Measurement and correlation of solubility of ethylparaben in pure and binary solvents and thermodynamic properties of solution

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Summary

Solubility data of bioactive compound such as ethylparaben (EtP) are important for the scientific and community. Therefore, in present study, solubility, solution thermodynamics and solute-solvent interactions (at molecular level) of EtP in nine cosolvent mixtures (1-propanol \( {n-PrOH} \) (1) + methanol (MeOH) (2)) including pure solvent (methanol and 1-propanol) at three different temperatures, i.e. \( (T = 283.2 \text{ K}, 298.2 \text{ K}, \text{ and } 313.2 \text{ K}) \) and constant pressure \( (p = 0.1 \text{ MPa}) \) were studied.

Experimental solubility of EtP (expressed in mole fraction) was observed highest in \( n-PrOH \) at 313.2 K, so, mole fraction solubility of EtP \( (x_i) \) increases when temperature arises and increases with \( n-PrOH \) proportion increasing. Ideal solubilities of EtP were estimated using their thermal parameters at three different temperatures. Ideal solubilities of EtP were observed similar to experimental solubilities of EtP at each temperature. With the help of ideal solubilities of EtP, activity coefficients were estimated. Based on estimated values of activity coefficients, highest interactions at molecular level were observed in rich-MeOH mixtures. Apparent thermodynamic analysis data showed endothermic and enthalpy-driven dissolution of EtP in each solvent and mixture studied. Solubility behavior was adequately correlated by means of the van’t Hoff and Yalkowsky-Roseman models combined.

Key words: Ethylparaben, solubility, van’t Hoff, Yalkowsky-Roseman, cosolvent.
Resumen

Determinación y correlación de la solubilidad del etilparabeno en disolventes puros y binarios y propiedades termodinámicas de solución

La solubilidad de compuestos bioactivos como el etilparabeno (EtP) es importante para la comunidad científica. Por lo tanto, en el presente estudio se reportan la solubilidad, termodinámica de solución e interacciones soluto-solvente (a nivel molecular) del EtP en nueve mezclas de cosolventes {1-propanol (n-PrOH) (1) + metanol (MeOH) (2)} incluyendo los solventes puros (metanol y 1-propanol) a tres temperaturas diferentes, (T = 283,2 K, 298,15 K y 313,2 K) y a presión constante (p = 0,1 MPa). La solubilidad experimental más alta del EtP (expresadas en fracción molar) se registró en n-PrOH a 313,15 K, así, la solubilidad en fracción molar de EtP aumenta cuando la temperatura aumenta y la proporción de n-PrOH aumentan.

Las solubilidades ideales de EtP se estimaron utilizando los parámetros térmicos a tres temperaturas diferentes. Las solubilidades ideales de EtPa son similares a las solubilidades experimentales de EtP a cada temperatura. A partir de las solubilidades ideales de EtP se estimaron los coeficientes de actividad y sobre la base de los valores estimados de los coeficientes de actividad, se define que las interacciones más altas a nivel molecular se registraron en mezclas ricas en MeOH. Los datos aparentes del análisis termodinámico mostraron un proceso endotérmico con conducción entálpica para el EtP cada uno de los solventes y mezclas de solventes estudiados. El comportamiento de solubilidad se correlacionó adecuadamente mediante los modelos de van’t Hoff y Yalkowsky-Roseman combinados.

Palabras clave: Etilparabeno, solubilidad, van’t Hoff, Yalkowsky-Roseman, cosolvente.

Introduction

Parabens, esters of para-hydroxybenzoic acid, have an alkyl group like methyl, ethyl, propyl, butyl, heptyl or benzoyl and are been utilized as preservatives in cosmetics, pharmaceutical products, food items for as they possess anti-microbial and anti-fungal properties [1]. Nowadays, parabens are considered dangerous, by its endocrine disruption potential, which includes modification of hormone synthesis and their metabolism [2]. Studies have shown that parabens have estrogen agonist action and they can also cause male infertility [3].
Ethylparaben (EtP, see figure 1, ethyl 4-hydroxybenzoate, C₉H₁₀O₃) is used in soap and detergents, eyeliner, perfumes, shampoos, tint, foundations, deodorants, pre-shaving lotions, moisturizers [4]. Parabens found in aqueous sources are mainly due to the discharges from wastewater treatment plants [2].

![Figure 1. Molecular structure of ethylparaben.](image)

In this context, solubility studies have become an important tool for the development of decontamination strategies. In addition, they also allow the development of more precise mathematical models, which lead to predict solubility and reduce the number of experimental tests, that entails reducing the environmental impact, due to a decrease in the volume of pollutant discharges to bodies of water [5, 6].

The other hands, the mathematical models are the easy and fast ways to estimate drugs solubility, and therefore, they also offer an important alternative in the pharmaceutical industry. Nevertheless, these models are optimized through the generation of experimental data, which allow for rational modifications [7-9].

The main goal of this paper is to evaluate the solution thermodynamic of EtP in {1-propanol + methanol} cosolvent mixtures, based on thermodynamic definitions. Thus, this work is similar to the ones presented previously in the literature for some drugs in cosolvent mixtures [10-14].

**Experimental**

**Reagents**

In this research, EtP (Sigma-Aldrich, USA; compound 3, purity at least 0.990 in mass fraction), MeOH (Merck A.R., Germany); the solvent component 2, purity at least 0.998 in mass fraction) n-PrOH (Merck A.R., Germany; the solvent component 1, purity at least 0.998 in mass fraction); EtOH (Merck A.R., Germany; solvent used for dilutions).
Preparation of solvent mixtures

All \{n-\text{PrOH} (1) + \text{MeOH} (2)\} solvent mixtures were prepared by mass in quantities of 40.00 g, using an analytical balance with sensitivity ± 0.1 mg (RADWAG AS 220. R2, Poland). The mass fractions of \text{n-PrOH} (1), \( w_1 \), of the nine mixtures prepared varied by 0.10 from 0.10 to 0.90.

Solubility determinations

An excess amount of EtP was added to approximately 40.00 g of each binary \{n-\text{PrOH} (1) + \text{MeOH} (2)\} solvent mixture or neat EtP, in stoppered dark glass flasks. The flasks were transferred to cooling thermostats (cryostats) (Medingen K-22/T100, Germany) maintained at 313.15 (±0.05) K for at three days to reach the saturation equilibrium. After this time, the supernatant solutions were filtered at isothermal conditions (Millipore Corp. Swinnex®-13, USA) to ensure that they were free of particulate matter before sampling for analysis. Drug concentrations were determined after appropriate gravimetric dilution with ethanol by measuring the UV light absorbance at the wavelength of maximum absorbance, 268 nm (UV/VIS EMC-11-UV spectrophotometer, Germany), and interpolation from a previously constructed UV spectrophotometric gravimetric calibration curve following a validated method. All the solubility experiments were performed at least three times. Later, the thermostats temperature was adjusted at 308.15 K during two days allowing the respective EtP precipitation, finally the temperature led to 283.15 K.

Results and discussion

Equilibrium solubility of EtP in aqueous-cosolvent mixtures

The experiment results in \text{n-PrOH}, \text{MeOH} and the mixtures of \text{n-PrOH} and \text{MeOH} are presented in table 1 and plotted in figure 2. The solubility value in pure solvents and the mixtures with a fixed composition increased with the rise of temperature. Moreover, in the two studied pure solvents, the solubility largest one was found in \text{n-PrOH} and lowest in \text{MeOH} at the determined temperature. As can be seen, the solubility of EtP in the mixtures of \{n-\text{PrOH} (1) + \text{MeOH} (2)\} increases to a maximum with the increasing the composition of cosolvent \text{n-PrOH} up to pure \text{n-PrOH}. The results show that the solubility of EtP can be improved by cosolvents. Table 1 via footnotes c and d shows that our parabens solubility values in neat solvents are in good agreement with those reported in the literature. The different reported solubility values for parabens vary in some extent. This could be due to differences in analyzed polymorphic crystals, equilibration times, or the analytical techniques employed [15].
Figure 2. Experimental mole fraction solubility of EtP in \{n-PrOH (1) + MeOH (2)\} mixtures at different temperatures; (● = 283.15 K; ▲ = 298.15 K; ◆ = 313.15 K).

Table 1. Experimental mole fraction solubility of EtP in \{n-PrOH (1) + MeOH (2)\} mixtures at different temperatures.

<table>
<thead>
<tr>
<th>(w_1)*</th>
<th>283.15 K</th>
<th>298.15 K</th>
<th>313.15 K</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.0597±0.0012</td>
<td>0.1283±0.0019(^b)</td>
<td>0.2142±0.0021(^b)</td>
</tr>
<tr>
<td>0.10</td>
<td>0.0623±0.0016</td>
<td>0.132±0.004</td>
<td>0.2173±0.0012</td>
</tr>
<tr>
<td>0.20</td>
<td>0.06307±0.00016</td>
<td>0.1364±0.0018</td>
<td>0.22048±0.00033</td>
</tr>
<tr>
<td>0.30</td>
<td>0.0701±0.0011</td>
<td>0.1407±0.0032</td>
<td>0.2237±0.006</td>
</tr>
<tr>
<td>0.40</td>
<td>0.0754±0.0011</td>
<td>0.1452±0.0016</td>
<td>0.22690±0.00028</td>
</tr>
<tr>
<td>0.50</td>
<td>0.0800±0.0010</td>
<td>0.150±0.003</td>
<td>0.23018±0.00026</td>
</tr>
<tr>
<td>0.60</td>
<td>0.0849±0.0019</td>
<td>0.1544±0.0019</td>
<td>0.2335±0.007</td>
</tr>
<tr>
<td>0.70</td>
<td>0.0940±0.0009</td>
<td>0.1593±0.0021</td>
<td>0.237±0.004</td>
</tr>
<tr>
<td>0.80</td>
<td>0.0996±0.0012</td>
<td>0.164±0.004</td>
<td>0.240±0.005</td>
</tr>
<tr>
<td>0.90</td>
<td>0.1054±0.0023</td>
<td>0.1695±0.0021</td>
<td>0.244±0.006</td>
</tr>
<tr>
<td>1.00</td>
<td>0.1077±0.0013</td>
<td>0.1748±0.0021(^c)</td>
<td>0.247±0.006(^c)</td>
</tr>
</tbody>
</table>

*a* \(w_1\) is the mass fraction of n-PrOH in the cosolvent mixture free of solute.

\(^b\) Reported mole fraction solubility values in neat MeOH (2) at 298.15 K: \(x_3=0.135\) [16]; \(x_3=0.136\) [4] and 313.15 K: \(x_3=0.208\) [16].
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Reported mole fraction solubility values in neat n-PrOH (1) at a 298.15 K: $x_1 = 0.176$ and 313.15 K: $x_1 = 0.229$ [16].

Activity coefficients

Table 2 shows the EtP (3) activity coefficients $\gamma_3$, calculated as the quotient $x_{3-id}/x_3$ from the respective solubility values presented in table 1 in all cases these values are quite approximate than 1 particularly in methanol-rich mixtures and low temperatures. From $\gamma_3$ values a rough estimate of solute-solvent intermolecular interactions can be made by considering the following expression [17]:

$$
\gamma_3 = \left( e_{11} + e_{33} - 2e_{13} \right) V_3 \phi_1^2 \left( RT \right)^{-1}
$$

(1)

Where subscript 1 stands for the solvent mixture: {n-PrOH (1) + MeOH (2)}, $e_{11}$, $e_{33}$ and $e_{13}$ represent the solvent-solvent, solute-solute and solvent-solute interaction energies, respectively; $V_3$ is the molar volume of the super-cooled liquid solute, whereas, $\phi_1$ is the volume fraction of the solvent. As commonly used, for relatively low $x_3$ values, $V_3 \phi_1^2 / RT$ may be considered as constant. Thus, $\gamma_3$ depends mainly on $e_{11}$, $e_{33}$ and $e_{13}$ [17]. The $e_{11}$ and $e_{13}$ terms are unfavorable for solubility and dissolution, whereas the $e_{13}$ term favors the dissolution process. The contribution of the $e_{33}$ term could be considered as constant in all the mixtures.

Table 2. EtP (3) activity coefficients ($\gamma_3$) in {n-PrOH (1) + MeOH (2)} cosolvent mixtures at several temperatures.

<table>
<thead>
<tr>
<th>$w_1$</th>
<th>283.15 K</th>
<th>298.15 K</th>
<th>313.15 K</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.869</td>
<td>1.207</td>
<td>1.332</td>
</tr>
<tr>
<td>0.10</td>
<td>0.906</td>
<td>1.245</td>
<td>1.351</td>
</tr>
<tr>
<td>0.20</td>
<td>0.918</td>
<td>1.284</td>
<td>1.371</td>
</tr>
<tr>
<td>0.30</td>
<td>1.020</td>
<td>1.325</td>
<td>1.391</td>
</tr>
<tr>
<td>0.40</td>
<td>1.098</td>
<td>1.366</td>
<td>1.411</td>
</tr>
<tr>
<td>0.50</td>
<td>1.164</td>
<td>1.409</td>
<td>1.431</td>
</tr>
<tr>
<td>0.60</td>
<td>1.235</td>
<td>1.453</td>
<td>1.452</td>
</tr>
<tr>
<td>0.70</td>
<td>1.369</td>
<td>1.499</td>
<td>1.473</td>
</tr>
<tr>
<td>0.80</td>
<td>1.449</td>
<td>1.546</td>
<td>1.494</td>
</tr>
<tr>
<td>0.90</td>
<td>1.535</td>
<td>1.595</td>
<td>1.516</td>
</tr>
<tr>
<td>1.00</td>
<td>1.567</td>
<td>1.645</td>
<td>1.538</td>
</tr>
</tbody>
</table>

$w^i$ is the mass fraction of n-PrOH in the cosolvent mixture free of solute.
This is a particularly interesting case, the values of \( \gamma_3 \), are very approximate to the unit. Therefore, solute-solvent interactions favor the process of solubility in all cases. In general, the activity coefficients diminish as the temperature rises, and therefore, the solution processes become “more ideal”.

**Apparent thermodynamic quantities of dissolution**

From solubility data, the thermodynamic functions are calculated solution. So, the standard molar enthalpy changes of solution, \( \Delta_{\text{soln}}^\circ H^\circ \) is obtained from the slope of a \( \ln x_3 \) vs. \( 1/T-1/T_{hm} \) plot. Over the limited temperature interval (283.15 to 313.15 K) the heat capacity change of solution may be assumed to be constant, hence \( \Delta_{\text{soln}}^\circ H^\circ \) should be valid for the mean harmonic temperature, \( T_{hm} = 297.6 \) K [17-19].

\[
\Delta_{\text{soln}} H^\circ = -R \left( \frac{\partial \ln x_3}{\partial \left( \frac{1}{T} - \frac{1}{T_{hm}} \right)} \right)_p
\]  

The apparent standard Gibbs energy change for the solution process (\( \Delta_{\text{soln}} G^\circ \)) considering the approach proposed by Krug et al., is calculated at 297.6 K by means of [17, 18]:

\[
\Delta_{\text{soln}} G^\circ = -RT \times \text{Intercept}
\]  

The standard molar entropy changes for the solution process, \( \Delta_{\text{soln}} S^\circ \), at the mean harmonic temperature, \( T_{hm} = 297.6 \) K is then

\[
\Delta_{\text{soln}} S^\circ = \frac{\Delta_{\text{soln}} H^\circ - \Delta_{\text{soln}} G^\circ}{T_{hm}}
\]

Table 3 presents the standard molar thermodynamic functions for dissolution of EtP (3) in all the \{n-PrOH (1) + MeOH (2)\} solvent mixtures.

The standard Gibbs free energy of solution is positive in all cases as is the enthalpy of solution; therefore the process is always endothermic [20]. In figure 3 show change of enthalpy versus the mole fraction of n-PrOH. In this case, it is not observed, the typical behavior of aqueous mixtures, where the enthalpy, initially increases, and then decreases [21, 22]. So, from the pure MeOH up to the pure n-PrOH the enthalpy of solution tends to decrease that is responsible for increasing the solubility.
Table 3. Apparent thermodynamic functions relative to solution process of EtP in \{n-PrOH (1) + MeOH (2)\} cosolvent mixtures at 297.15 K.

<table>
<thead>
<tr>
<th>(w_1^a)</th>
<th>(\Delta_{\text{soln}} G^o) (kJ mol(^{-1}))</th>
<th>(\Delta_{\text{soln}} H^o) (kJ mol(^{-1}))</th>
<th>(\Delta_{\text{soln}} S^o) (J mol(^{-1}) K(^{-1}))</th>
<th>(T\Delta_{\text{soln}} S^o) (kJ mol(^{-1}))</th>
<th>(\xi_H)</th>
<th>(\xi_{TS})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>5.29±0.11</td>
<td>31.5±2.7</td>
<td>88±8</td>
<td>26.2±2.3</td>
<td>0.546</td>
<td>0.454</td>
</tr>
<tr>
<td>0.10</td>
<td>5.22±0.11</td>
<td>30.8±2.8</td>
<td>86±8</td>
<td>25.6±2.4</td>
<td>0.546</td>
<td>0.454</td>
</tr>
<tr>
<td>0.20</td>
<td>5.17±0.13</td>
<td>30.8±3.2</td>
<td>86±9</td>
<td>25.7±2.8</td>
<td>0.546</td>
<td>0.454</td>
</tr>
<tr>
<td>0.30</td>
<td>5.05±0.10</td>
<td>28.6±2.5</td>
<td>79±7</td>
<td>23.5±2.1</td>
<td>0.548</td>
<td>0.452</td>
</tr>
<tr>
<td>0.40</td>
<td>4.95±0.09</td>
<td>27.1±2.2</td>
<td>75±6</td>
<td>22.2±1.8</td>
<td>0.550</td>
<td>0.450</td>
</tr>
<tr>
<td>0.50</td>
<td>4.86±0.08</td>
<td>26.0±2.0</td>
<td>71±6</td>
<td>21.2±1.7</td>
<td>0.551</td>
<td>0.449</td>
</tr>
<tr>
<td>0.60</td>
<td>4.78±0.08</td>
<td>24.9±1.9</td>
<td>68±5</td>
<td>20.2±1.6</td>
<td>0.553</td>
<td>0.447</td>
</tr>
<tr>
<td>0.70</td>
<td>4.65±0.05</td>
<td>22.7±1.2</td>
<td>61.7±3.1</td>
<td>18.1±1.0</td>
<td>0.557</td>
<td>0.443</td>
</tr>
<tr>
<td>0.80</td>
<td>4.57±0.04</td>
<td>21.7±1.1</td>
<td>57.5±2.9</td>
<td>17.1±0.9</td>
<td>0.559</td>
<td>0.441</td>
</tr>
<tr>
<td>0.90</td>
<td>4.48±0.04</td>
<td>20.6±1.0</td>
<td>54.2±2.6</td>
<td>16.1±0.8</td>
<td>0.561</td>
<td>0.439</td>
</tr>
<tr>
<td>1.00</td>
<td>4.43±0.06</td>
<td>20.5±1.4</td>
<td>54±4</td>
<td>16.0±1.1</td>
<td>0.561</td>
<td>0.439</td>
</tr>
<tr>
<td>Ideal</td>
<td>5.570±0.006</td>
<td>20.87±0.15</td>
<td>51.4±0.4</td>
<td>15.3±0.1</td>
<td>0.577</td>
<td>0.423</td>
</tr>
</tbody>
</table>

\(w_1^a\) is the mass fraction of n-PrOH in the cosolvent mixture free of solute.

The entropy of solution is positive in all solvent mixtures and neat solvent, indicating the entropy as driving the solution process. The \(\Delta_{\text{soln}} S^o\) values decrease nonlinearly from pure MeOH up to n-PrOH where the lower entropic value is obtained.

The relative contributions by enthalpy (\(\xi_H\)) and entropy (\(\xi_{TS}\)) toward the solution processes are given by equations (5) and (6) [23]:

\[
\xi_H = \frac{\left|\Delta_{\text{soln}} H^o\right|}{\left|\Delta_{\text{soln}} H^o\right| + T \left|\Delta_{\text{soln}} S^o\right|}
\]

\[
\xi_{TS} = \frac{\left|\Delta_{\text{soln}} S^o\right|}{\left|\Delta_{\text{soln}} H^o\right| + T \left|\Delta_{\text{soln}} S^o\right|}
\]
The main contributor to the (positive) standard molar Gibbs energy of solution of EtP, in all cases, is the (positive) enthalpy ($\zeta_H > 0.546$).

### Enthalpy-Entropy Compensation of EtP

There are several reports in the literature that have demonstrated enthalpy-entropy compensation effects for the solubility of drugs in aqueous cosolvent mixtures. This analysis has been used in order to identify the mechanism of the cosolvent action. Weighted graphs of $\Delta_{\text{soln}}H^\circ$ as a function of $\Delta_{\text{soln}}G^\circ$ at the mean temperature permit such an analysis [24, 25].

Figure 4 shows that EtP (3) in the \{n-PrOH (1) + MeOH (2)\} solvent system presents a non-linear $\Delta_{\text{soln}}H^\circ$ vs. $\Delta_{\text{soln}}G^\circ$ curve with a variable negative slope in the interval from $w_1=0.10$ up to $w_1 = 0.20$. In all cases, a variable positive slope is obtained with exception of mixtures with 0.1 and 0.2, a trend that is not common in these systems. Accordingly, the driving mechanism for solubility is the enthalpy, probably due to better solvation of the drug by n-PrOH molecules.
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**Figure 4.** $\Delta_{\text{soln}} H^\circ$ vs. $\Delta_{\text{soln}} G^\circ$ enthalpy-entropy compensation plot for solubility of EtP in {n-PrOH (1) + MeOH (2)} cosolvent mixtures at 297.15 K.

**Computational validation**

The $x$ values of EtP in the {n-PrOH (1) + MeOH (2)} solvent mixtures were fitted/correlated using two combined computational models namely van’t Hoff and Yalkowsky-Roseman. Thus, from four data can determine a high quantity of solubility values, between temperatures and compositions extremes. The van’t Hoff model (VH) solubilities in various solvent mixtures including neat solvents were determined with the help of Eq. 7 [26, 27]:

$$\ln x_{i} = A + \frac{B}{T}$$

(7)

Here, the terms $A$ and $B$ are the coefficients of model.

The logarithmic solubilities of Yalkowsky-Roseman (YR) model for a solute in the different solvent mixtures including neat solvents were determined with the help of Eq. 8 [28-33]:

$$\ln x_{3,1+2} = w_1 \ln x_{3,1} + w_2 \ln x_{3,2}$$

(8)

Here, $x_{3,1}$ and $x_{3,2}$ are the mole fraction solubility of the solute in the mono-solvents 1 and 2; $w_1$ and $w_2$ denote the mass fractions of pure-solvents 1 and 2 in the mixture free of solute.

Combining the two models would have Eq. 9:

$$\ln x_{3,1+2} = w_1 \left( A_1 + \frac{B_1}{T} \right) + w_2 \left( A_2 + \frac{B_2}{T} \right)$$

(9)
This combination is interesting, because the VH model predicts solubility by varying the temperature but with a constant cosolvent composition, and the YR model, allows to calculate the solubility in a range of cosolvent composition but in an isothermal manner. The combination develops a model, which allows varying both the cosolvent composition and the temperature. The mean relative deviation (MRD) is used as an error criterion [34]:

$$MRD = \frac{100}{N} \sum \left( \frac{x_3^{\text{exp}} - x_3^{\text{cal}}}{x_3^{\text{exp}}} \right)$$

(10)

Where, $N$ is the number of data in each set, and $x_3^{\text{exp}}$ and $x_3^{\text{cal}}$ are experimental and calculated solubility values.

The resulted equation for solubility prediction of EtP at different temperatures and composition (cosolvent mixtures), is as follow:

$$\ln x_{3,1+2} = w_1 \left( 6.5 \pm 0.3 - \frac{2461 + 105}{T} \right) + w_2 \left( 10.6 \pm 0.5 - \frac{3785 \pm 174}{T} \right)$$

(11)

Table 4. Calculated molar solubility of EtP in {n-PrOH (1) + MeOH (2)} mixtures at different temperatures.

<table>
<thead>
<tr>
<th>$w_1$</th>
<th>283.15 K</th>
<th>RD$^b$</th>
<th>298.15 K</th>
<th>RD$^b$</th>
<th>313.15 K</th>
<th>RD$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.061</td>
<td>3.01</td>
<td>0.120</td>
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$^a$ $w_1$ is the mass fraction of n-PrOH in the cosolvent mixture free of solute.

$^b$ Relative deviation $RD = \frac{x_3^{\text{exp}} - x_3^{\text{cal}}}{x_3^{\text{exp}}}$
List of extracted data sets, their related x values calculated by Eq. 11, and produced MRD values are tabulated in table 4. For total 33 data points the overall MRD value is 3.48%. The prediction error is within an acceptable range, where 30% error is accepted for correlating the solubility data in the pharmaceutical area [34-36].

The main advantage of the proposed model is that it does not require any experimental solubility data in mixed solvents.

Just four experimental solubility data points in mono-solvents and desired temperature. It almost provides good results, which might show its applicability in solubility prediction (figure 5). These characteristics make it a suitable model for solubility prediction of EtP in \{n-PrOH (1) + MeOH (2)\} mixture from 283.15 K up to 313.15 K and any solvent mixture.

**Figure 5.** Experimental solubility data versus predicted solubility data for 33 studied solubility data points of EtP in \{n-PrOH (1) + MeOH (2)\} mixtures.

**Conclusions**

The solubility of EtP in the investigated mixture solvents increased with the temperature increasing, these results indicate that the dissolution process is endothermic; therefore, the obtained thermodynamic functions are helpful to understand the dissolution process of EtP in the different organic solvents. Improving solubility prediction methods or making them easy to use is highly demanded in the pharmaceutical industries. In this work, we have showed the utility of the combined model van’t Hoff and
Yalkowsky-Roseman might be helpful in solubility prediction of EtP with acceptable error in {n-PrOH (1) + MeOH (2)} mixtures.

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**Disclosure statement**

No potential conflict of interest was reported by the authors.

**References**


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