Solubility and thermodynamic function of apremilast in different (Transcutol + water) cosolvent mixtures: Measurement, correlation and molecular interactions

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ARTICLE INFO

Article history:
Received 17 March 2017
Received in revised form 5 June 2017
Accepted 2 July 2017
Available online 8 July 2017

Keywords:
Apremilast
Activity coefficient
Cosolvent mixture
Solubility
Thermodynamics

ABSTRACT

The solubility of apremilast (APM) in different “Transcutol\textsuperscript{b} + water” cosolvent mixtures was determined and correlated at “T=298.2 K–318.2 K” and “p=0.1 MPa”. The experimental solubilities of APM were determined and correlated with “Apelblat, van’t Hoff, Yalkowsky and Jouyban–Acree equations”. The maximum solubilities of APM in mole fraction were obtained in neat Transcutol \( (2.53 \times 10^{-2} \text{ at } T=318.2 \text{ K}) \). Based on activity coefficients, strong molecular interactions were obtained between APM and neat Transcutol in comparison with APM and neat water. “Apparent thermodynamic analysis” showed an “endothermic and entropy-driven dissolution” of APM.

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Introduction

Apremilast (APM) [Fig. 1; IUPAC name: "(S)-N-(2-[(1-(3-ethoxy-4-methoxyphenyl)-2-methane sulfonylethyl]-1,3-dioxo-2,3-dihydro-1H-isindol-4-yl)acetamide" and CAS registry number: 608141-41-9] occurs as a slightly yellow to off-white crystalline solid with molecular formula and molar mass of \( C_{26}H_{32}N_2O_7S \) and 460.50 g mol\(^{-1}\), respectively [1,2]. It has been reported as an active inhibitor of type-4 cyclic nucleotide phosphodiesterase and recommended in the treatment of psoriatic arthritis and plaque arthritis [3–5]. It is practically insoluble/poorly soluble in water [3,6]. Only tablet dosage forms of APM are available in the market [3,6,7]. Due to poor solubility in water, its oral bioavailability is very poor which is around 20–33% [6]. The development of liquid dosage forms of APM is great challenge for pharmaceutical industries due its poor solubility in water. The solubility data and thermodynamic functions of poorly soluble drugs in aqueous-cosolvent mixtures had great role in the design of liquid dosage forms of such drugs for clinical use [8–10]. It has been reported that most of the drugs existing in the market show poor solubility in water [11]. Hence, the solubility data and thermodynamic functions of these drugs in aqueous-cosolvent mixtures must be determined in order to produce complete phsyicochemical information about these drugs [10,11]. The IUPAC name of Transcutol\textsuperscript{b} is “2-(2-ethoxyethoxy) ethanol” [12]. Recently, Transcutol has been proven as a great cosolvent in the solubilization of various poorly soluble drugs in an aqueous media [12–15]. Literature survey revealed that only extended release tablet dosage form of APM had been evaluated for the enhancement of its oral bioavailability [2]. Other dosage forms and cosolvency technique have not been evaluated for solubility/dissolution enhancement of APM. Recently, we reported the solubility of APM in eleven different neat solvents including neat water and neat Transcutol at temperatures “\( T=298.2 \text{ K–318.2 K} \)” and pressure “\( p=0.1 \text{ MPa} \)” [16]. However, the solubility data and thermodynamic function of APM in any aqueous-cosolvent mixture or “Transcutol + water” cosolvent mixtures have not been reported till date. Therefore, in this work, the solubilities of APM in mole fraction in different “Transcutol + water” cosolvent mixtures including neat solvents were determined by a static equilibrium method at “\( T=298.2 \text{ K–318.2 K} \)” and “\( p=0.1 \text{ MPa} \)”.

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thermodynamic analysis” on measured solubility data of APM was also performed in order to obtain dissolution behavior of APM in different “Transcutol + water” cosolvent mixtures including neat solvents. The molecular interactions between APM and cosolvent mixtures were determined by the determination of activity coefficients of APM. The solubility data obtained in this work would be useful in preformulation studies and dosage form design of APM.

Experimental

Materials

APM “(mass fraction purity: 0.998 by HPLC)” was obtained from “Beijing Mesochem Technology Co. Ltd. (Beijing, China)”. Transcutol® “(mass fraction purity: 0.999 by GC)” was obtained from “Gattefosse (Lyon, France)”. Water was obtained from “Milli-Q unit”. The information about these materials along with their sources and purity are listed in Table 1.

Analysis of APM by HPLC-UV method

The analysis of APM in solubility samples was carried out using reversed phase HPLC coupled with ultra-violet (UV) detector at 254 nm [16]. The separation of APM was performed at T = 298.2 K using “Waters HPLC system (Waters, USA)”. The column “Nucleodur (150 × 4.6 mm, 5 μm) RP C8 column” was used for the quantification of APM. The mobile phase was used for the quantification was composed of the binary mixture of methanol and ethanol (2:1 v/v). The elution of APM was carried out at a flow rate of 1.0 mL min⁻¹ at 254 nm. The volume of injection was 10 μL. The proposed analytical methodology was validated well in terms of “linearity, precision, accuracy, sensitivity, reproducibility and robustness”. All validation parameters for the quantification of APM were within the prescribed limits.

Determination of APM solubility in “Transcutol + water” cosolvent mixtures

The solubility of APM against mass fraction of Transcutol (m = 0.1–0.9; m is the mass fraction of Transcutol in “Transcutol + water” cosolvent mixtures) in different “Transcutol + water” cosolvent mixtures including neat solvents [water (m = 0.0) and Transcutol (m = 1.0)] was determined at “T = 298.2 K–318.2 K” and “p = 0.1 MPa”. Static equilibrium method was applied for the determination of solubility of APM [17]. The excess amount of APM was added in known quantities of each “Transcutol + water” cosolvent mixture including neat solvents in glass vials. Each experiment was carried out in triplicate manners. The resultant mixtures were vortexed for about 5 min and transferred to the “OLS 200 Grant Scientific Biological Shaker (Grant Scientific, Cambridge, UK)” at the shaking speed of 100 rpm for 3 days. After 3 days, the samples were taken out from the shaker and allowed to settle the particles of APM for about 24 h [18]. After 24 h settling of APM particles, the supernatants from each sample were taken carefully, diluted suitably with mobile phase and subjected for the analysis of APM content by HPLC-UV method at 254 nm. The experimental solubilities of APM as mole fraction (xₑ) were determined using Eqs. (1) and (2) [10,19]:

\[
xₑ = \frac{m₁ / M₁}{m₁ / M₁ + m₂ / M₂}
\]

(1)

\[
xₑ = \frac{m₁ / M₁ + m₂ / M₂ + m₃ / M₃}{m₁ / M₁ + m₂ / M₂ + m₃ / M₃}
\]

(2)

Here, m₁ is the mass of APM (g) and m₂ and m₃ are the masses of Transcutol and water (g), respectively. M₁ is the molar mass of APM (g mol⁻¹) and M₂ and M₃ are the molar masses of Transcutol and water (g mol⁻¹), respectively.

Eq. (1) was applied for the determination of xₑ values of APM in neat solvents (Transcutol and water) and Eq. (2) was applied for the determination of xₑ values of APM in “Transcutol + water” cosolvent mixtures.

Results and discussion

Solubility data of APM

The xₑ values of APM determined by a static equilibrium method in different “Transcutol + water” cosolvent mixtures including neat solvents at “T = 298.2 K–318.2 K” and “p = 0.1 MPa” are furnished in Table 2. The solubility data of APM in different “Transcutol + water” cosolvent mixtures with respect to temperature have not been reported in literature. However, the solubility of APM in neat water and neat Transcutol has been reported in literature [6,16]. The solubility of APM as mole fraction in water at “T = 298.2 K” was obtained as 2.74 × 10⁻⁹ [6]. The solubility of APM as mole fraction in water at “T = 298.2 K” was recorded as 4.15 × 10⁻⁷ in this work. The solubility of APM in water recorded in this work was in similar magnitude with reported one [6]. Recently, the mole fraction solubility of APM in neat water at “T = 298.2 K” has been reported as

![Chemical structure of APM](image)

**Fig. 1. Chemical structure of APM.**

**Table 1** Information about the materials used in this work.

<table>
<thead>
<tr>
<th>Material</th>
<th>Molecular formula</th>
<th>Molar mass (g mol⁻¹)</th>
<th>CAS Registry no.</th>
<th>Purification method</th>
<th>Mass fraction purity</th>
<th>Analysis method</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>APM</td>
<td>C₂₂H₂₈N₂O₇S</td>
<td>460.50</td>
<td>608141-41-9</td>
<td>None</td>
<td>0.998</td>
<td>HPLC</td>
<td>Beijing Mesochem Ltd.</td>
</tr>
<tr>
<td>Transcutol</td>
<td>C₁₀H₁₄O₃</td>
<td>134.17</td>
<td>111-90-0</td>
<td>None</td>
<td>0.999</td>
<td>GC</td>
<td>Gattefosse</td>
</tr>
<tr>
<td>Water</td>
<td>H₂O</td>
<td>18.07</td>
<td>7732-18-5</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>Milli-Q</td>
</tr>
</tbody>
</table>

Apremilast (APM); high performance liquid chromatography (HPLC); gas chromatography (GC).
4.30 × 10⁻⁷ [16]. The mole fraction solubility of APM in neat water at "T = 298.2 K" was recorded as 4.15 × 10⁻⁷ in this study. The mole fraction solubility of APM in neat Transcutol at "T = 298.2 K" has been reported as 1.58 × 10⁻² [16]. The mole fraction solubility of APM in neat water and neat Transcutol at "T = 298.2 K" were very close with literature values [16]. The graphical correlation between experimental and literature solubilities of APM in neat water and neat Transcutol at "T = 298.2 K−318.2 K" are presented in Figs. 2 and 3, respectively. Figs. 2 and 3 indicated good graphical correlation between experimental and literature solubility values of APM in neat water and neat Transcutol. These results showed that the results of this study were in good agreement with those reported in literature.

The solubility data furnished in Table 2 indicated that the xₑ values of APM at constant pressure (0.1 MPa) were increasing with increase in temperature and m value of Transcutol in "Transcutol + water" cosolvent mixtures. The maximum xₑ value of APM was recorded in neat Transcutol (2.53 × 10⁻² at "T = 318.2 K"). However, the minimum xₑ value of APM was recorded in neat water (4.15 × 10⁻⁷ at "T = 298.2 K"). The maximum xₑ value of APM in Transcutol was possible due to the lower polarity of Transcutol in comparison with higher polarity of water [12−14]. The influence of the m value of Transcutol on natural logarithmic xₑ values (ln xₑ) of APM at "T = 298.2 K−318.2 K" was also investigated and results are shown in Fig. 4. Fig. 4 indicated that an increase in the m value of Transcutol in "Transcutol + water" cosolvent mixtures resulted in the linear increase in the logarithmic solubilities of APM at each temperature level. The xₑ value of APM was significantly enhanced from neat water to neat Transcutol at each temperature level evaluated. The enhancement in the solubility of APM in neat Transcutol was around 37108 fold higher than the solubility of APM in neat water at "T = 298.2 K" (room temperature). The addition of a small quantity of Transcutol in water resulted in significant improvement in the solubility of APM. Due to this fact, Transcutol could be used as a potent solubilizer/cosolvent in solubilization of APM in water. Based on the solubility data of APM recorded in this work, APM was considered as practically insoluble in neat water and freely soluble in neat Transcutol at "T = 298.2 K" [11,12].

### Ideal solubilities and activity coefficients of APM at different temperatures

The ideal solubility of APM (xₑ) was determined using Eq. (3) [20]:

\[
\ln x^{id} = \frac{-\Delta H_{fus}(T_{fus} - T)}{R T_{fus} T} + \frac{\Delta C_p}{R} \left(\frac{T_{fus} - T}{T} + \ln \left(\frac{T}{T_{fus}}\right)\right)
\]  

Here, R is the universal gas constant and ΔC_p is the difference between the molar heat capacity of the crystalline solid form and hypothetical super-cooled liquid form [20,21]. T_fus is the fusion temperature of APM which was obtained as 432.02 K by differential scanning calorimetry (DSC). ΔH_fus is the fusion enthalpy for APM which was obtained as 13.09 kJ mol⁻¹ by DSC analysis. It was proposed that ΔC_p may be equal to the entropy of fusion (ΔS_fus) [22,23] which has been clarified previously in literature [24].
Hence, the $\Delta S_{\text{fus}}$ value for APM was determined using Eq. (4) [20]:

$$\Delta S_{\text{fus}} = \frac{\Delta H_{\text{fus}}}{T_{\text{fus}}}$$  \hspace{1cm} (4)

Using Eq. (4), the value of $\Delta S_{\text{fus}}/\Delta C_p$ was obtained as $30.30 \text{ J mol}^{-1} \text{ K}^{-1}$. Using Eq. (3), the $x^{\text{vdW}}$ values for APM were determined and obtained values are furnished in Table 2.

In this work, the values of $T_{\text{fus}}$, $\Delta H_{\text{fus}}$ and $\Delta C_p$ for APM were recorded as $432.02 \text{ K}$, $13.09 \text{ kJ mol}^{-1}$ and $30.30 \text{ J mol}^{-1} \text{ K}^{-1}$, respectively. The values of $T_{\text{fus}}$, $\Delta H_{\text{fus}}$ and $\Delta C_p$ for APM were obtained as $432.02 \text{ K}$, $13.09 \text{ kJ mol}^{-1}$ and $30.30 \text{ J mol}^{-1} \text{ K}^{-1}$, respectively in our previous work [16]. These values for APM were in good agreement with literature values.

The activity coefficients ($\gamma$) for APM in different “Transcutol + water” cosolvent mixtures including neat solvents were determined using Eq. (5) [20,23]:

$$\gamma = \frac{x^{\text{vdW}}}{x_{e}}$$  \hspace{1cm} (5)

The values of $\gamma$ for APM in different “Transcutol + water” cosolvent mixtures including neat solvent at “$T=298.2 \text{ K}$–$318.2 \text{ K}$” are furnished in Table 3. With the help of $\gamma$ values of APM, the molecular interactions between solute and solvent molecules have been described.

From data furnished in Table 3, it was observed that the values of $\gamma$ for APM were maximum in neat water at each temperature level evaluated. However, the values of $\gamma$ for APM were minimum in neat Transcutol at each temperature level evaluated. The values of $\gamma$ for APM were found to be decreased with the rise in temperature in all “Transcutol + water” cosolvent mixtures including neat solvents. The values of $\gamma$ for APM were also found to be decreased significantly from neat water to neat Transcutol at each temperature level evaluated. The maximum $\gamma$ values for APM in neat water were possible due to the minimum solubility of APM in water and higher polarity of water. Based on these results, it was concluded that the solvation/solute-solvent molecular interactions of APM were higher in neat Transcutol in comparison with neat water.

**Correlation of experimental solubilities of APM**

The $x_{e}$ values of APM determined by a static equilibrium method were correlated with three different semiempirical equations including “Apelblat, van’t Hoff, Yalkowsky-Roseman and Jouyban–Acree” equations [9,25–30]. The “van’t Hoff” solubilities ($x^{\text{van h}}$) of APM in different “Transcutol + water” cosolvent mixtures including neat solvents were determined using Eq. (6) [9]:

$$\ln x^{\text{van h}} = a + \frac{b}{T}$$  \hspace{1cm} (6)

Here, the symbols “a and b” are the parameters of van’t Hoff equation which were determined by the graphs plotted between the $\ln x_{e}$ values of APM and $1/T$.

The correlation of $x_{e}$ values of APM with $x^{\text{van h}}$ values of APM was performed in terms of root mean square deviations (RMSD) and determination of coefficients ($R^2$). The RMSD values for APM were determined using Eq. (7) [13]:

$$\text{RMSD} = \left[ \frac{1}{N} \sum_{i=1}^{N} \left( \frac{x^{\text{exp}} - x^{\text{cal}}}{x_{e}} \right)^{2} \right]^{1/2}$$  \hspace{1cm} (7)

Here, $N$ is the number of experimental points.

**Table 3** Activity coefficients ($\gamma$) of APM in different (Transcutol + water) mixtures ($m$) at $T=298.2 \text{ K}–318.2 \text{ K}$.

<table>
<thead>
<tr>
<th>$m$</th>
<th>$\gamma$</th>
<th>$T=298.2 \text{ K}$</th>
<th>$T=303.2 \text{ K}$</th>
<th>$T=308.2 \text{ K}$</th>
<th>$T=313.2 \text{ K}$</th>
<th>$T=318.2 \text{ K}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>625000.0</td>
<td>472000.0</td>
<td>357000.0</td>
<td>292000.0</td>
<td>243000.0</td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>212921.4</td>
<td>164736.8</td>
<td>128026.2</td>
<td>106552.6</td>
<td>89164.8</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>75600.0</td>
<td>59600.0</td>
<td>46500.0</td>
<td>39300.0</td>
<td>33200.0</td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>26600.0</td>
<td>21000.0</td>
<td>16900.0</td>
<td>14300.0</td>
<td>12300.0</td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td>9210.0</td>
<td>7540.0</td>
<td>6130.0</td>
<td>5270.0</td>
<td>4590.0</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>3230.0</td>
<td>2660.0</td>
<td>2200.0</td>
<td>1890.0</td>
<td>1700.0</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>1120.0</td>
<td>961.0</td>
<td>811.0</td>
<td>711.0</td>
<td>638.0</td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td>393.0</td>
<td>342.0</td>
<td>295.0</td>
<td>261.0</td>
<td>235.0</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td>137.0</td>
<td>122.0</td>
<td>106.0</td>
<td>95.1</td>
<td>88.2</td>
<td></td>
</tr>
<tr>
<td>0.9</td>
<td>48.0</td>
<td>43.4</td>
<td>38.8</td>
<td>35.4</td>
<td>32.8</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>16.8</td>
<td>15.6</td>
<td>14.2</td>
<td>13.0</td>
<td>12.2</td>
<td></td>
</tr>
</tbody>
</table>
The results of van’t Hoff correlation along with van’t Hoff parameters, RMSD and R² values of APM in different “Transcutol + water” cosolvent mixtures including neat solvents are furnished in Table 4. The RMSD values for APM in different “Transcutol + water” cosolvent mixtures including neat solvents were recorded in the range of (0.37–2.47) %. The maximum value of RMSD for APM was recorded in neat water (2.47%). However, the minimum value of RMSD for APM was recorded in neat Transcutol (0.37%). The mean value of RMSD for APM was obtained as 1.44% with relative standard deviation (RSD) value of 0.52. The R² values for APM were recorded in the range of 0.9954–0.9997. The mean value of R² for APM was obtained as 0.9974 with RSD value of 0.0015. These results showed good correlation of experimental solubilities of APM with “van’t Hoff equation”.

The “Apeblat solubilities (x[^Apeblat])” of APM in different “Transcutol + water” cosolvent mixtures including neat solvents were determined using Eq. (8) [24,25]:

\[
\text{ln} x_{\text{Apeblat}} = A + \frac{B}{T} + \text{Cln}(T)
\]  
(8)

Here, the symbols “A, B and C” are the parameters of “Apeblat equation” which were determined by applying nonlinear multivariate regression analysis of x[^C] values of APM furnished in Table 2 [9]. The x[^C] values of APM were correlated with x[^Apeblat] values of APM again in terms of RMSD and R².

The results of Apeblat correlation along with Apeblat parameters, RMSD and R² values for APM in different “Transcutol + water” cosolvent mixtures are furnished in Table 5. However, the graphical correlation between x[^C] and x[^Apeblat] values of APM at different temperatures are shown in Fig. 5. Fig. 5 showed good graphical correlations at each temperature level evaluated. The RMSD values for APM in different “Transcutol + water” cosolvent mixtures including neat solvents were recorded in the range of (0.51–3.96) %. The maximum value of RMSD for APM was recorded in neat water (3.96%). However, the minimum value of RMSD for APM was recorded at m = 0.9 of Transcutol in “Transcutol + water” cosolvent mixtures (0.51%). The mean value of RMSD for APM was obtained as 1.16% with RSD value of 0.84. The R² values for APM were recorded in the range of 0.9986 to 0.9997. The mean value of R² for APM was obtained as 0.9993 with RSD value of 0.0003. These results showed good correlation of experimental solubilities of APM with “Apeblat equation”.

The “logarithmic solubilities of Yalkowsky” equation (log x[^Yalkowsky]) for APM in different “Transcutol + water” cosolvent mixtures including neat solvents were determined using Eq. (9) [27]:

\[
\log x_{\text{Yalkowsky}} = m_1 \log x_1 + m_2 \log x_2
\]  
(9)

Here, “x₁ and x₂” are the solubilities of APM as mole fractions in neat solvent 1 (Transcutol) and neat solvent 2 (water), respectively; and “m₁ and m₂” are the mass fractions (g) of neat solvent 1 (Transcutol) and neat solvent 2 (water) in the absence of APM, respectively.

The RMSD values for APM in different “Transcutol + water” cosolvent mixtures were recorded in the range of (0.43–1.42) % (Table 6). The maximum value of RMSD for APM was recorded at m = 0.1 of Transcutol in “Transcutol + water” cosolvent mixtures (1.42%). However, the minimum value of RMSD for APM was recorded at m = 0.9 of Transcutol in “Transcutol + water” cosolvent mixtures (0.43%). The mean value of RMSD for APM was obtained as 0.98% with RSD value of 0.41. These results showed good correlation of experimental solubilities of APM with “Yalkowsky equation”.

For the solubility correlation of solutes in binary solvent mixtures, various cosolvency equations have been reported but “Jouyban–Acree equation” has been reported as the most accurate and precise one [28–30]. Therefore, “Jouyban–Acree” equation was applied for solubility correlation of APM in this work.

The “Jouyban–Acree” solubility (x[^JouybanAcree]) of APM in different “Transcutol + water” cosolvent mixtures was determined using Eq. (10) [31–33]:

\[
x_{\text{JouybanAcree}} = m_1 \ln x_1 + m_2 \ln x_2 + \frac{m_1 m_2}{T} \sum_{i=1}^{2} J_i (m_1 - m_2)
\]  
(10)

Here, the symbol J_i represents the constant of “Jouyban–Acree” equation. The value of constant J_i was determined by no-intercept regression analysis [34,35]. By putting the value of constant J_i, the trained version of Eq. (10) for present data set can be expressed using Eq. (11):

\[
x_{\text{JouybanAcree}} = m_1 \ln x_1 + m_2 \ln x_2 + 187.88 m_1 m_2
\]  
(11)

The x[^C] values of APM were correlated with x[^JouybanAcree] values in terms of RMSD.

The “Jouyban–Acree” equation reproduced the solubility data of APM with the RMSD value of <1.0% which was more accurate and precise than other equations evaluated.

The combination of “Jouyban–Acree” equation with “van’t Hoff” equation can produce more comprehensive computation and it can
be expressed using Eq. (12) [34,35]:
\[
\ln x_m = m_1 \left( A_1 + \frac{B_1}{T} \right) + m_2 \left( A_2 + \frac{B_2}{T} \right) + \frac{m_1 m_2}{T} \sum_{i=0}^{2} f_i (m_1 - m_2)
\]
(12)

Here, the symbols \( A_i, B_i, A_2, B_2 \) and \( f_i \) are the constants of Eq. (12). The trained version of Eq. (12) can be expressed using Eq. (13):
\[
\ln x_m = m_1 \left( 3.63 - \frac{2327}{T} \right) + m_2 \left( 3.10 - \frac{5298.60}{T} \right) + \frac{97.20 m_1 m_2}{T}
\]
(13)

Eq. (13) reproduced the solubility data of APM with the RMSD value of <0.8%. The main advantage of "Jouyban–Acree" equation is that it is a predictive equation and hence no more experimental data are required for the solubility prediction of APM at different solvent compositions and temperatures [34].

**Apparent thermodynamic analysis**

The dissolution behavior of APM in different “Transcutol + water” cosolvent mixtures including neat solvents was evaluated by “apparent thermodynamic analysis” of solubility data of APM.

<table>
<thead>
<tr>
<th>( M )</th>
<th>( \Delta_{	ext{sol}}H^\circ [\text{kJ mol}^{-1}] )</th>
<th>( \Delta_{	ext{sol}}G^\circ [\text{kJ mol}^{-1}] )</th>
<th>( \Delta_{	ext{sol}}S^\circ [\text{J mol}^{-1} \text{K}^{-1}] )</th>
<th>( R^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>44.10</td>
<td>36.10</td>
<td>25.99</td>
<td>0.9957</td>
</tr>
<tr>
<td>0.1</td>
<td>41.02</td>
<td>33.45</td>
<td>24.57</td>
<td>0.9965</td>
</tr>
<tr>
<td>0.2</td>
<td>39.18</td>
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<td>30.30</td>
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*The relative uncertainties are \( u(\Delta_{	ext{sol}}H^\circ) = 0.25 \text{ kJ mol}^{-1} \), \( u(\Delta_{	ext{sol}}G^\circ) = 0.37 \text{ kJ mol}^{-1} \), and \( u(\Delta_{	ext{sol}}S^\circ) = 0.06 \text{ J mol}^{-1} \text{ K}^{-1} \).*

Different “apparent standard thermodynamic parameters” namely “standard apparent enthalpy (\( \Delta_{	ext{sol}}H^\circ \))”, standard apparent Gibbs free energy (\( \Delta_{	ext{sol}}G^\circ \)) and standard apparent entropy (\( \Delta_{	ext{sol}}S^\circ \)) were determined for the evaluation of dissolution behavior of APM. The “\( \Delta_{	ext{sol}}H^\circ \)” values for dissolution behavior of APM in different “Transcutol + water” cosolvent mixtures including neat solvents were determined at the “mean harmonic temperature (\( T_{\text{HN}} \))” of

![Fig. 4. Influence of \( m \) value of the Transcutol on ln \( x_m \) values of APM at temperatures \( T = 298.2 \text{ K} – 318.2 \text{ K} \).](image-url)
including “van’t Hoff analysis” with the help of Eq. (14) [19,36]:

$$\left(\frac{\partial \ln x_c}{\partial \left(\frac{1}{T} - \frac{1}{T_{hm}}\right)}\right)_p = -\frac{\Delta_{sol}H^0}{R}$$  

(14)

The “$$\Delta_{sol}H^0$$” values for APM dissolution in different “Transcutol + water” cosolvent mixtures including neat solvents were calculated from the slopes of graphs constructed between in $$x_c$$ values of APM and $$\frac{1}{T} - \frac{1}{T_{hm}}$$.

The “$$\Delta_{sol}G^0$$” values for APM dissolution in different “Transcutol + water” cosolvent mixtures including neat solvents were also determined at $$T_{hm}$$ value of 308 K using “Krug et al. analysis” with the help of Eq. (15) [37]:

$$\Delta_{sol}G^0 = -RT_{hm} \times \text{intercept}$$  

(15)

Here, the intercept value for APM in each cosolvent mixture including neat solvents was determined from “van’t Hoff plot” described under “van’t Hoff analysis”.

Finally, the “$$\Delta_{sol}S^0$$” values for APM dissolution in different “Transcutol + water” cosolvent mixtures including neat solvents were determined by applying the combined approaches of “van’t Hoff” and Krug et al. analysis” with the help of Eq. (16) [20,37,38]:

$$\Delta_{sol}S^0 = \frac{\Delta_{sol}H^0 - \Delta_{sol}G^0}{T_{hm}}$$  

(16)

The resulting data of “apparent thermodynamic analysis” for APM dissolution in different “Transcutol + water” cosolvent mixtures including neat solvents are furnished in Table 7.

The “$$\Delta_{sol}H^0$$” values for APM dissolution different “Transcutol + water” cosolvent mixtures including neat solvents were recorded positive values in the range of (19.37–44.10) kJ mol$$^{-1}$$. The mean “$$\Delta_{sol}H^0$$” value for APM dissolution was recorded as 31.82 kJ mol$$^{-1}$$ with RSD value of 0.25. The “$$\Delta_{sol}G^0$$” values for APM dissolution were found to be decreasing with increase in the $$m$$ value of Transcutol in “Transcutol + water” cosolvent mixtures and the $$x_c$$ value of APM. The maximum “$$\Delta_{sol}H^0$$” value for APM dissolution was recorded in neat water (44.10 kJ mol$$^{-1}$$) that was possible due to minimum solubility of APM in neat water. However, the minimum “$$\Delta_{sol}H^0$$” value for APM dissolution was recorded in neat Transcutol (19.37 kJ mol$$^{-1}$$) that was possible due to maximum solubility of APM in neat Transcutol. The “$$\Delta_{sol}G^0$$” values for APM dissolution in different “Transcutol + water” cosolvent mixtures including neat solvents were also recorded positive values in the

![Graph](Image)

**Fig. 5.** Correlation of ln $$x_c$$ values of APM with Apelblat equation in different “Transcutol + water” mixtures at “T=298.2 K–318.2 K” (Apelblat solubilities of APM are represented by solid lines and experimental solubilities of APM are represented by the symbols).
range of (10.03–36.10) kJ mol\(^{-1}\). The mean “\(\Delta_{\text{sol}}G^0\) value” for APM dissolution was recorded as 8.64 kJ mol\(^{-1}\) with RSD value of 0.37. The “\(\Delta_{\text{sol}}G^0\) values” for APM dissolution were also found to be decreasing with increase in the \(m\) value of Transcutol in “Transcutol + water” cosolvent mixtures and the \(x_p\) value of APM. The maximum and minimum “\(\Delta_{\text{sol}}G^0\) values” for APM dissolution were also recorded in neat water (36.10 kJ mol\(^{-1}\)) and neat Transcutol (10.03 kJ mol\(^{-1}\)), respectively. The minimum “\(\Delta_{\text{sol}}G^0\) values” for APM dissolution were also possible due to higher solubility values of APM in neat Transcutol in comparison with its minimum solubility values in water. The positive “\(\Delta_{\text{sol}}H^0\) and “\(\Delta_{\text{sol}}S^0\) values” for APM dissolution in different “Transcutol + water” cosolvent mixtures including neat solvents indicated an “endothermic dissolution” of APM [14,15]. The “\(\Delta_{\text{sol}}S^0\) values” for APM dissolution in different “Transcutol + water” cosolvent mixtures including neat solvents were also recorded as positive values in the range of \((24.57–30.38)\) mol\(^{-1}\) K\(^{-1}\). The mean “\(\Delta_{\text{sol}}S^0\) value” for APM dissolution was recorded as 28.48 kJ mol\(^{-1}\) with RSD value of 0.06. The positive “\(\Delta_{\text{sol}}S^0\) values” for APM dissolution showed an “entropy-driven dissolution” of APM in all “Transcutol + water” cosolvent mixtures including neat solvents [39]. Overall, the dissolution behavior of APM was recorded as an “endothermic and entropy-driven” in all “Transcutol + water” cosolvent mixtures including neat solvents [39,40].

**Solvation behavior of APM in “Transcutol + water” cosolvent mixtures**

For the evaluation of “solvation behavior/cosolvent action” for APM in different “Transcutol + water” cosolvent mixtures including neat solvents, an “enthalpy-entropy compensation analysis” was conducted [39,41]. This analysis was conducted by plotting the weighted graphs of “\(\Delta_{\text{sol}}H^0\)” vs. “\(\Delta_{\text{sol}}G^0\)” at \(T_{\text{m}}\) value of 308 K [41]. The weighted graphs of “\(\Delta_{\text{sol}}H^0\)” vs. “\(\Delta_{\text{sol}}G^0\)” are shown in Fig. 6. Fig 6 showed that APM in all “Transcutol + water” cosolvent mixtures including neat solvents indicated linear “\(\Delta_{\text{sol}}H^0\)” vs. “\(\Delta_{\text{sol}}G^0\)” plot with a positive slope value of greater than 1.0 with \(R^2\) value of greater than 0.99. Hence, the “driving mechanism” for solvation behavior of APM was considered as an “enthalpy-driven” in all “Transcutol + water” cosolvent mixtures including neat solvents. This observation was probably due to excellent solvation of APM in Transcutol molecules as compared to its solvation behavior in water molecules [15]. The solvation behavior of APM recorded in this work was similar to those recorded for the solvation behavior of “istain, reserpine and vanillin” in various “Transcutol + water” cosolvent mixtures including neat solvents [9,14,15] (Figs. 5 and 6).

**Conclusion**

In the current research work, the solubilities of APM in different “Transcutol + water” cosolvent mixtures including neat solvents were measured at “\(T = 298.2\) K–318.2 K” and “\(p = 0.1\) MPa”. The solubilities of APM were determined by a static equilibrium method and correlated with “van’t Hoff, Apelblat, Yalkowsky and Jouyban–Acree” equations. The solubilities of APM in mole fraction were found to be increasing with increase in temperature and the \(m\) value of Transcutol in all “Transcutol + water” cosolvent mixtures including neat solvents. The maximum and minimum solubilities of APM in mole fraction were recorded in neat Transcutol and neat water, respectively at each temperature level evaluated. The experimental solubilities of APM in mole fraction were correlated well with “Apelblat, van’t Hoff, Yalkowsky and Jouyban–Acree” equations in all “Transcutol + water” cosolvent mixtures including neat solvents. The results of activity coefficients indicated higher molecular interactions between APM and Transcutol molecules in comparison with APM and water molecules. “Apparent thermo-dynamic analysis” indicated an “endothermic and entropy-driven” dissolution behavior of APM in all “Transcutol + water” cosolvent mixtures including neat solvents. “Enthalpy-entropy compensation” analysis showed that the solvation behavior of APM was “enthalpy-driven” in all “Transcutol + water” cosolvent mixtures including neat solvents.

**Conflict of interest**

The authors state that they do not have any conflict of interest associated with this manuscript.
Acknowledgements

This project was financially supported by King Saud University, Vice Deanship of Research Chairs, Kayyali Chair for Pharmaceutical industry through the grant number FN-2016.

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