Solubility of Lovastatin in Ethyl Acetate, Propyl Acetate, Isopropyl Acetate, Butyl Acetate, *sec*-Butyl Acetate, Isobutyl Acetate, *tert*-Butyl Acetate, and 2-Butanone, between (285 and 313) K

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A material-conserving analytical solubility measurement technique, with in-line reversed HPLC separation protocol, was employed to measure the mole fraction solubility of lovastatin in methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, *sec*-butyl acetate, *tert*-butyl acetate, acetone, and 2-butanone between (285 and 313) K. We examine three methods for the estimation of the ideal solubility of lovastatin by using different approximations for the difference between the heat capacity of the solid and the liquid at the melting point $\Delta C_P = C_P^{\mathrm{L}} - C_P^{\mathrm{S}}$. The solubility data were combined with calculated ideal solubility data to determine the activity coefficients of lovastatin which are then fitted to a van't Hoff form equation to obtain estimated values of the partial molar enthalpy of mixing, $\Delta_{\mathrm{mix}}H^{\infty}$, and partial molar entropy of mixing, $\Delta_{\mathrm{mix}}S^{\infty}$, respectively. Thermodynamic consistency was confirmed when $\Delta C_P = C_P^{\mathrm{L}} - C_P^{\mathrm{S}}$ was used in the ideal solubility calculation.

Introduction

Selection of industrial-relevant solvent, a function of solubility, is one of the most important steps for the development of efficient liquid−liquid extraction and crystallization processes in the pharmaceutical industry.[1−9]

Optimization of extraction, chromatography, and crystallization processes requires screening of numerous solvent systems for which the solubility of the compound of interest has to be measured as a function of temperature. Correlating solubility data requires knowledge of the ideal solubility of the solute whose calculation requires estimation of the difference in the molar heat capacity at constant pressure of the solid and the hypothetical supercooled liquid form of the solute, $\Delta C_P = C_P^{\mathrm{L}} - C_P^{\mathrm{S}}$. Since this parameter is usually not known exactly, three assumptions have been commonly used in the literature: (i) ΔC_P has negligible dependence on temperature, and it can be approximated by its value at the melting temperature, $\Delta C_P = \Delta C_P(T_{\mathrm{m}})$, (ii) ΔC_P can be considered to be zero, and (iii) ΔC_P is equated to the molar entropy of fusion $\Delta S^{\mathrm{fus}}(T_{\mathrm{m}})$. In our previous work described elsewhere,[4] we develop a material-conserving analytical method with in-line reversed-phase HPLC protocol to measure the equilibrium solubility of lovastatin in a family of alcohols. We measured the melting enthalpy, melting temperature, and heat capacities of the solid and liquid of the solutes between (270 and 520) K. We combined and used the data to show that only the first assumption gave thermodynamically consistent activity coefficients for lovastatin, particularly at temperatures far from the melting point.

In this work, we extend our study by measuring the mole fraction solubility of lovastatin in methyl acetate, propyl acetate, isopropyl acetate, *sec*-butyl acetate, isobutyl acetate, *tert*-butyl acetate, and 2-butanone between (285 and 313) K. Additionally, we validate our solubility measurement technique by comparing our data to literature values for solubility of lovastatin in ethyl acetate, butyl acetate, and acetone.

Lovastatin (structure shown in Figure 1) belongs to a class of the most powerful lipid lowering drug compounds, called the statins.[8] 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. Lovastatin is isolated from fermentation broth via extraction and is then purified by a sequence crystallization.[8] Results obtained from this study will be of relevance to estimation of solubility of lovastatin in various organic solvents for crystallization process development.

Theory. The temperature dependence of mole fraction equilibrium solubility of crystalline nonelectrolyte solute in solvent is described by the thermodynamic relationship[10]

$$\ln x_1 = \ln x_1^{\mathrm{id}} - \ln \gamma_1 = \frac{\Delta_{\mathrm{fus}}H}{RT}\left[\frac{T - T_{\mathrm{m}}}{T_{\mathrm{m}}}\right] + \int_{T_{\mathrm{m}}}^{T} \frac{\int_{T_{\mathrm{m}}}^{T} (C_P^{\mathrm{L}} - C_P^{\mathrm{S}})\mathrm{d}T}{RT^2}\mathrm{d}T - \ln \gamma_1 \quad (1)$$

Here x_1, x_1^{id}, γ_1, T_{m}, $\Delta_{\mathrm{fus}}H[= H\mathrm{L}(T_{\mathrm{m}}) - H\mathrm{S}(T_{\mathrm{m}})]$, $\Delta C_P[= C_P^{\mathrm{L}} - C_P^{\mathrm{S}}]$, R, and T represent the mole fraction solubility of the solute (denoted as component 1) in solution, ideal mole fraction solubility of the solute, activity coefficient of the solute in solution, melting temperature of the solute, enthalpy change of melting of the pure solute at its melting temperature, difference in the molar heat capacity (at constant pressure) of the solid and the supercooled liquid of the solute at the solution temperature, the gas constant, and the absolute temperature of the solution, respectively. In the above, C_P^{L}, and C_P^{S}, represent

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the molar heat capacities of the liquid and solid forms for lovastatin, respectively. Because the solubility or equilibrium mole fraction of lovastatin in most of the solvents studied is very low (in the order of 10^{-3} mole fraction), it is assumed that the last term in eq 1 denotes the infinite dilution activity coefficient, $\ln \gamma_1^{\infty}$.

In eq 1, the ideal mole fraction solubility $\ln x_1^{id}$ can be estimated with knowledge of T_m, $\Delta_{fus}H$, and ΔC_P. If the actual solute solubility is available, the activity coefficient can then be obtained by subtracting the measured solubility from the ideal solubility through eq 1. Conversely, if the activity coefficient is known, one can estimate solute solubility via eq 1. Note that the activity coefficient can be expressed as[10]

$$\ln \gamma_1^{\infty} = \frac{\Delta_{mix}H^{\infty}}{RT} - \frac{\Delta_{mix}S^{\infty}}{R} \quad (2)$$

where $\Delta_{mix}H^{\infty}$ and $\Delta_{mix}S^{\infty}$ represent the partial molar enthalpy of mixing and partial molar entropy of mixing of the solute at infinite dilution, respectively, and are assumed to be temperature independent.

Given that ΔC_P values for a large number of substances are not readily available, in order to estimate ideal solubility of a solute, the following three assumptions have been proposed and commonly made in the literature.[11−16]

Assumption I: In this assumption, ΔC_P is assumed to be independent of temperature and equal to the value at the melting temperature of the solute[14,15]

$$\Delta C_P = \Delta C_P(T_m) = C_P^{L}(T_m) - C_P^{S}(T_m) \quad (3)$$

If eq 3 is substituted into eq 1, we obtain

$$\ln x_1^{id} = \frac{\Delta_{fus}H}{RT_m}\left[1 - \frac{T_m}{T}\right] + \frac{\Delta C_P}{R}\left[\frac{T_m}{T} - 1 + \ln\left(\frac{T}{T_m}\right)\right] \quad (4)$$

Assumption II: In this assumption, the quantity ΔC_P is assumed negligible and considered to be zero.[11,12] Substituting $\Delta C_P = 0$ into eq 1 simplifies to,

$$\ln x_1^{id} = \frac{\Delta_{fus}H}{RT_m}\left(1 - \frac{T_m}{T}\right) \quad (5)$$

Assumption III: In this assumption, ΔC_P is approximated to be equal to the entropy of fusion at the melting point, that is, $\Delta C_P = \Delta_{fus}S$. This approach has been used in the literature[11−16] and, as noted by Pappa et al.,[17] is based on the observation by Hildebrand and Scott that in the case of ideal solubility $\ln x_1^{id}$ is linearly related to $\ln T$.

Hence, if we set $\Delta C_P = \Delta_{fus}S = \Delta_{fus}H/T_m$ and substitute it into eq 4, we obtain

$$\ln x_1^{id} = \frac{-\Delta_{fus}H}{RT_m} \ln\left(\frac{T_m}{T}\right) \quad (6)$$

Yalkowsky et al.[13] concluded that assumption II provides a better fit for naphthalene, phenanthrene, fluorene, and anthracene in benzene and thus must be preferred over assumption III. Recently, Pappa et al. highlighted some of the limitations of the assumptions II and III when used to interpret solubility data.[17]

In our previous work, reported elsewhere,[4] we demonstrated the importance of using the right assumption in calculating ideal solubility of lovastatin, particularly at temperatures far below the melting point of the solute. We employed a van't Hoff-like analysis to conclusively show that both assumption II and III give thermodynamically inconsistent partial molar enthalpies of mixing. Continuing on that finding, we extend the thermodynamic analysis to experimentally determined mole fraction solubility of lovastatin in methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, *sec*-butyl acetate, isobutyl acetate, *tert*-butyl acetate, 2-butanone, and acetone between (285 and 313) K.

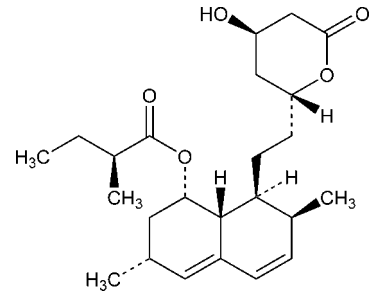

Figure 1. Chemical structure of lovastatin.

Experimental Section

Materials. Crystalline lovastatin powder ($C_{24}H_{36}O_5$; MW 404.54) manufactured by Merck and Co., Inc., with mass fraction purity (determined by HPLC) of 99.8 % was used for this study. HPLC analytical grade reagent solvents (each > 99.5 % purity), methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, *sec*-butyl acetate, isobutyl acetate, *tert*-butyl acetate, acetone, and 2-butanone, were used for the experiments. The mass fraction purity of the solvents was confirmed by gas chromatography to be > 99.5 %. Water mass fraction was determined by Karl Fisher titration to be $< 5 \cdot 10^{-3}$.

Equipment. The equipment included a Wrist Action, Burrel, model 75 mechanical shaker and Mettler AE 160 digital analytical balances, with sensitivity of 0.01 mg. Analytical scale solubility experiments were performed using an Agilent HP-1100 HPLC system composed of a quaternary pump, a column, and an autosampler thermostat and variable wavelength detector.

Experimental Methods. Solubility Measurement. Details for the solubility measurement techniques and the HPLC analytical method are provided elsewhere.[4] 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. Analysis time was 7 min, and the column was flushed after each run. The effluent from the column was monitored at 205 nm. The mobile phase was directed through the sampling needle and the sampling loop to the column, to ensure complete loading of the sample to the column. Each run was carried out in triplicate, from which the average was taken. On the basis of the standard deviation of the triplicate runs, the uncertainty for determining the components in the assay was ± 5 %.

Results and Discussion

Temperature-Dependent Equilibrium Mole Fraction Solubility of Lovastatin. The measured mole fraction solubility of lovastatin in ethyl acetate, butyl acetate, and acetone obtained by us agrees with literature values[9] within the limits of the uncertainty of our analytical method, ± 5 % (Figure 2A). This indicates that our solubility measurement technique[4] is reasonably good (i.e., a maximum deviation of ± 5 % from the literature values is reasonable since the solutes and solvents were obtained from different sources).

Measured temperature-dependent mole fraction equilibrium solubilities of lovastatin in the solvents between (285 and 313)

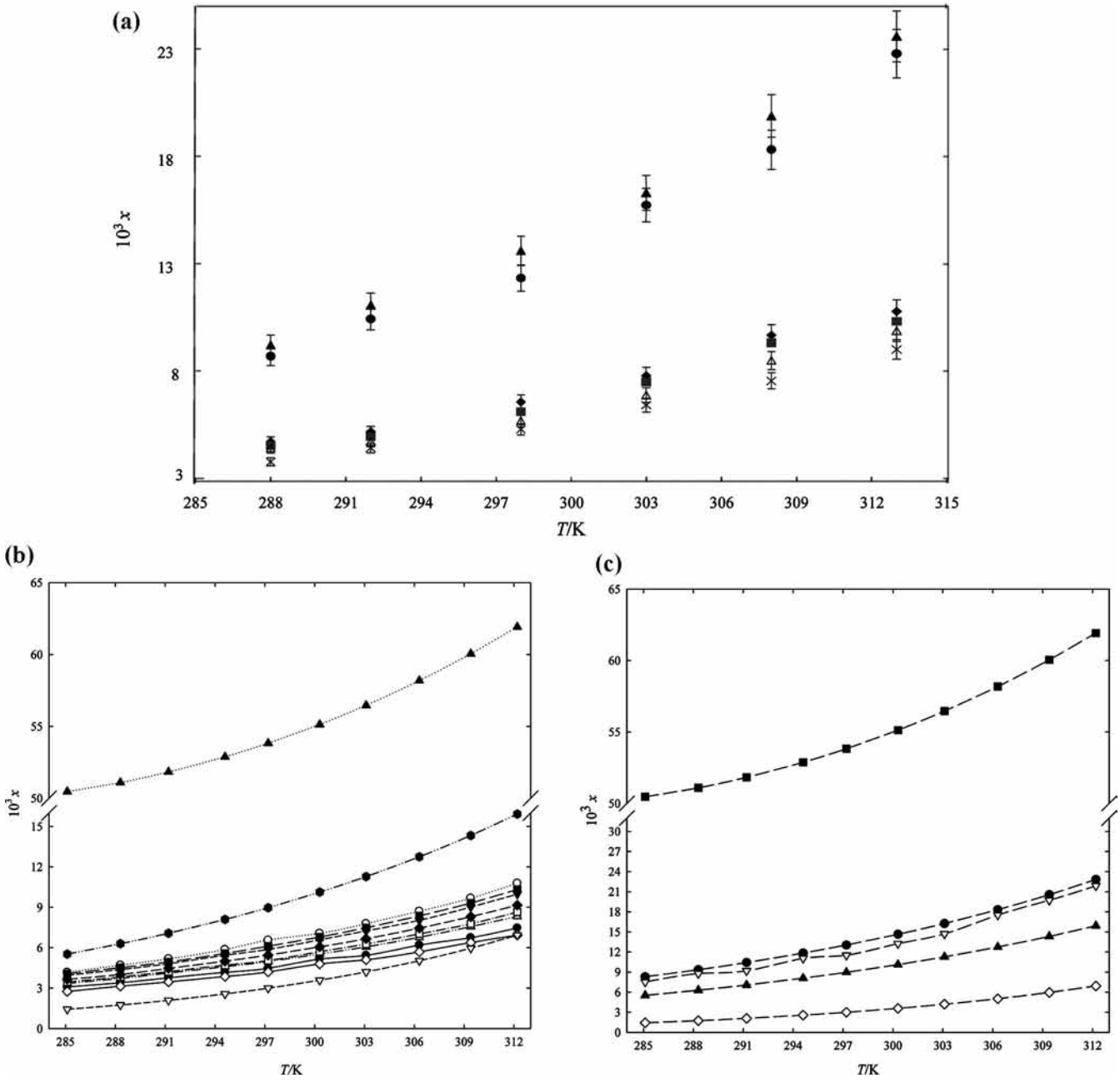

Figure 2. (A) Comparison of the present work mole fraction solubility x of lovastatin with literature values: ◆, ethyl acetate (this work); △, ethyl acetate (ref 9); ■, butyl acetate (this work); *, butyl acetate (ref 9); ▲, acetone (this work); ●, acetone (ref 9). (B) Mole fraction solubility x of lovastatin in different solvents: ●, methyl acetate; ○, ethyl acetate; ▼, propyl acetate; △, isopropyl acetate; ■, butyl acetate; □, isobutyl acetate; ◆, *sec*-butyl acetate; ◇, *tert*-butyl acetate; ▲, calculated ideal solubility using assumption I; ▽, calculated ideal solubility using assumption II; ⬢, calculated ideal solubility using assumption III. (C) Mole fraction solubility x of lovastatin in different solvents: ▽, 2-butanone; ●, acetone; ■, calculated ideal solubility using assumption I; ◇, calculated ideal solubility using assumption II; ▲, calculated ideal solubility using assumption III.

K are presented in Table 1 and graphically displayed in Figure 2B and 2C, along with theoretical ideal mole fraction solubility values estimated using assumptions I, II, and III.

For each solvent studied, the equilibrium solubility mole fraction of lovastatin increases with temperature, indicating that the dissolution of lovastatin in the solvents followed an endothermic process. It is of interest to note that the ideal solubility calculated from assumption I is always higher than the actual experimentally determined values (Figure 2B and 2C). In contrast, values of ideal solubility estimated from assumption II are consistently lower than the actual values suggesting that the resulting activity coefficients are lower than unity. This result is problematic as one expects the activity coefficient of lovastatin in these solvents to be greater than one. Similarly, Figure 2C shows that values of ideal solubility calculated based on assumption III for acetone and 2-butanone are again lower than the actual values. These observations indicate that for the lovastatin−solvent systems considered here assumptions II and III lead to thermodynamically inconsistent results and highlight the importance of the assumption used for estimating the ΔC_P term in calculating ideal solubility.

van't Hoff-Like Analysis of the Activity Coefficient Data. The activity coefficient of lovastatin in different organic solvents at infinite dilution, $\ln \gamma_1^{\infty}$, as a function of temperature, was calculated for the solvents in which solubility of lovastatin was low, using eq 1 in the same manner as reported in our previous work,[4] with the ideal solubility estimated from eq 4 to eq 6 for the three different assumptions. It is worth noting that the infinite

Table 1. Mole Fraction Solubility Data of Lovastatin in Different Organic Solvents and at Different Temperatures

T/K	methyl acetate	ethyl acetate	propyl acetate	isopropyl acetate	butyl acetate	isobutyl acetate	*sec*-butyl acetate	*tert*-butyl acetate	acetone	2-butanone
					$10^3\ x_1$					
285.1	3.09	4.17	3.95	3.35	4.07	3.45	3.65	2.75	8.31	7.52
288.3	3.40	4.70	4.38	3.72	4.52	3.83	4.01	3.14	9.36	8.78
291.2	3.76	5.17	4.81	4.12	4.94	4.22	4.46	3.46	10.43	9.18
294.6	4.17	5.86	5.44	4.59	5.57	4.70	5.00	3.86	11.84	11.05
297.2	4.47	6.56	5.87	4.97	6.11	5.04	5.45	4.20	13.04	11.51
300.3	5.15	7.06	6.58	5.53	6.79	5.70	6.06	4.79	14.64	13.24
303.1	5.43	7.78	7.24	6.06	7.48	6.27	6.66	5.10	16.26	14.70
306.3	6.19	8.70	8.03	6.77	8.36	7.02	7.45	5.69	18.32	17.51
309.4	6.74	9.67	9.01	7.56	9.31	7.77	8.30	6.38	20.56	19.72
312.2	7.46	10.78	9.97	8.32	10.32	8.64	9.15	6.93	22.83	21.86

dilution assumption could not be applied to the acetone and 2-butanone since the mole fraction solubilities were slightly high. Hence data from these solvents were excluded from the van't Hoff analysis.

van't Hoff plots of $\ln \gamma_1^\infty$ versus $1/T$ are made and displayed in Figures 3A, 3B, and 3C for assumptions I, II, and III, respectively. The activity coefficients are fitted to eq 2 to determine the partial molar enthalpy of mixing, $\Delta_{mix}H^\infty$, and partial molar entropy of mixing, $\Delta_{mix}S^\infty$, of the solute, which are displayed in Tables 2a, 2b, and 2c, for assumptions I, II, and III, respectively, along with values of the absolute average relative deviation (AARD). AARD is defined as

$$\text{AARD} = \frac{1}{N}\sum\left[\left|\frac{\gamma_1^\infty - \gamma_{1(\text{Corr})}^\infty}{\gamma_1^\infty}\right|\right] \tag{7}$$

where N is the number of data points obtained in each set which equal the number of temperatures used and $\gamma_{1\ (\text{Corr})}^{\infty}$ is the correlated value.

For assumption I, the slope of $\ln \gamma_1^\infty$ and $1/T$ plots for all mixtures exhibits a positive slope (Figure 3A and Table 2a) indicating that the partial molar enthalpy of mixing $\Delta_{mix}H^\infty$ is greater than zero, consistent with positive values of enthalpy of mixing and expected of the organic nonpolar system considered here. However, for assumptions II and III, the slopes are negative, erroneously suggesting that the enthalpy of mixing is negative (Figures 3B and 3C and Tables 2b and 2c). Additionally, for nonionic solute−solvent systems, as are the cases being studied here, it is expected that mixing would lead to an increase in randomness and hence an increase in entropy (i.e., $\Delta_{mix}S^\infty > 0$). However, for assumptions II and III, $\Delta_{mix}S^\infty < 0$ (also erroneously), suggesting that there is rather a decrease in entropy upon mixing (Tables 2b and 2c), thus consistent with the conclusion of our previous study[4] and the aforementioned observation (from the previous section) that assumptions II and III lead to $\gamma_1^\infty < 1$. The results here again indicate that only assumption I yields thermodynamic consistent results. Accordingly, as concluded in our earlier research, the choice of ΔC_P for modeling solubility data, particularly for temperatures far from the melting temperature, is very important.[4]

Nonrandom Two-Liquid (NRTL) Activity Coefficient Model. Existing activity coefficient models such as the nonrandom two-liquid (NRTL) model have been used successfully as tools to provide versatile thermodynamic frameworks to correlate existing experimental data.[10] The model NRTL interaction parameters can be determined using a small set of experimental datapoints, and once parametrized, the model can be employed to predict information such as solubility, limiting activity coefficient, and the Gibb excess enthalpy of mixing. Here, we use the NRTL model to correlate our experimental data, to generate the interaction parameters for lovastatin in the solvents studied.

The NRTL equation introduced by Renon and Prausnitz is a three-parameter equation, expressed as[10]

$$\ln \gamma_1 = x_2^2\left[\frac{\tau_{12}G_{12}}{(x_2 + x_1G_{12})^2} + \tau_{21}\left(\frac{G_{21}}{x_1 + x_2G_{21}}\right)^2\right] \tag{8}$$

Here

$$G_{12} = \exp(-\alpha\tau_{12}) \text{ and } G_{21} = \exp(-\alpha\tau_{21}) \tag{9}$$

and

$$\tau_{12} = \frac{b_{12}}{RT} \text{ and } \tau_{21} = \frac{b_{21}}{RT} \tag{10}$$

where b_{12} and b_{21} are interaction parameters specific to a particular pair of species, independent of temperature and composition, and the parameter α is a measure of the nonrandomness of the mixture.[10] Using an optimum α value of 0.4 for our data, we regressed measured values of lovastatin mole fraction solubility against $\ln x_1 = \ln x_1^{id} - \ln \gamma_1$ with the activity coefficient given by eq 8 to eq 10 and the ideal solubility represented by eq 4. It must be noted that the value of 0.40 is within the range of values commonly found for correlating solubility data (i.e., α ranges between 0.20 and 0.47).[10]

Best fit values of b_{12} and b_{21} were obtained by minimizing the average relative deviation (ARD) defined below

$$\text{ARD} = \frac{1}{N}\sum\left[\left|\frac{x_1 - x_{1\ (\text{Calcd})}}{x_1}\right|\right] \tag{11}$$

where N is the number of data points obtained in each set which equal the number of temperatures used and $x_{1(\text{Calcd})}$ is the calculated value from the NRTL equation. Best fit values of the interaction parameters are displayed in Table 3. The results indicate that good correlations were achieved for all the solvents studied.

Conclusion

In this study, we have continued on our previous work to employ a material-conserving solubility measuring technique to determine the mole fraction solubility of lovastatin in ten different pure organic solvents: methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, *sec*-butyl acetate, *tert*-butyl acetate, acetone, and 2-butanone, between (285 and 313) K (shown in Table 1). We found that the dissolution of lovastatin in each of these solvents is endothermic; that is, its equilibrium solubility increases with increasing temperature.

Comparison of the values of ideal solubility estimated using assumption II ($\Delta C_P = 0$) and assumption III ($\Delta C_P = \Delta_{fus}S$)

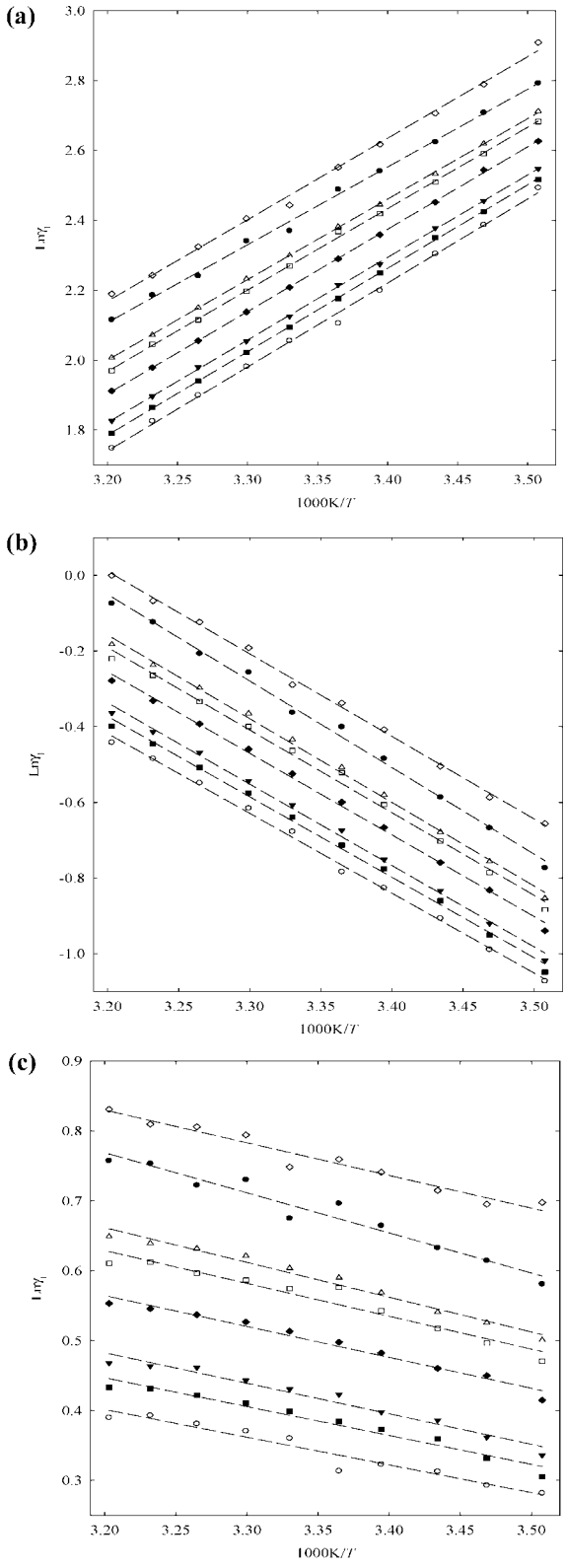

Figure 3. (A) van't Hoff plot of temperature-dependent activity coefficients at infinite dilution using assumption I (eq 4): ●, methyl acetate; ○, ethyl acetate; ▼, propyl acetate; △, isopropyl acetate; ■, butyl acetate; □, isobutyl acetate; ♦, *sec*-butyl acetate; ◇, *tert*-butyl acetate; - - -, linear fit. (B) van't Hoff plot of temperature-dependent activity coefficients at infinite dilution using assumption II (eq 5): ●, methyl acetate; ○, ethyl acetate; ▼, propyl acetate; △, isopropyl acetate; ■, butyl acetate; □, isobutyl acetate; ◆, *sec*-butyl acetate; ◇, *tert*-butyl acetate; - - -, linear fit. (C) van't Hoff plot of temperature-dependent activity coefficients at infinite dilution using assumption III (eq 9): ●, methyl acetate; ○, ethyl acetate; ▼, propyl acetate; △, isopropyl acetate; ■, butyl acetate; □, isobutyl acetate; ◆, *sec*-butyl acetate; ◇, *tert*-butyl acetate; - - -, linear fit.

Table 2a. Correlative Values of $\Delta_{mix}S^{\infty}$ and $\Delta_{mix}H^{\infty}$ Obtained from Linear van't Hoff Fit of ln γ_1 to 1/T (Using Assumption I; Equation 4), along with AARD Values (Equation 11)

	$\Delta_{mix}S^{\infty}$/J·mol^{-1}	$\Delta_{mix}H^{\infty}$/J·mol^{-1}	100 AARD
methyl acetate	42	18799	0.34
ethyl acetate	49	19980	0.36
propyl acetate	48	19647	0.13
isopropyl acetate	45	19140	0.10
butyl acetate	49	19847	0.09
isobutyl acetate	46	19373	0.17
sec-butyl acetate	47	19606	0.08
tert-butyl acetate	44	19389	0.38

Table 2b. Correlative Values of $\Delta_{mix}S^{\infty}$ and $\Delta_{mix}H^{\infty}$ Obtained from Linear van't Hoff Fit of ln γ_1 to 1/T (Using Assumption II; Equation 5), along with AARD Values (Equation 11)

	$\Delta_{mix}S^{\infty}$/J·mol^{-1}	$\Delta_{mix}H^{\infty}$/J·mol^{-1}	100 AARD
methyl acetate	−60	−19024	5.09
ethyl acetate	−53	−17544	1.37
propyl acetate	−54	−17884	1.86
isopropyl acetate	−58	−18392	2.80
butyl acetate	−53	−17685	1.63
isobutyl acetate	−57	−18159	2.74
sec-butyl acetate	−55	−17926	1.86
tert-butyl acetate	−58	−18142	3.88

Table 2c. Correlative Values of $\Delta_{mix}S^{\infty}$ and $\Delta_{mix}H^{\infty}$ Obtained from Linear van't Hoff Fit of ln γ_1 to 1/T (Using Assumption III; Equation 9), along with AARD Values (Equation 11)

	$\Delta_{mix}S^{\infty}$/J·mol^{-1}	$\Delta_{mix}H^{\infty}$/J·mol^{-1}	100 AARD
methyl acetate	−22	−4772	1.48
ethyl acetate	−14	−3295	2.08
propyl acetate	−16	−3632	1.65
isopropyl acetate	−19	−4139	1.09
butyl acetate	−15	−3432	1.32
isobutyl acetate	−18	−3909	1.24
sec-butyl acetate	−16	−3678	1.07
tert-butyl acetate	−19	−3889	1.45

Table 3. Values of the Binary Interaction Parameters for the NRTL Model and Average Relative Deviation (ARD) from the Measured Equilibrium Mole Fraction of Lovastatin in Different Solvents

	b_{12}	b_{21}	100 ARD
methyl acetate	−3406	16106	0.55
ethyl acetate	−3222	14835	0.76
propyl acetate	−3264	15125	0.98
isopropyl acetate	−3347	15712	0.50
butyl acetate	−3241	14970	0.45
isobutyl acetate	−3339	15634	0.88
sec-butyl acetate	−3300	15384	0.67
tert-butyl acetate	−3453	16413	0.68
acetone	−2840	12003	1.93
2-butanone	−2933	12714	2.51

yields activity coefficients less than unity, giving thermodynamically inconsistent activity coefficient values. van't Hoff plot analysis further shows that these two assumptions lead to thermodynamic inconsistent partial molar enthalpy changes of mixing. Hence, for the lovastatin−solvent systems considered in this study, we recommend that assumption I (eq 4) should be used to estimate the ideal solubility.

Measured solubility values were successfully fitted to the NRTL activity coefficient model generated interaction parameters for predicting solubility of lovastatin in the solvents studied herein.

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