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Scientific research article

Thermodynamic analysis and preferential solvation of metronidazole solubility in methanol-water and ethanol-water cosolvent mixtures at different temperatures

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SUMMARY

Introduction: Solubility is one of the most important physicochemical properties because it is related to some industrial processes such as: formulation, preformulation, purification and quantification. **Objective:** This paper presents the thermodynamic analysis of the solubility of metronidazole in methanol-water and ethanol-water cosolvent mixtures at seven temperatures. **Methodology:** From solubility data, the thermodynamic functions of solution and mixture are calculated and analysed using the Perlovich graphical method. On the other hand, an enthalpy-entropy compensation analysis is performed, and the preferential solvation parameters are calculated using the inverse Kirkwood-Buff integral (IKBI) method. **Results:** The result of the calculations performed indicates that the dissolution process of metronidazole is endothermic with entropic preference, where the addition of methanol and ethanol has a positive cosolvent effect in intermediate and water-rich mixtures. With regard to preferential solvation, the results are not entirely conclusive, since, except in intermediate mixtures, the values of the preferential solvation parameter are less than 0.01, so that negligible preferential solvation takes place.

Keywords: Solubility, metronidazole, solution thermodynamics, enthalpy-entropy compensation, preferential solvation.

RESUMEN

Análisis termodinámico y solvatación preferencial de la solubilidad del metronidazol en mezclas cosolventes metanol-agua y etanol-agua a diferentes temperaturas

Introducción: La solubilidad es una de las propiedades fisicoquímicas más importantes, puesto que está relacionada con algunos procesos industriales, como: formulación, preformulación, purificación y cuantificación. **Objetivo:** Este trabajo presenta el análisis termodinámico de la solubilidad del metronidazol en mezclas de cosolventes metanol + agua y etanol + agua a siete temperaturas diferentes. **Metodología:** A partir de los datos de solubilidad, se calcularon y analizaron las funciones termodinámicas de la solución y la mezcla mediante el método gráfico de Perlovich. Por otro lado, se realiza un análisis de compensación entalpía-entropía y se calculan los parámetros de solvatación preferencial mediante el método de la integral inversa de Kirkwood-Buff (IKBI). **Resultados:** Los cálculos realizados indican que el proceso de disolución del metronidazol es endotérmico con favorecimiento entrópico, la adición de metanol y etanol tiene un efecto cosolvente positivo en mezclas intermedias y ricas en agua. En cuanto al parámetro de solvatación preferencial, los resultados no son del todo concluyentes, ya que, salvo en las mezclas intermedias, los valores del parámetro de solvatación preferencial son inferiores a 0,01, por lo que se concluye que se tiene una solvatación preferencial despreciable.

***Palabras Clave*:** Solubilidad, metronidazol, termodinámica de soluciones, compensación entalpía-entropía, solvatación preferencial.

RESUMO

Análise termodinâmica e solvatação preferencial da solubilidade do metronidazol em misturas de metanol-água e etanol-água a diferentes temperaturas

Introdução: A solubilidade é uma das propriedades físico-químicas mais importantes, pois está relacionada com vários processos industriais, nomeadamente formulação, pré-formulação, purificação e quantificação. **Objetivo:** O presente trabalho apresenta a análise termodinâmica da solubilidade do metronidazol em misturas de metanol + água e etanol + água em sete temperaturas diferentes. **Metodologia:** A partir dos dados de solubilidade, as funções termodinâmicas da solução e da mistura foram calculadas e analisadas com recurso ao método gráfico de Perlovich. Além disso, é efetuada uma análise de troca de entalpia-entropia e os parâmetros de solvatação preferenciais são calculados utilizando o método integral inverso de Kirkwood-Buff (IKBI). **Resultados:** Os cálculos indicam que o processo de dissolução do metronidazol é endotérmico com favorecimento entrópico, e que a adição de metanol e etanol tem um efeito positivo de co-solvente em misturas intermédias e ricas em água. No que se refere ao parâmetro de solvatação preferencial, os resultados não são totalmente conclusivos, uma vez que, exceto nas misturas intermédias, os valores do parâmetro de solvatação preferencial são inferiores a 0,01, pelo que se conclui que a solvatação preferencial é desprezível.

Palavras-chave: solubilidade, metronidazol, termodinâmica de soluções, compensação entalpia-entropia, solvatação preferencial.

1. INTRODUCTION

Metronidazole (MET) (Figure 1) is a widely used antibiotic and antiprotozoal medication. Since its introduction in France in 1960, this essential drug has become integral to treating a variety of infections, including bacterial vaginosis, pelvic inflammatory disease, and parasitic

infections such as giardiasis, trichomoniasis, and amebiasis. Its versatility is further demonstrated by its use in treating anaerobic infections, Crohn's disease, Helicobacter pylori infections, and as a prophylactic agent after surgery. With multiple formulations—oral, topical, and intravenous—metronidazole continues to play a critical role in modern medicine, ranking among the most commonly prescribed medications globally [1,2].

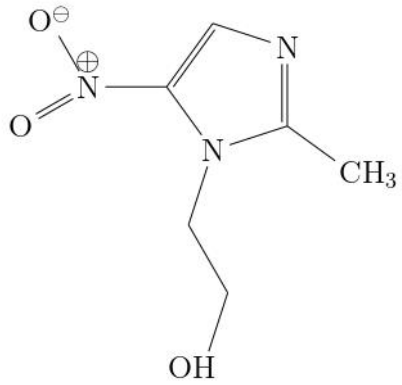

Figure 1. Molecular structure of metronidazole ($C_6H_9N_3O_3$; 2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethanol; CAS Number 443-48-1).

While the therapeutic potential of metronidazole is well-recognized, a critical factor that governs its clinical efficacy is its solubility and bioavailability [3, 4].

Water (solvent 2) is the most used solvent in pharmaceutical formulations, renowned for its safety, biocompatibility, and ability to dissolve polar compounds. As a universal solvent, water facilitates the dissolution of APIs, ensuring their bioavailability and therapeutic efficacy [5, 6]. It is particularly critical for oral drug formulations, where aqueous solubility governs the rate of drug dissolution and absorption in the gastrointestinal tract [7]. Additionally, water (W, solvent 2) is indispensable in parenteral, ophthalmic, and topical formulations, where purity and compatibility with physiological systems are paramount [8]. Methanol (MeOH, solvent 1^a), though less commonly employed than water due to its toxicity at higher concentrations, is a valuable cosolvent in pharmaceutical applications [9]. Its low molecular weight and high polarity make it an effective agent for dissolving hydrophobic drugs and enhancing the solubility of poorly water-soluble APIs. In laboratory settings, methanol is widely used in chromatographic analyses and quality control of drugs, including metronidazole, to ensure their compliance with pharmacopoeial standards [10, 11]. Ethanol (EtOH, solvent 1^b) serves a dual purpose in the pharmaceutical industry: as a solvent and as an antimicrobial preservative [12, 13]. Its compatibility with water and ability to dissolve both hydrophilic and hydrophobic substances make it a preferred cosolvent in liquid formulations, such as syrups, tinctures, and elixirs [14, 15]. Ethanol also plays a role in enhancing the bioavailability of drugs with poor aqueous solubility by modifying the solubility profile of APIs in mixed-solvent systems [6, 16–18].

The solubility of a drug is a key determinant of its therapeutic efficacy, particularly for oral dosage forms, which constitute many pharmaceutical products [19–21]. Poorly soluble drugs often face challenges such as low bioavailability, variable absorption, and suboptimal therapeutic outcomes. Factors influencing solubility, including pH levels, polarity, and dissolution dynamics, are critical considerations in drug formulation and delivery. Effective drug absorption and bioavailability hinge on the drug's ability to dissolve in gastrointestinal fluids

and traverse biological membranes. Poorly soluble drugs may exhibit erratic absorption patterns, leading to inconsistent therapeutic outcomes [22, 23].

The thermodynamic analysis allows us to evaluate the energetics related to the possible molecular interactions between the different molecules present in the solution; this information is relevant for the rational design of dosage forms, the optimization of industrial processes and the development of strategies for the decontamination of matrices such as water, soil and waste materials [24–26].

The preferential solvation analysis of drugs in co-solvent mixtures may be performed through the method of inverse Kirkwood–Buff integrals (IKBI). It expresses the local compositions near to the solute with respect to the different components present in the co- solvent solutions [18, 27]. This method depends on the value of the standard molar Gibbs energies of transfer of the solute from neat water to the cosolvent mixtures and the excess molar Gibbs energy of mixing for the solute-free mixtures. So, this treatment is of very importance in pharmaceutical sciences in understanding the molecular interactions between solute and solvent, because many solubility studies developed have been focused toward correlating or modelling the solubilities and the possible prediction in mixed solvents from the solubilities in the neat solvents [28]. Nevertheless, just a few of them have been intended to analyse the local environment around the drug molecules describing the local fraction of the solvent components (1 or 2) in the surrounding of solute [29].

2. METHODOLOGY

Experimental mole fraction solubility data (x_3) for metronidazole (component 3) in binary cosolvent mixtures of {methanol (1) + water (2)} and {ethanol (1) + water (2)} across a range of temperatures (specify range, e.g., from 293.15 K to 313.15 K) were sourced from a previously published scientific study [30].

Based on these solubility data, the apparent standard thermodynamic functions associated with the dissolution process were calculated [31]. The apparent standard Gibbs free energy of solution ($\Delta_{soln}G°$) it was determined according to Gibbs and van't Hoff equations based on the modification of Krug. The apparent standard enthalpy of solution ($\Delta_{soln}H°$) was derived using the modified van't Hoff equation by assessing the slope of the graphical representation of $\ln x_3$ plotted against $T^{-1} - T_{hm}^{-1}$. Where T_{hm} denotes the mean harmonic temperature over the experimental temperature interval. Consequently, the apparent standard entropy of solution ($\Delta_{soln}S°$) was computed at the temperature T_{hm} using the fundamental Gibbs relationship [32–36].

An enthalpy-entropy compensation analysis was conducted to explore the potential linear correlation between the enthalpy and entropy changes governing the solution process. This involved plotting $\Delta_{soln}H°$ against $\Delta_{soln}G°$ evaluated at the mean harmonic temperature T_{hm}. The linearity and the slope derived from this plot were analysed to characterize the compensation effect and potentially infer the molecular mechanisms driving the dissolution [37–39].

Furthermore, the preferential solvation of metronidazole by the constituent solvents within the mixtures (water and methanol/ethanol) was investigated employing the Inverse Kirkwood-Buff Integrals (IKBI) methodology [40–42].

3. RESULTS AND DISCUSSION

The solubilities of MET in mixtures of {MeOH (1[a]) + W (2)} and {MeOH (1[b]) + W (2)} (Figure 2) provided by Yu *et al.* [30].

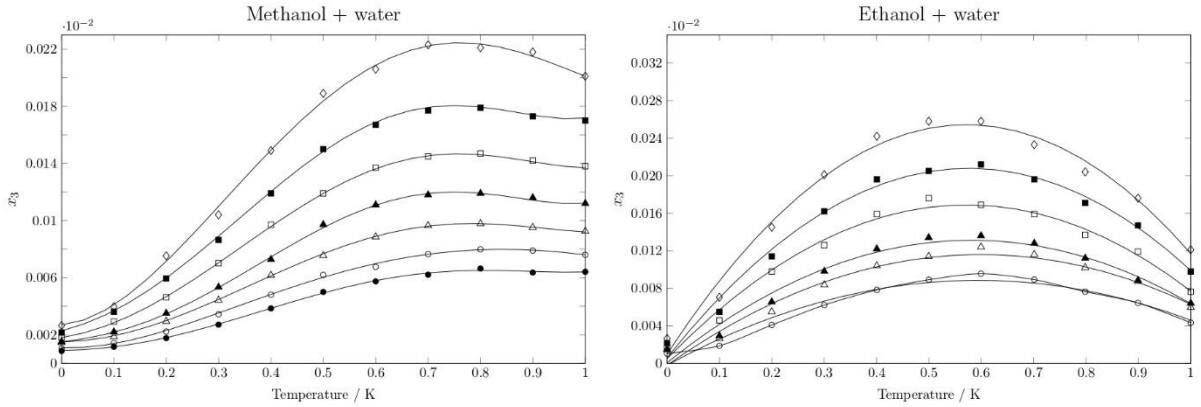

Figure 2. Solubility of MET in mole fraction (x_3) in {MeOH (1[a]) + W (2)} and {EtOH (1[b]) + W (2)} cosolvent mixtures: ●= 293.15 K; ○= 298.15 K; Δ= 303.15 K; ▲= 308.15 K; ■= 313.15 K; □= 318.15 K; ◊= 323.15 K. From [30].

According to Figure 2, the solubility of MET in {MeOH (1[a]) + W (2)} and {EtOH (1[b]) + W (2)} increases with increasing temperature, indicating an endothermic process [27, 28]. Furthermore, in both cosolvent mixtures, the cosolvent (MeOH and EtOH) influences the profile of the solubility isotherms. In mixtures {MeOH (1[a]) + W (2)}, except for 298.15 K, the maximum solubility is reached in a cosolvent mixture (between x_1=0.7 and x_1=0.9); in mixtures {EtOH (1[b]) + W (2)}, the maximum solubility is reached in a cosolvent mixture [43, 44].

When analysing the behaviour of the solubility isotherms as a function of the solubility parameter of the cosolvent system, a behaviour similar to that of sulfadiazine is observed at {MeOH (1[a]) + W (2)} [35] and {EtOH (1[b]) + W (2)} [31]. MET with a calculated solubility parameter of 25.6 $MPa^{1/2}$ (Table 1) reach it maximum solubility in {MeOH (1[a]) +W (2)} mixtures of δ_{1+2}=31-35 $MPa^{1/2}$ and in {EtOH (1[b])+W (2)} mixtures with δ_{1+2}=35.4 $MPa^{1/2}$.

Table 1. Fedor's methods applied to calculate partial and total solubility parameters of MET [45]

Group	#	$\Delta U°$ (kJ·mol^{-1})	$V°$ (cm^3·mol^{-1})
-CH_3	1	4.71	33.5
–CH_2–	2	2·4.94 = 9.88	2·16.1 = 32.2
–CH=	1	4.31	13.5
–OH	1	29.8	10
–NO_2	1	15.36	32
–N=	1	11.7	5
>N–	1	4.2	-9.0
Conjugation in ring	2	2·1.67=3.34	2·-2.2=-4.4
Ring closure [3] 5 atoms	1	1.05	16
	∑	84.35	128.80
		$\delta_2 = (84350/128.80)^{1/2} = 25.6$ $MPa^{1/2}$	

3.1. Thermodynamic functions of solution

From solubility data [30], the thermodynamic functions of solutions are calculated. Table 2 and Table 3 present the standard molar thermodynamic functions for dissolution of MET (3) in {MeOH (1[a]) + W (2)} and {EtOH (1[b]) + W (2)} cosolvent mixtures.

The mathematical expressions for calculating the apparent thermodynamic functions of a solution according to the Gibbs and van't Hoff equations based on the modification of Krug *et al.* are [46–48]:

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

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

and

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

where $\Delta_{\text{soln}}H^{\circ}$, $\Delta_{\text{soln}}G^{\circ}$ and $\Delta_{\text{soln}}S^{\circ}$ denote the enthalpy, Gibbs energy and entropy of the solution, respectively. T_{hm} denotes the harmonic average of the study temperatures, and R denotes the universal constant of the gases. The intercept corresponds to the linear equation of the plot of ln x_3 vs ($T^{-1} - T_{\text{hm}}^{-1}$) [49, 50].

The contribution of the energy factors (solution enthalpy) and organizational aspects (entropy) to the Gibbs energy of the solution can be obtained using equations 4 and 5 [51, 52].

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

$$\zeta_{TS} = |T\Delta_{\text{soln}}S^{\circ}|(|\Delta_{\text{soln}}H^{\circ}| + |T\Delta_{\text{soln}}S^{\circ}|)^{-1} \quad (5)$$

Thus, Tables 2 and 3, presents the thermodynamic analysis results of the MET dissolution processes in {MeOH (1[a]) + W (2)} and {EtOH (1[b]) + W (2)} mixtures.

Table 2. Standard thermodynamic functions of the MET solution in {MeOH (1[a]) + W (2)} mixtures at T_{hm} = 307.3 K

x_1[a]	$\Delta_{\text{soln}}G^{\circ}$/ kJ·mol^{-1}	$\Delta_{\text{soln}}H^{\circ}$/ kJ·mol^{-1}	$\Delta_{\text{soln}}S^{\circ}$/ J·mol^{-1}·K^{-1}	$T\Delta_{\text{soln}}S^{\circ}$/ kJ·mol^{-1}	ζ_H	ζ_{TS}
0.00	16.54	28.45	38.74	11.91	0.705	0.295
0.10	15.58	34.24	60.71	18.66	0.647	0.353
0.20	14.35	38.46	78.46	24.11	0.615	0.385
0.30	13.33	36.14	74.21	22.81	0.613	0.387
0.40	12.48	35.96	76.43	23.49	0.605	0.395
0.50	11.86	35.34	76.39	23.47	0.601	0.399
0.60	11.55	34.65	75.17	23.10	0.600	0.400
0.70	11.35	33.69	72.68	22.33	0.601	0.399
0.80	11.30	32.04	67.49	20.74	0.607	0.393
0.90	11.37	32.22	67.84	20.85	0.607	0.393
1.00	11.45	30.96	63.49	19.51	0.613	0.387
Ideal	7.87	22.97	49.13	15.10	0.603	0.397

[a]x_1 is the molar fraction of methanol in the cosolvent mixture free of solute.

Table 3. Standard thermodynamic functions of the MET solution in {EtOH (1^b) + W (2)} mixtures at T_{hm} = 310.0 K

x_1[a]	$\Delta_{soln}G°$/ kJ·mol^{-1}	$\Delta_{soln}H°$/ kJ·mol^{-1}	$\Delta_{soln}S°$/ J·mol^{-1}·K^{-1}	$T\Delta_{soln}S°$/ kJ·mol^{-1}	ζ_H	ζ_{TS}
0.00	16.44	28.53	39.00	12.09	0.702	0.298
0.10	14.43	44.03	95.51	29.60	0.598	0.402
0.20	12.49	42.44	96.64	29.96	0.586	0.414
0.30	11.55	38.63	87.37	27.08	0.588	0.412
0.40	11.00	37.25	84.68	26.25	0.587	0.413
0.50	10.78	34.89	77.81	24.12	0.591	0.409
0.60	10.71	32.30	69.66	21.59	0.599	0.401
0.70	10.90	31.35	65.99	20.46	0.605	0.395
0.80	11.25	31.64	65.77	20.39	0.608	0.392
0.90	11.69	32.71	67.84	21.03	0.609	0.391
1.00	12.69	32.34	63.41	19.66	0.622	0.378
Ideal	7.57	23.34	50.90	15.78	0.597	0.403

[a]x_1 is the molar fraction of ethanol in the cosolvent mixture free of solute.

The Gibbs energy of solution is positive in all cases and decreases as the polarity of the system decreases from pure water to pure methanol in the {MeOH (1^a) + W (2)} mixtures; in the {EtOH (1^b) + W (2)} mixture it initially has the same behaviour as in the {MeOH (1^a)+W(2)} mixture, decreasing from pure water to the mixture x_1=0. 6, from this mixture the Gibbs energy of the solution shows an increase up to pure EtOH, because the solubility decreases, possibly due to the effects of the change in polarity of the medium, making it less favourable in terms of MET. In mixtures {MeOH (1^a) + W (2)} the standard enthalpy of solution increases from pure water to the mixture x_1 = 0.2 and then decreases from this mixture to pure MeOH, possibly due to an increase in solute-solvent molecular interactions caused by the addition of MeOH; the initial increase may be due to the destructuring of the water around the non-polar groups of MET. It is important to note that the standard enthalpy of a solution is positive in all cases, indicating an endothermic process, which inhibits the dissolution process. However, unlike the positive enthalpy values, the standard entropy of the solution also has positive values, favouring the dissolution process [53, 54]. This favourability is lower in pure water, possibly because water adopts a highly organised structure around hydrophobic molecules, which maximises the interactions between its own molecules (hydrophobic hydration) and promotes the formation of 'clathrate-like structures', reducing the entropy of the system [55].

In terms of the contribution of energetic and organisational factors, the enthalpy of the solution is the most important contributor to the Gibbs energy values of the solution in all cases.

In mixtures {EtOH (1^b) + W (2)} the standard enthalpy of solution increases from pure water to the mixture x_1 = 0.1, then decreases from this mixture to the mixture x_1= 0.7, then increases, behaving randomly. As with the mixtures {MeOH (1^a) + W (2)}, the enthalpy is positive, which favours the solution process, but with a strong entropic favoring.

Analysis of the Perlovich plot (Figure 3) shows that all values are in the first sector ($\Delta_{soln}H° > T\Delta_{soln}S° > 0$), indicating that the standard enthalpy of solution is a major contributor to the Gibbs energy of solution in the two cosolvent systems [56–59].

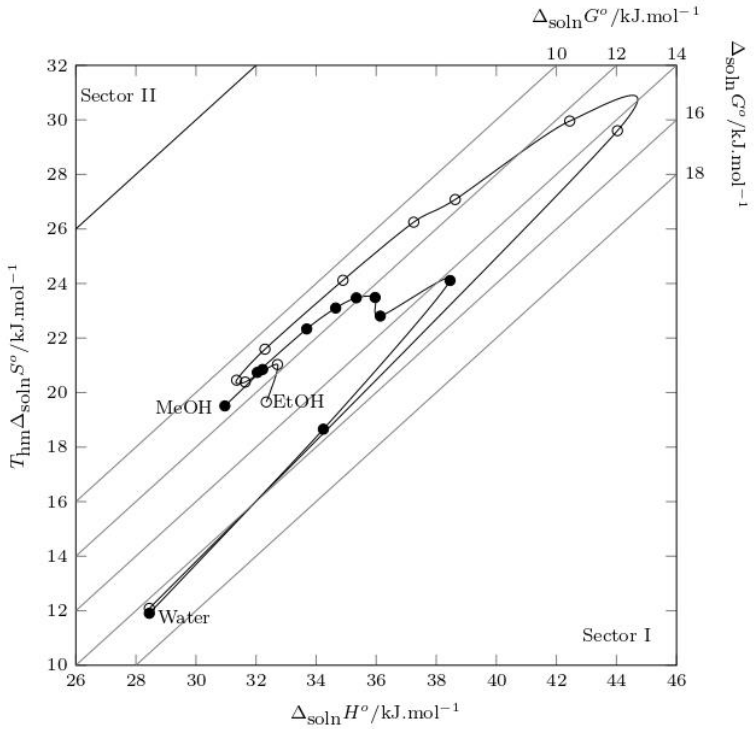

Figure 3. Relationship between the enthalpy and entropic terms of solutions functions of MET in {MeOH (1[a]) + W (2)} and {EtOH (1[b]) + W(2)} cosolvent mixtures. The isoenergetic curves of $\Delta_{soln}G°$ function are marked by dotted lines.

3.2. Thermodynamic functions of mixing

In general, the solution process can be described by three sub-processes [60] (Figure 4):

- Drug fusion process: In a hypothetical process, the drug changes phase, transforming into a super-cooled liquid. Technically, this process requires energy supply, which is why it is unfavourable for the solution process.
- Cavity formation: Although the solvent does not present a phase change, the solvent molecules must disintegrate, forming a cavity to house the solute molecule; this process also requires energy investment (endothermic process) and is therefore unfavourable for the solution process.
- Mixing process: Once the drug is in a liquid state and the cavity has been formed in the solvent, the solute molecule is housed in the solvent cavity, forming the solution. This process is exothermic, which favours the solution process.

Mathematically, the solution process can be described as

$$\Delta_{soln}f^o = \Delta_{mix}f^o + \Delta_{fus}f^{Thm} \quad (6)$$

Thus, the thermodynamic mixing functions are calculated as follows:

$$\Delta_{mix}f^o = \Delta_{soln}f^o - \Delta_{fus}f^{Thm} \quad (7)$$

where f represents the Gibbs energy, enthalpy or entropy of mixing and f_{fus} represent the thermodynamic functions of the fusion of MET (3) and its cooling to the harmonic mean temperature, 307.3 K (MeOH) and 310.0 K (EtOH). As it has been described previously in the literature, in this research study, the $\Delta_{soln}f°$ values for the ideal solution processes were used instead of $\Delta_{fus}f^{Thm}$.

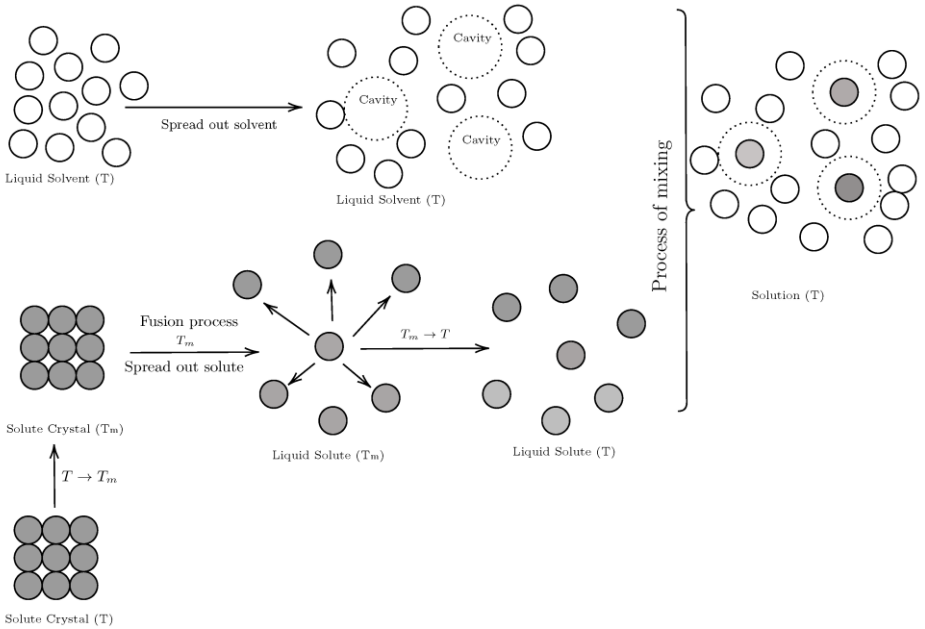

Figure 4. Diagram of hypothetical mixing process (solution formation) [25]

Table 4. Thermodynamic functions of mixing of MET (3) in {MeOH (1[a]) + W (2)} cosolvent mixtures at 307.3 K.

x_1 [a]	$\Delta_{mix}G°$/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	8.67	5.48	-10.39	-3.19
0.10	7.71	11.27	11.58	3.56
0.20	6.48	15.49	29.32	9.01
0.30	5.46	13.16	25.08	7.71
0.40	4.60	12.99	27.30	8.39
0.50	3.99	12.37	27.25	8.38
0.60	3.68	11.68	26.04	8.00
0.70	3.48	10.71	23.54	7.23
0.80	3.43	9.07	18.36	5.64
0.90	3.50	9.25	18.71	5.75
1.00	3.58	7.99	14.36	4.41

[a]x_1 is the mass fraction of MeOH (1[a]) in the {MeOH (1[a]) + W (2)} mixtures free of MET (3).

Table 5. Thermodynamic functions of mixing of MET (3) in {EtOH (1[b]) + W (2)} cosolvent mixtures at 310.0 K.

x_1 [a]	$\Delta_{mix}G°$/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	8.87	5.18	-11.90	-3.69
0.10	6.86	20.69	44.61	13.83
0.20	4.92	19.10	45.74	14.18
0.30	3.98	15.29	36.46	11.30
0.40	3.44	13.91	33.78	10.47
0.50	3.21	11.55	26.91	8.34
0.60	3.14	8.95	18.76	5.81
0.70	3.33	8.01	15.09	4.68
0.80	3.69	8.30	14.87	4.61
0.90	4.12	9.37	16.94	5.25
1.00	5.12	9.00	12.51	3.88

[a]x_1 is the mass fraction of EtOH (1[b]) in the {EtOH (1[a]) + W (2)} mixtures free of MET (3).

The thermodynamic mixing functions of MET in mixtures of cosolvents {MeOH (1[a]) + W (2)} and {EtOH (1[b]) + W (2)} at T_{hm} are given in Tables 4 and 5. The Gibbs energy is positive in all cases and decreases from pure water up to x_1 = 0.80 in mixtures {MeOH (1[a]) + W (2)} and x_1= 0.60 in mixtures {EtOH (1[b]) + W (2)}, then shows a slight increase up to pure alcohol (MeOH and EtOH). As for the enthalpy of the mixture, an increase is observed from pure water up to x_1 = 0.2 in mixtures {MeOH (1[a])+W(2)} and x_1 = 0.10 in mixtures {EtOH (1[b])+W(2)}; from this mixture up to x_1 = 0.80 in mixtures {MeOH (1[a]) + W (2)} and x_1 = 0.70 in mixtures {EtOH (1[b]) + W (2)}, the enthalpy decreases, indicating that the addition of MeOH or EtOH to the system favours the dissolution process by reducing the energy required to form a cavity between the solvent molecules. This is possibly due to the fact that water-water molecular interactions are much more energetic than W-MeOH, W-EtOH, MeOH-MeOH or EtOH interactions. Therefore, the formation of cavities in intermediate and alcohol-rich mixtures requires less energy. The entropy of the mixture is positive, except for pure water, due to the molecular interactions between the MET and water that cause the water to structure around the non-polar groups of this drug. Thus, starting from the cosolvent mixture x_1 = 0.1 to pure MeOH or pure EtOH, the solution process is favoured by the entropy of the mixture.

3.3. Enthalpy-entropy compensation

Changes in the free energy landscape upon tethering can be attributed to changes in entropy or enthalpy. Very often the changes in entropy and enthalpy are coupled. In many cases, a perturbation produced by a change in the solvent composition, leads to a change in the enthalpy of solution processes is correlated with a similar change in entropy in what is commonly referred to as "entropy–enthalpy compensation" [37, 46, 61, 62]. Entropy–enthalpy compensation is reported for many chemical processes and is often accounted for as a general thermodynamic principle. In this case, analysis has been used to identify the mechanism of the cosolvent action [63]. Figure 5 shows that MET in {MeOH (1[a]) + W (2)} and {EtOH (1[b]) + W (2)} cosolvent mixtures at 307.3 K for {MeOH (1[a]) + W (2)} and 310.0 K for {EtOH (1[b]) + W (2)} presents a non-linear $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$ curves. In cosolvent mixtures {MeOH (1[a]) + W (2)}, a positive slope is present in the interval from x_1= 0.70 to x_1=0.20, indicating that the driving mechanism of solubility is enthalpic; in the intervals from MeOH to x_1=0.70 and from x_1=0. 20 to pure water the trend has a negative slope, indicating entropic driving in these intervals; as for mixtures {EtOH (1[b]) + W (2)}, there are two continuous regions with enthalpic driving between pure EtOH and x_1=0.10, from this cosolvent composition to pure water the solution process is driven by entropy.

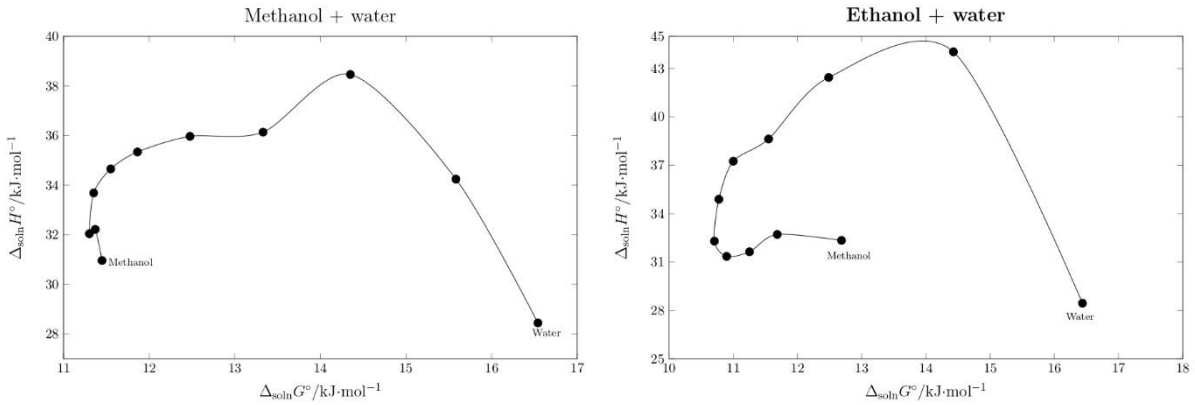

Figure 5. $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$ enthalpy-entropy compensation plot for solubility of MET in {MeOH (1[a]) + W (2)} and {EtOH (1[b]) + W (2)} cosolvent mixtures.

3.4. Preferential solvation

Although the thermodynamic analyses provide information of considerable importance for understanding the dissolution process of the drug, they do not provide information about the actual molecular environment of the drug in cosolvent mixtures [64–66]. The inverse Kirkwood-Buff integral (IKBI) approach identifies the local composition around the MET molecules for each of the solvents making up the mixture (W + MeOH and W + EtOH) based on the solubility data and the excess Gibbs energy of the free cosolvent mixtures of MET. This can be attributed to the preferential solvation of MET in the {MeOH (1) + W (2)} and {EtOH (1) + W (2)} cosolvent mixture, which depends both on the molecular interactions of MET with W, MeOH and EtOH, and on the interactions between the solvents described by the excess Gibbs energy of the mixture (in the absence of MET), taking into account the competitive molecular interactions of the three components (MET, W, MeOH or EtOH) in the solution process.

The results of this study are expressed in terms of the preferential solvation parameters $\delta x_{1,3}$ for MET (3) by the components of the W (2), MeOH (1^a) and EtOH (1^b) mixture as [67,68]:

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3}, \tag{8}$$

where x_1 is the mole fraction of 1 in the original solute-free mixture and $x_{1,3}^{L}$ is the local mole fraction of 1 in the MET molecule environment. If $\delta x_{1,3} > 0$, MET will be surrounded in considerable proportion by MeOH or EtOH (solvated preferentially by the MeOH or EtOH) when compared with the proportion of MeOH or EtOH in the original mixture.

The mathematical expressions for the application of the IKBI model proposed by Professor Ben-Naim restructured by Professor Marcus are described as follows [69,70]:

$$\delta x_{1,3} = x_1 x_2 \left(G_{1,3} - G_{2,3}\right)\left(x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}\right)^{-1} \tag{9}$$

$$G_{1,3} = RT\kappa_T - V_3 + x_2 V_2 D Q^{-1} \tag{10}$$

$$G_{2,3} = RT\kappa_T - V_3 + x_1 V_1 D Q^{-1} \tag{11}$$

$$V_{cor} = 2522.5\left[r_3 + 0.1363\sqrt[3]{x_1^L V_1 + (1 - x_1^L)V_2} - 0.085\right]^3 \tag{12}$$

$$D = \left(d\Delta_t G_{3,2\rightarrow 1+2}^{o}/dx_1\right)_{T,P} \tag{13}$$

$$Q = RT + x_1 x_2 \left(d^2 G_{1,2}^{E}/dx_2^2\right)_{T,P}, \tag{14}$$

where $G_{1,3}$ and $G_{2,3}$ denote the Kirkwood–Buff integrals ($cm^3\ mol^{-1}$), which are obtained from the thermodynamic data according to equations 10 and 11, and V_{cor} denotes the volume of correlation around MET within which preferential solvation occurs. κ_T is the isothermal compressibility of the mixtures (in GPa^{-1}) [71]. V_3 is the partial molar volume of the solute, and V_1 and V_2 are the volumes of the solvents ($cm^3\ mol^{-1}$). $G_{3,2\rightarrow 1+2}^{o}$ is the Gibbs energy of solute transfer from water to each cosolvent mixture, and $G_{1,2}^{E}$ is the excess Gibbs energy of the cosolvent MET-free {MeOH (1^a) + W (2)} and {EtOH (1^b) + W (2)} cosolvent mixtures. All the thermodynamic values required at 298.15 K for IKBI calculations in these mixtures were taken from the literature [72].

In Figure 6 and Table 6 the behaviour of $\delta x_{1,3}$ and other properties of preferential solvation in the function of the MeCN molar fraction at 298.15 K is denoted. The tendency of the solvation parameter is similar to that in other drugs, where the maximum solubility is reached in a cosolvent mixture and not in a pure solvent.

Figure 6 shows the Gibbs energy of transfer behaviour of MET from neat water to {MeOH (1^a) + W (2)} cosolvent mixtures at 307.3 K and from neat water to {EtOH (1^b) + W (2)} cosolvent mixtures at 310.0 K.

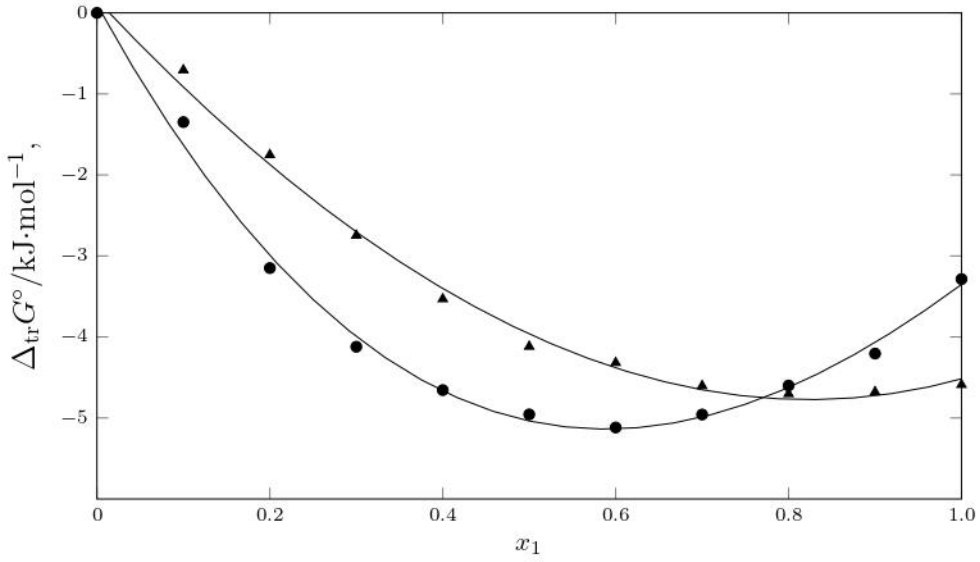

Figure 6. Gibbs energy of transfer of MET from neat water to {MeOH (1^a) + W (2)} cosolvent mixtures (▲) and from neat water to {ETOH (1^b) + W (2)} cosolvent mixtures (●).

The equations that represent the trend correspond to a second and third order polynomial (Equation 15 and 16).

$$\Delta_{tr}G^0_{3,2\rightarrow 1^a+2} = RT\ln\left(\frac{x_{3,2}}{x_{3,1^a+2}}\right) = 7.13x_{1a}^2 - 11.88x_{1a} + 0.19 \quad (15)$$

$$\Delta_{tr}G^0_{3,2\rightarrow 1^b+2} = RT\ln\left(\frac{x_{3,2}}{x_{3,1^b+2}}\right) = -4.63x_{1b}^3 + 20.60x_{1b}^2 - 19.42x_{1b} + 0.10 \quad (16)$$

According to equations 8 and 9, *D* is calculated as the derivative of Gibbs energy of transfer as a function of x_1 (Equation 17, 18).

$$D = \left(\frac{\partial \Delta_{tr}G^0_{(3,2\rightarrow 1a+2)}}{\partial x_{1a}}\right)_{T,p} = 14.26x_{1a} - 11.88 \quad (17)$$

$$D = \left(\frac{\partial \Delta_{tr}G^0_{(3,2\rightarrow 1b+2)}}{\partial x_{1b}}\right)_{T,p} = -13.89x_{1b}^2 + 41.2x_{1a} - 19.42 \quad (18)$$

In Figure 6 and Tables 6 and 7 the behaviour of $\delta x_{1,3}$ and other properties of preferential solvation in the function of the MeOH or EtOH molar fraction at 298.15 K is denoted. The tendency of the solvation parameter is like that in other drugs, where the maximum solubility is reached in a cosolvent mixture and not in a pure solvent.

Table 6. Some properties associated to preferential solvation of MET (3) in {MeOH (1[a]) + W (2)} mixtures at T_{hm} = 298.15 K.

x_1[a]	D/kJ.mol^{-1}	$G_{1,3}$/cm^3.mol^{-1}	$G_{2,3}$/cm^3.mol^{-1}	V_{cor}/cm^3.mol^{-1}	$100\delta x_{1,3}$
0.00	-11.89	-214.30	-127.67	672.61	0.00
0.10	-10.46	-196.38	-143.33	708.97	-0.85
0.20	-9.03	-184.40	-157.63	748.09	-0.73
0.30	-7.60	-173.87	-170.94	790.01	-0.10
0.40	-6.17	-162.58	-180.52	833.54	0.65
0.50	-4.74	-150.30	-181.68	876.63	1.10
0.60	-3.32	-139.02	-171.89	917.92	1.03
0.70	-1.89	-131.02	-154.00	958.08	0.59
0.80	-0.46	-126.75	-132.97	999.01	0.11
0.90	0.97	-125.30	-111.04	1041.91	-0.14
1.00	2.40	-125.71	-86.31	1085.19	0.00

[a] x_1 is the mole fraction of MeOH (1) in the {MeOH (1[a]) + W (2)} mixtures free of MET (3).

Table 7. Some properties associated to preferential solvation of MET (3) in {EtOH(1[b]) + W (2)} mixtures at T_{hm} = 298.15 K.

x_1[a]	D/kJ.mol^{-1}	$G_{1,3}$/cm^3.mol^{-1}	$G_{2,3}$/cm^3.mol^{-1}	V_{cor}/cm^3.mol^{-1}	$100\delta x_{1,3}$
0.00	-19.42	-269.27	-127.67	672.73	0.00
0.10	-15.44	-250.13	-168.68	734.90	-1.31
0.20	-11.74	-219.36	-199.40	811.84	-0.52
0.30	-8.31	-188.36	-212.38	891.74	0.73
0.40	-5.17	-162.48	-206.72	966.77	1.37
0.50	-2.30	-141.79	-179.11	1034.84	1.07
0.60	0.29	-124.80	-116.74	1095.71	-0.20
0.70	2.61	-112.35	-4.36	1151.58	-2.12
0.80	4.64	-110.64	110.98	1213.43	-3.09
0.90	6.40	-118.98	121.02	1289.80	-1.81
1.00	7.88	-125.94	60.59	1368.34	0.00

[a] x_1 is the mole fraction of EtOH (1) in the {EtOH (1[b]) + W (2)} mixtures free of MET (3).

The $\delta x_{1,3}$ values vary non-linearly in both cosolvent mixtures (Figure 7). With respect to mixture {MeOH (1[a]) + W (2)}, the addition of MeOH (1) to W (2) tends to make the $\delta x_{1,3}$ values of this drug negative from pure water (2) to the mixture of 0.30 in mole fraction of MeOH (1), reaching minimum values close to -0.010 in the mixture with 0.1 in mole fraction of methanol (1). Possibly the structuring of the water molecules around the non-polar groups of MET by hydrophobic hydration contributes to the reduction of the net $\delta x_{1,3}$ to negative values in these water-rich mixtures.

In mixtures with a composition of $0.30 < x_1 < 0.9$, the local mole fractions of methanol (1[a]) are higher than those of water (2). Thus, the effect of the cosolvent may be related to the disruption of the ordered structure of water by hydrogen bonding around the nonpolar moieties of the drug, as noted above. The highest preferential solvation by the co-solvent reaches a maximum value at x_1 = 0.50 ($\delta x_{1,3}$ close to 0.011 at 293.15 K).

MET in cosolvent mixtures {EtOH (1[b]) + W (2)} shows analogous behaviour, solvating in water- and ethanol-rich mixtures.

According to the preferential solvation results, it is assumed that in intermediate compositions MET (3) acts as a Lewis acid with methanol (1) and ethanol molecules, because these cosolvents are more basic than water, i.e. the Kamlet-Taft hydrogen bond acceptor parameters for MeOH and EtOH are $\beta = 0.62$ and $\beta = 0.77$, respectively, and 0.47 for water [73]. However, the specific solute-solvent interactions remain unclear despite the developed treatments.

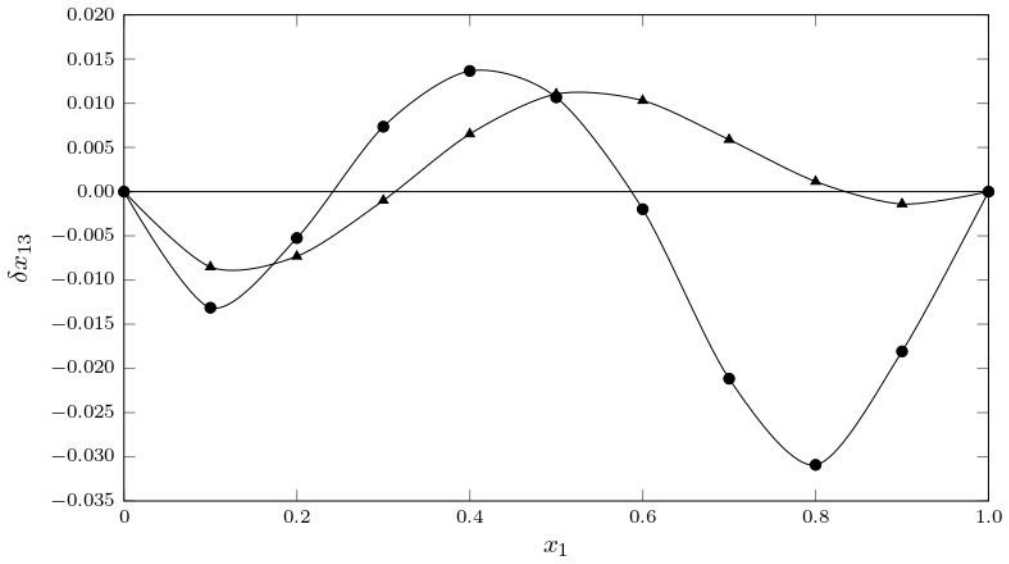

Figure 7. $\delta x_{1,3}$ values for MET (3) in {MeOH (1[a]) + W (2)}(▲) and {EtOH (1[b]) + W (2)}(●) co-solvent mixtures at 298.15 K.

4. CONCLUSIONS

The findings indicate that the dissolution process of metronidazole is endothermic and favoured by entropy. The addition of both methanol and ethanol demonstrated a positive cosolvent effect, particularly in intermediate and water-rich mixtures, enhancing the solubility of metronidazole. Regarding preferential solvation, the results were not entirely conclusive. While some preferential solvation by the cosolvents (methanol or ethanol) was observed, especially in intermediate mixtures where the local mole fractions of the alcohol were higher than water, the values of the preferential solvation parameter.

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CONFLICT OF INTEREST

All authors report that they do not have any conflicts of interest.

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