

Article

Effect of Ethanol on the Equilibrium Solubility and Apparent Specific Volume of Sodium Sulfamethazine in Aqueous Systems at Several Temperatures

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Abstract

The main objective of this research was to determine and correlate the equilibrium solubility of sodium sulfamethazine (NaSMT) in several {ethanol (1) + water (2)} mixtures reported in mass/volume and mass/mass percentages at different temperatures, as well as the density of saturated solutions. NaSMT solubility decreases with decreasing temperature, and also decreases non-linearly with the addition of ethanol to water at every temperature. Logarithmic solubility was adequately correlated with a bivariate model involving temperature and mixture composition. Solubility values were also well correlated with some Jouyban–Acree-based models. Moreover, an adapted version of the Jouyban–Acree model was used to represent the density of the saturated systems at different temperatures. Furthermore, the apparent specific volumes of NaSMT at saturation were also calculated from densities of saturated solutions and cosolvent mixtures free of drug at every mixture composition and temperature. These findings provide valuable insights into the solubility and volumetric behavior of NaSMT that could be useful for improving pharmaceutical formulation processes.

Keywords: sodium sulfamethazine; aqueous ethanolic mixtures; solubility; cosolvency; apparent specific volume



Academic Editor: Masashi Hojo

Received: 15 May 2026

Revised: 22 June 2026

Accepted: 9 July 2026

Published: 14 July 2026

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1. Introduction

As widely reported in the literature, the exhaustive physicochemical characterization of dissolved pharmaceuticals plays a crucial role in all R&D stages of homogenous liquid pharmaceutical dosage forms, in particular of those presented in small volumes intended for parenteral administration, like ampules, because these products commonly supply high doses of drugs [1–4].

Sodium sulfamethazine (IUPAC name: sodium (4-aminophenyl)sulfonyl-(4,6-dimethylpyrimidin-2-yl)azanide; CAS number: 1981-58-4; molecular formula: $C_{12}H_{13}N_4NaO_2S$;

molar mass: 300.31 g/mol; NaSMT; Figure 1) is an antimicrobial drug compound employed in the treatment of certain infections caused by different microorganisms [5–7]. Despite the wide use of NaSMT in therapeutics, its physicochemical behavior in aqueous solutions is still being studied. Select physicochemical studies regarding this drug have been reported in the literature. For example, the equilibrium solubility values expressed in molarity and mole fraction as well as the respective thermodynamic quantities of dissolution and mixing in several ethanol–water mixtures have been reported [8,9]. Moreover, its equilibrium solubility and apparent specific volumes at saturation in {propylene glycol (1) + water (2)} mixtures at 25.0 °C have also been reported [10]. Apparent molar volumes at several NaSMT concentrations have been determined at several temperatures in neat water and other aqueous systems [11–13]. Several other physicochemical properties of NaSMT have been reported in water at various drug concentrations and temperatures including the molar electrical conductivity, the calorimetric enthalpy of dissolution and the viscosity [14–16]. The aforementioned investigations demonstrate the main role of the hydrophilic and hydrophobic hydration processes of this drug in the observed physicochemical magnitudes obtained in aqueous media.

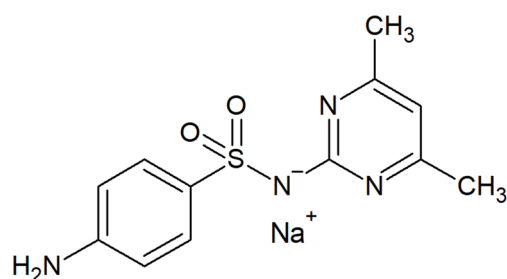


Figure 1. Molecular structure of sodium sulfamethazine (NaSMT).

From an industrial viewpoint, the systematic searching, acquisition, and systematization of equilibrium solubility values and volumetric contributions of drugs and excipients at saturation in aqueous and non-aqueous solvent mixtures are fundamental for theoretical and practical purposes. This is because different cosolvent blends are currently being used in the purification of pharmaceutical ingredients by recrystallization. Moreover, solvent mixtures are also considered in dosage form preformulation studies, as well as in the development and preparation of homogeneous liquid medicines [16,17]. For these reasons, it is important for the chemical and pharmaceutical communities to systematically determine the equilibrium solubility and specific volume contribution of all pharmaceuticals.

To provide the pharmaceutical industry with additional experimental values, we have determined the equilibrium solubility, expressed in mass/volume (% m/v) and mass/mass (% m/m) percentages, as well as the apparent specific volume (φ_V^{sp} /mL/g) at saturation of NaSMT in several aqueous–ethanolic binary mixtures at seven equidistant temperatures from 5.0 to 35.0 °C. Thus, this research expands the available database of these properties reported earlier for other analogous drugs in the same binary mixtures and temperatures, namely sodium sulfadiazine and sodium sulfamerazine [17,18]. Here we indicate “equilibrium solubility” to differentiate it from “kinetic solubility” that is commonly used in pharmaceutical sciences before saturation as a mean of dissolution rate [1–3].

2. Methods

2.1. Reagents and Materials

NaSMT provided by Sigma-Aldrich, Burlington, MA, USA (mass fraction purity > 0.99), absolute ethanol (CAS number: 64-17-5; molecular formula: C₂H₆O; molar mass:

46.07 g/mol; density, $\rho = 0.7854$ g/mL at 25.0 °C; dielectric constant, $\epsilon = 24.1$ at 25.0 °C), provided by Merck, Darmstadt, Germany (mass fraction purity > 0.995) and laboratory distilled water (CAS number: 7732-18-5; molecular formula: H₂O; molar mass: 18.02 g/mol; density, $\rho = 0.9970$ g/mL at 25.0 °C; dielectric constant, $\epsilon = 78.5$ at 25.0 °C) (conductivity < 2 μ S/cm) were studied in this research.

2.2. Cosolvent Mixtures Preparation

Aqueous ethanolic cosolvent mixture preparation was performed gravimetrically in quantities of 100.00 g with ethanol mass fractions (w_1) in compositions from $w_1 = 0.10$ to $w_1 = 0.90$ varying by 0.10 in mass fraction to study the NaSMT solubility in nine binary mixtures and both pure solvents.

2.3. NaSMT Solubility Determination

NaSMT solubility was determined by following the same classical shake-flask method and UV–vis spectrophotometry procedures [19,20] used before for studying the behavior of sodium sulfadiazine and sodium sulfamerazine [17,18]. Briefly, an excess of NaSMT was added to 50 mL of each solvent system in stoppered dark glass flasks. Then, the solid–liquid mixtures were stirred in a mechanical shaker (Burrel, Wrist Action Shaker, Model 75, Pittsburgh, PA, USA) at room temperature for at least four hours. After this stirring, the flasks were kept at 35.0 ± 0.05 °C in some recirculating thermostatic baths (Neslab RTE 10 Digital One Thermo Electron Company, Waltham, MA, USA) with sporadic stirring for at least three days until saturation is reached. After this time, the supernatant dispersions were filtered (at isothermal conditions) using 0.45 μ m pore diameter cartridges to ensure that they were free of undissolved particulate matter before sampling for composition analysis. NaSMT concentrations at saturation were determined by measuring UV absorbance after appropriate gravimetric aqueous dilution and interpolation from a previously established UV spectrophotometric calibration curve (UV/Vis BioMate 3 Thermo Electron Company spectrophotometer, Waltham, MA, USA). Then, the thermostatic bath temperature was decreased in successive steps of 5.0 °C following the same procedures indicated above until reaching the lowest research temperature of 5.0 °C. All solubility experiments were performed at least three times. Moreover, to facilitate the transformation of NaSMT solubility values between volumetric and gravimetric concentration scales [2,21] and to allow the calculation of apparent specific volumes of NaSMT at saturation, the density of the saturated solutions was determined at every temperature using a digital density meter (DMA 45 Anton Paar, Graz, Austria) connected to a recirculating thermostatic bath (Neslab RTE 10 Digital One Thermo Electron Company, Waltham, MA, USA). All calculations, correlations, and graphs were performed and prepared using different tools of MS Excel® v. 2013.

3. Results and Discussion

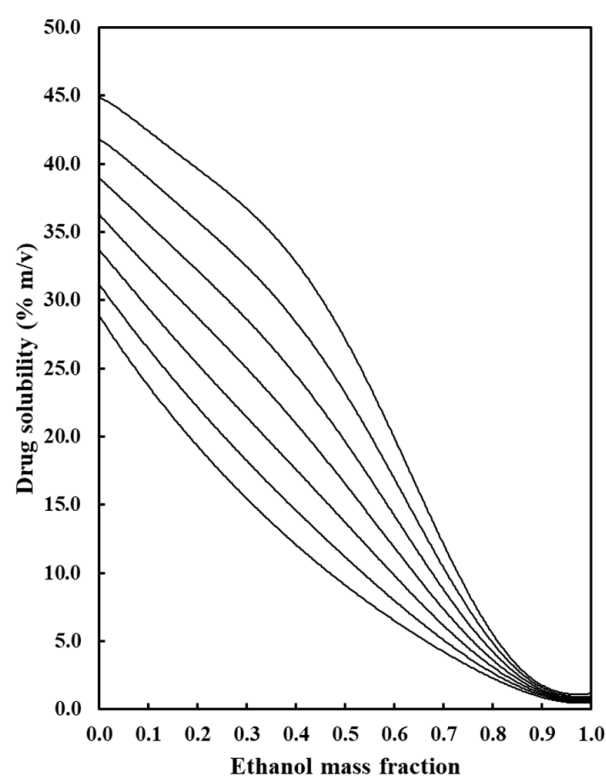
3.1. Experimental Solubility of NaSMT at Different Temperatures and Mixture Compositions

Table 1 summarizes the experimental mass/volume percentage (% m/v) solubilities of NaSMT in the aqueous ethanol mixtures as a function of both solvent system composition and temperature. As a visual aid, % m/v solubilities are depicted as a function of mixture compositions at all temperatures in Figure 2. NaSMT equilibrium solubility increases with increasing temperature, but it decreases with increase in ethanol proportion in the mixtures at all temperatures. The respective trends were adjusted to regular polynomials in the fourth degree in all cases [22–24]. Moreover, % m/v solubilities of NaSMT are depicted for all mixture compositions as a function of temperature in Figure 3, with linear, parabolic or hyperbolic NaSMT increases in solubility.

Table 1. Equilibrium solubility of sodium sulfamethazine in aqueous ethanolic mixtures at different temperatures expressed in mass/volume percentage (% m/v).

w_1 ^a	Temperature (°C) ^b						
	5.0	10.0	15.0	20.0	25.0	30.0	35.0
0.00	28.92	31.19	33.72	36.32	38.99	41.85	44.91
0.10	23.67	26.40	29.41	32.42	35.52	38.94	42.40
0.20	19.44	22.30	25.37	28.75	32.30	35.73	39.58
0.30	15.34	18.14	21.40	25.13	28.58	32.71	37.00
0.40	12.09	14.52	17.56	20.75	24.40	28.21	32.54
0.50	9.17	11.35	13.80	16.70	19.68	23.03	27.10
0.60	6.48	7.85	9.71	11.78	14.21	17.23	20.10
0.70	4.22	5.12	6.23	7.41	8.86	10.33	12.17
0.80	2.28	2.66	3.05	3.53	4.049	4.68	5.24
0.90	0.890	1.04	1.19	1.34	1.52	1.73	1.92
1.00	0.509	0.578	0.673	0.755	0.837	0.930	1.14

^a w_1 is the mass fraction of ethanol in the binary mixtures free of sodium sulfamethazine. ^b Mean relative uncertainty in mass/volume percentage solubility is 2.0%.

**Figure 2.** Equilibrium solubility of sodium sulfamethazine expressed in mass/volume percentage in some aqueous ethanolic mixtures as a function of ethanol mass fraction at different temperatures. Trends from top to bottom: 35.0 °C, 30.0 °C, 25.0 °C, 20.0 °C, 15.0 °C, 10.0 °C, and 5.0 °C.

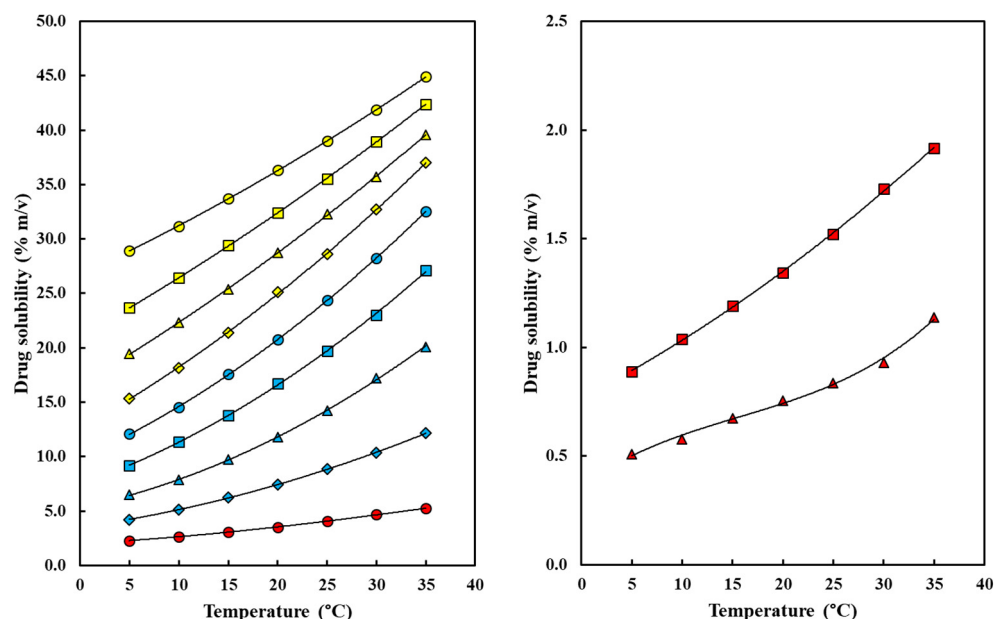


Figure 3. Equilibrium solubility of sodium sulfamethazine in some aqueous ethanolic mixtures as a function of temperature expressed in mass/volume percentage. ●: neat water; ■: $w_1 = 0.10$; ▲: $w_2 = 0.20$; ◆: $w_1 = 0.30$; ●: $w_1 = 0.40$; ■: $w_1 = 0.50$; ▲: $w_2 = 0.60$; ◆: $w_1 = 0.70$; ●: $w_1 = 0.80$; ■: $w_1 = 0.90$; ▲: neat ethanol.

All logarithmic % m/v solubility values of NaSMT (compound 3) in {ethanol (compound 1) + water (compound 2)} systems ($\ln S_{3,1+2}$) were correlated as the bivariate polynomial model shown as Equation (1), where w_1 denotes the mass fraction of ethanol in the solvent mixtures free of drug and the temperature (t) is expressed in degrees Celsius ($^{\circ}\text{C}$). Obtained statistical parameters were as follows: adjusted $r^2 = 0.9936$; mean standard error = 0.1042; and statistical F value = 2377. This bivariate model allows the calculation of NaSMT solubility with a mean percentage deviation (MPD %) of 8.2%—as calculated with Equation (2), where S_3^{Calc} and S_3^{Obs} are the calculated and experimental solubility NaSMT values, respectively [22–24].

$$\ln S_{3,1+2} = 3.06(\pm 0.04) + 0.0280(\pm 0.0012) \cdot t(^{\circ}\text{C}) - 3.00(\pm 0.58) \cdot w_1 + 11.1(\pm 2.5) \cdot w_1^2 - 21.0(\pm 3.9) \cdot w_1^3 + 9.0(\pm 1.9) \cdot w_1^4 \quad (1)$$

$$\text{MPD}\% = \frac{\sum_{i=1}^n 100 \cdot \left| \frac{S_3^{\text{Calc}} - S_3^{\text{Obs}}}{S_3^{\text{Obs}}} \right|}{n} \quad (2)$$

Regarding the solubility of NaSMT in other aqueous cosolvent systems, Figure 4 allows comparison when ethanol is exchanged for propylene glycol as a cosolvent at 25.0°C . As observed, propylene glycol exhibits a better solubilizing power due to its higher polarity relative to ethanol, as described by its dielectric constant, i.e., 32.0 [2,25].

Figure 5 shows that all NaSMT % m/v solubilities at 25.0°C are higher than those reported earlier for sodium sulfamerazine [18] in all mixture compositions but lower than the solubility of sodium sulfadiazine in water-rich mixtures [17]. Thus, aqueous solubility of these sodium sulfonamides decreases in the following order: sodium sulfadiazine > NaSMT > sodium sulfamerazine.

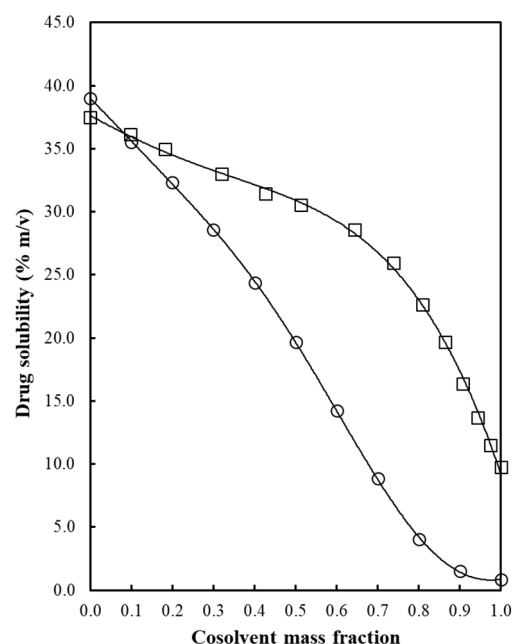


Figure 4. Equilibrium solubility of sodium sulfamethazine expressed in mass/volume percentage in some aqueous-cosolvent mixtures as a function of the cosolvent mass fraction free of solute at 25.0 °C. ○: {ethanol (1) + water (2)} mixtures (this work). □: {propylene glycol (1) + water (2)} mixtures (calculated from values reported in [10]).

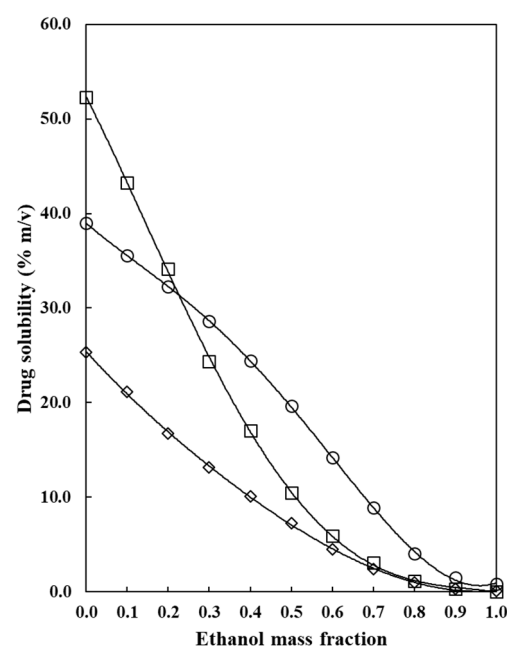


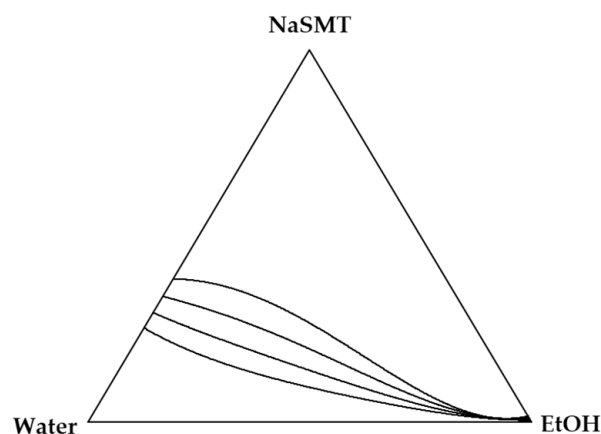
Figure 5. Equilibrium solubility of sodium sulfadiazine (□), sodium sulfamerazine (◇) and sodium sulfamethazine (○) expressed in mass/volume percentage in some aqueous ethanolic mixtures as a function of ethanol mass fraction free of solute at 25.0 °C.

Table 2 summarizes the experimental mass/mass percentage solubilities of NaSMT in aqueous mixtures of ethanol as a function of mixture composition and temperature. Moreover, % m/m solubilities are depicted as a function of mixture compositions at four temperatures in Figure 6 as a Gibbs–Roozeboom triangular graph [26,27]. It is important to note that mass fraction solubilities are required for calculating the apparent specific volumes of NaSMT as indicated below.

Table 2. Equilibrium solubility of sodium sulfamethazine in aqueous ethanolic mixtures at different temperatures expressed in mass/mass percentage (% m/m).

w_1 ^a	Temperature (°C) ^b						
	5.0	10.0	15.0	20.0	25.0	30.0	35.0
0.00	25.38	27.34	29.49	31.68	33.95	36.38	38.90
0.10	21.54	23.88	26.50	29.09	31.77	34.66	37.61
0.20	18.25	20.82	23.57	26.51	29.55	32.65	35.97
0.30	14.83	17.45	20.50	23.85	26.98	30.71	34.51
0.40	12.00	14.39	17.29	20.28	23.73	27.29	31.29
0.50	9.41	11.60	14.08	16.91	19.88	23.17	27.06
0.60	6.94	8.36	10.29	12.48	15.00	18.04	20.93
0.70	4.68	5.67	6.90	8.20	9.82	11.41	13.44
0.80	2.62	3.07	3.54	4.11	4.72	5.47	6.15
0.90	1.06	1.24	1.43	1.62	1.85	2.11	2.35
1.00	0.629	0.720	0.843	0.949	1.06	1.18	1.45

^a w_1 is the mass fraction of ethanol in the binary mixtures free of sodium sulfamethazine. ^b Mean relative standard deviation in mass percentage solubility is 2.0%.

**Figure 6.** Equilibrium solubility of sodium sulfamethazine expressed in mass fraction in aqueous ethanolic mixtures at different temperatures. Trends from top to bottom: 35.0 °C, 25.0 °C, 15.0 °C, and 5.0 °C.

Moreover, Figure 7 also allows the comparison of equilibrium solubilities of NaSMT and its analogues, sodium sulfadiazine [17] and sodium sulfamerazine [18], using a Gibbs–Roozeboom triangular graph [26,27].

The Jouyban–Acree model provided a promising and accurate representation of the solubility data in mixed solvent systems at different temperatures. Its accuracy could be affected by a number of parameters including the expressions of the solvent composition and solubilities. The effects of solubility units are systematically investigated in a previous work [28], and the effects of solubility expression units of NaSMT in aqueous alcoholic mixtures at different temperatures are studied in this work. The obtained results are listed in Table 3, and as shown, the model constants varied with different solubility units; however, there was no significant difference among the MPD% values except for mole fraction solubility. It should be noted that the solvent composition is expressed as mass fraction for the results reported in Table 3.

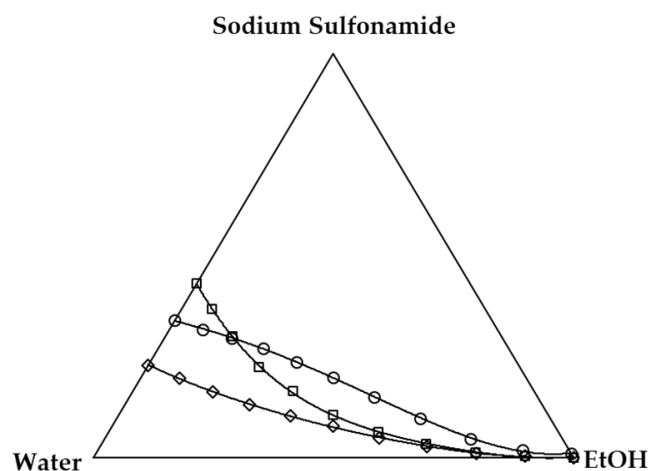


Figure 7. Equilibrium solubility of drugs expressed as mass fraction in aqueous ethanolic mixtures at 25.0 °C. Sodium sulfadiazine ($\square$), sodium sulfamerazine ($\diamond$), and sodium sulfamethazine ($\circ$).

Table 3. Jouyban–Acree and Jouyban–Acree–van’t Hoff model parameters for equilibrium solubility of sodium sulfamethazine in aqueous ethanolic mixtures at different temperatures.

Jouyban–Acree Model								
Scale					J_0	J_1	J_2	MPD% *
Molar					1362.820	345.798	−695.770	11.2
Mole fraction					856.552	412.536	−261.135	4.5
% mass/volume					1362.820	345.798	−695.770	11.2
% mass/mass					1327.509	360.732	−655.065	10.7
Jouyban–Acree–van’t Hoff Model								
Scale	A_1	B_1	A_2	B_2	J_0	J_1	J_2	MPD% *
Molar	1.495	−2192.268	2.178	−1257.603	1363.114	345.721	−695.035	11.3
Mole fraction	4.706	−1984.852	1.021	−423.962	856.422	411.849	−261.459	4.6
% mass/volume	7.200	−2192.268	7.883	−1257.603	1362.917	345.721	−695.528	11.3
% mass/mass	7.716	−2276.771	7.621	−1220.763	1327.171	360.392	−655.910	10.8

* MPD, mean percentage deviation.

Figure 8 depict the equilibrium solubility of NaSMT expressed as molarity and mole fraction in these aqueous ethanolic mixtures at all temperatures. As expected, the shape of solubility profiles expressed in molarity is the same as that shown in Figure 2 (% m/v) because both of them are volumetric scales. However, the shape of profiles expressed in mole fraction are different because this scale is gravimetric and involves the molar masses of the solute and solvents [2]. As observed in these scales, in all cases, NaSMT solubility decreases with the addition of ethanol to water, as expected, because the dielectric constants of the mixtures free of salt are decreasing as the ethanol proportion increases. In this way, the capacity of the solvent mixture to separate ionic charges decreases. Moreover, the capacity of the solvent mixture components to solvate the respective ions is also reduced [29]. Therefore, strong ion–dipole interactions that favor the saline drug solubility are present mainly in water-rich mixtures at all temperatures studied.

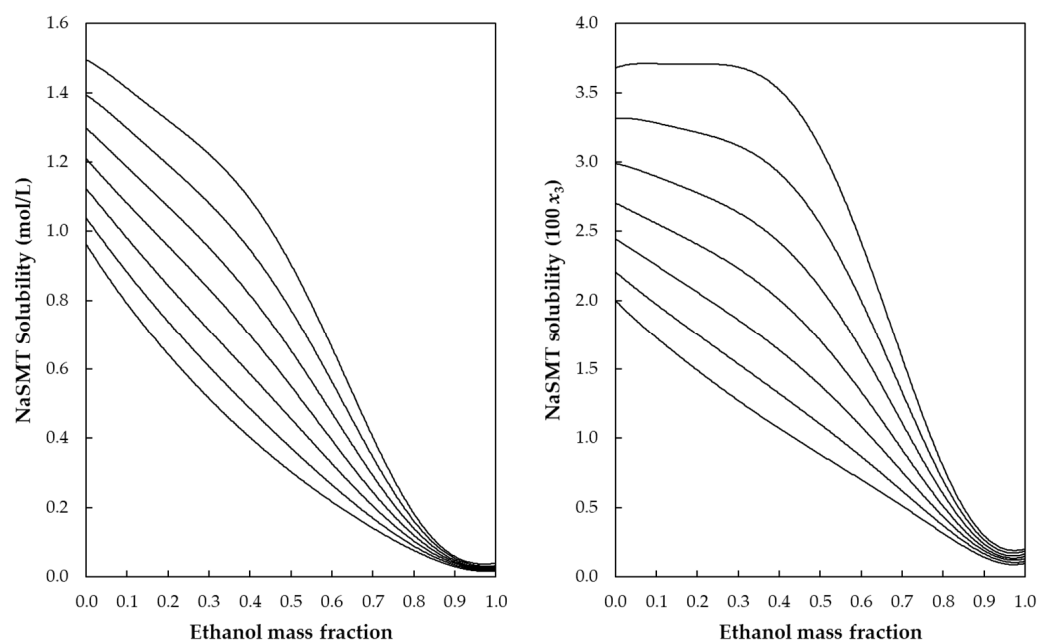


Figure 8. Equilibrium solubility of sodium sulfamethazine expressed in molarity (**left**) and mole fraction (**right**) in some aqueous ethanolic mixtures as a function of ethanol mass fraction at different temperatures. Trends from top to bottom: 35.0 °C, 30.0 °C, 25.0 °C, 20.0 °C, 15.0 °C, 10.0 °C, and 5.0 °C.

3.2. Apparent Specific Volume of NaSMT at Saturation

As described earlier in the literature, knowledge of the volumetric contribution of drugs and excipients after their dissolutions in aqueous cosolvent mixtures, as a function of system composition and temperature, is fundamental from both practical and theoretical viewpoints. Thus, a well-known property of pharmaceutical solutes in saturated solutions is its apparent specific volume (ϕ_V^{sp}), which is obtained using Equation (3) [30–32]:

$$\phi_V^{\text{sp}} = \frac{w_3 + w_{1+2}(1 - \rho_{1+2+3}/\rho_{1+2})}{w_3\rho_{1+2+3}} \quad (3)$$

Here, w_3 and w_{1+2} are the mass fractions of NaSMT (3) and the {ethanol (1) + water (2)} mixture in every saturated solution, respectively, whereas, ρ_{1+2+3} and ρ_{1+2} are the densities of the saturated solution and the cosolvent mixture free of NaSMT, respectively. The density values of the NaSMT-saturated solutions in all studied cosolvent mixtures and neat solvents at all temperatures are summarized in Table 4 and depicted in Figure 9. Regarding the behavior of the saturated mixtures, the density values decrease with the ethanol proportion in the mixtures (Table 4 and Figure 9) because ethanol is the component exhibiting the lowest density and because the NaSMT solubility decreases as the ethanol proportion increases in these aqueous mixtures. Regarding the effect of increasing temperature, the density of the saturated systems increases in pure water and in mixtures of $0.10 \leq w_1 \leq 0.70$. This is because the effect of NaSMT solubility increase is more important than the density decrease of the solvent systems free of the drug. Otherwise, the density of saturated systems decreases with increasing temperature in the solvent systems of $0.80 \leq w_1 \leq 1.00$, demonstrating the main role of density decrease of solvent systems with increasing temperature compared with the NaSMT solubility increase due to the low drug solubilities observed in these solvent systems.

Table 4. Density of saturated solutions of sodium sulfamethazine in aqueous ethanolic mixtures (ρ_{1+2} /g/mL) at different temperatures.

w_1 ^a	Temperature (°C) ^b						
	5.0	10.0	15.0	20.0	25.0	30.0	35.0
0.00	1.1395	1.1406	1.1435	1.1465	1.1485	1.1505	1.1546
0.10	1.0992	1.1055	1.1098	1.1147	1.1181	1.1233	1.1274
0.20	1.0655	1.0712	1.0764	1.0844	1.0934	1.0945	1.1005
0.30	1.0342	1.0400	1.0438	1.0538	1.0596	1.0651	1.0722
0.40	1.0071	1.0094	1.0157	1.0231	1.0281	1.0338	1.0400
0.50	0.9753	0.9779	0.9800	0.9873	0.9902	0.9940	1.0014
0.60	0.9335	0.9399	0.9435	0.9435	0.9477	0.9548	0.9600
0.70	0.9024	0.9035	0.9033	0.9031	0.9022	0.9052	0.9054
0.80	0.8690	0.8655	0.8623	0.8594	0.8584	0.8558	0.8531
0.90	0.8372	0.8353	0.8327	0.8270	0.8226	0.8191	0.8153
1.00	0.8086	0.8024	0.7985	0.7957	0.7901	0.7861	0.7827

^a w_1 is the mass fraction of ethanol in the binary mixtures free of sodium sulfamethazine. ^b Mean uncertainty in density of saturated solutions is 0.0010 g/mL.

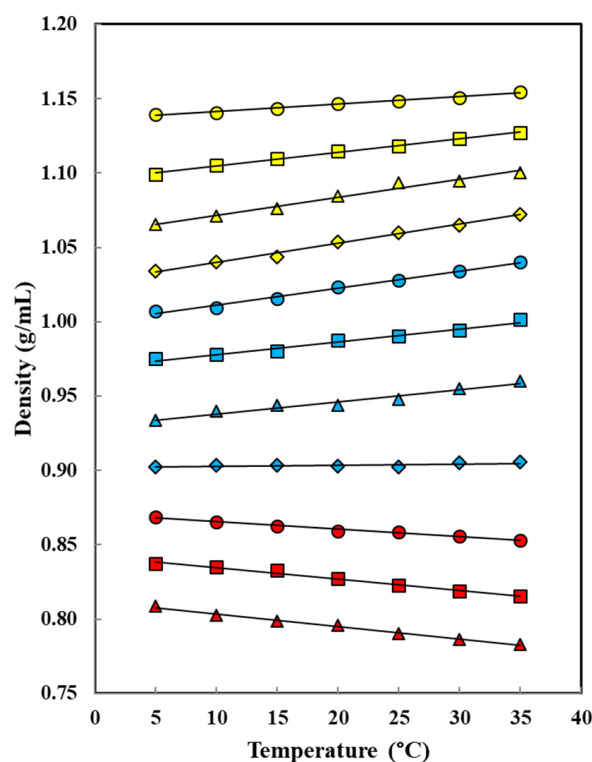
**Figure 9.** Density of saturated solutions of sodium sulfamethazine in some aqueous ethanolic mixtures as a function of temperature. ●: neat water; ■: $w_1 = 0.10$; ▲: $w_1 = 0.20$; ◆: $w_1 = 0.30$; ●: $w_1 = 0.40$; ■: $w_1 = 0.50$; ▲: $w_1 = 0.60$; ◆: $w_1 = 0.70$; ●: $w_1 = 0.80$; ■: $w_1 = 0.90$; ▲: neat ethanol.

Table 5 summarizes the difference between the densities of the NaSMT-saturated solutions and the aqueous ethanolic mixtures free of drug at different temperatures. Densities of binary mixtures free of NaSMT were taken numerically from the literature [33,34].

Table 5. Difference in density of saturated solutions of sodium sulfamethazine and aqueous ethanolic mixtures free of drug ($\Delta\rho/\text{g/mL}$) at different temperatures.

w_1 ^a	Temperature (°C) ^b						
	5.0	10.0	15.0	20.0	25.0	30.0	35.0
0.00	0.1395	0.1408	0.1443	0.1483	0.1515	0.1548	0.1606
0.10	0.1132	0.1205	0.1262	0.1329	0.1379	0.1446	0.1507
0.20	0.0915	0.0986	0.1056	0.1158	0.1268	0.1306	0.1393
0.30	0.0714	0.0800	0.0866	0.1001	0.1087	0.1177	0.1281
0.40	0.0611	0.0666	0.0764	0.0879	0.0960	0.1061	0.1159
0.50	0.0496	0.0557	0.0616	0.0735	0.0802	0.0881	0.0997
0.60	0.0295	0.0399	0.0467	0.0524	0.0605	0.0719	0.0807
0.70	0.0216	0.0267	0.0297	0.0354	0.0385	0.0460	0.0507
0.80	0.0121	0.0130	0.0130	0.0160	0.0192	0.0211	0.0220
0.90	0.0057	0.0082	0.0089	0.0090	0.0094	0.0097	0.0095
1.00	0.0062	0.0041	0.0033	0.0062	0.0048	0.0050	0.0060

^a w_1 is the mass fraction of ethanol in the binary mixtures free of sodium sulfamethazine. ^b Mean uncertainty in density differences is 0.0015 g/mL.

Figure 10 depicts a comparison of densities for all saturated solutions and the respective cosolvent mixtures free of NaSMT at 25.0 °C. Careful examination of Figure 10 reveals that all of the saturated solutions exhibit densities higher than those of the cosolvent mixtures free of NaSMT because this drug exhibits higher density compared with all respective solvent systems. As observed, density differences decrease as the ethanol proportion decreases in the mixtures as a consequence of NaSMT solubility decrease. Moreover, density differences increase with increasing temperature from pure water to the mixture of $w_1 = 0.80$ owing to the increase in NaSMT solubility. However, in the mixture of $w_1 = 0.90$ and in pure ethanol, the differences follow erratic tendencies.

An adapted version of the Jouyban–Acree model was presented for modeling the physicochemical properties of the solvent mixtures at different temperatures, including their density values [35]. The model could be trained using the solute-free density values of the solvent mixtures at various temperatures, because the small effect of the dissolved drug on the numerical values of the density of the saturated solution could be ignored, in particular in the case of organic salts in ethanol-rich mixtures. The trained model using the NaSMT-free mixtures of {ethanol (1) + water (2)} mixtures is as follows [18]:

$$\ln \rho_{m,T} = w_1 \ln \rho_{1,T} + w_2 \ln \rho_{2,T} + \frac{1.048 \cdot w_1 w_2}{t(^{\circ}\text{C}) + 273.15} \quad (4)$$

Equation (4) was used to predict the density of the NaSMT in {ethanol (1) + water (2)} mixtures employing the experimental density of the drug in neat ethanol and water at each temperature of interest with the MPD of 1.0% [18]. Using the same prediction procedure, the MPD for NaSMT is 0.9%.

The calculated apparent specific volumes of NaSMT at saturation (φ_V^{sp}) as functions of mixture composition and temperature are summarized in Table 6. Moreover, as a visual aid, Figures 11 and 12 depict this property as a function of the {ethanol (1) + water (2)} mixture composition and temperature, respectively. It is important to note that significant φ_V^{sp} values are obtained from pure water to the mixture of $w_1 = 0.80$, while in the mixture of $w_1 = 0.90$, very low φ_V^{sp} values are observed at 10.0 and 15.0 °C; moreover, in pure ethanol, a negative φ_V^{sp} value is observed, i.e., −0.28 mL/g.

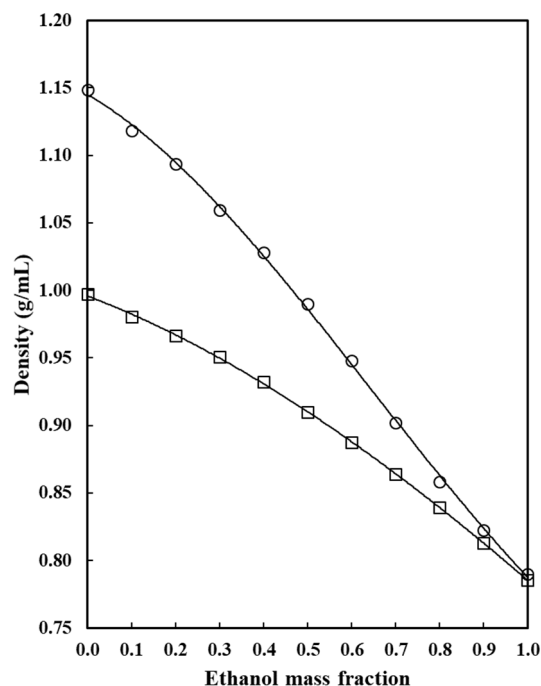


Figure 10. Density of saturated solutions of sodium sulfamethazine (○) and density of aqueous ethanolic mixtures free of drug (□) in aqueous ethanolic mixtures as a function of mixture composition at 25.0 °C.

Table 6. Apparent specific volume of sodium sulfamethazine at saturation (ϕ_V^{sp} / mL/g) in several aqueous ethanolic mixtures at several temperatures.

w_1 ^a	Temperature (°C) ^b						
	5	10	15	20	25	30	35
0.00	0.518	0.549	0.573	0.593	0.613	0.633	0.646
0.10	0.529	0.552	0.580	0.601	0.624	0.642	0.660
0.20	0.544	0.573	0.601	0.616	0.629	0.658	0.674
0.30	0.555	0.582	0.622	0.631	0.652	0.676	0.692
0.40	0.523	0.574	0.602	0.616	0.651	0.673	0.697
0.50	0.496	0.552	0.603	0.613	0.651	0.681	0.701
0.60	0.602	0.547	0.579	0.623	0.647	0.660	0.681
0.70	0.554	0.547	0.599	0.602	0.655	0.646	0.682
0.80	0.549	0.599	0.675	0.650	0.628	0.658	0.699
0.90	0.437	0.254	0.303	0.403	0.467	0.544	0.628
1.00	<i>−0.280</i> ^c	0.364	0.641	0.227	0.548	0.592	0.604

^a w_1 is the mass fraction of ethanol in the binary mixtures free of sodium sulfamethazine. ^b Mean uncertainty in the apparent specific volume of sodium sulfamethazine is 0.009 mL/g. ^c Value in italics is not considered for analysis because it is a negative value.

As observed, NaSMT ϕ_V^{sp} values increase continuously with increasing solution temperature in the composition interval of $0.00 \leq w_1 \leq 0.50$. From $w_1 = 0.60$ to $w_1 = 0.80$ the behavior is slightly erratic, perhaps because of the experimental uncertainty associated with one or two of the experimental values. The behavior appears more erratic; however, in $w_1 = 0.90$ and in neat ethanol, it is fully erratic at the lower four temperatures. In fact, the apparent specific volume of sodium sulfamethazine is negative at 5 °C. Regarding the variation in the NaSMT ϕ_V^{sp} values with the ethanol proportion in the mixtures at constant

temperature, the behavior is also erratic, particularly at 5.0 °C, where the observed trend is clearly different compared with those observed at other temperatures. As observed, the more erratic φ_V^{sp} values are observed in those systems and conditions exhibiting the lower solubilities, which implies smaller differences in densities of saturated solutions and mixtures.

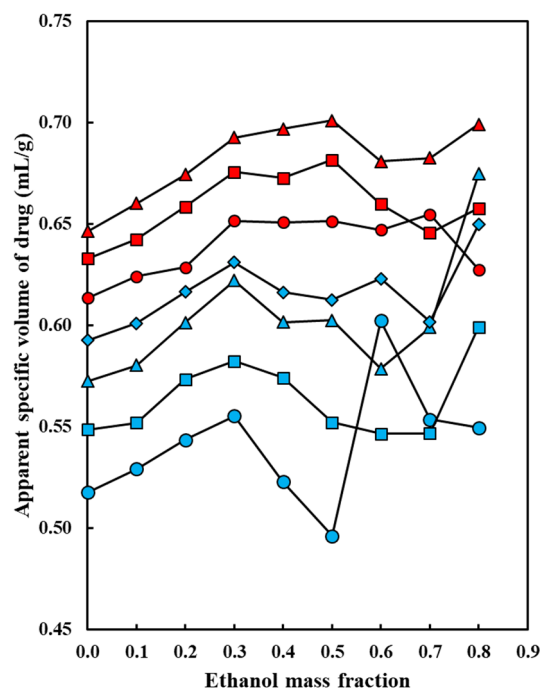


Figure 11. Apparent specific volume of sodium sulfamethazine at saturation in aqueous alcoholic mixtures as a function of ethanol mass fraction at several temperatures. ●: 5.0 °C; ■: 10.0 °C; ▲: 15.0 °C; ◆: 20.0 °C; ●: 25.0 °C; ■: 30.0 °C; ▲: 35.0 °C.

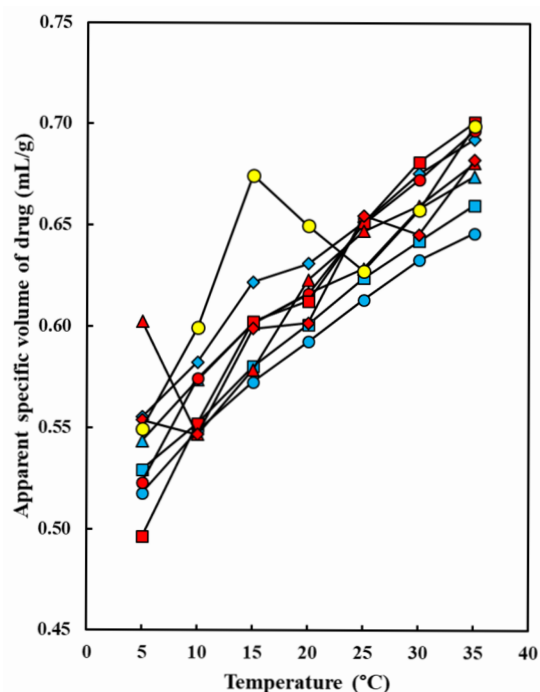


Figure 12. Apparent specific volume of sodium sulfamethazine at saturation in aqueous alcoholic mixtures as a function of temperature. ●: neat water; ■: $w_1 = 0.10$; ▲: $w_2 = 0.20$; ◆: $w_1 = 0.30$; ●: $w_1 = 0.40$; ■: $w_1 = 0.50$; ▲: $w_1 = 0.60$; ◆: $w_1 = 0.70$; ●: $w_1 = 0.80$.

The main technological purpose of determining the ϕ_V^{sp} values of drugs and excipients is to verify if this property is almost constantly independent of temperature and mixture composition. Thus, in this ternary (or binary in the case of pure solvents) system, in the interval of $0.00 \leq w_1 \leq 0.80$, the global mean ϕ_V^{sp} value is 0.615 (± 0.051) mL/g (with relative standard deviation, RSD = 8.33%). As clearly observed, this relative deviation exceeds 5.0%, indicating that, in some cases, it is better to study the effect of mixture composition and temperature on this property in order to obtain more reliable values during the different stages associated with the research and development of homogeneous liquid pharmaceutical dosage forms [36–39].

4. Conclusions

From all topics discussed previously, it can be concluded that the NaSMT solubility in {ethanol (1) + water (2)} mixtures is strongly dependent on temperature and the cosolvent mixture composition. NaSMT equilibrium solubility increases with increasing temperature, but decreases with an increase in the proportion of ethanol in the mixtures at all temperatures studied. This is because the dielectric constant of the mixtures free of NaSMT is lower as the ethanol proportion increases. Thus, the capacity of the solvent mixture to separate ionic charges decreases. Moreover, the capacity of the solvent mixture components to solvate the respective ions is also reduced. Mass/volume percentage logarithmic solubility is adequately correlated with a multivariate model involving a linear effect of temperature and a fourth-degree polynomial effect of mixture composition. Furthermore, the apparent specific volume (ϕ_V^{sp}) of NaSMT at saturation is also dependent on temperature and ethanol proportion in the mixtures. Thus, a global mean NaSMT ϕ_V^{sp} value of 0.615 (± 0.051) mL/g is obtained in the mixture composition interval of $0.00 \leq w_1 \leq 0.80$. Moreover, it can be said that both the solubility and volumetric data presented in this report expand the physicochemical information on the behavior of saline drugs in mixed aqueous solutions [29,40].

Author Contributions: Conceptualization, D.R.D., F.M., M.Á.P., A.J. and W.E.A.J.; methodology, D.R.D.; software, D.R.D., F.M. and A.J.; validation, D.R.D., F.M., M.Á.P., T.S., A.J. and W.E.A.J.; formal analysis, D.R.D., F.M., M.Á.P., A.J. and W.E.A.J.; investigation, D.R.D., F.M., M.Á.P., T.S., A.J. and W.E.A.J.; resources, F.M.; data curation, D.R.D., F.M., T.S. and A.J.; writing—original draft preparation, D.R.D., F.M. and A.J.; writing—review and editing, D.R.D., F.M., M.Á.P., A.J. and W.E.A.J.; visualization, F.M.; supervision, F.M., A.J. and W.E.A.J.; project administration, F.M.; funding acquisition, F.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All generated and required physicochemical data are reported in this manuscript.

Acknowledgments: We thank the Department of Pharmacy of the Universidad Nacional de Colombia for providing us the reagents, equipment, and laboratories used in this research.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CAS	Chemical Abstract Service
MPD%	Mean percentage deviation

NaSMT	Sodium sulfamethazine
RSD	Relative standard deviation
R&D	Research and Development
w_1	Mass fraction of ethanol
w_{1+2}	Mass fraction of solvent mixture
w_3	Mass fraction of solute
x_3	Mole fraction of solute
% m/m	Mass/mass percentage
% m/v	Mass/volume percentage
ϵ	Dielectric constant
φ_V^{sp}	Apparent specific volume
ρ	Density

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