Solubility of Form B Pravastatin Sodium in (Water + 2-Propanol)

Chun-Yan Jia, Qiu-Xiang Yin,* Jun-Bo Gong, and Jing-Kang Wang

School of Chemical Engineering and Technology, State Key Laboratory of Chemical Engineering (Tianjin University), Tianjin 300072, People's Republic of China

The solubilities of pravastatin sodium of form B in (water + 2-propanol) 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

The chemical (3*R*,5*R*)-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-6-hydroxy-2-methyl-8-[(2*S*)-2-methylbutanoyl]oxy-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoic acid, of chemical structure shown in Figure 1, is commonly and herein after known as pravastatin. It is a member of the class of pharmaceutical compounds called statins that are medications effective at lowering serum cholesterol levels in patients with atherosclerosis and hypercholesteremia. Sixteen polymorphic forms of crystal pravastatin sodium have been reported.[1–4] Details of pravastatin sodium have been reported in the previous article by Jia et al.[5]

In polymorphic study it has been found that pravastatin sodium in form A can transform to form B in (water + 2-propanol) with almost 100 % yield.[6] It is a good method for producing form B pravastatin sodium. To understand and control the transformation process well and to get the maximum product, solubility data of form A and form B pravastatin sodium in aqueous 2-propanol mixtures are needed. The former have been reported in previous literature[7] but the latter have not. In this work, the solubilities of the form B pravastatin sodium in (water + 2-propanol) at temperatures between (278 and 323) K were measured using the isothermal method.[5,8–11] A laser-monitoring observation technique was used to determine the dissolution of the solute.

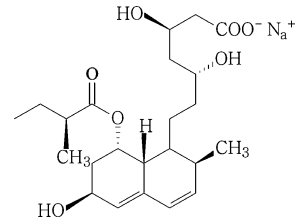

Figure 1. Chemical structure of pravastatin sodium.

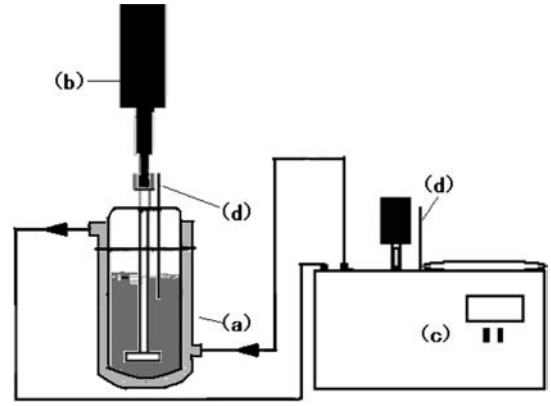

Figure 2. Experimental setup for production of form B: (a) jacketed crystallizer; (b) mechanical stirrer; (c) thermostat bath; (d) thermometer.

Experimental Section

Materials. Crystalline powder pravastatin sodium in form A with a mass fraction purity of greater than 99.5 % obtained from Shanghai Tianwei Pharmaceutical (molar mass of 446.52 $g \cdot mol^{-1}$ and molecular formula $C_{23}H_{35}NaO_7$), China, was used as received and used without further purification. 2-Propanol (obtained from Tianjin Chemical Reagent, China) used for experiments was of analytical reagent grade and was dehydrated with molecular sieves before use. The mass fraction purity was greater than 99.5 %. Distilled deionized water was used.

Form B pravastatin sodium was obtained with the apparatus shown in Figure 2 with the following procedure: 600 cm^3 of distilled deionized water and isopropanol (in a volume ratio of 20:1) was transferred to the crystallizer. The stirrer of the crystallizer was set to revolve at a rate of 150 rpm, and the thermostat bath was set to a temperature of about 308 K. When the temperature of the solvent mixture was steady, preweighed pravastatin sodium powder in form A was added to the crystallizer to make the solution saturated. The powder dissolved instantaneously, followed by form B crystal nucleus appearing and then growing. After about 1 h, the slurry was filtered through a 0.2 μm membrane. The sample was dried in a vacuum oven at 333 K for 24 h and analyzed by HPLC. The purity was above 99.0 %.

Apparatus and Procedure. The solubility of pravastatin sodium was determined with an isothermal method using the apparatus described in the literature.[11] The masses of the samples and solvents were determined using an analytical balance (Metler Toledo AB204-N, Switzerland) with an uncertainty of 0.0001 g. The experiments were performed in a cylindrical double-jacketed glass vessel having a working volume of 100 cm^3 in which the temperature was controlled to ± 0.05 K with a thermostat (Wanda/sida instrument HC2010, China). A magnetic stir bar was used for turbulent mixing of suspension. A laser-monitoring system (purchased from the 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 were used to examine the dissolution of the solute.

* Corresponding author. Fax: +86-22-27374971. E-mail: qxyin@tju.edu.cn.

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Table 1. Mean Values of the Measured Solubility, x_A, of Form B Pravastatin Sodium in (Water + 2-Proponal) at Temperatures, T, and the Standard Deviation, S, and Differences $(x_A - x_A^{calcd})/x_A$ where $-x_A^{calcd}$ was Obtained from Equation 5

T/K	100S	x_A	$100((x_A - x_A^{calcd})/x_A)$	T/K	100S	x_A	$100((x_A - x_A^{calcd})/x_A)$
			$x_B = 0.182$				
278	0.75	0.00237	8.56	303	0.64	0.00582	−8.18
283	0.86	0.00299	8.93	308	0.48	0.00762	−0.16
288	0.38	0.00346	1.89	313	0.32	0.00936	1.75
293	0.62	0.00423	0.70	318	0.92	0.01100	−0.14
298	0.50	0.00503	−2.58	323	0.66	0.01319	0.52
			$x_B = 0.143$				
278	0.69	0.00136	4.87	303	1.02	0.00415	−2.12
283	0.53	0.00181	7.85	308	0.35	0.00504	−4.18
288	0.36	0.00225	5.26	313	0.63	0.00614	−5.22
293	0.67	0.00286	5.54	318	0.73	0.00781	−1.12
298	0.68	0.00345	1.55	323	0.71	0.00990	3.09
			$x_B = 0.118$				
278	0.68	0.00083	7.77	303	0.49	0.00268	−5.47
283	0.94	0.00112	9.85	308	0.82	0.00342	−4.69
288	0.74	0.00131	−1.05	313	0.74	0.00441	−2.07
293	0.53	0.00173	0.61	318	0.74	0.00566	0.73
298	0.46	0.00215	−2.96	323	0.68	0.00707	1.48
			$x_B = 0.100$				
278	0.39	0.00060	18.50	303	0.73	0.00200	−2.03
283	0.51	0.00077	13.77	308	0.81	0.00255	−3.56
288	0.19	0.00095	6.10	313	0.69	0.00333	−1.80
293	0.48	0.00121	1.94	318	0.91	0.00435	0.75
298	0.49	0.00152	−2.83	323	0.64	0.00550	0.78
			$x_B = 0.077$				
278	0.95	0.00042	13.72	303	0.71	0.00148	−1.85
283	0.54	0.00051	3.58	308	0.16	0.00188	−3.71
288	0.57	0.00069	4.32	313	0.51	0.00246	−1.68
293	0.41	0.00091	3.56	318	0.81	0.00320	0.51
298	0.46	0.00117	1.25	323	0.49	0.00406	0.93
			$x_B = 0$				
278	0.67	0.00021	−6.03	303	0.33	0.00086	1.30
283	0.51	0.00029	−2.26	308	0.29	0.00109	0.84
288	0.76	0.00036	−8.62	313	0.62	0.00141	3.15
293	0.77	0.00047	−8.68	318	0.64	0.00175	2.13
298	0.86	0.00067	1.30	323	0.25	0.00209	−2.06

The measurements were obtained sequentially by the addition of known masses of solute to a stirred solution at a constant temperature. The procedure was as follows: A predetermined mass of solute (m_1) and solvent (m_2, about 20 g) were transferred to the jacketed vessel, and the solution was stirred at a fixed temperature. After a time of about 600 s, additional solute (about (0.1 to 0.3) mg) was introduced to the vessel. The addition of solute was repeated until the solute could not be completely dissolved within the time interval of 600 s. The dissolution of the solute was monitored by a laser beam. When the solute dissolved completely, the solution was clear, and the laser intensity penetrated the solution at maximum intensity. The total amount of the solute added (including the last addition) was used to compute the solubility. The integrated error in the solubility was estimated to be 1 %. The same solubility experiment was conducted between three and five times, and the mean values were used to calculate the mole fraction solubility, x_A, from the 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 by eq 2

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

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 molar masses of the solute, water, and 2-propanol, respectively.

Table 2. Parameters of Equations 5 and 6 for Form B Pravastatin Sodium x_B in (Water + 2-Proponal)

x_B	a	b	10^2rmsd
0.182	6.79172	−3593.453	4.84
0.143	7.73145	−3998.109	4.54
0.118	8.69635	−4413.211	4.76
0.100	9.69235	−4813.726	7.76
0.077	9.35374	−4802.888	5.05
0	7.80885	−4508.786	4.63

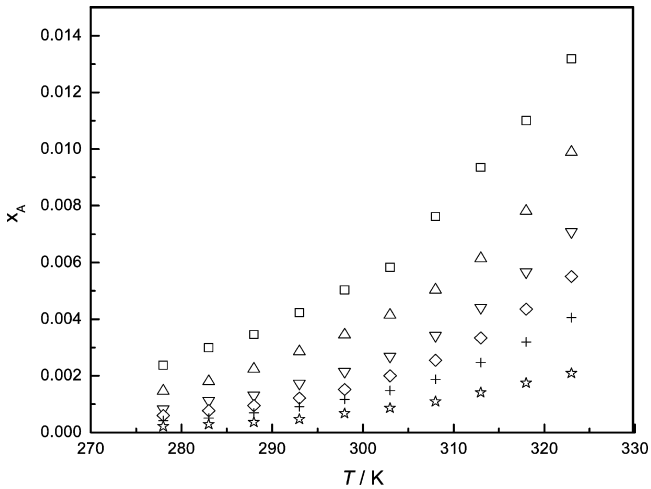

Figure 3. Mole fraction solubility of form B pravastatin sodium in (water + 2-proponal) between (278 and 323) K: □, $x_B = 0.182$; △, $x_B = 0.143$; ▽, $x_B = 0.118$; ◇, $x_B = 0.1$; +, $x_B = 0.077$; ☆, $x_B = 0$.

Results and Discussion

The mean value of the measured solubility of form B pravastatin sodium in (water + 2-propanol), listed in Table 1, was determined at temperatures from (278 to 333) K and are shown in Figure 3. The standard deviation, *S*, also listed in Table 1, was obtained from

$$S = \left\{ \frac{1}{N-1} \sum_{i=1}^{N} (x_{Ai} - x_A)^2 \right\}^{1/2} \quad (3)$$

where N is the repeating number of measurements under the same condition, x_{Ai} is the measured solubility, and x_A is the mean value of the measured solubility.

It is common to describe the solid−liquid equilibrium data with a semiempirical expression of the modified Apelblat equation[12] that represents the solubility data.[13–16] This equation is as follows

$$\ln x_A = a + \frac{b}{(T/\mathrm{K})} + c \ln(T/\mathrm{K}) \quad (4)$$

where T is temperature and a, b, and c are parameters. This semiempirical equation was used to correlate the experimental solubility data of form B pravastatin sodium in (water + 2-propanol).

When the solubility data are plotted as $\ln(x_1)$ as a function of $1/T$, the result is almost linear with parameter c of eq 4 about zero and gives

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

The deviations between the experimental results and results estimated from eq 5 with values of parameters a and b in Table 2 are presented in Table 1, where the root-mean-square deviations (rmsd), also in Table 2, are defined by eq 6

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

where N is the number of experimental points with given solvent mixtures and x_{Ai}^{calcd} represents the solubility calculated from eq 4.

From Table 1, it can be seen that the measurements show good reproducibility with most of the standard deviation below 0.01. Within the temperature range of measurements, the solubility of pravastatin sodium in (water + 2-propanol) increases with the increasing temperature. In addition, the solubility of form B pravastatin sodium depends on the polarity of the solvents to a great degree. As we all know, water is of stronger polarity than 2-propanol.[17] Along with the increase in water in solvent mixtures, the polarity of solvents increases, and the solubility of pravastatin sodium rises sharply.

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 accords with the empirical rule "like dissolves like".

By comparing the solubility data of form B pravastatin sodium with that of form A from previous literature[7] under the same conditions, it is obvious that the former is much smaller. The solubility difference is the driving force for the polymorphic transformation.[6] The solubility data can help us to understand and control the transformation process.

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