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Solubility and thermodynamics of *6-phenyl-4,5-dihydropyridazin-3(2H)-one* in various neat solvents at different temperatures

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ABSTRACT

Pyridazinone derivatives have been investigated either pre-clinically or clinically in the treatment of various cardiovascular diseases. The main problems associated with these drugs are the poor aqueous solubility and toxicity. Therefore, in the current study, the solubility of pyridazinone derivative i.e. *6-phenyl-4,5-dihydropyridazin-3(2H)-one* [coded as PDP-6] was determined in eleven different neat solvents at temperatures "$T = 293.2$ K to 313.2 K" and "atmospheric pressure $p = 0.1$ MPa". Experimental mole fraction solubilities of PDP-6 were correlated well with van't Hoff and Apelblat models with mean percent deviation of <6.0%. The mole fraction solubilities of PDP-6 at "$T = 313.2$ K" were recorded highest in dimethyl sulfoxide [DMSO] (6.77×10^{-1}) followed by 2-(2-ethoxyethoxy) ethanol (Transcutol®) (5.24×10^{-1}), polyethylene glycol-400 [PEG-400] (8.47×10^{-2}), ethyl acetate [EA] (1.45×10^{-2}), ethylene glycol [EG] (1.09×10^{-2}), propylene glycol [PG] (1.03×10^{-2}), 2-butanol (7.78×10^{-3}), 1-butanol (7.68×10^{-3}), ethanol (6.96×10^{-3}), isopropyl alcohol [IPA] (6.51×10^{-3}) and water (1.61×10^{-6}) and similar trend was also recorded at all five different temperatures investigated. "Apparent thermodynamic analysis" on mole fraction solubilities of PDP-6 indicated an endothermic dissolution of PDP-6 in all neat solvents studied. Based on these data, PDP-6 has been proposed as practically insoluble in water, sparingly soluble in ethanol, IPA, EG, PG, EA, 1-butanol and 2-butanol, soluble in PEG-400 and very soluble in DMSO and Transcutol®.

1. Introduction

Cardiovascular diseases including hypertension are the common disorders of Saudi Arabia [1]. Pyridazinone derivatives have great potential in the treatment of cardiovascular disorders [1,2]. Many of the cardio-protective pyridazinone derivatives are either under clinical trials or clinical use such as "imazodan [3,4], CI-930 [4,5] pimobendan [4,6], indolidan [4,7], levosimendan [4,8], SK&F-93741 [4,9], Y-590 [4,10], Meribendan [11], NSP-804 [12], NSP-805 [12], bemoradan [13,14], senazodan [15], amipizone [4,14], prinoxodan [16], SKF 95654 [17], siguazodan [18] and KF 15232" [18]. The main problems associated with these compounds are their toxicity and weak solubilization power in an aqueous media [1]. Weak solubilization power of these compounds in water creates plenty of problems in their formulation development. The IUPAC name of pyridazinone derivative evaluated in this work is *6-phenyl-4,5-dihydropydazin-3(2H)-one* [coded as PDP-6]. This novel antihypertensive compound was obtained as a white crystalline powder with the molecular formula and molar mass of $C_{10}H_{10}N_2O$ and 174.19 g mol^{-1}, respectively (Fig. 1) [1,2].

This compound (PDP-6) has been investigated as a potential antihypertensive agent in literature [1]. The solubility data of newly synthesized compounds and existing drugs in different neat solvents are important in "their purification, recrystallization, drug discovery processes and formulation development" [19–24]. Therefore, it is of utmost importance to measure the solubility of PDP-6 in various neat solvents including "aqueous and organic solvents". The most commonly used neat solvents for solubility enhancement of weakly soluble drugs are "ethanol, propylene glycol (PG) and polyethylene glycol-400 (PEG-400)" [25–27]. Recently, the potential of 2-(2-ethoxyethoxy) ethanol (Transcutol®) has also been investigated for solubility enhancement of several weakly soluble drug molecules [28–30]. The solubility data of pyridazinone derivatives are poorly reported in literature. Recently, we reported the solubility data of PDP-6 in various "Transcutol + water" mixtures at temperatures "$T = 293.2$ K to 313.2 K" and pressure "$p = 0.1$ MPa" [31]. However, the solubilities and "apparent thermodynamic function" of PDP-6 in other neat solvents have not been reported. Therefore, in the current study, the mole fraction solubilities of PDP-6 in eleven different neat solvents including "water, ethanol,

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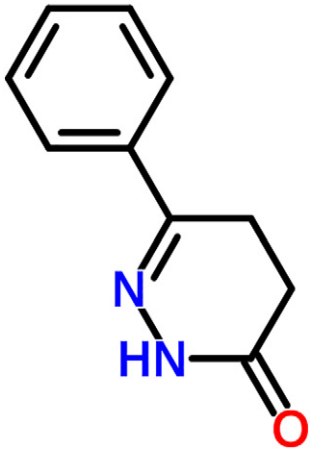

Fig. 1. Molecular structure of PDP-6 (molar mass: 174.19 g mol^{-1}).

Transcutol, PEG-400, PG, ethylene glycol (EG), isopropanol (IPA), ethyl acetate (EA), 1-butanol, 2-butanol and dimethyl sulfoxide (DMSO)" were measured at "$T = 293.2$ K to 313.2 K" and "$p = 0.1$ MPa". Neat solvents are also known as pure solvents which are being used without any solvent and they have high purities [19,20]. Temperature ranges were selected randomly at the interval of 5 K in order to obtain good data. This temperature range was selected in such a manner that the higher temperature should not exceed the melting point of drug. "Apparent thermodynamic analysis" on solubilities of PDP-6 was also performed using "van't Hoff and Krug et al. analysis". The solubility data of PDP-6 obtained in this study could be useful in "recrystallization, purification, pre-formulation studies and formulation development" of PDP-6.

2. Experimental

2.1. Materials

PDP-6 was synthesized and characterized in the "Laboratory of Pharmaceutical Chemistry, Northern Border University, Rafha, Saudi Arabia". Ethyl alcohol (IUPAC name: ethanol), 1-butyl alcohol (IUPAC name: 1-butanol), 2-butyl alcohol (IUPAC name: 2-butanol) and IPA (IUPAC name: isopropanol) were obtained from "Sigma-Aldrich (St. Louis, MO)". Transcutol® [IUPAC name: 2-(2-ethoxyethoxy)ethanol] was obtained from "Gattefosse (Lyon, France)". PEG-400 (IUPAC name: polyethylene glycol-400), PG (IUPAC name: 1,2-propanediol), EA (IUPAC name: ethyl acetate), DMSO (IUPAC name: dimethyl sulfoxide) and EG (IUPAC name: 1,2-ethanediol) were obtained from "Fluka Chemica (Buchs, Switzerland)". Water was obtained from "Milli-Q unit in the laboratory". The details of all these materials are listed in Supplementary Table 1 (Table S1).

2.2. Synthesis, characterization and identification of compound PDP-6

The synthesis of compound PDP-6 was performed in a two steps. In the first step, anhydrous aluminium chloride (0.125 M) was reacted with a solution of succinic anhydride (0.1 M) prepared in benzene (50 mL) to produce 3-benzoylpropionic acid which was purified by recrystallization with methanol. In the second step, 3-benzoylpropionic acid (0.01 M) was reacted with a solution of hydrazine hydrate (0.015 M) in ethanol to produce PDP-6 which was purified by recrystallization with ethanol. The detail procedure about synthesis of various pyridazinone derivatives including PDP-6 is presented in our previously published article [1]. The scheme for the synthesis of PDP-6 in two different steps is given in Supplementary Fig. 1 (Fig. S1). The synthesized compound PDP-6 was characterized in terms of yield, purity, melting point, FT-IR spectra, ^{1}H NMR spectra, ^{13}C NMR spectra and elemental analysis. The melting point of PDP-6 was determined using an open capillary tube method. The melting point of PDP-6 has been reported as (152 to 154) °C in literature [1]. In this work, the melting point of PDP-6 by an open capillary tube method was also recorded as (152 to 154) °C. The melting point of PDP-6 in this work was similar to its reported value. The yield of synthesized compound was recorded as 80%. The purity of PDP-6 was confirmed by elemental analysis and thin layer chromatography [1]. The structure elucidation of PDP-6 was based on FT-IR spectra, ^{1}H NMR spectra, ^{13}C NMR spectra and elemental analysis. FT-IR spectra of PDP-6 are presented in Fig. S2. The characteristics FT-IR peaks of PDP-6 were appeared at 3220 cm^{-1} (N—H), 3100 cm^{-1} (C—H), 1680 cm^{-1} (C═O), 1610 cm^{-1} (C═N) and 1510 cm^{-1} (C═C). ^{1}H NMR spectra of PDP-6 are presented in Fig. S3. ^{1}H NMR spectra of PDP-6 were identified on the basis of "multiplicity, chemical shifts and coupling constant". The characteristics ^{1}H NMR peaks of compound were observed at 2.44, 2.89, 7.40, 7.74 and 10.99 ppm. ^{13}C NMR spectra of PDP-6 are presented in Fig. S4. The characteristics ^{13}C NMR peaks of compound were observed at 167.02, 149.34, 135.90, 129.19, 128.42, 125.56, 125.31, 25.94 and 21.85 ppm. The results of elemental analysis of PDP-6 are presented in Table S2. The mass fractions (%) in terms of C, H and N were very close with their calculated mass fractions. Analytical and spectral characterization of the compound PDP-6 was in good agreement with the composition of the synthesized compound.

2.3. Analysis of compound PDP-6

The quantification of PDP-6 was carried out with the help of "reversed phase high performance liquid chromatography (RP-HPLC)" equipped with ultra-violet (UV) detector at 310 nm. All analysis was performed at 298.2 K using "HPLC system (Waters, USA)". The analysis of PDP-6 was performed using "Nucleodur (150 × 4.6 mm) RP C_8 column with 5 μm particle size". The binary mixture of ethanol and methanol (1:1%) was used as the mobile phase. The elution of PDP-6 was carried out at a flow rate of 1.0 mL min^{-1} at 310 nm. The volume of injection was 10 μL. The calibration curve was constructed between the concentration of PDP-6 and measured peak area. The calibration curve of PDP-6 was recorded linear in the concentration range of (1 − 100) μg g^{-1} with coefficient of determination (R^2) value of 0.9995. The equation of regression was recorded as $y = 22{,}058x + 3172.8$; in which x is the concentration of PDP-6 and y is the measured peak area of PDP-6.

2.4. Determination of PDP-6 solubility

The solubility of PDP-6 in eleven different neat solvents was determined by shake flask method reported by Higuchi and Connors [32]. The experiments were carried out at "$T = 293.2$ to 313.2 K" and "$p = 0.1$ MPa". The excess amount of PDP-6 was added in known quantities of each neat solvent in triplicates. The obtained samples were transferred to biological shaker (Julabo, PA) at 100 rpm for the period of 72 h. In order to optimize equilibrium time for PDP-6, preliminary solubility studies were performed at 24, 48, 72, 96 and 120 h and solubility of PDP-6 was measured at each time internal. It was observed that the change in the solubility of PDP-6 was negligible after 72 h. Therefore, 72 h was selected as an optimized equilibrium time for PDP-6. After 72 h, each sample was taken out from the biological shaker and allowed to settle PDP-6 particles for 24 h [33]. Centrifugation and filtration were avoided in this process because both processes could change the solubility data of PDP-6 at different temperatures. Moreover, all solid particles were settled completely after 24 h. Around 0.10 g of supernatants from each neat solvent were carefully withdrawn, diluted 100 times (dilution ratio was 1:100) with mobile phase (except in case of water, DMSO and Transcutol). No dilution was performed in case of water and supernatants were diluted 10,000 times (dilution ratio was 1:10,000) in case of DMSO and Transcutol. The samples were subjected for the analysis of

PDP-6 content by HPLC-UV method at 310 nm. The experimental mole fraction solubilities of PDP-6 (x_e) were calculated using Eq. (1) [28]:

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

In which, m_1 and m_2 are the masses of PDP-6 and respective neat solvent, respectively. M_1 and M_2 are the molar masses of PDP-6 and respective neat solvent, respectively.

The x_e value of PDP-6 was also verified by the gravimetric method [34]. The solubility of PDP-6 in Transcutol and DMSO at $T = 298.2$ K was measured by gravimetric method. Drug-solvent mixtures were prepared as stated above for shake flask method. Each drug-solvent mixture was heated at $T = 298.2$ K with continuous stirring till equilibrium reached. The equilibrium time for gravimetric method was optimized by the determination of the concentration of PDP-6 at 2, 4, 6, 8 and 12 h. After 6 h, the change in the concentration of PDP-6 was recorded as negligible. Hence, 6 h was selected as an equilibrium time for this method. After 6 h of stirring, the solution was kept at $T = 298.2$ K for some time in order to get settling of particles. The supernatant from each sample was taken, filtered and the known amount of each sample was transferred in pre weighted vial (m_0). This vial was reweighted in order to determine the mass of each sample (m_3). Each vial was then kept in an oven at $T = 323.2$ K for the evaporation of the solvent. After the complete dryness of the mass of the vial, the vial was reweighed (m_4). When the constant value of the mass was obtained, the final mass for each sample was determined (m_4–m_0). All the weights were determined using an electronic balance (Mettler Toledo AM50, Switzerland) with an uncertainty of ±0.0001 g. Each measurement was carried out in triplicates manner. The x_e value of PDP-6 was determined using Eq. (2) [34,35]:

$$x_e = \frac{m_4 - m_0/M_1}{m_4 - m_0/M_1 + m_3 - m_4/M_2} \quad (2)$$

3. Results and discussion

3.1. Experimental solubility data of PDP-6

Experimentally determined x_e values of PDP-6 in eleven different neat solvents at "$T = 293.2$ K to 313.2 K" and "$p = 0.1$ MPa" are presented in Table 1.

In literature, we reported the solubility data of PDP-6 in different "Transcutol + water" cosolvent mixtures at "$T = 293.2$ K to 313.2 K" and "$p = 0.1$ MPa" [31]. However, the solubilities of PDP-6 in other neat solvents have not been reported so far. The mole fraction solubility of PDP-6 in neat water at "$T = 298.2$ K" has been reported as 9.10×10^{-7} [31]. In this work, the mole fraction solubility of PDP-6 in neat water at "$T = 298.2$ K" was obtained as 9.18×10^{-7} which was very close to its reported value. The graphical comparison between literature and experimental solubility of PDP-6 in water at "$T = 293.2$ K to 313.2 K" is presented in Fig. 2 which showed excellent graphical correlation at all five temperatures investigated. The mole fraction solubility of PDP-6 in neat Transcutol at "$T = 298.2$ K" has been reported as 4.53×10^{-1} [31]. In this work, the mole fraction solubility of PDP-6 in neat Transcutol at "$T = 298.2$ K" was obtained as 4.51×10^{-1} which was also very close to its reported value. The graphical comparison between literature and experimental solubility of PDP-6 in Transcutol at "$T = 293.2$ K to 313.2 K" is presented in Fig. 3 which also showed excellent graphical correlation at all five temperatures investigated. Overall, these results indicated that solubility data of PDP-6 obtained in this work were in good agreement with literature.

From data presented in Table 1, it can be seen that the x_e values of PDP-6 were increasing with increase in temperature in each neat solvent evaluated. The x_e values of PDP-6 at "$T = 313.2$ K" were recorded highest in DMSO (6.77×10^{-1}) followed by Transcutol (5.24×10^{-1}), PEG-400 (8.47×10^{-2}), EA (1.45×10^{-2}), EG (1.09×10^{-2}), PG (1.03×10^{-2}), 2-butanol (7.78×10^{-3}), 1-butanol (7.68×10^{-3}), ethanol (6.96×10^{-3}), IPA (6.51×10^{-3}) and water (1.61×10^{-6}) and similar trend was also recorded at all five different temperatures investigated. It was observed that the x_e values of PDP-6 in DMSO, Transcutol and PEG-400 were significantly higher in comparison with its x_e values in other neat solvents including water. In general, the x_e values of PDP-6 were significantly higher in neat solvents with functional groups such as —OH, —SO_2— or O—C═O (DMSO, Transcutol, PEG-400, EA, EG, PG, 2-butanol, 1-butanol, ethanol and IPA) in comparison with water. This observation was probably due to the fact that PDP-6 is having some functional groups such as —NH and C═O which could have strong molecular interaction/solvation with neat solvents with functional groups of —OH, —SO_2— or O—C═O. The x_e values of PDP-6 in 1-butanol and 2-butanol were not significantly different at each temperature investigated. It was because of their similar molecular structures, molar masses and dielectric constants/polarities. The x_e values of PDP-6 in other alcoholic solvents such as PG and EG were also observed in similar magnitude because both of the neat solvents have two —OH groups with similar dielectric constants/polarities. The x_e values of PDP-6 in other neat solvents such as ethanol and IPA were also obtained in similar magnitude due to the presence of single —OH group in both neat solvents and their polarities are also similar. However, the x_e values of PDP-6 in "DMSO, Transcutol and PEG-400" were significantly higher in comparison with its x_e values in other neat solvents investigated. This observation was possible due to higher molar mass and lower polarities of DMSO, Transcutol and PEG-400 in comparison with other neat solvents including water [33]. Based on solubility data of current study, PDP-6 has been proposed as practically insoluble in water, sparingly soluble in ethanol, IPA, EG, PG, EA, 1-butanol and 2-butanol, soluble in PEG-400 and very soluble in DMSO and Transcutol [30,33]. The solubility

Table 1
Experimental mole fraction solubilities (x_e) of PDP-6 in different neat solvents (S) at "$T = 293.2$ K to 313.2 K and "$p = 0.1$ MPa"[a].

S	x_e				
	$T = 293.2$ K	$T = 298.2$ K	$T = 303.2$ K	$T = 308.2$ K	$T = 313.2$ K
Water	7.24×10^{-7}	9.18×10^{-7}	1.13×10^{-6}	1.37×10^{-6}	1.61×10^{-6}
Ethanol	4.07×10^{-3}	4.66×10^{-3}	5.29×10^{-3}	6.07×10^{-3}	6.96×10^{-3}
IPA	3.10×10^{-3}	3.78×10^{-3}	4.60×10^{-3}	5.55×10^{-3}	6.51×10^{-3}
EG	7.40×10^{-3}	8.36×10^{-3}	9.21×10^{-3}	1.01×10^{-2}	1.09×10^{-2}
(*RS*)-PG	6.54×10^{-3}	7.32×10^{-3}	8.46×10^{-3}	9.51×10^{-3}	1.03×10^{-2}
PEG-400	5.85×10^{-2}	6.46×10^{-2}	7.09×10^{-2}	7.80×10^{-2}	8.47×10^{-2}
Transcutol	4.23×10^{-1}	4.51×10^{-1}	4.76×10^{-1}	5.02×10^{-1}	5.24×10^{-1}
1-Butanol	4.74×10^{-3}	5.30×10^{-3}	6.01×10^{-3}	6.70×10^{-3}	7.68×10^{-3}
(*RS*)-2-Butanol	5.12×10^{-3}	5.55×10^{-3}	6.18×10^{-3}	6.87×10^{-3}	7.78×10^{-3}
EA	8.78×10^{-3}	9.94×10^{-3}	1.11×10^{-2}	1.28×10^{-2}	1.45×10^{-2}
DMSO	6.37×10^{-1}	6.47×10^{-1}	6.58×10^{-1}	6.68×10^{-1}	6.77×10^{-1}

[a] The standard uncertainties u are $u(T) = 0.08$ K, $u(p) = 0.003$ MPa and $u_r(x_e) = 1.45\%$.

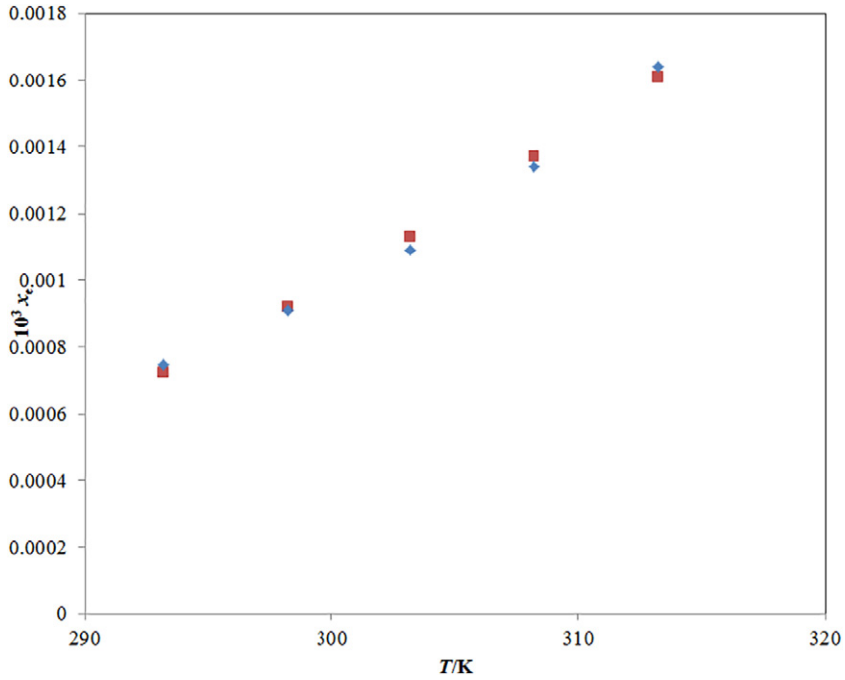

Fig. 2. Comparison of experimental solubilities of PDP-6 in water with literature values at five different temperatures; the symbol ■ represents the experimental solubilities of pure PDP-6 and the symbol ◆ represents the solubility values of PDP-6 taken from reference [31].

data of PDP-6 could be useful in "recrystallization, purification, pre-formulation studies and formulation development" of PDP-6.

In order to verify the solubility data of PDP-6 measured by shake flask method, the x_e values of PDP-6 in Transcutol and DMSO at $T = 298.2$ K were also determined by gravimetric method. Comparative x_e values of PDP-6 in Transcutol and DMSO $T = 298.2$ K are listed in Table 2. The x_e values of PDP-6 in both solvents were in similar magnitude which indicated the shake flask method used for the measurement of x_e values of PDP-6 in Transcutol, DMSO and other neat solvents was accurate and precise.

3.2. Hildebrand solubility parameter for PDP-6 and neat solvents

In the current study, Hildebrand solubility parameter (δ) for PDP-6 and neat solvents was determined by "Fedors group substitution method" with the help of Eq. (3) [36]:

$$\delta = \left[\left(\sum U^0\right)/\left(\sum V\right)\right]^{1/2} \quad (3)$$

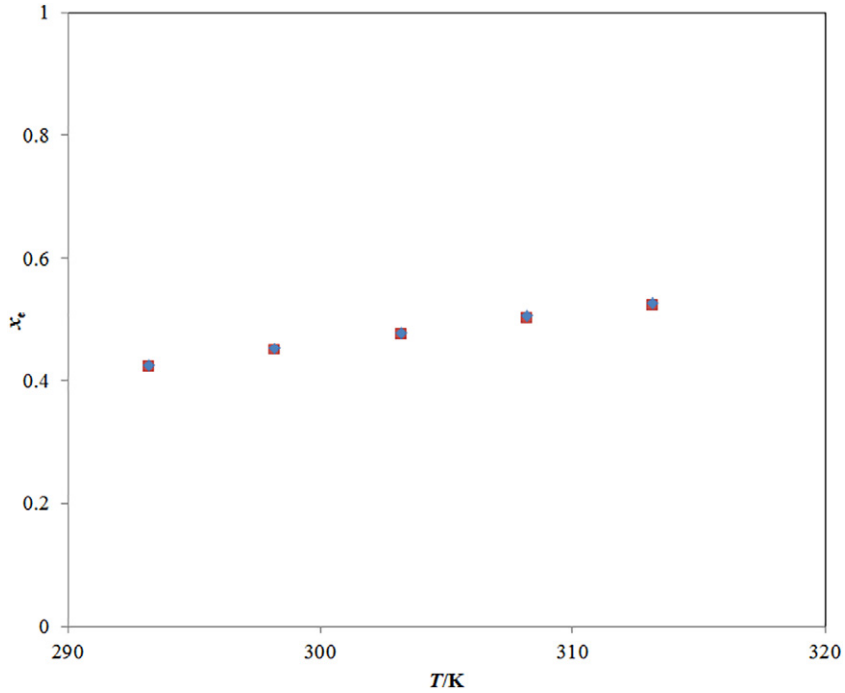

Fig. 3. Comparison of experimental solubilities of PDP-6 in Transcutol with literature values at five different temperatures; the symbol ■ represents the experimental solubilities of PDP-6 and the symbol ◆ represents the solubility values of PDP-6 taken from reference [31].

Table 2
The x_e values of PDP-6 in Transcutol and DMSO measured by gravimetric and shake flask methods at $T = 298.2$ K.

Solvent	Gravimetric method	Shake flask method
Transcutol	4.47×10^{-1}	4.51×10^{-1}
DMSO	6.44×10^{-1}	6.47×10^{-1}

In which, U^0 and V are the energy of vaporization and molar volume, respectively. With the help of the values of U^0 and V, δ values for various neat solvents have been reported in literature [37–39]. The δ values of neat solvents investigated in this work are also reported in literature [33]. However, δ value of PDP-6 has not been reported previously in literature. Therefore, it was determined in this work. The calculation of δ value for PDP-6 using "Fedors group substitution method" is listed in Table 3. The calculated δ value for PDP-6 and reported δ values for different neat solvents are presented in Table S3.

The δ value for PDP-6 was calculated as 25.71 $MPa^{1/2}$. The calculated δ value of PDP-6 indicated that it had lower polarity. The x_e values of PDP-6 were higher in neat solvents with lower or medium δ values such as "DMSO, Transcutol, PEG-400, EA, EG, PG, 2-butanol, 1-butanol, ethanol and IPA" because PDP-6 had lower polarity. However, the x_e value of PDP-6 was lowest in water due to highest δ value of water.

3.3. Correlation of x_e values of PDP-6

The x_e values of PDP-6 determined in the current study were correlated with two mathematical models including "Apelblat and van't Hoff models" [33,40,41]. The "Apelblat solubility (x^{Apl})" of compound PDP-6 was calculated and correlated using Eq. (4) [40,41]:

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

In which, the parameters "*A, B* and *C*" are the model parameters of "Apelblat model" presented in Eq. (4). Apelblat parameters were determined using "nonlinear multivariate regression analysis" of x_e values of PDP-6 listed in Table 1 using MS Excel program 2010 [33]. The correlation of x_e values of PDP-6 with its x^{Apl} values was carried out in terms of the mean percent deviations (*MPD*) and R^2 values. The *MPD* values between x_e and x^{Apl} of PDP-6 were determined using Eq. (5) [42]:

$$MPD = \frac{100}{N} \sum \frac{(x^{Apl} - x_e)}{x^{Apl}} \tag{5}$$

In which, N is the number of experimental data points.

The graphical correlation and curve fitting between natural logarithmic x_e ($\ln x_e$) and $\ln x^{Apl}$ values of PDP-6 in each neat solvent as a function of $1/T$ is presented in Fig. 4. The results presented in Fig. 4 indicated excellent correlation/curve fitting between $\ln x_e$ and $\ln x^{Apl}$ values of PDP-6. The parameters of "Apelblat correlation" are presented in Table 4. The *MPD* values in eleven different neat solvents were recorded as (1.17 to 5.27) %. The *MPD* value was recorded highest in 2-butanol (5.27%) followed by "1-butanol, water, EG, PG, EA, IPA, ethanol, DMSO, PEG-400 and Transcutol". However, the R^2 values for PDP-6 were recorded as 0.9957 to 0.9998. These results indicated good correlation of x_e values of PDP-6 with "Apelblat model".

The "van't Hoff model solubility ($x^{van't}$)" of PDP-6 was calculated using Eq. (6) [33]:

$$\ln x^{van't} = a + \frac{b}{T} \tag{6}$$

In which, the parameters "*a* and *b*" are the model parameters of "van't Hoff model" presented in Eq. (6). The values of "*a* and *b*" were determined by plotting $\ln x_e$ values of PDP-6 as a function of $1/T$.

The correlation of x_e values of PDP-6 with its $x^{van't}$ values was performed in terms of *MPD* and R^2 values.

The graphical correlation and curve fitting between $\ln x_e$ and $\ln x^{van't}$ values of PDP-6 in each neat solvent against $1/T$ was found to be similar as discussed for Apelblat correlation (figure not shown). The parameters of van't Hoff correlation are presented in Table 5.

The *MPD* values in eleven different neat solvents were recorded as (0.00 to 0.80) %. The *MPD* value was recorded highest in EA (0.80%) followed by "DMSO, water, 1-butanol, IPA, Transcutol, PG, PEG-400, EG, ethanol and 2-butanol". However, the R^2 values for PDP-6 were recorded as 0.9922 to 0.9998. These results again indicated good correlation of x_e values of PDP-6 with "van't Hoff model".

3.4. Apparent thermodynamic analysis

The dissolution thermodynamics of PDP-6 in eleven different neat solvents was studied by "apparent thermodynamic analysis" of solubilities of PDP-6. Two different apparent thermodynamic parameters including "apparent standard enthalpy ($\Delta_{sol}H^0$)" and "apparent standard Gibbs energy ($\Delta_{sol}G^0$)" were determined by "apparent thermodynamic analysis". The "$\Delta_{sol}H^0$ values" for PDP-6 dissolution in each neat solvent were determined at "mean harmonic temperature (T_{hm})" of 303 K with the help of "van't Hoff analysis" using Eq. (7) [43,44]:

$$\left(\frac{\partial \ln x_e}{\partial \left({}^{1}/_{T} - {}^{1}/_{T_{hm}} \right)} \right)_P = - \frac{\Delta_{sol}H^0}{R} \tag{7}$$

With the help of Eq. (7), the "$\Delta_{sol}H^0$ values" were determined by plotting $\ln x_e$ values of PDP-6 against ${}^{1}/_{T} - {}^{1}/_{T_{hm}}$. The "van't Hoff plots" in each neat solvent were recorded as linear with R^2 values of 0.9922 to 0.9998.

The "$\Delta_{sol}G^0$ values" for PDP-6 dissolution were also measured at T_{hm} of 303 K with the help of Krug et al. analysis using Eq. (8) [45]:

$$\Delta_{sol}G^0 = -RT_{hm} \times intercept \tag{8}$$

In which, the values of intercept for each neat solvent were determined from "van't Hoff plot" plotted between $\ln x_e$ values of PDP-6 and ${}^{1}/_{T} - {}^{1}/_{T_{hm}}$.

The results of "apparent thermodynamic analysis" for PDP-6 dissolution in eleven different neat solvents are presented in Table 6.

It was observed that the "$\Delta_{sol}H^0$ values" for PDP-6 dissolution in eleven different neat solvents were obtained as positive values in the range of (2.36 to 30.55) kJ mol^{-1}. The "$\Delta_{sol}H^0$ value" for PDP-6 dissolution was obtained highest in water (30.55 kJ mol^{-1}) followed by IPA (28.55 kJ mol^{-1}), ethanol (20.37 kJ mol^{-1}), EA (19.32 kJ mol^{-1}), 1-butanol (18.31 kJ mol^{-1}), PG (18.08 kJ mol^{-1}), 2-butanol (15.99 kJ mol^{-1}), EG (15.07 kJ mol^{-1}), PEG-400 (14.17 kJ mol^{-1}),

Table 3
Determination of internal energy (ΔU^0), molar volume (V) and Hildebrand solubility parameters (δ) of PDP-6 at $T = 298.2$ K using Fedors method [35].

Atom or group	Group number	ΔU^0/kJ·mol^{-1}	V/cm^3·mol^{-1}
—CH_2—	2	$2 \times 4.94 = 9.88$	$2 \times 16.1 = 32.2$
>C=	1	$1 \times 4.31 = 4.31$	$5.5 \times -1.0 = -5.5$
>C=O	1	$1 \times 17.4 = 17.4$	$1 \times 10.8 = 10.8$
=N—	1	$1 \times 11.75 = 11.75$	$1 \times 5 = 5$
—NH—	1	$1 \times 12.6 = 12.6$	$1 \times 4.5 = 4.5$
Phenyl ring	1	$1 \times 31.9 = 31.9$	$1 \times 71.4 = 71.4$
Ring closure, 5 or more atoms	1	$1 \times 1.05 = 1.05$	$1 \times 16.0 = 16.0$
Total		$\sum \Delta U^0 = 88.89$	$\sum V = 134.4$
		$\delta = (88{,}890/134.4)^{1/2} = 25.71$ $MPa^{1/2}$	

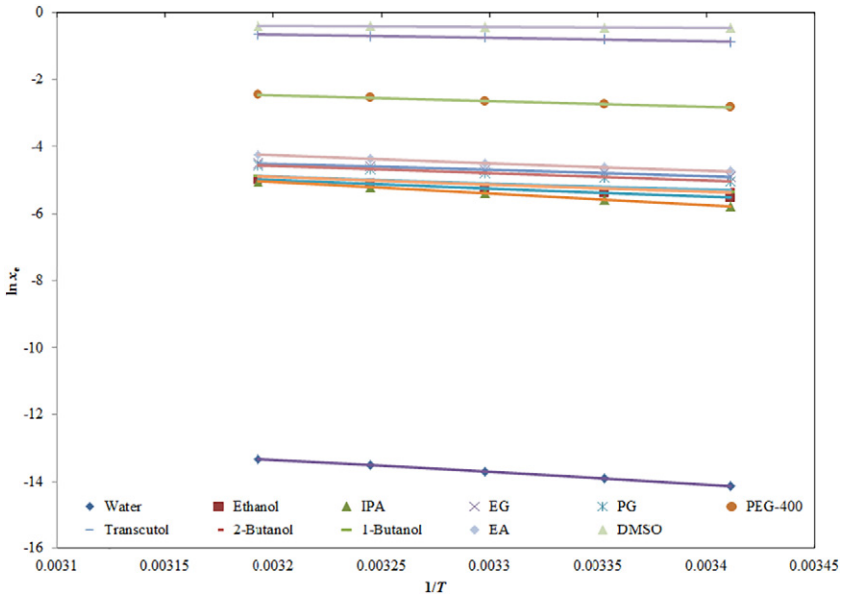

Fig. 4. Correlation of experimental natural logarithmic solubilities (ln x_e) of PDP-6 with Apelblat model in eleven different neat solvents as a function of 1/*T*; symbols represent the experimental ln x_e values of PDP-6 and the solid lines represent the ln x^{Apl} values calculated by Apelblat model.

Transcutol (8.17 kJ mol^{-1}) and DMSO (2.36 kJ mol^{-1}). Generally, the "$\Delta_{sol}H^0$ values" for PDP-6 dissolution were obtained lower for neat solvents with higher x_e values such as DMSO, Transcutol and PEG-400. However, the "$\Delta_{sol}H^0$ values" for PDP-6 dissolution were obtained higher for neat solvents with lower x_e values such as water, IPA, ethanol, EG, PG, 1-butanol and 2-butanol.

The "$\Delta_{sol}G^0$ values" for PDP-6 dissolution in eleven different neat solvents were also obtained as positive values in the range of (1.05 to 34.55) kJ mol^{-1}. The "$\Delta_{sol}G^0$ value" for PDP-6 dissolution was also obtained highest in water (34.55 kJ mol^{-1}) followed by IPA (13.58 kJ mol^{-1}), ethanol (13.19 kJ mol^{-1}), 1-butanol (12.88 kJ mol^{-1}), 2-butanol (12.79 kJ mol^{-1}), PG (12.06 kJ mol^{-1}), EG (11.82 kJ mol^{-1}), EA (11.29 kJ mol^{-1}), PEG-400 (6.67 kJ mol^{-1}), Transcutol (1.88 kJ mol^{-1}) and DMSO (1.05 kJ mol^{-1}) and the results of "$\Delta_{sol}G^0$ values" for PDP-6 dissolution were in good agreement with experimental solubilities of PDP-6 in eleven different neat solvents. The positive values of "$\Delta_{sol}H^0$ and $\Delta_{sol}G^0$" in all neat solvents indicated an endothermic dissolution of PDP-6 in all neat solvents studied. The lower values of "$\Delta_{sol}H^0$ and $\Delta_{sol}G^0$" in DMSO, Transcutol and PEG-400 indicated that relatively lower energies are required for the solubilization of PDP-6 in DMSO, Transcutol and PEG-400 in comparison with other neat solvents studied. The positive values of $\Delta_{sol}H^0$ in all eleven different neat solvents were possible due to weak electrostatic interactions between PDP-6-solvent molecules in comparison with strong electrostatic interactions between PDP-6-PDP-6 and solvent-solvent molecules.

4. Conclusion

In the current study, the mole fraction solubilities of a novel antihypertensive drug PDP-6 in eleven different neat solvents were determined at "T = 293.2 K to 313.2 K" and "p = 0.1 MPa". The experimental solubilities of PDP-6 were found to be increasing with increase in temperature in all eleven different neat solvents studied. Experimental solubilities of PDP-6 were correlated well with "van't Hoff and Apelblat models" with MPD < 6.0%. The mole fraction solubilities of PDP-6 at "T = 313.2 K" were recorded highest in DMSO followed by Transcutol, PEG-400, EA, EG, PG, 2-butanol, 1-butanol, ethanol, IPA and water and similar trend was also recorded at all five different temperatures investigated. The results of "apparent thermodynamic analysis" indicated an "endothermic dissolution" of PDP-6 in all neat solvents studied.

Conflict of interest

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

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Table 4
Apelblat parameters (*A*, *B* and *C*), R^2 and *MPD* (%) values for PDP-6 in different neat solvents (*S*).

S	*A*	*B*	*C*	R^2	*MPD* (%)
Water	291.94	−16,930.90	−43.71	0.9998	4.13
Ethanol	−116.58	2939.82	17.78	0.9998	2.04
(*RS*)-PG	64.70	−4990.07	−9.28	0.9957	2.56
PEG-400	1.31	−1630.83	0.24	0.9997	1.17
Transcutol	67.95	−3939.41	−9.74	0.9995	1.08
EG	159.83	−8972.45	−23.61	0.9994	3.87
IPA	70.98	−6373.79	−9.68	0.9994	2.49
1-Butanol	−154.65	4875.73	23.35	0.9990	5.03
(*RS*)-2-Butanol	−299.74	11,665.47	44.83	0.9994	5.27
EA	−171.46	5558.70	26.01	0.9993	2.54
DMSO	−2.87	−131.52	0.50	0.9992	1.20

Table 5
van't Hoff model parameters (*a* and *b*), R^2 and *MPD* (%) values for PDP-6 in different neat solvents (*S*).

S	*a*	*b*	R^2	*MPD* (%)
Water	−1.58	−3675.90	0.9976	0.59
Ethanol	2.85	−2451.20	0.9992	0.09
(*RS*)-PG	2.39	−2175.50	0.9957	0.17
PEG-400	2.97	−1705.00	0.9998	0.13
Transcutol	2.49	−983.50	0.9980	0.18
EG	1.28	−1813.10	0.9968	0.12
IPA	5.94	−3435.40	0.9994	0.42
1-Butanol	2.15	−2203.00	0.9976	0.49
(*RS*)-2-Butanol	1.27	−1924.20	0.9922	0.00
EA	3.18	−2325.40	0.9978	0.80
DMSO	0.51	−284.53	0.9993	0.78

Table 6
Apparent thermodynamic parameters ($\Delta_{sol}H^0$ and $\Delta_{sol}G^0$) and R^2 values for PDP-6 dissolution in different neat solvents (*S*)[x].

S	$\Delta_{sol}H^0$/kJ mol^{-1}	$\Delta_{sol}G^0$/kJ mol^{-1}	R^2
Water	30.55	34.55	0.9976
Ethanol	20.37	13.19	0.9992
(*RS*)-PG	18.08	12.06	0.9957
PEG-400	14.17	6.67	0.9998
Transcutol	8.17	1.88	0.9980
EG	15.07	11.82	0.9968
IPA	28.55	13.58	0.9994
1-Butanol	18.31	12.88	0.9975
(*RS*)-2-Butanol	15.99	12.79	0.9922
EA	19.32	11.29	0.9978
DMSO	2.36	1.05	0.9993

[x] The relative uncertainties are $u(\Delta_{sol}H^0) = 0.46$ kJ mol^{-1}, $u(\Delta_{sol}G^0) = 0.73$ kJ mol^{-1}.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.molliq.2017.05.032.

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