Transfer Thermodynamics of Triclosan from Water to Organic Solvents with Different Hydrogen Bonding Capability

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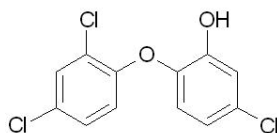
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SUMMARY. The thermodynamic functions Gibbs energy, enthalpy and entropy for the dissolution and mixing processes of triclosan (TS) in water are presented. These quantities were calculated by means of the van't Hoff and Gibbs equations from solubility values determined at temperatures ranging between 293.15 and 313.15 K. In addition, the corresponding thermodynamic quantities of the drug transfer processes from water to different organic solvents displaying different hydrogen bonding capability were also calculated. In all the evaluated cases, Gibbs energy of transfer comprised negative values, indicating the preference of TS for all the organic media evaluated. Nevertheless, enthalpy and entropy of transfer assumed positive or negative values according to every specific system. It was clear that hydrogen bonding plays a significant role in the dissolution and transfer processes of this antibacterial agent.

INTRODUCTION

Triclosan (TS, 5-chloro-2-(2,4-dichlorophe-noxi)-phenol, 289.55 g.mol⁻¹, Fig. 1), is a potent synthetic bactericide and fungicide agent with notable chemical stability and persistent activity [1]. The accepted mechanism of antimicrobial action is the diffusion across the cytoplasm and the inhibition of the synthesis of RNA, lipids and proteins [2]. Other studies, suggested that TS effectively inhibits enzymes involved in the metabolism of lipids of *Escherichia coli* [3,4]. Due to these features, TS has been extensively used along the years in a diversity of topical applications [2]. In 1997 it was approved by the FDA for use in oral care products such as toothpastes and its application gained even more impact with the development of mouthwashes and oth-er formulations for plaque prevention and control of periodontal disease [5-7]. In 2003, Ethicon Inc. has introduced poly(lactic-glycolic acid) biodegradable surgical sutures coated with TS (Vicryl® Plus) [8].

One important limitation in the development of TS-loaded topical products is the poor aqueous solubility of the drug [9]. This behavior stems from its high hydrophobicity. On the other hand, the presence of one aromatic –OH group that is ionizable at pH > [10] enables better solubilization under alkaline pH conditions. However, such alkalinity is incompatible with the vast majority of pharmaceutical applications. Several approaches were investigated in order to improve the apparent solubility of TS in neutral aqueous medium. Some investigators designed complexes with β-cyclodextrins and studied the effect of ionization and polymers nature on the formation of aggregates and higher-order complexes [10-12]. Grove *et al.* investigated other molecular complexes, micelles and the *in situ* formation of organic salts [13]; finding showed that the solubilizers studied increased the solubility of TS from

Figure 1. Molecular structure of triclosan.

80- to 6000-fold; furthermore, although the bacteriostatic efficacy of TS was significantly increased when solubilized with N-methylglucamine, L-arginine, and ethanolamine, increased solubilization did not increase the effectiveness of TS for all solubilizers tested [13]. Maestrelli *et al.* developed chitosan-hydroxypropylcyclodextrin nanocarriers and investigated the water-solubilization of TS [14]; findings showed a 20-fold increase in the solubility of the drug [14]. In another work, Steinberg *et al.* [15] reported on the development of ethylcellulose TS-containing buccal patches for sustained release of the drug; the device effectively released TS following a Higuchi model and affected the viability of *Streptococcus mutans,* a frequent pathogen in periodontal disease.

More recently, we evaluated the solubilization of TS by means of inclusion into poloxamine (a four-arms poly(ethylene oxide)-poly(propylene oxide) block copolymer) polymeric micelles in a broad range of pH values and polymer concentrations [16,17]. Apparent solubility values increase up to 4 orders of magnitude. Moreover, the hydrogen bonding ability played a central role in the drug-nanocarrier interaction. Thus, ionized TS (at pH ~12) displayed a weaker affinity for the micelle and this phenomenon rendered lower solubilization extents when compared to lower pH values [16,17]. More importantly, TS-loaded systems showed antibacterial activity *in vitro* against a broad spectrum of pathogens, including two representative clinical pathogens: methicilin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis.* Finally, the activity was assessed on biofilms of *Staphylococcus epidermidis* a bacterium highly recurrent in biomaterial-centered infections (BCI), with encouraging results [17].

On the other hand, it has well described that the profuse use of this agent has raised important environmental concerns due to its accumulation in wastewater streams [18,19]. As in the case of pre-formulation and formulation process of pharmaceutical dosage forms, toxicity to aquatic life and appearance in drinking water is directly related to its solubility in water.

The fundamental aspects of the aqueous dissolution and transfer processes of this drug from water to organic solvents (e.g., thermodynamic quantities) were not thoroughly investigated. In this context, the present work studied the TS solution thermodynamics in water and the thermodynamics of transfer from water to several model organic solvents with different hydrogen capability used for Quantitative Structure-Activity Relationships (QSAR) studies. The goal of the present work was to present a more complete and systematic insight on the properties of dissolution and transfer for this drug. The TS solubility in water was determined at temperatures ranging between 293.15 and 313.15 K. From these values, the thermodynamic quantities of aqueous solution were calculated by means of van't Hoff and Gibbs equations. Moreover, thermodynamic quantities of transfer to octanol (ROH), isopropyl myristate (IPM), chloroform (CLF), and heptane (HPT), were also calculated based on solution thermodynamics values reported in the literature [20]. Octanol has been used as standard organic medium for partition experiments in the development of QSAR studies, because the octanol-water partition coefficient (log P) is an important parameter for modeling biological membranes and predicting the fate, transport and distribution of drugs [21]. Isopropyl myristate is best related to skin/transdermal absorption because its polar and nonpolar nature mimics the complex nature (semipolar matrix) of the skin [22,23]. Chloroform is an organic solvent acting mainly as hydrogen donor in establishing hydrogen bonds. Heptane is a lipophilic hydrocarbon solvent, purely nonpolar, interacting by London forces, enabling the evaluation of solute-solvent non-specific interactions [24].

MATERIAL AND METHODS
Materials
In this investigation the following reagents and materials were used: triclosan was a kind gift of Ciba C.S. (Bogotá, Colombia); distilled water, conductivity < 2 µS cm⁻¹; Millipore Corp. Millex®-13 mm filters.

Aqueous solubility determinations
TS was added in excess to water (20 cm³) in dark flasks. The solid–liquid mixtures were then stirred in a mechanical shaker (Wrist Action, Burrel, model 75), for 1 h. Samples were then allowed to stand in water baths (Magni Whirl Blue M. Electric Company) kept at all temperatures studied for at least 7 days to reach the equilibrium (this equilibrium time was established by quantifying the drug concentration until a constant value was obtained). Once at equilibrium, supernatant solutions were filtered (at isothermal conditions) in order to remove insoluble particles before analysis. Drug concentrations were determined by measuring the ab-

sorbance followed by the interpolation in a UV calibration curve for TS (UV/VIS BioMate 3 Thermo Electron Company) at 283 nm. In order to allow the conversion between volumetric and gravimetric 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) [25] obtaining density values equal to neat water at all temperatures. All experiments were made at least three times and averaged.

RESULTS AND DISCUSSION

It is important to consider that due to the presence of phenolic –OH groups, TS behaves in solution mainly as a Lewis acid and can establish hydrogen bonds with proton-acceptor functional groups present in the aqueous and organic solvents (particularly, free electron pairs in oxygen atoms present in –OH and >C=O groups) [20].

Ideal and Experimental Aqueous Solubility of TS

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

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

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 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 [26]. Since the experimental determination of ΔC_{p} is difficult, its value is usually approximated to the entropy of fusion, ΔS_{fus} (calculated as $\Delta H_{\mathrm{fus}}/T_{\mathrm{fus}}$), and thus, this treatment was made in this work.

Table 1 summarizes the aqueous experimental solubility values of TS, expressed in molarity

and mole fraction, in addition to the ideal solubility calculated by means of Eq. [**1**] from values reported by Veiga *et al.* (ΔH_{fus} = 17.75 kJ mol⁻¹ and T_{fus} = 331.1 K) [27]. In general, the coefficient of variation for experimental solubility determinations was smaller than 1.5 %.

Our aqueous solubility values are in agreement with those reported by Raghavan *et al.* at 298.15 K (3.80 × 10⁻⁵ mol L⁻¹, 33% lower) [28] and by Yalkowsky & Le [29] at 293.15 K (3.454 × 10⁻⁵ mol L⁻¹, 20% lower), whereas they are not concordant with that reported by Loftson & Hreinsdórrir [30] at room temperature (1.7 × 10⁻⁴ mol L⁻¹, almost six-fold lower). It is possible that the little discrepancies found with respect to the first two research groups may be attributed to the different analytical methodologies employed in the studies. According to Jouyban, the possible reasons for such differences in solubilities reported by different authors arise from: 1) solute purity, 2) equilibration time, 3) temperature, 4) analysis method, 5) laboratory technique, 6) typographical error, 7) polymorphism, and 8) enantiomeric forms [31]; nevertheless, in the present case the main reasons for the discrepancies found are unclear.

TS Activity Coefficients

The solute activity coefficient in the solution (γ_2) is calculated as X_2^{id} / X_2 and it is an indication of the deviation presented by TS from its ideal behavior [32]. Table 1 also shows the aqueous TS activity coefficients. From the γ_2 values an approximate estimation of solute-solvent intermolecular interactions can be made by considering the Eq. [**2**]:

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

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 $(V_2\phi_1^2RT)_{T,P}$ may be con-

Temp. / K	10^5 Mol L⁻¹	$10^7 X_2$	X_2^{id}	$10^{-5} \gamma_2$
293.15	2.32 (0.04)	4.20 (0.07)	0.4565	10.88
298.15	2.860 (0.014)	5.168 (0.025)	0.5091	9.85
303.15	3.734 (0.014)	6.755 (0.025)	0.5668	8.39
308.15	4.55 (0.05)	8.24 (0.07)	0.6299	7.64
313.15	5.37 (0.06)	9.74 (0.11)	0.6987	7.17

Table 1. Experimental solubility of triclosan in water expressed in molarity and mole fraction including ideal solubility and drug activity coefficients at several temperatures.

sidered approximately constant at the same temperature, and then γ_2 depends almost exclusively on w_{11}, w_{22} and w_{12}. While the term w_{12} favors the solution process, both w_{11} and w_{22} terms are unfavorable for solubility [33]. The contribution of w_{22} represents the work necessary to transfer drug molecules from the solid to the vapor state and, therefore, it is constant at all the temperatures studied. By comparing γ_2 showed in Table 1 with those determined in organic solvents (CLF = 1.23, IPM = 10.7, ROH = 20.4 and HPT = 17.8 at 298.15 K) [20], it is clear that the term w_{12} in water is the lowest among all the solvents. Conversely, w_{11} in water is the strongest among all the solvents considered in this study (because it is the most polar solvent), which leads to γ_2 values near to 10^6 at the same temperature.

Thermodynamic Functions of TS Aqueous Solution

According to van't Hoff analysis, the apparent standard enthalpy change of solution is obtained from the slope of the respective ln X_2 vs. $1/T$ plot. Nevertheless, in several 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 generated by statistical treatments used when enthalpy-entropy compensation analyses are carried out. For this reason, the mean harmonic temperature (T_{hm}) is used in van't Hoff analysis. T_{hm} is calculated as:

$$n / \sum_{i=1}^{n} (1/T)$$

where n is the number of temperatures studied [34]. In the present case the T_{hm} value obtained is just 303 K. The modified expression more widely used is the Eq. [3] [35],

$$\left(\frac{\partial \ln X_2}{\partial \left(1/T - 1/T_{hm} \right)} \right)_P = -\frac{\Delta H^0_{soln}}{R} \qquad [3]$$

Figure 2 shows the modified van't Hoff plot for TS solubility in pure water where a linear model with good determination coefficient was obtained.

The apparent standard Gibbs energy change for the solution process (ΔG^0_{soln}), considering the approach proposed by Krug et al. [34] is calculated by means of Eq. [4]:

$$\Delta G^0_{soln} = RT_{hm} \times \text{intercept} \qquad [4]$$
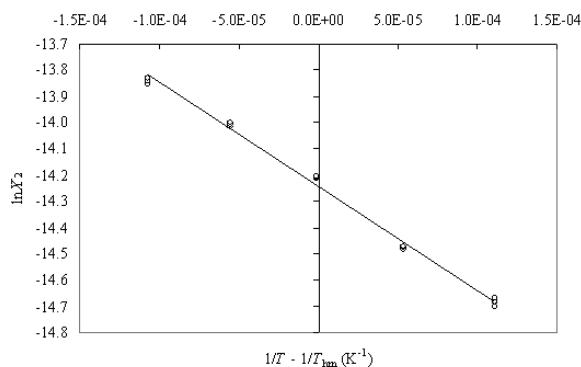
Figure 2. Van't Hoff plot of the aqueous solubility of triclosan expressed in mole fraction. The linear model obtained is: ln X_2 = -14.243 (± 0.006) − 3956 (± 77) $(1/T − 1/T_{hm})$, with adjusted r^2 = 0.995, typical error = 0.023, and n = 15.

in which the intercept used is that one obtained in the analysis by treatment of ln X_2 as a function of $1/T − 1/T_{hm}$. Finally, the apparent standard entropic change for solution process (ΔS^0_{soln}) is obtained from the respective ΔH^0_{soln} and ΔS^0_{soln} values by using Eq. [5]:

$$\Delta S^0_{soln} = \frac{\left(\Delta H^0_{soln} - \Delta G^0_{soln} \right)}{T_{hm}} \qquad [5]$$

Table 2 summarizes the apparent standard thermodynamic functions for experimental solution process of TS in water including those functions for the ideal process. In order to calculate these quantities some common methods to calculate propagation of uncertainties were used [36].

It is found that the standard Gibbs energy of solution and the enthalpy change of solution are positive, being the solution process thus endothermic. Thus, the entropy of solution is negative in neat water indicating neither enthalpy- nor entropy-driven solubilization.

With the aim to compare the relative contributions by enthalpy (%ζ_H) and by entropy (%ζ_{TS}) toward the solution process, Eqs. [6] and [7] were employed, respectively [37,38].

$$\%\zeta_H = 100 \cdot \frac{\left| \Delta H^0_{soln} \right|}{\left| \Delta H^0_{soln} \right| + \left| T\Delta S^0_{soln} \right|} \qquad [6]$$

$$\%\zeta_{TS} = 100 \cdot \frac{\left| T\Delta S^0_{soln} \right|}{\left| \Delta H^0_{soln} \right| + \left| T\Delta S^0_{soln} \right|} \qquad [7]$$

Process	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}	%ζ_H [a]	%ζ_{TS} [a]
Aqueous	35.9	32.9	−9.9	−2.99	91.7	8.3
Ideal	1.43	16.24	48.9	14.8	52.3	47.7

Table 2. Thermodynamic quantities for solution process of triclosan in water and for ideal process at 303 K. [a] ζ_H and %ζ_{HS} are the relative contributions by enthalpy and entropy toward Gibbs energy of solution. These values were calculated by means of equations (6) and (7), respectively.

From Table 2 it follows that the main contributor to standard Gibbs energy of solution process of TS in water is the enthalpy (%ζ_H value is greater than 91%). This result is remarkably different to those obtained in organic solvents where the enthalpy and entropy contributions were almost similar [20].

Thermodynamic Functions of Mixing

On the other hand, the drug solution process may be represented by the following hypothetic stages [39], Solute$_{(Solid)}$ → Solute$_{(Liquid)}$ → Solute$_{(Solution)}$, where the respective partial processes toward the solution are solute fusion and solute-solvent mixing at the same temperature (303 K) and they allow to calculate the partial thermodynamic contributions to the overall solution process by means of Eqs. [**8**] and [**9**], respectively.

$$\Delta H^0_{soln} = \Delta H^{303}_{fus} + \Delta H^0_{mix} \qquad [\mathbf{8}]$$

$$\Delta S^0_{soln} = \Delta S^{303}_{fus} + \Delta S^0_{mix} \qquad [\mathbf{9}]$$

ΔH^{303}_{fus} and ΔS^{303}_{fus} representing the thermodynamic functions of fusion at harmonic temperature (303 K). Thus, the ΔH^{303}_{fus} value is calculated from $\Delta H^T_{fus} = \Delta H^{MP}_{fus} − \Delta C_p (T_{fus} − T)$, using ΔH^{MP}_{fus} instead of ΔC_p, obtaining the value of

16.24 kJ mol^{-1}, which is coincident with the enthalpic change for an ideal solution process (Table 2). In contrast, the entropy of fusion at 303 K (53.6 J mol^{-1}·K^{-1}) is not coincident with the entropy of an ideal solution at this temperature (48.9 J mol^{-1} K^{-1}). Therefore, in this analysis, the ΔS^{0id}_{soln} value was used instead of ΔS^{303}_{fus}. Table 3 summarizes the thermodynamic functions of mixing determined in this investigation for TS in water and those reported in the literature for some organic solvents [20].

The partial contributions by an ideal solution (related to the solute fusion process) and mixing processes, to the enthalpy and entropy of drug solution, show that ΔH^{0id}_{soln} and ΔS^{0id}_{soln} are positive (Table 2), while the contribution of the thermodynamic functions relative to mixing process toward the solution in water process is variable, that is, ΔH^0_{mix} positive; whereas the entropy of mixing (ΔS^0_{mix}) is negative. This fact is thus interesting because in other cases, such as some analgesic drugs, mixing enthalpy and entropy values are both negative [26,39]. As a comparison, Table 3 also summarizes the results obtained for TS mixing in different organic solvents.

It is well known that the net variation in ΔH^0_{mix} values results from the contribution of several kinds of interactions. Thus, the enthalpy of cavity formation (required for solute accommodation) is endothermic because energy must

Solvent	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}	%ζ_H [a]	%ζ_{TS} [a]
Water	34.4	16.6	−58.7	−17.8	48.3	51.7
CLF	0.35	8.1	25.7	7.8	51.1	48.9
IPM	6.00	−3.3	−30.8	−9.32	26.3	73.7
ROH	5.24	117.1	369	111.9	51.2	48.8
HPT	6.52	45.0	127.0	38.5	53.9	46.1

Table 3. Thermodynamic quantities for mixing process of triclosan in water and the organic solvents under study at 303 K. [a] %ζ_H and %ζ_{TS} are the relative contributions by enthalpy and entropy toward Gibbs energy of mixing. These values were calculated by means of equations analogous to (6) and (7), respectively.

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 [40]. The structuring of water molecules around the non-polar groups of solutes (hydrophobic hydration) contributes to lower the net heat of mixing to relatively small or even negative values in aqueous solutions, but it is not the case for TS in pure water (Table 3).

Thermodynamic Quantities of Transfer of TS From Water to Organic Solvents

To contribute with the generation and systematization of the thermodynamic quantities of transfer useful in QSAR studies in medicinal and environmental chemistry, the values for the transfer of TS from water to organic solvents were calculated as the difference between the mixing functions reported for the organic solvents [20] and those obtained for aqueous media (Table 3) by means of Eq. [10], where, Ψ represents G, H or S. Findings are summarized in Table 4. It is important to note that under neutral pH the molecular form of TS without dissociation predominates and thus, the transfer of the non-dissociate drug should be considered.

$$\Delta\Psi^0_{w\rightarrow org} = \Delta\Psi^0_{mix-org} - \Delta\Psi^0_{mix-w} \qquad [10]$$

It is also important to note that, although thermodynamics of transfer is studied mainly by determining the equilibrium partition coefficients ($K_{o/w}$) [21,24], the equation [10] is often used when the experimental determination of $K_{o/w}$ values is difficult or impossible. In this context, according to Table 4 the transfer process of this drug from water to all organic solvents is spontaneous ($\Delta G^0_{w\rightarrow org} <0$), indicating the preference of TS for organic media.

In the hypothetic process of transfer of the drug from water to organic solvents, besides Gibbs energy, the enthalpic and entropic changes associated are also important and imply respectively, the energetic requirements and the molecular randomness (increase or decrease in the molecular disorder) involved in the net transfer. As is shown in Table 4, except for TS transfer to IPM, in all cases the entropic contribution is the most relevant parameter, stressing the key role of the hydrophobic effect toward these drug transfer processes. In general terms, the behavior presented in each phase, before and after the transfer process, should be considered independently. Since initially the solute is present in water, then, it is necessary to create a cavity in the organic medium in order to accommodate the solute after the transfer process. This is an endothermic event, since an energy supply is necessary to separate the organic solvent molecules. When the solute molecules are accommodated within the organic phase an amount of energy is released due to the generation of solute-organic solvent interactions. This event implies an entropy increase in this organic medium due to the liquid-liquid solute-solvent mixing process. On the other hand, the original cavities occupied by the drug in the aqueous phase have been now occupied by water molecules; this phenomenon taking place after a certain number of solute molecules have migrated from the aqueous to the organic phase up to reach the equilibrium. This event produces an energy release due to the formation of water-water interactions. However, depending on the moieties present in the molecular structure of the drug, it is also necessary to consider the possible disruption of the water structure, that is, the water molecules organized around the alkyl or aromatic groups (hydrophobic hydration). This event in particular implies an intake of energy, in addition to a local entropy increase by the separation of some water

Solvent	ΔG^0_{mix} / kJ mol^{-1} [a]	ΔH^0_{mix} / kJ mol^{-1} [a]	ΔS^0_{mix} / J mol^{-1} K^{-1} [a]	$T\Delta S^0_{mix}$ / kJ mol^{-1} [a]	%ζ_H [b]	%ζ_{TS} [b]
CLF	−34.1	−8.5	84.4	25.6	24.9	75.1
IPM	−28.4	−19.9	27.9	8.5	70.1	29.9
ROH	−29.2	100.5	427.7	129.7	43.7	56.3
HPT	−27.9	28.4	185.7	56.3	33.5	66.5

Table 4. Thermodynamic quantities for transfer of triclosan from water to organic solvents under study at 303 K. [a] These magnitudes were calculated as $\Delta\Psi^0_{w\rightarrow org} = \Delta\Psi^0_{mix-org} - \Delta\Psi^0_{mix-w}$, where Ψ is G, H or S. [b] %ζ_H and %ζ_{TS} are the relative contributions by enthalpy and entropy toward Gibbs energy of transfer. These values were calculated by means of equations analogous to (6) and (7), respectively.

molecules which originally were associated among them by hydrogen bonding [41]. Hence, it would be very important to determine experimentally the previously discussed thermodynamic quantities of transfer, by means of the determination of partition coefficients, and to confront the apparent values presented in Table 4.

It is also necessary to take in consideration here that the partitioning experiments are carried out at low drug concentrations where the solute-solute interactions are not present [24]; whereas, in the solubility analysis these interactions would be present in the organic solvents, due to the relatively high solubility values, and therefore, the thermodynamic quantities also include these interactions, in addition to solute-solvent ones.

Nevertheless, in order to clarify and understand the specific interactions presented between this drug and the aqueous and the organic solvents studied, it would be very important to dispose information about UV, IR and NMR spectral data, and DSC and dissolution calorimetric values, among others.

CONCLUSIONS

From the previously exposed analysis, in general terms it could be concluded that TS has mainly a lipophilic behavior but in turn it is not certainly a hydrophobic drug. Based on the thermodynamic quantities of transfer obtained, it is apparent that the hydrogen bonding plays an important role in the drug transfer process from water into the organic phase, and that they are too different among all the organic solvents studied. Finally, it could be said that physico-chemical values reported here would be useful for understanding the pharmaceutical behavior and performance of this drug in modern dosage forms as well as in biological and environmental media.

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