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 (ϕV sp) of sodium sulfonamides at saturation were also calculated in all the mixtures. The average ϕV sp values are as follows: 0.663 cm³ g⁻¹ for Na.SDZ, 0.723 cm³ g⁻¹ for Na.SMR, and 0.740 cm³ g⁻¹ for Na.SMT, with a variation lower than 5.0% in each case.

Keywords:
Sodium sulfonamides
Propylene glycol
Solubility
Apparent specific volume
Jouyban–Acree model

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-pyrimidinylbenzene-sulfonamide sodium salt, CAS RN: [68-35-9]), sodium sulfamethazine...
(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: 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 co-solvent of the twelve binary mixtures prepared varied by 0.100 from \( x_1 = 0.025 \) 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 co-solvent 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 \( \pm 0.05 \) 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 Thermoelectron 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 Antkon Paar, Austria) connected to a recirculating thermostatic bath (Neslab RTE 10 Digital One Thermo Electron Company, USA) at 298.15 \( \pm 0.05 \) 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

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th>Formula</th>
<th>Molar mass/g mol⁻¹</th>
<th>Source</th>
<th>Purity in mass fraction a</th>
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<td>Sodium sulfadiazine</td>
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<td>272.26</td>
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<td>0.980</td>
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<td>Sodium sulfamerazine</td>
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<td>C₁₁H₁₁NaO₃SNa</td>
<td>286.29</td>
<td>Sigma-Aldrich, USA</td>
<td>0.980</td>
</tr>
<tr>
<td>Sodium sulfamethazine</td>
<td>1981-58-4</td>
<td>C₁₂H₁₃N₄O₂SNa</td>
<td>300.31</td>
<td>Sigma-Aldrich, USA</td>
<td>0.980</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>57-55-6</td>
<td>C₃H₈O₂</td>
<td>76.09</td>
<td>Dow Chemical Co., USA</td>
<td>0.995</td>
</tr>
<tr>
<td>Water</td>
<td>7732-18-5</td>
<td>H₂O</td>
<td>18.02</td>
<td>Obtained by distillation</td>
<td>1.000</td>
</tr>
</tbody>
</table>

a All reagents were used as received without further purification.
is clear that the solubility of these drugs is higher in PG (1) + water (2) compared with ethanol (1) + water (2) mixtures which could be attributed to the difference in dielectric constant of the cosolvent considered, i.e. 32 and 24 at 298.15 K for PG and ethanol, respectively [24]. The higher the dielectric constant of the solvent mixture is the higher the capability of electrolyte dissociation is; therefore, the dissolution extent of salt form of drugs is higher with the dielectric constant [17,25,26].

On the other hand, Fig. 3 compares the logarithmic experimental solubility of the sodium sulfonamides with the solubility of the respective molecular sulfonamides in PG (1) + water (2) mixtures at 298.15 K [14]. In all cases the solubility of sodium salts is higher than those for the non-dissociate compounds. It indicates a great participation of the ion-dipole interactions toward the dissolution processes of these drugs.

3.2. Solubility calculations with the Jouyban–Acree model

Previous investigations showed that the Jouyban–Acree model is the most accurate model among the available cosolvency models for calculating drug solubility in mixed solvents [27,28]. This equation is

\[
x_{1}^{ah} = 100 x_{1}^{hc} \text{ mol dm}^{-3} \\
\begin{array}{cccccccc}
\text{Na.SDZ} & \text{Na.SMR} & \text{Na.SMT} & \text{Na.SDZ} & \text{Na.SMR} & \text{Na.SMT} \\
0.000 & 4.80 & 1.83 & 2.83 & 1.930 & 0.882 & 1.249 \\
0.025 & 4.47 & 2.67 & 2.91 & 1.752 & 1.132 & 1.203 \\
0.050 & 4.28 & 3.16 & 2.99 & 1.616 & 1.222 & 1.163 \\
0.100 & 4.04 & 3.71 & 3.15 & 1.404 & 1.253 & 1.099 \\
0.150 & 3.72 & 4.11 & 3.32 & 1.208 & 1.245 & 1.047 \\
0.200 & 3.49 & 4.48 & 3.54 & 1.048 & 1.233 & 1.017 \\
0.300 & 3.15 & 4.43 & 3.90 & 0.821 & 1.068 & 0.952 \\
0.400 & 2.72 & 3.84 & 4.04 & 0.631 & 0.836 & 0.863 \\
0.500 & 2.54 & 3.34 & 3.94 & 0.522 & 0.662 & 0.754 \\
0.600 & 2.21 & 2.89 & 3.76 & 0.412 & 0.523 & 0.655 \\
0.700 & 2.10 & 2.49 & 3.39 & 0.357 & 0.414 & 0.545 \\
0.800 & 1.95 & 2.16 & 3.05 & 0.304 & 0.331 & 0.455 \\
0.900 & 1.91 & 1.77 & 2.75 & 0.273 & 0.253 & 0.382 \\
1.000 & 1.86 & 1.37 & 2.50 & 0.246 & 0.182 & 0.324 \\
\end{array}
\]

\(a \) \(x_1\) is the mole fraction of propylene glycol (1) in the propylene glycol (1) + water (2) mixtures free of drug (3).

\(b\) Standard uncertainties are \(u(T) = 0.05\) K, \(u(p) = 2.2\) kPa, \(u(x_1) = 0.0003\). Average relative standard uncertainties in solubility, \(u_r(x_3)\) and \(u_r(mol dm^{-3})\), are 0.02 (or 2.0%).

\(c\) Na.SDZ, Na.SMR, and Na.SMT, are sodium sulfadiazine, sodium sulfamerazine, and sodium sulfamethazine, respectively.

<table>
<thead>
<tr>
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<td>4.80</td>
<td>1.83</td>
<td>2.83</td>
<td>1.930</td>
<td>0.882</td>
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<td>3.15</td>
<td>1.404</td>
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<td>3.72</td>
<td>4.11</td>
<td>3.32</td>
<td>1.208</td>
<td>1.245</td>
<td>1.047</td>
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<td>0.952</td>
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<td>0.412</td>
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<td>2.10</td>
<td>2.49</td>
<td>3.39</td>
<td>0.357</td>
<td>0.414</td>
<td>0.545</td>
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<td>0.800</td>
<td>1.95</td>
<td>2.16</td>
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<td>0.304</td>
<td>0.331</td>
<td>0.455</td>
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<tr>
<td>0.900</td>
<td>1.91</td>
<td>1.77</td>
<td>2.75</td>
<td>0.273</td>
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</tr>
<tr>
<td>1.000</td>
<td>1.86</td>
<td>1.37</td>
<td>2.50</td>
<td>0.246</td>
<td>0.182</td>
<td>0.324</td>
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</tbody>
</table>

Fig. 2. Solubility of sodium sulfonamides (3) expressed in mole fraction in cosolvent (1) + water (2) mixtures at 298.15 K. Filled circles: propylene glycol (1) + water (2) mixtures. Empty circles: ethanol (1) + water (2) mixtures.

Fig. 3. Logarithmic solubility of sodium sulfonamides (3) and molecular sulfonamides (3) expressed in mole fraction in propylene glycol (1) + water (2) mixtures at 298.15 K. Filled circles: sodium sulfonamides. Empty circles: molecular sulfonamides.
applicable to binary solvent mixtures at various temperatures and is [29]:

$$\log c_{\text{Sat}} - c_{\text{Exp}} = x_1 \log c_{1,\text{Sat}} + x_2 \log c_{2,\text{Sat}} + \frac{x_1 x_2}{\sum_{i=0}^{2} i(x_1 - x_2)^i}$$

(1)

where $c_{\text{Sat}}$ is the solute (mol dm$^{-3}$ or mole fraction) solubility in the solvent mixtures at temperature $T (K)$, $x_1$ and $x_2$ are the mole fractions of the solvents 1 and 2 in the absence of the solute, $c_{1,\text{Sat}}$ and $c_{2,\text{Sat}}$ denote (mol dm$^{-3}$) solubility of the solute in the solvents 1 and 2, respectively. The $J$ terms are the constants of the model and are computed by regressing $\log c_{\text{Sat}} - x_1 \log c_{1,\text{Sat}} - x_2 \log c_{2,\text{Sat}}$ against $x_1 x_2 x_i (x_1 - x_2)$ with intercept and using a no intercept least square analysis [30]. Eq. (1) provided reasonably accurate calculations for solubility of polar and non-polar solutes in binary solvent mixtures at various temperatures [27,28]. The molar solubility data is fitted to Eq. (1), and the obtained model constants and mean percentage deviations are listed in Table 3. Mean percentage deviations (MPD) were calculated by using Eq. (2), where $N$ is the number of mixtures considered in each case, i.e. 12. MPD values are also reported in Table 3.

$$\text{MPD} = \frac{100}{N} \sum \left( \frac{c_{\text{Sat}} - c_{\text{Exp}}}{c_{\text{Sat}} - c_{\text{Exp}}} \right)$$

(2)

The overall MPDs of 2.0% for both solubility data units (i.e. molar and mole fraction) indicate that the model is capable of correlating the solubility of salt forms of drugs and the obtained correlation errors are acceptable. The main restriction of Eq. (1) for practical uses in the pharmaceutical industries is the existence of the $J$ terms requiring a number of experimental solubility data in mixed solvents for computing their numerical values. To provide an alternative solution for this limitation, a trained version of the Jouyban–Acree model was presented for predicting the solubility of drugs in PG + water mixtures at various temperatures as:

$$\log c_{\text{Sat}} - c_{\text{Exp}} = x_1 \log c_{1,\text{Sat}} + x_2 \log c_{2,\text{Sat}} + \frac{x_1 x_2}{37.03 + 319.49(x_1 - x_2)}$$

(3)

which is able to predict the solubility with acceptable accuracy [31]. When solubility of the investigated drugs in this work was predicted using Eq. (3) the overall MPD of 21.4% and 24.5% were obtained respectively for molar and mole fraction solubilities. Considering 24% of previous report for solubility of 27 drugs in PG + water mixtures, the obtained prediction errors are acceptable [28].

An adapted version of the Jouyban–Acree model was used to represent the density of mixed solvents and/or saturated solutions of drugs in the solvent mixtures as has been shown in earlier works [32–34]. According to these findings, it is possible to train the Jouyban–Acree model using the density data of a solvent mixture at various temperatures and then use it for prediction of the solute saturated solution in the solvent mixtures by employing the density values of the solute saturated solutions in the mono-solvents 1 and 2 (Table 4). When the model is trained using the density of solute free solvent mixtures, the obtained equation is:

$$\log \phi_{\text{Sat}} = x_1 \log \phi_{1,\text{Sat}} + x_2 \log \phi_{2,\text{Sat}} + \frac{x_1 x_2}{28.92 - 31.27(x_1 - x_2) + 26.99(x_1 - x_2)^2}$$

(4)

which predicts the density of drug saturated solutions of sodium sulfonamides with the overall MPD of 2.3%.

3.3. Apparent specific volume of sodium sulfonamides at saturation

The volumetric contribution of drugs in solution is relevant from practical and theoretical points of view. A well considered property of drugs at saturation is the apparent specific volume ($\phi_D^b$) [35], calculated according to the Eq. (5):

$$\phi_D^b = \frac{w_2 + w_{1,2}(1 - \rho_{\text{Sat}}/\rho_{1+2})}{w_2 \rho_{\text{Sat}}}$$

(5)

where, $w_2$ and $w_{1,2}$ are the mass fractions of solute and cosolvent mixture at drug saturation, respectively; whereas, $\rho$ and $\rho_{1+2}$ are the densities of the saturated solution and co-solvent mixture. The density of the co-solvent mixtures free of drug at 298.15 K were taken from the literature [36]. The density and the apparent specific volumes of the sodium sulfonamides at the same temperature are also presented in Table 4. If the results in all the mono and mixed solvents are considered, the average $\phi_D^b$ values are as follows: 0.663 (±0.016) cm$^3$ g$^{-1}$ for Na.SDz, 0.723 (±0.039) cm$^3$ g$^{-1}$ for Na.SMR, and 0.740 (±0.030) cm$^3$ g$^{-1}$ for Na.SMT. In general, the variation of $\phi_D^b$ with the mixture composition is lower than 5.0%. This variation is normally accepted in the design of liquid pharmaceutical dosage forms [16,25].

Table 4

<p>| Volumetric properties of the saturated solutions of sodium sulfonamides (3) in propylene glycol (1) + water (2) mixtures at 298.15 K and local atmospheric pressure of 73.9 kPa. |
|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>$\phi_D^b$ cm$^3$ g$^{-1}$</th>
<th>Na.SDz</th>
<th>Na.SMR</th>
<th>Na.SMT</th>
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<td>1.0558</td>
<td>1.0495</td>
</tr>
</tbody>
</table>

$^a$ $x_1$ is the mole fraction of propylene glycol (1) in the propylene glycol (1) + water (2) mixtures free of drug (3).

$^b$ Standard uncertainties are $u(T) = 0.05$ K, $u(p) = 2.2$ kPa, $u(x_1) = 0.0003$. Average standard uncertainty in density of the saturated solutions is $u(\rho_{\text{Sat}}) = 0.0008$ cm$^3$ g$^{-1}$. Average standard uncertainty in apparent specific volumes at saturation is $u(\phi_D^b) = 0.0015$ cm$^3$ g$^{-1}$.

$^c$ Na.SDz, Na.SMR, and Na.SMT, are sodium sulfadiazine, sodium sulfamerazine, and sodium sulfamethazine, respectively.

$^d$ Density values calculated from those reported by Jiménez and Martínez [36].
4. Conclusions

From that discussed previously it can be concluded that the solution processes of the three sodium sulfonamides in all the PG (1) + water (2) mixtures studied are highly dependent on the mixture composition and that the Jouyban–Acree model correlates adequately with the solubility of these salt form of drugs in those mixtures. The variation of apparent specific volume of the drugs with the mixture composition is lower than 5.0%, which is normally accepted in the design and development of homogeneous liquid pharmaceutical dosage forms. Ultimately, it can be established that the data presented in this report expand the physicochemical information about salt form of drugs in aqueous cosolvent mixtures and generate good information about the solubilization of sodium sulfonamides using a pharmaceutically accepted cosolvent.

Acknowledgments

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References