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Effect of Ethanol on the Solubility and Apparent Specific Volume of Sodium Sulfadiazine in Aqueous Mixtures

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Abstract: The main objective of this research was to correlate the equilibrium solubility of sodium sulfadiazine in several {ethanol (EtOH, 1) + water (2)} mixtures reported in mass/volume and mass/mass percentages at different temperatures. Aqueous solubility of sodium sulfadiazine decreases almost linearly with decreasing temperature, but it decreases non-linearly with the addition of EtOH to water. Logarithmic solubility was adequately correlated with a bivariate model involving temperature and mixture composition. These solubility results were also well correlated with the Jouyban–Acree-based models. Moreover, an adapted version of the Jouyban–Acree model was used to represent the density of the saturated solvent mixtures at different temperatures. Furthermore, the apparent specific volumes of this drug at saturation were also calculated from densities of saturated solutions and cosolvent mixtures free of drug as well as from the respective mixture compositions. These findings provide valuable insights into the solubility and volumetric behavior of sodium sulfadiazine, which could be useful for pharmaceutical formulation and process optimization.

Keywords: sodium sulfadiazine; aqueous alcoholic mixtures; solubility; cosolvency; apparent specific volume

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1. Introduction

It is well-known that the exhaustive physicochemical characterization of drugs in dissolution plays a crucial role in all stages associated with the R&D of homogenous liquid pharmaceutical dosage forms, especially those intended for parenteral administration in small volumes like ampules, because these products supply high doses of active pharmaceutical ingredients [1–4].

Sodium sulfadiazine (sodium [(4-aminophenyl)sulfonyl](2-pyrimidinyl)azanide, NaSD, Figure 1) is a drug extensively used for the treatment of certain infections caused by several kinds of microorganisms [5–7]. Although NaSD is widely used in therapeutics, its physicochemical information regarding its behavior in aqueous solutions is not yet complete. However, some physicochemical studies have been reported in the literature. Thus, the molar and mole fraction equilibrium solubility as well as the respective dissolution and

mixing thermodynamic quantities in some ethanol–water blended solvents have been reported [8–10]. Moreover, its equilibrium solubility and apparent specific volumes at saturation in different {cosolvent (1) + water (2)} mixtures at 25.0 °C have also been reported, involving propylene glycol, formamide, *N*-methylformamide, *N*,*N*-dimethylformamide, dimethyl sulfoxide, *N*-methyl-2-pyrrolidone, 1,4-dioxane, and methanol [11,12]. On the other hand, apparent molar volumes at several drug concentrations have been determined at several temperatures in aqueous–cosolvent media [13,14]. Ultimately, the molar electrical conductivity of this saline drug has also been studied as a function of drug concentration as a function of temperature [15]. All these investigations have demonstrated the role of hydrophilic and hydrophobic hydration processes of this drug on the observed physicochemical magnitudes in aqueous media.

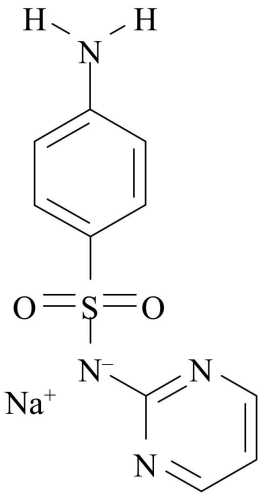

Figure 1. Molecular structure of sodium sulfadiazine (NaSD).

From a pharmaceutical viewpoint, the systematic searching, acquisition, and systematization of equilibrium solubility values and volumetric contributions of active pharmaceutical ingredients and excipients at saturation conditions in aqueous and non-aqueous cosolvent mixtures are very significant for theoretical and practical purposes. This is because cosolvent blends are frequently employed in pharmaceutical ingredient purification methods, dosage form preformulation studies, and the development and preparation of homogeneous liquid medicines, as already mentioned [16,17]. Therefore, it is almost mandatory for the global chemical and pharmaceutical community to systematically determine the solubility and specific volume contribution of every pharmaceutical agent.

Otherwise, the study of molar and specific volumes of every kind of pharmaceutical solute has been carried out basically with the aim of facilitating the design of liquid medicines on the one hand and also as an aid to proposing mechanisms for the transferring processes of drugs through biological membranes. Within the first group, studies have been carried out focused on the generation of useful information in the design of drug delivery systems, and as an example, the determination of partial specific volumes and critical micellar concentrations of surfactants from density measurements of their aqueous solutions [18]; in a similar way, these determinations facilitate the proposal of novel calculation methods of partial molar volumes of surfactants dispersed at the micellar level owing to the difficulty observed in determining experimentally this property under extreme conditions [19]. However, from density measurements, the apparent specific volumes of poly(ethylene oxide), poly(butylene oxide), poly(propylene oxide), and octadecyl chains in the micellar state as a function of temperature have been calculated and reported [20]. Moreover, Sarazin and Francois, analyzing various polymers in solvents of differing molec-

ular size and polarity, confirmed the dependence of their apparent specific volume on polymer molecular weight and solvent molar volume [21]. Moreover, it is noteworthy that use of apparent specific volumes is relevant in chemical analysis varying from milk food science to blood biochemistry [22,23]. On the other hand, molar volumes are required to calculate Hildebrand solubility parameters as required for the estimation of the solubility of organic compounds [24,25]. Thus, partial molar volumes and solubility parameters of compounds of pharmaceutical interest such as some esters have been studied [26]. Specifically, regarding the penetration of biological membranes, the solubility and partial molar volume of the ophthalmological drug physostigmine in binary mixtures of isopropanol–isopropyl myristate have been studied as an aid in clarifying the effects of these solvents on the penetration of physostigmine through biological membranes [27].

The extended theory of regular solutions has been applied to explain and estimate the percutaneous absorption of different non-electrolytes or undissociated weak electrolytes by studying the solubility and partial molar volumes of these solutes in certain solvents, with the aim of finding application in the design of dermal controlled release systems. Some of these solutes correspond to certain alkanoic acids, theophylline, and adenosine, among others [28–30].

In the research field related to identifying action mechanisms of active ingredients, the effect of volumetric properties has also been studied, as shown in the case of volatile anesthetics such as halothane, which have been evaluated for compressibility, molar volume, and partial molar volume in different solvents [31,32]. More recently, the partial molar volumes of some local anesthetics like lidocaine in water and ethanol were evaluated experimentally, and from these values the corresponding transfer volumes were calculated, and the respective interpretation was made in terms of solute–solvent interactions highlighting the role of the hydrophobicity of the compounds on the binding to the cell membrane [33].

Other compounds of pharmaceutical interest studied include sodium salicylate, methyl orange, tryptophan, phenol and propranolol hydrochlorides, procaine, pilocarpene and ephedrine, whose volumes and apparent molal compressibilities have been determined as a contribution to the clarification of solute–solvent interactions in QSAR studies [34]. A similar investigation was performed with tetracycline hydrochloride and chlortetracycline involving determining the partial molal volumes and compressibilities, interaction coefficients, and several thermodynamic activation parameters from ultrasonic speed, density, and viscosity measurements [35]. Furthermore, the partial molal volumes at infinite dilution of different phenyl alkylamines have also been reported [36]. Moreover, the volumetric properties of several other compounds, including active ingredients and excipients, have also been studied [37–41]. Otherwise, apparent specific volumes have been correlated with primary tastes as well as with specific tastes like amino acids and sweetener agents [42–48].

In this way, the present research studied the mass/volume (% m/v) and mass/mass (% m/m) percentages, equilibrium solubility, and apparent specific volume (φ_V^{sp}/mL/g) at saturation of NaSD (solute identified as component 3) in several aqueous–alcoholic binary mixtures at different temperatures from 5.0 to 35.0 °C. Thus, this research expands the available database of these properties reported earlier for other drugs and excipients in several binary and ternary aqueous–cosolvent mixtures that include some non-electrolyte organic compounds and active organic salts. These compounds and solvent systems include propranolol·HCl in aqueous binary mixtures of 1,4-dioxane, acetonitrile, polyethylene glycol 400, propylene glycol, and methanol at 25.0 °C [49]; sodium naproxen, procaine·HCl, and lysine clonixinate in (propylene glycol + water) [50] and (methanol + water) [51] mixtures at 25.0 °C; lidocaine·HCl·H_2O in aqueous binary mixtures of polyethylene glycol 200, ethanol, and propylene glycol at 25.0 °C [52]; and sodium diclofenac in aqueous binary mixtures of formamide, *N*-methylformamide, and *N*,*N*,-dimethylformamide at 25.0 °C [53].

All these reported physicochemical values of pharmaceutical compounds could be used for improving research and development activities.

Thus, it is noteworthy that these basic physicochemical properties of solid compounds in aqueous solutions have been key factors long time ago in the design of liquid dosage forms like syrups, elixirs, and injectable solutions, as well as in predicting the biological behavior of drugs [54,55].

2. Methods

The equilibrium solubility values of NaSD (CAS number: 547-32-0, molecular formula: $C_{10}H_9N_4NaO_2S$, molar mass: 272.26 g/mol, provider: Sigma-Aldrich, Burlington, MA, USA, mass fraction purity > 0.99) in binary mixtures of ethanol (CAS number: 64-17-5, molecular formula: C_2H_6O, molar mass: 46.07 g/mol, provider: Merck, Darmstadt, Germany, mass fraction purity > 0.995) and water (CAS number: 7732-18-5, obtained by distillation, conductivity < 2 μS/cm) as a function of mixture composition and temperature were expressed in molarity and mole fraction earlier [10,11]. Thus, these solubility values were determined at seven temperatures from 5.0 to 35.0 °C in EtOH mass fractions (w_1) from w_1 = 0.10 to w_1 = 0.90 varying by 0.10, studying nine binary mixtures and both pure solvents.

Classical shake-flask method and UV–vis spectrophotometry were employed for solubility determinations [56,57]. An excess of NaSD was added to 50 mL of each cosolvent mixture in stoppered dark glass flasks. 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, the flasks were kept at 35.0 ± 0.05 °C in recirculating thermostatic baths (Neslab RTE 10 Digital One, Thermo Electron Company, Waltham, MA, USA) with sporadic stirring at least for three days until equilibrium is obtained. After this time, the supernatant solutions were filtered (at isothermal conditions) using 0.45 μm pore diameter cartridges to ensure that they were free of particulate matter before sampling. NaSD concentrations at saturation were determined by measuring UV absorbance after appropriate gravimetric dilution with pure water and interpolation from a UV spectrophotometric calibration curve (UV/Vis BioMate 3 spectrophotometer, Thermo Electron Company, Waltham, MA, USA). Then, the temperature was diminished in successive steps of 5.0 °C following the same procedures indicated above to reach 5.0 °C as the lowest research temperature. All the solubility experiments were run at least in triplicate.

Moreover, in order to facilitate the transformation between volumetric and gravimetric concentration scales [2,58] and allow the calculation of apparent specific volumes of NaSD, the density of the saturated solutions at every temperature was determined with 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 plots were performed with different tools of MS Excel® v. 2013.

3. Results and Discussion

3.1. Experimental Solubility at Different Temperatures and Mixture Compositions

Table 1 summarizes the experimental mass/volume percentage solubilities of NaSD in the aqueous mixtures of ethanol as a function of the mixtures' composition and temperature. As visual help, % m/v solubilities are depicted as a function of mixture compositions at all temperatures in Figure 2. As observed, NaSD solubility increases with temperature rising, but it diminishes with the increasing EtOH proportion in the mixtures at all temperatures. The respective trends were adjusted to regular polynomials in the fourth degree in all cases [59–61]. Moreover, % m/v solubilities are depicted at all mixture compositions as a

function of temperature in Figure 3, observing linear NaSD solubility increasing in all the solvent systems [59–61].

Table 1. Equilibrium solubility of sodium sulfadiazine in aqueous alcoholic 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	46.90	48.33	49.73	51.06	52.29	53.72	55.15
0.10	37.05	38.66	40.24	41.72	43.28	44.74	46.14
0.20	27.53	29.14	30.84	32.39	34.14	35.72	37.35
0.30	18.92	20.19	21.63	23.06	24.34	25.81	27.30
0.40	12.89	13.89	14.93	15.89	17.06	18.21	19.22
0.50	7.82	8.35	9.08	9.79	10.50	11.15	11.92
0.60	4.43	4.79	5.15	5.49	5.92	6.33	6.73
0.70	2.35	2.52	2.69	2.88	3.05	3.23	3.42
0.80	0.904	0.954	1.01	1.05	1.10	1.15	1.19
0.90	0.248	0.260	0.272	0.282	0.293	0.304	0.312
1.00	0.036	0.037	0.038	0.039	0.040	0.041	0.043

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

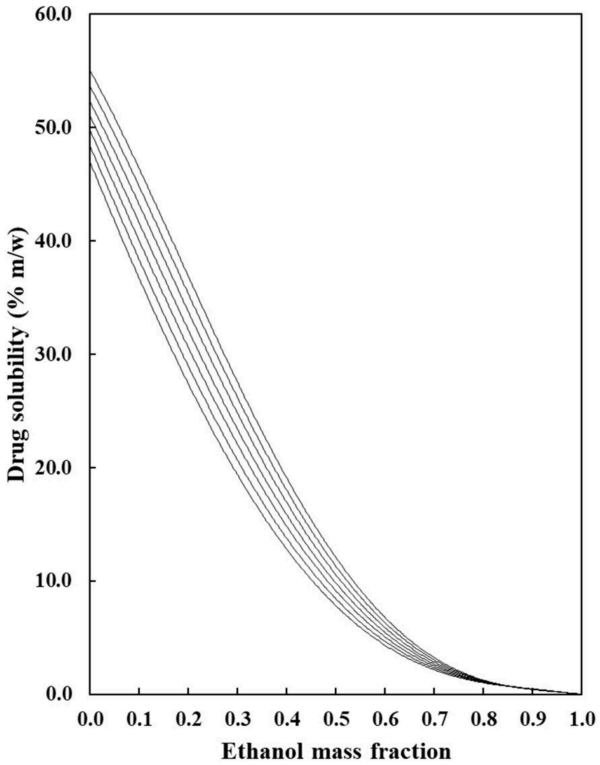

Figure 2. Equilibrium solubility of sodium sulfadiazine expressed in mass/volume percentage in some aqueous alcoholic mixtures as a function of the ethanol mass fraction at different temperatures. Trends from top to bottom: 35.0 °C, 30.0 °C, 25.0 °C, 20.0 °C, 15.0 °C, 10.0 °C, and 5.0 °C.

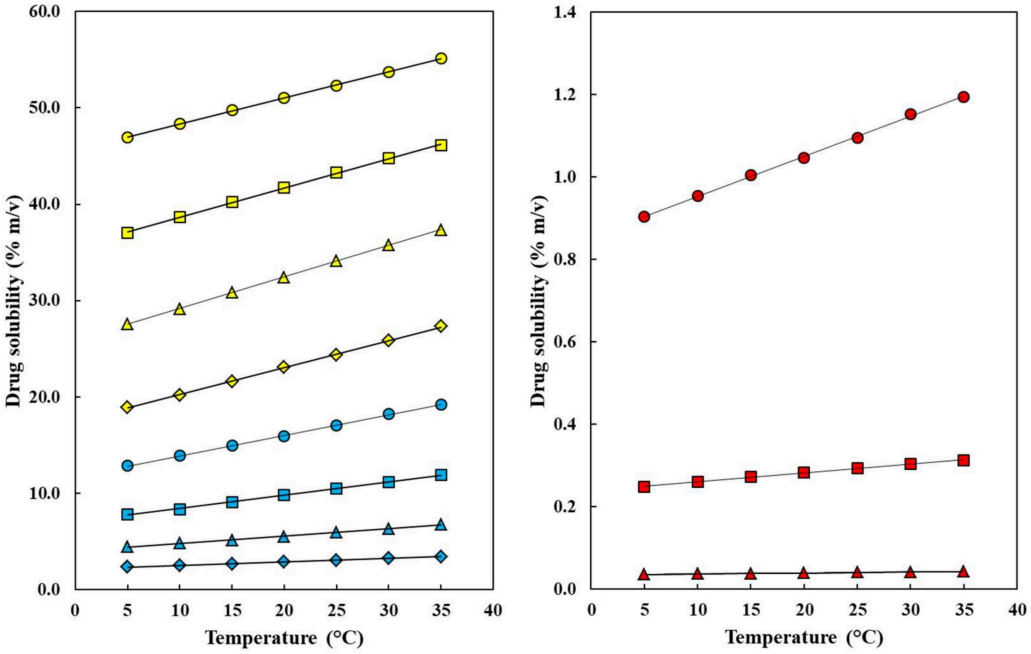

Figure 3. Equilibrium solubility of sodium sulfadiazine in some aqueous alcoholic mixtures as a function of temperature expressed in mass/volume percentage. ○: neat water; □: w_1 = 0.10; △: w_2 = 0.20; ◇: w_1 = 0.30; ●: w_1 = 0.40; ■: w_1 = 0.50; ▲: w_2 = 0.60; ◆: w_1 = 0.70; ●: w_1 = 0.80; ■: w_1 =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

On the other hand, all logarithmic % m/v solubility values of NaSD (compound 3) in {ethanol (compound 1) + water (compound 2)} ($\ln S_{3,1+2}$) 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 (°C). Obtained statistical parameters were as follows: r^2 = 0.9997, mean standard error = 0.0400, and statistical F value = 45,526. This model allows the calculation of NaSD solubility with a mean percentage deviation (MPD %) of 3.0%—as calculated with Equation (2), where $S_3^{\text{Calculated}}$ and S_3^{Observed} are the calculated and experimental solubility NaSD values, respectively [59–61]. It is worth noting that this MPD is slightly higher than the mean relative uncertainty in mass/volume percentage solubility of 2.0% (Table 1), demonstrating the usefulness of this correlation model.

$$\begin{aligned}\ln S_{3,1+2} &= 3.714 + 0.0102(\pm 0.0005)\cdot t(^{\circ}\text{C}) - 0.769(\pm 0.223)\cdot w_1 \\ &\quad -10.04(\pm 0.98)\cdot w_1^2 + 16.46(\pm 1.50)\cdot w_1^3 - 12.80(\pm 0.75)\cdot w_1^4\end{aligned} \quad (1)$$

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

On the other hand, Table 2 summarizes the experimental mass/mass percentage solubilities of NaSD in the aqueous mixtures of ethanol as a function of both the mixtures' composition and temperature. Moreover, as a visual help, % m/m solubilities are depicted as a function of mixture compositions at four temperatures in Figure 4 as a Gibbs–Roozeboom triangular graph [62,63]. It is noteworthy that mass fraction solubilities are required for calculating apparent specific volumes of NaSD as indicated below.

Table 2. Equilibrium solubility of sodium sulfadiazine in aqueous alcoholic 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	39.14	40.18	41.19	42.18	43.13	44.12	45.07
0.10	32.22	33.38	34.53	35.61	36.70	37.74	38.72
0.20	25.08	26.30	27.54	28.69	30.03	31.21	32.44
0.30	18.01	19.11	20.18	21.30	22.33	23.51	24.65
0.40	12.77	13.66	14.56	15.37	16.40	17.41	18.28
0.50	8.07	8.58	9.27	9.93	10.60	11.20	11.92
0.60	4.75	5.13	5.51	5.87	6.31	6.74	7.16
0.70	2.62	2.82	3.01	3.24	3.43	3.65	3.87
0.80	1.04	1.11	1.17	1.22	1.29	1.36	1.42
0.90	0.297	0.313	0.329	0.343	0.358	0.374	0.386
1.00	0.044	0.046	0.048	0.050	0.051	0.053	0.055

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

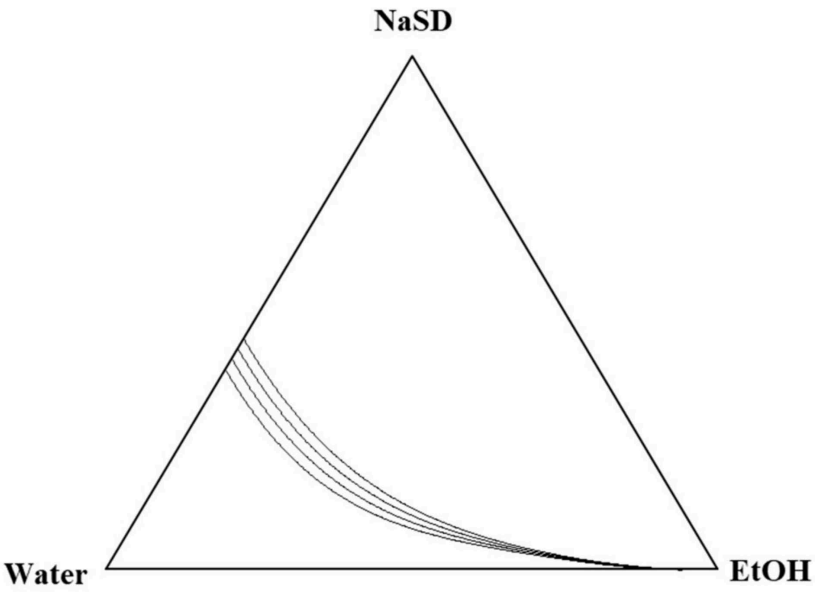

Figure 4. Equilibrium solubility of sodium sulfadiazine expressed in mass/mass percentage in some aqueous alcoholic mixtures as a function of the mixture composition at different temperatures. Trends from top to bottom: 35.0 °C, 25.0 °C, 15.0 °C, and 5.0 °C.

The effects of solubility units on the accuracy of the cosolvency model of Jouyban–Acree and Jouyban–Acree–van't Hoff models are investigated [64], and the obtained results are listed in Table 3. As it has been shown in Table 3, the model constants varied with different solubility units; however, there is no big difference among the MPD% values. This is in agreement with the findings reported in a previous study [64].

Table 3. Jouyban–Acree and Jouyban–Acree–van't Hoff models parameters for equilibrium solubility of sodium sulfadiazine in aqueous alcoholic mixtures at different temperatures.

Jouyban–Acree Model								
Scale					J_0	J_1	J_2	**MPD%**
Molar					2251.523	1343.278	912.184	7.1
Mole fraction					1951.167	1365.791	966.519	6.9
% mass/volume					2261.926	1362.768	939.024	8.1
% mass/mass					2257.024	1395.509	937.151	7.3
Jouyban–Acree–van't Hoff Model								
Scale	A_1	B_1	A_2	B_2	J_0	J_1	J_2	**MPD%**
Molar	−3.893	−770.676	2.191	−457.996	2251.206	1342.885	911.391	7.1
Mole fraction	−7.346	−598.184	−0.816	−662.826	1950.841	1365.970	965.703	6.9
% mass/volume	−1.595	−482.387	5.495	−457.990	2262.116	1363.003	939.497	8.1
% mass/mass	−0.885	−621.286	5.114	−402.209	2256.757	1395.700	936.483	7.3

MPD, mean percentage deviation.

3.2. Apparent Specific Volume of Sodium Sulfadiazine at Saturation

As widely described in the literature, the complete knowledge of the volumetric contribution of drugs and excipients after dissolution in aqueous cosolvent mixtures as a function of systems composition and temperature is very important from practical and theoretical viewpoints. Thus, a well-described property of every pharmaceutical solute in saturated solutions is its apparent specific volume (φ_V^{sp}), which is commonly calculated by means of Equation (3) [49–51]:

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

Here, w_3 and w_{1+2} are the mass fractions of the solute (3) and the {ethanol (1) + water (2)} mixture in the saturated solution, respectively. Furthrmore, ρ_{1+2+3} and ρ_{1+2} are the densities of the saturated solution and the cosolvent mixture free of solute, respectively.

The density values of the NaSD saturated solutions in all the cosolvent mixtures and neat solvents at all temperatures are shown in Table 4 and Figure 5.

Regarding the saturated mixtures, the density values diminish with the ethanol proportion in the mixtures (Table 4 and Figure 5) because ethanol is the compound exhibiting the lowest density and also because NaSD solubility decreases as the ethanol proportion increases in the mixtures. Regarding temperature increasing, the density of saturated systems increases in pure water and the mixtures of $0.10 \leq w_1 \leq 0.60$ because the effect of NaSD concentration increasing at saturation is more important than the density decreasing of the solvent systems free of drug as shown in Figure 6. Otherwise, the density of saturated systems decreases with temperature increasing in the solvent systems of $0.70 \leq w_1 \leq 1.00$, demonstrating the main role of density diminishing of solvent systems with temperature increasing compared with the NaSD solubility increasing owing to the low drug solubilities observed in these solvent systems.

Table 4. Density of saturated solutions of sodium sulfadiazine in aqueous alcoholic 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	1.1983	1.2028	1.2074	1.2106	1.2124	1.2175	1.2236
0.10	1.1498	1.1583	1.1652	1.1714	1.1793	1.1855	1.1918
0.20	1.0979	1.1078	1.1197	1.1289	1.1369	1.1446	1.1513
0.30	1.0507	1.0565	1.0716	1.0826	1.0898	1.0980	1.1074
0.40	1.0097	1.0172	1.0257	1.0341	1.0403	1.0462	1.0518
0.50	0.9686	0.9738	0.9796	0.9858	0.9904	0.9957	1.0001
0.60	0.9321	0.9337	0.9347	0.9357	0.9374	0.9382	0.9401
0.70	0.8967	0.8945	0.8924	0.8899	0.8881	0.8857	0.8831
0.80	0.8669	0.8629	0.8583	0.8545	0.8500	0.8494	0.8410
0.90	0.8359	0.8321	0.8269	0.8221	0.8173	0.8122	0.8073
1.00	0.8035	0.7990	0.7946	0.7910	0.7873	0.7835	0.7793

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

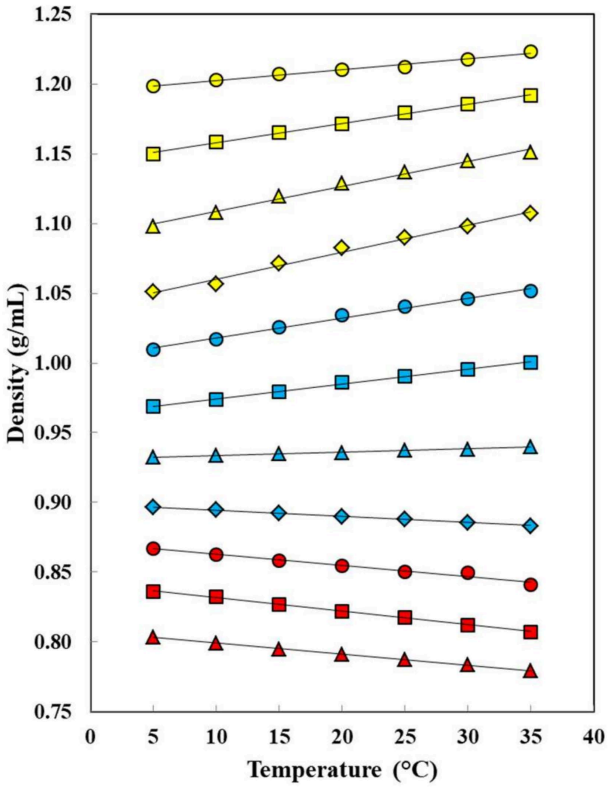

Figure 5. Density of saturated solutions of sodium sulfadiazine in some aqueous alcoholic mixtures as a function of temperature. ○: neat water; □: w_1 = 0.10; △: w_2 = 0.20; ◇: w_1 = 0.30; ●: w_1 = 0.40; ■: w_1 = 0.50; ▲: w_2 = 0.60; ◆: w_1 = 0.70; ●: w_1 = 0.80; ■: w_1 = 0.90; ▲: neat ethanol.

Moreover, Table 5 summarizes the difference in densities of saturated solutions of sodium sulfadiazine and aqueous alcoholic mixtures free of drug at different temperatures. It is noteworthy that densities of binary mixtures free of drug shown in Figure 6 were taken numerically from the literature [65,66]. It is important to note that volumetric and acoustic measurements have also been used for characterizing (EtOH + water) mixtures, demonstrating that the enhanced packing efficiency of ethanol in water at low concentrations is

affected by the formation of cage-like structures around the hydrophobic moiety; however, at high concentrations, linear chains or rings of ethanol molecules are formed, changing its mode of packing within the 3D structure of water [67].

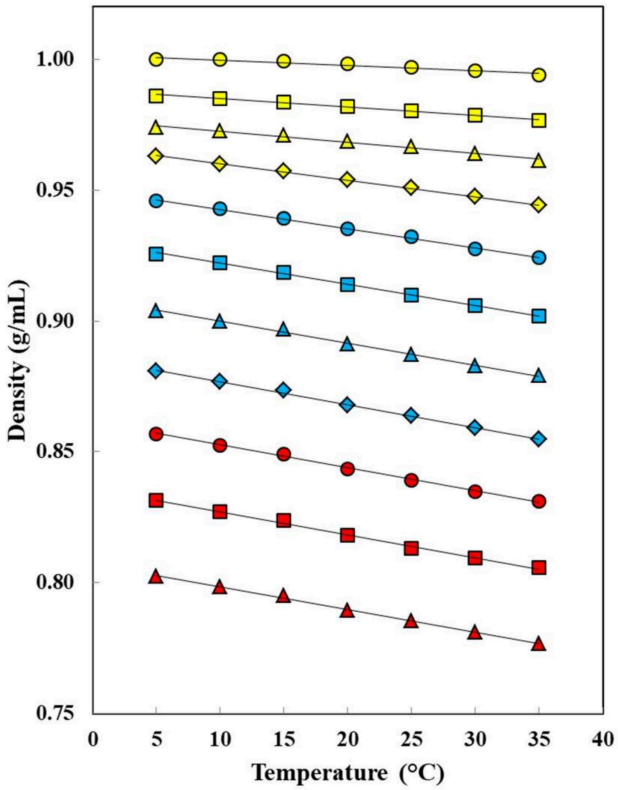

Figure 6. Density of some aqueous alcoholic mixtures free of sodium sulfadiazine as a function of temperature. ○: neat water; □: w_1 = 0.10; △: w_2 = 0.20; ◇: w_1 = 0.30; ●: w_1 = 0.40; ■: w_1 = 0.50; ▲: w_2 = 0.60; ◆: w_1 = 0.70; ●: w_1 = 0.80; ■: w_1 = 0.90; ▲: neat ethanol.

Table 5. Difference in density of saturated solutions of sodium sulfadiazine and aqueous alcoholic mixtures free of drug ($\Delta\rho$/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	0.1983	0.2030	0.2082	0.2124	0.2154	0.2218	0.2296
0.10	0.1638	0.1733	0.1816	0.1896	0.1991	0.2068	0.2151
0.20	0.1239	0.1352	0.1489	0.1603	0.1703	0.1807	0.1901
0.30	0.0879	0.0965	0.1144	0.1288	0.1389	0.1506	0.1633
0.40	0.0637	0.0744	0.0864	0.0989	0.1082	0.1185	0.1277
0.50	0.0429	0.0516	0.0612	0.0720	0.0804	0.0898	0.0984
0.60	0.0281	0.0337	0.0379	0.0446	0.0502	0.0553	0.0608
0.70	0.0159	0.0177	0.0188	0.0222	0.0244	0.0265	0.0284
0.80	0.0100	0.0104	0.0090	0.0110	0.0108	0.0147	0.0099
0.90	0.0044	0.0050	0.0031	0.0041	0.0041	0.0028	0.0015
1.00	0.0011	0.0007	−0.0006	0.0015	0.0020	0.0024	0.0026

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

Otherwise, as an example, Figure 7 allows the visual comparison of densities for all the saturated solutions and the respective cosolvent mixtures free of sodium sulfadiazine

at 25.0 °C. Moreover, Figure 8 allows the comparison of densities of saturated solutions in pure water regarding the water free of sodium sulfadiazine at different temperatures from 5.0 to 35.0 °C.

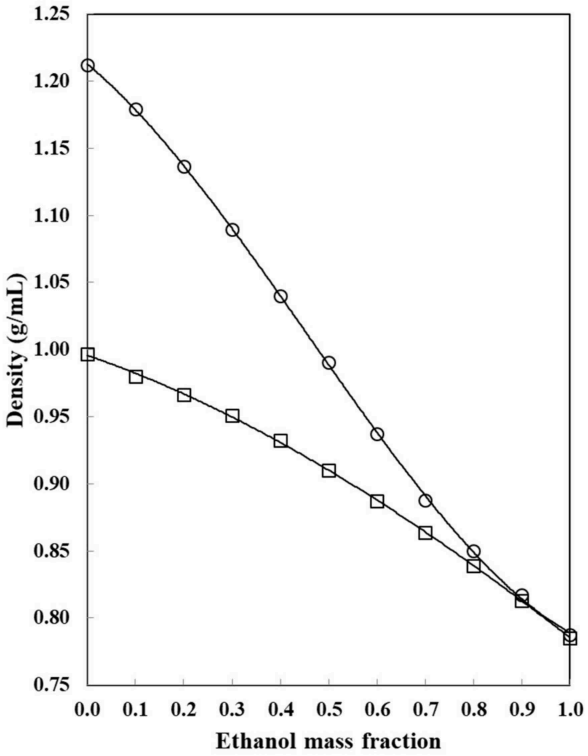

Figure 7. Density of saturated solutions of sodium sulfadiazine (○) and density of aqueous alcoholic mixtures free of drug (□) in some aqueous alcoholic mixtures as a function of the mixtures composition at 25.0 °C.

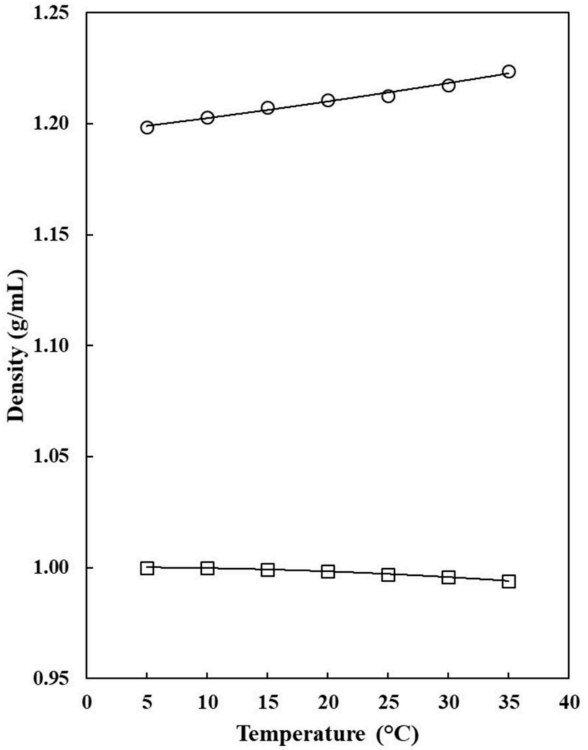

Figure 8. Density of saturated solutions of sodium sulfadiazine in pure water (○) and density of pure water free of drug (□) as a function of temperature.

As expected, all saturated solutions exhibit density values higher than those of the cosolvent mixtures free of sodium sulfadiazine, which indicates that this drug is denser than all the respective solvent systems.

As observed, density differences decrease as the ethanol proportion decreases in the mixtures owing to the NaSD solubility decreasing. Moreover, density differences increase with the temperature arising from pure water to the mixture of w_1 = 0.70 owing to the increase in the NaSD solubility. In mixtures from w_1 = 0.80 to pure EtOH, the differences follow erratic tendencies where differences in uncertainty are significant.

An adopted version of the Jouyban–Acree model could be used to represent the physico-chemical properties of the solvent mixtures at different temperatures, including density values [68]. Because of the ignorable effects of the dissolved solute on the density of the saturated solutions of poorly soluble drugs, one may use the trained model using solute-free solvent mixtures and then predict the density of the saturated solutions employing the experimental density of the saturated solutions in the neat mono-solvents. The trained model using the NaSD-free mixtures of aqueous alcoholic mixtures is as follows:

$$\ln \rho_{m,T} = w_1 \ln \rho_{1,T} + w_2 \ln \rho_{2,T} + \frac{1.048 w_1 w_2}{T} \quad (4)$$

This model predicted the density of the NaSD saturated solutions with the MPD % of 1.6%.

Otherwise, the calculated apparent specific volumes of NaSD at saturation (φ_V^{sp}) as functions of mixture composition and temperature are summarized in Table 6. Moreover, as visual help Figures 9 and 10 depict this property as a function of (EtOH + water) 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 = 0.70, while from w_1 = 0.80 to pure EtOH, negative φ_V^{sp} values are observed, some of them being too high, like −6.40 mL/g. For this reason, only the first φ_V^{sp} values are considered for discussion.

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

w_1 [a]	Temperature (°C) [b]						
	5	**10**	**15**	**20**	**25**	**30**	**35**
0.00	0.577	0.580	0.582	0.585	0.590	0.590	0.587
0.10	0.566	0.560	0.558	0.556	0.551	0.550	0.547
0.20	0.565	0.551	0.533	0.521	0.518	0.513	0.511
0.30	0.556	0.544	0.492	0.463	0.452	0.440	0.425
0.40	0.535	0.493	0.448	0.404	0.392	0.376	0.363
0.50	0.487	0.414	0.355	0.289	0.258	0.215	0.194
0.60	0.404	0.330	0.293	0.211	0.171	0.142	0.110
0.70	0.365	0.339	0.346	0.264	0.230	0.209	0.198
0.80 [c]	*−0.120*	*−0.102*	*0.127*	*−0.060*	*0.013*	*−0.333*	0.209
0.90 [c]	*−0.915*	*−1.129*	*−0.170*	*−0.553*	*−0.506*	0.111	0.657
1.00 [c]	*−2.483*	*−1.243*	*3.243*	*−3.582*	*−5.040*	*−6.136*	*−6.430*

[a] w_1 is the mass fraction of ethanol in the binary mixtures free of sodium sulfadiazine. [b] Mean uncertainty in the apparent specific volume of sodium sulfadiazine is 0.009 mL/g. [c] Values in italics are not considered for analysis owing negative or low values.

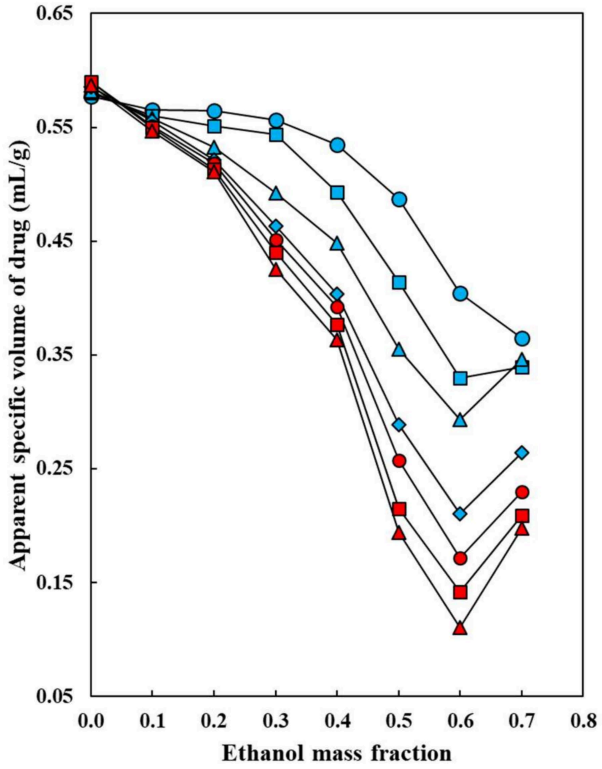

Figure 9. Apparent specific volume of sodium sulfadiazine at saturation in aqueous alcoholic mixtures as a function of ethanol mass fraction at several temperatures. ●: 5.0 °C; ■: 10.0 °C; ▲: 15.0 °C; ♦: 20.0 °C; ●: 25.0 °C; ■: 30.0 °C; ▲: 35.0 °C.

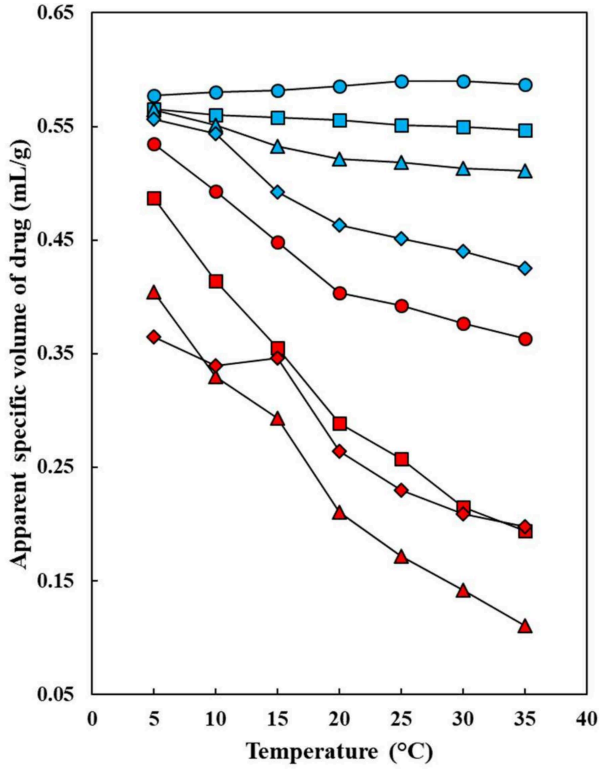

Figure 10. Apparent specific volume of sodium sulfadiazine at saturation in aqueous alcoholic mixtures as a function of temperature. ●: neat water; ■: w_1 = 0.10; ▲: w_2 = 0.20; ♦: w_1 = 0.30; ●: w_1 = 0.40; ■: w_1 = 0.50; ▲: w_1 = 0.60; ♦: w_1 = 0.70.

As observed, φ_V^{sp} values diminish as the EtOH proportion decreases in the mixtures from 0.590 mL/g in pure water to 0.171 mL/g in the mixture of w_1 = 0.60, but it increases again to 0.230 mL/g in the mixture of w_1 = 0.70. Moreover, φ_V^{sp} values apparently increase with the temperature rising in pure water, but these values decrease in the composition interval $0.10 \leq w_1 \leq 0.70$.

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. However, in this ternary (or binary in the case of pure solvents) system, it is observed that in the interval of $0.20 \leq w_1 \leq 0.70$, the φ_V^{sp} values change significantly with temperature. In this way, only in the cases of pure water and the mixture of w_1 = 0.10 no significant changes with temperature are obtained as follows: φ_V^{sp} = 0.584 (±0.005) mL/g (with relative standard deviation, RSD = 0.83%) in pure water and φ_V^{sp} = 0.555 (±0.007) mL/g (with RSD = 1.20%).

Regarding reported literature φ_V^{sp} values of NaSD in some other aqueous cosolvent binary solvent systems, our present φ_V^{sp} values in {ethanol (1) + water (2)} at 25.0 °C are significantly lower. In particular, if considering that the following mean φ_V^{sp} values were reported earlier: 0.617 (±0.013) mL/g (RSD = 2.06%) in {dimethyl sulfoxide (1) + water (2)} mixtures, 0.591 (±0.009) mL/g (RSD = 1.54%) in {methanol (1) + water (2)} mixtures, 0.598 (±0.009) mL/g (RSD = 1.51%) in {*N*-methyl-2-pyrrolidone (1) + water (2)} mixtures, 0.588 (±0.011) mL/g (RSD = 1.82%) in {1,4-dioxane (1) + water (2)} mixtures, 0.705 (±0.024) mL/g (RSD = 3.45%) in {formamide (1) + water (2)} mixtures, 0.668 (±0.012) mL/g (RSD = 1.76%) in {*N*-methylformamide (1) + water (2)} mixtures, and 0.659 (±0.015) mL/g (RSD = 2.22%) in {*N*,*N*-dimethylformamide (1) + water (2)} mixtures, respectively, when considering all the possible mixtures in almost all the binary systems [12].

As it is clearly observed, the relative deviations are higher than 1.0% in almost all binary solvent mixtures but lower than 2.50%, which is commonly accepted during the different stages associated with research and development of homogeneous liquid pharmaceutical dosage forms [69–72].

4. Conclusions

From all topics discussed previously, it can be concluded that the NaSD solubility in (EtOH + water) mixtures is strongly dependent on temperature and the cosolvent mixture composition. NaSD equilibrium solubility increases with temperature rising, but diminishes with the EtOH proportion increasing in the mixtures at all temperatures studied. Mass/volume percentage logarithmic solubility is adequately correlated with a multivariate model involving a linear effect of temperature and a polynomial effect of mixture composition. Furthermore, the apparent specific volume (φ_V^{sp}) of NaSD at saturation is also dependent on temperature and ethanol proportion in the mixtures. Thus, φ_V^{sp} values diminish as the EtOH proportion decreases in the mixtures from 0.590 mL/g in pure water to 0.171 mL/g in the mixture of w_1 = 0.60, but it increases again to 0.230 mL/g in the mixture of w_1 = 0.70. Moreover, φ_V^{sp} values apparently increase with the temperature rising in pure water, but these values decrease in the composition interval $0.10 \leq w_1 \leq 0.70$. Further, it can be said that the solubility and volumetric data presented in this report expand the physicochemical information about the behavior of saline drugs in mixed aqueous solutions. As described deeply in the literature, this information is highly in demand in the pharmaceutical and chemical laboratories where drug solubilization and/or desolubilization and volumetric contributions toward dissolution processes are required in many industrial processes.

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Abbreviations

The following abbreviations are used in this manuscript:

CAS	Chemical Abstract Service
EtOH	Ethanol
MPD%	Mean percentage deviation
NaSD	Sodium sulfadiazine
RSD	Relative standard deviation
% m/m	Mass/mass percentage
% m/v	Mass/volume percentage
φ_V^{sp}	Apparent specific volume

References

1. Rubino, J.T. Cosolvents and cosolvency. In *Encyclopedia of Pharmaceutical Technology*; Swarbrick, J.C., Boylan, J., Eds.; Marcel Dekker: New York, NY, USA, 1988; Volume 3, pp. 375–398.
2. Martin, A.; Bustamante, P.; Chun, A.H.C. *Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences*, 4th ed.; Lea & Febiger: Philadelphia, PA, USA, 1993; pp. 221–235.
3. Yalkowsky, S.H. *Solubility and Solubilization in Aqueous Media*; American Chemical Society and Oxford University Press: New York, NY, USA, 1999; pp. 180–235.
4. Florence, A.T.; Attwood, D. *Physicochemical Principles of Pharmacy*, 5th ed.; Pharmaceutical Press: London, UK, 2011; pp. 53–88.
5. Budavari, S.; O'Neil, M.J.; Smith, A.; Heckelman, P.E.; Obenchain, J.R., Jr.; Gallipeau, J.A.R.; D'Arecea, M.A. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 13th ed.; Merck & Co., Inc.: Whitehouse Station, NJ, USA, 2001; p. 1586.
6. Gelone, S.; O'Donell, J.A. Anti-Infectives. In *Remington: The Science and Practice of Pharmacy*, 21st ed.; Gennaro, A.R., Ed.; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2005; pp. 1630–1633.
7. MacDougall, C. Sulfonamides, trimethoprim-sulfamethoxazole, quinolones, and agents for urinary tract infections. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 13th ed.; Brunton, L.L., Hilal-Dandan, R., Knollmann, B.C., Eds.; McGraw-Hill: New York, NY, USA, 2017; pp. 1011–1021.
8. Delgado, D.R.; Martínez, F. Thermodynamic study of the solubility of sodium sulfadiazine in some ethanol + water cosolvent mixtures. *Vitae* **2010**, *17*, 191–198.
9. Delgado, D.R.; Martínez, F.; Fakhree, M.A.A.; Jouyban, A. Study of the solubility of some sodium sulfonamides in ethanol + water cosolvent mixtures and correlation with the Jouyban-Acree model. *Biomed. Int.* **2011**, *2*, 5–11.
10. Delgado, D.R.; Vargas, E.F.; Martínez, F. Thermodynamics of mixing of some sodium sulfonamides in ethanol + water cosolvent mixtures. *Vitae* **2011**, *18*, 192–200. [CrossRef]
11. Muñoz, M.M.; Rodríguez, C.J.; Delgado, D.R.; Peña, M.Á.; Jouyban, A.; Martínez, F. Solubility and saturation apparent specific volume of some sodium sulfonamides in propylene glycol + water mixtures at 298.15 K. *J. Mol. Liq.* **2015**, *211*, 192–196. [CrossRef]

12. Muñoz, M.M.; Martinez, F.; Delgado, D.R.; Jouyban, A.; Acree, W.E., Jr. Equilibrium solubility and apparent specific volume at saturation of sodium sulfadiazine in some aqueous cosolvent mixtures at 298.2 K. *Phys. Chem. Liq.* **2021**, *59*, 40–52. [CrossRef]
13. Delgado, D.R.; Vargas, E.F.; Martínez, F. Apparent molar volumes of some sodium sulfonamides in water at several concentrations and temperatures. *J. Solution Chem.* **2011**, *40*, 1955–1963. [CrossRef]
14. Rodríguez, G.A.; Martínez, F.; Vargas, E.F. Volumetric and acoustic properties of some sodium sulfonamides in dilute aqueous solutions at several temperatures. *J. Chem. Thermodyn.* **2018**, *118*, 159–164. [CrossRef]
15. Galindres, D.M.; Rodríguez, G.A.; Martínez, F.; Vargas, E.F. Molar electrical conductivity of sodium sulfonamides in aqueous solution at several temperatures. *J. Mol. Liq.* **2019**, *287*, 110984. [CrossRef]
16. Gong, Y.; Grant, D.J.W.; Brittain, H.G. Principles of Solubility. In *Solvent Systems and Their Selection in Pharmaceutics and Biopharmaceutics*; Augustijns, P., Brewster, M.E., Eds.; American Association of Pharmaceutical Scientists; Springer: New York, NY, USA, 2007; pp. 1–27.
17. Jouyban, A. *Handbook of Solubility Data for Pharmaceuticals*; CRC Press: Boca Raton, FL, USA, 2010; pp. 69–505.
18. Farhadieh, B. Determination of CMC and partial specific volume of Polysorbates 20, 60, and 80 from densities of their aqueous solutions. *J. Pharm. Sci.* **1973**, *62*, 1685–1688. [CrossRef]
19. Yalkowsky, S.H.; Zografi, G. Calculation of partial molal volume in micellar systems. *J. Pharm. Sci.* **1972**, *61*, 793–795. [CrossRef]
20. Sommer, C.; Pedersen, J.S.; Stein, P.C. Apparent specific volume measurements of poly(ethylene oxide), poly(butylene oxide), poly(propylene oxide), and octadecyl chains in the micellar state as a function of temperature. *J. Phys. Chem. B* **2004**, *108*, 6242–6249. [CrossRef] [PubMed]
21. Sarazin, D.; Francois, J. Apparent specific volumes of polymers in dilute solutions. *Polymer* **1983**, *24*, 547–552. [CrossRef]
22. Ford, T.F.; Ramsdell, G.A.; Alexander, T.G. Apparent specific volume of the calcium caseinate–calcium phosphate complex in milk. *J. Dairy Sci.* **1959**, *42*, 397–408. [CrossRef]
23. DeMoll, E.; Cox, D.J.; Daniel, E.; Riggs, A.F. Apparent specific volume of human hemoglobin: Effect of ligand state and contribution of heme. *Anal. Biochem.* **2007**, *363*, 196–203. [CrossRef] [PubMed]
24. Hildebrand, J.H.; Prausnitz, J.M.; Scott, R.L. *Regular and Related Solutions*; Van Nostrand Reinhold: New York, NY, USA, 1970; t
25. Martin, A.; Bustamante, P. El parámetro de solubilidad en las ciencias farmacéuticas. *Anal. Real Acad. Farm.* **1989**, *55*, 175–202.
26. Liron, Z.; Cohen, S. Densitometric determination of the solubility parameter and molal volume of compounds of medicinal relevance. *J. Pharm. Sci.* **1983**, *72*, 499–504. [CrossRef]
27. Pardo, A.; Shiri, Y.; Cohen, S. Partial molal volumes and solubilities of physostigmine in isopropanol:isopropyl myristate solvents in relation to skin penetrability. *J. Pharm. Sci.* **1991**, *80*, 567–572. [CrossRef]
28. Liron, Z.; Cohen, S. Percutaneous absorption of alkanoic acids II: Application of regular solution theory. *J. Pharm. Sci.* **1984**, *73*, 538–542. [CrossRef]
29. Kadir, R.; Stempler, D.; Liron, Z.; Cohen, S. Delivery of theophylline into excised human skin from alkanoic acid solutions: A "push-pull" mechanism. *J. Pharm. Sci.* **1987**, *76*, 774–779. [CrossRef]
30. Kadir, R.; Stempler, D.; Liron, Z.; Cohen, S. Penetration of theophylline and adenosine into excised human skin from binary and ternary vehicles: Effect of a nonionic surfactant. *J. Pharm. Sci.* **1989**, *78*, 149–153. [CrossRef]
31. Cohen, S.; Goldschmid, A.; Shtacher, G.; Srebrenik, S. Non-specific inhalation stimulants as a special case in the theory of anesthesia. In *Molecular and Quantum Pharmacology*; Bergmann, E., Pullman, B., Eds.; D. Keidel Publishing Company: Dordrecht, Holland, 1974; pp. 537–548.
32. Fukushima, K.; Kamaya, H.; Ueda, I. High pressure and anesthesia: Compressibility, molal volume, and partial molal volume of volatile anesthetics. *J. Pharm. Sci.* **1990**, *79*, 893–896. [CrossRef] [PubMed]
33. Iqbal, M.; Jamal, M.A.; Ahmed, M.; Ahmed, B. Partial molar volumes of some drugs in water and ethanol at 35 °C. *Can. J. Chem.* **1994**, *72*, 1076–1079. [CrossRef]
34. Iqbal, M.; Verall, R.E. Apparent molar volume and adiabatic compressibility studies of aqueous solutions of some drug compounds at 25 °C. *Can. J. Chem.* **1989**, *67*, 727–735. [CrossRef]
35. Pandey, J.D.; Mishra, K.; Shukla, A.; Rai, R.D. Ultrasonic and thermodynamic studies of tetracyclines in solutions. *Can. J. Chem.* **1987**, *65*, 303–306. [CrossRef]
36. Shahidi, F. Partial molar volumes of phenalkylamines and their physiologically active derivatives in water. *Can. J. Chem.* **1987**, *65*, 1924–1926. [CrossRef]
37. Leduc, P.A.; Fortier, J.L.; Desnoyers, J.E. Apparent molal volumes, heat capacities, and excess enthalpies of *n*-alkylamine hydrobromides in water as a function of temperature. *J. Phys. Chem.* **1974**, *78*, 1217–1225. [CrossRef]
38. Rodríguez, H.; Soto, A.; Arce, A.; Khoshkbarchi, M.K. Apparent molar volume, isentropic compressibility, refractive index, and viscosity of DL-Alanine in aqueous NaCl solutions. *J. Solution Chem.* **2003**, *32*, 53–63. [CrossRef]
39. Ruso, J.M.; Gonzalez-Perez, A.; Prieto, G.; Sarmiento, F.A. Volumetric study of two related amphiphilic beta-blockers as a function of temperature and electrolyte concentration. *Colloids Surf. B Biointerfaces* **2004**, *11*, 165–175. [CrossRef]

40. Sadeghi, R.; Ziamajidi, F. Volumetric and isentropic compressibility behavior of aqueous solutions of (polyvinylpyrrolidone + sodium citrate) at T = (283.15 to 308.15) K. *J. Chem. Thermodyn.* **2007**, *39*, 1118–1124. [CrossRef]
41. Banipal, T.S.; Singh, H.; Banipal, P.K. Volumetric and viscometric properties of some sulfa drugs in aqueous solutions of sodium chloride at *T* = (288.15 to 318.15) K. *J. Chem. Eng. Data* **2010**, *55*, 3872–3881. [CrossRef]
42. Birch, G.G.; Kemp, S.E. Apparent specific volumes and tastes of amino acids. *Chem. Senses* **1989**, *14*, 249–258. [CrossRef]
43. Spillane, W.J.; Morini, G.; Birch, G.G. Determination of apparent molar volumes (AMV) and capacity factors (kw) for sweet and non-sweet sulphamates, correlation between AMV values, and Corey-Pauling-Koltun volumes and relative sweetness correlations. *Food Chem.* **1992**, *44*, 337–342. [CrossRef]
44. Birch, G.G.; Karim, R.; Lopez, A. Novel aspects of structure-activity relationships in sweet taste chemoreception. *Food Qual. Prefer.* **1994**, *5*, 87–93. [CrossRef]
45. Birch, G.G.; Parke, S.; Siertsema, R.; Westwell, J.M. Specific volumes and sweet taste. *Food Chem.* **1996**, *56*, 223–230. [CrossRef]
46. Birch, G.G.; Parke, S.; Siertsema, R.; Westwell, J.M. Importance of molar volumes and related parameters in sweet taste chemoreception. *Pure Appl. Chem.* **1997**, *69*, 685–692. [CrossRef]
47. Lopez-Chavez, A.; Birch, G.G. The hydrostatic and hydrodynamic volumes of polyols in aqueous solutions and their sweet taste. *Chem. Senses* **1997**, *22*, 149–161. [CrossRef] [PubMed]
48. Birch, G.G.; Haywood, K.A.; Hanniffy, G.G.; Coyle, C.M.; Spillane, W.J. Apparent specific volumes and tastes of cyclamates, other sulfamates, saccharins and acesulfame sweeteners. *Food Chem.* **2004**, *84*, 429–435. [CrossRef]
49. Cárdenas, Z.J.; Jiménez, D.M.; Martínez, F. Solubility and saturation apparent volume of Propranolol Hydrochloride in some binary aqueous cosolvent mixtures at 298.15 K. *J. Chem. Eng. Data* **2015**, *60*, 1520–1525. [CrossRef]
50. Jiménez, D.M.; Cárdenas, Z.J.; Martínez, F. Solubility and apparent specific volume of some pharmaceutical salts in propylene glycol + water mixtures at 298.15 K. *Chem. Eng. Commun.* **2016**, *203*, 1013–1019. [CrossRef]
51. Muñoz, M.M.; Almanza, O.A.; Peña, M.Á.; Jouyban, A.; Martínez, F.; Acree, W.E., Jr. Solubility and apparent specific volume at saturation of some pharmaceutical salts in methanol + water mixtures at 298.15 K. *J. Mol. Liq.* **2016**, *220*, 842–847. [CrossRef]
52. Echeverry, L.C.; Muñoz, M.M.; Tinjacá, D.A.; Martinez, F.; Peña, M.A.; Rahimpour, E.; Jouyban, A.; Acree, W.E., Jr. Equilibrium solubility and apparent specific volume of lidocaine.HCl.H_2O in some {cosolvent (1) + water (2)} mixtures at 298.2 K. *Phys. Chem. Liq.* **2019**, *57*, 679–688. [CrossRef]
53. Muñoz, M.M.; Romdhani, A.; Tinjacá, D.A.; Martinez, F.; Echeverry, L.C.; Peña, M.A.; Rahimpour, E.; Jouyban, A.; Acree, W.E., Jr. Equilibrium solubility and apparent specific volume at saturation of sodium diclofenac in {formamide (1)/*N*-methylformamide (1)/or *N*,*N*,-dimethylformamide (1) + water (2)} mixtures at 298.2 K. *Phys. Chem. Liq.* **2019**, *58*, 446–455. [CrossRef]
54. Nail, S.; Hem, S.L. Physical-chemical principles. In *Pharmaceutics and Pharmacy Practice*; Banker, G.S., Chalmers, R.K., Eds.; Lippincott: Philadelphia, PA, USA, 1982; pp. 47–84.
55. Wells, J.I. *Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances*; Ellis Horwood, Ltd.: Chichester, UK, 1988; pp. 21–102.
56. Higuchi, T.; Connors, K. *Advances in Analytical Chemistry and Instrumentation*; Interscience Publishers, Inc.: New York, NY, USA, 1965.
57. Mader, W.J.; Higuchi, T. Phase solubility analysis. *C R C Crit. Rev. Anal. Chem.* **1970**, *1*, 193–215. [CrossRef]
58. Ansel, H.C.; Stoklosa, M.J. *Pharmaceutical Calculations*, 12th ed.; Lippincott, Williams & Wilkins: Baltimore, MD, USA, 2006; pp. 79–98.
59. Bevington, P.R. *Data Reduction and Error Analysis for the Physical Sciences*; McGraw-Hill Book, Co.: New York, NY, USA, 1969.
60. Carstensen, J.T. *Modeling and Data Treatment in the Pharmaceutical Sciences*; Technomic Publishing Co., Inc.: Lancaster, PA, USA, 1996.
61. Barrante, J.R. *Applied Mathematics for Physical Chemistry*, 2nd ed.; Prentice Hall, Inc.: Upper Saddle River, NJ, USA, 1998.
62. Palatnik, L.S.; Landau, A.I. *Phase Equilibria in Multicomponent Systems*; Holt, Rinehart and Winston, Inc.: New York, NY, USA, 1964; pp. 2–3.
63. Gamboa, R. *Diagramas Ternarios: Teoría y Ejercicios*; Dextra Editorial S.L.: Madrid, Spain, 2018.
64. Rahimpour, E.; Alvani-Alamdari, S.; Acree, W.E., Jr.; Jouyban, A. Drug solubility correlation using the Jouyban–Acree model: Effects of concentration units and error criteria. *Molecules* **2022**, *27*, 1998. [CrossRef] [PubMed]
65. Jiménez, J.; Manrique, J.; Martínez, F. Effect of temperature on some volumetric properties for ethanol + water mixtures. *Rev. Colomb. Cienc. Quím. Farm.* **2004**, *33*, 145–155.
66. Rodríguez, G.A.; Delgado, D.R.; Martínez, F.; Khoubnasabjafari, M.; Jouyban, A. Volumetric properties of some pharmaceutical binary mixtures at low temperatures and correlation with the Jouyban-Acree model. *Rev. Colomb. Cienc. Quím. Farm.* **2011**, *40*, 222–239.
67. Parke, S.A.; Birch, G.G. Solution properties of ethanol in water. *Food Chem.* **1999**, *67*, 241–246. [CrossRef]
68. Jouyban, A.; Acree, W.E., Jr. A single model to represent physico-chemical properties of liquid mixtures at various temperatures. *J. Mol. Liq.* **2011**, *323*, 115054. [CrossRef]

69. Carstensen, J.T. *Theory of Pharmaceutical Systems. I. General Principles*; Academic Press, Inc.: New York, NY, USA, 1972; pp. 1–55.
70. Allen, L.V., Jr.; Ansel, H.C. *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*, 10th ed.; Wolters Kluwer: Philadelphia, PA, USA, 2014; pp. 396–444.
71. Álvarez-Lorenzo, C.; Concheiro-Nine, Á. Aseguramiento de la calidad. In *Tratado de Tecnología Farmacéutica. Volumen III: Formas de Dosificación*; Martínez-Pacheco, R., Ed.; Editorial Sintesis: Madrid, Spain, 2017; pp. 369–439.
72. Murdan, S. Solutions. In *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, 6th ed.; Taylor, K.M.G., Aulton, M.E., Eds.; Elsevier Ltd.: Amsterdam, The Netherlands, 2022; pp. 386–396.