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Solubility of lovastatin in a family of six alcohols: Ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, and 1-octanol

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ABSTRACT

Accurate experimental determination of solubility of active pharmaceutical ingredients (APIs) in solvents and its correlation, for solubility prediction, is essential for rapid design and optimization of isolation, purification, and formulation processes in the pharmaceutical industry. An efficient material-conserving analytical method, with in-line reversed HPLC separation protocol, has been developed to measure equilibrium solubility of lovastatin in ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, and 1-octanol between 279 and 313 K. Fusion enthalpy ΔH^{fus}, melting point temperature, T_m, and the differential molar heat capacity, ΔC_P, were determined by differential scanning calorimetry (DSC) to be 43,136 J/mol, 445.5 K, and 255 J/(mol K), respectively. In order to use the regular solution equation, simplified assumptions have been made concerning ΔC_P, specifically, $\Delta C_P = 0$, or $\Delta C_P = \Delta S$. In this study, we examined the extent to which these assumptions influence the magnitude of the ideal solubility of lovastatin, and determined that both assumptions underestimate the ideal solubility of lovastatin. The solubility data was used with the calculated ideal solubility to obtain activity coefficients, which were then fitted to the van't Hoff-like regular solution equation. Examination of the plots indicated that both assumptions give erroneous excess enthalpy of solution, H^{∞}, and hence thermodynamically inconsistent activity coefficients. The order of increasing ideality, or solubility of lovastatin was butanol > 1-propanol > 1-pentanol > 1-hexanol > 1-octanol.

1. Introduction

Solubility is one of the most fundamental physiochemical properties that is particularly useful to a wide variety of applications important to the biological, chemical, pharmaceutical and environmental industries. Accurate solubility data are needed for process and product design including production and purification of pharmaceutical compounds, formulation, controlled drug delivery systems, bio-separations, precipitation/crystallization processes, chemical reaction systems, pollution prevention and remediation, and food processing. There is a vast amount of literature reporting the results of drug solubility measurements in organic solvents (Jouyban et al., 1998, 2002a,b; Kolar et al., 2002; Frank et al., 1999; Tiziana et al., 2007; Mirmehrabia et al., 2004; Huang et al., 2005; Ruckenstein and Shulgin, 2002, 2003, 2004; Rubino and Obeng, 1991; Adjei et al., 1980). But, many more combinations of solvent and solute remain to be investigated. This is because the current experimental method for measuring drug solubility is tedious, time consuming, and usually require large amounts of pure solute which are often unavailable or can be very expensive.

At the interface between drug discovery and preclinical candidate selection, solubility measurement and correlation have to satisfy the needs of both drug discovery and product development. Especially for low solubility compounds, extended solubility data, in both aqueous and organic pharmaceutically relevant solvents, are needed to select suitable pre-formulation strategy for subsequent pharmacokinetics and pharmacodynamics (PK/PD) and toxicology studies (Tiziana et al., 2007). Crystallization as a unit operation in the pharmaceutical industry serves the dual purpose of isolation and purification of the active pharmaceutical ingredient (API). And, because the compounds of interest are often labile, solution crystallization is the primary method of crystallization in comparison to other crystallization techniques such as heat melt. With increasing complexity of API molecules, enhanced analytical techniques to detect impurities, and ever-decreasing timelines for drug development, the challenges in crystallization process design and optimization have grown significantly over the years. In consideration of limited material supply at early stage of drug

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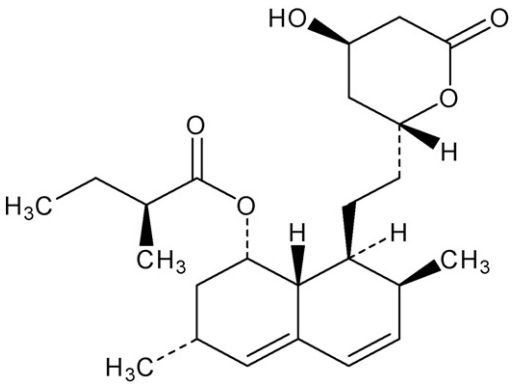

Fig. 1. Chemical structure of lovastatin.

development, and the need to identify the proper solvent and temperature range for crystallization as quickly as possible, prediction of solubility based on limited experimental data is gaining more attentions (Herrador and Gonzalez, 1997).

In this work, we experimentally measure and correlate temperature dependence of equilibrium solubility of lovastatin in a family of alcohols. Additionally, we measured the melting temperature, enthalpy change of fusion and differential molar heat capacity at the melting point of lovastatin. We use these data to calculate the ideal solubility of lovastatin and estimate its infinite dilution limiting activity coefficient in different alcohols. We showed that in order to obtain experimentally consistent activity coefficient data for lovastatin, accurate differential heat capacity must be used.

2. Theory

Lovastatin (structure shown in Fig. 1) belongs to a class of the most powerful lipid lowering drug compounds, called the statins (Istvan and Deisenhofer, 2001). Their mode of action is through inhibition of the (3*S*)-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Using competition, statins specifically inhibit HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevolanate, which is an early rate-limiting step in cholesterol biosynthesis in the body. The resulting decrease in intracellular cholesterol results in compensatory increase in cholesterol uptake by means of low-density lipoprotein (LDL) receptors and concomitant decrease in plasma cholesterol. Statins are the treatment of choice for management of hypercholestrolaemia because of their proven efficacy and safety profile (Palinski, 2000; Javernik et al., 2003; Greenberg et al., 2004; Kim et al., 1999; Vincenzi et al., 2003; Strode et al., 1999; Shachter, 2004; Elder, 1988; Sutherland et al., 2003; Manzoni et al., 1998).

Seven statins are now approved for clinical use in at least one country (Shachter, 2004): lovastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, prevastatin, and pitavastatin. Lovastatin (a.k.a. butanioc acid 2-methyl-1,2,3,7,8,8*a*-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl) ethyl]-1-naphalenyl ester) is a natural product, a secondary metabolite, derived from fermentation of *Aspergillus terreus* (Elder, 1988; Sutherland et al., 2003; Manzoni et al., 1998). It is also a key raw material for synthesis of simvastatin. Following isolation of the lovastatin crude product, the compound is purified by various crystallization sequences prior to milling to finished product, and subsequent formulation as drug (Elder, 1988).

Very little has been reported in the literature about the solubility of statins in organic solvents. Recently, Sun et al. (2005) employed the synthetic method, using a laser monitoring observation technique to measure the solubility of lovastatin in acetone, ethyl acetate, butyl acetate, ethanol, and methanol at different temperatures.

The temperature dependence of solute solubility is described by the thermodynamic relationship (Prausnitz et al., 1986):

$$\ln x_1 = \ln x_1^{\mathrm{id}} - \ln \gamma_1 \tag{1}$$

where $\ln x_1^{\mathrm{id}}$ represents the ideal solubility of solute 1 defined by

$$\ln x_1^{\mathrm{id}} = \left[\frac{\Delta H^{\mathrm{fus}}(T_{\mathrm{m}})}{RT_{\mathrm{m}}} - \frac{\Delta C_{\mathrm{P}}}{R}[1+\ln T_{\mathrm{m}}]\right] + \left[\left(\frac{\Delta C_{\mathrm{P}} T_{\mathrm{m}}}{R} - \frac{\Delta H^{\mathrm{fus}}(T_{\mathrm{m}})}{R}\right)\right]\frac{1}{T} + \frac{\Delta C_{\mathrm{P}}}{R}\ln T \tag{2}$$

Here x_1, γ_1, T_{m}, $\Delta H^{\mathrm{fus}}(T_{\mathrm{m}})$, ΔC_{P}, R, and T represent the solubility mole fraction of the solute (denoted as component 1) in solution, activity coefficient of the solute in solution, melting temperature of the solute, enthalpy of fusion of the pure solute at melting temperature, differential molar heat capacity of the pure solute (that is, the difference between the molar heat capacity of the solid and the liquid at their melting temperature), gas constant, and temperature, respectively. Because the solubility or equilibrium mole fraction of lovastatin in the alcohols is very low (of the order of 10^{-3}), it is assumed that the last term in Eq. (1) denotes the infinite dilution activity coefficient $\ln \gamma_1^{\infty}$.

Note that $\ln x_1^{\mathrm{id}}$ is temperature-dependent and can be determined from pure solute properties, namely, T_{m}, $\Delta H^{\mathrm{fus}}(T_{\mathrm{m}})$ and ΔC_{P}. The influence of the solvent on solute solubility is accounted for by the activity coefficient $\ln \gamma_1^{\infty}$ which quantifies the interaction between the solvent and solute molecules.

To accurately quantify the temperature dependence of equilibrium solubility x_1 using Eq. (1), it is necessary to know how $\ln \gamma_1^{\infty}$ varies with temperature. It is frequently assumed that, over a narrow temperature range, the activity coefficient follows a van't Hoff-like equation or the so-called regular solution approximation (Prausnitz et al., 1986), and that is

$$\ln \gamma_1^{\infty} = \frac{\bar{H}_1^{\mathrm{E},\infty}}{RT} - \frac{\bar{S}_1^{\mathrm{E},\infty}}{R} = \frac{\Delta H^{\infty}}{RT} - \frac{\Delta S^{\infty}}{R} \tag{3}$$

where $\bar{H}_1^{\mathrm{E},\infty}$, $\bar{S}_1^{E,\infty}$, ΔH^{∞} and ΔS^{∞} represent the limiting partial excess enthalpy, partial excess entropy, enthalpy of mixing and entropy of mixing, respectively, are considered to be temperature-independent. For cases where solubility increases with temperature (i.e., endothermic dissolution) one would expect the activity coefficient to decrease with increasing temperature. Thus, a plot of $\ln \gamma_1^{\infty}$ versus $1/T$ should yield a straight line with a positive slope ($\Delta H^{\infty}/R$). The opposite trend is expected to hold if the solubility decreases with increasing temperature (i.e., exothermic dissolution process). And, for entropically driven dissolution process, the intercept, ($\Delta S/R$), would be positive.For cases where ΔH^{∞} and ΔS^{∞} are not known, Eq. (3) can be expressed in terms of empirical constants, A and B:

$$\ln \gamma_1^{\infty} = \frac{\Delta H^{\infty}}{RT} - \frac{\Delta S^{\infty}}{R} = A + \frac{B}{T} \tag{4}$$

Combining Eq. (4) with Eqs. (1) and (2), and rearranging, derives:

$$\ln x_i = \left[\frac{\Delta H^{\mathrm{fus}}(T_{\mathrm{m}})}{RT_{\mathrm{m}}} - \frac{\Delta C_{\mathrm{P}}}{R}[1+\ln T_{\mathrm{m}}] - A\right] + \left[\left(\frac{\Delta C_{\mathrm{P}} T_{\mathrm{m}}}{R} - \frac{\Delta H^{\mathrm{fus}}(T_{\mathrm{m}})}{R}\right) - B\right]\frac{1}{T} + \frac{\Delta C_{\mathrm{P}}}{R}\ln T \tag{5}$$

$$\ln x_1 = a + \frac{b}{T} + c \ln T \tag{6}$$

where

$$a = \frac{\Delta H^{\text{fus}}(T_{\text{m}})}{RT_{\text{m}}} - \frac{\Delta C_{\text{P}}}{R}[1 + \ln T_{\text{m}}] - A \tag{7}$$

$$b = \left(\frac{\Delta C_{\text{P}} T_{\text{m}}}{R} - \frac{\Delta H^{\text{fus}}(T_{\text{m}})}{R} \right) - B \tag{8}$$

$$c = \frac{\Delta C_{\text{P}}}{R} \tag{9}$$

Eq. (6) is known as the Apelblat equation (Apelblat and Manzurola, 1999) and is frequently used to correlate solubility. The parameters a, b and c can be obtained by regressing Eq. (6) against experimental data and the regression procedure usually gives excellent fit to the solubility data (Sun et al., 2005; Ren and Wang, 2004; Ren et al., 2004; Niea and Wang, 2005; Niea et al., 2006; Wang et al., 2005; Roberts et al., 1994; Jiang et al., 2000; Liu et al., 2005). However, information on the activity coefficient $\ln \gamma_1^{\infty}$ cannot be easily extracted owing to the fact that the quantities A and B of Eq. (3) cannot be accurately obtained from the regressed constants a and b via of Eq. (6). The difficulty lies in the fact that the differential heat capacity ΔC_{P} is not readily available experimentally or through the best fit values of $c = \Delta C_{\text{P}}/R$. It is worthy of note that, for the same solute compound (with identical crystalline properties), the value of the fitted parameter c should remain constant regardless of the dissolving solvent since it is a pure solute property. Results in the literature show that the fitted parameter $c = \Delta C_{\text{P}}/R$, for a solute dissolving in different solvents, not only does not remain constant, but varies widely by 50%, and in some cases up to 300%. Such significant discrepancy indicates inconsistency in the fitted values of the parameters of a, b, and c, and makes it extremely difficult to obtain activity coefficients from the solubility data.

Given that ΔC_{P} for a large number of substances are not readily available, the following two assumptions have been made regarding the differential specific molar heat capacity at constant pressure (Neau and Flynn, 1990):

(I) ΔC_{P} is assumed negligible and can be considered to be zero, in which case, Eq. (1) simplifies to

$$\ln x_1 = \frac{-\Delta H^{\text{fus}}(T_{\text{m}})}{R} \left(\frac{T_{\text{m}} - T}{T_{\text{m}} T} \right) - \ln(\gamma_i^{\infty}) \tag{10}$$

(II) ΔC_{P} may be approximated by the entropy of fusion, ΔS. This assumption leads to the following expression for the equilibrium solubility:

$$\ln x_1 = \frac{-\Delta H^{\text{fus}}(T_{\text{m}})}{RT_{\text{m}}} \ln \left(\frac{T_{\text{m}}}{T} \right) - \ln(\gamma_i^{\infty}) \tag{11}$$

Eqs. (10) and (11) have been employed in several studies to fit experimentally measured solubility data (Neau and Flynn, 1990). The ideal solubility, x_1^{id}, for either cases would simply be the first term in each equation. Neau and Flynn (1990) investigated the validity of each of the two assumptions using a homologous series of n-alkyl paraminobenzoates, and concluded that the second assumption was more valid for this class of compounds. These results suggested that the contribution of heat capacity to the predicted ideal solubility is not negligible in these substances.

In this paper, we measure the melting temperature, heat of fusion, and differential molar heat capacity of lovastatin via differential scanning calorimetry (DSC). Given these quantities, we calculate the ideal solubility of lovastatin and examine the validity of the assumptions given by Eqs. (10) and (11). Additionally, we measure the equilibrium solubility of lovastatin in six alcohols: ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, and 1-octanol and determine the activity coefficient lovastatin at infinite dilution, $\ln \gamma_1^{\infty}$ by subtracting the measured solubility from the ideal solubility, that is

$$\ln \gamma_1^{\infty} = \ln x_1^{\text{id}} - \ln x_1^{\text{Exp}} \tag{12}$$

where x_1^{Exp} represents the experimentally measured equilibrium solubility of lovastatin in the solvent of study.

We further examine if the infinite dilution activity coefficient, $\ln \gamma_1^{\infty}$, follows a van't Hoff-like behavior, and whether it can be represented by Eqs. (1) and (2); Eqs. (10) and (2); and/or Eqs. (11) and (2).

3. Experimental

3.1. Materials

Crystalline lovastatin powder ($C_{24}H_{36}O_5$; MW 404.54) obtained from Alexis Biochemicals, with mass purity, determined by HPLC, of 99.8 wt% was used for this study. HPLC analytical grade reagent solvents (each >99.5% purity): methanol, ethanol, 1-propanol, 1-butanol, 1-hexanol, 1-pentanol, and 1-octanol were obtained from Fisher Scientific, then dried with molecular sieves before use. The purity of the solvents was confirmed by gas chromatography to be >99.5%. Water content was determined by Karl Fisher titration to be <0.005 wt%.

3.2. Equipment

Wrist Action, Burrel, model 75 mechanical shaker; Mettler AE 160 digital analytical balances, sensitivity 0.01 mg; 2910 Modulated DSC, TA Instruments differential scanning calorimeter; DSC822e, Mettler-Toledo differential scanning calorimeter. Analytical scale solubility experiments were performed using an Agilent HP-1100 HPLC system composed of a quaternary pump, column and autosampler thermostat and variable wavelength detector with detection monitored at 205 nm. A set of five standard lovastatin stock solutions were prepared by appropriate dilution of a stock solution, then used to generate a calibration curve (with regression coefficient better than 0.999). The calibration curve was used to determine the equilibrium concentrations of lovastatin upon sampling and analysis.

4. Experimental methods

4.1. Solubility determination

An analytical method with approach to equilibrium from oversaturation strategy (Alsenz et al., 2007) was employed for the saturation solubility measurement. This method was designed to ensure minimum material was used, and also to identify if any of the solvents being studied causes modification of the structure of lovastatin (stability). For solubility measurement with each solvent, about 150 mg of lovastatin (an excess of substance) was added to several 2 mL HPLC vials, containing 1.5 mL of the pertinent solvent. The mixtures were stirred in a mechanical shaker, maintained at $40 \pm 0.1\,^{\circ}\text{C}$, for 24 h. Visual inspection was carefully made to ensure there were excess lovastatin solids in the mixture, indicating saturation had been reached. The vials were then loaded into the thermostat-temperature-controlled autosampler of the HPLC and the temperature was lowered to the desired temperature (at a cooling rate of $0.25\,^{\circ}\text{C/h}$). Upon reaching the desired temperature, the mixture was allowed to equilibrate for 24–48 h (although

our experimental results indicated that 12 h was sufficient for complete equilibration and settling of un-dissolved solute). Thereafter, the solution was sampled then analyzed via the reversed phase method to determine the equilibrium concentration, as well as to ensure lovastatin was stable in the pertinent solvent.

To avoid any potential differential temperature driven precipitation upon sampling, the HPLC sampling needle was stored in the thermostat-temperature-controlled HPLC autosampler compartment with the samples. This ensured that its temperature was same as that of the sample. Additionally, the needle was positioned to allow careful sampling of 2 μL solution from the top middle portion of the vial; this ensured that the settled solids were not disturbed. Furthermore, each vial was sampled and analyzed in triplicates to ensure that the system was equilibrium at the point of sampling. The method was validated by comparing our results with literature values for equilibrium solubility of lovastatin in ethanol (Sun et al., 2005).

4.2. Reversed phase analytical methods

All samples were analyzed by reversed phase analytical HPLC with UV detection. The column used for the reversed phase analysis (Symmetry®, 4.6 mm i.d. × 50 mm, packed with silica-C-8, 3.5 μm particle diameter) was obtained from Waters Corporation, and maintained at 60 °C.

All elutions were carried out at 4.5 mL/min; mobile phase conditions were started isocratically with 70% 0.01 M H_3PO_4 (in water) and 30% acetonitrile for 1 min, followed by a linear gradient to 70% acetonitrile in 3 min, after which the column was flushed with 100% acetonitrile for 1 min, then re-equilibrated with the 70% 0.01 M H_3PO_4 (in water) and 30% acetonitrile for 2 min prior to the next injection (i.e., total run time was 7 min). For each run, the mobile was directed through the sampling needle sample loop into the column, to ensure complete loading of the sample to the column. Concentration of the lovastatin solute was calculated based on a calibration curve, and the value was used to calculate the equilibrium solubility mole fraction, x_1 as

$$x_1 = \frac{M_1}{M_1 + M_2} \tag{13}$$

where M_1 and M_2 represent the moles of the solute and solvent, respectively.

4.3. Thermal analysis

Around 5 mg of lovastatin powder was put in a hermetic DSC pan. For each DSC experiment, an empty DSC pan was used as a blank reference. The samples were scanned from 0 to 230 °C at a heating rate of 2 °C/min. The heat of fusion, melting temperature and differential specific heat were determined from the DSC data with STAR Thermal Analysis Software (Mettler-Toledo Inc., USA).

5. Results and discussion

5.1. Analytical results

The solubility measurement technique in this study was validated by comparing the temperature-dependent equilibrium mole fraction of lovastatin in ethanol, with the results obtained by Sun et al. (2005). At slightly elevated temperature (>300 K), a second peak was observed for the lovastatin–methanol system. The spectra of the second peak varied slightly from that obtained with the pure lovastatin, suggesting modification to the compound has occurred at these temperatures. An isolate of the second peak was analyzed via NMR and mass spectroscopy, and was analyzed to be a derivative

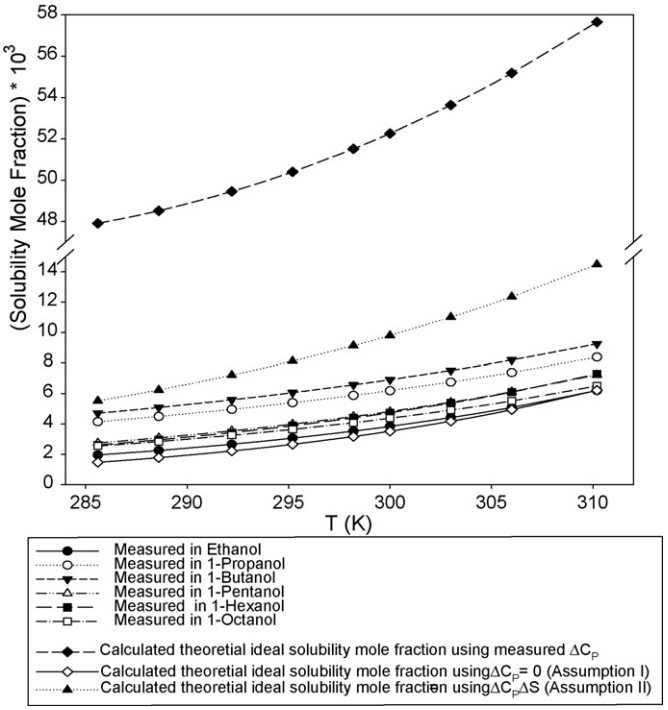

Fig. 2. Calculated ideal solubility with measured ΔC_P, and those calculated from assumption I ($\Delta C_P = 0$) and assumption II ($\Delta C_P = \Delta S$), and measured equilibrium solubility of lovastatin in different alcohols at different temperatures.

of the original compound, indicating that lovastatin is not stable in methanol, at elevated temperatures, for extended period. It is worthy to note that solubility of lovastatin in methanol exists in the literature (Sun et al., 2005); it is possible that the degradation was not observed because of different solubility measurement technique employed in that study. Lovastatin was relatively stable in all the other alcohols employed in this study.

5.2. Calorimetric data

The melting temperature and heat of fusion of the lovastatin crystalline powder was measured by differential scanning calorimetry to be 445.5 ± 0.5 K, and 43,136 J/mol, respectively. The values are in good agreement with literature values (Elder, 1988; Souza et al., 2007). The differential molar heat capacity, $\Delta\overline{C_P}$, was also measured by DSC to be 255 J/(mol K), employing a similar protocol used by Neau and Flynn (1990).

5.3. Ideal solubility $\ln x_1^{id}$ of lovastatin

The ideal solubility of lovastatin $\ln x_1^{id}$ can be determined from Eq. (2) using the values of ΔH^{fus}, T_m, and ΔC_P measured in this work. It is of interest to examine the accuracy of the approximate ideal solubilities calculated with Eq. (10) (assumption I) and Eq. (11) (assumption II) by comparing them to the values determined from Eq. (2). The calculated ideal solubility values are displayed in Fig. 2 together with the experimentally measured solubility data, and the correlated solubility data are displayed in Table 1. Fig. 2 shows that both assumption I ($\Delta C_P = 0$) and assumption II ($\Delta C_P = \Delta S^{fus}$) underestimate the calculated theoretical ideal solubility of lovastatin, with assumption I being the most impacted. This is consistent with observation reported for other compounds (Neau and Flynn, 1990; Gracin et al., 2002), suggesting that ΔC_P has a significant contribution to the ideal solubility of lovastatin particularly at temperatures

Table 1
Mole fraction solubility data of lovastatin in different alcohols at different temperatures

T (K)	$X_1 \times 10^3$	T (K)	$X_1 \times 10^3$	T (K)	$X_1 \times 10^3$
Ethanol (this work)					
286.15	2.0574	296.65	3.2270	307.15	5.4305
289.15	2.3045	301.65	4.0839	309.15	5.8507
291.10	2.5077	304.55	4.6648	310.55	6.2596
Ethanol (Sun et al.)					
278.25	1.4020	294.95	2.9810	307.80	5.5360
283.30	1.7970	298.15	3.5290	313.05	7.0940
288.25	2.2560	303.05	4.4600	318.65	9.3260
1-Propanol					
286.15	4.2104	301.65	6.4980	307.15	7.5945
289.15	4.5126	304.55	7.1873	309.15	8.0885
291.10	4.8848	305.65	7.3603	310.55	8.4415
1-Butanol					
285.70	4.6046	301.20	7.0227	308.70	8.6850
288.70	4.9877	304.10	7.6196	310.10	9.0410
290.65	5.2554	305.20	7.8606		
296.20	6.1126	306.70	8.2028		
1-Pentanol					
289.15	3.1213	299.20	4.6819	307.15	6.4004
291.10	3.3974	304.55	5.7108	309.15	6.9139
295.5	4.0441	305.65	6.1291	310.55	7.3787
1-Hexanol					
293.8500	3.6267	300.65	4.9080	312.00	7.6794
295.8500	3.9958	303.90	5.6535		
298.9500	4.5493	308.90	7.0345		
1-Octanol					
285.70	2.5518	301.20	4.6741	308.70	6.1930
288.70	2.7800	304.10	4.9997	310.10	6.5927
290.65	3.1255	305.20	5.1493		
296.20	3.9135	306.70	5.6685		

far from the solute melting temperature. It is worth noting that the calculated theoretical ideal solubility of lovastatin using assumption I is actually lower than the experimentally determined equilibrium mole fraction for each of the solvent investigated.

For all cases, solubility of lovastatin increases with increasing temperature, indicating dissolution of lovastatin in the alcohols followed an endothermic process. It is interesting to note that, solubility of lovastatin increases with increasing alkyl chain length (from ethanol to 1-butanol) and then decreases as the carbon chain length increases. This interesting behavior is probably a consequence of the interactions between solute–solvent. Studies are in progress to measure solubility of lovastatin in branched alky-chained alcohols. The data will be used in conjunction with molecular simulation to elucidate the nature of these interactions.

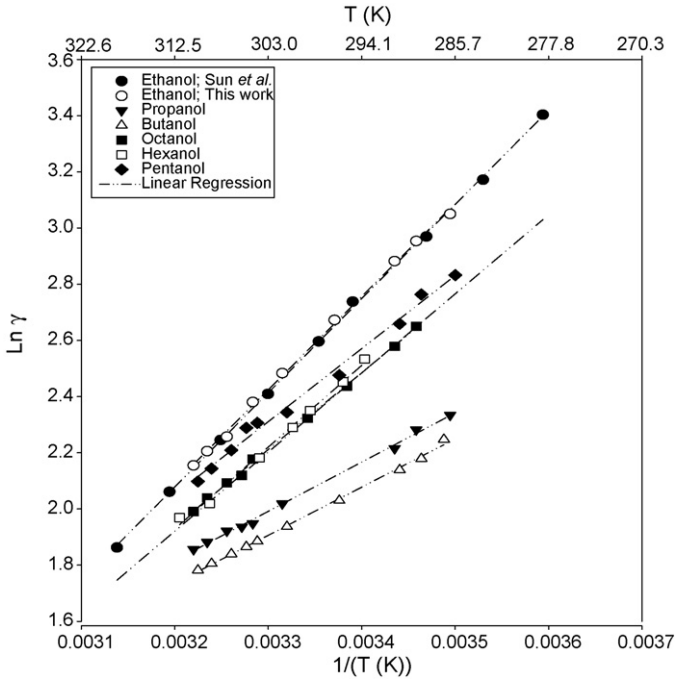

Fig. 3. van't Hoff plot of temperature-dependent activity coefficient at infinite dilution data for lovastatin in different alcohols.

5.4. Activity coefficient of lovastatin $\ln \gamma_1^\infty$

The activity coefficient of lovastatin in different alcohols at infinite dilution $\ln \gamma_1^\infty$ as a function of temperature can be obtained from Eqs. (1), (2) and (12) using the experimentally measured T_m, ΔH^{fus} (T_m), ΔC_P, and equilibrium solubility x_1^{Exp}. Values of $\ln \gamma_1^\infty$ against $1/T$ are plotted in Fig. 3. It is seen that the coefficient $\ln \gamma_1^\infty$ for all lovastatin–alcohol mixture follows van't Hoff's relation, Eq. (4):

$$\ln \gamma_1^\infty = A + \frac{B}{T}$$

where A and B can be identified as $\Delta S^\infty/R$ and $\Delta H^\infty/R$, respectively. A simple linear relationship between $\ln \gamma_1^\infty$ and $1/T$ is observed confirming that ΔH^∞ is reasonably constant over the temperature range considered. The goodness of fit is excellent as evidenced from the regression coefficient $r^2 > 0.995$ (see Table 2). Since the solubility of lovastatin in the alcohols studied herein increases with temperature, the slope of $\ln \gamma_1^\infty$ and $1/T$ plots for all mixtures exhibit a positive slope indicating that $\Delta H^\infty > 0$, consistent with endothermic dissolution.

Table 2
Values of the activity coefficient parameters, A and B obtained from van't Hoff's plots, and regression coefficients

	$\ln \gamma_1^\infty = A + B/T$								
	Measured ΔC_P (Fig. 3)			Assumption I: $\Delta C_P = 0$ (Fig. 4)			Assumption II: $\Delta C_P = \Delta S_{fus}$ (Fig. 5)		
	$A = \Delta S^\infty/R$	$B = \Delta H^\infty/R$	Regression coeff. r^2	$A = \Delta S^\infty/R$	$B = \Delta H^\infty/R$	Regression coeff. r^2	$A = \Delta S^\infty/R$	$B = \Delta H^\infty/R$	Regression coeff r^2
Ethanol[a]	−8.6461	3351.4	0.9996	3.7035	−1183.4	0.9695	−1.0970	579.4	0.9410
Ethanol[b]	−8.5321	3320.1	0.9986	3.7485	−1189.5	0.9723	−1.0251	563.5	0.9174
1-Propanol	−3.7883	1751.5	0.9979	8.5195	−2766.7	0.9990	3.7351	−1010.3	0.9939
1-Butanol	−3.7509	1714.3	0.9970	8.5541	−2302.3	0.9994	3.7708	−1046.6	0.9966
1-Pentanol	−6.8130	2734.7	0.9990	5.3302	−1733.0	0.9964	0.6098	3.710	0.0017
1-Hexanol	−7.3862	2911.0	0.9951	4.4323	−1457.9	0.9894	−0.1619	240.4	0.6693
1-Octanol	−6.2117	2600.0	0.9981	6.0645	−1925.4	0.9840	1.2690	−1660	0.3268

[a] Sun et al.'s data.
[b] This work.

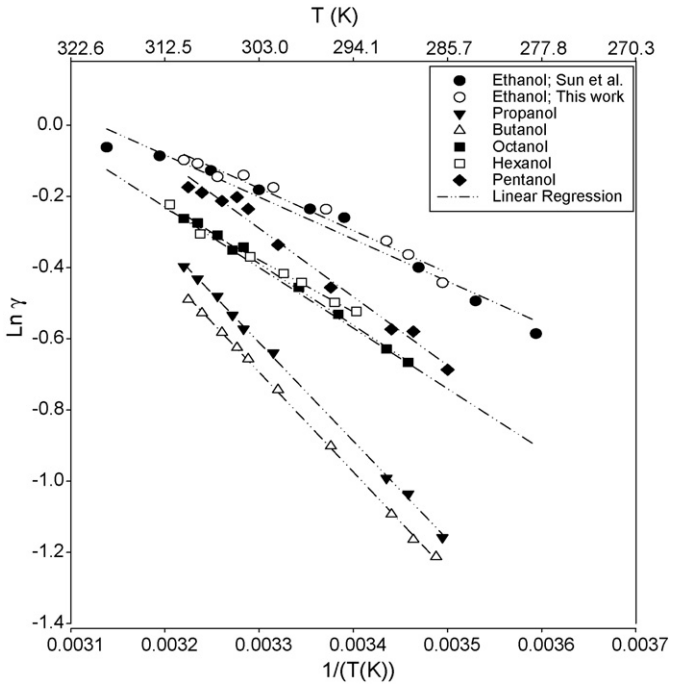

Fig. 4. van't Hoff plot temperature-dependent activity coefficient at infinite dilution data for lovastatin in different alcohols using the assumption I ($\Delta C_P = 0$).

We now examine the influence of assumptions I and II on the activity coefficient $\ln \gamma_1^\infty$. If we use the ideal solubility calculated from Eq. (10) (assumption I, $\Delta C_P = 0$) to determine $\ln \gamma_1^\infty$ via Eq. (12), the resulting activity coefficients of lovastatin in the various alcohols are displayed in Fig. 4. As in the previous case, van't Hoff plot of $\ln \gamma_1^\infty$ versus $1/T$ shows linear correlation (Fig. 4 and Table 2).

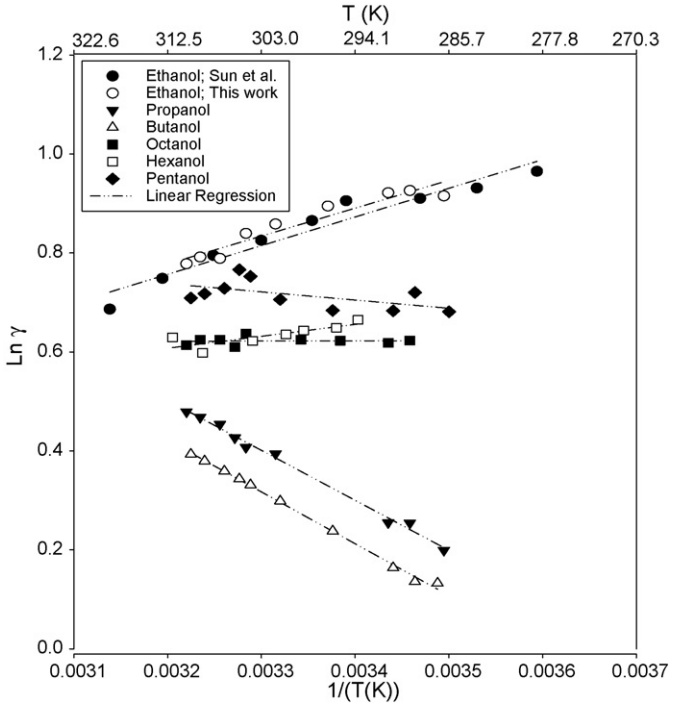

Fig. 5. van't Hoff plot of temperature-dependent activity coefficient at infinite dilution data for lovastatin in different alcohols using assumption II ($\Delta C_P = \Delta S$).

However, each straight line has a negative slope suggesting that the activity coefficient increases with increasing temperature (i.e., solubility decreases with increasing temperature or exothermic dissolution process). This contradicts the actual experimental data in which solubility increases with increasing temperature. Therefore, the $\Delta C_P = 0$ assumption leads to activity coefficients $\ln \gamma_1^\infty$ that are inconsistent with solubility data and is not applicable for correlating temperature-dependent equilibrium data for lovastatin in alcohols.

In the case of assumption II, $\Delta C_P = \Delta S$ and Eq. (11), we find that van't Hoff plot of $\ln \gamma_1^\infty$ versus $1/T$ shows almost linear curves with scattered correlation. Some of these curves exhibit negative slope, whereas others had positive slope (Fig. 5 and Table 2). Similar to the previous case, the $\Delta C_P = \Delta S$ assumption II again yields activity coefficients that are inconsistent with solubility data, and is not applicable for correlating temperature-dependent equilibrium data for lovastatin in alcohols.

6. Conclusion

In this study, equilibrium solubility of lovastatin in ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, and 1-octanol was measured between 279 and 313 K (displayed in Table 1). The solubility measurement method employed a material-conserving analytical technique, coupled with in-line reversed HPLC separation protocol to ensure compound stability in solvent of study. A possible degradation of lovastatin in methanol was discovered at elevated temperatures. We found that the dissolution of lovastatin is endothermic, that is, its equilibrium solubility increases with increasing temperature.

Lovastatin's enthalpy of fusion at its melting temperature ΔH^{fus}, melting point temperature, T_m, and the differential molar heat capacity ΔC_P were also determined via DSC. We examine and conclude that ΔC_P has a significant contribution to the ideal solubility of lovastatin, Eq. (2) and the commonly used approximations which consider $\Delta C_P = 0$ (assumption I of Eq. (10)) and $\Delta C_P = \Delta S^{fus}$ (assumption II of Eq. (11)) introduce significant errors in the predicted ideal solubility. With accurate values of the lovastatin ideal solubility x^{id}, we have successfully obtained the limiting activity coefficient $\ln \gamma_1^\infty$ of lovastatin at infinite dilution in the alcohols studied here. We found that the activity coefficient follows the van't Hoff equation, i.e., $\ln \gamma_1^\infty = A + B/T$. Values of $A = \Delta S^\infty/R$ and $B = \Delta H^\infty/R$ are obtained and tabulated in Table 2. The value of the parameter B is positive indicating that the activity coefficient decreases with increasing temperature, consistent with endothermic dissolution. We found that if $\Delta C_P = 0$ or $\Delta C_P = \Delta S^{fus}$ is assumed, the quantity $B = \Delta H^\infty/R$ can be negative implying exothermic dissolution which is inconsistent with the temperature dependence of lovastatin solubility. This finding again point to the fact that correct values of ΔC_P must be used to determine ideal solubility and activity coefficient. Molecular and thermodynamic modeling studies are being pursued to quantify and elucidate the observations obtained in this work.

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