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Solubility determination and thermodynamic data of apigenin in binary {Transcutol® + water} mixtures

Faiyaz Shakeel*, Sultan Alshehri, Nazrul Haq, Ehab Elzayat, Mohamed Ibrahim, Mohammad A. Altamimi, Kazi Mohsin, Fars K. Alanazi, Ibrahim A. Alsarra

Kayyali Chair for Pharmaceutical Industries, Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh, 11451, Saudi Arabia

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ABSTRACT

Solubility and thermodynamic data of apigenin (APG) in binary {2-(2-ethoxyethoxy)ethanol (Transcutol®) + water} mixtures were obtained in this work. The mole fraction solubilities (x_e) of APG in binary {Transcutol® + water} mixtures were measured at temperature $T = 298.15$ K to318.15 K and atmospheric pressure $p = 0.1$ MPa. Solubility values of APG determined in this study were fitted well with four different computational models namely "van't Hoff, Apelblat, Yalkowsky and Jouyban-Acree" models with root mean square deviations of < 4.0%. The maximum x_e value of APG was recorded in neat Transcutol® (0.382 at $T = 318.15$ K). However, the minimum x_e value of APG was recorded in neat water (1.01×10^{-6} at $T = 298.15$ K). The values of activity coefficients were also determined for the evaluation of solute-solvent molecular interactions and results suggested higher solute-solvent molecular interaction in APG-Transcutol in comparison with other combinations studied. Apparent thermodynamic analysis suggested endothermic and entropy-driven dissolution of APG in all binary {Transcutol® + water} mixtures studied. Enthalpy-entropy compensation analysis suggested enthalpy-driven mechanism as the main mechanism for solvation behavior of APG.

1. Introduction

Apigenin (APG) (Fig. 1; IUPAC name: 5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one; molecular formula: $C_{15}H_{10}O_5$; molar mass: 270.24 g mol^{-1} and CAS registry number: 520-36-5) occurs as a light yellow crystalline powder (Xiao et al., 2011; Zhang et al., 2012). It is poorly soluble bioflavonoid which is commonly present in most of the fruits and vegetables (Peterson and Dwyer, 1995; Shukla and Gupta, 2010; Shakeel et al., 2017a). It shows several biological activities including antioxidant, anti-inflammatory and anticancer activities in animal models (Takahashi et al., 1998; Gates et al., 2007; Tong et al., 2007; Gates et al., 2009; Funakoshi-Tago et al., 2011; Horvathova et al., 2013). It has been reported as poorly soluble in water due to which its dissolution rate and bioavailability are poor (Shakeel et al., 2017a). Various formulation approaches were evaluated for solubility, dissolution rate and bioavailability enhancement of APG in literature (Al Shaal et al., 2011; Arsic et al., 2011; Das et al., 2013; Ding et al., 2013; Zhai et al., 2013; Zhao et al., 2013; Zhang et al., 2013; Shen et al., 2014; Huang et al., 2016; Zhao et al., 2016; Jangdey et al., 2017; Telange et al., 2017). Different bioflavonoids isolated from various plant sources have weak solubilization capacity in an aqueous media including water (Shakeel et al., 2016, 2017a). Therefore, the solubilities of these bioflavonoids in "aqueous-cosolvent" binary mixtures have significant importance in the development of their dosage forms for human use (Shakeel et al., 2015a, 2016). The solubilization power of Transcutol® has been proved recently in solubility improvement of several weakly soluble natural drugs including "isatin, vanillin and reserpine" (Shakeel et al., 2015a, 2015b, 2015c). Transcutol® is used as an excipient in various pharmaceutical/food products and up to 10% concentration has been reported as safe for these formulations (Ether, 2013). The main side effects of Transcutol® in humans are central nervous system disorders, respiratory disorders and skin irritation (Ether, 2013). The solubility data and thermodynamics of APG in twelve different neat solvents including "water, methanol, ethanol, isopropanol, ethylene glycol, propylene glycol, 1-butanol, 2-butanol, ethyl acetate (EA), polyethylene glycol-400, dimethyl sulfoxide and Transcutol®" at temperatures $T = 298.15$ K to 318.15 K and atmospheric pressure $p = 0.1$ MPa have been reported in literature (Shakeel et al., 2017a). The solubility data of APG in seven different neat solvents namely "water, methanol, ethanol, 1-propanol, 1-butanol, acetone and EA" at $T = 288.2$ K to 328.2 K and atmospheric pressure were also recorded (Xiao et al., 2011). The solubility data of APG in

* Corresponding author.
E-mail address: faiyazs@fastmail.fm (F. Shakeel).

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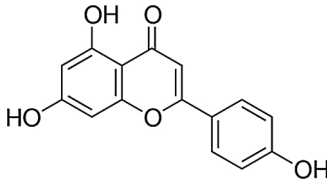

Fig. 1. Molecular structure of APG.

binary (ethanol + water) mixtures at T = 273.2 K to 323.2 K" and atmospheric pressure were also determined (Xiao et al., 2010). However, the solubility data and thermodynamics of APG in binary {Transcutol® + water} mixtures have not been reported. Hence, aim of this study was to determine the solubilities of APG in binary {Transcutol® + water} mixtures (including neat solvents) by a static equilibrium method at T = 298.15 K to 318.15 K under atmospheric pressure. Dissolution thermodynamic parameters of APG were also calculated using apparent thermodynamic analysis.

2. Materials and methods

2.1. Materials

Apigenin "(mass fraction purity > 0.99 by HPLC)" and Transcutol® "[IUPAC name: 2-(2-ethoxyethoxy)ethanol and mass fraction purity of > 0.99 by GC]" were obtained from "Beijing Mesochem Technology Co. Pvt. Ltd. (Beijing, China)" and "Gattefosse (Lyon, France)", respectively. Chromatographic grade acetonitrile "(mass fraction purity of > 0.99 by GC)" was obtained from "Sigma Aldrich (St. Louis, MO, USA)". 0.05 M ammonium phosphate buffer for chromatographic analysis was obtained in the laboratory. The water used in this study was deionized water and obtained from "Milli-Q water purification unit". The information of materials is given in Table 1.

2.2. Determination of APG solubility in binary {Transcutol® + water} mixtures

The solubility of APG with respect to mass fraction value of Transcutol® (m = 0.0 to 1.0; m is the mass fraction of Transcutol® in binary {Transcutol® + water} mixtures) in binary {Transcutol® + water} mixtures including neat solvents was measured at T = 298.15 K to 318.15 K under atmospheric pressure. The solubility of APG in mole fraction was determined using a static equilibrium method reported in literature (Higuchi and Connors, 1965). In order to perform these experiments, the excess quantity of crystalline APG was added in known amount of each {Transcutol® + water} mixture including neat solvents. Each experiment was conducted in triplicates manners. The resultant mixtures were vortexed for 5 min and transferred to the "OLS 200 Grant Scientific Biological Shaker (Grant Scientific, Cambridge, UK)" which was shaken at a speed of 100 rpm for 72 h (Shakeel et al., 2017a). After 72 h, each sample was withdrawn carefully from the shaker and allowed to settle APG particles for 24 h in order to obtain complete settling of particles (Shakeel et al., 2015c, 2017a). The supernatants were then withdrawn carefully from each sample, diluted and subjected for the quantification of APG content by validated ultra-performance liquid chromatography-ultra violet (UPLC-UV) method at 336 nm (Shakeel et al., 2017a). Mixture of 0.05 M ammonium formate buffer: acetonitrile (72:28% v/v) was used as mobile phase for UPLC analysis of APG. The "experimental mole fraction solubilities (x_e)" of APG were then determined using Eqs. (1) and (2) (Shakeel et al., 2013; Sunsandee et al., 2013):

$$x_e = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

$$x_e = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (2)$$

Here, m_1 is the mass of APG (g) and m_2 and m_3 represent the masses of Transcutol® (g) and water (g), respectively. M_1 represent the molar mass of APG (g mol^{-1}) and M_2 and M_3 represent the molar masses of Transcutol® (g mol^{-1}) and water (g mol^{-1}), respectively. Eq. (1) is applicable for the calculation of x_e values of APG in neat solvents (Transcutol® and water) and Eq. (2) is applicable for the calculation of x_e values of APG in {Transcutol® + water} mixtures.

3. Results and discussion

3.1. Experimental solubility data of APG with literature comparison

The x_e values of APG in binary {Transcutol® + water} mixtures (including neat solvents) at T = 298.15 K to 318.15 K under atmospheric pressure are furnished in Table 2. The solubilities of APG in mole fraction in neat water and neat Transcutol® at various temperatures and atmospheric pressure have been reported in literature (Xiao et al., 2011; Shakeel et al., 2017a). However, the solubilities of APG in mole fraction in binary {Transcutol® + water} mixtures at various temperatures are not available in literature. The solubility of APG in mole fraction in water at T = 298.2 K has been reported as 1.03×10^{-6} (Xiao et al., 2011) and 1.04×10^{-6} (Shakeel et al., 2017a). Solubility of APG in mole fraction in water at T = 298.2 K was obtained as 1.01×10^{-6} in the present study. The solubility of APG in mole fraction in neat Transcutol® at T = 298.2 K has been reported as 0.334 by Shakeel et al. (Shakeel et al., 2017a). But solubility of APG in mole fraction in neat Transcutol® at T = 298.2 K was obtained as 0.336 in the present study. Solubilities of APG in mole fraction in neat water and neat Transcutol® obtained in this work were similar to those reported in literature. The graphical correlation between experimental and reported solubilities of APG in neat water and neat Transcutol® at T = 298.15 K to 318.15 K are also presented in supplementary Figs. 1 and 2 (Figs. S1 and S2), respectively. Figs. S1 and S2 showed good correlation/curve fitting of experimental solubilities with reported ones in both neat solvents at T = 298.15 K to 318.15 K. These results suggested good agreement of experimental solubility data of APG with reported ones.

Generally, the x_e values of APG at constant pressure i.e. atmospheric pressure were recorded as increasing with the rise in temperature and increase in the m value of Transcutol® in binary {Transcutol® + water} mixtures. The solubility enhancement of bioactive compounds with the rise in temperature has been reported very well in literature (Shakeel et al., 2015a, 2015b). Therefore, our results were obtained in similar trend as reported previously with respect to temperature. Maximum x_e

Table 1
Materials information and their sources.

Materials	Molecular formula	Molar mass (g mol^{-1})	CAS Registry no.	Purification method	Mass fraction purity	Analysis method	Source
APG	$C_{15}H_{10}O_5$	270.24	520 − 36-5	None	> 0.99	HPLC	Beijing MesochemTechnology
Transcutol®	$C_6H_{14}O_3$	134.17	111 − 90-0	None	> 0.99	GC	Gattefosse
Acetonitrile	C_2H_3N	41.05	75 − 05-8	None	> 0.99	GC	Sigma Aldrich
Water	H_2O	18.07	7732 − 18-5	None	–	–	Milli-Q

Apigenin (APG), high performance liquid chromatography (HPLC) and gas chromatography (GC).

Table 2
The x_e values of APG against mass fraction value of Transcutol® (m) in binary {Transcutol® + water} mixtures at T = 298.15 K to 318.15 K and p = 0.1 MPa[a].

m	x_e				
	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K	T = 318.15 K
0.0	1.01×10^{-6}	1.31×10^{-6}	1.70×10^{-6}	2.23×10^{-6}	3.07×10^{-6}
0.1	3.67×10^{-6}	4.52×10^{-6}	5.75×10^{-6}	7.45×10^{-6}	9.93×10^{-6}
0.2	1.32×10^{-5}	1.64×10^{-5}	1.99×10^{-5}	2.48×10^{-5}	3.26×10^{-5}
0.3	4.53×10^{-5}	5.50×10^{-5}	6.70×10^{-5}	8.17×10^{-5}	1.01×10^{-4}
0.4	1.67×10^{-4}	1.96×10^{-4}	2.33×10^{-4}	2.77×10^{-4}	3.42×10^{-4}
0.5	5.88×10^{-4}	6.77×10^{-4}	7.83×10^{-4}	9.12×10^{-4}	1.10×10^{-3}
0.6	2.11×10^{-3}	2.40×10^{-3}	2.69×10^{-3}	3.04×10^{-3}	3.57×10^{-3}
0.7	7.46×10^{-3}	8.21×10^{-3}	9.11×10^{-3}	1.03×10^{-2}	1.18×10^{-2}
0.8	2.62×10^{-2}	2.81×10^{-2}	3.07×10^{-2}	3.35×10^{-2}	3.70×10^{-2}
0.9	9.44×10^{-2}	9.93×10^{-2}	1.07×10^{-1}	1.12×10^{-1}	1.20×10^{-1}
1.0	3.36×10^{-1}	3.46×10^{-1}	3.59×10^{-1}	3.70×10^{-1}	3.82×10^{-1}
x^{idl}	8.03×10^{-4}	9.38×10^{-4}	1.09×10^{-3}	1.27×10^{-3}	1.47×10^{-3}

[a] The standard uncertainties u are u(T) = 0.15 K, $u_r(m)$ = 0.1%, $u(p)$ = 0.003 MPa and $u_r(x_e)$ = 1.42%.

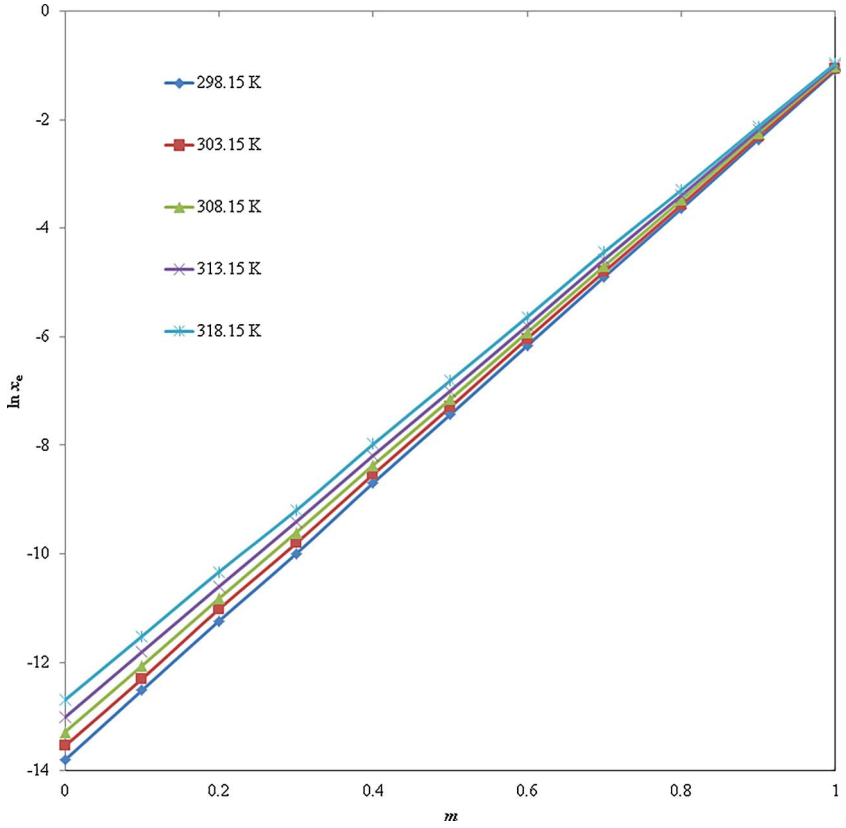

Fig. 2. Impact of m value of the Transcutol® on ln x_e values of APG at different temperatures.

value of APG was recorded in neat Transcutol® (0.382 at T = 318.15 K). However, the minimum one was recorded in neat water (1.01×10^{-6} at T = 298.15 K). The maximum x_e value of APG in neat Transcutol® could be possible due to lower value of dielectric constant/polarity of Transcutol® in comparison with higher value of dielectric constant/polarity of water (Shakeel et al., 2015a, 2015b). The influence of the m value of Transcutol® on logarithmic mole fraction solubility of APG at T = 298.15 K to 318.15 K was also investigated and results are shown in Fig. 2. It was noted that the increase in the m value of Transcutol® in binary {Transcutol® + water} mixtures resulted in the enhancement of logarithmic solubilities of APG significantly at each temperature level investigated. The maximum solubility of APG was recorded in neat Transcutol®. Therefore, the enhancement in m value of Transcutol® resulted in enhancement in solubility of APG in binary {Transcutol® + water} mixtures. These results were in good agreement with those reported for solubility of bioactive compounds such as isatin, reserpine and vanillin in binary {Transcutol® + water} mixtures (Shakeel et al., 2015a, 2015b, 2015c). It was also recorded that the x_e values of APG were enhanced significantly from pure/neat water to pure/neat Transcutol®. The addition of a small amount of Transcutol® in water resulted in significant enhancement in solubility of APG. Therefore, Transcutol® could be used as a potential cosolvent in solubilization of APG in water. Based on these results, APG has been proposed as very soluble in pure/neat Transcutol® and poorly soluble in pure/neat water (Shakeel et al., 2015a, 2015b).

3.2. Ideal solubilities and solute-solvent molecular interactions

The ideal solubility for APG (x^{idl}) was calculated with the help of Eq. (3) (Ruidiaz et al., 2010):

Table 3
The values of γ_i for APG in binary {Transcutol® + water} mixtures (m) at T = 298.15 K to 318.15 K.

m	γ_i				
	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K	T = 318.15 K
0.0	792.00	714.00	643.00	570.00	480.00
0.1	219.02	207.49	189.92	170.48	148.30
0.2	61.10	57.30	54.80	51.10	45.20
0.3	17.70	17.00	16.30	15.50	14.60
0.4	4.80	4.79	4.70	4.58	4.31
0.5	1.37	1.39	1.40	1.39	1.34
0.6	0.38	0.39	0.40	0.42	0.41
0.7	0.10	0.11	0.12	0.12	0.12
0.8	3.00×10^{-2}	3.30×10^{-2}	3.50×10^{-2}	3.70×10^{-2}	3.90×10^{-2}
0.9	8.00×10^{-3}	9.00×10^{-3}	1.00×10^{-2}	1.10×10^{-2}	1.20×10^{-2}
1.0	2.00×10^{-3}	2.00×10^{-3}	3.00×10^{-3}	3.00×10^{-3}	3.00×10^{-3}

Table 4
The van't Hoff model coefficients (a and b), R^2 and *RMSD* values for APG in binary {Transcutol® + water} mixtures.

m	a	b	R^2	*RMSD* (%)
0.0	3.60	−5197.70	0.9960	2.58
0.1	3.29	−4722.50	0.9939	2.73
0.2	2.92	−4227.00	0.9945	2.52
0.3	2.68	−3785.70	0.9988	1.10
0.4	2.57	−3366.10	0.9950	1.80
0.5	2.42	−2946.40	0.9938	1.77
0.6	2.05	−2453.90	0.9944	1.66
0.7	2.39	−2180.90	0.9905	1.69
0.8	1.85	−1641.10	0.9936	0.94
0.9	1.42	−1130.30	0.9967	0.93
1.0	0.93	−605.06	0.9982	0.81

$$\ln x^{idl} = \frac{-\Delta H_{fus}(T_{fus} - T)}{RT_{fus}T} + \left(\frac{\Delta C_p}{R}\right)\left[\frac{T_{fus} - T}{T} + \ln\left(\frac{T}{T_{fus}}\right)\right] \quad (3)$$

Here, R represents the universal gas constant (R = 8.314 J mol^{-1} K^{-1}) and ΔC_p represents the difference in the molar heat capacity of solid state with that of liquid state (Hildebrand et al., 1970; Ruidiaz et al., 2010). The symbols T_{fus} and ΔH_{fus} are the fusion/melting temperature and molar fusion enthalpy of APG, respectively. The values of T_{fus}, ΔH_{fus} and ΔC_p for APG were taken as 639.72 K, 49.66 kJ mol^{-1} and 77.62 J mol^{-1} K^{-1}, respectively from literature (Shakeel et al., 2017a). With the help of Eq. (3), the x^{idl} values for APG were calculated and its values are listed in Table 2.

The activity coefficients (γ_i) for APG in binary {Transcutol® + water} mixtures were calculated with the help of Eq. (4) (Manrique et al., 2008; Ruidiaz et al., 2010):

$$\gamma_i = \frac{x^{idl}}{x_e} \quad (4)$$

The values of γ_i for APG in binary {Transcutol® + water} mixtures at T = 298.15 K to 318.15 K are listed in Table 3. It can be seen that the physical values of γ_i for APG were larger in water at each temperature studied. While, the values of γ_i for APG were much smaller in Transcutol® at each temperature studied. The values of γ_i for APG were recorded as decreasing from neat water to neat Transcutol® significantly at each temperature studied. The larger γ_i values for APG in neat water could due to the lowest mole fraction solubility of APG in water and maximum dielectric constant of water. Based on the values of γ_i recorded in this study, it can be concluded that the maximum solute-solvent molecular interactions of APG were seen in neat Transcutol® as compared with water and other combinations studied.

3.3. Correlation of experimental solubility data of APG

The x_e values of APG obtained in this study were fitted with four different computational models namely "van't Hoff, Apelblat, Yalkowsky-Roseman and Jouyban-Acree" models (Yalkowsky and Roseman, 1981; Apelblat and Manzurola, 1999; Manzurola and Apelblat, 2002; Jouyban, 2008; Sardari and Jouyban, 2013; Sotomayor et al., 2013; Shakeel et al., 2015c). The "van't Hoff model solubility ($x^{van,t}$)" of APG in binary {Transcutol® + water} mixtures (including neat solvents) was determined using Eq. (5) (Shakeel et al., 2015c):

$$\ln x^{van't} = a + \frac{b}{t} \quad (5)$$

Here, the symbols "a and b" represent the model parameters of Eq. (5) and these parameters were obtained by constructing graphs between ln x_e values of APG and of 1/T.

The correlation of x_e values of APG with $x^{van't}$ values of APG was performed in terms of root mean square deviations (*RMSD*) and determination of coefficients (R^2). The *RMSD* values for APG were calculated using its standard formula reported in literature (Shakeel et al., 2015c).

The resulting data of this correlation for APG in binary {Transcutol® + water} mixtures including neat solvents are presented in Table 4. The *RMSD* values in binary {Transcutol® + water} mixtures (including pure/neat solvents) were recorded as (0.81–2.73) %. The maximum *RMSD* value for APG was obtained at m = 0.1 of Transcutol® (2.73%). However, the minimum value of *RMSD* was obtained in neat Transcutol® (0.81%). The R^2 values for APG were obtained as 0.9905–0.9988. These results showed good correlation of experimental solubility data of APG with "van't Hoff model".

The "Apelblat model solubility (x^{Apl})" of APG in binary {Transcutol® + water} mixtures (including neat solvents) was determined with the help of Eq. (6) (Apelblat and Manzurola, 1999; Manzurola and Apelblat, 2002):

$$\ln x^{Apl} = A + \frac{B}{T} + C\ln(T) \quad (6)$$

Here, the symbols "A, B and C" represent the parameters in Eq. (6) and these parameters were calculated by nonlinear multivariate regression analysis of x_e values of APG listed in Table 2 (Shakeel et al., 2015c). The correlation of x_e values of APG with x^{Apl} values of APG was carried out in terms of *RMSD* and R^2.

The results of this correlation for APG in binary {Transcutol® + water} mixtures are presented in Table 5. The graphical correlation between x_e and x^{Apl} values of APG are presented in Fig. 3 which presented good graphical correlation/curve fitting. The *RMSD* values for APG in binary {Transcutol® + water} mixtures (including pure/neat solvents) were obtained as (0.59–3.27) %. The maximum *RMSD* value for APG was obtained at m = 0.1 of Transcutol® (3.27%). However, the minimum one was recorded at m = 0.5 of Transcutol® (0.59%). The R^2 values for APG were obtained in the range of 0.9974–0.9999. These results again showed good correlation of

Table 5
Apelblat model coefficients (*A*, *B* and *C*), R^2 and *RMSD* for APG in binary {Transcutol® + water} mixtures.

m	*A*	*B*	*C*	R^2	*RMSD* (%)
0.0	−722.88	27996.15	107.97	0.9998	1.25
0.1	−795.35	31766.39	118.69	0.9996	3.27
0.2	−682.33	27081.95	101.84	0.9996	2.24
0.3	−286.67	9437.86	43.00	0.9999	1.56
0.4	−520.31	20524.28	77.71	0.9998	1.32
0.5	−509.14	20426.79	76.03	0.9998	0.59
0.6	−389.62	15441.70	58.21	0.9993	1.44
0.7	−469.22	19366.15	70.09	0.9998	1.93
0.8	−260.80	10359.24	39.03	0.9988	3.17
0.9	−62.17	1776.68	9.45	0.9974	0.88
1.0	−4.74	−344.39	0.84	0.9983	1.80

experimental data of APG with "Apelblat model".

The "logarithmic solubility of Yalkowsky model (log x^{Yal})" for APG in binary {Transcutol® + water} mixtures including neat solvents was calculated using Eq. (7) (Yalkowsky and Roseman, 1981):

$$Logx^{Yal} = m_1 logx_1 + m_2 logx_2 \quad (7)$$

Here, "x_1 and x_2" represent the solubilities of APG in mole fractions in neat solvent 1 (Transcutol®) and neat solvent 2 (water), respectively; and "m_1 and m_2" represent the mass fractions of neat Transcutol® and neat water in the absence of APG, respectively.

The results of this calculation for APG in binary {Transcutol® + water} mixtures including neat solvents are listed in Table S1. The *RMSD* values for APG in binary {Transcutol® + water} mixtures were obtained as (0.86–2.17) %. The maximum *RMSD* value for APG was obtained at m = 0.7 of Transcutol® (2.17%). However, the minimum one was obtained at m = 0.5 of Transcutol® (0.86%). These results again showed good correlation of experimental data of APG with "Yalkowsky model".

The "Jouyban-Acree model solubility ($x_{m,T}$)" of APG in binary {Transcutol® + water} mixtures was determined with the help of Eq. (8) (Jouyban et al., 2006; Jouyban and Acree, 2006; Khoubnasabjafari et al., 2016):

$$\ln x_{m,T} = m_1 \ln x_1 + m_2 \ln x_2 + \left[m_1 m_2 \sum_{i=0}^{2} \frac{J_i}{T} (m_1 - m_2)^i \right] \quad (8)$$

Here, the symbol J_i is the model parameter of Eq. (8) which was determined by no-intercept regression analysis (Jouyban-Gharamaleki and Hanaee, 1997; Jouyban et al., 2012). The trained version of Eq. (8) with respect to present data set can be expressed using Eq. (9):

$$\ln x_{m,T} = m_1 \ln x_1 + m_2 \ln x_2 + \frac{29.74 m_1 m_2}{T} \quad (9)$$

The x_e values of APG were fitted with $x_{m,T}$ values in terms of *RMSD*. Eq. (9) reproduced the solubility data of APG with the *RMSD* value < 1.50% which was more accurate and precise than other models.

More comprehensive computation can be generated by the combination of "Jouyban-Acree" model with "van't Hoff" model with the help of Eq. (10) (Nozohouri et al., 2017; Shakeel et al., 2017b):

$$\ln x_{m,T} = m_1 \left(A_1 + \frac{B_1}{T} \right) + m_2 \left(A_2 + \frac{B_2}{T} \right) + \left[\frac{m_1 m_2}{T} \sum_{i=0}^{2} J_i (m_1 - m_2)^i \right] \quad (10)$$

Here, the symbols A_1, B_1, A_2, B_2 and J_i represent the model parameters of Eq. (10). The trained version of Eq. (10) can be expressed using Eq. (11):

$$\ln x_{m,T} = m_1 \left(0.93 - \frac{605.06}{T} \right) + m_2 \left(3.60 - \frac{5197.70}{T} \right) + \frac{22.32 m_1 m_2}{T} \quad (11)$$

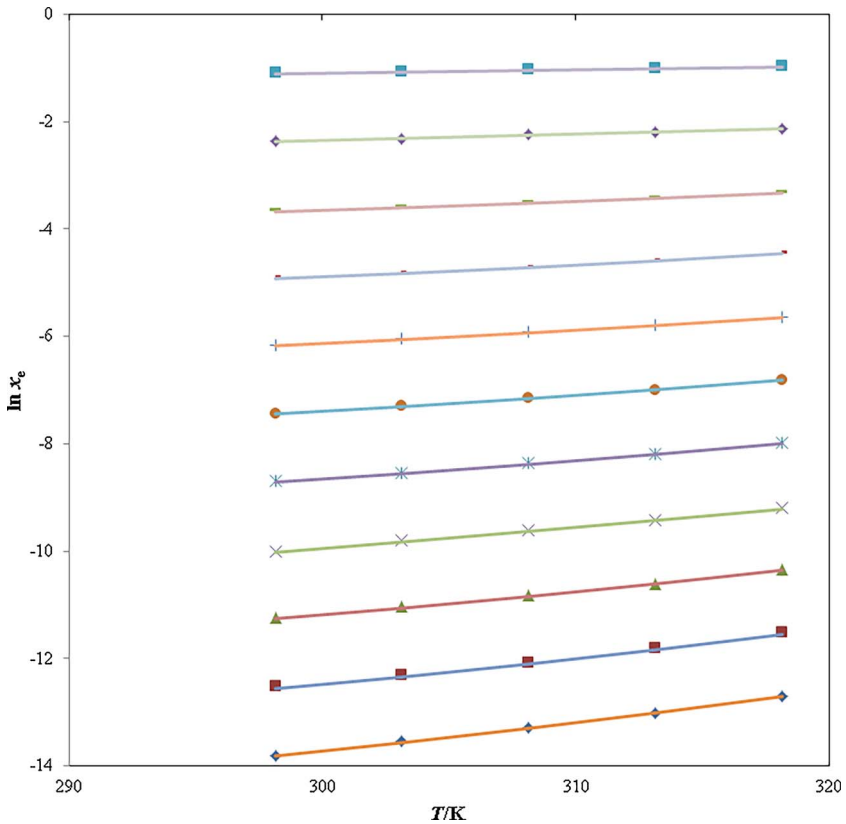

Fig. 3. Correlation of ln x_e values of APG with Apelblat model in binary {Transcutol® + water} mixtures at T = 298.15 K to 318.15 K (Apelblat solubilities are represented by solid lines and experimental solubilities of APG are represented by symbols).

Eq. (11) reproduced the solubility data of APG with the *RMSD* value of < 1.0%. These results were more accurate than other models studied.

3.4. Apparent thermodynamic analysis

Dissolution properties of APG in binary {Transcutol® + water} mixtures were determined using "apparent thermodynamic analysis". Various apparent standard thermodynamic parameters including "standard apparent enthalpy ($\Delta_{sol}H^0$), standard apparent Gibbs free energy ($\Delta_{sol}G^0$) and standard apparent entropy ($\Delta_{sol}S^0$)" were determined in order to evaluate the dissolution thermodynamic properties of APG. The $\Delta_{sol}H^0$ values for APG dissolution in binary {Transcutol® + water} mixtures were obtained at the mean harmonic temperature (T_{hm}) of 307.98 K using "van't Hoff analysis" with the help of Eq. (12) (Ruidiaz et al., 2010; Holguín et al., 2012):

$$\left(\frac{\partial ln x_e}{\partial\left(1/T - 1/T_{hm}\right)}\right)_P = -\frac{\Delta_{sol}H^0}{R} \quad (12)$$

The $\Delta_{sol}H^0$ values for APG dissolution in binary {Transcutol® + water} mixtures were calculated from the slopes of graphs which were plotted between ln x_e values of APG and $1/T - 1/T_{hm}$.

The $\Delta_{sol}G^0$ values for APG dissolution in binary {Transcutol® + water} mixtures were also calculated at T_{hm} value of 307.98 K by applying "Krug et al. analysis" approach using Eq. (13) (Krug et al., 1976):

$$\Delta_{sol}G^0 = -RT_{hm} \times intercept \quad (13)$$

Here, the intercept values for each sample were obtained from van't Hoff plot explained under "van't Hoff analysis".

The $\Delta_{sol}S^0$ values for APG dissolution in binary {Transcutol® + water} mixtures were calculated by applying the combined principles of "Van't Hoff and Krug et al. analysis" using Eq. (14) (Krug et al., 1976; Ruidiaz et al., 2010; Holguín et al., 2012):

$$\Delta_{sol}S^0 = \frac{\Delta_{sol}H^0 - \Delta_{sol}G^0}{T_{hm}} \quad (14)$$

The values for APG dissolution in binary {Transcutol® + water} mixtures are furnished in Table 6.

The $\Delta_{sol}H^0$ values for APG dissolution in binary {Transcutol® + water} mixtures were obtained as (5.02–43.19) kJ mol^{-1}. The $\Delta_{sol}H^0$ values for APG dissolution were observed as decreasing with increase in the *m* value of Transcutol® in binary {Transcutol® + water} mixtures and the x_e value of APG. The maximum $\Delta_{sol}H^0$ value for APG dissolution was obtained in neat water (43.19 kJ mol^{-1}). While, the minimum $\Delta_{sol}H^0$ value for APG dissolution was recorded in neat Transcutol® (5.02 kJ mol^{-1}). The $\Delta_{sol}G^0$ values for APG dissolution in binary {Transcutol® + water} mixtures were recorded as (2.62–33.97) kJ mol^{-1}. The $\Delta_{sol}G^0$ values for APG dissolution were also recorded as decreasing with increase in the *m* value of Transcutol® in binary {Transcutol® + water} mixtures and the x_e value of APG. The maximum and minimum $\Delta_{sol}G^0$ values for APG dissolution were also obtained in neat water (33.97 kJ mol^{-1}) and neat Transcutol® (2.62 kJ mol^{-1}), respectively. The minimum $\Delta_{sol}H^0$ and $\Delta_{sol}G^0$ values for APG dissolution might be due to maximum solubility values of APG in neat Transcutol® as compared to its minimum solubility values in neat water. The positive $\Delta_{sol}H^0$ and $\Delta_{sol}G^0$ values for APG dissolution in binary {Transcutol® + water} mixtures suggested an "endothermic dissolution" of APG in all {Transcutol® + water} mixtures (Shakeel et al., 2015b, 2015c).

The $\Delta_{sol}S^0$ values for APG dissolution in binary {Transcutol® + water} mixtures were obtained as (8.45–29.93) J mol^{-1} K^{-1}, suggesting entropy-driven dissolution of APG in all {Transcutol® + water} mixtures. The mean $\Delta_{sol}H^0$, $\Delta_{sol}G^0$ and $\Delta_{sol}S^0$ values for APG dissolution were obtained as 24.36 kJ mol^{-1}, 18.28 kJ mol^{-1} and 19.80 J mol^{-1} K^{-1} with relative uncertainties of 0.50, 0.56 and 0.32, respectively. Overall, the positive values of $\Delta_{sol}H^0$, $\Delta_{sol}G^0$ and $\Delta_{sol}S^0$ for APG dissolution suggested endothermic and entropy-driven dissolution of APG in all {Transcutol® + water} mixtures (Shakeel et al., 2015a, 2015b, 2017b).

3.5. Enthalpy-entropy compensation analysis for solvation behavior of APG

The solvation behavior of APG in binary {Transcutol® + water} mixtures was studied using an "enthalpy-entropy compensation analysis" (Holguín et al., 2012; Shakeel et al., 2015b). This analysis was conducted by constructing the weighted plots of $\Delta_{sol}H^\circ$ vs. $\Delta_{sol}G^\circ$ at T_{hm} value of 307.98 K (Shakeel et al., 2015b). The resulting data of "enthalpy-entropy compensation analysis" are furnished in Fig. 4. It can be seen that APG in all binary {Transcutol® + water} mixtures presented linear $\Delta_{sol}H^\circ$ vs. $\Delta_{sol}G^\circ$ curve with a positive slope value of greater than 1.0 with R^2 value of greater than 0.99 (Fig. 4). Hence, the "driving mechanism" for APG solvation has been proposed as an "enthalpy-driven" in all binary {Transcutol® + water} mixtures. This observation could be possible due to greater solvation of APG in neat Transcutol® molecules as compared to its solvation mechanism in the molecules of neat water (Shakeel et al., 2015c). This solvation behavior of APG in binary {Transcutol® + water} mixtures was similar to that reported for solvation behavior of apremilast, vitamin D3, dihydropyrimidine derivative, ibrutinib, isatin and vanillin in binary {Transcutol® + water} mixtures (Shakeel et al., 2015b, 2015c, 2015d; Almarri et al., 2017; Shakeel et al., 2017c, 2017d).

4. Conclusion

The solubilities of poorly aqueous soluble APG in binary {Transcutol® + water} mixtures (including pure/neat solvents) were measured at T = 298.15 K to 318.15 K under atmospheric pressure. The mole fraction solubilities of APG were recorded as increasing with the rise in temperature and increase in the *m* value of Transcutol® in binary {Transcutol® + water} mixtures (including neat solvents). The maximum and minimum solubilities of APG in mole fraction were obtained in neat Transcutol® and neat water, respectively at each temperature studied. The experimental solubility values of APG were fitted well with "van't Hoff, Apelblat, Yalkowsky and Jouyban-Acree" models with *RMSD* value of < 4.0% in all {Transcutol® + water} mixtures (including neat solvents). The values of activity coefficients suggested higher solute-solvent molecular interaction in APG-Transcutol® in comparison with other combinations studied. The dissolution behavior of APG was recorded as endothermic and entropy-driven in all binary {Transcutol® + water} cosolvent mixtures studied. Enthalpy-entropy compensation analysis suggested enthalpy-driven mechanism as the

Table 6
The values of various thermodynamic quantities ($\Delta_{sol}H^0$, $\Delta_{sol}G^0$ and $\Delta_{sol}S^0$) for APG dissolution in binary {Transcutol® + water} mixtures[a].

Parameters	*m* = 0.0	*m* = 0.1	*m* = 0.2	*m* = 0.3	*m* = 0.4	*m* = 0.5	*m* = 0.6	*m* = 0.7	*m* = 0.8	*m* = 0.9	*m* = 1.0
$\Delta_{sol}H^0$/kJ mol^{-1}	43.19	39.24	35.12	31.46	27.97	24.48	20.39	18.12	13.63	9.39	5.02
$\Delta_{sol}G^0$/kJ mol^{-1}	33.97	30.83	27.66	24.59	21.39	18.28	15.13	11.98	8.90	5.74	2.62
$\Delta_{sol}S^0$/J mol^{-1} K^{-1}	29.93	27.28	24.23	22.27	21.36	20.13	17.08	19.91	15.36	11.83	8.45

[a] The average uncertainties are u($\Delta_{sol}H^0$) = 0.50 kJ mol-1, u($\Delta_{sol}G^0$) = 0.56 kJ mol-1 and u($\Delta_{sol}S^0$) = 0.32 J mol-1 K-1.

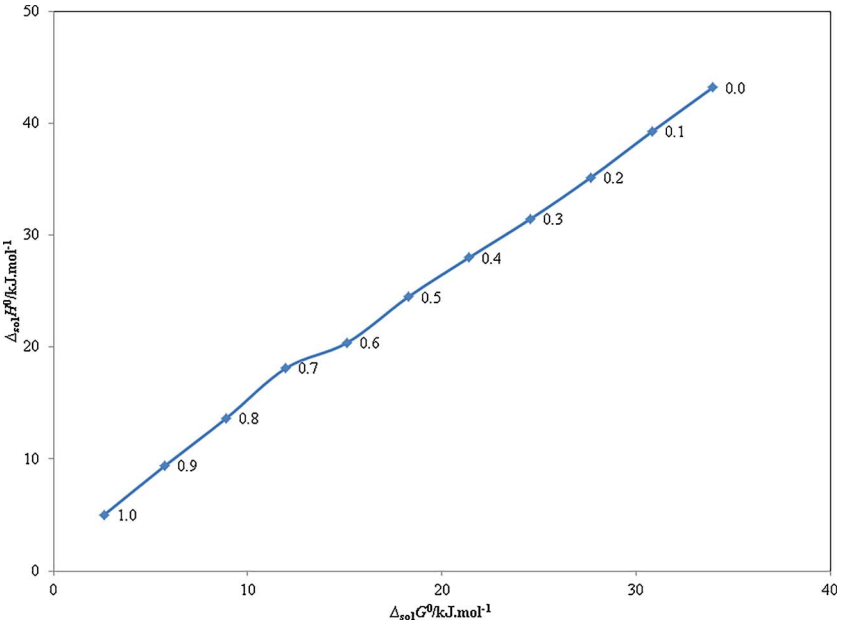

Fig. 4. $\Delta_{sol}H^0$ vs. $\Delta_{sol}G^0$ enthalpy-entropy compensation analysis for solubility of APG in binary {Transcutol® + water} mixtures at T_{hm} of 307.98 K.

main mechanism for solvation behavior of APG. Transcutol® was found to be a potential solubilizer in solubility enhancement of APG in water, therefore it could be used as a good cosolvent for APG. The solubility data of APG obtained in this study could be useful in pre-formulation studies and formulation design of APG in pharmaceutical and food industries.

Conflict of interest

"The authors report no conflict of interest associated with this manuscript".

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.indcrop.2018.02.047.

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