2466 *J. Chem. Eng. Data* **2008,** *53,* 2466–2468

Solubility of Pravastatin Sodium in Water, Methanol, Ethanol, 2-Propanol, 1-Propanol, and 1-Butanol from (278 to 333) K

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The solubilities of pravastatin sodium in water, methanol, ethanol, 2-propanol, 1-propanol, and 1-butanol from (278 to 333) K were measured. A laser monitoring observation technique was used to determine the dissolution of the solid phase in the solid + liquid mixture. The experimental data were correlated with a semiempirical equation. The solubilities in the six solvents decrease in the following order: water > methanol > ethanol > 1-propanol > 1-butanol > 2-propanol.

Introduction

Pravastatin ([1*S*-[1α(*β**,*γ**)2α,6α,8*β*(*R**),8aα]]-1,2,6,7,8,8a-hexahydro,*β*,*γ*,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthalene-heptanoic acid), whose chemical structure is shown in Figure 1, is a member of the class of pharmaceutical compounds called statins. Statins currently are the most effective medications for lowering serum cholesterol levels in patients with atherosclerosis and hypercholesteremia. Pravastatin sodium, the monosodium salt of pravastatin, can exist in hydrated, anhydrous, solvated, and unsolvated forms[1] (CASRN 81131-70-6).

Previously, pravastatin sodium was available only in the amorphous form. In recent years, the preparation of pravastatin sodium in the crystal form has been reported.[1,2] In comparison with the amorphous form, the crystalline substances have many advantages: their physical as well as chemical properties are better defined, and they are more stable.

It has been found that different polymorphic forms of pravastatin sodium can be obtained in the crystallization process by using different solvents.[1] To select the proper solvent and to design an optimized research process, it is necessary to know the solubility of pravastatin sodium in different solvents. In this work, its solubilities of the title compound in water, methanol, ethanol, 2-propanol, 1-propanol, and 1-butanol at temperatures between (298 and 333) K were measured using the isothermal method.[3−6] A laser monitoring observation technique was used to determine the dissolution of the solute.

Experimental Section

Materials. Crystalline powder pravastatin sodium of form A with a mass fraction higher than 99.5 % obtained from Shanghai Tianwei Pharmaceutical Co. Ltd. (Mw 446.52, molecular formula $C_{23}H_{35}NaO_7$), China, was used as received without further purification. Water, methanol, ethanol, 2-propanol, 1-propanol, and 1-butanol (purchased from Tianjin Chemical Reagent Co., China) used for experiments were of analytical reagent grade and were dehydrated with molecular sieves before use. Their mass fraction was higher than 99.5 %. Distilled deionized water was used.

Apparatus and Procedure. The solubility of pravastatin sodium was measured by the isothermal method, and the experimental apparatus used was similar to that described in detail in the literature.[6] The experiments were performed in a cylindrical double-jacketed glass vessel having a working volume of 100 mL, in which the temperature was controlled to

Table 1. Solubility of Pravastatin Sodium in Different Pure Solvents from (278 to 333) K

T/K	10^3x_1	$100(x_1 - x^{\text{calcd}}/x_1)$	T/K	10^3x_1	$100(x_1 - x^{\text{calcd}}/x_1)$
			water		
278.4	9.11	1.3	308	40.89	−0.436
283	11.93	−1.91	313	47.72	−1.94
288	16.24	−0.88	318	55.28	−2.06
293	21.65	0.96	323	64.19	0.16
298	28.52	4.25	328	72.3	1.16
303	34.31	1.21	333	84.14	6.98
			methanol		
277.8	22.46	2.65	302.9	37.32	−1.37
283	24.48	1.67	308	41.75	−3.64
287.9	26.95	1.34	313	49.21	−0.94
293	30.09	1.14	318	58.8	2.53
297.8	32.62	−2.1	324	68.67	0.06
			ethanol		
278	3.1	4.83	308	4.63	1.77
283	3.25	2.13	313	4.93	6.84
288	3.46	0	318	5.69	4.50
293	3.66	−0.01	323	6.92	−1.91
298	4.06	−3.33	328	7.93	−1.33
303	4.29	−0.36	333	9.42	−3.34
			2-propanol		
278	0.605	1.36	303	1.03	0.8
283	0.684	3.49	308	1.1	−4.33
288	0.753	2.67	318	1.41	−3.36
293	0.818	0.2	322.9	1.64	−1.87
298	0.903	−1	327.9	1.9	2.09
			1-propanol		
278	2.08	−10.6	308	3.43	−4.88
283	2.16	−0.78	313	4.49	−1.17
288	2.19	0.48	318	6.2	3.92
293	2.27	−1.37	328	12.16	6.61
298	2.38	−7.3	333	15.78	−4.16
303	2.74	−8.2			
			1-butanol		
278.1	1.08	−3.07	308	2.23	−0.28
283	1.18	0.52	313	2.9	−6.51
288	1.27	−0.26	318.2	3.45	2.16
293	1.44	1.61	323	4.08	−2.91
298	1.59	−1.53	328	4.93	−8.56
303	1.78	−5.65			

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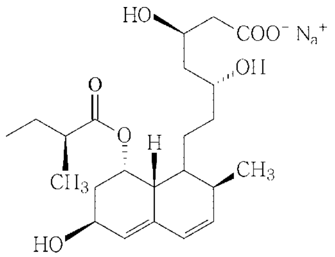

Figure 1. Chemical structure of pravastatin sodium.

be constant within 0.05 K through a thermostatted bath (Wanda/sida instrument HC2010, China). A magnetic stir bar was used for turbulent mixing of suspension. The dissolution of the solute was examined by the intensity of the laser beam that penetrated through the suspension. The laser monitoring system (purchased from Physics Department of Peking University) consisted of a laser generator (type JD-3, China), a photoelectric switch (type model 271, China), and a light intensity display.

The masses of the samples and solvents were determined using an analytical balance (Metler Toledo AB204-N, Switzerland) with an accuracy of 0.0001 g. This method is based on sequentially adding known masses of solute to a stirred solution kept at a fixed temperature. Predetermined masses of solute and solvent were transferred into the jacketed vessel. The solvent transferred into the vessel was overweight. After stirring at a fixed temperature for 10 min, an additional solute of known mass {about (0.1 to 0.3) mg} was introduced into the vessel with continuous stirring. This procedure was repeated until the solute was completely dissolved within the interval of addition of 20 min. Then, the total amount of the solute added (including the last addition) was used to compute the solubility. The dissolution of the solute was monitored by a laser beam. When the solute dissolved completely, the solution was clear, and the laser intensity that penetrated through the solution attained its maximum. Otherwise, the solute was believed not to be dissolved completely. The same solubility experiment was conducted three times, and the mean values were used to calculate the mole fraction solubility x_1 based on the following equation

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \tag{1}$$

where m_1 and m_2 represent the masses of the solute and solvent and M_1 and M_2 are the molecular weights of the solute and the solvent, respectively.

Results and Discussion

The solubility data of pravastatin sodium in water, methanol, ethanol, 2-propanol, 1-propanol, and 1-butanol from (278 to 333) K are listed in Table 1 and more visually given in Figure 2. For the sake of the practical application, it is common to describe the solid−liquid equilibrium data with a theoretical semiempirical expression. It has been found that the modified Apelblat equation[7] can fit the solubility data very well for several solid−liquid equilibrium systems.[8−11] Here, this semiempirical equation was tentatively used to correlate the experimental solubility data of pravastatin sodium in the six solvents under consideration.

The solubility of a solid in a liquid may be expressed in a very general manner by

$$\ln x_1 = -\frac{\Delta H_{\mathrm{f},1}}{RT_{\mathrm{f},1}}\left(\frac{T_{\mathrm{f},1}}{T} - 1\right) - \frac{\Delta C_{p\mathrm{f},1}}{R}\left(\frac{T_{\mathrm{f},1}}{T} - 1\right) + \frac{\Delta C_{p\mathrm{f},1}}{R}\ln\frac{T_{\mathrm{f},1}}{T} - \ln\gamma_1 \tag{2}$$

where x_1, γ_1, $\Delta H_{\mathrm{f},1}$, $\Delta C_{p\mathrm{f},1}$, $T_{f,1}$, R, and T stand for the mole fraction of solute, activity coefficient, enthalpy of fusion, difference in the solute heat capacity between the solid and liquid at the melting temperature, melting temperature of the solute, gas constant, and equilibrium temperature in the saturated solution, respectively. For regular solutions, the activity coefficient is given by

$$\ln\gamma_1 = A + \frac{B}{(T/\mathrm{K})} \tag{3}$$

where A and B stand for empirical constants. Introducing γ_1 from previous equations into eq 2 with subsequent rearrangements results in the equation

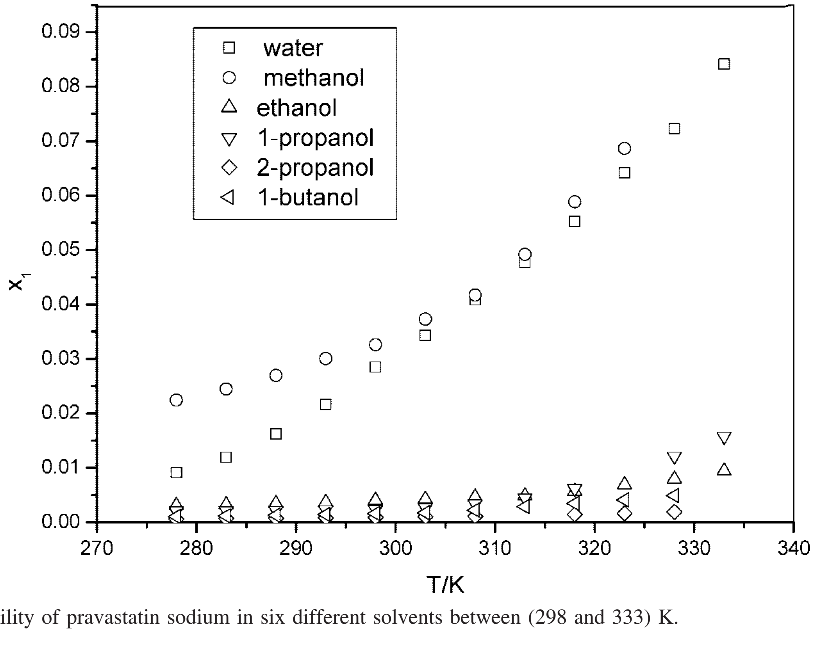

Figure 2. Mole fraction solubility of pravastatin sodium in six different solvents between (298 and 333) K.

$$\ln x_1 = \left[\frac{\Delta H_{\mathrm{f},1}}{RT_{\mathrm{f},1}} + \frac{\Delta C_{p\mathrm{f},1}}{R}(1 + \ln T_{\mathrm{f},1}) - A\right] - \left[B + \left(\frac{\Delta H_{\mathrm{f},1}}{RT_{\mathrm{f},1}} + \frac{\Delta C_{p\mathrm{f},1}}{R}\right)T_{\mathrm{f},1}\right]\frac{1}{T} - \frac{\Delta C_{p\mathrm{f},1}}{R}\ln T \quad (4)$$

which can be written as

$$\ln x_1 = a + \frac{b}{(T/\mathrm{K})} + c\ln(T/\mathrm{K}) \quad (5)$$

The deviations between the experimental and calculated results are also presented in Table 1. The values of parameters a, b, and c in eq 5 and the root-mean-square deviations (rmsd) defined by eq 6 are listed in Table 2. It can be seen that the calculated solubilities show good agreement with the experimental values.

$$\mathrm{rmsd} = \left\{\frac{1}{N}\sum_{i=1}^{N}\left(\frac{x_{1i}^{\mathrm{calcd}} - x_{1i}}{x_{1i}}\right)^2\right\}^{1/2} \quad (6)$$

where N is the number of experimental points and x_{1i}^{calcd} and x_{1i} represent the solubility calculated from eq 5 and the experimental value, respectively.

From Table 1, it can be seen that within the temperature range of measurements the solubilities of pravastatin sodium in water, methanol, ethanol, 2-propanol, 1-propanol, and 1-butanol increase with increasing temperature without exception. In addition, the solubilities of pravastatin sodium in water and methanol are much higher than those in the other four solvents. Referred to the fact that the polarities of the six solvents used in the experiments decrease in the following order, water(100) > methanol(76.2) > ethanol(65.4) > 1-propanol(61.7) > 1-butanol(60.2) > 2-propanol(54.6),[12] in accord with the solubilities order, it can be concluded that the bigger the polarity of the solvent used, the higher the solubility of the title compound. This can be due to the ion−dipole type interaction between the salt form solvents and the protic solute. This interaction gets stronger as the polarity of the solvent gets larger. As can be seen from Table 1, there is a sudden increase of the solubility in 1-propanol at higher temperature. The reason for this is maybe that the added pravastatin sodium reacted with the solvent. This is to be determined in the following study. From Figure 1, it can be seen that pravastatin sodium is a compound with high polarity, which is led by two carboxyls and three hydroxyls in the molecule. That is to say the solubility behavior of pravastatin sodium just accords with the empirical rule, “like dissolves like”.

Table 2. Parameters of Equation 2 for Pravastatin Sodium in Different Pure Solvents

solvent	a	b	c	10^2 rmsd
water	437.79	−23095.8	−63.87	2.66
methanol	−264.94	9800.77	40.13	1.99
ethanol	−396	16190.79	59	3.24
2-propanol	−155.46	4909.77	23.17	2.46
1-propanol	−1197.36	51088.13	179.03	5.53
1-butanol	−637.02	25916.05	95.42	3.99

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Received for review March 22, 2008. Accepted July 9, 2008.

JE800196K