

SOLVENT EFFECTS, SOLVATION BEHAVIOR, AND THERMODYNAMICS OF ARTESUNATE IN ALCOHOL-WATER MIXTURES

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ABSTRACT. The solubility of Artesunate (ART) in three different alcohol-water solvent mixtures was investigated using the KAT-LSER model. These mixtures were methanol (MeOH) + water, ethanol (EtOH) + water, and 2-propanol (2-PrOH) + water. Hydrogen bond acidity (α), hydrogen bond basicity (β), the cavity term, and solvent polarity were the primary factors influencing solubility. The parameter $\delta x_{1,ART}$ was obtained by applying the inverse Kirkwood-Buff integrals (IKBI) approach to analyze the preferential ART solvation. The findings of this study demonstrate that artesunate (ART) is preferentially solvated by water in binary mixtures of alcohol and water, indicating a stronger local interaction between ART molecules and water than with alcohol. To better understand the dissolution behavior of ART, important thermodynamic characteristics, including dissolution and transfer enthalpy, Gibbs free energy, and entropy, were carefully investigated for a range of solvent compositions. The evaluation of these parameters and an enthalpy-entropy compensation analysis revealed that changes in ART solubility within the alcohol (1) + water (2) mixtures are mainly controlled by enthalpy, highlighting the energetic contributions of solute-solvent interactions. Such knowledge is essential for guiding solvent selection and formulation strategies, ultimately enhancing ART's bioavailability, therapeutic performance, and stability in pharmaceutical and personal care product development.

KEY WORDS: Artesunate, Mixed solvents, Solvent effect, IKBI method, Preferential solvation

INTRODUCTION

A sesquiterpene lactone endoperoxide first isolated from the herb *Artemisia annua*, artesunate is a semi-synthetic derivative of artemisinin. Its molecular weight is 384.42 g/mol, its chemical structure is shown in Figure 1, and its chemical formula is $C_{19}H_{28}O_8$. Artesunate is a white to off-white crystalline powder that dissolves slowly in water but readily in ethanol and dimethyl sulfoxide. It is chemically characterized by a 1,2,4-trioxane ring, critical for its pharmacological activity. This endoperoxide bridge generates reactive oxygen species within the malaria parasite, leading to rapid parasitic death. Biologically, artesunate exhibits potent antimalarial activity [1], particularly against *Plasmodium falciparum*, including multidrug-resistant strains. It acts rapidly and is especially effective in severe malaria cases. Additionally, recent studies have reported its potential anticancer [2, 3], antiviral [4, 5] and anti-inflammatory properties [6], further highlighting its pharmacological versatility. Artesunate is a crucial part of the artemisinin-based combination treatments (ACTs) that the World Health Organization recommends for treating malaria because of its quick action [7, 8], safety profile, and wide therapeutic window. Due to its growing applicability in different therapeutic areas, it is a molecule of ongoing interest in pharmaceutical research and medication development [9-11].

Furthermore, comprehending the molecular interactions that control artesunate's solubility and stability in pharmaceutical formulations requires understanding the thermodynamic features

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of its dissolution in pure and binary solvents. Gibbs free energy, enthalpy, and entropy of dissolution are examples of thermodynamic parameters that offer essential information on the kind of interactions between solutes and solvents, the spontaneity of the dissolution process, and the energy changes related to solvation [12-14]. Evaluating artesunate in binary solvent systems, such as alcohol–water mixtures, further allows for optimizing solvent environments to enhance solubility and bioavailability. Additionally, preferential solvation analysis using models like the inverse Kirkwood–Buff integrals (IKBI) offers a molecular-level understanding of whether artesunate is more stabilized by one solvent component than another in mixed systems [12-14]. This knowledge is crucial for designing effective drug delivery systems, improving formulation strategies, and ensuring the therapeutic efficacy of artesunate in various dosage forms.

The solubility of artesunate (ART) in aqueous solutions of several organic solvents, such as methanol, ethanol, isopropanol, and propylene glycol (PG), was recently investigated by Xu *et al.* [15] throughout a temperature range of 278.15–318.15 K at a pressure of 101.1 kPa. Although their study effectively captured the solubility trends of ART through thermodynamic modeling, it did not address key aspects such as specific solvent–solute interactions, transfer thermodynamic properties, and preferential solvation behavior within these binary solvent systems. These limitations underscore the need for a more in-depth investigation into ART's solid–liquid equilibrium (SLE) to support its optimal utilization in pharmaceutical formulation development.

Using experimental solubility data for Artesunate (ART) in alcohol-water combinations made of methanol, ethanol, and 2-propanol, Xu *et al.* [15], set the groundwork for this study. This study expands the understanding of Artesunate's behavior through several key advancements: (1) Examining molecular interactions: The study uses the KAT-LSER model. This complex instrument permits a thorough analysis of how specific molecular characteristics and intermolecular forces impact the dissolution process. (2) Clarifying solubility mechanisms: To analyze preferred solvation in mixed solvent systems, the study uses the Inverse Kirkwood-Buff Integrals (IKBI) approach, a potent tool. (3) Thermodynamic driver analysis: A thorough assessment of critical thermodynamic parameters, including entropy, Gibbs free energy, and dissolution/transfer enthalpy, is part of the study. To better understand the thermodynamic forces that determine Artesunate's solubility and stability in solution, this investigation aims to identify the energy parameters driving the solvation process.

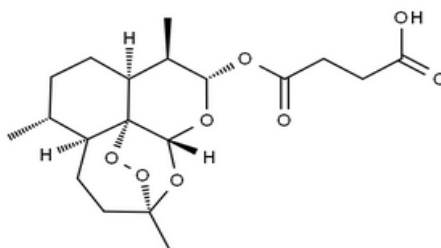


Figure 1. Structure of Artesunate (ART) molecule.

COMPUTATIONAL SECTION

KAT-LSER model

The KAT-LSER model is a computational framework that Kamlet and co-workers developed. It quantifies the functions of particular chemical interactions to link solvent parameters with solute dissolution behavior [16]. The model evaluates solvent characteristics such as polarity/polarizability (π^*), hydrogen bond acidity (α), hydrogen bond basicity (β), and cavity formation energy to comprehend how solvent-solvent and solute-solvent interactions govern

solubility ($V_s \delta_H^2$). KAT-LSER uses these parameters to determine the primary forces influencing dissolution in mixed solvent systems, such as dipolar interactions, hydrogen bonding, or hydrophobic effects. At 298.15 K, the KAT-LSER model employs Equation 1 to correlate solute-solvent interactions with mole fraction solubility (x). In this Equation, V_s represents the solute's molecular volume, δ_H is the Hildebrand solubility parameter, T is the absolute temperature, c_i is a solvent-independent coefficient, and R is the universal gas constant [17].

$$\ln(x) = c_0 + c_1\alpha + c_2\beta + c_3\pi^* + c_4\left(\frac{V_s\delta_H^2}{100RT}\right) \quad (1)$$

where T is the temperature in Kelvin, R is the gas constant, and V_s is the solute's molar volume, which is $318.334 \text{ cm}^3\cdot\text{mol}^{-1}$.

Dissolution and transfer of property

Calculations of the thermodynamic properties ($\Delta H_{\text{sol}}^\circ$, $\Delta S_{\text{sol}}^\circ$ and $\Delta G_{\text{sol}}^\circ$) can be performed using solute solubility data obtained in different binary mixed solvents. The standard molar enthalpy of dissolution can then be derived using the Van't Hoff Equation, as shown below [18]:

$$\Delta H_{\text{sol}}^\circ = -R \left(\frac{\partial \ln(x_1)}{\partial (1/T - 1/T_{\text{mean}})} \right) = -R \times \text{slope} \quad (2)$$

The standard molar Gibbs energy ($\Delta G_{\text{sol}}^\circ$) is expressed as [19]:

$$\Delta G_{\text{sol}}^\circ = -RT_{\text{mean}} \times \text{intercept} \quad (3)$$

The intercept is determined from the plot of $\ln(x_1)$ versus $(1/T - 1/T_{\text{mean}})$. The standard molar entropy of solvation, $\Delta S_{\text{sol}}^\circ$, is then calculated using the following relation [20]:

$$\Delta S_{\text{sol}}^\circ = \frac{\Delta H_{\text{sol}}^\circ - \Delta G_{\text{sol}}^\circ}{T_{\text{mean}}} \quad (4)$$

$$T_{\text{mean}} = n / \sum_{i=1}^n \frac{1}{T_i} \quad (5)$$

The harmonic mean temperature (T_{mean}) was calculated from the experimental conditions using Equation 5 [21]. In the Equation, x_1 is the mole fraction solubility of ART, and R is the universal gas constant ($8.314 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$). For this investigation, T_{mean} was fixed at 305.41 K.

Equations 6 and 7 [22, 23] were used to determine the enthalpy ($\% \xi_H$) and entropy ($\% \xi_{TS}$) contributes to the typical dissolution Gibbs energy ($\Delta G_{\text{sol}}^\circ$), in order to explain the thermodynamic driving forces of ART dissolution in aqueous-alcoholic solutions. This calculation was performed to determine if the dissolution process is mainly enthalpy- or entropy-driven, and thus reveal the molecular mechanisms of solubility.

$$\% \xi_H = \frac{|\Delta H_{\text{sol}}^\circ|}{|\Delta H_{\text{sol}}^\circ| + |T \cdot \Delta S_{\text{sol}}^\circ|} \times 100 \quad (6)$$

$$\% \xi_{TS} = \frac{|T \cdot \Delta S_{\text{sol}}^\circ|}{|\Delta H_{\text{sol}}^\circ| + |T \cdot \Delta S_{\text{sol}}^\circ|} \times 100 \quad (7)$$

Artesunate's (ART) solvation was investigated by calculating the standard Gibbs energy ($\Delta_{\text{tr}} G_{\text{ART},2 \rightarrow 1+2}^\circ$), enthalpy ($\Delta_{\text{tr}} H_{\text{ART},2 \rightarrow 1+2}^\circ$), and entropy ($\Delta_{\text{tr}} S_{\text{ART},2 \rightarrow 1+2}^\circ$) of transfer from aqueous co-solvent mixtures (1 + 2) to pure water (2) using Equations 8, 9, and 10 [24, 25]. This approach allowed for a detailed evaluation of how co-solvent interactions, such as hydrogen bonding, hydrophobic effects, and solvation-shell restructuring, affect ART's solubility and stability in mixed-solvent environments. It also facilitated differentiation between enthalpic and entropic contributions to solute-solvent compatibility during co-solvency.

$$\Delta_{tr}G_{ART,2 \rightarrow 1+2}^o = RT \ln \left(\frac{x_{ART,2}}{x_{ART,1+2}} \right) \quad (8)$$

$$\Delta_{tr}H_{ART,2 \rightarrow 1+2}^o = \Delta_{sol}H_{ART,1+2}^o - \Delta_{sol}H_{ART,2}^o \quad (9)$$

$$\Delta_{tr}S_{ART,2 \rightarrow 1+2}^o = (\Delta_{tr}H_{ART,2 \rightarrow 1+2}^o - \Delta_{tr}G_{ART,2 \rightarrow 1+2}^o)/T \quad (10)$$

$x_{ART,2}$ and $x_{ART,1+2}$ show ART's mole % solubility in aqueous co-solvent mixtures (1+2) and pure water (2), respectively, while $\Delta_{sol}H_{ART,2}^o$ and $\Delta_{sol}H_{ART,2 \rightarrow 1+2}^o$ represent the enthalpic contributions: $\Delta_{sol}H_{ART,2}^o$ for the standard molar enthalpy of solution in pure water and $\Delta_{sol}H_{ART,2 \rightarrow 1+2}^o$ for the change during transfer to the co-solvent system.

Preferential solvation

A theoretical technique for analyzing solutions and characterizing the spatial organization of solvent components surrounding a solute is the method of inverse Kirkwood-Buff integrals (IKBI). Preferential solvation occurs when a drug in a binary solvent mixture is surrounded more by one solvent than the other, leading to a solvation shell with a different composition than the overall solvent. The preferential solvation parameter is used to quantify this deviation in the local solvent composition, providing insight into the specific interactions that govern solubility and stability. Notably, the parameter $\delta x_{1,ART}$ shows that the solubility properties of ART in combinations such as MeOH–water, EtOH–water, and 2-PrOH–water are enhanced by organic solvents [12, 26-33].

$$\delta x_{1,MOx} = x_{1,ART}^L - x_1 = -\delta x_{2,ART} \quad (11)$$

Here, x_i denotes the mole fraction of alcohol in the first alcohol and water binary combination prior to the addition of ART, while $x_{1,ART}^L$ represents the local mole fraction of alcohol in the immediate solvation shell surrounding the ART molecules. A negative value of $x_{1,ART}^L$ indicates preferential solvation of ART by water, whereas a positive value suggests that alcohol molecules predominantly surround the solute. These preferential solvation parameters are calculated using equations derived from the Kirkwood-Buff Inverse Integrals (IKBI) method [12, 26, 34-36].

$$\delta x_{1,ART} = \frac{x_1 x_2 (G_{1,ART} - G_{2,ART})}{x_1 G_{1,ART} + x_2 G_{2,ART} + V_{cor}} \quad (12)$$

with,

$$G_{1,ART} = RTk_T - V_{ART} - x_2 V_2 D/Q \quad (13)$$

$$G_{2,ART} = RTk_T - V_{ART} + x_1 V_1 D/Q \quad (14)$$

$$V_{cor} = 2522.5 \left[r_{ART} + 0.1363 (x_{1,ART}^L \bar{V}_1 + x_{2,ART}^L \bar{V}_2)^{1/3} - 0.085 \right]^3 \quad (15)$$

The isothermal compressibility (k_T) of alcohol–water mixtures is typically estimated using a weighted average of the pure solvents' compressibility values per mole fraction. In these systems, V_{ART} relates to artesunate's molar volume, whereas V_1 and V_2 indicate the water's and the cosolvent's (alcohol) partial molar quantities, respectively.

The derivative of the standard molar Gibbs energy for transferring ART ($\Delta_{tr}G_{ART,2 \rightarrow 1+2}^o$) from pure water (2) to a binary solvent mixture (1+2), which varies with solvent composition, is calculated using function D. Function Q defines the second derivative of this transfer Gibbs energy with respect to the water mole fraction. These relationships are mathematically expressed in Equations 16 and 17, as outlined in references [12, 14, 37].

$$D = \left(\frac{\partial \Delta_{tr} G_{ART,2 \rightarrow 1+2}^o}{\partial x_1} \right)_{T,P} \quad (16)$$

$$Q = RT + x_1 x_2 \left[\frac{\partial^2 G_{1+2}^{Exc}}{\partial x_2^2} \right]_{T,P} \quad (17)$$

$$r_{ART} = \sqrt[3]{\frac{3 \times 10^{21} V_{ART}}{4\pi N_{AV}}} \quad (18)$$

Avogadro's constant is written as N_{AV} , and r_{ART} represents the radius of ART. In mixed solvent systems, the isothermal compressibility (k_T) of a pure component i can be estimated using Equation 19. This is because the term RTk_T has a negligible effect on IKBI calculations [12, 26-30].

$$k_T = x_1 k_{T,1}^o + x_2 k_{T,2}^o \quad (19)$$

wherein x_i signifies the mole fraction of component i in the mixture, and $k_{T,i}^o$ refers to the isothermal compressibility of the pure component i [38]. Since $\delta x_{1,ART}$ and V_{cor} are interdependent, as indicated by Equations 12 and 15 must be determined simultaneously through an iterative solution method.

RESULTS AND DISCUSSION

KAT-LSER model

Using the KAT-LSER model to forecast ART's solubility in MeOH–water, EtOH–water, and 2-PrOH–water mixtures at 293.15 K, the impact of solvents on ART solubility was further investigated. The solvatochromic parameters α , β , π^* , and δ_H —descriptors that are described in Table S1 of the supplementary material and that were obtained from previous studies [35, 39-42] were used to make this prediction. Tables S2–S5 summarize the F-test statistics and regression coefficients (c_i) obtained using multiple linear regression analysis (MLRA).

$$\ln(x) = -3.931 + 6.930\alpha - 4.685 \left(\frac{V_s \delta_H^2}{100RT} \right) \quad (20)$$

$$R^2 = 0.99; F = 338.61$$

$$\ln(x) = -5.579 + 7.620\pi^* - 4.491 \left(\frac{V_s \delta_H^2}{100RT} \right) \quad (21)$$

$$R^2 = 0.99; F = 555.03$$

$$\ln(x) = -11.226 + 5.660\beta + 3.267\pi^* - 1.870 \left(\frac{V_s \delta_H^2}{100RT} \right) \quad (22)$$

$$R^2 = 1.00; F = 6871.05$$

The most effective descriptive model is identified by the highest F-statistic, following Ref [43]. This selection criterion is based on the statistical principle that a more reliable LSER equation should exhibit a higher and reduced standard deviation of its coefficients and an overall correlation value (R^2). The multiple linear regression analyses (MLRA) for all analyzed binary mixed solvents are described by Equations 20-22. The results emphasize a significant correlation between solvent acidity and the cavity term and the solubility of ART in the studied MeOH + water binary solvent mixtures. This correlation is further substantiated by Table S2 and Equation 20.

For MeOH-water mixtures (Table S2, Equation 20), hydrogen bond acidity (α) is the main factor influencing solubility variation (59.99%), with the cavity term also playing a significant role

(40.34%). In contrast, dipolarity/polarizability (π^*) dominates the solvent effect in ethanol-water systems (Table S3, Equation 21), contributing 62.92%, while the cavity term contributes 37.08%. 2-propanol-water mixtures (Table S4, Equation 22) show hydrogen bond basicity (β) as the primary influence on solvent impact (52.42%), with dipolarity/polarizability (π^*) and cavity interactions contributing 30.26 % and 17.32 %, respectively. These results, derived from the model coefficients, demonstrate that the relative importance of solvent parameters changes substantially across different binary solvent systems.

Dissolution and transfer properties

The data in Table 1 demonstrates the dissolving process's thermodynamic character, highlighting entropy and enthalpy contributions. The transfer of ART from water to mixed solvents is further explained in Tables 2 and 3, highlighting the energetic and entropic changes associated with these transitions. By analyzing these Tables, one can infer the solute-solvent interactions, the influence of solvent composition on the dissolution process, and the driving forces behind the transfer of ART between different solvent environments. For instance, the trends in $\Delta H_{\text{sol}}^\circ$ and $\Delta H S_{\text{sol}}^\circ$. Table 1 suggests how changes in solvent composition affect the energy required for dissolution and the degree of order or disorder in the system. The positive standard molar Gibbs free energy ($\Delta G_{\text{sol}}^\circ$) indicates that dissolution is non-spontaneous under the conditions studied. However, the consistently positive standard molar entropy ($\Delta S_{\text{sol}}^\circ$) values across all binary mixed solvents suggest that entropy predominantly drives the dissolution.

Table 1. Thermodynamic Properties of dissolution of ART in Alcohol (1) + Water (2) Mixtures at Specified Temperature $T=305.41$ K and 101.3 kPa.

x_1	$\Delta_{\text{sol}}H^\circ$ (kJ·mol ⁻¹)	$\Delta_{\text{sol}}G^\circ$ (kJ·mol ⁻¹)	$\Delta_{\text{sol}}S^\circ$ (J·mol ⁻¹ ·K ⁻¹)	% ξ_H	% ξ_{TS}
MeOH (1) + water (2)					
0.000	36.404	25.780	34.786	77.41	22.59
0.059	31.622	21.802	32.153	76.30	23.70
0.123	27.723	19.009	28.533	76.08	23.92
0.194	25.329	17.115	26.898	75.51	24.49
0.273	23.194	15.789	24.247	75.80	24.20
0.360	21.100	14.824	20.549	77.08	22.92
0.458	19.728	14.074	18.513	77.72	22.28
0.567	18.462	13.457	16.388	78.67	21.33
0.692	16.901	12.878	13.173	80.77	19.23
0.835	15.674	12.392	10.745	82.69	17.31
1.000	14.672	12.079	8.493	84.98	15.02
EtOH (1) + water (2)					
0.000	36.404	25.780	34.786	77.41	22.59
0.042	32.795	22.420	33.971	75.97	24.03
0.089	30.004	19.887	33.129	74.78	25.22
0.144	27.889	18.013	32.334	73.85	26.15
0.207	25.927	16.616	30.487	73.58	26.42
0.281	24.603	15.577	29.554	73.16	26.84
0.370	23.715	14.795	29.208	72.67	27.33
0.477	22.796	14.187	28.189	72.59	27.41
0.610	22.060	13.661	27.499	72.43	27.57

0.779	21.390	13.197	26.826	72.30	27.70
1.000	20.909	12.797	26.562	72.05	27.95
2-PrOH (1) + water (2)					
0.000	36.404	25.780	34.786	77.41	22.59
0.032	34.253	28.144	20.000	84.87	15.13
0.070	32.159	22.124	32.857	76.22	23.78
0.114	30.256	20.505	31.925	75.63	24.37
0.167	28.508	19.086	30.849	75.16	24.84
0.231	27.124	17.940	30.073	74.70	25.30
0.310	25.684	17.006	28.413	74.75	25.25
0.412	24.715	16.337	27.435	74.68	25.32
0.545	24.192	15.841	27.345	74.34	25.66
0.730	23.292	15.479	25.583	74.88	25.12
1.000	23.561	15.168	27.483	73.73	26.27
^a x_1 is the mole fraction of alcohol (1) in alcohol (1) + water (2) co-solvent mixtures free of ART					

Table 2. Gibbs Free Energy of Transfer ($\Delta_{tr}G_{\text{ART},2 \rightarrow 1+2}^0$ (kJ·mol⁻¹)) of ART from neat water (2) to alcohol (1)-water (2) mixtures at various temperatures.

MeOH (1) + water (2)					
^a x_1	293.15 K	298.15 K	303.15 K	313.15 K	318.15 K
0.000	0.000	0.000	0.000	0.000	0.000
0.059	-4.009	-4.001	-3.982	-3.960	-3.944
0.123	-6.842	-6.825	-6.782	-6.722	-6.691
0.194	-8.756	-8.735	-8.678	-8.609	-8.563
0.273	-10.112	-10.084	-10.006	-9.916	-9.854
0.360	-11.116	-11.081	-10.982	-10.834	-10.778
0.458	-11.892	-11.848	-11.731	-11.592	-11.490
0.567	-12.534	-12.485	-12.350	-12.191	-12.083
0.692	-13.149	-13.091	-12.937	-12.743	-12.619
0.835	-13.662	-13.598	-13.424	-13.218	-13.070
1.000	-14.003	-13.933	-13.740	-13.513	-13.358
EtOH (1) + water (2)					
	293.15 K	298.15 K	303.15 K	313.15 K	318.15 K
0.000	0.000	0.000	0.000	0.000	0.000
0.042	-3.369	-4.001	-3.362	-3.355	-3.349
0.089	-5.910	-6.825	-5.897	-5.884	-5.870
0.144	-7.791	-8.735	-7.771	-7.753	-7.732
0.207	-9.209	-10.084	-9.177	-9.136	-9.108
0.281	-10.250	-11.081	-10.212	-10.166	-10.131
0.370	-11.041	-11.848	-10.997	-10.955	-10.902
0.477	-11.661	-12.485	-11.610	-11.552	-11.503
0.610	-12.193	-13.091	-12.135	-12.072	-12.015
0.779	-12.663	-13.598	-12.600	-12.539	-12.465
1.000	-13.066	-13.933	-12.999	-12.935	-12.865
2-PrOH (1) + water (2)					
	293.15 K	298.15 K	303.15 K	313.15 K	318.15 K
0.000	0.000	0.000	0.000	0.000	0.000
0.032	-1.876	-1.878	-1.866	-1.861	-1.854
0.070	-3.675	-3.678	-3.655	-3.643	-3.628
0.114	-5.303	-5.307	-5.275	-5.257	-5.234
0.167	-6.721	-6.747	-6.700	-6.671	-6.629
0.231	-7.897	-7.887	-7.835	-7.809	-7.781

0.310	-8.838	-8.843	-8.775	-8.737	-8.680
0.412	-9.517	-9.523	-9.445	-9.401	-9.335
0.545	-10.016	-10.025	-9.936	-9.885	-9.843
0.730	-10.392	-10.403	-10.303	-10.246	-10.166
1.000	-10.645	-10.733	-10.624	-10.565	-10.488

As shown in Table 1, both enthalpy ($\Delta H_{\text{sol}}^{\circ}$) and entropy ($\Delta S_{\text{sol}}^{\circ}$) contribute to the standard molar Gibbs free energy of solution ($\Delta G_{\text{sol}}^{\circ}$). According to the findings, enthalpy is the primary factor influencing the Gibbs energy for ART dissolution in binary solvent mixtures of MeOH/water, EtOH/water, and 2-PrOH/water. With enthalpy's percentage contribution ($\% \xi_H$) being at least 72.05% of the total. This highlights the thermodynamic dominance of enthalpy over entropy in these particular systems.

Table 3. Transfer enthalpies ($\text{kJ}\cdot\text{mol}^{-1}$) and entropies ($\text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$) of ART from neat water (2) to alcohol (1) + water (2) solvent mixtures at 303.15 K.

MeOH (1) + water (2)			EtOH (1) + water (2)			2-PrOH (1) + water (2)		
a_{X_1}	$\Delta_{tr}H_{\text{ART}}^{\circ}$	$\Delta_{tr}S_{\text{ART}}^{\circ}$	a_{X_1}	$\Delta_{tr}H_{\text{ART}}^{\circ}$	$\Delta_{tr}S_{\text{ART}}^{\circ}$	a_{X_1}	$\Delta_{tr}H_{\text{ART}}^{\circ}$	$\Delta_{tr}S_{\text{ART}}^{\circ}$
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.059	-4.782	-2.639	0.042	-3.609	-0.815	0.032	-2.151	-0.940
0.123	-8.681	-6.264	0.089	-6.400	-1.659	0.070	-4.245	-1.946
0.194	-11.075	-7.907	0.144	-8.515	-2.454	0.114	-6.148	-2.880
0.273	-13.210	-10.569	0.207	-10.477	-4.288	0.167	-7.896	-3.945
0.360	-15.304	-14.257	0.281	-11.801	-5.242	0.231	-9.280	-4.767
0.458	-16.676	-16.312	0.370	-12.689	-5.581	0.310	-10.720	-6.416
0.568	-17.942	-18.446	0.477	-13.608	-6.591	0.412	-11.689	-7.402
0.692	-19.503	-21.659	0.610	-14.344	-7.287	0.545	-12.212	-7.508
0.835	-20.730	-24.100	0.779	-15.014	-7.963	0.730	-13.112	-9.266
1.000	-21.732	-26.363	1.000	-15.495	-8.234	1.000	-12.843	-7.320

^a X_1 is the mole fraction of alcohol (1) in alcohol (1) + water (2) co-solvent mixtures free of ART.

The transfer parameters in Tables 2 and 3 reveal the relative affinities of ART for the mixed solvents compared to pure water, offering insights into preferential solvation. The transfer properties of ART are detailed in Tables 2 and 3. For the binary mixtures of MeOH/EtOH/2-PrOH (1) + water (2), the Gibbs free energy of transfer ($\Delta_{tr}G_{\text{ART},2\rightarrow1+2}^{\circ}$) values are initially negative and become more negative as the co-solvent concentration rises. This finding indicates a thermodynamic preference for transferring ART from pure water to the mixed solvents. This pattern aligns with the information shown in Table 2. Furthermore, the results indicate that the solubilization of ART is adversely affected by increasing the mole fraction of alcohol in the binary systems of MeOH (1) + water (2), EtOH (1) + water (2), and 2-PrOH (1) + water (2) [44].

Preferential solvation

The Gibbs free energy ($\Delta_{tr}G_{\text{ART},2\rightarrow1+2}^{\circ}$) related to ART's transition from its pure water state to a water-and-alcohol-mixed solvent is calculated using Equation 8.

$$\Delta_{tr}G_{\text{ART},2\rightarrow1+2}^{\circ} = a + bx_1 + cx_1^2 + dx_1^3 + ex_1^4 \quad (23)$$

The $\Delta_{tr}G_{\text{ART},2\rightarrow1+2}^{\circ}$ values for five specific temperatures (293.15, 298.15, 303.15, 313.15, and 318.15 K) are displayed in Table 2 and were correlated using Equation 23. The coefficients derived from these equations are provided in Table S5 within the supplemental materials. To

calculate D using Equation 24, the molar proportion of organic solutes within the solutions is necessary. Table S6 shows that the variance in mole fraction for all alcohols is consistently 0.05.

$$D = b + 2cx_1 + 3dx_1^2 + 4ex_1^3 \quad (24)$$

The excess molar Gibbs energies have to be found to obtain the Q values of mixing ($G_{1,2}^{Exc}$) at 298.15 K for each of the three co-solvent + water systems. Equations 25-27 were employed to obtain these $G_{1,2}^{Exc}$ values (expressed in $\text{J}\cdot\text{mol}^{-1}$) using literature values [12] for MeOH + water, EtOH + water, and 2-PrOH + water combinations. The variable x_1 represents the molar percentage of the co-solvent.

$$G_{1,2}^{Exc} = x_1(1 - x_1)[1200 - 87(1 - 2x_1) + 330(1 - 2x_1)^2] \quad (25)$$

$$G_{1,2}^{Exc} = x_1(1 - x_1)[2907 - 777(1 - 2x_1) + 494(1 - 2x_1)^2] \quad (26)$$

$$G_{1,2}^{Exc} = x_1(1 - x_1)[3843 - 984(1 - 2x_1) + 98(1 - 2x_1)^2] \quad (27)$$

Equation 28 is used to calculate the $G_{1,2}^{Exc}$ values at different temperatures. In this equation, T_1 represents one temperature, while T_2 represents 298.15 K. The solvent's extra molar enthalpy combinations is denoted as $H_{1,2}^{Exc}$, according to the reference [12].

$$G_{1,2}^{Exc}(T_2) = G_{1,2}^{Exc}(T_1) - T \int_{T_1}^{T_2} H_{1,2}^{Exc} d\left(\frac{1}{T}\right) \approx \frac{T_2}{T_1} G_{1,2}^{Exc}(T_1) + H_{1,2}^{Exc} \left(1 - \frac{T_2}{T_1}\right) \quad (28)$$

The relationship between the co-solvent component and $H_{1,2}^{Exc}$ for mixtures of MeOH (1) + water (2), EtOH (1) + water (2), and 2-PrOH (1) + water (2), Equations 29, 30, and 31. Excess molar enthalpy values can be derived from these equations using existing literature data [12], provided the mole fraction of water is available.

$$H_{1,2}^{Exc} = x_1(1 - x_1)[-3102 + 2040(1 - 2x_1) - 2213(1 - 2x_1)^2] \quad (29)$$

$$H_{1,2}^{Exc} = x_1(1 - x_1)[-1300 + 3567(1 - 2x_1) - 4971(1 - 2x_1)^2] \quad (30)$$

$$H_{1,2}^{Exc} = x_1(1 - x_1)[854 + 5167(1 - 2x_1) - 7243(1 - 2x_1)^2] \quad (31)$$

Q values for these systems at different temperatures are listed in Supplementary Tables S7–S9. At 298.15 K, the k_T values are 1.248 GPa^{-1} (MeOH), 1.153 GPa^{-1} (EtOH), 1.332 GPa^{-1} (2-PrOH), and 0.457 GPa^{-1} (water), with their corresponding RTk_T values [38]. Equation 34 calculates the molar volume of the combination (V) using M_1 values of 32.04 g/mol (MeOH), 46.07 g/mol (EtOH), 60.10 g/mol (2-PrOH), and an M_2 value of 18.02 g/mol (water).

$$\bar{V}_1 = V + x_2 \frac{dV}{dx_1} \quad (32)$$

$$\bar{V}_2 = V - x_1 \frac{dV}{dx_1} \quad (33)$$

$$V = \frac{x_1 M_1 + x_2 M_2}{\rho} \quad (34)$$

Apart from considering the partial molar values of ART, the mixtures are often regarded as pure compounds [26, 31, 45-48]. In essence, these mixtures act like pure substances under the same circumstances. Equation 18 was used to get the solute radius, which was 0.331 nm . Table S8 in the supplemental materials contains the $\bar{V}_1$ and $\bar{V}_2$ values for the mixtures of MeOH (1) + water (2), EtOH (1) + water (2), and 2-PrOH (1) + water (2) at 298.15 K.

The Kirkwood-Buff integrals were calculated using Equation 13 and 14 ($G_{1,\text{ART}}$ and $G_{2,\text{ART}}$) for 2-PrOH/water, MeOH/water, and EtOH/water, the three binary combinations. At intervals of 0.05, the integrals were computed at co-solvent ratios. Tables S13–S15 show that all $G_{2,\text{ART}}$ values

for ART are negative. The 2-PrOH (1) + water (2) mixture has the highest $G_{2,ART}$ values at $x_1 = 0.70$ - 0.75 across the studied temperature range. The combinations of MeOH (1) + water (2) and EtOH (1) + water (2) the maximum $G_{2,ART}$ values are observed at $x_1 = 0.75$. The negative $G_{1,ART}$ values for ART indicate a strong interaction between ART and both water and alcohols in the solutions. For mixtures with higher water content ($0 < x_1 < 0.10$), $G_{1,ART}$ subscript is positive, but it becomes negative for all other compositions from 293.15 to 313.15 K, as detailed in Tables S13–S15 suggests that water molecules preferentially interact with both solutes in alcohol-rich mixtures.

Table 4. Values of V_{cor} and $\delta x_{1,ART}$ for ART in MeOH (1) + water (2) mixtures at different temperatures.

$^a x_1$	V_{cor} (cm ³ .mol ⁻¹)					100 $\delta x_{1,ART}$				
	293.15 K	298.15 K	303.15 K	313.15 K	318.15 K	293.15 K	298.15 K	303.15 K	313.15 K	318.15 K
0	1173	1174	1174	1175	1177	0.00	0.00	0.00	0.00	0.00
0.05	1209	1210	1211	1212	1214	1.57	1.56	1.54	1.52	1.48
0.1	1243	1244	1244	1247	1249	2.58	2.55	2.51	2.49	2.40
0.15	1274	1275	1275	1278	1280	3.10	3.06	3.01	2.98	2.82
0.2	1302	1303	1304	1308	1309	3.23	3.18	3.13	3.09	2.85
0.25	1330	1331	1332	1336	1337	3.07	3.02	2.95	2.91	2.59
0.3	1356	1357	1359	1363	1364	2.74	2.68	2.61	2.56	2.18
0.35	1382	1384	1385	1390	1391	2.34	2.28	2.20	2.15	1.75
0.4	1409	1410	1412	1417	1419	1.98	1.92	1.84	1.79	1.38
0.45	1436	1438	1440	1446	1447	1.73	1.68	1.61	1.56	1.15
0.5	1464	1466	1469	1475	1477	1.64	1.59	1.52	1.48	1.06
0.55	1493	1496	1498	1505	1507	1.66	1.62	1.56	1.52	1.08
0.6	1522	1526	1528	1535	1538	1.73	1.70	1.64	1.61	1.15
0.65	1552	1555	1558	1565	1569	1.75	1.73	1.69	1.67	1.20
0.7	1580	1584	1588	1595	1599	1.67	1.65	1.62	1.62	1.19
0.75	1608	1613	1617	1624	1634	1.44	1.44	1.42	1.41	1.85
0.8	1636	1640	1645	1652	1663	1.09	1.08	1.07	1.07	1.52
0.85	1663	1668	1673	1679	1691	0.65	0.65	0.64	0.63	1.01
0.9	1690	1695	1700	1707	1718	0.22	0.22	0.21	0.20	0.43
0.95	1718	1724	1729	1735	1746	-0.07	-0.07	-0.07	-0.08	-0.02
1	1749	1754	1760	1766	1778	0.00	0.00	0.00	0.00	0.00

^a x_1 is the mole fraction of MeOH (1) in MeOH (1) + water (2) co-solvent mixtures free of ART.

Table 5. Values of V_{cor} and $\delta x_{1,ART}$ for ART in EtOH (1) + water (2) mixtures at several temperatures.

$^a x_1$	V_{cor} (cm ³ .mol ⁻¹)					100 $\delta x_{1,ART}$				
	293.15 K	298.15 K	303.15 K	313.15 K	318.15 K	293.15 K	298.15 K	303.15 K	313.15 K	318.15 K
0	1172	1173	1174	1177	1179	0.00	0.00	0.00	0.00	0.00
0.05	1242	1244	1244	1248	1250	1.77	1.78	1.78	1.79	1.79
0.1	1305	1308	1309	1314	1317	3.02	3.07	3.10	3.19	3.23
0.15	1361	1364	1367	1373	1377	3.66	3.73	3.80	3.95	4.02
0.2	1411	1414	1418	1424	1428	3.71	3.79	3.85	3.99	4.07
0.25	1457	1460	1463	1470	1473	3.32	3.37	3.40	3.48	3.53
0.3	1501	1503	1506	1512	1515	2.68	2.69	2.70	2.69	2.70
0.35	1544	1545	1548	1555	1557	2.02	2.00	1.98	1.92	1.90
0.4	1588	1589	1592	1599	1601	1.53	1.48	1.45	1.35	1.33
0.45	1635	1636	1638	1646	1648	1.32	1.25	1.22	1.09	1.07
0.5	1685	1685	1688	1695	1697	1.47	1.37	1.34	1.17	1.15

0.55	1737	1737	1739	1747	1749	1.99	1.84	1.78	1.56	1.53
0.6	1792	1790	1793	1800	1802	2.76	2.56	2.48	2.17	2.13
0.65	1846	1843	1846	1853	1856	3.59	3.33	3.24	2.86	2.82
0.7	1897	1893	1897	1904	1909	4.10	3.84	3.77	3.38	3.36
0.75	1941	1936	1943	1949	1956	3.91	3.71	3.69	3.38	3.42
0.8	1977	1971	1981	1988	1997	2.90	2.77	2.82	2.62	2.72
0.85	2009	2003	2014	2023	2033	1.45	1.38	1.44	1.32	1.42
0.9	2044	2038	2050	2060	2071	0.24	0.20	0.24	0.16	0.24
0.95	2085	2082	2094	2105	2116	-0.27	-0.29	-0.27	-0.30	-0.26
1	2134	2139	2146	2161	2171	0.00	0.00	0.00	0.00	0.00

^a x_1 is the mole fraction of EtOH (1) in EtOH (1) + water (2) co-solvent mixtures free of ART.

Table 6. Values of V_{cor} and $\delta x_{1,ART}$ values for ART in 2-PrOH (1) + water (2) mixtures at several temperatures.

^a x_1	V_{cor} (cm ³ .mol ⁻¹)					100 $\delta x_{1,ART}$				
	293.15 K	298.15 K	303.15 K	313.15 K	318.15 K	293.15 K	298.15 K	303.15 K	313.15 K	318.15 K
0	1173	1173	1174	1175	1173	0.00	0.00	0.00	0.00	0.00
0.05	1272	1278	1279	1278	1272	1.50	1.75	1.73	1.46	1.45
0.1	1362	1381	1383	1371	1362	2.59	3.62	3.58	2.57	2.56
0.15	1445	1483	1484	1457	1445	3.28	5.59	5.48	3.30	3.30
0.2	1521	1582	1582	1536	1521	3.60	7.60	7.31	3.66	3.67
0.25	1592	1678	1672	1609	1592	3.63	9.46	8.76	3.71	3.73
0.3	1659	1761	1748	1677	1659	3.46	10.61	9.28	3.52	3.53
0.35	1724	1821	1802	1742	1724	3.19	10.11	8.34	3.19	3.19
0.4	1788	1857	1841	1806	1788	2.95	7.81	6.27	2.84	2.81
0.45	1853	1888	1881	1871	1853	2.91	5.19	4.25	2.65	2.58
0.5	1923	1931	1929	1938	1923	3.30	3.50	2.99	2.76	2.63
0.55	1999	1984	1986	2009	1999	4.37	2.68	2.40	3.27	3.02
0.6	2082	2041	2046	2082	2082	6.05	2.28	2.13	3.97	3.59
0.65	2159	2100	2106	2149	2159	7.36	2.01	1.94	4.38	3.89
0.7	2213	2158	2165	2208	2213	6.88	1.72	1.70	4.07	3.61
0.75	2249	2215	2222	2258	2249	4.83	1.36	1.37	3.11	2.80
0.8	2284	2270	2278	2305	2284	2.63	0.94	0.95	1.91	1.75
0.85	2325	2326	2334	2353	2325	1.01	0.49	0.50	0.85	0.79
0.9	2375	2382	2389	2406	2375	0.09	0.09	0.09	0.13	0.12
0.95	2431	2438	2446	2461	2431	-0.22	-0.14	-0.14	-0.16	-0.16
1	2491	2497	2505	2520	2491	0.00	0.00	0.00	0.00	0.00

^a x_1 is the mole fraction of 2-PrOH (1) in 2-PrOH (1) + water (2) co-solvent mixtures free of ART.

The V_{cor} and $\delta x_{1,ART}$ values for all solvent mixtures at different temperatures are presented in Tables 4-6. Additionally, the connection between $\delta x_{1,ART}$ and solvent composition is depicted in Figure 2. As demonstrated in Figure 2, there is an inverse relationship between changes in the co-solvent composition and the corresponding changes in $\delta x_{1,ART}$ for each aqueous mixture.

As shown in Figure 2 and detailed in Tables 4 and 6, when compared to their bulk compositions throughout the mole fraction range of $0.00 < x_1 < 1.00$, the MeOH (1) + water (2) and 2-PrOH (1) + water (2) systems show more significant local mole fractions of MeOH/EtOH/or 2-PrOH near ART. This implies that ART is preferentially solvated by MeOH/EtOH/or 2-PrOH. The positive values of the preferential solvation parameter support this, $\delta x_{1,ART}$. This solvation occurs as MeOH/EtOH/or 2-PrOH displaces water molecules near ART's nonpolar region. Two distinct solvation maxima are observed at the studied temperatures. In the MeOH (1) + water (2) system, the first maximum is at $x_1 = 0.20$, with $\delta x_{1,ART}$ ranging from $(2.85 \text{ to } 3.23) \times 10^{-2}$, and the

second is at $x_1 = 0.60$, with values from $(1.20 \text{ to } 1.75) \times 10^{-2}$. A similar trend appears in the EtOH (1) + water (2) system, where the first maximum is at $x_1 = 0.20$, with $\delta x_{1,ART}$ values from $(3.79 \text{ to } 4.07) \times 10^{-2}$, and the second maximum is at $x_1 = 0.60$, with $\delta x_{1,ART}$ varying from $(3.36 \text{ to } 4.10) \times 10^{-2}$. A similar trend is observed in the 2-PrOH (1) + water (2) system, where the first maximum is at $x_1 = 0.25\text{--}0.30$, with $\delta x_{1,ART}$ values from $(3.73 \text{ to } 10.61) \times 10^{-2}$, and the second maximum is at $x_1 = 0.65$, with $\delta x_{1,ART}$ varying from $(1.94 \text{ to } 7.36) \times 10^{-2}$.

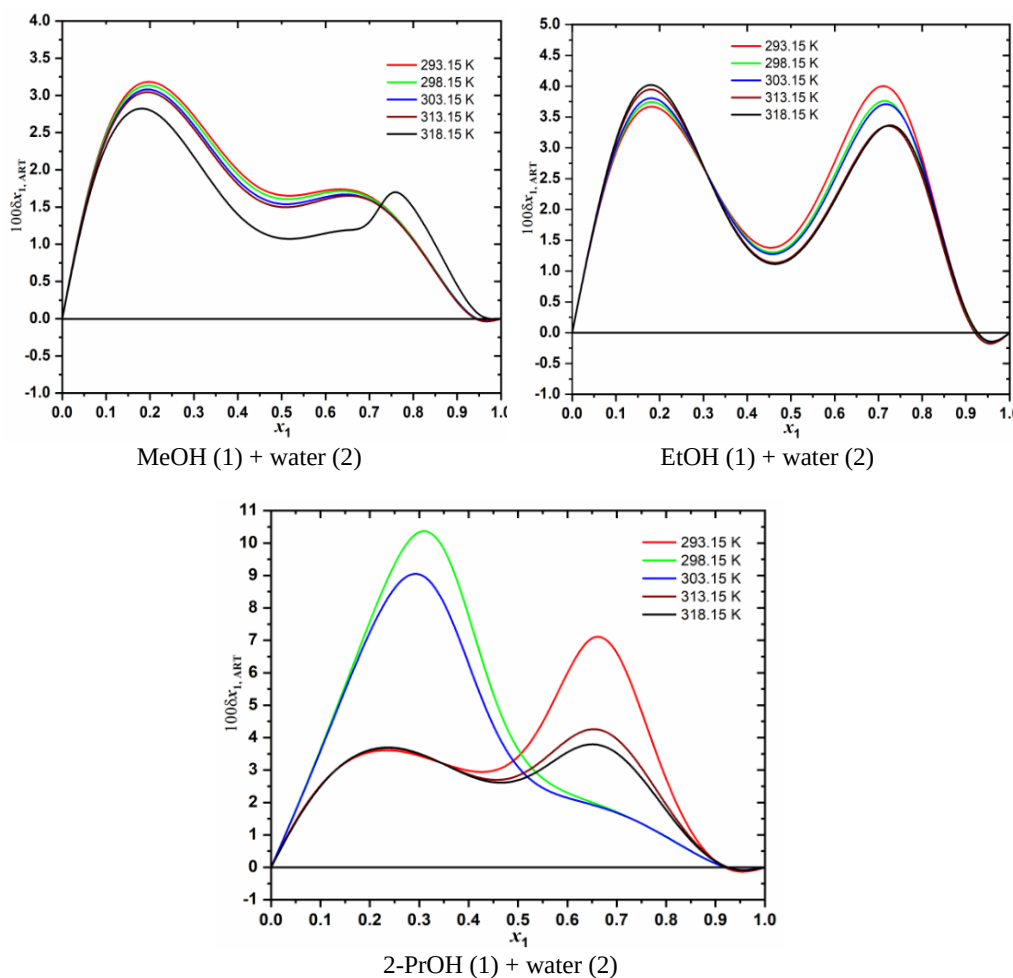


Figure 2. Plot of $\delta x_{1,ART}$ values of ART from pure water to MeOH (1) + water (2), EtOH (1) + water (2), and 2-PrOH (1) + water (2) mixtures at several temperatures.

At all studied temperatures, in the composition range of $0.90 < x_1 < 1.00$, neither EtOH nor water exhibits a notable preferential solvation effect on ART, as evidenced by $\delta x_{1,ART}$ values consistently remaining below 1.0×10^{-2} . This pattern suggests that propagating experimental errors, rather than actual preferred solvation processes, are more likely to be the cause of the reported values [49, 50].

Understanding the positive $\delta x_{1,ART}$ values in aqueous alcoholic mixtures present greater challenges within this framework. To elucidate why specific compounds act as hydrogen donors, their Lewis acid characteristics during interactions with alcohol molecules can be analyzed. This pattern suggests that propagating experimental errors, rather than actual preferred solvation processes, are more likely to be the cause of the reported values [49, 50]. With β values rising from 0.47 (water) to 0.66 (MeOH), 0.75 (EtOH), and 0.84 (2-PrOH). This heightened basicity of alcohols contrasts with water's more excellent acidity than MeOH, EtOH, and 2-PrOH.

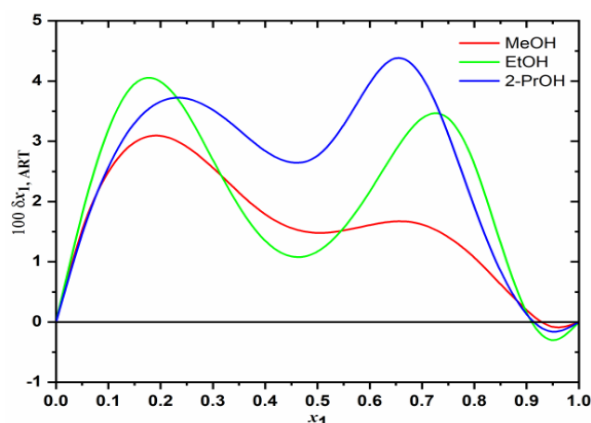


Figure 3. Plot of $\delta x_{1,ART}$ values of ART in alcohol (1) + water (2) mixtures at 313.15 K.

At 313.15 K, Figure 3 presents the preferential solvation behavior of ART in binary mixtures of methanol–water, ethanol–water, and 2–propanol–water. Across all solvent systems, ART consistently demonstrates a stronger affinity for water over the alcohol component. However, the degree of solvation differs among the mixtures: 2–propanol–water exhibits the most effective solvation, followed by ethanol–water, with methanol–water showing the least efficiency.

The maximum solvation of the solute varies with the specific composition of each binary solvent system. In methanol–water mixtures, the maximum solvation occurs when the mole fraction of MeOH (x_1) is 0.20, resulting in a $\delta x_{1,ART}$ value of 3.09×10^{-2} . A similar maximum for the EtOH–water system is also observed at $x_1 = 0.20$, though with a slightly higher $\delta x_{1,ART}$ of 3.99×10^{-2} . The 2-PrOH–water system differs significantly, reaching maximum solvation at a much higher 2-propanol content of $x_1 = 0.65$, where $\delta x_{1,ART}$ is 4.38×10^{-2} , the highest among the three systems.

CONCLUSIONS

The key factors influencing the solubility behavior of artesunate (ART) were effectively identified by the KAT-LSER model in binary solvent systems involving MeOH–water, EtOH–water, and 2-PrOH–water. Specifically, the findings demonstrated that hydrogen bond acidity (α), basicity (β), and dipolarity/polarizability (π^*) all had a considerable impact on the solubility of ART in these combinations and cavity effects. In addition, the local mole fractions surrounding ART might be quantitatively determined by applying the IKBI technique and combining it with experimental solubility data. The results showed that between 293.15 and 313.15 K, alcohol tended to solvate ART more preferentially in these binary systems. Moreover, the extent of preferential solvation ($\delta x_{1,ART}$) decreases with declining solvent polarity, underscoring the role of polarity in solvation dynamics. The enthalpy–entropy compensation analysis showed that ART's solvation mechanism

shifts from entropy-driven to enthalpy-driven with increasing alcohol content. In contrast, ART dissolution in pure alcohol–water systems remain enthalpy-controlled. These findings offer deeper insight into the solvation behavior of ART in mixed solvents and have important implications for optimizing its formulation in pharmaceutical and chemical applications.

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Data availability

The supporting data for this study is available from the authors upon request.

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