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Solubility and thermodynamic/solvation behavior of *6-phenyl-4,5-dihydropyridazin-3(2H)-one* in different (Transcutol + water) mixtures

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ABSTRACT

Pyridazinone derivatives are useful cardiovascular drugs which suffer from weak aqueous solubility and toxicity problems. Hence, in this work, the solubility of pyridazinone derivative i.e. *6-phenyl-4,5-dihydropyridazin-3(2H)-one* (PDP-6) was measured in various "2-(2-ethoxyethoxy)ethanol (Transcutol®) + water" mixtures at temperatures "$T = 293.2$ K to 313.2 K and pressure "$p = 0.1$ MPa". The experimental solubilities of PDP-6 were correlated with "Apelblat, Van't Hoff and Yalkowsky models" in terms of mean percent deviations and coefficient of determination. The highest solubilities of PDP-6 as mole fraction were obtained in pure Transcutol (5.27×10^{-1} at $T = 313.2$ K). However, the lowest one was obtained in pure water (7.45×10^{-7} at $T = 293.2$ K). "Apparent thermodynamic analysis" of solubilities of PDP-6 as mole fraction indicated an "endothermic dissolution" of PDP-6 in all "Transcutol + water" mixtures due to its positive values. "Enthalpy-entropy compensation" analysis indicated that the solvation of PDP-6 was "enthalpy-driven" in all "Transcutol + water" mixtures evaluated. Based on the results of the current study, PDP-6 has been proposed as practically insoluble in water and very soluble in Transcutol at $T = 298.2$ K.

1. Introduction

Hypertension and other cardiovascular disorders are very common problems in the population of Saudi Arabia [1]. In the last decade, pyridazinone derivatives have been proven good candidates in the management of these diseases [1,2]. Several pyridazinone derivatives have been approved or under clinical trials for the treatment of cardio-vascular diseases [3–7]. With respect to formulation development of pydazinone derivatives, poor water-solubility and toxicity of these compounds are the main hurdles. The chemical name of pyridazinone derivative investigated in current research work is *6-phenyl-4,5-dihydropydazin-3(2H)-one* [PDP-6]. PDP-6 (Fig. 1, CAS Registry number: 1011-46-7, molecular formula: $C_{10}H_{10}N_2O$ and molar mass: 174.19 g mol^{-1}) was synthesized, identified, characterized well and found to be a potent antihypertensive agent in our previous articles [1,2].

Most of the new chemical entities (NCE) and existing drugs in the market present poor water-solubility problems [8]. Therefore, the solubilities and thermodynamic analysis of NCE in "aqueous-cosolvent" binary solvent systems must be measured in order to obtain complete physicochemical information of these compounds [9,10]. Such type of experimental data had significant role in the dosage form design of these compounds for clinical use [9–11]. The chemical name of Transcutol® has been proposed *2-(2-ethoxyethoxy) ethanol* [10]. In the recent years, Transcutol had shown great potential in solubilization of several poorly water-soluble drugs [10–14]. The solubility data and thermodynamic analysis of pyridazinone derivatives have been reported rarely in literature. Moreover, the solubilities and thermodynamic analysis of PDP-6 in any aqueous-cosolvent mixture have not been presented in literature so far. Hence, in the current research work, the solubilities of PDP-6 as mole fraction in different "Transcutol + water" binary compositions including mono solvents were determined at temperatures "$T = 293.2$ K to 313.2 K" and pressure "$p = 0.1$ MPa". This temperature range was randomly selected at the interval of 5.0 K with uncertainty of ± 0.1 K in this work. "Apparent thermodynamic analysis" and enthalpy-entropy compensation analysis were also performed in order to evaluate the dissolution and solvation behavior of PDP-6 in different "Transcutol + water" binary compositions/mixtures including mono solvents. The solubility data of the current research work could

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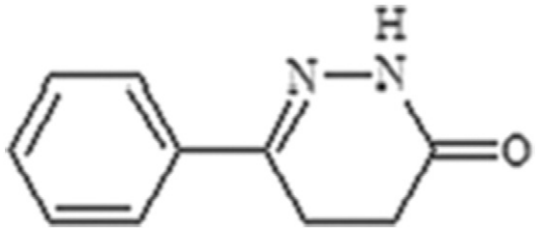

Fig. 1. Chemical structure of PDP-6.

be useful in "purification, recrystallization and formulation development" of PDP-6.

2. Experimental

2.1. Materials

PDP-6 "(mass fraction purity > 0.98 by HPLC)" was synthesized and characterized in the "Laboratory of Pharmaceutical Chemistry, Northern Border University, Rafha, Saudi Arabia" [1]. Transcutol® "(mass fraction purity of >0.99 by GC)" was obtained from "Gattefosse (Lyon, France)". Water was collected from "Milli-Q unit. The source and purity of materials are presented in Table 1.

2.2. Analysis of PDP-6 by HPLC

The analysis of PDP-6 in all sample matrices was performed using reversed phase HPLC at ultra-violet (UV) mode at 310 nm. The separation of PDP-6 was carried out at $T = 298.2$ K using "Waters HPLC system (Waters, USA)". The column used for analysis of PDP-6 was "Nucleodur (150 × 4.6 mm, 5 μm) RP C_8 column". The green mobile phase was used for analysis which was composed of the binary mixture of methanol and ethanol (1:1% v/v). The elution of PDP-6 was performed at a flow rate of 1.0 mL min^{-1} at the wavelength of 310 nm. The injection volume for all sample matrices was 10 μL. The proposed HPLC method was validated in terms of linearity, precision, accuracy, sensitivity, reproducibility and robustness. All validation parameters for the analysis of PDP-6 were recorded satisfactory.

2.3. Measurement of PDP-6 solubility in "Transcutol + water" mixtures

The solubility of PDP-6 against mass fraction of Transcutol ($m = 0.1$ to 0.9; m is the mass fraction of Transcutol in "Transcutol + water" mixtures) in different "Transcutol + water" mixtures including mono solvents [water ($m = 0.0$) and Transcutol ($m = 1.0$] was determined at "$T = 293.2$ K to 313.2 K" and "$p = 0.1$ MPa". A reported shake flask method of Higuchi and Connors (1965) was used for solubility determination of PDP-6 [15]. The excess amount of PDP-6 was added in known amounts of each "Transcutol + water" mixture including mono solvents in order to obtain the concentrated suspensions of PDP-6. Each experiment was repeated three times. The obtained concentrated suspensions of PDP-6 were vortexed for 5 min and transferred to the biological shaker (Julabo, PA) at shaking speed of 100 rpm for 72 h. After 72 h, the samples were taken out from the biological shaker and allowed to settle the particles of PDP-6 for 24 h [16]. Centrifugation and filtration were not used to obtain the supernatants because these processes could change the actual solubility values of PDP-6 in different "Transcutol + water" mixtures at different temperatures. The supernatants were taken carefully, diluted with mobile (wherever applicable) phase and subjected for the quantification of PDP-6 content by reversed phase HPLC method described above. The experimental solubilities of PDP-6 in mole fraction (x_e) were calculated with the help of Eq. (1) and (2) [17,18]:

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

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

In which, m_1 is the mass of PDP-6 and m_2 and m_3 are the masses of Transcutol and water, respectively. M_1 is the molar mass of PDP-6 and M_2 and $M3$ are the molar masses of Transcutol and water, respectively.

Eq. (1) is applicable for the calculation of x_e values of PDP-6 in mono solvent (Transcutol and water) and Eq. (2) is applicable for the calculation of x_e values of PDP-6 in "Transcutol + water" mixtures.

3. Results and discussion

3.1. Experimental solubilities of PDP-6

The x_e values of PDP-6 in different "Transcutol + water" mixtures including mono solvents at "$T = 293.2$ K to 313.2 K" and "$p = 0.1$ MPa" are listed in Table 2. Temperature-dependent solubility data of PDP-6 in different "Transcutol + water" mixtures or any mono solvent have not been reported.

It was observed from Table 2 that the x_e values of PDP-6 at constant pressure of 0.1 MPa were increasing with the rise in temperature and increase in m value of Transcutol in "Transcutol + water" mixtures. The highest x_e value of PDP-6 was obtained in mono solvent Transcutol (5.27×10^{-1} at "$T = 313.2$ K"). However, the lowest one was obtained in mono solvent water (7.45×10^{-7} at "$T = 293.2$ K"). The highest x_e value of PDP-6 in mono solvent Transcutol was due to the lower dielectric constant/polarity of Transcutol in comparison with higher dielectric constant/polarity of water [12,13]. The impact of the m value of Transcutol on natural logarithmic x_e values ($\ln x_e$) of PDP-6 at "$T = 293.2$ K to 313.2 K" was also evaluated and resulting data are shown in Fig. 2. The results presented in Fig. 2 showed that an increase in the m value of Transcutol in "Transcutol + water" mixtures resulted in the linear enhancement in the solubilities of PDP-6 at each temperature evaluated. The x_e value of PDP-6 was significantly increased from neat water to neat Transcutol at each temperature investigated. This enhancement in neat Transcutol was around 497,802 fold higher than neat water at standard room temperature i.e. $T = 298.2$ K. It was also observed that addition of a small amount of Transcutol in water resulted in significant enhancement in solubility of PDP-6. Due to significant enhancement in solubility of PDP-6 by addition of a small amount of Transcutol in water, it could be used as a potent solubilizer/cosolvent in solubilization of PDP-6 in an aqueous media such as water. Based on the solubility data of this work, PDP-6 has been proposed as very soluble in neat Transcutol and practically insoluble in neat water at $T = 298.2$ K [13,14].

Table 1
Information regarding materials used in the experimental work.

Material	Molecular formula	Molar mass (g mol^{-1})	CAS Registry no.	Purification method	Mass fraction purity	Analysis method	Source
PDP-6	$C_{10}H_{10}N_2O$	174.19	1011-46-7	Recrystallization	>0.98	HPLC	Synthesized
Transcutol	$C_6H_{14}O_3$	134.17	111-90-0	None	>0.99	GC	Gattefosse
Water	H_2O	18.07	7732-18-5	None	–	–	Milli-Q

6-Phenyl-4,5-dihydropydazin-3(2H)-one (PDP-6), high performance liquid chromatography (HPLC) and gas chromatography (GC).

Table 2
The x_e values of PDP-6 against m value of Transcutol in various "Transcutol + water" mixtures at "$T = 293.2$ K to 313.2 K" and "$p = 0.1$ MPa"[a].

m	x_e				
	$T = 293.2$ K	$T = 298.2$ K	$T = 303.2$ K	$T = 308.2$ K	$T = 313.2$ K
0.0	7.45×10^{-7}	9.10×10^{-7}	1.09×10^{-6}	1.34×10^{-6}	1.64×10^{-6}
0.1	2.83×10^{-6}	3.42×10^{-6}	4.02×10^{-6}	4.87×10^{-6}	5.86×10^{-6}
0.2	1.09×10^{-5}	1.28×10^{-5}	1.50×10^{-5}	1.78×10^{-5}	2.10×10^{-5}
0.3	4.01×10^{-5}	4.68×10^{-5}	5.41×10^{-5}	6.36×10^{-5}	7.40×10^{-5}
0.4	1.54×10^{-4}	1.77×10^{-4}	1.99×10^{-4}	2.31×10^{-4}	2.66×10^{-4}
0.5	5.65×10^{-4}	6.45×10^{-4}	7.25×10^{-4}	8.29×10^{-4}	9.33×10^{-4}
0.6	2.16×10^{-3}	2.41×10^{-3}	2.66×10^{-3}	3.00×10^{-3}	3.45×10^{-3}
0.7	8.01×10^{-3}	8.87×10^{-3}	9.72×10^{-3}	1.09×10^{-2}	1.19×10^{-2}
0.8	3.02×10^{-2}	3.31×10^{-2}	3.59×10^{-2}	3.91×10^{-2}	4.18×10^{-2}
0.9	1.14×10^{-1}	1.23×10^{-1}	1.31×10^{-1}	1.41×10^{-1}	1.50×10^{-1}
1.0	4.25×10^{-1}	4.53×10^{-1}	4.78×10^{-1}	5.07×10^{-1}	5.27×10^{-1}

[a] The standard uncertainties u are $u(T) = 0.10$ K, $u_r(m) = 0.1\%$, $u(p) = 0.003$ MPa and $u_r(x_e) = 1.22\%$.

3.2. Correlation of x_e values of PDP-6

In order to obtain the correlation and curve fitting of the x_e values of PDP-6, these values were fitted with three different semiempirical models namely "Van't Hoff, Apelblat and Yalkowsky-Roseman" models [14,19–21]. The "Van't Hoff" solubility ($x^{Van't}$) of PDP-6 in different "Transcutol + water" mixtures including mono solvents was calculated using Eq. (3) [14]:

$$\ln x^{Van't} = a + \frac{b}{T} \tag{3}$$

In which, the symbols "a and b" are the model parameters of Van't Hoff model. These parameters were determined by plotting the ln x_e values of PDP-6 against of $1/T$.

The correlation between x_e and $x^{Van't}$ values of PDP-6 was carried out by the calculation of mean percent deviations (*MPD*) and determination of coefficients (R^2). The *MPD* values for PDP-6 were calculated using its standard formula reported in literature [22]

The results of Van't Hoff parameters along with *MPD* and R^2 values of PDP-6 in different "Transcutol + water" mixtures including mono solvents are listed in Table 3. The *MPD* values for PDP-6 in different "Transcutol + water" mixtures including mono solvents were obtained as very low for Van't Hoff model (0.01 to 0.14). The highest value of *MPD* for PDP-6 was obtained at $m = 0.7$ of Transcutol (0.14). The R^2 values for PDP-6 were obtained as 0.9960 to 0.9995. These results indicated good correlation of experimental solubilities of PDP-6 with "Van't Hoff model".

The "Apelblat model" solubility (x^{Apl}) of PDP-6 in various "Transcutol + water" systems including mono solvents was determined using Eq. (4) [19,20]:

$$\ln x^{Apl} = A + \frac{B}{T} + C \ln (T) \tag{4}$$

In which, the symbols "A, B and C" are the parameters of Apelblat model. These parameters (A, B and C) were determined by nonlinear multivariate regression analysis of x_e values of PDP-6 listed in Table 2 [14]. The correlation between x_e and x^{Apl} values of PDP-6 was carried out again in terms of *MPD* and R^2.

The values of Apelblat parameters along with *MPD* and R^2 values for PDP-6 in different "Transcutol + water" mixtures are listed in Table 4.

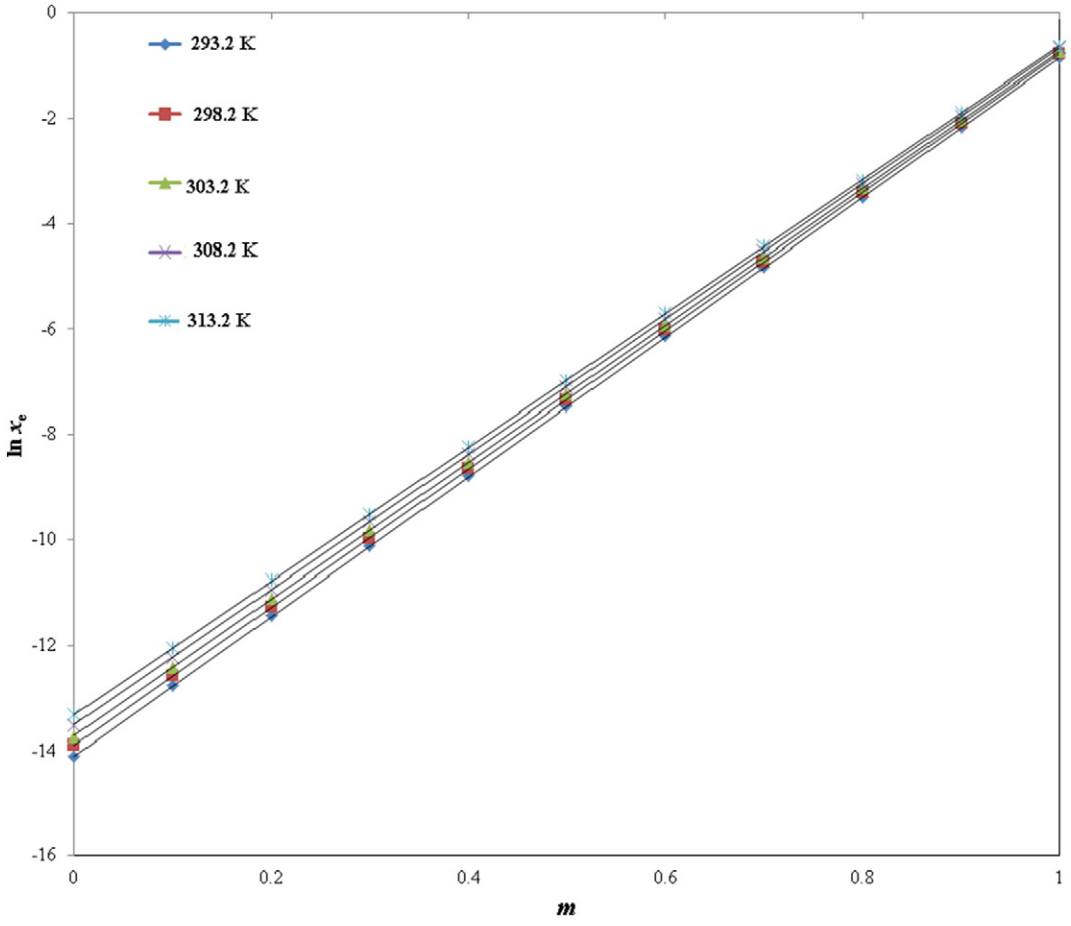

Fig. 2. Impact of m value of the Transcutol on ln x_e values of PDP-6 at five different temperatures i.e. "$T = 293.2$ K to 313.2 K".

Table 3
Van't Hoff coefficients (*a* and *b*), R^2 and *MPD* values for PDP-6 in different "Transcutol + water" mixtures.

m	*a*	*b*	R^2	*MPD* (%)
0.0	−1.75	−3624.60	0.9982	0.04
0.1	−1.44	−3323.40	0.9985	0.01
0.2	−1.14	−3017.00	0.9991	0.01
0.3	−0.53	−2814.10	0.9991	0.02
0.4	−0.26	−2498.90	0.9980	0.07
0.5	0.37	−2302.20	0.9995	0.07
0.6	0.65	−1993.50	0.9979	0.04
0.7	1.41	−1829.60	0.9984	0.14
0.8	1.63	−1505.10	0.9989	0.07
0.9	2.11	−1255.10	0.9986	0.03
1.0	2.54	−994.31	0.9960	0.04

The graphical correlation between x_e and x^{Apl} values of PDP-6 are presented in Fig. 3 which presented excellent graphical correlation/curve fitting. The *MPD* values for PDP-6 in different "Transcutol + water" mixtures including mono solvents were obtained as 0.38 to 5.32. The highest *MPD* value for PDP-6 was obtained at $m = 0.1$ of Transcutol (5.32). However, the lowest one was obtained in neat Transcutol (0.38). The R^2 values were obtained as 0.9974 to 0.9999. These results again indicated good correlation of experimental solubilities of PDP-6 with "Apelblat model".

The "logarithmic solubility of Yalkowsky" model ($\log x^{Yal}$) in different "Transcutol + water" mixtures including mono solvents was calculated using Eq. (5) [21]:

$$\mathrm{Log}x^{Yal} = m_1\ logx_1 + m_2\ logx_2 \tag{5}$$

In which, "x_1 and x_2" represent the solubilities of PDP-6 as mole fractions in mono solvent 1 (Transcutol) and mono solvent 2 (water), respectively; and "m_1 and m_2" are the mass fractions of mono solvent 1 (Transcutol) and mono solvent 2 (water) in the absence of PDP-6, respectively.

The results of this calculation for PDP-6 in different "Transcutol + water" mixtures including mono solvents are listed in Table 5. This correlation was carried out in terms of *MPD*. The *MPD* values for PDP-6 in different "Transcutol + water" mixtures were obtained as 3.44 to 17.60. The highest *MPD* value was obtained at $m =$ 0.7 of Transcutol (17.60). However, the lowest one was obtained at $m = 0.5$ of Transcutol (3.44). These results again indicated good correlation of experimental solubilities of PDP-6 with "Yalkowsky model".

3.3. Apparent thermodynamic analysis for dissolution of PDP-6

The dissolution analysis of PDP-6 in various "Transcutol + water" mixtures including mono solvents was performed by "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 measured to evaluate thermodynamic behavior of PDP-6. The "$\Delta_{sol}H^0$ values" for dissolution behavior of PDP-6 in various "Transcutol + water" mixtures including mono solvents were measured at "mean harmonic temperature (T_{hm})" of 303 K by applying "Van't Hoff analysis" using Eq. (6) [23,24]:

$$\left(\frac{\partial \ln x_e}{\partial\left({}^{1}/_{T} - {}^{1}/_{T_{hm}}\right)}\right)_P = -\frac{\Delta_{sol}H^0}{R} \tag{6}$$

In which, the symbol *R* represent the universal gas constant. The "$\Delta_{sol}H^0$ values" for PDP-6 dissolution in different "Transcutol + water" mixtures including mono solvents were obtained from the slopes of graphs plotted between ln x_e values of PDP-6 and ${}^{1}/_{T} - {}^{1}/_{T_{hm}}$.

The "$\Delta_{sol}G^0$ values" for PDP-6 dissolution in various "Transcutol + water" mixtures including mono solvents were also determined at T_{hm} of 303 K by applying "Krug et al. analysis" using Eq. (7) [25]:

$$\Delta_{sol}G^0 = -RT_{hm} \times intercept \tag{7}$$

In which, the intercept value for each sample matrices was determined from Van't Hoff plot discussed under "Van't Hoff analysis".

Finally, the "$\Delta_{sol}S^0$ values" for PDP-6 dissolution in various "Transcutol + water" mixtures including mono solvents were determined by applying the combined approach of "Van't Hoff and Krug et al. analysis" using Eq. (8) [23–25]:

$$\Delta_{sol}S^0 = \frac{\Delta_{sol}H^0 - \Delta_{sol}G^0}{T_{hm}} \tag{8}$$

The results of "apparent thermodynamic analysis" for dissolution behavior of PDP-6 in different "Transcutol + water" mixtures including mono solvents are presented in Table 6.

The "$\Delta_{sol}H^0$ values" for dissolution of PDP-6 in different "Transcutol + water" mixtures including mono solvents were obtained as positive values in the range of (8.26 to 30.12) kJ·mol^{-1}. The "$\Delta_{sol}H^0$ values" for PDP-6 dissolution were found to be decreasing with increase in the *m* value of Transcutol in "Transcutol + water" mixtures and the x_e value of PDP-6. The highest "$\Delta_{sol}H^0$ value" for PDP-6 dissolution was obtained in mono solvent water (30.12 kJ·mol^{-1}). However, the lowest "$\Delta_{sol}H^0$ value" for PDP-6 dissolution was obtained in mono solvent Transcutol (8.26 kJ·mol^{-1}). The "$\Delta_{sol}G^0$ values" for PDP-6 dissolution in various "Transcutol + water" mixtures including mono solvents were also obtained positive values in the range of (1.86 to 34.56) kJ·mol^{-1}. The "$\Delta_{sol}G^0$ values" for PDP-6 dissolution were also found to be decreasing with increase in the *m* value of Transcutol in "Transcutol + water" mixtures and the x_e value of PDP-6. The highest and lowest "$\Delta_{sol}G^0$ values" for PDP-6 dissolution were also obtained in mono solvent water (34.56 kJ·mol^{-1}) and mono solvent Transcutol (1.86 kJ·mol^{-1}), respectively. The lowest "$\Delta_{sol}H^0$ and $\Delta_{sol}G^0$ values" for PDP-6 dissolution were possible due to higher solubility values of PDP-6 in mono solvent Transcutol in comparison with its lower solubility values in mono solvent water. The positive "$\Delta_{sol}H^0$ and $\Delta_{sol}G^0$ values" for PDP-6 dissolution in various "Transcutol + water" mixtures including mono solvents indicated an "endothermic dissolution" of PDP-6 in all "Transcutol + water" mixtures including mono solvents [12,13]. The "$\Delta_{sol}S^0$ values" for PDP-6 dissolution in different "Transcutol + water" mixtures including mono solvents were recorded as negative values at $m = 0.0$ to 0.4 of Transcutol in "Transcutol + water" mixtures and positive values at $m = 0.5$ to 1.0 of Transcutol in "Transcutol + water" mixtures.

Table 4
Apelblat coefficients (*A*, *B* and *C*), R^2 and *MPD* for PDP-6 in different "Transcutol + water" mixtures.

m	*A*	*B*	*C*	R^2	*MPD* (%)
0.0	−232.54	6793.25	34.37	0.9993	3.41
0.1	−174.00	4465.48	25.69	0.9993	5.32
0.2	−176.87	4915.32	26.17	0.9999	0.55
0.3	−144.32	3676.31	21.41	0.9997	3.30
0.4	−145.57	4060.58	21.64	0.9989	3.99
0.5	−55.43	216.27	8.31	0.9996	4.39
0.6	−147.62	4700.51	22.08	0.9994	2.92
0.7	−78.01	1755.49	11.82	0.9987	0.65
0.8	68.24	-4513.11	-9.91	0.9996	2.62
0.9	48.40	-3345.76	-6.89	0.9992	3.69
1.0	67.68	-3935.94	-9.70	0.9974	0.38

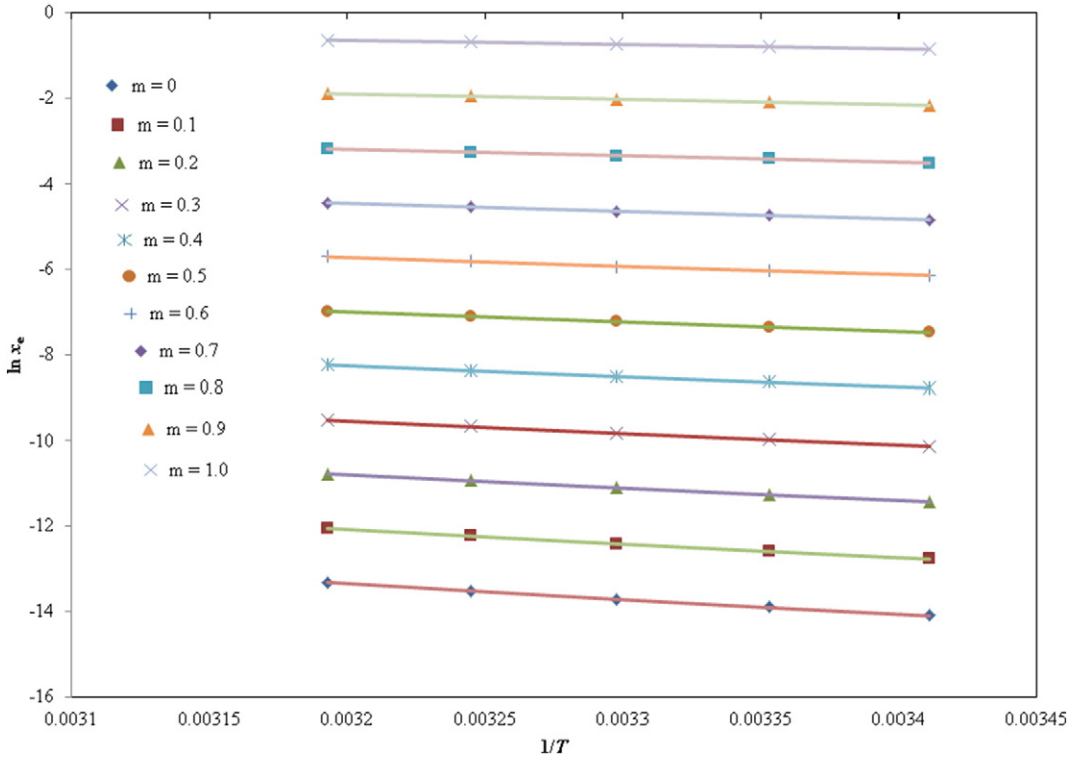

Fig. 3. Correlation/curve fitting of ln x_e values of PDP-6 with Apelblat model in various "Transcutol + water" mixtures at "T = 293.2 K to 313.2 K" (Apelblat solubilities are represented by solid lines and experimental solubilities of PDP-6 are represented by symbols).

3.4. Solvation behavior of PDP-6 in "Transcutol + water" mixtures

For the investigation of "solvation behavior and cosolvent action" for PDP-6 in different "Transcutol + water" mixtures including mono solvents, an "enthalpy-entropy compensation analysis" was performed [24,26]. "Enthalpy-entropy compensation analysis" was performed by making the weighted graphs of "$\Delta_{sol}H°$ vs. $\Delta_{sol}G°$" at T_{hm} value of 303 K [26]. The results of this analysis are presented in Fig. 4. From results presented in Fig. 4, it was observed that PDP-6 in all "Transcutol + water" mixtures including mono solvents presented linear "$\Delta_{sol}H°$ vs. $\Delta_{sol}G°$" graph with a positive slope value > 1.0 with R^2 value > 0.99. Therefore, the "driving mechanism" for solvation behavior of PDP-6 was proposed as an "enthalpy-driven" in all "Transcutol + water" mixtures including mono solvents. Such observation was possible due to excellent solvation of PDP-6 in Transcutol molecules in comparison with its solvation behavior in water molecules [13]. The solvation behavior of PDP-6 obtained in this work was similar to those recorded for solvation behavior of "ibrutinib, istain and vanillin" in various "Transcutol + water" mixtures including mono solvents [12–14].

Table 5
Log x^{Yal} values of PDP-6 calculated by log-linear model of Yalkowsky in different "Transcutol + water" mixtures at "T = 293.2 K to 313.2 K".

m	Log x^{Yal}					*MPD* (%)
	T = 293.2 K	T = 298.2 K	T = 303.2 K	T = 308.2 K	T = 313.2 K	
0.1	−5.52	−5.47	−5.39	−5.31	−5.23	6.99
0.2	−4.97	−4.90	−4.83	−4.75	−4.68	17.12
0.3	−4.40	−4.33	−4.26	−4.19	−4.13	5.84
0.4	−3.82	−3.76	−3.70	−3.64	−3.58	15.42
0.5	−3.24	−3.19	−3.14	−3.08	−3.03	3.44
0.6	−2.67	−2.62	−2.57	−2.52	−2.48	10.70
0.7	−2.09	−2.05	−2.01	−1.96	−1.93	17.60
0.8	−1.52	−1.48	−1.44	−1.40	−1.37	6.18
0.9	−0.94	−0.91	−0.88	−0.85	−0.82	9.03

Table 6
The $\Delta_{sol}H^0$, $\Delta_{sol}S^0$, $\Delta_{sol}G^0$ and R^2 values for PDP-6 dissolution in different "Transcutol + water" mixtures calculated by apparent thermodynamic analysis[b].

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}	30.12	27.62	25.07	23.39	20.77	19.13	16.57	15.20	12.51	10.43	8.26
$\Delta_{sol}G^0$/kJ·mol^{-1}	34.56	31.27	27.97	24.73	21.43	18.20	14.91	11.65	8.38	5.10	1.86
$\Delta_{sol}S^0$/J·mol^{-1} K^{-1}	−14.62	−12.04	−9.55	−4.41	−2.20	3.07	5.46	11.72	13.60	17.57	21.12
R^2	0.9982	0.9985	0.9991	0.9991	0.9980	0.9995	0.9979	0.9984	0.9989	0.9986	0.9961

[b] The average uncertainties are $u(\Delta_{sol}H^0)$ = 0.37 kJ·mol^{-1}, $u(\Delta_{sol}G^0)$ = 0.59 kJ·mol^{-1} and $u(\Delta_{sol}S^0)$ = 4.54 J·mol^{-1} K^{-1}.

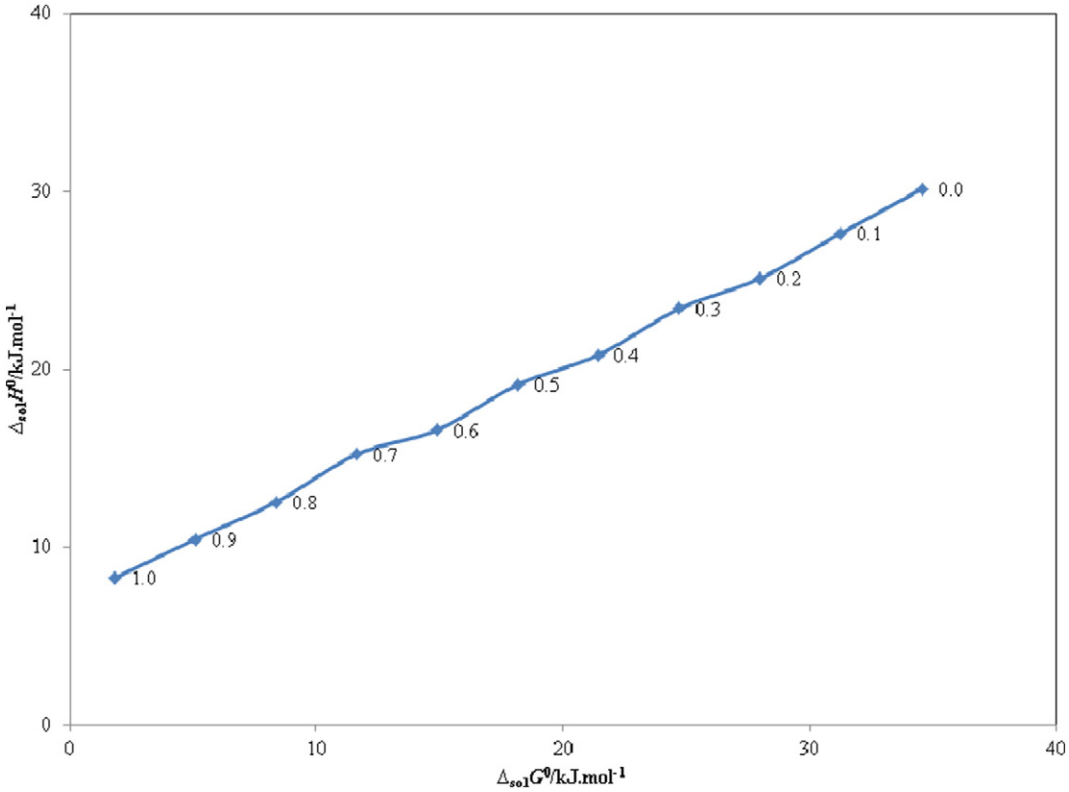

Fig. 4. $\Delta_{sol}H^0$ vs. $\Delta_{sol}G^0$ enthalpy-entropy compensation analysis for solubility of PDP-6 in various "Transcutol + water" mixtures at T_{hm} value of 303 K.

4. Conclusion

In this work, the solubilities of a novel antihypertensive drug PDP-6 in various "Transcutol + water" mixtures including mono solvents were determined at "$T = 293.2$ K to 313.2 K" and "$p = 0.1$ MPa". The solubilities of PDP-6 as mole fraction were found to be increased with increase in temperature and the m value of Transcutol in all "Transcutol + water" mixtures including mono solvents. The highest and lowest solubilities of PDP-6 as mole fraction were obtained in mono solvent Transcutol and mono solvent water, respectively at each temperature investigated. The experimental solubilities of PDP-6 as mole fraction were correlated and fitted better with "Apelblat, Van't Hoff and Yalkowsky" models in all "Transcutol + water" mixtures including mono solvents. "Apparent thermodynamic analysis" showed an endothermic dissolution behavior of PDP-6 in all "Transcutol + water" mixtures including mono solvents. "Enthalpy-entropy compensation" analysis indicated that the solvation behavior of PDP-6 was "enthalpy-driven" in all "Transcutol + water" mixtures including mono solvents evaluated.

Conflict of interest

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

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