1.0**	**-30.8±3.21**	**-170.47±13.48**	**20.19±7.04**	**37.66**	**0.962**
Propylene glycol	0.2	37.83±3.71	96.22±10.15	9.98±5.41	57.38	0.952
	0.4	37.08±3.54	107.82±10.28	4.87±0.94	53.50	0.951
	0.6	39.56±3.78	123.96±11.33	2.48±0.88	51.61	0.945
	0.8	38.70±3.89	123.97±10.98	1.61±0.82	51.06	0.995
	1.0	24.64±2.90	79.02±8.47	0.99±0.31	51.03	0.889
Ethanol	0.2	70.73±8.86	0.206±0.051	8.97±2.85	53.88	0.999
	0.4	21.30±2.55	0.072±0.022	-0.24±0.11	49.71	0.961
	0.6	13.56±1.43	0.050±0.019	-1.33±0.28	47.66	0.972
	0.8	11.26±1.29	0.043±0.016	-1.59±0.23	46.70	0.984
	1.0	19.52±2.05	0.070±0.025	-1.35±0.52	48.33	0.999
Ethylene glycol	0.2	55.44±6.05	141.83±13.56	13.01±1.08	56.64	0.990
	0.4	29.28±2.88	67.88±7.15	8.98±1.54	59.05	0.917
	0.6	41.00±3.95	113.61±10.57	7.02±2.52	54.68	0.972
	0.8	44.62±3.22	131.95±11.29	5.15±1.05	53.06	0.992
	1.0	47.38±3.58	146.67±13.74	3.51±1.13	51.92	0.985

ΔH^o_{soln}; ΔG^o_{soln}: $kJ\ mol^{-1}$; ΔS^o_{soln}: $J\ K^{-1}\ mol^{-1}$

When the same process is observed in ethanol, ethylene glycol and propylene glycol, the solubility process in these solvents is not spontaneous in all proportions. But with decreasing X_W, the process becomes more spontaneous. For the ethylene glycol and propylene glycol cosolvents, the endothermic character clearly decreases with increasing percentage of co-solvent in the mixture. For ethanol this trend is not as clear. The entropy change is positive when the cosolvent is present in the solution.

Thermodynamic parameters and calculated values presented similar trends to those observed by Gantiva et al. [13, 17]. Figure 5 shows the modified van't Hoff plots for different water-ethanol mixtures.

Enthalpy-entropy compensation

Krug et al. [25] established that the graphic representation of ΔH versus ΔG to t_{hm} allows the identification of the mechanism of the co-solvent action. When this kind of graphic presents positive slopes, it indicates that the enthalpy drives the process, whereas when the slope is negative, the leading force of the process is the entropy. Some author shave reported non-linear graphics [31].

It is also possible to determine the enthalpy-entropy compensation using graphics ΔH versus $T\Delta S$. In this case, when the process is governed by the enthalpy, the slope of this graph has a value greater than one, whereas when the process is determined by the entropy, the slope value is lower than one [5].
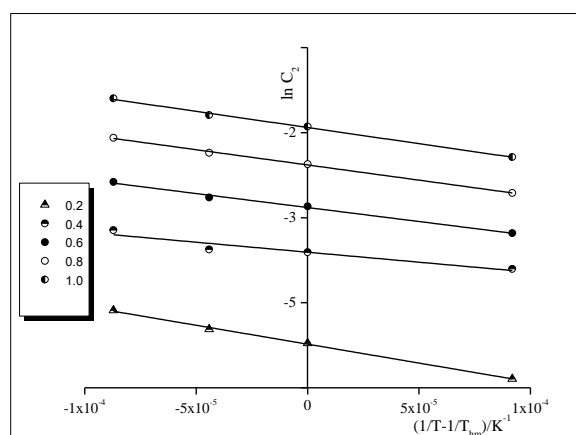
Fig. 5: Graphic representation of Van't Hoff modified expression

From plotting ΔH versus ΔG (at t_{hm}) for aqueous cosolvent mixtures, we obtained a straight line for the water-ethanol (y=-0.431x + 6.141; R^2=0.944), water-ethylene glycol (y=-4.91x + 70.30; R^2=0.983) and water-propylene glycol (y=-3.52x + 43.08; R^2=0.894) mixtures. The slopes obtained showed a negative value indicating that, in this case, the process is dominated by entropy. Gantiva et al. obtained non-linear graphs for KET in aqueous mixtures of propylene glycol [17] and ethanol [13]. This difference could be attributed to the use of different experimental techniques for determining solubility.

Confirming the results mentioned above, the graph of enthalpy changes (ΔH) versus the product of entropy changes by mean harmonic temperature (T_{hm}, ΔS) presented the following settings for the three analyzed systems for water-etanol y= 0.866x + 5.907, R^2=0.947; for water- ethylene glycol y=0.843x + 12.083, R^2= 0.998 and for water- propylene glycol y=0.806x +10.16, R^2=0.986. As it can be observed, the slope values slopes were lower than one, which indicates that the process is driven by organizational character (ΔS). In Figure 6 we show the graphs obtained lines obtained for binary mixtures of ethylene glycol and propylene glycol.
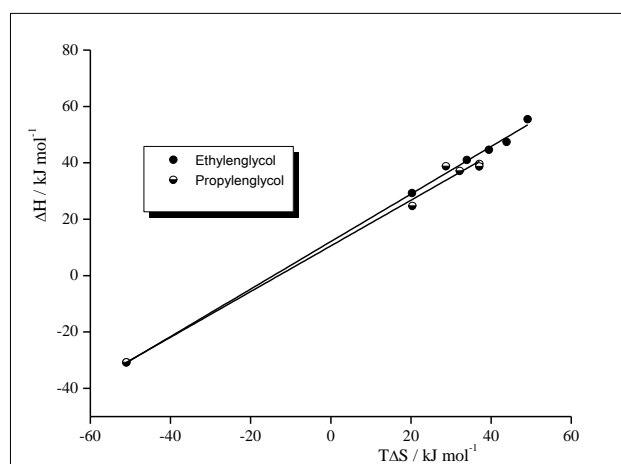

Fig. 6: Enthalpy- entropy compensation

CONCLUSION

The results obtained in this work from solubility determinations of KET are consistent with those shown by other authors with the use of spectroscopic parameters. Therefore, we may conclude that the solubility data allows us to obtain good results in relation to the information on the interactions that occur in the process of solvation.

KET is a relatively non-polar drug; in consequence, it is more soluble in pure organic solvents than in water and in water-organic solvent mixtures. Their solubility depends on the interaction polarity/polarizability, with a positive effect, and on the cohesive forces of solvents that occurs primarily through the Hildebrand solubility parameter, with a negative effect. Nevertheless, the solubility of KET also depends on other factors that have a minor influence on the process.

The analysis of the solubilization processes in binary aqueous systems shows a non-ideal behavior and a significant influence of solvent-solvent interactions, determining the solubility. The results show that for all ratios of aqueous organic solvent mixtures, KET is preferentially solvated by the organic cosolvent but not as much as would have been suggested by the differences in the solvation abilities of the net solvent components. This is due to the existence of an interaction between water and the organic cosolvent. These solvents establish two types of interactions with water: the hydrophobic hydration, i.e. the accumulation of water around apolar parts of cosolvent, and furthermore, solvents having one or more hydroxyl groups, which may form hydrogen bonds with water, reinforcing its structure and causing a decrease in solute- solvent interactions.

In the analysis related to temperature, it can be concluded that the process of dissolution in water-cosolvent mixtures of ethanol, ethylene glycol and propylene glycol, the enthalpy of solution is positive. Therefore, the process is always endothermic or unfavorable, i.e., solute-solute and/or solvent-solvent interactions predominate. They are entropically unfavorable.

Considering the three systems, the energy of formation of the cavity decreases as the solvent polarity decreases, favoring these solute-solvent interactions.

The analysis of the enthalpy-entropy compensation suggests that the process of solubilization of KET in aqueous mixtures of ethanol, ethylene glycol and propylene glycol is driven by the entropy.

It may be concluded that the data presented in this study enhance existing information related to the physicochemical behavior of KET in different pure organic solvents and in their aqueous mixtures. This information is very useful for designing pharmaceutical of liquid dosage forms.

ACKNOWLEDGMENT

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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