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Solubility of bosentan in polyethylene glycol 400 + water mixtures: Experimental and mathematical computations

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Abstract

Background**.** To discover the optimal solvent amounts for using in a particular application, it is vital to achieve some useful information in regard with suitable pure or mixed solvent and drugs equilibrium solubility in them. It is known that the low water solubility of drugs such as bosentan (BST) negatively effects its in vitro and in vivo kinetics of dissolution, affecting in turn and its bioavailability along with making several difficulties around designing of its liquid formulations.

Methods**.** Solubility of BST in some mixtures of polyethylene glycol 400 (PEG 400) and water was experimentally determined at T = (293.15 to 313.15) K by using a common shake-flask technique followed by Uv-visible spectroscopic method. The experimental solubility data at 298.15 K and w_1=0.0, 0.5 and 1.0 at other temperatures were then correlated by cosolvency models including the Jouyban-Acree, the Jouyban-Acree-van't Hoff, and the double log-log models and some un-measured solubility data are predicted based on the obtained trained models.

Results. The results presented that the aqueous solubility of BST is increased by increasing mass fraction of PEG 400 as well as increasing temperature and reached the maximum value in neat PEG 400 at 313.15 K.

Conclusion. The BST solubility in water improved by addition of PEG 400 into it. According to the average relative deviations obtained from the back-computed data with trained models which were < 8.0%, it concluded that the selected modes were able to predict the un-measured data with high reliability.

Keywords: Solubility; Bosentan; Polyethylene glycol 400; Cosolvency models

Introduction

Bosentan (BST, Figure 1) is a twin endothelin receptor antagonist utilized inside the treatment of pulmonary arterial hypertension with an elimination half-life of 5 h. [1] It has a low water solubility (1 g. L^{-1}, $pK_a = 5.8$ and log $P = 4.94$) and categorized as a class II based on the BSC classification. [2] Low values of bioavailability of BST (≈ 50%) and its solubility in water lead to variable blood concentration of it. [3] Considering to its application in therapeutic and its low solubility in water as well as low bioavailability, it is vital to measures BST solubility in various pharmaceutical solvent mixtures to formulate the liquid dosage forms.

"Figure 1"

Several ways have been used to increases solubility of BST in water involving cosolvency, complexation, micellization and pH adjustments. [4-8] Among these methods, cosolvency is received more attention from scientific community due to its convenience, cost effectiveness and simplicity. [9-13] Most of drugs are nonpolar molecules and for enhancing their aqueous solubility, it is essential to diminishes the polarity of solvent systems and increment the drug's solubility by addition of one more less polar solvent to water. [14]

Up to now, the increment of BST solubility in water by cosolvency approach has been investigated by addition of C_2H_5OH, [13] polyethylene glycol 200 (PEG 200) [11] and propylene glycol. [12] However, there is no report for BST solubility in water in the presence of PEG 400. In continuation of previous works [11-13] in regard with the extension of BST solubility in water as an essential data in pharmaceutical industry, here, the solubility profile of BST was assessed in binary (PEG 400 + water) solvent mixtures. PEG is well-known as a low-toxic passive material (with a systemic absorption < 0.5%) and different medicinal application. [15] In the current work, the solubility data for BST in the selected mixtures of PEG 400 and water (*i.e.* all fractions at 298.15 K and $w_1 = 0.0$, 0.5 and 1.0 for other temperatures) are measured followed then by their correlations with different cosolvency models such as the Jouyban-Acree, Jouyban-Acree-van't Hoff, and the double log-log. The performance of trained models is compared by computing average relative deviation (*ARD*%) for back-calculated data. In the next attempt, the rest of untested data are predicted based on the obtained trained model at 298.15 K.

Chemicals and procedure

Chemicals

BST (purity of 99.7 in wt.%) was obtained from Danesh Pharmaceutical Company (Tehran, Iran) as its mono-hydrate form. PEG (the average molar mass of 400, purity of 98.0 in wt.%) was supplied from Merck. To prepare solutions, C_2H_5OH (purity of 93.5 in wt.%, Jahan Alcohol Teb, Iran) and double distilled deionized water (conductivity < 0.1 μS cm^{-1}) was employed. The all materials were used as supplied by companies without any more purification.

Determination of BST solubility

At the first, binary {PEG 400 (1) + water (2)} mixtures were constructed with polymer mass fraction (w_1) of 0.1 to 0.9 for studies at 298.15 K and w_1 = 0.5 at 293.15, 303.15, 308.15 and 313.15 K through mixing proper amounts of both solvent by utilizing an analytical balance (Shimadzu, 321-34553, Shimadzu Co., Japan, precision of $\pm 10^{-4}$ g). To measure the solubility of BST in the abovementioned solutions, a shake-flask method [16] was utilized along with determination of maximum value of BST with Uv-visible spectrophotometer (Shimadzu UV-1800, Kyoto, Japan). Excess values of BST were added within the volumetric flask composed of 2.0 g of pure PEG 400, pure water and then as-constructed solutions of PEG 400 + water, stoutly sealed and placed in an incubator (Kimia Idea Pardaz Azerbaijan, Tabriz, Iran) on a shaker (Behdad, Tehran, Iran) to shake at working temperatures for 72 h. Temperature uncertainty was about 0.1 K. After equilibrating, the solid phase was eliminated by centrifuging supernatants of saturated solutions at 10000 rpm for 20 min followed by dilution with C_2H_5OH:H_2O (70:30% v/v) and recording its absorbance at 273 nm. The molar solubility of BST ($C_{m,\,T}$/ mol L^{-1}) in the saturated solutions was achieved by the help of calibration curve. The reported solubility data were the mean of three repetitive experiments.

Computational section

The experimental $C_{m,\,T}$ values of BST in the binary solutions of PEG 400 and water (*i.e.* w_1 = 0.0 to w_1 = 1.0 at 298.15 K and w_1 = 0.0, 0.5, and 1.0 at the other working temperatures) were correlated with three accurate cosolvency models of Jouyban-Acree, the Jouyban-Acree-van't Hoff and the double log-log. Agreeing to acceptable ability of these models in solubility prediction and some previously reported ones, the solubility in w_1 = 0.1, 0.2, 0.3, 0.4, 0.6, 0.7, 0.8 and 0.9 were predicted.

van't Hoff equation

Eq. (10) describes dependence of the $C_{\mathrm{m,T}}$ values respect to temperature: [17]

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

where A and B correspond to the model parameters.

Jouyban-Acree model

Dependence of the experimental $C_{\mathrm{m,T}}$ values respect to solvent composition and temperature is illustrated with the Jouyban-Acree model. [18]

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

here $C_{m,T}$, $C_{1,T}$ and $C_{2,T}$ are BST molar solubility in the solvent systems, pure PEG 400 and pure water, respectively, at temperature T/K and J_{i} terms as the model constants are achieved from a simple regression analysis, [19] w_1 and w_2 denote to mass fraction of pure PEG 400 and pure water in each binary mixture, respectively.

Jouyban-Acree- van't Hoff model

By replacing Eq. (1) within Eq. (2), one more accurate predictive model is provided as Eq. (3), [20] wherein A_1, B_1, A_2 and B_2 relate to the van't Hoff model constants and J_i terms were determined using regression of $(\ln C_{m,T} - w_1(A_1 + \frac{B_1}{T}) - w_2(A_2 + \frac{B_2}{T})$ against $\frac{w_1.w_2}{T}$, $\frac{w_1.w_2(w_1 - w_2)}{T}$, and $\frac{w_1.w_2(w_1 - w_2)^2}{T}$.

$$\ln C_{m,T} = w_1\left(A_1 + \frac{B_1}{T}\right) + w_2\left(A_2 + \frac{B_2}{T}\right) + \frac{w_1 w_2}{T} \sum_{i=0}^{2} J_i.(w_1 - w_2)^i \tag{3}$$

The double log-log model

The double log-log model divides the measured $C_{m,T}$ values to two parts, as presented in Eqs. (4) and (5). [21]

$$\ln[\ln(C_m / C_2)] = \ln[\ln((C_m)_{0.5} / C_2)] + B\ln(w_1 / w_2) \tag{4}$$

for $0 < w_1 \leq 0.5$

$$\ln[\ln(C_1 / C_m)] = \ln[\ln(C_1 /(C_m)_{0.5})] + b\ln(w_2 / 0.5) \tag{5}$$

for $0 < w_2 \leq 0.5$

in which C_1 and C_2 are the molar solubility in the pure PEG 400 and pure water, $(C_m)_{0.5}$ is the molar solubility in PEG 400 + water at $w_1 = 0.5$ and B and b are the model parameters.

Model accuracy

The *ARD*% of the back-calculated values of $C_{m,T}$ were determined to reports the accuracy of each model.

$$ARD\% = \frac{100}{N}\sum\left(\frac{\left|C^{\exp} - C^{cal}\right|}{C^{\exp}}\right) \tag{6}$$

here, the experimental molar solubility of BST, the back-calculated solubilities from each model and the number of data points are denoted as $C^{\exp}$, C^{cal} and *N*, respectively.

Results and discussions

BST solubility measurement and correlation

The experimental molar values of BST ($C_{m,T}$) in neat water and PEG 400 at 293.15 to 313.15 K and their mixtures with w_1 = 0.1 to 0.9 at 298.15 K and w_1 = 0.5 at 293.15, 303.15, 308.15 and 313.15 K along with the standard deviation (*SD*) of three replications are reported in Table

1. It is clear that BST solubility is increased by increasing PEG 400 portion and temperature with the minimum and maximum values determined in pure water at 293.15 K (5.414×10^{-6} mol L^{-1}) and for neat PEG 400 at 313.15 K (0.427 mol L^{-1}). This means that, the solubility of BST in pure PEG 400 is 78927.91 times higher than that of pure water. Considering to the presence of a water molecule in the crystalline structure of BST, it is expected that some water is released in the solution after dissolving of BST and affected on the reported mass fractions of PEG 400 at different temperatures in Table 1. Aiming to the released water amount in each mixtures, the real mass fractions of PEG 400 were calculated at different temperatures and the results are in the order: 0.0, 0.4999 and 0.9997 at 293.15 K instead of 0.0, 0.5 and 1.0, respectively; 0.0, 0.0999, 0.1999, 0.2999, 0.3999, 0.4999, 0.5999, 0.6999, 0.7999, 0.8999 and 0.9999 at 298.15 K instead of 0.0, 0.1, 0.2,0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1, respectively; 0.0, 0.4999 and 0.9997 at 303.15 K instead of 0.0, 0.5 and 1.0, respectively; 0.0, 0.4999 and 0.9996 at 308.15 K instead of 0.0, 0.5 and 1.0, respectively; 0.0, 0.4999 and 0.9996 at 313.15 K instead of 0.0, 0.5 and 1.0, respectively. These calculations present that the released water from BST dissolving in the studied mixtures has not significantly affected the mass fractions of PEG 400. Hence, the apparent mass fractions of PEG 400, *i.e.* 0.0, 0.1, 0.2 ,0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0 are reported in Table 1.

"Table 1"

Also, the measured solubility of BST in water at different temperature was compared with those reported in the literature [11] and the results are collected in Table 2. According to this Table, there is a good consistency between two series of solubility data.

"Table 2"

The influenc of PEG molar mass on the solubility of BST were survayed by comparing the current data with the ones reported in the literature for the (PEG 200 + water) systems (11) in

Figure 2. As presented in this figure, the solubility of BST is highly dependent on the PEG molar masses, especially at high mass fractions and it represents the same trend in both systems. This means that, the $C_{m,T}$ values of BST in PEG 200 + water mixtures are also enhanced with an increment PEG 200 portion and temperature reaching the maximum value in pure PEG 200. However, the maximum solubility of BST in the neat PEG 400 at 313.15 K (≈ 0.427 mol L^{-1}) is 3.1 times higher than that of mono-solvent of PEG 200 at the same condition (≈ 0.139 mol L^{-1}). This result indicates the molar solubility of BST in water is more improved in the presence of PEG 400.

"Figure 2"

The methods utilized to estimate the drugs solubility are experimental measurements and/or prediction methods. The experimental techniques are usually tedious, time-consuming and costly leading to some limitations in detection and development of novel drugs and this issue may be resolved by using mathematical predictive methods. In this respect, herein, to presents the applicability of the mathematical methods for prediction of BST molar solubilities, contrary to previous works about BST solubility in the (cosolvent + water) mixtures, the least number of experimental data were measured using the aforementioned way and fitted with some mathematical models including the Jouyban-Acree and the Jouyban-Acree-van't Hoff which introduced as simple and accurate models in the literature. [22] To this reason, the experimental values of $C_{m,T}$ given in Table 1 were utilized to train Eqs. (2) and (3). The trained models are as follow:

$$\ln x_m = w_1 \ln x_1 + w_2 \ln x_2 - 637.650\frac{w_1.w_2}{T} - 1996.517\frac{w_1.w_2(w_1-w_2)}{T} + 1059.889\frac{w_1.w_2(w_1-w_2)^2}{T} \quad (7)$$

$$\ln x_m = w_1(4.395 - \frac{1639.169}{T}) + w_2(2.570 - \frac{4290.250}{T}) \\ -630.322\frac{w_1.w_2}{T} - 2065.223\frac{w_1.w_2(w_1-w_2)}{T} + 1179.687\frac{w_1.w_2(w_1-w_2)^2}{T} \quad (8)$$

The overall *ARDs*% (*OARDs*%) ± SDs for back-calculated data are 4.8% ± 5.2 and 6.2% ± 4.6 for the Jouyban-Acree and Jouyban-Acree-van't Hoff models, respectively. The low *ARDs*% obtained for the back-calculated data show that these models have enough reliability to predict solubility data. So, the $C_{m,T}$ values of BST in untested mixtures are predicted with Eqs. (7) and (8) along with reporting the results in Table 3.

"Table 3"

Another model that can be used for the correlation/prediction is the double log-log model. The experimental solubilities at 298.15 K in the current work are also correlated to this model and trained model can be shown as the following equations.

$$\ln[\ln(C_m / C_2)] = \ln[\ln((C_m)_{0.5} / C_2)] + 0.465 \ \ln(w_1 / w_2) \quad (9)$$

for $0 < w_1 \leq 0.5$

$$\ln[\ln(C_1 / C_m)] = \ln[\ln(C_1 /(C_m)_{0.5})] + 0.772 \ \ln(w_2 / 0.5) \quad (10)$$

for $0 < w_2 \leq 0.5$

The overall *ARDs*% (*OARDs*%) ± SDs for back-calculated data are 8.0% ± 4.6 and 6.5% ± 5.2 for Eqs. (9) and (10), respectively. In the following the previous calculation, this trained model is also used for solubility prediction in other temperatures. In this study, we have the $C_{m,T}$ values in w_1 = 0.0, 0.5 and 1 for other temperatures. On the other hand, this model divides the data set in two parts and use the data in w_1 = 0.5 and each pure solvent for the prediction. The predicted solubility data are also reported in Table 3. Recent studies uncovered that by determination sufficient solubility data points and their training with an accurate model, it is possible to predict the solubility data at other solvent compositions and temperatures. [23] This ability can be cosidered as a stronght point for these models that can be helpful in the pharmacetical industries. Figure 3 visually presents the predicted solubility values of BST using the Jouyban-Acree, Jouyban-Acree-van't Hoff and double log-log models along with the experimental solubilities of BST at w_p = 0.0, 0.5 and 1.0 at T = (293.15, 303.15, 308.15 and 313.15) K. As shown in this figure, these models have acceptable accuracies to predict the solubility values of BST in the untested solvent.

"Figure 3"

Moreover, a generally trained mathematical model derived from Yalkowsky model was reported for prediction the solubility of drugs in water in the presence of PEG 400. The trained version of this model is: [24]

$$\ln x_m = \ln x_2 + w_1(1.704 \log P + 2.902) \tag{11}$$

For training Eq. (11), the reported $C_{m,T}$ values in Table 1 is not utilized and the only used data are the aqueous solubility datum at 298.15 K. The *OARD*% for back-calculated data with Eq. (11) is 28.4% ± 20.2. The main limitation of the Yalkowsky model is that it was developed for room temperature data, however, by mixing Eq. (11) with Eq. (1), one may obtain an extended version to represent the solubility data at different temperatures. The extended model is: [25]

$$\ln C_{m,T} = w_1\left(A_1 + \frac{B_1}{T}\right) + w_2\left(A_2 + \frac{B_2}{T}\right) \tag{12}$$

in Eq. (12), A and B correspond to the model parameters computed using regression of the solubility in each pure solvent at different temperatures. Due to the linearity of Eq. (12), one may compute the A and B terms, using only two data points in each mono-solvents. The A_2 and

B_2 terms were already reported in the literature (see Eq. (15) of Ref. [12]), when the measured solubility data at 293.15 and 313.15 K in neat PEG 400 were used to the compute A_1 and B_1 terms, the obtained model is:

$$\ln C_{m,T} = w_1\left(4.395 - \frac{1639.169}{T}\right) + w_2\left(6.003 - \frac{5335.676}{T}\right) \tag{13}$$

which predicted the reported solubility data in the investigated PEG 400 + water mixtures at working temperatures with the ARD% of 41.1% ± 41.5 (N=21). It is obvious that we used only two new experimental data points for this prediction. To provide more accurate predictions, one may use a trained version of the Jouyban-Acree-van't Hoff model by combining Eq. (13) with the *J* terms calculated for the aqueous solubility data of BST in the presence of PEG 200 at working temperatures employing only three data points at 298.15 K (see Eq. (13) of ref. [11]). The combined model is:

$$\begin{aligned}\ln C_{m,T} &= w_1\left(4.395 - \frac{1639.169}{T}\right) + w_2\left(6.003 - \frac{5335.676}{T}\right) \\ &\quad -888.681\frac{w_1.w_2}{T} - 942.138\frac{w_1.w_2(w_1 - w_2)}{T} - 1714.647\frac{w_1.w_2(w_1 - w_2)^2}{T}\end{aligned} \tag{14}$$

The *ARD*% for the back-computed values of $C_{\mathrm{m,T}}$ in PEG 400 + water at working temperatures with Eq. (14) is 20.1% ± 20.6 (N=21).

Conclusions

The BST molar solubilities in neat water, PEG 400 and their mixtures at polymer mass fraction of 0.5 at 293.15, 303.15, 308.15 and 318.15 K and also in binary mixtures of PEG 400 and water with polymer mass fraction of 0.1 to 0.9 at 298.15 K were experimentally determined. Then, the current data were represented with the Jouyban-Acree, Jouyban-Acree-van't Hoff, and the double log-log models to obtain their trained models for prediction the solubility of

BST values in untested mixtures at each working temperature, *i.e*. binary mixtures with polymer mass fractions of 0.1, 0.2, 0.3, 0.4, 0.6, 0.7, 0.8 and 0.9 at 293.15, 303.15, 308.15 and 313.15 K. The overall average relative deviation values for back-calculated data were 4.8% and 6.2% for the Jouyban-Acree and Jouyban-Acree-van't Hoff models, respectively, along with the 8.0% and 6.5% for double log-log models. This study is more uncovered that by measuring sufficient solubility data points and their training with an accurate model, it was possible to predict the solubility data at other solvent compositions and temperatures in accordance with the ones recent reported in the literature. Finally, we checked the previously trained models for BST solubility prediction, where acceptable predictions were made revealing that these models can be used in industrial applications.

Conflict of interests

The authors declare no conflict of interest.

Author contributions

Parisa Jafari: Formal analysis, Investigation, Writing original draft.

Abolgasem Jouyban: Conceptualization, Writing, Review and editing, Supervision.

Elaheh Rahimpour: Writing-review and editing.

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Table 1. Experimental molar solubility values ($C_{m,T}$) as the average of three experiments (± standard deviation) measured for the BST in the binary mixtures of PEG 400 and water at various temperatures.

$w_1{}^a$	$C_{m,T}$ (mol L^{-1})
	293.15 K
0.0	5.41 (± 0.249) × 10^{-6}
0.5	8.54 (± 0.049) × 10^{-4}
1.0	3.01 (± 0.002) × 10^{-1}
	298.15 K
0.0	7.82 (± 0.148) × 10^{-6}
0.1	4.11 (± 0.130) × 10^{-5}
0.2	1.14 (± 0.096) × 10^{-4}
0.3	2.20 (± 0.069) × 10^{-4}
0.4	4.36 (± 0.523) × 10^{-4}
0.5	9.76 (± 0.038) × 10^{-4}
0.6	2.48 (± 0.035) × 10^{-3}
0.7	5.73 (± 0.016) × 10^{-3}
0.8	1.73 (± 0.001) × 10^{-2}
0.9	6.37 (± 0.001) × 10^{-2}
1.0	3.28 (± 0.001) × 10^{-1}
	303.15 K
0.0	9.55 (± 0.027) × 10^{-6}
0.5	1.02 (± 0.006) × 10^{-3}
1.0	3.74 (± 0.001) × 10^{-1}
	308.15 K
0.0	1.21 (± 0.003) × 10^{-5}

0.5	1.24 (± 0.002) × 10^{-3}
1.0	3.98 (± 0.002) × 10^{-1}
	313.15 K
0.0	1.40 (± 0.002) × 10^{-5}
0.5	1.32 (± 0.001) × 10^{-3}
1.0	4.27 (± 0.002) × 10^{-1}

[a] w_1 is mass fraction of PEG 400 in the binary (PEG 400 + water) mixtures in the absence of BST.

[b] The solubility of BST in neat water obtained from the Ref. (11).

Table 2. Molar solubility values ($C_{m,T}$) of BST in water at various temperatures obtained from Ref. [11].

10^5. $C_{m,\,T}$ (mol L^{-1})				
293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.490 (± 0.140)	0.744 (±0.140)	0.939 (± 0.330)	1.13 (± 0.090)	1.38 (± 0.110)

Table 3. Predicted molar solubility values by the trained Jouyban-Acree, the Jouyban-Acree-van't Hoff, and the double log-log models for some non-measured solubility data in mixtures of PEG 400 and water

w_1	$C_{m, T}$ (mol L^{-1})		
	Jouyban-Acree	Jouyban-Acree-van’t Hoff	Double log-log
		293.15	
0.1	2.66×10^{-5}	2.95×10^{-5}	3.34×10^{-5}
0.2	8.03×10^{-5}	8.90×10^{-5}	7.70×10^{-5}
0.3	1.82×10^{-4}	1.98×10^{-4}	1.64×10^{-4}
0.4	3.64×10^{-4}	3.87×10^{-4}	3.58×10^{-4}
0.6	1.68×10^{-3}	1.73×10^{-3}	2.16×10^{-3}
0.7	4.57×10^{-3}	4.68×10^{-3}	5.77×10^{-3}
0.8	1.50×10^{-2}	1.60×10^{-2}	1.67×10^{-2}
0.9	6.30×10^{-2}	6.40×10^{-2}	5.53×10^{-2}
		303.15	
0.1	4.47×10^{-5}	4.55×10^{-5}	5.14×10^{-5}
0.2	1.30×10^{-4}	1.33×10^{-4}	1.11×10^{-4}
0.3	2.87×10^{-4}	2.90×10^{-4}	2.22×10^{-4}
0.4	5.62×10^{-4}	5.59×10^{-4}	4.56×10^{-4}
0.6	2.48×10^{-3}	2.41×10^{-3}	2.59×10^{-3}
0.7	6.52×10^{-3}	6.34×10^{-3}	6.96×10^{-3}
0.8	2.10×10^{-2}	2.00×10^{-2}	2.03×10^{-2}
0.9	8.20×10^{-2}	8.00×10^{-2}	6.79×10^{-2}
		308.15	
0.1	5.51×10^{-5}	5.60×10^{-5}	6.40×10^{-5}
0.2	1.58×10^{-4}	1.62×10^{-4}	1.37×10^{-4}
0.3	3.43×10^{-4}	3.48×10^{-4}	2.74×10^{-4}
0.4	6.64×10^{-4}	6.66×10^{-4}	5.59×10^{-4}
0.6	2.86×10^{-3}	2.82×10^{-3}	3.09×10^{-3}
0.7	7.40×10^{-3}	7.32×10^{-3}	8.13×10^{-3}
0.8	2.30×10^{-2}	2.30×10^{-2}	2.31×10^{-2}
0.9	8.90×10^{-2}	9.00×10^{-2}	7.52×10^{-2}
		313.15	
0.1	6.28×10^{-5}	6.84×10^{-5}	7.16×10^{-5}
0.2	1.78×10^{-4}	1.95×10^{-4}	1.52×10^{-4}
0.3	3.86×10^{-4}	4.16×10^{-4}	3.00×10^{-4}
0.4	7.48×10^{-4}	7.90×10^{-4}	6.04×10^{-4}
0.6	3.20×10^{-3}	3.28×10^{-3}	3.29×10^{-3}
0.7	8.24×10^{-3}	8.42×10^{-3}	8.68×10^{-3}
0.8	2.60×10^{-2}	2.60×10^{-2}	2.47×10^{-2}
0.9	9.70×10^{-2}	1.00×10^{-1}	8.05×10^{-2}

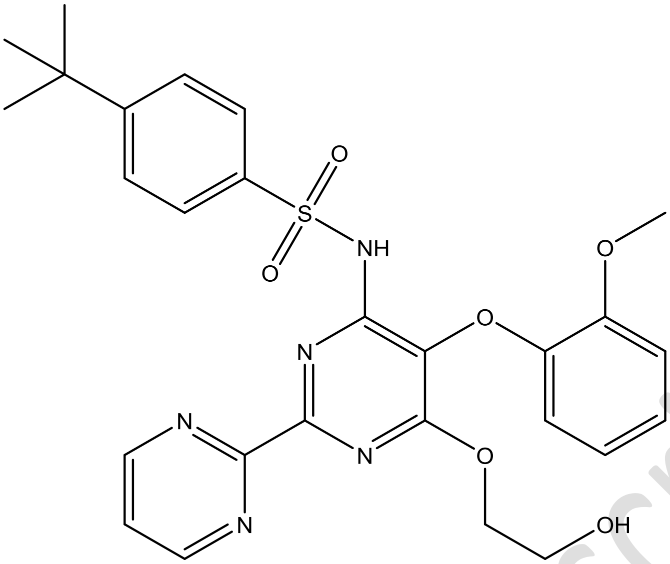


Figure 1. Molecular structure of BST.

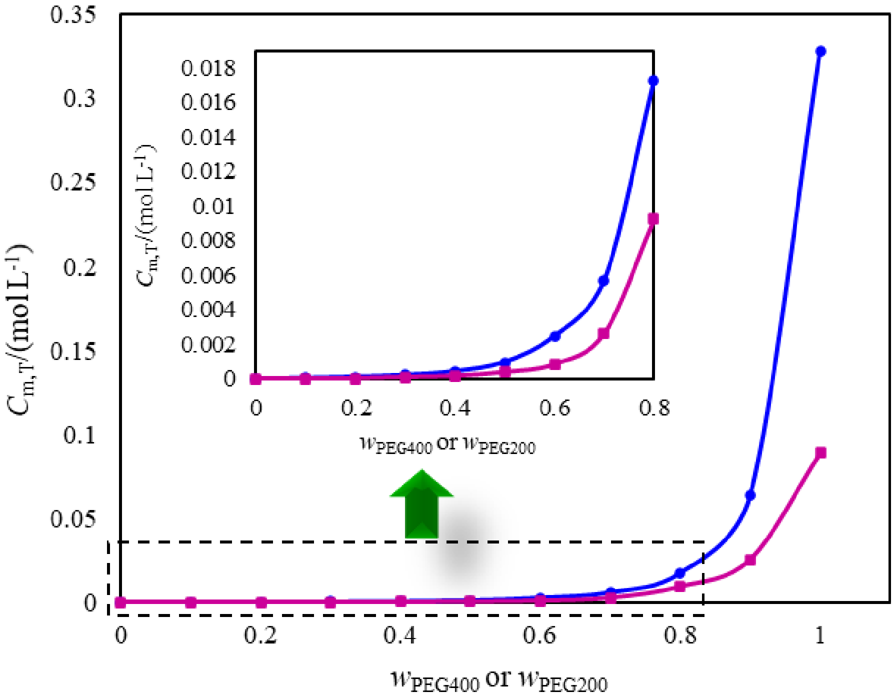
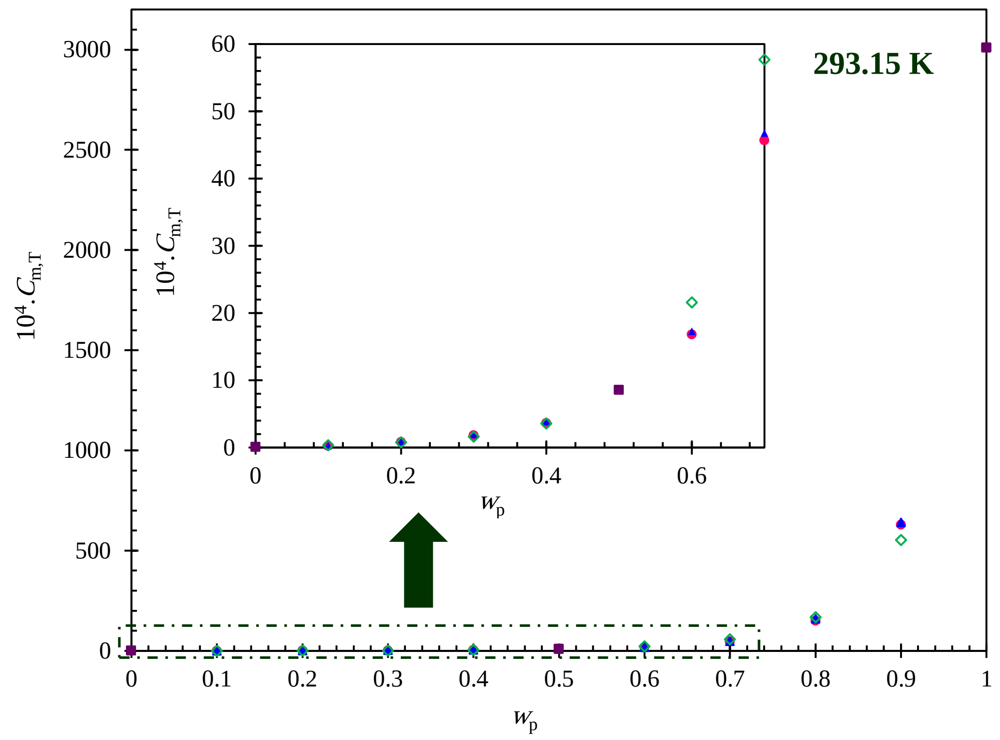
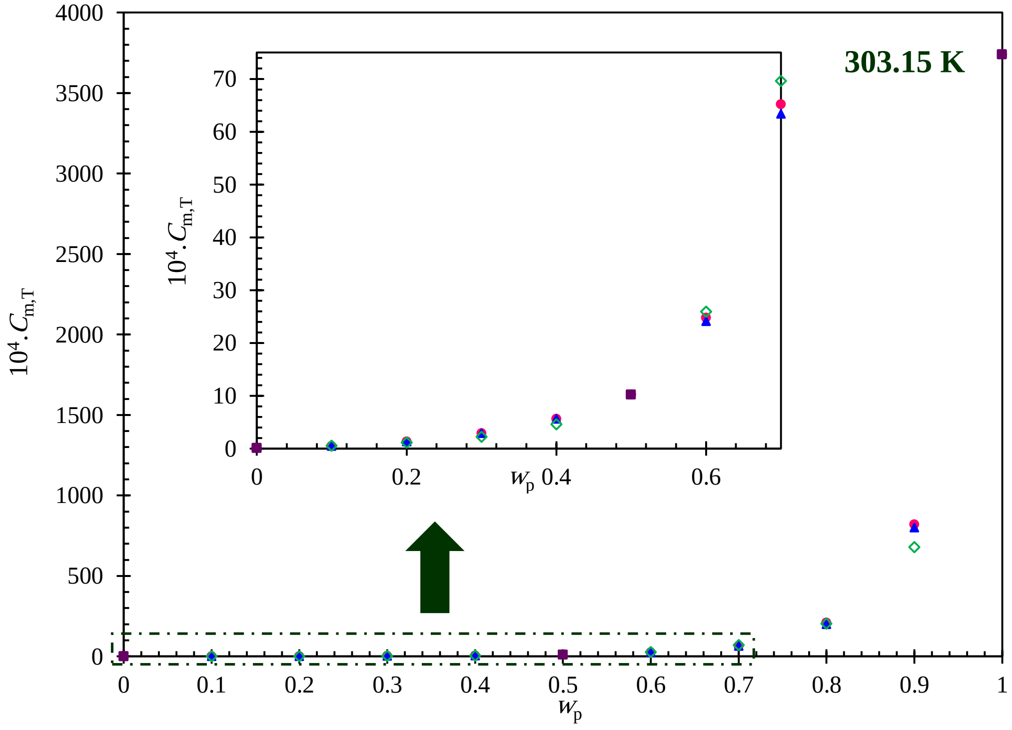
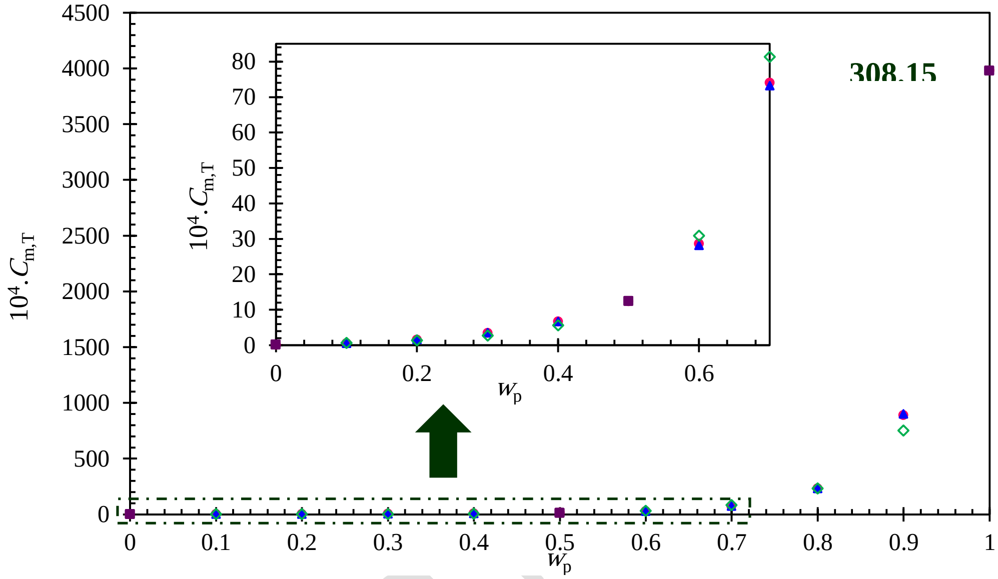


Figure 2. Molar solubility of BST ($C_{m, T}$) in the binary (PEG 400 + water) mixtures at various temperatures and those obtained from Ref. (11) for PEG 200 + water mixtures.


293.15 K
10⁴·C_m,T
3000
2500
2000
1500
1000
500
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
w_p
60
50
40
30
20
10
0
0
0.2
0.4
0.6
w_p


303.15 K
10⁴·C_m,T
4000
3500
3000
2500
2000
1500
1000
500
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
w_p
70
60
50
40
30
20
10
0
0
0.2
w_p 0.4
0.6


308.15
$10^4.C_{m,T}$
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
w_p
80
70
60
50
40
30
20
10
0
0.2
0.4
0.6

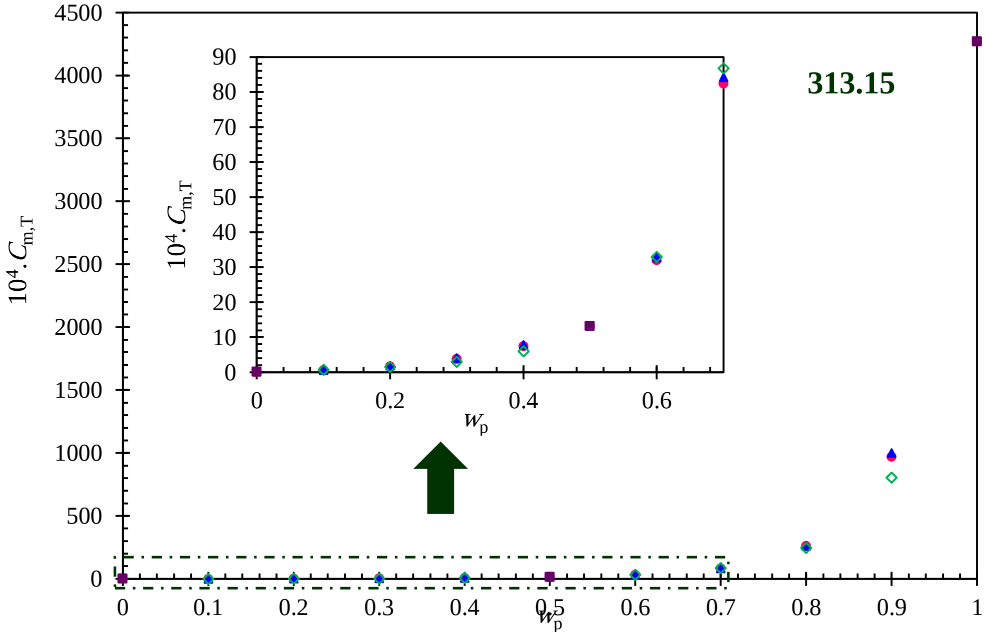

313.15
$10^4.C_{m,T}$
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
w_p
90
80
70
60
50
40
30
20
10
0
0.2
0.4
0.6

Figure 3. The predicted solubility values of BST using the Jouyban-Acree, Jouyban-Acree-van't Hoff and double log-log models along with the experimental solubilities of BST at w_p = 0.0, 0.5 and 1.0 at T = (293.15, 303.15, 308.15 and 313.15) K: (■), experimental values; (●), predicted values with Jouyban-Acree; (▲), predicted values with Jouyban-Acree-van't Hoff, and (◊) predicted values with double log-log.