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# Solubility and Thermodynamics of Clonazepam in (1-Propanol/2-Propanol) and Water Binary Solvent Mixtures at (293.15 to 313.15) K

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In this study, the solubility of clonazepam (CZP) in binary solvent mixtures of (1-propanol + water) and (2-propanol + water) at five different temperatures was investigated. The solubility of CZP was assessed using the shake-flask technique, while the concentrations of CZP in the solutions were measured utilizing a UV-Vis spectrophotometer. The obtained solubility data were analyzed using the main mathematical models available in this context. The experimental data obtained for CZP dissolution encompassed various thermodynamic properties, including $\Delta G°$, $\Delta H°$, $T\Delta S°$, and $\Delta S°$. These properties offer valuable insights into the energetic aspects of the dissolution process. The results revealed that the solubility of CZP in both binary solvent mixtures increased with increasing alcohol concentration and temperature. The mathematical models provided accurate predictions of the solubility of CZP in these binary solvent systems (*MRDs*% were less than 14.3). Based on the thermodynamic analysis, it was determined that the dissolution of CZP in the examined mixtures is endothermic. Furthermore, the inverse Kirkwood-Buff integrals revealed the presence of preferential hydration of CZP in mixtures that were rich in water as well as those rich in cosolvent.

**Keywords:** Clonazepam, Cosolvency method, Mathematical computations, Thermodynamic properties

## INTRODUCTION

Clonazepam (CZP, the molecular structure is depicted in Fig. 1) is a benzodiazepine drug that is commonly used as an anticonvulsant, muscle relaxant, and anxiolytic agent [1]. However, its low solubility in water can limit its bioavailability and effectiveness in oral drug formulations. Therefore, improving the solubility of CZP is of great interest in pharmaceutical research. Solubility plays a pivotal role in

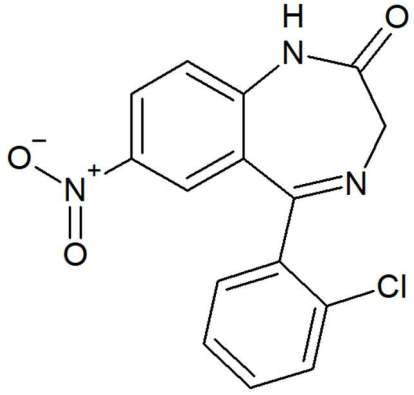


**Fig. 1.** Molecular structure of clonazepam (CZP).

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pharmaceutical sciences and is frequently utilized to inform decisions concerning the destiny of a drug candidate. Solubility data are crucial in drug development as they are essential for drug evaluation of solid-phase characteristics, formulation, and establishing correlations between *in vivo* and *in vitro* data [2]. Solubility in non-aqueous solvents is also significant in drug synthesis and purification processes, as well as in the development of pharmaceutical analysis [3,4].

One challenge in drug development is the solubilization of poorly soluble drugs [5]. Various methods have been developed for solubilizing drugs. Binary solvent systems are commonly used in the pharmaceutical industry to improve the solubility and bioavailability of poorly soluble drugs [6]. Cosolvency refers to the process of blending an organic solvent, which is capable of miscible with water, in order to reduce the polarity of the water used for dissolution and subsequently enhance the solubility of a drug. Actually, a mixture of two solvents can provide higher solubility than individual solvents. This method has the advantages of ease of use and solubilization power [7].

On the other hand, efforts have been devoted to predicting physicochemical properties in pharmaceutical sciences, including the use of mathematical models for estimating drug solubility in water-cosolvent mixtures [8]. These models use statistical analysis to identify correlations between the solubility of the drug and various parameters such as the cosolvent type, concentration, and temperature. These correlations can then be used to predict drug solubility in water-cosolvent mixtures.

The choice of solvent system and its composition can have a significant impact on the solubility of a drug. Therefore, selecting an appropriate binary solvent system is a crucial step in drug development. Among the various binary solvent systems, the (1-propanol + water) and (2-propanol + water) mixtures have gained attention due to their good solubilizing power for many drugs [9,10]. However, the solubility of CZP in (1-propanol + water) and (2-propanol + water) mixtures has not been studied. Therefore, this research aims to investigate the solubility of CZP in (1-propanol + water) and (2-propanol + water) mixtures at various temperatures ranging from 20 °C to 40 °C.

The acquired data from this study can offer valuable insights into the solubilizing capacity of (1-propanol + water) and (2-propanol + water) mixtures for CZP and help optimize the formulation of CZP-based drug products. Additionally, this research can also contribute to the understanding of the solubility behavior of other drugs in binary solvent systems. The comparison of the solubility of CZP in (1-propanol + water) and (2-propanol + water) mixtures can also provide insights into the effect of the type of alcohol on the solubility behavior of CZP. In addition to the experimental investigation, this study also employs mathematical models for predicting the solubility of CZP in these binary solvent systems. These models can be used for predicting solubility in mixed solvent systems and can also be used to calculate other physicochemical properties.

## MATERIALS AND METHOD

### Materials

The CZP used in this study was obtained as a gift from Sobhan Pharmaceutical (Iran) and had a purity of 99.7%. 2-Propanol and 1-propanol with purity of ≥ 99.5% were from Scharlau Chemie (Spain). Deionized water was from Shahid Ghazi Pharmaceutical.

### CZP Solubility Determination

The solubility of CZP in binary solvent mixtures consisting of (1-propanol + water) and (2-propanol + water) was determined using a shake-flask approach. To conduct the experiment, an extra amount of CZP was introduced into 5-ml tubes that already contained pre-mixed solvents with a total mass of 3.0 g at intervals of 0.1, ranging from 0.1 to 0.9 in mass fractions. Taking into account initial findings on dissolution rates, the tubes were subsequently placed on a shaker and incubated for a predetermined duration. Following 72 h, the system reached a state of solid-liquid equilibrium, resulting in solubility, and the saturated mixtures were centrifuged. After centrifugation, an aliquot of the clear upper solutions was taken and the concentrations of CZP were determined by measuring the absorbance at 310 nm using a UV-Vis spectrophotometer (Cecil BioAquarius 7250 CE, UK). This absorbance data was then utilized to calculate the concentrations of CZP; in the case of concentrate solutions, dilution using ethanol 50% (v/v) was made. The saturated solutions' density was determined utilizing a 1.5 ml pycnometer along with an analytical

balance, which had a precision of 0.0001 g.

## Mathematical Models

This study employed various mathematical models to analyze solubility data in relation to temperature and solvent compositions. The main available solubility models involve van't Hoff, Jouyban-Acree, modified Wilson, Jouyban-Acree-van't Hoff, and mixture response surface (MRS) models. The dissolution process of the solute in a specific solvent mixture was described by the van't Hoff equation (Eq. (1)), which relates it to temperature. Empirical solubility data can be described by Eqs. (2) and (3), which linked solubility data to both temperatures of mixtures and solvent properties. Eq. (4) (MRS model) was employed to connect the solubility of the drug at different solvent ratios at a given temperature. Lastly, Eq. (5) (the modified Wilson model) was a non-linear equation used to fit the obtained data, taking into account the composition of the blend at a specific temperature.

$$\ln x = A + \frac{B}{T} \tag{1}$$

$$\ln x_m = \beta_1 w_1' + \beta_2 w_2' + \beta_3 \left(\frac{1}{w_1'}\right) + \beta_4 \left(\frac{1}{w_2'}\right) + \beta_5 w_1'.w_2' \tag{2}$$

$$\ln x_{m,T} = w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + \frac{w_1.w_2}{T} \sum_{i=0}^{2} J_i.(w_1 - w_2)^i \tag{3}$$

$$\ln x_{m,T} = w_1 \left(A_1 + \frac{B_1}{T}\right) + w_2 \left(A_2 + \frac{B_2}{T}\right) + \frac{w_1.w_2}{T} \sum_{i=0}^{2} J_i.(w_1 - w_2)^i \tag{4}$$

$$-\ln x_m = 1 - \frac{w_1[1 + \ln x_1]}{w_1 + w_2 \lambda_{12}} - \frac{w_2[1 + \ln x_2]}{w_1 \lambda_{21} + w_2} \tag{5}$$

Here the solubilities of the CZP in mono-solvents 1, 2, and the solvent blend are represented by $x_1$, $x_2$, and $x_m$, respectively, while $w_1$ and $w_2$ are denoted as the mass fractions of solvents 1 and 2. The mean relative deviation (*MRD*%) (Eq. (6)) is employed to express the accuracy of the models' prediction.

$$MRD\% = \frac{100}{N} \sum \left( \frac{|Calculated\ Value - Observed\ Value|}{Observed\ Value} \right) \tag{6}$$

The value of *N* denotes the number of data points.

## Calculation of Thermodynamic Parameters

To determine the thermodynamic functions of CZP in studied solvent mixtures, a thermodynamic analysis was conducted using the van't Hoff equation. The thermodynamic parameters of interest included the standard dissolution enthalpy ($\Delta H°$), the standard dissolution entropy ($\Delta S°$), and the Gibbs free energy change ($\Delta G°$). The $\Delta H°$ value in binary solvent mixtures was calculated using the van't Hoff equation, which can be represented as follows:

$$\frac{\partial \ln x}{\partial \left(\frac{1}{T} - \frac{1}{T_{hm}}\right)_p} = -\frac{\Delta H^\circ}{R} \tag{7}$$

The value of $\Delta H°$ was determined by plotting $\ln x$ against $\frac{1}{T} - \frac{1}{T_{hm}}$ (Eq. (7)). The slope of this plot was used to calculate $\Delta H°$. At the temperatures of 293.2-313.2 K, the heat capacity change of the solution was assumed to be constant. Therefore, $\Delta H°$ was considered valid for the harmonic mean temperature ($T_{hm}$) value of 303.0 K. The $\Delta G°$ and $\Delta H°$ values for the solubilization of CZP in the solvents blend were calculated using the intercept and slope of the plot of Eq. (7), respectively. To obtain $\Delta S°$, the Eq. (8) was employed, utilizing the $\Delta H°$ and $\Delta G°$ [11]:

$$\Delta S° = \frac{\Delta H° - \Delta G°}{T_{hm}} \tag{8}$$

Since both entropy and enthalpy contribute to dissolution, their individual contributions ($\zeta_{TS}$ and $\zeta_H$) can be expressed using Eqs. (9) and (10) [12]:

$$\zeta_{TS} = \frac{|T\Delta S^\circ|}{(|\Delta H^\circ| + |T\Delta S^\circ|)} \tag{9}$$

$$\zeta_H = \frac{|\Delta H^\circ|}{(|\Delta H^\circ| + |T\Delta S^\circ|)} \tag{10}$$

# RESULTS AND DISCUSSIONS

## Solubility of CZP in Aqueous Binary Mixtures

The solubility of CZP in the (1-propanol + water) and (2-

propanol + water) mixtures can be analyzed based on the experimental data provided in Table 1. Table 1 presents obtained solubility data at investigated temperatures and concentrations of the cosolvent (1-propanol or 2-propanol) in mole fraction scale ($x_{m,T}$) with the corresponding standard deviation. In the (2-propanol + water) mixture, the minimum solubility of CZP occurs in the neat water ($w_1$ = 0.0). In neat water, the solubility gradually increases with rising temperature. For instance, at 293.2 K, the mole fraction solubility is $6.89 \times 10^{-7}$, while at 313.2 K, it reaches $1.61 \times 10^{-6}$. Conversely, the maximum solubility occurs in the 2-propanol-mass fraction of 0.9 ($w_1$ = 0.9). At this 2-propanol-mass fraction, the solubility also increases with temperature. For example, at 293.2 K, the solubility is $8.14 \times 10^{-4}$ and at 313.2 K, it is $1.57 \times 10^{-3}$. Therefore, the solubility ranges achievable in the (2-propanol + water) mixture can be determined by the difference between the minimum and maximum solubility values.

Similarly, in the (1-propanol + water) mixture, the minimum solubility of CZP occurs at the neat water ($w_1$ = 0.0). The solubility increases gradually with rising temperature, just like in the (2-propanol + water) mixture.

**Table 1.** Experimental Mole Fraction Solubility ($x_{m,T}$) Values as the Mean of Three Experiments (± SD) Measured for CZP in Solvent Mixtures at Different Temperatures

| $w_1$[a] | 293.2 K | 298.2 K | 303.2 K | 308.2 K | 313.2 K |
|---|---|---|---|---|---|
| 2-Propanol + water | | | | | |
| 0.00 | $6.89\ (\pm0.25) \times 10^{-7}$ | $9.02\ (\pm0.50) \times 10^{-7}$ | $1.02\ (\pm0.02) \times 10^{-6}$ | $1.27\ (\pm0.05) \times 10^{-6}$ | $1.61\ (\pm0.09) \times 10^{-6}$ |
| 0.10 | $1.98\ (\pm0.06) \times 10^{-6}$ | $3.35\ (\pm0.15) \times 10^{-6}$ | $4.66\ (\pm0.20) \times 10^{-6}$ | $5.61\ (\pm0.14) \times 10^{-6}$ | $6.34\ (\pm0.28) \times 10^{-6}$ |
| 0.20 | $7.20\ (\pm0.30) \times 10^{-6}$ | $1.06\ (\pm0.05) \times 10^{-5}$ | $1.52\ (\pm0.06) \times 10^{-5}$ | $2.65\ (\pm0.06) \times 10^{-5}$ | $3.00\ (\pm0.07) \times 10^{-5}$ |
| 0.30 | $3.50\ (\pm0.05) \times 10^{-5}$ | $4.51\ (\pm0.07) \times 10^{-5}$ | $6.22\ (\pm0.30) \times 10^{-5}$ | $8.48\ (\pm0.17) \times 10^{-5}$ | $1.01\ (\pm0.02) \times 10^{-4}$ |
| 0.40 | $1.21\ (\pm0.04) \times 10^{-4}$ | $1.39\ (\pm0.02) \times 10^{-4}$ | $1.81\ (\pm0.03) \times 10^{-4}$ | $2.13\ (\pm0.07) \times 10^{-4}$ | $2.67\ (\pm0.08) \times 10^{-4}$ |
| 0.50 | $2.29\ (\pm0.05) \times 10^{-4}$ | $2.68\ (\pm0.04) \times 10^{-4}$ | $3.39\ (\pm0.04) \times 10^{-4}$ | $3.97\ (\pm0.18) \times 10^{-4}$ | $4.62\ (\pm0.10) \times 10^{-4}$ |
| 0.60 | $4.05\ (\pm0.16) \times 10^{-4}$ | $4.59\ (\pm0.11) \times 10^{-4}$ | $5.58\ (\pm0.11) \times 10^{-4}$ | $6.49\ (\pm0.16) \times 10^{-4}$ | $7.63\ (\pm0.13) \times 10^{-4}$ |
| 0.70 | $6.08\ (\pm0.12) \times 10^{-4}$ | $7.07\ (\pm0.16) \times 10^{-4}$ | $8.53\ (\pm0.10) \times 10^{-4}$ | $9.86\ (\pm0.25) \times 10^{-4}$ | $1.12\ (\pm0.02) \times 10^{-3}$ |
| 0.80 | $7.97\ (\pm0.19) \times 10^{-4}$ | $9.08\ (\pm0.15) \times 10^{-4}$ | $1.10\ (\pm0.02) \times 10^{-4}$ | $1.29\ (\pm0.03) \times 10^{-3}$ | $1.44\ (\pm0.01) \times 10^{-3}$ |
| 0.90 | $8.14\ (\pm0.24) \times 10^{-4}$ | $9.60\ (\pm0.14) \times 10^{-4}$ | $1.21\ (\pm0.03) \times 10^{-4}$ | $1.41\ (\pm0.07) \times 10^{-3}$ | $1.57\ (\pm0.03) \times 10^{-3}$ |
| 1.00 | $4.82\ (\pm0.11) \times 10^{-4}$ | $5.88\ (\pm0.02) \times 10^{-4}$ | $6.98\ (\pm0.23) \times 10^{-4}$ | $8.68\ (\pm0.27) \times 10^{-4}$ | $1.07\ (\pm0.05) \times 10^{-3}$ |
| 1-Propanol + water | | | | | |
| 0.00 | $6.89\ (\pm0.25) \times 10^{-7}$ | $9.02\ (\pm0.05) \times 10^{-7}$ | $1.02\ (\pm0.02) \times 10^{-6}$ | $1.27\ (\pm0.05) \times 10^{-6}$ | $1.61\ (\pm0.09) \times 10^{-6}$ |
| 0.10 | $2.62\ (\pm0.09) \times 10^{-6}$ | $4.83\ (\pm0.18) \times 10^{-6}$ | $5.41\ (\pm0.03) \times 10^{-6}$ | $7.86\ (\pm0.31) \times 10^{-6}$ | $8.08\ (\pm0.23) \times 10^{-6}$ |
| 0.20 | $1.50\ (\pm0.01) \times 10^{-5}$ | $2.04\ (\pm0.05) \times 10^{-5}$ | $2.95\ (\pm0.12) \times 10^{-5}$ | $3.35\ (\pm0.08) \times 10^{-5}$ | $4.13\ (\pm0.09) \times 10^{-5}$ |
| 0.30 | $6.66\ (\pm0.21) \times 10^{-5}$ | $8.82\ (\pm0.16) \times 10^{-5}$ | $1.13\ (\pm0.13) \times 10^{-4}$ | $1.45\ (\pm0.04) \times 10^{-4}$ | $1.66\ (\pm0.03) \times 10^{-4}$ |
| 0.40 | $1.59\ (\pm0.06) \times 10^{-4}$ | $2.09\ (\pm0.10) \times 10^{-4}$ | $2.41\ (\pm0.05) \times 10^{-4}$ | $3.16\ (\pm0.07) \times 10^{-4}$ | $3.72\ (\pm0.03) \times 10^{-4}$ |
| 0.50 | $3.02\ (\pm0.12) \times 10^{-4}$ | $3.77\ (\pm0.07) \times 10^{-4}$ | $4.53\ (\pm0.14) \times 10^{-4}$ | $5.40\ (\pm0.07) \times 10^{-4}$ | $6.48\ (\pm0.19) \times 10^{-4}$ |
| 0.60 | $5.10\ (\pm0.21) \times 10^{-4}$ | $5.92\ (\pm0.24) \times 10^{-4}$ | $7.03\ (\pm0.28) \times 10^{-4}$ | $8.36\ (\pm0.20) \times 10^{-4}$ | $9.63\ (\pm0.33) \times 10^{-4}$ |
| 0.70 | $7.09\ (\pm0.28) \times 10^{-4}$ | $8.50\ (\pm0.19) \times 10^{-4}$ | $1.04\ (\pm0.01) \times 10^{-3}$ | $1.23\ (\pm0.03) \times 10^{-3}$ | $1.38\ (\pm0.04) \times 10^{-3}$ |
| 0.80 | $1.00\ (\pm0.02) \times 10^{-3}$ | $1.20\ (\pm0.02) \times 10^{-3}$ | $1.41\ (\pm0.04) \times 10^{-3}$ | $1.70\ (\pm0.04) \times 10^{-3}$ | $1.87\ (\pm0.05) \times 10^{-3}$ |
| 0.90 | $1.22\ (\pm0.04) \times 10^{-3}$ | $1.49\ (\pm0.02) \times 10^{-3}$ | $1.79\ (\pm0.06) \times 10^{-3}$ | $2.13\ (\pm0.05) \times 10^{-3}$ | $2.29\ (\pm0.03) \times 10^{-3}$ |
| 1.00 | $1.08\ (\pm0.03) \times 10^{-3}$ | $1.33\ (\pm0.04) \times 10^{-3}$ | $1.48\ (\pm0.06) \times 10^{-3}$ | $1.83\ (\pm0.04) \times 10^{-3}$ | $1.99\ (\pm0.06) \times 10^{-3}$ |

[a]$w_1$ is the mass fraction of 2-propanol/1-propanol in (2-propanol/1-propanol and water) mixtures in the absence of CZP.

The maximum solubility, on the other hand, is also in the 1-propanol-mass fraction of 0.9 ($w_1$ = 0.9). With increasing temperature, the solubility also increases.

Overall, in both mixtures, the solubility of CZP tends to increase with higher concentrations of the respective cosolvent (2-propanol or 1-propanol) and elevated temperatures. These solubility behaviors can be attributed to specific molecular interactions and solvation effects between CZP, the cosolvent, and water within the mixtures [13]. These interactions have a significant impact on the solubility of CZP and contribute to the observed solubility behavior in these cosolvency systems. The differences in solubility of CZP in 1-propanol and 2-propanol can be attributed to their structural dissimilarities and the resulting variations in molecular interactions with CZP and water [14]. 1-Propanol, also known as n-propanol, has a linear structure with a single hydroxyl (-OH) group attached to the end of a carbon chain. On the other hand, 2-propanol, also known as isopropanol, has a branched structure with a hydroxyl group attached to the middle carbon atom. The solubility of a solute like CZP in distinct alcohol-based solvents could be influenced bytheir molecular structures and the interactions which they form with the cosolvent and the surrounding water molecules [15]. In the case of CZP, which is a nonpolar drug (log$P$ = 2.41), it tends to exhibit better solubility in nonpolar solvents and may experience different solubility behavior in 1-propanol and 2-propanol due to their subtle structural differences.

At a temperature of 298.15 K, the dielectric constants of 2-propanol and 1-propanol are 19.0 and 21.7, respectively [16]. Comparatively, the dielectric constant of 1-propanol is higher than that of 2-propanol. This parameter serves as a valuable indicator of a liquid polarity. 1-Propanol has a linear molecular structure with a longer hydrocarbon chain compared to 2-propanol, which has a branched structure. This difference in molecular structure affects the polarity of the alcohol. 1-Propanol is slightly more polar than 2-propanol due to the presence of the longer hydrocarbon chain, which contains more polarizable electrons. Therefore, it is expected that the solubility of hydrophobic CZP is high in 2-propanol compared to 1-propanol but the obtained data indicate a controversial result.

When CZP is introduced to the (1-propanol + water) mixture, it can form a variety of interactions with both 1-propanol and water molecules. Hydrogen bonding can occur between the polar functional groups in CZP and the hydroxyl group in 1-propanol, further enhancing solubility. Although 2-propanol can still form hydrogen bonds with CZP and water, the branched structure may hinder some interactions, leading to a slightly different solubility behavior compared to 1-propanol [14]. Furthermore, the solubility of CZP is also affected by the cosolvent-water interactions. The presence of cosolvents in water can disrupt the hydrogen bonding network among water molecules. In turn, this can impact the solvation of CZP and lead to variations in its solubility behavior in the alcohol-water mixtures [17].

Moreover, Fig. 2 depicts the molar solubility of CZP in (2-propanol + water) and (1-propanol + water) at all temperatures under research. Solubility data expressed in moles per liter could be useful for the design of liquid formulations because it is easily converted to mass/volume percent (% m/v) that is used for expressing drug concentrations in pharmaceutical liquid products. On the other hand, it is interesting to note that maximal solubilities in molarity are observed in the mixture of $w_1$ = 0.8 in (2-propanol + water) mixtures but in the mixture of $w_1$ = 0.9 in (1-propanol + water) mixtures, whereas, in mole fraction, they are observed in the mixtures of $w_1$ = 0.9 for both cosolvents. The distinction observed with 2-propanol arises from the definitions of different concentration scales. Molarity, being a semi-empirical volumetric scale, takes into account only the moles of the solute without considering the moles of the solvent. On the other hand, the moles of both the solute and the solvent within the saturated mixture are considered in the mole fraction scale, which in turn is considered a gravimetric scale [18].

In order to evaluate the polarity of CZP Fig. 3 depicts the mole fraction solubility of this drug as a function of the Hildebrand solubility parameter of the cosolvent mixtures ($\delta_{1+2}$/MPa$^{1/2}$) in both 2-propanol and 1-propanol aqueous mixtures at 298.2 K. The $\delta_{1+2}$ values were determined following the methodology outlined in the literature [19]. Based on observations, the highest level of solubility is obtained in solvent mixtures of $\delta_{1+2}$ values near to 25.5-26.5 MPa$^{1/2}$, which apparently can propose a $\delta_3$ value of 26 MPa$^{1/2}$ for CZP. However, using the Fedors group-contribution method [20], a $\delta_3$ value of 28 MPa$^{1/2}$ is obtained as summarized in Table 2. Thus, it is demonstrated that not

only polarity is involved in equilibrium solubility but other solute and solvent properties as well.

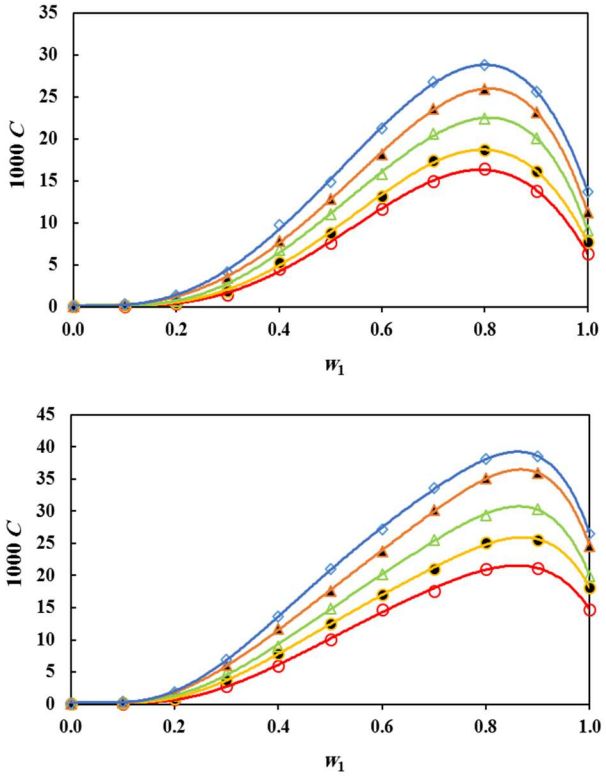


**Fig. 2.** Experimental molar solubility ($C$, M) of CZP in solvent mixtures at different temperatures. Top: (2-Propanol + water). Bottom: (1-Propanol + water). ○: 293.2 K; ●: 298.2 K; Δ: 303.2 K; ▲: 308.2 K; ◊: 313.2 K.

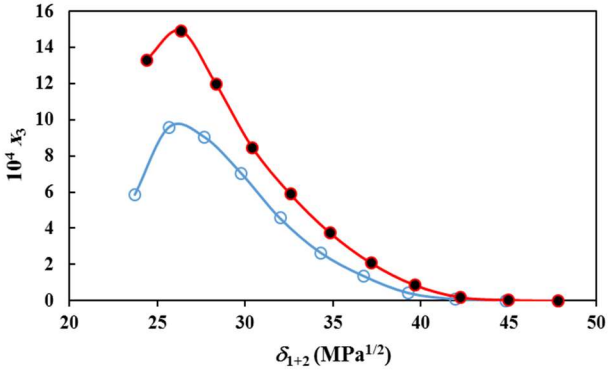


**Fig. 3.** Experimental mole fraction solubility ($x_3$) of CZP as a function of the Hildebrand solubility parameter of the cosolvent mixtures at 298.2 K. ○: (2-Propanol + water); ●: (1-Propanol + water).

On the other hand, to discuss the results based on Tables 3-6, the different mathematical models used for evaluating the solubility and solubility prediction of CZP in the solvent mixtures of (2-propanol + water) and (1-propanol + water) were analyzed. The *MRD*% values and the power of prediction of each model for the solubility data were considered. In Table 3, the parameters of the van't Hoff model and the corresponding *MRD*% for CZP are displayed for both binary mixtures. The *MRD*% values indicate the accuracy of the model's predictions. The *MRD*% values for CZP solubility in the mixtures of (2-propanol + water) and (1-propanol + water) are 2.2 and 2.1, respectively. These

**Table 2.** Application of the Fedors Method to Estimate Internal Energy, Molar Volume, and Hildebrand Solubility Parameter of CZP

| Group | Group number | $\Delta U°$ (kJ mol$^{-1}$) | $V°$ (cm$^3$ mol$^{-1}$) |
|---|---|---|---|
| –$CH_2$– | 1 | 4.94 | 16.1 |
| >C= | 1 | 4.31 | -5.5 |
| Phenylene | 1 | 31.90 | 52.4 |
| Trisubstituted phenyl | 1 | 31.90 | 33.4 |
| 7 atoms ring closure | 1 | 1.05 | 16.0 |
| –Cl attached to C with double bond | 1 | 9.24 | 24.0 |
| –N= | 1 | 11.70 | 5.0 |
| –CONH– | 1 | 33.50 | 9.5 |
| –$NO_2$ aromatic | 1 | 15.36 | 32.0 |
| | | $\Sigma\Delta U° = 143.90$ | $\Sigma V = 182.9$ |
| | | $\delta_3 = (143{,}900/182.9)^{1/2} = 28.05$ MPa$^{1/2}$ | |

*MRD*% values represent the average relative deviation between the predicted solubility values using the van't Hoff model and the experimental solubility data. Lower *MRD*% values indicate better prediction accuracy. In this case, both mixtures show relatively low *MRD*% values, indicating that the van't Hoff model provides a reasonably good prediction of CZP solubility in these systems. Table 4 presents the parameters calculated for the Jouyban-Acree and Jouyban-Acree-van't Hoff models. The *MRD*% values for CZP solubility in the mixtures of (2-propanol + water) and (1-propanol + water) are 11.2, 11.0, and 9.8, 10.2, respectively. The *MRD*% values for both mixtures are relatively higher compared to the van't Hoff model, indicating slightly less accurate predictions. However, the differences in *MRD%* between the two models are small, suggesting similar prediction performance. Table 5 provides the MRS model constants at different temperatures and the corresponding *MRD*% for CZP solubility in both mixtures. *MRD*% values for back-calculated CZP solubility in the mixtures of (2-propanol + water) and (1-propanol + water) are 8.0 and 14.3, respectively. These *MRD*% values indicate relatively good predictions for CZP solubility, especially in the mixture of (2-propanol + water). The overall *MRD*% values indicate reasonably accurate predictions, although slightly higher compared to the van't Hoff model. Table 6 displays the modified Wilson model parameters at different temperatures and the corresponding *MRD*% values. The *MRD*% values for back-calculated CZP solubility in the mixtures of (2-propanol + water) and (1-propanol + water) are 8.9 and 8.6, respectively. The *MRD*% values are relatively low, indicating good predictive performance for both mixtures. In summary, based on the *MRD*% values, the van't Hoff model appears to have the best prediction accuracy among the models considered. However, the differences in *MRD*% values between the models are generally small, suggesting that they all provide reasonably accurate predictions for CZP solubility in the binary mixtures. It is worth noting that the choice of the most appropriate model depends on various factors such as the specific system under investigation and the range of conditions.

In the next step, for evaluation of the prediction power of Jouyban-Acree-van't Hoff model for solubility data, the model was trained using minimum data points *i.e.*, solubility data for mono-solvents at low and high temperatures and solvent mixtures of 0.3, 0.5 and 0.7 at 298.2 K and the rest data in other mass fractions and other temperatures were predicted using the trained model. The prediction *MRDs*% for various temperatures of the (2-propanol + water) system were 16.3, 8.9, 8.8, 10.0, and 9.4 and (1-propanol + water) system were 18.5, 10.4, 9.7, 11.3, and 11.2 for 293.2, 298.2, 303.2, 308.2 and 313.2 K, respectively.

**Table 3.** The van't Hoff Model Parameters and the Corresponding *MRD*% for CZP in Two Binary Mixtures of (2-Propanol + Water) and (1-Propanol + Water)

| $w_1$ | 2-Propanol + water | | | 1-Propanol + water | | |
|---|---|---|---|---|---|---|
| | *A* | *B* | *MRD*% | *A* | *B* | *MRD*% |
| 0.00 | -1.432 | -3736.692 | 2.7 | -1.407 | -3744.354 | 2.7 |
| 0.10 | 4.909 | -5249.824 | 1.0 | 4.550 | -5057.652 | 1.2 |
| 0.20 | 11.817 | -6935.182 | 5.8 | 4.776 | -4643.517 | 4.2 |
| 0.30 | 6.947 | -5046.941 | 2.7 | 4.992 | -4275.504 | 2.9 |
| 0.40 | 3.456 | -3665.309 | 2.5 | 4.514 | -3883.416 | 2.5 |
| 0.50 | 2.881 | -3304.138 | 1.6 | 3.728 | -3466.205 | 0.7 |
| 0.60 | 2.269 | -2960.665 | 1.2 | 2.535 | -2968.444 | 0.7 |
| 0.70 | 2.388 | -2871.600 | 0.9 | 3.431 | -3129.303 | 1.7 |
| 0.80 | 2.532 | -2836.138 | 1.7 | 3.140 | -2942.713 | 1.4 |
| 0.90 | 3.555 | -3125.409 | 2.5 | 3.468 | -2976.642 | 2.7 |
| 1.00 | 4.746 | -3634.290 | 1.2 | 2.856 | -2834.809 | 2.6 |
| Overall *MRD*% | | | 2.2 | | | 2.1 |

**Table 4.** Parameters Calculated for the Jouyban-Acree, and Jouyban-Acree-van't Hoff Model for CZP Solubility in Two Binary Mixtures of (2-Propanol + Water) and (1-Propanol + Water)

| | Jouyban-Acree | | Jouyban-Acree-van't Hoff | |
|---|---|---|---|---|
| 2-Propanol + water | $J_0$ | 3033.297 | $A_1$ | 4.746 |
| | $J_1$ | 370.640 | $B_1$ | -3634.290 |
| | $J_2$ | 0[a] | $A_2$ | -1.432 |
| | | | $B_2$ | -3736.692 |
| | | | $J_0$ | 3032.730 |
| | | | $J_1$ | 370.729 |
| | | | $J_2$ | 0[a] |
| *MRD%* | | 11.2 | | 11.0 |
| | Jouyban-Acree | | Jouyban-Acree-van't Hoff | |
| 1-Propanol + water | $J_0$ | 2986.392 | $A_1$ | 2.856 |
| | $J_1$ | -736.079 | $B_1$ | -2834.809 |
| | $J_2$ | 0[a] | $A_2$ | -1.407 |
| | | | $B_2$ | -3744.354 |
| | | | $J_0$ | 2986.272 |
| | | | $J_1$ | -735.322 |
| | | | $J_2$ | 0[a] |
| *MRD*% | | 9.8 | | 10.2 |

[a]Not statistically significant ($p$-value > 0.05).

**Table 5.** The MRS Model Constants at the Investigated Temperatures and the *MRD*% for Back-calculated CZP Solubility in Two Binary Mixtures of (2-Propanol + Water) and (1-Propanol + Water)

| Binary system | $T$ (K) | $\beta_1$ | $\beta_2$ | $\beta_3$ | $\beta_4$ | $\beta_5$ | *MRD*% |
|---|---|---|---|---|---|---|---|
| 2-Propanol + water | 293.2 | -7.694 | -15.632 | -0.021 | 0[a] | 13.114 | 8.7 |
| | 298.2 | -7.439 | -14.862 | 0.011 | 0[a] | 11.719 | 8.0 |
| | 303.2 | -6.922 | -14.155 | -0.008 | 0[a] | 10.216 | 6.4 |
| | 308.2 | -7.047 | -13.908 | 0[a] | 0[a] | 10.864 | 8.6 |
| | 313.2 | -6.888 | -13.709 | 0[a] | 0[a] | 10.735 | 8.3 |
| | Overall *MRD*% | | | | | | 8.0 |
| 1-Propanol + water | 293.2 | -7.006 | -14.568 | 0[a] | 0[a] | 10.803 | 13.4 |
| | 298.2 | -6.814 | -14.125 | 0[a] | 0[a] | 10.455 | 13.2 |
| | 303.2 | -6.708 | -13.973 | 0[a] | 0[a] | 10.792 | 16.2 |
| | 308.2 | -6.397 | -13.167 | -0.015 | 0[a] | 9.263 | 12.1 |
| | 313.2 | -6.449 | -13.533 | 0[a] | 0[a] | 10.763 | 16.7 |
| | Overall *MRD*% | | | | | | 14.3 |

[a]Not statistically significant ($p$-value > 0.05).

**Table 6.** The modified Wilson Model Parameters at the Investigated Temperatures and the *MRD*% for Back-calculated CZP Solubility in Two Binary Mixtures of (2-Propanol + Water) and (1-Propanol + Water)

| *T* (K) | 2-Propanol + water | | | 1-Propanol + water | | |
|---|---|---|---|---|---|---|
| | $\lambda_{12}$ | $\lambda_{21}$ | *MRD*% | $\lambda_{12}$ | $\lambda_{21}$ | *MRD*% |
| 293.2 | 2.768 | 1.300 | 13.8 | 1.568 | 1.716 | 10.9 |
| 298.2 | 2.514 | 1.368 | 8.9 | 1.337 | 1.885 | 7.7 |
| 303.2 | 2.348 | 1.493 | 7.5 | 1.331 | 1.973 | 7.5 |
| 308.2 | 2.036 | 1.628 | 7.2 | 1.241 | 2.062 | 8.2 |
| 313.2 | 1.991 | 1.631 | 7.1 | 1.335 | 2.008 | 8.6 |
| Overall *MRD*% | | | 8.9 | | | 8.6 |

The density of the CZP-saturated solutions in both binary mixtures was determined (Table 7). This information was essential for transforming the molar concentration of CZP to the mole fraction solubility. By considering the density, the solubility values were accurately represented in terms of the mole fraction, which provides a more comprehensive understanding of the solubility behavior of CZP in the binary solvent systems. This additional step further strengthens the reliability and validity of the experimental findings and facilitates the comparison and interpretation of the results in the context of other studies and theoretical models.

The density as another physicochemical property was also shown as a mathematical equation. For this purpose, the Jouyban-Acree model was correlated using the density data reported in Table 7 and the trained model was given the following equation.

$$\ln\rho_{m,T} = w_1\ln\rho_{1,T} + w_2\ln\rho_{2,T} + 31.258\frac{w_1.w_2}{T} \quad (11)$$

$$\ln\rho_{m,T} = w_1\ln\rho_{1,T} + w_2\ln\rho_{2,T} + 14.581\frac{w_1.w_2}{T} - 6.068\frac{w_1.w_2\,(w_1-w_2)}{T} + 7.326\ \frac{w_1.w_2\,(w_1-w_2)^2}{T} \quad (12)$$

Equations (11) and (12) were the trained models for density data of CZP saturated solutions in two binary mixtures of (2-propanol + water) and (1-propanol+ water), respectively. The *MRD*% for back-calculated data were 0.3 and 0.1% for Eqs. (11) and (12) demonstrate a strong capability of the Jouyban-Acree model in predicting density values.

## Apparent Thermodynamic Properties of CZP Dissolution

Table 8 presents the apparent thermodynamic functions of the solubilization of CZP in both examined binary mixtures at $T_{hm}$ = 303.0 K. These functions include $\Delta G°$, $\Delta H°$, $\Delta S°$, $T\Delta S°$, $\zeta_H$, and $\zeta_{TS}$. The positive values of $\Delta G°$ indicate the non-spontaneity of the dissolution, while the positive values of $\Delta H°$ suggest an endothermic process where heat is absorbed during dissolution. Additionally, the positive values of $\Delta S°$ (except for $w_1$ = 0) indicate an increase in entropy, and the positive values of $T\Delta S°$ highlight the favorable contribution of entropy to the dissolution. Therefore, based on these thermodynamic parameters, it is obvious that the dissolution of CZP in the (2-propanol + water) and (1-propanol + water) mixtures is favorable by decreasing positive $\Delta G°$, driven by an increase in entropy, and accompanied by the absorption of heat.

## Enthalpy-entropy Compensation Analysis

The phenomenon known as enthalpy-entropy compensation has been employed to elucidate the relationship between the changes in $\Delta H°$ and $\Delta S°$ observed in a series of related reactions. These reactions are primarily influenced by alterations in water solvation [21]. Enthalpy-entropy compensation refers to the phenomenon where an increase in entropy is counterbalanced by a concurrent reduction in enthalpy [22]. The compensation effect leads to a linear correlation between enthalpy and entropy when changes in solubility occur due to variations in cosolvent

**Table 7.** Measured Density (g cm$^{-3}$) of CZP Saturated Solutions in Two Binary Mixtures of (2-Propanol + Water) and (1-Propanol+ Water) at Different Temperatures

| $w_1$ | 293.2 K | 298.2 K | 303.2 K | 308.2 K | 313.2 K |
|---|---|---|---|---|---|
| 2-Propanol + water | | | | | |
| 0.00 | 1.013 ±0.003 | 1.004 ±0.003 | 1.002 ±0.003 | 0.999 ±0.001 | 0.997 ±0.003 |
| 0.10 | 1.002 ±0.001 | 0.999 ±0.002 | 0.988 ±0.001 | 0.979 ±0.001 | 0.976 ±0.001 |
| 0.20 | 0.988 ±0.001 | 0.983 ±0.001 | 0.973 ±0.001 | 0.964 ±0.001 | 0.962 ±0.001 |
| 0.30 | 0.968 ±0.002 | 0.966 ±0.001 | 0.955 ±0.001 | 0.946 ±0.002 | 0.942 ±0.001 |
| 0.40 | 0.944 ±0.001 | 0.943 ±0.001 | 0.931 ±0.002 | 0.922 ±0.001 | 0.920 ±0.002 |
| 0.50 | 0.923 ±0.003 | 0.919 ±0.002 | 0.908 ±0.001 | 0.899 ±0.001 | 0.898 ±0.001 |
| 0.60 | 0.898 ±0.001 | 0.896 ±0.001 | 0.884 ±0.003 | 0.875 ±0.001 | 0.873 ±0.001 |
| 0.70 | 0.876 ±0.002 | 0.873 ±0.001 | 0.861 ±0.001 | 0.853 ±0.001 | 0.848 ±0.001 |
| 0.80 | 0.853 ±0.001 | 0.848 ±0.002 | 0.837 ±0.001 | 0.829 ±0.002 | 0.826 ±0.002 |
| 0.90 | 0.828 ±0.002 | 0.824 ±0.001 | 0.813 ±0.001 | 0.805 ±0.001 | 0.801 ±0.001 |
| 1.00 | 0.795 ±0.002 | 0.791 ±0.001 | 0.785 ±0.001 | 0.779 ±0.001 | 0.775 ±0.002 |
| 1-Propanol + water | | | | | |
| 0.00 | 1.013 ±0.003 | 1.004 ±0.003 | 1.002 ±0.001 | 0.999 ±0.001 | 0.997 ±0.003 |
| 0.10 | 0.998 ±0.001 | 0.991 ±0.001 | 0.990 ±0.001 | 0.984 ±0.004 | 0.977 ±0.001 |
| 0.20 | 0.987 ±0.001 | 0.979 ±0.001 | 0.974 ±0.001 | 0.971 ±0.003 | 0.965 ±0.001 |
| 0.30 | 0.966 ±0.001 | 0.961 ±0.001 | 0.956 ±0.001 | 0.952 ±0.004 | 0.945 ±0.001 |
| 0.40 | 0.947 ±0.001 | 0.941 ±0.001 | 0.936 ±0.001 | 0.933 ±0.003 | 0.926 ±0.001 |
| 0.50 | 0.926 ±0.003 | 0.920 ±0.001 | 0.917 ±0.001 | 0.912 ±0.002 | 0.905 ±0.001 |
| 0.60 | 0.905 ±0.001 | 0.900 ±0.001 | 0.896 ±0.001 | 0.893 ±0.003 | 0.885 ±0.001 |
| 0.70 | 0.884 ±0.004 | 0.881 ±0.001 | 0.877 ±0.001 | 0.873 ±0.002 | 0.866 ±0.001 |
| 0.80 | 0.868 ±0.001 | 0.862 ±0.001 | 0.858 ±0.001 | 0.856 ±0.003 | 0.849 ±0.001 |
| 0.90 | 0.846 ±0.002 | 0.841 ±0.001 | 0.836 ±0.001 | 0.835 ±0.004 | 0.828 ±0.001 |
| 1.00 | 0.825 ±0.001 | 0.820 ±0.001 | 0.817 ±0.001 | 0.814 ±0.002 | 0.807 ±0.004 |

composition. In other words, an unfavorable change in enthalpy is offset by a favorable change in entropy, allowing the process to proceed. The analysis of enthalpy-entropy compensation offers a valuable approach to understanding and explaining interaction mechanisms [23]. By examining the thermodynamic consequences of molecular interactions between solutes and solvents, particularly the formation of hydrogen bonds, it becomes possible to gain insights into these processes [24,25]. There are two graphical models commonly used to evaluate enthalpy-entropy compensation [26]: (i) plotting $\Delta H°$ against $\Delta G°$, where negative slopes in the linear relationship suggest that the driving force is primarily entropic, while positive slopes indicate that the driving force is enthalpic, and (ii) plotting $\Delta H°$ against $T\Delta S°$, where slopes > 1.0 show enthalpy driving and < 1.0 display entropic driving. However, the validity of linear correlations between changes in $\Delta H°$ and changes in $\Delta S°$ has been questioned by Krug *et al.* [27] due to proportional errors in measurements of $\Delta H°$ and $\Delta S°$. Therefore, they suggested an alternative method of plotting $\Delta H°$ against changes in free energy $(\Delta G°)$ at an estimated temperature of $T_{hm}$ (the harmonic mean of the experimental temperature). This approach allows for uncorrelated errors in slope and intercept estimation.

Figure 4, which depicts the enthalpy-entropy compensation plots based on the $\Delta H°$ vs. $\Delta G°$ for the solubility of CZP in (2-propanol + water) and (1-propanol + water) mixtures at $T_{hm}$ = 303.0 K, provide insights into the

**Table 8.** Apparent Thermodynamic Functions of Dissolution of CZP in Two Binary Mixtures of (2-Propanol + Water) and (1-Propanol + Water) at $T_{hm}$ = 303.0 K

| $w_1$ | $\Delta G°$ (kJ mol$^{-1}$) | $\Delta H°$ (kJ mol$^{-1}$) | $\Delta S°$ (J K$^{-1}$ mol$^{-1}$) | $T\Delta S°$ (kJ mol$^{-1}$) | $\zeta_H$ | $\zeta_{TS}$ |
|---|---|---|---|---|---|---|
| 2-Propanol + water | | | | | | |
| 0.00 | 34.68 | 31.07 | -11.91 | -3.61 | 0.896 | 0.104 |
| 0.10 | 31.28 | 43.65 | 40.81 | 12.37 | 0.779 | 0.221 |
| 0.20 | 27.89 | 57.66 | 98.25 | 29.77 | 0.659 | 0.341 |
| 0.30 | 24.46 | 41.96 | 57.77 | 17.50 | 0.706 | 0.294 |
| 0.40 | 21.77 | 30.47 | 28.73 | 8.71 | 0.778 | 0.222 |
| 0.50 | 20.21 | 27.47 | 23.96 | 7.26 | 0.791 | 0.209 |
| 0.60 | 18.90 | 24.62 | 18.86 | 5.72 | 0.812 | 0.188 |
| 0.70 | 17.86 | 23.88 | 19.86 | 6.02 | 0.799 | 0.201 |
| 0.80 | 17.20 | 23.58 | 21.05 | 6.38 | 0.787 | 0.213 |
| 0.90 | 17.03 | 25.98 | 29.56 | 8.96 | 0.744 | 0.256 |
| 1.00 | 18.26 | 30.22 | 39.46 | 11.96 | 0.717 | 0.283 |
| 1-Propanol + water | | | | | | |
| 0.00 | 34.68 | 31.07 | -11.91 | -3.61 | 0.896 | 0.104 |
| 0.10 | 30.59 | 42.09 | 37.95 | 11.50 | 0.785 | 0.215 |
| 0.20 | 26.57 | 38.50 | 39.36 | 11.93 | 0.763 | 0.237 |
| 0.30 | 22.97 | 35.62 | 41.75 | 12.65 | 0.738 | 0.262 |
| 0.40 | 20.92 | 32.29 | 37.55 | 11.38 | 0.739 | 0.261 |
| 0.50 | 19.43 | 28.82 | 31.00 | 9.39 | 0.754 | 0.246 |
| 0.60 | 18.30 | 24.70 | 21.15 | 6.41 | 0.794 | 0.206 |
| 0.70 | 17.37 | 26.13 | 28.90 | 8.76 | 0.749 | 0.251 |
| 0.80 | 16.56 | 24.37 | 25.81 | 7.82 | 0.757 | 0.243 |
| 0.90 | 16.01 | 24.63 | 28.47 | 8.63 | 0.741 | 0.259 |
| 1.00 | 16.37 | 23.69 | 24.15 | 7.32 | 0.764 | 0.236 |

contributions of $\Delta S°$ and enthalpy $\Delta H°$ to the dissolution process. In Fig. 4, for the (2-propanol + water) mixture, we can observe a general positive slope if a correlation line between all data points is plotted which indicates enthalpy driven process, while local negative slopes from mass fractions of 0.0-0.2 and 0.8-0.9 can be observed which implies the solubility enhancement is entropy driven. Similarly, a general positive slope in Fig. 4 for the (1-propanol + water) mixture can be observed which shows enthalpy is the main contributor to solubility progression. There are negative slopes from 0.0-0.1 and 0.6-0.7, and at these points, the solubility is driven by entropy. The enthalpy-entropy compensation phenomenon suggests that in these binary solvent mixtures, changes in enthalpy and entropy are interconnected and tend to compensate for each other. The increase in $\Delta H°$ during dissolution is offset by a corresponding increase in $\Delta S°$, resulting in a linear relationship between both of them. The dimensionless factors $\zeta_H$ and $\zeta_{TS}$, mentioned in Table 8, quantitatively reflect the contributions of enthalpy and entropy to the dissolution process. A higher value of $\zeta_H$ indicates a greater enthalpic contribution, while a higher value of $\zeta_{TS}$ indicates a stronger entropy-driven dissolution. Therefore, based on the enthalpy-entropy compensation plots, it can be inferred that both

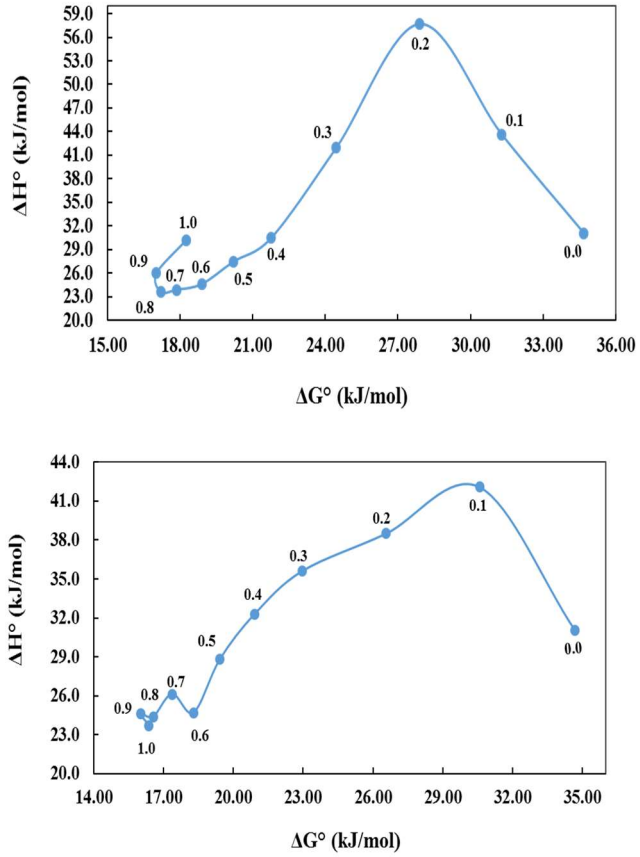


**Fig. 4.** Enthalpy-entropy compensation plot for the solubility of CZP at $T_{hm}$ = 303.0 K in Top: (2-Propanol + water). Bottom: (1-Propanol + water). The solid points correspond to the mass fraction of organic solvent in the binary solvent mixtures (before the addition of CZP).

entropy and enthalpy play significant roles in the dissolution process of CZP in the (2-propanol + water) and (1-propanol + water) mixtures.

## Preferential Solvation of CZP

The parameters for preferential solvation of CZP (referred to as compound 3) by 2-propanol (or 1-propanol) molecules (identified here as compound 1) in various {cosolvent (1) + water (2)} mixtures ($\delta x_{1,3}$), are characterized as follows [28,29]:

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \tag{13}$$

In the given context, $x_{1,3}^{L}$ is the local mole fraction of 2-propanol (or 1-propanol) within the molecular environment of CZP, while $x_1$ represents the bulk mole fraction of 2-propanol (or 1-propanol) in the initial {cosolvent (1) + water (2)} binary solvent mixture without CZP present. Thus, if $\delta x_{1,3} > 0$ CZP molecules are preferentially solvated by 2-propanol (or 1-propanol) molecules in the respective dissolution. Oppositely, when $\delta x_{1,3} < 0$, CZP molecules exhibit preferential solvation by water molecules. The $\delta x_{1,3}$ values were derived from the inverse Kirkwood-Buff integrals (IKBI) as previously described [28,29]:

$$\delta x_{1,3} = \frac{x_1 x_2 \left(G_{1,3} - G_{2,3}\right)}{x_1 G_{1,3} + x_2 G_{2,3} + V_{\text{cor}}} \tag{14}$$

with,

$$G_{1,3} = RT\kappa_T - \overline{V}_3 + x_2 \overline{V}_2 \left(\frac{D}{Q}\right) \tag{15}$$

$$G_{2,3} = RT\kappa_T - \overline{V}_3 + x_1 \overline{V}_1 \left(\frac{D}{Q}\right) \tag{16}$$

$$V_{\text{cor}} = 2522.5\left(r_3 + 0.1363\left(x_{1,3}^{L}\overline{V}_1 + x_{2,3}^{L}\overline{V}_2\right)^{1/3} - 0.085\right)^3 \tag{17}$$

where $\kappa_T$ denotes the isothermal compressibility of the aqueous-2-propanol (or 1-propanol) mixtures. In the dissolution process, $\overline{V}_1$ represents the partial molar volume of 2-propanol (or 1-propanol), $\overline{V}_2$ represents the partial molar volume of water, and $\overline{V}_3$ represents the partial molar volume of CZP. The value of the function $D$ is determined by applying Eq. (18), which incorporates the Gibbs energies associated with the transfer of CZP from water to the mixtures of aqueous-cosolvent. The function $Q$ is calculated as defined in Eq. (19) involves the excess Gibbs energy of mixing of 2-propanol (or 1-propanol) and water. $V_{\text{cor}}$ represents the correlation volume, while $r_3$ corresponds to the molecular radius of CZP. In this case, the approximate calculation of $r_3$ was performed using Eq. (20), where $N_{\text{Av}}$

represents the Avogadro number.

$$D = \left( \frac{\partial \Delta_{tr} G^{o}_{3,2\rightarrow 1+2}}{\partial x_1} \right)_{T,p} \quad (18)$$

$$Q = RT + x_1 x_2 \left( \frac{\partial^2 G^{Exc}_{1+2}}{\partial x_2^2} \right)_{T,p} \quad (19)$$

$$r_3 = \left( \frac{3 \cdot 10^{21} V_3}{4\pi N_{Av}} \right)^{1/3} \quad (20)$$

$V_{cor}$ values are obtained after iteration processes due to their dependency on the local mole fractions of 2-propanol (or 1-propanol) and water in the vicinity of the CZP molecules. Therefore, these iterative processes involved substituting $\delta x_{1,3}$ and $V_{cor}$ into Eqs. (13), (14), and (17) to recompute the $x^L_{1,3}$ values, repeating the calculations until constant values of $V_{cor}$ were achieved.

Figure 5 illustrates the apparent Gibbs energies of transfer of CZP from neat water to aqueous-2-propanol (or 1-propanol) mixtures ($\Delta_{tr} G^{o}_{3,2\rightarrow 1+2}$) at 298.2 K. The values of $\Delta_{tr} G^{o}_{3,2\rightarrow 1+2}$ were determined using the following equation based on the mole fraction solubility data presented in Table 1:

$$\Delta_{tr} G^{o}_{3,2\rightarrow 1+2} = RT \ln \left( \frac{x_{3,2}}{x_{3,1+2}} \right) \quad (21)$$

Obtained $\Delta_{tr} G^{o}_{3,2\rightarrow 1+2}$ values were correlated by means of the quotient polynomial shown as Eqs. (22) and (23) for (2-propanol + water) and (1-propanol + water) systems, respectively. The statistical parameters obtained for Eq. (22) were: adjusted $r^2 = 0.997$, typical error = 0.330, and $F = 1124$, whereas for Eq. (23) were: adjusted $r^2 = 0.997$, typical error = 0.327, and $F = 1192$.

$$\Delta_{tr} G^{o}_{3,2\rightarrow 1+2} = \frac{0.186 - 123.388 x_1}{1 + 3.705 x_1 + 2.943 x_1^2} \quad (22)$$

$$\Delta_{tr} G^{o}_{3,2\rightarrow 1+2} = \frac{0.201 - 178.034 x_1}{1 + 7.169 x_1 + 1.672 x_1^2} \quad (23)$$

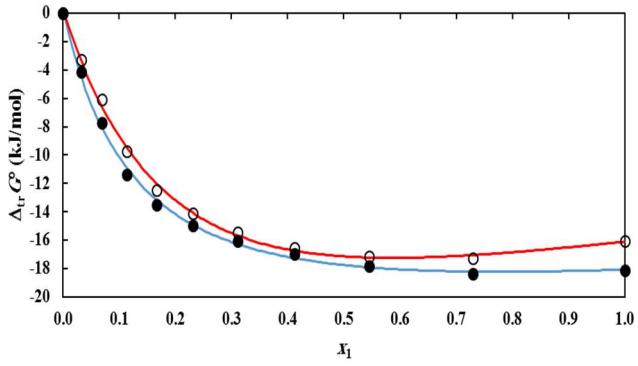


**Fig. 5.** Gibbs energy of transfer of CZP (3) from neat water (2) to {cosolvent (1) + water (2)} mixtures at 298.2 K. ○: (2-Propanol + water); ●: (1-Propanol + water).

The $D$ values presented in Table 9 were computed as the first derivatives of Eqs. (22) and (23) when solved using composition steps of $x_1 = 0.05$. In the investigated mixtures of water and 2-propanol (or 1-propanol), the $Q$, $RT\kappa_T$, $\overline{V}_1$ and $\overline{V}_2$ values at 298.2 K were taken from [30]. Otherwise, the $\overline{V}_3$ value for CZP was assumed to be identical to the one computed using the Fedors method, namely 182.9 $cm^3 \cdot mol^{-1}$ (as shown in Table 2). Moreover, the CZP $r_3$ value was computed as 0.417 nm. Furthermore, at 298.2 K, Table 9 provides a comprehensive overview of the preferential solvation parameters of CZP by 2-propanol (or 1-propanol) molecules, denoted as $\delta x_{1,3}$.

In Fig. 6, the $\delta x_{1,3}$ values of CZP exhibit a nonlinear trend with respect to the proportion of 2-propanol (or 1-propanol) in the solvent mixtures, as indicated by the mole fraction of 2-propanol (or 1-propanol) prior to the addition of the solute. Initially, when 2-propanol (or 1-propanol) is added to neat water as the solvent, the $\delta x_{1,3}$ values of CZP become negative within the composition range of $0.00 < x_1 < 0.19$. The most significant negative $\delta x_{1,3}$ values were achieved in the mixture with a composition of $x_1 = 0.05$. In 2-propanol mixtures, the corresponding $\delta x_{1,3}$ value reached $-4.67 \times 10^{-2}$, while in 1-propanol mixtures, it reached $-4.27 \times 10^{-2}$. Absolute values of these parameters are higher than $1.0 \times 10^{-2}$ and therefore, $\delta x_{1,3}$ values are regarded as consequences of realistic preferential solvation effects instead of being merely consequences of uncertainties propagation in IKBI analyses

**Table 9.** Some Properties Associated with Preferential Solvation of CZP (3) in some {Cosolvent (1) + Water (2)} Mixtures at 298.2 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 $\delta x_{1,3}$ |
|---|---|---|---|---|---|
| 2-Propanol + water | | | | | |
| 0.00 | -124.08 | -1083.0 | -181.8 | 826 | 0.00 |
| 0.05 | -86.64 | -797.8 | -311.7 | 830 | -4.67 |
| 0.10 | -61.51 | -620.0 | -379.9 | 896 | -4.39 |
| 0.15 | -44.12 | -503.5 | -416.4 | 985 | -2.00 |
| 0.20 | -31.77 | -424.0 | -436.2 | 1071 | 0.31 |
| 0.25 | -22.83 | -367.6 | -446.5 | 1148 | 2.05 |
| 0.30 | -16.24 | -326.3 | -451.0 | 1218 | 3.26 |
| 0.35 | -11.33 | -294.6 | -450.6 | 1282 | 4.01 |
| 0.40 | -7.62 | -268.8 | -443.4 | 1341 | 4.33 |
| 0.45 | -4.79 | -246.1 | -423.7 | 1393 | 4.19 |
| 0.50 | -2.63 | -223.6 | -378.4 | 1439 | 3.40 |
| 0.55 | -0.96 | -199.0 | -285.9 | 1474 | 1.74 |
| 0.60 | 0.33 | -173.7 | -132.8 | 1501 | -0.73 |
| 0.65 | 1.32 | -156.0 | 34.9 | 1529 | -3.02 |
| 0.70 | 2.09 | -152.9 | 126.4 | 1572 | -3.90 |
| 0.75 | 2.69 | -158.8 | 128.2 | 1628 | -3.49 |
| 0.80 | 3.14 | -166.1 | 88.9 | 1688 | -2.59 |
| 0.85 | 3.49 | -171.8 | 43.5 | 1747 | -1.71 |
| 0.90 | 3.75 | -175.6 | 3.7 | 1804 | -0.98 |
| 0.95 | 3.93 | -178.0 | -28.2 | 1858 | -0.42 |
| 1.00 | 4.07 | -179.6 | -53.4 | 1911 | 0.00 |
| 1-Propanol + water | | | | | |
| 0.00 | -179.47 | -1490.3 | -181.8 | 828 | 0.00 |
| 0.05 | -96.28 | -760.9 | -303.8 | 835 | -4.27 |
| 0.10 | -58.75 | -532.1 | -339.1 | 911 | -3.14 |
| 0.15 | -38.72 | -436.3 | -365.1 | 991 | -1.48 |
| 0.20 | -26.82 | -391.8 | -398.3 | 1067 | 0.15 |
| 0.25 | -19.19 | -371.8 | -445.7 | 1144 | 1.93 |
| 0.30 | -14.03 | -363.7 | -510.1 | 1222 | 4.07 |
| 0.35 | -10.39 | -356.2 | -581.3 | 1300 | 6.42 |
| 0.40 | -7.73 | -335.5 | -622.4 | 1369 | 7.99 |
| 0.45 | -5.74 | -297.2 | -592.3 | 1418 | 7.62 |
| 0.50 | -4.21 | -256.0 | -508.3 | 1452 | 5.90 |
| 0.55 | -3.03 | -225.5 | -420.7 | 1485 | 4.12 |
| 0.60 | -2.09 | -206.8 | -353.0 | 1522 | 2.79 |
| 0.65 | -1.34 | -195.7 | -303.8 | 1563 | 1.85 |
| 0.70 | -0.73 | -188.7 | -263.8 | 1605 | 1.13 |
| 0.75 | -0.23 | -183.5 | -218.0 | 1648 | 0.44 |
| 0.80 | 0.17 | -178.4 | -140.3 | 1688 | -0.40 |
| 0.85 | 0.51 | -175.5 | -52.2 | 1731 | -1.00 |
| 0.90 | 0.79 | -177.8 | -70.3 | 1782 | -0.60 |
| 0.95 | 1.02 | -179.7 | -116.6 | 1833 | -0.18 |
| 1.00 | 1.21 | -180.4 | -143.6 | 1882 | 0.00 |

[a] $x_1$ is the mole fraction of cosolvent (1) in the {cosolvent (1) + water (2)} mixtures free of CZP (3).

[31,32]. Thus, this result could be considered as a consequence of the preferential hydration of CZP. The negative values of $\delta x_{1,3}$ can be attributed to the potential involvement of structured water molecules surrounding the aromatic groups (as depicted in Fig. 1) through hydrophobic hydration. This hydrophobic hydration effect is believed to play a significant role in reducing $\delta x_{1,3}$ to negative values.

In the mixtures composition interval of $0.19 < x_1 < 0.58$ for 2-propanol mixtures and $0.19 < x_1 < 0.77$ for 1-propanol mixtures the local mole fractions of 2-propanol (or 1-propanol) around CZP molecules are higher than those in the bulk aqueous-cosolvent mixtures. The highest positive $\delta x_{1,3}$ values are observed in the mixture with a composition of $x_1 = 0.40$ with $\delta x_{1,3} = 4.33 \times 10^{-2}$ for 2-propanol mixtures and $\delta x_{1,3} = 7.99 \times 10^{-2}$ for 1-propanol mixtures, being these values are also greater than $|1.0 \times 10^{-2}|$. Therefore, these maximum positive values can be attributed to the preferential solvation effects of CZP by 2-propanol (or 1-propanol) molecules within this range of mixture compositions, CZP exhibits characteristics of a Lewis acid in front of 2-propanol (or 1-propanol) molecules by means of its cyclic amide groups, whose hydrogen atom would potentially interact with the lone pairs of electrons of the oxygen atoms of 2-propanol (or 1-propanol) by establishing hydrogen bonding. It is crucial to note that both 2-propanol and 1-propanol demonstrate a higher tendency to act as Lewis bases compared to water. This behavior is supported by their hydrogen bond acceptor parameters, $\beta$, which are 0.84 for 2-propanol, 0.90 for 1-propanol, and 0.47 for water [33].

Finally, in the intervals of $0.58 < x_1 < 1.00$ for 2-propanol mixtures and $0.77 < x_1 < 1.00$ for 1-propanol mixtures $\delta x_{1,3}$ values are negative again, indicating preferential solvation of CZP by water molecules. The most significant negative $\delta x_{1,3}$ values were observed in the mixture with a composition of $x_1 = 0.85$ with $\delta x_{1,3} = -1.00 \times 10^{-2}$ for 1-propanol and $x_1 = 0.70$ with $\delta x_{1,3} = -3.90 \times 10^{-2}$ for 2-propanol mixtures. In these cosolvent-rich mixtures, where CZP is predominantly solvated by water, the drug is likely to act primarily as a Lewis base towards water molecules. This can be attributed to the fact that water exhibits a higher Lewis acidic behavior compared to both alcohols. This difference in Lewis acidity is characterized by their Kamlet-Taft hydrogen bond donor parameters, α, with water having a value of 1.17, while 1-propanol and 2-propanol have values of 0.84 and 0.76, respectively [33]. It is conjecturable that better solubilizing power of 1-propanol mixtures regarding 2-propanol mixtures could also be associated with better preferential solvation of CZP by 1-propanol in terms of its higher positive $\delta x_{1,3}$ magnitude and higher composition interval of preferential solvation by this cosolvent.

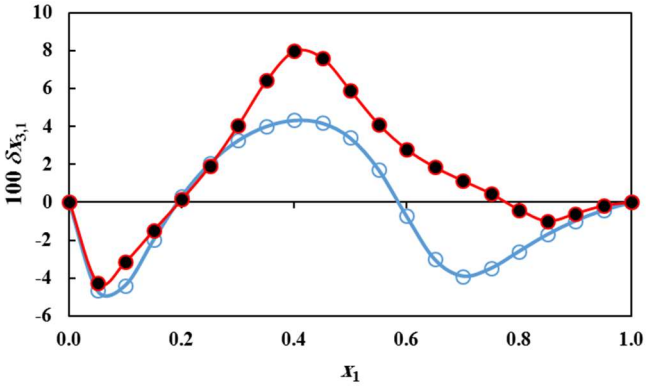


**Fig. 6.** Preferential solvation parameters ($\delta x_{1,3}$) of CZP (3) by cosolvent in some {cosolvent (1) + water (2)} mixtures at 298.2 K. ○: (2-Propanol + water); ●: (1-Propanol + water).

## CONCLUSION

In this study, we investigated the solubility and thermodynamics of CZP in binary solvent mixtures of (1-propanol + water) and (2-propanol + water) over a range of temperatures. Our findings revealed that both (2-propanol + water) and (1-propanol + water) mixtures exhibited enhanced solubility of CZP compared to neat water. Moreover, the solubility of CZP increased with increasing alcohol concentration and temperature in both solvent systems. The mathematical models employed in this study, including the van't Hoff, Jouyban-Acree, MRS, Jouyban-Acree-van't Hoff, and modified Wilson models, provided accurate predictions of CZP solubility in the studied binary solvent mixtures. These models can be valuable tools for estimating CZP solubility in other solvent systems and for calculating relevant thermodynamic parameters. Thermodynamic analysis indicated that the dissolution of CZP in the studied solvent mixtures was an endothermic process, suggesting an increased energy requirement for CZP to dissolve in these

systems. This knowledge can aid in the design and optimization of CZP-based drug formulations, as it provides insights into the solubility behavior and thermodynamic characteristics of CZP. Notably, our results demonstrated that (1-propanol + water) mixtures exhibited higher solubilizing power for CZP compared to (2-propanol + water) mixtures at all temperatures studied. This finding suggests that (1-propanol + water) mixtures could be particularly advantageous for enhancing the solubility of CZP and potentially improving its bioavailability in oral drug formulations.

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