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Solution Thermodynamics of 6-Methylcoumarin in Aqueous Media at Several pH Values

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***SUMMARY*. Based on van't Hoff and Gibbs equations, thermodynamic functions Gibbs energy, enthalpy, and entropy of solution and mixing of 6-methylcoumarin in water at pH 1.2, 6.8, and 7.4, were evaluated from solubility values determined at five temperatures from 293.15 to 313.15 K. The solubility at all pH values was almost the same demonstrating a slight effect of pH on this physicochemical property. All the thermodynamic quantities of solution were positive indicating endothermic and entropy-driving dissolution processes at all pH values studied. The results were discussed in terms of solvent-solute and solvent-solvent interactions, mainly hydrophobic hydration around non-polar groups of this drug.**

INTRODUCTION

Aqueous solubility of drugs is a very important consideration during the physicochemical characterization of pharmaceutical compounds, as also it is during the design and development of new pharmaceutical dosage forms. Moreover, temperature-solubility dependence of drugs allows carrying out the respective thermodynamic analysis, which simultaneously provides a possible explanation of the molecular mechanisms that are involved in the dissolution processes [1].

On the other hand, coumarins (compounds with a 1,2-benzopyrone nucleus), are part of an important group of heterocyclic metabolites widely distributed in plant species [2]. There are reported different kinds of coumarins since it is possible to make several chemical substitutions on carbons 3 to 8. This chemical diversity involves multiple biological and pharmacological properties, such as antiviral, anticoagulant, antibacterial, anticancer, antihelmintic, anti-inflammatory, and antioxidant, among others activities [3-5].

6-Methylcoumarin (Fig. 1, molar mass 160.17 g/mol, CAS Number: 92-48-8) is a simple coumarin used as flavoring agent, which has exhibited promising anti-inflammatory activity on *in vivo* models as carrageenan-induced paw edema and zymosan air pouch. *In vitro,* this compound has exhibited properties of leukocyte degranulation and also inhibition of myeloperoxidase enzyme activity [6]. This drug is a white crystal solid with coconut-like odor.

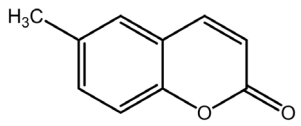

Figure 1. Molecular structure of 6-methylcoumarin.

As most anti-inflammatory drugs, 6-methylcoumarin has low solubility in aqueous solution not only in physiological media but also in those relevant to the development and assessment of pharmaceutical dosage forms [7]. For this reason, in order to develop an oral solid dosage form of 6-methylcoumarin, dissolution profiles at pH 1.2, 6.8, and 7.4 should be performed and

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its necessary guaranteed sink conditions in every dissolution media.

Despite the *in vitro* or *in vivo* dissolution of drugs contained in solid dosage forms is a kinetic process, it depends strongly on the equilibrium solubility in the aqueous media under consideration [8]. Therefore, the main objective of this study was to evaluate the effect of pH on aqueous solubility of 6-methylcoumarin and on its respective solution thermodynamics in USP buffers of pH 1.2, 6.8 and 7.4. The analysis was based on van't Hoff method, including the respective contributions by the mixing of the hypothetically melted drug with the solvent during the dissolution processes. This investigation expands the concepts developed previously in our research groups about the solubility of the more classical analgesic drugs naproxen and ibuprofen [9,10].

MATERIALS AND METHODS

Reagents

6-Methylcoumarin (Sigma-Aldrich, U.S.A.), potassium chloride (Scharlau, Spain), potassium phosphate monobasic (Scharlau, Spain), hydrochloric acid (Panreac, Spain) and distilled water with conductivity lower than 2 µS/cm were used in this work.

Buffers preparation

Buffers of pH 1.2, 6.8, and 7.4 were prepared according to the specifications for dissolution media reported in the American Pharmacopeia, USP [11].

Solubility determination

An excess of 6-methylcoumarin was added to 10 mL each aqueous media (pH-metric controlled buffers of pH 1.2, 6.8, and 7.4) in dark stoppered glass flasks. Solid-liquid mixtures were placed on a mechanical stirred thermostatic bath kept at 313.15 ± 0.05 K for at least three days to reach the saturation equilibrium. This equilibrium time was established by quantifying the drug concentration up to obtain a constant value, as indicated as follows. After this time the supernatant solutions were filtered (Millipore Corp. Swinnex®-13 filter units, U.S.A.) at isothermal conditions to ensure that they were free of particulate matter before sampling. Drug concentrations were determined by measuring absorbance after appropriate aqueous dilution and interpolation from previously constructed UV spectrophotometry calibration curves at λ_{max} = 275 nm for 6-methylcoumarin at pH 1.2, 6.8, and 7.4 (UV/VIS Optimus spectrophotometer). After the procedure already described the temperature was decreased in 5.0 K and therefore, it was stabilized in 308.15 K during at least one day allowing the precipitation of the drug dissolved in excess and analyzing the drug concentration in equilibrium. This procedure was repeated decreasing temperature in 5.0 K up to reach 293.15 K. All the solubility experiments were run at least in triplicate. In order to make the equivalence between molarity and mole fraction concentration scales, the density of the saturated solutions was determined with a digital density meter (DMA 45 Anton Paar) connected to recirculating thermostatic baths (Neslab RTE 10 Digital One Thermo Electron Company) according to procedures used in the literature [12].

Calorimetric study

Melting point and enthalpy of fusion of 6-methylcoumarin were determined by DSC studies (Shimadzu DSC-60). Thermal analysis was performed in a sealed aluminum pan at a heating rate of 10 K/min in a dynamic nitrogen atmosphere (50 cm^3/min). Nearly 2.0 mg of drug was used. The equipment was calibrated using Indium as standard [13].

RESULTS AND DISCUSSION

6-Methylcoumarin is a cyclic lactone (Fig. 1), and therefore, it acts in solution mainly as a Lewis base in order to establish hydrogen bonds with the proton-donor groups present in water; on the other hand, it could also interact by the weak London forces due to its non-polar groups [14]. On the other hand, it is also important to consider that this drug has not ionizable groups, just in opposite way to naproxen and ibuprofen, which were studied previously in similar pH conditions, and that exhibit acidic behavior due to their carboxylic acid groups. Therefore, no dissociation is expected for 6-methylcoumarin with the pH variation in aqueous media.

Ideal solubility

The ideal solubility of a crystalline solute is calculated by Eq. [**1**]:

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

where X_2^{id} is the ideal solubility of the solute as mole fraction, $\Delta_{fus}H$ 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 universal gas constant (8.314 J/mol.K), and ΔC_p is the difference between the molar heat capacity of the

x_2^{id}				
293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.346	0.387	0.432	0.482	0.536

Table 1. Ideal solubility of 6-methylcoumarin at several temperatures.

crystalline form and the molar heat capacity of the hypothetical supercooled liquid form, both at the solution temperature [1]. Since ΔC_p cannot be easily determined, in this investigation is assumed that ΔC_p may be approximated to the entropy of fusion ($\Delta_{fus}S$). The experimental calorimetric values obtained were: T_{fus} = 344.1 K and $\Delta_{fus}H$ = 18.95 kJ/mol.

Table 1 summarizes the ideal solubility of 6-methylcoumarin at all temperatures considered. Ideal solubilities are relatively high (greater than 0.35) if they are compared with the ones reported for any other anti-inflammatory drugs where values from 1 x 10^{-2} to 1 x 10^{-3} are commonly found, *i.e.* 1.479 x 10^{-2} for piroxicam [15], 1.684 x 10^{-2} for indomethacin [16], 4.098 x 10^{-2} for naproxen [9], 5.989 x 10^{-2} for acetaminophen [1], and 3.079 x 10^{-3} for meloxicam [17]. This is because 6-methylcoumarin exhibits low values of melting point and enthalpy of fusion in comparison with all these drugs, just as it also happens with the other analgesic drugs ibuprofen and ketoprofen. For this reason, the ideal solubilities of these two drugs are also high, *i.e.* 0.2607 for ibuprofen [10] and 0.2392 for ketoprofen [18].

Experimental solubility

Table 2 summarizes the experimental solubilities of 6-methylcoumarin, expressed as molarities and mole fractions at pH 1.2, 6.8, and 7.4. According to this table, the drug solubility increases with the temperature but this property is apparently invariant with pH. For this reason a two-way analysis of variance (ANOVA) was made by comparing the solubility obtained in different pH values media at five temperatures [19]. Thus, Tables 3 and 4 show the ANOVA results, where some differences are observed and therefore the pH affects in some extent the solubility of 6-methylcoumarin in these aqueous media.

In order to make comparisons among the aqueous solubilities of 6-methylcoumarin and

pH	10^3 Mol/L				
	293.15 K	**298.15 K**	**303.15 K**	**308.15 K**	**313.15 K**
1.2	2.82 (0.03)	3.56 (0.07)	3.99 (0.03)	4.74 (0.03)	6.02 (0.08)
6.8	2.90 (0.05)	3.52 (0.07)	4.29 (0.04)	4.94 (0.02)	5.91 (0.06)
7.4	3.00 (0.06)	3.55 (0.01)	4.10 (0.11)	4.86 (0.03)	5.85 (0.13)
pH	$10^5 x_2$				
	293.15 K	**298.15 K**	**303.15 K**	**308.15 K**	**313.15 K**
1.2	5.08 (0.05)	6.41 (0.12)	7.19 (0.05)	8.53 (0.06)	10.84 (0.14)
6.8	5.22 (0.09)	6.33 (0.12)	7.72 (0.07)	8.89 (0.04)	10.64 (0.11)
7.4	5.40 (0.12)	6.38 (0.01)	7.38 (0.21)	8.73 (0.06)	10.51 (0.24)

Table 2. Experimental solubility of 6-methylcoumarin in aqueous media at pH 1.2, 6.8, and 7.4, expressed in molarity and mole fraction at several temperatures.

Source of variation	% of total variation	P value	P value summary	Significant?	DF	Sum-of-squares	Mean square	F
Interaction	0.47	< 0.0001	***	Yes	8	2.36 E-7	2.95 E-8	7.092
Column Factor	0.13	0.0022	**	Yes	2	6.28 E-8	3.14 E-8	7.552
Row Factor	99.15	< 0.0001	***	Yes	4	4.93 E-5	1.23 E-5	2961

Table 3. Statistical analysis of the solubility of 6-methylcoumarin at several pH values. Two-ways ANOVA *p < 0.05; ** p < 0.01; *** p < 0.001.

Row Factor	Difference	95% CI of diff.	t	P value	Summary
		pH 1.2 *vs.* pH 6.8			
293.15	8.64 E-5	-8.15 E-5 to 2.54 E-4	1.641	P > 0.05	ns
298.15	-3.44 E-5	-2.02 E-4 to 1.34 E-4	0.653	P > 0.05	ns
303.15	2.99 E-4	1.31 E-4 to 4.67 E-4	5.681	P < 0.001	***
308.15	2.08 E-4	3.97 E-5 to 3.76 E-4	3.943	P < 0.01	**
313.15	-1.02 E-4	-2.69 E-4 to 6.64 E-5	1.928	P > 0.05	ns
		pH 1.2 *vs.* pH 7.4			
293.15	1.85 E-4	1.70 E-5 to 3.53 E-4	3.511	P < 0.01	**
298.15	-7.46 E-6	-1.75 E-4 to 1.60 E-4	0.142	P > 0.05	ns
303.15	1.14 E-4	-5.38 E-5 to 2.82 E-4	2.168	P > 0.05	ns
308.15	1.20 E-4	-4.76 E-5 to 2.88 E-4	2.284	P > 0.05	ns
313.15	-1.69 E-4	-3.37 E-4 to -1.28 E-6	3.213	P < 0.05	*
		pH 6.8 *vs.* pH 7.4			
293.15	9.85 E-5	-6.94 E-5 to 2.66 E-4	1.870	P > 0.05	ns
298.15	2.69 E-5	-1.41 E-4 to 1.95 E-4	0.511	P > 0.05	ns
303.15	-1.85 E-4	-3.53 E-4 to -1.71 E-5	3.514	P < 0.01	**
308.15	-8.74 E-5	-2.55 E-4 to 8.06 E-5	1.659	P > 0.05	ns
313.15	-6.77 E-5	-2.36 E-4 to 1.00 E-4	1.285	P > 0.05	ns

Table 4. Effect of the pH and temperature on the solubility of 6-methylcoumarin in aqueous media. *p < 0.05; ** p < 0.01; *** p < 0.001; Bonferroni test.

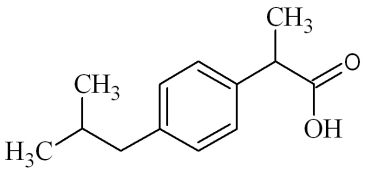

Figure 2. Molecular structure of ibuprofen.

other anti-inflammatory drug studied on similar experimental pH conditions and with similar ideal solubilities, according to the literature, the only available drug is ibuprofen (Fig. 2) [9]. Nevertheless, because the solubility of ibuprofen is pH dependent due to its dissociation in alkaline media, the comparison is made only at pH 1.2 where the non-dissociate form predominates [9]. In this way, at 298.15 K the solubilities in mole fraction are 6.41 x 10^{-5} and 4.53 x 10^{-6} for 6-methylcoumarin and ibuprofen, respectively. Thus, there is a difference of almost one order of magnitude, and therefore, this big difference should be due to different solvent-solute and/or solvent-solvent interactions since both drugs have similar solute-solute interactions as it is indicated by the ideal solubilities.

Solubility parameter

Hildebrand solubility parameter is a polarity index widely used to describe a lot of pharmaceutical physicochemical events and phenomena, including drugs solubility as the most studied [20]. According to the literature, this polarity index is useful for solutes and solvents, and therefore, the smaller the difference of the solubility parameters between solute and solvent is, the higher the solubility of the solute in the solvent is [14,20]. Hildebrand solubility parameter (δ) is calculated as indicated in Eq. [**2**]:

$$\delta = \left(\frac{\Delta_{vap} H^\circ - RT}{V_{liq}} \right)^{1/2} \qquad [\mathbf{2}]$$

where $\Delta_{vap}H^\circ$ and V_{liq} are the standard enthalpy of vaporization and the molar volume of the liquid considered, respectively. Although the Hildebrand solubility parameter as polarity index was originally developed for non-polar solutes and solvents, its use has been extended to include several aqueous systems [20]. Nevertheless, for solid compounds the Eq. [**2**] is not applicable and therefore some theoretical methods of estimation of δ are widely used in the literature [20]. In this way, Fedors method [21] is based on groups' contribution and it is the most widely used for pharmaceutical purposes [22]. For this reason, Tables 5 and 6 show the solubility parameters for 6-methylcoumarin and ibuprofen, *i.e.* 22.4 and 20.9 $MPa^{1/2}$, respectively. The δ value for water is 47.9 $MPa^{1/2}$, so, the δ difference

Group or atom	Quantity	ΔU (kJ/mol)	V (cm^3/mol)
$-CH_3$	1	4.71	33.5
–CH=	2	2 x 4.31 = 8.62	2 x 13.5 = 27.0
Trisubstituted phenyl	1	31.9	33.4
–COO–	1	18.0	18.0
Ring closure	1	1.05	16.0
		ΔU_{total} = 64.28	V_{total} = 127.9
		$\delta_{total} = (64{,}280/127.9)^{1/2}$ = 22.4 MPa$^{1/2}$	

Table 5. Application of the group contribution method of Fedors for estimate interne energy, molar volume, and total Hildebrand solubility parameter of 6-methylcoumarin.

Group or atom	Quantity	ΔU (kJ/mol)	V (cm^3/mol)
$-CH_3$	3	3 x 4.71 = 14.13	3 x 33.5 = 100.5
$-CH_2-$	1	4.94	16.1
>CH–	2	2 x 3.43 = 6.86	2 x –1.0 = –2.0
Phenylene (p)	1	31.9	52.4
–COOH	1	27.6	28.5
		ΔU_{total} = 85.43	V_{total} = 195.5
		$\delta_{total} = (85{,}430/195.5)^{1/2}$ = 20.9 MPa$^{1/2}$	

Table 6. Application of the group contribution method of Fedors for estimate interne energy, molar volume, and total Hildebrand solubility parameter of ibuprofen.

between solvent and solute with 6-methylcoumarin is lower than with ibuprofen. Thus, this could explain in some way the greater solubility of 6-methylcoumarin in water at pH 1.2 with respect to ibuprofen.

Activity coefficients

The big difference obtained between ideal and experimental solubilities in aqueous media is a consequence of the deviations presented by 6-methylcoumarin with respect to the ideal behavior. One descriptor of these deviations is the drug activity coefficient (γ_2), which is calculated as X_2^{id} / X_2 [1]. γ_2 values at all pH values studied are presented in Table 7. From these values a rough estimate of solute-solvent intermolecular interactions can be made by considering Eq. [**3**]:

$$\ln \gamma_2 = (w_{11} + w_{22} - 2w_{12}) \frac{V_2 \phi_1^2}{RT} \qquad [3]$$

where w_{11}, w_{22} and w_{12} represent the water-water, 6-methylcoumarin-6-methylcoumarin and water-6-methylcoumarin 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. Because the drug solubility is too low the term ($V_2\phi_1^2$ /*RT*) is constant at the same temperature, and therefore γ_2 depends almost exclusively on w_{11}, w_{22} and w_{12} [23]. The w_{11} and w_{22} terms are unfavorable for

pH	γ_2				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
1.2	6822	6046	6015	5649	4946
6.8	6631	6116	5605	5420	5040
7.4	6418	6074	5862	5522	5102

Table 7. Activity coefficients of 6-methylcoumarin in aqueous media at pH 1.2, 6.8, and 7.4, at several temperatures.

solubility, while the w_{12} term favors the aqueous solution process of 6-methylcoumarin. The term w_{11} is high for water (δ = 47.9 MPa$^{1/2}$) [22]. On the other hand, the term w_{22} is relatively low for 6-methylcoumarin based on the low values obtained for T_{fus} and $\Delta_{fus}H$ values. For these reasons, w_{12} would be low in order to obtain high γ_2 values such as those presented in Table 7. According to this table, γ_2 values for 6-methylcoumarin are near to 6 x 10^4 indicating clearly non ideal behavior of this drug in water. These values are different with respect to the ones reported for ibuprofen at pH 1.2 (near to 6 x 10^5) because of the big difference in experimental solubilities [10].

Thermodynamic functions of solution

According to the literature, weighted graphs based on the variation of the natural logarithm of solubility as a function of reciprocal absolute temperature allows to obtain the apparent enthalpic change of solution ($\Delta_{soln}H°$) through the classical van't Hoff equation if the drug solubility is relatively low, as it occur in the case of 6-methylcoumarin in these aqueous media (Table 2). Nevertheless, in more recent treatments, the mean harmonic temperature (T_{hm}) has been introduced into the van't Hoff equation in order to facilitate the regression treatment of solubility values [24]. When temperature intervals from 293.15 K to 313.15 K (varying in 5.00 K) are evaluated the T_{hm} value obtained is just 303.0 K [25]. Thus the modified expression can be written as follows (Eq. [**4**]):

$$\left(\frac{\partial \ln X_2}{\partial\left(1/T - 1/T_{hm}\right)}\right)_p = -\frac{\Delta_{soln}H°}{R} \qquad [4]$$

Fig. 3 shows the modified van't Hoff plots for 6-methylcoumarin in aqueous media at all pH values. Linear models with good determination coefficients were obtained in both systems studied as it is shown in Table 8. For this reason, the Eq. [**4**] is useful to estimate the $\Delta_{soln}H°$ values.

The standard Gibbs energy change for the solution process ($\Delta_{soln}G°$) has been traditionally

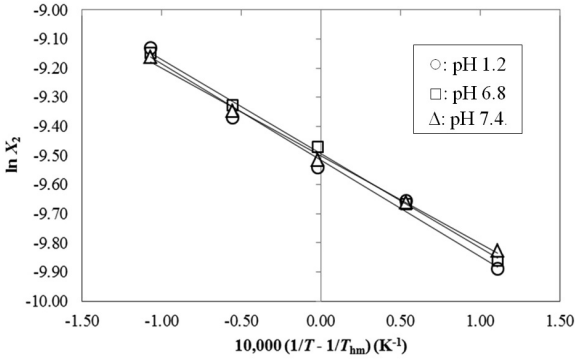

Figure 3. Van't Hoff plot of the 6-methylcoumarin solubility at several pH values.

calculated in literature as: $-RT\ 1nX_2$ [26,27]. Nevertheless considering the approach proposed by Krug *et al.* [24] this property is more appropriately calculated by means of Eq. [**5**]:

$$\Delta_{soln}G° - RT_{hm} \times \text{intercept} \qquad [5]$$

in which, the intercept used is the one obtained from ln X_2 *vs.* 1/T – 1/T_{hm} plots (Fig. 3).

The standard entropic change for solution process ($\Delta_{soln}S°$) is obtained from the respective $\Delta_{soln}H°$ and $\Delta_{soln}G°$ values by using Eq. [**6**]:

$$\Delta_{soln}S° = \frac{\left(\Delta_{soln}H° - \Delta_{soln}G°\right)}{T_{hm}} \qquad [6]$$

Table 9 summarizes the apparent standard thermodynamic functions for experimental solution process of 6-methylcoumarin in all aqueous media, including the ones relative to the ideal process. In order to calculate the thermodynamic magnitudes of experimental dissolution processes some methods for estimating propagation of errors were used [28,29]. It is found that the standard Gibbs energy of solution is positive in all cases; *i.e.,* the solution process apparently is not spontaneous, which may be explained in terms of the concentration scale used (mole fraction), where the reference state is the ideal solution having the unit as concentration of 6-methylcoumarin, that is, the solid pure solute. It is important to note that real thermodynamic

pH	Intercept	Slope	Adjusted r^2	Typical error	*N*
1.2	-9.516 (0.009)	-3309 (115)	0.9833	0.0344	15
6.8	-9.494 (0.004)	-3237 (54)	0.9961	0.0162	15
7.4	-9.501 (0.006)	-3021 (73)	0.9918	0.0219	15

Table 8. Some statistical parameters of the linear regression analysis in modified van't Hoff plots of 6-methylcoumarin solubility at pH 1.2, 6.8, and 7.4.

pH	$\Delta_{soln}G°$ / kJ/mol	$\Delta_{soln}H°$ / kJ/mol	$\Delta_{soln}S°$ / J/mol.K	$T\Delta_{soln}S°$ / kJ/mol	$\%\xi_H$ [a]	$\%\xi_{TS}$ [a]
1.2	24.0 (0.3)	27.5 (1.0)	11.7 (0.4)	3.54 (0.13)	88.6	11.4
6.8	23.9 (0.3)	26.9 (0.5)	9.9 (0.2)	3.00 (0.06)	90.0	10.0
7.4	23.9 (0.4)	25.1 (0.6)	3.9 (0.1)	1.18 (0.03)	95.5	4.5
Ideal	0.29	16.7	54.1	16.4	50.4	49.6

Table 9. Thermodynamic quantities relative to solution processes of 6-methylcoumarin in aqueous media at pH 1.2, 6.8, and 7.4, including ideal process at 303.0 K. [a] $\%\xi_H$ and $\%\xi_{TS}$ are the relative contributions by enthalpy and entropy toward Gibbs energy of solution. These values were calculated by means of Eqs. [**8**] and [**9**], respectively.

function indicating the spontaneity of the solution process is the reduction of Gibbs energy ($\Delta_{soln}G$), according with Eq. [**7**]:

$$\Delta_{soln}G = \Delta_{soln}G° + RT \ln X_2 \quad [7]$$

The enthalpy and entropy of solution is positive at all pH values, and therefore the process is always endothermic and driven by the entropy. $\Delta_{soln}H°$ and $\Delta_{soln}S°$ diminish as the pH increases but the reasons for these behaviors are not clear by considering that the molecular structure of this drug does not change with the pH due to the lack of dissociable groups. On the other hand, with the aim to compare the relative contributions by enthalpy ($\%\xi_H$) and by entropy ($\%\xi_{TS}$) toward the solution process, Eqs. [**8**] and [**9**] were employed, respectively [30].

$$\%\zeta_H = 100\frac{|\Delta_{soln}H°|}{|\Delta_{soln}H°| + |T\Delta_{soln}S°|} \quad [8]$$

$$\%\zeta_{TS} = 100\frac{|T\Delta_{soln}S°|}{|\Delta_{soln}H°| + |T\Delta_{soln}S°|} \quad [9]$$

Table 9 shows that the main contributor to standard Gibbs energy of experimental dissolution processes of 6-methylcoumarin at all pH values is the enthalpy ($\%\xi_H > 88\%$), whereas for the respective ideal solution process the contribution is almost equivalent for enthalpy and entropy. On the other hand, the enthalpy contribution increases as the pH increases. Otherwise, a notorious difference with respect to ibuprofen behavior at pH 1.2 is observed ($\%\xi_H = 64\%$) although the reasons are not clear [10].

Thermodynamic functions of mixing

The solution process may be represented by the following hypothetic stages [17]:

$$Solute_{(Solid)} \rightarrow Solute_{(Liquid)}\ at\ T_{fus} \rightarrow Solute_{(Liquid)}\ at\ T_{hm} \rightarrow Solute_{(Solution)}$$

where the solution stages are solute fusion, cooling the liquid solute to the harmonic mean temperature T_{hm} (303.0 K), and the subsequent mixing of the hypothetical super-cooled liquid solute with the solvent at this temperature. This approximation makes possible to calculate the partial thermodynamic contributions to solution process by means of Eqs. [**10**] and [**11**]:

$$\Delta_{soln}H° = \Delta_{fus}H^{303} + \Delta_{mix}H° \quad [10]$$

$$\Delta_{soln}S° = \Delta_{fus}H^{303} + \Delta_{mix}S° \quad [11]$$

where $\Delta_{fus}H^{303}$ and $\Delta_{fus}S^{303}$ represent the thermodynamic functions of fusion process at harmonic temperature (303.0 K). Nevertheless, for practical purposes, $\Delta_{soln}H°\text{-id}$ and $\Delta_{soln}S°\text{-id}$ values (Table 9) were used instead of $\Delta_{fus}H^{303}$ and $\Delta_{fus}S^{303}$ as has been done previously with other drugs [9,10,15-18]. In Table 10 the thermodynamic functions of mixing of 6-methylcoumarin are summarized.

By analyzing the partial contributions by ideal solution (related to 6-methylcoumarin fusion process) and liquid mixing processes, to the enthalpy and entropy of solution, it is found that $\Delta_{soln}H°\text{-id}$ and $\Delta_{soln}S°\text{-id}$ values are positive (Table 9), but on the other hand, the contribution of the thermodynamic functions relative to mixing process toward the solution process is variable, *i.e.* $\Delta_{mix}H°$ is positive at all pH values, whereas the entropy of mixing ($\Delta_{mix}S°$) is negative in all pH values. Accordingly, the enthalpies and entropies of mixing are in general unfavorable and therefore, according to tables 9 and 10, the dissolution process of 6-methylcoumarin is driven by the overall entropy of solution in all the buffers studied.

It is important to keep in mind that the net variation in $\Delta_{soln}H°$ values results from the contribution of several kinds of interactions. Thus, the enthalpy of cavity formation is endothermic because some energy must be supplied to over-

pH	$\Delta_{mix}G°$ / kJ/mol	$\Delta_{mix}H°$ / kJ/mol	$\Delta_{mix}S°$ / J/mol.K	$T\Delta_{mix}S°$ / kJ/mol	$\%\zeta_H$ [a]	$\%\zeta_{TS}$ [a]
1.2	23.7	10.8	-42.4	-12.8	45.8	54.2
6.8	23.6	10.2	-44.2	-13.4	43.3	56.7
7.4	23.6	8.4	-50.2	-15.2	35.7	64.3

Table 10. Thermodynamic quantities relative to mixing process of 6-methylcoumarin in aqueous media at pH 1.2, 6.8, and 7.4, at 303.0 K. [a] $\%\zeta_H$ and $\%\zeta_{TS}$ are the relative contributions by enthalpy and entropy toward Gibbs energy of mixing. These values were calculated by means of equations analogous to Eqs. [**8**] and [**9**], respectively.

come the cohesive forces of the solvent. This process decreases solubility. On the other hand, in the case of non-electrolyte drugs as 6-methylcoumarin, the enthalpy of solute-solvent interaction is exothermic and it is originated mainly from the van der Waals and Lewis acid-base interactions. The structuring of water molecules around the nonpolar groups of any kind of solute (hydrophobic hydration) contributes to decrease the net heat of mixing to small or even negative values in aqueous solutions [31]. This fact is not clearly observed in the case of 6-methylcoumarin in buffers at all pH values because this property is positive (Table 10).

On the other hand, the water-structuring process also contributes to decrease the entropy of mixing, which is observed for this drug at all pH values (Table 10). As was said previously, 6-methylcoumarin could interact with water by hydrogen bonding and hydrophobic hydration around hydrocarbon moieties (Fig. 1), and these events imply an entropy diminishing [32].

CONCLUSIONS

Based on all topics already discussed, in special those regarding for γ_2, it could be concluded that 6-methylcoumarin exhibits non ideal behavior in all the aqueous solutions studied. On the other hand, the pH affects slightly the solubility and solution thermodynamics of this drug although the molecular reasons involved are not clear because this drug does not present dissociation in aqueous media, and therefore, the molecular structure remains constant despite the pH value. Finally, the values presented in this report expand the physicochemical information about analgesic drugs in aqueous media.

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REFERENCES

1. Jiménez, J.A. & F. Martínez (2006) *J. Braz. Chem. Soc.* **17**: 125-34.
2. Kleiner, H.E., X. Xia, J. Sonoda, J. Zhang, E. Pontius, J. Abey, *et al.* (2008) *Toxicol. Appl. Pharmacol.* **232**: 337-50.
3. Hoult, J.R.S. & M. Payá (1996) *Gen. Pharmacol. Vasc. Sys.* **27**: 713-22.
4. Torres, R., F. Faini, B. Modak, F. Urbina, C. Labbé & J. Guerrero (2006) *Phytochemistry* **67**: 984-7.
5. Wu C.-R., M.-Y. Huang, Y.-T. Lin, H.-Y. Ju & H. Ching (2007) *Food Chem.* **104**: 1464-71.
6. Vergel-Blanco, N.E. (2010) *"Estudio de la actividad anticonvulsivante de metabolitos secundarios tipo cumarina",* Ph.D. Thesis, Universidad Nacional de Colombia, Bogotá D.C.
7. Budavari, S., M.J. O'Neil, A. Smith, P.E. Heckelman, J.R. Obenchain Jr, J.A.R. Gallipeau, *et al.* (2001) *"The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals",* 13th edition, Merck & Co., Inc., Whitehouse Station, NJ.
8. Florence, A.T. & D. Atwood (1998) *"Physicochemical Principles of Pharmacy",* 3rd edition, MacMillan Press Ltd., London.
9. Mora, C.P. & F. Martínez (2006) *Phys. Chem. Liq.* **44**: 585-96.
10. Aragón, D.M., J.E. Rosas & F. Martínez (2011) *Lat. Am. J. Pharm.* **30**: 1720-7.
11. *US Pharmacopeia,* 32nd edition (2009) The United States Pharmacopeial Convention, Inc., Rockville, MD.
12. Rodríguez, G.A., D.R. Delgado, F. Martínez, M.A.A. Fakhree & A. Jouyban (2012) *J. Solution Chem.* **41**: 1477-94.
13. McCauley S.A. & H.G. Brittain (1995) "Thermal methods of analysis", in *"Physical Characterization of Pharmaceutical Solids"* (H.G. Brittain, ed.) Marcel Dekker, Inc., New York, chap. 8, pp. 223-51.
14. Martin, A., P. Bustamante & A.H.C. Chun (1993) *"Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences",* 4th edition, Lea & Febiger, Philadelphia.
15. Sotomayor, R.G., A.R. Holguín, A. Romdhani,

F. Martínez & A. Jouyban (2013) *J. Solution Chem.* **42**: 358-71.
16. Cantillo, E.A., D.R. Delgado & F. Martínez (2013) *J. Mol. Liquids* **181**: 62-7.
17. Delgado, D.R., A.R. Holguín, O.A. Almanza, F. Martínez & Y. Marcus (2011) *Fluid Phase Equilib.* **305**: 88-95.
18. Gantiva, M., A. Yurquina & F. Martínez (2010) *J. Chem. Eng. Data* **55**: 113-8.
19. Bolton S. & C. Bon (2003) *"Pharmaceutical Statistics: Practical and Clinical Applications",* 4th edition, CRC Press, New York.
20. Martin, A. & P. Bustamante (1989) *Anal. Real Acad. Farm.* **55**: 175-202.
21. Fedors, R.F. (1974) *Polymer Eng. Sci.* **14**: 147-54.
22. Barton, A.F.M. (1991) *"Handbook of Solubility Parameters and Other Cohesion Parameters",* 2nd edition, CRC Press, New York, p. 103.
23. Kristl, A. & G. Vesnaver (1995) *J. Chem. Soc. Faraday Trans.* **91**: 995-8.
24. Krug, R.R., W.G. Hunter & R.A. Grieger (1976) *J. Phys. Chem.* **80**: 2341-51.
25. Bustamante, P., S. Romero, A. Peña, B. Escalera & A. Reillo (1998) *J. Pharm. Sci.* **87**: 1590-6.
26. Martínez, F. & A. Gómez (2001) *J. Solution Chem.* **30**: 909-23.
27. Garzón, L.C. & F. Martínez (2004) *J. Solution Chem.* **33**: 1379-95.
28. Bevington, P.R. (1969) *"Data Reduction and Error Analysis for the Physical Sciences",* McGraw-Hill Book Co., New York, pp. 56-65.
29. Barrante, J.R. (1998) *"Applied Mathematics for Physical Chemistry",* 2nd edition, Prentice Hall, New Jersey, pp. 179-91.
30. Perlovich, G.L., S. V. Kurkov & A. Bauer-Brandl (2003) *Eur. J. Pharm. Sci.* **19**: 423-32.
31. Romero, S., A. Reillo, B. Escalera & P. Bustamante (1996) *Chem. Pharm. Bull.* **44**: 1061-4.
32. Yalkowsky, S.H. (1999) *"Solubility and Solubilization in Aqueous Media",* American Chemical Society and Oxford University Press, New York.