Budesonide Solubility in 2-Propanol+ Water Mixtures at T = (293.2 to 313.2) K: Experimental Measurement, Thermodynamic Analysis and Mathematical Modeling

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ABSTRACT: *A shake-flask method was used to investigate the solubility and thermodynamic properties of budesonide (BDS) in the temperature scope of 293.2-313.22 K in aqueous mixtures of 2-propanol. There are two categories of mathematical models used to fit the experimental data: linear and non-linear cosolvency mathematical models, such as the van't Hoff's model, Yalkowsky's equation, CNIBS/R–K model, Buchowski, and Ksiazczak equation, modified Wilson model, the Williams-Amidon excess Gibbs energy model, and two Jouyban-Acree models: the Jouyban-Acree and the Jouyban-Acree-van't Hoff. The experimental data for BDS solubility at 298.1 K was also represented with KAT-LSER model. Using back-calculated solubility data, mean relative deviations (MRDs %) of used models were calculated to illustrate fitness and accuracy. Furthermore, van't Hoff and Gibbs equations have been applied to describe how BDS dissolves in binary solvent mixtures with entropy, enthalpy, and Gibbs free energy included.*

KEYWORDS: *Budesonide, Solubility, 2-Propanol, Aqueous mixtures, Cosolvency, Thermodynamic behavior.*

INTRODUCTION

Budesonide (BDS, sold under the brand name Pulmicort), a potent synthetic corticosteroid, was approved by the FDA on January 14, 2013 to treat mild to moderate ulcerative colitis (UC). [1]. Patients with mild-moderate and distal UC can benefit from this treatment in oral and rectal forms. It is used topically to treat IBD, as well as to induce remission in Crohn's Disease (CD) patients who suffer from disease distribution involving the distal ileum and

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right colon [2,3]. In addition, studies have shown that BDS can be used in the treatment of some other illnesses containing autoimmune hepatitis, asthma, eosinophilic esophagitis, rhinitis, Berger's disease, Chronic Obstructive Pulmonary Disease (COPD) and inflammatory bowel disease [4-6].

The COVID-19 outbreak, which is regarded as the most serious problem of humanity since the start of World War II, was first detected in Wuhan City, Hubei Province, China, on December 19, 2019. SARS-CoV-2 infection is responsible for this new type of pneumonia [7,8]. As a result of SARS-CoV-2 infection, patients may suffer from fatigue, fever, and dry cough. World Health Organization (WHO) recommendations include using a mask, keeping social distance, and washing hands frequently. In addition to vaccines, some drugs such as remdesivir, favipiravir, ribavirin, penciclovir, lopinavir/ritonavir, hydroxychloroquine and chloroquine and arbidol are potentially therapeutic for the treatment of COVID-19 [9]. A recent research study showed that BDS reduced COVID-19-related urgent care or hospitalization, resulting in shorter recovery times, quicker self-reported clinical recovery, and a steep reduction in fever. However, BDS has also been shown to reduce rhinovirus replication in vitro. The results suggest that adult people with early COVID-19 might benefit from treatment and the extreme pressure on the healthcare system might be reduced by treating early COVID-19 [10].

BDS, in Class II of the biopharmaceutics classification system, are practically insoluble in water with a solubility of about 16 μg/mL, and possess log$P$ of 2.32 [11]. These features at physiological pH in the intestinal region may lead to reduced dissolution and therapeutic potential of BDS. It is due to liver biotransformation that three potential metabolites can be produced, resulting in BDS's low oral bioavailability of about 10%, effectual systemic removal and a great hepatic clearance [12-14]. Also, BDS is effective and safe in treating respiratory diseases such as asthma by way of inhalation, but its solubility in aqueous solutions can impact its systemic absorption and the rate at which it leaves the respiratory tract by way of cough and mucociliary clearance [15,16]. Given the widespread use of BDS in various diseases, especially COVID-19, as well as limitations in its physicochemical properties, it is important to conduct studies to improve the existing properties.

Drug solubility can be utilized to procure drug formulations, characterization of solid phases, improvement of purity and also yield with recrystallization comparison of experiments in vitro and in vivo and developing pharmaceutical analysis techniques, by testing the solubility of drugs in various types of solvents, including aqueous and non-aqueous solutions [17-20]. Furthermore, the study of different factors influencing the solubility of the drug in a solvent, such as the polarity, dielectric constant, cosolvents, temperature, and pH allow the scientist and research to select the appropriate solvent for using during the different stages in the research, development, and industrial processes [21]. It is worth mentioned that the details of the solubility process and a description of a drug's structure and intermolecular forces may be useful in the following cases: i) introducing of the appropriate separation processes, ii) finding a high separation ratio, iii) predicting the dividing of molecules of drugs in immiscible and nonimmiscible phases, and iv) acquire the suitable solvent system to extract drugs and drug-like molecules from a variety of biological samples [22].

In the case of drugs with low aqueous solubility such as BDS in class II biopharmaceutics with 16 μg/mL, solubilization allows us to enhance the bioavailability, reduce doses, improve efficiencies and develop chemical processes *e.g.* methods based on crystallization and chromatographic separation/purification [23, 24]. On the other hand, improving the solubility of BDS can lead to decrease variability in T_{max} and C_{max}. As you know, reaching faster to Minimum Effective level Concentration (MEC) is a critical point for therapeutic efficacy [13].

Various techniques have been used to alter the drugs solubility including i) cosolvency method, ii) procedures based on size reduction, iii) approach of solid dispersion, iv) salt formation of drug, v) method based on crystal engineering, vi) using of surfactants and complexation, vii) pH adjustments of solutions, viii) chemical modifications on the structure of drugs, ix) emulsions production, x) production of liposomes, xi) micronization, xii) hydrotropic, etc [19-21]. Among these methods, cosolvency is a popular method to increase the solubility, particularly of drugs that are poorly water-soluble. It is a simple and easily applicable method widely used in the pharmaceutical industry [25,26]. In the cosolvency method, the solvent selection step is crucial to the design and formulation process [27,28]. Nevertheless, solubility measurements in all possible solvent mixtures have two major limitations including time-consuming procedure

and low feasibility [19,20]. As an alternative approach and to overcome these limitations, several mathematical models were introduced to predict the drugs solubility when mixed with water and cosolvents. Another goal is to find the optimal concentration of cosolvents to maximize drug solubility. Until now, the solubility of special drugs in various cosolvent mixtures (including aqueous and non-aqueous solutions) has been predicted using several models by our group, and their accuracies were compared with each other [20,27,29-31].

With the use of interpolation and the least of data points for solubility, various theoretical and semi-empirical models have been considered to predict drug solubility in different conditions of solvent ratio and temperature [19]. In studies, the Jouyban-Acree model has been found to have advantages over the rest in the point view of good predictability across a wide range of temperatures and solvent composition [20,26,32].

The BDS solubility in aqueous mixtures of polyethylene glycol 400 (PEG400) [33], N-methyl-2-pyrrolidone (NMP) and ethanol [35], some non-aqueous mono-solvents [36] and six mono solvents including i) ethyl acetate, ii) ethanol, iii) acetone, iv) carbon tetrachloride, v) water and vi) n-hexane [37], has been reported in previous studies. Aiming to present an appropriate and best solvent system special for BDS, experimental measurements of the BDS solubility were carried out at various temperatures in 2-propanol aqueous mixture. Our systematic investigation in field of solubility of drugs in mixed systems for various applications at laboratory and industrial scale continues with this study. In the following, the experiment solubility data are correlated/back-calculated with the CNIBS/R–K model, Yalkowsky's equation, Buchowski, and Ksiazczak equation, modified Wilson model, the Williams-Amidon excess Gibbs energy model, and two Jouyban-Acree models: the Jouyban-Acree and the Jouyban-Acree-van't Hoff, as a comprehensive investigation, were performed. A KAT-LSER model was also investigated to show BDS solubility properties at 298.2 K. Additionally, BDS dissolved in 2-propanol + water was evaluated for its apparent thermodynamic data.

EXPERIMENTAL SECTION

Materials

BDS (obtained from Lirok Pharma, Tehran, Iran with 0.98 mass fraction purity), 2-propanol (obtained from Scharlau Chemie, Spain with 0.995 mass fraction purity), distilled water (Lab made) and ethanol (obtained from Jahan Alcohol Teb, Arak, Iran with 0.935 mass fraction purity) in order to dilution the solution before spectrophotometric determination were the materials applied throughout this work. The chemicals were used without further purification as obtained directly from manufacturers.

Solubility determination

In this study, we used the famous shake-flask approach as common technique based on solid-liquid equilibrium to investigation solubility of BDS in 2-propanol aqueous binary mixture [38]. The additional of BDS was first added into vials containing mixtures of various solvents in the range of 0.1 to 0.9% in mass fractions. In the next step, exactly for 48 hours, the primed vials were shaken using a shaker (Heidolph® Unimax 1010 Orbital Shaker) placed in an incubator (Heidolph® Model 1000 Incubator Heating Unit) having a temperature-control system that operates between 293.2 and 313.2 K (with a 0.2K uncertainty). After equilibrium was reached, the syringe filters (0.22 μm) were applied to remove the solid phase. In the following, sample solutions were diluted with the appropriate amount of ethanol, and the absorbance of the ready mixture at 242 nm was measured for drug contents applied with UV–Vis spectrophotometer (Shimadzu, Kyoto, Japan). After diluted solutions were tested for absorbance, the concentration of BDS in saturated solutions was interpolated in accordance with the calibration curve. The average of the experimental data points was determined after measuring all data points in triplicate.

Thermodynamic analysis of dissolution

It has been proven which there is a correlation between dissolution process of solubility and the absorption and ΔH° known as freedom of heat, and ΔS° known as changes in entropy () [33,39]. To obtain the essential data in the dissolution procedure of BDS, the Gibbs and in the study of BDS dissolution in 2-propanol aqueous mixtures, van't Hoff's equations were applied. In the present study ΔH°, ΔS° and ΔG° respectively known as the dissolution standard enthalpy, standard entropy of process and changes in Gibbs free energy were computed as apparent thermodynamic functions to investigate the BDS dissolution behavior in the binary solvent mixture of

{2-propanol (1) + water (2)}. The general form of the modified version of van't Hoff's equation can be written as [40]:

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

In Eq. (1), C, T_{hm} and T denote molar solubility of drug in the desired cosolvent mixture, the mean harmonic temperature and the absolute temperature based on the Kelvin unit, respectively. The ideal gas constant is show by R.

The symbol T_{hm} represents the mean harmonic temperature that was written pursuant to

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

While the number of investigated temperatures is indicated by the sign n. As a result of temperature variations between 293.2 and 313.2 K, 303.0 K was obtained as the T_{hm} value.

Based on Eq. (3) and (4), the values of ΔH° related to solutions from intercept of the plot of ln x vs $1/T - 1/T_{hm}$ and ΔG° of solutions from the slope of the plot of ln x vs $1/T - 1/T_{hm}$, were obtained, respectively [40].

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

$$\Delta G^\circ = -RT_{hm}.\ \text{intercept} \quad (4)$$

At T_{hm} value of 303.0 K, Gibbs's equation was used to compute the ΔS° in the dissolution process:

$$\Delta G^\circ = \Delta H^\circ - T_{hm}\Delta S^\circ \quad (5)$$

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

The relative contributions of ζ_H *(*related to the enthalpy*)* and ζ_{TS} *(*related to the entropy*)* to ΔG°, for dissolution procedure of BDS in the binary solvent mixture of {2-propanol (1) + water (2)} were calculated by the following equations [41].

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

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

Computational validation

Eight commonly used mathematical models such as i) van't Hoff's model, ii) CNIBS/R–K model, iii) Yalkowsky's equation, iv) modified Wilson model, v) Buchowski, and Ksiazczak equation, vi) Williams-Amidon excess Gibbs energy model and two Jouyban-Acree models: vii) the Jouyban-Acree and viii) the Jouyban-Acree-van't Hoff, are used to correlate BDS investigational solubility data in 2-propanol aqueous mixtures.

The following equations are detailed:

The van't Hoff equation

Using van't Hoff's formula we can create a correlation between solubility of given solute and temperature at a specific solvent ratio as follows [42]:

$$\ln C_T = A + \frac{B}{T} \quad (9)$$

The parameters of the equation are A and B.

It is noteworthy that by utilizing Eq. (10), it is possible to investigate temperature-dependent solubility data for drugs by using a modified van't Hoff's equation [43].

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

A and B are the constants of the model, and using Eq. (2), T_{hm} (mean harmonic temperature) is calculated.

The CNIBS/R–K model

Based on the log-linear Yalkowsky and Redlich–Kister extension, Acree in 1992 developed the combined nearly ideal binary solvent/Redlich–Kister model to relate the value of solute solubility in binary isothermal solvent mixtures [44].

Model equation is presented in the following common form:

$$ln C_{m,T} = w_1 \ln C_{1,T} + w_2 \ln C_{2,T} + w_1.w_2 \sum_{i=0}^{2} J_i.(w_1 - w_2)^i \quad (11)$$

Herein C_1 and C_2, C_m and w_1 and w_2 are solubilities of solute in neat solvents 1 and 2, the binary mixture's solute solubility and solvent 1 and solvent 2 mass fractions when the solute is absent, respectively. Also, J_i as the model constant is calculated by regressing $ln C_{m,T} - (w_1 \ln x_{1,T} + w_2 \ln x_{2,T})$ versus w_1w_2, w_1w_2 $(w_1 - w_2)$ and w_1w_2 $(w_1 - w_2)^2$.

Yalkowsky model

In Yalkowsky's equation, the solubility of solute in pure solvents correlates very well with the solute solubility in different mixture of solvent.

Calculate it using Eq. (12) [45]:

$$lnC_m = w_1 lnC_1 + w_2 lnC_2 \quad (12)$$

Rearranging the model would result in Eq. (13):

$$lnC_m = lnC_2 + \left(ln\frac{C_1}{C_2}\right)w_1 = lnC_2 + \sigma\ .w_1 \quad (13)$$

Here the model constant, σ, can be defined based on a direct correlation among the log P and σ as shown in the equation below [46]:

$$\sigma = M.logP + N \quad (14)$$

M and N are the constants of cosolvent. Replace σ of Eq. (14) with Eq. (13) can lead to a new predictive model as Eq. (15):

$$lnC_m = lnC_2 + (M.logP + N)\,w_1 \quad (15)$$

Based on this equation, the solubility of a drug (BDS in this study) in aqueous mixtures can be computed applying common *M*, *N*, log *P* values and investigational aqueous solubility of the drug.

Jouyban-Acree model

This model as a multiple linear cosolvency mode, is among the most precise models for binary solvent systems [20].

In this model binary mixed solvent's solubility is determined by the relationship between the Temp. and composition of the solvent. In general, the model is showed by Eq. (16) [47]:

$$\ln C_{m,T} = w_1.\ln C_{1,T} + w_2.\ln C_{2,T} + \frac{w_1.w_2}{T}\sum_{i=0}^{2} J_i.(w_1 - w_2)^i \quad (16)$$

Herein $C_{m,T}$,$C_{1,T}$and$C_{2,T}$, are defined as solvent mixture's solubility of BDS, BDS solubility in the pure solvents 1and 2 at temperature *T* (Kelvin), respectively [47].

J_i is the constants of equation that can been produced by regressing $\ln C_{m,T} - w_1.\ln C_{1,T} - w_2.\ln C_{2,T}$ versus $\frac{w_1.w_2}{T}$, $\frac{w_1.w_2(w_1-w_2)}{T}$ and $\frac{w_1.w_2(w_1-w_2)^2}{T}$.

Jouyban-Acree- van't Hoff model

By combining the Jouyban-Acree equation and van't Hoff's models a most precise mathematical model has been developed analyzing data on drug solubility in a solution mixture [48].

The mentioned model is expressed as [48]:

$$lnC_{m,T} = w_1\left(A_1 + \frac{B_1}{T}\right) + w_2\left(A_2 + \frac{B_2}{T}\right) + \frac{w_1w_2}{T}\sum_{i=0}^{2} J_i(w_1 - w_2)^i \quad (17)$$

As a linear regression is used to obtain the equation coefficients, A_1, B_1, A_2, B_2, and J_i. Based on data on temperature-dependent solubility in aqueous mixture of 2-propanol, A and B terms could be calculated and J_i terms are obtained by regressing $((lnC_{m,T} - w_1\left(A_1 + \frac{B_1}{T}\right) - w_2\left(A_2 + \frac{B_2}{T}\right)))$ versus $\frac{w_1.w_2}{T}$, $\frac{w_1.w_2(w_1-w_2)}{T}$, and $\frac{w_1.w_2(w_1-w_2)^2}{T}$.

The modified version of Eq. (18), that proposed by *Sun et al*. can be given as [49].

$$lnC_{m,T} = D_1 + \frac{D_2}{T} + D_3w_1 + D_4\frac{W_1}{T} + D_5\frac{w_1^2}{T} + D_6\frac{w_1^3}{T} + D_7\frac{w_1^4}{T} \quad (18)$$

In which a regression analysis is used to compute constants of model D_1 through D_7.

Modified Wilson model

For all investigated temperatures, in addition to the linear mathematical models, non-linear equations like the mentioned model can be used for correlating, predicting and fitting the obtained data of solubility [20,50].

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

$$-lnc_m = 1 - \frac{w_1(1 + lnC_1)}{w_1 + w_2\lambda_{12}} - \frac{w_2(1 + lnC_2)}{w_1\lambda_{21} + w_2} \quad (19)$$

Here, the constants of model including Λ_{12} and Λ_{21} are obtained via an analysis based on nonlinear least squares.

Buchowski–Ksiazczak equation

Buchowski et al. originally proposed this non-linear/ activity coefficient mathematical model which also known as Λh equation [51]. With only two adjustable parameters, it can be applied to systems with equilibrium between solid and liquid phases with suitable relationship results. Molecular systems featuring strong polarities and strong interactions are suited to this model approach.

Table S1: Kamlet- Abboud -Taft parameters π* (dipolarity-polarizability), α (hydrogen bond donor parameter) and β (hydrogen bond donor parameter) and Hildebrand solubility parameter, δ_H, of the investigated solvent mixtures at 298.15 K.

2-Propanol (1) + water (2)					Ethanol (1) + water (2)				NMP (1) + water (2)			
w_1[a]	π*[b]	β [b]	α [b]	δ_H [c]	π*	β	α	δ_H	π*	β	α	δ_H
0.00	1.09	0.47	1.17	47.82	1.09	0.47	1.17	47.82	1.09	0.47	1.17	47.82
0.10	1.10	0.50	1.04	44.80	1.08	0.52	0.99	45.12	1.12	0.56	1.03	45.36
0.20	1.08	0.57	0.88	41.94	1.05	0.57	0.79	42.59	1.13	0.62	0.91	42.9
0.30	0.95	0.64	0.82	39.22	0.97	0.62	0.72	40.20	1.13	0.65	0.79	40.49
0.40	0.86	0.67	0.81	36.66	0.90	0.66	0.72	37.84	1.13	0.66	0.7	38.01
0.50	0.80	0.71	0.81	34.20	0.83	0.70	0.75	35.66	1.13	0.67	0.61	35.54
0.60	0.76	0.72	0.81	31.87	0.79	0.71	0.75	33.59	1.12	0.68	0.53	33.05
0.70	0.72	0.74	0.80	29.66	0.74	0.72	0.75	31.60	1.1	0.69	0.42	30.55
0.80	0.67	0.76	0.79	27.54	0.69	0.74	0.78	29.72	1.07	0.71	0.31	28.03
0.90	0.62	0.79	0.78	25.51	0.63	0.75	0.80	27.86	1.01	0.74	0.17	25.51
1.00	0.48	0.84	0.76	23.58	0.54	0.75	0.86	26.13	0.92	0.77	0.00	22.96

[a] w_1 is the mass fraction of solvent (1) in the cosolvency system free of the solute.
[b] Kamlet-Taft parameters are taken from literature for aqueous mixtures of ethanol and 2-propanol[56] , NMP[57].
[c] δ_H values for pure solvents are obtained from the Hoy solubility parameter software[58], and for binary mixtures are estimated as a function of the mass fraction of solvents by $\omega_1\delta_{H1} + \omega_2\delta_{H2}$ in the mixture.

The Buchowski, and Ksiazczak (ʎh) equation can be written as:

$$ln\left[1+\frac{\lambda(1-C)}{C}\right]=\lambda h\left[\frac{1}{T}-\frac{1}{T_{hm}}\right] \quad (20)$$

Here ʎ and h are the model constants.

The excess Gibbs energy model of Williams–Amidon

As another cosolvency model, Williams-Amidon excess Gibbs energy model can be presented as follows [52]:

$$\begin{aligned}\ln C_m = {} & w_1 \ln C_1 + w_2 \ln C_2 - A_{1-2} w_1 w_2 \\ & (2\,w_1 - 1)\left(\frac{V_s}{V_1}\right) + (2\,A_{2-1})\,w_1^2 w_2\left(\frac{V_s}{V_2}\right) + \\ & 3D_{12} w_1^2 w_2^2\left(\frac{V_s}{V_2}\right) + a_2 w_1 w_2^2\left(\frac{V_s}{V_2}\right) + a_1 w_1^2 w_2\end{aligned} \quad (21)$$

Here A_{1-2}, A_{2-1}, α_1, α_2 and D_{12} are defined as the terms related to interactions between solvent and solvent as well as solvent and solute. Also, V_1, V_2, and V_s denote the cosolvent molar volume, water molar volume and solute molar volume, respectively. Using data obtained from experimental solubility study, interaction terms between the solute-solvent and solvent -solvent are derived.

KAT-LSER model

This model is utilized for correlating the solubility of solute in pure solvents and solute solubility in mixed solvents at 298.15 K [53, 54]. In this equation, the polarity of solvent is divided into three empirical constants related to solvent according to the crucial parameters of solvatochromic, i.e. π*, β and α that defined as the solvent dipolarity/polarizability, measures a solvent's basicity and acidity, respectively.

The KAT-LSER model is given as:

$$\log C = c_0 + c_1.\pi^* + c_2.\beta + c_3.\alpha + c_4.\left(\frac{V_s\delta_H^2}{100RT}\right) \quad (22)$$

Here $c_{i=0\text{-}4}$ is the model factors, the term $\left(\frac{V_s\delta_H^2}{100RT}\right)$ refers to the cavity term that originated from interaction energy between solvent molecules [27]. Also, $V_s\delta_H^2$, V_s, δ_H, R and T are cavity terms that defined as the solute accommodation energy, solute molar volume, solvent Hildebrand solubility constant, ideal gas parameter and the specific temperature of solution. Table S1 and S2 summarize KAT parameters of investigated binary mixture and mono solvent, respectively.

The combined van't Hoff equation

A new combined van't Hoff's model with the well-known parameters of solubility (*i.e.* Abraham, Hansen and Catalan solvation parameters) is described [55]. The trained model with noteworthy contributions for studied parameters is obtained from the general form of the model:

$$\begin{aligned}\ln x = {} & \left(\alpha_0 + \sum_{i=1}^{5}\alpha_{i,AP}AP_i + \sum_{i=1}^{3}\alpha_{i,HP}HP_i + \sum_{i=1}^{4}\alpha_{i,CP}CP_i\right) + \\ & \left(\frac{\beta_0+\sum_{i=1}^{5}\beta_{i,AP}AP_i+\sum_{i=1}^{3}\beta_{i,HP}HP_i+\sum_{i=1}^{4}\beta_{i,CP}CP_i}{T}\right)\end{aligned} \quad (23)$$

Table S2: Kamlet- Abboud -Taft parameters π* (dipolarity-polarizability), α (hydrogen bond donor parameter) and β (hydrogen bond donor parameter) and Hildebrand solubility parameter, δ_H, of the investigated mono solvents at 298.15 K.

Solvent	π^{*a}	β^a	α^a	$\delta_H{}^b$
1-Propanol	0.52	0.9	0.84	24.45
Acetonitrile	0.75	0.4	0.19	24.4
Ethyl acetate	0.5	0.5	0	18.2
1,4-Dioxane	20.5	0.55	0.37	0
Ethylene glycol	0.92	0.52	0.9	33.11
Methanol	0.7	0.7	1.1	29.6
N-Methyl-2-pyrrolidone	0.92	0.77	0	22.96
Propylene glycol	0.83	0.78	0.76	30.22
Acetic acid	0.64	0.45	1.12	13.5

[a] Kamlet-Taft parameters are taken from literature for mono solvents of 1-Propanol, Acetonitrile and Ethyl acetate [59], 1,4-Dioxane, Ethylene glycol, Methanol, N-Methyl-2-pyrrolidone and Propylene glycol [60] and Acetic acid [61].

[b] δ_H values for pure solvents are obtained from the Hoy solubility parameter software [58], and for binary mixtures are estimated as a function of the mass fraction of solvents by $\omega_1\delta_{H1} + \omega_2\delta_{H2}$ in the mixture.

Where the model constants are α and β terms and also Abraham (AP_i), Hansen (HP_i) and Catalan (CP_i) solvation parameters were utilized as terms of interaction between solute and solvent.

Model accuracy

Eqs. (9) to (23) are used to fit and correlate with BDS experimental molar solubility in aqueous mixture of 2-propanol at various temperatures. The %MRD (mean relative deviation) between the back-calculated and the experimental values are computed by Eq. (24) and applied for the study of the accuracy of the correlate.

$$\%\,MRD = \frac{100}{N}\sum\left(\frac{|Calculated\ value - Observed\ value|}{Observed\ value}\right) \quad (24)$$

The N indicates how many experimental data points are included in each set.

RESULTS AND DISCUSSIONS

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

In Table 1, BDS molar solubility values ± standard deviations for binary mixtures of 2-propanol and water in the temperature range 293.2 - 313.2 Kelvin are presented. The solubility measurements for three times are used to calculate the mean in an experiment with *RSD*% value of <10. At 293.2 K, neat water shows the lowest molar solubility of BDS in aqueous mixtures of 2-propanol (3.62 (±0. 127) × 10^{-5} mol/L), while at 313.2 K, in 0.8 mass fraction of 2-propanol shows the highest (1.17 (±0.038) × 10^{-1} mol/L). Our findings for solubility of BDS in pure solvent (2-propanol and water) are consistent with the reported data in a previous work [36]. Based on Table 1's data, the BDS molar solubility rises with enhancing temperature and 2-propanol mass fraction, so that after adding 2-propanol, the value reached its maximum at 0.8 mass fraction at all temperatures then decreased as 2-propanol was added further. Observed patterns for solubility are influenced by the mixed solvents polarity. In the presence of a cosolvent like 2-propanol, the polarity of water will decrease and its polarity will be suitable for dissolving a drug like BDS with a log P of 2.32 (according to the principle of "like dissolves like"). From the literature, dielectric constants related to aqueous mixture of 2-propanol (1) were collected [62] and summarized in Table 2. As can be observed, BDS becomes more soluble when the polarity of the solvent mixtures decreases. Also in order to the drug solubility and respective polarities dependency study, Fedors' method was used to estimate BDS's internal energy, molar volume, and Hildebrand solubility parameter, so that these parameters are obtained 192.57 kJ/mol , 371.4 cm^3/mol and 0.720 $MPa^{1/2}$, respectively [63, 64] (Table 3). Nevertheless, solubility is determined by various factors such as polarity, interactions available at intermolecular scale, hydrogen bonds, and van der Waals' interactions of solute-solvent as well as between a solvent and a solvent. Therefore, it is extremely difficult to explain a solute's solubility behavior with only one factor. Based on the results obtained in the present investigation, the polarity of solvents can play a significant role in the solubility of BDS.

UP to now, the BDS molar solubility is studied in four binary systems including PEG 400- water [33], ethanol-water [35] and NMP-Water [34]. The comparison between BDS solubility data across various reported binary systems is shown in Fig. 1. As can be seen, there are two solubility profiles for the examined systems: systems containing ethanol-water and 2-propanol-water denote a maximal fraction of cosolvent; while in systems containing PEG 400-water and NMP-water with increasing mass fraction of cosolvent, their solubility rises linearly. NMP - water system determines maximum solubility values.

Table 1: Experimental molar solubility ($C_{m,T}^{sat}$) values {as the mean of three experiments measured (± standard deviation)} for BDS (3) in 2-propanol (1) + water (2) solvent mixtures at various temperatures.

w_1[a]	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00	3.62 (±0. 127) × 10^{-5}	4.44 (±0.048) × 10^{-5}	5.20 (±0. 122) × 10^{-5}	5.93 (±0.166) × 10^{-5}	6.73 (±0.333) × 10^{-5}
0.10	1.55 (±0. 073) × 10^{-4}	1.78 (±0. 072) × 10^{-4}	2.34 (±0. 147) × 10^{-5}	2.79 (±0.192) × 10^{-4}	3.19 (±0.133) × 10^{-4}
0.20	6.71 (±0.057) × 10^{-4}	7.27 (±0.066) × 10^{-4}	8.51 (±0.148) × 10^{-4}	1.05 (±0.046) × 10^{-3}	1.17 (±0.030) × 10^{-3}
0.30	2.30 (±0. 099) × 10^{-3}	2.70 (±0. 078) × 10^{-3}	3.29 (±0.116) × 10^{-3}	4.06 (±0.152) × 10^{-3}	4.50 (±0.244) × 10^{-3}
0.40	7.48 (±0. 143) × 10^{-3}	8.70 (±0.086) × 10^{-3}	9.47 (±0. 148) × 10^{-3}	1.11 (±0.034) × 10^{-2}	1.27 (±0.060) × 10^{-2}
0.50	2.00 (±0. 094) × 10^{-2}	2.23 (±0. 077) × 10^{-2}	2.65 (±0. 115) × 10^{-2}	3.22 (±0.156) × 10^{-2}	3.62 (±0.149) × 10^{-2}
0.60	4.20 (±0. 083) × 10^{-2}	5.30 (±0. 116) × 10^{-2}	5.98 (±0. 069) × 10^{-2}	7.26 (±0.053) × 10^{-2}	8.26 (±0.323) × 10^{-2}
0.70	6.44 (±0. 096) × 10^{-2}	7.73 (±0. 384) × 10^{-2}	8.51 (±0.511) × 10^{-2}	9.67 (±0.229) × 10^{-2}	1.05 (±0.051) × 10^{-1}
0.80	7.71 (±0.091) × 10^{-2}	8.93 (±0.331) × 10^{-2}	9.84 (±0.169) × 10^{-2}	1.09 (±0.007) × 10^{-1}	1.17 (±0.038) × 10^{-1}
0.90	5.84 (±0.135) × 10^{-2}	6.97 (±0.113) × 10^{-2}	7.94 (±0.378) × 10^{-2}	9.47 (±0.478) × 10^{-2}	1.06 (±0. 009) × 10^{-1}
1.00	3.67 (±0.139) × 10^{-2}	4.21 (±0.106) × 10^{-2}	4.82 (±0.082) × 10^{-2}	5.41 (±0.034) × 10^{-2}	6.09 (±0.119) × 10^{-2}

[a] ***w_1* is mass fraction of 2-propanol (1) in the 2-propanol (1) + water (2) mixtures in the absence of BDS (3).**

Table 2: Molar solubility profile {mean of three experiments (± SD)} of BDS and dielectric constant of the solvent mixtures of 2-propanol (1) + water (2) at 298.2 K.

w_1	Dielectric constant	Solubility (mol/L) values {mean of three experiments (± SD)}
0.00	78.5	44 (±0.048) × 10^{-5}
0.10	71.4	1.78 (±0. 072) × 10^{-4}
0.20	64.1	7.27 (±0.066) × 10^{-4}
0.30	56.9	2.70 (±0. 078) × 10^{-3}
0.40	49.7	8.70 (±0.086) × 10^{-3}
0.50	42.5	2.23 (±0. 077) × 10^{-2}
0.60	35.3	5.30 (±0. 116) × 10^{-2}
0.70	28.7	7.73 (±0. 384) × 10^{-2}
0.80	23.7	8.93 (±0.331) × 10^{-2}
0.90	20.3	6.97 (±0.113) × 10^{-2}
1.00	18	4.21 (±0.106) × 10^{-2}

Table 3: Using the Fedors' method to estimate BDS's internal energy, molar volume, and Hildebrand solubility parameter

Group	Group number	ΔU° / kJ mol^{-1}	V / cm^3 mol^{-1}
CH_3	3	14.1075	100.5
CH_2	7	34.5268	112.7
CH	6	20.5656	-6
-CH=	3	12.9162	40.5
C=	1	4.3054	-5.5
Ring closure 5 or more atoms	5	5.225	80
co	2	34.694	21.6
0	2	6.688	7.6
OH	2	59.5232	20
Σ ΔU°= 192.5517 , Σ V= 371.4 , δ3=(192.5517/371.4)$^{1/2}$=0.720 $MPa^{1/2}$			

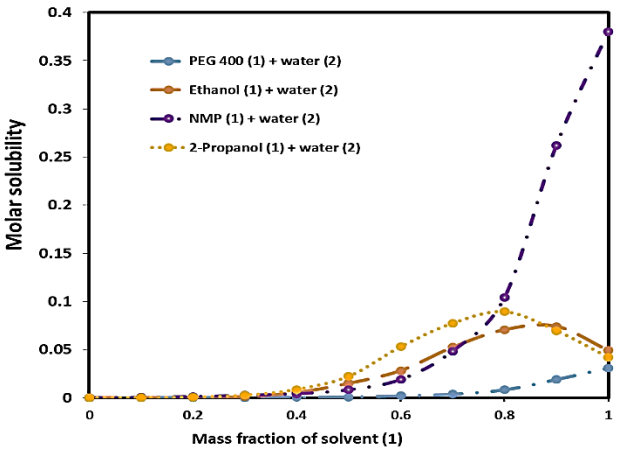

Fig. 1: A comparison of BDS solubility profiles in various reported cosolvency

Furthermore, an analysis of the solubilization efficiency of different cosolvents used for BDS is presented in Table 4. There are two factors that contribute to the efficacy of cosolvents for solubilization; (i) the power and efficacy of solubilization expressed by Yalkowsky's parameter (σ) as Eq. (25) [65]:

$$\sigma = \log\left(\frac{C_c}{C_s}\right) \tag{25}$$

and (ii) a new definition for power of solubilization (ω) as Eq. (26) [66]:

$$\omega = \frac{\log\left(\frac{C_{m,max}}{x_s}\right)}{w_{1,max}} \tag{26}$$

In which C_c and C_s are defined as the drug solubility related to cosolvent and solvent, respectively. Also $C_{m,max}$ is the highest drug solubility of cosolvent-water mixture while $w_{1,max}$ shows the cosolvent mass fraction that produces the greatest solubility.

As shown in Table 4, the having the same value for both ω and σ are found for binary mixtures of NMP - water and PEG 400 - water which means that BDS maximal solubility is revealed in the NMP and PEG 400 as cosolvents. On the other hand, the solubilization power based on ω shows a maximum value for 2-propanol + water system demonstrating that 2-propanol, as a solubilizer, can benefit for its employ as a cosolvent in formulations of various drugs.

Thermodynamic analysis

With the aim of calculating the apparent thermodynamic quantities of BDS dissolution, van't Hoff

Table 4: Evaluation of the solubilization powers of varying cosolvent systems used for BDS solubility study.

Solvent mixtures	δ	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

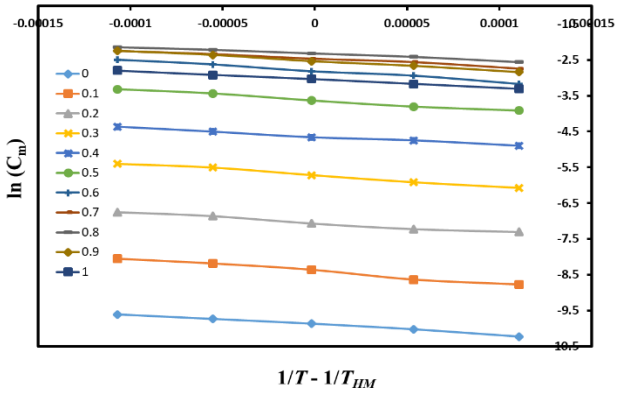

Fig. 2: van't Hoff plots of the experimental molar solubility of BDS in the binary mixtures of 2-propanol and water (2)

plots is drawn for the BDS solubility in aqueous mixture of 2-propanol and neat solvents (Fig. 2). A correlation coefficient of greater than 0.991 was obtained in all cases, indicating parabolic trends [67-69]. Based on demonstration in Section 2.3 and through a well-established connection, the apparent enthalpies and Gibbs energies at T_{hm} = 303.0 K were computed by using Eq. (5) and Eq. (6) from respective slopes and intercepts, respectively. The ΔH°, ΔS°, and ΔG° as thermodynamic parameters of BDS dissolution process in binary mixture of 2-propanol (1) + water (2) is calculated from van't Hoff's model and Gibbs's equation. Table 5 shows the values obtained at T_{hm} equal with 303.0 K. According to the positive values of ΔH°, ΔS° and ΔG°, BDS dissolution was observed in every case endothermic, entropy-driven and evidently not spontaneous, respectively. It should be noted that ΔS° in neat water has negative values. On the other hand, the highest value of ΔH° in w_1 = 0.5 and the lowest value of ΔH° in w_1 = 0.8 were obtained 38.64 and 15.77 kJ/mol, respectively. Also, the maximum and lowermost positive values related to ΔS° in w_1 = 0.5 and w_1 =0.2 were observed 96.98 and 15.26 J/K.mol, respectively. The range of ΔG° changes was found 24.95- 5.88 kJ/mol while maximum amount was produced in a mixture containing high levels of BDS solubility.

Table 5: Dissolution behavior of BDS (3) in 2-Propanol (1) + water (2) mixtures at T_{hm} as based on apparent thermodynamic parameters

w_1	ΔG° (kJ/mol)	ΔH° (kJ/mol)	ΔS° (J/K.mol)	TΔS° (kJ/mol)	ζ_H	ζ_{TS}
0.00	24.95(±0.04)	23.37(±2.85)	-5.21(±9.52)	-1.58(±2.89)	0.937	0.063
0.10	21.19(±0.01)	28.85(±3.19)	25.26(±10.53)	7.66(±3.19)	0.790	0.210
0.20	17.77(±0.01)	22.40(±0.32)	15.26(±1.10)	4.63(±0.33)	0.829	0.171
0.30	14.44(±0.07)	26.75(±0.87)	40.57(±2.89)	12.31(±0.88)	0.685	0.315
0.40	11.69(±0.03)	19.95(±0.72)	27.24(±2.47)	8.27(±0.75)	0.707	0.293
0.50	9.21(±0.05)	38.64(±1.96)	96.98(±6.28)	29.42(±1.91)	0.568	0.432
0.60	7.08(±0.02)	25.50(±1.47)	60.70(±4.89)	18.42(±1.48)	0.581	0.419
0.70	6.23(±0.05)	18.50(±1.38)	40.44(±4.59)	12.27(±1.39)	0.601	0.399
0.80	5.88(±0.04)	15.77(±0.97)	32.60(±3.28)	9.89(±0.99)	0.615	0.385
0.90	6.38(±0.04)	22.86(±1.42)	54.32(±4.71)	16.48(±1.43)	0.581	0.419
1.00	7.68(±0.03)	19.36(±0.94)	38.49(±3.00)	11.68(±0.91)	0.624	0.376

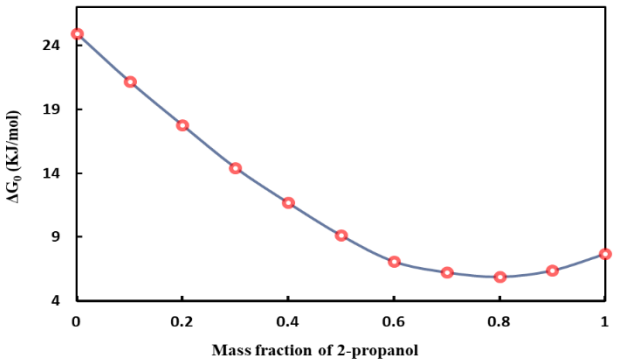

Fig. 3: Gibbs energy for transfer of BDS (3) from pure water (2) to 2-propanol (1) + water (2) mixtures at 303.4 K

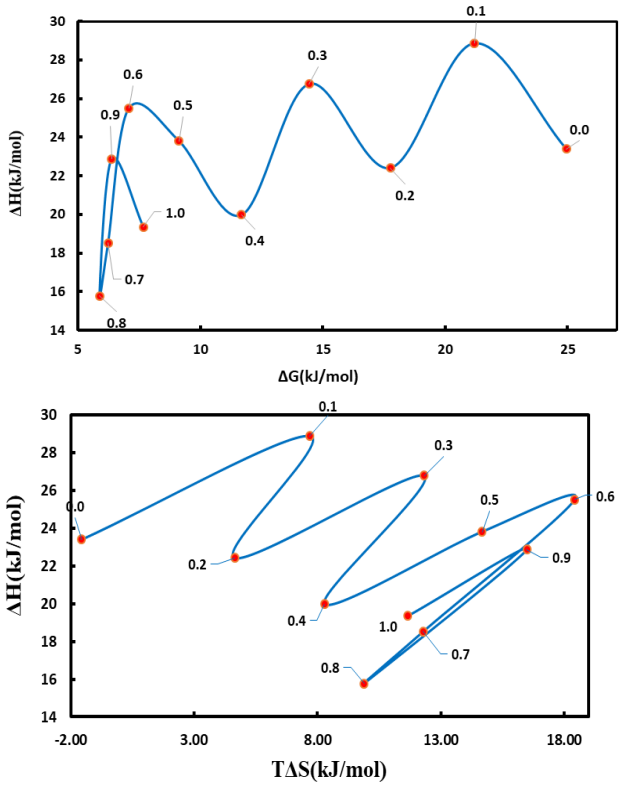

Fig. 4. ΔH° vs ΔG° and ΔH° vs TΔS° enthalpy–entropy compensation plots for the solubility of BDS in 2-propanol (1) + water (2) mixtures at 303.4 K (T_{hm}). The points denote the mass fraction of 2-propanol (1) in the 2-propanol (1) + water (2) mixtures before the addition of solute (BDS, 3).

As can be seen from Fig. 3, in the presence of higher 2-propanol proportions, the ΔG° value decreases, reaching a minimum value at 0.8 mass fraction. This is because as drug solubility increases, the dissolution process becomes more favorable. The values for ζ_H and ζ_{TS} are also shown in Table 5. In every case, BDS dissolution process was primarily driven by the ΔH° ($\zeta_H > \zeta_{TS}$ and $\zeta_H > 0.560$). It can be concluded that in all solvent mixtures, the dissolution process of BDS indicated great energetic requirements for dominating the cohesive force of solute-solvent [70].

ΔH° versus ΔG° and ΔH° versus TΔS° enthalpy–entropy compensation plots of BDS at different temperatures also revealed the mechanism of dissolution [43]. Based on Fig. 4, there is a nonlinear relationship between ΔH° and ΔG° the r solubility of BDS in the various ratios of 2-propanol aqueous mixture. These results show that the regions revealing positive and negative parts of the slopes related to the curve between ΔH° and ΔG° originate from the decreasing and increasing the role of entropy in the dissolution process of BDS, respectively. On the other hand, decreasing and increasing the influence of enthalpy in the dissolution process of BDS, lead to the regions revealing positive and negative part of the slopes between ΔH° and TΔS°.

Table 6: van't-Hoff model constants and the corresponding MRD% for the back-calculated solubility of BDS in the binary mixtures of 2-propanol (1) + water (2).

w_1	A	B	MRD%
0.00	-0.61	-2812.43	1.6
0.10	3.058	-3472.13	2.9
0.20	1.852	-2695.79	2.7
0.30	4.898	-3218.57	1.8
0.40	3.296	-2402.64	1.3
0.50	5.827	-2862.81	2.0
0.60	7.317	-3068.32	2.0
0.70	4.878	-2226.94	1.7
0.80	3.93	-1897.52	1.5
0.90	6.547	-2750.25	1.2
1.00	4.633	-2326.48	0.3
Overall			1.7

Table 7: The CNIBS/R–K model constants and the corresponding MRD% for back calculated BDS solubility in the binary mixtures of 2-propanol (1) + water (2) at investigated temperatures

w_1	J_0	J_1	J_2	MRD%
293.2	11.324	3.136	0[a]	2.4
298.2	11.243	3.672	0[a]	2.9
303.2	11.217	3.259	0[a]	3.6
308.2	11.458	2.994	0[a]	4.2
313.2	11.405	2.875	0[a]	4.7
Overall				3.6

Table 8: ln C^{Yal} values of BDS computed by Yalkowsky model in the binary mixtures of 2-propanol (1) + water (2) at investigated temperatures T = 298.2 K

w_1	ln C^{Yal} (298.2 K)
0.00	-10.02
0.10	-9.34
0.20	-8.65
0.30	-7.97
0.40	-7.28
0.50	-6.6
0.60	-5.91
0.70	-5.22
0.80	-4.54
0.90	-3.85
1.00	-3.17
MRD%	67.5

Table 9: The Jouyban-Acree and Jouyban-Acree-van't-Hoff models constants for BDS solubility in the binary mixtures of 2-propanol (1) + water (2).

	Jouyban-Acree		Jouyban-Acree-van't Hoff	
2-Propanol + water	J_0	3430.970	A_1	4.633
	J_1	966.412	B_1	-2326.482
	J_2	0[a]	A_2	-0.610
			B_2	-2812.428
			J_0	3430.933
			J_1	965.973
			J_2	0[a]
R^2	0.998		0.999	
F	17315.22		17697.776	
P	<0.001		<0.001	
MRD%	5.7		5.8	

Solubility modeling

In the aqueous mixture of 2-propanol, experimental molar solubility data of BDS are fitted to various cosolvency mathematical models including linear and nonlinear ones such as the i) van't Hoff's model, ii) CNIBS/R–K model, iii) Yalkowsky's equation, two Jouyban-Acree models: iv) Jouyban-Acree equation, v) Jouyban-Acree- van't Hoff's model, vi) modified version of Wilson model, vii) Buchowski, and Ksiazczak equation and viii) Williams-Amidon excess Gibbs energy model and the constants related to models with *MRDs* % of back-calculated solubility data are listed in Tables 6–11.

Solubility data of BDS from the back-calculated for all investigated models showed low *MRDs*% (<19.0%). The Yalkowsky's model with MRD = 67.5% was an exception. It is apparent that a comparison of various equations' error levels cannot be performed, because some models such the van't Hoff's model is used for temperature-dependent prediction of solubility in the equal value of solvent ratio, in contrast to that, some models like Yalkowsky, CNIBS/R–K model, ʎh equation, and the modified version of Wilson model calculate the solubility of the mixture in various solvents ratio in isothermal conditions. Whereas, at different temperatures and solvent mixtures, the Jouyban-Acree and Jouyban-Acree-van't Hoff models can be used to predict solubility data. If we want to discuss briefly, using Eq. (9) the overall back-calculated *MRDs* for van't Hoff model were obtained 1.7 % (Table 6). As seen in Table 7, the CNIBS/R–K model models show reasonable overall *MRDs*% for back-calculated solubility data at 293.2, 298.2, 303.2, 308.2, and 313.2 K are 2.4%, 2.9%, 3.6%,

Table 10: Modified Wilson model' parameters at evaluated temperatures from 293.2 to 313.2 K and the relevant MRD% for back-calculated BDS solubility in mixed solvents of 2-propanol (1) and water (2).

T/K	λ_{12}	λ_{21}	MRD%
293.2	10.62	2.13	17.4
298.2	13.13	2.15	20.0
303.2	14.02	2.23	18.2
308.2	16.45	2.36	18.2
313.2	18.49	2.42	19.0
Overall			18.6

4.2% and 4.7%, respectively. The overall *MRD* is 3.6%. The overall *MRD* is 3.6%. On the other hand, based on the Yalkowsky model (Table 8), the obtained *MRD*% values for the back-calculated BDS solubility at 298.2 K was 67.5%.

In 1998, the Jouyban–Acree model was suggested as a solution to the problem of temperature dependence within the CNIBS/RK model [71]. According to the Jouyban-Acree model, the general MRD% at 293.2-313.2 K is 5.7%, while for the Jouyban-Acreevan't Hoff model, it is 4.6%.

In addition, experimental solubility data of BDS were fitted with the recently modified version of Jouyban-Acree-van't Hoff model (Eq. (18)). With a *p*-value less than 0.001, D_1, D_2, D_3, D_4, D_5 and D_7 are found to be statistically significant coefficients (Eq. (27)). The overall *MRD* is 5.1%.

$$lnC_{m,T} = 1.858 - \frac{3559.995}{T} + 4.580\, w_1 + 3135.369\frac{w_1}{T} - 464.013\frac{w_1^2}{T} - 1994.052\frac{w_1^3}{T} \quad (27)$$

Data with the fewest fittings, *i.e.* at 293.2 and 313.2 K, data on solubility in 2-propanol and water and in solvent mixtures containing 0.3, 0.5 and 0.7 mass fractions of 2-propanol at 298.2 K, was also employed to study the prediction abilities of the Jouyban- Acree-van't Hoff model. There is a semi-predictive aspect to the equation above. For this purpose, Eq. (17) is trained by applying these least experimental solubility data and next the solute solubility values related to another 2-propanol mass fractions were computed by utilizing the mentioned trained models. The overall back-calculated *MRD*% is obtained 1.26%. In isothermal conditions, the Ʌh equation and modified version of Wilson model that were used to prediction of solute solubility at different mixed solutions,

Table 11: The Ʌh equation parameters and the relevant MRD% for the back-calculated solubility of BDS in mixed solvents of 2-propanol (1) and water (2).

w_1	λ	h	MRD%
0.00	0.500	0.570	0.3
0.10	0.501	3.162	2.9
0.20	0.502	9.645	4.1
0.30	0.509	42.318	2.8
0.40	0.521	93.643	2.4
0.50	0.569	300.876	3.3
0.60	0.698	735.091	1.5
0.70	0.708	702.246	1.2
0.80	0.708	664.554	0.8
0.90	0.770	927.585	1.1
1.00	0.608	417.879	0.9
Overall			1.9

obtain the overall *MRD*s% of 18.6 and 1.9, respectively (Tables 10 and 11).

In continuation, the model constants were correlated to the Williams-Amidon excess Gibbs energy model and the following results were obtained:

$$ln\, C_m = w_1\, ln\, C_1 + w_2 ln\, C_2 + 0.505(2\, w_1 - 1)\left(\frac{V_s}{V_1}\right) + 0.013 w_1^2 w_2^2 \left(\frac{V_s}{V_2}\right) + 21.564 w_1^2 w_2 \quad (28)$$

In which the back-calculated *MRD*% value was found 3.9%.

Lastly, the KAT-LSER model was used to predicting solubility at 298.2 K in i) binary aqueous mixture of NMP, ethanol and 2-propanol and ii) mono solvents such as n-propyl alcohol, acetic acid, isopropyl alcohol, ethylene glycol, ethyl acetate, acetonitrile, ethanol, methanol, NMP, 1,4-dioxane, propylene glycol and water. Furthermore, the combined van't Hoff's equation is utilized for BDS solubility representation in the pure solvents mentioned above.

Eq. (29) presents the trained models for data related to solubility of BDS at 298.2 K in the binary systems mentioned.

$$\log C_T = -6.030(\pm 1.46) + 1.014(\pm 0.30)\,\pi^* + 4.490(\pm 1.56)\,\beta - 0.854(\pm 0.19)\left(\frac{V_s \delta_H^2}{100RT}\right) \quad (29)$$

The overall back-calculated *MRDs*% are 41.3 for ethanol-water, 33.9 for NMP-water and 72.3 for 2-propanol-water, respectively (with an overall *MRDs*% of 49.2).

Moreover, Eq. (30) shows the trained model for data related to solubility of BDS at 298.2 K in the pure solvents mentioned above.

$$\begin{aligned} log\, C_T = &-1.640(\pm 0.644) + 1.509(\pm 0.823)\,\pi^* \\ &+ 1.311(\pm 0.594)\,\beta \\ &- 1.579(\pm 0.219)\left(\frac{V_s \delta_H^2}{100RT}\right) \end{aligned} \quad (30)$$

The trained combined van't Hoff equation with BDS solubility parameters in the studied mono solvents are also shown in Eq. (31).

If we have a comparison between the KAT-LSER model and the combined version of van't Hoff equation, the overall back-calculated *MRDs*% were obtained 5.4 vs 3.1 for 1-propanol, 66.8 vs 5.6 for 1,4-dioxane, 134.6 vs 1.3 for 2-propanol, 7.0 vs 4.8 for acetic acid, 61.0 vs 4.3 for acetonitrile, 80.4 vs 4.9 for ethylene glycol, 139.1 vs 13.1 for ethyl acetate, 1.1 vs 10.3 ethanol, 74.9 vs 2.0 for methanol, 37.7 vs 1.5 for propylene glycol and 18.7 vs 2.0 for water, respectively. The overall *MRDs*% for Eq. (30) and Eq. (31) are 53.2 and 4.8, respectively. A conclusion can be drawn from the obtained data that the combined version of van't Hoff equation has a better efficacy than KAT-LSER model for solubility correlation in mentioned mono solvents. It should be said that the KAT-LSER model is intended primarily to apply at a temperature of 298.2 K, so its inability to be applied in other temperatures is a significant limitation for this model.

CONCLUSIONS

Under atmospheric pressure, our measurements of the BDS solubility were performed by shake-flask approach as is commonly done in various solvent mixtures of 2-propanol (1) + water (2) within the range of temperature changes from 293.2 to 313.2 K to expand the experimental solubility database for BDS. Several cosolvency models were investigated linearly and nonlinearly in order to fit/back calculate and an examination of the accuracy of the result of computed solubility was conducted by calculating the *MRD*%. Outcomes shows that all investigated models produce *MRDs*% of less than 19%, which falls within the acceptable error range. Based on the results, it appears that Jouyban-Acree has the best ability to regress the solubility data in general due to extending the calculation to a variety of temperatures and solvent compositions. Moreover, the apparent thermodynamic parameters related to dissolution of BDS are discussed and considered as well. According to the computed apparent thermodynamic properties, BDS dissolution occurs in an aqueous mixture of 2-propanol under endothermic and entropic conditions. Pharmaceutical companies can benefit from the physicochemical data provided in the present study regarding BDS in mixtures of cosolvents and water.

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$$\begin{aligned} \ln C = \quad & (-41.44 - 30.65\,e + 4.87\,s - 2.16\,b - 0.74\,\delta_d + 100.86\,SP) \\ & + \left(\frac{\begin{array}{c} -8382.14 + 3180.26\,c + 2549.30\,e + 549.68\,\delta_d + 54.33\,\delta_p + 466.93\,\delta_h - 20987.94\,SP \\ +2429.05\,Sdp - 9719.06\,SA + 4405.56\,SB \end{array}}{T}\right) \end{aligned} \quad (31)$$

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REFERENCES

[1] Abdalla M.I., Herfarth H., Budesonide for the Treatment of Ulcerative Colitis, *Expert Opin. Pharmacother*, **17(11):** 1549-1559 (2016).

[2] Lichtenstein G.R., Hanauer S.B., Sandborn W.J., Management of Crohn's Disease in Adults, *Am. J. Gastroenterol.*, **104(2):** 465-483 (2009).

[3] Kuenzig M.E., Rezaie A., Seow C.H., Otley A.R., Steinhart A.H., Griffiths A.M., Kaplan G.G., Benchimol E.I., Budesonide for Maintenance of Remission in Crohn's Disease, *Cochrane Database Syst. Rev.*, **2014(8):** CD002913 (2014).

[4] Johansson S.-Å., Andersson K.-E., Brattsand R., Gruvstad E., Hedner P., Topical and Systemic Glucocorticoid Potencies of Budesonide and Beclomethasone Dipropionate in Man, *Eur. J. Clin. Pharmacol*., **22(6):** 523-529 (1982).

[5] Juniper E.F., Kline P.A., Vanzieleghem M.A., Ramsdale E.H., O'byrne P.M., Hargreave F.E., Effect of Long-Term Treatment with an Inhaled Corticosteroid (Budesonide) on Airway Hyperresponsiveness and Clinical Asthma in Nonsteroid-Dependent Asthmatics, *Am. Rev. Respir. Dis.*, **142(4)**: 832-836 (1990).

[6] Rawla P., Sunkara T., Thandra K.C., Gaduputi V., Efficacy and Safety of Budesonide in the Treatment of Eosinophilic Esophagitis: Updated Systematic Review and Meta-Analysis of Randomized and Non-Randomized Studies, *Drugs in R. D.*, **18(4)**: 259-269 (2018).

[7] Femere R., Aronson J., Chloroquine and Hydroxychloroquine in Covid-19, BMJ., **2020:** 369 (2020).

[8] Khoubnasabjafari M., Jouyban A., Mahdavi A.M., Namvar L., Esalatmanesh K., Hajialilo M., Dastgiri S., Soroush M., Safiri S., Khabbazi A., Prevalence of COVID-19 in Patients with Rheumatoid Arthritis (RA) Already Treated with Hydroxychloroquine (HCQ) Compared with HCQ-Naive Patients with RA: A Multicentre Cross-Sectional Study, *Postgrad. Med. J*., **98(2):** 92-93 (2022).

[9] Huang B., Ling R., Cheng Y., Wen J., Dai Y., Huang W., Characteristics and Therapeutic Options of the Coronavirus Disease 2019, *Mol. Ther. Methods Clin. Dev*., **18:** 367-375 (2020).

[10] Ramakrishnan S., Nicolau D.V., Langford B., Mahdi M., Jeffers H., Mwasuku C., Krassowska K., Fox R., Binnian I., Glover V., Inhaled Budesonide in the Treatment of Early COVID-19 (STOIC): a Phase 2, Open-Label, Randomised Controlled Trial, *Lancet Respir. Med.*, **9(7):** 763-772 (2021).

[11] Daley-Yates P.T., Inhaled Corticosteroids: Potency, dose Equivalence and Therapeutic Index, *Br. J. Clin. Pharmacol*., **80(3):** 372-380 (2015).

[12] Ali H.S., York P., Blagden N., Soltanpour S., Acree Jr W.E., Jouyban A., Solubility of Budesonide, Hydrocortisone, and Prednisolone in Ethanol+ Water Mixtures at 298.2 K, *J. Chem. Eng. Data*., **55(1):** 578-582 (2010).

[13] Bhatt H., Naik B., Dharamsi A., Solubility Enhancement of Budesonide and Statistical Optimization of Coating Variables for Targeted Drug Delivery, *Int. J. Pharm*., **2014:** 262194 (2014).

[14] Spencer C.M., McTavish D., Budesonide: A Review of its Pharmacological Properties and Therapeutic Efficacy in Inflammatory Bowel Disease, *Drugs*., **50(5):** 854-872 (1995).

[15] Hvizdos K.M., Jarvis B., Budesonide inhalation suspension: A Review of its Use in Infants, Children and Adults with Inflammatory Respiratory Disorders, *Drugs*., **60(5):** 1141-1178 (2000).

[16] Dalby C., Polanowski T., Larsson T., Borgström L., Edsbäcker S., Harrison T.W., The Bioavailability and Airway Clearance of the Steroid Component of Budesonide/Formoterol and Salmeterol/Fluticasone after Inhaled Administration in Patients with COPD and Healthy Subjects: A Randomized Controlled Trial, *Respir. Res*., **10(1):** 1-11 (2009).

[17] Di L., Fish P.V., Mano T., Bridging Solubility Between Drug Discovery and Development, *Drug Discov. Today.*, **17(9-10):** 486-495 (2012).

[18] Zhou L., Yang L., Tilton S., Wang J., Development of a High Throughput Equilibrium Solubility Assay Using Miniaturized Shake-Flask Method in Early Drug Discovery, *J. Pharm. Sci*., **96(11):** 3052-3071 (2007).

[19] Mohamadian E., Hamidi S., Martínez F., Jouyban A., Solubility Prediction of Deferiprone in N-Methyl-2-Pyrrolidone+ Ethanol Mixtures at Various Temperatures Using a Minimum Number of Experimental Data, *Phys. Chem. Liquids*., **55(6):** 805-816 (2017).

[20] Rahimpour E., Mohammadian E., Acree Jr W.E., Jouyban A., Computational Tools for Solubility Prediction of Celecoxib in the Binary Solvent Systems, *J. Mol. Liq*., **299:** 112129 (2020).

[21] Khan A.D., Singh L., Various Techniques of Bioavailability Enhancement: A Review, *J. Drug Deliv. Ther*., **6(3):** 34-41 (2016).

[22] Hu Y., Liu Z., Yuan X., Zhang X., Molecular Mechanism for Liquid–Liquid Extraction: Two-Film Theory Revisited, *AIChE Journal*., **63(6):** 2464-2470 (2017).

[23] Eixarch H., Haltner-Ukomadu E., Beisswenger C., Bock U., Drug Delivery to the Lung: Permeability and Physicochemical Characteristics of Drugs as the Basis for a Pulmonary Biopharmaceutical Classification System (pBCS), *J. Epithel. Biol. Pharmacol*., **3(1):** 1-14 (2010).

[24] Hastedt J.E., Bäckman P., Clark A.R., Doub W., Hickey A., Hochhaus G., Kuehl P.J., Lehr C.-M., Mauser P., McConville J., Scope and Relevance of a Pulmonary Biopharmaceutical Classification System AAPS/FDA/USP Workshop March 16-17th, 2015 in Baltimore, MD, *AAPS Open.*, **2:** 1 (2016).

[25] Jouyban A., Review of the Cosolvency Models for Predicting Solubility of Drugs in Water-Cosolvent Mixtures, *J. Pha. Pha. Sci*., **11(1):** 32-58 (2008).

[26] Jouyban-Gharamaleki A., Valaee L., Barzegar-Jalali M., Clark B., Acree Jr W., Comparison of Various Cosolvency Models for Calculating Solute Solubility in Water–Cosolvent Mixtures, *Int. J. Pha.*, **177(1):** 93-101 (1999).

[27] Mohammadian E., Foroumadi A., Hasanvand Z., Rahimpour E., Zhao H., Jouyban A., Simulation of Mesalazine Solubility in the Binary Solvents at Various Temperatures, *J. Mol. Liq*., **357:** 119160 (2022).

[28] Mohammadian E., Rahimpour E., Barzegar-Jalali M., Dadmand S., Martinez F., Jouyban A., Solubility of Celecoxib in 1-Propanol+ Water Mixtures at T=(293.2–313.2) K: Experimental Data and Thermodynamic Analysis, *Ph. Chem. Liquids*., **58(2):** 175-183 (2020).

[29] Mohammadian E., Barzegar-Jalali M., Rahimpour E., Solubility Prediction of Lamotrigine in Cosolvency Systems Using Abraham and Hansen Solvation Parameters, *J. Mol. Liq*., **276:** 675-679 (2019).

[30] Hatefi A., Jouyban A., Mohammadian E., Acree Jr W.E., Rahimpour E., Prediction of Paracetamol Solubility in Cosolvency Systems at Different Temperatures, *J. Mol. Liq*., **273:** 282-291 (2019).

[31] Mohammadian E., Jouyban A., Barzegar-Jalali M., Acree Jr W.E., Rahimpour E., Solubilization of Naproxen: Experimental Data and Computational Tools, *J. Mol. Liq.*, **288:** 110985 (2019).

[32] Ruidiaz M.M.A., Rodríguez D.S.J., Neita R.P.C., Cristancho B.D.M., Martínez R.F., Performance of the Jouyban-Acree Model for Correlating the Solubility of Indomethacin and Ethylhexyl Triazone in Ethyl Acetate+ Ethanol Mixtures, *Vitae*., **17(3):** 309-316 (2010).

[33] Mohammadian E., Rahimpour E., Martinez F., Jouyban A., Budesonide Solubility in Polyethylene Glycol 400+ Water at Different Temperatures: Experimental Measurement and Mathematical Modelling, *J. Mol. Liq*., **274:** 418-425 (2019).

[34] Barzegar-Jalali M., Rahimpour E., Martinez F., Jouyban A., Determination and Mathematical Modelling of Budesonide Solubility in N-Methyl-2-Pyrrolidone+ Water Mixtures from T= 293.2 to 313.2 K, *Phys Chem Liquids*., **56(6):** 834-842 (2018).

[35] Mohammadian E., Rahimpour E., Martinez F., Jouyban A., Solubility of Budesonide in {Ethanol+ Water} Mixtures from T=(293.2 to 313.2) K: Experimental Measurement and Mathematical Modelling, *Phys Chem Liquids*., **56(6):** 751-758 (2018).

[36] Barzegar-Jalali M., Jouyban A., Mohammadian E., Martinez F., Rahimpour E., Budesonide Solubility in some Non-Aqueous Mono-Solvents at Different Temperatures: Measurements and Mathematical Correlation with Abraham Model, *J. Mol. Liq*., **269:** 461-466 (2018).

[37] Mota F.L., Carneiro A.P., Queimada A.J., Pinho S.P., Macedo E.A., Temperature and Solvent Effects in the Solubility of Some Pharmaceutical Compounds: Measurements and Modeling, *Eur. J. Pharm. Sci*., **37(3-4):** 499-507 (2009).

[38] Acree B., "Toxicity and Drug Testing", InTech, Kenya (2012).

[39] Wei T., Wang C., Du S., Wu S., Li J., Gong J., Measurement and Correlation of the Solubility of Penicillin V Potassium in Ethanol+ Water and 1-Butyl Alcohol+ Water Systems, *J. Chem. Eng. Data*, **60(1):** 112-117 (2015).

[40] Vahdati S., Shayanfar A., Hanaee J., Martínez F., Acree W.E., Jouyban A., Solubility of Carvedilol in Ethanol+ Propylene Glycol Mixtures at Various Temperatures, *Ind. Eng. Chem. Res*., **52(47):** 16630-16636 (2013).

[41] Perlovich G.L., Kurkov S.V., Bauer-Brandl A., Thermodynamics of Solutions: II. Flurbiprofen and Diflunisal as Models for Studying Solvation of Drug Substances, *Eur. J. Pharm. Sci*., **19(5):** 423-432 (2003).

[42] Zhou C., Shi X., Wang H., An N., Measurement and Correlation of Solubilities of Trans-Ferulic Acid in Solvents, *J. Ind. Eng. Chem*., **58(11):** 2705 (2007).

[43] Gantiva M., Martínez F., Thermodynamic Analysis of the Solubility of Ketoprofen in some Propylene Glycol+ Water Cosolvent Mixtures, *Fluid Ph. Equilibria*., **293(2):** 242-250 (2010).

[44] Acree W.E., Mathematical Representation of Thermodynamic Properties: Part 2. Derivation of the Combined Nearly Ideal Binary Solvent (NIBS)/Redlich-Kister Mathematical Representation from a Two-Body and Three-Body Interactional Mixing Model, *Thermochim. Acta*., **198(1):** 71-79 (1992).

[45] S.H. Yalkowsky T.J.R., Techniques of Solubilization of Drugs, M. Dekker, New York (1981).

[46] Valvanix S., Yalkowsky S.H., Roseman T., Solubility and Partitioning IV: Aqueous Solubility and Octanol-Water Partition Coefficients of Liquid Nonelectrolytes, *J. Pharm. Sci*., **70(5):** 502-507 (1981).

[47] Jouyban A., Acree W.E., Mathematical Derivation of the Jouyban-Acree Model to Represent Solute Solubility Data in Mixed Solvents at Various Temperatures, *J. Mol. Liq*., **256:** 541-547 (2018).

[48] Jouyban A., Fakhree M.A., Acree W.E., Comment on Measurement and Correlation of Solubilities of (Z)-2-(2-Aminothiazol-4-yl)-2-Methoxyiminoacetic Acid in Different Pure Solvents and Binary Mixtures of Water+(Ethanol, Methanol, or Glycol), *J. Chem. Eng. Data*., **57(4):** 1344-1346 (2012).

[49] Sun H., Li M., Jia J., Tang F., Duan E., Measurement and Correlation of the Solubility of 2, 6-Diaminohexanoic Acid Hydrochloride in Aqueous Methanol and Aqueous Ethanol Mixtures, *J. Chem. Eng. Data*, **57(5):** 1463-1467 (2012).

[50] Jouyban-Gharamaleki A., The modified Wilson Model and Predicting Drug Solubility in Water-Cosolvent Mixtures, *Chem. Pharm. Bull*., **46(6):** 1058-1061 (1998).

[51] Buchowski H., Ksiazczak A., Pietrzyk S., Solvent Activity Along a Saturation Line and Solubility of Hydrogen-Bonding Solids, *J. Phys. Chem*., **84(9):** 975-979 (1980).

[52] Williams N., Amidon G., Excess Free Energy Approach to the Estimation of Solubility in Mixed Solvent Systems II: Ethanol–Water Mixtures, *J. Pharm. Sci*., **73(1):** 14-18 (1984).

[53] Li X., Zhu Y., Zhang X., Farajtabar A., Zhao H., Solubility, Preferential Solvation, and Solvent Effect of Micoflavin in Aqueous Mixtures of Dimethylsulfoxide, Isopropanol, Propylene Glycol, and Ethanol, *J. Chem. Eng. Data*., **65(4):** 1976-1985 (2020).

[54] Li W., Farajtabar A., Wang N., Liu Z., Fei Z., Zhao H., Solubility of Chloroxine in Aqueous Co-Solvent Mixtures of N, N-Dimethylformamide, Dimethyl Sulfoxide, N-Methyl-2-Pyrrolidone and 1, 4-Dioxane: Determination, Solvent Effect and Preferential Solvation Analysis, *J. Chem. Thermodyn*., **138:** 288-296 (2019).

[55] Jouyban A., Rahimpour E., Karimzadeh Z., A New Correlative Model to Simulate the Solubility of Drugs in Mono-Solvent Systems at Various Temperatures, *J. Mol. Liq*., **343:** 117587 (2021).

[56] Zhang C., Jouyban A., Zhao H., Farajtabar A., Acree W.E., Equilibrium Solubility, Hansen Solubility Parameter, Dissolution Thermodynamics, Transfer Property and Preferential Solvation of Zonisamide in Aqueous Binary Mixtures of Ethanol, Acetonitrile, Isopropanol and N, N-Dimethylformamide, *J. Mol. Liq*., **326:** 115219 (2021).

[57] Li W., Farajtabar A., Xing R., Zhu Y., Zhao H., Solubility of D-histidine in Aqueous Cosolvent Mixtures of N, N-Dimethylformamide, Ethanol, Dimethyl Sulfoxide, and N-Methyl-2-Pyrrolidone: Determination, Preferential Solvation, and Solvent Effect, *J. Chem. Eng. Data.*, **65(4):** 1695-1704 (2020).

[58] Aerts J., "The Hoy Solubility Parameter Calculation Software", Germany: Computer Chemistry Counsultancy, Singen, Germany (2005).

[59] Maitra A., Bagchi S., Study of Solute–Solvent and Solvent–Solvent Interactions in Pure and Mixed Binary Solvents, *J. Mol. Liq*., **137(1-3):** 131-137 (2008).

[60] Islam T., Islam Sarker M.Z., Uddin A.H., Yunus K.B., Prasad R., Mia M.A.R., Ferdosh S., Kamlet Taft Parameters: A Tool to Alternate the Usage of Hazardous Solvent in Pharmaceutical and Chemical Manufacturing/Synthesis-A Gateway Towards Green Technology, *Anal. Chem. Lett*., **10(5):** 550-561 (2020).

[61] Sherwood J., Granelli J., McElroy C.R., Clark J.H., A method of Calculating the Kamlet–Abboud–Taft Solvatochromic Parameters Using COSMO-RS, *Molecules*, **24(12):** 2209 (2019).

[62] Akerlof G., Dielectric Constants of some Organic Solvent-Water Mixtures at Various Temperatures, *J. Am. Chem. Soc*., **54(11):** 4125-4139 (1932).

[63] Fedors R.F., A Method for Estimating both the Solubility Parameters and Molar Volumes of Liquids, Polym, *Eng. Sci.*, **14(2):** 147-154 (1974).

[64] Rezaei H., Rahimpour E., Martinez F., Zhao H., Jouyban A., Study and Mathematical Modeling of Caffeine Solubility in N-Methyl-2-Pyrrolidone+ Ethylene Glycol Mixture at Different Temperatures, *J. Mol. Liq.*, **341:** 117350 (2021).

[65] Li A., Yalkowsky S.H., Predicting Cosolvency. 1. Solubility Ratio and Solute Log K ow, *Eng. Chem. Res*., **37(11):** 4470-4475 (1998).

[66] Jouyban A., Fakhree M., A New Definition of Solubilization Power of a Cosolvent, *Int. J. Pharm. Sci.*, **63(4):** 317-318 (2008).

[67] Bevington P.R., Robinson D.K., "Data Reduction and Error Analysis for the Physical Sciences" McGraw-Hill, New York **19692**: 235 (1969).

[68] Carstensen J.T., "Modeling and Data Treatment in the Pharmaceutical Sciences", CRC Press (1996).

[69] Krug R., Hunter W., Grieger R., Enthalpy-Entropy Compensation. 2. Separation of the Chemical from the Statistical Effect, *J. Phys. Chem*., **80(21):** 2341-2351 (1976).

[70] Martínez F., Peña M.Á., Bustamante P., Thermodynamic Analysis and Enthalpy–Entropy Compensation for the Solubility of Indomethacin in Aqueous and non-Aqueous Mixtures, *Fluid Ph. Equilibria*., **308(1-2):** 98-106 (2011).

[71] Jouyban-Gharamaleki A., Acree W., Comparison of Models for Describing Multiple Peaks in Solubility Profiles, Int. J. Pharm. **167(1-2)**: 177-182 (1998).