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Thermodynamic Analysis of the Solubility of Sulfadiazine in (Acetonitrile + 1-Propanol) Cosolvent Mixtures from 278.15 K to 318.15 K

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Abstract: Drug solubility is one of the most significant physicochemical properties as it is related to drug design, formulation, quantification, recrystallization, and other processes, so understanding it is crucial for the pharmaceutical industry. In this context, this research presents the thermodynamic analysis of the solubility of sulfadiazine (SD) in cosolvent mixtures {acetonitrile + 1-propanol} at 9 temperatures (278.15 K–318.15 K), which is a widely used drug in veterinary therapy, and two solvents of high relevance in the pharmaceutical industry, respectively . The solubility of SD, in cosolvent mixtures {acetonitrile + 1-propanol} is an endothermic process where the maximum solubility was reached in pure acetonitrile at 318.15 K and the minimum in 1-propanol at 278.15 K. Although the solubility parameters of acetonitrile and propanol were similar, the addition of acetonitrile to the cosolvent mixture leads to a positive cosolvent effect on the solubility of DS. As for the thermodynamic functions of the solution, the process is strongly influenced by enthalpy, and according to the enthalpy–entropy compensation analysis, the process is enthalpy-driven in intermediate to rich mixtures in 1-propanol and entropy-driven in mixtures rich in acetonitrile.

Keywords: sulfadiazine; solubility; cosolvent; thermodynamics; acetonitrile; 1-propanol

1. Introduction

Sulfadiazine (SD, $C_{10}H_{10}N_4O_2S$, CAS Number: 68-35-9, Figure 1) is a broad-spectrum, fast-acting, synthetic bacteriostatic agent effective against most gram-positive and many gram-negative bacteria; it is used in human and veterinary therapy for the treatment of infections [1,2].

Since one of the main difficulties in developing drugs made with SD is the low aqueous solubility of this [3–10], solubility studies in cosolvent systems are highly relevant as they allow for the identification of the most suitable solvents or solvent mixtures to improve the solubility of the drug [11]. The solubility of SD in different cosolvent mixtures of pharmaceutical interest has been reported, such as: acetonitrile+methanol [2], ethanol+water [3,12], methanol+water [13], 1,4-dioxane+water [4], propylene glycol+water [14], ethylene glycol+water [15], N-methyl-2-pyrrolidone+water [5], and water-N,N-dimethylformamide [7].

In addition, experimental solubility data have been correlated with some mathematical models, which have allowed one to optimize processes [6,16–18].
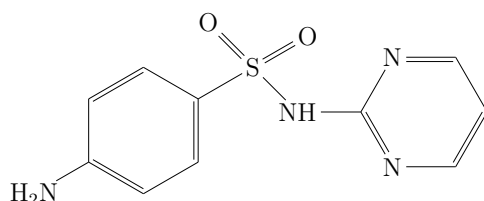

Figure 1. Molecular structure of the sulfadiazine.

Although a large number of solubility data have been reported for SD in different cosolvent mixtures, the generation of new data allows one to understand the possible mechanisms involved in the dissolution process, as well as to compare and identif which factors improve drug solubility.

In this context, the solubility data of SD in cosolvent mixtures acetonitrile (1) + 1-propanol (2), two solvents with a similar solubility parameter, are reported (δ_1 = 24.8 MPa$^{1/2}$ and δ_2 = 24.9 [19]). Both acetonitrile (MeCN) and 1-propanol (n-PrOH) are solvents widely used in the industry; acetonitrile is an aprotic solvent used in the pharmaceutical industry in the manufacture of pharmaceutical products and in analytical processes (HPLC). On the other hand, 1-propanol is an alcohol miscible with water and is classified as a class 3 residual solvent, i.e., it has a low toxic potential for humans [20]. Solubility studies in these pure solvents and their cosolvent mixtures would provide useful information in industrial processes.

In addition, a thermodynamic analysis and the entalphic-entropic compensation of the SD solution process in MeCN + nPrOH mixtures is performed.

2. Materials and Methods
2.1. Reagents

Table 1 reports the reagents used in the development of this research.

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

Chemical Name	CAS [a]	Source	Purity in Mass Fraction	Analytic Technique [b]
Sufadiazine	57-83-0	Sigma-Aldrich, Burlington, MA, USA	>0.990	HPLC
Acetonitrile	75-05-8	Merck Millipore, Burlington, MA, USA	0.998	GC
1-Propanol	71-23-8	Merck Millipore, Burlington, MA, USA	0.998	GC
Ethanol	64-17-5	Merck Millipore, Burlington, MA, USA	0.998	GC

[a] Chemical Abstracts Service Registry Number. [b] HPLC is high-performance liquid chromatography; GC is gas chromatography.

2.2. Preparation of Solvent Mixtures

Nineteen cosolvent mixtures of acetonitrile + 1-propanol from 0.05 through 0.95 in mass fraction were prepared using an analytical balance (RADWAG AS 220.R2, Torun, Poland) of 4 decimal places (sensitivity ±0.0001 g). Samples were prepared in amber glass vials with a capacity of 15 mL. For each concentration, 3 samples of approximately 10.00 ± 0.00 g each were prepared.

2.3. Solubility Determination

The procedure of the flask agitation method proposed by Higuchi and Connors was followed [21–23]. Initially, the pure solvents or cosolvent mixtures were saturated by adding sufficient SD to each flask (see previous section) to obtain two phases. Subsequently, each solution was deposited in a thermostatted circulation bath at each of the 9 study temperatures

(278.15 K, 283.15 K, 288.15 K, 293.15 K, 298.15 K, 303.15 K, 308.15 K, 313.15 K, and 318.15 K) during 48 h. Later, an aliquot of each sample was taken and filtered through a 0.45 μm membrane; then, a gravimetric dilution was performed with absolute ethanol, and the concentration of the solution was measured by UV/Vis spectrophotometry (UV/VIS EMC-11- UV spectrophotometer, Dresden, Germany) at 268 nm (wavelength of maximum absorbance).

2.4. Calorimetric Study

The enthalpy and melting temperature of four SD samples were determined by differential scanning calorimetry (DSC 204 F1 Phoenix, Dresden, Germany). A mass of approximately 10.0 mg of each sample was deposited in an aluminum crucible and placed in the calorimeter under a nitrogen flow of 10 mL·min^{-1}. The heating cycle was developed from 300 to 575 K, with a heating ramp of 10 K·min^{-1}.

3. Results and Discussion

3.1. Experimental Mole Fraction Solubility (x_3)

Table 2 reports the mole fraction solubility of SD in cosolvent mixtures {MeCN + 1-PrOH} at nine temperatures (278.15 K, 283.15 K, 288.15 K, 293.15 K, 298.15 K, 303.15 K, 308.15 K, 313.15 K, and 318.15 K). With increasing temperature, the solubility of SD increases, indicating an endothermic dissolution process. Concerning the cosolvent effect, solubility usually depends on the polarity of the solvent, so the maximum solute solubility is reached in the solvent or cosolvent mixture with a solubility parameter similar to the solute.

In this case, the solubility parameter of MeCN and PrOH are similar, so it is complex to elucidate the relationship between the polarity of the solvent medium (the quasi-constant solubility parameter, between 24.8 and 24.9 MPa$^{1/2}$) and the SD (28.89 MPa$^{1/2}$ [3]). Therefore, regarding the solubility parameter, one alternative is to consider the three-dimensional solubility parameter [24], which means the dispersion force (d), polar force (p), and hydrogen-bonding force (h). In this way, PrOH (δ_d = 14.1 MPa$^{1/2}$, δ_p = 10.1 MPa$^{1/2}$, and δ_h = 17.1 MPa$^{1/2}$ [19]) differs the most from MeCN (δ_d = 10.3 MPa$^{1/2}$, δ_p = 11.1 MPa$^{1/2}$, and δ_h = 19.6 MPa$^{1/2}$ [19]) in δ_d, so the increase in SD solubility with increasing PrOH concentration in the cosolvent mixture is possibly due to the increase in non-polar interactions between PrOH and SD.

On the other hand, when evaluating the solubility behavior of SD considering the Kamlet–Taft acidity scale α [25], SD behaves as an acid against MeCN (α = 0.29 ± 0.06 [25]), which is a more basic solvent than 1-PrOH (α = 0.766 ± 0.013 [25]).

An important factor to consider is the possible formation of polymorphs since this phenomenon affects drug solubility [26]. For this purpose, the solid phases of the original sample and the phases in the equilibrium with pure MeCN, pure 1-PrOH, and in the cosolvent mixture $w_{0.50}$ were evaluated (Figure 2).

Table 3 shows the experimental values of the enthalpy and fusion temperatures of the samples evaluated and some of the values taken from the literature. It is observed that the values from the original sample and those from the solid phase in equilibrium were similar, indicating that there were no polymorphic changes; furthermore, the results agree with those reported by other authors.

Table 2. Experimental solubility of sulfadiazine (3) in {acetoitrile (1) + 1-propanol (2)} cosolvent mixtures expressed in mole fraction ($10^4 x_3$) at different temperatures and p = 96 kPa ^{ac}.

w_1 ^{b}	Temperature/K								
	278.15	283.15	288.15	293.15	298.15	303.15	308.15	313.15	318.15
0.00	0.152	0.210	0.275	0.388	0.471	0.587	0.721	0.913	1.097
0.05	0.179	0.228	0.288	0.394	0.490	0.588	0.740	0.938	1.187
0.10	0.203	0.254	0.326	0.407	0.518	0.650	0.821	1.038	1.303
0.15	0.226	0.285	0.362	0.455	0.577	0.720	0.907	1.140	1.431
0.20	0.250	0.317	0.401	0.503	0.635	0.789	0.990	1.241	1.543
0.25	0.281	0.346	0.435	0.536	0.675	0.843	1.055	1.310	1.642
0.30	0.312	0.389	0.486	0.599	0.744	0.926	1.144	1.424	1.753
0.35	0.353	0.433	0.538	0.662	0.816	0.992	1.242	1.520	1.875

Table 2. *Cont.*

w_1 [b]	Temperature/K								
	278.15	283.15	288.15	293.15	298.15	303.15	308.15	313.15	318.15
0.40	0.407	0.495	0.603	0.731	0.890	1.093	1.324	1.614	1.974
0.45	0.472	0.572	0.699	0.837	1.011	1.211	1.461	1.760	2.092
0.50	0.562	0.661	0.791	0.941	1.126	1.326	1.577	1.871	2.253
0.55	0.679	0.804	0.949	1.106	1.292	1.523	1.783	2.085	2.402
0.60	0.900	1.035	1.189	1.363	1.572	1.792	2.073	2.384	2.716
0.65	1.021	1.168	1.343	1.535	1.731	1.982	2.250	2.556	2.890
0.70	1.269	1.440	1.611	1.795	2.032	2.279	2.560	2.859	3.208
0.75	1.585	1.743	1.946	2.161	2.404	2.636	2.977	3.286	3.655
0.80	1.916	2.098	2.316	2.554	2.833	3.062	3.422	3.754	4.198
0.85	2.306	2.525	2.783	3.024	3.382	3.684	4.055	4.446	4.946
0.90	2.673	2.964	3.314	3.671	4.037	4.468	4.945	5.427	5.972
0.95	2.966	3.279	3.696	4.126	4.615	5.139	5.818	6.518	7.442
1.00	3.162	3.849	4.653	5.323	6.022	6.663	7.748	8.649	9.352

[a] p is the atmospheric pressure in Neiva, Colombia. [b] w_1 is the mass fraction of acetonitrile (1) in the acetonitrile (1) + 1-propanol (2) mixtures free of sulfadiazine (3) . [c] Standard uncertainty in p is $u(p) = 3.0$ kPa. Average relative standard uncertainty in w_1 is $u_r(w_1) = 0.0008$. Standard uncertainty in T is $u(T) = 0.10$ K. Average relative standard uncertainties in x_3 is $u_r(x_{3(1+2)}) = 0.025$.
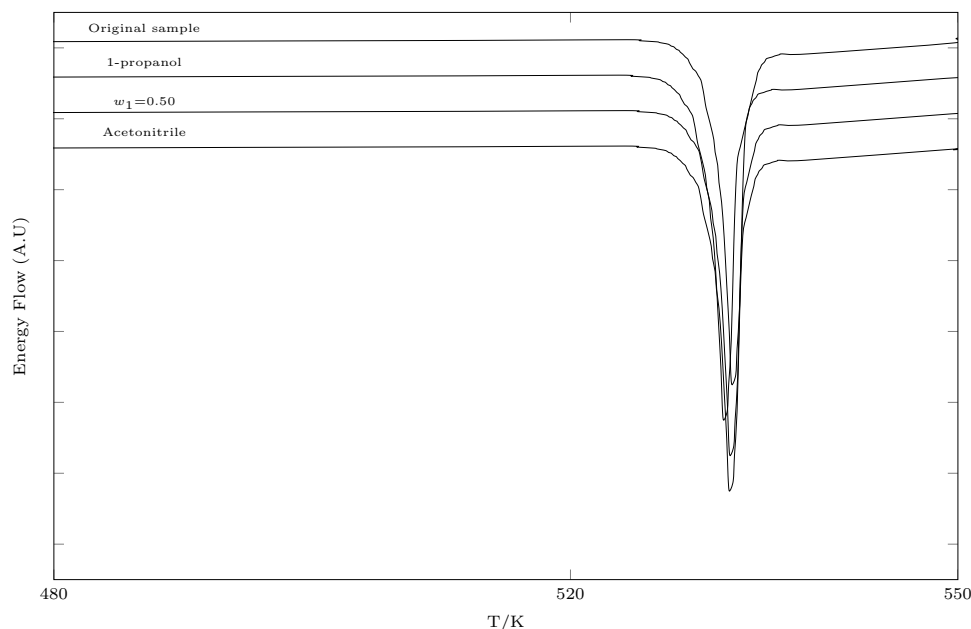

Figure 2. DSC thermograms of sulfadiazine.

Table 3. The thermophysical properties of SD obtained by the DSC.

Sample	Enthalpy of Fusion, $\Delta_{fus}H$/kJ·mol^{-1}	Melting Point T_{fus}/K	Ref.
Original sample	44.36 ± 0.5	532.6 ± 0.5	This work
	44.352	532.7	[27]
	44.35	520.4	[28]
	31.21	538.7	[29]
		538.8	[29]
		534.0	[30]
		531.0	[30]
		532.4	[2]
		532.6	[15]
1-Propanol	44.23 ± 0.5	533.1 ± 0.5	This work
$w_{0.50}$	44.45 ± 0.5	531.8 ± 0.5	This work
Acetonitrile	44.63 ± 0.5	532.4 ± 0.5	This work

3.2. Ideal Solubility and Activity Coefficients

The possible molecular interactions that occur during the SD dissolution process in MeCN + 1-PrOH cosolvent mixtures can be evaluated through the activity coefficients.

Firstly, the ideal solubility is calculated by the Equation (1) [31], where T and T_m (in K), $\Delta_m H$ is the solute enthalpy of fusion (in kJ mol^{-1}), R is the gas constant (in kJ·mol^{-1}·K^{-1}), and ΔC_p is the differential heat capacity of fusion (in kJ·K^{-1}·mol^{-1}) [10]. Some researchers such as Hildebrand et al. [32], Neau and Flynn [33], Neau et al. [34], and Opperhuizen et al. [35] assume ΔC_p as the entropy of fusion ($\Delta_m S$), which is calculated as $\Delta_m H / T_m$

$$\ln x_3^{id} = -\frac{\Delta_m H}{R}\left(\frac{T_m - T}{T_m T}\right) + \frac{\Delta C_p}{R}\left(\frac{T_m - T}{T}\right) - \frac{\Delta C_p}{R}\ln\left(\frac{T_m}{T}\right) \tag{1}$$

Once the ideal solubility has been calculated, Equation (2) is used to calculate the activity coefficient (γ_3) from the experimental solubility (x_3) data [32,36].

$$\gamma_3 = \frac{x_3^{id}}{x_3} \tag{2}$$

Finally, from Equation (3), γ_3 can be interpreted in terms of molecular interactions [37,38]. Then, e_{11} and e_{33} represent the solvent–solvent and solute–solute iteration energy, respectively, where e_{11} is related to the MeCN-MeCN, 1-PrOH-1-PrOH, and MeCN-PrOH interactions. On the other hand, e_{13} represents the solute–solvent interaction energy, i.e., MeCN-SD, 1-PrOH-SD, and MeCN-SD-1-PrOH .

When the solution process behaves ideally $e_{11} = e_{22} = e_{33}$, the values of γ_3 greater than 1 indicate that e_{11} and e_{22} control the solution process [39,40].

$$\ln \gamma_3 = (e_{11} + e_{33} - 2e_{13})\frac{V_3 \phi_1^2}{RT} \tag{3}$$

Table 4. Activity coefficient of sulfadiazine (3) in {acetonitrile (1) + 1-propanol (2)} cosolvent mixtures at different temperatures and pressure p = 0.096 MPa [a].

w_1 [b]	Temperature/K								
	278.15	283.15	288.15	293.15	298.15	303.15	308.15	313.15	318.15
0.00	99.13	85.70	77.99	65.65	63.99	60.63	58.11	53.93	52.59
0.05	84.04	78.98	74.30	70.00	65.49	60.58	56.63	52.48	48.61
0.10	74.19	70.73	65.77	62.60	58.24	54.78	51.08	47.46	44.28
0.15	66.68	63.11	59.26	55.88	52.23	49.44	46.24	43.21	40.34
0.20	60.09	56.77	53.50	50.63	47.48	45.10	42.33	39.70	37.40
0.25	53.51	52.02	49.28	47.50	44.62	42.21	39.74	37.59	35.15
0.30	48.31	46.26	44.09	42.45	40.53	38.44	36.65	34.59	32.92
0.35	42.63	41.53	39.84	38.45	36.92	35.87	33.75	32.41	30.78
0.40	37.01	36.33	35.54	34.82	33.87	32.58	31.66	30.51	29.23
0.45	31.92	31.45	30.65	30.42	29.82	29.40	28.70	27.98	27.59
0.50	26.79	27.22	27.07	27.04	26.77	26.84	26.59	26.32	25.62
0.55	22.16	22.36	22.57	23.00	23.33	23.37	23.51	23.62	24.03
0.60	16.72	17.38	18.02	18.67	19.17	19.87	20.22	20.66	21.25
0.65	14.74	15.40	15.95	16.58	17.41	17.96	18.63	19.27	19.97
0.70	11.86	12.49	13.30	14.18	14.83	15.62	16.38	17.23	17.99
0.75	9.49	10.32	11.01	11.78	12.54	13.50	14.08	14.99	15.79
0.80	7.85	8.57	9.25	9.96	10.64	11.62	12.25	13.12	13.74
0.85	6.53	7.12	7.70	8.42	8.91	9.66	10.34	11.08	11.67
0.90	5.63	6.07	6.47	6.93	7.47	7.97	8.48	9.07	9.66
0.95	5.07	5.49	5.80	6.17	6.53	6.93	7.21	7.56	7.75
1.00	4.76	4.67	4.60	4.78	5.00	5.34	5.41	5.69	6.17

[a] p is the atmospheric pressure in Neiva, Colombia. [b] w_1 is the mass fraction of acetonitrile (1) in the {acetonitrile (1) + 1-propanol (2)} mixtures free of sulfadiazine (3).

According to the data reported in Table 4, the increase in temperature favors the solute–solvent interactions in general. Moreover, when analyzing the influence of cosolvent

composition, it is deduced that MeCN-SD interactions are more favorable than 1-PrOH-SD interactions.

3.3. Thermodynamic Functions of Solution

The thermodynamic solution functions (Table 5), enthalpy ($\Delta_{\text{soln}}H^\circ$), Gibbs energy ($\Delta_{\text{soln}}G^\circ$), and entropy of solution ($\Delta_{\text{soln}}S^\circ$) (in kJ·mol^{-1}) were calculated by the Gibbs–van't Hoff–Krug model from the SD experimental solubility data (Table 2) [41,42] by means of the Equations (4)–(6).

$$\Delta_{\text{soln}}H^\circ = -R\left(\frac{\partial \ln x_3}{\partial\left(T^{-1} - T_{\text{hm}}^{-1}\right)}\right)_p \tag{4}$$

$$\Delta_{\text{soln}}G^\circ = -RT_{\text{hm}}.\text{intercept} \tag{5}$$

$$\Delta_{\text{soln}}S^\circ = (\Delta_{\text{soln}}H^\circ - \Delta_{\text{soln}}G^\circ)T_{\text{hm}}^{-1} \tag{6}$$

where T_{hm} is the harmonic temperature (in K) and R is the gas constant (kJ·mol^{-1}·K^{-1}).

The contributions of enthalpy and entropy to the Gibbs energy ζ_H and ζ_{TS} were calculated using the Equations (7) and (8)

$$\zeta_H = |\Delta_{\text{soln}}H^\circ|(|T\Delta_{\text{soln}}S^\circ| + |\Delta_{\text{soln}}S^\circ|)^{-1} \tag{7}$$

$$\zeta_{TS} = 1 - \zeta_H \tag{8}$$

Table 5. Thermodynamic functions of the solution process of sulfadiazine (3) in {acetonitrile (1) + 1-propanol (2)} co-solvent mixtures at T_{hm} = 297.6 K [a].

w_1 [b]	$\Delta_{\text{soln}}G^\circ$/ (kJ·mol^{-1})	$\Delta_{\text{soln}}H^\circ$ (kJ·mol^{-1})	$\Delta_{\text{soln}}S^\circ$ (J·mol^{-1}·K^{-1})	$T_{\text{hm}}\Delta_{\text{soln}}S^\circ$ (kJ·mol^{-1})	ζ_H [c]	ζ_{TS} [c]
0.00	24.79	36.09	37.94	11.29	0.76	0.24
0.05	24.70	34.77	33.83	10.07	0.78	0.22
0.10	24.43	34.27	33.07	9.84	0.78	0.22
0.15	24.17	33.95	32.85	9.77	0.78	0.22
0.20	23.94	33.43	31.89	9.49	0.78	0.22
0.25	23.76	32.56	29.56	8.80	0.79	0.21
0.30	23.52	31.76	27.69	8.24	0.79	0.21
0.35	23.30	30.71	24.89	7.41	0.81	0.19
0.40	23.07	29.03	20.05	5.97	0.83	0.17
0.45	22.78	27.41	15.58	4.64	0.86	0.14
0.50	22.51	25.50	10.03	2.99	0.90	0.10
0.55	22.15	23.28	3.79	1.13	0.95	0.05
0.60	21.68	20.37	−4.40	−1.31	0.94	0.06
0.65	21.43	19.14	−7.71	−2.29	0.89	0.11
0.70	21.04	17.00	−13.58	−4.04	0.81	0.19
0.75	20.62	15.43	−17.47	−5.20	0.75	0.25
0.80	20.23	14.33	−19.83	−5.90	0.71	0.29
0.85	19.79	13.97	−19.56	−5.82	0.71	0.29
0.90	19.34	14.79	−15.29	−4.55	0.76	0.24
0.95	18.99	16.82	−7.29	−2.17	0.89	0.11
1.00	18.43	19.73	4.34	1.29	0.94	0.06

[a] Average relative standard uncertainty in w_1 is $u_r(w_1) = 0.0008$. Standard uncertainty in T is $u(T) = 0.10$ K. Average relative standard uncertainty in apparent thermodynamic quantities of real dissolution processes are $u_r(\Delta_{\text{soln}}G^\circ) = 0.015$, $u_r(\Delta_{\text{soln}}H^\circ) = 0.019$, $u_r(\Delta_{\text{soln}}S^\circ) = 0.024$, and $u_r(T\Delta_{\text{soln}}S^\circ) = 0.024$. [b] w_1 is the mass fraction of acetonitrile (1) in the {acetonitrile (1) + 1-propanol (2)} mixtures free of sulfadiazine (3). [c] ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward the apparent Gibbs energy of dissolution.

As the concentration of MeCN in the cosolvent mixtures increases, the solution Gibbs energy decreases from pure 1-PrOH to pure MeCN. The solution enthalpy decreases from pure 1-PrOH to $w_{0.85}$, and from this mixture to pure MeCN, the enthalpy of the solution increases. The enthalpy decrease in 1-PrOH-rich and intermediate mixtures is probably due

to solvent–solvent bond breaking, which agrees with the increase in solubility. However, in MeCN-rich mixtures, the enthalpy increases possibly due to the MeCN tendency to form micro-cluster [43], which leads to the formation of MeCN-MeCN bonds and increases the enthalpy of the solution.

The solution entropy follows a similar pattern as the enthalpy of the solution, decreasing from pure 1-PrOH to $w_{0.85}$ and then increasing to pure MeCN. Finally, when analyzing the solution enthalpy and entropy contribution to the Gibbs energy, the energetic component, i.e., the solution enthalpy, is the main source (>71%). This was verified by Perlovich's analysis (Figure 3) since when plotting $\Delta_{soln}H^\circ$ vs. $T\Delta_{soln}S^\circ$, all of the values were recorded in the sector I ($\Delta_{soln}H^0 > T\Delta_{soln}S^\circ$) and the sector VIII ($\Delta_{soln}H^\circ > 0$, $T\Delta_{soln}S^\circ < 0$, $|\Delta_{soln}H^\circ| > |T\Delta_{soln}S^\circ|$), indicating an enthalpic conduction of the dissolution process [44,45].
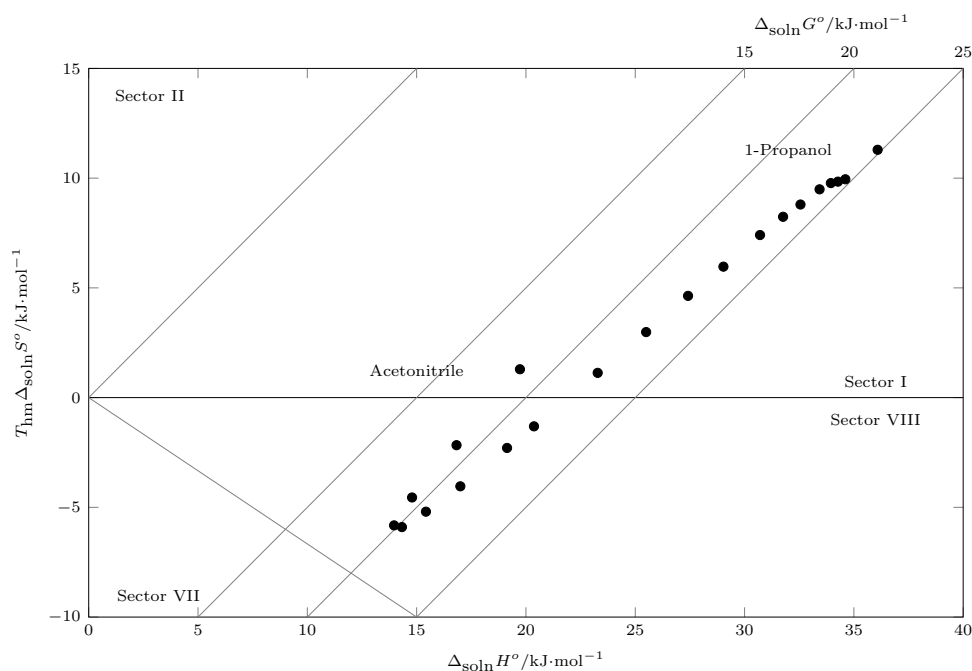
Figure 3. Relation between enthalpy ($\Delta_{soln}H^\circ$) and entropy ($T_{hm}\Delta_{soln}S^\circ$) in terms of the process of sulfadiazine (3) solution in {MeCN (1) + 1-PrOH (2)} cosolvent mixtures at 297.6 K. The isoenergetic curves for $\Delta_{soln}G^\circ$ are represented by dotted lines.

3.4. Thermodynamic Functions of Mixing

The solution process involves the change of state of the solute ($Solute_{solid,T} \rightarrow Solute_{solid,T_m} \rightarrow Solute_{liquid,T_m} \rightarrow Solute_{Liquid,T}$); the molecular reorganization of the solvent to form a cavity to house the solute; and the mixing process (Table 6), which involves the molecular interaction between the solute and the solvent to form the solution ($Solute_{liquid,T} \rightarrow Solute_{soln}$) [31,46,47]. The solution process can be described by Equation (9)

$$\Delta_{sol}f^\circ = \Delta_{mix}f^\circ + \Delta_m f^\circ \tag{9}$$

Clearing $\Delta_{mix}f^\circ$ Equation (9), we obtain:

$$\Delta_{mix}f^\circ = \Delta_{soln}f^\circ - \Delta_m f^\circ \tag{10}$$

The mixing Gibbs energy was positive in each case and decreased from pure 1-PrOH to pure MeCN. This indicates that as the concentration of MeCN in the cosolvent mixtures increases, lower energy is required to generate the cavity where the solute is accommodated. The enthalpy of mixing decreases from 1-PrOH to $w_{0.85}$, and from this cosolvent composition to pure MeCN it increases. Similarly, the entropy of mixing was negative in each case and behaved similarly to the enthalpy of mixing. In general, from 1-PrOH up to

$w_{0.50}$, the solution process is disfavored by the thermodynamic mixing functions, and from $w_{0.55}$ up to MeCN, the solution process is favored by the mixing enthalpy.

According to Perlovich's analysis (Figure 4) from 1-PrOH up to $w_{0.30}$, the mixing process is driven by the enthalpy of mixing (Sector VIII: $\Delta_{mix}H° > 0$, $T\Delta_{mix}S° < 0$, $|\Delta_{mix}H°| > |T\Delta_{mix}S°|$); from $w_{0.30}$ to $w_{0.50}$ (Sector VII: $\Delta_{mix}H° > 0$, $T\Delta_{mix}S° < 0$, $|\Delta_{mix}H°| < |T\Delta_{mix}S°|$) and from $w_{0.50}$ to pure MeOH (Sector VI: $\Delta_{mix}H° < 0$, $T\Delta_{mix}S° < 0$, $|\Delta_{mix}H°| < |T\Delta_{mix}S°|$), the process is driven by the entropy of mixing [44,45].

Table 6. Thermodynamic functions relative to mixing processes of sulfadiazine (3) in {acetonitrile (1) + 1-propanol (2)} co-solvent mixtures at $T_{hm} = 297.6$ K [a].

w_1 [b]	$\Delta_{mix}G°$ (kJ·mol^{-1})	$\Delta_{mix}H°$ (kJ·mol^{-1})	$\Delta_{mix}S°$ (J·mol^{-1}·K^{-1})	$T\Delta_{mix}S°$ (kJ·mol^{-1})
0.00	13.51	11.24	−7.62	−2.27
0.05	13.41	9.92	−11.74	−3.49
0.10	13.14	9.42	−12.50	−3.72
0.15	12.88	9.10	−12.72	−3.78
0.20	12.65	8.58	−13.67	−4.07
0.25	12.47	7.71	−16.00	−4.76
0.30	12.23	6.91	−17.88	−5.32
0.35	12.01	5.86	−20.67	−6.15
0.40	11.78	4.18	−25.51	−7.59
0.45	11.49	2.57	−29.99	−8.92
0.50	11.22	0.65	−35.53	−10.57
0.55	10.86	−1.57	−41.77	−12.43
0.60	10.39	−4.48	−49.96	−14.87
0.65	10.14	−5.71	−53.27	−15.85
0.70	9.75	−7.85	−59.15	−17.60
0.75	9.33	−9.42	−63.03	−18.76
0.80	8.94	−10.52	−65.39	−19.46
0.85	8.50	−10.88	−65.13	−19.38
0.90	8.05	−10.06	−60.86	−18.11
0.95	7.70	−8.02	−52.85	−15.73
1.00	7.14	−5.12	−41.22	−12.27

[a] Average relative standard uncertainty in w_1 is $u_r(w_1) = 0.0008$. Standard uncertainty in T is $u(T) = 0.10$ K. Average relative standard uncertainties in apparent thermodynamic quantities of real dissolution processes are $u_r(\Delta_{mix}G°) = 0.015$, $u_r(\Delta_{mix}H°) = 0.019$, $u_r(\Delta_{mix}S°) = 0.024$, and $u_r(T\Delta_{mix}S°) = 0.024$. [b] w_1 is the mass fraction of acetonitrile (1) in the {acetonitrile (1) + 1-propanol (2)} mixtures free of sulfadiazine (3).
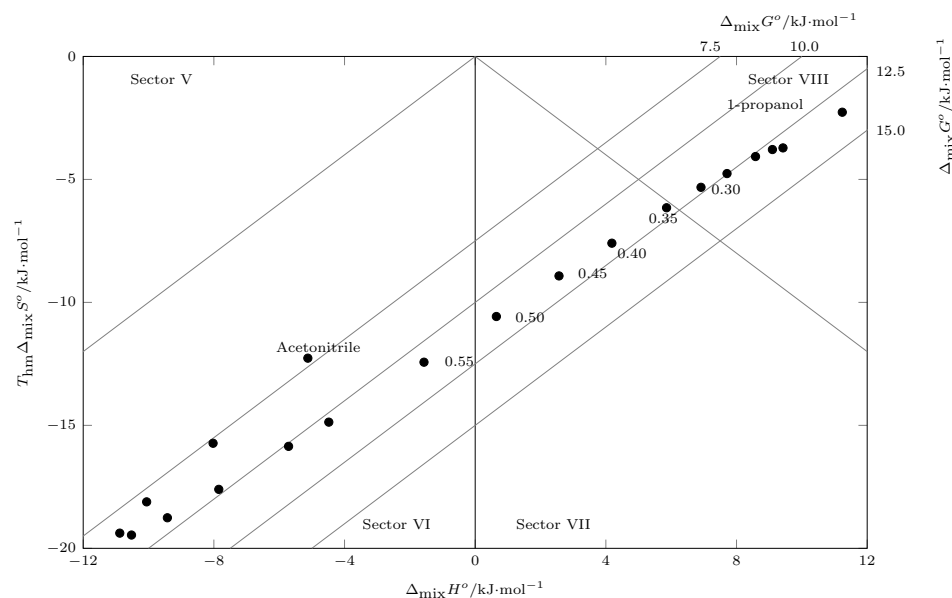

Figure 4. Relation between enthalpy ($\Delta_{mix}H°$) and entropy ($T_{hm}\Delta_{mix}S°$) of the process mixing of sulfadiazine (3) in {MeCN (1) + 1-PrOH (2)} cosolvent mixtures at 297.6 K. The isoenergetic curves for $\Delta_{mix}G°$ are represented by dotted lines.

3.5. Enthalpy–Entropy Compensation Analysis

Enthalpy–entropy compensation is defined by Ryde as the cancellation of an entropy increase, generated by the non-covalent interaction of two molecules (solute–solvent), by a simultaneous decrease in enthalpy [48]. This phenomenon creates a linear enthalpy–entropy relationship when changes in solubility occur as a consequence of changes in cosolvent composition (Figure 5). Therefore, an adverse enthalpy change is compensated for by a favorable entropy change that allows for the process to occur.

According to Sharp, when $\Delta_{soln}G°$ changes are present, there is a linear relationship between $\Delta_{soln}H°$ and $T\Delta_{soln}S°$, which is a strong enthalpy–entropy compensation indicator [49].

Following this, by analyzing the enthalpic–entropic compensation of the drug solution process in cosolvent mixtures, the mechanisms involved in the solution process can be identified. This can be done by evaluating the thermodynamic effects of the solute–solvent molecular interactions, such as the formation of hydrogen bonds [6,50,51].

The enthalpy–entropy compensation can be evaluated through two graphic models: (i) $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$, where negative slopes indicate entropic driving and positive slopes enthalpy driving; and (ii) $\Delta_{soln}H°$ vs. $T\Delta_{soln}S°$, where slopes >1.0 indicate enthalpy driving and slopes <1.0 indicate entropic driving. Hence, according to Figures 5 and 6, from 1-PrOH to $w_{0.85}$, the process is driven by the enthalpy of solution, and from $w_{0.85}$ to pure MeCN, the process is driven by entropy.
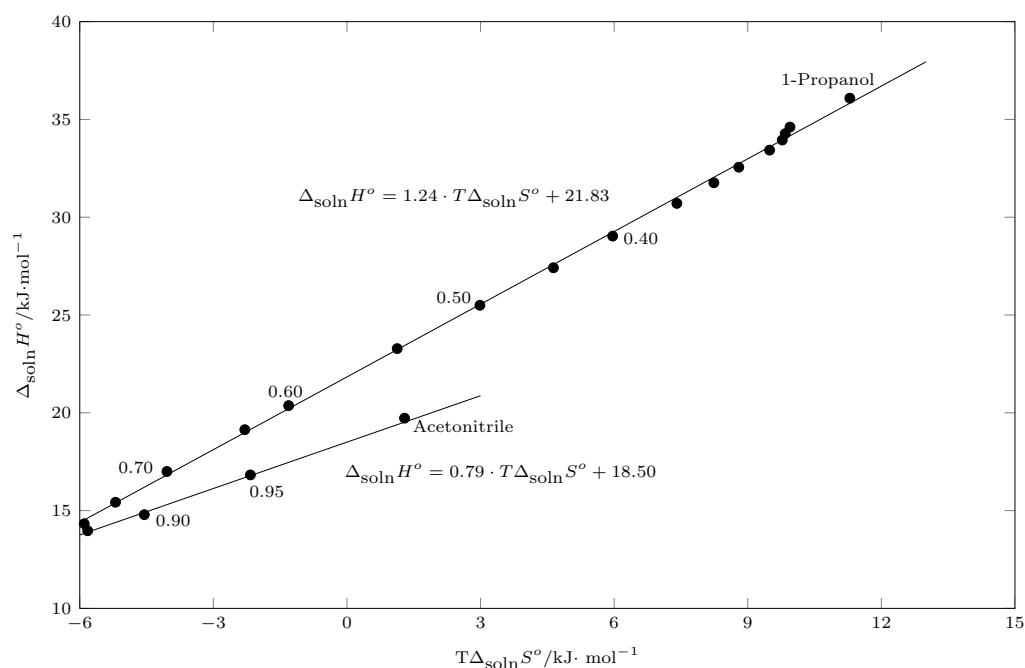

Figure 5. Enthalpy–entropy compensation plot for the solubility of SD (3) in {MeCN(1) + 1-PrOH(2)} mixtures at T_{hm} = 297.6 K.
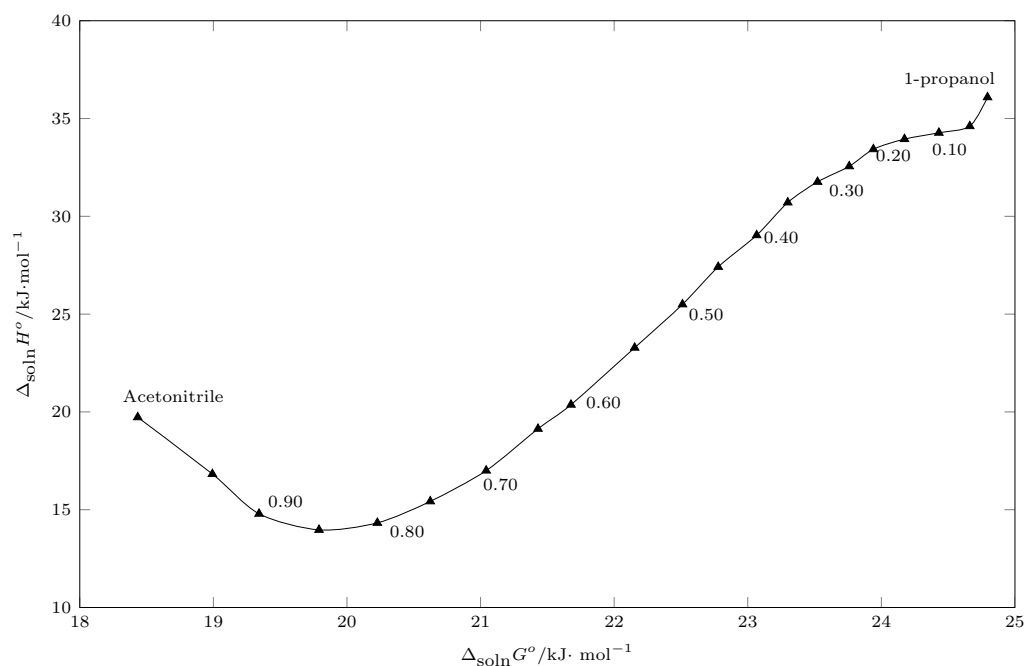
Figure 6. Enthalpy–entropy compensation plot for the solubility of SD (3) in {MeCN(1) + 1-PrOH (2)} mixtures at T_{hm} = 297.6 K.

4. Conclusions

The solubility of sulfadiazine in acetonitrile + 1-propanol cosolvent mixtures is an endodermal process, and it is dependent on the cosolvent composition. Sulfadiazine tends to present an acidic character relative to acetonitrile, increasing its solubility as the concentration of acetonitrile increases. In the latter, the lowest values of the activity coefficient were obtained, indicating quasi-ideal behavior in MeCN-rich mixtures.

Regarding the thermodynamic functions of solution , the solution Gibbs energy is highly dependent on the enthalpy values, and overall the solution process is favored by entropy in 1-propanol-rich mixtures. The mixing process is driven by the enthalpy in 1-propanol-rich and intermediate mixtures, and in acetonitrile-rich mixtures, the mixing process is driven by the entropy.

Finally, according to the enthalpy–entropy compensation analysis, the process is driven by the enthalpy in acetonitrile-rich and intermediate mixtures and by the entropy in 1-propanol-rich mixtures.

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

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