Solubility of Simvastatin and Lovastatin in Mixtures of Dichloromethane and Supercritical Carbon Dioxide

Dong-Joon Oh and Byung-Chul Lee*

Department of Chemical Engineering and Nano-Bio Technology, Hannam University, 461-6 Jeonmin-dong, Yuseong-gu, Daejeon 305-811, Korea

Sung-Joo Hwang

College of Pharmacy, Chungnam National University, 220 Kung-dong, Yuseong-gu, Daejeon 305-764, Korea

The phase behavior of simvastatin and lovastatin drugs, which are well-known to be effective drugs for hypercholesterolemia therapy, in solvent mixtures of dichloromethane (DCM) and supercritical carbon dioxide (CO_2) was investigated to present a guideline for establishing operating conditions in the particle formation of the drugs by a supercritical antisolvent recrystallization process utilizing DCM as a solvent and CO_2 as an antisolvent. The solubilities of the statin drugs in the DCM + CO_2 mixtures were determined as functions of temperature, pressure, and solvent composition by measuring the cloud points of the ternary mixtures of simvastatin + DCM + CO_2 and lovastatin + DCM + CO_2 at various conditions using a high-pressure phase equilibrium apparatus equipped with a variable-volume view cell. The solubility data of simvastatin and lovastatin are presented in the mixtures of DCM + CO_2 with the DCM mole fractions between 0.18 and 0.34 at temperatures from 303.25 K to 333.25 K and at pressures up to about 45 MPa. The ternary mixtures exhibited the cloud point phase behavior of a typical lower critical solution temperature phase behavior. The solubility of the drug increased as the DCM composition in solution and the system pressure increased at a fixed temperature. A lower solubility of the drug was obtained at a higher temperature. Simvastatin was more soluble than lovastatin in the mixtures of DCM + CO_2.

Introduction

Supercritical fluid (SCF) technology has recently gained great attention in the field of pharmaceutical industries.[1,2] Particularly, the microparticle formation of biodegradable polymers, bioactive agents, and water-insoluble drugs by a SCF process has been studied by many researchers.[3−5] In pharmaceutical industries, it is very important to make water-insoluble drugs of micro- or nanosize because their bioavailability depends upon their particle size and polymorphism. Drug microparticles are currently being prepared by jet milling, freeze drying, and solvent evaporation. However, those methods have many problems such as thermal degradation of drugs by friction, excessive energy consumption, and residual organic solvent in drugs. Thus, SCF processes have recently gained great attention as a new and environmentally benign method of preparing drug microparticles of less than 10 μ.[6,7] They have many advantages such as no thermal degradation, no mechanical damage, and no residual solvent problem. The core work in the particle formation of a water-insoluble drug using the SCF processes such as a supercritical antisolvent (SAS) recrystallization[8,9] and a rapid expansion of supercritical solution[10,11] is to obtain the microparticles of various sizes and shapes by controlling the supersaturation and nucleation rates of the drug in the SCF with a change of solvent strength. For the preparation of the drug microparticles by a SCF process, it is important to know the location of the phase boundaries in the solution of drug and SCF.

In this work, simvastatin and lovastatin were selected as target drugs. Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus* and is well-known to be an effective drug for hypercholesterolemia therapy. It is used to reduce the total amounts of cholesterol, LDL (bad) cholesterol, triglycerides, and apolipoprotein B (a protein needed to make cholesterol) in blood, and it is used to increase the level of HDL (good) cholesterol in blood. Lovastatin is also a cholesterol-lowering agent isolated from a strain of *Aspergillus terreus*. After oral ingestion, the statin drugs are hydrolyzed to the corresponding β-hydroxyacid form, which is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. Simvastatin and lovastatin are a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water and freely soluble in dichloromethane, chloroform, methanol, and ethanol.

For the purpose of selecting a solvent and an antisolvent used in the particle formation of the statin drugs by an SAS recrystallization process, dichloromethane (DCM) and carbon dioxide (CO_2) were tested. From our preliminary work, it was observed that the statin drugs were insoluble in nonpolar CO_2 at pressures as high as 80 MPa but were completely soluble in polar DCM. Consequently, DCM is an excellent solvent for the statin drugs, whereas CO_2 acts as an antisolvent for the same solutes. This work is focused on determining the feasibility of dissolving the statin drugs in mixtures of DCM + CO_2. The solubility of the statin drugs in the mixtures of DCM and CO_2 was determined by measuring the cloud points of the ternary

* Corresponding author. E-mail: bclee@hannam.ac.kr.

10.1021/je700019h CCC: $37.00
Published on Web 05/23/2007

Table 1. Physicochemical Characteristics of Simvastatin and Lovastatin

generic name	simvastatin	lovastatin
CAS registry no.	79902-63-9	75330-75-5
synonym	[1*S*-(1α,3α,7*β*,8*β*(2*S**,4*S**),8a*β*)]-2,2-dimethylbutanoic acid 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl ester	[1*S*-(1α(*R**),3α,7*β*,8*β*(2*S**,4*S**),8a*β*)]-2-methylbutanoic acid 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl ester
chemical formula	$C_{25}H_{38}O_5$	$C_{24}H_{36}O_5$
molecular weight	418.57	404.55
melting point	135∼138 °C	174.5 °C (under N_2)
water solubility	0.765 mg/L @ 25 °C (estimated value)	−

mixtures of drug + DCM + CO_2 at different temperatures and compositions. The cloud point pressures were measured using a high-pressure phase equilibrium apparatus equipped with a variable-volume view cell. The phase behavior data produced in this work would be useful for establishing operating conditions in the particle formation of the statin drugs by an SAS recrystallization process which utilizes DCM as a solvent and CO_2 as an antisolvent.

Experimental Section

Materials. The simvastatin (99.8 % purity) and lovastatin (99.9 % purity) drugs were obtained from Kyongbo Pharm. Co. (Asan, Chungnam, Korea) and Lupin Ltd. (India), respectively. The general chemical information and some physical properties of the statin drugs are given in Table 1, and their chemical structures are shown in Figure 1. DCM and CO_2 used as solvent and antisolvent were obtained from Aldrich Chemical Co. and Myung-Sin General Gas Co. (Yangsan, Gyeongnam, Korea), respectively, and their certified purities were 99.99 mass %. The drugs and chemicals were used as received without further purification.

Apparatus and Procedure. The phase behavior of the statin drugs in the mixtures of DCM and CO_2 was measured using a high-pressure apparatus equipped with a variable-volume view cell. A main feature of using the variable-volume cell apparatus is that the concentration of the system is kept constant during the experiment. A detailed description of the experimental apparatus and procedure is given in our previous publications.[12−14] The apparatus consists of a view cell equipped with a sapphire window and a movable piston, a pressure generator (High-Pressure Equipment Co., model 50-6-15), a borescope (Olympus model R080-044-000-50), a magnetic stirring system, and an air bath. The cylindrical view cell has dimensions of 16 mm i.d. by 70 mm o.d. and an internal working volume of about 31 cm^3. The system pressure is measured using a piezoresistive pressure transmitter (Keller Druckmesstechnik, type PA-25HTC/8585-1000, ± 0.1 MPa accuracy). The system temperature is measured to within ± 0.1 K by an RTD probe inserted into the cell.

The solubilities of the statin drugs in DCM + CO_2 at various temperatures and pressures were determined by measuring the cloud points of the solutions with different compositions. A mixture of the drug + DCM + CO_2 is prepared and then compressed until it becomes a homogeneous single-phase solution. The solid drug completely dissolves in DCM + CO_2. The single-phase solution is then depressed. When the solution reaches a cloud point, it becomes cloudy and the drug begins to precipitate from the solution. Therefore, the cloud point represents the phase transition from the single-phase to the two-phase solution and is the boundary between the complete dissolution and precipitation of the drug in DCM + CO_2.

The experiment for measuring the cloud point was performed by the following procedure. The cell was purged with enough CO_2 gas to remove any entrapped air present in the cell. A certain amount of the drug was loaded into the cell along with

Table 2. Experimental Data of Cloud Points of Simvastatin (1) in DCM (2) + CO_2 (3)

			cloud point pressure, *P*/MPa			
m_1[a]	x_1[b]·10^3	x_2[c]	303.25 K	313.25 K	323.25 K	333.25 K
0.050	0.603	0.179	10.3	13.5	16.8	20.2
	0.575	0.227	8.0	10.7	13.5	16.3
	0.541	0.267	6.5	8.3	10.5	13.0
	0.518	0.307	bubble[d]	6.4	8.2	9.9
	0.490	0.338	bubble	bubble	6.6	8.1
0.075	0.910	0.180	13.3	17.9	22.3	27.8
	0.865	0.226	10.7	14.5	18.1	23.2
	0.818	0.269	8.5	11.5	14.6	18.6
	0.776	0.307	6.4	8.8	11.1	13.9
	0.737	0.339	bubble	6.6	8.5	10.3
0.100	1.219	0.181	17.5	22.5	28.5	34.5
	1.146	0.227	14.8	19.3	24.7	30.0
	1.088	0.269	12.3	16.2	21.2	25.6
	1.034	0.307	10.2	13.5	17.5	21.8
	0.979	0.338	7.7	10.5	14.0	17.9
0.125	1.523	0.181	22.1	27.3	32.8	39.4
	1.434	0.227	19.3	24.0	29.4	35.2
	1.366	0.270	16.4	20.5	25.2	30.5
	1.290	0.306	13.6	17.0	21.3	26.2
	1.222	0.338	11.1	13.8	17.4	21.9

[a] Amount of drug loaded into the system in grams. [b]Solubility of drug in DCM + CO_2; x_1 = (mole of drug)/(mole of drug + mole of DCM + mole of CO_2). [c]Mole fraction of DCM in solution; x_2 = (mole of DCM)/(mole of drug + mole of DCM + mole of CO_2). [d]Bubble point behavior observed.

Table 3. Experimental Data of Cloud Points of Lovastatin (1) in DCM (2) + CO_2 (3)

			cloud point pressure, *P*/MPa			
m_1[a]	x_1[b]·10^3	x_2[c]	303.25 K	313.25 K	323.25 K	333.25 K
0.050	0.631	0.182	16.8	21.5	26.2	30.4
	0.590	0.225	13.3	17.3	21.3	25.1
	0.564	0.268	10.5	13.9	17.1	20.1
	0.537	0.306	8.1	10.8	13.5	16.3
	0.504	0.337	6.8	8.8	10.8	12.8
0.075	0.951	0.180	19.5	24.4	29.6	34.3
	0.889	0.227	15.8	20.2	24.5	28.1
	0.847	0.270	13.2	16.8	20.2	23.5
	0.808	0.308	11.2	13.1	16.2	19.7
	0.762	0.338	9.5	11.8	14.1	16.5
0.100	1.251	0.180	24.0	29.3	34.6	40.7
	1.197	0.229	20.6	25.2	29.8	34.4
	1.110	0.265	17.9	21.8	25.9	30.0
	1.060	0.304	15.6	18.9	22.2	25.5
	1.024	0.342	14.0	16.6	19.2	22.0
0.125	1.552	0.178	27.3	32.9	38.5	44.8
	1.479	0.226	23.9	28.9	33.8	38.9
	1.373	0.262	21.3	25.6	29.8	34.3
	1.350	0.306	18.9	22.5	26.1	29.1
	1.283	0.342	17.3	20.3	23.9	26.5

[a] Amount of drug loaded into the system in grams. [b]Solubility of drug in DCM + CO_2; x_1 = (mole of drug)/(mole of drug + mole of DCM + mole of CO_2). [c]Mole fraction of DCM in solution; x_2 = (mole of DCM)/(mole of drug + mole of DCM + mole of CO_2).

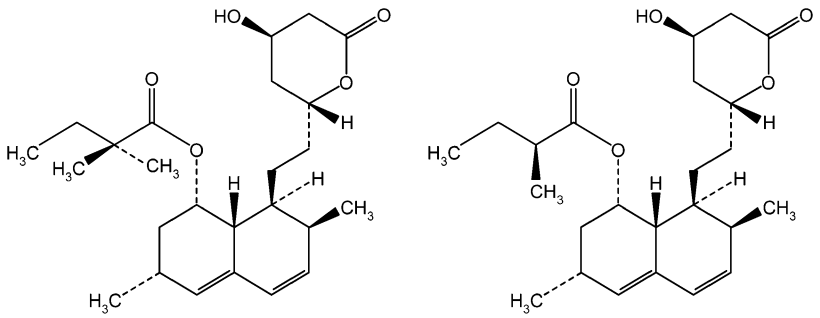

Figure 1. Chemical structure of the drugs studied in this work.

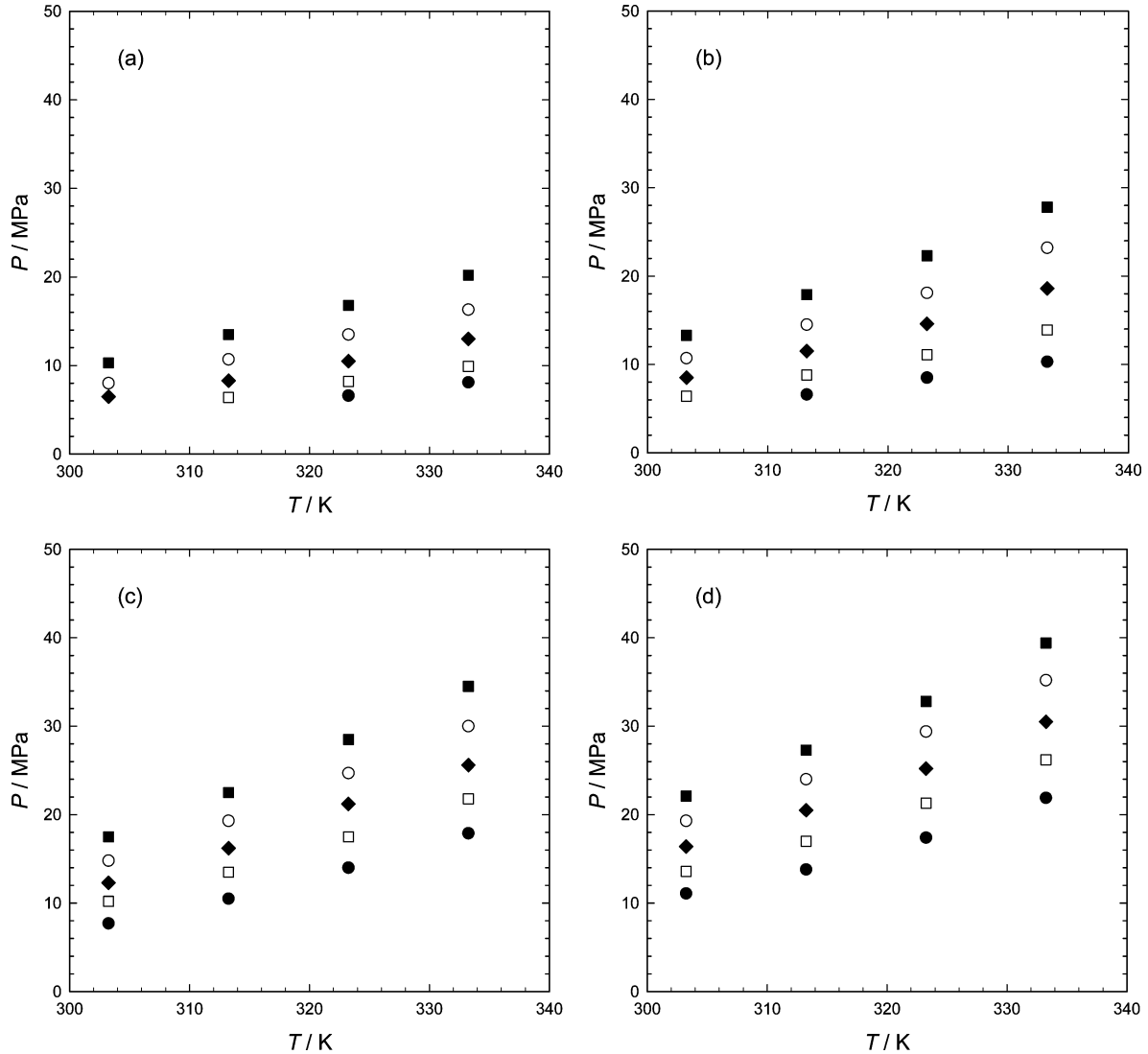

Figure 2. $P-T$ isopleths of cloud points of simvastatin in mixtures of DCM + CO_2. (a) $m_1 = 0.050$ g; ■, $x_1 = 0.603 \cdot 10^{-3}$, $x_2 = 0.179$; ○, $x_1 = 0.575 \cdot 10^{-3}$, $x_2 = 0.227$; ◆, $x_1 = 0.541 \cdot 10^{-3}$, $x_2 = 0.267$; □, $x_1 = 0.518 \cdot 10^{-3}$, $x_2 = 0.307$; ●, $x_1 = 0.490 \cdot 10^{-3}$, $x_2 = 0.338$. (b) $m_1 = 0.075$ g; ■, $x_1 = 0.910 \cdot 10^{-3}$, $x_2 = 0.180$; ○, $x_1 = 0.865 \cdot 10^{-3}$, $x_2 = 0.226$; ◆, $x_1 = 0.818 \cdot 10^{-3}$, $x_2 = 0.269$; □, $x_1 = 0.776 \cdot 10^{-3}$, $x_2 = 0.307$; ●, $x_1 = 0.737 \cdot 10^{-3}$, $x_2 = 0.339$. (c) $m_1 = 0.100$ g; ■, $x_1 = 1.219 \cdot 10^{-3}$, $x_2 = 0.181$; ○, $x_1 = 1.146 \cdot 10^{-3}$, $x_2 = 0.227$; ◆, $x_1 = 1.088 \cdot 10^{-3}$, $x_2 = 0.269$; □, $x_1 = 1.034 \cdot 10^{-3}$, $x_2 = 0.307$; ●, $x_1 = 0.979 \cdot 10^{-3}$, $x_2 = 0.338$. (d) $m_1 = 0.125$ g; ■, $x_1 = 1.523 \cdot 10^{-3}$, $x_2 = 0.181$; ○, $x_1 = 1.434 \cdot 10^{-3}$, $x_2 = 0.227$; ◆, $x_1 = 1.366 \cdot 10^{-3}$, $x_2 = 0.270$; □, $x_1 = 1.290 \cdot 10^{-3}$, $x_2 = 0.306$; ●, $x_1 = 1.222 \cdot 10^{-3}$, $x_2 = 0.338$.

a stirring bar. DCM was injected into the cell using a gastight syringe, and then the piston was positioned immediately. The amounts of the drug and DCM loaded into the cell were determined using a sensitive balance (AND model HM-300) measurable to ± 0.1 mg. About 3 g to 7 g of DCM was loaded into the cell, depending on the desired DCM composition. CO_2 was charged into the cell using a high-pressure cylinder. The amount of CO_2 introduced into the cell was determined by weighing the sample cylinder both before and after loading using a balance (Precisa model 1212 M SCS) with an accuracy of ±

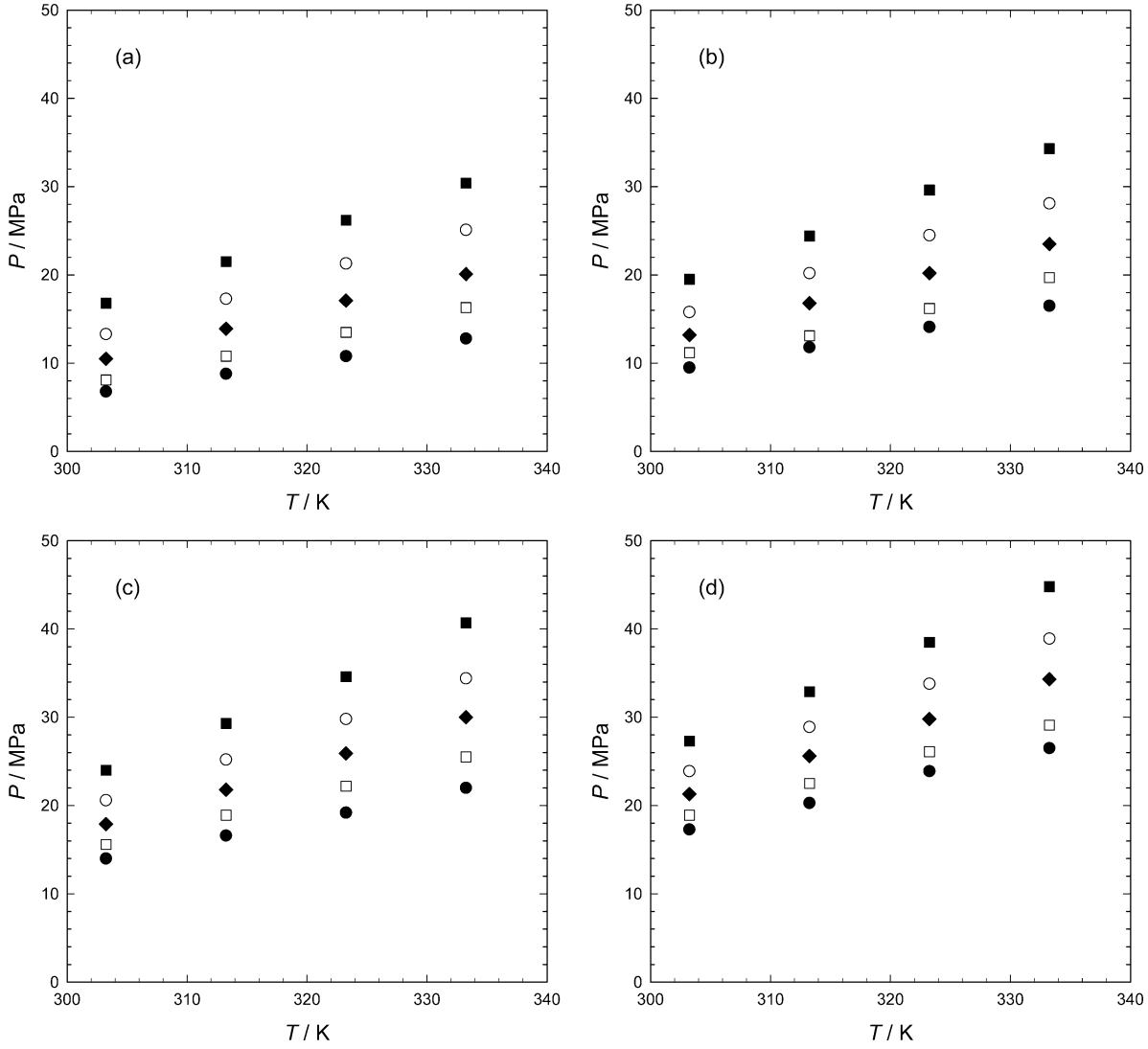

Figure 3. $P-T$ isopleths of cloud points of lovastatin in mixtures of DCM + CO_2. (a) $m_1 = 0.050$ g; ■, $x_1 = 0.631 \cdot 10^{-3}$, $x_2 = 0.182$; ○, $x_1 = 0.590 \cdot 10^{-3}$, $x_2 = 0.225$; ◆, $x_1 = 0.564 \cdot 10^{-3}$, $x_2 = 0.268$; □, $x_1 = 0.537 \cdot 10^{-3}$, $x_2 = 0.306$; ●, $x_1 = 0.504 \cdot 10^{-3}$, $x_2 = 0.337$. (b) $m_1 = 0.075$ g; ■, $x_1 = 0.951 \cdot 10^{-3}$, $x_2 = 0.180$; ○, $x_1 = 0.889 \cdot 10^{-3}$, $x_2 = 0.227$; ◆, $x_1 = 0.847 \cdot 10^{-3}$, $x_2 = 0.270$; □, $x_1 = 0.808 \cdot 10^{-3}$, $x_2 = 0.308$; ●, $x_1 = 0.762 \cdot 10^{-3}$, $x_2 = 0.338$. (c) $m_1 = 0.100$ g; ■, $x_1 = 1.251 \cdot 10^{-3}$, $x_2 = 0.180$; ○, $x_1 = 1.197 \cdot 10^{-3}$, $x_2 = 0.229$; ◆, $x_1 = 1.110 \cdot 10^{-3}$, $x_2 = 0.265$; □, $x_1 = 1.060 \cdot 10^{-3}$, $x_2 = 0.304$; ●, $x_1 = 1.024 \cdot 10^{-3}$, $x_2 = 0.342$. (d) $m_1 = 0.125$ g; ■, $x_1 = 1.552 \cdot 10^{-3}$, $x_2 = 0.178$; ○, $x_1 = 1.479 \cdot 10^{-3}$, $x_2 = 0.226$; ◆, $x_1 = 1.373 \cdot 10^{-3}$, $x_2 = 0.262$; □, $x_1 = 1.350 \cdot 10^{-3}$, $x_2 = 0.306$; ●, $x_1 = 1.283 \cdot 10^{-3}$, $x_2 = 0.342$.

1 mg. To minimize the amount of CO_2 lost when charging it into the cell, a fine and short feed line (0.03 in. i.d., 10 cm long) was used and heated by a heat gun. Approximately 7 g of CO_2 was charged into the cell for each run. The total dead volume of the feed line and fittings used to charge CO_2 into the view cell was estimated to be about 0.24 cm^3. It was calculated by weighing the amount of CO_2 gas entrapped in the feed line and fittings and then dividing it by the CO_2 gas density at the gas loading pressure and temperature. The amount of CO_2 gas lost during charging was estimated to be about 0.028 g and was deducted when calculating the CO_2 composition. The uncertainty analysis for the composition measurement for each component was performed in accordance with the ISO guidelines.[15] The average uncertainty values of the compositions in mole fraction were estimated to be $3.1 \cdot 10^{-6}$ for drug and $7.8 \cdot 10^{-5}$ for DCM and $3.7 \cdot 10^{-4}$ for CO_2.

The solution in the cell was compressed by moving the piston located within the cell using the pressure generator and well agitated by the magnetic stirrer. At the same time, the system was heated to a desired temperature. As the pressure generator pressurized water, the compressed water displaced the piston to the window side to decrease the cell volume and thus raise the pressure in the cell. As the pressure increased, the drug dissolved in the solvent of DCM + CO_2 and the mixture in the cell finally became a single phase. Once the system reached thermal equilibrium and the solution was maintained at a single phase, the pressure was then slowly reduced at about 0.5 MPa/min until the solution became cloudy. At a constant temperature, the cloud point indicating the single-phase to two-phase transition was defined as the pressure at which it was no longer possible to visually observe the stirring bar.[12] Every measurement was repeated at least twice for consistent measurements. Reproducibility of the cloud point pressure was within ± 0.2 MPa. The system temperature was raised, and the above procedure was repeated, thus creating a pressure−temperature ($P-T$) cloud point curve for a solvent mixture of DCM and CO_2 with a certain amount of the drug dissolved.

Results and Discussion

The solubilities of the simvastatin and lovastatin drugs in the solvent mixtures of DCM and CO_2 were investigated as functions of temperature, pressure, and DCM composition.

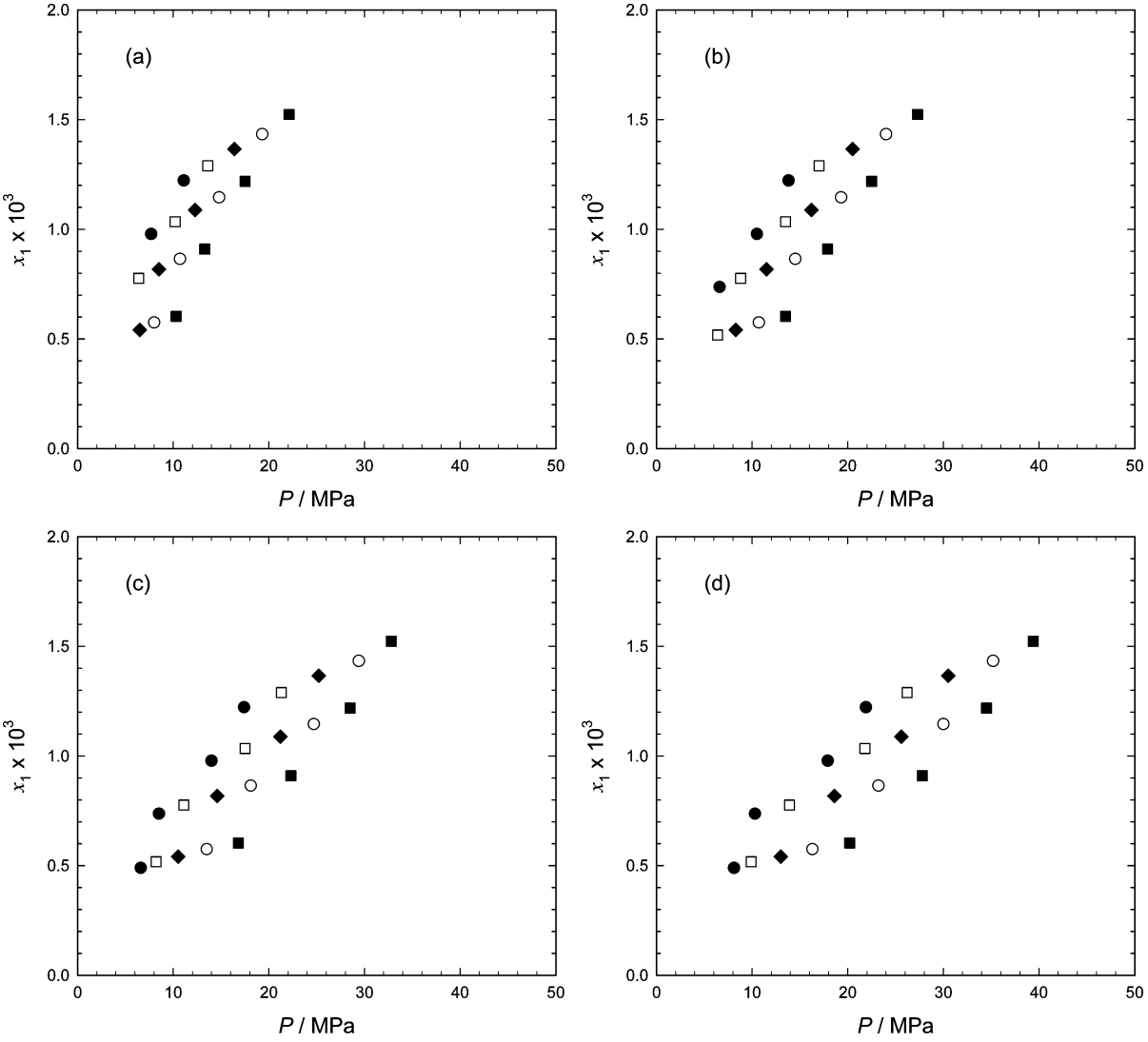

Figure 4. Solubility of simvastatin in mixtures of DCM + CO_2 as a function of pressure and DCM composition at different temperatures: (a) 303.25 K; (b) 313.25 K; (c) 323.25 K; (d) 333.25 K. For all the figures, the symbols are the DCM composition in solution: ■, $x_2 \approx 0.18$; ○, $x_2 \approx 0.23$; ◆, $x_2 \approx 0.27$; □, $x_2 \approx 0.31$; ●, $x_2 \approx 0.34$.

Cloud point pressures of the systems of simvastatin + DCM + CO_2 and lovastatin + DCM + CO_2 were measured at various conditions of temperature and DCM composition for different amounts of the drug loaded into the cell. The experimental cloud point data are given in Tables 2 and 3 for simvastatin and lovastatin, respectively. As shown in the tables, the amount of the drug loaded into the cell varied arbitrarily from 0.05 g to 0.125 g to determine the solubility of the drug in the mixture of DCM and CO_2. The DCM composition in the solution changed from 0.18 to 0.34 mole fractions. The solubility of the drug (component 1) in the solvent mixture of DCM (component 2) and CO_2 (component 3) is expressed as the mole fraction of the drug of the total.

Figures 2 and 3 show the $P-T$ isopleths of the cloud points of the simvastatin and lovastatin drugs in the DCM + CO_2 mixtures at different amounts of the drugs loaded, respectively. In these figures, above each cloud point is the single-phase region, and below the point is the two-phase region. In other words, the cloud point is the phase boundary showing whether the solute drug is completely soluble in the DCM + CO_2 mixture. Therefore, the composition of the solute drug at the cloud point is its solubility in the DCM + CO_2 mixture. As shown in Figures 2 and 3, the cloud point pressure increased as the temperature increased, indicating that the system exhibited a typical lower critical solution temperature (LCST) behavior. In other words, as the temperature increased, a higher pressure was needed to obtain a single-phase solution from a two-phase solution. At a given temperature, as the DCM composition in the mixed solvent increased and the drug composition decreased, the cloud point curve was shifted to lower pressures so that the single-phase region of drug−solvent miscibility enlarged. CO_2 is not a good solvent to dissolve the simvastatin drug, and DCM is a good solvent for the drug due to the hydrogen bonding between the hydrogen atom in DCM and the ester group in the simvastatin and lovastatin drugs.[12,13] Therefore, addition of DCM to CO_2 caused an increase of the dissolving power of the solvent mixture. This can be attributed to the increase of the solvent polarity by the increase of DCM composition in the solvent mixture. Consequently, DCM acted as a solvent and CO_2 acted as an antisolvent.

Figures 4 and 5 show the solubilities (x_1) of the drugs as a function of pressure and DCM composition (x_2) at four different temperatures for simvastatin and lovastatin, respectively. Obviously, the solubility of the drug increased with increasing system pressure at a fixed temperature and DCM composition. At a given pressure and temperature, the solubility of the drug increased as the DCM composition in solution increased. A

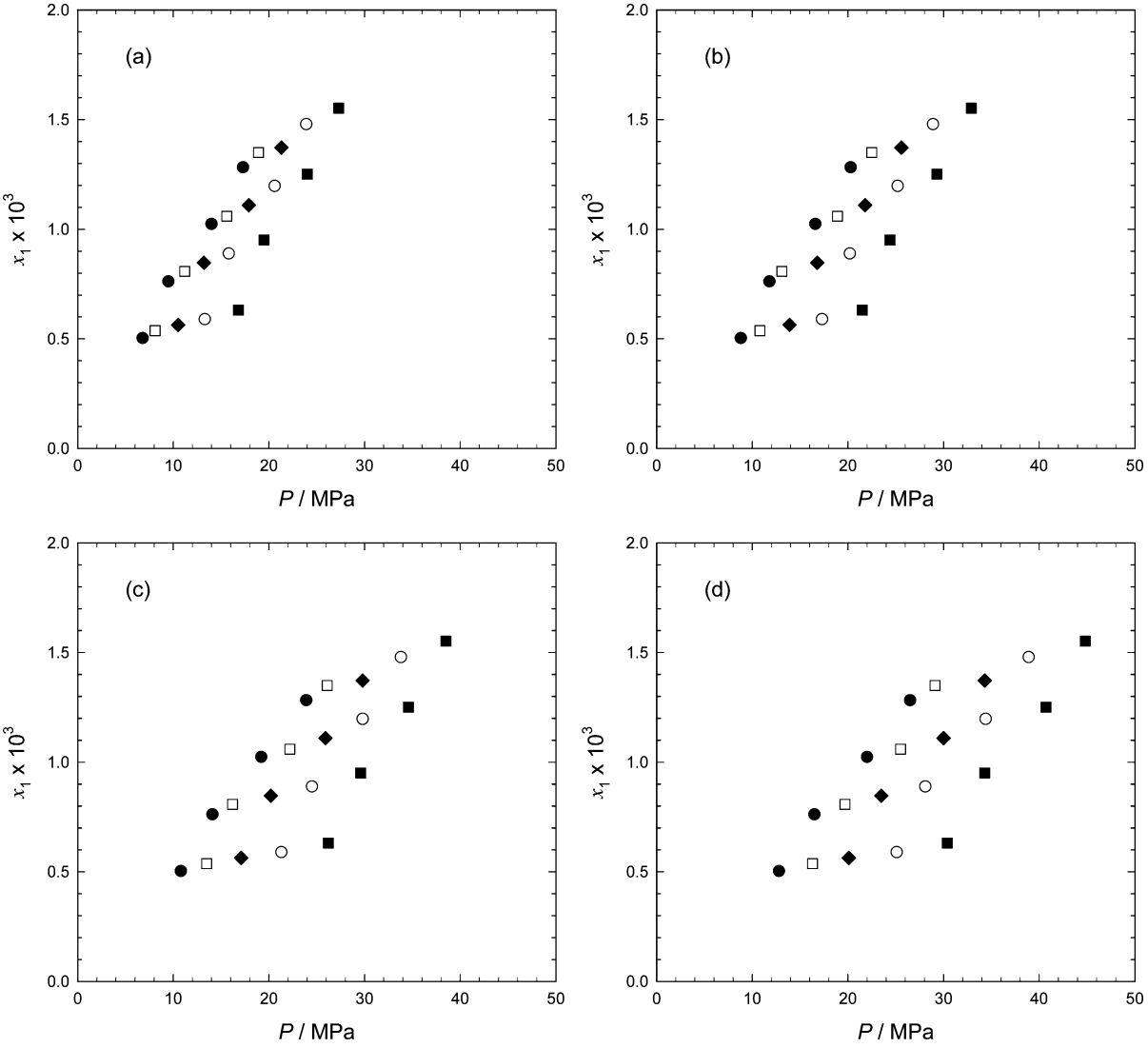

Figure 5. Solubility of lovastatin in mixtures of DCM + CO_2 as a function of pressure and DCM composition at different temperatures: (a) 303.25 K; (b) 313.25 K; (c) 323.25 K; (d) 333.25 K. For all the figures, the symbols are the DCM composition in solution: ■, $x_2 \approx 0.18$; ○, $x_2 \approx 0.23$; ◆, $x_2 \approx 0.27$; □, $x_2 \approx 0.31$; ●, $x_2 \approx 0.34$.

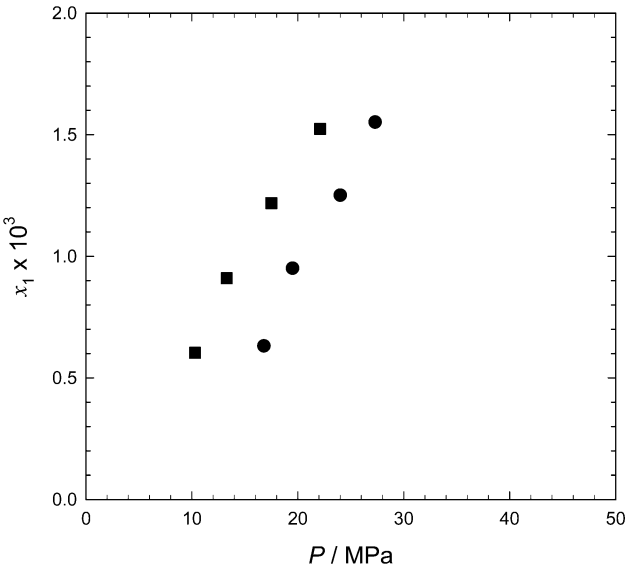

Figure 6. Comparison of solubilities between simvastatin and lovastatin in mixtures of DCM + CO_2 at 303.25 K and $x_2 \approx 0.18$: ■, simvastatin; ●, lovastatin.

lower solubility of the drug was observed at a higher temperature, as compared at the same DCM composition and pressure.

Figure 6 compares the solubilities of simvastatin and lovastatin in the mixture of DCM + CO_2 as a function of pressure at the temperature of 303.25 K and the DCM composition of 0.18. The solubilities of simvastatin were higher than those of lovastatin at a given pressure. It means that simvastatin is more soluble than lovastatin in the mixtures of DCM + CO_2. The phase behavior data produced in this work would be useful for establishing operating conditions in the particle formation of the water-insoluble statin drugs by the supercritical antisolvent recrystallization process which utilizes DCM as a solvent and CO_2 as an antisolvent.

Conclusions

The solubility of the water-insoluble simvastatin and lovastatin drugs in solvent mixtures of DCM and supercritical CO_2 was investigated as a function of temperature, pressure, and solvent composition by measuring the cloud points of the ternary mixtures of simvastatin + DCM + CO_2 and lovastatin + DCM + CO_2. The ternary mixtures exhibited the cloud point phase behavior of a typical LCST phase behavior; the pressure necessary to maintain the solution in a single-phase region

increased with increasing temperature. The solubility of the drug increased as the DCM composition in solution and the system pressure increased at a fixed temperature. A lower solubility of the drug was obtained at a higher temperature, as compared at the same DCM composition and pressure. Simvastatin was more soluble than lovastatin in the mixtures of DCM + CO_2. DCM acted as a solvent and CO_2 acted as an antisolvent for the simvastatin and lovastatin drugs. The phase behavior data produced in this work would be a guideline for establishing operating conditions in the particle formation of the statin drugs by a supercritical recrystallization process.

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Received for review January 12, 2007. Accepted April 13, 2007. This work was supported by the Energy Conservation Technology Program (2004-E-ID12-P-05-3-010) of the Korea Energy Management Corporation and Ministry of Commerce, Industry and Energy, Korea.

JE700019H