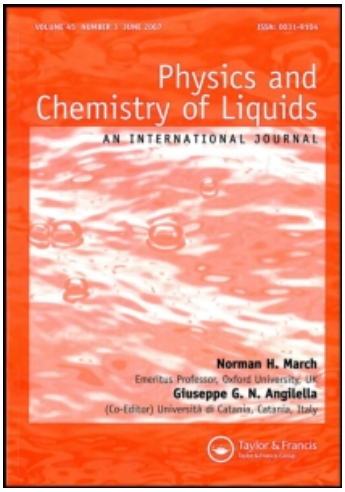

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Estimation of the Solubility of Sulfonamides in Aqueous Media from Partition Coefficients and Entropies of Fusion

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ESTIMATION OF THE SOLUBILITY OF SULFONAMIDES IN AQUEOUS MEDIA FROM PARTITION COEFFICIENTS AND ENTROPIES OF FUSION

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Semi empirical equation developed by Yalkowsky and Valvani, and another equation extended by Jain and Yalkowsky were used to estimate the aqueous solubility S_w, of some sulfonamides using experimental octanol–water partition coefficients P, entropies of fusion ΔS_f, and melting points t_m, determined by DSC measurements. The calculated solubilities were compared with those experimentally determined. When experimental ΔS_f and t_m were used, the S_w calculated values were in good agreement in most cases.

Keywords: Sulfonamides; Solubility; Partition coefficient; Yalkowsky–Valvani and Jain–Yalkowsky equations

INTRODUCTION

The effect of the aqueous solubility in the dissolution and transport of drugs is very well documented [1]. For these reasons several methods for the estimation and prediction of solubilities have been developed. These methods arise from equations that involve other physicochemical properties of solutes such as molar volumes, partition coefficients and melting temperatures [2], chromatographic retention parameters [3] as well as other methods that include calculated molecular

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properties such as molecular surface area [4], molecular volume [5] and molecular connectivity [6].

At present there are other approaches that involve neural network models [7], Monte Carlo simulations [8], and semi empirical quantum mechanical methods which make use of properties such as dipole moments, charge distribution, geometric parameters [9], and some extended linear solvation relationships (LSER) [10]. Also some applications of thermodynamics of mobile disorder [11] and extended regular solutions theory can be used [12,13].

As to the methods that include other experimental physicochemical properties of solutes, the earlier investigations were performed by Hansch *et al.* [14], who developed a basic relationship (Eq. (1)) between the molar aqueous solubility (S_w), and the octanol–water partition coefficient (P), for 156 liquid substances.

$$\log S_w = -1.339 \log P_c + 0.978 \tag{1}$$

Since almost every pharmaceutical interesting solute is solid, Yalkowsky and Valvani [1] have extended Eq. (1) including terms relative to the melting of the solute (Considering the basic model of dissolution as melting of the solute and its further mixing with the solvent [15,16]). They also demonstrated that the entropy of melting (ΔS_f), may be calculated [2,17]. Consequently they have established the relationship shown in Eq. (2).

$$\log S_w = -1.00 \log P_c - 1.11 \Delta S_f (t_m - 25)/1364 + 0.54 \tag{2}$$

The previous relationship was developed by means of multiple linear regression analysis of experimental values of S_w, calculated values of P, experimental values of ΔS_f (in entropy units: cal mole^{-1} K^{-1}), and melting temperature t_m, in °C, from 167 compounds. For rigid molecules, these authors propose a constant value of ΔS_f of 56.5 J mole^{-1} K^{-1}, and by means of regression analysis of S_w, calculate P, and t_m for 155 compounds and established Eq. (3).

$$\log S_w = -1.05 \log P_c - 0.012\, t_m + 0.87 \tag{3}$$

Equations (2) and (3) have been widely used for estimation of the aqueous solubility of some important pharmaceutical compounds

such as barbiturate derivatives with good results [18]. Nevertheless in the case of some guanine derivatives these equations do not give good results [19].

By means of a more complete thermodynamic analysis and by using data from a set of 580 pharmaceutically, environmentally, and industrially relevant compounds, Jain and Yalkowsky [20] have extended Eq. (3) to obtain Eq. (4).

$$\log S_w = -1.031 \log P_c - 0.0120\, t_m + 0.679 \tag{4}$$

The aim of this paper is to evaluate the validity of Yalkowsky–Valvani and Jain–Yalkowsky equations for the estimation of the aqueous solubility of some structurally related sulfonamides used as antiinfective agents.

EXPERIMENTAL

Materials

Sulfonamides: sulfanilamide (SA) Merck; sulfapyridine (SP), sulfadiazine (SD), sulfamerazine (SMR); sulfamethazine (SMT) Sigma Chemical Co.; sulfacetamide (SCM), sulfathiazole (STL); sulfamethoxazole (SMX) USP Quality [21]. Solvents: octanol extra pure (ROH) Merck; distilled water (W) conductivity $< 2\,\mu S$, Laboratory of Industrial Pharmacy. Others: absolute ethanol A.R. Merck; potassium chloride A.R. Merck; sodium mono and dihydrogen phosphates A.R. Merck; citric acid and sodium hydroxide A.R. Merck; sodium acetate and acetic acid A.R. Merck; indium DSC standard. Millipore Corp. Swinnex®-13 filter units.

Equipment

Magni Whirl Blue M. Electric Company water baths; Wrist Action, Burrel, model 75 mechanical shaker; Mettler AE 160 and Sartorius K200D digital analytical balances, sensitivities of 0.1 mg and 0.01 mg respectively; DMA 35 Anton Paar digital density meter; Unicam

UV–VIS UV2 – 100 v 4.00 spectrophotometer; 2910 Modulated DSC, TA Instruments differential scanning calorimeter; micro pipettes.

Methods

Calorimetric Studies

Melting points and enthalpies of fusion, in addition to purity analysis were determined by DSC. All thermal analysis measurements were performed at a heating rate of 10°C per minute in a dynamic nitrogen atmosphere (50 mL per minute). Approximately 4 mg of each sulfonamide were used. The equipment was calibrated using indium as standard [22]. All thermal analyses were carried out at least three times.

Solubility Determinations

Nearly 100 mg of each sulfonamide (an excess of substance) were added to 20 mL of solvent in glass flasks. The mixtures were then stirred in a mechanical shaker for 1 h. Samples were allowed to stand in water baths kept at 25.0 ± 0.1°C for 72 h [23]. After this time the supernatant solutions were filtered to ensure that the solutions were particulate matter free before sampling. The solution concentrations were determined by measuring UV absorbances after appropriate dilution and interpolation from previously constructed calibration curves for each sulfonamide. All solubility experiments were repeated at least three times. The density of the saturated solutions was determined by using a digital density meter according to a previously reported procedure to facilitate the conversion of the concentration scales (molarity-mole fraction) [24].

Partitioning Studies

Both solvents were mutually saturated before performing the experiments. Solutions of well known concentration, about 5×10^{-5} M of sulfonamides, were prepared in aqueous buffer solutions adjusted to the isoelectric points and pH 7.4 at ionic strength of 0.15 mole L^{-1}. Then 10.0 mL of octanol were added to 10.0 mL of the aqueous sulfonamide solution in glass flasks. The mixtures were then stirred in a mechanical

shaker for one hour. Samples were allowed to stand in water baths kept at $25.0 \pm 0.1^{\circ}C$ for at least 72 h. After this time the aqueous phases were isolated and the concentrations were determined by measuring the UV absorbances as previously described. The partition coefficients were calculated by mass balance. All the partitioning experiments were repeated at least three times.

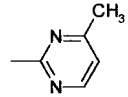
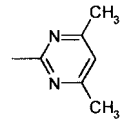
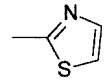
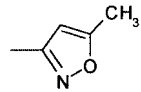
RESULTS AND DISCUSSION

The molecular structures of each sulfonamide, their abbreviations, and some of their physicochemical properties are summarized in Table I. The melting points and enthalpies of fusion were determined from DSC thermograms. The pK_{a1} and pK_{a2} were corrected to ionic strength values, $\mu = 0.15\,\text{mole}\,L^{-1}$, similar to the gastrointestinal tract value [25], by means of the Debye–Hückel equation [26] from Bell and Roblin data [27] and Budavari *et al.* [28] and Moffat *et al.* [29] for sulfacetamide. For sulfamethoxazole, only pK_{a2} has been published [29] and therefore a pK_{a1} average value with respect to other sulfonamides was used. This assumption is valid since Foernzler and Martin [30] showed from molecular orbital calculations that the electronic charge is approximately constant at the N4 position (primary amine group).

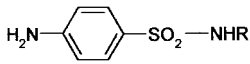
The solubility and the partitioning of sulfonamides in water were determined at the isoelectric point pI, where $pI = (pK_{a1} + pK_{a2})/2$, since they are pH dependent (the studied compounds are amphoteric). The sulfonamides have their lowest solubility and their highest partition coefficient at pI because the molecular compound without dissociation dominates [31]. Each pH value was regulated by acetate, citrate or phosphate buffers having β capacity between 0.01 and 0.02 using pK_a values corrected to $\mu = 0.15\,\text{mole}\,L^{-1}$.

Table II summarizes the melting point, enthalpy and entropy of fusion of the sulfonamides. All T_m values obtained are in good agreement with those reported in the literature [28,29]. The enthalpy and entropy of fusion reported in the literature are scarce, and have been obtained by differential thermal analysis (DTA). It may be seen that all the entropies of fusion differ from $56.5\,\text{J}\,\text{mole}^{-1}\,K^{-1}$, the value proposed by Yalkowsky and Valvani for rigid molecules.

TABLE I Some physicochemical properties of the sulfonamides evaluated

Sulfonamide	*Abbr.*	*R*[a]	*MW*[b]	pK_{a1}[c]	pK_{a2}[c]	*pI*[d]	λ_{max}[b,e]
Sulfanilamide	SA	–H	172.2	2.54	10.28	6.41	258 262
Sulfacetamide	SCM	–CO–CH_3	214.2	1.94	5.26	3.60	269 271
Sulfapyridine	SP		249.3	2.74	8.29	5.52	261 270
Sulfadiazine	SD		250.3	2.14	6.34	4.24	264 270
Sulfamerazine	SMR		264.3	2.24	6.92	4.58	263 270
Sulfamethazine	SMT		278.3	2.54	7.22	4.88	262 270
Sulfathiazole	STL		255.3	2.54	6.98	4.76	283 289
Sulfamethoxazole	SMX		253.3	2.5	5.45	4.0	267 269

[a]Substituent on the basic structure of sulfanilamide:



[b]Units: molecular weight (g $mole^{-1}$), and λ_{max}(nm).
[c]Corrected to $\mu = 0.15$ mole L^{-1} by means of the Debye–Hückel equation [26].
[d]$pI = (pK_{a1}+pK_{a2})/2$.
[e]First value in water at the isoelectric point and second in absolute ethanol.

This behavior may be attributed to the thermal analysis method used, since our values were obtained by DSC, a quantitative method, while Yalkowsky and Valvani used DTA, which is considered a semiquantitative method. The former is more appropriate for the determination of specific and molar enthalpies of fusion. Our values are generally greater than those reported by Yang and Guillory [32], and Sunwoo and Eisen [33], but in SD and SMR, our values are almost identical to those obtained by Maury *et al.* [34] by using DSC measurements.

TABLE II Properties of melting of the sulfonamides evaluated by DSC. (Values in parentheses: *SD*)

Compd	*MP*	ΔH_f	ΔS_f
SA	162.2	23.28 (0.79)	53.47 (1.82)
SCM	182.0	29.76 (0.41)	65.40 (0.90)
SP	189.5	40.47 (0.14)	87.48 (0.30)
SD	259.5	44.25 (0.38)	83.08 (0.70)
SMR	235.3	41.27 (0.98)	81.15 (1.92)
SMT	195.8	39.22 (0.71)	83.63 (1.51)
STL	199.8	30.25 (0.97)	63.96 (2.05)
SMX	167.5	33.76 (0.25)	76.63 (0.57)

Units: melting point (°C), ΔH_f (kJ mole^{-1}) ($\pm$ *SD*), and ΔS_f (J mole $^{-1}$ K^{-1}) ($\pm$ *SD*).

TABLE III Partition coefficient, experimental solubilities in water and octanol, ideal solubilities and activity coefficients in water and octanol at 25°C. (Values in parentheses: *SD*)

Compd	*Properties*							
	P	*Solubility (10^5)*						
		S_w	S_o	X_w	X_o	$X^2{}_i$	γ_w	γ_o
SA	0.192 (0.001)	4274 (159)	321.3 (7.9)	77.65	50.79	5186	66.8	102.1
SCM	0.643 (0.008)	3871 (35)	932.8 (8.1)	70.51	147.6	1591	22.6	10.8
SP	0.995 (0.002)	104.9 (2.7)	50.37 (2.33)	1.901	7.981	300.9	158.3	37.7
SD	0.826 (0.016)	26.82 (0.31)	8.801 (0.209)	0.487	1.394	38.62	79.4	27.7
SMR	1.406 (0.010)	80.12 (1.52)	43.52 (1.91)	1.450	6.895	102.1	70.4	14.8
SMT	1.811 (0.015)	160.0 (6.6)	159.6 (2.3)	2.896	25.29	314.0	108.4	12.4
STL	1.101 (0.010)	179.6 (7.3)	59.87 (3.04)	3.251	9.486	1098	337.7	115.8
SMX	8.222 (0.026)	147.0 (2.6)	611.9 (29.2)	2.664	96.91	1223	459.1	12.6

Table III summarizes the experimental solubilities in water and octanol in molarity (S_w and S_o) and mole fraction (X_w and X_o), as well as the ideal solubilities (X_i^2). In addition, the respective activity coefficients in water (γ_w) and octanol (γ_o) calculated from real and ideal solubilities are presented.

The logarithms of the experimental aqueous solubility and partitioning values for sulfonamides at 25°C, and the solubilities calculated by Eqs. (2)–(4) are presented in Table IV. The differences between experimental and calculated values are also presented, as $\log S_{w(\text{exp})} - \log S_{w(\text{calc})}$.

Deviations lower than 0.40 log units are found when Eq. (2) is used except for SP, STL, and SA. In SA the difference is close to 1.20 log units, whereas the experimental and calculated values differ in more

TABLE IV Partition coefficient, aqueous experimental and calculated solubilities as decimal logarithms, and respective deviations at 25°C

Compd	*log* P_C	*log* S_w	*Calculated log* S_w			*Deviation (as* Δ *log* S_w*)*[a]		
			Eq. (2)	*Eq. (3)*	*Eq. (4)*	*Eq. (2)*	*Eq. (3)*	*Eq. (4)*
SA	−0.717	−1.369	−0.171	−0.324	−0.236	−1.198	−1.045	−1.133
SCM	−0.192	−1.412	−1.265	−1.112	−0.979	−0.147	−0.300	−0.433
SP	−0.002	−2.979	−2.258	−1.402	−1.252	−0.721	−1.577	−1.727
SD	−0.083	−3.572	−3.167	−2.157	−1.882	−0.405	−1.415	−1.690
SMR	−0.148	−3.096	−2.929	−2.109	−1.568	−0.167	−0.987	−1.528
SMT	−0.258	−2.796	−2.495	−1.751	−1.052	−0.301	−1.045	−1.744
STL	−0.042	−2.746	−1.678	−1.572	−1.316	−1.068	−1.174	−1.430
SMX	−0.915	−2.833	−2.498	−2.101	−1.973	−0.335	−0.732	−0.860

[a]Calculated as log $S_{w(\text{exp})}$ − log $S_{w(\text{calc})}$.

than 1.0 log unit (with the exception of SCM) when Eq. (3) and (4) are used. These differences are greater with Eq. (4). This shows that it is not valid to use a constant value for the entropy of fusion (56.5 J mole^{-1} K^{-1}), which is lower than those obtained for all studied sulfonamides except for SA.

The difference between the experimental S_w and the values calculated by Eq. 2 may be explained if it is assumed that the solutes show ideal behavior, that is, the activity coefficients in octanol γ_o are unity [2]. This assumption is not valid as it may be seen in Table III, where all compounds have γ_o greater than 10. Particularly, SA and STL show γ_o greater than 100. For this reason, these compounds present the largest deviations with respect to the experimental S_w (1.198 and 1.068 log units, respectively).

The previous reasoning may also explain the low deviation for SCM because the respective γ_w and γ_o values are the smallest of all sulfonamides, that is, SCM shows the most ideal behavior in water and octanol.

If a difference lower than 0.30 log units is considered as valid for the estimation of S_w [19], then only the aqueous solubilities of SCM, SMR and SMT calculated by Eq. (2) are valid, as well as S_w for SCM calculated by Eq. (3). In all other cases, the evaluated equations do not give a reasonable estimation of this physicochemical property. Since a difference of 0.30 log units indicates a limit between twice and half the values of solubility in the non-logarithmic scale, these equations are not valid for quantitative estimations.

In addition to the assumption that $\gamma_o = 1$, Yalkowsky and Valvani assume that the effect of the partial miscibility between octanol and water on the activity coefficients is not significant upon phenomena such as solubility and partitioning, which is not valid in the case of solutes such as guanine derivatives and the studied sulfonamides (semipolar compounds). For these solutes the activity coefficients are different in pure solvents than in those mutually saturated [35,36].

From the previous analysis it may be concluded that the Yalkowsky–Valvani and Jain–Yalkowsky equations need refinement before they can yield reasonable estimations of the aqueous solubility of the studied sulfonamides.

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