Solubility of Lovastatin in Acetone, Methanol, Ethanol, Ethyl Acetate, and Butyl Acetate between 283 K and 323 K

Hua Sun, Jun-bo Gong,* and Jing-kang Wang

School of Chemical Engineering and Technology, Tianjin University, Tianjin 3001072, People's Republic of China

The solubilities of lovastatin in acetone, methanol, ethanol, ethyl acetate, and butyl acetate between 283 K and 323 K were measured using a synthetic method. A laser monitoring observation technique was used to determine the disappearance of the solid phase in a solid + liquid mixture. The experimental solubility data was correlated with an empirical equation.

Introduction

Lovastatin (CAS no. 75330-75-5) is butanioc acid 2-methyl-1,2,3,7,8,8a-hexahydro-3, 7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphalenyl ester. It is a white or almost white powdered crystal. Lovastatin is also known as a (3*S*)-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) inhibitor and is used as an antihypercholesterolemic agent. At the same time, it is also a key material for the production of simvastatin (CAS no. 79902-63-9), a stronger HMG-CoA reductase inhibitor.[1] In industry, lovastatin is generated by fermentation. Then it is separated and purified by extraction, lactonization, and crystallization in series. In the final purification step, the lovastatin is recrystallized from solution.[2,3] To determine the proper solvent and to design an optimized separation process, it is necessary to know its solubility in different solvents.[4] However, no experimental solubility data of lovastatin in solvents has been reported. In this paper, a laser monitoring observation technique was used to measure the solubilities of lovastatin in acetone, ethyl acetate, butyl acetate, ethanol, and methanol. In this paper, a synthetic method was used to determine the solubility data of lovastatin.[5,6] By this method, solubility data can be obtained much faster and more readily than with an analytical method.[7,8]

Experimental Sections

Materials. White crystalline lovastatin powder ($C_{24}H_{36}O_5$, MW 404.54) was obtained from Blue Treasure Pharmaceutical Co., Ltd., China, and had a melting point of (452.15 ± 0.5) K. Its mass fraction purity, determined by HPLC according to USP27,[9] is higher than 99.5%. It was dried under vacuum at 313.15 K for 24 h and stored in a desiccator. Acetone, ethyl acetate, butyl acetate, ethanol, and methanol (obtained from Tianjin Chemical Reagent Co., Ltd., China) were analytical reagent grade and dehydrated with molecular sieves before use. The mass fraction purities of these five solvents, determined by gas chromatography, are higher than 99.5%. Lovastatin is stable in these five solvents.

Apparatus and Procedure. The solubility of lovastatin was measured by a synthetic method. The laser monitoring observation technique was used to determine the disappearance of the last crystal particles in the solid + liquid mixture. The laser set consists of a laser generator, a photoelectric transformer, and a digital display. The experiment was performed in a cylindrical double-jacketed glass vessel. The volume of this vessel was 150 mL. This vessel was maintained at a desired temperature by circulating water from a water bath with a thermoelectric controller. A condenser was connected to the vessel to prevent the solvents from evaporating. A mercury-in-glass thermometer was inserted into the inner chamber of the vessel with an uncertainty of ±0.05 K. An analytical balance (Metler Toledo AB204-N) with an uncertainty of ±0.0001 g was used. The mixtures of solute and solvent in the vessel were stirred with a magnetic stirrer.

In the experiments, the solubility was determined by the last crystal disappearance method. This method is based on sequentially adding known masses of a solid to a stirred solution kept at a predetermined temperature. During the experiments, the glass vessel was monitored by a laser beam. When the solute dissolved completely, the solution was clear, and the laser intensity penetrating through the vessel reached its maximum. If the solute could not dissolve completely, then the laser beam was scattered by the undissolved solute particles in the solution, and the penetrating laser intensity was below the maximum. Predetermined amounts of solute and solvent were trans-

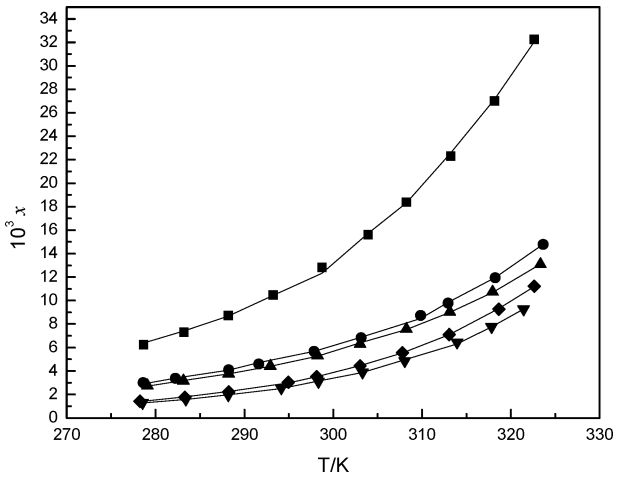

Figure 1. Mole fraction solubility of lovastatin x in different solvents: ■, acetone; ●, ethyl acetate; ▲, *n*-butyl acetate; ▼, methanol; ◆, ethanol.

* To whom correspondence should be addressed. E-mail: junbo_gong@yahoo.com.cn. Fax: 0086-22-27374971.

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Table 1. Mole Fraction Solubility x of Lovastatin in Pure Solvents

T/K	10^3x^{exptl}	10^3x^{calcd}	T/K	10^3x^{exptl}	10^3x^{calcd}	T/K	10^3x^{exptl}	10^3x^{calcd}	T/K	10^3x^{exptl}	10^3x^{calcd}
					Acetone						
278.65	6.375	6.242	303.95	15.73	15.60	293.25	10.43	10.47	318.15	27.16	27.01
283.20	7.416	7.307	308.25	18.32	18.39	298.75	12.33	12.83	322.65	32.06	32.26
288.20	8.692	8.723	313.25	22.59	22.30						
					Ethyl Acetate						
278.60	2.911	3.010	303.15	6.881	6.840	291.65	4.713	4.586	318.25	11.97	11.94
282.25	3.397	3.373	309.85	8.492	8.724	297.85	5.684	5.672	323.65	14.81	14.79
288.25	4.078	4.094	312.95	9.872	9.786						
					Butyl Acetate						
279.10	2.727	2.766	303.05	6.403	6.290	292.95	4.410	4.417	317.95	10.69	10.74
283.15	3.190	3.164	308.25	7.541	7.570	298.25	5.279	5.312	323.35	13.12	13.09
288.25	3.763	3.759	313.15	9.004	9.028						
					Ethanol						
278.25	1.402	1.412	303.05	4.460	4.438	294.95	2.981	3.039	318.65	9.326	9.275
283.30	1.797	1.776	307.80	5.536	5.549	298.15	3.529	3.528	322.65	11.19	11.22
288.25	2.256	2.229	313.05	7.094	7.112						
					Methanol						
278.55	1.277	1.303	303.30	3.863	3.883	294.15	2.514	2.553	317.85	7.770	7.768
283.40	1.595	1.595	308.05	4.959	4.855	298.35	3.147	3.089	321.45	9.292	9.256
288.20	1.971	1.961	313.95	6.293	6.434						

Table 2. Parameters of Equation 1 for Lovastatin in Pure Solvents

solvent	A	B	C	10^4rmsd
acetone	−217. 2	6658	33.43	2.532
ethyl acetate	−260.4	8719	39.66	1.159
butyl acetate	−185.9	5393	28.53	0.5514
ethanol	−211. 3	5621	32.78	0.3567
methanol	−280.9	8794	43.12	0.7295

ferred into the inner chamber of the vessel. The solid + liquid mixture was stirred at a fixed temperature for 1 h. The quantity of solvent was a small excess. Then additional solute of known mass, from about (3 to 5) mg, was introduced into the vessel with continuous stirring. This procedure was repeated until the last addition of solute could not dissolve completely. The interval of addition was 30 min. This process lasted more than 6 h. Then the total amount of the solute used was recorded, and the solubility expressed in mole fraction was calculated. The uncertainty of the experimental solubility values is estimated to be 3%.

Results and Discussion

The solubilities of lovastatin (x^{exptl}) in acetone, ethyl acetate, butyl acetate, ethanol, and methanol at different temperatures are presented in Table 1 and more visually expressed in Figure 1.

The temperature dependence of lovastatin solubility in pure solvents was described by the modified empirical equation[10,11]

$$\ln x = A + \frac{B}{(T/\mathrm{K})} + C \ln(T/\mathrm{K}) \qquad (1)$$

where x is the mole fraction solubility of lovastatin, T is the absolute temperature, and A, B, C are the parameters. The calculated solubility values of lovastatin (x^{calcd}) are also given in Table 1. The values of parameters A, B, C and the root-mean-square deviations (rmsd) are listed in Table 2. The rmsd is defined as the following

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

where N is the number of experimental points; x_i^{calcd} represents the solubilities calculated from eq 1; and x_i^{exptl} represents the experimental values of solubility.

From Table 1 and Table 2, we can draw the following conclusions: (1) the solubilities of lovastatin in acetone, ethyl acetate, butyl acetate, ethanol, and methanol all increase with increasing temperature. (2) The solubility of lovastatin in acetone is higher than that in ethyl acetate, butyl acetate, ethanol, and methanol. The solubility of lovastatin in methanol is the lowest. (3) These experimental data were able to be regressed by eq 1 for each solvent.

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Supporting Information Available:

Parameters of the fitting equation. This material is available free of charge via the Internet at http://pubs.acs.org.

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