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Solubility and saturation apparent specific volume of some sodium sulfonamides in propylene glycol + water mixtures at 298.15 K

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ABSTRACT

Equilibrium solubility of sodium sulfadiazine (Na.SDZ), sodium sulfamerazine (Na.SMR), and sodium sulfamethazine (Na.SMT), was determined in aqueous binary mixtures of propylene glycol (PG) at 298.15 K. If the solubility values expressed in both concentration scales are considered, i.e. mole fraction and molarity, in water-rich mixtures the solubility decrease as: Na.SDZ > Na.SMT > Na.SMR, whereas, in PG-rich mixtures the observed order is: Na.SMT > Na.SDZ > Na.SMR. In all cases the solubility in neat water is higher than those in neat PG. Correlation of the solubility data obtained was made by means of the Jouyban–Acree model for all the sodium sulfonamides. Otherwise, apparent specific volumes (ϕ_V^{sp}) of sodium sulfonamides at saturation were also calculated in all the mixtures. The average ϕ_V^{sp} values are as follows: 0.663 $cm^3\ g^{-1}$ for Na.SDZ, 0.723 $cm^3\ g^{-1}$ for Na.SMR, and 0.740 $cm^3\ g^{-1}$ for Na.SMT, with a variation lower than 5.0% in each case.

1. Introduction

Sodium sulfonamides are drugs extensively used for the treatment of certain infections caused by several kinds of microorganisms [1]. Although sodium sulfonamides are still used in therapeutics, the physicochemical information about their aqueous solutions is not complete, however several physicochemical studies have been reported in the literature [2]. In this way, the solubility and solution thermodynamics of the sodium salts of sulfadiazine, sulfamerazine, and sulfamethazine (Fig. 1), in ethanol (1) + water (2) mixtures have been presented in the literature [3–5]. Moreover, the apparent molar volumes in water and ethanol have also been studied as a function of drug concentration at 298.15 K [6,7].

In similar way, it is well known that parenteral homogeneous liquid formulations supply high doses of drug in small volumes, and thus, the solubility of drugs and their occupied volumes in solution are very important at industrial level, because they facilitate the design process of pharmaceutical dosage forms [8]. Moreover, the use of pharmaceutical salts is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs [9,10].

As has been already described, 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 [11,12]. For these reasons, it is important to determine systematically the solubility of pharmaceutical compounds and thus, the main objective of this study is to evaluate the effect of the cosolvent composition on the solubility and apparent specific volume at saturation of the sodium salts of sulfadiazine, sulfamerazine, and sulfamethazine in propylene glycol (1) + water (2) mixtures at 298.15 K. In this way, this study is similar to that presented previously about the solubility and apparent specific volumes of propranolol hydrochloride in several cosolvent (1) + water (2) mixtures at the same temperature [13]. It is noteworthy that the solubility of these three sulfonamides as molecular compounds has been recently reported in the literature [14], and thus, the respective comparison between salts and non-dissociate compounds is also made in this research.

2. Experimental

2.1. Reagents and materials

Sodium sulfadiazine (Na.SDZ, 4-Amino-*N*-2-pyrimidinylbenzenesulfonamide sodium salt, CAS RN: [68-35-9]), sodium sulfamerazine

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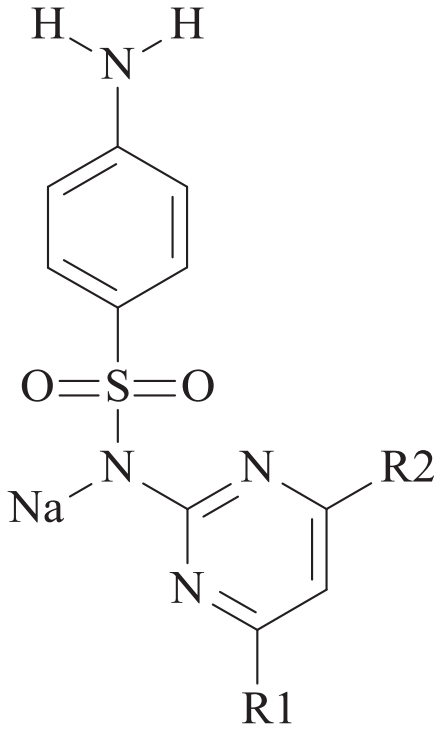

Fig. 1. Molecular structure of sodium sulfonamides. Na.SDZ: R1 = H, R2 = H; Na.SMR: R1 = CH_3, R2 = H; Na.SMT: R1 = CH_3, R2 = CH_3. It is noteworthy that the established bond between sodium cation and sulfonamide anion is ionic instead of covalent.

(Na.SMR, 4-Amino-*N*-(4-methyl-2-pyrimidinyl)benzenesulfonamide sodium salt, CAS RN: [127-58-2]), and sodium sulfamethazine (Na.SMT, 4-Amino-*N*-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide sodium salt, CAS RN: [1981-58-4]) used were in agreement with the quality requirements for sodium sulfadiazine indicated in the American Pharmacopeia, USP [15]. Propylene glycol USP (PG, CAS RN: [57-55-6]) [15], distilled water (CAS: 7732-18-5; conductivity <2 μS cm^{-1}), molecular sieve (Merck, numbers 3 and 4, Germany) intended to desiccate PG, and Millipore Corp. Swinnex®-13 filter units (USA), were also used. Source and purity of the reagents studied are presented in Table 1.

2.2. Solvent mixture preparation

All PG (1) + water (2) solvent mixtures were prepared by mass, using an Ohaus Pioneer TM PA214 (USA) analytical balance with sensitivity ± 0.1 mg, in quantities of 30.00 g. The mole fractions of cosolvent of the twelve binary mixtures prepared varied by 0.100 from $x_1 = 0.100$ to 0.900 to cover all the rank of compositions; moreover, mixtures with $x_1 = 0.025$, 0.050 and 0.150, were also studied.

2.3. Solubility determinations

The procedures followed in this research were similar to the ones used previously for studying these drugs in ethanol (1) + water (2) mixtures [3–5]. Briefly, an excess of sodium sulfonamide was added to approximately 10 g of each cosolvent mixture or neat solvent, in stoppered dark glass flasks. The flasks with the solid–liquid mixture were placed in an ultrasonic bath (Elma® E 60 H Elmasonic, Germany) during 15 min and later they were placed with stirring in a thermostatic mechanical shaker (Julabo SW23, Germany) kept at 298.15 (±0.05) K at least for five days to reach the saturation equilibrium. After this time the supernatant solutions were filtered to ensure that they were free of particulate matter before sampling. Sodium sulfonamide concentrations were determined after appropriate gravimetric aqueous dilution by measuring the UV light absorbance at 259 nm for Na.SDZ or 261 nm for Na.SMR and Na.SMT (UV/VIS BioMate 3 Thermo Electron Company spectrophotometer, USA) and interpolation from previously constructed UV spectrophotometric calibration curves. All the solubility experiments were run in triplicate at least. In order to make the equivalence between mole fraction and molarity (mol dm^{-3}) concentration scales, the density of the saturated solutions was determined with a digital density meter (DMA 45 Anton Paar, Austria) connected to a recirculating thermostatic bath (Neslab RTE 10 Digital One Thermo Electron Company, USA) at 298.15 (±0.05) K [16]. Densities were also used to calculate the volumetric contribution of the drug in the saturated solutions. The computations were carried out using Microsoft Excel.

3. Results and discussion

3.1. Experimental solubility of sodium sulfonamides

Table 2 summarizes the experimental solubility of the three sodium sulfonamides in all the PG (1) + water (2) mixtures at 298.15 K, expressed in mole fraction and mol dm^{-3}, respectively. In almost all cases the relative standard deviations were smaller than 2.0%. If the mole fraction scale is considered, initially the drug solubility increases with the PG proportion reaching maximum values in PG (1) + water (2) mixtures and later it decreases up to neat PG, except with Na.SDZ, where drug solubility decreases from neat water to neat PG. Otherwise, in the three cases the drug solubility is higher in water than PG by considering both concentration scales, mole fraction and molarity. On the other hand, if the molarity scale is considered the solubility behavior is different compared with mole fraction because the drug solubility decrease from neat water to neat PG for Na.SDZ and Na.SMT, whereas for Na.SMR this property increases from water up to the mixture with $x_1 = 0.100$ and later it decreases until the neat PG. This apparently contradictory behavior is a consequence of the definitions of the respective scales [17]. Similar behaviors have been reported in the literature for other salt form of drugs in ethanol (1) + water (2) mixtures [18–22]. From an empirical point of view the solubility of these salt form of drugs in the mixtures studied could be considered as varying from freely soluble to soluble, i.e. that the parts of solvent required to dissolve one part of solute varies from 1 to 10 in the first case and from 10 to 30 in the second [17].

Fig. 2 compares the experimental solubility of the sodium sulfonamides in PG (1) + water (2) and ethanol (1) + water (2) mixtures at 298.15 K [3]. The respective solubility trends were adjusted to regular polynomial models in order four [23]. For all the drugs the solubility decreases continuously from neat water to neat ethanol. Otherwise, it

Table 1
Source and purities of the compounds used in this research.

Compound	CAS	Formula	Molar mass/g mol^{-1}	Source	Purity in mass fraction[a]
Sodium sulfadiazine	68-35-9	$C_{10}H_9N_4O_2SNa$	272.26	Sigma-Aldrich, USA	0.980
Sodium sulfamerazine	127-58-2	$C_{11}H_{11}N_4O_2SNa$	286.29	Sigma-Aldrich, USA	0.980
Sodium sulfamethazine	1981-58-4	$C_{12}H_{13}N_4O_2SNa$	300.31	Sigma-Aldrich, USA	0.980
Propylene glycol	57-55-6	$C_3H_8O_2$	76.09	Dow Chemical Co., USA	0.995
Water	7732-18-5	H_2O	18.02	Obtained by distillation	1.000

[a] All reagents were used as received without further purification.