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## Thermodynamic Solubility and Density of Sildenafil Citrate in Ethanol and Water Mixtures: Measurement and Correlation at Various Temperatures

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**Abstract**

Solubility of sildenafil citrate (SC) in binary aqueous mixtures of ethanol (EtOH) were studied at 293.2, 298.2, 303.2, 308.2 and 313.2 K. Density of the SC saturated solutions over the entire solvent composition and temperature range was measured using a pycnometer. The effect of solvent composition on solubility, enthalpy, entropy and Gibbs energy were studied according to van't Hoff and Gibbs equations. The experimental solubility and densities were used to estimate solubility in the investigated solvent system using the van't Hoff and Jouyban-Acree model.

**Key words:** Solubility, density, sildenafil citrate, solvent mixture, Jouyban-Acree model, van't Hoff equation.

## 1. Introduction

Sildenafil is a selective phosphodiesterase-5 inhibitor used in the treatment of erectile dysfunction (ED) and pulmonary arterial hypertension. Sildenafil citrate (SC) is an ampholyte with  $pK_a$  values of 4 (pyridinium ion) and 8.8 (benzimidazole) [5]. Sildenafil is marketed as the citrate salt and is 40% orally bioavailable and the low bioavailability is due to its low aqueous solubility (4.1 mg/mL in water), [1,2].

Solubility is an essential physicochemical aspect of liquid dosage forms. The pharmaceutical industry faces considerable challenges associated with low aqueous solubility of drugs and drug-like molecules. Various techniques such as cosolvency, drug complexation, pH adjustment and salt formation are effective methods available for solubility improvement. For cosolvency approaches, solvent selection plays an important role in the design and formulation strategy. Ethanol (EtOH), a short chain alcohol co-solvent, is frequently used for solubility improvement of poorly soluble drugs [6,7].

New methods to better facilitate solubility prediction are continuously being developed. Various methods and approaches to predict solubility in cosolvent mixtures have been previously developed [8]. The Jouyban-Acree model is one such versatile model with good predictability power over broad temperature range and solvent composition [9-12].

The aim of the present work is to measure the mole fraction solubility and density of SC in EtOH + water mixtures at 293.2, 298.2, 303.2, 308.2 and 313.2 K. The effect of solvent composition on solubility, enthalpy, entropy and Gibbs free energy were studied. The experimental solubility and density data was correlated with the Jouyban-Acree model and van't Hoff equation.

## 2. Materials and Method

### 2.1. Materials

SC was obtained from Damavand Darou Pharmaceutical company (Semnan, Iran). EtOH of analytical grade was purchased from Scharlau Chemie (Spain). Distilled water (Lab made) was used throughout this study. All chemicals were used as obtained.

### 2.2. Solubility determination

The mole fraction solubility of SC in EtOH + water mixtures was measured according to Higuchi and Connors shake-flask method [13, 14]. Solubility was determined by equilibrating excess amounts of SC in glass vials containing 10 g of each solvent mixtures (mass fraction  $w_1=0.1-0.9$ ) or neat solvent ( $w_1=1.0$ ) using a shaker (Behdad, Tehran, Iran). Samples were placed in an incubator (Kimia Idea Pardaz Azarbayjan (KIPA) Co., Tabriz, Iran) at specified temperatures and allowed to equilibrate for 55 hrs. Equilibration was verified by solute concentration measurements at different times. All experiments were carried out by the isothermal saturation method at several temperature points (293.2, 298.2, 303.2, 308.2, and 313.2 K). At the end of the equilibration time, the solid phase was removed by filtration using syringe filters (0.45  $\mu\text{m}$ ), diluted and analyzed spectrophotometrically (Biotech-Ultraspec 2000, England) at 290 nm. The solution concentrations were calculated using a calibration curve and the dilution factors. Solutions were diluted with neat EtOH (1:1) if required. All solubility determinations were performed in triplicates.

### 2.3. Thermodynamic analysis

Thermodynamic solubility could be studied by evaluating enthalpy and entropy changes [15]. For non-ideal systems enthalpy and entropy of mixing can be determined experimentally from the enthalpy and entropy of solution [16]. Thermodynamic changes were measured at mean harmonic temperature  $T_{hm}$  by means of:

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

where  $n$  is the number of temperatures analyzed. The modified van't Hoff equation was used to calculate  $\Delta H_{soln}^{\circ}$ :

$$\frac{\partial \ln X}{\partial \left( \frac{1}{T} - \frac{1}{T_{hm}} \right)_p} = - \frac{\Delta H_{soln}^{\circ}}{R} \quad (2)$$

where  $X$  is the mole fraction solubility in the cosolvent system,  $T$  and  $R$  are the absolute temperature (K) and gas constant, respectively [17]. The standard solution enthalpies  $\Delta H_{soln}^{\circ}$  were calculated using the van't Hoff equation [17]:

$$d(\ln X) / dT = \Delta H_{soln}^{\circ} / RT^2 \quad (3)$$

The apparent standard Gibbs energies  $\Delta G_{soln}^{\circ}$  that take place during the solubilization process were determined at  $T_{hm}$  considering the following approach [17]:

$$\Delta G_{soln}^{\circ} = -RT_{hm} \cdot \text{intercept} \quad (4)$$

Standard entropic changes in the solution process  $\Delta S_{soln}^{\circ}$  can be obtained by [17]:

$$\Delta G_{\text{soln}}^{\circ} = \Delta H_{\text{soln}}^{\circ} - T_{hm} \Delta S_{\text{soln}}^{\circ} \quad (5)$$

$$\Delta S_{\text{soln}}^{\circ} = \frac{(\Delta H_{\text{soln}}^{\circ} - \Delta G_{\text{soln}}^{\circ})}{T_{hm}} \quad (6)$$

The relative contributions of enthalpy ( $\zeta H$ ) and entropy ( $\zeta S$ ) to Gibbs energy of solution process is calculated by the following relation [17]:

$$\zeta H = \frac{|\Delta H_{\text{soln}}^{\circ}|}{(|\Delta H_{\text{soln}}^{\circ}| + |T\Delta S_{\text{soln}}^{\circ}|)} \quad (7)$$

$$\zeta S = \frac{|T\Delta S_{\text{soln}}^{\circ}|}{(|\Delta H_{\text{soln}}^{\circ}| + |T\Delta S_{\text{soln}}^{\circ}|)} \quad (8)$$

#### 2.4. Density measurement

Densities of saturated SC solutions at different temperatures ( $T=293.2, 298.2, 303.2, 308.2, 313.2$  K) were measured using a 5 mL pycnometer. The reliability of the pycnometer was checked using density measurement of double distilled water at 298.2 K and compared with previous data. The mass of the filtered solutions was measured with the uncertainty of  $\pm 0.0001$  g. The relative standard deviation (RSD) of the density measurements were less than 2%.

#### 2.5. Computational validation

The general Jouyban-Acree model for solute solubility prediction in binary solvent mixtures at various temperatures is defined as [18]:

$$\log_{10} C_{m,T}^{sat} = w_1 \cdot \log_{10} C_{1,T}^{sat} + w_2 \cdot \log_{10} C_{2,T}^{sat} + \frac{w_1 \cdot w_2}{T} \cdot \sum_{i=0}^2 J_i \cdot (w_1 - w_2)^i \quad (9)$$

where  $C_{m,T}^{sat}$  is the molar solubility of SC in the solvent mixtures at temperature  $T$  (Kelvin),  $w_1$  and  $w_2$  are the mass fractions of mono solvents 1 and 2.  $C_{1,T}^{sat}$  and  $C_{2,T}^{sat}$  are solubility of solute in the mono-solvents 1 and 2,  $J_i$  is the constant obtained by regressing

$$(\log C_{m,T}^{Sat} - w_1 \log C_{1,T}^{Sat} - w_2 \log C_{2,T}^{Sat}) \text{ against } \frac{w_1 w_2}{T}, \frac{w_1 w_2 (w_1 - w_2)}{T}, \text{ and } \frac{w_1 w_2 (w_1 - w_2)^2}{T} \quad [19].$$

The van't Hoff equation was used to relate the logarithm of SC solubility as a linear function of the reciprocal of the absolute temperature  $T$  [20] by:

$$\log C_T^{Sat} = A + \frac{B}{T} \quad (10)$$

Where  $C_{m,T}^{Sat}$  is the SC solubility ( $\text{mol}\cdot\text{L}^{-1}$ ),  $A$  and  $B$  are constants calculated using a least square analysis. In practice most real solutions express non-ideal behavior; thus the standard enthalpy and entropy for solution process must be taken into consideration, consequently Eq 10 becomes:

$$\log C_T^{Sat} = \frac{\Delta H_{\text{soln}}^{\circ}}{RT} + \frac{\Delta S_{\text{soln}}^{\circ}}{R} \quad (11)$$

Where  $\Delta H_{\text{soln}}^{\circ}$  and  $\Delta S_{\text{soln}}^{\circ}$  are the enthalpy and entropy of solution, respectively [21].

Application of the van't Hoff equation to Jouyban-Acree model can provide a fully predictive model after training with a number of experimental solubility data points. Thus the combined equation becomes:

$$\log_{10} C_{m,T}^{sat} = w_1 \left( A_1 + \frac{B_1}{T} \right) + w_2 \left( A_2 + \frac{B_2}{T} \right) + \frac{w_1 w_2}{T} \sum_{i=0}^2 J_i \cdot (w_1 - w_2)^i \quad (12)$$



where  $A_1$ ,  $B_1$ ,  $A_2$  and  $B_2$  are constants of the van't Hoff equation obtained by regression analysis of the SC solubility in mono-solvents at various temperatures.

Correlation of the measured SC solubility was evaluated by mean relative deviation (MRD) between the calculated and observed solubility values using the following equation:

$$MRD = \frac{100}{N} \sum \left( \frac{|C_{m,T}^{Calculated} - C_{m,T}^{Observed}|}{C_{m,T}^{Observed}} \right) \quad (13)$$

in which  $N$  is the number of data points in each set.

### 3. Results and Discussions

#### 3.1. Experimental solubility

The temperature-dependent solubility of SC in mono and binary solvent mixtures was assessed at 293.2, 298.2, 303.2, 308.2 and 313.2 K and the obtained experimental mole fraction solubility data of SC in the mixtures are listed in Table 1. The results of solubility data are also shown in Figure 1 to provide a general picture of variations of the data with respect to solvent composition and temperature. There was good agreement between the previously published solubility data of SC in ethanol (1.3 g·L<sup>-1</sup>) and water (4.1 g·L<sup>-1</sup>) at 298.2 K [3] and the solubilities of SC in ethanol (1.3 g·L<sup>-1</sup>) and water (4.4 g·L<sup>-1</sup>) determined in the present study. The curves were concave downwards and reached a maximum value (high end at  $w_1=0.5$  or 0.4) at 313.3 K after which solubility decreased to a minimum of 1.79 g·L<sup>-1</sup> in neat EtOH at 293.2 K. Solubility in neat water was found to be 1.10 g·L<sup>-1</sup>. It is well accepted that a solute will dissolve well in a solvent with similar polarity or solubility parameter [21, 22]. Mole fraction

solubility depends on several factors including chemical structure, solvent polarity, temperature and co-solvent ratio [23].

The shape of a solubility profile can help to optimize co-solvent ratio for maximum solubility enhancement. Various active pharmaceutical ingredients have shown different solubility profile in aqueous mixtures of EtOH. Solubility of dihydromyricetin, ibrutinib and fuasterone increases linearly with mole fraction of EtOH [10, 23, 24]. While for naproxen, phenacetin and salicylic acid drug solubility reaches a maximum point and decrease with further addition of EtOH [17, 26, 27]. Solubility of a solute is at its maximum in solvents with similar polarity or solubility parameter. The oldest rule of solubility “like dissolve like” indicates that solute will better dissolve in solvent with similar intermolecular forces which minimize energy changes during preparation of solution [21, 22]. This can help explain the concave solubility pattern observed ethanol, water mixtures.

Solubility of SC in hexane, toluene, 1-butanol and dichloroethane has been studied at various temperatures. It was found that solubility increased as a function of temperature in all solvents. SC mole fraction solubility at 293.2 K was in the following order with respect to their dielectric constants: Toluene (2.38) > hexane (1.89) > 1-butanol (17.5) > dichloroethane (10.35). It was found that besides dielectric constant and dipole moment other factors may contribute to SC solubility. The temperature dependence solubility has been described previously by the modified Apelblat and Buchowski-Ksiazczak equation [25].

### 3.2. Thermodynamic analysis

Table 2 represents the standard molar thermodynamic functions for SC solubility in all EtOH and water solvent mixtures. In the temperature range studied (293.2, 298.2, 303.2, 308.2, 313.2 K) the  $T_{hm}$  value was calculated as 303.2 K. Maximum solubility was obtained in the  $w_1=0.5$  EtOH at temperature of 313.5 K.

From Table 2 it is seen that  $\Delta H_{soln}^{\circ}$  value in all solvent mixtures was recorded as positive and in neat water and EtOH was found to be 37.7 and 30.2 kJ mol<sup>-1</sup>, respectively.  $\Delta H_{soln}^{\circ}$  and  $\Delta S_{soln}^{\circ}$  increase nonlinearly from  $w=0$  to  $w=0.4$  of EtOH where it reaches its maximum enthalpy and entropy values and then decreases thereafter. The positive values for  $\Delta H_{soln}^{\circ}$  and  $\Delta S_{soln}^{\circ}$  indicate an endothermic and entropy-driven dissolution of SC in water and EtOH mixtures.

Gibbs energy of mixing ( $\Delta G_{mix}^{\circ}$ ) is negative in the range of -7.83 and -2.63 kJ mol<sup>-1</sup>. The lower  $\Delta G_{mix}^{\circ}$  values at  $w_1=0.5$  indicate higher SC solubility in the stated solvent systems. These results are in accordance with the solubility data of SC in co-solvent mixtures.

The van't Hoff plots were constructed between  $\ln X$  and  $(\frac{1}{T} - \frac{1}{T_{hm}})$  and slopes were calculated for each cosolvent mixture. The values of %  $\zeta_H$  and %  $\zeta_{TS}$  indicate that the main contributor to the mole Gibbs energy is entropy. To evaluate the mechanism of co-solvent action, the enthalpy-entropy compensation was obtained by plotting  $\Delta H_{soln}^{\circ}$  as a function of  $\Delta G_{soln}^{\circ}$ . The graph of  $\Delta H_{soln}^{\circ}$  as a function of  $\Delta G_{soln}^{\circ}$  and  $T\Delta S_{soln}^{\circ}$  at the harmonic temperature is demonstrated in Fig 2a and b. The curves represents variable positive and negative slope in all co-solvent ratios. Three regions are exhibited; from pure water up to  $w_1=0.1$  with negative slope (1), followed by a positive slope of up to  $w_1=0.4$  (2) and from this point to neat ethanol

(3) the slope becomes negative again. This indicates that the driving force for the dissolution is entropy in the first and third region, which implies water-structure loosening and enthalpy driven in the second region by the co-solvent as presented by the solubility data [28].

### 3.3. Experimental density

Table 3 lists the densities of saturated SC solutions at various solvent systems and temperatures. The overall results show that the densities of neat water represent the highest density at 0.811 (g cm<sup>-3</sup>) at 313.2 K. At constant temperatures, the densities of the aqueous ethanolic mixtures were increased as the amount of water increased. At fixed composition the densities of the aqueous mixtures followed a slight decrease as the temperature was increased. The linear model can thus be used to fit the density of solvent mixture at various temperatures.

#### 3.3.1. Correlation of Solubility and density data of sildenafil citrate saturated solution to Jouyban-Acree model

The experimental solubility data were fitted to Jouyban–Acree model. Model constants were computed using least square analysis resulting in:

$$\log_{10} C_{m,T}^{sat} = w_1 \cdot \log_{10} C_{1,T}^{sat} + w_2 \cdot \log_{10} C_{2,T}^{sat} + 2049.6 \frac{w_1 \cdot w_2}{T} + 1289.7 \frac{w_1 \cdot w_2}{T} (w_1 - w_2) \quad (14)$$

$$R^2=0.994 \quad F=4236 \quad p<0.001 \quad \text{MRD}=8.4\%$$

The above equation was used to predict the experimental solubilities, with MRD of 8.4%. Predictive power of the combined Jouyban-Acree and van't Hoff equation using two

experimental solubility data (SC solubility in mono-solvents 1 and 2 i.e. EtOH and water at minimum and maximum temperatures) were correlated with the ideal solution equation of van't Hoff thus modifying the equation and yielding:

$$\log_{10} C_{m,T}^{sat} = w_1 \cdot \log_{10} \left( 2.4 - \frac{1895.1}{T} \right) + w_2 \cdot \log_{10} \left( 1.2 - \frac{1512.4}{T} \right) + 1989.9 \frac{w_1 \cdot w_2}{T} + 1315.8 \frac{w_1 \cdot w_2}{T} (w_1 - w_2)$$

(15)

$$R^2=0.992 \quad F=3462 \quad p<0.001 \quad \text{MRD}=10.0\%$$

The trained equation was employed to predict the remaining solubility data points with a MRD value of 10.0 % ( $N=55$ ).

Trained version of Jouyban-Acree model was employed to predict the density of SC saturated solution in the solvent mixtures:

$$\log_{10} \rho_{m,T} = w_1 \cdot \log_{10} \rho_{1,T} + w_2 \cdot \log_{10} \rho_{2,T} - 30.808 \frac{w_1 \cdot w_2}{T} - 18.274 \frac{w_1 \cdot w_2}{T} (w_1 - w_2) + 13.890 \frac{w_1 \cdot w_2}{T} (w_1 - w_2)^2$$

(16)

Density of saturated SC solution was predicted with slight deviation ( $5.6\% \pm 3.7$ ). The combined version of the Jouyban-Acree model and the Abraham salvation parameters has been previously investigated to predict the density of solvent mixtures with relatively good accuracy [29]. Based on the experimental solubility and density data, the trained versions of the van't Hoff and Jouyban-Acree models were employed. The applicability of this model and its simplicity makes this method a reliable model for the prediction of drug solubility at various temperatures and solvent composition.

#### 4. Conclusion

As part of a continuing investigation of the thermodynamic properties of solvent mixtures and drug solubility, this work reports density and solubility of SC in aqueous mixtures of EtOH at various temperatures. The aim of this work was to investigate the ability of the Jouyban-Acree model to predict SC solubility in binary aqueous mixture and to explore its solubilization behavior with respect to thermodynamic concepts. Solubility of SC is reported in aqueous binary mixtures of EtOH at five temperatures in order to select a relatively better solvent composition and optimize drug solubility. The Jouyban-Acree model show good reliability to predict SC solubility in various binary solvent mixtures at the studied temperature ranges. MRD values obtained show good correlation between experimental and predicted solubility values.

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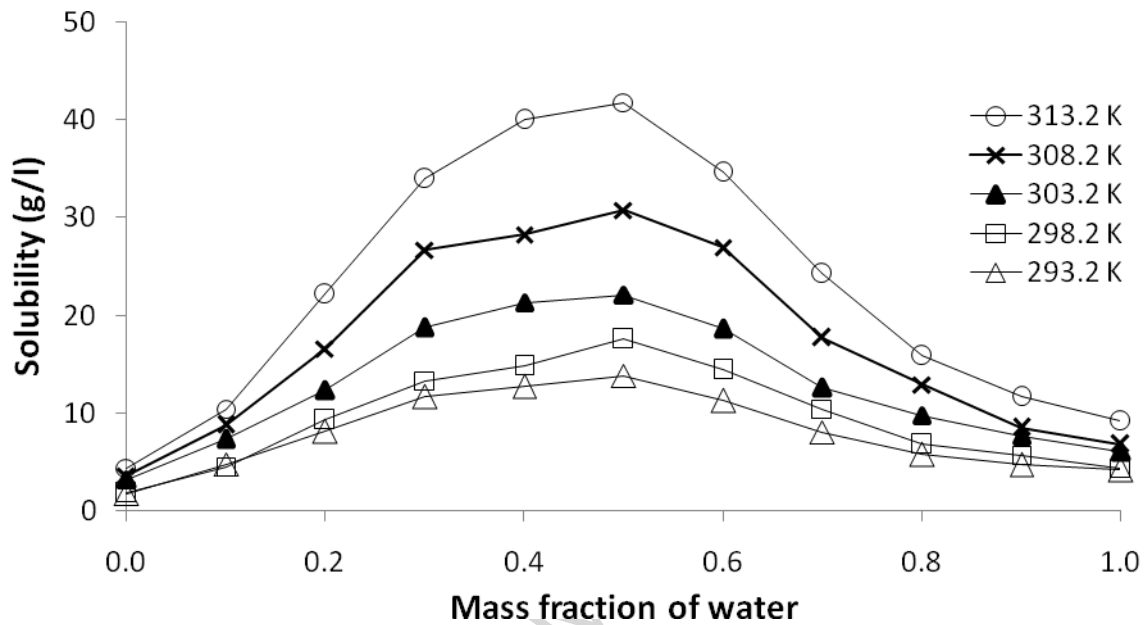
This report is a part of the results of F.H. Pirhayati's Pharm.D thesis submitted to the Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

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**Figure 1.** The g/L solubility of SC in EtOH + water mixtures at various temperatures.

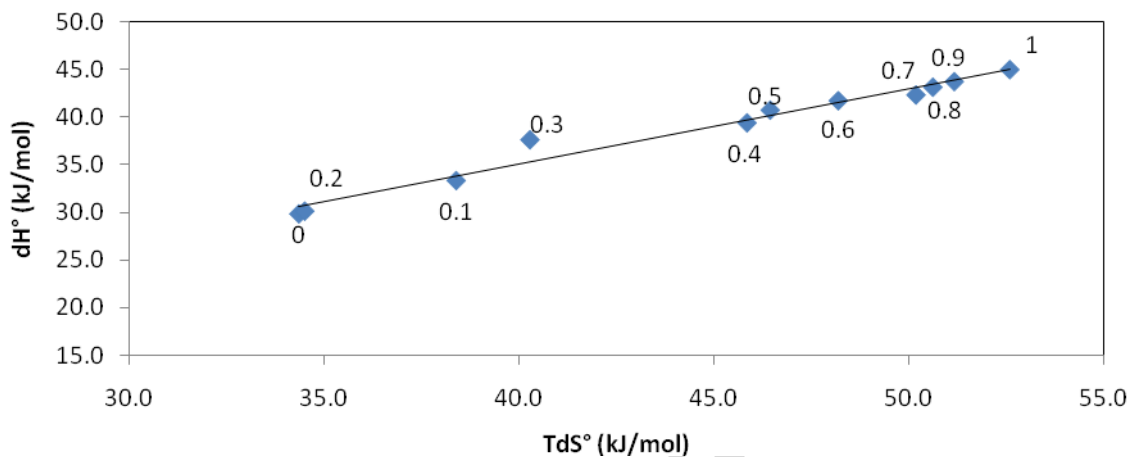


Figure 2a

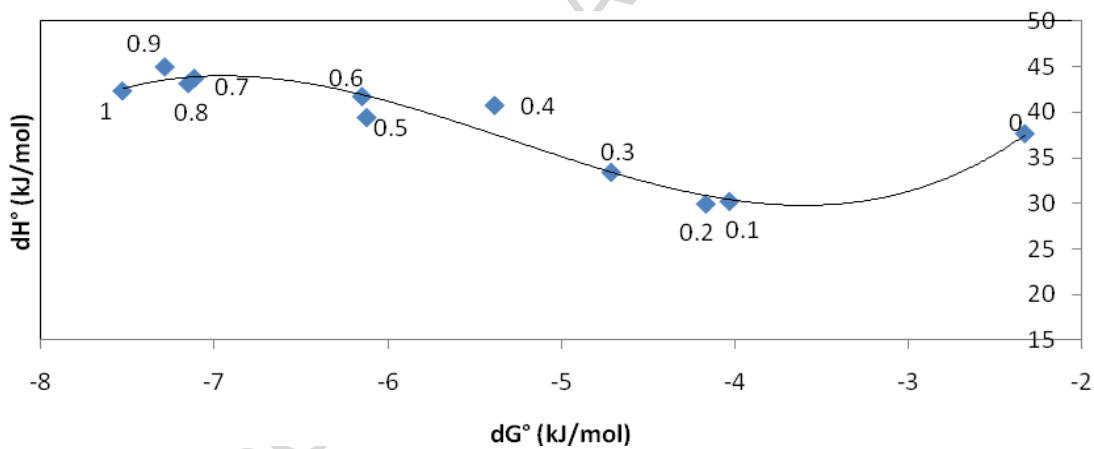


Figure. 2b

**Figure 2.**  $\Delta H_{\text{soln}}^\circ$  versus  $\Delta G_{\text{soln}}^\circ$  (a) and  $T\Delta S_{\text{soln}}^\circ$  (b) enthalpy-entropy compensation plots for solubility of SC in the binary solvent system of EtOH and water at 303.0 K ( $T_{hm}$ ).

**Table 1.** The mole fraction solubility of SC in various ethanol mass fractions ( $w_1$ ) in mixed solvents at different temperatures

$w_1$	293.2	298.2	303.2	308.2	313.2
0.00	$1.50 \times 10^{-4}$	$1.60 \times 10^{-4}$	$2.70 \times 10^{-4}$	$3.03 \times 10^{-4}$	$3.84 \times 10^{-4}$
0.10	$3.77 \times 10^{-4}$	$3.55 \times 10^{-4}$	$5.59 \times 10^{-4}$	$6.78 \times 10^{-4}$	$7.72 \times 10^{-4}$
0.20	$5.80 \times 10^{-4}$	$6.57 \times 10^{-4}$	$8.56 \times 10^{-4}$	1.16E-03	$1.62 \times 10^{-3}$
0.30	$7.59 \times 10^{-4}$	$8.56 \times 10^{-4}$	$1.19 \times 10^{-3}$	1.71E-03	$2.28 \times 10^{-3}$
0.40	$7.50 \times 10^{-4}$	$8.62 \times 10^{-4}$	$1.22 \times 10^{-3}$	1.63E-03	$2.43 \times 10^{-3}$
0.50	$7.35 \times 10^{-4}$	$9.21 \times 10^{-4}$	$1.14 \times 10^{-3}$	1.59E-03	$2.28 \times 10^{-3}$
0.60	$5.35 \times 10^{-4}$	$6.73 \times 10^{-4}$	$8.56 \times 10^{-4}$	1.24E-03	$1.67 \times 10^{-3}$
0.70	$3.38 \times 10^{-4}$	$4.31 \times 10^{-4}$	$5.11 \times 10^{-4}$	$7.21 \times 10^{-4}$	$1.03 \times 10^{-3}$
0.80	$2.12 \times 10^{-4}$	$2.47 \times 10^{-4}$	$3.50 \times 10^{-4}$	$4.61 \times 10^{-4}$	$5.90 \times 10^{-4}$
0.90	$1.52 \times 10^{-4}$	$1.84 \times 10^{-4}$	$2.37 \times 10^{-4}$	$2.63 \times 10^{-4}$	$3.76 \times 10^{-4}$
1.00	$1.16 \times 10^{-4}$	$1.19 \times 10^{-4}$	$1.59 \times 10^{-4}$	$1.79 \times 10^{-4}$	$2.51 \times 10^{-4}$

**Table 2.** Thermodynamic functions of dissolution of mixing of SC in various mass ratio of EtOH in water.

$w_1$	$\Delta G^\circ$ (kJ mol <sup>-1</sup> )	$\Delta H^\circ$ (kJ mol <sup>-1</sup> )	$\Delta S^\circ$ (J.K <sup>-1</sup> .mol <sup>-1</sup> )	$T\Delta S^\circ$ (kJ mol <sup>-1</sup> )	$\zeta H$	$\zeta S$
0.00	-2.63	37.7	133.0	40.3	48.3	51.7
0.10	-4.46	29.9	113.4	34.4	46.5	53.5
0.20	-6.42	39.4	151.3	45.9	46.2	53.8
0.30	-7.45	43.2	167.1	50.6	46.0	54.0
0.40	-7.58	45.0	173.6	52.6	46.1	53.9
0.50	-7.83	42.4	165.6	50.2	45.8	54.2
0.60	-7.41	43.8	168.9	51.2	46.1	53.9
0.70	-6.45	41.7	159.1	48.2	46.4	53.6
0.80	-5.68	40.8	153.3	46.4	46.7	53.3
0.90	-5.01	33.4	126.7	38.4	46.5	53.5
1.00	-4.33	30.2	113.9	34.5	46.7	53.3

**Table 3.** Measured density ( $\text{g cm}^{-3}$ ) of SC saturated solutions of various ethanol mass fractions ( $w_1$ ) in mixed solvents at various temperatures

$w_1$	293.2	298.2	303.2	308.2	313.2
0.00	0.997	0.999	1.011	0.999	1.013
0.10	0.984	0.978	0.997	0.984	0.999
0.20	0.971	0.968	0.979	0.973	0.986
0.30	0.959	0.955	0.966	0.955	0.972
0.40	0.942	0.939	0.949	0.943	0.958
0.50	0.922	0.920	0.930	0.925	0.936
0.60	0.902	0.897	0.908	0.899	0.912
0.70	0.880	0.875	0.885	0.874	0.887
0.80	0.858	0.854	0.862	0.850	0.866
0.90	0.833	0.819	0.836	0.820	0.816
1.00	0.823	0.802	0.812	0.801	0.811

## Highlights

- Experimental solubility of sildenafil citrate in ethanol +water at 5 temperatures
- Determination of properties of the dissolution process,  $\Delta S^\circ$ ,  $\Delta G^\circ$ ,  $\Delta H^\circ$
- Applicability of the Jouyban-Acree model and van't Hoff equation in prediction

ACCEPTED MANUSCRIPT