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Solubilization and thermodynamic properties of simvastatin in various micellar solutions of different non-ionic surfactants: Computational modeling and solubilization capacity

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Abstract

The aim of this work was to solubilize simvastatin (SIM) using different micellar solutions of various non-ionic surfactants such as Tween-80 (T80), Tween-20 (T20), Myrj-52 (M52), Myrj-59 (M59), Brij-35 (B35) and Brij-58 (B58). The solubility of SIM in water (H_2O) and different micellar concentrations of T80, T20, M52, M59, B35 and B58 was determined at temperatures $T = 300.2$ K to 320.2 K under atmospheric pressure $p = 0.1$ MPa using saturation shake flask method. The experimental solubility data of SIM was regressed using van't Hoff and Apelblat models. The solubility of SIM (mole fraction) was recorded highest in M59 (1.54×10^{-2}) followed by M52 (6.56×10^{-3}), B58 (5.52×10^{-3}), B35 (3.97×10^{-3}), T80 (1.68×10^{-3}), T20 (1.16×10^{-3}) [the concentration of surfactants was 20 mM in H_2O in all cases] and H_2O (1.94×10^{-6}) at $T = 320.2$ K. The same results were also recorded at each temperature and each micellar concentration of T80, T20, M52, M59, B35 and B58. "Apparent thermodynamic analysis" showed endothermic and entropy-driven dissolution/solubilization of SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58.

Introduction

Simvastatin (SIM) {molecular structure: Fig 1; chemical name: [(1S,3R,7S,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl] 2,2-dimethylbutanoate; molecular formula: $C_{25}H_{38}O_5$; molar mass: 418.57 g mol^{-1} and CASRN: 79902-63-9) occurs as a white to off-white crystalline powder [1, 2]. It is a lipid lowering agent which belongs to statins family and powerful inhibitor of (3,5)-hydroxy-3-methylglutaryl coenzyme A (HMGr-CoA) reductase [3, 4]. Due to HMGr-CoA reductase inhibitory activity, it is used to treat and control hyper-cholesterolaemia in humans [5–7]. It shows very poor bioavailability (< 5.0%) upon oral administration which may be attributed to its poor solubility in water, low intestinal uptake and extensive first pass metabolism [2, 8, 9].

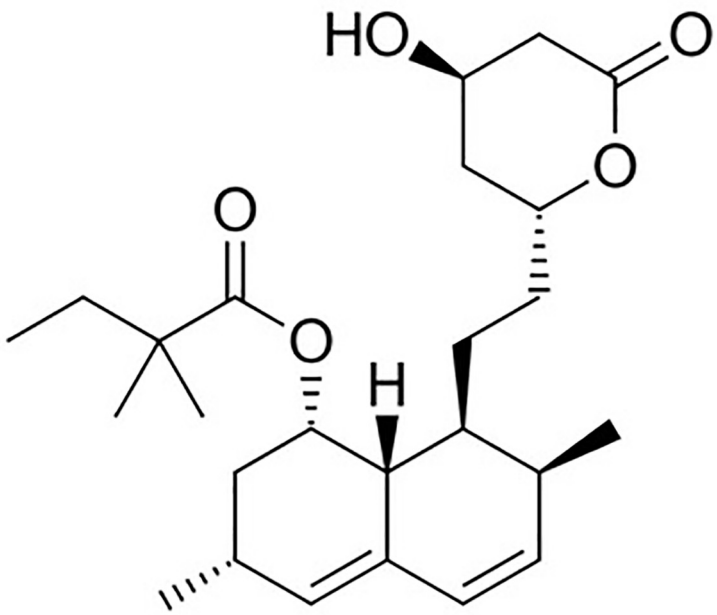

Fig 1. Molecular structure of simvastatin (SIM).

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Majority of the pharmaceutical products contain one or more types of surfactants [10, 11]. Surfactants have the ability to form colloidal-sized micelles in certain liquids and hence capable in enhancing the solubility of drugs [11, 12]. Around 40% of newly synthesized active pharmaceutical ingredients lack the required aqueous solubility [13]. Therefore, surfactants have gained much interest for enhancing the solubility of poorly soluble drugs in an aqueous media [10–14]. Several solubility enhancement techniques such as cyclodextrin complexation [15, 16], solid dispersions [17–19], self-emulsifying drug delivery system [20], self-microemulsifying drug delivery system [21, 22], self-nanoemulsifying drug delivery system [8], nanoencapsulation [23, 24], supercritical fluid techniques [25] and drug-dendrimer complex [26] were investigated in solubility/dissolution enhancement of SIM. However, solid dispersion technology has been investigated most widely in solubility enhancement of SIM [2, 17–19, 27].

There is lack of temperature dependent solubility data of statins in literature. The solubilities (mole fraction) of statin drugs like lovastatin in some organic solvents such as acetone, methanol, ethanol, ethyl acetate and butyl acetate at temperature T = 283 K to 323 K under atmospheric pressure p = 0.1 MPa are reported elsewhere [28]. The solubilities of SIM (mole fraction) in various alcohols such as ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol and 1-octanol at T = 286.15 K to 310.15 K are also available [1]. The micellar solubilization of drugs is one of the useful techniques which is being applied in solubility enhancement of weakly aqueous-soluble drug compounds [11, 29, 30]. Micellar solubilization of several poorly water-soluble drugs such as SIM, itraconazole, danazol, fenofibrate and androstane has been studied [12, 31, 32]. Temperature dependent solubilities of SIM in micellar solutions of various non-ionic surfactants such as Tween-80 (T80), Tween-20 (T20), Myrj-52 (M52), Myrj-59 (M59), Brij-35 (B35) and Brij-58 (B58) are not reported elsewhere. Therefore, the aim of this work was to determine the solubility of SIM in various molar concentrations of T80, T20, M52, M59, B35 and B58 in comparison with its solubility in water (H_2O) at T = 300.2 K to 320.2 K and p = 0.1 MPa. The dissolution/solubilization behavior of SIM in different molar concentrations of T80, T20, M52, M59, B35 and B58 was investigated by apparent thermodynamic analysis. All studied surfactants are non-ionic surfactants which are safe for human use.

They have potential for enhancing the solubility of poorly soluble drugs via micelle formation. Hence, the studied surfactants were selected for the solubilization of SIM in this work.

Materials and methods

Materials

SIM was obtained from Riyadh Pharmaceuticals (Riyadh, Saudi Arabia). T80 (IUPAC name: polyoxyethylene (20) sorbitan monooleate) and T20 (IUPAC name: polyoxyethylene (20) sorbitan monolaurate) were obtained from BDH Chemicals Ltd. Co. (Poole, England, UK). M52 (IUPAC name: polyoxyethylene (40) stearate), M59 (IUPAC name: polyoxyethylene (100) stearate), B35 (IUPAC name: polyoxyethylene (23) lauryl ether) and B58 (IUPAC name: polyoxyethylene (20) cetyl ether) were obtained from Sigma Aldrich (St. Louis, MO, USA). Chromatography grade acetonitrile (IUPAC name: cyanomethane) and formic acid (IUPAC name: methanoic acid) were obtained from E-Merck (Darmstadt, Germany). H_2O of high purity (deionized H_2O) was collected from Milli-Q Water Purification Unit.

Quantification of SIM by UPLC-UV analysis

"Waters Acquity® H-class Ultra-Performance Liquid Chromatography (UPLC)" apparatus connected with a "Waters diode-array-ultra-violet detector (DAD-UV) (Waters, MA, USA)" was applied for quantification of SIM at 237 nm. The quantification was carried out at reverse-phase isocratic elution mode using "Acquity® UPLC BEH C_{18} column (2.1 x 50 mm, 1.7 μm)" which was acquired from "Waters (Waters Inc., Bedford, MA, USA)". The binary mixture of 0.1% formic acid and acetonitrile (25:75, v/v) was used as mobile phase which was delivered with a flow rate of 0.3 mL min^{-1}. The volume of injection was 1 μL. The quantification of SIM was performed at 237 nm. The column temperature was maintained at "T = 313.2 K". The UPLC response of SIM was obtained at retention time of 1.12 min with a total run time of 1.5 min. The "Masslynx software" was utilized for data analysis.

Calibration and regression

The measured UPLC response of SIM was plotted against its concentrations in order to obtain calibration and regression. The calibration plot of SIM was observed linear in the range of (10 to 500.0) ng g^{-1}. The coefficient of determination (R^2) and equation for regression line were recorded as 0.9990 and UPLC area = 225.43*concentration—502.98. The proposed UPLC-UV method was validated in terms of "linearity, accuracy, precision, robustness, sensitivity, reproducibility and specificity". The results of validation parameters were obtained within the recommended limits of International Council for Harmonization guidelines [33].

Solid state characterization of pure and SIM equilibrated with water

The solid phases of SIM in pure and equilibrated samples (equilibrated with water) were characterized by differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) studies. The pure SIM was original SIM powder which was used before solubility studies. The equilibrated SIM was recovered from water after solubility studies. The equilibrated SIM was recovered by slow evaporation of water and stored at an ambient temperature till further use. The characterization of solid phases was performed for the investigation of physical form and probable transformation of SIM into polymorphs/solvates/hydrates after equilibrium. DSC thermogram of SIM in pure and equilibrated forms was obtained using "DSC-8000 Instrument (Perkin Elmer, MA, USA)". The whole DSC assembly was connected with chiller and auto-sampler. Before DSC experiments, the calibration of instrument was performed using pure

indium. Accurately weighed 5.40 mg of pure SIM and 5.20 mg of equilibrated SIM were taken and transferred into an aluminium pan which was sealed hermetically. DSC spectra for SIM in both samples was recorded in the temperature range of T = 303.2 K to 573.2 K with heating rate of 10.0 K min^{-1}. The flow for nitrogen for this analysis was set at 20 mL min^{-1}.

PXRD spectra of SIM in both samples were obtained with the help of "Ultima IV Diffractometer (Rigaku Inc. Tokyo, Japan)" in the 2θ range of 3–60˚ at a scan speed of 0.5˚ min^{-1}. The tube anode utilized for PXRD measurements was "Cu with Ka = 0.1540562 nm mono chromatized with a graphite crystal (Rigaku Inc., Tokyo, Japan)". PXRD spectra of SIM in both samples were recorded at tube voltage and tube current of 40 kV and 40 mA, respectively.

Measurement of SIM solubility in H_2O and various micellar solutions of different non-ionic surfactants

The solubilities of SIM (mole fraction) in H_2O and different micellar solutions of T80, T20, M52, M59, B35 and B58 were measured using a saturation shake flask technique propose by Higuchi and Connors [34]. The solubility of SIM was measured at T = 300.2 K to 320.2 K under atmospheric pressure. The excess quantity of pure SIM was added into known quantities of H_2O and various micellar solutions (1, 5, 10 and 20 mM) of T80, T20, M52, M59, B35 and B58. Each experiment was performed in triplicates manner. Each drug-surfactant/drug-H_2O mixture was vortexed using a Vortex mixer (Thermo Fisher Scientific, Waltham, MA, USA) for about 5 min. The samples were then kept in the WiseBath® WSB Shaking Water Bath (Model WSB-18/30/-45, Daihan Scientific Co. Ltd., Seoul, Korea). The speed of shaker was maintained at 100 rpm and temperature was varied from 300.2 K to 320.2 K. The equilibrium time was optimized as 72 h by preliminary investigations. After 72 h, each drug-surfactant/drug-H_2O mixture was taken out from the WSB shaking Water bath. The samples were centrifuged using a Remi Centrifuge (Remi Sales & Eng. Ltd., Mumbai, India) at 5000 rpm for about 20 min at ambient temperature i.e. T = 298.2 K. The supernatants were withdrawn, filtered using Whatman filter paper (Sigma Aldrich, St. Louis, MO, USA), diluted (wherever applicable) and subjected for the quantification of SIM by UPLC-UV technique at 237 nm. The experimental mole fraction solubility (x_e) values of SIM were obtained using Eq (1) [35, 36]:

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

In which, m_1 and m_2 represent the amounts of SIM (g) and H_2O/surfactant (g), respectively. M_1 and M_2 represent the molecular weights of SIM (g mol^{-1}) and H_2O/surfactant (g mol^{-1}), respectively.

Results and discussion

Solid state characterization of pure and equilibrated SIM

The solid phases of SIM in both samples were characterized for the investigation their physical form and possible transformation of SIM into polymorphs/solvates/hydrates after equilibrium. DSC thermograms of SIM in pure and equilibrated samples are shown in Fig 2A and 2B, respectively. DSC thermogram of SIM in pure form presented a crystalline endothermic peak at melting/fusion temperature (T_{fus}) of 412.95 K. The values of fusion enthalpy (ΔH_{fus}) and fusion entropy (ΔS_{fus}) for pure SIM were obtained as 28.38 kJ mol^{-1} and 68.72 J mol^{-1} K^{-1}, respectively (Fig 2A). The equilibrated SIM was recovered from slow evaporation of water. DSC thermogram of SIM in equilibrated form (the SIM equilibrated with water) also

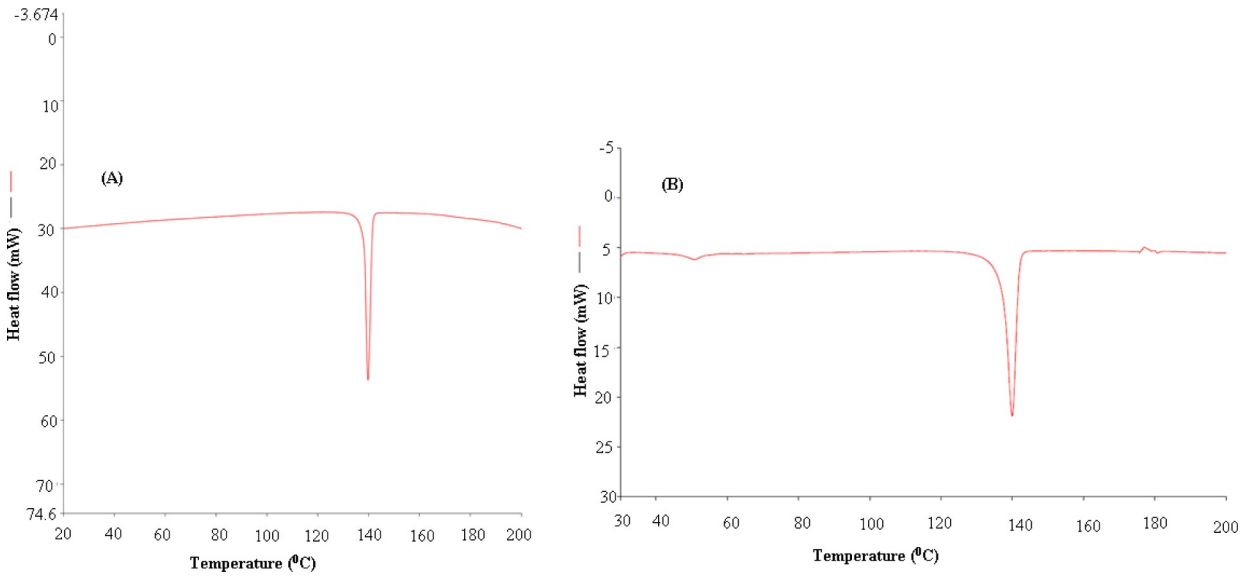

Fig 2. Differential scanning calorimetry (DSC) spectra of (A) pure SIM and (B) equilibrated SIM recovered from water after slow evaporation.

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presented a crystalline endothermic peak at T_{fus} of 413.18 K. The values of ΔH_{fus} and ΔS_{fus} for equilibrated SIM were obtained as 28.58 kJ mol^{-1} and 69.19 J mol^{-1} K^{-1}, respectively (Fig 2B). The DSC spectra and various thermal parameters such as T_{fus}, ΔH_{fus} and ΔS_{fus} of pure SIM very closed with those of equilibrated SIM. The results of DSC analysis indicated crystalline nature of SIM in both samples. Although, the peak intensities of pure and equilibrated SIM were slightly different, but their thermal parameters were almost closed to each other. The difference in peak intensity might be due to the fact that different amounts of pure and equilibrated SIM were taken for DSC analysis. Similar DSC spectra for pure and equilibrated SIM suggested no transformation of SIM into amorphous/polymorphic/solvate form after equilibrium. The T_{fus} and ΔH_{fus} values of pure SIM have been reported as 410.92 K and 24.46 kJ mol^{-1}, respectively [1]. The T_{fus} and ΔH_{fus} values of pure SIM were obtained as 412.95 K and 28.38 kJ mol^{-1}, respectively in the present study. These thermal parameters of present work were found to be closed with literature values [1].

The PXRD spectra of pure and equilibrated SIM are shown in Fig 3A and 3B, respectively. PXRD spectra of SIM in pure sample presented different crystalline peaks at various 2 θ values,

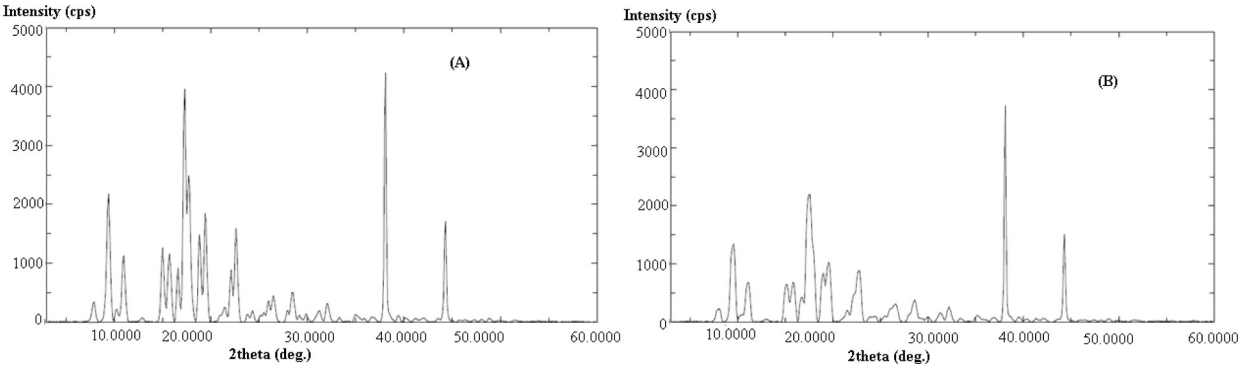

Fig 3. Powder X-ray diffraction (PXRD) spectra of (A) pure SIM and (B) equilibrated SIM recovered from water after slow evaporation.

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also suggesting crystalline nature of SIM (Fig 3A). PXRD spectra of SIM in equilibrated form also presented different crystalline peaks at similar 2 θ values (Fig 3B). Similar PXRD spectra of pure and equilibrated SIM again suggested crystalline nature of SIM in both samples and no transformation of SIM into amorphous/polymorphic/solvate form after equilibrium. Based on DSC and PXRD results, we can say that the crystal form of SIM was similar in water and most probably on studied surfactants as no transformation of SIM was recorded after equilibrium.

Experimental solubilities of SIM in H_2O and various micellar solutions of different non-ionic surfactants

The experimental solubility (x_e) values of SIM in H_2O and various micellar solutions (1, 5, 10 and 20 mM) of T80, T20, M52, M59, B35 and B58 at three different temperatures T = 300.2 K, 310.2 K and 320.2 K and p = 0.1 MPa are presented in Table 1. Saturated solubility of SIM in H_2O at ambient temperature i.e. T = 298.2 K has been reported elsewhere [19, 27]. Micellar solubilization of SIM in polyglycerol diisostearate ethoxylates surfactants has also been reported [12]. However, temperature-dependent solubilities of SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 are not reported so far. Murtaza reported

Table 1. Mole fraction solubility (x_e) values of simvastatin (SIM) in water (H_2O) and various micellar solutions of different non-ionic surfactants at T = 300.2 K to 320.2 K and p = 0.1 MPa[a].

Samples	x_e		
	T = 300.2 K	T = 310.2 K	T = 320.2 K
H_2O	7.57×10^{-7}	1.29×10^{-6}	1.94×10^{-6}
1 mM T80	9.37×10^{-5}	1.29×10^{-4}	1.77×10^{-4}
5 mM T80	5.00×10^{-4}	6.36×10^{-4}	8.27×10^{-4}
10 mM T80	7.34×10^{-4}	9.32×10^{-4}	1.18×10^{-3}
20 mM T80	1.08×10^{-3}	1.35×10^{-3}	1.68×10^{-3}
1 mM T20	4.69×10^{-5}	6.42×10^{-5}	8.80×10^{-5}
5 mM T20	1.94×10^{-4}	2.52×10^{-4}	3.31×10^{-4}
10 mM T20	4.84×10^{-4}	6.45×10^{-4}	8.06×10^{-4}
20 mM T20	7.18×10^{-4}	9.13×10^{-4}	1.16×10^{-3}
1 mM M52	2.75×10^{-4}	3.72×10^{-4}	4.78×10^{-4}
5 mM M52	1.54×10^{-3}	1.90×10^{-3}	2.33×10^{-3}
10 mM M52	3.60×10^{-3}	4.29×10^{-3}	5.20×10^{-3}
20 mM M52	4.67×10^{-3}	5.62×10^{-3}	6.56×10^{-3}
1 mM M59	4.92×10^{-4}	6.61×10^{-4}	9.17×10^{-4}
5 mM M59	2.28×10^{-3}	2.84×10^{-3}	3.54×10^{-3}
10 mM M59	6.01×10^{-3}	7.03×10^{-3}	8.44×10^{-3}
20 mM M59	1.15×10^{-2}	1.33×10^{-2}	1.54×10^{-2}
1 mM B35	1.35×10^{-4}	1.87×10^{-4}	2.53×10^{-4}
5 mM B35	3.43×10^{-4}	5.48×10^{-4}	8.15×10^{-4}
10 mM B35	1.13×10^{-3}	1.39×10^{-3}	1.76×10^{-3}
20 mM B35	2.71×10^{-3}	3.25×10^{-3}	3.97×10^{-3}
1 mM B58	9.11×10^{-5}	1.37×10^{-4}	1.94×10^{-4}
5 mM B58	2.55×10^{-4}	3.36×10^{-4}	4.55×10^{-4}
10 mM B58	4.34×10^{-4}	5.57×10^{-4}	7.55×10^{-4}
20 mM B58	3.74×10^{-3}	4.47×10^{-3}	5.52×10^{-3}
x^{idl}	7.16×10^{-2}	9.39×10^{-2}	1.22×10^{-1}

[a]The relative uncertainties u_r are $u_r(T)$ = 0.016, $u_r(p)$ = 0.003 and $u_r(x_e)$ = 0.014.

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the saturated solubility of SIM in H_2O at T = 298.2 K as 30.00 μg mL^{-1} (converted to 7.57 x 10^{-7} in mole fraction) [27]. However, Craye et al. reported the saturated solubility of SIM in H_2O at T = 298.2 K as 1.74 μg mL^{-1} (converted to 7.49 x 10^{-8} in mole fraction) [19]. The mole fraction solubility of SIM in H_2O at T = 298.2 K was not determined directly in the present work. The mole fraction solubility of SIM in H_2O at T = 298.2 K was determined from extrapolation of curve plotted between ln x_e and 1/T and obtained as 7.08 x 10^{-7} in our work. Solubility of SIM in H_2O recorded in this study was much closed with that reported by Murtaza [27]. However, it was much deviated from solubility of SIM reported by Craye et al. [19].

The influence of temperature on logarithmic solubilities of SIM is presented in Fig 4. It was observed from experimental data that the logarithmic solubility values of SIM were increasing

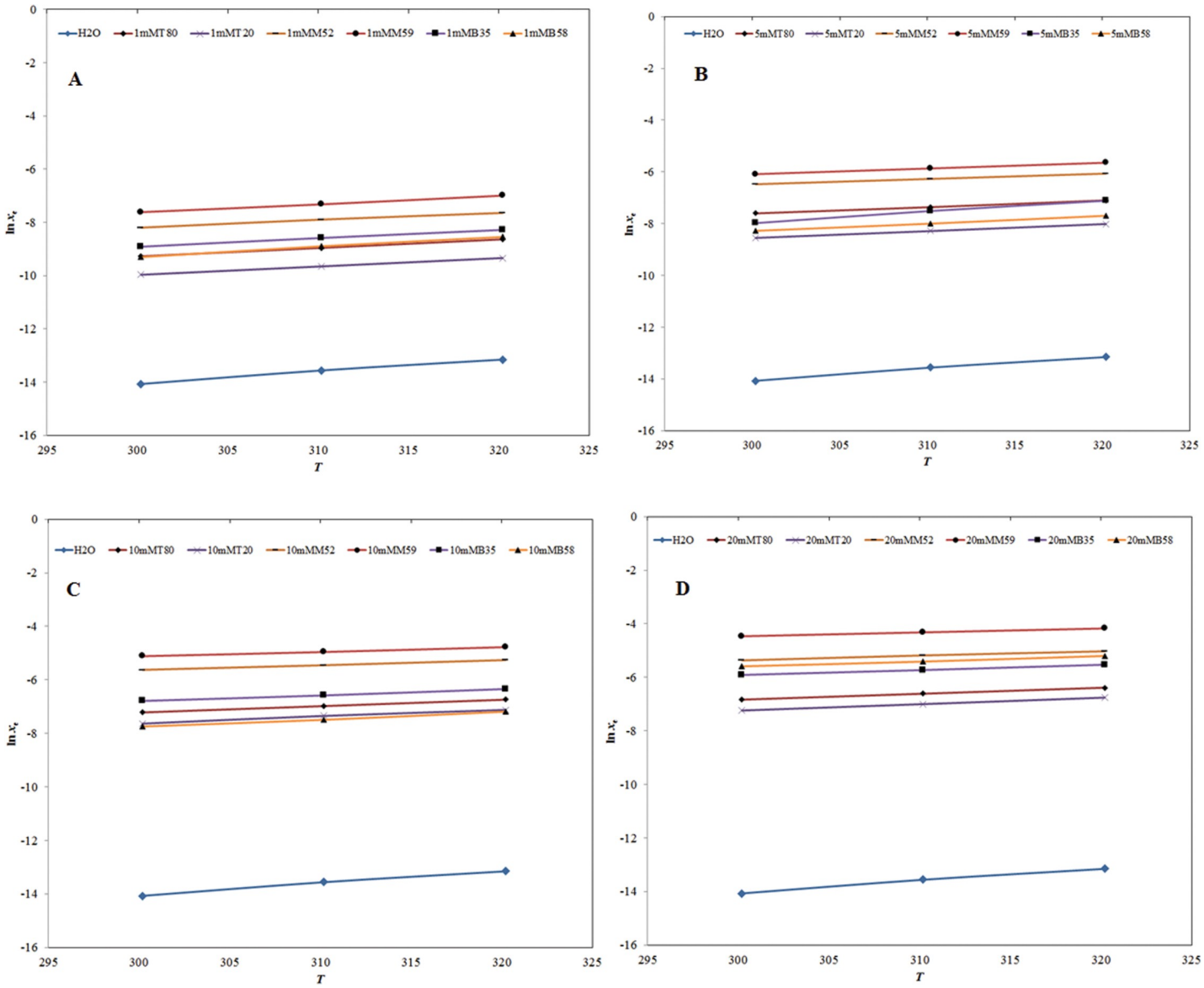

Fig 4. Influence of temperature on logarithmic solubility (ln x_e) values of SIM in (A) H_2O and 1 mM molar solution of various non-ionic surfactants and (B) H_2O and 5 mM molar solution of various non-ionic surfactants. Influence of temperature on ln x_e values of SIM in (C) H_2O and 10 mM molar solution of various non-ionic surfactants and (D) H_2O and 20 mM molar solution of various non-ionic surfactants.

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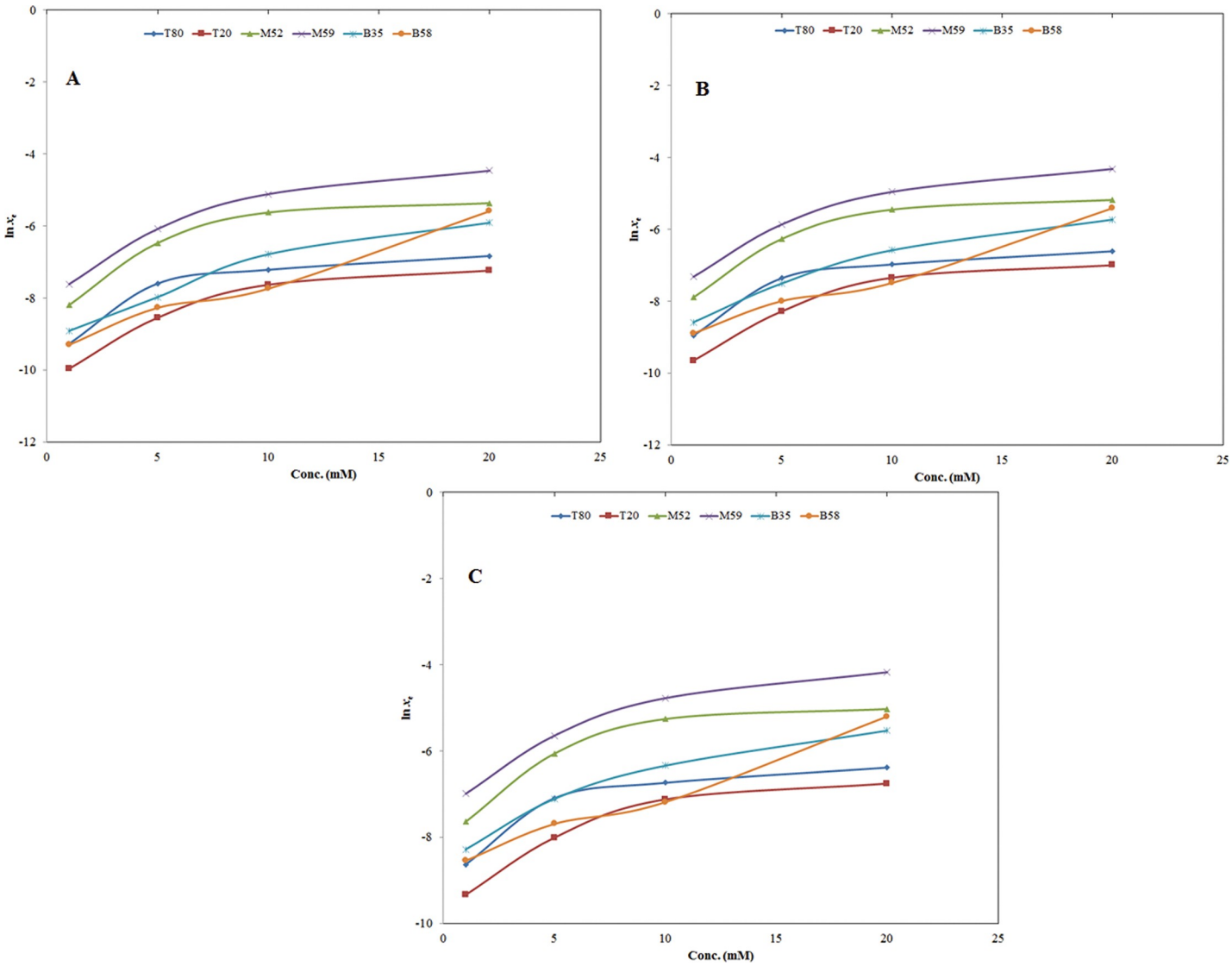

Fig 5. Influence of molar concentrations of different non-ionic surfactants on ln x_e values of SIM at (A) T = 300.2 K, (B) T = 310.2 K and (C) T = 320.2 K.

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linearly with increase in temperature in H_2O and four different micellar solutions of T80, T20, M52, M59, B35 and B58 (Fig 4). The results of influence of temperature on solubility of SIM were accordance with those reported for several weakly water soluble drugs [35–39].

The influence of molar concentrations of various non-ionic surfactants on logarithmic solubilities of SIM at three different temperatures is presented in Fig 5. It was found that the logarithmic solubility values of SIM were increasing non-linearly with increase in the molar concentrations of T80, T20, M52, M59, B35 and B58 at each temperature studied. The x_e values of SIM recorded highest in M59 (1.54×10^{-2}) followed by M52 (6.56×10^{-3}), B58 (5.52×10^{-3}), B35 (3.97×10^{-3}), T80 (1.68×10^{-3}), T20 (1.16×10^{-3}) [the concentration of surfactants was 20 mM in H_2O in all cases] and H_2O (1.94×10^{-6}) at T = 320.2 K. The same results were also obtained at each temperature and four different micellar solutions of T80, T20, M52, M59, B35 and B58. The x_e values of SIM were much higher in M59 in comparison with H_2O. The maximum x_e values of SIM in M59 might be possible due to similar polarity of SIM and M59. Due

to the highest solubility of SIM in 20 mM M59, it can be used as a solubilizer in liquid formulation design of SIM.

Solubility parameter for SIM, H_2O and different surfactants

In this work, Hansen solubility parameter (δ) for SIM, H_2O, T80, T20, M52, M59, B35 and B58 was obtained using Eq (2) [40–42]:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (2)$$

In which, the symbol δ is the total Hansen solubility parameter for solute/solvent. However, the symbols δ_d, δ_p and δ_h represent dispersion, polar and hydrogen-bonded Hansen solubility parameters, respectively. The δ, δ_d, δ_p and δ_h values were obtained by putting "simplified molecular-input line-entry system (SMILES)" of each component using "HSPiP software (version 4.1.07)" The SMILES of each compound is easily available in the compound database. The calculated values of δ, δ_d, δ_p and δ_h are presented in Table 2. From "HSPiP software", the value of δ for SIM was obtained as 18.70 $MPa^{1/2}$ which suggesting that SIM had lower polarity. The δ value for three different non-ionic surfactants i.e. M52, M59 and B58 was recorded as 18.70 $MPa^{1/2}$. However, the value of δ for T80, T20, B35 and H_2O was obtained as 21.30, 22.10, 18.90 and 47.80 $MPa^{1/2}$, respectively. The x_e values of SIM were obtained higher in M59, M52 and B35 which was possible due to same δ values for SIM, M59, M52 and B58 (Table 2). However, the x_e value of SIM was recorded lowest in H_2O which attributed the maximum δ value (47.80 $MPa^{1/2}$) of H_2O. Overall, the results of Hansen solubility parameters suggested good agreement of experimental solubility data of SIM with their polarities/solubility parameters.

Determination of drug solubilization efficiency

The drug solubilization efficiency for different micellar solutions of various non-ionic surfactants was determined as the molar solubilization capacity (S_c) using Eq (3) [31, 32]:

$$S_c = \frac{S_t - S_W}{C_S - CMC} \times 1000 \quad (3)$$

In which, S_t is the measured SIM solubility in the presence of surfactants, S_w is the intrinsic water solubility of SIM, C_s is the molar surfactant concentration and CMC is the critical micelle concentration of surfactant. The values of solubilization capacity for SIM in different micellar solutions of various non-ionic surfactants were determined at "T = 300.2 K" and results are presented in Table 3. The solubilization capacity for SIM was found to be lower in all micellar solutions of T80, T20, B35 and B58 compared to various micellar solutions of M52

Table 2. Hansen solubility parameters for SIM, H_2O and different non-ionic surfactants at T = 298.2 K calculated using HSPiP software.

Components	Hansen solubility parameters			
	δ_d/$MPa^{1/2}$	δ_p/$MPa^{1/2}$	δ_h/$MPa^{1/2}$	δ/$MPa^{1/2}$
SIM	46.60	6.60	5.70	18.70
T80	14.80	8.60	12.70	21.30
T20	14.90	9.40	13.30	22.10
M52	16.10	3.90	7.90	18.40
M59	16.10	3.90	7.90	18.40
B35	9.00	9.70	13.50	18.90
B58	10.10	8.80	12.60	18.40
H_2O	15.50	16.00	42.30	47.80

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Table 3. SIM solubilization capacity in various micellar solutions of different non-ionic surfactants at T = 300.2 K.

Surfactant	Solubilization capacity (mM M^{-1})
1 mM T80	29.40
5 mM T80	68.10
10 mM T80	51.90
20 mM T80	39.10
1 mM T20	51.30
5 mM T20	23.30
10 mM T20	35.30
20 mM T20	27.20
1 mM M52	102.0
5 mM M52	145.0
10 mM M52	174.0
20 mM M52	113.0
1 mM M59	62.60
5 mM M59	89.00
10 mM M59	125.0
20 mM M59	122.0
1 mM B35	72.90
5 mM B35	49.30
10 mM B35	90.60
20 mM B35	112.0
1 mM B58	41.50
5 mM B58	37.40
10 mM B58	34.70
20 mM B58	166.0

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and M59. The best solubilization capacity (x = 174.0) was found in 10 mM micellar solution of M52.

Theoretical/ideal solubilities

Theoretical/ideal solubility of solute/SIM (x^{idl}) was obtained using Eq (4) [43, 44]:

$$\ln x^{idl} = \frac{-\Delta H_{fus}(T_{fus} - T)}{RT_{fus}T} + \left(\frac{\Delta C_p}{R}\right)\left[\frac{T_{fus} - T}{T} + \ln\left(\frac{T}{T_{fus}}\right)\right] \quad (4)$$

In which, R represents the universal gas constant and ΔC_p represents the differential molar heat capacity of solute/SIM [43–45]. Other symbols in Eq (4) were defined previously in the article.

The values of T_{fus}, ΔH_{fus} and ΔC_p for solute/SIM were obtained as 412.95 K, 28.38 kJ mol^{-1} and 68.72 J mol^{-1} K^{-1}, respectively from DSC/thermal analysis of SIM. The x^{idl} values for solute/SIM were obtained using Eq (4) and these values at three different temperatures are presented in Table 1. Theoretical/ideal solubilities of SIM were compared with experimental solubilities at each temperature. It was noticed that theoretical/ideal solubility of SIM was significantly higher than SIM solubility in H_2O and various micellar solutions (1, 5, 10 and 20 mM) of T80, T20, M52, M59, B35 and B58 at each temperature investigated. Theoretical/ideal solubility of SIM was also recorded as increasing significantly with increase in temperature, suggesting the dissolution behavior of SIM was endothermic process [1].

Model solubilities and curve fitting

The experimental solubilities of SIM were modelled/curve fitted with the help of van't Hoff and Apelblat models [38, 46, 47]. Apelblat model solubility (x^{Apl}) of SIM in H_2O and various micellar solutions (1, 5, 10 and 20 mM) of T80, T20, M52, M59, B35 and B58 was calculated using of Eq (5) [46, 47]:

$$\ln x^{Apl} = A + \frac{B}{T} + C\ln(T) \tag{5}$$

In which, *A*, *B* and *C* represent the coefficients/parameters of Apelblat model which were obtained by applying "nonlinear multivariate regression analysis" of experimental solubilities of SIM listed in Table 1 [48]. The x_e of SIM were modelled/curve fitted with Apelblat solubilities of SIM using root mean square deviations (*RMSD*) and R^2. *RMSD* values between experimental and Apelblat solubilities of SIM were obtained using Eq (6) [35]:

$$RMSD = \left[\frac{1}{N}\sum_{i=1}^{N}\left(\frac{x^{Apl} - x_e}{x_e}\right)^2\right]^{\frac{1}{2}} \tag{6}$$

In which, *N* represents the number of experimental data points used in the study. The graphical correlation/curve fitting between logarithmic experimental solubilities ($\ln x_e$) and logarithmic Apelblat solubilities ($\ln x^{Apl}$) of SIM in H_2O and 1 mM and 5 mM micellar solution of T80, T20, M52, M59, B35 and B58 against reciprocal of absolute temperature ($1/T$) is presented in Fig 6A and 6B, respectively.

However, the curve fitting between $\ln x_e$ and $\ln x^{Apl}$ of SIM in H_2O and 10 mM and 20 mM micellar solution of T80, T20, M52, M59, B35 and B58 against $1/T$ is presented in Fig 6C and 6D, respectively. The results showed in Fig 6A–6D suggested good correlation/curve fitting between $\ln x_e$ and $\ln x^{Apl}$ values of SIM in H_2O and different micellar solutions of T80, T20, M52, M59, B35 and B58. The resulting data of this correlation/fitting are listed in Table 4. *RMSD* values for SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 were obtained as (0.16 to 5.84) %. An average *RMSD* for this correlation was found to be 0.60%. The R^2 values for SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 were obtained in the range of 0.9957 to 0.9999. The results presented in Table 4 in terms of *RMSD* and R^2 suggested good correlation of experimental data of SIM with Apelblat model.

The van't Hoff model solubility ($x^{van't}$) of SIM in H_2O and various micellar solutions (1, 5, 10 and 20 mM) of T80, T20, M52, M59, B35 and B58 was obtained using Eq (7) [38]:

$$\ln x^{van't} = a + \frac{b}{T} \tag{7}$$

In which, *a* and *b* represent the coefficients/parameters of van't Hoff model which were obtained by least square method.

The experimental solubilities of SIM were modelled/curve fitted with van't Hoff solubilities of SIM using *RMSD* and R^2. The curve fitting between logarithmic experimental solubilities and logarithmic van't Hoff solubilities of SIM in H_2O and 1 mM and 5 mM micellar solution of T80, T20, M52, M59, B35 and B58 against $1/T$ is shown in S1 and S2 Figs, respectively. However, the curve fitting between logarithmic experimental solubilities and logarithmic van't Hoff solubilities of SIM in H_2O and 10 mM and 20 mM micellar solution of T80, T20, M52, M59, B35 and B58 against $1/T$ is presented in S3 and S4 Figs, respectively. The data presented in S1–S4 Figs also showed good correlation/curve fitting between experimental and model

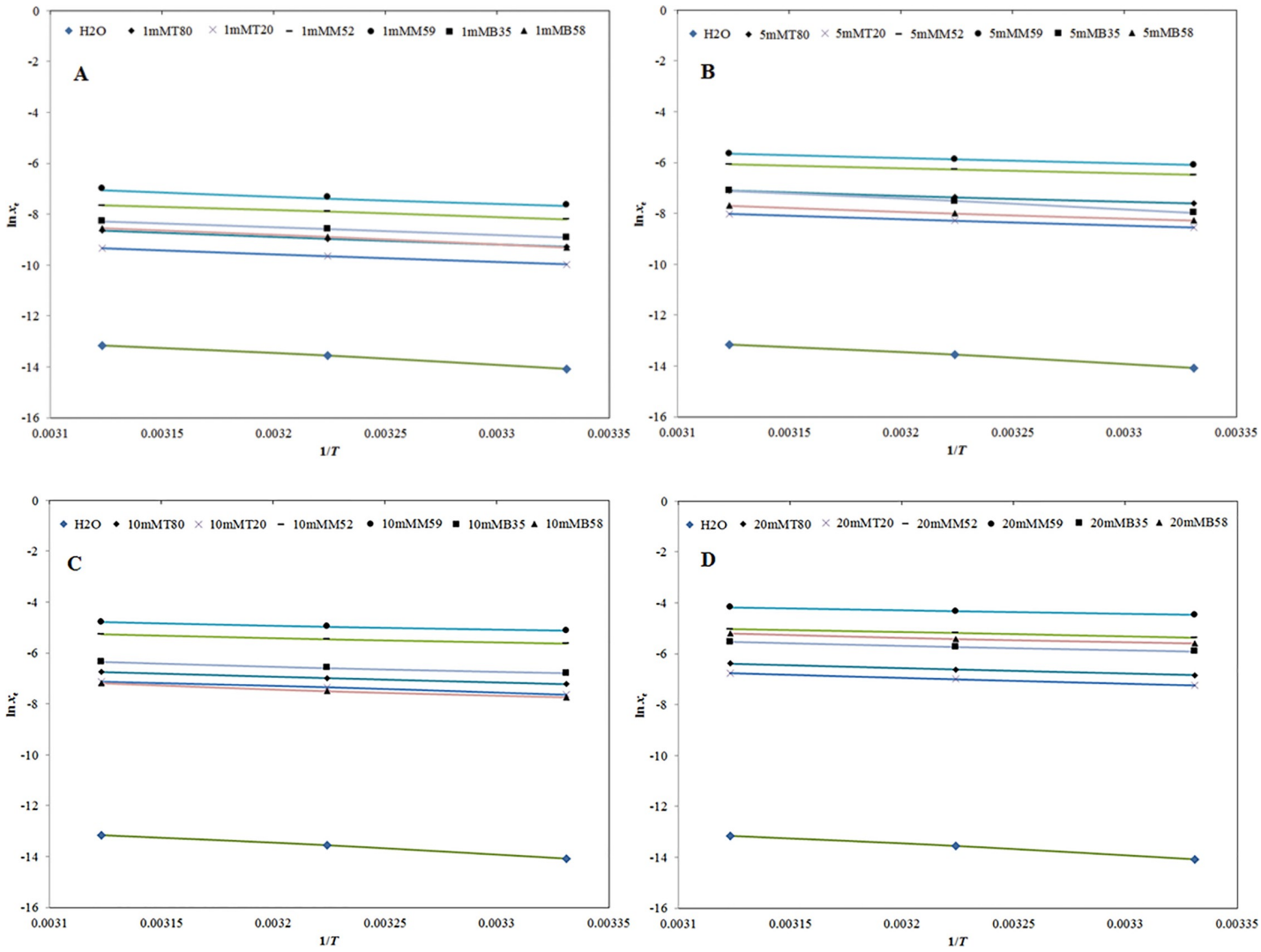

Fig 6. Correlation of ln x_e values of SIM with "Apelblat model" in (A) H_2O and 1 mM molar solution of various non-ionic surfactants and (B) H_2O and 5 mM molar solution of various non-ionic surfactants as a function of $1/T$; symbols represent the experimental solubilities of SIM and solid lines represent the solubilities of SIM calculated by "Apelblat model". Correlation of ln x_e values of SIM with "Apelblat model" in (C) H_2O and 10 mM molar solution of various non-ionic surfactants and (D) H_2O and 20 mM molar solution of various non-ionic surfactants as a function of $1/T$; symbols represent the experimental solubilities of SIM and solid lines represent the solubilities of SIM calculated by "Apelblat model".

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solubilities of SIM in H_2O and different micellar solutions of T80, T20, M52, M59, B35 and B58. The resulting data of this correlation are presented in Table 5. The *RMSD* values for SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 were obtained as (0.23 to 1.74) %. An average *RMSD* for this correlation was predicted as 0.78%. The R^2 values for SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 were recorded as 0.9944 to 1.0000. The results presented in Table 5 in terms of *RMSD* and R^2 again suggested good correlation of experimental data of SIM with van't Hoff model.

Apparent thermodynamics

Apparent thermodynamics is helpful in evaluation of various thermodynamic parameters, which could ultimately determine the dissolution behavior in case of real solutions and

Table 4. The parameters of Apelblat model (*A*, *B* and *C*) along with determination coefficient (R^2) and root mean square deviation (% *RMSD*) for SIM in H_2O and various micellar solutions of different non-ionic surfactants.

Samples	*A*	*B*	*C*	R^2	*RMSD* (%)	Overall *RMSD* (%)
H_2O	647.42	-34175.10	-96.00	0.9968	0.64	
1 mM T80	-181.54	5330.48	27.08	0.9998	0.37	
5 mM T80	-311.63	11940.19	46.32	0.9987	0.43	
10 mM T80	-103.18	2473.20	15.37	0.9999	0.24	
20 mM T80	-113.47	3086.68	16.89	0.9999	0.33	
1 mM T20	-155.24	4127.85	23.05	0.9999	0.44	
5 mM T20	-176.33	5533.73	26.18	0.9998	0.23	
10 mM T20	408.99	-21253.40	-60.62	0.9960	0.37	
20 mM T20	-127.46	3570.18	18.99	0.9999	0.21	
1 mM M52	309.92	-16896.90	-45.90	0.9978	0.28	
5 mM M52	-85.63	1970.57	12.72	0.9999	0.22	0.60
10 mM M52	-248.25	9672.29	36.88	0.9984	0.26	
20 mM M52	171.06	-9500.15	-25.38	0.9982	0.16	
1 mM M59	-410.22	15997.45	61.23	0.9985	5.84	
5 mM M59	-108.27	2914.14	16.21	0.9999	0.46	
10 mM M59	-299.01	12145.24	44.42	0.9970	0.57	
20 mM M59	-73.76	2004.46	10.97	0.9999	0.27	
1 mM B35	74.36	-6399.34	-10.86	0.9998	0.22	
5 mM B35	391.42	-21901.50	-57.22	0.9985	0.53	
10 mM B35	-401.65	16360.83	59.66	0.9969	0.81	
20 mM B35	-243.08	9359.92	36.11	0.9986	0.19	
1 mM B58	307.96	-17678.60	-48.29	0.9987	0.31	
5 mM B58	-341.94	12988.89	50.90	0.9988	0.65	
10 mM B58	-575.75	23887.41	85.62	0.9957	0.40	
20 mM B58	-364.22	14921.47	54.15	0.9966	0.60	

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solubilization in case of non-ideal solutions [49]. Hence, the dissolution/solubilization behavior of SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 were determined by applying "apparent thermodynamic analysis" on solubilities (mole fraction) of SIM. Accordingly, three different thermodynamic parameters including "apparent standard dissolution enthalpy ($\Delta_{sol}H^0$), apparent standard Gibbs free energy ($\Delta_{sol}G^0$) and apparent standard dissolution entropy ($\Delta_{sol}S^0$)" for SIM dissolution/solubilization were determined using this analysis. The $\Delta_{sol}H^0$ values for SIM dissolution/solubilization in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 were determined at mean harmonic temperature (T_{hm}) by applying van't Hoff analysis using Eq (8) [43, 49]:

$$\left(\frac{\partial ln\, x_e}{\partial\left({}^{1}/_{T} - {}^{1}/_{T_{hm}}\right)}\right)_{P} = -\frac{\Delta_{sol}H^0}{R} \tag{8}$$

The value of T_{hm} was calculated as 309.98 K using its reported formula [41]. The $\Delta_{sol}H^0$ values for SIM dissolution/solubilization in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 were obtained by van't Hoff plots plotted between ln x_e values of SIM and ${}^{1}/_{T} - {}^{1}/_{T_{hm}}$.

The $\Delta_{sol}G^0$ values for dissolution/solubilization behavior of SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 were also obtained at T_{hm} of 309.98 K by

Table 5. The parameters of van't Hoff model (*a* and *b*) along with R^2 and % *RMSD* for SIM in H_2O and various micellar solutions of different non-ionic surfactants.

Samples	*a*	*B*	R^2	*RMSD* (%)	Overall *RMSD* (%)
H_2O	0.62	-4407.80	0.9977	1.74	
1 mM T80	0.93	-3066.30	0.9995	0.57	
5 mM T80	0.45	-2421.40	0.9979	0.90	
10 mM T80	0.42	-2294.20	0.9997	0.31	
20 mM T80	0.32	-2149.50	0.9996	0.33	
1 mM T20	0.08	-3019.90	0.9996	0.51	
5 mM T20	0.04	-2582.60	0.9994	0.57	
10 mM T20	0.55	-2456.10	0.9971	1.12	
20 mM T20	0.47	-2316.80	0.9996	0.36	
1 mM M52	0.68	-2664.80	0.9986	0.84	
5 mM M52	0.10	-1974.60	0.9997	0.37	0.78
10 mM M52	0.24	-1763.00	0.9975	0.68	
20 mM M52	0.06	-1630.50	0.9989	0.46	
1 mM M59	2.32	-2987.20	0.9976	1.23	
5 mM M59	0.94	-2111.70	0.9996	0.53	
10 mM M59	0.30	-1628.80	0.9959	0.87	
20 mM M59	0.19	-1398.90	0.9996	0.25	
1 mM B35	1.18	-3030.50	1.0000	0.23	
5 mM B35	5.87	-4157.40	0.9991	1.14	
10 mM B35	0.32	-2137.80	0.9957	1.02	
20 mM B35	0.19	-1835.30	0.9978	0.72	
1 mM B58	2.80	-3634.10	0.9993	0.84	
5 mM B58	1.02	-2793.60	0.9981	1.30	
10 mM B58	1.10	-2658.80	0.9944	1.71	
20 mM B58	0.62	-1868.60	0.9954	1.07	

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Krug et al. analysis with the help of Eq (9) [50]:

$$\Delta_{sol}G^0 = -RT_{hm} \times intercept \quad (9)$$

In which, the intercept value for SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 was calculated from van't Hoff plot discussed under van't Hoff analysis.

Finally, the $\Delta_{sol}S^0$ values for dissolution/solubilization behavior of SIM were obtained using the combined approaches of van't Hoff and Krug et al. analysis with the help of Eq (10) [43, 49, 50]:

$$\Delta_{sol}S^0 = \frac{\Delta_{sol}H^0 - \Delta_{sol}G^0}{T_{hm}} \quad (10)$$

The calculated values of these thermodynamic parameters for dissolution/solubilization behavior of SIM in H_2O and different micellar solutions of T80, T20, M52, M59, B35 and B58 at T_{hm} of 309.98 K are presented in Table 6.

The $\Delta_{sol}H^0$ values for SIM dissolution/solubilization in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 were recorded as (11.62 to 36.64) kJ mol^{-1}. The $\Delta_{sol}H^0$ value for SIM dissolution was recorded highest in H_2O (36.64 kJ mol^{-1}). However, the lowest $\Delta_{sol}H^0$ value (11.62 kJ mol^{-1}) for SIM solubilization was obtained in 20 mM micellar

Table 6. Apparent thermodynamic quantities ($\Delta_{sol}H^0$, $\Delta_{sol}G^0$ and $\Delta_{sol}S^0$) along with R^2 values for SIM in H_2O and various micellar solutions of different non-ionic surfactants at T_{hm} of 309.98 K[a].

Samples	$\Delta_{sol}H^0$/kJ mol^{-1}	$\Delta_{sol}G^0$/kJ mol^{-1}	$\Delta_{sol}S^0$/J mol^{-1} K^{-1}	R^2
H_2O	36.64	35.03	5.17	0.9977
1 mM T80	25.48	23.08	7.76	0.9995
5 mM T80	20.12	18.95	3.79	0.9979
10 mM T80	19.07	17.98	3.50	0.9997
20 mM T80	17.86	17.30	2.68	0.9996
1 mM T20	25.10	24.87	0.72	0.9996
5 mM T20	21.46	21.34	0.39	0.9994
10 mM T20	20.41	18.98	4.60	0.9971
20 mM T20	19.25	18.03	3.94	0.9996
1 mM M52	22.15	20.39	5.67	0.9986
5 mM M52	16.41	16.15	0.83	0.9997
10 mM M52	14.65	14.03	2.00	0.9975
20 mM M52	13.55	13.38	0.55	0.9989
1 mM M59	24.86	18.84	19.32	0.9976
5 mM M59	17.55	15.11	7.86	0.9996
10 mM M59	13.53	12.75	2.52	0.9959
20 mM M59	11.62	11.13	1.60	0.9996
1 mM B35	25.19	22.14	9.81	1.0000
5 mM B35	34.55	19.41	48.85	0.9991
10 mM B35	17.77	16.93	2.70	0.9957
20 mM B35	15.25	14.74	1.64	0.9978
1 mM B58	30.20	22.97	23.32	0.9993
5 mM B58	23.22	20.58	8.49	0.9981
10 mM B58	22.10	19.23	9.15	0.9943
20 mM B58	15.53	13.91	5.21	0.9954

[a]The relative uncertainties are $u(\Delta_{sol}H^0) = 0.30$, $u(\Delta_{sol}G^0) = 0.26$ and $u(\Delta_{sol}S^0) = 1.40$

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concentration of M59. Overall, the low values of $\Delta_{sol}H^0$ were obtained at each micellar concentration of M59 investigated. The average value of $\Delta_{sol}H^0$ for SIM dissolution/solubilization was found out 20.94 kJ mol^{-1} with uncertainty of 0.30. The lowest $\Delta_{sol}H^0$ value for SIM solubilization in 20 mM micellar concentration of M59 was possible due to the highest solubility (mole fraction) of SIM in 20 mM micellar concentration of M59. While, the highest $\Delta_{sol}H^0$ value for SIM dissolution in H_2O was attributed to the lowest solubility of SIM in H_2O. The $\Delta_{sol}G^0$ values for SIM dissolution/solubilization in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 were recorded as (11.13 to 35.03) kJ mol^{-1}. The $\Delta_{sol}G^0$ value for SIM dissolution was also recorded highest in H_2O (35.03 kJ mol^{-1}). However, the lowest $\Delta_{sol}G^0$ value (11.13 kJ mol^{-1}) for SIM solubilization was obtained in 20 mM micellar concentration of M59. Overall, the low values of $\Delta_{sol}G^0$ were also obtained at each micellar concentration of M59 investigated. The average value of $\Delta_{sol}G^0$ for SIM dissolution/solubilization was found out 18.68 kJ mol^{-1} with uncertainty of 0.26. In comparison, lower values of $\Delta_{sol}H^0$ and $\Delta_{sol}G^0$ were obtained in 20 mM micellar concentration of M59, indicating that minimum energies are used for the solubilization of SIM in M59. The results of enthalpy and Gibbs free energy measurements were in accordance with solubility data of SIM in H_2O and various micellar solutions of different non-ionic surfactants. The positive values of apparent standard enthalpy ($\Delta_{sol}H^0 > 0$) and apparent standard Gibbs energy ($\Delta_{sol}G^0 > 0$) in all samples suggested an

endothermic dissolution/solubilization behavior of SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 [38, 51]. The positive values of $\Delta_{sol}H^0$ and $\Delta_{sol}G^0$ might be due to the formation of new bond energy of attraction between the drug and solvent molecules [49]. The $\Delta_{sol}S^0$ values for SIM dissolution/solubilization in H_2O and different micellar solutions of T80, T20, M52, M59, B35 and B58 were also recorded as positive values in the range of (0.39 to 48.55) J mol^{-1} K^{-1}. The average $\Delta_{sol}S^0$ value for SIM dissolution/solubilization was recorded as 7.28 J mol^{-1} K^{-1} with uncertainty of 1.40. The positive $\Delta_{sol}S^0$ values for SIM showed an entropy-driven dissolution/solubilization behavior of SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 [51]. Finally, the dissolution/solubilization behavior of SIM was found to be endothermic and entropy-driven in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 [36, 38, 51].

Conclusions

The objective of this work was to solubilize SIM using different micellar solutions of various non-ionic surfactants including T80, T20, M52, M59, B35 and B58. The solubility (mole fraction) of SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58 was determined at three different temperatures i.e. T = 300.2 K, 310.2 K and 320.2 K under atmospheric pressure. The results of DSC and PXRD analysis suggested crystalline nature of SIM before and after equilibrium. The solubilities (mole fraction) of SIM were regressed well with van't Hoff and Apelblat equations. With increase in temperature, the solubility of SIM was found to be enhanced significantly in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58. The solubility of SIM (mole fraction) was recorded highest in M59 (20 mM) followed by M52 (20 mM), B58 (20 mM), B35 (20 mM), T80 (20 mM), T20 (20 mM) and H_2O at T = 320.2 K. The same results were also recorded at each temperature and four different micellar solutions of T80, T20, M52, M59, B35 and B58. The results of "apparent thermodynamic analysis" showed an endothermic and entropy-driven dissolution/solubilization of SIM in H_2O and various micellar solutions of T80, T20, M52, M59, B35 and B58. Overall, these results suggested that various micellar solution of non-ionic surfactants could be successfully used in solubilization of poorly water soluble drugs such as SIM.

Supporting information

S1 Fig. Correlation of ln x_e values of SIM with van't Hoff model in H_2O and 1 mM molar solution of various non-ionic surfactants as a function of 1/T; symbols represent the experimental solubilities of SIM and solid lines represent the solubilities of SIM calculated by van't Hoff model.
(DOCX)

S2 Fig. Correlation of ln x_e values of SIM with van't Hoff model in H_2O and 5 mM molar solution of various non-ionic surfactants as a function of 1/T; symbols represent the experimental solubilities of SIM and solid lines represent the solubilities of SIM calculated by van't Hoff model.
(DOCX)

S3 Fig. Correlation of ln x_e values of SIM with van't Hoff model in H_2O and 10 mM molar solution of various non-ionic surfactants as a function of 1/T; symbols represent the experimental solubilities of SIM and solid lines represent the solubilities of SIM calculated by van't Hoff model.
(DOCX)

S4 Fig. Correlation of ln x_e values of SIM with van't Hoff model in H_2O and 20 mM molar solution of various non-ionic surfactants as a function of 1/T; symbols represent the experimental solubilities of SIM and solid lines represent the solubilities of SIM calculated by van't Hoff model.
(DOCX)

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