THERMODYNAMIC MAGNITUDES OF MIXING AND SOLVATION OF ACETAMINOPHEN IN ETHANOL + WATER COSOLVENT MIXTURES

por

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Resumen

Jiménez, J. & F. Martínez: Thermodynamic magnitudes of mixing and solvation of acetaminophen in ethanol + water cosolvent mixtures. Rev. Acad. Colomb. Cienc. **30** (114): 87-99, 2006. ISSN 0370-3908.

A partir de valores de solubilidad a diferentes temperaturas mediante las ecuaciones de Gibbs y van't Hoff se calcularon las funciones termodinámicas, energía libre, entalpía y entropía, para los procesos de solución, mezcla y solvatación de acetaminofén (ACF) en mezclas cosolventes etanol + agua (EtOH + W). La solubilidad fue más alta en mezclas del 90% de EtOH a todas las temperaturas estudiadas, lo que demuestra la importancia del efecto cosolvente en este sistema. La solvatación del fármaco es mayor en la medida que se incrementa la proporción de EtOH en las mezclas. Mediante análisis de compensación entálpica-entrópica se obtuvo un comportamiento más complejo que el descrito previamente en la literatura. Desde el agua pura hasta el 10% m/m de EtOH y desde el 90% de EtOH hasta el etanol puro se encontró una conducción entrópica, mientras que en las otras mezclas se encontró conducción entálpica. Estos hechos podrían explicarse en términos de la pérdida de estructura del agua y en una disminución de la energía de cavidad en el solvente al incrementar la proporción de EtOH. Sin embargo, en las mezclas ricas en EtOH los mecanismos intermoleculares involucrados en el proceso de solución deben ser más complejos involucrando a otras propiedades fisicoquímicas.

Palabras clave: Acetaminofén, solubilidad, termodinámica de soluciones, solvatación.

Abstract

Based on van't Hoff and Gibbs equations the thermodynamic functions free energy, enthalpy, and entropy of solution, mixing and solvation of acetaminophen in ethanol + water cosolvent mixtures, were evaluated from solubility data determined at several temperatures. The solubility was greater at 90% m/m of ethanol at all temperatures studied. This result shows clearly the cosolvent

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effect present in this system. The solvation of this drug in the mixtures increases as the ethanol proportion is also increased. By means of enthalpy-entropy compensation analysis, a more complex behavior for solution was found with respect to that exposed previously in literature. From 0% up to 10% m/m of ethanol and from 90% up to 100% of ethanol, entropy driving was found, while from 20% up to 60% of ethanol, enthalpy driving was found. These facts would be explained in terms of a losing of water-structure in addition to a diminishing in the energy required for cavity formation in the solvent for mixtures from 20% up to 60% of ethanol. Nevertheless in the ethanol-rich mixtures the intermolecular mechanisms involved in the solution process should be more complex including other physicochemical considerations.

Key words: Acetaminophen, solubility, solution thermodynamics, solvation.

Introduction

Acetaminophen is an analgesic and antipyretic drug widely used in modern therapeutics. This drug is specially indicated in the treatment of several minor diseases presented by pediatric patients (**Lund W.**, 1994; **Roberts II LJ & Morrow JD,** 2001). In the Colombian market it is commercially available as tablets, syrups and concentrates, but it is not available as parenteral products (**Rosenstein-Ster, E.,** 2004). The later products recently have been asked for by physicians and other care practitioners. Injectable homogeneous liquid formulations supply relatively high doses of drug in small volumes. For this reason, some physicochemical properties such as the solubility and the occupied volumes by the drugs and other components in the solution are very important because they facilitate the design process of pharmaceutical dosage forms (**Lund W.,** 1994; **Pérez, C. *et al.*,** 2003).

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 (**Rubino JC.,** 1988; **Yalkowsky SH.,** 1999). Although several methods of calculating the solubility are available nowadays, these methods do not explain fully the mechanism of cosolvent action in mixtures. On the other hand, almost all of these methods in general do not consider the effect of temperature on this fundamental property. For these reasons it is important to determine systematically the solubility of drugs, in order to obtain complete information about physicochemical data for pharmaceutical systems. This information facilitates widely the labor of pharmacists associated to research and development of new products in pharmaceutical industry (**Jiménez F. & Martínez F.,** 1995). Temperature-solubility dependence permits to realize the respective thermodynamic analysis, which, at its time, permits inside the molecular mechanisms, involved toward the solution processes (**Garzón LC. & Martínez F.,** 2004).

The main objective of this study was to evaluate the effect of the cosolvent composition on solubility and solution thermodynamics of acetaminophen in ethanol + water cosolvent mixtures based on van't Hoff method, including the respective contributions by mixing and solvation of this drug toward the solution processes. Ethanol and propylene glycol are the cosolvents more widely used in the development of liquid pharmaceutical dosage forms (**Rubino, JC.,** 1988). The present investigation is a continuation and expansion of those developed with this drug by **Grant, DJW. *et al*.** (1984), **Etman MA. & Naggar VF.** (1990), **Bustamante P. *et al*.** (1995, 1998), and **Pérez DC. *et al*.** (2003), among others.

Experimental

Materials

Acetaminophen USP (ACP) (**US Pharmacopeia,** 1994); absolute ethanol A.R., Merck (EtOH); distilled water (W), conductivity < 2 μS, Laboratory of Pharmaceutics of the Universidad Nacional de Colombia; molecular sieve Merck (numbers 3 and 4); Millipore Corp. Swinnex®-13 filter units.

Solubility determinations

An excess of ACP was added to 20 mL of each cosolvent mixture evaluated in glass flasks. The cosolvent mixtures were prepared by mass in quantities close to 100.0 g varying in 10.00% m/m (Mettler Toledo PB302, sensitivity ± 0.01 g). The solid-liquid mixtures were then stirred in a (Wrist Action, Burrel, model 75) mechanical shaker for 1 hour. Samples were then allowed to stand in (Magni Whirl Blue M. Electric Company) water baths kept at the appropriate temperature ± 0.05ºC. All samples were maintained at least for 48 hours to reach the equilibrium.

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 refractive indexes (Abbe Carlzeiss Jena refractive meter) after appropriate dilution and interpolation from previously constructed calibration curves for ACP in each cosolvent mixture (**Pérez DC.,** ***et al***. 2003).

All the solubility experiments were repeated at least three times and the results were averaged. In order to permit conversion between molarity and mole fraction concentration scales, the density of the saturated solutions was determined with a digital density meter (DMA 45 Anton Paar, precision ± 0.0001 g cm^{-3}).

Results and discussion

In Table 1, the molecular structure of ACP and some of their physicochemical properties are summarized. The melting point and enthalpy of fusion were reported by **Bustamante P.** ***et al.*** (1995) while the enthalpy of sublimation was reported by **Williams D.** ***et al.*** (2004). Accordingly to **Romero S.** ***et al***. (1996) this drug act in solution mainly as a Lewis acid in order to establish hydrogen bonds with proton-acceptor functional groups in the solvents (oxygen in -OH groups). **Dearden JC.** (1972) demonstrated that both functional groups of this drug (-NH and -OH) were involved in complex formation with the carbonyl group of antipyrine. On the other hand, ACP could also act as a proton-acceptor compound by means of its carbonyl and -OH moieties.

Ideal and Experimental Solubility of ACP

The ideal solubility of a crystalline solute in a liquid solvent can be calculated by Eq. (1):

$$\ln X_2^{\mathrm{id}} = -\frac{\Delta H_{\mathrm{fus}}(T_{\mathrm{fus}} - T)}{RT_{\mathrm{fus}}T} + \left(\frac{\Delta C_{\mathrm{p}}}{R}\right)\left[\frac{(T_{\mathrm{fus}} - T)}{T} + \ln\left(\frac{T}{T_{\mathrm{fus}}}\right)\right] \qquad (1)$$

where X_2^{id} is the ideal solubility of the solute as mole fraction, ΔH_{fus} is the molar enthalpy of fusion of the pure solute (at the melting point), T_{fus} is the absolute melting point, T is the absolute solution temperature, R is the gas constant (8.314 J mol^{-1} K^{-1}), and 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 (**Hildebrand JH.** ***et al***. 1970). Since ΔC_{p} cannot be easy experimentally determined, one of the following assumptions has to be made: (a) ΔC_{p} is negligible and can be considered zero or (b) ΔC_{p} may be approximated to the entropy of fusion, ΔS_{fus}. In this investigation the later consideration is assumed.

Table 2 summarizes the experimental solubilities of ACP, expressed in molarity 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 all cases the coefficients of variation for solubility were smaller than 2.0 %. On the other hand, Fig. 1 shows the solubility expressed in mole fraction at all temperatures evaluated. It can be seen the cosolvent effect on solubility since a maximum is obtained at 90 % m/m of EtOH at all temperatures.

The tendency obtained in mole fraction solubilities is in good agreement with that presented by **Bustamante P.** ***et al***. (1995). It should be considered that these authors used volumetric fractions in the preparation of cosolvent mixtures while in the present work only mass fractions were used, obtaining different compositions in both investigations. It may be observed that the highest solubility value in mole fraction for ACP was obtained in the 90% m/m of EtOH mixture at 40.0°C, while the lowest value was found in water at 20.0°C.

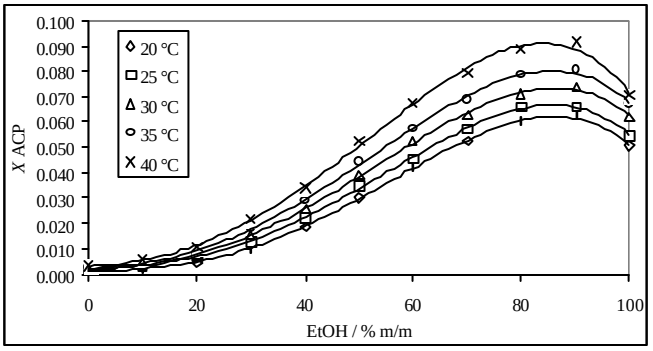


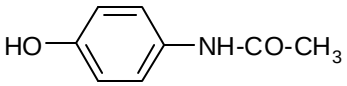
Figure 1. Solubility of ACP in EtOH + W cosolvent mixtures expressed in mole fraction at several temperatures.

Thermodynamic Functions of Solution

It is well known that the making of weighted graphs based on the logarithm of solubility as a function of reciprocal absolute temperature permits to obtain the apparent enthalpic change of solution ($\Delta H_{\mathrm{soln}}^{0\mathrm{app}}$) by means of van't Hoff equation (Eq. 2):

$$\left(\frac{\partial \ln X_2}{\partial(1/T)}\right)_P = -\frac{\Delta H_{\mathrm{soln}}^{0\mathrm{app}}}{R} \qquad (2)$$

Table 1. Some physicochemical properties of ACP.

Molecular structure (a)	Molar mass / g mol^{-1} (a)	Melting point / K (b)	ΔH_{fus} / kJ mol^{-1} (b)	ΔH_{subl} / kJ mol^{-1} (c)
	151.16	442.3	26.25	238.85

(a) Taken from **Budavari** et al. (2001).

(b) Taken from **Bustamante** et al. (1995).

(c) Taken from **Williams** et al. (2004).

Table 2. Experimental solubility of ACP in EtOH + W cosolvent mixtures expressed in molarity and mole fraction including ideal solubility at several temperatures.

EtOH / % m/m	Mol L^{-1} (a)				
	20.0 °C	25.0 °C	30.0 °C	35.0 °C	40.0 °C
0	0.0837	0.1015	0.1141	0.1390	0.1701
10	0.1226	0.1640	0.1909	0.2199	0.2812
20	0.2170	0.3127	0.3406	0.3914	0.474
30	0.434	0.539	0.620	0.718	0.852
40	0.685	0.795	0.903	1.019	1.174
50	0.968	1.092	1.219	1.351	1.545
60	1.178	1.262	1.415	1.537	1.750
70	1.291	1.389	1.496	1.622	1.816
80	1.297	1.401	1.494	1.618	1.797
90	1.177	1.234	1.362	1.465	1.623
100	0.826	0.886	0.993	1.062	1.115
EtOH / % m/m	Mole fraction x 10^2 (a)				
	20.0 °C	25.0 °C	30.0 °C	35.0 °C	40.0 °C
0	0.152	0.185	0.209	0.256	0.315
10	0.243	0.327	0.382	0.442	0.570
20	0.470	0.687	0.751	0.870	1.065
30	1.049	1.323	1.540	1.81	2.18
40	1.87	2.22	2.54	2.91	3.42
50	3.02	3.47	3.94	4.45	5.21
60	4.19	4.55	5.20	5.75	6.74
70	5.24	5.72	6.25	6.88	7.91
80	6.00	6.58	7.10	7.81	8.88
90	6.25	6.61	7.41	8.09	9.13
100	5.04	5.46	6.20	6.68	7.05
ideal	5.308	5.989	6.744	7.580	8.503

(a) In all cases the coefficients of variation (CV) were smaller than 2.0 %.

Nevertheless, in more recent treatments some corrections have been introduced in order to diminish the propagation of errors, and therefore, to separate the chemical effects from those due only to statistical treatments used in compensation plots. For this reason, the mean harmonic temperature (T_{hm}) is used in van' Hoff analysis. T_{hm} is calculated as (**Krug RR *et al.***, 1976):

$$T_{hm} = \frac{n}{\sum_{i}^{n}(1/T)} \qquad (3)$$

where n is the number of temperatures studied. In our case the T_{hm} value obtained is just 303 K. The corrected expression more widely used (**Bustamante P. *et al***. 1998) is the following:

$$\left(\frac{\partial \ln X_2}{\partial(1/T - 1/T_{hm})}\right)_P = -\frac{\Delta H^{0app}_{soln}}{R} \qquad (4)$$

As an example, Fig. 2 shows the modified van't Hoff plot for ACP in mixtures having 30% and 40% m/m of EtOH. In general, linear models with good correlation coefficients were obtained in all cases studied.

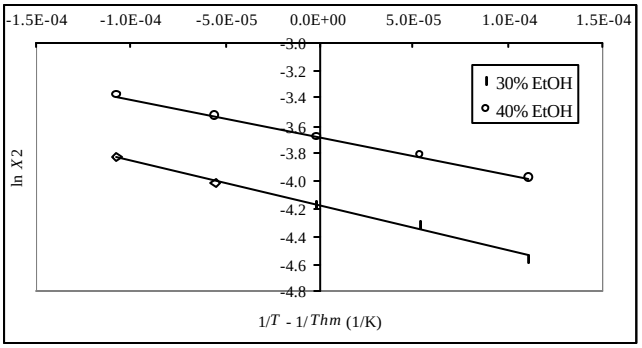


Figure 2. Temperature dependence for solubility of ACP in some EtOH + W cosolvent mixtures expressed in mole fraction.

For non-ideal solutions, the slope obtained in Eq. (4) does not give directly the heat of solution. For this reason it is necessary to consider the variation of solute thermodynamic activity (a_2) with concentration at constant temperature and pressure (**Hollenbeck RG.,** 1980; **Bustamante P. *et al.*** 1998). Then, the enthalpic change of solution is calculated from:

$$\Delta H^{0}_{soln} = \Delta H^{0app}_{soln}\left(\frac{\partial \ln a_2}{\partial \ln X_2}\right)_{T,P} \qquad (5)$$

in which, the second term of the right side (**Manzo RH & Ahumada AA.,** 1990; **Bustamante P *et al.*** 1998), is calculated by means of:

$$\left(\frac{\partial \ln a_2}{\partial \ln X_2}\right)_{T,P} = 1 - \frac{2f_2}{X_1}\ln\left(\frac{a_2^{sat}}{X_2^{sat}}\right) \qquad (6)$$

The term "sat" indicates the saturation. Since in the previous equation the solute volumetric fraction (f_2) is required, then this property would be calculated from the apparent specific volume of solute (ASV_2) at saturation, and the mixture composition. ASV_2 is calculated by means of:

$$ASV_2 = \frac{m_2 + m_1(1 - SV_1\tilde{n})}{m_2\tilde{n}} \qquad (7)$$

where, m_2 and m_1 are the masses of solute and solvent at saturation, respectively, SV_1 is the specific volume of solvent, and ρ is the solution density. Although in a more refined treatment, the partial specific volume of solute instead of ASV_2 should be used, the procedure proposed here is also adequate.

Since ACP is solid, then the thermodynamic activity at saturation is equal to ideal solubility (X_2^{id}) (**Yalkowsky SH.,** 1999), and therefore it follows that:

$$\left(\frac{\partial \ln a_2}{\partial \ln X_2}\right)_{T,P} = 1 - \frac{2f_2}{X_1}\ln\left(\frac{X_2^{id}}{X_2^{sat}}\right) \qquad (8)$$

The term (X_2^{id}/X_2) in Eq. (8) is equal to the solute activity coefficient in the solution (g_2) and it is an indication of the deviation presented by this one in front to ideal behavior. Table 3 shows the experimental % m/v solubilities, saturated solution densities, cosolvent mixtures densities, solute volume fractions, solute activity coefficients, and correction factors at 30.0°C. This temperature is nearest to 303 K. In order to calculate the g_2 and ($\partial \ln a_2/\partial \ln X_2$) values some propagation of errors methods were used (**Schoemaker DP. & Garland GW.,** 1968; **Bevington, PR** 1969).

From the g_2 values presented in Table 3 a rough estimate of solute-solvent intermolecular interactions can be made by considering the following expression:

$$\ln g_2 = (w_{11} + w_{22} - 2w_{12}) \frac{V_2 f_1^2}{RT} \qquad (9)$$

where w_{11}, w_{22} y w_{12} represent the solvent-solvent, solute-solute and solvent-solute interaction energies, respectively; V_2 is the molar volume of the supercooled liquid solute, and finally, f_1 is the volume fraction of the solvent. In a first approach the term ($V_2 f_1^2 / RT$) may be considered approximately constant at the same temperature, and then g_2 depends almost exclusively on w_{11}, w_{22} and w_{12} (**Martínez F. & Gómez A.,** 2001). The w_{11} and w_{22} terms are unfavorable for solubility, while the w_{12} term favors the solution process.

It can be seen in Eq. (9) that the contribution of w_{22} represents the work necessary to take molecules from solid state to the vapor state and therefore it is constant in all mixtures. On the other hand, **Romero S. *et al***. (2004) have demonstrate recently by using calorimetric, spectroscopic, and crystallographic techniques that ACP solid phase in excess keeps its original crystalline properties in saturated solutions in several cosolvent mixtures varying in polarity and Lewis acid-base character. Although an increase of 8 °C in the melting point has been reported for ACP solid phase at equilibrium with saturated solutions having cosolvent proportions greater than 50 % v/v (**Bustamante P. *et al.*** 1995), according to these authors, for practical purposes it may be considered that the contribution of the solid phase toward the overall process is constant for this drug in the different saturated solutions studied.

The term w_{11} is highest in water (Hildebrand solubility parameter δ = 23.0 cal$^{1/2}$ cm$^{-3/2}$) while it is comparatively smaller in EtOH (δ = 13.0 cal$^{1/2}$ cm$^{-3/2}$) (**Martín A. *et al.*** 1993). The pure water and water-rich mixtures having larger g_2 values imply high w_{11} and low w_{12} values. On the other hand, in EtOH-rich mixtures (having g_2 values close to 1.0), the w_{11} values are relatively low but the w_{12} values are higher. According to this fact, the solvation of ACP is higher in EtOH-rich mixtures.

The apparent standard free energy change for the solution process (ΔG_{soln}^{0app}) has been traditionally calculated in literature as:

$$\Delta G_{soln}^{0app} = -RT \ln X_2 \qquad (10)$$

Nevertheless considering the approach proposed by **Krug RR. *et al***. (1976), this property is more appropriately calculated by means of:

$$\Delta G_{soln}^{0app} = -RT_{hm} \quad \text{intercept} \qquad (11)$$

in which, the intercept used is that one obtained in the analysis by treatment of ln X_2 as a function of $1/T - 1/T_{hm}$ (Eq. 4). This thermodynamic function is also corrected using the factor $(\partial \ln a_2/\partial \ln X_2)_{T,P}$ in order to express it in terms of solute thermodynamic activity instead of solute concentration.

The standard entropic change for solution process (ΔS_{soln}^0) is obtained from the respective and ΔG_{soln}^0 values by using:

$$\Delta S_{soln}^0 = \frac{\left(\Delta H_{soln}^0 - \Delta G_{soln}^0\right)}{T_{hm}} \qquad (12)$$

Table 4 summarizes the corrected standard thermodynamic functions for experimental solution process of ACP in all cosolvent mixtures including those functions for the ideal process. In order to calculate the thermodynamic magnitudes of experimental solution some propagation of errors methods were used (**Schoemaker DP. & Garland GW.,** 1968; **Bevington PR.,** 1969). It is found that the standard free 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 unity as concentration of ACP, that is, the solid pure solute.

The enthalpy of solution is positive in all cases, therefore the process is always endothermic. The entropy of solution is also positive in all cases, indicating entropy driving on overall the solution processes. The ΔH_{soln}^0 value in water is in good agreement with those presented by **Grant DJW. *et al.*** (1984) and **Bustamante P. *et al.*** (1995), that is, 23.7 and 22.5 kJ mol^{-1}, respectively. The value for the same property in EtOH is also in good agreement with that one presented by **Bustamante P. *et al.*** (1995). The values obtained in the mixtures are not comparables because the cosolvent compositions are not the same. The ΔH_{soln}^0 values vary nonlinearly with EtOH composition showing a maximum at 10 % m/m of cosolvent.

Table 3. Solubility of ACP expressed in % m/v, saturated solution and solvent densities, solute volumetric fraction, solute activity coefficient, and activity variation factor in EtOH + W cosolvent mixtures at 30.0°C.

EtOH / % m/m	ACP / % m/v (a)	r / g cm^{-3} (b)	r_0 / g cm^{-3}	f_2	g_2	$\left(\frac{\partial \ln a_2}{\partial \ln X_2}\right)$
0	1.72	0.9990	0.9957	0.0140	32.3	0.902
10	2.89	0.9846	0.9787	0.0235	17.7	0.865
20	5.15	0.9752	0.9639	0.0417	8.98	0.816
30	9.37	0.9682	0.9474	0.0770	4.38	0.769
40	13.6	0.9617	0.9277	0.1104	2.66	0.779
50	18.4	0.9547	0.9059	0.1496	1.71	0.832
60	21.4	0.9455	0.8829	0.1713	1.296	0.906
70	22.6	0.9308	0.8592	0.1798	1.079	0.971
80	22.6	0.9125	0.8347	0.1773	0.950	1.020
90	20.6	0.8839	0.8094	0.1623	0.910	1.033
100	15.0	0.8425	0.7811	0.1136	1.088	0.980

(a) In all cases CV were smaller than 2.0 %.
(b) In all cases standard deviations were smaller than 0.0002 g cm^{-3}.

Table 4. Thermodynamic functions relative to solution process of ACP in EtOH + W cosolvent mixtures including ideal process at 303 K.

EtOH / % m/m	ΔG^0_{soln} / kJ mol^{-1}	ΔH^0_{soln} / kJ mol^{-1}	ΔS^0_{soln} / J mol^{-1} K^{-1}	$T\Delta S^0_{soln}$ / kJ mol^{-1}	$\%z_H$ (a)	$\%z_{TS}$ (a)
0	13.95 (0.28)	24.4 (0.8)	34.4 (1.3)	10.4 (0.4)	70.0	30.0
10	12.16 (0.24)	26.6 (1.0)	47.6 (2.1)	14.4 (0.6)	64.8	35.2
20	10.07 (0.20)	23.4 (1.5)	44.0 (3.0)	13.3 (0.9)	63.7	36.3
30	8.09 (0.16)	20.9 (0.5)	42.2 (1.4)	12.8 (0.4)	62.0	38.0
40	7.21 (0.14)	17.6 (0.4)	34.4 (1.1)	10.4 (0.3)	62.9	37.1
50	6.78 (0.14)	17.0 (0.5)	33.8 (1.2)	10.2 (0.4)	62.4	37.6
60	6.74 (0.13)	16.4 (0.7)	31.8 (1.5)	9.6 (0.5)	63.0	37.0
70	6.75 (0.13)	14.9 (0.7)	27.0 (1.4)	8.2 (0.4)	64.6	35.4
80	6.76 (0.14)	14.9 (0.7)	26.7 (1.3)	8.1 (0.4)	64.7	35.3
90	6.77 (0.14)	15.1 (0.7)	27.6 (1.4)	8.4 (0.4)	64.4	35.6
100	6.93 (0.14)	13.1 (0.7)	20.3 (1.1)	6.1 (0.3)	68.0	32.0
ideal	6.80	17.98	36.90	11.18	61.7	38.4

(a) $\%z_H$ and $\%z_{TS}$ are the relative contributions by enthalpy and entropy toward Free energy of solution. These values were calculated by means of equations (13) and (14), respectively.

With the aim to compare the relative contributions by enthalpy ($\%\zeta_H$) and by entropy ($\%\zeta_{TS}$) toward the solution process, equations (13) and (14) were employed respectively.

$$\%\zeta_H = 100\frac{\left|\Delta H^0_{soln}\right|}{\left|\Delta H^0_{soln}\right| + \left|T\Delta S^0_{soln}\right|} \qquad (13)$$

$$\%\zeta_{TS} = 100\frac{\left|T\Delta S^0_{soln}\right|}{\left|\Delta H^0_{soln}\right| + \left|T\Delta S^0_{soln}\right|} \qquad (14)$$

From Table 4 it follows that in all cases the main contributor to standard free energy of solution process of ACP is the enthalpy (greater than 60 % in all cases).

Thermodynamic Functions of Mixing

The solution process may be represented by the following hypothetic stages (**Martínez F. & Gómez A.,** 2001):

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

where, the respective partial processes toward the solution are fusion and mixing at the same temperature (303 K), which permits calculate the partial thermodynamic contributions to solution process by means of equations (15) and (16), respectively.

$$\Delta H^0_{soln} = \Delta H^{303}_{fus} + \Delta H^0_{mix} \qquad (15)\}$$

$$\Delta S^0_{soln} = \Delta S^{303}_{fus} + \Delta S^0_{mix} \qquad (16)$$

where, ΔH^{303}_{fus} and ΔS^{303}_{fus} represent the thermodynamic functions of fusion process at harmonic temperature (303 K). ΔH^{303}_{fus} was calculated from $\Delta H^T_{fus} = \Delta H^{MP}_{fus} - \Delta C_p(T_{fus} - T)$, using ΔS^{MP}_{fus} instead of ΔC_p obtaining a value of 17.98 kJ mol^{-1} which is coincident with the enthalpic change for ideal solution. In contrast, the entropy of fusion at 303 K (59.35 J mol^{-1} K^{-1}) is not coincident with the entropy of ideal solution at this temperature (36.90 J mol^{-1} K^{-1}), nevertheless, for practical purposes in this analysis, the ΔS^{0id}_{soln} value was used instead of ΔS^{303}_{fus}. In Table 5 the thermodynamic functions of mixing of ACP are summarized.

By analyzing the partial contributions by ideal solution (related to solute fusion process) and mixing processes to the enthalpy and entropy of solution, it is found that ΔH^{303}_{fus} and ΔS^{303}_{fus} are positive (Table 4), while the contribution of the thermodynamic functions relative to mixing process toward the solution process is variable, that is, ΔH^0_{mix} is positive in those mixtures with EtOH content up to 30 % m/m and negative for all other mixtures, while the entropy of mixing (ΔS^0_{mix}) is positive in mixtures containing 10, 20 and 30% of EtOH, but negative in all other mixtures. It can be concluded that in general the solution process of this drug is driven mainly by the entropy of solution.

The net variation in ΔH^0_{mix} values results from the contribution of several kinds of interaction. The enthalpy of cavity formation 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. Nevertheless, this is not observed in the case of ACP in water (Table 5).

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. This fact is observed in Table 5, where ΔH^0_{mix} is more negative over 40 % of cosolvent. According to **Romero S. *et al.*** (1996) in the initial portion of the solubility curve, the hydrogen bonding of ACP will increase with EtOH concentration. At large cosolvent proportions, 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.

For comparative purposes, Fig. 3 shows the thermodynamic functions of mixing, ΔG^0_{mix}, ΔH^0_{mix}, and $T\Delta S^0_{mix}$. All functions vary nonlinearly with composition showing maxima for enthalpy and entropy at 10 % of EtOH.

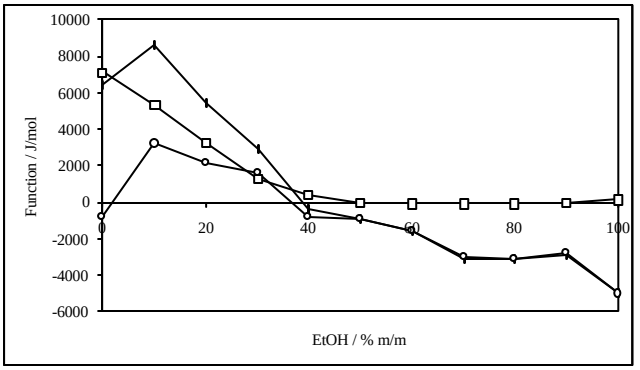


Figure 3. Thermodynamic functions relative to mixing process of ACP in EtOH + W cosolvent mixtures at 303 K. (ΔG^0_{mix} : squares; ΔH^0_{mix} : rhombic; $T\Delta S^0_{mix}$: circles).

In order to verify the effect of cosolvent composition on the thermodynamic function driving the solution process Table 6 summarizes the thermodynamic functions of transfer of ACP from more polar solvent to those less polar. These new functions were calculated as the differences between thermodynamic magnitudes of mixing between the less polar mixtures and the more polar mixtures.

If the addition of EtOH to water is considered, it happens the following: At 10% of EtOH ($\Delta G^0_{1\to 2} < 0$ and $\Delta H^0_{1\to 2} > 0$) the solubility process is driven by the entropy increase due to loss of water-structure around the nonpolar moieties of ACP. From 20 % up to 60% of EtOH ($\Delta G^0_{1\to 2} < 0$ and $\Delta H^0_{1\to 2} < 0$) the solution processes are driven by enthalpy, probably due to solvation of ACP, particularly in mixtures containing 20, 30, and 40% of EtOH. From 70 up to 90% of EtOH the contributions by enthalpy and entropy are practically the same in each one of the mixtures. This fact leads to $\Delta G^0_{1\to 2}$ values practically equal to 0 kJ mol^{-1}.

On the other hand, for these latter mixtures (considering the enthalpy and entropy of transfer values, that is, $\Delta H^0_{1\to 2} < 0$ and $\Delta S^0_{1\to 2} < 0$ for 70 and 80 % of EtOH, and $\Delta H^0_{1\to 2} > 0$ and $\Delta S^0_{1\to 2} > 0$ for 90% of EtOH), it follows that enthalpy drives the solution process in the former mixtures (70 and 80% of EtOH), while entropy drives the process in the latter mixture (90% of EtOH).

Finally, if the addition of water to EtOH is considered, then, at 10 % of water (90% of EtOH) the increase of solubility is explained by an increase of entropy, which is not easily explained ($\Delta G^0_{2\to 1} < 0$ and $\Delta H^0_{2\to 1} > 0$).

Thermodynamic Functions of Solvation

In addition to previous fusion-mixing subprocesses, the solution process may also be represented by the following hypothetic stages (**Perlovich GL. *et al.*** 2003 and 2004):

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

where, the respective partial processes toward the solution in this case are sublimation and solvation, which permits calculate the partial thermodynamic contributions to solution process by means of equations (17) and (18), respectively, while the free energy of solvation is calculate by means of Eq. (19):

$$\Delta H^0_{soln} = \Delta H^0_{subl} + \Delta H^0_{solv} \qquad (17)$$

$$\Delta S^0_{soln} = \Delta S^0_{subl} + \Delta S^0_{solv} \qquad (18)$$

$$\Delta G^0_{soln} = \Delta G^0_{subl} + \Delta G^0_{solv} \qquad (19)$$

where, ΔH^0_{subl} = 238.85 kJ mol^{-1} was taken from **Williams D. *et al.*** (2004), and therefore, the function ΔH^0_{solv} was calculated from ΔH^0_{soln} values presented in Table 4. The respective entropy of sublimation was calculated as $\Delta S^0_{subl} = (\Delta H^0_{subl} - \Delta G^0_{subl})/T$ at 303 K, where $\Delta G^0_{subl} = -RT\ln(P/P_0)$ with P = 7.9 x 10^{-9} mmHg at 303 K and P_0 = 760 mmHg, then ΔG^0_{subl} = 63.71 kJ mol^{-1}, and therefore ΔS^0_{subl} = 577.7 J mol^{-1} K^{-1} at the same temperature. In Table 7 the thermodynamic functions of solvation are presented, while on the other hand, with the aim to compare the relative contributions by enthalpy (%ζ_H) and entropy (%ζ_{TS}) toward the solvation process, two equations analogous to Eq. (13) and (14) were employed.

From the values of %ζ_H and %ζ_{TS} presented in Table 7 it follows that the main contributing force to standard free energy of the solvation process of ACP in all the cosolvent mixtures is the enthalpy (%ζ_H are greater than 56% in all cases).

Because that not only the main driving force of solvation process of drug compounds is important, but also the balance between specific and non-specific solute-solvent interactions as well, therefore, parameters which describe the relative ratio of specific and non-specific solute-solvent interaction in terms of enthalpies ($\%e_H$) and in terms of entropies ($\%e_S$), were used according to the following definitions introduced by **Perlovich GL. *et al.*** (2003 and 2004):

$$\%e_H = 100\left|\frac{\Delta H^0_{spec}}{\Delta H^0_{non-spec}}\right| \qquad (20)$$

$$\%e_S = 100\left|\frac{\Delta S^0_{spec}}{\Delta S^0_{non-spec}}\right| \qquad (21)$$

where,

$$\Delta H^0_{spec} = \Delta H^0_{soln(solvent-i)} - \Delta H^0_{soln(cyclohex)} = \Delta H^0_{soln(cyclohex\,«\,solvent-i)}$$
$$\Delta H^0_{non-spec} = \Delta H^0_{soln(cyclohex)} - \Delta H^0_{subl} = \Delta H^0_{solv(cyclohex)}$$

$$\Delta S^0_{spec} = \Delta S^0_{soln(solvent-i)} - \Delta S^0_{soln(cyclohex)} = \Delta S^0_{soln(cyclohex\,«\,solvent-i)}$$
$$\Delta S^0_{non-spec} = \Delta S^0_{soln(cyclohex)}$$

Cyclohexane was chosen as an "inert" solvent, which interacts with drug molecules solely by nonspecific interactions (dispersion forces), while the cosolvent mixtures interact with ACP by specific interactions such as hydrogen bonding. Benzene and hexane have also been used as inert solvents in the study of naproxen (**Perlovich GL. *et al.*** 2004) although important differences have been found between these two solvents, indicating some effect of pi electrons and planar geometry of benzene on non-specific interactions of that drug.

Solubility data for ACP in cyclohexane was taken from **Baena Y. *et al.*** (2004). Those data were analyzed according to equations (4), (11), and (12) founding the following values for apparent thermodynamic functions: $\Delta H^{0app}_{soln(CH)}$ = 38.1 kJ mol^{-1}, $\Delta G^{0app}_{soln(CH)}$ = 25.61 kJ mol^{-1}, and $\Delta S^{0app}_{soln(CH)}$ = 41.2 J mol^{-1} K^{-1}. The apparent specific volume of ACP in cyclohexane obtained by using densities of solvent and saturated solutions lead to a negative value (due to very scarce solubility and uncertainty in density measurements). For this reason, in order to calculate the $(\partial \ln a_2/\partial \ln X_2)_{T,P}$ for ACP in this solvent, the molar volume of drug was calculate by means of **Fedors RF** method (1974) obtaining a value of 124.4 cm^3 mol^{-1}. From this value and the solubility at 303 K, the value obtained for $(\partial \ln a_2/\partial \ln X_2)_{T,P}$ using Eq. (8) was 0.9994. Since this value is included into the uncertainty obtained in thermodynamic functions of solution, then, the apparent values were used instead of corrected values.

The $\%e_H$ and $\%e_S$ values for ACP solvation are also presented in Table 7. These values indicate that during dissolution of ACP in all mixtures studied, the specific solute-solvent interactions (hydrogen bonding, mainly) do not affect the entropic term of free energy with respect to non-specific interactions, although it is less insignificant as the EtOH proportion in the mixture is increased. With regard to the enthalpic term in all cases the non-specific solute-solvent interactions predominate.

Enthalpy-Entropy Compensation of Solution

Bustamante P. *et al*. (1995 and 1998) have demonstrated some chemical compensation effects for the solubility of several drug compounds in aqueous cosolvent mixtures. This analysis was used in order to identify the mechanism of the cosolvent action. The making of weighted graphs of ΔH^0_{soln} as a function of ΔG^0_{soln} at mean harmonic temperature permits to observe similar mechanisms for the solution process according to tendencies obtained (**Leffler JE & Grunwald E.** 1963; **Tomlinson E.** 1983).

For solubility of ACP in EtOH + W mixtures, **Bustamante P. *et al.*** (1995) obtained a nonlinear trend using seven cosolvent compositions including the pure solvents. They data were adjusted to a parabolic regression model obtaining a maximum for 20% v/v of EtOH. From 0 up to 20% v/v 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.

On the other hand, Fig. 4 shows our corrected ΔH^0_{soln} and ΔG^0_{soln} values obtaining a trend slightly more complex compared with that presented by **Bustamante P. *et al***. (1995). It is necessary kept in mind that these authors used volume fractions in cosolvent mixtures whereas in the present work mass fractions were used, which leads to study different compositions. Moreover, **Bustamante P. *et al.*** (1995) used apparent thermodynamic functions without correction. For these reasons it is possible that trends obtained in both investigations have been different.

Table 5. Thermodynamic functions relative to mixing process of ACP in EtOH + W cosolvent mixtures at 303 K.

EtOH / % m/m	ΔG^0_{mix} / kJ mol^{-1}	ΔH^0_{mix} / kJ mol^{-1}	ΔS^0_{mix} / J mol^{-1} K^{-1}	$T\Delta S^0_{mix}$ / kJ mol^{-1}	$\%z_H$ (a)	$\%z_{TS}$ (b)
0	7.15	6.4	–2.5	–0.8	89.5	10.5
10	5.36	8.6	10.7	3.2	72.7	27.3
20	3.28	5.4	7.1	2.1	71.7	28.3
30	1.30	2.9	5.3	1.6	64.3	35.7
40	0.41	–0.4	–2.5	–0.8	31.9	68.1
50	–0.02	–1.0	–3.1	–0.9	50.5	49.5
60	–0.05	–1.6	–5.1	–1.5	50.8	49.2
70	–0.05	–3.1	–9.9	–3.0	50.4	49.6
80	–0.04	–3.1	–10.2	–3.1	50.3	49.7
90	–0.03	–2.8	–9.3	–2.8	50.3	49.7
100	0.13	–4.9	–16.6	–5.0	49.4	50.6

(a) $\%z_H$ and $\%z_{TS}$ are the relative contributions by enthalpy and entropy toward Free energy of mixing. These values were calculated by means of equations (13) and (14), respectively.

Table 6. Thermodynamic functions of transfer of ACP from more polar solvents to less polar solvents in EtOH + W cosolvent mixtures at 303 K.

EtOH / % m/m		$\Delta G^0_{1\to2}$ /	$\Delta H^0_{1\to2}$ /	$\Delta S^0_{1\to2}$ /	$T\Delta S^0_{1\to2}$ /
Medium 1	Medium 2	kJ mol^{-1}	kJ mol^{-1}	J mol^{-1} K^{-1}	kJ mol^{-1}
0	10	–1.79	2.2	13.2	4.0
10	20	–2.08	–3.2	–3.6	–1.1
20	30	–1.98	–2.5	–1.7	–0.5
30	40	–0.89	–3.3	–7.9	–2.4
40	50	–0.43	–0.6	–0.5	–0.2
50	60	–0.04	–0.6	–2.0	–0.6
60	70	0.00	–1.5	–4.9	–1.5
70	80	0.01	–0.1	–0.2	–0.1
80	90	0.01	0.3	0.9	0.3
90	100	0.16	–2.1	–7.3	–2.2

These magnitudes were calculated as $\Delta\Psi^0_{1\to2} = \Delta\Psi^0_{mix(Medium\ 2:less\ polar)} - \Delta\Psi^0_{mix(Medium1:\ more\ polar)}$, where Ψ is *G*, *H* or *S*.

Table 7. Thermodynamic functions relative to solvation process of ACP in EtOH + W cosolvent mixtures at 303 K.

EtOH / % m/m	ΔG^0_{solv} / kJ mol^{-1}	ΔH^0_{solv} / kJ mol^{-1}	ΔS^0_{solv} / J mol^{-1} K^{-1}	$T\Delta S^0_{solv}$ / kJ mol^{-1}	$\%z_H$ (a)	$\%z_{TS}$ (a)	$\%e_H$ (b)	$\%e_S$ (b)
0	–49.76	–214.5	–543.3	–164.6	56.6	43.4	6.8	1.2
10	–51.55	–212.3	–530.2	–160.6	56.9	43.1	5.7	1.1
20	–53.63	–215.5	–533.8	–161.7	57.1	42.9	7.3	0.5
30	–55.61	–218.0	–535.5	–162.3	57.3	42.7	8.6	0.2
40	–56.50	–221.2	–543.4	–164.6	57.3	42.7	10.2	1.2
50	–56.93	–221.8	–543.9	–164.8	57.4	42.6	10.5	1.3
60	–56.96	–222.5	–545.9	–165.4	57.4	42.6	10.8	1.6
70	–56.96	–223.9	–550.8	–166.9	57.3	42.7	11.5	2.5
80	–56.95	–224.0	–551.0	–167.0	57.3	42.7	11.6	2.5
90	–56.94	–223.7	–550.1	–166.7	57.3	42.7	11.4	2.4
100	–56.78	–225.8	–557.5	–168.9	57.2	42.8	12.5	3.6

(a) $\%z_H$ and $\%z_{TS}$ are the relative contributions by enthalpy and entropy toward Free energy of solvation. These values were calculated by means of equations (13) and (14), respectively.

(b) $\%e_H$ and $\%e_S$ are the relative ratio of specific and non specific solute-solvent interactions expressed in terms of enthalpy and entropy. These values were calculated by means of equations (20) and (21), respectively.

Fig. 4 shows fully that this solute-cosolvent system does not present linear ΔH^0_{soln} - ΔG^0_{soln} compensation in all compositions studied. Nevertheless, if an interval from 10 % up to 60 % of EtOH is considered an apparent linear trend is observed with positive slope. Accordingly to this graph it follows that from 0 up to 10% of EtOH and from 90% up to 100 % of EtOH the dominant mechanism for solubility is the entropy, while from 10% up to 60 % of EtOH the dominant mechanism is enthalpy. Finally, from 70% up to 90% of EtOH it is not easy to determine which thermodynamic function dominates the solution process.

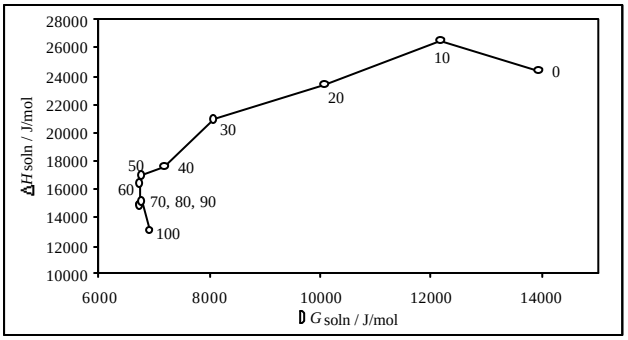


Figure 4. Enthalpy-entropy compensation plot for solubility of ACP in EtOH + W cosolvent mixtures at 303 K.

Other Considerations

In order to verify the effect of specific (hydrogen bonding) and nonspecific interactions, **Romero S** et al. (1996) proposed an approach based upon the acidic and basic solubility parameters of **Karger BL *et al.*** (1976) to describe solubility curves in binary cosolvent mixtures. The model developed is especially useful for systems that present two solubility peaks. The equation has the form:

$$\ln X_2 = c_0 + c_1\delta_1 + c_2\delta_1^2 + c_3\delta_{1a} + c_4\delta_{1b} + c_5\delta_{1a}\delta_{ib} \quad (22)$$

where, δ_1 is the Hildebrand solubility parameter of the solvent mixtures and δ_{1a} and δ_{1b} are the Karger acidic and basic parameters of the solvent mixtures. These values were calculated for each cosolvent mixture from the expression: $\delta_{mix} = \sum \delta_i \phi_i$, where δ_i is the value of the pure solvent and ϕ_i is the volume fraction of the solvent in the cosolvent mixture. The contribution of the solid phase is included as constant in the intercept. Eq. (22) was used by **Romero S. *et al.*** (1996) in order to fit the experimental solubilities of ACP at 25°C in ethanol + water and ethanol + ethyl acetate mixtures obtaining the following regression model:

$$\ln X_2 = -20.6 + 1.28\delta_1 - 0.023\delta_1^2 + 0.46\delta_{1b} - 0.027\delta_{1a}\delta_{1b} \quad (23)$$

in which, the statistical parameters are: r^2 = 0.97, S.D. = 0.25 and n = 26, expressing the solubility parameters in $MPa^{1/2}$. The signs obtained in coefficients of Eq. (23) are in good agreement with their expected effect on solubility, that is, the negative intercept is related to the energy need to overcome the cohesion interactions of the solute crystal lattice (unfavorable for solubility), while the positive signs on δ_1 and δ_{1b} are related to solubility-favorable nonspecific and specific interactions (ACP as acid and solvent as base), respectively. On the other hand, the sign is negative (unfavorable) for the parameters related to solvent-solvent interactions, δ_1^2 and $\delta_{1a}\delta_{1b}$. For ACP, the term δ_{1a} of Eq. (22) is not significant statistically (Eq. 23), suggesting that this drug behaves mainly as Lewis acid (proton donating) toward the cosolvent in the mixtures evaluated.

Conclusions

From all discussed previously it can be concluded that the solution process of ACP in EtOH + W mixtures is very complex and highly dependent on cosolvent composition. The solvation of this drug is greater for EtOH-rich mixtures which favor the solubility. Finally, it can be said that our data amply the physicochemical information about drugs useful in the design of homogeneous liquid pharmaceutical dosage forms.

Acknowledgments

We thank the Banco de la República and the DIB-DINAIN of the Universidad Nacional de Colombia (UNC) for the financial support. Additionally we thank the Department of Pharmacy of UNC for facilitating the equipment and laboratories used.

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Recibido el 29 de septiembre de 2005.

Aceptado para su publicación el 13 de diciembre de 2005.