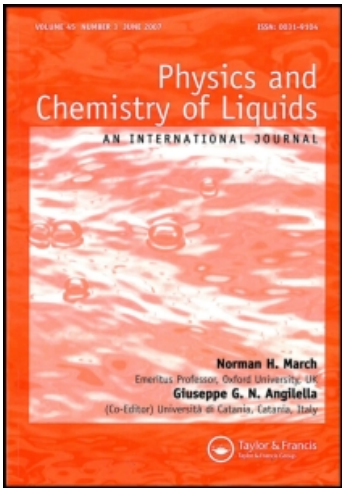

Physics and Chemistry of Liquids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713646857

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To cite this Article Pacheco, Diana P. and Martínez, Fleming(2007) 'Thermodynamic analysis of the solubility of naproxen in ethanol + water cosolvent mixtures', Physics and Chemistry of Liquids, 45: 5, 581 — 595
To link to this Article: DOI: 10.1080/00319100701313862
URL: http://dx.doi.org/10.1080/00319100701313862

Physics and Chemistry of Liquids
Vol. 45, No. 5, October 2007, 581–595

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Thermodynamic analysis of the solubility of naproxen in ethanol + water cosolvent mixtures

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(*Received 1 August 2006; in final form 3 March 2007*)

By using the van't Hoff and Gibbs equations the thermodynamic functions free energy, enthalpy, and entropy of solution, mixing, and solvation of naproxen (NAP) in ethanol (EtOH) + water (W) cosolvent mixtures, were evaluated from solubility data determined at several temperatures. The solubility was greater in pure ethanol and lower in water at all temperatures studied. This result shows the cosolvent effect present in this system. The solvation of this drug in the mixtures increases as the EtOH proportion is also increased in the mixtures. By means of enthalpy–entropy compensation analysis, nonlinear ΔH^0_{soln} *versus* ΔG^0_{soln} compensation with negative slope from pure water up to 30% EtOH and positive slope from 30% EtOH up to 70% EtOH was obtained. Over 70% EtOH the behavior was more complex. Accordingly to these results it follows that the dominant mechanism for solubility of NAP in water-rich mixtures is the entropy, probably due to water-structure loosing by EtOH; whereas, over 30% EtOH the dominant mechanism is the enthalpy probably due to NAP solvation increase by EtOH molecules.

Keywords: Naproxen; Solubility; Solution thermodynamics; Solvation

1. Introduction

Naproxen (NAP) is a nonsteroidal anti-inflammatory drug (NSAID) derived of propionic acid used widely as analgesic and antipyretic, although it is also used for relief of symptoms of rheumatoid arthritis and osteoarthritis in addition to treatment of dysmenorrheal, among other applications. Like other NSAIDs its mechanism of action likely relates to its inhibition of prostaglandin synthesis [1,2]. Although NAP is used widely nowadays in therapeutics, the physicochemical information about properties such as solubility and molar volume for this drug is not widely available. In the Colombian market it is commercially available as tablets, capsules, and suspensions, as well as being available as a gel intended for topic use and injectable solution intended

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ISSN 0031-9104 print/ISSN 1029-0451 online © 2007 Taylor & Francis
DOI: 10.1080/00319100701313862

for intramuscular administration [3]. Injectable homogeneous liquid formulations supply relatively high doses of drugs 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 [4,5].

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 [6,7]. 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 the pharmaceutical industry [8]. Temperature–solubility dependence allows realizing the respective thermodynamic analysis, which, on the other hand, also allows inquiring into the molecular mechanisms involved in the solution process [9].

The main objective of this study was to evaluate the effect of the cosolvent composition on solubility and solution thermodynamics of NAP in ethanol (EtOH) + water (W) cosolvent mixtures, based on the van't Hoff method, including the respective contributions by mixing and solvation of this drug toward the solution processes. EtOH and propylene glycol (PG) are the cosolvents more widely used in the development of liquid pharmaceutical dosage forms [6]. This report extends the information presented for this drug in other solvent systems by Perlovich *et al*. [10] and by Mora and Martínez [11], among others.

2. Experimental

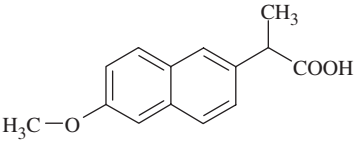
2.1. *Materials*

Naproxen USP quality [12]; absolute ethanol A.R., Merck (EtOH); distilled water (W), conductivity $< 2\,\mu S$, Laboratory of Pharmaceutics of the Universidad Nacional de Colombia; molecular sieve Merck (numbers 3 and 4); Millipore Corp. Swinnex®-13 filter units.

2.2. *Solubility determinations*

An excess of NAP 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% EtOH (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 h. Samples were then allowed to stand in water baths (Magni Whirl Blue M. Electric Company) kept at $40.00 \pm 0.05^{\circ}C$ at least for 5 days to reach the equilibrium (this equilibrium time was established by quantifying the drug concentration to obtain 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.

Table 1. Some physicochemical properties of NAP.

Molecular structure[a]	Molar mass ($g\,mol^{-1}$)[a]	Melting point (K)[b]	ΔH_{fus} ($kJ\,mol^{-1}$)[b]	ΔH_{subl} ($kJ\,mol^{-1}$)[b]
	230.26	427.6	31.5 (2.1)	128.3 (0.5)

[a]Taken from Budavari *et al*. [13].
[b]Taken from Perlovich *et al*. [10].

Concentrations were determined by measuring absorbance after appropriate dilution and interpolation from a previously constructed UV spectrophotometry calibration curve for NAP in alcohol USP at 271 nm (UV/Vis BioMate 3 Thermo Electron Corp. spectrophotometer) according to a validated methodology (using a concentration interval from 5.0 to 50.0 $\mu g\,mL^{-1}$ obtaining a coefficient of variation of 1.58% in the analysis of intermedium accuracy). After the procedure already described, the temperature was decreased in 5.0°C and therefore, it was stabilized at 35.0°C at least during 2 days, allowing the precipitation of the drug dissolved in excess and quantifying the drug concentration in equilibrium. These procedures were developed varying in 5.0°C up to 20.0°C. All solubility analyses 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 $\pm 0.0001\,g\,cm^{-3}$).

3. Results and discussion

In table 1, the molecular structure of NAP and some of their physicochemical properties are summarized. The melting point, the enthalpy of fusion, and the enthalpy of sublimation were reported by Perlovich *et al*. [10]. This drug acts 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). On the other hand, NAP could also act as a proton-acceptor compound by means of its carbonyl, hydroxyl, and methoxyl moieties.

3.1. *Ideal and experimental solubility of NAP*

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

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

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 ($8.314\,\mathrm{J\,mol^{-1}\,K^{-1}}$), 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 [14]. Since ΔC_p cannot be easily experimentally determined it is usually assumed that it may be approximated to the entropy of fusion, ΔS_{fus}.

Table 2 summarizes the experimental solubilities of NAP, expressed in molarity and mole fraction, in addition to the ideal solubilities calculated by means of equation (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%.

It may be observed that the highest solubility value in mole fraction for NAP was obtained in pure EtOH at 40.0°C, while the lowest value was found in water at 20.0°C. The solubility of NAP in pure EtOH at 25.0°C is moderately different with respect to the value reported by Perlovich *et al.* [10], that is, 1.07×10^{-2} in mole fraction. Unfortunately, there is not any other solubility value for this drug in these solvents, reported in literature, and therefore no other direct comparison is possible. On the other hand, Mora and Martínez [11] presented the solution thermodynamics of NAP in aqueous buffer at pH 1.2 and ionic strength adjusted at $0.15\,\mathrm{mol\,L^{-1}}$, with potassium chloride. The solubility value presented in this buffer at 25.0°C in mole fraction was 1.492×10^{-6}, which is lower compared with that presented in table 2, in water at the same temperature.

3.2. *Thermodynamic functions of solution*

According to van't Hoff analysis, the apparent standard enthalpy change of solution is obtained from the slope of a $\ln X_2$ *versus* $1/T$ plot. Nevertheless, in recent thermodynamic treatments some corrections have been introduced in the van't Hoff equation in order to diminish the propagation of errors, and therefore, to separate the chemical effects from those due only to statistical treatments used. For this reason, the mean harmonic temperature (T_{hm}) is used in van' Hoff analysis. T_{hm} is calculated as: $n/\sum_{i=1}^{n}(1/T)$, where n is the number of temperatures studied [15]. In the present case, the T_{hm} value obtained is just 303 K. The corrected expression more widely used is the following [16]:

$$\left(\frac{\partial \ln X_2}{\partial(1/T - 1/T_{hm})}\right)_P = -\frac{\Delta H^{0app}_{soln}}{R}. \tag{2}$$

As an example, figure 1 shows the modified van't Hoff plot for NAP in pure EtOH and in mixtures having 90 and 80% of EtOH. In general, linear models with good determination coefficients were obtained in all cases studied.

For nonideal solutions, the slope obtained in equation (2) does not give directly the real heat of solution. For this reason, sometimes it is necessary to consider the variation of solute thermodynamic activity (a_2) with concentration (X_2) at constant temperature and pressure [16]. Then, the standard enthalpic change of solution (ΔH^0_{soln}) is calculated by using the equation: $\Delta H^0_{soln} = \Delta H^{0app}_{soln} \times (\partial \ln a_2/\ln X_2)_{T,P}$, in which, the second term of the right side according to Manzo and Ahumada [17], is calculated by means of:

$$\left(\frac{\partial \ln a_2}{\partial \ln X_2}\right)_{T,P} = 1 - \frac{2\phi_2}{X_1}\ln\left(\frac{a_2^{sat}}{X_2^{sat}}\right). \tag{3}$$

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

EtOH (% in mass)	20.0°C	25.0°C	30.0°C	35.0°C	40.0°C
	mol L^{-1}[a]				
0	$2.39\ (0.04) \times 10^{-4}$	$2.84\ (0.06) \times 10^{-4}$	$3.27\ (0.06) \times 10^{-4}$	$3.64\ (0.21) \times 10^{-4}$	$4.23\ (0.22) \times 10^{-4}$
10	$2.68\ (0.06) \times 10^{-4}$	$3.58\ (0.12) \times 10^{-4}$	$4.712\ (0.021) \times 10^{-4}$	$6.32\ (0.16) \times 10^{-4}$	$7.34\ (0.13) \times 10^{-4}$
20	$6.15\ (0.28) \times 10^{-4}$	$8.59\ (0.10) \times 10^{-4}$	$1.15\ (0.03) \times 10^{-3}$	$1.59\ (0.05) \times 10^{-3}$	$2.03\ (0.10) \times 10^{-3}$
30	$2.433\ (0.012) \times 10^{-3}$	$3.807\ (0.011) \times 10^{-3}$	$5.30\ (0.06) \times 10^{-3}$	$6.752\ (0.022) \times 10^{-3}$	$8.95\ (0.06) \times 10^{-3}$
40	$9.822\ (0.026) \times 10^{-3}$	$1.281\ (0.015) \times 10^{-2}$	$1.72\ (0.03) \times 10^{-2}$	$2.261\ (0.022) \times 10^{-2}$	$2.56\ (0.08) \times 10^{-2}$
50	$2.585\ (0.008) \times 10^{-2}$	$3.33\ (0.05) \times 10^{-2}$	$4.214\ (0.020) \times 10^{-2}$	$5.290\ (0.009) \times 10^{-2}$	$6.39\ (0.06) \times 10^{-2}$
60	$5.463\ (0.028) \times 10^{-2}$	$6.68\ (0.04) \times 10^{-2}$	$8.68\ (0.03) \times 10^{-2}$	0.1060 (0.0005)	0.1360 (0.0014)
70	$9.34\ (0.03) \times 10^{-2}$	0.1141 (0.0011)	0.1411 (0.0014)	0.1730 (0.0005)	0.2032 (0.0016)
80	0.1353 (0.0005)	0.1701 (0.0010)	0.209 (0.003)	0.2591 (0.0008)	0.2992 (0.0016)
90	0.1793 (0.0008)	0.2182 (0.0018)	0.2655 (0.0008)	0.3276 (0.0024)	0.3781 (0.0006)
100	0.2079 (0.0028)	0.2476 (0.0019)	0.3215 (0.0013)	0.3728 (0.0014)	0.4469 (0.0024)
	Mole fraction[a]				
0	$4.31\ (0.24) \times 10^{-6}$	$5.13\ (0.11) \times 10^{-6}$	$5.91\ (0.12) \times 10^{-6}$	$6.60\ (0.38) \times 10^{-6}$	$7.68\ (0.40) \times 10^{-6}$
10	$5.23\ (0.11) \times 10^{-6}$	$7.01\ (0.23) \times 10^{-6}$	$9.24\ (0.04) \times 10^{-6}$	$1.24\ (0.03) \times 10^{-5}$	$1.443\ (0.026) \times 10^{-5}$
20	$1.30\ (0.06) \times 10^{-5}$	$1.824\ (0.021) \times 10^{-5}$	$2.44\ (0.07) \times 10^{-5}$	$3.40\ (0.10) \times 10^{-5}$	$4.34\ (0.21) \times 10^{-5}$
30	$5.638\ (0.027) \times 10^{-5}$	$8.842\ (0.026) \times 10^{-5}$	$1.235\ (0.014) \times 10^{-4}$	$1.578\ (0.005) \times 10^{-4}$	$2.100\ (0.014) \times 10^{-4}$
40	$2.509\ (0.007) \times 10^{-4}$	$3.28\ (0.04) \times 10^{-4}$	$4.41\ (0.08) \times 10^{-4}$	$5.85\ (0.06) \times 10^{-4}$	$6.64\ (0.20) \times 10^{-4}$
50	$7.365\ (0.024) \times 10^{-4}$	$9.51\ (0.13) \times 10^{-4}$	$1.213\ (0.006) \times 10^{-3}$	$1.532\ (0.003) \times 10^{-3}$	$1.861\ (0.017) \times 10^{-3}$
60	$1.758\ (0.009) \times 10^{-3}$	$2.160\ (0.012) \times 10^{-3}$	$2.832\ (0.010) \times 10^{-3}$	$3.484\ (0.016) \times 10^{-3}$	$4.51\ (0.05) \times 10^{-3}$
70	$3.433\ (0.012) \times 10^{-3}$	$4.222\ (0.022) \times 10^{-3}$	$5.27\ (0.05) \times 10^{-3}$	$6.526\ (0.019) \times 10^{-3}$	$7.74\ (0.06) \times 10^{-3}$
80	$5.747\ (0.024) \times 10^{-3}$	$7.30\ (0.05) \times 10^{-3}$	$9.05\ (0.14) \times 10^{-3}$	$1.138\ (0.004) \times 10^{-2}$	$1.330\ (0.008) \times 10^{-2}$
90	$8.95\ (0.08) \times 10^{-3}$	$1.100\ (0.009) \times 10^{-2}$	$1.357\ (0.005) \times 10^{-2}$	$1.700\ (0.013) \times 10^{-2}$	$1.985\ (0.004) \times 10^{-2}$
100	$1.242\ (0.018) \times 10^{-2}$	$1.494\ (0.012) \times 10^{-2}$	$1.976\ (0.009) \times 10^{-2}$	$2.323\ (0.010) \times 10^{-2}$	$2.836\ (0.017) \times 10^{-2}$
Ideal	3.527×10^{-2}	4.098×10^{-2}	4.748×10^{-2}	5.489×10^{-2}	6.330×10^{-2}

[a]In almost all cases the coefficients of variation (CV) were smaller than 3.0%.

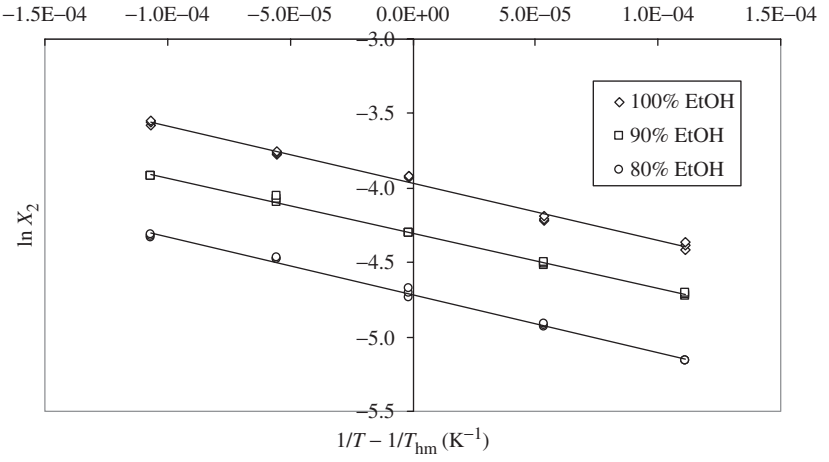


Figure 1. Temperature dependence for solubility of NAP in some EtOH + W cosolvent mixtures expressed in mole fraction.

The term "sat" indicates the saturation. Since in the previous equation the solute volumetric fraction (ϕ_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 $[m_2 + m_1(1 - SV_1\rho)]/(m_2\rho)$, where, m_2 and m_1 are the masses of solute and solvent at saturation, respectively, SV_1 is the specific volume of solvent (calculated as the reciprocal of density for the pure cosolvent mixture), and ρ is the NAP solution density. Although, in a more refined treatment, the partial specific volume of solute instead of ASV_2 should be used, the procedure proposed is also adequate [4,5].

Since NAP is solid, then the thermodynamic activity at saturation is equal to ideal solubility (X_2^{id}) [7], and therefore it follows that:

$$\left(\frac{\partial \ln a_2}{\partial \ln X_2}\right)_{T,P} = 1 - \frac{2\phi_2}{X_1}\ln\left(\frac{X_2^{id}}{X_2^{sat}}\right). \tag{4}$$

The term (X_2^{id}/X_2) in equation (4) is equal to the solute activity coefficient in the solution (γ_2) and it is an indication of the deviation presented by this one in front to ideal behavior [9]. Table 3 shows the experimental solubilities as % in mass, saturated solution densities, cosolvent mixtures densities [18], 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 γ_2 and $(\partial \ln a_2/\partial \ln X_2)_{T,P}$ values some propagation of errors methods were used [19,20].

From the γ_2 values presented in table 3 a rough estimate of solute–solvent intermolecular interactions can be made by considering the following expression:

$$\ln \gamma_2 = (w_{11} + w_{22} - 2w_{12})\frac{V_2\phi_1^2}{RT} \tag{5}$$

where w_{11}, w_{22} and w_{12} represent the solvent–solvent, solute–solute and solvent–solute interaction energies, respectively; V_2 is the molar volume of the supercooled liquid

Table 3. Solubility of NAP expressed in % in mass, 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 (% in mass)	NAP (% in mass)[a]	ρ (g cm^{-3})[b]	ρ_0 (g cm^{-3})[c]	ϕ_2	γ_2	$(\partial \ln a_2/\partial \ln X_2)$
0	7.56×10^{-3}	0.9953	0.9957	4.438×10^{-4}	8030	0.9920
10	1.109×10^{-2}	0.9785	0.9787	3.152×10^{-4}	5141	0.9946
20	2.74×10^{-2}	0.9639	0.9639	3.816×10^{-4}	1536	0.9944
30	0.129	0.9470	0.9474	1.676×10^{-3}	384.4	0.9801
40	0.425	0.9291	0.9277	2.748×10^{-3}	107.6	0.9743
50	1.068	0.9083	0.9059	8.100×10^{-3}	39.14	0.9405
60	2.25	0.8877	0.8829	1.725×10^{-2}	16.76	0.9025
70	3.738	0.8689	0.8592	2.655×10^{-2}	9.01	0.8826
80	5.65	0.8502	0.8347	3.898×10^{-2}	5.25	0.8696
90	7.362	0.8305	0.8094	4.951×10^{-2}	3.50	0.8743
100	9.153	0.8087	0.7811	5.943×10^{-2}	2.40	0.8937

[a]In almost all cases CV were smaller than 3.0%.
[b]In all cases SD were smaller than 0.0002 g cm^{-3}.
[c]From Jiménez *et al.* [18].

solute, and finally, ϕ_1 is the volume fraction of the solvent. In a first approach, the term $(V_2\phi_1^2/RT)_{T,P}$ may be considered approximately constant at the same temperature, and then γ_2 depends almost exclusively on w_{11}, w_{22}, and w_{12} [4,5]. 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 equation (5) 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.

The term w_{11} is highest in water (Hildebrand solubility parameter $\delta = 47.05\,\text{MPa}^{1/2}$), while it is comparatively smaller in EtOH ($\delta = 26.59\,\text{MPa}^{1/2}$) [21]. The pure water and water-rich mixtures having larger γ_2 values imply high w_{11} and low w_{12} values. On the other hand, in EtOH-rich mixtures (having γ_2 values near to 2.5), the w_{11} values are relatively low but the w_{12} values are higher. According to this fact, the solvation of NAP is higher in EtOH-rich mixtures.

The standard free energy change for the solution process (ΔG^0_{soln}), considering the approach proposed by Krug *et al.* [15] and 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, is calculated by means of:

$$\Delta G^0_{soln} = -RT_{hm} \times \text{intercept} \times \left(\frac{\partial \ln a_2}{\partial \ln X_2}\right)_{T,P} \tag{6}$$

in which, the intercept used is that one obtained in the analysis by treatment of $\ln X_2$ as a function of $1/T - 1/T_{hm}$ equation (2).

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

$$\Delta S^0_{soln} = \frac{(\Delta H^0_{soln} - \Delta G^0_{soln})}{T_{hm}}. \tag{7}$$

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

EtOH (% in mass)	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})	$\%\zeta_H$[a]	$\%\zeta_{TS}$[a]
0	30.13 (0.03)	21.3 (1.3)	−29.0 (1.7)	−8.8 (0.5)	70.8	29.2
10	29.10 (0.03)	39.5 (1.4)	34.4 (1.3)	10.4 (0.4)	79.1	20.9
20	26.61 (0.02)	46.0 (1.0)	63.9 (1.4)	19.4 (0.4)	70.4	29.6
30	22.38 (0.03)	48.1 (1.4)	84.9 (2.5)	25.7 (0.8)	65.2	34.8
40	19.04 (0.03)	37.6 (1.4)	61.3 (2.3)	18.6 (0.7)	66.9	33.1
50	15.95 (0.01)	33.5 (0.5)	57.9 (0.8)	17.6 (0.3)	65.6	34.4
60	13.37 (0.01)	32.5 (0.6)	63.3 (1.2)	19.2 (0.4)	62.9	37.1
70	11.69 (0.01)	27.8 (0.4)	53.1 (0.8)	16.1 (0.3)	63.3	36.7
80	10.33 (0.01)	28.2 (0.6)	59.0 (1.3)	17.9 (0.4)	61.2	38.8
90	9.48 (0.01)	27.1 (0.4)	58.1 (1.0)	17.6 (0.3)	60.6	39.4
100	8.93 (0.02)	28.6 (0.8)	64.8 (1.7)	19.6 (0.5)	59.3	40.7
Ideal	7.68	22.31	48.3	14.63	60.4	39.6

[a]$\%\xi_H$ and $\%\zeta_{TS}$ are the relative contributions by enthalpy and entropy toward free energy of solution. These values were calculated by means of equations (8) and (9), respectively.

Table 4 summarizes the corrected standard thermodynamic functions for experimental solution process of NAP 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 [19,20]. 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 unit as concentration of NAP, that is, the solid pure solute. In the same way, as it was presented for NAP solubility in pure water and buffer pH 1.2, the thermodynamic functions of solution are also different between both aqueous media, that is, 33.35 kJ mol^{-1} for free energy, 30.0 kJ mol^{-1} for enthalpy, and −10.9 J mol^{-1} K^{-1}, for entropy, in aqueous buffer at pH 1.2 and 303 K [11], which are very different with respect to those for pure water (table 4). These differences would be explained in terms of a possible water-structure increase by effect of potassium chloride, which in consequence, diminishes entropy and therefore the solubility of IBP by a "squeezing-out" effect.

The enthalpy of solution is positive in all cases, therefore the process is always endothermic. The entropy of solution is negative for water, whereas it is positive in EtOH-rich mixtures, indicating entropy driving on overall the solution process for the latter mixtures. The ΔH^0_{soln} values increase nonlinearly from pure water up to 30% EtOH and diminish with EtOH proportion from this mixture up to 70% EtOH. Over this later mixture, the enthalpy of solution remains almost constant.

Perlovich *et al*. [10] determined the enthalpy of solution of NAP in EtOH by solution calorimetry obtaining the value 25.3 ± 0.3 kJ mol^{-1}, which is almost coincident with that presented in table 4 obtained by van't Hoff method. On the other hand, the respective entropy of solution presented by the same authors was 47.3 J mol^{-1} K^{-1} [10], which is moderately different with respect to that presented in table 4. The discrepancies found between both reports would be attributed to differences in the methods used for obtaining the enthalpy of solution.

With the aim to compare the relative contributions by enthalpy ($\%\zeta_H$) and by entropy ($\%\zeta_{TS}$) toward the solution process, equations (8) and (9) were employed, respectively [10,22]:

$$\%\zeta_H = 100\frac{\left|\Delta H^0_{soln}\right|}{\left|\Delta H^0_{soln}\right| + \left|T\Delta S^0_{soln}\right|} \tag{8}$$

$$\%\zeta_{TS} = 100\frac{\left|T\Delta S^0_{soln}\right|}{\left|\Delta H^0_{soln}\right| + \left|T\Delta S^0_{soln}\right|} \tag{9}$$

From table 4 it follows that in all mixtures the main contributor to standard free energy of solution process of NAP is the enthalpy (greater than 60% in almost all cases). It is interesting to note that enthalpy and entropy contributions for EtOH-rich mixtures are almost equal to ideal process.

3.3. *Thermodynamic functions of mixing*

The solution process may be represented by the following hypothetic stages [4,5]:

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

where, the respective partial processes toward the solution are solute fusion and mixing at the same temperature (303 K), which permits to calculate the partial thermodynamic contributions to overall solution process by means of equations (10) and (11), respectively.

$$\Delta H^0_{soln} = \Delta H^{303}_{fus} + \Delta H^0_{mix} \tag{10}$$

$$\Delta S^0_{soln} = \Delta S^{303}_{fus} + \Delta S^0_{mix} \tag{11}$$

where, ΔH^{303}_{fus} and ΔS^{303}_{fus} represent the thermodynamic functions of fusion process at harmonic temperature (303 K). According to Mora and Martínez [11], ΔH^{303}_{fus} is 22.32 kJ mol^{-1}, which is coincident with the enthalpic change for ideal solution (table 2). In contrast, the entropy of fusion at 303 K (73.7 J mol^{-1} K^{-1}) is not coincident with the entropy of ideal solution at this temperature (48.3 J mol^{-1} K^{-1}). For this reason, for practical purposes in this analysis, the ΔS^{0id}_{soln} value was used instead of ΔS^{303}_{fus} as it was made previously with this drug [11]. In table 5, the thermodynamic functions of mixing of NAP 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 almost all mixtures but negative for pure water, while the entropy of mixing (ΔS^0_{mix}) is positive in almost all mixtures but negative in pure water and in 10% EtOH mixture. 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 except for 10% EtOH. For pure water, the solution process is driven by the enthalpy of mixing (negative value: table 5).

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

EtOH (% in mass)	ΔG^0_{mix} ($kJ\,mol^{-1}$)	ΔH^0_{mix} ($kJ\,mol^{-1}$)	ΔS^0_{mix} ($J\,mol^{-1}\,K^{-1}$)	$T\Delta S^0_{mix}$ ($kJ\,mol^{-1}$)	$\%\zeta_H$[a]	$\%\zeta_{TS}$[a]
0	22.45	−1.0	−77.3	−23.4	4.0	96.0
10	21.42	17.2	−13.9	−4.2	80.3	19.7
20	18.93	23.7	15.6	4.7	83.3	16.7
30	14.70	25.8	36.6	11.1	69.9	30.1
40	11.36	15.3	13.0	4.0	79.5	20.5
50	8.27	11.2	9.6	2.9	79.3	20.7
60	5.69	10.2	15.0	4.5	69.3	30.7
70	4.01	5.5	4.8	1.5	79.0	21.0
80	2.65	5.9	10.7	3.3	64.5	35.5
90	1.80	4.8	9.8	3.0	61.6	38.4
100	1.25	6.3	16.5	5.0	55.6	44.4

[a]$\%\zeta_H$ and $\%\zeta_{TS}$ are the relative contributions by enthalpy and entropy toward free energy of mixing. These values were calculated by means of equations analogous to equations (8) and (9), respectively.

The net variation in ΔH^0_{mix} values results from the contribution of several kinds of interaction. 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 it is the case of pure water (table 5).

As it 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 lower as the proportion of cosolvent increases in both water-rich and EtOH-rich mixtures. According to Romero *et al.* [23] in the initial portion of the solubility curve, the hydrogen bonding of the drug will increase with EtOH concentration (from pure water up to 30% EtOH). At large cosolvent proportions (from 70% 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.

For comparative purposes, figure 2 shows the thermodynamic functions of mixing, ΔG^0_{mix}, ΔH^0_{mix}, and $T\Delta S^0_{mix}$. Free energy diminishes as EtOH proportion increases in the mixtures, whereas enthalpy and entropy, initially increase from pure water up to 30% EtOH and diminish over this composition.

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 NAP from more polar solvents 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 30% of EtOH ($\Delta G^0_{1\to2} < 0$, $\Delta H^0_{1\to2} > 0$, and $\Delta S^0_{1\to2} > 0$) the solubility process is driven by the entropy due to water-structure loosing by EtOH, while beyond this composition ($\Delta G^0_{1\to2} < 0$, $\Delta H^0_{1\to2} < 0$, and $\Delta S^0_{1\to2} < 0$) in almost all cases, the solubility process is

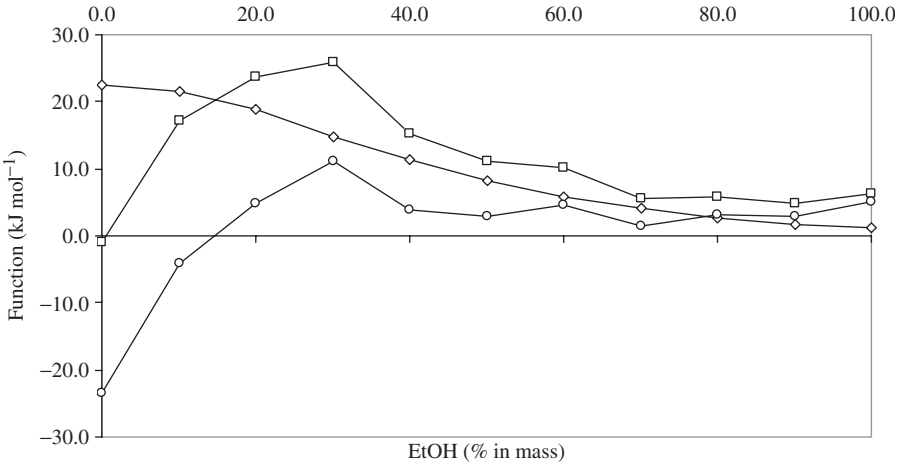


Figure 2. Thermodynamic functions relative to mixing process of NAP in EtOH + W cosolvent mixtures at 303 K. (ΔG^0_{mix}: rhombic; ΔH^0_{mix}: squares; $T\Delta S^0_{mix}$: circles).

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

Medium 1	Medium 2	$\Delta G^0_{1\rightarrow 2}$ (kJ mol^{-1})	$\Delta H^0_{1\rightarrow 2}$ (kJ mol^{-1})	$\Delta S^0_{1\rightarrow 2}$ (J mol^{-1} K^{-1})	$T\Delta S^0_{1\rightarrow 2}$ (kJ mol^{-1})
EtOH (% in mass)					
0	10	−1.03	18.2	63.4	19.2
10	20	−2.49	6.5	29.5	9.0
20	30	−4.22	2.1	21.0	6.4
30	40	−3.34	−10.5	−23.6	−7.1
40	50	−3.10	−4.1	−3.4	−1.0
50	60	−2.58	−1.0	5.4	1.6
60	70	−1.68	−4.8	−10.2	−3.1
70	80	−1.36	0.4	5.9	1.8
80	90	−0.85	−1.1	−0.9	−0.3
90	100	−0.55	1.5	6.7	2.0

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

enthalpy driven. This later behavior is probably due to increase in solvation of NAP by EtOH molecules.

3.4. *Thermodynamic functions of solvation*

In addition to previous fusion-mixing subprocesses, the solution process may also be represented by the following hypothetic stages [10,22]:

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

where, the respective partial processes toward the solution in this case are solute sublimation and solvation, which permits to calculate the partial thermodynamic

contributions to solution process by means of equations (12) and (13), respectively, while the free energy of solvation is calculated by means of equation (14):

$$\Delta H^0_{\text{soln}} = \Delta H^0_{\text{subl}} + \Delta H^0_{\text{solv}} \tag{12}$$

$$\Delta S^0_{\text{soln}} = \Delta S^0_{\text{subl}} + \Delta S^0_{\text{solv}} \tag{13}$$

$$\Delta G^0_{\text{soln}} = \Delta G^0_{\text{subl}} + \Delta G^0_{\text{solv}} \tag{14}$$

where, $\Delta H^0_{\text{subl}} = 128.3\,\text{kJ mol}^{-1}$ was taken from Perlovich *et al*. [10], and therefore, the function ΔH^0_{solv} was calculated from ΔH^0_{soln} values presented in table 4. Free energy and entropy of sublimation, according to Mora and Martínez [11] are $57.32\,\text{kJ mol}^{-1}$ and $234.3\,\text{J mol}^{-1}\,\text{K}^{-1}$ at 303 K, respectively. 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 ($\%\zeta_{\text{H}}$) and entropy ($\%\zeta_{\text{TS}}$) toward the solvation process, two equations analogous to equations (8) and (9) were employed.

From the values of $\%\zeta_{\text{H}}$ and $\%\zeta_{\text{TS}}$ presented in table 7, it follows that the main contributing force to standard free energy of the solvation process of NAP in all the cosolvent mixtures is the enthalpy, especially for EtOH-rich mixtures ($\%\zeta_{\text{H}}$ are greater than 57% in all cosolvent mixtures).

Because not only the main driving force of solvation process of drug compounds is important, but also the balance between specific and nonspecific solute–solvent interactions as well, therefore, parameters which describe the relative ratio of specific and nonspecific solute–solvent interaction in terms of enthalpies ($\%\varepsilon_{\text{H}}$) and in terms of entropies ($\%\varepsilon_{\text{S}}$), were used according to the following definitions introduced by Perlovich *et al*. [10,22]:

$$\%\varepsilon_{\text{H}} = 100\left|\frac{\Delta H^0_{\text{spec}}}{\Delta H^0_{\text{nonspec}}}\right| \tag{15}$$

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

EtOH (% in mass)	ΔG^0_{solv} (kJ mol^{-1})	ΔH^0_{solv} (kJ mol^{-1})	ΔS^0_{solv} ($\text{J mol}^{-1}\,\text{K}^{-1}$)	$T\Delta S^0_{\text{solv}}$ (kJ mol^{-1})	$\%\zeta_{\text{H}}$[a]	$\%\zeta_{\text{TS}}$[a]	$\%\varepsilon_{\text{H}}$[b]	$\%\varepsilon_{\text{S}}$[b]
0	−27.19	−107.0	−263	−79.8	57.3	42.7	51.1	126.0
10	−28.22	−88.8	−200	−60.6	59.4	40.6	25.4	69.2
20	−30.71	−82.3	−170	−51.6	61.5	38.5	16.3	42.7
30	−34.94	−80.2	−149	−45.3	63.9	36.1	13.3	23.9
40	−38.28	−90.7	−173	−52.4	63.4	36.6	28.1	45.0
50	−41.37	−94.8	−176	−53.4	63.9	36.1	33.9	48.1
60	−43.95	−95.8	−171	−51.8	64.9	35.1	35.3	43.3
70	−45.63	−100.5	−181	−54.9	64.7	35.3	42.0	52.4
80	−46.99	−100.1	−175	−53.1	65.3	34.7	41.4	47.1
90	−47.84	−101.2	−176	−53.4	65.5	34.5	42.9	47.9
100	−48.39	−99.7	−169	−51.4	66.0	34.0	40.9	41.9

[a]$\%\zeta_{\text{H}}$ and $\%\zeta_{\text{TS}}$ are the relative contributions by enthalpy and entropy toward free energy of solvation. These values were calculated by means of equations analogous to equations (8) and (9), respectively.
[b]$\%\varepsilon_{\text{H}}$ and $\%\varepsilon_{\text{S}}$ 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 (15) and (16), respectively.

$$\%\varepsilon_S = 100\left|\frac{\Delta S^0_{spec}}{\Delta S^0_{nonspec}}\right| \tag{16}$$

where, $\Delta H^0_{spec} = \Delta H^0_{soln(solvent-i)} - \Delta H^0_{soln(CH)} = \Delta H^0_{soln(CH\rightarrow solvent-i)}$; $\Delta H^0_{nonspec} = \Delta H^0_{soln(CH)} - \Delta H^0_{subl} = \Delta H^0_{solv(CH)}$; $\Delta S^0_{spec} = \Delta S^0_{soln(solvent-i)} - \Delta S^0_{soln(CH)} = \Delta S^0_{soln(CH\rightarrow solvent-i)}$; and $\Delta S^0_{nonspec} = \Delta S^0_{soln(CH)}$.

Cyclohexane (CH) was chosen as an "inert" solvent, which interacts with drug molecules solely by nonspecific interactions (dispersion forces), while the cosolvent mixtures interact with NAP by specific interactions such as hydrogen bonding. Benzene and hexane have also been used as inert solvents in the study of this drug [10], although important differences have been found between these two solvents, indicating some effect of π-electrons and planar geometry of benzene on nonspecific interactions of that drug.

Solution thermodynamics data for NAP in CH was taken from Mora and Martínez [11]. The respective values for apparent thermodynamic functions are: $\Delta H^{0app}_{soln(CH)} = 57.5\,kJ\,mol^{-1}$, $\Delta G^{0app}_{soln(CH)} = 23.75\,kJ\,mol^{-1}$, and $\Delta S^{0app}_{soln(CH)} = 111.5\,J\,mol^{-1}\,K^{-1}$. For NAP solubility in CH, the apparent values were used instead of corrected values as it was made previously in EtOH + W mixtures (table 4) because $(\partial \ln a_2/\partial \ln X_2)_{T,P}$ in CH is almost the unit [24].

The $\%\varepsilon_H$ and $\%\varepsilon_S$ values for NAP solvation are also presented in table 7. These values indicate that during dissolution of this drug in all mixtures studied, the specific solute–solvent interactions (hydrogen bonding, mainly) effectively affect the entropic term of free energy with respect to nonspecific interactions, especially in pure water, although it is also significant in all other cosolvent mixtures. With regard to the enthalpic term in all cases the nonspecific solute–solvent interactions predominate.

3.5. *Enthalpy–entropy compensation of solution*

Bustamante *et al*. [25,26] 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 [27,28].

For solubility of acetaminophen in EtOH + W mixtures, Bustamante *et al*. [25] 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% in volume of EtOH. From 0 to 20% in volume 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 NAP in the EtOH + W cosolvent system present nonlinear ΔH^0_{soln} *versus* ΔG^0_{soln} compensation with negative slope if an interval from pure water up to 30% EtOH (where the maximum is obtained) is considered. On the other hand, from this composition up to 70% EtOH positive slope is obtained. According to this graph it follows that the dominant mechanism for solubility is the entropy in the former

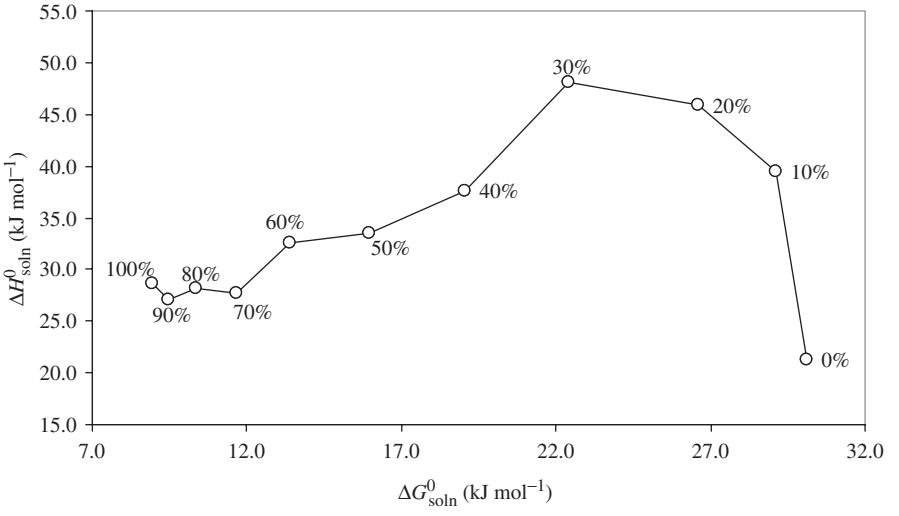


Figure 3. Enthalpy–entropy compensation plot for solubility of NAP in EtOH + W cosolvent mixtures at 303 K.

case implying water-structure loosing; whereas in the later case, the dominant mechanism is the enthalpy probably due to NAP solvation by EtOH molecules as it was already said. Over 70% EtOH the dominant mechanism is unclear due to uncertainty in the respective thermodynamic values.

From all topics discussed previously it can be concluded that the solution process of NAP in EtOH + W mixtures is complex depending on the cosolvent composition. 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 expands the physicochemical information about analgesic drugs in solution. As it was already said, this information is very useful in the design of homogeneous liquid pharmaceutical dosage forms, such as parenteral medications.

Acknowledgements

We thank 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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