Korean J. Chem. Eng., **23**(6), 1009-1015 (2006)

Phase behavior of water-insoluble simvastatin drug in supercritical mixtures of chlorodifluoromethane and carbon dioxide

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(*Received 1 May 2006 • accepted 16 May 2006*)

Abstract–Phase behavior data are presented for simvastatin, a water-insoluble drug, in supercritical solvent mixtures of chlorodifluoromethane ($CHClF_2$) and carbon dioxide (CO_2). The solubilities of the simvastatin drug in the solvent mixtures of $CHClF_2$ and CO_2 were determined by measuring the cloud point pressures using a variable-volume view cell apparatus as functions of temperature, solvent composition, and amount of the drug loaded into the solution. The cloud point pressure increased with increasing the system temperature. As the $CHClF_2$ composition in the solvent mixture increased, the cloud point pressure at a fixed temperature decreased. Addition of $CHClF_2$ to CO_2 caused an increase of the dissolving power of the mixed solvent for the simvastatin drug due to the increase of the solvent polarity. $CHClF_2$ acted as a solvent for simvastatin, while CO_2 acted as an anti-solvent. The cloud point pressure increased as the amount of the simvastatin drug in the solvent mixture increased. Consequently, the solubility of the simvastatin drug in the solvent mixture of $CHClF_2$ and CO_2 decreased with increasing the CO_2 content in the solvent mixture as well as with increasing the system temperature.

Key words: Simvastatin, Water-insoluble Drug, Solubility, Supercritical Fluid, Carbon Dioxide, Chlorodifluoromethane, Cloud Point Pressure

INTRODUCTION

Supercritical fluid (SCF) solvent is an attractive alternative to incompressible organic liquid solvents because they can have liquid-like dissolving power while exhibiting transport properties of a gas. SCF technology has recently gained considerable attention from the pharmaceutical industries [Fages et al., 2004; Ginty et al., 2005; Guney and Akgerman, 2002; Shekunov and York, 2000]. Particularly, the microparticle formation of biodegradable polymers, bioactive agents and water-insoluble drugs by an SCF process has been studied by many researchers [Datea and Patravale, 2004; Duarte et al., 2006; Kerc et al., 1999; Reverchon and Adami, 2006; Reverchon and Della Porta, 2003; Yeo and Kiran, 2005]. Pharmaceutically, it is very important to make water-insoluble drugs of micro- or nano-size, since 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 microns [Perrut et al., 2005; Reverchon and Spada, 2004; Rodier et al., 2005; Van Nijlen et al., 2003]. They have many advantages such as no thermal degradation, no mechanical damage, and no residual solvent problems. The core work in the particle formation of a water-insoluble drug using the SCF processes such as a supercritical anti-solvent (SAS) recrystallization [Bakhbakhi et al., 2006; Miguel et al., 2006; Song et al., 2002; Steckel et al., 2004; Won et al., 2005] and a rapid expansion of supercritical solution [Huang et al., 2005; Kwak et al., 2004; Thakur and Gupta, 2006; Turk et al., 2002] is to obtain 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 an SCF process it is important to know the location of the phase boundaries in the solution of drug and SCF. In this work, simvastatin was selected as the target drug.

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, while it is used to increase the level of HDL (good) cholesterol in blood. These actions may reduce the risk of hardening of the arteries, which can lead to heart attacks, stroke, and peripheral vascular disease. After oral ingestion, simvastatin is 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. The simvastatin drug is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water and freely soluble in methylene chloride, chloroform, methanol and ethanol.

Since simvastatin is a medicinal substance, the chemicals used to process it should be pharmacologically acceptable. For the purpose of selecting a solvent and an anti-solvent used in the particle formation of the simvastatin drug by an SAS recrystallization pro-

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cess, chlorodifluoromethane ($CHClF_2$) and carbon dioxide (CO_2) were tested. From our preliminary work, it was observed that the simvastatin was insoluble in nonpolar CO_2 but was soluble in polar $CHClF_2$. For example, it was not completely soluble in supercritical CO_2 at pressures as high as 80 MPa even for a very small amount of the drug, while it was readily soluble even in saturated liquid $CHClF_2$ at a room temperature. $CHClF_2$ hydrogen-bonds to molecules such as esters but does not hydrogen-bond to itself [Lee et al., 2003]. Thus it should be a better solvent for the simvastatin drug which contains an ester group. The polar moment in $CHClF_2$ interacts favorably with the polar moment of the ester group in the simvastatin drug [Lee et al., 2003]. The enhanced solubility of simvastatin in $CHClF_2$ can be attributed to hydrogen bonding between $CHClF_2$ and simvastatin. Consequently, $CHClF_2$ is an excellent solvent for the simvastatin solute, while CO_2 acts as an anti-solvent for the same solute. $CHClF_2$ is also highly volatile and nontoxic so that it is adequate to be used in the recrystallization process for the simvastatin.

This work is focused on determining the feasibility of dissolving the simvastatin drug in mixtures of $CHClF_2$+CO_2. In this article we present the phase behavior data for the simvastatin drug in supercritical mixtures of $CHClF_2$ and CO_2. The cloud point pressures were measured by using a high-pressure variable-volume view cell apparatus and were characterized as a function of $CHClF_2$ composition in the solvent mixture and temperature at different amounts of the simvastatin drug loaded. The phase behavior data produced in this work would be useful for establishing operating conditions in the particle formation of the simvastatin drug by an SAS recrystallization process which utilizes $CHClF_2$ as a solvent and CO_2 as an anti-solvent.

EXPERIMENTAL

1. Materials

The simvastatin drug used in this work was obtained from Kyongbo Pharmaceutical Co. (Korea) and its purity was 99.8%. The general chemical information and some physical properties of simvastatin are given in Table 1, and its chemical structure is shown in Fig. 1. $CHClF_2$ and CO_2 used as solvent and anti-solvent were obtained from Solvay Fluorides Inc. (Greenwich, CT) and Myung-Sin General Gas Co. (Yangsan, Gyeongnam, Korea), respectively, and their certified purities were 99.99 mass%. They were used as received without further purification.

2. Apparatus

Fig. 2 shows a schematic diagram of the experimental apparatus

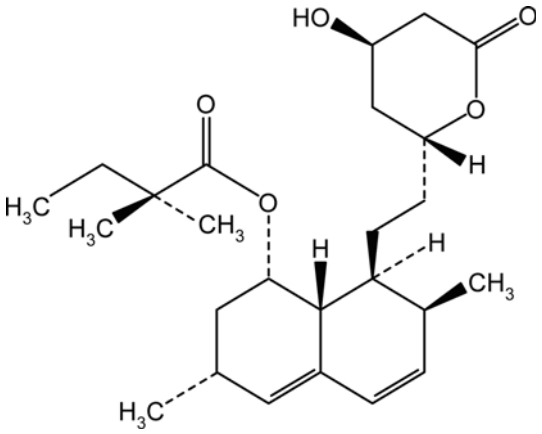

Fig. 1. Chemical structure of simvastatin drug.

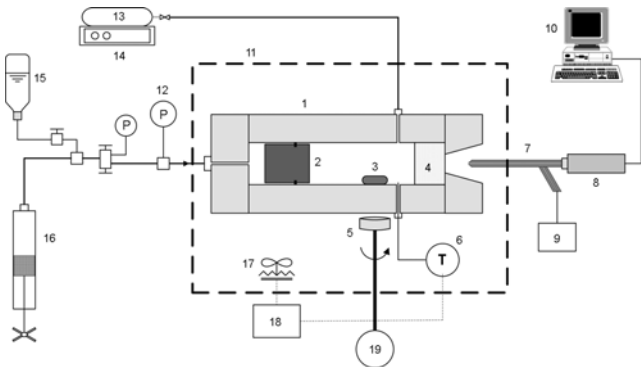

Fig. 2. A schematic diagram of the experimental apparatus.

1. Variable-volume view cel
2. Piston
3. Spin bar
4. Sapphire window
5. Magnetic stirrer
6. Temperature indicator
7. Borescope
8. CCD camera
9. Light source
10. Monitor
11. Air bath
12. Pressure transmitterl and indicator
13. Gas (CO_2 or $CHClF_2$) bomb
14. Balance
15. Water
16. Pressure generator
17. Heater and fan
18. Temperature controller
19. Motor

for measuring the cloud point behavior for simvastatin drug in a mixture of $CHClF_2$ and CO_2. The experimental apparatus used in this work is similar to that used by Lee and Kim [2002], Lee et al. [2000], and Lee et al. [2003]. The heart of the system is the high-pressure

Table 1. Physicochemical characteristics of simvastatin drug

Generic name	Simvastatin
CAS registry number	79902-63-9
Synonym	butanoic acid, 2,2-dimethyl-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-(1α,3α,7β,8β(2S*,4S*),8aβ)]
Chemical formula	$C_{25}H_{38}O_5$
Molecular weight	418.5722
Melting point	135-138 °C
Water solubility	0.765 mg/L @ 25 °C (estimated value)
log P (octanol-water)	4.68 (experimental value)

variable-volume view cell. The cell has dimensions of 16 mm i.d. by 70 mm o.d., and an internal working volume of about 31 cm^3. A movable piston is placed inside the cell to change the cell volume. A pressure generator (High Pressure Equipment Co. model 50-6-15) is used to pressurize water and thereby displace the piston. A change in the cell volume causes a change of the system pressure. A sapphire window (¾" diameter by ¾" thick) is inserted into the view cell for visual observation of the interior of the cell. The main feature of using the variable-volume cell apparatus is that the concentration of the system is kept constant during the experiment.

The system pressure is measured with a piezoresistive pressure transmitter (Keller Druckmesstechnik, type PA-25HTC/8585-1,000, 100 MPa max. pressure, ±0.1 MPa accuracy) installed on the pressurizing fluid (water) side between the pressure generator and the cell. Connecting the pressure transmitter directly to the solvent side of the cell can cause an uncertainty in the exact concentration of the solution due to dead volume. The system temperature is measured to within ±0.1 K by an RTD (Pt-100) probe inserted into the cell. An air bath is used to keep the system temperature constant.

A visual observation of the cell inside through the sapphire window is made by a borescope (Olympus model R080-044-000-50) and a CCD camera (WAT-202B) connected to a monitor. A cold light source (Olympus model ILK-5) is used to provide illumination inside the view cell. A magnetic stirring system is equipped under the cell body to agitate the fluid. A stirring bar in the cell is rotated by a samarium-cobalt magnet located below the cell, and the magnet is driven by an electric motor and an RPM controller.

3. Method

The experiment for measuring the cloud point behavior for simvastatin drug in a mixture of $CHClF_2$ and CO_2 was performed by the following procedure. A certain amount of the simvastatin drug was loaded into the cell, and then the stirring bar was placed inside the cell. The amount of the drug loaded into the cell was determined with a sensitive balance (AND model HM-300) measurable to ±0.1

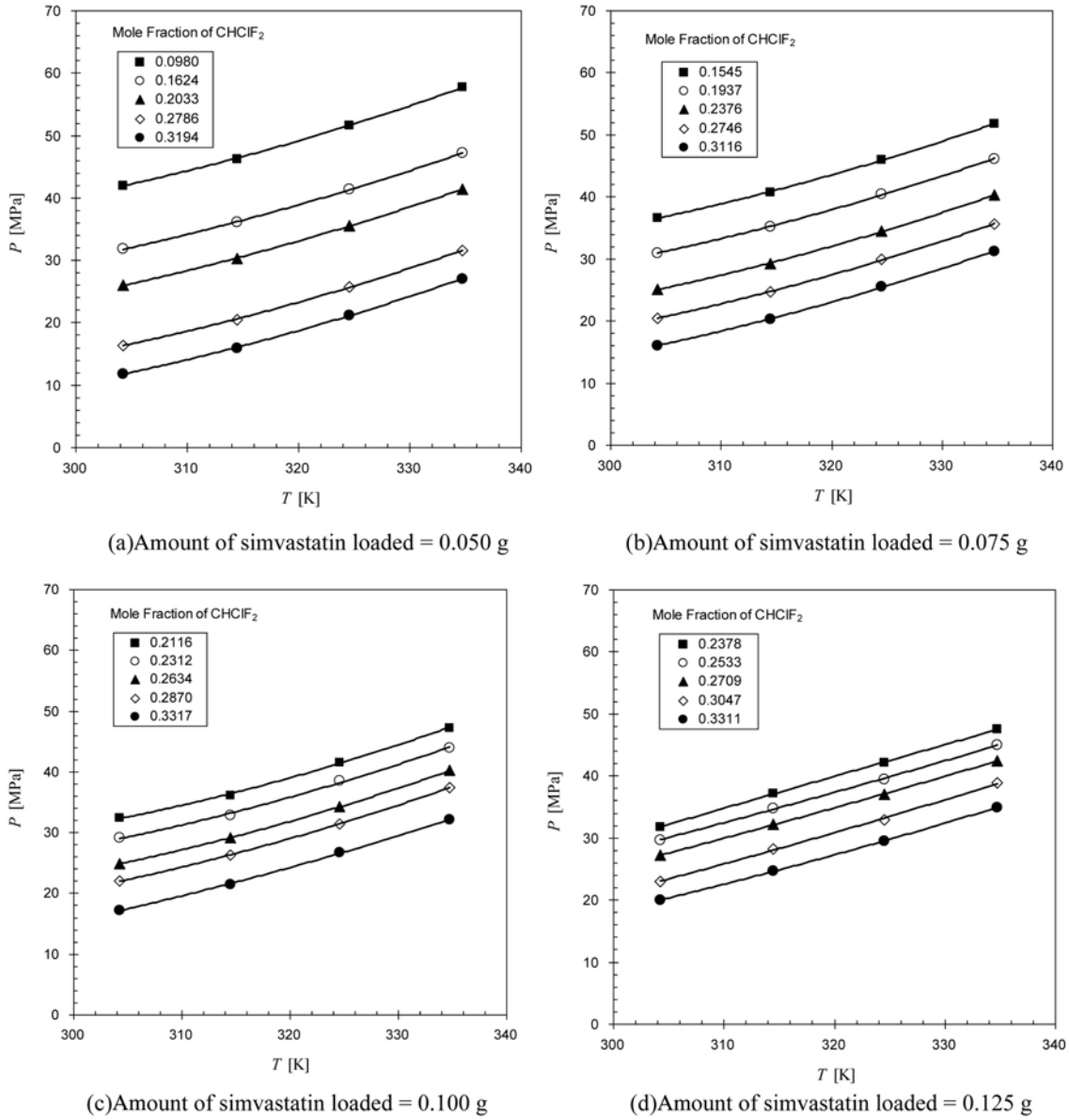

Fig. 3. P-T isopleths of cloud points of simvastatin drug in mixtures of $CHClF_2$+CO_2.

mg. After a piston was assembled into the cell, the cell was placed inside the air bath. The $CHClF_2$ and CO_2 were loaded into the cell by using a high-pressure sample cylinder. $CHClF_2$ was first loaded because its vapor pressure was lower than that of CO_2. The amounts of $CHClF_2$ and CO_2 introduced into the cell were determined by weighing the sample cylinders both before and after loading by using a balance (Precisa model 1212 M SCS) with an accuracy of ±1 mg.

The solution in the cell was compressed by moving the piston located within the cell using the pressure generator. As the pressure generator pressurizes water, the compressed water displaces the piston to the window side to decrease the cell volume and thus raises the pressure in the cell. As the pressure increases, the solution in the cell finally becomes a single homogeneous phase. At the same time the solution was well agitated by a stirring bar. The system was heated to a desired temperature. Once the system reached thermal equilibrium and the solution was maintained at a single phase, the pressure was then very slowly reduced 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 [Lee et al., 2000]. For obtaining consistent measurements, every measurement was repeated at least twice at each temperature.

The temperature of the system was raised in about 10 K increments, and the above procedure was repeated, thus creating a pressure-temperature (P-T) cloud point curve at a certain amount of the simvastatin drug loaded in a solvent mixture of a given composition. In this work the amount of the drug loaded varied arbitrarily from 0.05 g to 0.125 g in order to investigate the effect of the drug content on the phase behavior.

RESULTS AND DISCUSSION

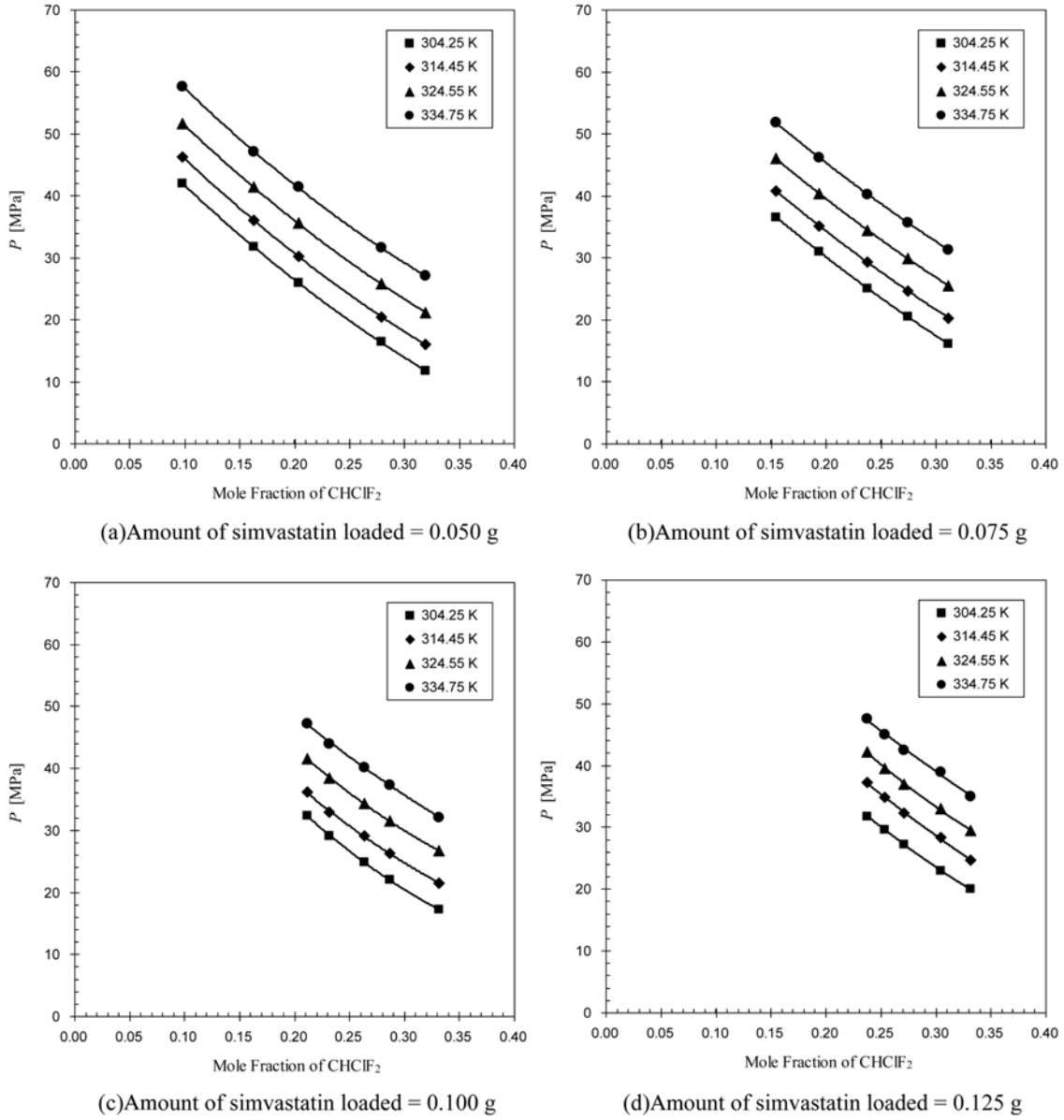

Fig. 4. Effect of $CHClF_2$ in the solvent mixture on cloud point pressures of simvastatin drug at various temperatures.

Cloud point pressures of the simvastatin drug in supercritical mixtures of $CHClF_2$ and CO_2 were investigated as functions of temperature, solvent composition, and the amount of the drug loaded. The experimental cloud point data are given in Table 1. Fig. 3 shows the P-T isopleths of the cloud points of the simvastatin in the mixed solvents of $CHClF_2$ and CO_2. The $CHClF_2$ composition in the solvent mixture ranged widely from 0.1 to 0.33 mole fractions on a drug-free basis. The amount of the simvastatin drug loaded into the solution was varied from 0.05 grams to 0.125 grams, to investigate the effect of the drug content in the solution on the cloud point behavior. Above each cloud point is the single-phase region, and below the point is the liquid-liquid two-phase region. Therefore, the cloud point curve is the phase boundary between the single and two phases on the P-T phase diagram. As shown in Fig. 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. The cloud point curves had similar slopes for all the $CHClF_2$ compositions.

As the $CHClF_2$ composition in the solvent increased at a given temperature, 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, while $CHClF_2$ is a good solvent for the drug due to the hydrogen bonding between the hydrogen atom in $CHClF_2$ and the ester group in the simvastatin. Therefore, addition of $CHClF_2$ to CO_2 caused an increase of dissolving power of the solvent mixture. This can be attributed to the increase of the solvent polarity by the increase of $CHClF_2$ composition in the solvent mixture. Consequently, $CHClF_2$ acted as a solvent and CO_2 acted as an anti-solvent. Fig. 4 shows the effect of $CHClF_2$ composition in the mixed solvent on the cloud point pressures at several temperatures for four different amounts of the drug loaded. The cloud point pressure decreased with increasing the $CHClF_2$ composition in the mixed solvent.

In this work, the factors, which affect the cloud point pressure of the simvastatin drug in $CHClF_2$+CO_2, are temperature, solvent composition, and the amount of the drug loaded into the solution. To examine more vividly the dependence of cloud point pressure on these three factors, the cloud point curves are shown in three-dimensional diagrams. For each plot given in Fig. 4, the cloud point pressures at several $CHClF_2$ mole fractions of solvent mixtures (0.24, 0.27, 0.30, and 0.33) were obtained by fitting the cloud point curves with polynomial equations and then determining the pressures corresponding to the $CHClF_2$ mole fractions from the curve fits for each temperature. A second-order polynomial equation was used in this work, and the correlation coefficients of the curve fits, which expressed the goodness of the fits, were greater than 0.998 for all cases.

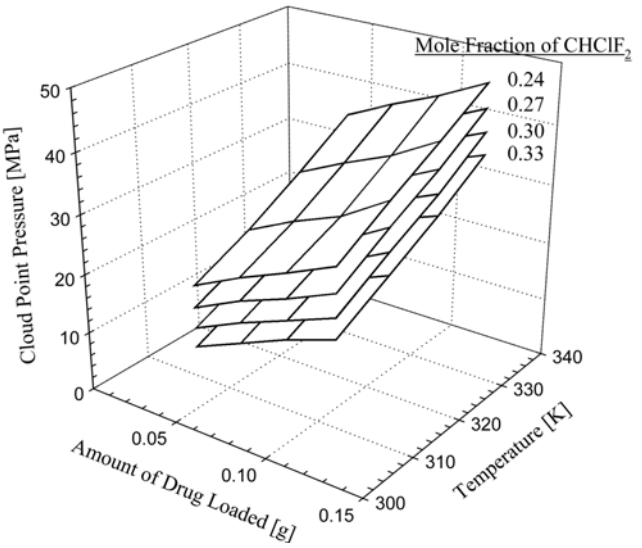

Fig. 6. Effect of amount of drug loaded and temperature on cloud point pressure at various mole fractions of $CHClF_2$ for simvastatin drug in mixtures of $CHClF_2$+CO_2.

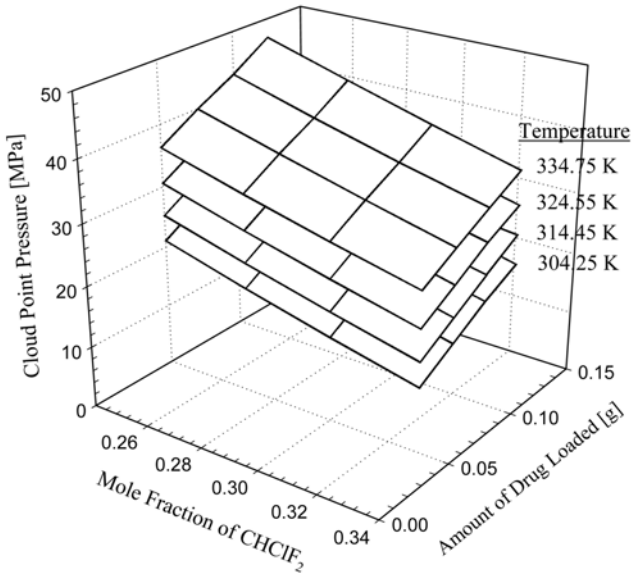

Fig. 5. Effect of $CHClF_2$ mole fraction and amount of drug loaded on cloud point pressure at various temperatures for simvastatin drug in mixtures of $CHClF_2$+CO_2.

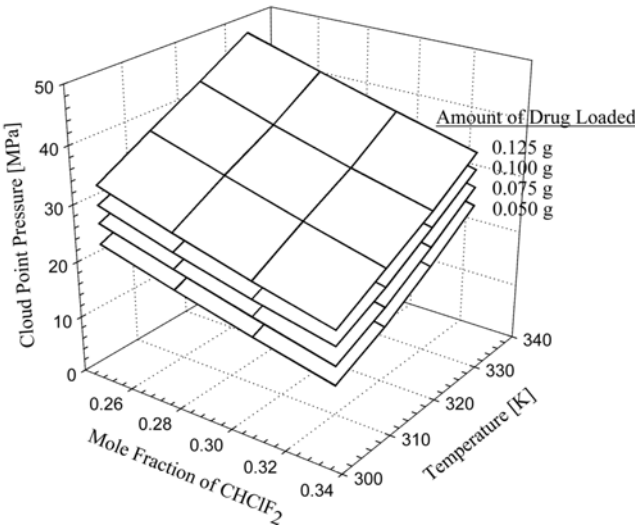

Fig. 7. Effect of $CHClF_2$ mole fraction and temperature on cloud point pressure at various amounts of drug loaded for simvastatin drug in mixtures of $CHClF_2$+CO_2.

Table 2. Experimental data of cloud points of simvastatin in mixtures of $CHClF_2$ and CO_2

Amount of simvastatin drug loaded [g]	Mole fraction of $CHClF_2$*	Cloud point pressure [MPa]			
		304.25 K	314.45 K	324.55 K	334.75 K
0.050	0.0980	42.0	46.3	51.7	57.7
	0.1624	31.8	36.1	41.4	47.2
	0.2033	26.0	30.3	35.6	41.4
	0.2786	16.4	20.5	25.8	31.6
	0.3194	11.8	16.0	21.2	27.1
0.075	0.1545	36.6	40.8	46.0	51.8
	0.1937	31.0	35.2	40.4	46.2
	0.2376	25.1	29.3	34.5	40.3
	0.2746	20.5	24.7	29.9	35.7
	0.3116	16.1	20.3	25.5	31.3
0.100	0.2116	32.4	36.2	41.6	47.3
	0.2312	29.1	32.9	38.5	44.0
	0.2634	24.9	29.1	34.3	40.2
	0.2870	22.0	26.3	31.5	37.4
	0.3317	17.2	21.5	26.7	32.1
0.125	0.2378	31.8	37.2	42.2	47.5
	0.2533	29.7	34.8	39.5	45.0
	0.2709	27.2	32.3	37.0	42.5
	0.3047	23.0	28.3	33.0	38.9
	0.3311	20.0	24.7	29.5	35.0

*Mole fraction of $CHClF_2$ in a mixed solvent of $CHClF_2$ and CO_2 on a drug-free basis.

Fig. 5 shows the effect of the $CHClF_2$ composition and the amount of the drug loaded into the solution on the cloud point pressure at four different temperatures in a three-dimensional space. The cloud point pressure increased with the decrease of the $CHClF_2$ composition in the solvent mixture and the increase of the amount of the drug loaded. The effect of the amount of the drug loaded and the temperature on the cloud point pressure at four different mole fractions of $CHClF_2$ in the solvent mixture is illustrated in Fig. 6 in a three-dimensional space. Fig. 7 also shows the change of the cloud point pressure as functions of the $CHClF_2$ mole fraction and the temperature at four different amounts of the drug loaded into the solution. For all cases of Fig. 5 to Fig. 7, the upper space of the cloud point pressure plane surface is the single-phase region and the lower space is the two-phase region.

CONCLUSIONS

The phase behavior of the water-insoluble simvastatin drug in a mixed solvent of $CHClF_2$ and CO_2 was investigated as a function of temperature, pressure, solvent composition, and the amount of the drug, The cloud point curves exhibited the characteristics of a typical lower critical solution temperature phase behavior; the pressure necessary to maintain the solution in a single-phase region increased with increasing the temperature. At a given temperature, the cloud point pressure decreased with increasing the $CHClF_2$ composition in the solvent mixture. Addition of $CHClF_2$ to CO_2 caused an increase of dissolving power of the solvent mixture due to the increase of the solvent polarity and enlarged the area of miscibility by shifting the cloud point curve to higher temperatures and lower pressures. The cloud point pressure increased with the amount of the drug loaded into the solution,. The phase behavior data produced in this work would be useful for establishing operating conditions in the particle formation of the simvastatin drug by a supercritical recrystallization process which utilizes $CHClF_2$ as a solvent and CO_2 as an anti-solvent.

ACKNOWLEDGMENTS

This work was supported by Grant No. R05-2002-000-00632-0 from the Basic Research program of the KOSEF.

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