

Article

Thermodynamic Insights into Isoniazid Solubility in PEG 300 + Water Mixtures

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Abstract

Solubility studies are essential for developing more efficient dosing processes and systems. The solubility of INH in a mixture of PEG 300 (1) + water (2) was evaluated at various temperatures using UV/Vis spectrophotometry and the shaking flask method. Solubility increased by 150% at 288.15 K and 298% at 318.15 K, reflecting the temperature dependence of solubility when transitioning from pure water to pure PEG 300. Generally, the solubility of INH is an endothermic process favoured by entropy. Its affinity increases with PEG 300 proportion in the mixtures, transitioning from an enthalpic to an entropic mechanism as it approaches the pure solvent. Ultimately, it is concluded that PEG 300 acts as an excellent, eco-friendly cosolvent that could help to optimise more sustainable pharmaceutical systems.

Keywords: solubility; isoniazid; PEG 300; cosolvent; solution thermodynamics

1. Introduction

Contemporary pharmaceutical process engineering is undergoing a crucial transition toward sustainability, guided by the principles of green chemistry [1]. In this context, the selection of solvent systems determines not only the efficiency of fundamental unit operations, such as crystallisation and purification, but also the environmental footprint of the industrial process [2]. Solubility is the physicochemical property that governs these mass transfer phenomena [3]. Cosolvency is one of the most effective, simple, and thermodynamically sound techniques for manipulating and optimising this property to improve drug solubility. This increases its strategic value when volatile and toxic organic solvents can be replaced with eco-friendly alternatives [4], such as polyethylene glycol 300 (PEG 300) and water. This makes it a priority strategy for reducing risks and operational costs.

In this context, water and polyethylene glycol (PEG) 300 are among the best eco-friendly alternatives because they are classified as green solvents due to their low toxicity, limited flammability, and high biocompatibility [5,6]. Water is an economical and safe



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solvent, and PEG 300 is an excellent cosolvent that improves the solubility of various poorly water-soluble therapeutic agents. Consequently, using these substances ensures direct alignment with the fundamental principles of green chemistry, facilitating sustainable innovation and ensuring strict regulatory compliance in the modern pharmaceutical industry [7].

Isoniazid (INH, Figure 1), a first-line drug for treating tuberculosis [8], requires rigorous thermodynamic characterisation to enable the rational design of new solvent systems and ensure the development of robust, scalable manufacturing processes. According to the World Health Organization, INH is of undeniable clinical importance and remains an indispensable tool in the global fight against multidrug-resistant mycobacterial strains. It is currently the most widely used therapeutic regimen to combat tuberculosis [9]. Solubility is a fundamental parameter that drives mass transport processes such as dissolution. The transfer rate depends directly on the concentration gradient established between the solid surface and the fluid interior [10]. The Noyes–Whitney equation mathematically describes this dynamic relationship, positing that the dissolution rate is proportional to the solute's saturation solubility [11,12]. This underscores that increasing solubility in mixtures such as PEG 300/water drastically optimises the drug's release kinetics and bioavailability [13]. So, water and PEG 300 are among the best eco-friendly alternatives due to their classification as green solvents, given their low toxicity, limited flammability, and high biocompatibility. Water is an economical and safe cosolvent, and PEG 300 is an excellent cosolvent that improves the solubility of various poorly water-soluble therapeutic agents. Consequently, using them ensures direct alignment with the fundamental principles of green chemistry, facilitating sustainable innovation and ensuring strict regulatory compliance in the modern pharmaceutical industry.

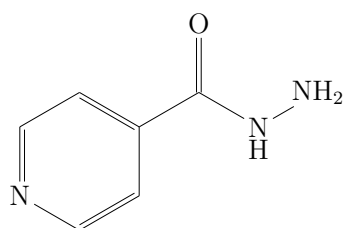


Figure 1. Molecular structure of isoniazid.

Consequently, the main objective of this study is to analyse the thermodynamic behaviour of isoniazid solubility in PEG 300 + water cosolvent mixtures at different temperatures.

2. Materials and Methods

2.1. Reagents

In this study, isoniazid (Sigma-Aldrich, Burlington, MA, USA; compound 3, with purities of at least 0.990 in mass fraction), polyethylene glycol 300 (Sigma-Aldrich, Burlington, MA, USA; solvent component 1, purity of at least 0.998 in mass fraction), and distilled water with conductivity $2.0 < \mu\text{S}/\text{cm}$ (solvent component 2) were used.

2.2. Preparation of Solvent Mixtures

Nineteen cosolvent mixtures of PEG 300 (substance 1) and water (substance 2) were prepared gravimetrically (mass fraction) from 0.05 to 0.95 using an analytical balance with sensitivity of ± 0.0001 g (RADWAG AS 220.R2, Toruń, Poland). Each of the cosolvent systems was prepared in an amber glass bottle with a capacity of 15 mL; 3 samples of 10.00 ± 0.00 g were prepared independently for each gravimetric concentration (See Supplementary File).

2.3. Solubility Determination

Solubility was determined according to the flowchart shown in Figure 2 [14]; for phase separation, syringe filters with a pore size of 0.45 μm were used, DSC analysis was performed using a Phoenix DSC 204 F1 (Dresden, Germany), and quantification was performed using an EMC-11-UV UV/VIS spectrophotometer (Dresden, Germany) (See Supplementary File).

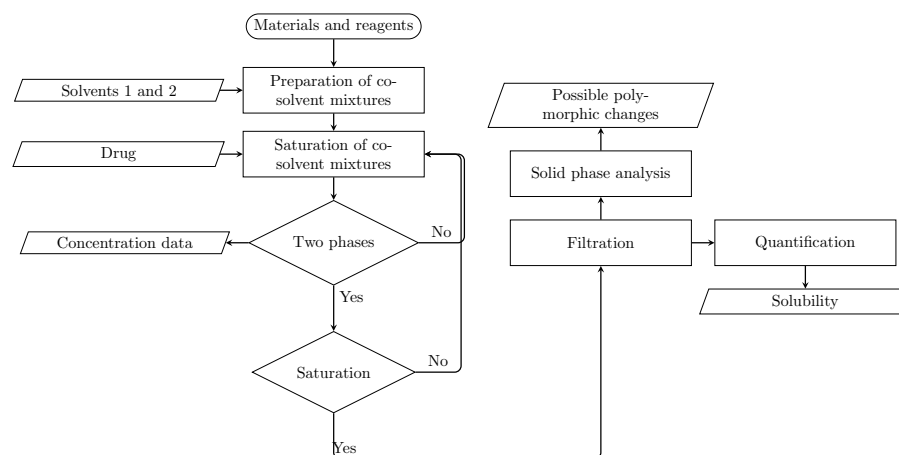


Figure 2. Flowchart of the experimental procedure for determining the solubility of drugs in cosolvent mixtures.

3. Results

The solubility of INH in the {PEG 300 (1) + water (2)} binary system (Table 1, Figure 3) exhibits behaviour characterised by a positive cosolvent effect and thermal (endothermic) dependence. As the temperature increases from 288.15 K to 318.15 K, the mole fraction of the drug progressively increases, indicating that energy input is necessary to overcome the cohesive forces of the crystalline solute and form cavities in the solvent matrix. In terms of composition, minimum solubility is observed in pure water, whereas maximum values are reached in pure PEG 300, suggesting that the molecular environment of PEG 300 is more favourable for the solvation of INH than the aqueous medium.

Table 1. Experimental solubility of INH (3) in {PEG 300 (1) + water (2)} cosolvent mixtures expressed as mole fraction (x_1) at different temperatures. Average relative uncertainty in mole fraction solubility is $u_r(x_3) = 0.025$; standard uncertainty in temperature is $u_r(T) = 0.05$ K. Experimental pressure $p = 0.1$ MPa. w_1 is the mass fraction of PEG 300 (1) in the {PEG 300 (1) + water (2)} mixtures free of INH, $u_r(w_1) = 0.001$.

w_1	288.15 K	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
0.00	0.0134 ¹	0.0165 ¹	0.0197 ¹	0.0238 ¹	0.0283 ¹	0.0338 ¹	0.0390 ¹
0.05	0.0136	0.0168	0.0205	0.0249	0.0295	0.0356	0.0421
0.10	0.0139	0.0176	0.0210	0.0258	0.0298	0.0368	0.0430
0.15	0.0144	0.0180	0.0213	0.0259	0.0308	0.0372	0.0439
0.20	0.0146	0.0184	0.0221	0.0264	0.0317	0.0375	0.0444
0.25	0.0149	0.0194	0.0226	0.0271	0.0323	0.0385	0.0452
0.30	0.0156	0.0191	0.0232	0.0280	0.0330	0.0394	0.0462
0.35	0.0162	0.0199	0.0236	0.0286	0.0344	0.0411	0.0470
0.40	0.0167	0.0202	0.0239	0.0292	0.0352	0.0418	0.0477
0.45	0.0172	0.0214	0.0247	0.0299	0.0358	0.0427	0.0484
0.50	0.0176	0.0216	0.0257	0.0301	0.0357	0.0430	0.0494
0.55	0.0180	0.0226	0.0264	0.0313	0.0368	0.0433	0.0503

Table 1. Cont.

w_1	288.15 K	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
0.60	0.0184	0.0230	0.0271	0.0321	0.0378	0.0452	0.0508
0.65	0.0190	0.0229	0.0271	0.0328	0.0392	0.0459	0.0516
0.70	0.0193	0.0237	0.0277	0.0333	0.0396	0.0467	0.0538
0.75	0.0197	0.0244	0.0286	0.0347	0.0411	0.0493	0.0554
0.80	0.0201	0.0248	0.0296	0.0363	0.0438	0.0522	0.0607
0.85	0.0202	0.0255	0.0310	0.0388	0.0475	0.0567	0.0668
0.90	0.0205	0.0266	0.0333	0.0422	0.0521	0.0631	0.0757
0.95	0.0206	0.0273	0.0355	0.0457	0.0579	0.0734	0.0931
1.00	0.0209	0.0281	0.0385	0.0528	0.0682	0.0907	0.1162

¹ This information was reported by Baracaldo-Santamaría et al. [15].

Adding PEG 300 could alter the structure of the water around the nonpolar groups of the solute, promoting dipole–dipole interactions and London dispersion forces with the aromatic ring [16–18]. The dynamics of this process may also be affected by the arrangement of the polymer chains. As temperature increases, the flexibility and conformation of the PEG chains may increase, facilitating solute–water interactions and generating an entropic gain that drives dissolution [19].

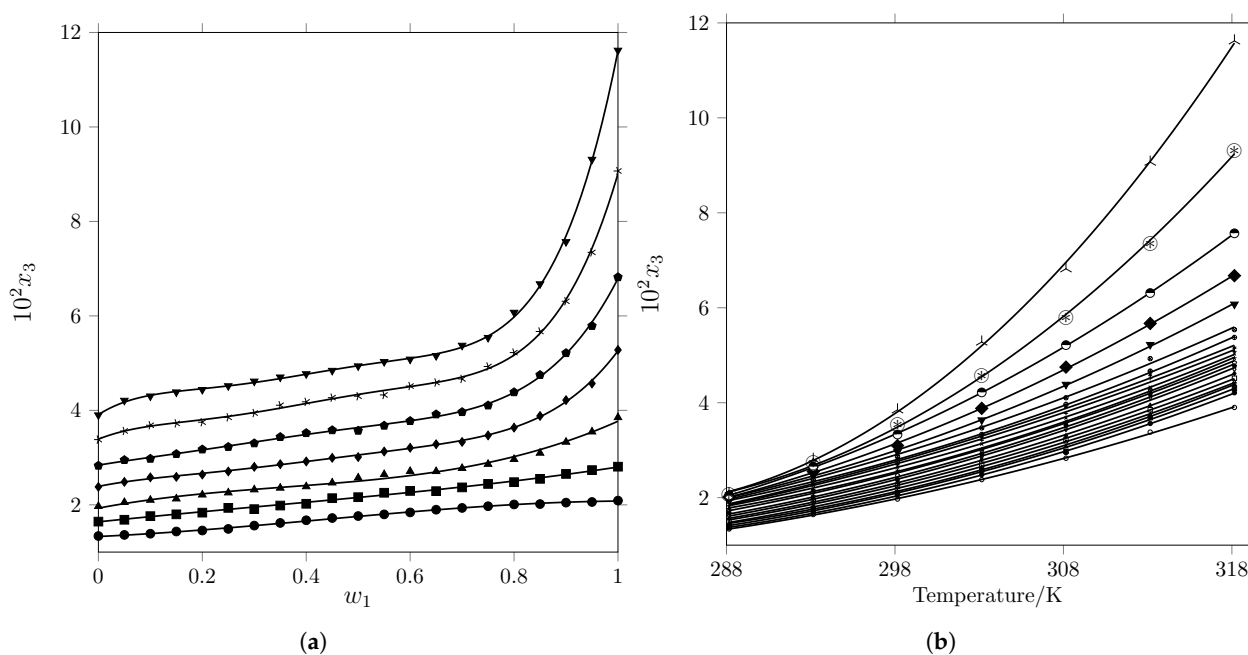


Figure 3. Solubility of INH in {PEG 300 (1) + water (2)} cosolvent mixtures. (a) The solubility behaviour of INH as a function of cosolvent composition (●: 288.15 K; ■: 293.15 K; ▲: 298.15 K; ◆: 303.15 K; ●: 308.15 K; ★: 313.15 K; ▼: 318.15 K). (b) The solubility behaviour of INH as a function of temperature (○: $w_{0.00}$, ●: $w_{0.05}$, ■: $w_{0.10}$, ▲: $w_{0.15}$, △: $w_{0.20}$, □: $w_{0.25}$, ◆: $w_{0.30}$, ◇: $w_{0.35}$, ●: $w_{0.40}$, ◇: $w_{0.45}$, ★: $w_{0.50}$, ×: $w_{0.55}$, +: $w_{0.60}$, *: $w_{0.65}$, ⊕: $w_{0.70}$, ⊗: $w_{0.75}$, ▼: $w_{0.80}$, ◆: $w_{0.85}$, ●: $w_{0.90}$, ⊗: $w_{0.95}$, ▲: $w_{1.00}$).

When the results of this study are compared with those obtained for PEG 200 [15] and PEG 400 [20], it can be seen that the process in PEG 400 + W is predominantly driven by entropy, due to the greater conformational freedom of its long chains. In the {PEG 300 (1) + water (2)} system, however, the enthalpic component becomes more significant, due to the density of specific interactions. Thus, PEG 300 acts as a thermodynamic transition point where solubility is modulated by balancing the structuring of the aqueous

network with the polymer's ability to stabilise the hydrazide group via hydrogen bonds and the pyridine ring via interactions in its ethylene regions.

3.1. Analysis of the Thermodynamic Functions of Dissolution and Mixing

The apparent thermodynamic functions of the dissolution and mixing processes were calculated using the Gibbs–van't Hoff–Krug model [21], according the following expressions: (1)–(5).

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

$$\Delta_{\text{soln}}G^{\circ} = -RT_{\text{hm}} \cdot \text{intercept} \quad (2)$$

$$\Delta_{\text{soln}}S^{\circ} = (\Delta_{\text{soln}}H^{\circ} - \Delta_{\text{soln}}G^{\circ})T_{\text{hm}}^{-1} \quad (3)$$

$$\zeta_H = |\Delta_{\text{soln}}H^{\circ}| (|T\Delta_{\text{soln}}S^{\circ}| + |\Delta_{\text{soln}}H^{\circ}|)^{-1} \quad (4)$$

$$\zeta_{TS} = 1 - \zeta_H \quad (5)$$

where $\Delta_{\text{soln}}H^{\circ}$ (in kJ/mol), $\Delta_{\text{soln}}G^{\circ}$ (in kJ/mol), and $\Delta_{\text{soln}}S^{\circ}$ (in kJ/mol·K) are the standard thermodynamic solution functions, namely enthalpy, Gibbs energy, and entropy of solution, assuming the reference state is the solution $x_3 = 1$. T is the study temperature (in K), T_{hm} is the harmonic mean temperature (in K), R is the gas constant (kJ/mol·K), and ζ_H and ζ_{TS} are the enthalpic and entropic contributions to the solution process.

The harmonic temperature is calculated as follows:

$$T_{\text{hm}} = \frac{n}{\sum_{i=1}^n \frac{1}{T_i}} \quad (6)$$

where n is the number of study temperatures (in this case $n = 8$).

From the van't Hoff–Krug equation,

$$\ln x_3 = a + m \left(\frac{1}{T} - \frac{1}{T_{\text{hm}}} \right) \quad (7)$$

$\Delta_{\text{soln}}H^{\circ}$ and $\Delta_{\text{soln}}G^{\circ}$ are calculated, according to Equations (1) and (2) using the values of m (slope) and a (intercept) of Equation (7).

The other hand, the dissolution process can be described in terms of three fundamental physicochemical subprocesses [22] (Figure 4). The first subprocess corresponds to the melting of the drug. This is a hypothetical stage in which the solute undergoes a phase change to become a supercooled liquid. Strictly speaking, this transition requires an energy input, or melting enthalpy. This makes it thermodynamically unfavourable for overall dissolution. The second subprocess involves the formation of a cavity within the solvent. Although the solvent does not undergo a phase change, its molecules must rearrange to create a space with sufficient volume to accommodate the solute molecule. This molecular restructuring also requires an energy input and is an endothermic process, which represents an unfavourable barrier to dissolution, as discussed in [23]. Finally, the mixing process takes place. Once the drug is in a hypothetical liquid state and a cavity has formed in the solvent, the solute occupies the space to consolidate the solution. This final stage is exothermic, driven by the formation of new solute–solvent interactions that release energy. This offsets the previous energy expenditure, favouring the dissolution process as a whole.

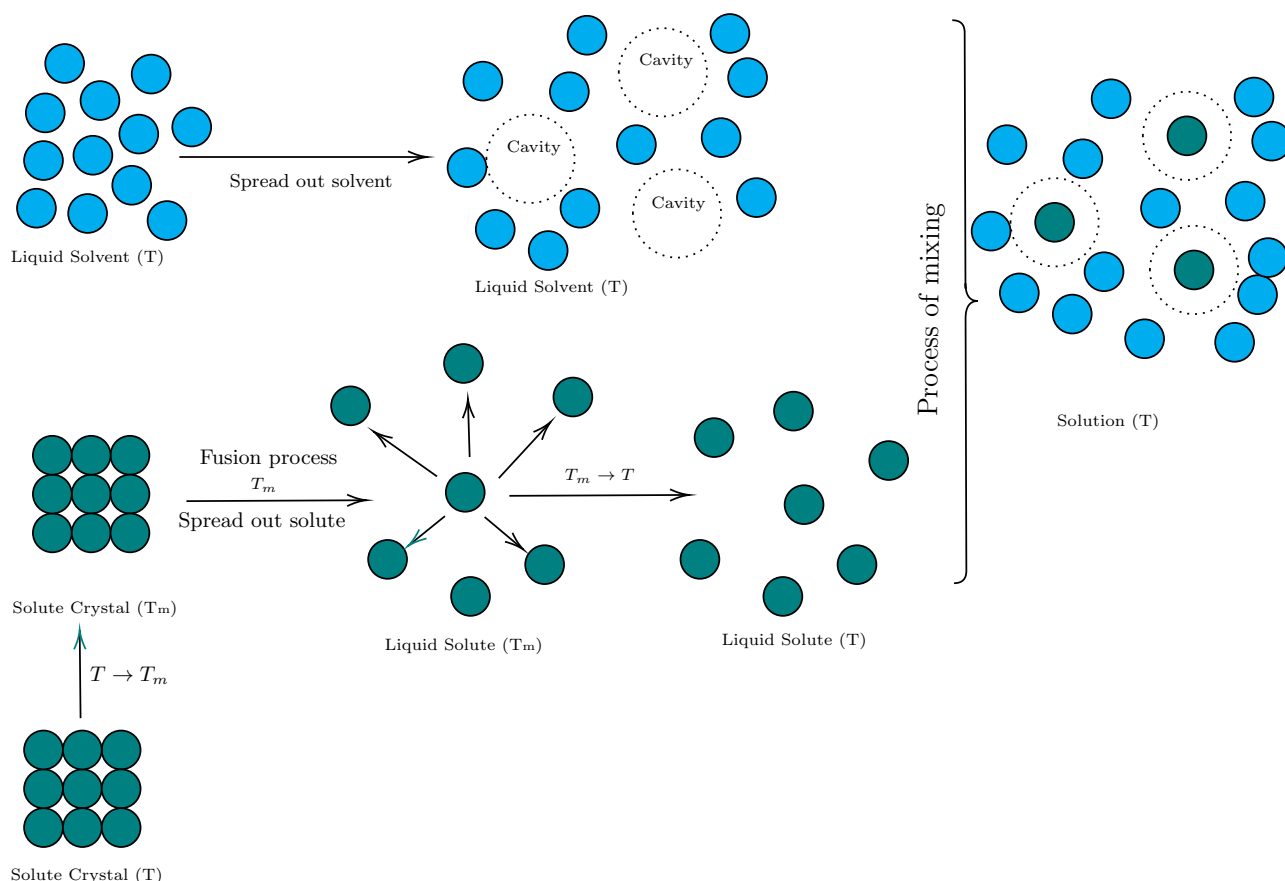


Figure 4. Diagram of hypothetical mixing process (solution formation).

The thermodynamic mixing functions are calculated as follows [14,20,24]:

$$\Delta_{\text{mix}} f^{\circ} = \Delta_{\text{soln}} f^{\circ} - \Delta_{\text{fus}} f^{T_{\text{hm}}} \quad (8)$$

$\Delta_{\text{fus}} f^{T_{\text{hm}}}$ is replaced by the thermodynamic functions relative to the ideal solution process, which are calculated from the ideal solubility at T_{hm} .

The standard thermodynamic functions of the solution are presented in Table 2. $\Delta_{\text{soln}} G^{\circ}$ decreases from 9.45 kJ/mol in pure water ($w_1 = 0.00$) to a minimum of 7.51 kJ/mol in pure PEG 300 ($w_1 = 1.00$). This systematic reduction in solution chemical potential indicates that the thermodynamic affinity of INH increases significantly (increased solubility of INH) as the proportion of the polymer in the mixture increases, thus validating the efficacy of PEG 300 as a cosolvent.

When this behaviour is broken down into its energetic and organisational components, it becomes apparent that the solution enthalpy ($\Delta_{\text{soln}} H^{\circ}$) is positive across the entire composition range, classifying the dissolution as an endothermic process [25]. However, the enthalpy trajectory is not linear; it initially decreases to a minimum of 25.71 kJ/mol at $w_1 = 0.55$, before rising sharply to 43.94 kJ/mol in the pure cosolvent. This initial decrease indicates that in water-rich mixtures, PEG 300 disrupts the three-dimensional network of water hydrogen bonds, thereby reducing the energy required to form the cavity that accommodates the solute [26,27]. Conversely, the sharp increase in polymer-rich regions is attributed to the high energy cost of separating the highly entangled PEG 300 chains and their strong intermolecular cohesive forces in their pure state. From an organisational perspective, the solution entropy ($\Delta_{\text{soln}} S^{\circ}$) is positive in all mixtures, favouring dissolution over the enthalpic barrier; the maximum value of this term is 120.29 J/mol · K in pure PEG 300 ($T\Delta_{\text{soln}} S^{\circ} = 36.43$ kJ/mol). This phenomenon indicates an entropy-driven process in

PEG-rich mixtures, where the conformational flexibility of the PEG 300 chains and deregulation generate an increase in configurational microstates, compensating for the mixing's high enthalpic cost. Finally, analysis of the relative contribution coefficients confirms that enthalpy ($\zeta_H \approx 0.605\text{--}0.547$) predominates over entropy ($\zeta_{TS} \approx 0.395\text{--}0.453$) in determining the magnitude of Gibbs energy. This confirms that, while entropy enables solubility in organic media by compensating for endothermicity, the net affinity of the system is predominantly governed by the energetic component of molecular interactions. Comparing the values of the thermodynamic functions of an ideal system reveals a significant deviation from ideal behaviour. The experimental enthalpy ranges from 25.71 to 43.94 kJ/mol. This value is significantly higher than the value for an ideal solution (18.7 kJ/mol), suggesting a higher energy cost. Similarly, the experimental entropies far exceed the ideal behaviour value of 37.5 J/mol·K. These thermodynamic differences demonstrate the presence of complex molecular interactions in the solution that are not accounted for in an ideal process.

Table 2. Thermodynamic functions of the solution process of INH (3) in {PEG 300 (1) + water (2)} cosolvent mixtures at T_{hm} .

w_1	$\Delta_{soln} G^\circ$ (kJ/mol)	$\Delta_{soln} H^\circ$ (kJ/mol)	$\Delta_{soln} S^\circ$ (J/mol·K)	$T\Delta_{soln} S^\circ$ (kJ/mol)	ζ_H	ζ_{TS}
0.00	9.45	27.29	58.91	17.84	0.605	0.395
0.05	9.35	28.57	63.47	19.22	0.598	0.402
0.10	9.28	28.42	63.22	19.14	0.598	0.402
0.15	9.23	28.19	62.60	18.96	0.598	0.402
0.20	9.18	27.97	62.06	18.79	0.598	0.402
0.25	9.11	27.58	60.99	18.47	0.599	0.401
0.30	9.06	27.56	61.11	18.50	0.598	0.402
0.35	8.98	27.44	60.95	18.46	0.598	0.402
0.40	8.93	27.15	60.17	18.22	0.598	0.402
0.45	8.86	26.47	58.16	17.61	0.600	0.400
0.50	8.82	26.11	57.08	17.29	0.602	0.398
0.55	8.75	25.71	56.00	16.96	0.603	0.397
0.60	8.69	25.80	56.50	17.11	0.601	0.399
0.65	8.65	25.94	57.10	17.29	0.600	0.400
0.70	8.59	26.03	57.58	17.44	0.599	0.401
0.75	8.51	26.51	59.47	18.01	0.596	0.404
0.80	8.39	28.34	65.90	19.96	0.587	0.413
0.85	8.24	30.62	73.88	22.37	0.578	0.422
0.90	8.05	33.27	83.28	25.22	0.569	0.431
0.95	7.82	38.09	99.95	30.27	0.557	0.443
1.00	7.51	43.94	120.29	36.43	0.547	0.453
Ideal ¹	7.58 ± 0.03	18.7 ± 0.17	37.5 ± 0.4	11.17 ± 0.11	0.627	0.373

¹ This information was reported by Baracaldo-Santamaría et al. [15].

Table 3 shows the standard thermodynamic mixing function values for the dissolution process of INH (3) in cosolvent mixtures of {PEG 300 (1) + water (2)}. The Gibbs free energy of mixing ($\Delta_{mix} G^\circ$) predominantly exhibits positive values, decreasing progressively from 1.87 kJ/mol in pure water to -0.07 kJ/mol in pure PEG 300. This trend suggests that, despite the thermodynamically unfavourable nature of the mixing process in aqueous media due to water's resistance to rearrangement, the solute–solvent affinity increases with the addition of the polymer. The mixing enthalpy ($\Delta_{mix} H^\circ$) is positive across the entire composition range, varying from 8.59 kJ/mol to a maximum of 25.24 kJ/mol. This endothermic nature indicates that the net INH–solvent interactions are weaker than the solvent–solvent and solute–solute interactions, which must be overcome to allow molecular

packing. There is a relative minimum in $\Delta_{\text{mix}}H^\circ$ around $w_1 = 0.55$ (7.01 kJ/mol), suggesting that, in these intermediate mixtures, cavity formation is less energetically costly since PEG 300–water interactions are weaker than those in pure water or pure polymer. The key driving force of the mixing process is entropy ($\Delta_{\text{mix}}S^\circ$), which is positive throughout the range and reaches extremely high values in pure PEG 300 (82.79 J/mol·K). The significant increase in entropy compensates for the enthalpy barrier, particularly in regions with a high polymer content. Thermodynamically, the INH/PEG 300 + water mixing process is classified as an entropy-driven phenomenon that is enthalpy-limited. Accordingly, the affinity of the drug for PEG 300 may be dominated by structural and conformational factors rather than stronger intermolecular interactions, indicating conformational freedom.

Table 3. Thermodynamic functions of the mixing process of INH (3) in {PEG 300 (1) + water (2)} cosolvent mixtures at Thm.

w_1	$\Delta_{\text{mix}}G^\circ$ (kJ/mol)	$\Delta_{\text{mix}}H^\circ$ (kJ/mol)	$\Delta_{\text{mix}}S^\circ$ (J/mol·K)	$T\Delta_{\text{mix}}S^\circ$ (kJ/mol)
0.00	1.87	8.59	21.41	6.67
0.05	1.77	9.87	25.97	8.05
0.10	1.70	9.72	25.72	7.97
0.15	1.65	9.49	25.10	7.79
0.20	1.60	9.27	24.56	7.62
0.25	1.53	8.88	23.49	7.30
0.30	1.48	8.86	23.61	7.33
0.35	1.40	8.74	23.45	7.29
0.40	1.35	8.45	22.67	7.05
0.45	1.28	7.77	20.66	6.44
0.50	1.24	7.41	19.58	6.12
0.55	1.17	7.01	18.50	5.79
0.60	1.11	7.10	19.00	5.94
0.65	1.07	7.24	19.60	6.12
0.70	1.01	7.33	20.08	6.27
0.75	0.93	7.81	21.97	6.84
0.80	0.81	9.64	28.40	8.79
0.85	0.66	11.92	36.38	11.20
0.90	0.47	14.57	45.78	14.05
0.95	0.24	19.39	62.45	19.10
1.00	−0.07	25.24	82.79	25.26

3.2. Enthalpy–Entropy Compensation (EEC) Analysis

Analysis of Figure 5a, which plots solution enthalpy ($\Delta_{\text{soln}}H^\circ$) against solution Gibbs energy ($\Delta_{\text{soln}}G^\circ$), reveals a non-linear trajectory with a reversal in slope at the critical point, $w_1 \approx 0.60$. This transition indicates the coexistence of two distinct solvation mechanisms. In the water-rich interval ($0.00 < w_1 < 0.60$), a positive slope is observed, denoting an enthalpy-driven process where the addition of PEG 300 disrupts the water’s hydrogen-bond network, reducing the energy cost of cavity formation [28]. Conversely, as we move towards pure PEG 300 from $w_1 \approx 0.60$, the slope becomes negative, indicating an entropy-driven process. In addition, Figure 5b provides validation of the phenomenon through the linear relationship between $\Delta_{\text{soln}}H^\circ$ and the entropy term $T\Delta_{\text{soln}}S^\circ$. Regarding the EEC effect, a linear correlation with a slope close to unity indicates that changes in enthalpy are almost entirely offset by changes in entropy, thereby maintaining variations in $\Delta_{\text{soln}}G^\circ$ within a narrow range [29]. The graph clearly identifies two zones with distinct slopes: 1.25 for the water-rich region and 0.939 for the PEG 300-rich region. A slope greater than one in the aqueous region confirms enthalpic dominance linked to disruption of the solvent structure. A slope less than one in the organic region, meanwhile, confirms an entropic

driving force associated with relaxation of the PEG chains and system reorganisation [30,31]. It is also important to note that this type of analysis must distinguish between real ‘chemical’ compensation and artificial ‘statistical’ compensation derived from the propagation of errors in van’t Hoff equations [29,32]. The clear inflection observed in Figure 5a and the robustness of the slopes in Figure 5b suggest that this is not a mathematical artefact, but rather reflects a genuine change in the solvation mechanism caused by transitioning from a rigidly structured medium (water) to a conformationally flexible one (PEG 300).

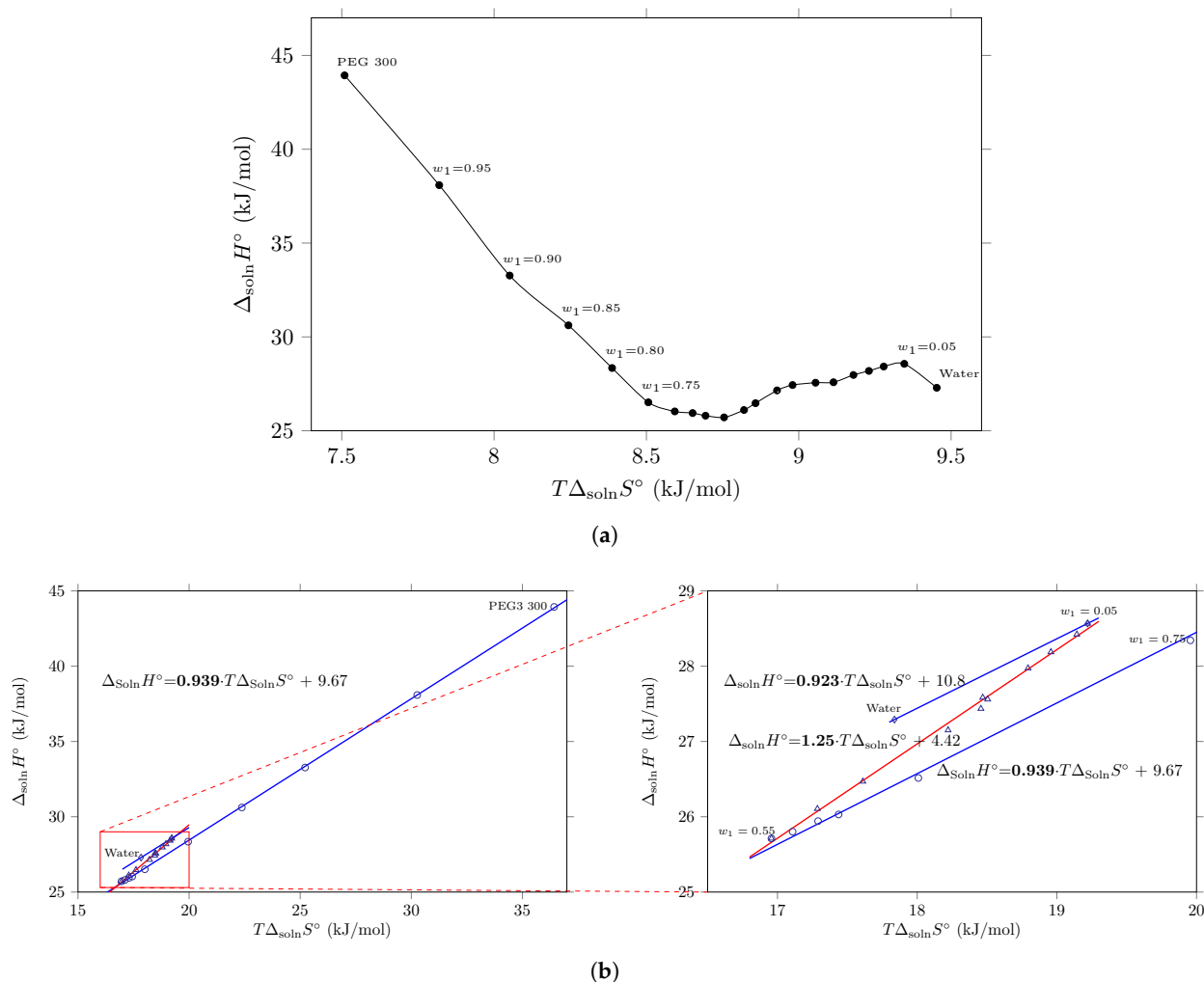


Figure 5. Enthalpic–entropic compensation corresponding to the solution process of the INH in PEG 300 + water at $T_{hm}/K = 302.82$. (a) Nonlinear relationship between $\Delta_{\text{soln}}H^\circ$ and $\Delta_{\text{soln}}G^\circ$. (b) Linear relationship between $\Delta_{\text{soln}}H^\circ$ and $T\Delta_{\text{soln}}S^\circ$.

4. Conclusions

The solubility of INH exhibits positive temperature dependence, classifying dissolution as an endothermic process across the entire composition range. A positive cosolvent effect was observed, whereby the chemical affinity (measured via the Gibbs free energy of solution, $\Delta_{\text{soln}}G^\circ$) increases with the polymer’s mass fraction, reaching a maximum in pure PEG 300 ($w_1 = 1.00$). Analysis of the standard solution functions reveals that, although the process is globally enthalpy-driven ($\zeta_H > 0.54$), it is favoured by entropy. In regions rich in PEG 300, the increase in microstates and the flexibility of the polymer chains offset the enthalpic cost of molecular separation. Finally, enthalpy–entropy compensation analysis shows nonlinear behaviour with an inflection point at $w_1 \approx 0.60$. This demonstrates a transition from an enthalpy-driven mechanism in aqueous mixtures to an entropy-driven

mechanism in organic media, confirming that PEG 300 is an efficient medium for designing sustainable pharmaceutical processes.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/liquids6030023/s1>, A detailed description of the experimental methodology is provided. Table S1: Source and purities of the compounds used in this research.

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Abbreviations

The following abbreviations are used in this manuscript:

a	Intercept
m	Slope
EEC	Enthalpy–entropy compensation
INH	Isoniazid
K	Kelvin
PEG	Polyethylene glycol
LD	Linear dichroism
R	Universal gas constant (8.314 J/K·mol)
$\Delta_{\text{soln}}H^\circ$	Standard Enthalpy of Solution
$\Delta_{\text{mix}}H^\circ$	Standard Enthalpy of Mixing
$\Delta_{\text{soln}}S^\circ$	Standard Entropy of Solution
$\Delta_{\text{mix}}S^\circ$	Standard Entropy of Mixing
$\Delta_{\text{soln}}G^\circ$	Standard Gibbs Energy of Solution
$\Delta_{\text{mix}}G^\circ$	Standard Gibbs Energy of Mixing
T	Temperature
T_{hm}	Harmonic temperature
W	Water
w_1	Mass fraction of PEG 300
x_3	Mole fraction of INH

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