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An environmentally benign HPLC-UV method for thermodynamic solubility measurement of vitamin D3 in various (Transcutol + water) mixtures

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ABSTRACT

In the current research work, an environmentally benign "reversed phase high-performance liquid chromatography (RP-HPLC)" method was developed and validated for thermodynamic solubility measurement of vitamin D3 in various [2-(2-ethoxyethoxy)ethanol (Transcutol®) + water] mixtures. The HPLC analysis of vitamin D3 was achieved using a Nucleodur (150 × 4.6 mm, 5 μm) column. The binary mixture of ethanol: methanol (50:50% v/v) was used as a mobile phase and delivered at a flow rate of 1.0 mL min^{-1}. The proposed HPLC-UV method was validated well for linearity (R^2 = 0.9997), selectivity, accuracy as % recovery (98.60–102.00%), precision (% *RSD* = 1.07–1.31), robustness and sensitivity. The potential of methodology was demonstrated by its application in thermodynamic solubility determination of vitamin D3 in different "Transcutol + water" mixtures at various temperatures. The "mole fraction solubilities (x_e)" of vitamin D3 were measured at temperature "T = 273.2 K to 298.2 K" and pressure "p = 0.1 MPa". Measured x_e values of vitamin D3 were correlated well with "Apelblat, van't Hoff and Yalkowsky" models. The highest x_e value of vitamin D3 was obtained in neat Transcutol (4.04×10^{-1} at T = 298.2 K) followed by lowest one in neat water (1.97×10^{-7} at T = 273.2 K). "Apparent thermodynamic analysis" of solubility values of vitamin D3 showed an "endothermic and entropy-driven dissolution" of vitamin D3. Overall, these results showed that the proposed HPLC-UV method could be successfully used for thermodynamic solubility determination of vitamin D3 in various "Transcutol + water" mixtures.

1. Introduction

Vitamin D3 (Fig. 1, IUPAC name: (3β,5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-3-ol, molecular formula: $C_{27}H_{44}O$, molar mass: 384.64 g mol^{-1} and CAS registry number: 67-97-0) is also known as "cholecalciferol" which is a fat-soluble vitamin and administered in the treatment of rickets [1–4]. Its active metabolite "25-hydroxyvitamin D3 (calcifediol)" plays a great role in the various biochemical processes [5–7]. It is one of the most common disorders in Saudi Arabia because >96% of Saudi's population is currently suffering from vitamin D3 deficiency [8,9].

Vitamin D3 has been reported as practically insoluble in water and practically insolubility is the major problem associated with its formulation development [10]. The log *P* (logarithm of apparent partition coefficient) value of vitamin D3 has been reported as 9.10 [11]. The maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) after oral administration of vitamin D3 have been reported as 37.74 nmol L^{-1} and 16.0 h, respectively in healthy human volunteers [12]. However, the plasma half-life and rate and extent of absorption (AUC_{0-t}) after oral administration of vitamin D3 have been reported as 43.47 h and 1814 nmol h L^{-1}, respectively [12].

Thermodynamic solubility data of poorly-water soluble compounds in various water-cosolvent mixtures are important in drug discovery processes, preformulation studies and formulation development [13–16]. Therefore, it is important to measure thermodynamic solubility data of vitamin D3 in various aqueous-cosolvent mixtures. The IUPAC name of Transcutol® has been proposed as "2-(2-ethoxyethoxy)ethanol" [15]. Recently, Transcutol has been investigated as a potential cosolvent for solubility enhancement of various poorly water-soluble compounds [13,15,17].

Recently, the solubility data of vitamin D3 in eleven different mono solvents including Transcutol and water at temperatures "T = 273.2 K to 298.2 K" and pressure "p = 0.1 MPa" have been reported by Almarri

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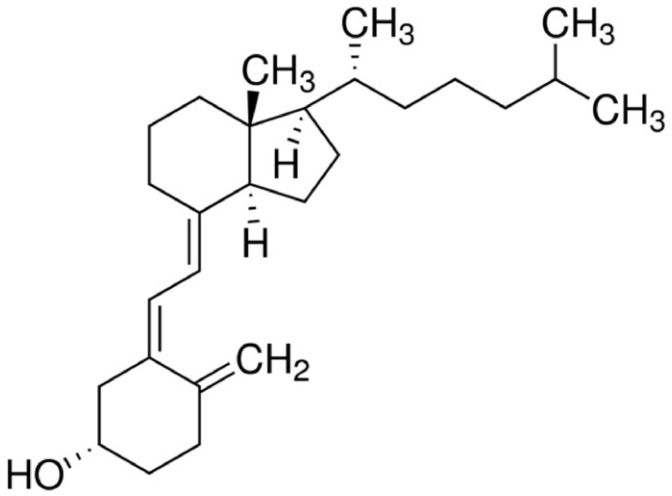

Fig. 1. Chemical structure of vitamin D3.

et al. [10]. Lian et al. also reported the solubility data of vitamin D3 in six organic solvents at "$T = 248.2$ K to 273.2 K" and "$p = 0.1$ MPa" [1].

Nevertheless, thermodynamic solubility data of vitamin D3 in various "Transcutol + water" mixtures have not been presented in literature or encyclopedia or any pharmacopoeia. Hence, in the current research work, the solubilities of vitamin D3 in mole fractions in various "Transcutol + water" mixtures were determined at "$T = 273.2$ K to 298.2 K" and "$p = 0.1$ MPa" by high performance liquid chromatography (HPLC) coupled with ultraviolet (UV) detector method. "Apparent thermodynamic analysis" on solubility data of vitamin D3 was also applied in order to investigate its dissolution and solvation behavior in various "Transcutol + water" mixtures. The proposed HPLC-UV method was validated in terms of different parameters such as "linearity, selectivity, accuracy, precision, sensitivity and robustness" for this purpose. The proposed analytical methodology could be useful in routine analysis of vitamin D3 in pharmaceutical and nutraceutical samples. Moreover, the solubility data of vitamin D3 recorded in this work could be useful in its pre-formulation studies and formulation development.

2. Experimental

2.1. Materials

Vitamin D3 was obtained from "Sigma Aldrich (St. Louis, MO)". Transcutol® [IUPAC name: 2-(2-ethoxyethoxy)ethanol] was obtained from "Gattefosse (Lyon, France)". Water was obtained from "Milli-Q unit". HPLC grades methyl alcohol (IUPAC name: methanol) and ethyl alcohol (IUPAC name: ethanol) were obtained from E-Merck (Darmstadt, Germany). The details of materials used in this work are furnished in Table 1.

2.2. Instrumentation and analytical conditions

Chromatographic analysis of vitamin D3 was carried out at $T = 298.2$ K using a "Waters HPLC system (Waters, USA) attached to a 1515 isocratic HPLC pump, 717 plus Autosampler, quaternary LC-10A VP pumps and a programmable 2487 dual λ absorbance UV-visible detector". The software used for data analysis was "Millennium (version 32)". The chromatographic separation of vitamin D3 was performed on "Nucleodur (150 mm × 4.6 mm, 5 μm) RP C8 column. The binary mixture of ethanol:methanol (50:50% v/v) was used as an environmentally benign mobile phase which was delivered a flow rate of 1.0 mL min^{-1}. The analysis was performed in UV mode at 254 nm. Waters Autosampler was used to inject samples (10 μL) into the HPLC system.

2.3. Standard solution of vitamin D3

Calibration/standard curve of vitamin D3 was prepared in the concentration range of (0.10 to 100) μg g^{-1}. The concentration of standard solution of vitamin D3 prepared was 100 μg g^{-1}. From this standard solution, serial dilutions were prepared by dilution of standard solution with mobile phase to obtain the concentrations of vitamin D3 in the range of (0.10 to 100) μg g^{-1}.

2.4. Method development

Various environmentally benign eluents were utilized as the environmentally benign mobile phases in order to develop a suitable RP-HPLC method for the quantification of vitamin D3 in pure form and thermodynamic solubility samples. Various criteria including method sensitivity, quantification time, chromatographic parameters, toxicity of solvents, the effort required for the preparation and cost of solvents were applied during method development. Based on these criteria, we had investigated methanol–water, methanol-ethyl acetate, ethanol-water, ethanol-ethyl acetate and ethanol-methanol as mobile phases at different proportions. Among the investigated mobile phases for analysis, a combination of ethanol:methanol (50:50% v/v) was finally selected as an eluent for further analysis of vitamin D3.

2.5. Method validation

The proposed analytical methodology was validated for various parameters including "linearity, selectivity, accuracy, precision and robustness [18, 19]". For the determination of linearity, calibration curves were plotted in the concentration range of (0.10 to 100) μg g^{-1}. The binary mixture of ethanol:methanol (50:50% v/v) was delivered at a flow rate of 1 mL min^{-1} for equilibration of the column. Vitamin D3 at different concentrations was analyzed at 254 nm. Each concentration of vitamin D3 was injected in triplicate manner. During this process, the peak area of each concentration of vitamin D3 was recorded. The calibration curves were plotted between the concentrations and measured peak areas.

The proposed HPLC-UV method was also evaluated for the selectivity. The selectivity of the method was determined by repeating 6 different injections of selected concentration of vitamin D3 (10 μg g^{-1}). Finally, the variations in chromatographic performance in terms of retention time and peak area were recorded and interpreted [18].

The accuracy as the % recovery was measured by reported standard addition method [20]. For accuracy measurements, 10 μg g^{-1} of the standard vitamin D3 solution was spiked with an extra 0, 50, 100 and

Table 1
A sample table for materials used in this work.

Material	Molecular formula	Molar mass (g mol^{-1})	CAS registry no.	Purification method	Mass fraction purity	Analysis method	Source
Vitamin D3	$C_{27}H_{44}O$	384.60	67-97-0	None	>0.98	HPLC	Sigma Aldrich
Transcutol	$C_6H_{14}O_3$	134.17	111-90-0	None	>0.99	GC	Gattefosse
Ethanol	C_2H_5OH	46.07	64-17-5	None	>0.99	GC	E-Merck
Methanol	CH_3OH	32.04	67-56-1	None	>0.99	GC	E-Merck
Water	H_2O	18.07	7732-18-5	None	–	–	Milli-Q

150% standard solution of vitamin D3 and were reanalyzed by the proposed HPLC-UV method. Each experiment was carried out in triplicate manner. Results of accuracy were interpreted in terms of "the percent of the relative standard deviation (% *RSD*), recovery (%) and standard error (*SE*)" at each concentration level.

With a view of determining the precision of the proposed HPLC-UV method, both intraday as well as intermediate precisions were measured. For the determination of intraday precision, the samples at four different concentrations of vitamin D3 (10, 15, 20 and 25 μg g^{-1}) were analyzed on the same day in triplicate manner. However, for the determination of intermediate precision, the proposed HPLC-UV method was assessed by repeating the same studies on three different days [19].

The sensitivity of proposed HPLC-UV method was determined in terms of the limit of detection (*LOD*) and the limit of quantification (*LOQ*). The *LOD* and *LOQ* were determined by standard deviation (*SD*) method. For the determination of *LOD* and *LOQ*, blank samples (samples without vitamin D3) were injected into the HPLC system in triplicates manner and the peak areas of each blank sample were recorded. *LOD* and *LOQ* were calculated with the help of slope (*S*) of the calibration curve and the *SD* of the peak area using Eqs. (1) and (2), respectively [20]:

$$LOD = 3.3 \times \frac{SD}{S} \tag{1}$$

$$LOD = 10 \times \frac{SD}{S} \tag{2}$$

The robustness of the proposed HPLC-UV method was determined in order to evaluate the deliberate changes in the set experimental conditions on the analysis of vitamin D3. The target concentration of vitamin D3 (10 μg g^{-1}) was selected for such studies. Robustness of this method was determined by comparing the changes observed in the chromatographic responses by changing the eluent flow rate from 1.0 to 0.90 and 1.10 mL min^{-1}, wavelength of detection from 254 nm to 250 nm and 258 nm and the percentage of ethanol/methanol in mobile phase from 50 to 45 and 55% [19,20].

2.6. Measurement of vitamin D3 solubility in "Transcutol + water" mixtures by proposed HPLC-UV method

The solubility of vitamin D3 against mass fraction of Transcutol (m = 0.1 to 0.9; m is the mass fraction of Transcutol in "Transcutol + water" mixtures) in different "Transcutol + water" mixtures including mono solvents neat water ($m = 0.0$) and neat Transcutol ($m = 1.0$) was determined at "T = 273.2 K to 298.2 K" and "p = 0.1 MPa". Solubility measurements were carried out using shake flask method of Higuchi & Connors [21]. Therefore, the excess amount of solid vitamin D3 was added in known amounts of each "Transcutol + water" mixture including mono solvents. Each experiment was carried out in triplicates manner. These drug-cosolvent mixtures were prepared carefully in amber colored glass vials because vitamin D3 has been reported as a photosensitive drug [22]. The resultant mixtures of drug-cosolvent were vortexed for 5 min in order to sure their nature as concentrated suspensions and transferred to biological shaker OLS 200 (Grant Scientific, Cambridge, UK) at 100 rpm for 48 h [10]. After 48 h, the samples were taken out from the shaker and allowed to settle vitamin D3 particles for 24 h [23]. The supernatants were carefully withdrawn from each sample, diluted suitably with mobile phase and subjected for the analysis of vitamin D3 content by the proposed HPLC-UV method at 254 nm.

The "experimental mole fraction solubilities (x_e)" of vitamin D3 were then calculated using Eqs. (3) and (4) [24,25]:

$$x_e = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \tag{3}$$

$$x_e = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \tag{4}$$

in which, m_1 is the mass of vitamin D3 and m_2 and m_3 are the masses of Transcutol and water, respectively. M_1 is the molar mass of vitamin D3 and M_2 and M_3 are the molar masses of Transcutol and water, respectively. Eq. (3) was applied for the calculation of x_e values of vitamin D3 in mono solvents (Transcutol and water) and Eq. (4) was applied for the calculation of x_e values of vitamin D3 in "Transcutol + water" mixtures.

3. Results and discussion

3.1. Method development

With a view to develop an environmentally benign HPLC-UV method for the analysis of vitamin D3, various combinations of mobile phases were investigated. It was observed that the combination of methanol-water and methanol-ethyl acetate as the eluents resulted in an asymmetric peak with poor chromatographic performance. Further, the combinations of ethanol-water and ethanol-ethyl acetate as another eluent systems resulted in a chromatograph with a poor peak but improved asymmetry. In order to obtain a good peak with better chromatographic

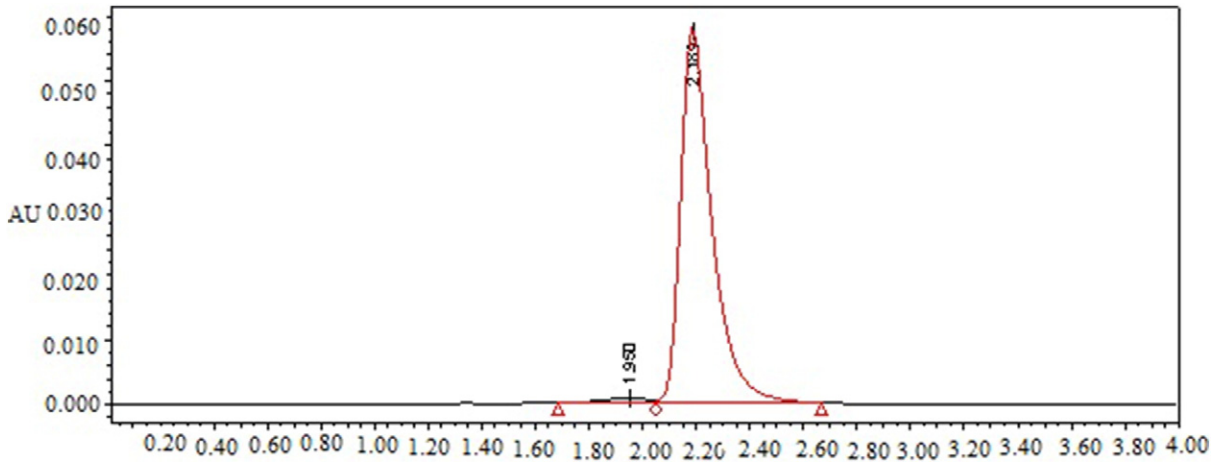

Fig. 2. Representative HPLC-UV chromatogram of vitamin D3 in binary mixture of ethanol:methanol (50:50% v/v).

Table 2
Linear regression analysis for the calibration curves of vitamin D3 ($n = 3$).

Parameters	Values
Linearity range	0.1–100 μg g^{-1}
Coefficient of determination ($R^2 \pm SD$)	0.9997 ± 0.0007
Regression equation	y = 22,977x + 2812.6
Slope ± *SD*	22,977 ± 76.58
Confidence interval of slope[a]	190.23
SE of slope	44.21
Slope without intercept	23,018
Intercept ± *SD*	2812.60 ± 34.14
Confidence interval of intercept[a]	84.81
Standard error of intercept	19.71

[a] 95% confidence interval.

Table 3
Selectivity of the proposed HPLC-UV method ($n = 6$).

Conc. (μg g^{-1})	Peak area	Mean area ± *SD*	*RSD* (%)	R_t (min)	Mean R_t ± *SD*	*RSD* (%)
10	221,022	221,805.80 ±	0.28	1.79	1.79 ±	1.65
	221,354	636.32		1.77	0.03	
	222,148			1.77		
	222,348			1.84		
	222,587			1.78		
	221,376			1.76		

Table 4
Accuracy of the proposed HPLC-UV method ($n = 3$).

Standard added to analyte (%)	Theoretical concentration (μg g^{-1})	Measured concentration (μg g^{-1}) ± *SD*	*RSD* (%)	*SE*	Recovery (%)
0	10	9.86 ± 0.12	1.21	0.06	98.60
50	15	14.77 ± 0.14	0.94	0.08	99.46
100	20	20.24 ± 0.18	0.88	0.10	101.20
150	25	25.50 ± 0.21	0.82	0.12	102.00

performance, the binary mixture of ethanol and methanol was investigated as an alternate mobile phase. Among several compositions of ethanol-methanol studied, the binary combination at 50:50% v/v was recorded to be the best with a sharp peak, appropriate retention time (R_t) and good asymmetry factor. Therefore, the combination of ethanol and methanol (50:50% v/v) was finally selected to obtain a fast and rapid analytical method for vitamin D3 with a rational run time (4 min), appropriate R_t (2.18 ± 0.02 min) and satisfactory tailing or asymmetry factor (Fig. 2).

3.2. Method validation

Linearity of the proposed HPLC-UV method was determined using linear regression analysis and R^2. The results of linear regression analysis for the calibration curve of vitamin D3 are presented in Table 2. The calibration curve of vitamin D3 was recorded linear in the concentration range of (0.10–100) μg g^{-1}. The regressed equation for calibration curve of vitamin D3 was obtained as y = 22,977x + 2812.6 with R^2 value of 0.9997. No significant variations were recorded in the slopes of standard curves of vitamin D3 ($P > 0.05$).

Table 6
Robustness of the proposed HPLC-UV method ($n = 3$).

Parameters	Mean area ± *SD*	*RSD* (%)	*SE*
Mobile phase composition (% v/v)			
45:55	205,432 ± 2015	0.98	1163.39
55:45	203,478 ± 1978	0.97	1142.03
Flow rate (mL min^{-1})			
1.10	213,345 ± 2234	1.04	1289.83
0.90	215,612 ± 2303	1.06	1329.67
Wavelength (nm)			
250	216,167 ± 1876	0.86	1083.14
258	214,234 ± 1985	0.92	1146.07

The results of selectivity of the proposed HPLC-UV method are presented in Table 3. The variations in R_t and peak area were recorded for selectivity determination. The magnitude of % *RSD* in peak area and R_t were obtained as 0.28 and 1.24, respectively. The lower values of % *RSD* in peak area and R_t indicated the selectivity of the proposed HPLC-UV method.

The accuracy of the proposed HPLC-UV method was measured by the standard addition method in terms of % recovery. The results are presented in Table 4. Good recoveries (98.46 to 102.00) % of the added drug were obtained at each concentration level investigated. These results indicated the accuracy of the proposed HPLC-UV method for analysis of vitamin D3.

The results of precisions as intraday and intermediate precisions were expressed in terms of % *RSD* and results are presented in Table 5. Lower values of % *RSD* (1.06 to 1.31) % were obtained for the proposed HPLC-UV method at four different concentration levels. These results indicated the precision of the proposed HPLC-UV method for the analysis of vitamin D3.

The *LOD* and *LOQ* of the proposed HPLC-UV method were determined by calculating the *SD* of the blank sample. The magnitude of *LOD* and *LOQ* of the proposed HPLC-UV method were obtained as 0.054 and 0.162 μg g^{-1}, respectively. The lower values of *LOD* and *LOQ* indicated the sensitivity of the proposed HPLC-UV method.

For the determination of robustness of the proposed HPLC-UV method, the *SD*, % *RSD* and *SE* of the peak areas for all variables at a concentration level of 10 μg g^{-1} are presented in Table 6. As a result of making small changes in the mobile phase composition, the wavelength of detection and flow rate, small magnitudes of *SD*, % *RSD* and *SE* were obtained. These results indicated the robustness of the proposed HPLC-UV method for the analysis of vitamin D3.

3.3. Experimental solubilities of vitamin D3 and possible literature comparison

The measured x_e values of vitamin D3 in various "Transcutol + water" mixtures including mono solvents at "T = 273.2 K to 298.2 K" and "p = 0.1 MPa" are listed in Table 7. The solubilities of vitamin D3 in mole fractions have been reported in eleven different mono solvents including Transcutol and water at "T = 273.2 K to 298.2 K" by Almarri et al. [10]. Liang et al. also reported the mole fraction solubility data of vitamin D3 in six different organic solvents at "T = 248.2 K 273.2 K" [1]. Nevertheless, the solubilities of vitamin D3 in different

Table 5
Precision of the proposed HPLC-UV method ($n = 3$).

Conc. (μg g^{-1})	Repeatability (intra-day precision)			Intermediate precision (inter-day)		
	Mean area ± *SD*	*RSD* (%)	*SE*	Mean area ± *SD*	*RSD* (%)	*SE*
10	231,124 ± 2845	1.23	1642.60	233,421 ± 3078	1.31	1777.13
15	324,214 ± 3654	1.12	2109.69	317,858 ± 3845	1.20	2219.97
20	470,142 ± 5010	1.06	2892.60	476,548 ± 5512	1.15	3182.44
25	561,245 ± 6023	1.07	3477.48	570,247 ± 6845	1.20	3952.07

Table 7
The x_e values of vitamin D3 against m value of Transcutol in various "Transcutol + water" mixtures at "$T = 273.2$ K to 298.2 K" and "$p = 0.1$ MPa"[a].

m	x_e				
	$T = 273.2$ K	$T = 278.2$ K	$T = 283.2$ K	$T = 288.2$ K	$T = 298.2$ K
0.0	1.97×10^{-7}	2.95×10^{-7}	4.38×10^{-7}	5.71×10^{-7}	1.06×10^{-6}
0.1	8.38×10^{-7}	1.23×10^{-6}	1.69×10^{-6}	2.24×10^{-6}	3.80×10^{-6}
0.2	3.57×10^{-6}	4.94×10^{-6}	6.74×10^{-6}	8.44×10^{-6}	1.42×10^{-5}
0.3	1.54×10^{-5}	2.03×10^{-5}	2.64×10^{-5}	3.25×10^{-5}	5.07×10^{-5}
0.4	6.39×10^{-5}	8.17×10^{-5}	1.06×10^{-4}	1.29×10^{-4}	1.84×10^{-4}
0.5	2.72×10^{-4}	3.34×10^{-4}	4.14×10^{-4}	4.79×10^{-4}	6.60×10^{-4}
0.6	1.17×10^{-3}	1.37×10^{-3}	1.63×10^{-3}	1.86×10^{-3}	2.40×10^{-3}
0.7	4.89×10^{-3}	5.56×10^{-3}	6.35×10^{-3}	6.96×10^{-3}	8.58×10^{-3}
0.8	2.07×10^{-2}	2.28×10^{-2}	2.50×10^{-2}	2.70×10^{-2}	3.11×10^{-2}
0.9	8.73×10^{-2}	9.20×10^{-2}	9.77×10^{-2}	1.03×10^{-1}	1.13×10^{-1}
1.0	3.68×10^{-1}	3.74×10^{-1}	3.83×10^{-1}	3.90×10^{-1}	4.04×10^{-1}

[a] The standard uncertainties u are $u(T) = 0.12$ K, $u_r(m) = 0.1\%$, $u(p) = 0.003$ MPa and $u_r(x_e) = 1.43\%$.

Table 8
Van't Hoff parameters (a and b), R^2 and MPD values for vitamin D3 in various "Transcutol + water" mixtures.

m	a	b	R^2	MPD (%)
0.0	4.47	−5430.40	0.9965	0.13
0.1	3.93	−4886.90	0.9972	0.08
0.2	3.75	−4447.20	0.9979	0.14
0.3	3.02	−3847.80	0.9989	0.50
0.4	3.01	−3456.00	0.9956	0.99
0.5	2.32	−2874.00	0.9971	0.54
0.6	1.86	−2350.10	0.9975	0.44
0.7	1.36	−1825.20	0.9976	0.15
0.8	0.97	−1324.20	0.9984	0.08
0.9	0.63	−838.39	0.9991	0.07
1.0	0.12	−306.98	0.9971	0.21

"Transcutol + water" mixtures at different temperatures have not been reported.

Generally, the x_e values of vitamin D3 were found to be increasing with the rise in temperature and increase in m value of Transcutol in "Transcutol + water" mixtures. The highest x_e value of vitamin D3 was obtained in neat Transcutol (4.04×10^{-1} at "$T = 298.2$ K"). However, the lowest one was obtained in neat water (1.97×10^{-7} at "$T = 298.2$ K"). The highest x_e value of vitamin D3 in neat Transcutol was probably due to the lower dielectric constant/polarity of Transcutol as compared with higher dielectric constant/polarity of water [13,15]. The impact of the m value of Transcutol on natural logarithmic x_e (ln x_e) values of vitamin D3 at "$T = 273.2$ K to 298.2 K" was also studied and results are presented in Fig. 3. It can be seen from Fig. 3 that with increase in the m value of Transcutol in "Transcutol + water" mixtures, the solubilities of vitamin D3 were also increasing linearly at each temperature studied. The x_e values of vitamin D3 were significantly enhanced from neat water to neat Transcutol. The addition of a small quantity of Transcutol in water resulted in significant increase in the solubility of vitamin D3. Hence, Transcutol could be utilized as a potential and physiologically compatible cosolvent in solubility enhancement of vitamin D3 in water. Based on the results obtained in the current research work, vitamin D3 has been considered as very soluble in neat Transcutol and practically insoluble in neat water [13,15].

3.4. Correlation/curve fitting of x_e values of vitamin D3

With the view to validate experimental solubilities of vitamin D3 measured by the proposed HPLC-UV method, the x_e values of vitamin D3 were correlated and fitted with three different semiempirical models including "Van't Hoff, Apelblat and Yalkowsky-Roseman" models [26–29]. The "Van't Hoff" solubilities ($x^{Van't}$) of vitamin D3 in various "Transcutol + water" mixtures including mono solvents were calculated using Eq. (5) [28]:

$$\ln x^{Van't} = a + \frac{b}{T} \tag{5}$$

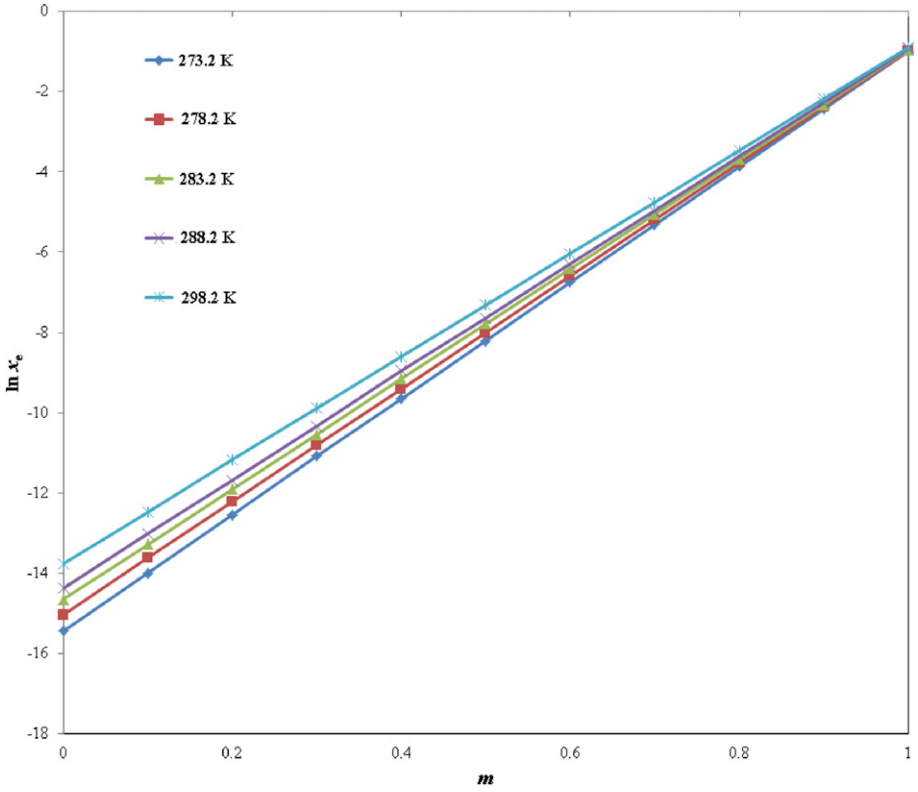

Fig. 3. Impact of m value of the Transcutol on ln x_e values of vitamin D3 at five different temperatures i.e. "$T = 273.2$ K to 298.2 K".

in which, the symbols "a and b" are the model parameters of Eq. (1) which were determined by plotting ln x_e values of vitamin D3 against of $1/T$.

The x_e values of vitamin D3 were correlated with $x^{Van't}$ values of vitamin D3 in terms of mean percent deviations (*MPD*) and R^2 values. The *MPD* values between x_e and $x^{Van't}$ for vitamin D3 were calculated using Eq. (6) [30]:

$$MPD = \frac{100}{N}\sum \frac{(x^{Van't} - x_e)}{x^{Van't}} \quad (6)$$

in which, N represents the total number of experimental data points which were 55 (11 different cosolvent mixtures at five different temperatures) in the current research work.

The resulting data of Van't Hoff correlation in various "Transcutol + water" mixtures are listed in Table 8. The *MPD* values in various "Transcutol + water" mixtures including mono solvents were obtained as (0.07 to 0.99) %. The highest *MPD* value for vitamin D3 was obtained at $m = 0.4$ of Transcutol (0.99%). However, the lowest value of *MPD* was obtained at $m = 0.9$ of Transcutol (0.07%). The R^2 values were for vitamin D3 were obtained as 0.9956 to 0.9991. These results in terms of R^2 and *MPD* indicated good correlation of x_e values of vitamin D3 with "Van't Hoff model".

The "Apelblat model" solubilities (x^{Apl}) of vitamin D3 in various "Transcutol + water" mixtures were determined using Eq. (7) [26,27]:

$$\ln x^{Apl} = A + \frac{B}{T} + C \ln(T) \quad (7)$$

in which, the symbols "A, B and C" are the model coefficients of Eq. (7) which were determined by nonlinear multivariate regression analysis of x_e values of vitamin D3 presented in Table 7 [28]. The x_e values of vitamin D3 were correlated/fitted with x^{Apl} values of vitamin D3 again in terms of *MPD* and R^2 values.

Table 9
Apelblat parameters (A, B and C), R^2 and *MPD* values for vitamin D3 in various "Transcutol + water" mixtures.

m	A	B	C	R^2	*MPD* (%)
0.0	537.56	−28,275.30	−80.12	0.9988	0.05
0.1	490.87	−25,753.90	−73.18	0.9994	0.93
0.2	301.57	−17,208.60	−44.76	0.9989	2.42
0.3	201.91	−12,369.60	−29.89	0.9995	2.97
0.4	464.29	−23,224.70	−69.33	0.9999	1.09
0.5	274.41	−14,533.80	−40.89	0.9993	8.28
0.6	223.53	−11,849.60	−33.31	0.9997	3.56
0.7	147.57	−8090.49	−21.97	0.9991	1.41
0.8	109.85	−5989.84	−16.36	0.9999	1.69
0.9	44.44	−2715.68	−6.58	0.9997	1.28
1.0	4.05	−475.36	−0.59	0.9973	1.94

The resulting data of Apelblat correlation in various "Transcutol + water" mixtures are listed in Table 9. The graphical representation and curve fitting between x_e and x^{Apl} values of vitamin D3 are shown in Fig. 4 which indicated good graphical correlation between experimental and calculated solubilities of vitamin D3. The *MPD* values in various "Transcutol + water" mixtures including mono solvents were obtained as (0.05 to 8.28) %. The highest *MPD* value for vitamin D3 was obtained at $m = 0.5$ of Transcutol (8.28%). However, the lowest one was obtained in neat water (0.05%). The R^2 values for vitamin D3 were obtained as 0.9973 to 0.9999. These results again indicated good correlation of x_e values of vitamin D3 with "Apelblat model".

The "logarithmic solubilities of Yalkowsky" models (log x^{Yal}) in various "Transcutol + water" mixtures were calculated using Eq. (8) [29]:

$$Logx^{Yal} = m_1 \log x_1 + m_2 \log x_2 \quad (8)$$

in which, "x_1 and x_2" are the solubilities of vitamin D3 in mole fractions in mono solvent 1 (Transcutol) and mono solvent 2 (water),

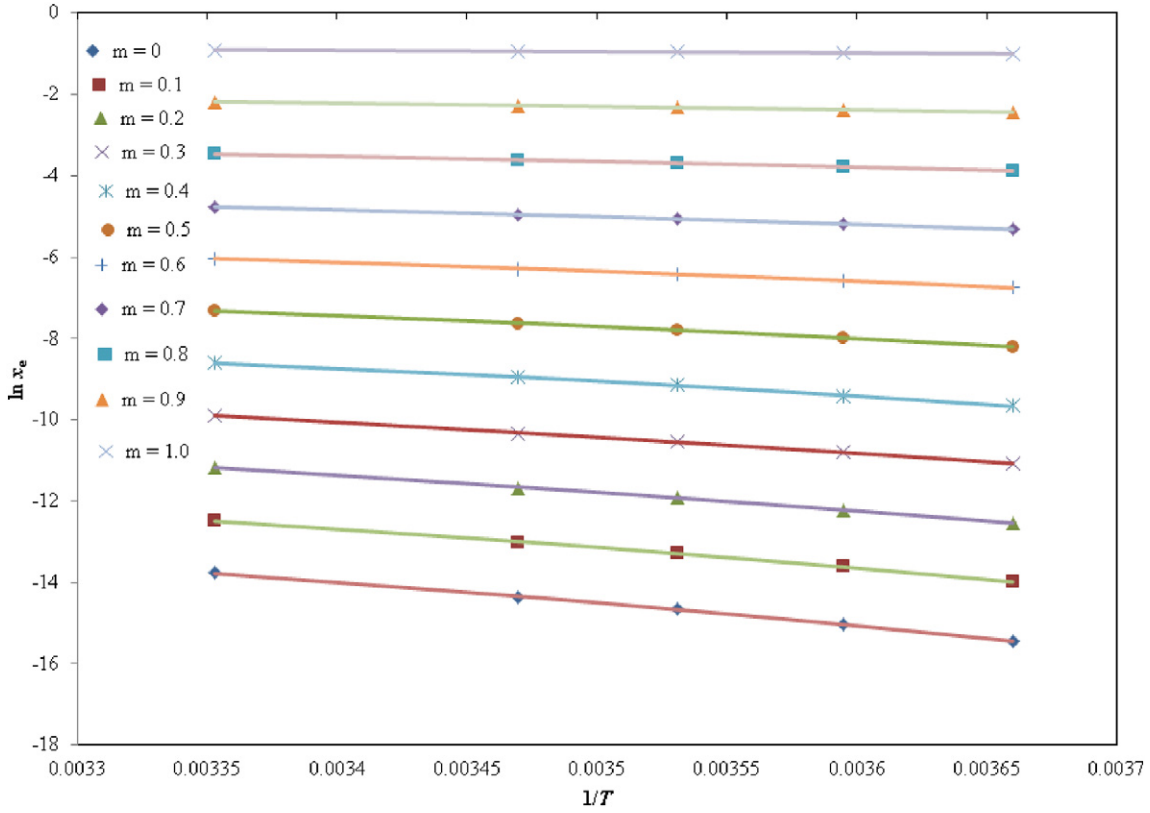

Fig. 4. Correlation/curve fitting of ln x_e values of vitamin D3 with Apelblat model in various "Transcutol + water" mixtures at "$T = 273.2$ K to 298.2 K" (Apelblat solubilities are represented by solid lines and experimental solubilities of vitamin D3 are represented by symbols.

Table 10
Log x^{Yal} values of vitamin D3 calculated by log-linear model of Yalkowsky in various "Transcutol + water" mixtures at "T = 273.2 K to 298.2 K".

m	Log x^{Yal}					*MPD* (%)
	273.2 K	278.2 K	283.2 K	288.2 K	298.2 K	
0.1	−6.07	−5.91	−5.76	−5.65	−5.41	4.48
0.2	−5.45	−5.30	−5.17	−5.07	−4.85	7.37
0.3	−4.82	−4.69	−4.57	−4.49	−4.30	10.55
0.4	−4.19	−4.08	−3.98	−3.90	−3.74	16.15
0.5	−3.56	−3.47	−3.38	−3.32	−3.18	8.89
0.6	−2.94	−2.86	−2.79	−2.74	−2.62	16.00
0.7	−2.31	−2.25	−2.19	−2.15	−2.06	4.83
0.8	−1.68	−1.64	−1.60	−1.57	−1.50	8.68
0.9	−1.06	−1.03	−1.01	−0.99	−0.95	5.03

respectively; and "m_1 and m_2" are the mass fractions of mono solvent 1 (Transcutol) and mono solvent 2 (water) in the absence of vitamin D3, respectively.

The resulting data of Yalkowsky model calculation in various "Transcutol + water" mixtures are presented in Table 10. Yalkowsky correlation was carried in terms of *MPD* only. The *MPD* values for vitamin D3 in various "Transcutol + water" mixtures were obtained as (4.48 to 16.15) %. The highest *MPD* value for vitamin D3 was obtained at m = 0.4 of Transcutol (16.15%). However, the lowest one was obtained at m = 0.1 of Transcutol (4.48%). These results again indicated good correlation of x_e values of vitamin D3 with "Yalkowsky model".

3.5. Dissolution behavior of vitamin D3 by apparent thermodynamic analysis

The dissolution behavior of vitamin D3 in various "Transcutol + water" mixtures was determined by "apparent thermodynamic analysis". Various "standard apparent thermodynamic parameters" such as "standard apparent enthalpy ($\Delta_{sol}H^0$), standard apparent Gibbs free energy ($\Delta_{sol}G^0$) and standard apparent entropy ($\Delta_{sol}S^0$)" were measured in order to evaluate dissolution behavior of vitamin D3. The "$\Delta_{sol}H^0$ values" for dissolution thermodynamics of vitamin D3 in various "Transcutol + water" mixtures were determined at "mean harmonic temperature (T_{hm})" of 283.94 K by applying "Van't Hoff analysis" using Eq. (9) [31,32]:

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

in which, the symbol R (8.314 J mol^{-1} K^{-1}) is the universal gas constant and other parameters have already been defined. The "$\Delta_{sol}H^0$ values" for vitamin D3 dissolution in various "Transcutol + water" mixtures were determined from the slopes of graphs plotted between ln x_e values of vitamin D3 and ${}^{1}/_{T} - {}^{1}/_{T_{hm}}$.

The "$\Delta_{sol}G^0$ values" for vitamin D3 dissolution in various "Transcutol + water" mixtures were also determined at T_{hm} of 283.94 K using Eq. (10) by applying "Krug et al. analysis" approach [33]:

$$\Delta_{sol}G^0 = -RT_{hm} \times \text{intercept} \tag{10}$$

in which, the intercept values for vitamin D3 in each cosolvent mixture were taken from Van't Hoff plot discussed in previous paragraph.

Finally, the "$\Delta_{sol}S^0$ values" for vitamin D3 dissolution in various "Transcutol + water" mixtures were determined by applying the combined approaches of "Van't Hoff and Krug et al. analysis" using Eq. (11) [31-33]:

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

The results of "apparent thermodynamic analysis" for dissolution behavior of vitamin D3 in various "Transcutol + water" mixtures are presented in Table 11.

The "$\Delta_{sol}H^0$ values" for vitamin D3 dissolution in various "Transcutol + water" mixtures were obtained as positive values in the range of (2.55 to 45.13) kJ mol^{-1}. The mean "$\Delta_{sol}H^0$ value" for vitamin D3 dissolution was recorded as 23.86 kJ mol^{-1} with relative standard deviation (*RSD*) value of 0.59. The "$\Delta_{sol}H^0$ values" of vitamin D3 were found to be decreasing linearly with increase in the m value of Transcutol in "Transcutol + water" mixtures and the x_e value of vitamin D3. The highest "$\Delta_{sol}H^0$ value" for vitamin D3 dissolution was obtained in neat water (45.13 kJ mol^{-1}). However, the lowest "$\Delta_{sol}H^0$ value" for vitamin D3 dissolution was obtained in neat Transcutol (2.55 kJ mol^{-1}). The "$\Delta_{sol}G^0$ values" for vitamin D3 dissolution in various "Transcutol + water" mixtures were also obtained as positive values in the range of (2.25 to 34.58) kJ mol^{-1}. The mean "$\Delta_{sol}G^0$ value" for vitamin D3 dissolution was recorded as 18.40 kJ mol^{-1} with *RSD* value of 0.58. The "$\Delta_{sol}G^0$ values" for vitamin D3 dissolution were also found to be decreasing linearly with increase in m value of Transcutol in "Transcutol + water" mixtures and the x_e value of vitamin D3. The highest and lowest "$\Delta_{sol}G^0$ values" for vitamin D3 dissolution were also obtained in neat water (34.58 kJ mol^{-1}) and neat Transcutol (2.25 kJ mol^{-1}), respectively. The lowest "$\Delta_{sol}H^0$ and $\Delta_{sol}G^0$ values" for vitamin D3 dissolution were possible due to higher solubilities of vitamin D3 in neat Transcutol in comparison with its lower solubilities in neat water. The positive "$\Delta_{sol}H^0$ and $\Delta_{sol}G^0$ values" for vitamin D3 dissolution in various "Transcutol + water" mixtures suggested an "endothermic dissolution" of vitamin D3 in all "Transcutol + water" mixtures studied [34,35]. The "$\Delta_{sol}S^0$ values" for vitamin D3 dissolution in various "Transcutol + water" mixtures were also obtained as positive values in the range of (1.02 to 37.13) J mol^{-1} K^{-1}. The mean "$\Delta_{sol}S^0$ value" for vitamin D3 dissolution was recorded as 19.23 J mol^{-1} K^{-1} with *RSD* value of 0.62. The positive "$\Delta_{sol}S^0$ value" indicated an "entropy-driven dissolution" of vitamin D3 in all "Transcutol + water" mixtures studied [35].

3.6. Solvation behavior of vitamin D3 in "Transcutol + water" mixtures

For the investigation of "solvation behavior and cosolvent action" for vitamin D3 in various "Transcutol + water" mixtures, an "enthalpy-entropy compensation analysis" was performed [32,36]. "Enthalpy-entropy compensation analysis" was performed by making the weighted plots of "$\Delta_{sol}H°$ vs. $\Delta_{sol}G°$" at T_{hm} value of 283.94 K [36]. The results of

Table 11
The $\Delta_{sol}H^0$, $\Delta_{sol}S^0$, $\Delta_{sol}G^0$ and R^2 values for vitamin D3 dissolution in various "Transcutol + water" mixtures calculated by apparent thermodynamic analysis[a].

Parameters	m = 0.0	m = 0.1	m = 0.2	m = 0.3	m = 0.4	m = 0.5	m = 0.6	m = 0.7	m = 0.8	m = 0.9	m = 1.0
$\Delta_{sol}H^0$/kJ mol^{-1}	45.13	40.61	36.95	31.97	28.72	23.88	19.53	15.16	11.00	6.96	2.55
$\Delta_{sol}G^0$/kJ mol^{-1}	34.58	31.34	28.10	24.86	21.61	18.40	15.14	11.94	8.70	5.48	2.25
$\Delta_{sol}S^0$/J mol^{-1} K^{-1}	37.13	32.65	31.19	25.06	25.03	19.31	15.44	11.35	8.11	5.23	1.02
R^2	0.9965	0.9972	0.9980	0.9989	0.9956	0.9972	0.9976	0.9976	0.9984	0.9991	0.9971

[a] The relative uncertainties are $u(\Delta_{sol}H^0)$ = 0.59 kJ mol^{-1}, $u(\Delta_{sol}G^0)$ = 0.58 kJ mol^{-1} and $u(\Delta_{sol}S^0)$ = 0.62 J mol^{-1} K^{-1}.

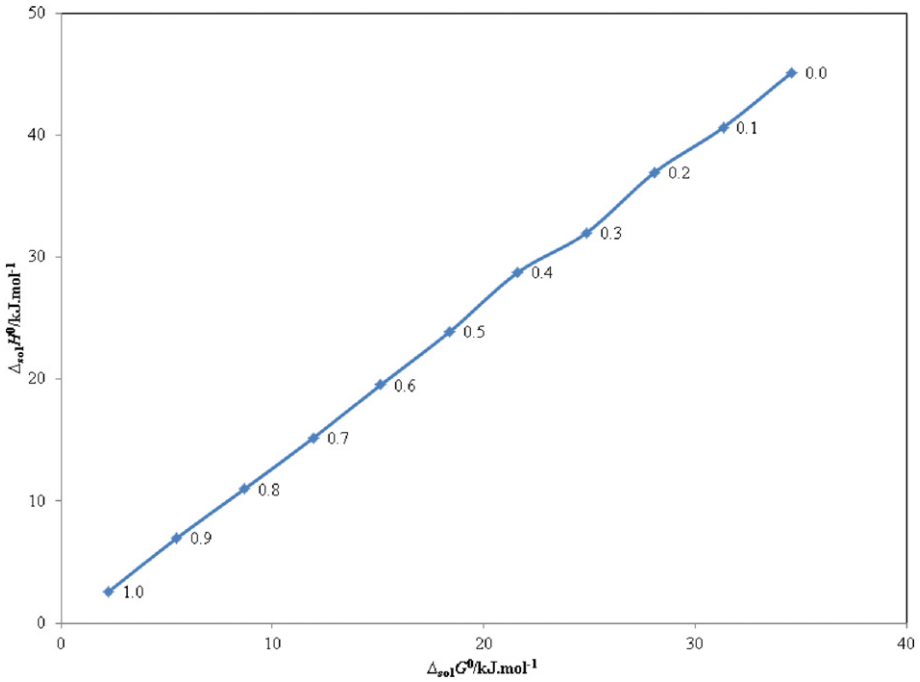

Fig. 5. $\Delta_{sol}H^0$ vs. $\Delta_{sol}G^0$ enthalpy-entropy compensation analyses for solubility of vitamin D3 in various "Transcutol + water" mixtures at T_{hm} value of 283.94 K.

this analysis are presented in Fig. 5. Fig. 5 indicated that vitamin D3 in all "Transcutol + water" mixtures including neat solvents showed linear "$\Delta_{sol}H°$ vs. $\Delta_{sol}G°$" plot with a positive slope value >1.0 with R^2 value of >0.99. Therefore, the "driving mechanism" for solvation behavior of vitamin D3 was proposed as an "enthalpy-driven" in all "Transcutol + water" mixtures including neat solvents i.e. Transcutol and water. This observation was possible due to an excellent solvation of vitamin D3 in Transcutol molecules in comparison with its solvation behavior in water molecules [35]. These results were in accordance with those reported for solvation behavior of ibrutinib in various "Transcutol + water" mixtures [37].

4. Conclusion

An environmentally benign HPLC-UV method was developed and validated for thermodynamic solubility determination of a fat-soluble vitamin (vitamin D3) in various "Transcutol + water" mixtures. The method was found to be selective, accurate, precise, sensitive and robust for the analysis of vitamin D3 in thermodynamic solubility samples. The solubilities of vitamin D3 in mole fractions in various "Transcutol + water" mixtures were determined using shake flask method at "T = 273.2 K to 298.2 K" and "p = 0.1 MPa". The solubilities of vitamin D3 in mole fractions were found to be increasing with increase in temperature and m value of Transcutol in all "Transcutol + water" mixtures studied. The highest and lowest solubilities of vitamin D3 were obtained in neat Transcutol and neat water, respectively by the proposed HPLC-UV method. The experimental solubilities of vitamin D3 were correlated/fitted well with three different semiempirical models including "Apelblat, Van't Hoff and Yalkowsky" models. "Apparent thermodynamic analysis" suggested an "endothermic and entropy-driven dissolution" of vitamin D3 in all "Transcutol + water" mixtures studied. "Enthalpy-entropy compensation" analysis suggested that the solvation behavior of vitamin D3 was "enthalpy-driven" in all "Transcutol + water" mixtures studied. Overall, these results suggested that the developed HPLC-UV method could be successfully applied for routine analysis of vitamin D3 in thermodynamic solubility samples.

Conflict of interest

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

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