Solubility of Form A Pravastatin Sodium in Aqueous 2-Propanol Mixtures

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The solubilities of pravastatin sodium of form A in aqueous 2-propanol mixtures from (278 to 323) K were measured. A laser monitoring observation technique was used to determine the dissolution of the solid phase in the solid + liquid mixtures. The experimental data were correlated with a semiempirical equation.

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. Fifteen polymorphic forms of crystal pravastatin sodium have been reported.[1–4] Details of the title compound and its solubility in six single solvents have been reported in the previous article by Chun-Yan Jia et al.[5] The melting temperature and fusion enthalpy of pravastatin sodium (form A) were 171 °C and −3.08 KJ·mol^{-1}, respectively.[4]

In polymorphic research, it has been found that pravastatin sodium of form A can transform to form B in aqueous 2-propanol mixtures in almost 100 % yield. It is a good method to produce form B pravastatin sodium. To research the transformation process further, solubility data of form A pravastatin sodium in the title solvent are needed. Publications about the solubility of pravastatin sodium have been reported for only pure solvents.[4,5] None of these are for solvent mixtures. In this work, the solubilities of the title compound in aqueous 2-propanol mixtures between (278 and 323) K were measured using the isothermal method.[6–9] A laser monitoring observation technique was used to determine the dissolution of the solute.

Experimental Section

Materials. Crystalline powder pravastatin sodium (MW 446.52, molecular formula $C_{23}H_{35}NaO_7$) with a mass fraction of higher than 99.5 % was obtained from Shanghai Tianwei Pharmaceutical, China, and was used as received without further purification. 2-Propanol (purchased from Tianjin Chemical Reagent, China) used for experiments was of analytical reagent grade and was dehydrated with molecular sieves before use. Its 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.[9] 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 be constant (fluctuates 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 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.

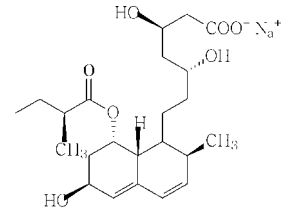

Figure 1. Chemical structure of pravastatin sodium.

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 (m_1) and solvent (m_2) were transferred to the jacketed vessel. The solvent transferred to 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 to 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 the solution attained its maximum. Otherwise the solute was believed to be not completely dissolved. An excess of 0.3 mg solute has little effect on the results. The uncertainty in the solubility values is estimated to be 0.1 %. The same solubility experiment was conducted three to five times, and the mean values were used to calculate the mole fraction solubility, x_A, on the basis of the following equation

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_B/M_B + m_C/M_C} \quad (1)$$

The composition of solvent mixtures (x_B) was defined as eq 2

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$$x_B = \frac{m_B/M_B}{m_B/M_B + m_C/M_C} \quad (2)$$

where m_A, m_B, and m_C represent the mass of the solute, water, and 2-propanol, respectively, and M_A, M_B, and M_C are the molecular weights of the solute, water, and 2-propanol, respectively.

Results and Discussion

The solubility data of pravastatin sodium in aqueous 2-propanol mixtures 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[10] can fit the solubility data very well for several solid−liquid equilibrium systems.[11–14] Here this semiempirical equation was tentatively used to correlate the experimental solubility data of pravastatin sodium in the aqueous 2-propanol mixtures under consideration.

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

$$\ln x_1 = -\frac{\Delta H_{f,1}}{RT_{f,1}}\left(\frac{T_{f,1}}{T} - 1\right) - \frac{\Delta C_{pf,1}}{R}\left(\frac{T_{f,1}}{T} - 1\right) + \frac{\Delta C_{pf,1}}{R} \ln \frac{T_{f,1}}{T} - \ln \gamma_1 \quad (3)$$

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

$$\ln \gamma_1 = A + \frac{B}{(T/\mathrm{K})} \quad (4)$$

where A and B stand for empirical constants. Introducing γ_1 from the previous equation to eq 3 with subsequent rearrangements results in the equation

$$\ln x_1 = \left[\frac{\Delta H_{f,1}}{RT_{f,1}} + \frac{\Delta C_{pf,1}}{R}(1 + \ln T_{f,1}) - A\right] - \left[B + \left(\frac{\Delta H_{f,1}}{RT_{f,1}} + \frac{\Delta C_{pf,1}}{R}\right)T_{f,1}\right]\frac{1}{T} - \frac{\Delta C_{pf,1}}{R} \ln T \quad (5)$$

Replacing x_1 with x_A, it can be written as

$$\ln x_A = a + \frac{b}{(T/\mathrm{K})} + c \ln(T/\mathrm{K}) \quad (6)$$

Considering that the solubility data plotted in the form of $\ln(x_1)$ versus $1/T$ are almost linear, parameter c should be close to zero. (As stated in the introduction, $-(\Delta C_{pf,1})/(R)$ should be about 0.37). Then, eq 6 can be written as

$$\ln x_A = a + \frac{b}{(T/\mathrm{K})} \quad (7)$$

The deviations between the experimental and calculated results are also presented in Table 1. The values of parameters a and b in eq 7 and the root-mean-square deviations (rmsd's) defined by eq 8 are listed in Table 2. It can be seen that the calculated solubilities show good agreement with the experimental values.

$$\mathrm{rmsd} = \left\{\frac{1}{N}\sum_{i=1}^{N}\left(\frac{x_{Ai}^{\mathrm{calcd}} - x_{Ai}}{x_{Ai}}\right)^2\right\}^{1/2} \quad (8)$$

where N is the number of experimental points and x_{Ai}^{calcd} and x_{Ai} represent the solubility calculated from eq 7 and the experimental value, respectively.

Table 1. Solubility of Pravastatin Sodium (A) in Water (B) and 2-Propanol (C) Mixtures from (278 to 323) K

T/K	x_A	$100((x_A - x_A^{\mathrm{calcd}})/(x_A))$	T/K	x_A	$100((x_A - x_A^{\mathrm{calcd}})/(x_A))$
		$x_B = 0.182$			
278	0.0063	− 1.89	303	0.0188	4.02
283	0.0081	1.12	308	0.0217	− 0.21
288	0.0100	0.83	313	0.0251	− 3.78
293	0.0122	0.09	318	0.0309	− 0.42
298	0.0151	1.46	323	0.0372	1.18
		$x_B = 0.143$			
278	0.0036	− 12.59	303	0.0123	− 0.60
283	0.0049	− 5.05	308	0.0150	− 0.91
288	0.0063	− 2.91	313	0.0188	2.15
293	0.0082	1.20	318	0.0220	− 1.00
298	0.0105	4.31	323	0.0267	0.06
		$x_B = 0.118$			
278	0.0026	3.45	303	0.0088	− 4.32
283	0.0035	5.32	308	0.0114	− 1.76
288	0.0047	7.82	313	0.015	2.99
293	0.0054	− 3.93	318	0.0186	2.57
298	0.0070	− 2.96	323	0.0220	− 1.89
		$x_B = 0.100$			
278	0.0018	4.18	303	0.0069	− 1.15
283	0.0025	6.94	308	0.0087	− 3.25
288	0.0035	11.26	313	0.0118	2.81
293	0.0043	4.51	318	0.0147	1.16
298	0.0052	− 3.40	323	0.0181	− 0.96
		$x_B = 0.077$			
278	0.0001	− 5.12	303	0.0047	− 0.58
283	0.0014	− 3.60	308	0.0062	− 0.02
288	0.0020	1.05	313	0.0081	0.44
293	0.0027	1.04	318	0.0104	− 0.01
298	0.0036	0.80	323	0.0133	− 0.07

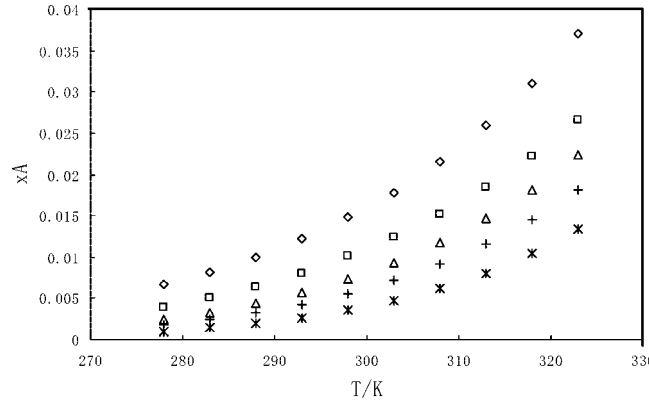

Figure 2. Mole fraction solubility of pravastatin sodium in aqueous 2-propanol mixtures between (278 and 323) K: ◇, $x_B = 0.182$; □, $x_B = 0.143$; △, $x_B = 0.118$; +, $x_B = 0.1$; *, $x_B = 0.077$.

Table 2. Parameters of Equation 7 for Form A Pravastatin Sodium in Aqueous 2-Proponal Mixtures

x_B	a	b	10^2 rmsd
0.182	7.47835	− 3482.468	1.99
0.143	8.01849	− 3760.427	4.68
0.118	9.72764	− 4368.76	4.08
0.1	10.58013	− 4710.115	4.96
0.077	11.36358	− 5065.549	2.06

From Table 1, it can be seen that within the temperature range of measurements the solubility of pravastatin sodium in aqueous 2-propanol mixtures increase with increasing temperature without exception. In addition, the solubility of the title compound depends on the polarity of the solvents to a great degree. As we all know, water is of a stronger polarity than is 2-propanol.[15] Along with the increase in water in solvent mixtures, the polarity of solvents increases, and the solubility of pravastatin sodium sharply rises.

From Figure 1, it can be seen that pravastatin sodium is a compound with high polarity, which is led by one carboxyl 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".

Literature Cited

(1) Keri, V. S.; Szabo, C.; Arvai, E. N.; Aronhime, J. Forms of Pravastatin Sodium. U.S. Patent 7,262,218, 2007.

(2) Pflaum; Z. Crystalline Sodium Salt of Pravastatin. U.S. Patent 6,740,775, May 25, 2004.

(3) Keri, V.; Nagyne Arvai, E.; Czovek, Z.; Kovacsne-Mezei, A.; Katai, I. V.; Katai, I. V.; Nemethne Racz, C. Methods of Making Pravastatin Sodium. U.S. Patent Application US 2006/0194984, 2007.

(4) Martín-Islán, A. P.; Cruzado, M. C.; Asensio, R.; Sainz-Diaz, C. I. Crystalline Polymorphism and Molecular Structure of Sodium Pravastatin. *J. Phys. Chem. B* **2006**, *110*, 26148–26159.

(5) Jia, C. Y.; Yin, Q. X.; Song, J. J.; Hou, G. Y.; Zhang, M. J. Solubility of Pravastatin Sodium in Water, Methanol, Ethanol, 2-Propanol, 1-Propanol, and 1-Butanol from (278 to 333) K. *J. Chem. Eng. Data* **2008**, *53*, 2466–2468.

(6) Nie, Q.; Wang, J. K.; Wang, Y. L.; Wang, S. Solubility of 11α-Hydroxy-16α,17α-Epoxyprogesterone in Different Solvents between 283 K and 323 K. *J. Chem. Eng. Data* **2005**, *50*, 989–992.

(7) Zhang, H. T.; Wang, J. K.; Chen, Y.; Nie, Q. Solubiliy of Sodium Cefotaxime in Aqueous 2-Propanol Mixtures. *J. Chem. Eng. Data* **2006**, *51*, 2239–2241.

(8) Liu, B. S.; Gong, J. B.; Wang, J. K.; Jia, C. Y. Solubility of Potassium Clavulanate in Ethanol, 1-Propanol, 1-Butanol, 2-Propanol, and 2-Methyl-1-propanol between 273 K and 305 K. *J. Chem. Eng. Data* **2005**, *50*, 1684–1686.

(9) Ren, G. B.; Wang, J. K.; Yin, Q. X.; Zhang, M. J. Solubilities of Proxetine Hydrochloride Hemihydrate between 286 K and 363 K. *J. Chem. Eng. Data* **2004**, *49*, 1671–1674.

(10) Apelblat, A.; Manzurola, E. Solubilities of *o*-Acetylsalicylic, 4-Aminosalicylic, 3,5-Dinitrosalicylic, and *p*-Toluic Acid, and Magnesium-DL-Aspartate in Water from $T = (278$ to 348) K. *J. Chem. Thermodyn.* **1999**, *31*, 85–91.

(11) Hao, H. X.; Wang, J. K.; Wang, Y. L. Solubility of Dexamethasone Dodium Phosphate in Different Solvents. *J. Chem. Eng. Data* **2004**, *49*, 1697–1698.

(12) Wang, L. C.; Wang, F. A. Solubility of Niacin in 3-Picoline + Water (287.65 to 359.15) K. *J. Chem. Eng. Data* **2004**, *49*, 155–156.

(13) Ren, B. Z.; Yuan, X. L.; Li, C.; Zhao, H. K. Solubility of Tripolycyanamid E and Cyanuric Acid in Ethanediol, *N*,*N*-Dimethylformamide, and *N*,*N*-Dimethylacetamide from (301.07 to 363.35) K. *J. Chem. Eng. Data* **2004**, *49*, 890–891.

(14) Wang, L. H.; Cheng, Y. Y. Solubility of Puerarin in Water, Ethanol, and Acetone from (288.2 to 328.2) K. *J. Chem. Eng. Data* **2005**, *50*, 1375–1376.

(15) Smallwood, I. M. *Handbook of Organic Solvent Properties*; Arnold: London, 1996.

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