J. Chem. Eng. Data **2010,** *55,* 113–118

Solution Thermodynamics of Ketoprofen in Ethanol + Water Cosolvent Mixtures

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Ketoprofen (KTP) is an anti-inflammatory drug widely used in therapeutics. By using the van't Hoff and Gibbs equations, the thermodynamic functions Gibbs energy, enthalpy, and entropy of solution and mixing for KTP in ethanol (EtOH) + water cosolvent mixtures were evaluated from solubility data determined at several temperatures. The solubility was greater in pure EtOH and lower in water at all temperatures studied. This behavior shows the cosolvent effect present in this system. By means of enthalpy−entropy compensation analysis, a nonlinear $\Delta_{\text{soln}}H^0$ vs $\Delta_{\text{soln}}G^0$ plot with negative slope from pure water up to 0.6 in mass fraction of EtOH and positive beyond this EtOH proportion was obtained. Accordingly to this result, it follows that the dominant mechanism for solubility of KTP in water-rich mixtures is the entropy, probably due to water-structure loosening around the drug nonpolar moieties by EtOH, whereas over 0.6 in mass fraction of EtOH, the dominant mechanism is the enthalpy probably due to the KTP solvation increase by EtOH molecules.

Introduction

Ketoprofen (KTP) is a nonsteroidal anti-inflammatory drug (NSAID) derived from propionic acid used widely as an analgesic and an antipyretic, among other indications. Like other NSAIDs, its mechanism of action likely relates to inhibition of prostaglandin synthesis.[1] In the Colombian market, it is commercially available as coated tablets and controlled release tablets for peroral administration, gel for topic use, and injectable solution for intramuscular administration.[2] Although KTP is used widely nowadays in therapeutics, the physicochemical information about properties such as solubility for this drug is not abundant. It is well-known that injectable homogeneous liquid formulations supply relatively high doses of drug in small volumes. For this reason, some physicochemical properties, such as the solubility of drugs and other formulation components, are very important because they facilitate the design process of pharmaceutical dosage forms.[3]

As has already been described, the solubility behavior of drugs in cosolvent mixtures is very important because cosolvent blends are frequently used in purification methods, preformulation studies, and pharmaceutical dosage forms design, among other applications.[4,5] For these reasons, it is important to determine systematically the solubility of drugs, to obtain complete information about physicochemical data of pharmaceutical systems. This information facilitates widely the labor of pharmacists associated to research and development of new products in the pharmaceutical industry.[6] Temperature−solubility dependence allows us to carry out the respective thermodynamic analysis, which, on the other hand, also permits inside the molecular mechanisms, involved toward the solution processes.[7]

The main objective of this study was to evaluate the effect of the cosolvent composition on solubility and solution thermodynamics of KTP in ethanol (EtOH) (1) + water (2) cosolvent mixtures based on the van't Hoff method, including the respective contributions by mixing of this drug toward the solution processes. EtOH and propylene glycol are the cosolvents more widely used in the development of liquid pharmaceutical dosage forms.[4,5] This report expands the information presented for this drug by Espitalier et al.,[8] Kommury et al.,[9] and Perlovich et al.[10]

Experimental Section

Materials. Ketoprofen (2-(3-benzoyl-phenyl)propionic acid, CAS 22071-15-14, KTP, (3)) used is in agreement with the quality requirements indicated in the American Pharmacopeia, USP.[11] KTP used was the racemate; absolute ethanol A.R., Merck (CAS 64-17-5, EtOH, (1)); distilled water (CAS 7732-18-5, (2)), conductivity < 2 $\mu\text{S}\cdot\text{cm}^{-1}$; molecular sieve Merck (numbers 3 and 4); Millipore Corp. Swinnex-13 filter units.

Cosolvent Mixture Preparation. All ethanol (1) + water (2) cosolvent mixtures were prepared in quantities of 40.00 g by mass using a Ohaus Pioneer TM PA214 analytical balance with sensitivity ± 0.1 mg, in mass fractions from 0.10 to 0.90 varying by 0.10, to study nine mixtures and the two pure solvents.

Solubility Determinations. An excess of KTP was added to 20 cm^3 of each cosolvent mixture, in stoppered dark glass flasks. Solid−liquid mixtures were placed on an ultrasonic bath (Elmasonic E 60 H) for 15 min and allowed with stirring in a thermostatic mechanical shaker (Julabo SW23) kept at (313.15 ± 0.05) K at least for five days to reach the equilibrium. This equilibrium time was established by quantifying the drug concentration until it became a constant value). After this time, the supernatant solutions were filtered (at isothermal conditions) to ensure that they were free of particulate matter before sampling. Drug concentrations were determined by measuring absorbance after appropriate dilution and interpolation from a previously constructed UV spectrophotometry calibration curve (UV/vis BioMate 3 Thermo Electron Company spectrophotom-

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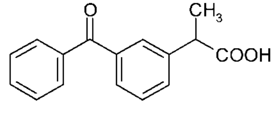
10.1021/je9002866 CCC: $40.75

Table 1. Some Physicochemical Properties of Ketoprofen (CAS: 22071-15-14)

Molecular structure [a]	Molar mass / g·mol^{-1} [a]	Melting point / K [b]	ΔH_{fus} / kJ·mol^{-1} [b]
	254.28	367.1	21.0

[a] From Budavari et al.[12] [b] From Perlovich et al.[10]

eter). After the procedure already described, the temperature was decreased by (5.00 ± 0.05) K, and therefore, it was stabilized at (308.15 ± 0.05) K during at least two days, allowing the precipitation of the drug dissolved in excess and quantifying the drug concentration in equilibrium. This procedure was repeated, decreasing the temperature by (5.00 ± 0.05) K to reach (293.15 ± 0.05) K. All the solubility experiments were run at least in triplicate. To make the equivalence between moles per liter and mole fraction concentration scales, the density of the saturated solutions was determined with a digital density meter (DMA 45 Anton Paar) connected to a recirculating thermostatic bath (Neslab RTE 10 Digital One Thermo Electron Company).

Results and Discussion

The molecular structures of KTP and some of their physicochemical properties are summarized in Table 1.[10,12] This drug acts in solution mainly as a Lewis acid to establish hydrogen bonds with proton-acceptor functional groups in the solvents (oxygen in −OH groups). On the other hand, KTP could also act as a proton-acceptor compound by means of its carbonyl and hydroxyl moieties.

Ideal and Experimental Solubility of KTP. The ideal solubility of a crystalline solute (3) in a liquid solvent can be calculated by eq 1

$$\ln x_3^{\mathrm{id}} = -\frac{\Delta_{\mathrm{fus}}H(T_{\mathrm{fus}} - T)}{RT_{\mathrm{fus}}T} + \left(\frac{\Delta C_p}{R}\right)\left[\frac{(T_{\mathrm{fus}} - T)}{T} + \ln\left(\frac{T}{T_{\mathrm{fus}}}\right)\right] \quad (1)$$

where x_3^{id} is the mole fraction ideal solubility of the solute; $\Delta_{\mathrm{fus}}H$ is the molar enthalpy of fusion of the pure solute (at the melting point); T_{fus} is the absolute melting temperature; T is the absolute solution temperature; R is the gas constant (8.314 J·mol^{-1}·K^{-1}); and ΔC_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.[6] Since ΔC_p cannot be easily experimentally determined, it is usually assumed that it may be approximated to the entropy of fusion, $\Delta_{\mathrm{fus}}S$.

Table 2 summarizes the experimental solubilities of KTP, expressed in moles per liter and mole fraction, in addition to the ideal solubilities calculated by means of eq 1, from ΔH_{fus}, and T_{fus} presented in Table 1. In almost all cases, the coefficients of variation for solubility were smaller than 3.0 %.

The highest mole fraction solubility, x_3, value for KTP was obtained in pure EtOH at 313.15 K, while the lowest value was found in water at 293.15 K. The solubility in pure EtOH, x_3 = (4.41 ± 0.12)·10^{-2} at 298.15 K, is moderately different with respect to the value reported by Perlovich et al.,[10] that is, 1.07·10^{-2}. On the other hand, the drug solubility values in pure water at 293.15 K, (3.210 ± 0.025)·10^{-4} mol·L^{-1}, and at 303.15 K, (5.46 ± 0.08)·10^{-4} mol·L^{-1}, are also moderately different with respect to the values reported by Espitalier et al.,[9] that is, 4.89·10^{-4} mol·L^{-1} at 293.25 K and 8.89·10^{-4} mol·L^{-1} at 303.15 K. Otherwise, the drug solubility in water at 298.15 K, (4.295 ± 0.042)·10^{-4} mol·L^{-1}, is not concordant with that reported by Kommury et al.,[8] that is, 5.58·10^{-3} mol·L^{-1}. Unfortunately, in the literature there are no reports of any other solubility value for this drug in these solvents, and therefore, no other direct comparison is possible. All the KTP solubility

Table 2. Experimental Solubility of Ketoprofen in Ethanol (1) + Water (2) Cosolvent Mixtures Expressed in Molarity and Mole Fraction Including Ideal Solubility at Several Temperatures

	S/mol·L^{-1}				
mass fraction of EtOH	T = 293.15 K	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K
0.00	3.210 (0.025)·10^{-4}	4.295 (0.042)·10^{-4}	5.46 (0.08)·10^{-4}	6.47 (0.10)·10^{-4}	7.57 (0.06)·10^{-4}
0.10	4.88 (0.08)·10^{-4}	6.60 (0.11)·10^{-4}	8.09 (0.09)·10^{-4}	9.46 (0.05)·10^{-4}	1.22 (0.05)·10^{-3}
0.20	1.000 (0.013)·10^{-3}	1.337 (0.013)·10^{-3}	1.684 (0.017)·10^{-3}	2.016 (0.020)·10^{-3}	2.671 (0.018)·10^{-3}
0.30	3.41 (0.14)·10^{-3}	4.39 (0.11)·10^{-3}	7.09 (0.26)·10^{-3}	1.047 (0.027)·10^{-2}	1.721 (0.026)·10^{-2}
0.40	9.01 (0.69)·10^{-3}	1.428 (0.050)·10^{-2}	2.559 (0.027)·10^{-2}	5.171 (0.033)·10^{-2}	7.045 (0.046)·10^{-2}
0.50	2.65 (0.17)·10^{-2}	4.77 (0.13)·10^{-2}	0.1049 (0.0026)	0.2038 (0.0023)	0.2906 (0.0008)
0.60	7.13 (0.54)·10^{-2}	0.133 (0.005)	0.243 (0.015)	0.523 (0.015)	0.822 (0.015)
0.70	0.133 (0.010)	0.263 (0.017)	0.447 (0.016)	0.787 (0.015)	1.170 (0.0012)
0.80	0.260 (0.013)	0.468 (0.015)	0.672 (0.010)	0.934 (0.005)	1.332 (0.009)
0.90	0.428 (0.006)	0.618 (0.015)	0.822 (0.011)	1.048 (0.008)	1.420 (0.015)
1.00	0.505 (0.008)	0.672 (0.015)	0.881 (0.004)	1.119 (0.012)	1.470 (0.011)

	mole fraction				
mass fraction of EtOH	T = 293.15 K	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K
0.00	5.77 (0.04)·10^{-6}	7.73 0.07)·10^{-6}	9.85 (0.14)·10^{-6}	1.169 (0.017)·10^{-5}	1.370 (0.013)·10^{-5}
0.10	9.48 (0.16)·10^{-6}	1.283 (0.023)·10^{-5}	1.573 (0.019)·10^{-5}	1.848 (0.009)·10^{-5}	2.384 (0.011)·10^{-5}
0.20	2.094 (0.028)·10^{-5}	2.807 (0.025)·10^{-5}	3.55 (0.03)·10^{-5}	4.27 (0.05)·10^{-5}	5.69 (0.04)·10^{-5}
0.30	7.75 (0.31)·10^{-5}	1.01 (0.03)·10^{-4}	1.63 (0.06)·10^{-4}	2.42 (0.06)·10^{-4}	4.00 (0.06)·10^{-4}
0.40	2.23 (0.17)·10^{-4}	3.59 (0.12)·10^{-4}	6.41 (0.07)·10^{-4}	1.309 (0.009)·10^{-3}	1.818 (0.012)·10^{-3}
0.50	7.21 (0.45)·10^{-4}	1.32 (0.04)·10^{-3}	2.93 (0.07)·10^{-3}	5.89 (0.07)·10^{-3}	8.72 (0.03)·10^{-3}
0.60	2.18 (0.15)·10^{-3}	4.18 (0.16)·10^{-3}	7.85 (0.52)·10^{-3}	1.84 (0.06)·10^{-2}	3.19 (0.07)·10^{-2}
0.70	4.64 (0.36)·10^{-3}	9.58 (0.67)·10^{-3}	1.71 (0.07)·10^{-2}	3.41 (0.08)·10^{-2}	5.82 (0.08)·10^{-2}
0.80	1.06 (0.06)·10^{-2}	2.06 (0.07)·10^{-2}	3.15 (0.06)·10^{-2}	4.89 (0.04)·10^{-2}	8.16 (0.08)·10^{-2}
0.90	2.13 (0.04)·10^{-2}	3.33 (0.10)·10^{-2}	4.77 (0.08)·10^{-2}	6.74 (0.07)·10^{-2}	0.1072 (0.0018)
1.00	3.06 (0.06)·10^{-2}	4.41 (0.12)·10^{-2}	6.27 (0.03)·10^{-2}	8.88 (0.14)·10^{-2}	0.1365 (0.0016)
ideal	0.2129	0.2392	0.2682	0.3001	0.3353

Table 3. Ketoprofen Activity Coefficients (γ_3) in Ethanol (1) + Water (2) Cosolvent Mixtures at Several Temperatures

mass fraction of EtOH	T = 293.15 K	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K
0.00	36870	30924	27216	25667	24471
0.10	22466	18646	17043	16243	14064
0.20	10168	8519	7548	7033	5895
0.30	2745	2368	1648	1241	839
0.40	955	666	418	229	184
0.50	295	181	91.4	51.0	38.4
0.60	97.9	57.2	34.2	16.3	10.5
0.70	45.9	25.0	15.7	8.8	5.8
0.80	20.0	11.6	8.5	6.1	4.1
0.90	10.0	7.2	5.6	4.5	3.1
1.00	7.0	5.4	4.3	3.4	2.5

values were greater than those reported for naproxen in the same mixtures,[6] whereas the same values were lower than those reported for ibuprofen in the mixtures with only one phase.[13] Like KTP, naproxen and ibuprofen are also NSAIDs derived from propionic acid.

Table 3 presents the solute activity coefficients γ_3, calculated as x_3^{id}/x_3, considering the respective solubility values presented in Table 2. The γ_2 values are a measure of nonideality for solution processes. From these values, a rough estimate of solute−solvent intermolecular interactions can be made by considering the following expression

$$\ln \gamma_3 = (w_{11} + w_{33} - 2w_{13})\frac{V_3\phi_1^2}{RT} \qquad (2)$$

where w_{11}, w_{33}, and w_{13} represent the solvent−solvent, solute−solute, and solvent−solute interaction energies, respectively; V_3 is the molar volume of the supercooled liquid solute; and finally, ϕ_1 is the volume fraction of the solvent. In a first approach, the term $(V_3\phi_1^2/RT)_{T,P}$ may be considered approximately constant at the same temperature, and then γ_3 depends almost exclusively on w_{11}, w_{33}, and w_{13}.[7,14] The w_{11} and w_{33} terms are unfavorable for solubility, while the w_{13} term favors the solution process. It can be seen in eq 2 that the contribution of w_{33} represents the work necessary to take molecules from the solid state to the vapor state, and therefore it is constant in all mixtures.

The term w_{11} is highest in water (Hildebrand solubility parameter $\delta = 47.05\ \mathrm{MPa}^{1/2}$), while it is comparatively smaller in EtOH ($\delta = 26.59\ \mathrm{MPa}^{1/2}$).[15] The pure water and water-rich mixtures having larger γ_3 values imply high w_{11} and low w_{13} values. On the other hand, in EtOH-rich mixtures (having γ_3 values near 5.0), the w_{11} values are relatively low, but the w_{13} values are higher. According to this fact, the solvation of KTP could be higher in EtOH-rich mixtures.

Thermodynamic Functions of Solution. According to the van't Hoff analysis, the apparent standard enthalpy change of solution ($\Delta_{\mathrm{soln}}H^{0\text{-app}}$) is obtained from the slope of a ln x_3 vs 1/T plot (eq 3).

$$\left(\frac{\partial \ln x_3}{\partial(1/T)}\right)_P = -\frac{\Delta_{\mathrm{soln}}H^{0\text{-app}}}{R} \qquad (3)$$

As an example, Figure 1 shows the van't Hoff plot for KTP in pure EtOH and in mixtures having 0.90 and 0.80 in mass fraction of EtOH. In general, linear models with good determination coefficients (r^2) were obtained in all cases studied, except for pure water and mixtures with 0.30 in mass fraction of EtOH, where parabolic models were obtained. The r^2 values were as follows: pure water, 0.999; 0.10 of EtOH, 0.990; 0.20 of EtOH, 0.994; 0.30 of EtOH, 0.996; 0.40 of EtOH, 0.989; 0.50 of EtOH, 0.991; 0.60 of EtOH, 0.994; 0.70 of EtOH, 0.997; 0.80 of EtOH, 0.994; 0.90 of EtOH, 0.996; and pure EtOH, 0.996.

The apparent standard Gibbs energy change for the solution process ($\Delta_{\mathrm{soln}}G^{0\text{-app}}$) is calculated by means of

$$\Delta_{\mathrm{soln}}G^{0\text{-app}} = -RT \ln x_3 \qquad (4)$$

Finally, the apparent standard entropic change for solution process ($\Delta_{\mathrm{soln}}S^{0\text{-app}}$) is obtained from the respective $\Delta_{\mathrm{soln}}H^{0\text{-app}}$ and $\Delta_{\mathrm{soln}}G^{0\text{-app}}$ values by using

$$\Delta_{\mathrm{soln}}S^{0\text{-app}} = \frac{(\Delta_{\mathrm{soln}}H^{0\text{-app}} - \Delta_{\mathrm{soln}}G^{0\text{-app}})}{T_{\mathrm{hm}}} \qquad (5)$$

Table 4 summarizes the apparent standard thermodynamic functions for the experimental solution process of KTP in all cosolvent mixtures including those functions for the ideal process at 303.15 K. To calculate the thermodynamic magnitudes of experimental solution, some propagation of errors methods were used.[16] It is found that the standard Gibbs energy of solution is positive in all cases; i.e., the solution process apparently is not spontaneous, which may be explained in terms of the concentration scale used (mole fraction), where the reference state is the ideal solution having the unit as concentration of KTP, that is, the solid pure solute.

The enthalpy of solution is positive in all cases; therefore, the process is always endothermic. In the same way, the entropy of solution is also positive indicating entropy drives overall the solution process for all the mixtures. The $\Delta_{\mathrm{soln}}H^{0\text{-app}}$ values increase nonlinearly from pure water up to 0.60 in mass fraction of EtOH and diminish beyond this EtOH proportion.

Perlovich et al.[10] determined the enthalpy of solution of KTP in EtOH by solution calorimetry obtaining the value (28.1 ± 0.2) kJ·mol^{-1}, which is very different with respect to that presented in Table 4, that is, (56.3 ± 1.0) kJ·mol^{-1}. On the other hand, the respective entropy of solution presented by the same authors was 71.4 J·mol^{-1}·K^{-1},[10] which is also very different with respect to that presented in Table 4, that is, (163

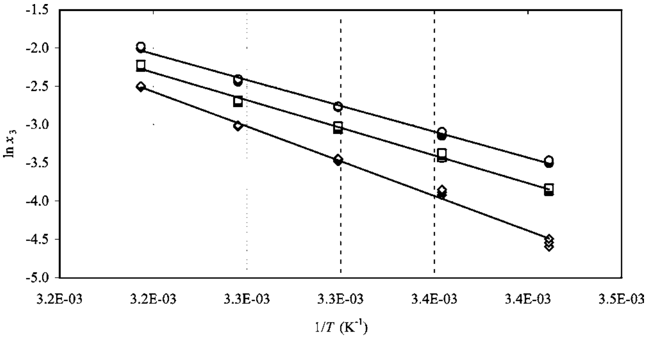


Figure 1. Temperature dependence for solubility of ketoprofen in some ethanol (1) + water (2) cosolvent mixtures expressed in mole fraction. (◇, 0.80 in mass fraction of EtOH; □, 0.90 in mass fraction of EtOH; ○, pure EtOH).

Table 4. Apparent Thermodynamic Functions Relative to Solution Process of Ketoprofen in Ethanol (1) + Water (2) Cosolvent Mixtures Including Ideal Process at 303.15 K

mass fraction of EtOH	$\Delta_{soln}G^{0\text{-app}}$ kJ·mol^{-1}	$\Delta_{soln}H^{0\text{-app}}$ kJ·mol^{-1}	$\Delta_{soln}S^{0\text{-app}}$ J·mol^{-1}·K^{-1}	$T\Delta_{soln}S^{0\text{-app}}$ kJ·mol^{-1}	ζ_H[a]	ζ_{TS}[a]
0.00	29.05 (0.03)	32.3 (1.1)	10.8 (0.4)	3.28 (0.12)	0.908	0.092
0.10	27.87 (0.02)	33.8 (0.9)	19.4 (0.5)	5.89 (0.16)	0.851	0.149
0.20	25.82 (0.02)	36.9 (0.8)	36.6 (0.8)	11.09 (0.23)	0.769	0.231
0.30	21.99 (0.05)	64.0 (2.1)	139 (5)	42.0 (1.4)	0.604	0.396
0.40	18.53 (0.06)	83.9 (2.4)	216 (6)	65.4 (1.9)	0.562	0.438
0.50	14.70 (0.06)	99.0 (2.6)	278 (7)	84.3 (2.3)	0.540	0.460
0.60	12.22 (0.05)	104.7 (2.2)	305 (7)	92.4 (2.0)	0.531	0.469
0.70	10.25 (0.04)	96.7 (1.6)	285 (5)	86.5 (1.4)	0.528	0.472
0.80	8.72 (0.04)	75.5 (1.6)	220 (5)	66.8 (1.5)	0.531	0.469
0.90	7.67 (0.02)	60.1 (1.1)	173 (3)	52.4 (0.9)	0.534	0.466
1.00	6.98 (0.02)	56.3 (1.0)	163 (3)	49.3 (0.9)	0.533	0.467
ideal	3.3	17.3	46.2	14.0	0.553	0.447

[a] ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward Gibbs energy of solution. These values were calculated by means of eqs 8 and 9, respectively.

± 3) J·mol^{-1}·K^{-1}. The discrepancies found between both reports would be attributed to differences in the experimental conditions used to obtain the enthalpy of solution.

With the aim to compare the relative contributions by enthalpy (ζ_H) and by entropy (ζ_{TS}) toward the solution process, eqs 6 and 7 were employed, respectively[17]

$$\zeta_H = \frac{|\Delta_{soln}H^{0\text{-app}}|}{|\Delta_{soln}H^{0\text{-app}}| + |T\Delta_{soln}S^{0\text{-app}}|} \tag{6}$$

$$\zeta_{TS} = \frac{|T\Delta_{soln}S^{0\text{-app}}|}{|\Delta_{soln}H^{0\text{-app}}| + |T\Delta_{soln}S^{0\text{-app}}|} \tag{7}$$

From Table 4, it follows that in all mixtures the main contributor to standard free energy of solution process of KTP is the enthalpy, in particular, for water-rich mixtures, where ζ_H values are greater than 0.77. It is interesting to note that enthalpy and entropy contributions for mixtures with 0.40 and 0.50 in mass fraction of EtOH are similar to those for ideal process.

Thermodynamic Functions of Mixing. The solution process may be represented by the following hypothetic stages[7]

$$\text{Solute}_{(\text{Solid})} \rightarrow \text{Solute}_{(\text{Liquid})} \rightarrow \text{Solute}_{(\text{Solution})}$$

where the respective partial processes toward the solution are solute fusion and mixing at the same temperature (303.15 K), which permits us to calculate the partial thermodynamic contributions to overall solution process by means of eqs 8 and 9, respectively.

$$\Delta_{soln}H^{0\text{-app}} = \Delta_{fus}H^{303.15} + \Delta_{mix}H^{0\text{-app}} \tag{8}$$

$$\Delta_{soln}S^{0\text{-app}} = \Delta_{fus}S^{303.15} + \Delta_{mix}S^{0\text{-app}} \tag{9}$$

where $\Delta_{fus}H^{303.15}$ and $\Delta_{fus}S^{303.15}$ represent the thermodynamic functions of fusion process at 303.15 K. $\Delta_{fus}H^{303.15}$ was calculated according to $\Delta_{fus}H_{MP} - \Delta C_p(T_{fus} - 303.15\text{ K})$, by using $\Delta_{fus}S^{MP}$ instead of ΔC_p, obtaining a value of 17.3 kJ·mol^{-1}, which is coincident with the enthalpic change for ideal solution (Table 2). In contrast, the entropy of fusion at 303.15 K (57.2 J·mol^{-1}·K^{-1}) is not coincident with the entropy of ideal solution at this temperature (46.2 J·mol^{-1}·K^{-1}). In this context, for practical purposes the $\Delta_{soln}S^{0\text{-id}}$ value was used instead of $\Delta_{fus}S^{303.15}$ in this analysis, as it was made previously with similar drugs.[6,13] Figure 2 shows the apparent thermodynamic functions of mixing, $\Delta_{mix}G^{0\text{-app}}$, $\Delta_{mix}H^{0\text{-app}}$, and $T\Delta_{mix}S^{0\text{-app}}$, at 303.15 K. Gibbs energy diminishes as EtOH proportion increases in the mixtures, whereas enthalpy and entropy initially increase from pure water up to 0.60 in mass fraction of EtOH and diminish over this composition.

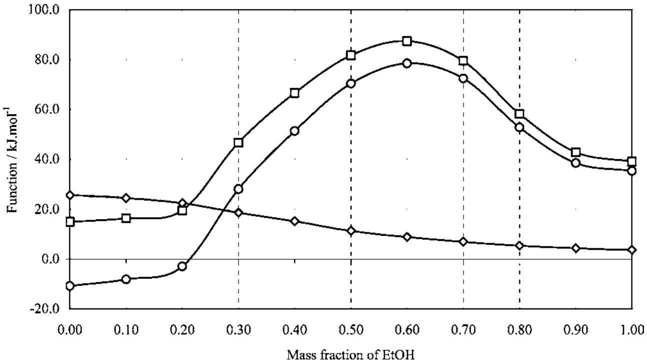


Figure 2. Apparent thermodynamic functions relative to the mixing process of ketoprofen in ethanol (1) + water (2) cosolvent mixtures at 303.15 K. (◇, $\Delta_{mix}G^{0\text{-app}}$; □, $\Delta_{mix}H^{0\text{-app}}$; ○, $T\Delta_{mix}S^{0\text{-app}}$).

The partial contributions by ideal solution (related to solute fusion process) and mixing processes to the enthalpy and entropy of drug solution shows that $\Delta_{soln}H^{0\text{-id}}$ and $\Delta_{soln}S^{0\text{-id}}$ are positive (Table 4), while the contribution of the thermodynamic functions relative to the mixing process toward the solution process is variable; that is, $\Delta_{mix}H^{0\text{-app}}$ is positive in all mixtures and pure solvents, whereas the entropy of mixing ($\Delta_{mix}S^{0\text{-app}}$) is positive in almost all mixtures but negative in pure water and mixtures with 0.10 and 0.20 in mass fraction of EtOH. It can be concluded that, in general, the solution process of this drug in EtOH-rich mixtures is driven mainly by the entropy of solution and/or entropy of mixing.

It is well-known that the net variation in $\Delta_{mix}H^{0\text{-app}}$ values results from the contribution of several kinds of interactions. The enthalpy of cavity formation (required for solute accommodation) is endothermic because energy must be supplied against the cohesive forces of the solvent. This process decreases solubility. On the other hand, the enthalpy of solute−solvent interaction is exothermic and results mainly from van der Waals and Lewis acid−base interactions. The structuring of water molecules around the nonpolar groups of solutes (hydrophobic hydration) contributes to lower the net heat of mixing to small or even negative values in aqueous solutions as is the case of pure water and mixtures with 0.10 and 0.20 in mass fraction of EtOH (Figure 2).

As was already said, the energy of cavity formation should be lower as the proportion of EtOH increases because the polarity of the medium decreases, a fact that favors solute−solvent interactions. Nevertheless, this fact is observed only in EtOH-rich mixtures (> 0.60 in mass fraction of EtOH), where $\Delta_{\text{mix}}H^{0\text{-app}}$ decreases as the proportion of cosolvent increases in the mixtures. According to Romero et al.,[18] in the initial portion of the solubility curve, the hydrogen bonding of the drug will increase with EtOH concentration (from pure water up to 0.60 in mass fraction of EtOH). At large cosolvent proportions (from 0.60 in mass fraction of EtOH up to pure EtOH), this interaction may be saturated, becoming a constant contribution. On the other hand, nonspecific and cavity effects are not saturated and vary with EtOH concentration.

Thermodynamic Functions of Transfer. To verify the effect of cosolvent composition on the thermodynamic function driving the solution processes, apparent thermodynamic functions of transfer of KTP from water to a mixture with 0.60 in mass fraction of EtOH (where $\Delta_{\text{soln}}H^{0\text{-app}}$ and $\Delta_{\text{soln}}S^{0\text{-app}}$ reach their highest values) and from this cosolvent mixture to pure ethanol were calculated. These values were calculated as the differences between the thermodynamic quantities of solution obtained in each solvent system. In both cases, the transfer of KTP from more polar medium to less polar medium is spontaneous because $\Delta^{\text{transf}}G^{0\text{-app}}$ is always negative. On the other hand, the following is observed: from pure water to 0.60 in mass fraction of EtOH ($\Delta^{\text{transf}}G^{0\text{-app}} = -16.84\ \text{kJ}\cdot\text{mol}^{-1}$, $\Delta^{\text{transf}}H^{0\text{-app}} = 72.3\ \text{kJ}\cdot\text{mol}^{-1}$, and $\Delta^{\text{transf}}S^{0\text{-app}} = 294\ \text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$), the solubility process is driven by the entropy (because $\Delta^{\text{transf}}H^{0\text{-app}} > 0$ and $\Delta^{\text{transf}}S^{0\text{-app}} > 0$), probably due to water-structure loosening by EtOH, whereas beyond this cosolvent composition ($\Delta^{\text{transf}}G^{0\text{-app}} = -5.24\ \text{kJ}\cdot\text{mol}^{-1}$, $\Delta^{\text{transf}}H^{0\text{-app}} = -48.4\ \text{kJ}\cdot\text{mol}^{-1}$, and $\Delta^{\text{transf}}S^{0\text{-app}} = -142\ \text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$), the solubility process is enthalpy driven (because $\Delta^{\text{transf}}H^{0\text{-app}} < 0$ and $\Delta^{\text{transf}}S^{0\text{-app}} < 0$). This latter behavior is probably due to an increase in solvation of KTP by EtOH molecules, as was already said.

Enthalpy−Entropy Compensation of Solution. Bustamante et al.[19,20] have demonstrated some chemical compensation effects for the solubility of several drug compounds in aqueous cosolvent mixtures. This analysis was used to identify the mechanism of the cosolvent action. The making of weighted graphs of $\Delta_{\text{soln}}H^{0\text{-app}}$ as a function of $\Delta_{\text{soln}}G^{0\text{-app}}$ permits us to observe similar mechanisms for the solution process according to tendencies obtained.[21,22]

For solubility of acetaminophen in ethanol + water mixtures, Bustamante et al.[20] obtained a nonlinear trend using seven cosolvent compositions including the pure solvents. Their data were adjusted to a parabolic regression model obtaining a maximum for 0.20 in volume fraction of EtOH. From 0 up to 0.20 in volume fraction of EtOH, a negative slope was obtained, while over this EtOH proportion, a positive slope was obtained. According to these authors, this fact implies a change from entropy driving to enthalpy driving toward the solution process.

Figure 3 shows fully that KTP in the EtOH (1) + water (2) cosolvent system presents nonlinear $\Delta_{\text{soln}}H^{0\text{-app}}$ vs $\Delta_{\text{soln}}G^{0\text{-app}}$ compensation with negative slope if an interval from pure water up to 0.60 in mass fraction of EtOH (where the maximum is obtained) is considered. On the other hand, beyond this EtOH composition, a positive slope is obtained. Accordingly to this graph, it follows that the dominant mechanism for solubility is the entropy in the former case probably implying water-structure loosening, whereas in the latter case, the dominant mechanism is the enthalpy probably due to KTP solvation by EtOH molecules as was already said.

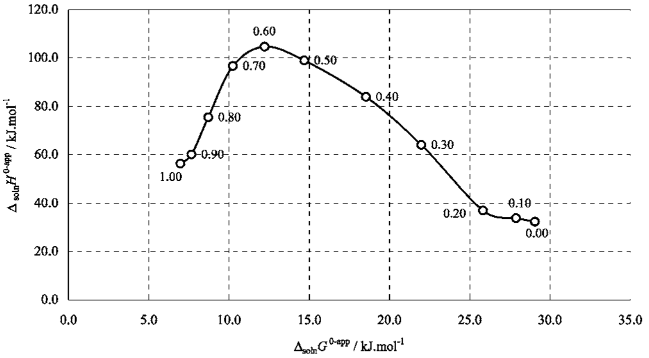


Figure 3. ΔH vs ΔG enthalpy−entropy compensation plot for solubility of ketoprofen in ethanol (1) + water (2) cosolvent mixtures at 303.15 K.

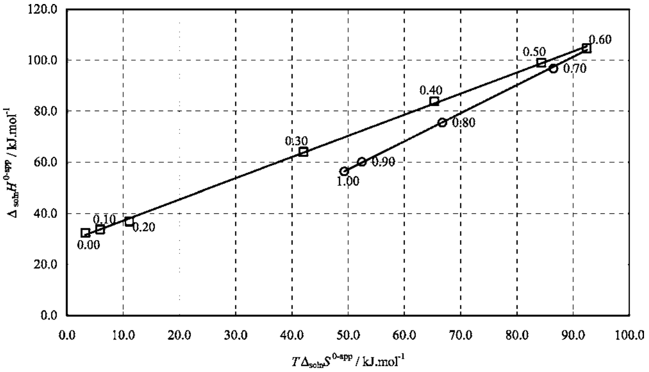


Figure 4. ΔH vs $T\Delta S$ enthalpy−entropy compensation plot for solubility of ketoprofen in ethanol (1) + water (2) cosolvent mixtures at 303.15 K.

Another interesting compensation graph is obtained by plotting $\Delta_{\text{soln}}H^{0\text{-app}}$ as a function of $T\Delta_{\text{soln}}S^{0\text{-app}}$ like that shown in Figure 4. Thus, two linear trends are obtained according to mixture composition. One of them corresponds to EtOH proportions varying from pure water up to 0.60 in mass fraction of EtOH obtaining the linear equation $\Delta_{\text{soln}}H^{0\text{-app}} = 0.831\ (0.009)\cdot T\Delta_{\text{soln}}S^{0\text{-app}} + 28.5\ (0.5)$, with r^2 adjusted, 0.999, and typical error, 0.819, and the other trend corresponding to compositions from 0.60 in mass fraction of EtOH to pure EtOH with the linear equation, $\Delta_{\text{soln}}H^{0\text{-app}} = 1.103\ (0.015)\cdot T\Delta_{\text{soln}}S^{0\text{-app}} + 1.9\ (1.0)$, with r^2 adjusted, 0.999, and typical error, 0.571. In these linear equations, $\Delta_{\text{soln}}H^{0\text{-app}}$ and $T\Delta_{\text{soln}}S^{0\text{-app}}$ are expressed in $\text{kJ}\cdot\text{mol}^{-1}$. Thus, linear equations with slopes lower than 1.0 correspond to entropy-driven processes, whereas those with slopes greater than 1.0 would be corresponding to enthalpy-driven solution processes.

Conclusions

From all topics discussed previously, it can be concluded that the solution process of KTP in EtOH (1) + water (2) mixtures is complex depending on the cosolvent composition. No linear enthalpy−entropy compensation was found for this drug in this cosolvent system. In this context, entropy driving was found for the solution processes in compositions from pure water to the mixture having 0.60 in mass fraction of EtOH, whereas for cosolvent mixtures beyond this EtOH proportion, enthalpy driving was found. The solvation of this drug is greater in EtOH-rich mixtures which favor the solubility. Finally, it can be said that the data presented in this report supply the physicochemical information about anti-inflammatory drugs in aqueous solutions. As was already said, this information is very useful in the design of homogeneous liquid pharmaceutical dosage forms, such as parenteral medications.

Acknowledgment

We thank the Department of Pharmacy of UNC for facilitating the equipment and laboratories used.

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Received for review March 20, 2009. Accepted June 4, 2009. We thank the DIB of the Universidad Nacional de Colombia (UNC) for the financial support.

JE9002866