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Solubility and thermodynamic parameters of apigenin in different neat solvents at different temperatures

Faiyaz Shakeel [a,b,*], Sultan Alshehri [a], Mohamed A. Ibrahim [a], Ehab M. Elzayat [a], Mohammad A. Altamimi [a], Kazi Mohsin [a], Fars K. Alanazi [a], Ibrahim A. Alsarra [a]

[a] Kayyali Chair for Pharmaceutical Industries, Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia
[b] Center of Excellence in Biotechnology Research (CEBR), King Saud University, P.O. Box 2460, Riyadh 11451, Saudi Arabia

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ABSTRACT

In the current study, the solubility of a poorly water-soluble bioflavonoid apigenin in twelve different neat solvents including "water, methanol, ethanol, isopropanol (IPA), ethylene glycol (EG), propylene glycol (PG), 1-butanol, 2-butanol, ethyl acetate (EA), dimethyl sulfoxide (DMSO), polyethylene glycol-400 (PEG-400) and Transcutol®" was measured at temperatures "$T = 298.2$ K to 318.2 K" and pressure "$p = 0.1$ MPa". The experimental solubilities of apigenin were measured by a static equilibrium method using ultra performance liquid chromatography at 336 nm. The measured solubilities of apigenin in mole fraction were correlated with "van't Hoff and Apelblat models". Good correlation was observed with both models with root mean square deviation values of <3.0% in all solvents evaluated. The solid state characterization of apigenin was performed using differential scanning calorimetry and thermal gravimetric analysis. The solubilities of apigenin in mole fraction were obtained highest in PEG-400 (4.27×10^{-1}) followed by DMSO (4.18×10^{-1}), Transcutol (3.83×10^{-1}), PG (1.50×10^{-2}), EG (8.22×10^{-3}), 1-butanol (9.18×10^{-4}), 2-butanol (8.90×10^{-4}), IPA (6.29×10^{-4}), ethanol (4.86×10^{-4}), EA (4.46×10^{-4}), methanol (2.96×10^{-4}) and water (3.08×10^{-6}) at "$T = 318.2$ K" and similar trend was recorded at each temperature evaluated. The solute-solvent interaction was described based on the polarity and activity coefficient. Apparent standard thermodynamic parameters of apigenin in twelve different neat solvents were determined using "apparent thermodynamic analysis" and results showed an "endothermic and entropy-driven dissolution" of apigenin in each solvent evaluated. Based on these results, PEG-400, DMSO and Transcutol were selected as the best solvents and water and methanol were selected as the anti-solvents for apigenin.

1. Introduction

Apigenin (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) is available commercially as a light yellow crystalline powder [1,2]. It is a bioflavonoid which is commonly present in most of the fruits and vegetables [3,4]. It has been found a potential bioactive compound against variety of diseases and investigated as a potent antioxidant [5], anticancer [6–12] and anti-inflammatory [13] bioactive compound. It has been reported as practically insoluble/poorly soluble in water [1,14]. Due to poor water solubility, its oral bioavailability is very poor [14]. It is commercially available in capsule dosage form which is marketed under the name of Swanson® for dietary supplement. The solubility data of natural bioactive compounds are poorly reported in literature. The solubility data of these compounds in the aqueous and organic solvents are important in their "extraction/separation, purification, recrystallization, drug discovery and formulation development" [15–20]. Hence, it is of great importance to measure the solubility of apigenin in the solvents which could be useful for its pharmaceutical and industrial applications. Different formulation approaches including cyclodextrin complexation [21], cyclodextrin-modified microemulsion [22], liposomes [23], ethosomes [24], phytosomes [25], transferosmes [26], nanocrystal [14,27], nanocapsule [28], polymeric micelles [29], nanoparticles [30] and self-microemulsifying drug delivery system [31] of apigenin have been investigated in literature for the enhancement of its solubility/dissolution rate, drug delivery potential, bioactivity and *in vivo* bioavailability. The solubility data of solid apigenin in seven different neat solvents including water, methanol, ethanol, 1-propanol, 1-butanol, acetone and ethyl acetate (EA) at temperature "$T = 288.2$ K to 328.2 K" and pressure "$p =$

* Corresponding author at: Kayyali Chair for Pharmaceutical Industries, Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.
E-mail address: faiyazs@fastmail.fm (F. Shakeel).

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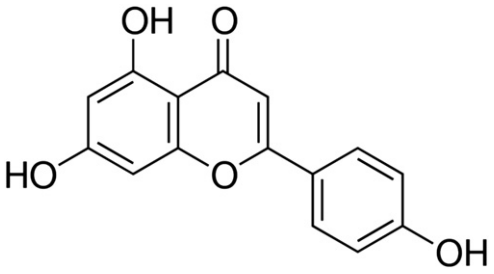

Fig. 1. Molecular structure of apigenin (molar mass: 270.24 g mol^{-1}).

0.1 MPa" are available in literature [1]. The solubility data of solid apigenin in various (ethanol + water) cosolvent mixtures at "T = 273.2 K to 323.2 K" and "p = 0.1 MPa" have also been reported in literature [32]. However, the solubility data of solid apigenin in neat solvents including "isopropyl alcohol (IPA), ethylene glycol (EG), propylene glycol (PG), polyethylene glycol-400 (PEG-400), 2-butanol, Transcutol® and dimethyl sulfoxide (DMSO)" have not been reported in literature. Therefore, in this work, the solubility of solid apigenin in twelve different neat solvents including "water, methanol, ethanol, Transcutol, PEG-400, PG, EG, IPA, 1-butanol, 2-butanol, EA and DMSO" were determined and correlated at "T = 298.2 K to 318.2 K" and "p = 0.1 MPa". "Apparent thermodynamic analysis" on measured solubility data of solid apigenin was also performed by "van't Hoff and Krug et al. analysis" in order to investigate the dissolution behavior of solid apigenin. Activity coefficients of solid apigenin were also determined for the evaluation of molecular interactions between apigenin and solvent molecules. The solubility data of solid apigenin obtained in this work would be useful in various industrial processes such as "extraction/separation, purification, recrystallization, drug discovery and formulation development" of apigenin.

2. Experimental

2.1. Materials

Apigenin was obtained from "Beijing Mesochem Technology Co. Pvt. Ltd. (Beijing, China)". Transcutol® [IUPAC name: 2-(2-ethoxyethoxy) ethanol] was procured from "Gattefosse (Lyon, France)". Methyl alcohol (IUPAC name: methanol), ethyl alcohol (IUPAC name: ethanol), IPA (IUPAC name: isopropanol), 1-butyl alcohol (IUPAC name: 1-butanol) and 2-butyl alcohol (IUPAC name: 2-butanol) were obtained from "Sigma Aldrich (St. Louis, MO)". EG (IUPAC name: 1,2-ethanediol), PG (IUPAC name: 1,2-propanediol), PEG-400 (IUPAC name: polyethylene glycol-400), EA (IUPAC name: ethyl ethanoate) and DMSO (IUPAC name: dimethyl sulfoxide) were obtained from "E-Merck (Darmstadt, Germany)". Water was collected from "Milli-Q water purification unit". The detailed information about these materials is furnished in supplementary Table 1 (Table S1).

2.2. UPLC analysis of apigenin

"Waters Acquity H-class ultra-performance liquid chromatography (UPLC)" system coupled with a Waters diode-array-ultra-violet detector (DAD-UV) by Aqcuity "UPLC (Waters, MA)" was applied for the analysis of apigenin. The chromatographic system was composed of quaternary solvent manager, sample manager (Aqcuity, UPLC Waters) with injection capacity of 10 μL and a column heater. The separation of apigenin was carried out on "Acquity UPLC BEH™ C_{18} column (2.1 × 50 mm, 1.7 μm, Waters, USA)" maintained at T = 313.2 K. The mobile phase was composed of 72:28% v/v ratio of 0.05 M ammonium formate buffer and acetonitrile (pH was maintained at 2.3 with orthophosphoric acid) which was pumped at an isocratic flow rate of 0.3 mL min^{-1}. The injection volume was set at 1.0 μL and the column oven temperature was maintained at T = 313.2 ± 2 K. The analysis was performed at 336 nm. The "EMPOWER software" was used for data acquisition and processing. The calibration curve was plotted between the concentration of apigenin and measured UPLC response. The calibration curve of apigenin was obtained linear in the concentration range of (0.5 to 25.0) μg g^{-1} with coefficient of determination (R^2) value of 0.9999. The regressed equation was obtained as $y = 252.61 \times -28.67$; in which y is the measured UPLC peak area of apigenin and x is the concentration of apigenin. The propose UPLC method was validated well in terms of "linearity, accuracy, precision, robustness, sensitivity, reproducibility and specificity".

Table 1
Measured solubilities (x_e) of apigenin as mole fraction in different neat solvents (S) at "T = 298.2 K to 318.2 K" and "p = 0.1 MPa"[a].

S	x_e				
	T = 298.2 K	T = 303.2 K	T = 308.2 K	T = 313.2 K	T = 318.2 K
Water	1.04×10^{-6}	1.33×10^{-6}	1.73×10^{-6}	2.27×10^{-6}	3.08×10^{-6}
Ethanol	2.50×10^{-4}	3.14×10^{-4}	3.58×10^{-4}	4.26×10^{-4}	4.86×10^{-4}
IPA	3.80×10^{-4}	4.27×10^{-4}	4.85×10^{-4}	5.51×10^{-4}	6.29×10^{-4}
EG	5.22×10^{-3}	5.73×10^{-3}	6.44×10^{-3}	7.32×10^{-3}	8.22×10^{-3}
PG	1.01×10^{-2}	1.12×10^{-2}	1.24×10^{-2}	1.37×10^{-2}	1.50×10^{-2}
PEG-400	3.97×10^{-1}	4.05×10^{-1}	4.13×10^{-1}	4.20×10^{-1}	4.27×10^{-1}
Transcutol	3.34×10^{-1}	3.45×10^{-1}	3.57×10^{-1}	3.71×10^{-1}	3.83×10^{-1}
1-Butanol	5.62×10^{-4}	6.30×10^{-4}	7.13×10^{-4}	8.08×10^{-4}	9.18×10^{-4}
2-Butanol	5.34×10^{-4}	6.03×10^{-4}	6.85×10^{-4}	7.81×10^{-4}	8.90×10^{-4}
EA	2.41×10^{-4}	2.84×10^{-4}	3.26×10^{-4}	3.94×10^{-4}	4.46×10^{-4}
DMSO	3.76×10^{-1}	3.84×10^{-1}	3.95×10^{-1}	4.07×10^{-1}	4.18×10^{-1}
Methanol	1.42×10^{-4}	1.72×10^{-4}	2.07×10^{-4}	2.49×10^{-4}	2.96×10^{-4}
x^{idl}	8.03×10^{-4}	9.38×10^{-4}	9.98×10^{-4}	1.09×10^{-3}	1.27×10^{-3}

[a] The standard uncertainties u are $u(T)$ = 0.12 K, $u(p)$ = 0.003 MPa and $u_r(x_e)$ = 1.48%.

2.3. Solid state characterization of apigenin by thermal analysis

The solid state characterization and possibility of polymorphic states of apigenin was evaluated by thermal analysis using "Differential Scanning Calorimetry (DSC)" and "Thermogravimetric Analysis (TGA)" techniques. DSC analysis of solid apigenin was performed using "DSC-8000 Instrument (Perkin Elmer, USA)" which was equipped with chiller (T = 253.2 K) and autosampler. The calibration of DSC apparatus was performed using pure indium at T = 283.2 K to 773.2 K. In order to perform DSC experiments, a mass of around 3.8 mg was accurately weighed and transferred to an aluminium pan which was hermetically sealed. DSC thermogram of pure apigenin was recorded under a nitrogen purge of 20 mL min^{-1} at a heating rate of 10.0 K min^{-1} with the temperature range from 303.2 K to 673.2 K.

TGA analysis of pure apigenin was carried out using "Pyris 1 TGA (Perkin Elmer, USA)" apparatus equipped with autosampler. TGA traces were also recorded at a heating rate of 10.0 K min^{-1} under a nitrogen purge of 20 mL min^{-1}. The temperature range was set from 313.2 K to 673.2 K. The sample of solid apigenin with an accurate mass of 2.273 mg was analyzed using platinum pan. The mass loss was calculated based on the original mass of sample.

2.4. Measurement of apigenin solubility

The solubility of apigenin in twelve different neat solvents including "water, methanol, ethanol, IPA, EG, PG, 1-butanol, 2-butanol, EA, DMSO, PEG-400 and Transcutol" was measured by static equilibrium method using UPLC/UV method described in above section [33]. Static equilibrium method is one of the commonly employed methods to achieve solid liquid equilibrium (SLE) of solutes [18,19,33,34]. Therefore, this method was used in this work. The solubility of apigenin in each solvent was measured at "T = 298.2 K to 318.2 K" and "p = 0.1 MPa". The excess amount of apigenin was added in known amounts of each neat solvent in triplicates manner. Each apigenin-solvent mixture was vortexed for about 5 min in order to obtain the concentrated suspensions of

apigenin. Each apigenin-solvent mixture was then transferred to the "OLS 200 Grant Scientific Biological Shaker (Grant Scientific, Cambridge, UK)" at 100 rpm for 72 h. The equilibrium time of 72 h was previously optimized in preliminary studies. After 72 h, each apigenin-solvent mixture was taken from the shaker and allowed to settle apigenin solid particles for overnight [20]. After overnight settling of apigenin solid particles, the supernatants were taken, diluted with mobile phase (wherever applicable) and subjected for the quantification of apigenin content by the proposed UPLC method at 336 described in above section. The experimental solubilities of apigenin (x_e) in mole fraction were calculated using Eq. (1) [35,36]:

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

In which, m_1 and m_2 represent the masses of apigenin and respective neat solvent (g), respectively. M_1 and M_2 represent the molar masses of apigenin and respective neat solvent (g mol^{-1}), respectively.

3. Results and discussion

3.1. Solid state characterization of apigenin by DSC and TGA

The solid state characterization and possibility of polymorphic states of apigenin was evaluated using DSC and TGA techniques. The representative DSC and TGA spectra of pure apigenin are shown in Figs. 2 and 3, respectively. The DSC thermogram of apigenin presented a sharp crystalline peak at fusion temperature (T_{fus}) of 639.72 K with fusion enthalpy (ΔH_{fus}) of 49.66 kJ mol^{-1} as shown in Fig. 2. The T_{fus} of apigenin has been reported as 639.56 K [21]. In this work, it was obtained as 639.72 K which was very close to the literature value. These results indicated that apigenin does not exist in different polymorphic forms and existed in pure crystalline form [21].

TGA spectra of pure apigenin indicated the mass loss at around at T = 615.53 K as shown in Fig. 3. This mass loss of apigenin was recorded due to decomposition of apigenin at T = 615.53 K. The mass loss of apigenin due to decomposition was obtained as 1.872% (w/w).

TGA results also showed that apigenin does not exist in different polymorphic forms and exist in pure crystalline form [21].

3.2. Experimental solubilities of apigenin with possible literature comparison

The x_e values of solid apigenin measured by a static equilibrium method using UPLC/UV technique in twelve different neat solvents at "T = 298.2 K to 318.2 K" and "p = 0.1 MPa" are presented in Table 1. The solubilities of solid apigenin at "T = 288.2 K to 328.2 K" and "p = 0.1 MPa" in various neat solvents including "water, methanol, ethanol, 1-propanol, 1-butanol, acetone and EA" have been reported by Xiao et al. [1]. However, the solubilities of solid apigenin at various temperatures in other neat solvents including "EG, PG, PEG-400, IPA, 2-butanol, Transcutol and DMSO" have not been reported in literature. The mole fraction solubility of solid apigenin in water at "T = 298.2 K" was recorded as 1.03×10^{-6} by Xiao et al. [1]. The mole fraction solubility of solid apigenin in water at "T = 298.2 K" was recorded as 1.04×10^{-6} in this work. The mole fraction solubility of solid apigenin in organic solvents methanol, ethanol, 1-butanol and EA at "T = 298.2 K" have been reported as 1.48×10^{-4}, 2.95×10^{-4}, 5.68×10^{-4} and 2.39×10^{-4}, respectively [1]. The mole fraction solubility of solid apigenin in organic solvents methanol, ethanol, 1-butanol and EA at "T = 298.2 K" were obtained as 1.42×10^{-4}, 2.50×10^{-4}, 5.62×10^{-4} and 2.41×10^{-4}, respectively in this work. The mole fraction solubility of solid apigenin in all these five solvents including water, methanol, ethanol, 1-butanol and EA obtained in this work was similar to those reported by Xiao et al. The mole fraction solubility of solid apigenin in 1-propanol at "T = 298.2 K" was recorded as 4.01×10^{-4} by Xiao et al. [1]. The mole fraction solubility of solid apigenin in 1-propanol was not measured in this work but it was measured in IPA which has similar structure, molar mass and polarity as reported for 1-propanol. The mole fraction solubility of solid apigenin in IPA at "T = 298.2 K" was recorded as 3.80×10^{-4} in this work. This value of solid apigenin was very close

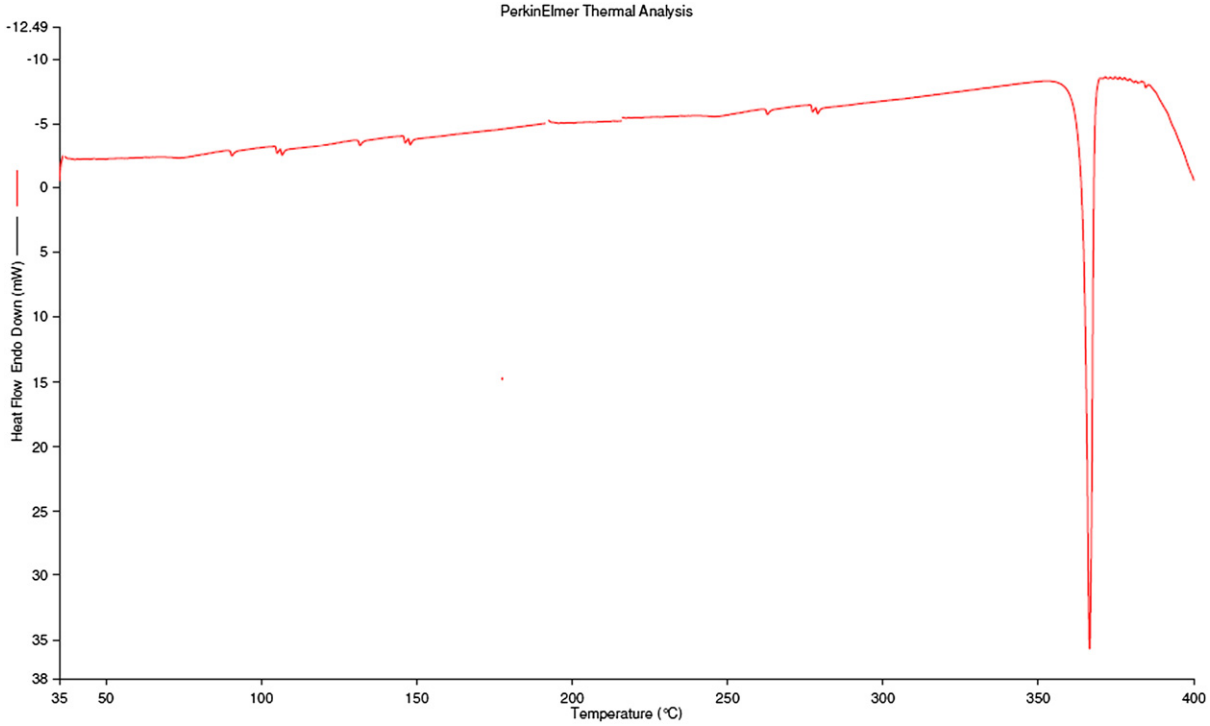

Fig. 2. DSC thermogram of solid apigenin.

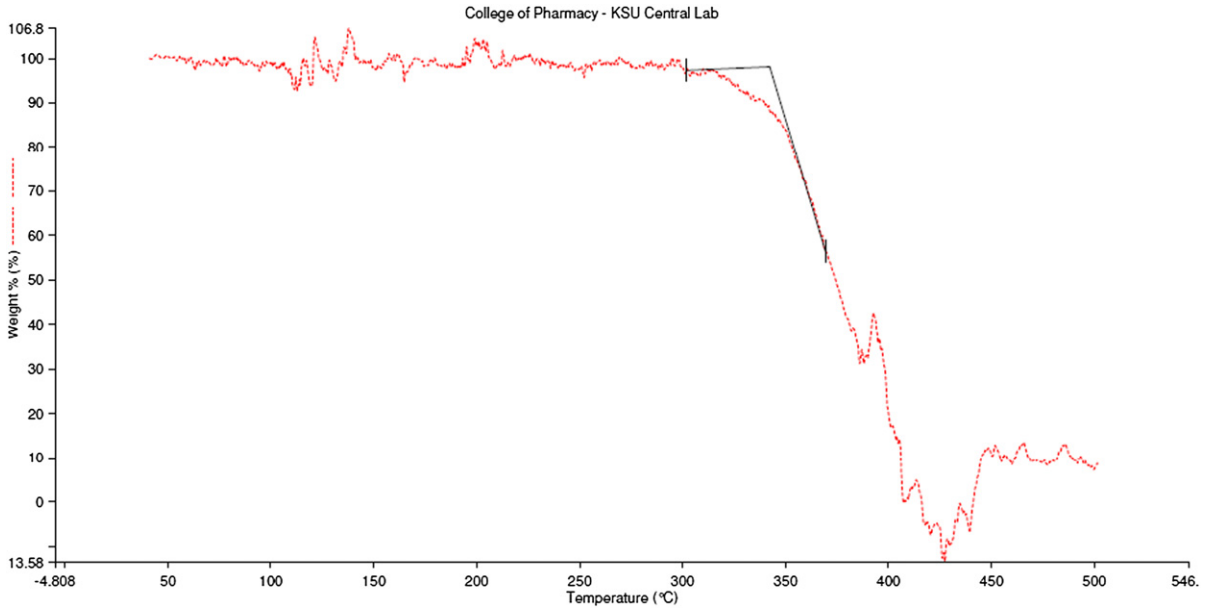

Fig. 3. TGA spectra of solid apigenin.

to reported value of 1-propanol. Overall, these results indicated good agreement of solubility data of this work with those reported in literature.

Generally, the x_e values of solid apigenin were observed as increasing with increase in temperature in all neat solvents evaluated as shown in Table 1. The x_e values of solid apigenin were obtained highest in PEG-400 (4.27×10^{-1}) followed by DMSO (4.18×10^{-1}), Transcutol (3.83×10^{-1}), PG (1.50×10^{-2}), EG (8.22×10^{-3}), 1-butanol (9.18×10^{-4}), 2-butanol (8.90×10^{-4}), IPA (6.29×10^{-4}), ethanol (4.86×10^{-4}), EA (4.46×10^{-4}), methanol (2.96×10^{-4}) and water (3.08×10^{-6}) at "$T = 318.2$ K" and similar trend was recorded at each temperature evaluated. The x_e values of solid apigenin were recorded in similar magnitude in PEG-400, Transcutol and DMSO. The x_e values of solid apigenin in PEG-400, Transcutol and DMSO were exceptionally higher than its x_e values in "water, methanol, ethanol, IPA, 1-butanol, 2-butanol, EG, PG and water". The highest x_e values of solid apigenin in PEG-400 were possibly due low dielectric constant/polarity, higher molar mass and low activity coefficients of PEG-400 as compared to high dielectric constant/polarity, low molar mass and high activity coefficients of water [37,38]. The x_e values of solid apigenin in different alcoholic organic solvents such as methanol, ethanol, IPA, 1-butanol and 2-butanol were also recorded in similar magnitude because the dielectric constants/polarities of all these alcoholic solvents are not significantly different [20]. The x_e values of solid apigenin in EG and PG were also obtained in similar magnitude due to their similar dielectric constants/polarities [36]. Based on these results, PEG-400, DMSO and Transcutol were selected as the best solvents and water and methanol were selected as the anti-solvents for apigenin.

3.3. Ideal solubilities and activity coefficients of apigenin

The ideal solubility of solid apigenin (x^{idl}) was calculated using Eq. (2) [39]:

$$\ln x^{idl} = \frac{-\Delta H_{fus}(T_{fus}-T)}{RT_{fus}T} + \left(\frac{\Delta C_p}{R}\right)\left[\frac{T_{fus}-T}{T} + \ln\left(\frac{T}{T_{fus}}\right)\right] \quad (2)$$

In which, all the symbols have already been defined in previous text except R and ΔC_p. Here, R is the universal gas constant and ΔC_p is the difference between the molar heat capacity of the crystalline solid form and that of the hypothetical super-cooled liquid form [39,40]. It has been generally assumed that ΔC_p may be set approximately as the entropy of fusion (ΔS_{fus}) [41,42]. The reasons for this hypothesis had already been discussed in the literature [43]. The value of ΔS_{fus} was calculated using Eq. (3) [39]:

$$\Delta S_{fus} = \frac{\Delta H_{fus}}{T_{fus}} \quad (3)$$

From DSC analysis, the value of T_{fus} for apigenin was obtained as 639.72 K and the value of ΔH_{fus} for apigenin was obtained as 49.66 kJ mol^{-1}. Using Eq. (3), the value of ΔS_{fus} or ΔC_p was obtained as 77.62 J mol^{-1} K^{-1}. For the calculation of x^{idl} values of solid apigenin, all the parameters of Eq. (2) are known now. Therefore, these values were calculated using Eq. (2) and resulting values are listed in Table 1.

The activity coefficients (γ) of solid apigenin in twelve different neat solvents were calculated using Eq. (4) [39,41]:

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

The calculated values of γ for solid apigenin in twelve different neat solvents at five different temperatures are presented in Table 2. From γ

Table 2
Activity coefficients (γ) of apigenin in different neat solvents (S) at "$T = 298.2$ K to 318.2 K".

S	γ				
	$T = 298.2$ K	$T = 303.2$ K	$T = 308.2$ K	$T = 313.2$ K	$T = 318.2$ K
Water	772.000	704.000	576.000	482.000	412.000
Ethanol	2.870	2.990	2.790	2.570	2.620
IPA	2.110	2.200	2.060	1.980	2.020
EG	0.150	0.160	0.150	0.140	0.150
PG	0.070	0.080	0.080	0.070	0.080
PEG-400	0.002	0.002	0.002	0.002	0.002
Transcutol	0.002	0.002	0.002	0.003	0.003
1-Butanol	1.430	1.490	1.400	1.350	1.380
2-Butanol	1.502	1.555	1.456	1.399	1.426
EA	3.330	3.300	3.060	2.770	2.840
DMSO	0.002	0.002	0.002	0.002	0.003
Methanol	5.640	5.460	4.810	4.390	4.290

values, the solute–solvent intermolecular interactions can be made with the help of Eq. (5) [44]:

$$\ln \gamma = \frac{(e_{11} + e_{33} - 2e_{13})V_3 \varnothing_1^2}{RT} \quad (5)$$

In which, subscript 1 stands for the respective neat solvent and e_{11}, e_{33} and e_{13} are the solvent–solvent, solute–solute and solvent–solute interaction energies, respectively. V_3 represents the molar volume of the super-cooled liquid solute and $\varnothing_1$ represent the volume fraction of the respective neat solvent.

For relatively low values of x_e, the term $V_3\varnothing_1^2/RT$ is considered as constant and hence γ values will depend mainly on e_{11}, e_{33} and e_{13} [44]. It has been reported in literature that the terms e_{11} and *e33* are unfavorable for solubility and the term e_{13} favors the solution process [39, 44]. The contribution of the term e_{33} could be considered as constant in all neat solvents. As a qualitative approach, the following analysis could be made based on the energetic quantities and magnitudes described in the Eq. (5):

The term e_{11} was highest in water and it was lowest in PEG-400. The value of e_{11} was obtained similar in PEG-400, Transcutol and DMSO because their x_e values were also recorded as similar. The values of e_{11} were also much lower in methanol, ethanol, IPA, 1-butanol, 2-butanol, EG, PG and EA in comparison with water. Neat water had larger γ values would imply high e_{11} and low e_{13} values. However, in PEG-400, Transcutol and DMSO (having low γ values), the e_{11} values were relatively low but the e_{13} values could be higher. Therefore, the solvation of solid apigenin could be higher in PEG-400, Transcutol and DMSO.

3.4. Correlation/curve fitting of x_e values of apigenin

The x_e values of solid apigenin were correlated/fitted with two different semiempirical models namely "Apelblat and van't Hoff models" [36,45,46]. The "Apelblat model solubility (x^{Apl})" of solid apigenin was calculated using Eq. (6) [45,46]:

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

Here, the symbols "*A*, *B* and *C*" are the parameters/coefficients of "Apelblat model" which were determined by "nonlinear multivariate regression analysis" of x_e values of solid apigenin listed in Table 1 [20]. The x_e values of solid apigenin were fitted/correlated with x^{Apl} values of solid apigenin in terms of "root mean square deviations (*RMSD*)" and R^2 values. The *RMSD* values between x_e and x^{Apl} of solid apigenin were determined using Eq. (7):

$$RMSD = \left[\frac{1}{N}\sum_{i=1}^{N}\left(\frac{x^{Apl} - x_e}{x_e}\right)^2\right]^{\frac{1}{2}} \quad (7)$$

Here, *N* represents the number of experimental temperature points which were five in the current research work. The representation of graphical correlation/curve fitting between natural logarithm x_e ($\ln x_e$) and $\ln x^{Apl}$ values of solid apigenin in twelve different neat solvents against $1/T$ is presented in Fig. 4. The resulting data presented in Fig. 4 showed good correlation/curve fitting between $\ln x_e$ and $\ln x^{Apl}$ values of solid apigenin in each neat solvent evaluated. The results of "Apelblat correlation" are listed in Table 3. The *RMSD* values in twelve different neat solvents were obtained in the range of (0.22 to 1.19) %. The *RMSD* value for solid apigenin was obtained maximum in EA (1.19%) followed by ethanol (1.08%), 1-butanol (0.78%), water (0.55%), EG (0.54%), Transcutol (0.40%), 2-butanol (0.39%), DMSO (0.38%), PEG-400 (0.30%), methanol (0.26%), IPA (0.23%) and PG (0.22%). The R^2 values for solid apigenin in twelve different neat solvents were obtained in the range of 0.9965 to 0.9999. The lower values of *RMSD* and higher values of R^2 for solid apigenin indicated good correlation of x_e values of solid apigenin with "Apelblat model".

The "van't Hoff model solubility ($x^{van't}$)" of solid apigenin was calculated using Eq. (8) [36]:

$$\ln x^{van't} = a + \frac{b}{T} \quad (8)$$

Here, the symbols "*a* and *b*" are the parameters/coefficients of "van't Hoff model" which were calculated by plotting $\ln x_e$ values of solid apigenin against $1/T$.

The x_e values of solid apigenin were correlated/fitted with $x^{van't}$ values again in terms of *RMSD* and R^2 values.

The representation of graphical correlation/fitting between x_e and $x^{van't}$ values of solid apigenin in twelve different neat solvents against $1/T$ is presented in Fig. S1. The resulting data presented in Fig. S1 indicated good correlation/curve fitting. The results of "van't Hoff correlation" are listed in Table 4. The *RMSD* values for solid apigenin in twelve different neat solvents were obtained in the range of (0.06 to 2.23) %. The *RMSD* value for solid apigenin was obtained maximum in water (2.23%) followed by ethanol (1.66%), EA (1.18%), EG (1.11%), IPA (0.73%), 1-butanol (0.68%), 2-butanol (0.64%), DMSO (0.27%), Transcutol (0.20%), PG (0.18%), methanol (0.15%) and PEG-400 (0.06%). The R^2 values for solid apigenin in twelve different neat solvents were obtained in the range of 0.9933 to 1.0000. The lower values of *RMSD* and higher values of R^2 for solid apigenin again showed good correlation of x_e values of solid apigenin with "van't Hoff model".

3.5. Apparent thermodynamic analysis

"Apparent thermodynamic analysis" on solubility data of solid apigenin was carried out for the investigation of dissolution thermodynamics of apigenin in twelve different neat solvents. Hence, various "apparent standard thermodynamic parameters" namely "apparent standard dissolution enthalpy ($\Delta_{sol}H^0$), apparent standard Gibbs free energy ($\Delta_{sol}G^0$) and apparent standard dissolution entropy ($\Delta_{sol}S^0$)" of apigenin dissolution were determined in this work. The "$\Delta_{sol}H^0$ values" for apigenin dissolution in twelve different neat solvents were determined at the "mean harmonic temperature (T_{hm})" of 308 K by applying "van't Hoff analysis" using Eq. (9) [39,47]:

$$\left(\frac{\partial \ln x_e}{\partial\left(1/T - 1/T_{hm}\right)}\right)_P = -\frac{\Delta_{sol}H^0}{R} \quad (9)$$

Here, all the symbols have already been defined in previous text. The "$\Delta_{sol}H^0$ values" for apigenin dissolution were determined by van't Hoff plots which were plotted between $\ln x_e$ values of solid apigenin against $1/T - 1/T_{hm}$. The results are presented in Fig. S2. These "van't Hoff plots" for apigenin dissolution in twelve different neat solvents were found to be linear with R^2 values in the range of 0.9934 to 1.0000 (Fig. S2).

The "$\Delta_{sol}G^0$ values" for apigenin dissolution were also determined at T_{hm} value of 308 K by applying "Krug et al. analysis" approach using Eq. (10) [48]:

$$\Delta_{sol}G^0 = -RT_{hm} \times intercept \quad (10)$$

Here, the value of intercept for solid apigenin in each solvent was obtained from "van't Hoff plot" constructed between $\ln x_e$ values of solid apigenin and $1/T - 1/T_{hm}$.

Finally, the "$\Delta_{sol}S^0$ values" for apigenin dissolution were determined by applying the combined approach of "van't Hoff and Krug et al.

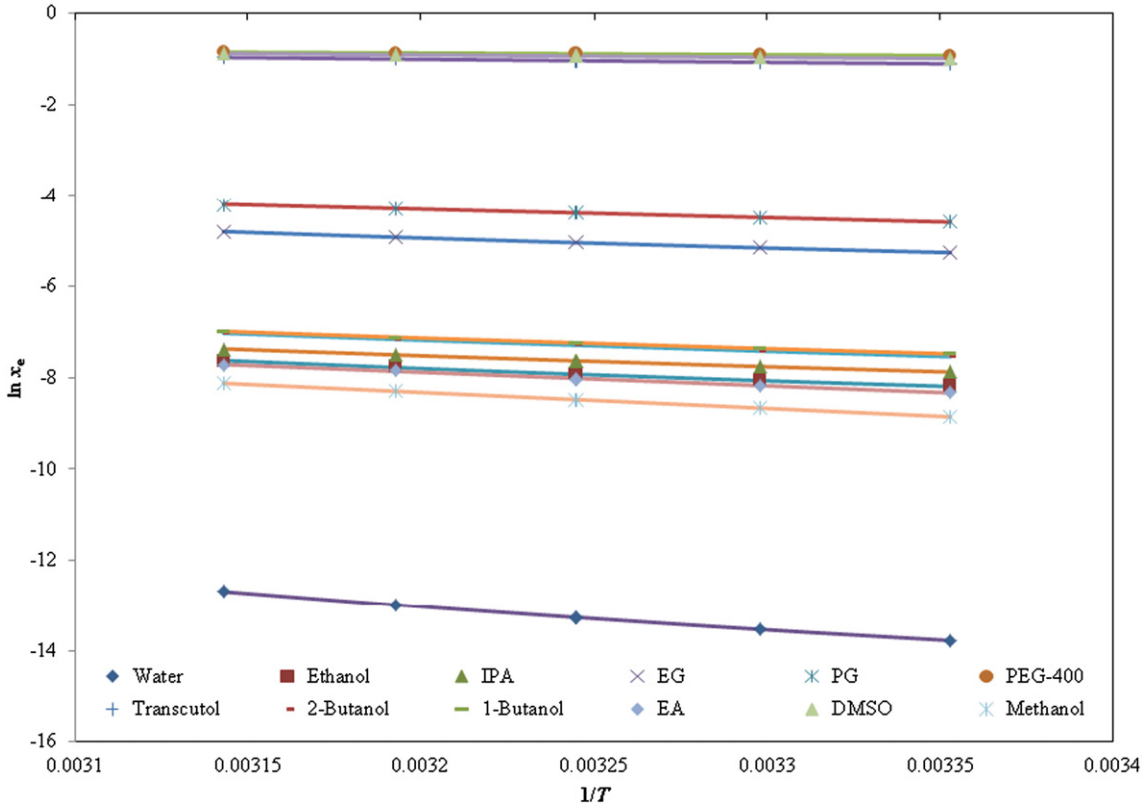

Fig. 4. Correlation of ln x_e values of apigenin with "Apelblat model" in twelve different neat solvents as a function of 1/T; symbols represent the experimental solubilities of apigenin and solid lines represent the solubilities of apigenin calculated by "Apelblat model".

analysis" using Eq. (11) [39,47,48]:

$$\Delta_{sol}S^0 = \frac{\Delta_{sol}H^0 - \Delta_{sol}G^0}{T_{hm}} \tag{11}$$

Thermodynamic quantities obtained from "apparent thermodynamic analysis" along with R^2 values for apigenin dissolution in twelve different neat solvents are listed in Table 5.

From "apparent thermodynamic analysis", it can be seen that the "$\Delta_{sol}H^0$ values" for apigenin dissolution in twelve different neat solvents were recorded as positive values in the range of (2.91 to 42.55) kJ mol^{-1}. The "$\Delta_{sol}H^0$ value" for apigenin dissolution was recorded maximum in water (42.55 kJ mol^{-1}) followed by methanol (29.04 kJ mol^{-1}), EA (24.59 kJ mol^{-1}), ethanol (22.27 kJ mol^{-1}), 2-butanol (20.20 kJ mol^{-1}), IPA (19.94 kJ mol^{-1}), 1-butanol (19.42 kJ mol^{-1}), EG (18.12 kJ mol^{-1}), PG (15.58 kJ mol^{-1}), Transcutol (5.51 kJ mol^{-1}), DMSO (4.24 kJ mol^{-1}) and PEG-400 (2.91 kJ mol^{-1}). The mean "$\Delta_{sol}H^0$ value" for apigenin dissolution was calculated as 18.70 kJ mol^{-1} with relative standard deviation (*RSD*) value of 0.59. The minimum "$\Delta_{sol}H^0$ value" for apigenin dissolution was recorded in PEG-400 that was possible due to the maximum solubility of apigenin in PEG-400. Generally, the results of $\Delta_{sol}H^0$ measurement were in good agreement with their experimental solubility data. The "$\Delta_{sol}G^0$ values" for apigenin dissolution in twelve different neat solvents were also recorded as positive values in the range of (2.26 to 33.93) kJ mol^{-1}. The "$\Delta_{sol}G^0$ value" for apigenin dissolution was also recorded maximum in water (33.93 kJ mol^{-1}) followed by methanol (21.73 kJ mol^{-1}), EA (22.52 kJ mol^{-1}), ethanol (20.26 kJ mol^{-1}), IPA (19.53 kJ mol^{-1}), 2-butanol (18.64 kJ mol^{-1}), 1-butanol

Table 3
The results of Apelblat correlation in terms of model parameters (*A*, *B* and *C*), R^2 and % *RMSD* values for apigenin in different neat solvents (*S*).

S	*A*	*B*	*C*	R^2	*RMSD* (%)
Water	−657.00 (0.01)	25,052.74 (0.01)	98.14 (0.01)	0.9999	0.55
Ethanol	−331.52 (NS)	12,508.48 (NS)	49.38 (NS)	0.9965	1.08
PG	1.86 (NS)	−1880.59 (NS)	−0.02 (NS)	0.9979	0.22
PEG-400	13.95 (NS)	−975.99 (NS)	−2.03 (NS)	0.9998	0.30
Transcutol	−26.69 (NS)	608.10 (NS)	4.13 (NS)	0.9988	0.40
EG	−267.21 (NS)	10,121.72 (NS)	40.01 (NS)	0.9983	0.54
IPA	−212.91 (0.05)	7342.02 (NS)	31.66 (0.05)	0.9998	0.23
1-Butanol	−189.81 (0.04)	6356.99 (NS)	28.25 (0.04)	0.9998	0.78
2-Butanol	−182.04 (0.04)	5920.18 (NS)	27.14 (0.04)	0.9998	0.39
EA	−24.04 (NS)	−1783.77 (NS)	37.57 (NS)	0.9970	1.19
DMSO	−45.10 (NS)	1584.09 (NS)	6.81 (NS)	0.9992	0.38
Methanol	−16.07 (NS)	−2618.01 (0.04)	1.91 (NS)	0.9999	0.26

The values in parentheses are *p* values for respective parameter and NS is not significant.

Table 4
The results of van't Hoff model in terms of model parameters (*a* and *b*), R^2 and % *RMSD* values for apigenin in different neat solvents (*S*).

S	*a*	*b*	R^2	*RMSD* (%)
Water	3.37	−5122.90	0.9966	2.23
Ethanol	0.76	−2675.30	0.9933	1.66
PG	1.69	−1876.10	0.9997	0.18
PEG-400	0.25	−350.79	0.9994	0.06
Transcutol	1.12	−663.77	0.9984	0.20
EG	2.04	−2182.10	0.9951	1.11
IPA	0.14	−2395.00	0.9982	0.73
1-Butanol	0.33	−2333.30	0.9985	0.68
2-Butanol	0.59	−2427.10	0.9987	0.64
EA	1.59	−2960.70	0.9970	1.18
DMSO	0.73	−510.79	0.9975	0.27
Methanol	2.83	−3488.30	1.0000	0.15

Table 5
Results of "apparent thermodynamic analysis" in terms of $\Delta_{sol}H^0$, $\Delta_{sol}G^0$, $\Delta_{sol}S^0$ and R^2 values for apigenin in different neat solvents (*S*).[b]

S	$\Delta_{sol}H^0$/kJ mol^{-1}	$\Delta_{sol}G^0$/kJ mol^{-1}	$\Delta_{sol}S^0$/Jmol^{-1} K^{-1}	R^2
Water	42.55	33.93	27.98	0.9967
Ethanol	22.27	20.26	6.51	0.9934
PG	15.58	11.25	14.06	0.9997
PEG-400	2.91	2.26	2.10	0.9988
Transcutol	5.51	2.63	9.35	0.9988
EG	18.12	12.89	16.98	0.9951
IPA	19.94	19.53	1.32	0.9983
1-Butanol	19.42	18.54	2.85	0.9986
2-Butanol	20.20	18.64	5.06	0.9988
EA	24.59	20.52	13.20	0.9970
DMSO	4.24	2.37	6.06	0.9975
Methanol	29.04	21.73	23.73	1.0000

[b] The relative uncertainties are $u(\Delta_{sol}H^0) = 0.59$ kJ mol^{-1}, $u(\Delta_{sol}G^0) = 0.61$ kJ mol^{-1} and $u(\Delta_{sol}S^0) = 0.80$ J mol^{-1} K^{-1}.

(18.54 kJ mol^{-1}), EG (12.89 kJ mol^{-1}), PG (11.25 kJ mol^{-1}), Transcutol (2.63 kJ mol^{-1}), DMSO (2.37 kJ mol^{-1}) and PEG-400 (2.26 kJ mol^{-1}). The mean "$\Delta_{sol}G^0$ value" for apigenin dissolution was calculated as 15.38 kJ mol^{-1} with *RSD* value of 0.61. The minimum "$\Delta_{sol}G^0$ value" for apigenin dissolution was also recorded in PEG-400 that was possible due to the maximum solubility of apigenin in PEG-400. The results of "$\Delta_{sol}G^0$" measurement for apigenin dissolution were also in good agreement with measured solubility data of apigenin. Relatively, lower values of $\Delta_{sol}H^0$ and $\Delta_{sol}G^0$ were obtained in PEG-400, DMSO and Transcutol which indicated that minimum energy is required for the solubilization of solid apigenin in these solvents. The positive values of "$\Delta_{sol}H^0$ and $\Delta_{sol}G^0$" in all neat solvents indicated an "endothermic dissolution" behavior of apigenin in all these solvents [20,36]. The "$\Delta_{sol}S^0$ values" for apigenin dissolution in twelve different neat solvents were also recorded as positive values in the range of (1.32 to 27.98) J mol^{-1} K^{-1}. The mean "$\Delta_{sol}S^0$ values" for apigenin dissolution was calculated as 10.76 J mol^{-1} K^{-1} with *RSD* value of 0.80. The positive "$\Delta_{sol}S^0$ values" indicated an "entropy-driven dissolution" of apigenin in all neat solvents evaluated [20]. Overall, the dissolution of solid apigenin was obtained as an "endothermic and entropy-driven" in all solvents investigated [20,36].

4. Conclusion

The solubility of a poorly soluble bioflavonoid apigenin was measured in twelve different neat solvents by a static equilibrium method at "$T = 298.2$ K to 318.2 K" and "$p = 0.1$ MPa". The solid state characterization of apigenin was carried out using DSC and TGA analysis. The measured solubility data of solid apigenin was and correlated well with "van't Hoff and Apelblat" models with *RMSD* values of <3.0% for both models. The solubility of solid apigenin was obtained as increasing with increase in temperature. The results of activity coefficients indicated better molecular interaction of apigenin with PEG-400, Transcutol and DMSO in comparison with other neat solvents evaluated. The solubility of solid apigenin in mole fraction was recorded maximum in PEG-400 followed by DMSO, Transcutol, PG, EG, 1-butanol, 2-butanol, IPA, ethanol, EA, methanol and water at "$T = 318.2$ K" and similar trend was recorded at each temperature evaluated. "Apparent thermodynamic analysis" of solubility data of solid apigenin indicated an "endothermic and entropy-driven dissolution" of solid apigenin in all solvents evaluated. Based on the results obtained in this work, PEG-400, DMSO and Transcutol were selected as the best solvents and water and methanol were selected as the anti-solvents for apigenin.

Conflict of interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.molliq.2017.03.057.

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