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Experimental measurement, thermodynamic analysis, and mathematical modeling for budesonide solubility in 1-propanol + water mixtures at $T = (293.2$ to $313.2)$ K

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Abstract

Budesonide (BDS) a steroid-based anti-inflammatory drug widely prescribed for various diseases, has a low aqueous solubility. In this study, we investigated cosolvency approach to study the thermodynamic specifications related to the solubility of BDS at the temperature range of 293.2–313.2 K in (1-propanol + water) mixtures applying the shaking flask method. The predictive power of different mathematical models for experimental data in the cosolvency systems was evaluated. For this purpose, the linear and nonlinear mathematical equations such as van't Hoff model (as a linear model), Buchowski-Ksiazczak equation (as a non-linear), CNIBS/R–K and MRS models (as a linear model for solvent composition at an isothermal condition), modified Wilson model (as a non-linear model for isothermal condition), the Jouyban-Acree model (as a model that considers temperature and solvent composition), and Jouyban-Acree-van't Hoff model (as a model with no further input data) were studied. Also, the Williams-Amidon excess Gibbs energy model was investigated. In addition, the related apparent thermodynamics of the BDS dissolution process in the desired temperature such as Gibbs free energy, enthalpy, and entropy, were computed by the corresponding equations. Moreover, based on the inverse Kirkwood-Buff integrals, it is demonstrated that BDS is preferentially solvated by water in water-rich mixtures. The accuracy of the fitness was evaluated with mean relative deviations (*MRDs%*) for back-calculated molar BDS solubility data. The result showed that the maximum solubility of BDS was obtained at 0.7 mass fraction of 1-propanol at all temperatures. Thermodynamic studies demonstrated that BDS dissolution procedures were obtained as endothermic and entropy-driven in almost all cases. The overall *MRDs%* values for the back-computed BDS solubility in the aqueous mixture of 1-propanol based on van't Hoff model, Buchowski-Ksiazczak equation, CNIBS/R–K model, modified Wilson model, Jouyban-Acree model, Jouyban-Acree-van't Hoff model, MRS model, and Williams-Amidon excess Gibbs energy model were found 1.93%, 1.80%, 11.68%, 33.32%, 12.30%, 9.24%, 10.70%, and 6.57%, respectively.

Highlights

- Study of BDS solubility profile in 1-propanol + water mixtures at 293.2 -313.2 K
- Prediction solubility with two Jouyban-Acree models: Jouyban-Acree equation and

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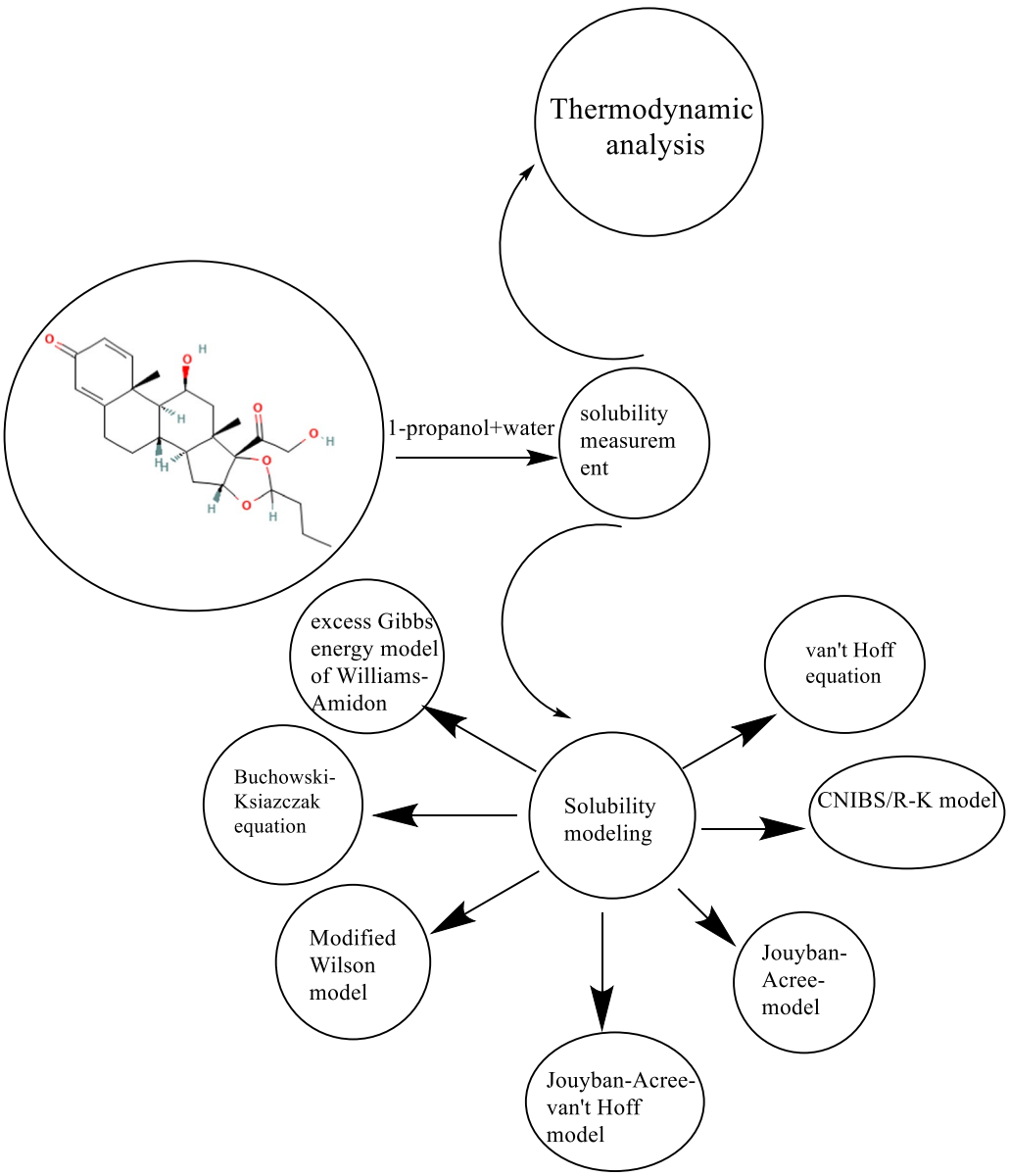
- Jouyban-Acree-van't Hoff model
- Representation of BDS solubility data with some linear and nonlinear cosolvency models
- Utilize the van't Hoff and Gibbs equations to compute thermodynamic parameters

Keywords Solubility, Budesonide, 1-Propanol, Cosolvency, Thermodynamics, Aqueous mixtures

Graphical Abstract



Introduction

Budesonide (BDS) is a synthetic corticosteroid obtained by modifying prednisolone through the addition of acetyl group at the 16α and 17α positions. These changes have turned the compound into a potent corticosteroid drug [1]. For this crystalline solid with a

molecular weight of 430.5 g/mol, log *P* was reported 1.9 [2]. Also, aqueous solubility of this drug was obtained at 0.045 mg/mL. It should be noted that high hepatic first-pass effect (80–90%) and plasma clearance (1.8–9 l/min) are the prominent features of this drug [3]. BDS in the rectal, nasal, respiratory, and oral dosage forms are widely used to treatment of allergic rhinitis (nasal), asthma (inhalation), emphysema, chronic bronchitis (inhalation), moderate crohn's disease (oral), ulcerative colitis (rectal), acute ulcerative proctitis (rectal), acute sinusitis, chronic rhinosinusitis (accompanied by inflammation of polyps), eosinophilic esophagitis, eosinophilic colitis, collagenous colitis, lymphocytic esophagitis, refractory celiac disease, primary biliary cholangitis, primary immunoglobulin a nephropathy, autoimmune hepatitis, croup, sarcoidosis and also for reducing bronchopulmonary dysplasia in very low birth weight babies [4–7]. COVID-19 as an important and serious disease for human society, since its outbreak can cause various symptoms in the patient including a dry and persistent cough, fever, fatigue, and lung involvement [2, 8]. Also, according to a meta-analysis study, COVID-19 can have side effects on various organs of the body, including the brain, liver, thyroid, heart, kidney, blood cells, gastrointestinal system, blood coagulation system, and skin [8]. Although vaccines have significantly reduced the spread of COVID-19, there have been limited treatment options to reduce the symptoms and effective treatment of COVID-19. Nevertheless, a strong response of the body's inflammatory system is observed in COVID-19.

Previous studies have shown that corticosteroids (such as BDS), reduce the body's inflammatory response. Also, they can be effective for the treatment, reduce the patient's symptoms, and prevent the progression of the disease [9]. A study conducted in 2021 presented that early administration of inhaled BDS minimizes the need for emergency medical care and can lead to faster recovery of COVID-19 patients [10]. Also, a clinical trial study in 2022 showed that the use of inhaled BDS along with oral fluvoxamine for COVID-19 patients decreases severe diseases and subsequently reduces the need for medical care [11]. According to the mentioned applications as well as COVID-19, investigating the physical and chemical characteristics of BDS can be extremely important.

The biopharmaceutics classification system (BCS) classified compounds based on aqueous solubility, dissolution, and rate of penetration in the intestinal environment [12]. Predictions based on this system can reduce the need for in vivo bioequivalence studies and save a lot of time and money in the development process of pharmaceutical formulations [13]. BDS in class II of BCS has low solubility and high permeability [12], so that insufficient amount of the this drug in the systemic blood circulation leads to poor bioavailability and a decrease in the drug effect at the site of drug action [14]. Due to liver biotransformation and high hepatic clearance, the oral bioavailability of BDS is about 10%. In other words, it may not show adequate therapeutic effect at physiological intestinal pH [15]. Wide applications of this drug in the treatment processes of various respiratory diseases such as asthma and COVID-19 can be limited by its physicochemical properties (such as solubility) [4, 10, 12]. It is necessary to mention that increasing the solubility of BDS can reduce the therapeutic dose and side effects. Also, increasing the bioavailability and reduce the variation in T_{max} (time to peak drug concentration in blood) and C_{max} (maximum blood concentration after administration of a drug) can be observed. It is necessary to mention, the low solubility of BDS may affect its therapeutic effect, systemic absorption, and mucociliary removal [16]. Therefore, increasing the BDS solubility can be very useful in solving the mentioned limitations. Also, increasing the BDS solubility is the first step to producing new formulations.

Drug solubility in pure solvents has an important role in the drug development process, new drug formulations, and analytical methods development [4, 17].

Increase in drug solubility depends on various factors such as polarity, type of solvent, dielectric constant, and pH. So, to select the most suitable solvent for drugs in industrial production, it is very important to consider factors affecting drugs solubility [18]. Various methods have been reported for increasing the solubility of poor soluble drugs in water, such as reduction of particle size, hydrotropic, nanofabrication, pH adjustment, supercritical fluid (SCF) process, sonocrystallization, complexation, solid dispersion, emulsifying systems, and cosolvency mixtures [19]**.** Among the mentioned methods, cosolvency is a common technique to increase the solubility of poorly soluble drugs in the field of pharmaceutical research [20].

The mechanism of the cosolvency method (adding some water-miscible solvent as a co-solvent) is as follows the cosolvent decreases the interfacial tension among the hydrophobic solute and the water. In other words, the cosolvent consists of two hydrophobic and hydrophilic parts, the hydrophobic part interacts with the solute that has low solubility, and the hydrophilic part interacts with the aqueous solvent [18]. So, with the balance created, increasing the solubility of drugs was observed.

The most important step in the cosolvency method is the choice of solvent [21, 22]. 1-Propanol (propyl alcohol) is miscible in water with properties such as colorless liquid, molecular weight of 60.10 g/mol, density of 0.803 mg/ml, and log *P* of 0.3. This solvent

mildly irritates the throat and eyes. On the other hand, it has wide applications in pharmaceutical production, cosmetics and hygiene industries, and the production of perfumery, antiseptic, and disinfectant agents [23]. Its miscibility with other polar solvents such as water and low toxicity are the salient features of this solvent. 1-Propanol has wide applications as a solvent especially for cellulose esters, resins, and disinfectants in the field of pharmaceutical research [24].

Previous studies have shown that experimental measurement of drug solubility had two basic limitations, such as low feasibility and time-consuming [25, 26]. Also, the high consumption of solvents in this process can be costly. To remove these restrictions, the drugs solubility prediction in the different mixtures of (cosolvents + water) with various mathematical models was introduced. There are various mathematical models for predicting the solubility of drugs at different temperatures and ratios of solvents [25]. Based on previous studies, the Jouyban-Acree model is one of the most appropriate equations with high precision and accuracy for the prediction solubility of different drugs [26]. Also, the use of this model and other combined models with the Jouyban-Acree model to predict the solubility of a wide range of drugs has been evaluated by our group [21, 26–29].

So far, BDS solubility has been investigated in the (i) aqueous mixtures of ethanol[30], *N*-methyl-2-pyrrolidone (NMP) [31], polyethylene glycol 400 (PEG-400) [2] and 2-propanol [4] and ii) some mono solvents such as ethyl acetate, acetone, n-hexane, carbon tetrachloride [32]. The most important limitation of previous studies is that some investigated solvents in high concentrations cause toxicity in the pharmaceutical formulations, limiting their practical applications. Also, the maximum amount of BDS solubility obtained is restricted in some cases and can be greatly improved. On the other hand, limited mathematical models have been used to predict BDS solubility. Finally, limited thermodynamic studies do not provide complete information on the dissolution process of BDS in solvent mixtures [33].

On the other hand, to extend the diversity of the existing experimental solubility data, find more efficient cosolvency systems compared to other methods of increasing solubility, complete thermodynamic studies, further investigate effective mechanisms in improving the solubility of BDS such as hydrogen bonding factors and solvent polarity, presenting the full predictive quantitative structure–property relationship (QSPR) equations to the solubility prediction of BDS, optimizing the solvent mixture ratio for BDS solubility, and reduction of experimental measurements of BDS solubility at laboratory and industrial scales, additional studies in the other solvent mixture are needed [34].

Up to the present, the solubility of various drugs including sulfamerazine, sulphadiazine, sulfamethazine, minoxidil, nisoldipine, clopidogrel hydrogen sulfate, pranlukast, oxcarbazepine, rebamipide, ribavirin, methimazole, candesartan, taltirelin, and carvedilol in binary mixed systems of 1-propanol has been investigated (for more details see Table 1S) [22, 35–44]. Alcohols are very important in the pharmaceutical industry because they have many uses as follows: having antimicrobial properties, astringent and cooling effects in topical products like gels, lotions, and creams, use in transdermal drug delivery to enhance the penetration of drugs through the skin and improving palatability in pediatric formulations [45–48]. 1-Propanol is one of the common alcohols used in the pharmaceutical industry. Also, water is the safest solvent for all pharmaceutical formulations and is used in nearly all liquid formulations. On the other hand, BDS, as a drug with low solubility in water, has many uses that are mentioned above. Due to the extensive applications of BDS, there is always a need to produce new formulations. For every new formulation, increasing the solubility in water is required. Among the various methods of improving the aqueous solubility of drugs, the cosolvency techniques have been more effective than others. Therefore, the aqueous cosolvent systems based on alcohol can be critical. Cosolvency systems can behave differently at different temperatures. Examining the thermodynamic behavior of BDS in cosolvent systems including alcohols at high and low temperatures can be very helpful. On the other hand, it is not possible to measure the solubility of BDS in all mass fractions of solvents and it will be very costly and time-consuming. Therefore, providing mathematical models for more accurate prediction of physicochemical properties at various temperatures in different stages of the pharmaceutical industry should be advantageous [49]. Also, these studies offer a complete perspective to find important and effective parameters in the solubility processes of BDS and predict the solubility of it and similar drugs in other alcoholic systems. It should be noted that the use of new alcohol to investigate the solubility of BDS, the use of linear and non-linear models for solubility prediction, and the comparison of the results obtained with previous works can be considered significant progress to complete the previous studies.

In the present study, we considered the BDS solubility in the 1-propanol + aqueous mixture at different temperatures. To expand available BDS solubility data for industrial and laboratory applications, 11 mass fractions of 1-propanol were evaluated to produce the maximum solubility of BDS. In the following, the experiment

solubility data are correlated/back-calculated with several mathematical methods counting the modified Wilson model, Williams-Amidon excess Gibbs energy model, Yalkowsky's equation, Buchowski and Ksiazczak equation, CNIBS/R–K model, MRS model, the and two Jouyban-Acree models: the Jouyban-Acree-van't Hoff and the Jouyban-Acree [43]. Also, the apparent thermodynamics of the BDS dissolution process such as Gibbs free energy, enthalpy, and entropy, in the desired temperature were calculated.

Materials and methods

Materials

BDS (Lirok Pharma, Tehran, Iran with 0.98 mass fraction purity), 1-propanol (Scharlau Chemie, Spain with 0.995 mass fraction purity), distilled water (Lab made), and ethanol (Jahan Alcohol Teb, Arak, Iran with 0.935 mass fraction purity and it was used to dilute the solution before spectrophotometric analysis) were the materials applied throughout this work. The chemicals provided by the companies were used without further purification process.

Solubility determination

In the present study, the shake flask technique was used as a routine method based on a solid–liquid equilibrium mechanism to study the BDS solubility in the binary mixture of (1-propanol + water) [50]. At first, vials including a mixture of different solvents with various mass fractions of the cosolvent ranging from 0.1 to 0.9 were prepared. In the next step, the excess amount of BDS was poured into the vials. Next, for exactly 48 h, the primed vials were shaken by applying a shaker (Heidolph® Unimax 1010 Orbital Shaker) inserted in an incubator (Heidolph® Model 1000 Incubator Heating Unit) containing a temperature-control between 293.2 and 313.2 K (± 0.2 K). After preparing saturated solutions at desired temperatures, the additional solid phase was separated by applying syringe filters (0.22 µm) (Potentiometric CheqSol and Standardized Shake-Flask Solubility Methods are Complimentary Tools in Physicochemical Profiling). Next, using the appropriate amount of ethanol, the sample solutions were diluted and a UV–Vis spectrophotometer (Shimadzu, Kyoto, Japan) was applied to read the absorbance at 242 nm.

In the next step, the BDS concentration of the mentioned saturated solutions was considered by the previously obtained calibration curve (y = 0.0272 x + 0.1003 with $R^2 = 0.9989$) and dilution factors (2 and 1500 for water and 1-propanol, respectively). The experiments were performed in three replicates. The mean of experimental molar solubility and *RSD%* were calculated for all measured data points.

Thermodynamic analysis of dissolution

The drug dissolution procedure is affected by several factors including enthalpy (ΔH°) and entropy (ΔS°). To understand the important information related to BDS solubility, the Gibbs and van't Hoff equations were applied to the BDS dissolution process in the mixture of (1-propanol + water).

The modified form of van't Hoff equations can be inscribed as [51]:

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

In this equation, the symbols are as follows:

C = molar solubility of the drug in the solvent (mono- or mixed-solvent), T = absolute temperature, T_{hm} = the mean harmonic temperature (Kelvin unit), and R = ideal gas constant.

The T_{hm} was calculated according to

$$T_{hm}=n/\sum_{i=1}^{n}(1/T) \tag{2}$$

Here, n indicates the number of examined temperatures. It is necessary to mention the difference in temperature from 293.2 to 313.2 K, T_{hm} value was obtained as 303.0 K.

According to Eqs. 3, 4, the ΔH° associated with solutions from interrupt of the scheme of ln C vs $1/T - 1/T_{hm}$ and ΔG° of solutions through the slope of the scheme of ln C vs $1/T - 1/T_{hm}$ were achieved, respectively [51].

$$\Delta H^{\circ}=-R\frac{\partial \ln C}{\partial(T^{-1}-T_{hm}^{-1})} \tag{3}$$

$$\Delta G^{\circ}=-RT_{hm}.intercept \tag{4}$$

At T_{hm} value of 303.0 K, the Gibbs equation was applied to calculate the ΔS° in the dissolution procedure:

$$\Delta G^{\circ}=\Delta H^{\circ}-T_{hm}\Delta S^{\circ} \tag{5}$$

$$\Delta S^{\circ}=\frac{(\Delta H^{\circ}-\Delta G^{\circ})}{T_{hm}} \tag{6}$$

The relative contributions of ζ_{TS} (associated with the entropy) and ζ_{H} (associated with the enthalpy) to ΔG°, for dissolution process of BDS in the 1-propanol-aqueous mixtures were determined through the following equations [52].

$$\zeta_{H}=\frac{\left|\Delta H^{\circ}\right|}{(\left|\Delta H^{\circ}\right|+\left|T\Delta S^{\circ}\right|)} \tag{7}$$

$$\zeta_{TS} = \frac{\left|T\Delta S^{\circ}\right|}{\left(\left|\Delta H^{\circ}\right| + \left|T\Delta S^{\circ}\right|\right)} \tag{8}$$

X-ray powder diffraction

The crystallinity of raw BDS, equilibrated in neat water, 1-propanol, and 50:50(water: 1-propanol) was investigated with the X-ray powder diffraction (XRD) analysis. By using above-mentioned shake flask method and an incubator equipped with a temperature-controlling system at 298.15 K for 48 h, XRD patterns were obtained for raw BDS, and the excess amounts of BDS equilibrated with the neat solvents of 1-propanol, water, and 50:50 (water: 1-propanol). In the next step, the saturated solution was removed using a filter. The bottom solid phases were obtained by rinsing the solid phase with deionized water at least three times, drying at 298.15 K for 96 h. Finally, their XRD patterns by instrument: Tongda TD-3700 (China) using target Material (anode): copper, radiation source: Cu Kalpha 1, wavelength: 1.5406 Angstrom, voltage: 30 kV, current: 20 mA, step size: 0.02 deg, and time per step: 0.5 s in the 2-theta range of 10° to 70° and 40 kV at ambient pressure, were recorded.

Computational validation

In this study, for prediction of the experimental data for BDS solubility in mixtures of (1-propanol + water) at various temperatures, several mathematical models including van't Hoff model, Yalkowsky equation, CNIBS/R–K model, Buchowski and Ksiazczak equation, modified Wilson model, two Jouyban-Acree models including Jouyban-Acree-van't Hoff and Jouyban-Acree, and Williams-Amidon excess Gibbs energy model were evaluated. The statistical analyses were performed by using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA).

The van't Hoff equation

The van't Hoff equation shown below is applied to check the correlation between the solubility of the desired solute and temperature in a certain solvent ratio [53]:

$$ln\, C_T = A + \frac{B}{T} \tag{9}$$

It should be noted that Eq. (10) as the modified van't Hoff equation, was applied to examine temperature-dependent solubility information of drugs [54].

$$ln\, C_T = A + B\left(\frac{1}{T} - \frac{1}{T_{hm}}\right) \tag{10}$$

Here, T_{hm} as mean harmonic temperature was computed with Eq. (2). Also, A and B are the constants of the equation.

The CNIBS/R–K model

The CNIBS/R-K model was introduced to show the correlation between the experimental solubility data of a special solute in the binary isothermal solvent mixtures [55].

$$\ln C_m = w_1 \ln C_1 + w_2 \ln C_2 + w_1.w_2 \sum_{i=0}^{2} J_i.(w_1 - w_2)^i \tag{11}$$

In this equation, C_1 C_2, and C_m represents the solute's solubility in neat solvents 1 and 2, and a binary mixture of solvents, respectively. Also, the mass fraction of solvent 1 and solvent 2 in the absence of solutes are indicated by symbols w_1 and w_2, respectively. It is necessary to mention, that J_i is the constant of the equation which is calculated by regressing $\ln C_m - (w_1 \ln C_1 + w_2 \ln C_2)$ versus w_1w_2, w_1w_2 $(w_1 - w_2)$, and w_1w_2 $(w_1 - w_2)^2$.

Jouyban-Acree model

This model is the most accurate equation for investigating solubility in binary solvent mixtures [20]. According to this model, the factors affecting the BDS solubility are temperature and solvent composition. The equation is shown below [56]:

$$\ln C_{m,T} = w_1.\ln C_{1,T} + w_2.\ln C_{2,T} + \frac{w_1.w_2}{T} \sum_{i=0}^{2} J_i.(w_1 - w_2)^i \tag{12}$$

The symbol T, $C_{m,T}$,$C_{1,T}$, and $C_{2,T}$ represents the temperature, and the BDS solubility in the different mass fractions of solvent, and pure solvents 1 and 2, respectively.

It can be noted that in this equation the temperature is reported in Kelvin units [56].

J_i is the constant which is calculated through regression $\ln C_{m,T} - w_1.\ln C_{1,T} - w_2.\ln C_{2,T}$ against $\frac{w_1.w_2}{T}$, $\frac{w_1.w_2(w_1 - w_2)}{T}$, and $\frac{w_1.w_2(w_1 - w_2)^2}{T}$.

Jouyban-acree-van't Hoff model

This equation as another most accurate models for calculating solubility is obtained from the combination of two Jouyban-Acree models and van't Hoff models.

The equation of this model is as follows [57]:

$$\ln C_{m,T} = w_1\left(A_1 + \frac{B_1}{T}\right) + w_2\left(A_2 + \frac{B_2}{T}\right) + \frac{w_1w_2}{T}\sum_{i=0}^{2} J_i(w_1 - w_2)^i \tag{13}$$

In this equation, coefficients A and B can be computed (with a linear regression) according to data related to the temperature-dependent solubility in the mixture of (1-propanol + water). The J_i terms are achieved by regressing

$((\ln C_{m,T} - w_1\left(A_1 + \frac{B_1}{T}\right) - w_2\left(A_2 + \frac{B_2}{T}\right))$ against $\frac{w_1.w_2}{T}$, $\frac{w_1.w_2(w_1-w_2)}{T}$, and $\frac{w_1.w_2(w_1-w_2)^2}{T}$ [58].

The revised form of Eq. (13), suggested by Sun et al. is as follows [59].

$$\ln C_{m,T} = D_1 + \frac{D_2}{T} + D_3 w_1 + D_4 \frac{W_1}{T} + D_5 \frac{w_1^2}{T} + D_6 \frac{w_1^3}{T} + D_7 \frac{w_1^4}{T} \quad (14)$$

In this equation, regression analysis is applied to calculate constants of formula including D_1 to D_7.

Modified Wilson model

For entire examined temperatures, further the linear mathematical pattern, non-linear model including the referred equation can be applied for forecasting and fitting the achieved information of solubility [26, 60].

Wilson's modified model is shown in the following form:

$$-\ln C_m = 1 - \frac{w_1(1+\ln C_1)}{w_1 + w_2\lambda_{12}} - \frac{w_2(1+\ln C_2)}{w_1\lambda_{21} + w_2} \quad (15)$$

In this equation, the constants of the equation, i.e. λ_{12} and λ_{21}, are achieved through nonlinear least squares analysis.

Buchowski–Ksiazczak equation

Buchowski–Ksiazczak model (also called λh equation) is one of the effective and suitable nonlinear models for modeling solid–liquid equilibrium systems. It is related to two physical parameters including λ and h. This equation provides better results in the field of data correlation and its efficiency has been confirmed by several studies [61]. Molecular systems with strong polarities and strong interactions have shown better responsiveness in this system.

The Buchowski- Ksiazczak (λh) equation is as follows:

$$\ln\left[1 + \frac{\lambda(1-C)}{C}\right] = \lambda h\left[\frac{1}{T} - \frac{1}{T_{hm}}\right] \quad (16)$$

the constants are λ and h.

The excess Gibbs energy model of Williams–Amidon

Williams-Amidon excess Gibbs energy equation is introduced as follows [62].

$$\ln C_m = w_1 \ln C_1 + w_2 \ln C_2 - A_{1-2} w_1 w_2 (2w_1 - 1)\left(\frac{V_s}{V_1}\right) + (2A_{2-1}) w_1^2 w_2 \left(\frac{V_s}{V_2}\right) + 3D_{12} w_1^2 w_2^2 \left(\frac{V_s}{V_2}\right) + \alpha_2 w_1 w_2^2 \left(\frac{V_s}{V_2}\right) + \alpha_1 w_1^2 w_2 \quad (17)$$

The parameters of this model are defined as follows, symbols indicating the interaction among solvent–solvent and solvent–solute are A_{1-2}, A_{2-1}, α_1, α_2, and D_{12}. Also, the symbols indicating the molar volume of cosolvent, water, and solute are V_1, V_2, and V_s respectively.

The mixture response surface (MRS) model

Based on the following equation with five constants, the MRS model correlatives the drug solubility data in different co-solvent mass fractions under isotherm condition [63].

In which, C_m and β_1–β_5 are the drug molar solubility in the equilibrated solutions and the model parameters, respectively.

$$\ln C_m = \beta_1 W_1' + \beta_2 W_2' + \beta_3\left(\frac{1}{W_1'}\right) + \beta_4\left(\frac{1}{W_2'}\right) + \beta_5 W_1' W_2'$$

It is necessary to mention that w_1 and w_2 can be computed by $w_1' = 0.96\, w_1 + 0.02$ and $w_2' = 0.96\, w_2 + 0.02$.

Model accuracy

In this study, several mentioned equations were used to evaluate of relationship between the experimental and calculated BDS solubility in the mixture of (1-propanol + water) at various temperatures. To estimate the accuracy of the investigated models, the *MRD%* parameters among the experimental values and back-calculated data were computed using the following equation.

$$\%MRD = \frac{100}{N}\sum\left(\frac{|Calculated\ value - Observed\ value|}{Observed\ value}\right) \quad (18)$$

The N is considered the number of tests in each set.

Results and discussions

Solubility of BDS in the mixed solvent of {1-propanol (1) + water (2)}

The molar solubility of BDS (mean ± *SD*) in the presence of binary solvent mixtures of 1-propanol and water in five different temperatures 293.2, 298.2, 303.2, 308.2, and 313.2 K is shown in Table 1. All the solubility measurements were performed with three repetitions of the experiment so that the *RSDs%* values were less than 5%. The lowest and highest molar solubility of BDS were obtained in neat water at 293.2 K ($3.62\ (\pm 0.13) \times 10^{-5}$) and in 0.7 mass fraction of 1-propanol at 313.2 K ($1.82\ (\pm 0.03) \times 10^{-1}$), respectively. Previous studies have shown that drug solubility in a co-solvent environment depends on factors such as solute–solvent interactions, solvent–solvent interactions, and molecular shapes and sizes. A drug as solute reaches its maximum solubility when it

Table 1 Experimental molar solubility ($C_{m,T}^{sat}$) values {as the mean of three experiments measured (± *SD*) [a]} for BDS (3) in {1-propanol (1) + water (2)} solvent mixtures at various temperatures (0.101 ± 0.002 MPa)

w_1 [b] (± 0.005)	293.2 ± 0.2 K	298.2 ± 0.2 K	303.2 ± 0.2 K	308.2 ± 0.2 K	313.2 ± 0.2 K	Ref
0.00	$3.62\ (\pm 0.13)\times 10^{-5}$	$4.44\ (\pm 0.05)\times 10^{-5}$	$5.20\ (\pm 0.12)\times 10^{-5}$	$5.93\ (\pm 0.17)\times 10^{-5}$	$6.73\ (\pm 0.33)\times 10^{-5}$	[2]
0.10	$1.27\ (\pm 0.06)\times 10^{-4}$	$1.89\ (\pm 0.05)\times 10^{-4}$	$2.05\ (\pm 0.10)\times 10^{-4}$	$2.47\ (\pm 0.11)\times 10^{-4}$	$2.74\ (\pm 0.10)\times 10^{-4}$	This work
0.20	$5.57\ (\pm 0.14)\times 10^{-4}$	$6.81\ (\pm 0.17)\times 10^{-4}$	$7.99\ (\pm 0.23)\times 10^{-4}$	$8.89\ (\pm 0.25)\times 10^{-4}$	$1.03\ (\pm 0.01)\times 10^{-3}$	This work
0.30	$2.20\ (\pm 0.09)\times 10^{-3}$	$2.45\ (\pm 0.07)\times 10^{-3}$	$2.81\ (\pm 0.13)\times 10^{-3}$	$3.54\ (\pm 0.16)\times 10^{-3}$	$4.09\ (\pm 0.10)\times 10^{-3}$	This work
0.40	$8.05\ (\pm 0.31)\times 10^{-3}$	$8.57\ (\pm 0.22)\times 10^{-3}$	$1.09\ (\pm 0.05)\times 10^{-3}$	$1.12\ (\pm 0.04)\times 10^{-2}$	$1.30\ (\pm 0.02)\times 10^{-2}$	This work
0.50	$2.50\ (\pm 0.07)\times 10^{-2}$	$2.82\ (\pm 0.12)\times 10^{-2}$	$3.09\ (\pm 0.14)\times 10^{-2}$	$3.61\ (\pm 0.08)\times 10^{-2}$	$3.97\ (\pm 0.08)\times 10^{-2}$	This work
0.60	$6.13\ (\pm 0.21)\times 10^{-2}$	$6.89\ (\pm 0.18)\times 10^{-2}$	$7.53\ (\pm 0.12)\times 10^{-2}$	$8.17\ (\pm 0.17)\times 10^{-2}$	$9.34\ (\pm 0.44)\times 10^{-2}$	This work
0.70	$1.29\ (\pm 0.03)\times 10^{-1}$	$1.44\ (\pm 0.04)\times 10^{-1}$	$1.57\ (\pm 0.07)\times 10^{-1}$	$1.69\ (\pm 0.06)\times 10^{-1}$	$1.82\ (\pm 0.03)\times 10^{-1}$	This work
0.80	$1.22\ (\pm 0.05)\times 10^{-1}$	$1.37\ (\pm 0.06)\times 10^{-1}$	$1.52\ (\pm 0.04)\times 10^{-1}$	$1.67\ (\pm 0.03)\times 10^{-1}$	$1.78\ (\pm 0.05)\times 10^{-1}$	This work
0.90	$1.15\ (\pm 0.01)\times 10^{-1}$	$1.29\ (\pm 0.01)\times 10^{-1}$	$1.42\ (\pm 0.06)\times 10^{-1}$	$1.55\ (\pm 0.04)\times 10^{-1}$	$1.64\ (\pm 0.03)\times 10^{-1}$	This work
1.00	$1.03\ (\pm 0.14)\times 10^{-1}$	$1.17\ (\pm 0.11)\times 10^{-1}$	$1.28\ (\pm 0.08)\times 10^{-1}$	$1.36\ (\pm 0.03)\times 10^{-1}$	$1.41\ (\pm 0.12)\times 10^{-1}$	[6]

[a] The mean uncertainty value of 0.0154 was obtained

[b] w_1 is mass fraction of 1-propanol (1) in the {1-propanol (1) + water (2)} mixtures in the absence of BDS (3)

has similar polarity and solubility parameters and also intermolecular forces in the co-solvent medium so that the minimum amount of energy changes occurs in the process of dissolution. The result of the influence of the mentioned factors in the dissolution process makes the drug reach its maximum solubility in a specific mass fraction of co-solvent [64].

It should be pointed out that the solubility data of BDS in pure water and 1-propanol solvents were obtained from the previous study of our group [5]. As shown in Table 1, at all temperatures, the lowest amount of solubility is related to pure water. In the following, with the increase of 1-propanol, the maximum amount of solubility values was obtained at 0.7 mass fraction at all temperatures. After 0.7 mass fraction, the BDS solubility reduction process continues until the pure solvent of 1-propanol. This process was repeatable at all temperatures. The observed pattern is due to the variation in the polarity of the solvent mixtures, so that at 0.7 mass fraction, the polarity decreases to a point that is suitable for dissolving BDS with a log *P* of 2.32. This phenomenon is based on the "like dissolves like" principle. The closer the log *P* for solute and solvents are to each other, the more the heat dissolution process occurs. In general, polar solutes dissolve better in polar solvents and non-polar solutes in non-polar solvents. Therefore, it can be expected that the solubility of the non-polar drug will increase in co-solvent mixtures with the increase in the mass fraction of non-polar co-solvent (log *P* for 1-propanol is equal to 0.329). From the literature, the dielectric constant of different mass fractions of an aqueous mixture of 1-propanol can be seen in Table 2 [65]. The dielectric constant decreases with the increase of the mass fraction of 1-propanol and reaches its lowest value in pure 1-propanol. The reported data show that BDS solubility increases with decreasing polarity. The decrease in the solubility of BDS after mass fraction 0.7 shows that the role of polarity for the dissolution process was less in the next mass fractions. In our previous study, for investigating BDS solubility and respective polarity dependency, BDS's internal energy, molar volume, and Hildebrand solubility parameter were obtained as 192.55 kJ mol^{-1}, 371.4 $cm^3 \cdot mol^{-1}$ and 22.77 $MPa^{1/2}$, respectively (based on Fedors' method, see Table S2) [4]. Therefore, it can be concluded that polarity, hydrogen bonds, and van der Waals' interactions of solute–solvent and solvent–solvent as interactions at the intermolecular scale affected drug solubility. The effect

Table 2 Mean BDS molar solubility ± *SD* and dielectric constant related to the solvent mixtures of {1-propanol (1) + water (2)} at 298.2 K

w_1 (± 0.005)	Dielectric constant	Solubility ($mol \cdot L^{-1}$) values {mean of three experiments (± *SD*)}[a]
0.00	78.5	$4.44\ (\pm 0.05)\times 10^{-5}$
0.10	71.8	$1.89\ (\pm 0.05)\times 10^{-4}$
0.20	64.9	$6.81\ (\pm 0.17)\times 10^{-4}$
0.30	57.7	$2.45\ (\pm 0.07)\times 10^{-3}$
0.40	50.3	$8.57\ (\pm 0.22)\times 10^{-3}$
0.50	43	$2.82\ (\pm 0.12)\times 10^{-2}$
0.60	36.4	$6.89\ (\pm 0.18)\times 10^{-2}$
0.70	30.7	$1.44\ (\pm 0.04)\times 10^{-1}$
0.80	26.1	$1.37\ (\pm 0.06)\times 10^{-1}$
0.90	22.7	$1.29\ (\pm 0.01)\times 10^{-1}$
1.00	20.1	$1.17\ (\pm 0.11)\times 10^{-1}$

[a] The mean uncertainty value of 0.0149 was obtained

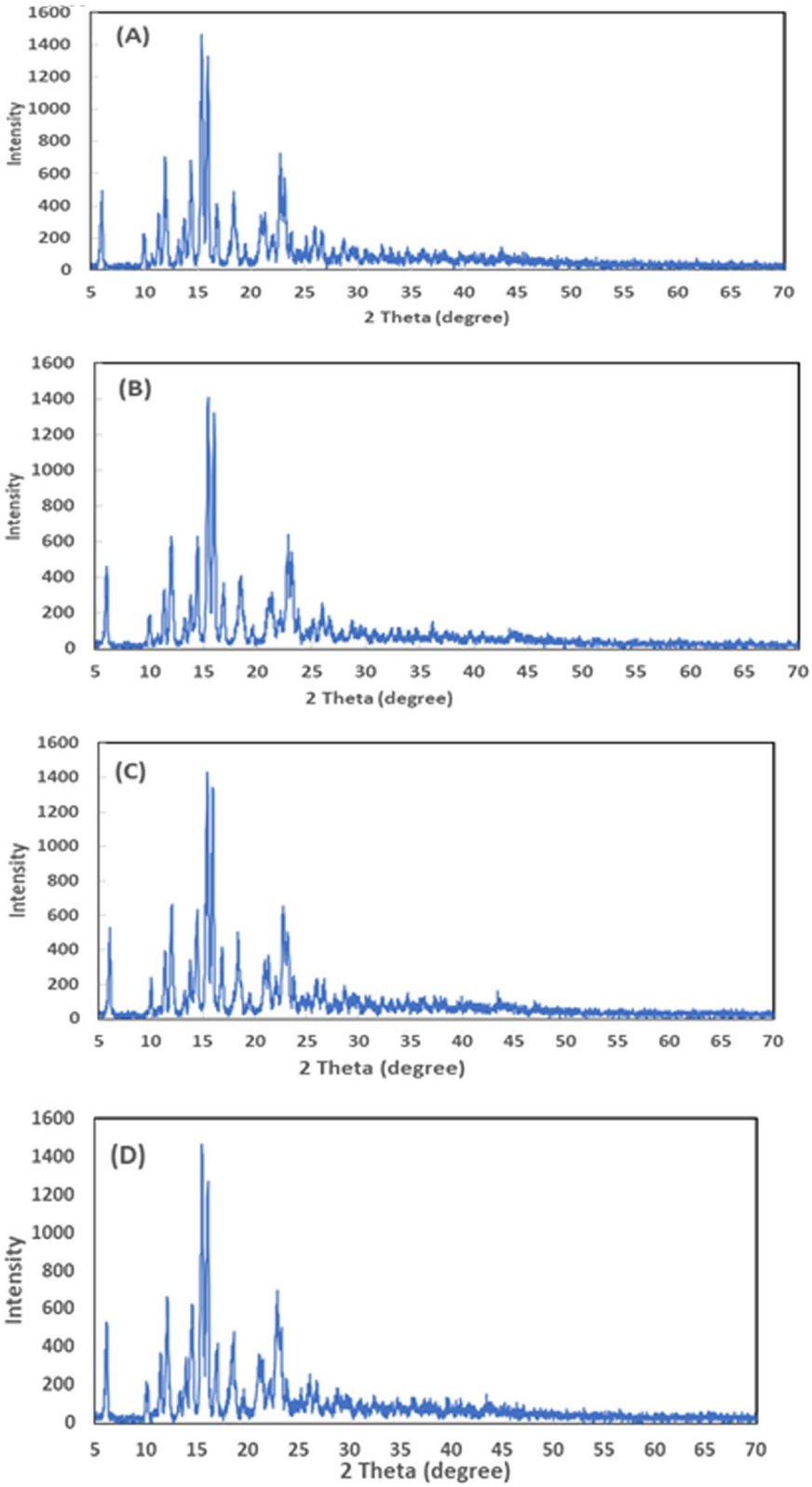


Fig. 1 XRD pattern of raw BDS (**A**) and equilibrated BDS in water (**B**), 1-propanol (**C**), and 50:50 (water: 1-propanol) (**D**)

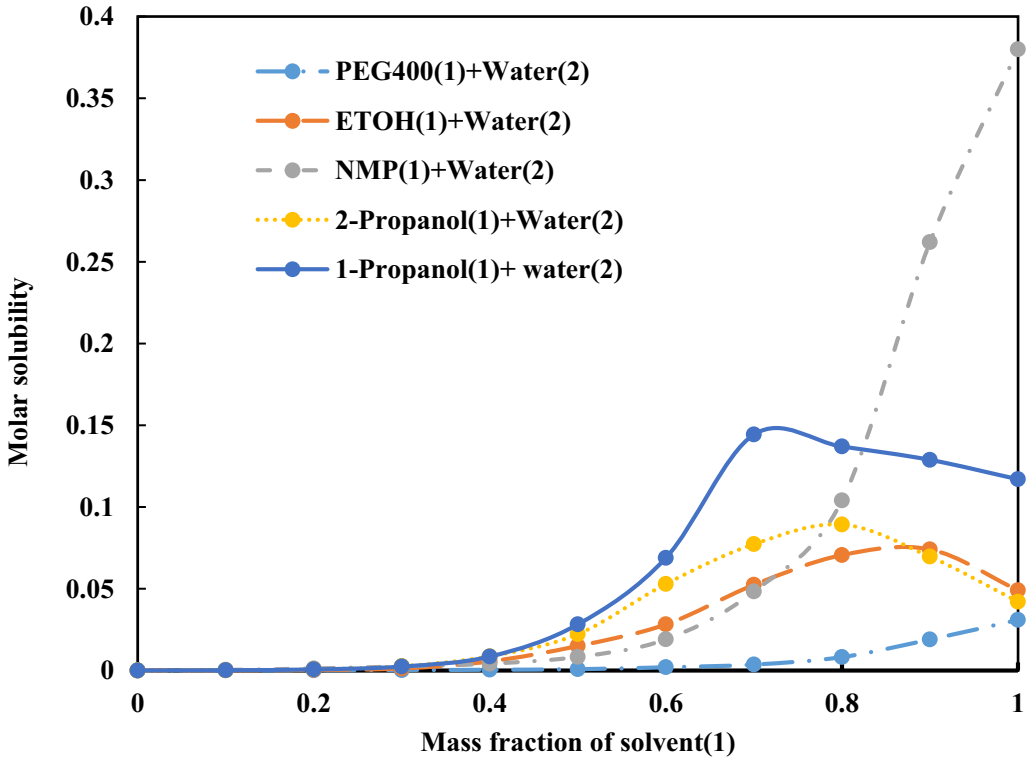


Fig. 2 Comprehensive comparison of BDS molar solubility in different reported cosolvency systems at 298.2 K. (PEG400 + water) [2], (EtOH + water) [30], (NMP + water) [31], (2-Propanol + water) [4], (1-Propanol + water (This work)

value of each of these parameters and other unknown parameters in the dissolution process for water and 1-propanol are specific values. Therefore, in each mass fraction of the co-solvent, the result of the influence of these parameters determines the BDS solubility value. Although it is difficult to decide on a single factor for solute's solubility behavior, BDS solubility appears to be most affected by polarity.

XRD analysis

In Fig. 1, the X pattern of the raw BDS and solids equilibrated with water, 1-propanol, and 50:50(water: 1-propanol) can be seen. The XRD patterns of solid BDS in equilibrium with the mentioned solvents showed that the same characteristic peaks with the raw material were found. Thereby, during the entire experiment, neither polymorph transformations nor solvate formations were observed.

Previous studies on BDS solubility in different systems have shown two trends: i) systems containing (ethanol + water) [30], (2-propanol + water) [4], and (1-propanol + water) (this work) denoted maximal BDS solubility in 0.9, 0.8, and 0.7 mass fractions of cosolvent, respectively, and ii) systems including (PEG 400 + water) [2] and (*N*-methyl-2-pyrrolidone (NMP) + water) [31] showed maximum BDS solubility in neat cosolvents, so that, a linear increase in BDS solubility with the growing mass fraction of cosolvent was observed. According to the studies conducted, the maximum amount of BDS solubility was obtained in the (NMP + water) system at 298.2 K (see Fig. 2).

In the solvents + co-solvents investigated systems in the temperature range of 293.2 to 313.2 K in mass fractions from 0.0 to 1.0 with an interval of $w_1 = 0.1$, the maximum solubility value (1.5×10^0 mol/L) for NMP was obtained at 313.2 K and the minimum solubility value (3.62×10^{-5} mol/L) for water was found at 293.2 K. Among the alcohols used to increase the solubility of BDS, including ethanol, 1-propanol, and 2-propanol as co-solvent, the most and least performance were related to 1-propanol and ethanol, respectively. In studies conducted to date, the dissolution process of BDS in mixtures of (PEG 400 + water), (2-propanol + water), and (ethanol + water) were endothermic ($\Delta H^\circ > 0$ in all cases) and entropy-driven ($\Delta S^\circ > 0$ in all cases, except in mono solvent of water). Mathematical modeling showed that the overall *MRDs%* for back-calculated solubility data of BDS based on the Jouyban-Acree model in the mixtures of (PEG 400 + water), (NMP + water), (2-propanol + water), and (ethanol + water) were

Table 3 Computing of the solubilization powers of different cosolvency systems used for BDS solubility study

Solvent mixtures	σ	ω
2-Propanol + water	2.98	4.13
NMP + water	3.98	3.98
PEG 400 + water	2.84	2.84
Ethanol + water	3.08	3.82
1-Propanol + water	2.83	4.36

obtained as 6.7%, 5.2%, 5.7%, and 6.6%, respectively. While overall *MRDs%* in these mixtures were obtained for Jouyban-Acree-van't-Hoff as 6.9%, 5.0%, 5.8%, and 6.5%, respectively. Among the models presented to predict the solubility of BDS, Yalkowsky-Roseman model, and modified Wilson model had higher *MRDs%* than others.

In the next step, the solubilization efficiency for various cosolvency systems applied for BDS solubility is showed in Table 3. Previous study shows that the efficacy of cosolvents for solubilization is affected by two parameters: (i) σ as Yalkowsky's parameter and (ii) ω as a new definition for the power of solubilization (Eqs. (19, 20)) [66, 67].

$$\sigma = log\left(\frac{C_c}{C_s}\right) \tag{19}$$

$$\omega = \frac{log\left(\frac{C_{m,max}}{x_s}\right)}{w_{1,max}} \tag{20}$$

In these equations C_c, C_s, $C_{m,max,}$, and $w_{1,max}$ are defined as drug solubility in cosolvent, drug solubility in the solvent, maximum drug solubility of cosolvent-water mixture, and cosolvent mass fraction with highest solubility.

Table 3 shows that the highest solubility of BDS was related to the NMP and PEG 400 as cosolvents, due to ω and σ having the same value in the (NMP + water) and (PEG 400 + water) binary mixtures. The data also show that based on the ω parameter with 4.36 (as a maximum value) in (1-propanol + water), 1-propanol can be recommended as a solubilizer for cosolvency systems in formulations of numerous drugs.

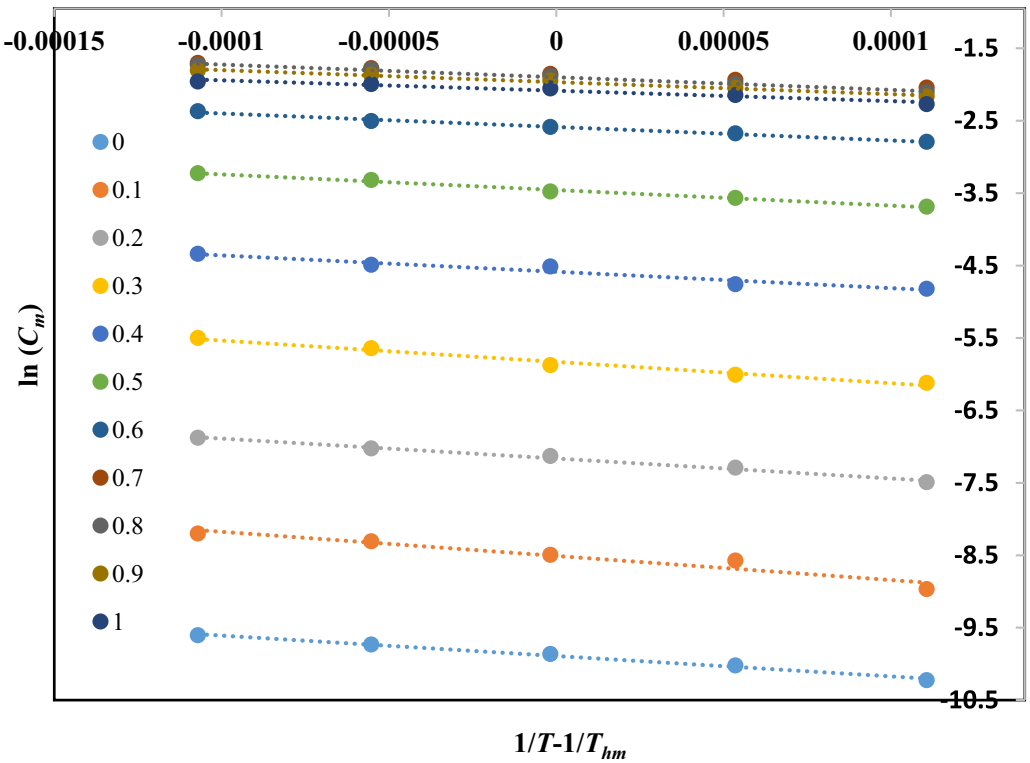


Fig. 3 Van't Hoff plots of the experimental molar solubility of BDS in the different mass fractions of 1-propanol (w_1 from 0.0 to 1.0)

Thermodynamic analysis

In continues, the van't Hoff plots for BDS solubility in pure 1-propanol, different mass fraction of 1-propanol and neat water is drawn for calculation of the apparent thermodynamic quantities of BDS dissolution (Fig. 3). Parabolic trends were obtained by correlation coefficients greater than 0.992 in all cases [22, 68]. Based on Eqs. (5, 6) which were explained in full before and according to the slope and intercept of the line at T_{hm} = 303.0 K, the apparent enthalpies and Gibbs energies were calculated. Table 4 shows the ΔH°, ΔS°, and ΔG° values for BDS dissolution in various aqueous mixtures of 1-propanol at T_{hm} equal to 303.0 K. The results show that the values of ΔH°, ΔS°, and ΔG° in every case are positive, indicating that BDS dissolution procedures were obtained as endothermic and entropy-driven in almost all cases. There is an exception with ΔS° in neat water exhibiting negative value. It is necessary to mention the maximum and minimum values of ΔH° in w_1 = 0.1 and w_1 = 1.0 were found at 27.67 and 11.94 kJ·mol^{-1}, respectively. Also, the highest value of ΔS° in w_1 = 0.3 and the lowest value of ΔS° in w_1 = 0.2 were observed as 32.40 and 15.8 J·mol^{-1}·K^{-1}, respectively. The range of ΔG° changes was found as 24.95–4.70 kJ·mol^{-1} so that the highest and lowest values of ΔG° were related to low and high levels of BDS solubility. As shown in Fig. 4, when 1-propanol proportions increase leading to lesser ΔG° values, reaching a minimum at 0.7 mass fraction. The reason for the observed trend is that a more favorable dissolution process leads to increasing BDS solubility.

The values for ζ_H and ζ_{TS} summarized in Table 4 show that the BDS dissolution process was contributed mainly by the ΔH° because $\zeta_H > \zeta_{TS}$ and $\zeta_H > 0.599$ were observed. Accordingly, we can conclude that BDS dissolution was dependent on the cohesive force of the solute–solvent mixture in all solvent mixtures [4, 69].

To further study the BDS dissolution process, ΔH° versus ΔG° and ΔH° versus $T\Delta S^{\circ}$ as enthalpy–entropy compensation plots of BDS at various temperatures were investigated [5]. According to Fig. 1S, a nonlinear relationship was observed for ΔH° and ΔG° related to BDS solubility in the various mass fractions of the (1-propanol + water) mixture. It is clearly understood that, in the ΔH° versus ΔG° curve, decreasing and improving the role of entropy in the BDS dissolution process led to positive and negative parts of the slopes, respectively. On the other hand, the analysis of the contribution of enthalpy and entropy in the dissolution process of BDS in the binary mixture of (1-propanol + water) can be investigated. Some linear correlations with different slopes in Fig. 1S indicated that both enthalpy-driven and entropy-driven processes contribute to BDS solubility. In mixtures with $0.1 \le w_1 \le 0.2$ and $0.3 \le w_1 \le 0.8$, the ΔH° versus ΔG° plots exhibited positive slopes, indicating that enthalpy effects mainly drove the BDS transfer in these mixtures. This decrease in enthalpy was accompanied by a corresponding decrease in Gibbs free energy, highlighting the enthalpic interactions between BDS and the solvent components as the main determinants of the transfer process. While for mixtures with $0.0 \le w_1 \le 0.1$, $0.2 \le w_1 \le 0.3$, and $0.8 \le w_1 \le 1.0$ the plot showed negative slopes indicating that entropy effects influenced principally the BDS transfer processes in these mixtures. In other words, the accompanying increase of ΔH° with the decrease of ΔG° in these mixtures means that in the dissolution process, entropic factors such as increased disorder or solvation effects were responsible for forcing the dissolution

Table 4 Apparent thermodynamic parameters for describing BDS dissolution behavior in {1-propanol (1) + water (2)} mixtures at T_{hm} = 303.0 K

w_1 (±0.005)	ΔG° (kJ·mol^{-1})	ΔH° (kJ·mol^{-1})	ΔS° (J·K^{-1}·mol^{-1})	$T\Delta S^{\circ}$ (kJ·mol^{-1})	ζ_H	ζ_{TS}
0.00	24.9 ± 1.0	23.4 ± 1.1	− 5.1 ± 0.3	− 1.5 ± 0.1	0.938	0.062
0.10	21.4 ± 0.9	27.6 ± 4.3	20.4 ± 3.3	6.2 ± 1.0	0.817	0.183
0.20	18.1 ± 0.7	22.8 ± 1.3	15.8 ± 1.1	4.8 ± 0.3	0.828	0.172
0.30	14.7 ± 0.6	24.5 ± 2.0	32.4 ± 2.9	9.8 ± 0.9	0.714	0.286
0.40	11.6 ± 0.5	18.9 ± 2.6	24.1 ± 3.4	7.3 ± 1.0	0.721	0.279
0.50	8.7 ± 0.3	17.9 ± 0.9	30.3 ± 1.9	9.2 ± 0.6	0.661	0.339
0.60	6.5 ± 0.3	15.5 ± 0.8	29.5 ± 2.0	8.9 ± 0.6	0.634	0.366
0.70	4.7 ± 0.2	12.9 ± 0.5	27.1 ± 1.5	8.2 ± 0.4	0.611	0.389
0.80	4.8 ± 0.2	14.5 ± 0.7	32.2 ± 2.1	9.7 ± 0.6	0.599	0.401
0.90	5.0 ± 0.2	13.8 ± 0.8	29.0 ± 2.0	8.8 ± 0.6	0.610	0.390
1.00	5.3 ± 0.2	11.9 ± 1.4	22.1 ± 2.8	6.7 ± 0.9	0.641	0.359

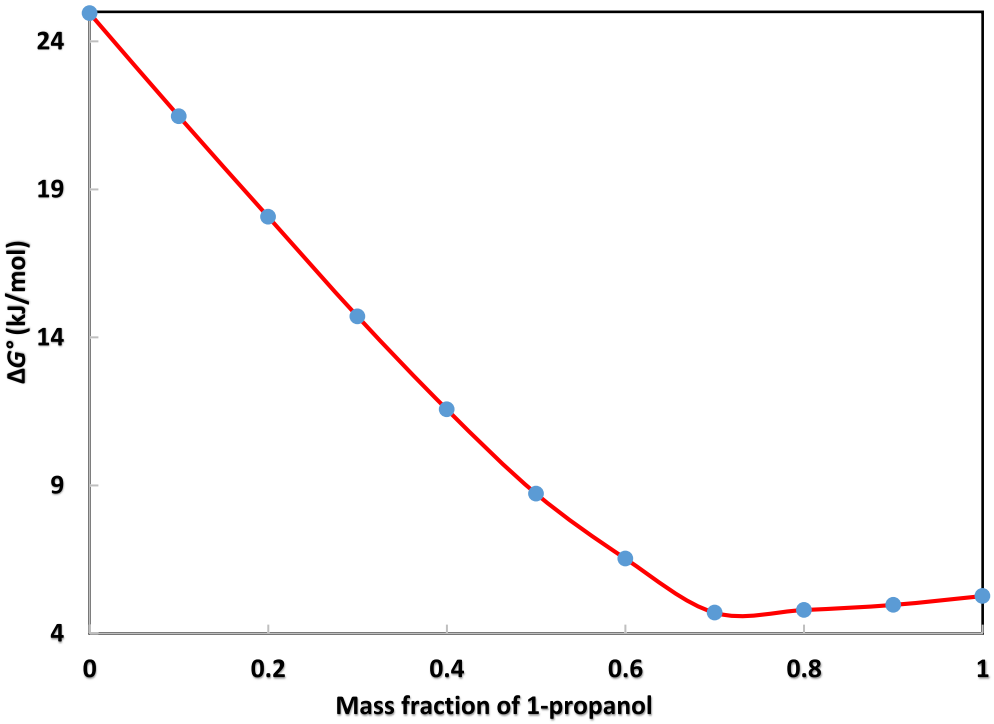


Fig. 4 Gibbs energy related to the transfer of BDS (3) from neat water (2) to aqueous mixture of 1-propanol (1) at 303.0 K

process. In addition, the positive and negative parts of the slopes in the ΔH° versus $T\Delta S^{\circ}$ curve originated from reducing and increasing the effect of enthalpy in the BDS dissolution process, respectively.

As shown, an increase in BDS solubility was observed at different temperatures in the range of 0.0 to 0.7 of mass fraction. On the other hand, in the mass fraction of 0.7 to 1.0, BDS solubility was decreased. According to Fig. 3, the value of ΔG° decreases between mass fractions from 0.0 to 0.7 and increases from 0.7 to 1.0. In mixtures with $0.0 \leq w_1 \leq 0.1$ and $0.2 \leq w_1 \leq 0.3$, two factors, namely ΔG° decreasing and ΔS° increasing, leading to increased BDS solubility. While in mixtures with $0.1 \leq w_1 \leq 0.2$ and $0.3 \leq w_1 \leq 0.7$, decreasing ΔG° and ΔH° caused BDS solubility increasing. On the other hand, for mixtures with composition intervals of $0.7 \leq w_1 \leq 0.8$ and $0.8 \leq w_1 \leq 1.0$ the observed decrease in BDS solubility is attributed to ΔG° and enthalpy increasing and ΔG° increasing vs decreasing entropy, respectively.

As indicated above, BDS solubility expressed in molarity (C, mol/L) in {1-propanol (1) + water (2)} mixtures at 298.2 K is summarized in Table 1. Nevertheless, density values of the saturated solutions were not determined in this research, and thus, a direct calculation of the BDS solubility expressed in mole fraction is not possible. For this reason, the volumetric contribution of BDS at saturation was considered as constant based on the Fedors molar volume reported in Table S2, *i.e.* 371.4 cm^3 mol^{-1}. Thus, starting from molarity drug concentration the volume contribution of BDS was subtracted to one liter, and the mass of (1-propanol + water) mixture was calculated by

Table 5 Mole fraction solubility and apparent Gibbs energies of dissolution and transfer of BDS in {1-propanol (1) + water (2)} mixtures at $T = 298.2$ K

w_1 [a]	x_1 [a]	x_3	$\Delta_{soln}G^{\circ}$ (kJ/mol)	$\Delta_{tr}G^{o}_{3,2\rightarrow 1+2}$ (kJ/mol)
0.00	0.0000	8.02×10^{-7}	34.80	0.00
0.10	0.0322	3.73×10^{-6}	30.99	−3.81
0.20	0.0697	1.48×10^{-5}	27.57	−7.23
0.30	0.1139	5.92×10^{-5}	24.14	−10.66
0.40	0.1666	2.32×10^{-4}	20.75	−14.05
0.50	0.2307	8.72×10^{-4}	17.47	−17.33
0.60	0.3102	2.48×10^{-3}	14.88	−19.92
0.70	0.4116	6.20×10^{-3}	12.60	−22.20
0.80	0.5453	6.97×10^{-3}	12.31	−22.49
0.90	0.7296	7.96×10^{-3}	11.98	−22.82
1.00	1.0000	9.10×10^{-3}	11.65	−23.15

[a] w_1 and x_1 are the mass and mole fractions of 1-propanol (1) in the {1-propanol (1) + water (2)} mixtures free of budesonide (3), respectively

using density values reported in the literature [70]. In this way, moles of all components were calculated and in turn, the mole fraction of BDS was also calculated at 298.2 K. These values are summarized in Table 5. Regarding, 1-propanol-aqueous mixtures is noteworthy that equilibrium solubility expressed in molarity at 298.2 K is obtained in the mixture of $w_1 = 0.70$ ($x_1 = 0.4116$) (Table 1), but when expressed in mole fraction, maximum solubility is observed in neat 1-propanol (Table 5). This is a consequence of the different physicochemical definitions being the molarity is a volumetric concentration scale that only considers the moles of solute whereas the mole fraction is a gravimetric scale taking into account both the moles of solute and solvent [71].

Otherwise, Table 5 recapitulates the apparent Gibbs energies of dissolution at 298.2 K that were calculated with Eq. (21) [72]. As observed all $\Delta_{soln}G^{\circ}$ are positive in all cases and diminish with the 1-propanol proportion owing to the respective BDS solubility increasing. This trend demonstrates the BDS preference by semipolar media.

$$\Delta_{soln}G^{\circ} = -RTlnx_3 \tag{21}$$

Moreover, because the molecular environment around BDS molecules is important to approach the mechanisms of dissolution processes, the preferential solvation parameters of BDS (identified here as compound 3) by 1-propanol molecules (identified here as compound 1) molecules in the different {1-propanol (1) + water (2)} mixtures are necessary. In this way, $\delta x_{1,3}$ are defined as indicated in Eq. (22) [73, 74]:

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \tag{22}$$

where $x_{1,3}^{L}$ is the local mole fraction of 1-propanol around the BDS molecules and x_1 is the bulk mole fraction of 1-propanol in the initial {1-propanol (1) + water (2)} binary solvent mixture free of BDS. Thus, if the $\delta x_{1,3}$ value is positive budesonide molecules are preferentially solvated by 1-propanol molecules in the respective dissolution. In contrast, BDS molecules are preferentially solvated by water molecules if this $\delta x_{1,3}$ parameter is negative. The values of $\delta x_{1,3}$ are commonly obtained from the inverse Kirkwood-Buff integrals (IKBI) as described in the literature based on the following physicochemical terms [73, 74]:

$$\delta x_{1,3} = \frac{x_1 x_2 \left(G_{1,3} - G_{2,3}\right)}{x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}} \tag{23}$$

with,

$$G_{1,3} = RT\kappa_T - \overline{V}_3 + x_2 \overline{V}_2 \left(\frac{D}{Q}\right) \tag{24}$$

$$G_{2,3} = RT\kappa_T - \overline{V}_3 + x_1 \overline{V}_1 \left(\frac{D}{Q}\right) \tag{25}$$

$$V_{cor} = 2522.5\left(r_3 + 0.1363\left(x_{1,3}^{L}\overline{V}_1 + x_{2,3}^{L}\,\overline{V}_2\right)^{1/3} - 0.085\right)^3 \tag{26}$$

Here, κ_T denotes the isothermal compressibility of the aqueous-1-propanol solvent systems. $\overline{V}_1$, $\overline{V}_2$, and $\overline{V}_3$ are respectively the partial molar volumes of 1-propanol, water, and BDS in the dissolutions. The function D, defined in Eq. (27), corresponds to the first derivative of the standard molar Gibbs energies of transfer of BDS from neat water to every aqueous-1-propanol mixture regarding the mole fraction of 1-propanol. The function Q, defined in Eq. (28), involves the second derivative of the excess molar Gibbs energy of mixing of 1-propanol and water (G_{1+2}^{Exc}) regarding the mole fraction of water. V_{cor} and r_3 are respectively the correlation volume and the molecular radius of BDS. Here, r_3 was roughly calculated by means of Eq. (29), where N_{Av} is the number of Avogadro.

$$D = \left(\frac{\partial \Delta_{tr}G_{3,2\to 1+2}^{o}}{\partial x_1}\right)_{T,p} \tag{27}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G_{1+2}^{Exc}}{\partial x_2^2}\right)_{T,p} \tag{28}$$

$$r_3 = \left(\frac{3 \cdot 10^{21} V_3}{4\pi N_{Av}}\right)^{1/3} \tag{29}$$

To obtain definitive V_{cor} values some iteration processes are required because they depend on the local mole fractions of 1-propanol and water around the BDS molecules in every solution. Thus, these iteration processes were performed by replacing $\delta x_{1,3}$ and V_{cor} in the Eqs. (22, 23, and 26) to recalculate the $x_{1,3}^{L}$ values until obtaining non-variant values of V_{cor}.

Table 5 and Fig. 4 show the apparent Gibbs energies of the transfer of BDS from neat water to all aqueous-1-propanol mixtures ($\Delta_{tr}G_{3,2\to 1+2}^{o}$) at 298.2 K. These $\Delta_{tr}G_{3,2\to 1+2}^{o}$ values were calculated from the experimental mole fraction solubility values reported in Table 1 by using:

$$\Delta_{tr}G^{o}_{3,2\rightarrow 1+2} = RTln\left(\frac{x_{3,2}}{x_{3,1+2}}\right) \quad (30)$$

Obtained $\Delta_{tr}G^{o}_{3,2\rightarrow 1+2}$ values were correlated by means of the regular polynomial shown as Eq. (31), whose statistical parameters were as follows: adjusted $r^2 = 0.999$, typical error = 0.219, and $F = 2900$.

$$\Delta_{tr}G^{o}_{3,2\rightarrow 1+2} = -0.16 - 113.03x_1 + 191.75x_1^2 - 101.69x_1^3 - 35.46x_1^4 + 35.43x_1^5 \quad (31)$$

The D values summarized in Table 6 were calculated as the first derivative of Eq. (31) solved in mixtures composition steps of $x_1 = 0.05$. For the studied aqueous-1-propanol mixtures, the Q, $RT\kappa_T$,and values at 298.2 K were taken from the literature [75]. In this research, the value was considered the same as the one calculated by using the Fedors method, *i.e.* 371.4 $cm^3 \cdot mol^{-1}$ [76]. Table 6 also shows that the $G_{1,3}$ and $G_{2,3}$ values are negative in all the mixed-solvent systems indicating affinity for both solvents, 1-propanol and water. The BDS r_3 value was calculated as 0.528 nm. As indicated above, V_{cor} values shown in Table 6 were obtained after three iterations. V_{cor} values increase with the 1-propanol-proportion in the mixtures because of the $\overline{V}_1$ values are higher than the $\overline{V}_2$ values in all cases. Additionally, Table 6 summarizes the preferential solvation parameters of BDS by 1-propanol molecules ($\delta x_{1,3}$) in all these mixtures at 298.2 K.

Figure 5 shows a non-linear variation of BDS $\delta x_{1,3}$ values regarding the 1-propanol-proportion in the solvent mixtures as expressed by the mole fraction of 1-propanol before BDS adding. Initially, the addition of 1-propanol to neat water as a solvent makes negative the $\delta x_{1,3}$ values of BDS in the composition interval of $0.00 < x_1 < 0.19$. The maximum negative $\delta x_{1,3}$ value is obtained in the mixture of $x_1 = 0.10$ with $\delta x_{1,3} = -2.85 \times 10^{-2}$, being its absolute value higher than 1.0×10^{-2}, which corresponds to the minimum values associated with real preferential solvation effects. Thus, these $\delta x_{1,3}$ values are considered a consequence of preferential solvation rather than a consequence of uncertainties propagation in IKBI calculations [77, 78]. Possibly the structuring of water molecules around the methyl and methylene groups of this drug compound by hydrophobic hydration contributes to the lowering of the net $\delta x_{1,3}$ to negative values in these water-rich mixtures.

In the mixtures composition interval of $0.19 < x_1 < 1.00$ the local mole fractions of 1-propanol around BDS molecules are higher than those in the bulk aqueous-1-propanol mixtures in the absence of this drug. The

Table 6 Some properties associated to preferential solvation of BDS (3) in {1-propanol (1) + water (2)} mixtures at $T = 298.2$ K

x_1[a]	D (kJ/mol)	$G_{1,3}$ (cm^3/mol)	$G_{2,3}$ (cm^3/mol)	V_{cor} (cm^3/mol)	100 $\delta x_{1,3}$
0.00	−113.03	−1194	−370	1295	0.00
0.05	−94.63	−940	−490	1333	−2.60
0.10	−77.85	−835	−579	1412	−2.85
0.15	−62.76	−783	−667	1508	−1.79
0.20	−49.38	−757	−769	1616	0.22
0.25	−37.74	−744	−890	1732	3.10
0.30	−27.83	−732	−1022	1852	6.65
0.35	−19.60	−700	−1125	1963	9.80
0.40	−12.98	−629	−1111	2038	10.33
0.45	−7.89	−529	−935	2071	7.62
0.50	−4.20	−444	−696	2092	4.13
0.55	−1.77	−396	−510	2125	1.68
0.60	−0.43	−375	−405	2174	0.40
0.65	0.03	−369	−367	2233	−0.03
0.70	−0.17	−371	−389	2299	0.20
0.75	−0.79	−378	−494	2373	1.10
0.80	−1.53	−389	−728	2455	2.71
0.85	−2.09	−390	−898	2520	3.15
0.90	−2.15	−376	−670	2557	1.23
0.95	−1.34	−370	−453	2604	0.18
1.00	0.73	−369	−347	2662	0.00

[a] x_1 is the mole fraction of 1-propanol (1) in the {1-propanol (1) + water (2)} mixtures free of budesonide (3)

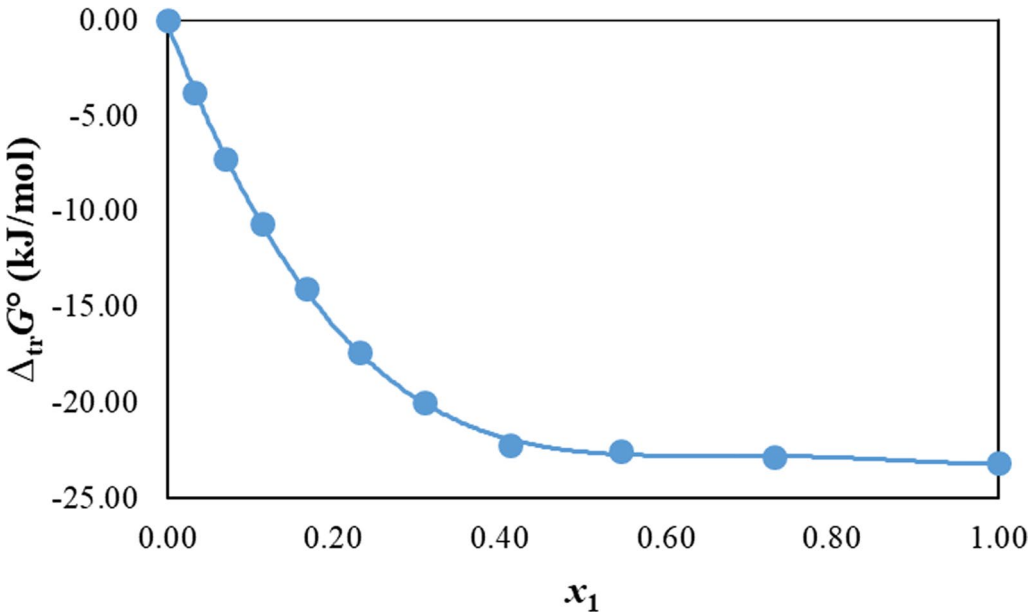


Fig. 5 Gibbs energy of transfer of BDS (3) from neat water (2) to {1-propanol (1) + water (2)} mixtures at $T = 298.2$ K

maximum positive $\delta x_{1,3}$ value is obtained in the mixture of $x_1 = 0.40$, with $\delta x_{1,3} = 0.1033$), which is higher than $|1.0 \times 10^{-2}|$, which means that it is a consequence of preferential solvation effects of BDS by 1-propanol molecules. In this composition interval, BDS could be acting as a Lewis acid in front of 1-propanol molecules by means of its hydroxyl groups, whose hydrogen atoms would be interacting with the unshared electron pairs of the oxygen atoms of 1-propanol establishing hydrogen bonding. It is important to keep in mind that 1-propanol exhibits a higher Lewis base behavior regarding pure water [79] Fig. 6.

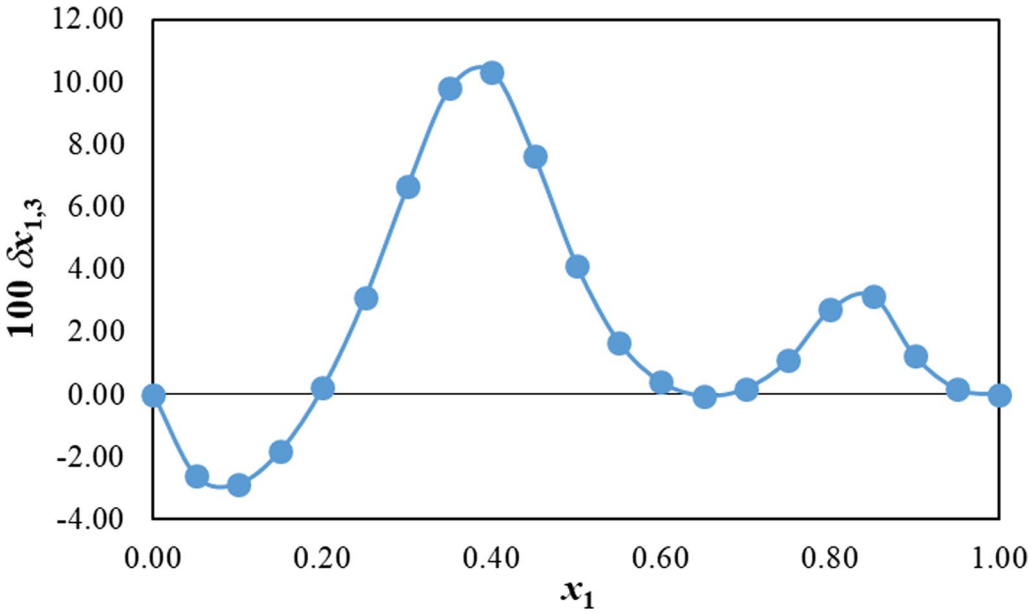


Fig. 6 Preferential solvation parameters ($\delta x_{1,3}$) of BDS (3) by 1-propanol (1) in {1-propanol (1) + water (2)} mixtures at $T = 298.2$ K

Solubility modeling

In the next step, we fit experimental molar BDS solubility data in (1-propanol + water) mixtures to van't Hoff model (as a linear model), Buchowski-Ksiazczak equation (as a non-linear), CNIBS/R–K model (as a linear model for solvent composition at isothermal condition), modified Wilson model (as a non-linear model for isothermal condition), the Jouyban-Acree model (as a model that considers temperature and solvent composition), and Jouyban-Acree-van't Hoff model (as a model with no further input data) were studied. Also, the Williams-Amidon excess Gibbs energy model was investigated. In Tables 7, 8, 9, 10, 11, 12 the constants related to mentioned models with *MRDs %* for back-computed BDS solubility data are presented.

The results obtained for the back-computed BDS solubility in the aqueous mixture of 1-propanol presented low *MRDs%* (< 13.0%) for all investigated models (except modified Wilson models with *MRD*s% equal to 33.32%). It is important to recall that some models including the van't Hoff model applied for the prediction of solubility in the same mass fraction of co-solvent at various temperatures while, other models like CNIBS/R–K model, λh equation, and the modified version of the Wilson model are used to solubility calculation in different mass fraction of solvent in isothermal conditions so, comparison of error levels of various equations cannot be benefited. Fortunately, newer and improved models such as Jouyban-Acree and Jouyban-Acree-van't Hoff models can be used to predict drug solubility in conditions of various temperature and mass fractions of solvent.

In brief, as the results of Table 7, the van't Hoff equation was able-well to the prediction of the BDS solubility so that the overall back-calculated *MRD%* was obtained at 1.93%. Also, based on the CNIBS/R–K model, the *MRDs%* for back-calculated BDS solubility data at 293.2, 298.2, 303.2, 308.2, and 313.2 K were found 11.47%, 13.03%, 1.98%, 11.68%, and 10.39%, respectively. While overall *MRD%* was obtained 11.68% (Table 8). One of the disadvantages of the Yalkowsky model is its dependence on temperature, so the Jouyban–Acree equation was recommended as a solution to the problem of temperature dependence [80]. It is necessary to mention that the general *MRD%* for back-calculated BDS solubility data from 293.2 to 313.2 K was obtained at 12.30%, while for the Jouyban-Acree-van't Hoff model, it was 9.24% (Table 9). In the next step, a modified version of Jouyban-Acree-van't Hoff model (Eq. (14) suggested by Sun et al.) was also evaluated. After excluding non-significant parameters, D_1, D_2, D_3, D_4, D_5 , and D_7 coefficients were found as statistically significant parameters with a p-value < 0.001 (see Eq. (32)). The overall *MRD%* for this model was 11.22%.

$$\begin{aligned} ln\, C_{m,T} = {} & 2.80(\pm 0.78) - \frac{3869.56(\pm 235.63)}{T} \\ & + 4622.36(\pm 121.21)\frac{w_1}{T} - 1159.61(\pm 210.28)\frac{w_1^2}{T} \\ & - 1117.08(\pm 114.80)\frac{w_1^4}{T} \end{aligned} \tag{32}$$

As mentioned before, the van't Hoff model as the most accurate equation cannot apply a trained model to a different solvent composition, while, the modified version of the Wilson model and λh equation is for conditions where the temperature is constant. Therefore, the modified Wilson model was also used to predict BDS solubility in different mixed solutions, so a little poor correlation was observed with an overall *MRD%* of 33.32% (Table 10), although the λh equation performed better with a general *MRD%* value of 1.8% (Table 11). On the other hand, pleased relationship outcomes were found

Table 7 The van't Hoff model parameters and MRD% related to the back-computed solubility of BDS in the aqueous mixture of 1-propanol (1)

w_1 (± 0.005)	*A*	*B*	*MRD*%
0.00	− 0.61	− 2812.43	1.64
0.10	2.48	− 3335.23	4.53
0.20	1.83	− 2725.51	1.73
0.30	3.64	− 2869.70	2.77
0.40	2.92	− 2275.28	3.27
0.50	3.68	− 2161.40	1.00
0.60	3.54	− 1855.52	1.11
0.70	3.28	− 1557.97	0.71
0.80	3.87	− 1748.05	1.10
0.90	3.51	− 1659.44	1.12
1.00	2.65	− 1436.00	2.22
Overall			1.93

Table 8 The CNIBS/R–K model parameters and the corresponding MRD% for back calculated solubility of BDS in the aqueous mixture of 1-propanol (1) at studied temperatures

T (± 0.2 K)	J_0	J_1	J_2	*MRD*%
293.2	12.486	7.385	0[a]	11.47
298.2	12.279	7.098	0[a]	13.03
303.2	12.172	6.859	0[a]	11.98
308.2	12.119	6.501	0[a]	11.68
313.2	12.068	6.147	0[a]	10.39
Overall				11.68

[a] Not statistically significant (p > 0.05)

Table 9 The Jouyban-Acree and Jouyban-Acree-van't-Hoff models constants for molar solubility of BDS in the aqueous mixture of 1-propanol (1)

	Jouyban-Acree		Jouyban-Acree-van't Hoff	
1-Propanol + water	J_0	3703.521	A_1	−2.086
	J_1	2061.998	B_1	−1436.00
	J_2	0[a]	A_2	−9.891
			B_2	−2812.428
			J_0	3114.500
			J_1	1191.212
			J_2	0[a]
R^2	0.998		1.00	
F	1369.824		18,623.186	
P	< 0.001		< 0.001	
MRD%	12.30		9.24	

[a] Not statistically significant (p > 0.05)

Table 10 The Modified Wilson constants and the corresponding MRDs% related to BDS solubility in the aqueous mixture of 1-propanol (1) at studied temperatures from 293.2 to 313.2 K

Modified Wilson model			*MRD*%
T (± 0.2 K)	λ_{12}	λ_{21}	
293.2	48.79	2.11	34.11
298.2	63.50	2.16	32.57
303.2	88.43	2.22	33.95
308.2	128.00	2.30	32.91
313.20	190.47	2.37	33.07
Overall			33.32

Table 11 The λh equation constants and the corresponding *MRD*% for the back-computed BDS solubility in the aqueous mixture of 1-propanol (1)

w_1 (± 0.005)	λ	*h*	MRD%
0.00	0.500	0.569	0.34
0.10	0.500	2.602	3.07
0.20	0.502	8.424	1.07
0.40	0.519	91.898	3.91
0.50	0.560	262.155	1.77
0.60	0.640	509.608	1.61
0.70	0.793	841.011	0.41
0.80	0.831	979.549	0.73
0.90	0.770	809.570	0.72
1.00	0.694	586.740	1.89
overall			1.80

through the MRS model for these considered systems (overall *MRD%* value of 10.70%) (Table 12). Finally, the Williams-Amidon excess Gibbs energy model was used to correlate the model constants. The following results (Eq. (33)) with a back-calculated *MRD%* value of 6.57% were found.

$$\begin{aligned} ln\, C_m = {} & w_1 lnC_1 + w_2 lnC_2 \\ & + 0.718(\pm 0.03)(2w_1 - 1)\left(\frac{V_s}{V_1}\right) \\ & + 0.059(\pm 0.01)w_1^2 w_2^2\left(\frac{V_s}{V_2}\right) \\ & + 0.233(\pm 0.01)w_1^2 w_2 \end{aligned} \quad (33)$$

The difference in the prediction power of mathematical models in various solvent mixtures is because the solubility process is complex and influenced by various factors such as the presence of multiple solvents, solute–solvent interaction, and temperature. In general, the greater the amount of available data lead to the higher the predictive power of mathematical models. It is important to mention that, linear and non-linear models, models for solvent composition at isothermal conditions, models for considering temperature and solvent composition, and models without input data have different accuracies for solubility prediction of various experimental data obtained. On the other hand, by using mathematical models that cover more effective physical and chemical parameters in the dissolution process, the prediction power will be better for most drugs and different solvents.

Conclusions

It is noteworthy that for the following reasons, more studies are needed (to complete our previous studies) (i) the difference in polarity between the drug and solvents causes a different behavior of the same drug to be seen in different solvents, (ii) different solvents can have different interactions with a particular drug, (iii) different solvents at high and low temperatures have their specific characteristics that affect the solubility of the drug, and there is the possibility of seeing unpredictable behavior in the solubility of the drugs, (iv) any mixture of solvent and co-solvent in a specific mass ratio reaches the maximum amount of drug solubility, and minor changes in mass fraction can lead to large differences in drug solubility, (v) different impurities present in different solvents have special effects on the drug solubility process, and (vi) the thermodynamic properties of solvent mixtures are complex and require more analysis [81]. Therefore, the use of a widely used alcohol (1-propanol) in the pharmaceutical industry, as well as the use of different linear

Table 12 The mixture response surface (MRS) model constants and the MRD% for back-computed BDS solubility in the aqueous mixture of {1-propanol (1) + water (2)} at investigated temperatures from 293.2 to 313.2 K

T (± 0.2 K)	β_1	β_2	β_3	β_4	β_5	MRD%
293.2	− 2.36	− 11.85	0.024	0	13.60	10.14
298.2	− 2.19	− 11.41	0.019	0	12.79	12.77
303.2	− 2.11	− 11.29	0.020	0	12.92	10.84
308.2	− 2.04	− 11.07	0.019	0	12.79	9.28
313.2	− 2.02	− 10.94	0.018	0	12.94	10.48
Overall						10.70

and non-linear models to predict solubility, along with examining thermodynamic properties, can be a significant innovation.

The present study was carried out based on the common method of shake-flask under atmospheric pressure. To expand the available data for BDS solubility in cosolvency systems, experimental BDS solubility in various solvent mixtures of {1-propanol (1) + water (2)} within the range of temperature 293.2–313.2 K were investigated. In the next step, several linear and non-linear models were used to predict BDS solubility, and their accuracy was measured by calculating *MRDs%*. The results noted that the used models had good and acceptable accuracy, and in most cases, the *MRDs%* values were lower than 13% obtained. The obtained *MRD%* values for the BDS solubility prediction with van't Hoff model, CNIBS/R–K model, modified Wilson model, Jouyban-Acree model, Jouyban-Acree-van't Hoff model, modified version of Jouyban-Acree-van't Hoff model, Buchowski–Ksiazczak equation (λh equation), MRS model, and Williams-Amidon excess Gibbs energy model were obtained 1.93%, 11.68%, 33.32%, 12.30%, 9.24%, 11.22%, 1.80% and 10.70%, 6.57%, respectively. The lowest and highest *MRD%* values were related to models Buchowski–Ksiazczak equation and the modified Wilson model, respectively. However, in a previous study, Jouyban-Acree model had better predictive power for different temperatures and ratios of solvents compared to others [82]. As mentioned, the Jouyban-Acree model needs experimental data to predict solubility (in neat solvents). To solve this limitation, Jouyban-Acree-van't model is presented, which does not require experimental data. Also, a modified version of the Jouyban-Acree-van't Hoff model is introduced. Comparing the results of these models shows that the Jouyban-Acree-van't Hoff model and its modified version have performed better in BDS solubility prediction (12.30% vs 9.24% and 11.22%).

To find detailed information about the mechanism of the thermodynamic process related to BDS dissolution, apparent thermodynamic parameters in an aqueous mixture of 1-propanol were investigated. According to the calculated apparent thermodynamic factors such as ΔG°, ΔH°, and ΔS°, under endothermic and entropic conditions, BDS dissolves in a 1-propanol aqueous mixture. Experimental data of mathematical modeling and thermodynamic factors obtained in the present study for BDS solubility in an aqueous mixture of 1-propanol can be useful for pharmaceutical companies, researchers, and medicinal chemists in the drug discovery and development fields. The comprehensive view that this study provides for these researchers in continuation of the previous research works is that the maximum amount of BDS solubility is created in lower mass fractions of cosolvent (0.7 vs 0.8 and 0.9) than in previous studies, which reduces the use of cosolvent. Also, positive values for ΔG°, ΔH°, and ΔS° factors have been similar to the studies. On the other hand, unlike previous studies that only evaluated linear or non-linear models, a comprehensive review of a wide range of mathematical models to predict BDS solubility is one of the salient features of the current study.

Previous studies have shown that water-miscible organic solvents can be used in the formulation of soft gelatin capsules for some drugs so a significant increase in the bioavailability of drugs was observed. Water-miscible solvent systems were applied in the complex excipients of oral solution and elixir formulations to achieve the desired concentration for low water-soluble drugs. Increasing the solubility of drugs that are poorly soluble in water leads to a decrease in the dosage, an increase in the acceptance of the drug by the patient, as well as a decrease in side effects. The organic solvents (such as PEG 400, PG(Propylene glycol), and ethanol) along with water in some injectable formulations in the pharmaceutical market were observed, although there is a possibility of precipitation, pain, inflammation, and hemolysis after injection. These formulations can be diluted at least twofold before injection. Therefore, studying the BDS solubility in (water + cosolvent) systems can significantly help

in creating a wide range of new formulations (soft gelatin capsules, oral, injectable, and controlled release formulations) of this drug to improve its pharmacokinetic properties [83].

Future perspective

The experimental measurement of BDS solubility was based on the reliable shake flask method and the *SD* values are shown in Table 1. In all cases, the *RSD%* value was less than 5%. The *MRDs%* more than 10% for solubility prediction of BDS can have several reasons as follows: (i) there is always the possibility of outliers in the measurement of experimental data due to different laboratory conditions and materials used as well as individual errors, (ii) more experimental data always lead to more accurate prediction of solubility, and (iii) according to the parameters used in mathematical models, their efficiency is different and some models are less accurate in predicting solubility in most studies. The limitations of the present study can be improved in future studies. Therefore, the examination of BDS solubility in other solvent mixtures with a wider temperature range, as well as, studies of several mathematical models predicting BDS solubility and thermodynamic behavior for BDS in the mentioned mixture can be suggested by this study. Also, the present study will guide future research to improve the selection of the best solvent mass fractions in the other solvent mixtures and temperatures to obtain maximum BDS solubility in future practical studies. These correlation models could imply neural networks and similar ones. On the other, time and cost of future studies will be reduced.

Supplementary Information

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Additional file 1.

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The datasets used or analyzed during the current study are available from the corresponding authors on reasonable request.

Declarations

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Consent for publications
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Competing interests
The authors declare no competing interests.

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