Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **26** (3): 344-354 (2007)

Trabajos originales

Recibido el 26 de julio de 2006
Aceptado el 28 de enero de 2007

Solubility of Ibuprofen in Some Ethanol + Water Cosolvent Mixtures at Several Temperatures

Juliana MANRIQUE and Fleming MARTÍNEZ*

Sección de Farmacotecnia, Departamento de Farmacia,
Universidad Nacional de Colombia, A.A. 14490, Bogotá D.C., Colombia.

SUMMARY. By using the van't Hoff and Gibbs equations the thermodynamic functions free energy, enthalpy, and entropy of solution, mixing and solvation of ibuprofen (IBP) in some 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 clearly the cosolvent effect present in this system. Depending on temperature, liquid phases' separation was found in mixtures from 30% in mass of EtOH up to 70% EtOH. The solvation of this drug in the mixtures increases as the EtOH proportion is also increased in those mixtures formed by only one liquid phase. By means of enthalpy-entropy compensation analysis, linear ΔH^0_{soln} vs. ΔG^0_{soln} compensation with positive slopes were obtained if composition intervals from pure water up to 20% EtOH and from 70% EtOH up to pure EtOH are considered. Accordingly to this result it follows that the dominant mechanism for solubility of IBP in this cosolvent system is the enthalpy probably due to solvation by EtOH molecules.

RESUMEN. "Solubilidad de Ibuprofeno en Función de la Temperatura en Algunas Mezclas Cosolventes Etanol + Agua". En este trabajo se calcularon las funciones termodinámicas energía libre, entalpía y entropía para los procesos de solución, mezcla y solvatación de ibuprofeno (IBP) en algunas mezclas cosolventes etanol (EtOH) + agua (W), mediante las ecuaciones de Gibbs y van't Hoff, utilizando valores de solubilidad a diferentes temperaturas. La solubilidad fue más alta en EtOH puro y más baja en agua pura a todas las temperaturas estudiadas, lo que demuestra la importancia del efecto cosolvente en este sistema. Dependiendo de la temperatura, se encontró separación de fases líquidas en mezclas desde el 30% en masa de EtOH hasta 70% de EtOH. La solvatación del fármaco es mayor en la medida que se incrementa la proporción de EtOH en las mezclas donde se presenta una sola fase líquida. Mediante análisis de compensación entálpica-entrópica, se obtuvieron gráficos lineales de ΔH^0_{soln} vs. ΔG^0_{soln} con pendientes positivas, considerando intervalos de composición desde el agua pura hasta el 20% de EtOH y desde el 70% de EtOH hasta el EtOH puro. De acuerdo a esto, se tiene que el mecanismo dominante en la solubilidad de IBP en este sistema cosolvente, es la entalpía, debido probablemente a la solvatación del fármaco por las moléculas de EtOH.

INTRODUCTION

Ibuprofen (IBP) is a non-steroidal anti-inflammatory drug (NSAID) derived of propionic acid widely used 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 indications. Like other NSAIDs its mechanism of action likely relates to its inhibition of prostaglandin synthesis [1,2]. Although IBP is used widely nowadays in therapeutics, the physicochemical information about properties such as solubility and molar volume for this drug is not abundant. In the Colombian market it is commercially available as tablets, syrups and concentrates, but it is not available as parenteral products [3]. 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 volumes occupied by the drugs and other components in the solution are very important

KEY WORDS: Ibuprofen, Solubility, Solution thermodynamics, Solvation.
PALABRAS CLAVE: Ibuprofeno, Solubilidad, Solvatación, Termodinámica de Soluciones.

* Autor a quien dirigir la correspondencia. *E-mail:* fmartinezr@unal.edu.co

ISSN 0326-2383

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 fully explain 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 widely facilitates the labor of pharmacists associated to research and development of new products in pharmaceutical industry [8]. Temperature-solubility dependence allows to realize the respective thermodynamic analysis, which, on the other hand, also permits inside the molecular mechanisms involved toward the solution processes [9].

The main objective of this study was to evaluate the effect of the cosolvent composition on solubility and solution thermodynamics of IBP in ethanol (EtOH) + water (W) cosolvent mixtures based on 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].

EXPERIMENTAL

In this investigation the following chemicals and materials were used: Ibuprofen USP [10]; 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. Millex® 0.45 μm PVDF, 25 mm filter units.

Solubility determinations

An excess of IBP 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 40.0 ± 0.05 °C at least for five days to reach the equilibrium (This equilibrium time was established by quantifying the drug concentration up to obtain a constant value). After this time, the supernatant solutions formed by only one liquid phases were filtered (at isothermal conditions) to ensure that they were free of particulate matter before sampling. Concentrations were determined by measuring absorbance after appropriate dilution and interpolation from previously constructed UV spectrophotometry calibration curves for IBP in alcohol USP (UV/Vis BioMate 3 Thermo Electron Corp. spectrophotometer). After the procedure already described the temperature was decreased in 5.0 °C and therefore it was stabilized in 35.0 °C during at least two 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 reach 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 ± 0.0001 $g.cm^{-3}$).

RESULTS AND DISCUSSION

In Table 1, the molecular structure of IBP 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.* [11]. 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). On the other hand, IBP could also act as a proton-acceptor compound by means of its carbonyl and –OH moieties.

Ideal and Experimental Solubility of IBP

The ideal solubility of a crystalline solute in a liquid solvent can be calculated by Eq. [**1**]:

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

where X^{id}_2 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 be-

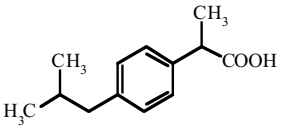
Molecular structure (a)	Molar mass / g mol^{-1} (a)	Melting point / K (b)	ΔH_{fus} / kJ mol^{-1} (b)	ΔH_{subl} / kJ mol^{-1} (b)
	230.26	347.15	25.50	115.8

Table 1. Some physicochemical properties of IBP. (**a**) Taken from Budavari *et al.* [12]. (**b**) Taken from Perlovich *et al.* [11].

tween the molar heat capacity of the crystalline form and the molar heat capacity of the hypothetical supercooled liquid form, both at the solution temperature [13]. Since ΔC_p cannot be easy experimentally determined it is usual assuming that it may be approximated to the entropy of fusion, ΔS_{fus}.

Table 2 summarizes the experimental solubilities of IBP, 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 almost all cases the coefficients of variation for solubility were smaller than 2.0%. Only one saturated liquid' phases at all temperatures were found for mixtures varying from pure water up to 20% EtOH and from 80% EtOH up to pure EtOH. Liquid phases' separations were found for the other cosolvent mixtures depending on temperature. This event has been reported for any other drugs, such as benzocaine, salicylic acid, and some parabens [14,15]. Apparently, it is present in some drugs having lower melting points and lower enthalpies of fusion.

It may be observed that the highest solubility value in mole fraction for IBP was obtained in pure EtOH at 40.0 °C, while the lowest value was found in water at 20.0 °C. The solubility of IBP in pure EtOH at 25.0 °C is not coincident with value reported by Perlovich *et al.* [16], that is, 0.0833. Unfortunately, there is not any other solubility value for this drug in these solvents, reported in literature, and therefore no direct comparison is possible.

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 vs. $1/T$ plot. Nevertheless, in recent thermodynamic treatments some modifications 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 in the development of enthalpy-entropy compensation plots as it will be seen in other paragraph. 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 [17]. In the present case the T_{hm} value obtained is just 303 K. The modified expression more widely used is the following [18]:

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

As an example, Fig. 1 shows the modified van't Hoff plot for IBP in the pure solvents and in mixtures having 10% and 80% of EtOH. In general, linear models with good determination coefficients were obtained in all cases studied,

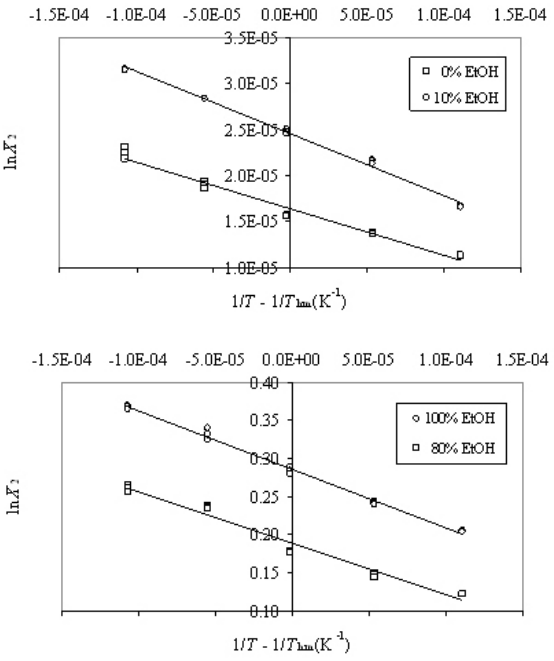


Figure 1. Temperature dependence for solubility of IBP in some EtOH + W cosolvent mixtures expressed in mole fraction.

EtOH / % m/m	Mol L^{-1} (a)				
	20.0 °C	**25.0 °C**	**30.0 °C**	**35.0 °C**	**40.0 °C**
0	6.218 (0.050) x 10^{-4}	7.544 (0.036) x 10^{-4}	8.534 (0.036) x 10^{-4}	1.049 (0.021) x 10^{-3}	1.235 (0.035) x 10^{-3}
10	8.471 (0.035) x 10^{-4}	1.097 (0.076) x 10^{-3}	1.261 (0.010) x 10^{-3}	1.442 (0.020) x 10^{-3}	1.601 (0.004) x 10^{-3}
20	2.787 (0.039) x 10^{-3}	3.315 (0.037) x 10^{-3}	3.760 (0.029) x 10^{-3}	4.095 (0.017) x 10^{-3}	4.538 (0.071) x 10^{-3}
30	-	-	-	-	-
40	-	-	-	-	-
50	0.0189 (0.0006)	-	-	-	-
60	0.6046 (0.0024)	0.8310 (0.0042)	1.095 (0.011)	-	-
70	1.474 (0.014)	1.757 (0.010)	2.084 (0.048)	2.473 (0.010)	-
80	1.968 (0.006)	2.205 (0.030)	2.470 (0.003)	2.881 (0.009)	3.031 (0.024)
90	2.313 (0.004)	2.546 (0.036)	2.817 (0.003)	3.057 (0.022)	3.208 (0.018)
100	2.323 (0.007)	2.559 (0.014)	2.822 (0.023)	3.090 (0.017)	3.209 (0.010)
EtOH / % m/m	**Mole fraction (a)**				
	20.0 °C	**25.0 °C**	**30.0 °C**	**35.0 °C**	**40.0 °C**
0	1.123 (0.090) x 10^{-5}	1.364 (0.006) x 10^{-5}	1.546 (0.006) x 10^{-5}	1.902 (0.038) x 10^{-5}	2.242 (0.064) x 10^{-5}
10	1.656 (0.007) x 10^{-5}	2.140 (0.007) x 10^{-5}	2.475 (0.020) x 10^{-5}	2.833 (0.039) x 10^{-5}	3.149 (0.007) x 10^{-5}
20	5.908 (0.082) x 10^{-5}	7.045 (0.080) x 10^{-5}	8.017 (0.020) x 10^{-5}	8.746 (0.037) x 10^{-5}	9.71 (0.15) x 10^{-5}
30	-	-	-	-	-
40	-	-	-	-	-
50	5.34 (0.18) x 10^{-4}	-	-	-	-
60	0.02154 (0.00010)	0.03107 (0.00028)	0.04313 (0.00057)	-	-
70	0.07152 (0.00010)	0.09168 (0.00008)	0.1190 (0.0045)	0.1589 (0.0002)	-
80	0.1218 (0.0006)	0.1462 (0.0034)	0.1765 (0.0004)	0.2367 (0.0016)	0.2608 (0.0046)
90	0.1771 (0.0005)	0.2074 (0.0055)	0.2522 (0.0005)	0.2963 (0.0046)	0.3280 (0.0044)
100	0.2045 (0.0010)	0.2410 (0.0024)	0.2840 (0.0046)	0.3398 (0.0042)	0.3671 (0.0024)
ideal	0.2245	0.2607	0.3020	0.3489	0.4023

Table 2. Experimental solubility of IBP in EtOH + W cosolvent mixtures expressed in molarity and mole fraction including ideal solubility at several temperatures. (**a**) In almost all cases the coefficients of variation (CV) were smaller than 2.0%.

that is, from pure water up to 20% EtOH and from 70% EtOH up to pure EtOH. The mixture of 70% EtOH presents liquid phases' separation at 40.0 °C, nevertheless, at the other four temperatures it is homogeneous, which permits the van't Hoff analysis.

For non-ideal solutions, the slope obtained in Eq. [**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 [18]. Then, the enthalpic change of solution (ΔH^0_{soln}) is calculated from: $\Delta H^{0app}_{soln} (\partial \ln a_2 / \partial \ln X_2)_{T,P}$, in which, the second term of the right side [18,19], is calculated by means of:

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

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, 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 is also adequate [4,5,20].

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

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

The term (X_2^{id}/X_2) in Eq. [**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. Table 3 shows the experimental % mass/volume solubilities, saturated solution densities, cosolvent mixtures densities [21], 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 ($\partial \ln a_2/\partial \ln X_2$) values some propagation of errors' methods were used [22,23].

According to literature the activity variation factor usually varies from 0.85 and 1.15 for solutes such as acetaminophen, phenacetin and nalidixic acid, among others [4,5,18,20]. For water-rich mixtures, for IBP this factor is near to unit, whereas for EtOH-rich mixtures, this factor is very different with respect to unit, in particular for 70% EtOH and 80% EtOH, that is, 0.0786 and 0.3285, respectively. Apparently, there are some cases where the Eq. [**4**] is not valid for correcting thermodynamic quantities. For this reason, in order to evaluate the effect of mixture composition on IBP solubility, the thermodynamic magnitudes without corrections will be used in the following analyses.

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:

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

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 solute, and finally, ϕ_1 is the volume fraction of the solvent. In a first approach the term ($V_2\phi_1^2/RT$) 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 Eq. [**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 δ = 23.0 cal$^{1/2}$ cm$^{-3/2}$) while it is comparatively smaller in EtOH (δ = 13.0 cal$^{1/2}$ cm$^{-3/2}$) [24]. 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 close to

EtOH / % m/m	IBP / % m/v (a)	ρ / g cm^{-3} (b)	ρ_0 / g cm^{-3} (c)	ϕ_2	γ_2	$\left(\frac{\partial \ln a_2}{\partial \ln X_2}\right)$
0	0.01761	0.9950	0.9957	0.00088	19534	0.9826
10	0.02979	0.9780	0.9787	0.00102	12202	0.9808
20	0.07758	0.9632	0.9639	0.00153	3767	0.9748
70	42.99	0.9147	0.8592	0.4357	2.539	0.0786
80	50.96	0.9145	0.8347	0.5149	1.711	0.3285
90	58.12	0.9141	0.8094	0.5887	1.197	0.7166
100	58.21	0.9099	0.7811	0.5804	1.063	0.9006

Table 3. Solubility of IBP expressed in % mass/volume, saturated solution and solvent densities, solute volumetric fraction, solute activity coefficient, and activity variation factor in some EtOH + W cosolvent mixtures at 30.0 °C. (**a**) In all cases CV were smaller than 2.0 %. (**b**) In all cases standard deviations were smaller than 0.0002 g cm^{-3}. (**c**) From Jiménez *et al.* [21].

1.0), the w_{11} values are relatively low but the w_{12} values are higher. According to this fact, the solvation of IBP is higher in EtOH-rich mixtures.

The apparent standard free energy change for the solution process (ΔG^{0app}_{soln}), considering the approach proposed by Krug *et al.* [17], is calculated by means of:

$$\Delta G^{0app}_{soln} = RT_{hm} \times \text{intercept} \qquad [6]$$

in which, the intercept used is that one obtained in the analysis by treatment of ln X_2 as a function of $1/T$ - $1/T_{hm}$ (Eq. [**2**]). Although the enthalpy obtained by using the Eq. [**2**] is the same obtained by means of the traditional method, the ΔG^{0app}_{soln} is slightly different with respect to that calculated by means of: $-RT_{hm} \times \ln X_2$ at 30.0 °C, because in the former case, it depend on all the solubility data, whereas in the traditional form, it depend solely on the value obtained at the specified temperature.

This thermodynamic function would be 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. Nevertheless, this function will be used without correction in the same way as it will be with the enthalpy of solution.

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:

$$\Delta S^0_{soln} = \frac{\left(\Delta H^0_{soln} - \Delta G^0_{soln}\right)}{T_{hm}} \qquad [7]$$

Table 4 summarizes the apparent standard thermodynamic functions for experimental solution process of IBP 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 also used [22,23]. 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 IBP, 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 negative for water-rich mixtures, 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 diminish nonlinearly with EtOH proportion from pure water up to 20% EtOH and from 70% EtOH up to pure EtOH.

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 [25,26]:

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

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

From Table 4 it follows that in water-rich mixtures the main contributor to standard free energy of solution process of IBP is the enthalpy (greater than 77% in all cases), while for EtOH-rich mixtures the enthalpy and entropy contributions are similar, although it is higher for enthalpy (near to 54%). It is interesting to note that enthalpy and entropy contributions for EtOH-rich mixtures are almost equal to ideal process.

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}	$\%\zeta_H$ (a)	$\%\zeta_{TS}$ (a)
0	27.83 (0.01)	26.2 (0.6)	-5.46 (0.12)	-1.65 (0.04)	94.1	5.9
10	26.80 (0.03)	23.9 (1.1)	-9.5 (0.4)	-2.88 (0.13)	89.2	10.8
20	23.84 (0.02)	18.5 (0.7)	-17.6 (0.7)	-5.32 (0.20)	77.7	22.3
70	5.34 (0.02)	39.8 (0.9)	113.9 (2.7)	34.5 (0.8)	53.6	46.4
80	4.31 (0.03)	30.6 (1.1)	87 (3)	26.3 (1.0)	53.8	46.2
90	3.53 (0.02)	24.3 (0.7)	68.5 (2.0)	20.8 (0.6)	53.9	46.1
100	3.20 (0.02)	23.1 (0.7)	65.8 (2.0)	19.9 (0.6)	53.7	46.3
ideal	3.02	22.25	63.46	19.23	53.6	46.4

Table 4. Apparent thermodynamic functions relative to solution process of IBP in some EtOH + W cosolvent mixtures including ideal process at 303 K. (**a**) $\%\zeta_H$ 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.

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 calculate the partial thermodynamic contributions to overall solution process by means of equations [**10**] and [**11**], respectively.

$$\Delta H^0_{\text{soln}} = \Delta H^{303}_{\text{fus}} + \Delta H^0_{\text{mix}} \qquad [\mathbf{10}]$$

$$\Delta S^0_{\text{soln}} = \Delta S^{303}_{\text{fus}} + \Delta S^0_{\text{mix}} \qquad [\mathbf{11}]$$

where, $\Delta H^{303}_{\text{fus}}$ and $\Delta S^{303}_{\text{fus}}$ represent the thermodynamic functions of fusion process at harmonic temperature (303 K). $\Delta H^{303}_{\text{fus}}$ was calculated from $\Delta H^{T}_{\text{fus}} = \Delta H^{\text{MP}}_{\text{fus}} - \Delta C_p(T_{\text{fus}} - T)$, using $\Delta S^{\text{MP}}_{\text{fus}}$ instead of ΔC_p obtaining a value of 22.25 kJ mol^{-1} which is coincident with the enthalpic change for ideal solution. In contrast, the entropy of fusion at 303 K (73.45 J mol^{-1} K^{-1}) is not coincident with the entropy of ideal solution at this temperature (63.46 J mol^{-1} K^{-1}), nevertheless, for practical purposes in this analysis, the $\Delta S^{0\text{id}}_{\text{soln}}$ value was used instead of $\Delta S^{303}_{\text{fus}}$. In Table 5 the thermodynamic functions of mixing of IBP 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 $\Delta H^{303}_{\text{fus}}$ and $\Delta S^{303}_{\text{fus}}$ 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 20% EtOH mixture, while the entropy of mixing (ΔS^0_{mix}) is positive in EtOH-rich mixtures but negative in water-rich mixtures. 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. For 20% EtOH mixture, the solution process is driven by the enthalpy of mixing (negative value: Table 5), while, for pure water and for 10% EtOH mixture, nor enthalpy or entropy driving is found for the solution process.

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. Nevertheless, this is not observed in the case of IBP in water-rich mixtures (Table 5), because ΔH^0_{mix} diminish as EtOH proportion increases.

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 lower as the proportion of cosolvent increases in both water-rich and EtOH-rich mixtures. According to Romero *et al.* [27] in the initial portion of the solubility curve, the hydrogen bonding of the drug will increase with EtOH concentration (from pure water up to 20% EtOH). At large cosolvent proportions (from 70% EtOH up to pure EtOH), this interaction may be saturated, becoming a constant contri-

EtOH / % m/m	ΔG^0_{mix}/ kJ mol^{-1}	ΔH^0_{mix}/ kJ mol^{-1}	ΔS^0_{mix}/ J mol^{-1} K^{-1}	$T\Delta S^0_{\text{mix}}$/ kJ mol^{-1}	$\%\xi_H$ (a)	$\%\xi_{TS}$ (a)
0	24.81	3.9	-68.9	-20.9	15.8	84.2
10	23.78	1.7	-73.0	-22.1	7.0	93.0
20	20.82	-3.7	-81.0	-24.5	13.2	86.8
70	2.32	17.6	50.4	15.3	53.5	46.5
80	1.28	8.4	23.4	7.1	54.2	45.8
90	0.51	2.0	5.0	1.5	57.2	42.8
100	0.18	0.9	2.4	0.7	55.5	44.5

Table 5. Thermodynamic functions relative to mixing process of IBP in some EtOH + W cosolvent mixtures at 303 K. (**a**) $\%\xi_H$ and $\%\xi_{TS}$ 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.

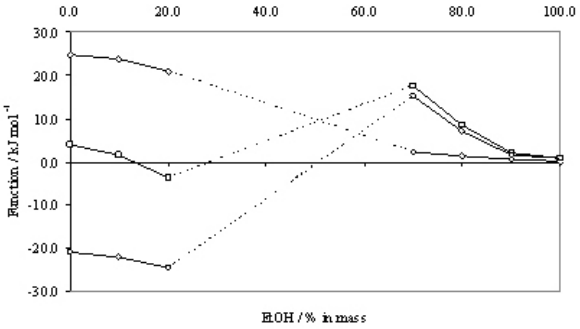


Figure 2. Thermodynamic functions relative to mixing process of IBP in some EtOH + W cosolvent mixtures at 303 K. (ΔG^0_{mix}: Rhombic; ΔH^0_{mix}: Squares; $T\Delta S^0_{mix}$: Circles).

bution. On the other hand, nonspecific and cavity effects are not saturated and vary with EtOH concentration.

For comparative purposes, Fig. 2 shows the thermodynamic functions of mixing, ΔG^0_{mix}, ΔH^0_{mix}, and $T\Delta S^0_{mix}$. If intervals from 0% EtOH up to 20% EtOH and from 70% EtOH up to 100% EtOH are considered, then all functions diminish nonlinearly with EtOH proportion. On the other hand, apparent increases in ΔH^0_{mix} and $T\Delta S^0_{mix}$ are presented from 20% EtOH up to 70% EtOH, which are not easily explained because of the liquid phases' separation presented in those mixtures.

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 IBP 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 20% 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 enthalpy, while from 70% EtOH up to pure EtOH ($\Delta G^0_{1\to2} < 0$, $\Delta H^0_{1\to2} < 0$, and $\Delta S^0_{1\to2} < 0$) the solubility process is enthalpy driven again. This behavior is probably due to increase in solvation of IBP by EtOH molecules.

Thermodynamic Functions of Solvation

In addition to previous fusion-mixing subprocesses, the solution process may also be represented by the following hypothetic stages [25,26]:

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

where, the respective partial processes toward the solution in this case are solute sublimation and solvation, which permits calculate the partial thermodynamic contributions to solution process by means of equations [**12**] and [**13**], respectively, while the free energy of solvation is calculate by means of Eq. [**14**]:

$$\Delta H^0_{soln} = \Delta H^0_{subl} + \Delta H^0_{solv} \qquad [\mathbf{12}]$$

$$\Delta S^0_{soln} = \Delta S^0_{subl} + \Delta S^0_{solv} \qquad [\mathbf{13}]$$

$$\Delta G^0_{soln} = \Delta G^0_{subl} + \Delta G^0_{solv} \qquad [\mathbf{14}]$$

where, ΔH^0_{subl} = 115.8 kJ mol^{-1} was taken from Ertel *et al.* [28], 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 = 2.82 x 10^{-5} mmHg at 303 K and P_0 = 760 mmHg, then ΔG^0_{subl} = 43.1 kJ mol^{-1}, and therefore ΔS^0_{subl} = 240.1 J mol^{-1} K^{-1} at the same temperature. In Table 7 the thermodynamic functions of solvation are presented, while on the other hand,

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	-1.03	-2.3	-4.1	-1.2
10	20	-2.97	-5.4	-8.0	-2.4
70	80	-1.04	-9.2	-27.0	-8.2
80	90	-0.77	-6.3	-18.4	-5.6
90	100	-0.33	-1.1	-2.6	-0.8

Table 6. Thermodynamic functions of transfer of IBP from more polar solvents to less polar solvents in some EtOH + W cosolvent mixtures at 303 K. These magnitudes were calculated as $\Delta\Psi^0_{1\to2} = \Delta\Psi^0_{mix(\text{Medium 2: less polar})} - \Delta\Psi^0_{mix(\text{Medium 1: more polar})}$, where Ψ is *G*, *H* or *S*.

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}	$\%\zeta_H$ (a)	$\%\zeta_{HS}$ (a)	$\%\varepsilon_H$ (b)	$\%\varepsilon_S$ (b)
0	-15.27	-89.6	-245.6	-74.4	54.6	45.4	35.0	103.7
10	-16.30	-91.9	-249.6	-75.6	54.8	45.2	38.4	106.5
20	-19.26	-97.3	-257.7	-78.1	55.5	44.5	46.5	111.9
70	-37.76	-76.0	-126.2	-38.2	66.5	33.5	14.4	22.7
80	-38.79	-85.2	-153.2	-46.4	64.7	35.3	28.3	41.1
90	-39.57	-91.5	-171.6	-52.0	63.8	36.2	37.9	53.5
100	-39.90	-92.7	-174.3	-52.8	63.7	36.3	39.6	55.3

Table 7. Thermodynamic functions relative to solvation process of IBP in some EtOH + W cosolvent mixtures at 303 K. (**a**) $\%\zeta_H$ and $\%\zeta_{TS}$ 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**) $\%\varepsilon_H$ and $\%\varepsilon_S$ 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.

with the aim to compare the relative contributions by enthalpy ($\%\zeta_H$) and entropy ($\%\zeta_{TS}$) toward the solvation process, two equations analogous to equations [**8**] and [**9**] were employed.

From the values of $\%\zeta_H$ and $\%\zeta_{TS}$ presented in Table 7 it follows that the main contributing force to standard free energy of the solvation process of IBP in all the cosolvent mixtures is the enthalpy, especially for EtOH-rich mixtures ($\%\zeta_H$ are greater than 54% in water-rich mixtures and greater than 63% in EtOH-rich mixtures).

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 ($\%\varepsilon_H$) and in terms of entropies ($\%\varepsilon_S$), were used according to the following definitions introduced by Perlovich *et al.* [25, 26]:

$$\%\varepsilon_H = 100\left|\frac{\Delta H^0_{spec}}{\Delta H^0_{non\text{-}spec}}\right| \qquad [\mathbf{15}]$$

$$\%\varepsilon_S = 100\left|\frac{\Delta H^0_{spec}}{\Delta H^0_{non\text{-}spec}}\right| \qquad [\mathbf{16}]$$

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

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 IBP by specific interactions such as hydrogen bonding. Benzene and hexane have also been used as inert solvents in the study of naproxen [26], although important differences have been found between these two solvents, indicating some effect of π-electrons and planar geometry of benzene on non-specific interactions of that drug.

Solubility data for IBP in CH was taken from Garzón & Martínez [9]. Those data were analyzed according to equations [**2**], [**6**], and [**7**] founding the following values for apparent thermodynamic functions: $\Delta H^{0app}_{soln(CH)}$ = 49.4 kJ mol^{-1}, $\Delta G^{0app}_{soln(CH)}$ = 4.75 kJ mol^{-1}, and $\Delta S^{0app}_{soln(CH)}$ = 147.4 J mol^{-1} K^{-1}. For IBP solubility in CH, the apparent values were used instead of corrected values as it was made previously in EtOH + W mixtures (Table 4).

The $\%\varepsilon_H$ and $\%\varepsilon_S$ values for IBP 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 non-specific interactions, although it is more significant as the EtOH proportion in the mixtures is increased from pure water up to 20% EtOH and from 70% EtOH up to pure EtOH. With regard to the enthalpic term in all cases the non-specific solute-solvent interactions predominate.

Enthalpy-Entropy Compensation of Solution

Bustamante *et al.* [18,29] have demonstrated some chemical compensation effects for the solubility of several drug compounds in aqueous cosolvent mixtures. This analysis was used in

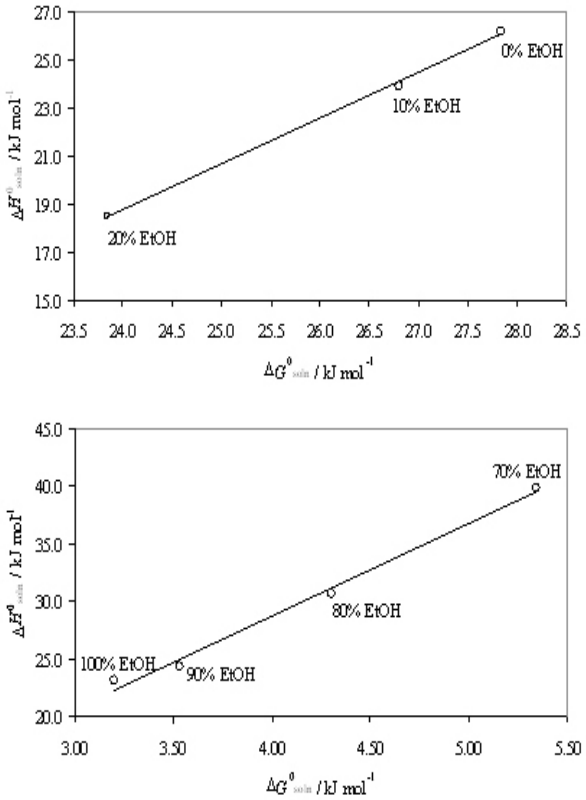


Figure 3. Enthalpy-entropy compensation plot for solubility of IBP in some EtOH + W cosolvent mixtures at 303 K.

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 [30,31].

For solubility of acetaminophen in EtOH + W mixtures, Bustamante *et al.* [29] 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 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 IBP in the EtOH + W cosolvent system present linear ΔH^0_{soln} vs. ΔG^0_{soln} compensation with positive slopes if intervals from pure water up to 20% EtOH and from 70% EtOH up to pure EtOH are considered again. Accordingly to this graph it follows that the dominant mechanism for solubility is the enthalpy probably due to IBP solvation by EtOH molecules as it was already said.

CONCLUSIONS

From all topics discussed previously it can be concluded that the solution process of IBP in EtOH + W mixtures is complex implying liquid phases' separations and it is 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 the data presented in this report amply the physicochemical information about drugs in solution. As it was already said this information is very useful in the design of homogeneous liquid pharmaceutical dosage forms.

Acknowledgments. 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.

REFERENCES

1. Roberts II, L.J. & J.D. Morrow (2001) "Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout", in *"Goodman & Gilman's. The Pharmacological Basis of Therapeutics",* 10th edition (J.G. Hardman, L.E. Limbird & A.G. Gilman, eds.) McGraw-Hill, New York, pages 703-5.
2. Hanson G.R. (2000) "Analgesic, antipyretic, and anti-inflammatory drugs", in *"Remington, The Science and Practice of Pharmacy",* 20th edition (A.R. Gennaro, ed.) Lippincott, Williams & Wilkins, Philadelphia, page 1457.
3. Rosenstein-Ster E. (2004) *"Diccionario de Especialidades Farmacéuticas",* 32ª edición, Thompson P.L.M., S.A., Bogotá.
4. Jiménez, J.A. & F. Martínez (2006) *J. Braz. Chem. Soc.* **17**: 125-34.
5. Jiménez, J.A. & F. Martínez (2006) *J. Solution Chem.* **35**: 335-52.
6. Rubino, J.T. (1988) "Cosolvents and cosolvency", in *"Encyclopedia of Pharmaceutical Technology",* (J. Swarbrick & J.C. Boylan, eds.) Marcel Dekker, New York, Vol 3, pages 375-98.
7. Yalkowsky, S.H. (1999) *"Solubility and Solubilization in Aqueous Media",* American Chemical Society and Oxford University Press, New York.
8. Jiménez, F. & F. Martínez (1995) *Rev. Col. Cienc. Quím. Farm.* **24**: 19-23.
9. Garzón, L.C. & F. Martínez (2004) *J. Solution Chem.* **33**: 1379-95.
10. US Pharmacopeia, 23rd edition, (1994). The United States Pharmacopeial Convention, Rockville, MD.

11. Perlovich, G.L., S.V. Kurkov, L.K. Hansen, & A. Bauer-Brandl (2004) *J. Pharm. Sci.* **93**: 654-66.
12. Budavari S, M.J. O'Neil, A. Smith, P.E. Heckelman, J.R. Obenchain Jr, J.A.R. Gallipeau & M.A. D'Arecea (2001) *"The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals",* 13th edition, Merck & Co., Inc., Whitehouse Station, NJ.
13. Hildebrand, J.H., J.M. Prausnitz & R.L. Scott (1970) *"Regular and Related Solutions",* Van Nostrand Reinhold, New York.
14. Peña, M.A., P. Bustamante, B. Escalera, A. Reíllo & J.M. Bosque-Sendra (2004) *J. Pharm. Biomed. Anal.* **36**: 571-8.
15. Paruta, A.N., B.J. Sciarrone & N.G. Lordi (1964) *J. Pharm. Sci.* **53**: 1349-53.
16. Perlovich, G.L., S.V. Kurkov, A.N. Kinchin & A. Bauer-Brandl (2004) *AAPS PharmSci.* **6**: Article 3. (http://www.aapspharmsci.org).
17. Krug, R.R., W.G. Hunter & R.A. Grieger (1976) *J. Phys. Chem.* **80**: 2341-51.
18. Bustamante, P., S. Romero, A. Peña, B. Escalera & A. Reillo (1998) *J. Pharm. Sci.* **87**: 1590-6.
19. Manzo, R.H. & A.A. Ahumada (1990) *J. Pharm. Sci.* **79**: 1109-15.
20. Jiménez J.A. & F. Martínez (2006) *Rev. Acad. Colomb. Cienc.* **30**: 87-99.
21. Jiménez, J., J. Manrique & F. Martínez (2004) *Rev. Col. Cienc. Quím. Farm.* **33**: 145-55.
22. Schoemaker, D.P. & G.W. Garland (1968) *"Experimentos de Fisicoquímica",* Unión Tipográfica Editorial Hispano Americana, México, pages 43-4.
23. Bevington, P.R. (1969) *"Data Reduction and Error Analysis for the Physical Sciences",* McGraw-Hill Book Co., New York, pages 56-65.
24. Sinko, P.J. (2006) *"Martin's Physical Pharmacy and Pharmaceutical Sciences",* 5th edition, Lippincott Williams & Wilkins, Philadelphia, pages 247-50.
25. Perlovich, G.L., S.V. Kurkov & A. Bauer-Brandl (2003) *Eur. J. Pharm. Sci.* **19**: 423-32.
26. Perlovich, G.L., S.V. Kurkov, A.N. Kinchin & A. Bauer-Brandl (2004) *Eur. J. Pharm. Biopharm.* **57**: 411-20.
27. Romero, S., A. Reillo, B. Escalera & P. Bustamante (1996) *Chem. Pharm. Bull.* **44**: 1061-4.
28. Ertel, K.D., R.A. Heasley, C. Koegel, A. Chakrabarti & J.T. Carstensen (1990) *J. Pharm. Sci.* **79**: 552.
29. Bustamante, P., S. Romero & A. Reillo (1995) *Pharm. Sci.* **1**: 505-7.
30. Leffler, J.E. & E. Grunwald (1963) *"Rates and Equilibria of Organic Reactions"*, Wiley, New York.
31. Tomlinson, E. (1983) *Int. J. Pharm.* **13**: 115-44.