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# Modeling, solubility, and thermodynamic aspects of sodium phenytoin in propylene glycol–water mixtures

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ABSTRACT

The solubility of sodium phenytoin in binary mixtures of propylene glycol and water at 298.2, 303.2, 308.2, and 313.2 K was measured. The effect of solvent composition on the thermodynamic properties of the dissolution process, including enthalpy, entropy, and Gibbs energy were studied based on van't Hoff analysis and the Gibbs equation. Experimental solubility was determined using the shake-flask method and the resulting data were correlated with the Jouyban–Acree model and with the Jouyban–Acree model in combination with the van't Hoff equation.



## 1. Introduction

Solubility is an essential physicochemical aspect in drug discovery and development. The pharmaceutical industry faces considerable challenges associated with the low aqueous solubility of drugs and drug-like molecules [1]. Poor solubility of a drug is always a challenge for the development of a suitable drug formulation and has a great impact on its oral bioavailability. The solubility of some drugs in neat water is too low; therefore, it is customary to increase drug solubility by various techniques, such as co-solvency, drug complexation, pH adjustments, and salt formation [2]. Co-solvency is a widely used solubility enhancement method. Propylene glycol (PG), one of the most frequently used pharmaceutically accepted co-solvents, increases solubility with the maximum observed solubility occurring between 70 and 90% PG [3]. In cases where a single method is not able to achieve the desired drug solubility, a combination of methods may be employed [4].

Phenytoin is a weak acid with a pKa of 8.33 and a poor aqueous solubility of $7.53 \times 10^{-5}$ mol $dm^{-3}$ [5]. It has been shown that this drug exhibits erratic absorption following oral administration as well as a highly variable bioavailability owing to its incomplete dissolution and poor aqueous solubility [6]. Low aqueous solubility may be overcome by salt formation, co-solvency, or complexation with cyclodextrins [7–10].

The solid-state properties of drug molecules (amorphous or polymorphs) directly influence their solubility and dissolution rate. A significant difference of up to several hundred times can be observed between the solubility of amorphous and crystalline materials. When a drug molecule forms a salt, physicochemical properties such as solubility, dissolution rate, and stability may be affected [11]. Salt formation together with co-solvency might provide an alternative method of solubilization of a poorly water-soluble drug such as phenytoin [12].

Studying the solubility behavior of drug molecules in solvents or co-solvent mixtures is useful to understand the solubilization process. There are various assays for determining drug solubility. Current strategies include thermodynamic and kinetic approaches. Thermodynamic (or equilibrium) solubility is often regarded as the true solubility of a compound and is considered as the gold standard in solubility studies and drug formulation. In this method, a solid compound is introduced into the dissolution medium and solubility is defined as a saturated solution in equilibrium. The thermodynamic method is labor-intensive, requires a large amount of drug, and the experiments could last for several days. The kinetic solubility assay is easily performed and deals with the precipitation of a pre-dissolved drug in a co-solvent system.

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This method allows rapid evaluation of drug solubility and is a common choice in drug discovery. The main drawback of this method is that it overestimates the solubility values compared to thermodynamic solubility. Thermodynamic solubility represents the crystalline phase whilst kinetic solubility relies on the amorphous phase and thus might mislead the scientist towards amorphous residues. This might explain the large differences in solubility obtained by the two methods. In both cases, solubility can be determined by HPLC-UV, LC-MS, or UV detection after filtration or spin-down to remove the insoluble drug [13–15].

Pharmaceutical scientists are continuously searching for new approaches to facilitate and improve the solubility prediction of drug molecules. There are various well-known co-solvency models that are available for predicting drug solubility in solvent mixtures [16]. The Jouyban–Acree model is a versatile model that provides acceptable predictability power over a broad range of temperatures and solvent compositions [17–20].

Based on these considerations, the aim of the present work is to study the effect of salt formation and co-solvency and to measure the mole fraction solubility of sodium phenytoin in PG–water mixtures at 298.2, 303.2, 308.2, and 313.2 K. Thermodynamic parameters involved in the process of solubility were calculated and the effect of solvent composition on the thermodynamic properties of the dissolution process, including enthalpy, entropy, and Gibbs energy, were studied. The experimental solubility data was also correlated with the Jouyban–Acree model and the van't Hoff equation.

## 2. Materials and methods

### 2.1. Materials

Sodium phenytoin (with mass fraction purity (m/m) of 0.993) was purchased from Alhavi Pharmaceutical Company (Tehran, Iran). PG (purity of 0.999 m/m) was obtained from Merck (Germany), and double distilled water was used as received in the lab. Ethanol with a purity of 96% v/v (or 0.935 m/m) was supplied by Jahan Teb Alcohol (Arak, Iran) and used as a diluent for saturated solutions prior to spectrophotometric analyses.

### 2.2. Solubility determination

The mole fraction solubility of sodium phenytoin in PG–water mixtures (mass fraction m = 0.10–0.90) including neat water ($w_1$ = 0.0) and neat PG ($w_1$ = 1.0) was measured using Higuchi and Connors' shake-flask method [21,22]. The solubility was determined by equilibrating excess amounts of sodium phenytoin in the solvent systems using a shaker (Behdad, Tehran, Iran). An excess amount of sodium phenytoin was added to glass vials containing approximately 30 g of each co-solvent mixture or neat solvent. Samples were placed in an incubator (Kimia Idea Pardaz Azarbayjan [KIPA] Co., Tabriz, Iran) at the specified temperature and allowed to equilibrate for 48 h.

All experiments were carried out by the isothermal saturation method at several temperature points (298.2 K, 303.2, 308.2, and 313.2 K). After spin down, the solid phase was removed by centrifugation at 13,000 rpm for 15 min (MSE Micro Center MSB010·CX2.5, Sanyo, Japan). Samples were then filtered and aliquots were analyzed spectrophotometrically (Biotech-Ultraspec 2000, England) at 220 nm for drug contents [23]. Solutions were diluted with ethanol 96% v/v if required. Solubility determinations were performed in triplicates.

### 2.3. Thermodynamic analysis

The thermodynamic solubility of poorly soluble drugs is measured by the shake-flask method of Higuchi and Connors. The thermodynamic solubility of a solute (solute–solution equilibrium) can be studied through solution enthalpy and entropy changes [24].

For non-ideal mixing, the solubility process can be approximately described by the following hypothetical process:

$$\text{Solute}_{(\text{solid})} \rightarrow \text{solute}_{(\text{liquid})} \rightarrow \text{solute}_{(\text{solution})}.$$

Therefore, the enthalpy and entropy of mixing can be determined experimentally from the enthalpy and entropy of solution [25]. During the solvation process, first the bond between the solute molecules breaks followed by the creation of a hole in the solvent for solute placement. These steps are enthalpically unfavorable and consume heat ($\Delta H^\circ > 0$). Then, the solute is placed in the solvent cavity, which is enthalpically favorable due to the solute–solvent interaction ($\Delta H^\circ < 0$) [26].

Thermodynamic changes of the solution are obtained by means of the harmonic temperature, $T_{\text{hm}}$, defined as:

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

where $n$ is the number of temperatures analyzed. The modified van't Hoff expression was used to calculate $\Delta H^\circ_{\text{soln}}$ in the molarity scale ($C$):

$$\frac{\partial \ln C}{\partial\left(\frac{1}{T}-\frac{1}{T_{hm}}\right)_p} = -\frac{\Delta H^\circ_{\text{soln}}}{R} \tag{2}$$

where $C$ is the molar solubility in the co-solvent system, $T$ is the absolute temperature (K), and $R$ represents the gas constant. This equation is based on the analysis of ln $C$ as a function of $\frac{1}{T}-\frac{1}{T_{\text{hm}}}$ [27]. Thus, the standard solution enthalpies $\Delta H^\circ_{\text{soln}}$were calculated from the slopes by using the van't Hoff equation, which is derived from the general equation as [27]:

$$d(\ln C)/dT = \Delta H^\circ_{\text{soln}}/RT^2 \tag{3}$$

The apparent standard Gibbs energies, $\Delta G^\circ_{\text{soln}}$, for the solubilization process were determined at $T_{\text{hm}}$ considering the approach [27]:

$$\Delta G^\circ_{\text{soln}} = -RT_{hm}\cdot\text{intercept} \tag{4}$$

The standard entropic change in the solution process, $\Delta S^\circ_{\text{soln}}$, is obtained as [27]:

$$\Delta G^\circ_{\text{soln}} = \Delta H^\circ_{\text{soln}} - T_{\text{hm}}\Delta S^\circ_{\text{soln}} \tag{5}$$

$$\Delta S^\circ_{\text{soln}} = \frac{\left(\Delta H^\circ_{\text{soln}} - \Delta G^\circ_{\text{soln}}\right)}{T_{\text{hm}}} \tag{6}$$

The relative contributions of enthalpy ($\zeta_H$) and entropy ($\zeta_{TS}$) to the Gibbs energy of the solution process are calculated using [27]:

$$\zeta_H = \frac{\left|\Delta H^\circ_{\text{soln}}\right|}{\left(\left|\Delta H^\circ_{\text{soln}}\right| + \left|T\Delta S^\circ_{\text{soln}}\right|\right)} \tag{7}$$

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

### 2.4. Computational validation

The Jouyban–Acree model for solute solubility prediction in binary solvent mixtures at various temperatures is expressed in a general way by [28]:

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

where $C_{m,T}^{sat}$ represents the solute's molar solubility in the solvent mixtures at temperature $T$ (K), and $w_1$ and $w_2$ are the mass fractions of solvents 1 and 2, respectively, in the absence of a solute. $C_{1,T}^{sat}$ and $C_{2,T}^{sat}$ are the solubilities of the solute in the mono-solvents 1 and 2, respectively, and $J_i$ represents the constants obtained by regressing $(\log C_{m,T}^{Sat} - w_1 \log C_{1,T}^{Sat} - w_2 \log C_{2,T}^{Sat})$ against $\frac{w_1 w_2}{T}$, $\frac{w_1 w_2 (w_1 - w_2)}{T}$, and $\frac{w_1 w_2 (w_1 - w_2)^2}{T}$ [29].

The relationship between temperature and the solubility in different solvents is described by the ideal solution equation. The van't Hoff equation relates the logarithm of the solubility of a solute as a linear function of the reciprocal of the absolute temperature $T$ [30], assuming that the ideal solution is given by:

$$\log C_T^{Sat} = A + \frac{B}{T} \tag{10}$$

where $C_{m,T}^{Sat}$ is the solubility of the solute (mol dm$^{-3}$), A and B are the model constants calculated using a least square analysis.

In practice, most real solutions exhibit non-ideal behavior; therefore, the enthalpy and entropy of mixing must be taken into consideration. The real solubility can be calculated from the expression:

$$\log C_T^{Sat} = \frac{\Delta H_d}{RT} + \frac{\Delta S_d}{R} \tag{11}$$

where $\Delta H_d$ and $\Delta S_d$ are the enthalpy and entropy of the solution, respectively [31].

The Jouyban–Acree model can be combined with van't Hoff equation to provide a fully predictive model after training with experimental solubility data. The combined equation is represented by:

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

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

To evaluate the accuracy of the predictions, the mean relative deviation (MRD) between the calculated and observed solubilities were computed using:

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

where $N$ denotes the number of data points in each set.

## 3. Results and discussion

### 3.1. Experimental solubility

The experimental temperature-dependent mole fraction solubility data of sodium phenytoin in monosolvent and co-solvent mixtures at 298.2, 303.2, 308.2, and 313.2 K are listed in Table 1 and graphically shown in Fig. 1. Drug solubility was found to be the lowest ($2.52 \times 10^{-2}$ mol dm$^{-3}$) in neat water at 298.2 K. The maximum solubility (1.308 mol dm$^{-3}$) of sodium phenytoin was observed in neat PG at 313.2 K. The mole fraction solubility of the drug in neat PG was significantly higher than that in neat water. This pattern is repeated for the solubility of sodium phenytoin in PG at all investigated temperatures. The lowest and highest solubility of the drug in neat water and neat PG was probably owing to the high and low polarity of water and PG, respectively. The mole fraction solubility of a solute depends on several issues, such as chemical structure, solvent polarity, temperature, and co-solvent ratio [32].

**Table 1**
Temperature dependencies of experimental molar solubility ($C_{m,T}^{Sat}$) of sodium phenytoin in various mass fractions ($w_1$) of propylene glycol (1) in aqueous mixtures.

| $w_1$ | 298.2 K | 303.2 K | 308.2 K | 313.2 K |
|---|---|---|---|---|
| 0.00 | 0.252 | 0.304 | 0.341 | 0.360 |
| 0.10 | 0.356 | 0.406 | 0.460 | 0.514 |
| 0.20 | 0.374 | 0.425 | 0.496 | 0.554 |
| 0.30 | 0.395 | 0.444 | 0.521 | 0.577 |
| 0.40 | 0.418 | 0.482 | 0.554 | 0.604 |
| 0.50 | 0.441 | 0.517 | 0.609 | 0.658 |
| 0.60 | 0.465 | 0.550 | 0.630 | 0.688 |
| 0.70 | 0.484 | 0.582 | 0.655 | 0.736 |
| 0.80 | 0.524 | 0.631 | 0.695 | 0.815 |
| 0.90 | 0.579 | 0.714 | 0.780 | 0.947 |
| 1.00 | 0.655 | 0.900 | 1.102 | 1.308 |

Fig. 2 compares the solubility of sodium phenytoin with that of phenytoin taken from Rubino et al. [9]. In aqueous solution, the solubility of sodium phenytoin is greater than that of phenytoin. In aqueous mixtures of PG, the solubility of sodium salt is more than that of its base form for all solvent compositions. However, for PG-rich compositions, the solubility values of the salt form are closer to that of the base form. These observations could be interpreted considering the better solvation of ionic species in water-rich compositions and greater solubility of base forms in PG-rich mixtures [9].

The solubility of sodium phenytoin in 10, 30, and 50% of PG in water was studied by Rubino and Thomas [12] and maximum solubility was found in 30% PG. This effect was found to be due to the formation of hydrate and solvates in aqueous systems, which cause precipitation of the acid form of the drug. The unusual trend in drug solubility was related to the change in the crystal solvation of the drug molecule from hexahydrate to monohydrate when the solvent was changed from 10% to 30% PG. High desolvation transition temperature corresponds to lower drug solubility. However experimental results showed exactly same transition temperature of 345 °C for 30% and 50% PG solvent systems [12]. A quantitative relationship on the effect of co-solvent system on the solubility of sodium phenytoin may not be achieved with only 3 data points and should require numerous ratios of solvent mixtures. In the present study 11 mass fractions of the solvent mixture at 4 different temperature range ($n = 44$) were used to study the solubility enhancement of sodium phenytoin. It is concluded that the mixture of propylene glycol and water system may enhance solubility of sodium salt of drug molecule under the studied conditions.

The solubility of phenytoin in water and ethanol mixtures has been studied in the presence of sodium dodecylsulphate (SDS; at concentrations below its critical micelle concentration (CMC) value). It was found that ethanol and SDS synergistically increased drug solubility by a factor

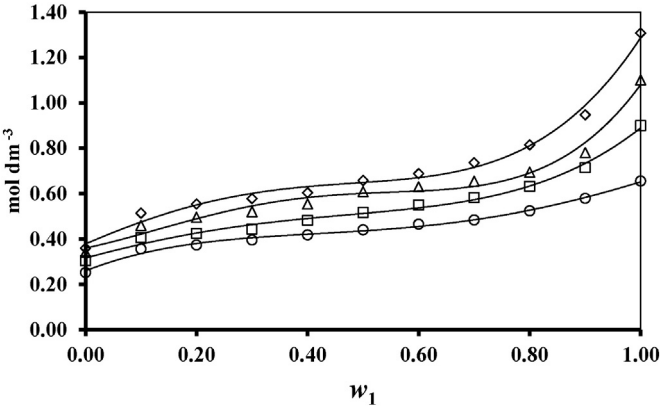


**Fig. 1.** Molar solubility of sodium phenytoin in propylene glycol (1) + water (2) mixtures at several temperatures. (○): 298.2 K; (□): 303.2 K; (△): 308.15 K; (◇): 313.15 K.

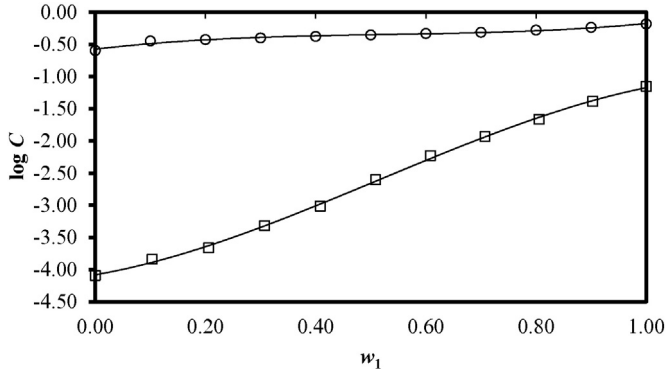


**Fig. 2.** Comparison of molar solubilities of phenytoin as molecular form (□, [9]) and its sodium salt (○, this work) in propylene glycol (1) + water (2) mixtures at 298.2 K.

of 7149. SDS at concentrations below its critical micelle concentration value acts as a secondary co-solvent and helps to enhance drug solubility [23]. The findings were consistent with previous findings of Rubino and co-workers [9].

The solubility of phenytoin as a function of polyethylene glycol 6000 (PEG 6000) and PVP k-30 has been studied. The enhancement in drug solubility was explained using the solubility parameter "$\delta$" to clarify different phenomena of regular solutions, such as solubility and dissolution. The solubility parameter can help in selecting the right co-solvent composition for the optimum level of solubility. The solubility parameters of phenytoin ($\delta$ = 24.99 $MPa^{1/2}$), PEG 6000 ($\delta$ = 19.8 $MPa^{1/2}$), and PVP k-30 ($\delta$ = 25 or 22.5 $MPa^{1/2}$) was calculated using Fedor's group contribution method [10]. It was suggested that the similar solubility parameter of the two materials leads to nearly identical energies of interaction and balance of mixing energy, thus facilitating the solubility and dissolution of phenytoin [4,10].

### 3.2. Apparent thermodynamic function of groups

Table 2 represents the standard molar thermodynamic function for sodium phenytoin solubility in all PG and water solvent mixtures. At the temperatures studied (298.15, 303.15, 308.15, and 313.15 K) the $T_{hm}$ value was calculated as 305.5 K.

Solubility increases with temperature in all cases, indicating that the dissolution process is endothermic. The highest solubility of sodium phenytoin was obtained in the neat PG at 313.5 K. The oldest rule of solubility 'like dissolve like' indicates that a solute will better dissolve in a solvent with similar intermolecular forces resulting in minimal changes of energy upon making the solution [4].

From Table 2, it can be seen that the $\Delta H^{\circ}_{soln}$ value for the drug in all solvent mixtures was recorded as positive and in neat water and neat PG was found to be 18.3 and 35.2 kJ $mol^{-1}$, respectively. The higher value for PG is probably owing to the weaker molecular or ionic interaction between drug and the solvent. $\Delta H^{\circ}_{soln}$ increases nonlinearly from neat water to neat PG.

The lowest and highest $\Delta S^{\circ}_{soln}$ values for the drug in all solvent mixtures were observed in neat water and neat PG with 50.5 and 115.2 J $K^{-1}$ $mol^{-1}$, respectively, indicating an entropy-driven dissolution of sodium phenytoin in all the solvent mixtures. The positive values for $\Delta H^{\circ}_{soln}$ and $\Delta S^{\circ}_{soln}$ indicate an endothermic and entropy-driven dissolution processes of sodium phenytoin in water and PG mixtures.

The positive value for $\Delta G^{\circ}$ in the range of 2.86 and 0.00 kJ $mol^{-1}$ indicates that the drug's dissolution is more favorable in neat PG compared with that in neat water. In this way, the lower $\Delta G^{\circ}$ values correspond to higher solubility and more favorable sodium phenytoin dissolution. The $\Delta G^{\circ}$ value was found to decrease with increasing mass fraction of PG. These results are in accordance with the solubility data of sodium phenytoin in co-solvent mixtures.

The endothermic effect of sodium phenytoin in the dissolution process ($\Delta H^{\circ}_{sol} > 0$) may be owing to the interactions between the solute and solvent molecules being weaker than those between the solvent molecules by one side and between the solute molecules in its solid state by the other. Thus, the new drug–solvent bond energy is not powerful enough to compensate for the energy needed to break the original association bond in various solvents, and the system needs to absorb heat from the surroundings as enthalpy increases. Previous investigations have indicated an exothermic reaction between PG and water [12,24].

The entropy increase during the dissolution process is caused by the solute disrupting the alignment of solvent molecules and therefore reducing the degree of order in various solvent systems, as well as, because of the passing from the more ordered state of the solid drug to the liquid phase in the solution [24].

The van't Hoff plots were constructed by considering ln $C$ and $\frac{1}{T} - \frac{1}{T_{hm}}$ and slopes were calculated for each co-solvent mixture. These plots were found to be linear with $R^2$ values in the range of >0.9941. In all cases, the main contributor to the positive standard molar Gibbs energy of the solution of sodium phenytoin is the positive enthalpy. The values of $\%\zeta_H$ and $\%\zeta_{TS}$ indicate that the main contributor to the mole Gibbs energy is enthalpy with values of $\%\zeta_H > 54\%$, indicating energetic predominance in the dissolution process. It is noteworthy that in neat PG the enthalpy and entropy contributions are the same. On the other hand, the graphs of $\Delta H^{\circ}$ as a function of $\Delta G^{\circ}$ and $T\Delta S^{\circ}$ at the harmonic temperature are shown in Figs 3a and 3b. The curve shown in Fig. 3a exhibits a variable negative slope in all co-solvent mixtures, indicating an entropy-driven transfer of sodium phenytoin from more polar to less polar systems. Furthermore, the trend shown in Fig. 3b, described by the linear equation $\Delta H^{\circ} = 4.048 + 0.875 \cdot T\Delta S^{\circ}$, exhibiting a positive slope lower than 1.0, also indicates an entropy-driven transfer of this drug under the same conditions. These kinds of plots have been successfully used in similar co-solvency studies with molecular forms of different drugs [33,34].

**Table 2**
Apparent thermodynamic quantities of dissolution of sodium phenytoin in various mass fractions of propylene glycol (1) and water (2) at 305.5 K.

| $w_1$ | $\Delta G^{\circ}$/ kJ $mol^{-1}$ | $\Delta H^{\circ}$/ kJ $mol^{-1}$ | $\Delta S^{\circ}$/ J $K^{-1}$ $mol^{-1}$ | $T\Delta S^{\circ}$/ kJ $mol^{-1}$ | $\%\zeta_H$ | $\%\zeta_{TS}$ |
|---|---|---|---|---|---|---|
| 0.00 | 2.86 | 18.3 | 50.5 | 15.4 | 54.24 | 45.76 |
| 0.10 | 2.14 | 19.0 | 55.2 | 16.9 | 52.99 | 47.01 |
| 0.20 | 1.99 | 20.7 | 61.2 | 18.7 | 52.52 | 47.47 |
| 0.30 | 1.87 | 20.1 | 59.7 | 18.3 | 52.43 | 47.56 |
| 0.40 | 1.67 | 19.2 | 57.5 | 17.6 | 52.27 | 47.72 |
| 0.50 | 1.46 | 21.1 | 64.4 | 19.7 | 51.80 | 48.20 |
| 0.60 | 1.34 | 20.3 | 61.9 | 18.9 | 51.71 | 48.28 |
| 0.70 | 1.22 | 21.3 | 65.8 | 20.1 | 51.47 | 48.52 |
| 0.80 | 1.06 | 22.1 | 68.8 | 21.0 | 51.23 | 48.76 |
| 0.90 | 0.75 | 24.3 | 77.2 | 23.6 | 50.78 | 49.21 |
| 1.00 | 0.00 | 35.2 | 115.2 | 35.2 | 50.00 | 50.00 |

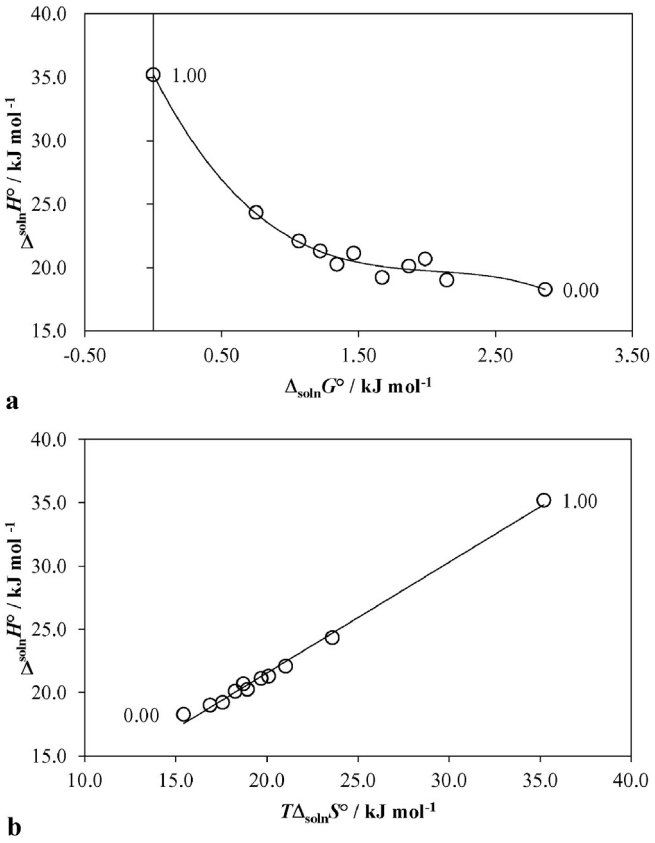


**Fig. 3.** $\Delta H°$ versus $\Delta G°$ (a) and $T\Delta S°$ (b) enthalpy-entropy compensation plots for solubility of sodium phenytoin in the binary solvent system of propylene glycol (1) and water (2) at 305.5 K ($T_{hm}$).

### 3.3. Validation of modeling approach

The solubility data was fitted to Eq. (9) and the model constants were computed using least square analysis resulting in:

$$\log_{10}C^{sat}_{m,T} = w_1.\log_{10}C^{sat}_{1,T} + w_2.\log_{10}C^{sat}_{2,T} + \frac{1142.377w_1.w_2}{T} + \frac{842.519w_1.w_2(w_1-w_2)}{T}. \quad (14)$$

The experimental solubilities were then back-calculated using Eq. (14) in its present form. The MRD value computed according to Eq. (13) was 12.7%. These results reveal that the equation is able to estimate solubility reasonably well with good accuracy. Eq. (14) could be modified by interpolation technique in order to estimate the solubility at different temperatures and solvent compositions of PG–water. The main limitation of Eq. (14) in its present form is that the predictions require experimental $C^{sat}_{1,T}$ and $C^{sat}_{2,T}$ values. In order to overcome this limitation, the solubilities of sodium phenytoin in the mono-solvents 1 and 2, i.e., PG and water, at various temperatures were used to determine the slope and intercept of the van't Hoff equation. These values were then substituted for $\log_{10}C^{sat}_{1,T}$ and $\log_{10}C^{sat}_{2,T}z$ in Eq. (14), thus modifying the equation and yielding:

$$\log_{10}C^{sat}_{m,T} = w_1\left(4.533-\frac{1739.369}{T}\right) + w_2\left(2.695-\frac{978.070}{T}\right) + \frac{1142.377w_1.w_2}{T} + \frac{842.519w_1.w_2(w_1-w_2)}{T} \quad (15)$$

The above modified equation was used to predict the experimental solubilities, resulting in an MRD of 13.7%. To show the predictive power of the combined Jouyban–Acree and van't Hoff equation, the minimum number of experimental data points was used to train the equation. The trained equation was then used to predict the remaining solubility data points with an MRD value of 25.6% ($N = 36$), this is reasonable considering the minimum number of data points used to train the equation.

The marginally improved fit of the equation for phenytoin in aqueous mixtures of ethanol (MRD = 13.9%) as listed in our previous paper [23] can be explained by the unionized form of the drug when compared to the salt form of the drug used in this study (MRD = 25.6%). The applicability of this model may not be same for all solid-state properties of solutes, however the simplicity and relative prediction accuracy of this model makes this method a reliable model for the prediction of drug solubility at various temperatures and solvent compositions.

## 4. Conclusion

The goal of this work was to investigate the predictability of the Jouyban–Acree model for the solubility of sodium phenytoin in binary aqueous mixtures and to understand its solubilization behavior by applying thermodynamic concepts. The solubility of sodium phenytoin is reported in aqueous binary mixtures of PG at four different temperatures. The thermodynamic aspects of the solubility process of sodium phenytoin in PG and water mixtures were studied in order to select the best solvent and optimize drug solubility. Results indicate that PG could be used as a compatible co-solvent for solubility enhancement for sodium phenytoin. The positive values for $\Delta S°$, $\Delta G°$, and $\Delta H°$ indicate endothermic, spontaneous, and enthalpy-driven dissolution of sodium phenytoin in all the PG and water co-solvent mixtures. This was found to be owing to the strong molecular interaction between drug and solvent. In addition, the change of dissolution enthalpy is the main contributor to the Gibbs energy of the dissolution process. From the modeling point of view, the Jouyban–Acree model shows good applicability in predicting solubility in various solvent mixtures and temperatures. These findings are supported by acceptable MRD values obtained when comparing the estimated and experimental solubilities.

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