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Cloud Points of Poly(L-lactide) in HCFC-22, HFC-23, HFC-32, HFC-125, HFC-143a, HFC-152a, HFC-227ea, Dimethyl Ether (DME), and HCFC-22 + CO_2 in the Supercritical State

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Cloud points were measured using the high-pressure variable-volume cell apparatus for poly(L-lactide) in chlorodifluoromethane (HCFC-22), trifluoromethane (HFC-23), difluoroethane (HFC-32), pentafluoroethane (HFC-125), 1,1,1-trifluoroethane (HFC-143a), 1,1-difluoroethane (HFC-152a), 1,1,1,2,3,3,3-heptafluoropropane (HFC-227ea), and dimethyl ether (DME), respectively. The cloud points were characterized as functions of pressure, temperature, and polymer molecular weight. Cloud point pressures of poly(L-lactide) were studied at temperature ranging up to 413.2 K for polymer concentrations of about 3 mass %. The phase behavior of poly(L-lactide) in DME, HCFC-22, and HFC-23 exhibited LCST (lower critical solution temperature) behavior, and that of poly(L-lactide) in HFC-32 and HFC-152a exhibited UCST (upper critical solution temperature) behavior. However, poly(L-lactide) had a low solubility in HFC-125, HFC-143a, and HFC-227ea even at 413.2 K and 150 MPa. In addition, the phase behavior of poly(L-lactide) was investigated as a function of CO_2 in a HCFC-22 + CO_2 mixture.

1. Introduction

Much attention has been placed on the use supercritical fluids as solvents in a variety of polymer processes including extractions, separations, fractionations, particle formations, and other reactions.[1−5] Interest stems primarily from the ability to change the bulk properties of supercritical fluids (e.g., density and solubility) dramatically with small variations in temperature and pressure such that supercritical fluids have liquidlike dissolving power while exhibiting the transport properties of a gas.[6] One application of chemists' and engineers' continuous research into supercritical fluids is the combining of supercritical and nanotechnology to form a nanometer-size particle of polymer in the supercritical state. Nanoparticle formation is categorized according to the use of supercritical fluids as solvents or antisolvents. Precipitation from a supercritical fluid solvent is called rapid expansion of a supercritical solution,[7] and a supercritical fluid that is used to lower the solubility of a solute in an organic solvent is called a supercritical antisolvent.[8] The latter precipitation process employs various equipment designs.

Of late, supercritical antisolvents have been studied extensively as a way of producing micro- to nanosize particles of drugs, polymers, and/or pigments. The phase behavior and solubility data of a chemical in various solvents in or near the supercritical state are important to the efficient design and production of nanoparticles of polymers via supercritical antisolvents. Recent studies in several fields have generated useful data as to the phase behavior of chemicals in various solvents; moreover, the phase behavior of polymer + supercritical fluid systems has been measured and is reported in refs 9 and 10. For this study, poly(L-lactide) was selected; it is used in sutures and dental, orthopedic, and drug delivery devices. This polymer is of interest in the area of tissue engineering. This paper presents phase behavior data for biodegradable and bioresorbable poly(L-lactide) in chlorodifluoromethane (HCFC-22), trifluoromethane (HFC-23), difluoroethane (HFC-32), pentafluoroethane (HFC-125), 1,1,1-trifluoroethane (HFC-143a), 1,1-difluoroethane (HFC-152a), 1,1,1,2,3,3,3-heptafluoropropane (HFC-227ea), dimethyl ether (DME), and an HCFC-22 + CO_2 mixture. The cloud points of these systems were measured as functions of polymer molecular weight at temperatures up to 370.2 K. The cloud point and solubility data obtained by this study comprise important thermodynamic properties of supercritical fluids because the supercritical antisolvent process is directly affected by solubility.

2. Experimental Section

Chemicals. Dimethyl ether (Aldrich Chemical Co.), HCFC-22 (Solvay Fluorides), HFCs (DuPont), and CO_2 (Duck Yang Co.) had a minimum purity of 99.9% and were used as received. The chemical structure of poly(L-lactide) is shown in Scheme 1. Table 1 lists the physical properties of the chemicals used in this study. Poly(L-lactide) was obtained from Biomaterials Research Center in KIST, Korea, that had weight-average molecular weights (M_w) of 2000, 80 000, 110 000, and 230 000, and number-average molecular weights (M_n) of 2500, 98 500, 135 500, and 283 000. Therefore, the polydispersity indexes (M_w/M_n) of poly(L-lactide) with these molecular weights were 1.2, 1.35, 1.38, and 1.51, respectively. The molecular weight and molecular weight distributions were determined by gel permeation chromatography (GPC) using a Waters 510

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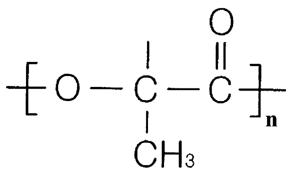
Table 1. Physical Properties of Solvents Used in This Study[14–15]

solvent	chemical formula	MW	T_c/K	P_c/MPa	dipole moment/D
carbon dioxide (CO_2)	CO_2	44.01	304.10	7.38	0.0
dimethyl ether (DME)	CH_3OCH_3	46.06	400.00	5.24	1.3
chlorodifluoromethane (HCFC-22)	$CHClF_2$	84.46	369.30	4.97	1.4
trifluoroethane (HFC-23)	CHF_3	70.01	299.07	4.84	1.6
difluoroethane (HFC-32)	CH_2F_2	52.02	356.26	5.78	2.0
pentafluoroethane (HFC-125)	C_2HF_5	120.03	339.33	3.62	1.5
1,1,1-trifluoroethane (HFC-143a)	CF_3CH_3	84.04	346.04	3.78	2.3
1,1-difluoroethane (HFC-152a)	CHF_2CH_3	66.05	386.41	4.52	2.2
1,1,1,2,3,3,3-heptafluoropropane (HFC-227ea)	CF_3CHFCF_3	170.03	375.95	2.98	1.5

Scheme 1. Chemical Structure of Poly(L-lactide)



$$\left[O-\underset{CH_3}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}} \right]_n$$

fluids unit, a Waters 717 plus autosampler, and a Waters 410 differential refractometer with a combination of three Shodex microstyagel columns with molecular weight exclusion limits of 1500/70 000/400 000 g/mol. The column was eluted with $CHCl_3$ (flow rate of 1.0 mL/min at 30 °C) and calibrated with polystyrene standards over a molecular weight range of 1000−350 000. Pasch et al.[11] reported that PS-calibrated GPC measurements overestimate the actual molecular weights of aliphatic polyesters by 50−100% (depending on their structures and molecular weights). Therefore, the actual molecular weights of poly(L-lactide) are expected to be less than those determined by GPC. ^1H NMR spectra were recorded at 25 °C using a Varian Unity Plus 300-MHz spectrometer in $CDCl_3$. TMS was used as an internal reference. Polymer signals were detected at 1.57 and 5.15 ppm.

Experimental Apparatus. The schematic diagram of the apparatus is shown in Figure 1. This apparatus was designed to measure the cloud point at temperatures to 373.2 K and pressures to 100 MPa. The reactor had an internal variable-volume view cell that allowed for change in cell volume and pressure via a movable piston. The variable-volume view cell was designed by ourselves and manufactured by our machine shop in KIST. A pressure generator (High-Pressure Equipment Co. model 376-30, pressure rating 206.8 MPa) was used to pressurize the contents of the cell. Visual observation of phenomena occurring inside the cell was made through a sapphire window (thickness = 19.2 mm, diameter = 19.2 mm) using a borescope (Olympus model R080-044-000-50) and a CCD camera (Watec, WAT-202B). These were connected to a VCR/TV (Anam Co.) monitor and computer. One advantage of using the variable-volume cell is that the concentration of the system remains constant during the experiment. A stirrer, rotated at variable speeds by an external magnet, was used to mix the solvent and poly(L-lactide) in the high-pressure reactor. A simple thermostatic air bath was used to maintain the system temperature to within ±0.1 K. The temperature in the reactor was measured with a K-type thermocouple and digital indicator (OMEGA Co.) calibrated by KRISS (Korea Institute of Standards and Science). The pressure in the reactor was measured to within ±0.1 MPa using a pressure transducer (SENSOTEC model TJE, a strain gauge-based sensor-bonded foil type, accuracy = ±0.1%) and a digital indicator (SENSOTEC model L20000WM1) calibrated by a dead weight gauge. A detailed description of the apparatus is given elsewhere.[9−10,12]

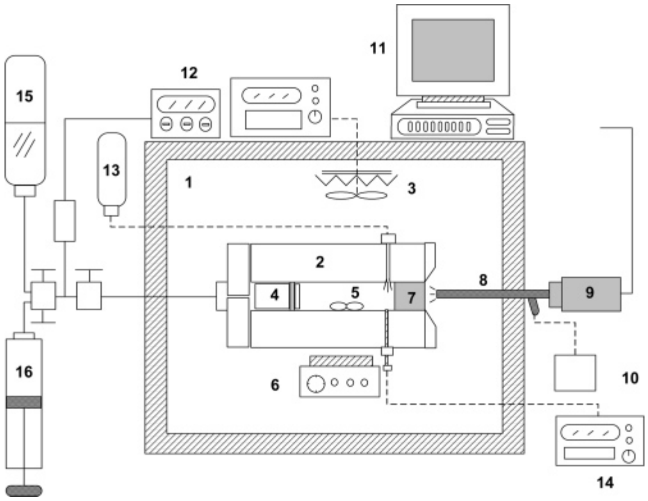


Figure 1. Schematic diagram of the experimental apparatus: (1) air bath, (2) variable-volume cell, (3) heater, (4) piston, (5) magnetic bar, (6) stirrer, (7) sapphire window, (8) borescope, (9) CCD camera, (10) light source, (11) TV/VCR, (12) pressure gauge, (13) temperature controller, (14) solvent reservoir, (15) water for pressurizing, and (16) pressure generator.

Experimental Procedure for Measuring the Cloud Points of Poly(L-lactide) in Various Solvents. The reactor cell was evacuated, and a certain amount of poly(L-lactide) was loaded into the cell. The amount of the poly(L-lactide) loaded into the cell was determined using a sensitive balance (OHAUS, E04130) measurable to ±0.1 mg. To remove any trapped air, the cell was purged a minimum of three times with low-pressure solvent (less than 0.3 MPa) at a very slow rate so that poly(L-lactide) in the cell was not disturbed and was avoided. A certain amount of liquid solvent, calculated as the difference between the initial and final mass of the sample cylinder, was charged into the cell through the inlet line using a balance (OHAUS, E04130) with an accuracy of ±0.1 mg. To minimize the amount of components lost when charging them into the cell, we used a fine, short inlet line (i.d. = $^1/_{16}$ in., length = 2.5 cm) and heated it with a heat gun for a sufficient period of time. The uncertainty in the solvent composition measurement was <0.02 mass %. The solution in the cell was compressed by moving the piston located in the cell; therefore, the pressure in the cell was increased continuously. The solution in the cell was agitated by the magnetic stirrer until it became an optically transparent single phase. Once the system reached thermal equilibrium and maintained a single phase, the pressure was slowly reduced until the solution became cloudy. The pressure was reduced at about 0.05 MPa/min as the cloud point pressure was approached, and the cloud points (pressures and temperatures) were measured. At the cloud point, it was not possible to observe the stir bar visually. To obtain consistent measurements, every measurement was re-

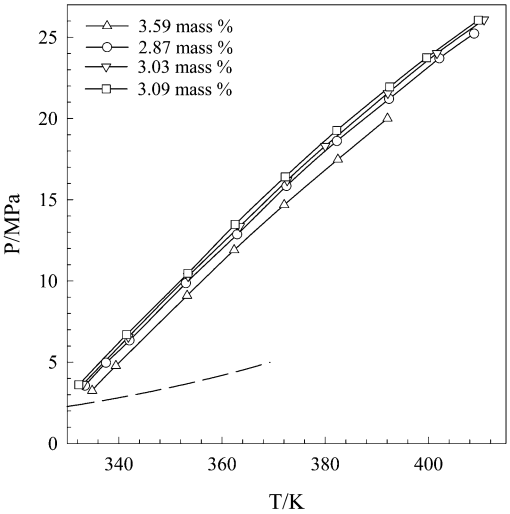


Figure 2. $P-T$ isopleths of cloud points of poly(L-lactide) (1) in HCFC-22 (2) at various polymer molecular weights: △, MW = 50 000;[9] ○, MW = 80 000; ▽, MW = 110 000; □, MW = 230 000, and - -, vapor pressure of HCFC-22.

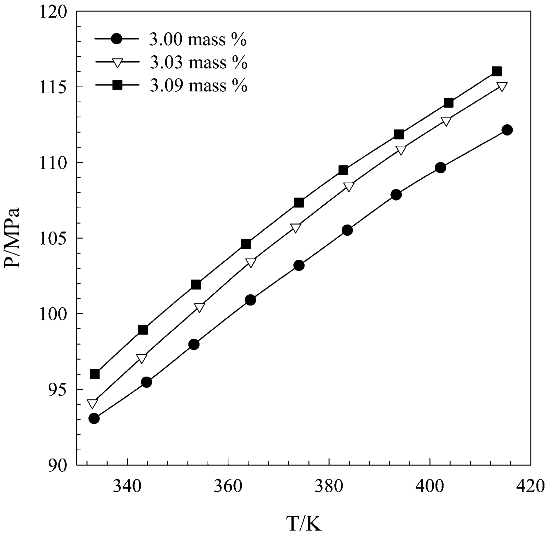


Figure 3. $P-T$ isopleths of cloud points of poly(L-lactide) (1) in HFC-23 (2) at various polymer molecular weights: ●, MW = 80 000; ▽, MW = 110 000; and ■, MW = 230 000.

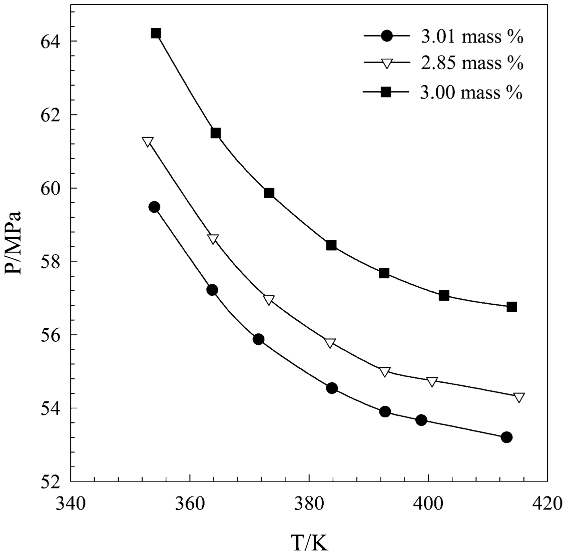


Figure 4. $P-T$ isopleths of cloud points of poly(L-lactide) (1) in HFC-152a (2) at various polymer molecular weights: ●, MW = 80 000; ▽, MW = 110 000; and ■, MW = 230 000.

peated at least three times at each temperature. The reproducibility of the cloud point pressures was within ±0.1 MPa. The temperature of the system was raised in ~10 K increments, and the above procedure was repeated, thus creating a pressure−temperature ($P-T$) cloud point curve at fixed poly(L-lactide) and solvents concentrations. The maximum temperature was set to about 413.2 K to avoid thermal degradation of the O-rings in the apparatus and polymers. After completing the measurement at a given temperature, the cell temperature was stabilized at a new value, and the experimental procedure was repeated.

3. Results and Discussions

The cloud points of poly(L-lactide) were measured at various pressures, temperatures, polymer molecular weights in HCFC-22, HFC-23, HFC-32, HFC-125, HFC-143a, HFC-152a, HFC-227ea, and dimethyl ether (DME) and in a HCFC-22 + CO_2 mixed solvent at various CO_2 concentrations. Poly(L-lactide) was soluble in HCFC-22, HFC-23, HFC-32, HFC-152a, and DME but not in HFC-143a, HFC-125, and HFC-227ea at pressures up to 150 MPa and temperatures up to 413.2 K. Figures 2−4 show $P-T$ isopleths of the cloud points of poly(L-lactide) in HCFC-22 (Figure 2), HFC-23 (Figure 3), and HFC-152a (Figure 4). Three molecular weights of poly(L-lactide) (MW = 80 000, 110 000, and 230 000) were used, although all were ~3 mass % in solution to eliminate any polymer concentration effects. All Figures show the cloud points of poly(L-lactide) according to changing polymer molecular weight. The area above the cloud point is the single-phase region for each system. Below the cloud point is the two-phase region (liquid−liquid phases) in which the solvent and poly(L-lactide) become separated. Figure 2 compares the results of experiment for poly(L-lactide) + HCFC-22 with that of a similar previous study from ref 9. Experimental and literature values agreed sufficiently such that the experimental apparatus was considered to be reliable for measuring the cloud point at high pressures. This system exhibited the characteristics of typical lower critical solution temperature (LCST) phase behavior.

The cloud point increased obviously with the molecular weight of poly(L-lactide) in solvents such as HCFC-22, HFC-23, and HFC-152a in the temperature range from 332.8 K to 416.8 K. However, from Table 2 it can be seen that at a given temperature the cloud point pressure of poly(L-lactide) in DME and HFC-32 was relatively insensitive to its molecular weight in the range of 80 000 to 110 000. The increase in solubility may have been attributed to the higher pressures that necessarily caused the solvent density to increase. These results suggest that poly(L-lactide) solubility is dependent on solvent density for these two systems. Among the five systems, cloud point data for poly(L-lactide) + HCFC-22, poly(L-lactide) + HFC-23, and poly(L-lactide) + DME exhibited lower critical solution temperature (LCST) behavior, and those for poly(L-lactide) + HFC-152a and poly(L-lactide) + HFC-32 showed upper critical solution temperature (UCST) behavior. In all cases, at a given temperature, the cloud point pressure of poly(L-lactide) in these solvents increased with increasing molecular weight of poly(L-lactide). This indicates that poly(L-lactide) becomes less soluble as its molecular weight increases. At constant temperature, the observed changes in the cloud points for the three molecular weights were less than 2 MPa in poly(L-lactide) +

Table 2. Experimental Data for Cloud Points: Poly(L-lactide) (1) in Various Solvents (2)

T/K	P/MPa	T/K	P/MPa	T/K	P/MPa
Poly(L-lactide) (1) in HCFC-22 (2)					
$\mathrm{MW}_1 = 80\,000$	$100\omega_1{}^a = 2.97$	$\mathrm{MW}_1 = 110\,000$	$100\omega_1 = 3.01$	$\mathrm{MW}_1 = 230\,000$	$100\omega_1 = 3.03$
333.4	3.6	333.1	3.7	332.3	3.6
337.5	5.0	341.9	6.6	341.5	6.7
342.1	6.3	353.4	10.3	353.4	10.5
353.0	9.9	363.5	13.4	362.5	13.5
362.9	12.9	372.6	16.2	372.2	16.4
372.5	15.8	380.0	18.3	382.2	19.3
382.3	18.6	392.1	21.6	392.5	22.0
392.4	21.2	401.7	24.0	399.6	23.7
402.1	23.7	410.8	26.1	409.7	26.1
408.8	25.2				
Poly(L-lactide) (1) in HFC-23 (2)					
$\mathrm{MW}_1 = 80\,000$	$100\omega_1 = 2.99$	$\mathrm{MW}_1 = 110\,000$	$100\omega_1 = 2.94$	$\mathrm{MW}_1 = 230\,000$	$100\omega_1 = 2.99$
333.4	93.1	333.1	94.1	333.6	96.1
343.8	95.5	342.9	97.1	343.2	99.0
353.2	98.0	354.3	100.5	353.6	101.9
364.5	100.9	364.5	103.4	363.6	104.6
374.1	103.2	373.4	105.7	374.1	107.4
383.7	105.5	384.0	108.5	382.8	109.5
395.3	107.9	394.3	110.9	393.9	111.9
402.1	109.7	403.3	112.8	403.8	114.0
415.3	112.1	414.3	115.1	413.3	116.0
Poly(L-lactide) (1) in HFC-32 (2)					
$\mathrm{MW}_1 = 80\,000$	$100\omega_1{}^a = 2.95$	$\mathrm{MW}_1 = 110\,000$	$100\omega_1 = 2.94$	$\mathrm{MW}_1 = 230\,000$	$100\omega_1 = 2.97$
344.4	91.6	342.5	93.6	334.6	111.3
354.1	85.6	352.6	86.8	336.8	108.0
363.7	81.8	364.1	82.1	345.0	99.5
373.9	79.5	373.6	80.0	352.8	93.0
383.3	78.1	382.2	78.7	365.0	87.4
393.4	77.2	391.6	77.8	374.5	84.8
402.8	77.0	402.5	77.4	384.2	83.1
412.7	77.0	416.8	77.3	393.7	82.1
				403.1	81.7
				413.1	81.4
Poly(L-lactide) (1) in HFC-152a (2)					
$\mathrm{MW}_1 = 80\,000$	$100\omega_1 = 3.01$	$\mathrm{MW}_1 = 110\,000$	$100\omega_1 = 2.98$	$\mathrm{MW}_1 = 230\,000$	$100\omega_1 = 3.00$
354.1	59.5	352.9	61.3	354.3	64.2
363.8	57.2	363.9	58.6	364.3	61.5
371.5	55.9	373.3	57.0	373.3	59.9
383.9	54.5	383.5	55.8	383.8	58.4
392.7	53.9	392.7	55.0	392.6	57.7
398.8	53.7	400.6	54.8	402.6	57.1
413.1	53.2	415.2	54.3	414.0	56.8
Poly(L-lactide) (1) in DME (2)					
$\mathrm{MW}_1 = 80\,000$	$100\omega_1 = 2.99$	$\mathrm{MW}_1 = 110\,000$	$100\omega_1 = 2.99$	$\mathrm{MW}_1 = 230\,000$	$100\omega_1 = 3.02$
333.1	3.6	331.4	3.1	332.8	6.3
343.1	6.5	343.1	6.6	342.5	9.0
353.2	9.3	353.9	9.3	354.0	12.0
363.5	11.9	362.1	11.5	364.1	14.5
373.2	14.3	374.0	14.5	372.9	16.7
382.8	16.6	382.8	16.5	381.4	18.6
392.6	18.8	392.0	18.5	393.1	21.2
401.2	20.5	402.7	21.0	401.7	23.0
410.4	22.6	412.6	22.8	411.6	24.9

[a] Mass fraction of poly(L-lactide) in solution.

HCFC-22, 3 MPa in poly(L-lactide) + DME, and 5 MPa in poly(L-lactide) + HFCs. Thus, the cloud point is sensitive to change in polymer molecular weight, but the cloud point pressure does not increase linearly with increasing molecular weight. Experimental data for the cloud point of poly(L-lactide) in five solvents are listed in Table 2. In Table 2, the mass fraction of poly(L-lactide), ω_1 in various solvents, is expressed as follows: ω_1 = (mass of poly(L-lactide))/(mass of poly(L-lactide) + mass of solvent); the solvents are HFC-22, HFC-23, HFC-32, HFC-152a, and DME, respectively. The cloud points of poly(L-lactide) in various solvents show a similar tendency with the molecular weight of poly(L-lactide). Therefore, Figure 5 summarizes the cloud point pressures of poly(L-lactide) (MW = 80 000) for each solvent. The maintenance of a single-phase region at pressures as low as 26 MPa and temperatures as high as 413.2 K indicates that both HCFC-22 and DME are effective solvents of poly(L-lactide). In the case of HCFC-22, this is explained by the hydrogen bond between Cl in HCFC-22 and the ester group in poly(L-lactide).[13] HFCs are less effective for dissolving poly(L-lactide), with HFC-152a having the strongest solvent power, HFC-32 the second, and HFC-23 the third. The dipole moments of the HFCs decrease in the same order.

Table 3. Experimental Data of Cloud Points: Poly(L-lactide) (MW = 2000) (1) in (1 − ω_3) HCFC-22 (2) + ω_3CO$_2$ (3)

T/K	P/MPa	T/K	P/MPa	T/K	P/MPa
		poly(L-lactide) (1) in HCFC-22 (2) + CO$_2$(3)			
$\omega_3{}^a = 0.00^b$	$100\omega_1{}^c = 2.88$	$\omega_3 = 18.61$	$100\omega_1{}^c = 2.96$	$\omega_3 = 53.16$	$100\omega_1{}^c = 3.02$
344.4	3.6	322.5	4.4	314.2	20.5
353.1	6.0	333.3	7.8	322.1	24.0
363.4	8.7	343.1	10.8	331.1	27.5
372.7	10.9	353.2	13.7	342.4	31.5
382.1	13.1	363.2	16.4	353.2	35.0
395.7	15.6	373.2	19.8	363.2	38.2
		383.2	22.2	373.2	41.5
		393.2	24.2	383.2	44.1

[a] Mass fraction of CO$_2$ in a mixed solvent of HCFC-22 + CO$_2$ on a polymer-free basis. [b] J. M. Lee's work.[11] [c] Poly(L-lactide) mass fraction of the total.

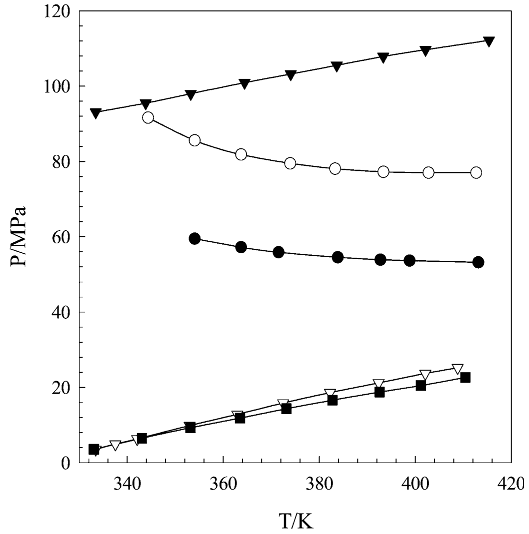


Figure 5. $P-T$ isopleths of cloud points of poly(L-lactide) (MW = 80 000) in various solvents: ■, DME; ▽, HCFC-22; ●, HFC-152a; ○, HFC-32; and ▼, HFC-23.

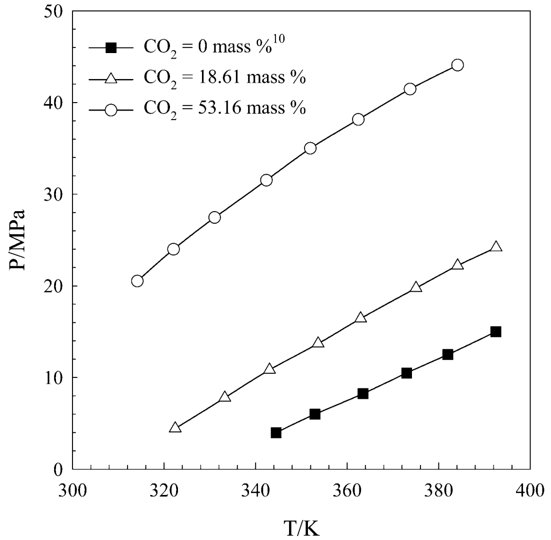


Figure 6. $P-T$ isopleths of cloud points of poly(L-lactide) (MW = 2000) (1) in an HCFC-22 (2) + CO$_2$ (3) mixed solvent (with CO$_2$ mass % on a polymer-free basis).

Figure 6 shows the phase behavior of poly(L-lactide) (MW = 2000) in HCFC-22 + CO$_2$. The concentration of poly(L-lactide) was about 3.0 mass %, and the compositions of CO$_2$ in the HCFC-22 + CO$_2$ mixture were 18.61 mass % and 53.16 mass %.

In Table 3, the mass fraction of CO$_2$ (ω_3) in HCFC-22 is expressed as follows: ω_3 = (mass of CO$_2$)/(mass of CO$_2$ + mass of HCFC-22). The mass fraction of poly(L-lactide) and (ω_1) in HCFC-22 is expressed as follows: ω_1 = (mass of poly(L-lactide))/(mass of poly(L-lactide) + mass of CO$_2$ + mass of HCFC-22). The addition of CO$_2$ to HCFC-22 caused a lowering of the dissolving power of the mixed solvent. Therefore, this can be attributed to the decrease in solvent polarity caused by the increase in CO$_2$ composition in this solvent. The cloud point for the higher CO$_2$ composition was four times that of poly(L-lactide) in pure HCFC-22, suggesting that the nonpolar CO$_2$ could not solubilize the polar polymer. The cloud point of poly(L-lactide) can thus be controlled with CO$_2$ as an antisolvent, and this can be applied to nanoparticle formation processes.

Conclusions

The phase behavior of poly(L-lactide) in HCFC-22, HFC-23, HFC-32, HFC-125, HFC-143a, HFC-152a, HFC-227ea, and dimethyl ether was investigated as a function of polymer molecular weight (2000, 80 000, 110 000, and 230 000). Poly(L-lactide) was soluble in HCFC-22, HFC-23, HFC-32, HFC-152a, and DME but not in HFC-143a, HFC-125, and HFC-227ea at pressures up to 150 MPa and temperatures up to 413.2 K. A variable-volume cell was used to measure the cloud points of poly(L-lactide) (~3.0 mass %). The cloud point data for poly(L-lactide) + HCFC-22, poly(L-lactide) + HFC-23, and poly(L-lactide) + DME exhibited LCST behavior, and those for poly(L-lactide) + HFC-32 and poly(L-lactide) + HFC-152a showed UCST behavior. Poly(L-lactide) was not soluble in HFC-125, HFC-143a, and HFC-227ea, even at pressures as high as 150 MPa and temperatures up to 413.2 K. DME and HCFC-22 better solubilized poly(L-lactide) than any of the HFCs. In the case of the phase behavior of poly(L-lactide) in the HCFC-22 + CO$_2$ mixed solvent, the cloud point pressure of poly(L-lactide) (MW = 2000) at a fixed temperature increased significantly as the CO$_2$ composition in the mixed solvent increased.

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