International Journal of Pharmaceutics 523 (2017) 410–417

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Solubility and thermodynamics of apremilast in different mono solvents: Determination, correlation and molecular interactions

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ARTICLE INFO

Article history:
Received 4 February 2017
Received in revised form 18 March 2017
Accepted 26 March 2017
Available online 28 March 2017

Keywords:
Apremilast
Activity coefficient
Antipsoriatic arthritis
Dissolution thermodynamics
Mono solvent
Solubility

ABSTRACT

The solubility data of recently launched poorly soluble antipsoriatic drug apremilast (APM) in any mono solvent or cosolvent mixtures with respect to temperature are not available in literature. Hence, in this research work, the solubility of APM in twelve different mono solvents namely "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 determined at temperatures "T = 298.2 K to 318.2 K" and pressure "p = 0.1 MPa". Experimental solubilities of APM in mole fraction were determined by a static equilibrium method using high performance liquid chromatography at 254 nm. Experimental solubilities of APM in mole fraction were correlated well with "Van't Hoff and Apelblat models". The solubilities of APM in mole fraction were recorded highest in DMSO (9.91×10^{-2}), followed by EA (2.54×10^{-2}), Transcutol (2.51×10^{-2}), PEG-400 (2.16×10^{-2}), PG (4.01×10^{-3}), EG (1.61×10^{-3}), IPA (4.96×10^{-4}), 1-butanol (4.18×10^{-4}), 2-butanol (3.91×10^{-4}), methanol (2.25×10^{-4}), ethanol (2.20×10^{-4}) and water (1.29×10^{-6}) at "T = 318.2 K" and similar results were also obtained at each temperature evaluated. The molecular interactions between solute and solvent molecules were evaluated by the determination of activity coefficients. Based on activity coefficients, the higher solute-solvents molecular interactions were recorded in APM-DMSO, APM-EA, APM-Transcutol and APM-PEG-400 in comparison with other combination of solute and solvents. "Apparent standard thermodynamic parameters" of APM indicated an "endothermic and entropy-driven dissolution" of APM in all mono solvents evaluated. Based on these results, APM was proposed as freely soluble in DMSO, EA and Transcutol, sparingly soluble in PEG0-400, slightly soluble in methanol, ethanol, IPA, EG, PG, 1-butanol and 2-butanol and practically insoluble in water. Hence, DMSO, EA and Transcutol were selected as the best solvents and water and ethanol were selected as the anti-solvents for APM.

1. Introduction

Apremilast (APM) [Fig. 1]; IUPAC name: *(S)-N-(2-[1-(3-ethoxy-4-methoxyphenyl)-2-methane* sulfonylethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl) acetamide; molecular formula: $C_{22}H_{24}N_2O_7S$; molar mass: 460.50 g mol^{-1} and CAS registry number: 608141-41-9 is available commercially as a light yellow to off-white crystalline powder (Man et al., 2009; Tang et al., 2016). It is an orally active small molecule inhibitor of type-4 cyclic nucleotide phosphodiesterase which is recently approved by United States Food and Drug Administration (USFDA) for the treatment of psoriatic arthritis and plaque arthritis (FDA, 2014; Schafer et al., 2014; Souto and Gomez-Reino, 2015). It produces multiple anti-inflammatory effects in comparison with other anti-inflammatory drugs (Tang et al., 2016). According to USFDA and European Medicines Agency (EMA) database, APM has been reported as practically insoluble in water (EMA, 2014; FDA, 2014). It is marketed under the trade name of Otezela® for the treatment of psoriatic arthritis and plaque arthritis (EMA, 2014; Tang et al., 2016). It is commercially available as the immediate release (IR) tablets in the strengths of 10, 20 and 30 mg (EMA, 2014; FDA, 2014). APM IR tablets show poor bioavailability due to its poor solubility in water after oral administration (EMA, 2014; Tang et al., 2016). Its oral bioavailability has been reported as 20–33% and absolute bioavailability was obtained as around 73% (EMA, 2014).

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http://dx.doi.org/10.1016/j.ijpharm.2017.03.067
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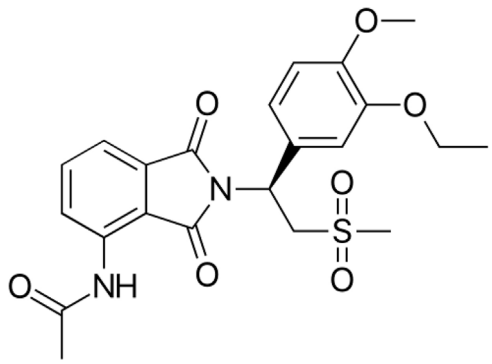

Fig. 1. Molecular structure of APM (molar mass: 460.50 g mol^{-1}); apremilst (APM).

Due to its poor solubility in water, its formulation development especially in terms of liquid dosage forms is very difficult. The solubility data of drugs/biomolecules in "aqueous and organic solvents" are important in their pre-formulation studies and formulation development (Anwer et al., 2014; Shakeel et al., 2015a, b, 2016; Alshora et al., 2016; Almarri et al., 2017). Therefore, it is of great importance to determine the solubility of APM properly in the solvents which could be useful for its pharmaceutical applications. Till date, only extended release tablet formulations of APM have been investigated both *in vitro* as well as *in vivo* in literature (Tang et al., 2016). No formulation technique or cosolvency model had been investigated for solubilization of APM in an aqueous media. The solubility (as mole fraction) of APM in water at room temperature (T = 298.2 K) has been reported as 2.74×10^{-7} by USFDA and EMA database (EMA, 2014; FDA, 2014). To the best of the knowledge of authors, the solubility data of APM in any organic solvent or cosolvent mixtures have not been reported in literature. Hence, in this research work, the solubility of solid APM in twelve different mono solvents namely "water, methanol, ethanol, Transcutol, polyethylene glycol-400 (PEG-400), propylene glycol (PG), ethylene glycol (EG), isopropanol (IPA), 1-butanol, 2-butanol, ethyl acetate (EA) and dimethyl sulfoxide (DMSO)" were determined at temperatures "T = 298.2 K to 318.2 K" and pressure "p = 0.1 MPa". "Apparent thermodynamic analysis" on experimental solubility data of APM was also carried out by "Van't Hoff and Krug et al. analysis" for the investigation of dissolution behavior of APM (Krug et al., 1976; Ruidiaz et al., 2010; Holguín et al., 2012). The molecular interactions between solute and solvent molecules were described by the determination of activity coefficients of APM. The solubility data of APM obtained in this research work would be useful in various industrial processes including "purification, recrystallization, drug discovery and formulation development" of APM especially in terms of liquid dosage forms.

2. Experimental

2.1. Materials

APM and Transcutol® [IUPAC name: 2-(2-ethoxyethoxy) ethanol] were obtained from "Beijing Mesochem Technology Co. Pvt. Ltd. (Beijing, China)" and "Gattefosse (Lyon, France)", respectively. 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)". Methyl alcohol (IUPAC name: methanol), ethyl alcohol (IUPAC name: ethanol), 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 used in this work was deionized water (specific conductivity was $<1.0\ \mu S\ cm^{-1}$) and obtained from "Milli-Q water purification unit". The information regarding all these materials is listed in Supplementary Table 1 (Table S1).

2.2. Quantification of APM

The quantification of APM was carried out using "reversed-phase high performance liquid chromatography (RP-HPLC)" method which was equipped with "ultra-violet (UV)" detector. All quantifications of APM were performed at "T = 298.2 K" using "Waters HPLC system (Waters, USA)". The column utilized for the quantification of APM was "Nucleodur (150 × 4.6 mm, 5 μm) RP C_8 column". The binary mixture of methanol and ethanol (2:1% v/v) was utilized as the mobile phase for the quantification of APM. The elution of APM was carried out with a flow rate of 1.0 mL min^{-1} at the wavelength of 254 nm. The injection volume of analysis was set at 10 μL. The stock solution of APM was prepared in the concentration of 200 μg g^{-1}. From this stock solution, the serial dilutions were made on mass/mass basis in order to obtain the concentration in the range of (0.1 to 100) μg g^{-1}. The standard plot was constructed between the concentration of APM (μg g^{-1}) and peak area obtained from HPLC analysis. The standard plot of APM was obtained linear in the concentration range of (0.1 to 100) μg g^{-1} with coefficient of determination (R^2) value of 0.9992. The regressed equation was obtained as peak area = 31007 * concentration – 24123. The proposed RP-HPLC method for the quantification of APM was validated in terms of "linearity, precision, accuracy, sensitivity, selectivity and robustness" and results were obtained as satisfactory.

2.3. Solid state characterization of APM

The solid state characterization of APM was carried out using "Differential Scanning Calorimetry (DSC)". This characterization was performed for the evaluation of the possibility of polymorphic transformations of APM. DSC analysis of solid APM was carried out using "DSC-60 Instrument (Shimadzu, Japan)". The samples of original APM (4 mg) were loaded in an aluminum pan and sealed with the help of aluminum lids using a crimper. The sample of original APM was then thermally scanned against an empty aluminum pan (reference) with lid. DSC analysis was performed at the temperature range of 298.2 K to 523.2 K at heating rate of 10.0 K min^{-1} under nitrogen purging with a flow rate of 40 mL min^{-1}. The thermal parameters of original APM were obtained and interpreted using "TA-60WS thermal analysis software (Shimadzu, Japan)".

2.4. Determination of APM solubility

The solubility of solid APM in twelve different mono solvents namely "water, methanol, ethanol, IPA, EG, PG, 1-butanol, 2-butanol, EA, DMSO, PEG-400 and Transcutol" was determined using a static equilibrium method (Higuchi and Connors, 1965). The solubility of solid APM as mole fraction in each mono solvent was determined at "T = 298.2 K to 318.2 K" and "p = 0.1 MPa". The studied temperatures (T = 298.2 K to 318.2 K) were selected randomly with the interval of 5 K with keeping in mind that the maximum studied temperature should not exceed the melting point of APM. The maximum temperature studied was 318.2 K which was much lower than its melting point (432.02 K). Therefore, the measurements were performed at these temperatures. The excess amount of solid APM was added in known amounts of each mono solvent in triplicates manner. Each APM-mono solvent mixture was vortexed for about 5 min and transferred to the "OLS 200 Grant Scientific Biological Shaker

(Grant Scientific, Cambridge, UK)" at the shaking speed of 100 rpm for the period of 3 days. The equilibrium time of 3 days was previously optimized. After 3 days, each APM-mono solvent mixture was removed from the biological shaker and allowed to settle APM solid particles for the period of 24 h (Shakeel et al., 2016). After 24 h settling of APM solid particles, the supernatants were taken, diluted suitably with mobile phase (wherever applicable) and subjected for the analysis of APM content by the proposed RP-HPLC method at 254 nm. The concentration of APM ($\mu g\,g^{-1}$) in solubility samples was determined by standard plot of APM discussed in section 2.2. Then, the experimental solubilities of APM (x_e) in mole fraction were determined using Eq. (1) (Almarri et al., 2017; Shakeel et al., 2017):

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

Here, the symbols m_1 and m_2 are the masses of solid APM and respective mono solvent (g), respectively. The symbols M_1 and M_2 are the molar masses of APM and respective mono solvent ($g\,mol^{-1}$), respectively.

3. Results and discussion

3.1. Solid state characterization of APM

DSC analysis on original APM was performed for the evaluation of the solid state characterization and polymorphic transformations of APM. The representative DSC spectra of original APM is presented in Fig. 2. DSC thermogram of original APM presented a sharp crystalline peak at the fusion temperature (T_{fus}) of 432.02 K with fusion enthalpy (ΔH_{fus}) of 13.09 $kJ\,mol^{-1}$ (Fig. 2). A sharp crystalline peak at 432.02 K indicated that original APM was in pure crystalline form. A single crystalline peak of APM indicated that it does not show the evidence of polymorphic transformations.

3.2. Experimental solubilities of APM

The x_e values of solid APM determined by a "static equilibrium method" using RP-HPLC technique in twelve different mono solvents at "T = 298.2 K to 318.2 K" and "p = 0.1 MPa" are listed in Table 1. The mole fraction solubility of APM in water at "T = 298.2 K" has been reported as 2.74×10^{-7} according to EMA database (EMA, 2014). The mole fraction solubility of APM in water at "T = 298.2 K" was obtained as 4.30×10^{-7} in the current research work. The mole fraction solubility of APM in water obtained in this work was deviated with that reported by EMA database (EMA, 2014). This deviation could be due to the differences in shaking speed, equilibrium time and method of analysis used for APM.

Generally, the x_e values of APM were found to be increasing with increase in temperature in all mono solvents evaluated (Table 1). The x_e values of APM were obtained maximum in DMSO (9.91×10^{-2}), followed by EA (2.54×10^{-2}), Transcutol (2.51×10^{-2}), PEG-400 (2.16×10^{-2}), PG (4.01×10^{-3}), EG (1.61×10^{-3}), IPA (4.96×10^{-4}), 1-butanol (4.18×10^{-4}), 2-butanol (3.91×10^{-4}), methanol (2.25×10^{-4}), ethanol (2.20×10^{-4}) and water (1.29×10^{-6}) at "T = 318.2 K" and similar results were also obtained at each temperature evaluated. The x_e values of APM were obtained in similar magnitude in four different mono solvents namely DMSO, EA, Transcutol and PEG-400. The x_e values of APM in

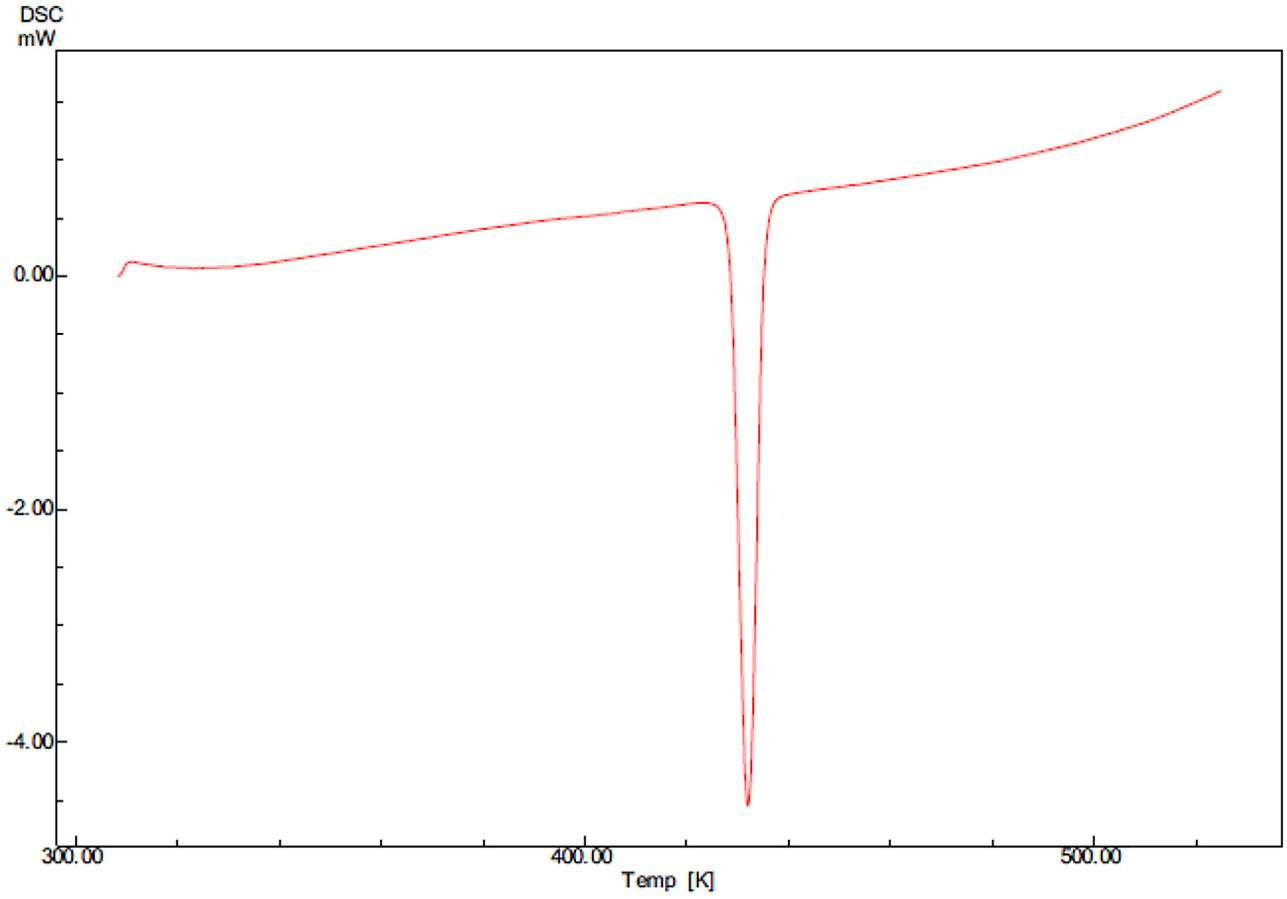

Fig. 2. DSC thermogram of solid APM; differential scanning calorimetry (DSC) and apremilast (APM).

Table 1
Experimental solubilities (x_e) of APM in mole fraction measured by a static equilibrium method in different mono 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	4.30×10^{-7}	5.87×10^{-7}	7.94×10^{-7}	1.02×10^{-6}	1.29×10^{-6}
Ethanol	6.63×10^{-5}	9.40×10^{-5}	1.30×10^{-4}	1.70×10^{-4}	2.20×10^{-4}
IPA	2.70×10^{-4}	3.13×10^{-4}	3.68×10^{-4}	4.28×10^{-4}	4.96×10^{-4}
EG	9.71×10^{-4}	1.11×10^{-3}	1.27×10^{-3}	1.41×10^{-3}	1.61×10^{-3}
PG	2.24×10^{-3}	2.53×10^{-3}	2.98×10^{-3}	3.42×10^{-3}	4.01×10^{-3}
PEG-400	9.82×10^{-3}	1.22×10^{-2}	1.51×10^{-2}	1.79×10^{-2}	2.16×10^{-2}
Transcutol	1.58×10^{-2}	1.75×10^{-2}	1.97×10^{-2}	2.23×10^{-2}	2.51×10^{-2}
1-Butanol	2.41×10^{-4}	2.82×10^{-4}	3.30×10^{-4}	3.75×10^{-4}	4.18×10^{-4}
2-Butanol	2.22×10^{-4}	2.57×10^{-4}	2.94×10^{-4}	3.38×10^{-4}	3.91×10^{-4}
EA	1.96×10^{-2}	2.08×10^{-2}	2.21×10^{-2}	2.37×10^{-2}	2.54×10^{-2}
DMSO	8.46×10^{-2}	8.85×10^{-2}	9.20×10^{-2}	9.57×10^{-2}	9.91×10^{-2}
Methanol	9.88×10^{-5}	1.21×10^{-4}	1.46×10^{-4}	1.77×10^{-4}	2.25×10^{-4}
x^{idl}	2.58×10^{-1}	2.75×10^{-1}	2.81×10^{-1}	2.92×10^{-1}	3.09×10^{-1}

Absolute temperature (T), pressure (p), apremilast (APM), ideal solubility of APM (x^{idl}), isopropyl alcohol (IPA), ethylene glycol (EG), propylene glycol (PG), polyethylene glycol-400 (PEG-400), ethyl acetate and dimethyl sulfoxide (DMSO)
[a] The standard uncertainties u are $u(T) = 0.11$ K, $u(p) = 0.003$ MPa and $u_r(x_e) = 1.38\%$.

DMSO, EA, Transcutol and PEG-400 were exceptionally higher in comparison with its x_e values in other mono solvents namely "water, methanol, ethanol, IPA, 1-butanol, 2-butanol, EG and PG". This observation could be possible because the polarity/dielectric constant of APM might be similar with that of DMSO, EA, Transcutol and PEG-400. Between ethanol and IPA, the x_e values of APM were higher in IPA because of slightly lower polarity/dielectric constant of IPA in comparison with ethanol (Shakeel et al., 2017). Between methanol and ethanol, the x_e values of APM were higher in ethanol because of slightly lower polarity/dielectric constant of ethanol in comparison with methanol (Almarri et al., 2017). Between EG and PG, the x_e values of APM were higher in PG because of slightly lower polarity/dielectric constant of PG in comparison with EG (Shakeel et al., 2016). The x_e values of APM in 1-butanol and 2-butanol were obtained in similar magnitude due to their similar molar masses, molecular structures and dielectric constants/polarities (Shakeel et al., 2017). Based on the results of this work, APM was considered as freely soluble in DMSO, EA and Transcutol, sparingly soluble in PEG0-400, slightly soluble in methanol, ethanol, IPA, EG, PG, 1-butanol and 2-butanol and practically insoluble in water. Therefore, DMSO, EA and Transcutol were selected as the best solvents and water and ethanol were selected as the anti-solvents for APM.

3.3. Ideal solubilities and activity coefficients for APM

The ideal solubility of APM (x^{idl}) was determined with the help of Eq. (2) (Ruidiaz et al., 2010):

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

Here, R represents the universal gas constant and ΔC_p is the molar heat capacity which can be expressed as $\Delta C_p = C_p$ (liq) $- C_p$ (solid) (Hildebrand et al., 1970; Ruidiaz et al., 2010). Other symbols in Eq. (2) have already been defined in previous text of this manuscript. It has been proposed that ΔC_p may be set approximately as the entropy of fusion [ΔS_{fus}] (Manrique et al., 2008; Aragón et al., 2009). The main reasons for such hypothesis had already been discussed previously in literature (Neau and Flynn, 1990). The value of ΔS_{fus} for APM was determined with the help of Eq. (3) (Ruidiaz et al., 2010):

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

From DSC analysis of original APM, the T_{fus} value for APM was recorded as 432.02 K and ΔH_{fus} value for APM was recorded as 13.09 kJ mol^{-1}. With the help of Eq. (3), the value of $\Delta S_{fus}/\Delta C_p$ was recorded as 30.30 J mol^{-1} K^{-1}. For the calculation of x^{idl} values of APM, all the parameters of Eq. (2) are known now. Hence, these values were determined with the help of Eq. (2) and resulting values are presented in Table 1.

The activity coefficients (γ) of APM in each mono solvent were determined with the help of Eq. (4) (Manrique et al., 2008; Ruidiaz et al., 2010):

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

The γ values for APM in each mono solvent at "T = 298.2 K to 318.2 K" are listed in Table 2. From γ values of APM, the molecular interactions between solute and solvent molecules can be described using Eq. (5) (Kristl and Vesnaver, 1995):

$$\ln\gamma = \frac{(e_{11} + e_{33} - 2e_{13})V_3\phi_1^2}{RT} \quad (5)$$

Here, the subscript 1 stands for the respective mono solvent and the symbols e_{11}, e_{33} and e_{13} are the solvent–solvent, solute–solute and solvent–solute interaction energies, respectively. The symbol V_3 represents the molar volume of the super-cooled liquid solute and ϕ_1 represent the volume fraction of the respective mono solvent.

For relatively low values of x_e, the term $V_3\phi_1^2/RT$ is proposed as constant and hence γ values will depend mainly on e_{11}, e_{33} and e_{13} (Kristl and Vesnaver, 1995). It has been proposed that the symbols e_{11} and e_{33} are unfavorable for solubility and the symbol e_{13} favors the solution process (Kristl and Vesnaver, 1995; Ruidiaz et al., 2010). The contribution of the symbol e_{33} could be considered as constant in all mono solvents because it is not favorable for the solubilization of solute in the solvent (Ruidiaz et al., 2010).

Based on these assumptions, the value of e_{11} was highest in water due to the largest value of γ for APM in water. However, its value was lowest in DMSO due to lowest value of γ for APM in DMSO. The value of e_{11} was slightly lower in Transcutol, EA and PEG-400 because the γ values of APM were slightly higher in these mono solvents in comparison with DMSO. The values of e_{11} were also much lower in other mono solvents namely methanol, ethanol, IPA, 1-butanol, 2-butanol, EG, PG and EA in comparison

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

S	x_e				
	T = 298.2 K	T = 303.2 K	T = 308.2 K	T = 313.2 K	T = 318.2 K
Water	602000.0	469000.0	355000.0	287000.0	240000.0
Ethanol	3900.0	2930.0	2170.0	1720.0	1410.0
IPA	959.0	879.0	766.0	683.0	625.0
EG	267.0	249.0	222.0	207.0	192.0
PG	116.0	109.0	94.7	85.3	77.2
PEG-400	26.3	22.5	18.5	16.3	14.2
Transcutol	16.4	15.8	14.3	13.1	12.3
1-Butanol	1070.0	977.0	854.0	779.0	740.0
2-Butanol	1166.2	1068.7	957.1	864.3	792.1
EA	13.2	13.3	12.7	12.3	12.2
DMSO	3.0	3.1	3.0	3.0	3.1
Methanol	2620.0	2270.0	1930.0	1650.0	1370.0

Absolute temperature (T), apremilast (APM), isopropyl alcohol (IPA), ethylene glycol (EG), propylene glycol (PG), polyethylene glycol-400 (PEG-400), ethyl acetate and dimethyl sulfoxide (DMSO).

with water because the value of γ for APM in these solvents was much lower than water. Neat water presented larger γ values would imply high (e_{11}-$2e_{13}$) values than other mono solvents evaluated. However, in DMSO, Transcutol, EA and PEG-400 (having low γ values), the (e_{11}-$2e_{13}$) values were relatively lower than water. Hence, the solute-solvent molecular interactions of APM could be higher in DMSO, Transcutol, EA and PEG-400 in comparison with other mono solvents evaluated.

3.4. Correlation of x_e values of APM

The x_e values of APM were correlated with two different mathematical models inluding "Apelblat and Van't Hoff models" (Apelblat and Manzurola, 1999; Manzurola and Apelblat, 2002; Shakeel et al., 2017). The "Apelblat model solubilities (x^{Apl})" of APM were determined with the help of Eq. (6) (Apelblat and Manzurola, 1999; Manzurola and Apelblat, 2002):

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

Here, the symbols "*A*, *B* and *C*" are the model parameters/coefficients of "Apelblat model". The values of these model parameters were determined by applying "nonlinear multivariate regression analysis" of x_e values of APM listed in Table 1 (Shakeel et al., 2016). The x_e values of APM were correlated with x^{Apl} values of APM via "root mean square deviations (*RMSD*)" and R^2 values. The *RMSD* for APM were determined with the help of 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, the symbol *N* is the number of experimental temperature points and other parameters have already been defined. The graphical correlation between natural logarithm x_e (ln x_e) and ln x^{Apl} values of APM in each mono solvent as a function of $1/T$ is shown in Fig. 3. The results of graphical correlation shown in Fig. 3 indicated good correlation between ln x_e and ln x^{Apl} values of APM in each mono solvent evaluated. The results of "Apelblat correlation" along with model parameters are listed in Table 3. The *RMSD* values in different mono solvents were recorded as (0.13 to 1.06) %. The *RMSD* value for APM was obtained maximum in methanol (1.06%) and minimum in DMSO (0.13%). The R^2 values for APM in different mono solvents were recorded as 0.9988 to 0.9999. The results of this correlation in terms of *RMSD* and R^2 indicated good correlation of x_e values of APM with "Apelblat model".

The "Van't Hoff model solubilities ($x^{Van't}$)" of APM were determined with the help of Eq. (8) (Shakeel et al., 2017):

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

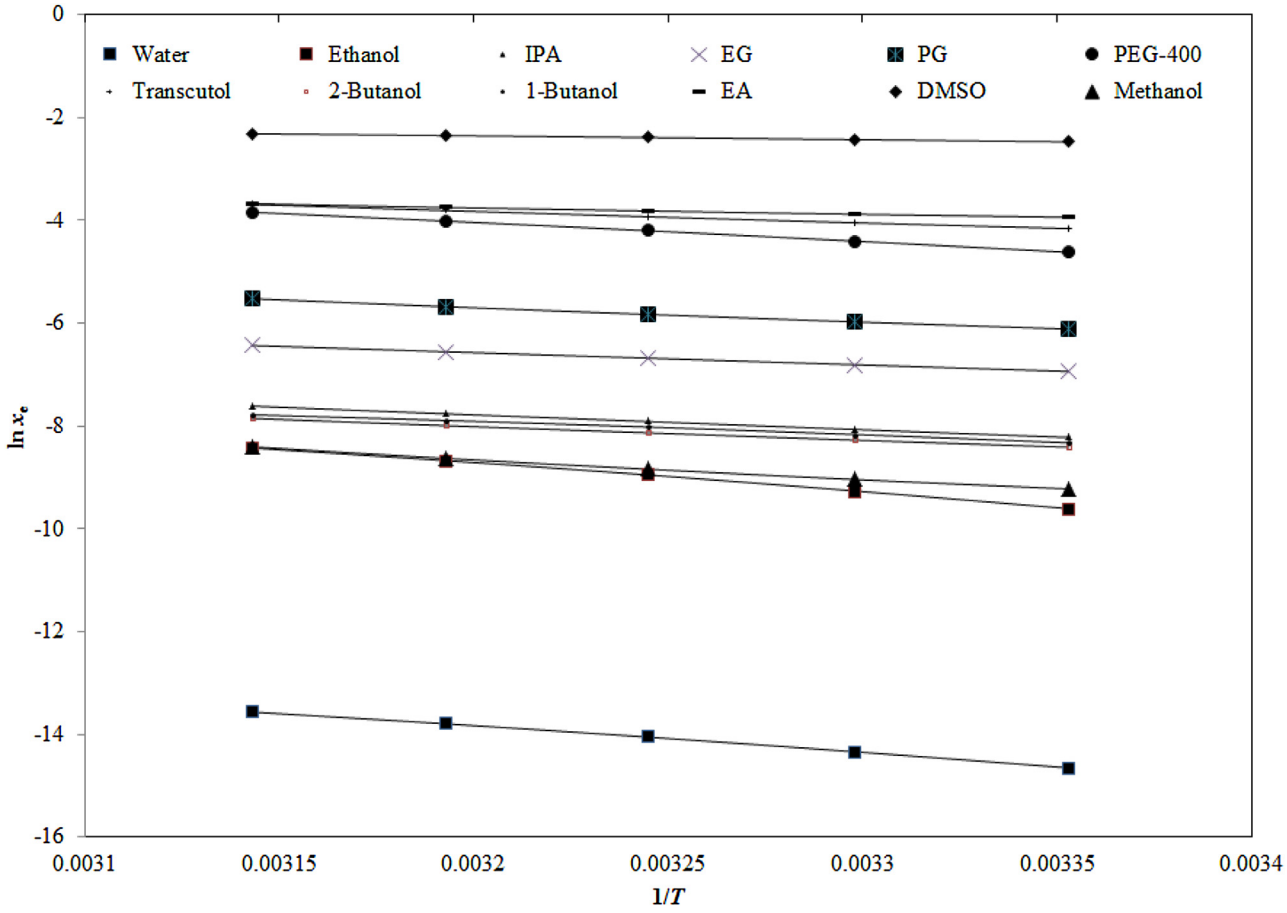

Fig. 3. Correlation of ln x_e values of APM with "Apelblat model" in twelve different mono solvents as a function of $1/T$; symbols represent the experimental solubilities of APM and solid lines represent the solubilities of APM calculated by "Apelblat model"; apremilst (APM); experimental natural logarithmic solubilities (ln xe); absolute temperature (T); isopropyl alcohol (IPA); ethylene glycol (EG); propylene glycol (PG); polyethylene glycol-400 (PEG-400); ethyl acetate and dimethyl sulfoxide (DMSO).

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

S	*A*	*B*	*C*	R^2	*RMSD* (%)
Water	482.94	−27139.00	−71.35	0.9998	0.65
Ethanol	593.44	−32347.60	−86.80	0.9997	0.83
PG	−249.57	8766.78	37.57	0.9988	0.76
PEG-400	212.15	−13055.40	−30.36	0.9991	0.78
Transcutol	−184.44	6352.73	27.90	0.9991	0.40
EG	−36.34	−680.51	5.56	0.9991	0.64
IPA	−62.89	49.40	9.56	0.9998	0.43
1-Butanol	327.50	−17565.10	−48.60	0.9999	0.51
2-Butanol	−130.85	3343.69	19.52	0.9998	0.39
EA	−168.39	6467.85	25.05	0.9997	0.32
DMSO	33.50	−2274.33	−4.97	0.9997	0.13
Methanol	−501.89	19255.72	75.13	0.9993	1.06

Apremilast (APM), coefficient of determination (R^2), root mean square deviations (*RMSD*), isopropyl alcohol (IPA), ethylene glycol (EG), propylene glycol (PG), polyethylene glycol-400 (PEG-400), ethyl acetate and dimethyl sulfoxide (DMSO).

Here, the symbols "*a* and *b*" are the model parameters of "Van't Hoff model". These model parameters were determined by plotting ln x_e values of APM as a function of $1/T$.

The x_e values of APM were correlated with $x^{van't}$ values of APM again via *RMSD* and R^2 values.

The graphical correlation between ln x_e and ln $x^{Van't}$ values of APM in each mono solvent as a function of $1/T$ is shown in Fig. S1. The results of graphical correlation shown in Fig. S1 indicated good correlation. The results of "Van't Hoff correlation" along with model parameters are listed in Table 4. The *RMSD* values for APM in different mono solvents were recorded as (0.14 to 2.08) %. The *RMSD* value for APM was recorded maximum in ethanol (2.08%) and minimum in DMSO (0.14%). The R^2 values for APM in different mono solvents were recorded as 0.9960 to 0.9996. The results of this correlation in terms of *RMSD* and R^2 values again indicated good correlation of x_e values of APM with "Van't Hoff model".

3.5. Apparent thermodynamic analysis

"Apparent thermodynamic analysis" on experimental solubilities of APM was performed for the evaluation of dissolution behavior/thermodynamics of APM in different mono solvents. Various "apparent standard thermodynamic parameters" such as "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 APM dissolution were determined by applying Van't Hoff and Krug et al. analysis approaches. The "$\Delta_{sol}H^0$ values" for APM dissolution in different mono solvents were measured at the "mean harmonic temperature (T_{hm})" of 308 K by applying "Van't Hoff analysis" with the help of Eq. (9) (Ruidiaz et al., 2010; Holguín et al., 2012):

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

According to Eq. (9), the "$\Delta_{sol}H^0$ values" for APM dissolution were determined by "Van't Hoff plots" which were plotted between ln x_e values of APM as a function of ${}^{1}/_{T}-{}^{1}/_{T_{hm}}$. The resulting data of "Van't Hoff plots" are presented in Fig. S2. These "Van't Hoff plots" for APM dissolution in different mono solvents were recorded as linear with R^2 values of 0.9961 to 0.9997 (Fig. S2).

The "$\Delta_{sol}G^0$ values" for APM dissolution were also measured at T_{hm} value of 308 K by applying "Krug et al. analysis" approach with the help of Eq. (10) (Krug et al., 1976):

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

Here, the value of intercept for APM in each mono solvent was determined from "Van't Hoff plot" presented in Fig. S2.

Finally, the "$\Delta_{sol}S^0$ values" for APM dissolution were measured by applying the combined approach of "Van't Hoff and Krug et al. analysis" with the help of Eq. (11) (Krug et al., 1976; Ruidiaz et al., 2010; Holguín et al., 2012):

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

All thermodynamic quantities were determined at equilibrium in this work. Because non-ideality of the solution was not considered in the determination of thermodynamic parameters, we called all these parameters as "apparent thermodynamic parameters". Thermodynamic quantities measured by "apparent thermodynamic analysis" along with R^2 values for APM dissolution in different mono solvents are listed in Table 5.

From "apparent thermodynamic analysis" on experimental solubilities of APM, it was observed that the "$\Delta_{sol}H^0$ values" for APM dissolution in different mono solvents were recorded as positive values in the range of (6.22 to 47.30) kJ mol^{-1}. The "$\Delta_{sol}H^0$ value" for APM dissolution was recorded maximum in ethanol and minimum in DMSO (6.22 kJ mol^{-1}). The mean "$\Delta_{sol}H^0$ value" for APM dissolution was obtained as 25.01 kJ mol^{-1} with relative standard deviation (*RSD*) value of 0.47. The minimum "$\Delta_{sol}H^0$ value" for APM dissolution was obtained in DMSO that could be due to the maximum solubility of APM in DMSO. The "$\Delta_{sol}G^0$ values" for APM dissolution in different mono solvents were also

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

S	*a*	*b*	R^2	*RMSD* (%)
Water	2.85	−5218.70	0.9981	1.69
Ethanol	9.45	−5682.30	0.9976	2.08
PG	3.22	−2786.10	0.9971	1.19
PEG-400	7.90	−3732.00	0.9986	1.05
Transcutol	3.31	−2227.80	0.9977	0.83
EG	1.09	−2395.30	0.9992	0.63
IPA	1.49	−2897.10	0.9996	0.41
1-Butanol	0.51	−2633.20	0.9967	1.18
2-Butanol	0.51	−2662.30	0.9994	0.48
EA	0.20	−1236.00	0.9960	0.53
DMSO	0.03	−747.15	0.9994	0.14
Methanol	3.65	−3844.90	0.9960	1.73

Apremilast (APM), coefficient of determination (R^2), root mean square deviations (*RMSD*) isopropyl alcohol (IPA), ethylene glycol (EG), propylene glycol (PG), polyethylene glycol-400 (PEG-400), ethyl acetate and dimethyl sulfoxide (DMSO).

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 APM in different mono solvents (*S*).[b]

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	43.44	36.06	23.97	0.9980
Ethanol	47.30	23.01	78.85	0.9975
PG	23.19	14.90	26.93	0.9973
PEG-400	31.06	10.78	65.83	0.9985
Transcutol	18.54	10.04	27.61	0.9978
EG	19.94	17.10	9.19	0.9992
IPA	24.11	20.26	12.52	0.9997
1-Butanol	21.92	20.67	4.03	0.9966
2-Butanol	22.16	20.81	4.37	0.9994
EA	10.29	9.74	1.76	0.9962
DMSO	6.22	6.11	0.34	0.9993
Methanol	32.01	22.59	30.58	0.9961

Apremilast (APM), coefficient of determination (R^2), apparent standard enthalpy ($\Delta_{sol}H^0$), apparent standard Gibbs free energy ($\Delta_{sol}G^0$), apparent standard entropy ($\Delta_{sol}S^0$), isopropyl alcohol (IPA), ethylene glycol (EG), propylene glycol (PG), polyethylene glycol-400 (PEG-400), ethyl acetate and dimethyl sulfoxide (DMSO)

[b] The relative uncertainties are $u(\Delta_{sol}H^0) = 0.47$ kJ mol^{-1}, $u(\Delta_{sol}G^0) = 0.45$ kJ mol^{-1} and $u(\Delta_{sol}S^0) = 1.05$ J mol^{-1} K^{-1}.

obtained as positive values in the range of (6.11 to 36.06) kJ mol^{-1}. The "$\Delta_{sol}G^0$ value" for APM dissolution was obtained maximum in water (36.06 kJ mol^{-1}) and minimum in DMSO (6.11 kJ mol^{-1}). The mean "$\Delta_{sol}G^0$ value" for APM dissolution was obtained as 17.67 kJ mol^{-1} with *RSD* value of 0.45. The minimum "$\Delta_{sol}G^0$ value" for APM dissolution was also obtained in DMSO that could be possible due to the maximum solubility of APM in DMSO. The results of "$\Delta_{sol}G^0$" measurement for APM dissolution were in good agreement with experimental solubility data of APM. Relatively, lower values of "$\Delta_{sol}H^0$ and $\Delta_{sol}G^0$" were recorded in DMSO, EA and Transcutol which indicated that lower energies are required for the solubilization of APM in DMSO, EA and Transcutol. The positive values of "$\Delta_{sol}H^0$ and $\Delta_{sol}G^0$" obtained for this work in all mono solvents indicated an "endothermic dissolution" behavior of APM in all these mono solvents (Shakeel et al., 2016, 2017).

The general equation for Gibbs energy is expressed using Eq. (12):

$$\Delta G = \Delta_{sol}G^0 + RT \ln x \quad (12)$$

In which, ΔG is Gibbs free energy and $\Delta_{sol}G^0$ is an apparent standard Gibbs energy. It has been reported that if $\Delta G > 0$ (i.e. positive values), the dissolution process will be non-spontaneous and if $\Delta G < 0$ (i.e. negative values), the dissolution process will be spontaneous (Zhao et al., 2016; Li et al., 2017). This case is valid when both ideality and non-ideality of solution are considered (Li et al., 2017). The values presented in Table 5 are positive values for $\Delta_{sol}G^0$ not for ΔG and hence the dissolution process was not non-spontaneous. At equilibrium (when non-ideality of solution is not considered), the value of $\Delta G = 0$ and Eq. (12) can be expressed using Eq. (13):

$$\Delta_{sol}G^0 = -RT \ln x \quad (13)$$

Gibbs energy obtained in equilibrium will be apparent standard Gibbs energy. According to Eq. (13), if $\Delta_{sol}G^0 > 0$ (means positive values), the dissolution process will be spontaneous now and if $\Delta G < 0$ (means negative values), the dissolution process will be non-spontaneous (Krug et al., 1976; Shakeel et al., 2015a,b). Therefore, the dissolution process in current research work was spontaneous.

The "$\Delta_{sol}S^0$ values" for APM dissolution in different mono solvents were also obtained as positive values in the range of (0.34 to 78.85) J mol^{-1} K^{-1}. The mean "$\Delta_{sol}S^0$ value" for APM dissolution was recorded as 23.83 J mol^{-1} K^{-1} with *RSD* value of 1.05. The positive "$\Delta_{sol}S^0$ values" for APM indicated an "entropy-driven dissolution" of APM in each mono solvent evaluated (Shakeel et al., 2016). Overall, the dissolution of APM was recorded as an "endothermic and entropy-driven" in all mono solvents investigated (Shakeel et al., 2016, 2017).

4. Conclusion

The solubility of a recently approved poorly soluble drug APM was determined in twelve different mono solvents using a static equilibrium method at "$T = 298.2$ K to 318.2 K" and "$p = 0.1$ MPa". The experimental solubility data of APM was correlated well with "Van't Hoff and Apelblat" models in terms of *RMSD* and R^2 values. The solubility of APM was found to be increasing with increase in temperature in each mono solvent evaluated. The physical values of activity coefficients obtained in this work indicated better molecular interaction of APM with Transcutol, EA, PEG-400 and DMSO. The solubility of APM in mole fraction was obtained maximum in DMSO, followed by EA, Transcutol, PEG-400, PG, EG, IPA, 1-butanol, 2-butanol, methanol, ethanol and water at "$T = 318.2$ K" and similar results were also obtained at each temperature evaluated. "Apparent thermodynamic analysis" of experimental solubility data of APM indicated an "endothermic and entropy-driven dissolution" of APM in each mono solvent evaluated. Based on these results, APM has been proposed as freely soluble in DMSO, EA and Transcutol, sparingly soluble in PEG0-400, slightly soluble in methanol, ethanol, IPA, EG, PG, 1-butanol and 2-butanol and practically insoluble in water. Hence, DMSO, EA and Transcutol were selected as the best solvents and water and ethanol were selected as the anti-solvents for APM.

Conflict of interest

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

Acknowledgement

"This project was financially supported by King Saud University, Vice Deanship of Research Chairs, Kayyali Chair for Pharmaceutical industry through the grant number FN-2016".

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijpharm.2017.03.067.

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