Solubility of Lovastatin in Acetone + Water Solvent Mixtures

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The solubilities of lovastatin in binary acetone + water solvent mixtures were determined by the synthetic method from (277.35 to 310.05) K by a laser monitoring observation technique. Results of these measurements were correlated by the semiempirical equation. For the nine mole fractions of acetone studied, a semiempirical equation was found to provide an accurate mathematical representation of the experimental data.

Introduction

Lovastatin (CAS No. 75330-75-5), a white crystal powder and named as [8-[2-(4-hydroxy-6-oxo-oxan-2-yl)ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl] 2-methylbutanoate, is an important drug as a (3*S*)-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) inhibitor and is used as an antihypercholesterolemic agent. The molecular structure can be seen from Figure 1. It is generated by a fermentation process and purified by extraction and crystallization in the final step.[1,2] In preferential crystallization, the solubilities of lovastatin in solvents are needed. Up to now, only a few experimental solubility data of lovastatin in some pure solvents were reported in the literature,[3] and no experimental solubility data of lovastatin in binary solvent mixtures were reported. In this work, the solubility of lovastatin in the binary system of acetone + water has been measured from (278.15 to 323.15) K at atmospheric pressure. The experimental data were correlated with a semiempirical equation.

Experimental Section

Materials. Acetone was obtained from Tianjin Chemical Reagent Co., Ltd., China. It was analytical reagent grade and dried with molecular sieves before use. A white crystalline powder of lovastatin was obtained from Blue Treasure Pharmaceutical Co., Ltd., China, and had a melting temperature of (452.15 ± 0.5) K. Its purity, determined by HPLC according to United States Pharmacopeial 27 edition (USP27), was higher than 0.995 (mass fraction). Water used in the experiments was double-distilled water.

Apparatus and Procedure. Solubilities were measured by a synthetic method.[4–6] The apparatus for the solubility measurement and the procedure are the same as those described in the literature[7] and are described only briefly here. A 100 mL jacketed vessel equipped with a condenser to prevent the solvent from evaporating was used to determine the solubility. The temperature was controlled to be constant through a thermostatted bath with an uncertainty of (± 0.02 K). A laser monitoring observation technique was used to determine the disappearance of the last crystal particles in the solid + liquid mixture at a known temperature. The masses of lovastatin and solvents were weighed using an analytical balance (Mettler Toledo AB204-N, Switzerland) with an uncertainty of (0.0001 g).

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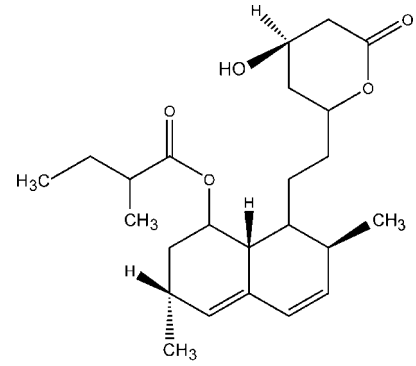

Figure 1. Structure of lovastatin.

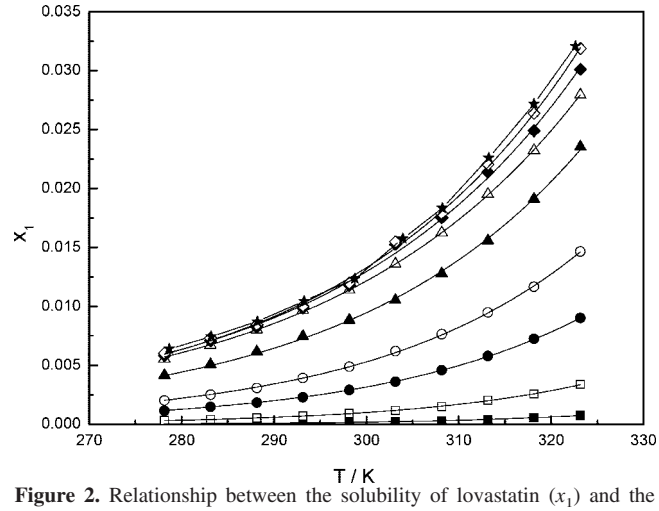

Figure 2. Relationship between the solubility of lovastatin (x_1) and the mole fraction of acetone in water (x_3) + acetone (x_2) solvent mixtures as a function of temperature: ■, $x_2 = 0.2$; □, $x_2 = 0.3$; ●, $x_2 = 0.4$; ○, $x_2 = 0.5$; ▲, $x_2 = 0.6$; Δ, $x_2 = 0.7$; ◆, $x_2 = 0.8$; ◇, $x_2 = 0.9$; ★, $x_2 = 1.0$.

The solubility of lovastatin was determined by the laser system.[7–9] During experiments, the fluid in the glass vessel was monitored by a laser beam. Predetermined solvents were placed in the inner cell of the vessel and were stirred continuously at a required temperature. Lovastatin was added to the vessel simultaneously. When the solute dissolved completely, the laser intensity passing through the vessel reached a maximum. Then additional solute of known mass {about (1 to 4) mg} was introduced into the vessel. This procedure was repeated until the passing laser intensity could not return to the maximum.

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Table 1. Mole Fraction Solubility (x_1) of Lovastatin in Binary Acetone (x_2) + Water (x_3) Mixtures in the Temperature Range (278 to 323) K

T/K	$10^3 x_i^{exptl}$	$10^2[(x_i^{exptl} - x_i^{calcd})/x_i^{exptl}]$	T/K	$10^3 x_i^{exptl}$	$10^2[(x_i^{exptl} - x_i^{calcd})/x_i^{exptl}]$	T/K	$10^3 x_i^{exptl}$	$10^2[(x_i^{exptl} - x_i^{calcd})/x_i^{exptl}]$
				$x_2 = 0.2$				
278.15	0.0468	3.42	298.15	0.1666	0.84	313.15	0.4046	2.72
283.15	0.0656	1.07	303.15	0.2243	1.56	318.15	0.5433	2.93
288.15	0.0905	0.11	308.15	0.3021	1.99	323.15	0.7401	1.39
293.15	0.1235	0.08						
				$x_2 = 0.3$				
278.15	0.3150	−5.33	298.15	0.912	−4.35	313.15	2.020	−4.72
283.15	0.4100	−4.71	303.15	1.160	−1.97	318.15	2.560	−2.40
288.15	0.5260	−2.81	308.15	1.500	−1.30	323.15	3.350	−3.33
293.15	0.6960	−3.99						
				$x_2 = 0.4$				
278.15	1.150	0.51	298.15	2.890	−0.64	313.15	5.780	−1.71
283.15	1.460	−0.64	303.15	3.600	0.16	318.15	7.230	−1.42
288.15	1.830	−0.49	308.15	4.590	−1.38	323.15	8.990	−0.59
293.15	2.290	−0.14						
				$x_2 = 0.5$				
278.15	2.000	1.65	298.15	4.880	−0.02	313.15	9.470	−0.39
283.15	2.500	1.13	303.15	6.180	−1.65	318.15	11.66	0.77
288.15	3.060	2.82	308.15	7.620	−0.63	323.15	14.63	0.01
293.15	3.910	0.19						
				$x_2 = 0.6$				
278.15	4.160	−3.49	298.15	8.830	−2.80	313.15	15.57	−1.35
283.15	5.070	−4.48	303.15	10.52	−1.03	318.15	19.09	−2.18
288.15	6.160	−4.99	308.15	12.78	−1.09	323.15	23.55	−3.55
293.15	7.440	−4.80						
				$x_2 = 0.7$				
278.15	5.540	2.53	298.15	11.40	−0.48	313.15	19.52	−0.62
283.15	6.690	0.61	303.15	13.61	−0.45	318.15	23.23	0.10
288.15	8.020	−0.32	308.15	16.25	−0.29	323.15	27.95	−0.20
293.15	9.660	−1.50						
				$x_2 = 0.8$				
278.15	5.820	−0.64	298.15	11.76	−0.17	313.15	21.38	−5.07
283.15	7.070	−2.66	303.15	15.24	−7.66	318.15	24.90	−1.97
288.15	8.230	−0.27	308.15	17.53	−3.65	323.15	30.10	−2.38
293.15	9.840	−0.33						
				$x_2 = 0.9$				
278.15	6.010	0.62	298.15	11.97	5.55	313.15	22.04	1.04
283.15	7.300	−0.67	303.15	15.47	−1.45	318.15	26.36	2.22
288.15	8.420	3.46	308.15	17.87	3.06	323.15	31.88	2.34
293.15	10.03	4.52						
				$x_2 = 1.0$				
278.65	6.375	−2.09	293.25	10.43	0.38	308.25	18.32	0.38
283.2	7.416	−1.47	298.75	12.33	4.06	313.25	22.59	−1.28
288.2	8.692	0.36	303.95	15.73	−0.83	318.15	27.16	−0.55
322.65	32.06	0.62						

The delay of two solute additions was 30 min. The total amount of the solute dissolved was recorded. The same solubility experiment was carried out three times. The mean values were used to calculate the solubility in mole fraction (x_1) based on eq 1, and the composition of solvent mixtures (x_2) was defined by eq 2

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (1)$$

$$x_2 = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \quad (2)$$

where m_1, m_2, and m_3 represent the mass of the solute, acetone, and water, respectively, and M_1, M_2, and M_3 are the molecular mass of the solute, acetone, and water, respectively. It is estimated that the uncertainty in solubility values is less than 3 %.

Results and Discussion

The solubilities of lovastatin in acetone−water mixtures at different temperatures are given in Table 1 and more visually expressed in Figure 1. The solubilities in pure acetone solvent ($x_2 = 1.0000$) were taken from the literature directly.[3] The temperature dependence of lovastatin at fixed solvent composition is described by the semiempirical equation.[8,10,11]

$$\ln x = A + \frac{B}{T/\mathrm{K}} + C \ln(T/\mathrm{K}) \quad (3)$$

where T is the absolute temperature; x_i is the solubility of lovastatin; and A, B, and C were three adjustable parameters of eq. 3.

The values of the parameters A, B, and C are presented in Table 2. The calculated results show satisfactory agreement with

Table 2. Parameters of Equation 3 for Lovastatin in Mixed Solvents

x_2	A	B	C	10^4 rmsd
0.2	−172.09	2647.44	27.12	0.0730
0.3	−172.16	3329.30	27.02	0.5425
0.4	−172.44	3971.87	26.90	0.5279
0.5	−172.39	4115.02	26.90	0.5611
0.6	−172.70	4562.70	26.79	3.6131
0.7	−172.90	4824.44	26.72	0.8359
0.8	−173.04	4774.44	26.78	6.1170
0.9	−172.90	4669.67	26.83	4.5127
1.0	−271.20	6658.00	33.43	2.5320

the experimental data. The root-mean-square deviations (rmsd) are defined in eq 4.

$$\mathrm{rmsd} = \left\{ \frac{\sum_{i=1}^{N} \left[\left(x_i^{\mathrm{calcd}} - x_i^{\mathrm{exptl}} \right) \right]^2}{N} \right\}^{1/2} \quad (4)$$

where N is the number of experimental points; x_i^{calcd} represents the solubilities calculated from eq 3; and x_i^{exptl} represents the experimental values of solubility.

From Table 1 and Table 2, the following conclusions can be reached: (1) the solubilities of lovastatin in binary acetone + water mixtures all increase with an increase of temperature. (2) The solubility of lovastatin decreases with an increase of water content in the mixed solvents. (3) These experimental data can be regressed by eq 3 for each solvent mixture. (4) The calculated solubilities of lovastatin show good agreement with the experimental values. The experimental solubility and correlation equation in this work can be used as essential data and models in the purification process of lovastatin.

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