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Solubility and thermodynamic function of vitamin D3 in different mono solvents

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ABSTRACT

In this study, the solubility of a fat soluble vitamin (vitamin D3) was measured in eleven different mono solvents including "water, ethanol, 2-propanol (IPA), 1-butanol, 2-butanol, 2-(2-ethoxyethoxy) ethanol [Transcutol®], ethylene glycol (EG), propylene glycol (PG), polyethylene glycol-400 (PEG-400), ethyl acetate (EA) and dimethyl sulfoxide (DMSO)" at temperatures "$T = 273.2$ K to 298.2 K" and "atmospheric pressure $p = 0.1$ MPa". Experimental solubility data of vitamin D3 in mole fraction were correlated well with "Van't Hoff and Apelblat models" with mean percent deviations of <5.0%. The solubilities of vitamin D3 in mole fraction at "$T = 298.2$ K" were obtained highest in Transcutol® (4.03×10^{-1}) followed by IPA (2.45×10^{-1}), EA (1.95×10^{-1}), 2-butanol (1.87×10^{-1}), ethanol (1.77×10^{-1}), 1-butanol (1.69×10^{-1}), PEG-400 (2.91×10^{-2}), DMSO (7.23×10^{-3}), PG (3.37×10^{-3}), EG (5.24×10^{-4}) and water (1.03×10^{-6}). Thermodynamic treatment of solubility data of vitamin D3 by "Apparent thermodynamic analysis" indicated an "endothermic and entropy-driven dissolution" of vitamin D3 in all mono solvents investigated. Based on the results of this study, vitamin D3 has been considered as practically insoluble in water, sparingly soluble in DMSO, PG and PEG-400, poorly soluble in EG and very soluble in ethanol, IPA, EA, 1-butanol, 2-butanol and Transcutol®.

1. Introduction

The IUPAC name of vitamin D3 (Fig. 1; molecular formula: $C_{27}H_{44}O$; molar mass: 384.64 g mol^{-1} and CAS registry number: 67-97-0) has been proposed as "*(3β,5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-3-ol*" [1]. It is also known as "cholecalciferol" which is categorized as a fat-soluble vitamin and used in the treatment of rickets [2–4]. It is inactive itself, but it metabolizes to give an active metabolite "25-hydroxyvitamin D3", which plays a significant role in the coordination of calcium and phosphorus homeostasis, healthy mineralization, growth and remodeling of bone [5–7].

In Saudi Arabia, the deficiency of vitamin D3 is very common due to lack of exposure to sunlight [8]. Around 96% of Saudi Arabia's population suffers from vitamin D3 deficiency due to lack of sunlight exposure [9]. Therefore, the required intake of vitamin D3 is very essential especially in Saudi Arabia [8,9].

Because vitamin D3 is a fat-soluble vitamin and hence its aqueous solubility is very low [3]. Poor aqueous solubility of vitamin D3 is the main problem associated with its formulation development.

The solubility and physicochemical data of drugs in different aqueous and organic solvents are important in "their purification, recrystallization, drug discovery processes and formulation development" [10–15]. Hence, it is of great importance to determine the solubility of vitamin D3 in various "aqueous and organic solvents". The commonly used solvents for solubilization of poorly-soluble drugs have been proposed as "ethanol, propylene glycol (PG) and polyethylene glycol-400 (PEG-400)" [16–18]. Nevertheless, the capability of 2-(2-ethoxyethoxy)ethanol [Transcutol®] and dimethyl sulfoxide (DMSO) have also been proven for solubilization of poorly-soluble drugs [19–23].

Various organic solvents such as ethyl acetate (EA), 2-propanone and methanol have been utilized for crystallization of vitamin D3 especially at lower temperatures. The solubility data of vitamin D3 in six different organic solvents including methanol, ethanol, EA, ethanenitrile, 2-propanone and 1-propanol at lower temperature range i.e. "$T = 248.2$ K to 273.2 K" and pressure "$p = 0.1$ MPa" have been reported in literature [1]. However, the solubility data of vitamin D3 in other mono solvents such as "water, Transcutol®, PEG-400, PG, ethylene

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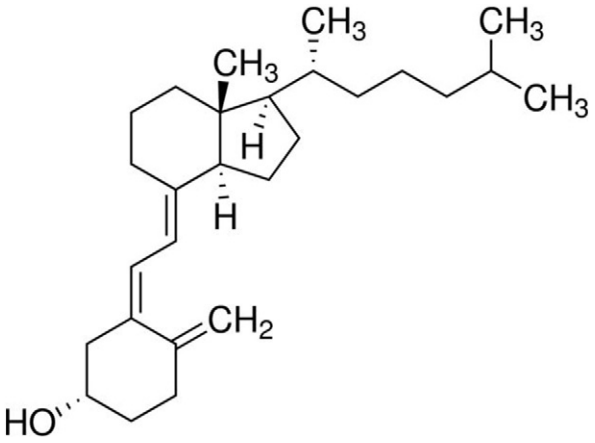

Fig. 1. Molecular structure of vitamin D3 (molar mass: 384.64 g mol^{-1}).

glycol (EG), isopropanol (IPA), 1-butanol, 2-butanol and DMSO" have not been reported in literature. Therefore, in this work, the solubilities of vitamin D3 as mole fraction in eleven different mono solvents including "water, ethanol, Transcutol®, PEG-400, PG, EG, IPA, EA, 1-butanol, 2-butanol and DMSO" were determined at "T = 273.2 K to 298.2 K and "p = 0.1 MPa". The temperature range of 273.2 K to 298.2 K was selected in this study because vitamin D3 has been reported as a photosensitive drug and its melting point is also reported as low (357 to 359) K [1, 24]. "Apparent thermodynamic analysis" of solubilities of vitamin D3 was also carried out with the help of "Van't Hoff and Krug et al. analysis". The solubility data of vitamin D3 obtained in this work could be helpful in "recrystallization, purification, pre-formulation studies and formulation development" of vitamin D3.

2. Experimental

2.1. Materials

Vitamin D3, PEG-400 (IUPAC name: polyethylene glycol-400), PG (IUPAC name: 1,2-propanediol), EA (IUPAC name: ethyl ethanoate), ethyl alcohol (IUPAC name: ethanol) and IPA (IUPAC name: isopropanol) were procured from "Sigma Aldrich (St. Louis, MO)". 1-Butyl alcohol (IUPAC name: 1-butanol), 2-butyl alcohol (IUPAC name: 2-butanol), DMSO (IUPAC name: dimethyl sulfoxide) and EG (IUPAC name: 1,2-ethanediol) were procured from "E-Merck (Darmstadt, Germany)". Transcutol® [IUPAC name: 2-(2-ethoxyethoxy)ethanol] was procured from "Gattefosse (Lyon, France)". Water used was deionized water which was obtained from "Milli-Q unit in the laboratory". The details of drug and all mono solvents are listed in supplementary Table 1 (Table S1).

2.2. Analysis of vitamin D3

The analysis of vitamin D3 was performed using "reversed phase high performance liquid chromatography (RP-HPLC)" equipped with ultra-violet (UV) detector at 254 nm. All analysis were carried out at T = 298.15 K using "HPLC system (Waters, USA)". The column used for analysis of vitamin D3 was "Nucleodur (150 × 4.6 mm, 5 μm) RP C_8 column. The binary mixture of ethanol and methanol (1:1%) was used as the mobile phase. The elution of vitamin D3 was performed at a flow rate of 1.0 mL min^{-1} at 254 nm. The volume of injection was 10 μL. The calibration curve was plotted between the concentration of vitamin D3 and measured peak area. The calibration curve of vitamin D3 was observed linear in the concentration range of (0.1–100) μg g^{-1} with coefficient of determination (R^2) of 0.9997. The equation of regression line was obtained as $y = 22{,}977x + 2812.6$; in which x is the concentration of vitamin D3 and y is the measured peak area of vitamin D3.

2.3. Determination of vitamin D3 solubility

The solubility of vitamin D3 in eleven different mono solvents was determined by shake flask method of Higuchi and Connors [25]. The experiments were carried out at "T = 273.2 to 298.2 K" and "p = 0.1 MPa". The excess amount of vitamin D3 was added in known quantities of each mono solvent in triplicates. Because vitamin D3 has been reported as photosensitive drug, drug-solvent mixtures were prepared in amber colored glass vials [24]. The obtained samples were transferred to biological shaker OLS 200 (Grant Scientific, Cambridge, UK) at 100 rpm for 48 h. For solubility measurement of vitamin D3 at "T = 273.2 K" and "T = 278.2 K", 10% of EG (as coolant) was added with 90% of water in biological shaker in order to maintain cooling temperatures. The lowest temperature sensitivity of OLS biological shaker was 273.2 K. Equilibrium time of 48 h was previously optimized by solubility measurement of vitamin D3 at 12, 24, 36, 48, 60 and 72 h. After 48 h, each sample was taken out from the biological shaker and allowed to settle vitamin D3 particles for 24 h [26]. Then, supernatants were carefully withdrawn, diluted with mobile phase and subjected for the analysis of vitamin D3 content by HPLC-UV method at 254 nm. The experimental mole fraction solubilities of vitamin D3 (x_e) were calculated using Eq. (1) [19]:

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

In which, m_1 and m_2 are the masses of vitamin D3 and respective mono solvent, respectively. M_1 and M_2 are the molar masses of vitamin D3 and respective mono solvent, respectively.

Table 1
Experimental solubilities (x_e) of vitamin D3 as mole fraction in different mono solvents (S) at "T = 273.2 K to 298.2 K" and "p = 0.1 MPa".[a]

S	x_e				
	T = 273.2 K	T = 278.2 K	T = 283.2 K	T = 288.2 K	T = 298.2 K
Water	1.87×10^{-7}	2.90×10^{-7}	4.22×10^{-7}	5.67×10^{-7}	1.03×10^{-6}
Ethanol	1.36×10^{-1}	1.44×10^{-1}	1.53×10^{-1}	1.62×10^{-1}	1.77×10^{-1}
IPA	1.90×10^{-1}	2.02×10^{-1}	2.15×10^{-1}	2.25×10^{-1}	2.45×10^{-1}
EG	1.13×10^{-4}	1.61×10^{-4}	2.34×10^{-4}	3.18×10^{-4}	5.24×10^{-4}
(*RS*)-PG	1.42×10^{-3}	1.76×10^{-3}	2.09×10^{-3}	2.49×10^{-3}	3.37×10^{-3}
PEG-400	1.35×10^{-2}	1.62×10^{-2}	1.91×10^{-2}	2.22×10^{-2}	2.91×10^{-2}
Transcutol	3.69×10^{-1}	3.75×10^{-1}	3.82×10^{-1}	3.90×10^{-1}	4.03×10^{-1}
1-Butanol	1.51×10^{-1}	1.57×10^{-1}	1.63×10^{-1}	1.69×10^{-1}	1.69×10^{-1}
(*RS*)-2-butanol	1.54×10^{-1}	1.61×10^{-1}	1.68×10^{-1}	1.76×10^{-1}	1.87×10^{-1}
EA	9.04×10^{-2}	1.09×10^{-1}	1.31×10^{-1}	1.50×10^{-1}	1.95×10^{-1}
DMSO	4.10×10^{-3}	4.69×10^{-3}	5.33×10^{-3}	6.01×10^{-3}	7.23×10^{-3}

[a] The standard uncertainties u are $u(T)$ = 0.10 K, $u(p)$ = 0.003 MPa and $u_r(x_e)$ = 1.41%.

3. Results and discussion

3.1. Experimental solubility data of vitamin D3 and its literature comparison

Experimentally measured x_e values of vitamin D3 in eleven different mono solvents at "$T = 273.2$ K to 298.2 K" and "$p = 0.1$ MPa" are listed in Table 1. The solubilities of vitamin D3 in six organic mono solvents including "methanol, ethanenitrile, EA, ethanol, 2-propanone and 1-propanol" at "$T = 248.2$ K to 273.2 K" and "$p = 0.1$ MPa have been reported in literature [1].

The x_e value of vitamin D3 in ethanol and EA at "$T = 273.2$ K" has been reported as 1.39×10^{-1} and 8.83×10^{-2}, respectively [1]. In the current study, the x_e value of vitamin D3 in ethanol and EA at "$T = 273.2$ K" was recorded as 1.36×10^{-1} and 9.04×10^{-2}, respectively. However, the x_e value of vitamin D3 in 1-propanol at "$T = 273.2$ K" has been reported as 1.93×10^{-1} [1]. In the current study, the x_e value of vitamin D3 in 1-propanol was not measured but it was measure in IPA i.e. 2-propanol. 1-Propanol and IPA are isomers of each other and they have similar molar masses and molecular structures. Therefore, their x_e values should also be similar. In the current study, the x_e value of vitamin D3 in IPA at "$T = 273.2$ K" was recorded as 1.90×10^{-1} which was very close to its x_e value in 1-propanol.

The x_e values of vitamin D3 in ethanol, EA and IPA obtained in this work were very close to their literature values. Hence, the results obtained in this work were in good agreement with those reported in literature.

From results listed in Table 1, it can be seen that the x_e values of vitamin D3 were increasing with the rise in temperature in each mono solvent investigated. The x_e values of vitamin D3 at "$T = 298.2$ K" were obtained highest in Transcutol® (4.03×10^{-1}) followed by IPA (2.45×10^{-1}), EA (1.95×10^{-1}), 2-butanol (1.87×10^{-1}), ethanol (1.77×10^{-1}), 1-butanol (1.69×10^{-1}), PEG-400 (2.91×10^{-2}), DMSO (7.23×10^{-3}), PG (3.37×10^{-3}), EG (5.24×10^{-4}) and water (1.03×10^{-6}).

The highest x_e values of vitamin D3 were obtained in Transcutol in comparison with its x_e values in other mono solvents including water. Generally, the x_e values of vitamin D3 were significantly higher in Transcutol, IPA, ethanol, 1-butanol, 2-butanol and EA in comparison with water. This observation was probably due to the fact that vitamin D3 is having some functional groups such as —OH which could have strong molecular interaction/solvation with mono solvents with functional groups of —OH. The x_e values of vitamin D3 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 vitamin D3 in other alcoholic solvents such as PG and EG were also observed in similar magnitude because both of the mono solvents have two —OH groups with similar dielectric constants/polarities. The x_e values of vitamin D3 in other mono solvents such as ethanol and IPA were also obtained in similar magnitude due to the presence of single —OH group in both mono solvents and their polarities are also similar. However, the x_e values of vitamin D3 in Transcutol, IPA, ethanol, 1-butanol, 2-butanol and EA were significantly higher in comparison with its x_e values in other mono solvents investigated. This observation was possible due to lower polarities of Transcutol, IPA, ethanol, 1-butanol, 2-butanol and EA in comparison with other mono solvents including water [26]. Based on solubility data of vitamin D3 obtained in this work, vitamin D3 has been proposed as practically insoluble in water, sparingly soluble in DMSO, PG and PEG-400, poorly soluble in EG and very soluble in ethanol, IPA, EA, 1-butanol, 2-butanol and Transcutol® [21,26]. The solubility data of vitamin D3 could be useful in "recrystallization, purification, pre-formulation studies and formulation development" of vitamin D3.

3.2. Correlation of experimental data of vitamin D3

The x_e values of vitamin D3 measured in this work were correlated/fitted with well-known "Apelblat and Van't Hoff models" [26–28]. The "Apelblat solubility (x^{Apl})" of vitamin D3 was determined and correlated with the help of Eq. (2) [27,28]:

$$\ln x^{Apl} = A + \frac{B}{T} + C\ \ln(T) \tag{2}$$

In which, the symbols "A, B and C" are the parameters/coefficients of "Apelblat model" [Eq. (2)]. These coefficients were determined by applying "nonlinear multivariate regression analysis" of x_e values of vitamin D3 furnished in Table 1 [26]. The correlation between x_e and x^{Apl} values of vitamin D3 was performed by the determination of the mean percent deviations (*MPD*) and R^2 values. The *MPD* values between x_e and x^{Apl} of vitamin D3 were determined with the help of Eq. (3) [29]:

$$MPD = \frac{100}{N} \sum \frac{(x^{Apl} - x_e)}{x^{Apl}} \tag{3}$$

In which, N is the total number of experimental data points which were 55 in this work.

The graphical representation and correlation between natural logarithmic x_e ($\ln x_e$) and $\ln x^{Apl}$ values of vitamin D3 in each mono solvent against $1/T$ is shown in Fig. 2. Fig. 2 showed an excellent correlation between $\ln x_e$ and $\ln x^{Apl}$ values of vitamin D3. The results of "Apelblat correlation" are listed in Table 2. The *MPD* values for vitamin D3 in eleven different mono solvents were obtained in the range of 0.26 to 4.78. The *MPD* value for vitamin D3 was obtained highest in ethanol (4.78) followed by "1-butanol, PEG-400, DMSO, Transcutol, PG, IPA, EA, EG, 2-butanol and water". However, the R^2 values for vitamin D3 were obtained in the range of 0.9982 to 0.9999. The higher values of R^2 and lower values of *MPD* indicated good correlation of x_e values of vitamin D3 with "Apelblat model".

The "Van't Hoff model solubility ($x^{van't}$)" of vitamin D3 was calculated with the help of Eq. (4) [26]:

$$\ln x^{van't} = a + \frac{b}{T} \tag{4}$$

In which, the symbols "a and b" are the parameters/coefficients of "Van't Hoff model" [Eq. (4)]. These parameters were determined by plotting $\ln x_e$ values of vitamin D3 against $1/T$.

The correlation between x_e and $x^{van't}$ values of vitamin D3 was carried out in terms of *MPD* and R^2 values. The graphical representation and correlation between $\ln x_e$ and $\ln x^{van't}$ values of vitamin D3 in each mono solvent against $1/T$ is shown in supplementary Fig. 1 (Fig. S1). Fig. S1 showed good graphical correlation between $\ln x_e$ and $\ln x^{van't}$ values of vitamin D3. The results of Van't Hoff correlation are listed in Table 3.

The *MPD* values for vitamin D3 in all mono solvents investigated were obtained in the range of 0.02 to 1.47. The *MPD* value for vitamin D3 was obtained highest in EG (1.47) followed by "EA, 2-butanol, 1-butanol, water, ethanol, DMSO, Transcutol, PG, PEG-400 and IPA". However, the R^2 values for vitamin D3 were obtained in the range of 0.9951 to 0.9985. The higher values of R^2 and lower values of *MPD* again indicated good correlation of x_e values of vitamin D3 with "Van't Hoff model".

3.3. Apparent thermodynamic analysis

The dissolution behavior of vitamin D3 in eleven different mono solvents was investigated by "apparent thermodynamic analysis" of solubilities of vitamin D3. For this purpose, three different apparent thermodynamic parameters such as "apparent standard enthalpy ($\Delta_{sol}H^0$)", "apparent standard Gibbs energy ($\Delta_{sol}G^0$)" and "apparent standard entropy ($\Delta_{sol}S^0$)" were calculated by "apparent

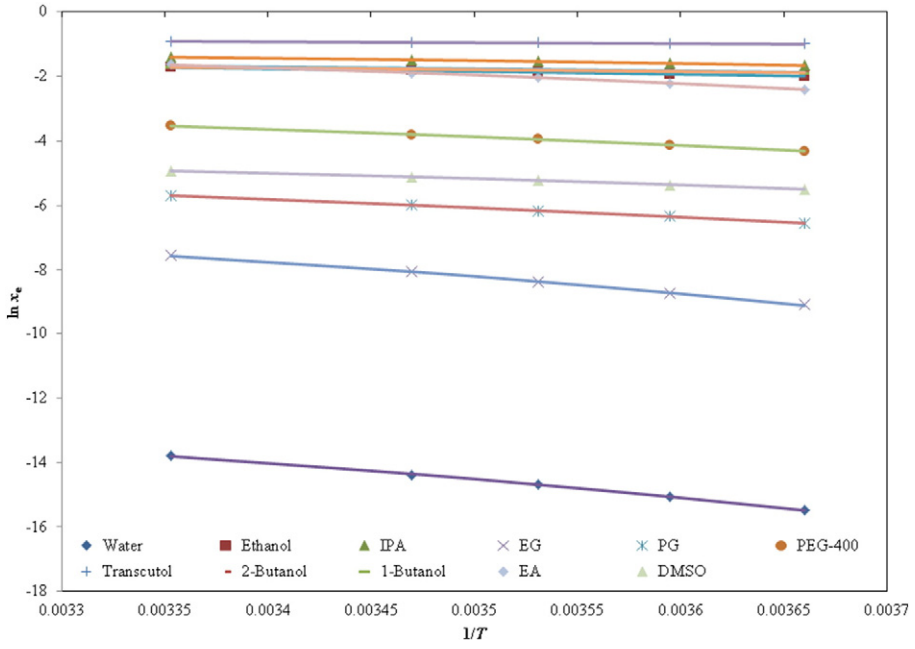

Fig. 2. Correlation of experimental natural logarithmic solubilities (ln x_e) of vitamin D3 with Apelblat model in different mono solvents as a function of $1/T$; symbols represent the experimental ln x_e values of vitamin D3 and the solid lines represent the ln x^{Apl} values calculated by Apelblat model.

thermodynamic analysis". The "$\Delta_{sol}H^0$ values" for vitamin D3 dissolution in each mono solvent were determined at "mean harmonic temperature (T_{hm})" of 283.94 K by applying "Van't Hoff analysis" with the help of Eq. (5) [30,31]:

$$\left(\frac{\partial \ln x_e}{\partial\left({}^{1}/_{T}-{}^{1}/_{T_{hm}}\right)}\right)_P = -\frac{\Delta_{sol}H^0}{R} \tag{5}$$

In which, R is the universal gas constant and other parameters have already been defined. Using Eq. (5), the "$\Delta_{sol}H^0$ values" for vitamin D3 were calculated by plotting ln x_e values of vitamin D3 against ${}^{1}/_{T}-{}^{1}/_{T_{hm}}$. The "Van't Hoff plots" in each mono solvent investigated were obtained as linear with R^2 values in the range of 0.9952 to 0.9985.

The "$\Delta_{sol}G^0$ values" for vitamin D3 dissolution were also calculated at T_{hm} of 283.94 K by applying Krug et al. analysis with the help of Eq. (6) [32]:

$$\Delta_{sol}G^0 = -RT_{hm} \times intercept \tag{6}$$

In which, the intercept value for each mono solvent was determined from "Van't Hoff plot" constructed between ln x_e values of vitamin D3 and ${}^{1}/_{T}-{}^{1}/_{T_{hm}}$.

Finally, the "$\Delta_{sol}S^0$ values" for vitamin D3 dissolution were calculated by applying the combined approaches of "Van't Hoff" and "Krug et al. analysis" using Eq. (7) [30–32]:

$$\Delta_{sol}S^0 = \frac{\Delta_{sol}H^0 - \Delta_{sol}G^0}{T_{hm}} \tag{7}$$

The resulting data of "apparent thermodynamic analysis" for vitamin D3 dissolution in each solvent are listed in Table 4.

From data listed in Table 4, it can be seen that the "$\Delta_{sol}H^0$ values" for vitamin D3 dissolution in eleven different mono solvents were observed as positive values in the range of (2.38 to 45.57) kJ mol^{-1}. The "$\Delta_{sol}H^0$ value" for vitamin D3 dissolution was observed highest in water (45.57 kJ mol^{-1}) followed by EG (41.79 kJ mol^{-1}), PG (23.24 kJ mol^{-1}), PEG-400 (21.01 kJ mol^{-1}), EA (20.73 kJ mol^{-1}), DMSO (15.43 kJ mol^{-1}), ethanol (7.21 kJ mol^{-1}), IPA (6.92 kJ mol^{-1}), 2-butanol (5.32 kJ mol^{-1}), 1-butanol (4.60 kJ mol^{-1}) and Transcutol (2.38 kJ mol^{-1}). In general, the "$\Delta_{sol}H^0$ values" for vitamin D3 dissolution were obtained lower for mono solvents with higher x_e values such as Transcutol, ethanol, IPA, 1-butanol and 2-butanol. However, the "$\Delta_{sol}H^0$ values" for vitamin D3 dissolution were obtained higher for mono solvents with lower x_e values such as water, EG, PG, PEG-400, EA and DMSO.

Table 2
Apelblat parameters (A, B and C), R^2 and MPD (%) values for vitamin D3 in different mono solvents (S).

S	A	B	C	R^2	MPD (%)
Water	650.17	−33,148.40	−97.02	0.9990	0.26
Ethanol	46.27	−2799.97	−6.77	0.9989	4.78
(*RS*)-PG	202.92	−11,333.30	−29.94	0.9995	2.64
PEG-400	246.67	−12,887.10	−36.33	0.9996	3.21
Transcutol	−19.38	546.53	2.92	0.9982	2.98
EG	706.74	−34,916.20	−104.81	0.9998	1.12
IPA	117.82	−5823.42	−17.49	0.9999	1.99
1-Butanol	38.29	−2188.63	−5.73	0.9993	4.73
(*RS*)-2-butanol	58.43	−3124.56	−8.71	0.9983	0.35
EA	345.30	−17,004.20	−50.88	0.9995	1.27
DMSO	223.43	−11,376.00	−33.38	0.9996	3.12

Table 3
Van't Hoff model parameters (a and b), R^2 and MPD (%) values for vitamin D3 in different mono solvents (S).

S	a	b	R^2	MPD (%)
Water	4.63	−5484.00	0.9958	0.34
Ethanol	1.18	−868.09	0.9982	0.32
(*RS*)-PG	3.69	−2796.70	0.9985	0.06
PEG-400	4.95	−2528.70	0.9976	0.02
Transcutol	0.05	−286.67	0.9969	0.08
EG	9.35	−5028.60	0.9952	1.47
IPA	1.39	−833.61	0.9952	0.02
1-Butanol	0.14	−553.72	0.9984	0.75
(*RS*)-2-butanol	0.47	−640.84	0.9965	0.77
EA	6.75	−2495.50	0.9951	1.44
DMSO	1.31	−1856.90	0.9963	0.24

Table 4
Apparent thermodynamic parameters ($\Delta_{sol}H^0$, $\Delta_{sol}G^0$ and $\Delta_{sol}S^0$) and R^2 values for vitamin D3 dissolution in different mono solvents (S).[a]

S	$\Delta_{sol}H^0$/kJ mol^{-1}	$\Delta_{sol}G^0$/kJ mol^{-1}	$\Delta_{sol}S^0$/J mol^{-1} K^{-1}	R^2
Water	45.57	34.65	38.47	0.9959
Ethanol	7.21	4.41	9.84	0.9982
(*RS*)-PG	23.24	14.52	30.70	0.9985
PEG-400	21.01	9.32	41.17	0.9976
Transcutol	2.38	2.26	0.42	0.9968
EG	41.79	19.73	77.69	0.9953
IPA	6.92	3.63	11.60	0.9953
1-Butanol	4.60	4.27	1.15	0.9984
(*RS*)-2-butanol	5.32	4.20	3.95	0.9965
EA	20.73	4.80	56.11	0.9952
DMSO	15.43	12.33	10.89	0.9963

[a] The relative uncertainties are $u(\Delta_{sol}H^0) = 0.84$ kJ mol^{-1}, $u(\Delta_{sol}G^0) = 0.54$ kJ mol^{-1} and $u(\Delta_{sol}S^0) = 1.21$ J mol^{-1} K^{-1}.

The "$\Delta_{sol}G^0$ values" for vitamin D3 dissolution in eleven different mono solvents were also recorded as positive values in the range of (2.26 to 34.65) kJ mol^{-1}. The "$\Delta_{sol}G^0$ value" for vitamin D3 dissolution was also recorded highest in water (34.65 kJ mol^{-1}) followed by EG (19.73 kJ mol^{-1}), PG (14.52 kJ mol^{-1}), DMSO (12.33 kJ mol^{-1}), PEG-400 (9.32 kJ mol^{-1}), EA (4.80 kJ mol^{-1}), ethanol (4.41 kJ mol^{-1}), 1-butanol (4.27 kJ mol^{-1}), 2-butanol (4.20 kJ mol^{-1}), IPA (3.63 kJ mol^{-1}) and Transcutol (2.26 kJ mol^{-1}). The results of "$\Delta_{sol}G^0$ values" for vitamin D3 dissolution were in good agreement with experimental solubilities of vitamin D3 in eleven different neat solvents. The positive values of "$\Delta_{sol}H^0$ and $\Delta_{sol}G^0$" in all mono solvents indicated an endothermic dissolution of vitamin D3 in all mono solvents studied. The lower values of "$\Delta_{sol}H^0$ and $\Delta_{sol}G^0$" in Transcutol, ethanol, IPA, 1-butanol and 2-butanol indicated that relatively lower energies are required for the solubilization of vitamin D3 in Transcutol, ethanol, IPA, 1-butanol and 2-butanol in comparison with other mono solvents investigated. The "$\Delta_{sol}S^0$ values" for vitamin D3 dissolution in eleven different mono solvents were also recorded positive values in all mono solvents investigated. The positive values of "$\Delta_{sol}S^0$" indicated an entropy-driven dissolution of vitamin D3 in all mono solvents investigated [26]. The positive values of "$\Delta_{sol}H^0$" in all mono solvents were possible due to strong electrostatic interactions between vitamin D3-solvent molecules in comparison with weak electrostatic interactions between vitamin D3-vitamin D3 and solvent-solvent molecules [12,26].

4. Conclusion

In this work, the solubilities of a fat soluble vitamin i.e. vitamin D3 as mole fraction in eleven different mono solvents were measured at "$T =$ 273.2 K to 298.2 K and "$p = 0.1$ MPa". The experimental solubility data of vitamin D3 were found to be increasing with the rise in temperature in each solvent studied. Experimental solubility data of vitamin D3 were correlated well with "Van't Hoff and Apelblat models" with MPD < 5.0%. The solubilities of vitamin D3 as mole fraction at "$T = 298.2$ K" were obtained highest in Transcutol followed by IPA, EA, 2-butanol, ethanol, 1-butanol, PEG-400, DMSO, PG, EG and water. The results of "apparent thermodynamic analysis" indicated an "endothermic and entropy-driven dissolution" behavior of vitamin D3 in each solvent studied.

Conflict of interest

"The authors state that they do not have any 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.2016.12.105.

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