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Thermodynamic analysis and preferential solvation of gatifloxacin in DMF + methanol cosolvent mixtures

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Summary

This paper presents the thermodynamic analysis of solubility of gatifloxacin in the N,N-Dimethylformamide (DMF) + methanol (MeOH) cosolvent system at 10 temperatures. From the solubility data, the thermodynamic functions of solution, mixing, and transfers are calculated and analyzed 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. The result of the performed calculations indicates that the gatifloxacin solution process is endothermic with entropic favor, where the addition of DMF has a positive cosolvent effect in all cases. Regarding preferential solvation, the results are not entirely conclusive, since in all cases the values of the preferential solvation parameter are less than 0.01, so that, negligible preferential solvation takes place.

Key words: gatifloxacin, solubility, *N,N*-dimethylformamide, IKBI, preferential solvation.

Resumen

Análisis termodinámico y solvatación preferencial de gatifloxacina en mezclas cosolventes DMF + metanol

Este artículo presenta el análisis termodinámico de la solubilidad de gatifloxacina en el sistema cosolvente de *N*,*N*-Dimetilformamida (DMF) + metanol (MeOH) a 10 temperaturas. A partir de los datos de solubilidad se calculan las funciones termodinámicas de solución, mezcla y transferencia. Para el análisis además se utiliza el método gráfico Perlovich. Por otro lado, se realiza un análisis de compensación entalpía-entropía y se calculan los parámetros de solvatación preferencial utilizando el método de las integrales inversas de Kirkwood-Buff (IIKB). Los resultados del análisis termodinámico indican que el proceso de solución de gatifloxacina es endotérmica con favorecimiento entrópico, donde la adición de DMF tiene un efecto cosolvente positivo en todos los casos. En cuanto a la solvatación preferencial, los resultados no son del todo concluyentes, debido a que en todos los casos los valores del parámetro de solvatación preferencial son menores a 0,01 indicando una solvatación insignificante.

Palabras clave: gatifloxacina, solubilidad, *N*,*N*-dimetilformamida, IIKBI, solvatación preferencial.

Introduction

Gatifloxacin (1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid; CAS: 112811-59-3) (figure 1) is an antibiotic agent and a member of the fourth-generation fluoroquinolone family. It works by inhibiting the bacterial enzymes DNA gyrase and topoisomerase IV [1, 2]. Gatifloxacin is effective against a broad spectrum of bacteria that may cause ocular infections in humans including endopthalmitis and conjunctivitis. Melo *et al.* found that gatifloxacin was effective against a range of both Gram positive and Gram negative microorganisms including anaerobes when tested in vitro, which transforms this drug into a dangerous agent for the aquatic systems, if used indiscriminately [3].

In addition, the pharmaceutical industry is a potential source of contamination, since most processes, such as synthesis, purification of raw materials, chemical analysis for quality assessment, and pre-formulation and formulation studies, tend to produce large masses of waste containing these chemical agents [4, 5].

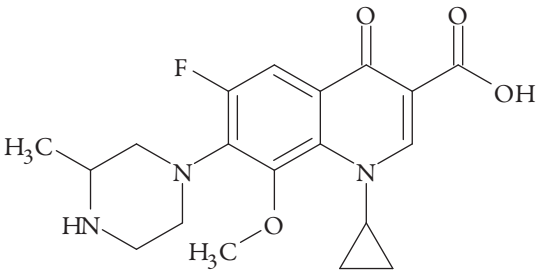

Figure 1. Molecular structure of gatifloxacin.

In this sense, the development of strategies that lead to the design of more environmental-friendly methodologies, focused on environmental management systems supported by ISO 14001, and leading to promoting the development of cleaner production practices have been consolidated as an important tool for the prevention and correction of contaminating processes [6, 7]. Thus, the generation of experimental data and the development of mathematical models that allow predicting properties such as solubility contribute greatly to reducing experimental tests, which in turn decreases the mass of pollutants (e.g., drugs, solvents, disposable material, and energy) produced in processes of the pharmaceutical industry [8, 9].

In this context, mathematical models tending to predict the solubility of drugs in different solvents and/or cosolvents mixtures at different temperatures have become an important tool for the pharmaceutical industry [10], not only for drugs but also for other large organic molecules, such as polycyclic aromatic hydrocarbons, which, like drugs, are also a source of contamination by the oil industry [11, 12]. Thus, based on thermodynamic properties, models such as the "nearly ideal binary solvent" approach by Acree *et al.* allow to successfully determine solubility in some types of cosolvent mixtures [13, 14]. Another model, which is an improvement of the previous one, is that proposed by Jouyban *et al.*, which involves polar and non-polar solvents [15, 16]. Other models based on area surfaces, contribution of UNIFAC groups, Hildebrand solubility parameters, and Kirkwood-Buff integrals have been proposed and refined to improve their predictability [17-20].

Thus, based on the solubility data of gatifloxacin in *N*,*N*-Dimethylformamide + methanol cosolvent mixtures, published by Wu *et al.* [21], and some data on the physicochemical properties of the drug (table 1) [22], the objective of the present work is perform a thermodynamic analysis and of preferential solvation.

Table 1. Physicochemical information of the gatifloxacin.

Chemicals	CAS reg. no.	molar mass / g mol^{-1}	Melting point / K	Melting enthalpy / kJ mol^{-1}
Gatifloxacin	112811-59-3	375.39	435.15[a]	34.95[a]

[a] *Ref* [22].

Results and discussion

Solubility of Gatifloxacin in DMF + methanol cosolvent mixtures

Figure 2 show the solubility of gatifloxacin (3) in DMF (1) + methanol (2) cosolvent mixtures, in this plot, can look an increase in solubility, as a consequence of an increase in temperature, which implies that the solution process in DMF (1) + methanol (2) cosolvent mixtures is favored by supplying energy to the system. This demonstrates that the process is endothermic [23, 24], where we can obtain the lowest solubility in pure methanol at 273.15 K (1.9 x 10^{-4}) and the maximum solubility in pure DMF (9.891 x 10^{-3}) at 318.15 K.

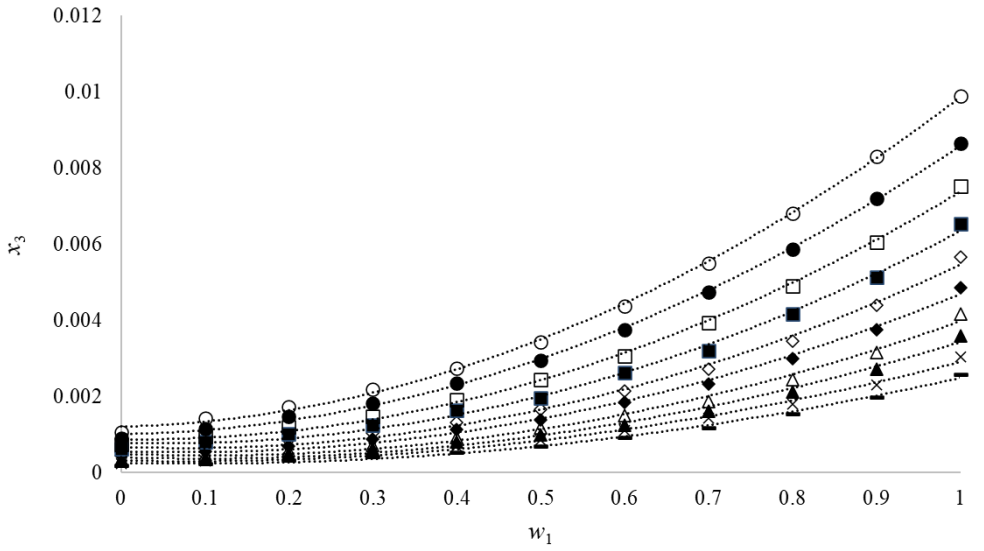

Figure 2. Solubility of gatifloxacin (3) expressed in molar fraction (x_3) in DMF (1) + methanol (2) cosolvent mixtures as a function of mass fraction at different temperatures. **-**: 273.15, **x**: 278.15 K; ▲: 283.15 K; Δ: 288.15 K; ♦: 293.15 K; ◊: 298.15 K; ▪: 303.15 K; □: 308.15 K; ●: 313.15 K; and ○: 318.15 K.

According to Hildebrand's theory, it would be expected that the maximum solubility would be reached in a cosolvent mixture and not in a pure solvent, as it happens in this case, because the polarity of la gatifloxacin (28.08 $MPa^{1/2}$ [25, 26]) (table 2) is between the polarity of DMF (24.1 $MPa^{1/2}$ [25]) and the polarity of methanol (29.7 $MPa^{1/2}$) [25].

Table 2. Application of the Fedors' method to estimate internal energy, molar volume, and Hildebrand solubility parameter of gatifloxacin (3) [25, 26].

Group	Group number	$V°$ / cm^3 mol^{-1}	$U°$ / kJ mol^{-1}
–NH–	1	4.5 x 1 = 4.5	8.4 x 1 = 8.4
>N–	2	-9 x 2 = -18	4.2 x 2 = 8.4
$–CH_3$	2	33.5 x 2 = 67	4.71 x 2 = 9.42
$–CH_2$	5	16.1 x 5 = 80.5	4.94 x 5 = 24.7
>CH–	3	-1 x 3 = -3	3.43 x 3 = 10.29
>C=	1	-5.5 x 1= -5.5	4.3 x 1 = 4.3
–C=O	1	10.8 x 1 = 10.8	17.4 x 1 = 17.4
–COOH	1	28.5 x 1 = 28.5	27.6 x 1 = 27.6
–O–	1	3.8 x 1 = 3.8	3.4 x 1 = 3.4
–F	1	18 x 1 = 18	4.19 x 1 = 4.19
Phenyl (pentasubstituted)	1	-4.6 x 1 = -4.6	31.9 x 1 = 31.9
Halogen attached to C atom with double bond	1	-	-0.2 x 4.19 = -0.84
Ring closure 5 or more atoms	2	16 x 2 = 32	1.05 x 2 = 2.10
Ring closure 3 or 4 atoms	1	18 x 1 = 18	3.14 x 1 = 3.14
Total		232.0	156.04
Solubility parameter			25.93 $MPa^{1/2}$

Activity coefficients

From the activity coefficients, the possible molecular interactions that govern the process of gatifloxacin solubility in the DMF + methanol cosolvent mixture can be inferior.

Table 3 presents the values of the activity coefficients in the DMF + methanol cosolvent system at nine temperatures calculated according to equation 1 [27], from the solubility data [21] and the ideal solubility calculated according to equation 2, which can be analyzed based on the solute-solute (e_{33}), solvent-solvent (e_{11}), and solute-solvent (e_{13}) molecular interactions using equation 3 [28]:

$$\gamma_3 = x_3^{id} / x_3 \tag{1}$$

$$\ln x_3^{id} = -\left\{\left[\Delta_{fus}H\left(T_{fus} - T\right)\right]\left[RT_{fus}T\right]^{-1}\right\} + \left\{\Delta C_P R^{-1}\left[\left(T_{fus} - T\right)T^{-1} + \left(\ln T - \ln T_{fus}\right)\right]\right\} \tag{2}$$

here x_3^{id} is the ideal solubility of the solute as mole fraction, $\Delta_{fus}H$ is the molar enthalpy of fusion of the pure solute (at the melting point), T_{fus} is the absolute melting point, T is the absolute solution temperature, R is the gas constant (8.314 J mol^{-1} K^{-1}), and ΔC_p is the difference between the molar heat capacity of the crystalline form and the molar heat capacity of the hypothetical super-cooled liquid form, both at the solution temperature. Since ΔC_p cannot be easy experimentally determined it is usual assuming that it may be approximated to the entropy of fusion, $\Delta_{fus}S$ [29,30].

$$\ln \gamma_3 = \left(e_{11} + e_{33} - 2e_{13}\right)V_3\varphi_1^2\left(RT\right)^{-1} \tag{3}$$

where V_3 is the molar volume of the supercooled liquid solute, and finally, ϕ_1 is the volumetric fraction of the solvent. A good approximation, for relatively low solubilities, is that the term $V_3\varphi^2{}_1/RT$ can be considered a constant, and therefore, ln γ_3 depends solely on $e_{11} + e_{33} - 2e_{13}$ [31]. The e_{11} and e_{33} terms are unfavorable for drug solubility and the term e_{13} favors the solubility thereof [32].

In all cases (table 3), the activity coefficients are greater than unity, which according to equation 3 [33], indicates that the solute-solute (e_{33}) and solvent-solvent (e_{11}) molecular interactions, which demerit the process of the solution, surpass the solute-solvent interactions, which favor the process.

In general, with an increase in temperature, the activity coefficients decrease and the cosolvent system's polarity decreases; thus, from pure methanol to the pure DMF, the activity coefficients decrease, showing a possible increase in the solute-solvent interactions, due to increased solubility of gatifloxacin (e_{13}).

Thermodynamic functions of solution

The standard thermodynamic functions of the solution (table 4) are calculated from the experimental solubility data and study temperatures. Thus, the mathematical expressions of Gibbs and van't Hoff, under Krug's approach, are presented as follows [4, 34, 35]:

$$T_{hm} = n / \sum_{i=1}^{n} 1/T_i \tag{4}$$

Table 3. Coefficient activity of gatifloxacin (3) in DMF (1) + methanol (2) cosolvent mixtures at different temperatures and pressure p = 0.1 MPa.

w_1 [a]	T / K									
	273.15	278.15	283.15	288.15	293.15	298.15	303.15	308.15	313.15	318.15
0.00	58.6	57.1	53.6	51.8	50.3	48.8	47.8	47.4	46.2	45.3
0.10	45.6	42.6	42.4	39.7	40.1	39.7	37.7	38.0	36.2	34.1
0.20	34.4	33.3	32.5	31.8	31.2	30.2	30.3	29.8	28.4	28.2
0.30	26.8	25.7	25.5	25.8	24.8	25.1	24.4	24.1	22.7	22.3
0.40	20.5	19.2	19.7	20.3	19.3	19.5	18.7	18.6	17.8	17.7
0.50	15.8	15.5	15.9	15.8	15.8	15.6	15.4	14.6	14.2	14.1
0.60	11.9	12.0	12.5	12.4	12.0	12.1	11.6	11.6	11.1	11.1
0.70	9.4	9.3	9.7	9.9	9.4	9.6	9.5	9.1	8.8	8.8
0.80	7.2	7.4	7.4	7.6	7.4	7.5	7.3	7.3	7.1	7.1
0.90	5.6	5.8	5.8	5.9	5.9	5.9	5.9	5.9	5.8	5.8
1.00	4.3	4.3	4.4	4.5	4.5	4.6	4.7	4.7	4.8	4.9

[a] w_1, mass fraction of DMF (1) in the gatifloxacin -free DMF (1) + methanol (2) mixture.

$$\Delta_{\text{soln}}H^{\circ} = -R\partial \ \text{In}\, x_3 / \partial\left(T^{-1} - T_{hm}^{-1}\right) \tag{5}$$

$$\Delta_{\text{soln}}G^{\circ} = -RT \times \text{intercept} \tag{6}$$

$$\Delta_{\text{soln}}S^{\circ} = T_{hm}^{-1}\left(\Delta_{\text{soln}}H^{\circ} - \Delta_{\text{soln}}G^{\circ}\right) \tag{7}$$

$$\xi_H = \left(\left|\Delta_{\text{soln}}H^{\circ}\right|\right)\left(\left|\Delta_{\text{soln}}H^{\circ}\right| + \left|T_{hm}\Delta_{\text{soln}}S^{\circ}\right|\right)^{-1} \tag{8}$$

$$\xi_{TS} = 1 - \xi_H \tag{9}$$

where T_{hm} is the harmonic temperature, $\Delta_{\text{soln}}G^{\circ}$ is the standard Gibbs energy of solution, $\Delta_{\text{soln}}H^{\circ}$ is the standard enthalpy of solution, and $\Delta_{\text{soln}}S^{\circ}$ is the standard entropy of solution. ξ_H y ξ_{TS} are the enthalpy and entropy contributions to the solution process and the intercept corresponds to the linear equation of the plot $\ln x_3$ vs. $(1/T - 1/T_{\text{hm}})$ [36, 37].

Table 4. Thermodynamic functions of solution of gatifloxacin (3) in DMF (1) + methanol (2) cosolvent mixtures at 294.95 K and pressure p = 0.1 MPa.

w_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}	ξ_H	ξ_{TS}
0.00	18.8	27.8	30.45	8.98	0.76	0.24
0.10	18.2	27.6	31.75	9.36	0.75	0.25
0.20	17.6	26.7	30.99	9.14	0.75	0.25
0.30	17.0	26.2	31.17	9.19	0.74	0.26
0.40	16.4	25.7	31.59	9.32	0.73	0.27
0.50	15.9	25.5	32.61	9.62	0.73	0.27
0.60	15.2	25.1	33.56	9.90	0.72	0.28
0.70	14.7	24.8	34.51	10.18	0.71	0.29
0.80	14.1	24.2	34.26	10.11	0.71	0.29
0.90	13.5	23.2	32.85	9.69	0.71	0.29
1.00	12.9	21.5	29.19	8.61	0.71	0.29
Ideal	9.2	23.7	49.07	14.47	0.62	0.38

[a] w_1 is mass fraction of DMF (1) in the gatifloxacin-free DMF (1) + methanol (2) mixture.

Gibbs energy is positive in all cases and decreases from pure methanol to pure DMF. As for the standard solution, it is positive in all cases, indicating an endothermic process, and decrease from pure methanol to pure DMF, possibly due to an increase in solute-solvent interactions, which is consistent with the gatifloxacin solubility increase in DMF-rich mixtures and pure DMF.

Regarding the standard solution entropy, it is positive in all cases, presenting an entropic favor to the gatifloxacin solution process in DMF + MeOH cosolvent mixtures.

From the results of equations 8 and 9, it can be concluded that the solution process is favored in all cases by enthalpy. A graphical method that allows corroborating the previously exposed is that developed by Perlovich (figure 3) (all values are within sector I: $\Delta_{soln}H° > T\Delta_{soln}S° > 0$ [38, 39]). Thus, the contribution of the solution's standard enthalpy to Gibbs energy values in all cases is greater than 71%, being greater in methanol-rich mixtures and less in DMF-rich mixtures.

Although there is an enthalpy predominance, the solution entropy promotes a decrease in Gibbs energy values, which generally favors the solution process.

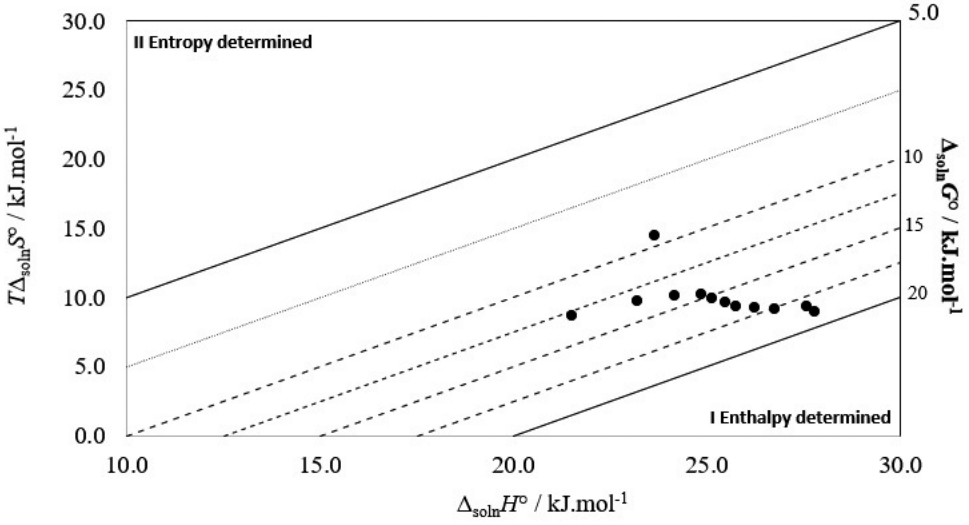

Figure 3. Relation between enthalpy ($\Delta_{soln}H°$) and entropy ($T\Delta_{soln}S°$) terms of the process of gatifloxacin solution in DMF (1) + methanol (2) cosolvent mixtures at 294.95 K. The isoenergetic curves for $\Delta_{soln}G°$ are represented by dotted lines.

Thermodynamic transfer functions

One way to identify the cosolvent effect on the thermodynamic behavior of the solution process is to analyze the transfer functions. Starting from a hypothetical transfer process from a medium of greater polarity to a medium of lower polarity, the thermodynamic transfer functions are calculated as [40]:

$$\Delta_{tr} f^0 = \Delta_{soln} f^0_{less\ polar} - \Delta_{soln} f^0_{more\ polar} \tag{10}$$

where, f represents thermodynamic functions, Gibbs energy, enthalpy, or entropy.

Table 5 shows the most representative values of the gatifloxacin transfer process from pure methanol to pure DMF. From the results of equation 10, a Perlovich plot [39] (figure 4) is drawn, which provides a good analysis of the results.

Thus, according to the Perlovich plot [4, 37, 39, 41, 42], from pure methanol to $w_{0.10}$ (Sector III $\Delta_{tr}H° < 0$, $T\Delta_{tr}S° > 0$, and $|T\Delta_{tr}S°| > |\Delta_{tr}H°|$) the process is driven by entropy; from $w_{0.10}$ to $w_{0.20}$ (Sector V $\Delta_{tr}H° < 0$, $T\Delta_{tr}S° < 0$, and $|T\Delta_{tr}S°| < |\Delta_{tr}H°|$) the process is driven by enthalpy; from $w_{0.20}$ to $w_{0.40}$ (Sector IV $\Delta_{tr}H° < 0$, $T\Delta_{tr}S° > 0$, and $|T\Delta_{tr}S°| < |\Delta_{tr}H°|$), the process is again driven by enthalpy; from $w_{0.40}$ to $w_{0.50}$ (Sector

Table 5. Thermodynamic functions of transfer of gatifloxacin (3) in DMF (1) + methanol (2) co-solvent mixtures at 294.95 K and pressure p = 0.1 MPa.

More polar→less polar	$\Delta_{tr}G°$ / kJ mol^{-1}	$\Delta_{tr}H°$ / kJ mol^{-1}	$\Delta_{tr}S°$ / J mol^{-1} K^{-1}	$T\Delta_{tr}S°$ / kJ mol^{-1}
[a]$w_{0.00}$→ $w_{0.10}$	-0.60	-0.22	1.3	0.38
$w_{0.10}$→ $w_{0.20}$	-0.60	-0.82	-0.8	-0.22
$w_{0.20}$→ $w_{0.30}$	-0.56	-0.50	0.2	0.05
$w_{0.30}$→ $w_{0.40}$	-0.63	-0.50	0.4	0.12
$w_{0.40}$→ $w_{0.50}$	-0.55	-0.25	1.0	0.30
$w_{0.50}$→ $w_{0.60}$	-0.62	-0.35	0.9	0.28
$w_{0.60}$→ $w_{0.70}$	-0.58	-0.30	0.9	0.28
$w_{0.70}$→ $w_{0.80}$	-0.60	-0.67	-0.2	-0.07
$w_{0.80}$→ $w_{0.90}$	-0.56	-0.98	-1.4	-0.42
$w_{0.90}$→ $w_{1.00}$	-0.60	-1.67	-3.7	-1.07

[a] w_1, mass fraction of DMF (1) in the gatifloxacin-free DMF (1) + methanol (2) mixture.

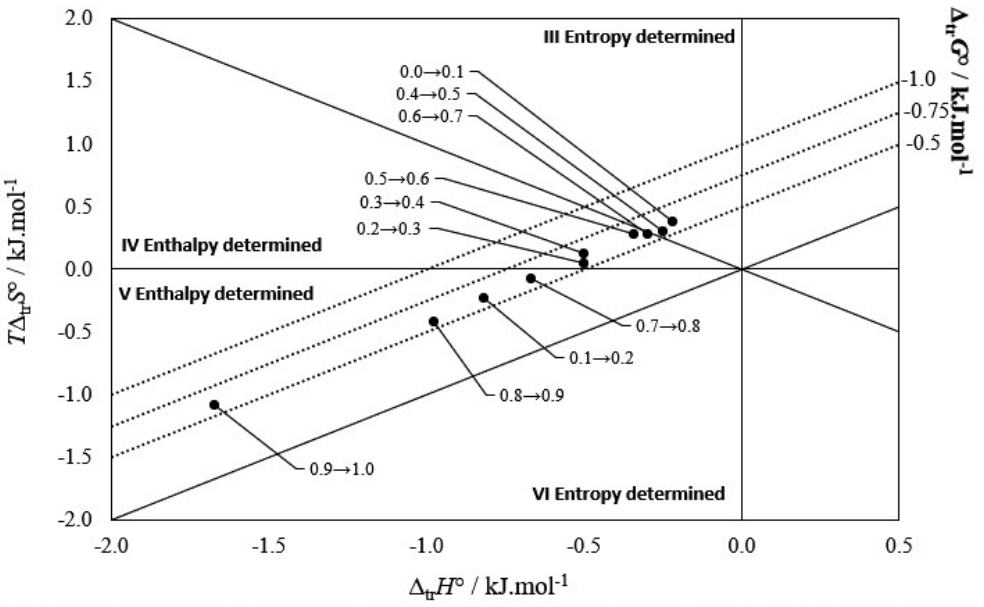

Figure 4. Relationship between the enthalpy ($\Delta_{tr}H°$) and entropy ($T\Delta_{tr}S°$) terms of the transfer process of gatifloxacin from more polar mixtures to less polar mixtures at 294.95 K. The isoenergetic curves of $\Delta_{tr}G°$ are represented by dotted lines.

III $\Delta_{tr}H° < 0$, $T\Delta_{tr}S° > 0$, and $|T\Delta_{tr}S°| > |\Delta_{tr}H°|$) the process is driven by entropy; from $w_{0.50}$ to $w_{0.70}$ (Sector IV $\Delta_{tr}H° < 0$, $T\Delta_{tr}S° > 0$, and $|T\Delta_{tr}S°| < |\Delta_{tr}H°|$), the process is driven by enthalpy and from $w_{0.70}$ to pure DMF (Sector V $\Delta_{tr}H° < 0$, $T\Delta_{tr}S° < 0$, and $|T\Delta_{tr}S°| < |\Delta_{tr}H°|$) the process continues to be driven by enthalpy.

So, in all cases there is an enthalpy favor (negative enthalpy), therefore there is an enthalpy conduction in the whole process, however, from $w_{0.10}$ to $w_{0.20}$ and from $w_{0.90}$ to DMF the entropy is negative, therefore, entropy disadvantages the transfer process. In other cases, entropy is positive, indicating that the solution process is favored by enthalpy and entropy.

Thermodynamic functions of the mixing

The solute behavior in the dissolution process can generally be divided into two stages, the solute fusion and its subsequent mixing with the solvent, so this hypothetical process can be represented according to the following scheme [43, 44]:

$$\text{Solute}_{(\text{Solid})} \text{ at } T \rightarrow \text{Solute}_{(\text{Solid})} \text{ at } T_{\text{fus}} \rightarrow \text{Solute}_{(\text{Liquid})} \text{ at } T_{\text{fus}} \rightarrow \text{Solute}_{(\text{Liquid})} \text{ at } T \rightarrow \text{Solute}_{(\text{Solution})} \text{ at } T$$

In this way, thermodynamic solution functions can be represented by the following equation:

$$\Delta_{\text{soln}} f^0 = \Delta_{\text{f}} f^0 + \Delta_{\text{mix}} f^0 \tag{11}$$

where, f represents the thermodynamic functions (G, H or S) and the subscripts ***f*** and **mix** represent fusion and mixing, respectively.

Thus, the mixing functions are determined as [45]:

$$\Delta_{\text{mix}} f^0 = \Delta_{\text{soln}} f^{0-T_{fm}} - \Delta_{\text{f}} f^0 \tag{12}$$

where $\Delta_{\text{f}} f°$ is replaced by the ideal thermodynamic functions, which are thus calculated as[46]

$$\Delta_{\text{mix}} G^{\text{o}} = \Delta_{\text{soln}} G^{\text{o}} + \Delta_{\text{soln}} G^{\text{o-id}} \tag{13}$$

$$\Delta_{\text{mix}} H^{\text{o}} = \Delta_{\text{soln}} H^{\text{o}} + \Delta_{\text{soln}} H^{\text{o-id}} \tag{14}$$

$$\Delta_{\text{mix}} S^{\text{o}} = \Delta_{\text{soln}} S^{\text{o}} + \Delta_{\text{soln}} S^{\text{o-id}} \tag{15}$$

Table 6 shows the thermodynamic mixing functions; from pure methanol to pure DMF, the mixing Gibbs energy decreases in value as the DMF concentration increases, whereby the DMF addition has a positive cosolvent effect, favoring the solvent-solvent interactions (e_{13}). As for the mixing enthalpy, it is positive from pure methanol to $w_1 = 0.8$, this factor it does not favor the dissolution process, it is observed that the enthalpy is greater in methanol-rich and intermediate mixtures possibly due to the fact that the formation of the cavity (required for solute accommodation) in these mixtures requires more energy. The foregoing may indicate that MeOH-MeOH interactions are stronger than those of DMF-DMF, In DMF-rich mixtures ($0.90 \leq w_1 \leq 1.00$), the enthalpy is negative, which favors the mixing process.

Regarding the entropy of the mixture, it is negative in all cases, which unfavors the mixing process.

Table 6. Thermodynamic functions of mixing gatifloxacin (3) in DMF (1) + methanol (2) cosolvent mixtures at 294.95 K and pressure $p = 0.1$ MPa.

w_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	9.6	4.1	-18.6	-5.5
0.10	9.0	3.9	-17.3	-5.1
0.20	8.4	3.1	-18.1	-5.3
0.30	7.9	2.6	-17.9	-5.3
0.40	7.2	2.1	-17.5	-5.2
0.50	6.7	1.8	-16.5	-4.9
0.60	6.1	1.5	-15.5	-4.6
0.70	5.5	1.2	-14.6	-4.3
0.80	4.9	0.5	-14.8	-4.4
0.90	4.3	-0.5	-16.2	-4.8
1.00	3.7	-2.1	-19.9	-5.9

[a] w_1, mass fraction of DMF (1) in the gatifloxacin -free DMF (1) + methanol (2) mixture.

From Perlovich's analysis (figure 5), it is concluded that in all cases the process is driven by entropy, both in the sector VII, from pure methanol to $w_1 = 0.80$ (sector VII: $\Delta_{mix}H° < T\Delta_{mix}S°$ and $|T\Delta_{mix}S°| > |\Delta_{mix}H°|$), and in the sector VI, from $w_1 = 0.90$ to pure DMF (sector VI: $\Delta_{mix}H° < 0$, $T\Delta_{mix}S° < 0$, and $|T\Delta_{mix}S°| > |\Delta_{mix}H°|$).

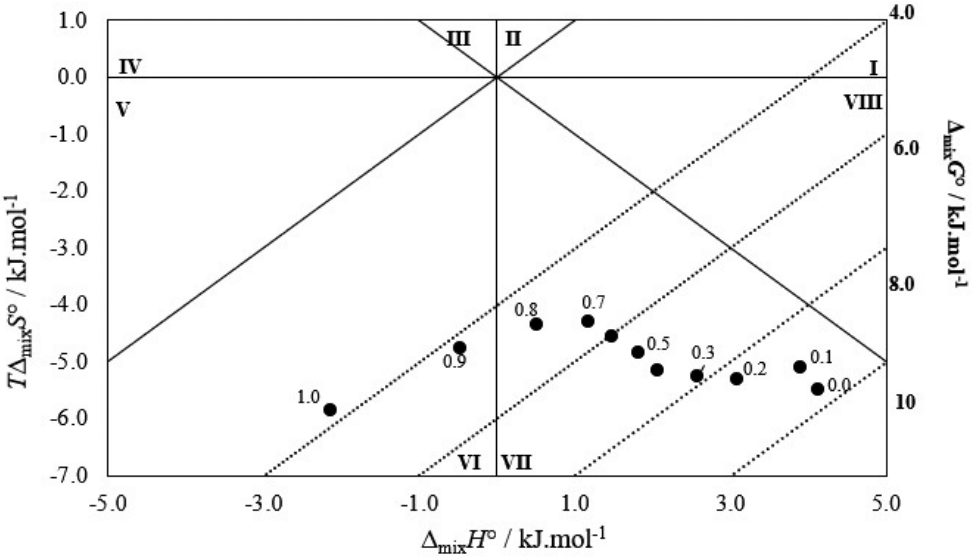

Figure 5. Relationship between the enthalpy ($\Delta_{mix}H°$) and entropy ($T\Delta_{mix}S°$) terms of the mixing process of gatifloxacin in DMF (1) + methanol (2) cosolvent mixtures at 294.95 K. The isoenergetic curves of $\Delta_{mix}G°$ are represented by dotted lines.

Enthalpy-entropy compensation

An analysis that identifies changes in the mechanism that controls the cosolvent action is that of enthalpy–entropy compensation, which is performed by plotting $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$, where in most cases, a nonlinear behavior is observed. Thus, this graphic analysis allows to identify the thermodynamic consequences of bond formation and rupture, where the hydrogen bond is the most relevant interaction [42, 47].

The plot interpretation ($\Delta_{soln}H°$ vs. $\Delta_{soln}G°$) is based on the sign of the slopes; thus, negative slopes indicate that the process is entropy-driven, which may be a consequence of the system's molecular rearrangement, while positive slopes indicate that the process is enthalpy-driven, which could be a consequence of changes in intermolecular interactions between the drug and solvents through hydrogen bonds and van der Waals forces such as the induced or permanent dipole–dipole interactions, and therefore, can be considered as quantitative indicator of changes in the intermolecular bond energies that occur during the interaction [48-50].

Figure 6 shows the behavior of gatifloxacin enthalpy-entropy compensation in the DMF + MeOH system. Thus, in all cases the solution process is driven by enthalpy.

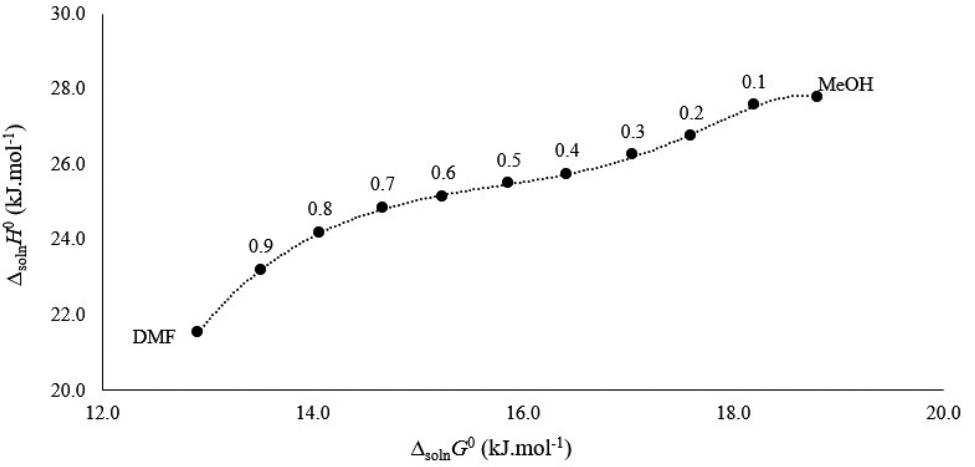

Figure 6. Enthalpy-entropy compensation graph $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$ for the solution process of gatifloxacin (3) in DMF (1) + methanol (2) cosolvent mixtures at 294.95 K.

Preferential solvation

An analysis that allows a more precise evaluation of molecular interactions and solvent composition in the immediate environment of solute molecules, is the mathematical model proposed by Ben-Naim denominating the inverse Kirkwood-Buff integral (IKBI) [51-53], which expresses its results according to the preferential solvation parameters $\delta x_{1,3}$ and $\delta x_{2,3}$, indicates the solute preference (3) for solvent (1) or (2) according to [10, 54, 55]:

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \tag{16}$$

where x_1 is the mole fraction of 1 in the cosolvent mixture and $x^{L}_{1,3}$, is the local mole fraction of 1 in the vicinity of the solute (3). If $\delta x_{1,3} > 0$, the solute is preferentially solvated by 1, and if $\delta x_{1,3} < 0$, the solute is preferentially solvated by 2. However, if $|\delta x_{1,3}| \leq 0.01$, the values are probably within the error of determination, indicating an insignificant preferential solvation. On the other hand, if $\delta x_{1,3} \approx x_2$, it means that $x^{L}_{1,3} = 1$ or a complete preferential solvation of 3 by 1 [10, 54].

The application expressions of the IKBI approach given by Ben-Naim are [56, 57]:

$$\delta x_{1,3} = \left[x_1(1-x_1)(G_{1,3} - G_{2,3})\right]\left[x_1 G_{1,3} + (1-x_1)G_{2,3} + V_{cor}\right]^{-1} \tag{17}$$

where $G_{1,3}$ and $G_{2,3}$ are the Kirkwood-Buff integrals (in cm^3 mol^{-1}) and V_{cor} is the volume of correlation around 3 (gatifloxacin), within which preferential solvation occurs. Thus, $G_{1,3}$ and $G_{2,3}$ are calculated as [58, 59]:

$$G_{1,3} = RT\kappa_T - V_3 + (1-x_1)V_2 DQ^{-1} \tag{18}$$

$$G_{2,3} = RT\kappa_T - V_3 + x_1 V_1 DQ^{-1} \tag{19}$$

and the correlation volume is calculated as [54, 60 ,61]:

$$V_{cor} = 2522.5\left[r_3 - 0.1363\sqrt[3]{\left(x_{1,3}^L V_1\right) + \left(x_{2,3}^L V_2\right)} - 0.085\right]^3 \tag{20}$$

where $\varkappa_T$ is the isothermal compressibility of DMF + MeOH mixtures (DMF: 0.698 GPa^{-1} [62], Methanol: 1.248 GPa^{-1} [63]), V_1 and V_2 are DMF and methanol Gadžurić *et al.* [64] and Kijevčanin *et al.* [65], V_3 is the molar volume of gatifloxacin (232 cm^3 mol^{-1}), r is the radius of the gatifloxacin molecule (0.4476 nm), and D and Q (in kJ mol^{-1}, as RT) are calculated using equations 21 and 22 [66, 67]:

$$D = d\Delta_t G_{3,2\to 1+2}^0 / dx_1 \tag{21}$$

$$Q = RT + x_1(1-x_1)\left(d^2 G_{1,2}^E / dx_2^2\right) \tag{22}$$

$\Delta_t G_{3,2\to 1+2}^0$ is the transfer Gibbs energy of gatifloxacin from the methanol to each DMF + MeOH cosolvent mixture (equation 23), and $G_{1,2}^E$ is the excess Gibbs energy of the cosolvent mixture of DMF + MeOH free of gatifloxacin (equation 24) [54, 68]:

$$\Delta_t G_{3,2\to 1+2}^0 = 0.6098x_1^2 - 6.5647x_1 + 0.0228 \tag{23}$$

$$G^E = x_2 x_1\left[-1264 + 67(1-2x_2)\right] \tag{24}$$

The values of D, $G_{1,3}$, $G_{2,3}$, V_{cor} and $\delta x_{1,3}$ are presented in table 7, and the behavior of $\delta x_{1,3}$ is presented in Figure 7. The $\delta x_{1,3}$ values show that the preferential solvation of gatifloxacin by both methanol (from pure methanol to $w_1 = 0.25$, $\delta x_{1,3}$ has negative values) and DMF (From $w_1 = 0.25$ to pure DMF, $\delta x_{1,3}$ has positive values) is insignificant, because all the $\delta x_{1,3}$ values are less than 0.01.

It could be expected (however, because the values of $\delta x_{1,3}$ are less than 0.01, the analyzes are not conclusive) that the gatifloxacin, it behaves as a Lewis base against the

methanol-rich medium because the methanol (β = 0.62 [69]) has a less basic character than DMF (β = 0.71 [70]) according to the β-scale of Taft and Kamlet, and like a Lewis acid against the DMF. Table 7. Some properties associated to preferential solvation gatifloxacin (3) in DMF (1) + MeOH (2) cosolvent mixtures at 313.15 K and pressure p = 0.096 MPa.

Table 7. Solubility and preferential solvation of gatifloxacin in DMF+ methanol mixtures at 313.15 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	-6.56	-274.5	-228.8	1485.1	0.000
0.05	-6.50	-270.2	-235.4	1521.3	-0.129
0.10	-6.44	-266.3	-241.7	1557.8	-0.169
0.15	-6.38	-262.7	-247.6	1594.3	-0.143
0.20	-6.32	-259.5	-253.2	1630.7	-0.073
0.25	-6.26	-256.5	-258.6	1667.0	0.028
0.30	-6.20	-253.8	-263.8	1702.9	0.146
0.35	-6.14	-251.3	-268.8	1738.6	0.270
0.40	-6.08	-249.0	-273.8	1773.9	0.394
0.45	-6.02	-246.9	-278.7	1808.9	0.510
0.50	-5.95	-244.9	-283.7	1843.4	0.613
0.55	-5.89	-243.1	-288.7	1877.5	0.699
0.60	-5.83	-241.4	-293.8	1911.3	0.762
0.65	-5.77	-239.9	-299.2	1944.5	0.801
0.70	-5.71	-238.4	-304.8	1977.4	0.811
0.75	-5.65	-237.0	-310.8	2009.8	0.789
0.80	-5.59	-235.6	-317.4	2041.7	0.731
0.85	-5.53	-234.3	-324.6	2073.2	0.631
0.90	-5.47	-233.0	-332.7	2104.1	0.482
0.95	-5.41	-231.6	-341.9	2134.5	0.276
1.00	-5.35	-230.2	-352.7	2164.3	0.000

[a] x_1, mole fraction of acetonitrile (1) in the gatifloxacin-free DMF (1) + methanol (2) mixture.

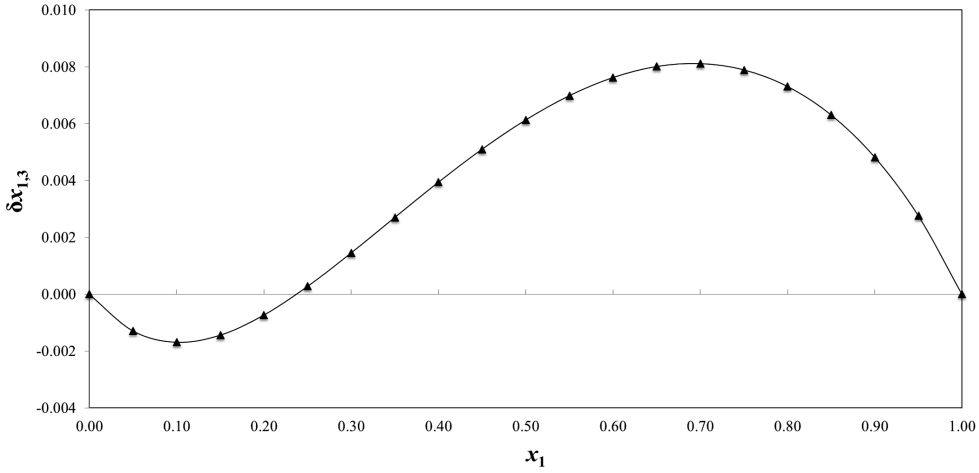

Figure 7. $\delta x_{1,3}$ values of gatifloxacin (3) in DMF (1) + methanol (2) mixtures at 313.15 K.

Conclusions

From thermodynamic analysis and preferential solvation of gatifloxacin in DMF + MeOH cosolvent mixtures, it is concluded that the solution process is endothermic with a marked enthalpy favor, which increases as the polarity of the cosolvent system decreases due to the addition of DMF, presenting a positive cosolvent effect that leads to increased gatifloxacin solubility. Finally, regarding gatifloxacin's preferential solvation, the results are not conclusive, because in all cases the values of the preferential solvation parameter are less than 0.01, so that, negligible preferential solvation takes place.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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