J. Chem. Eng. Data **2002,** *47,* 575−581

High-Pressure Phase Behavior of Poly(D,L-lactide) in Chlorodifluoromethane, Difluoromethane, Trifluoromethane, and 1,1,1,2-Tetrafluoroethane

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Phase behavior data at temperatures from 303.15 K to 373.15 K and at pressures from 3 MPa to 85 MPa are presented for poly(D,L-lactide) in chlorodifluoromethane, difluoromethane, trifluoromethane, and 1,1,1,2-tetrafluoroethane. The cloud point pressures were measured using a high-pressure equilibrium apparatus equipped with a variable-volume view cell, and were investigated as functions of temperature, polymer concentration, and polymer molecular weight. Chlorodifluoromethane was the solvent with the highest solvent power, while trifluoromethane was the solvent with the lowest solvent power. The solvent power of hydrofluorocarbon solvents of dissolving the poly(D,L-lactide) increased in the order trifluoromethane, difluoromethane, and 1,1,1,2-tetrafluoroethane in proportion to their dipole moments.

Introduction

Supercritical fluid solvents are an attractive alternative to incompressible organic liquid solvents, since they can have liquidlike dissolving power while exhibiting the transport properties of a gas.[1] They have been used in a variety of polymer processes such as extractions and separations, fractionations, and reactions. In particular, supercritical fluid technology has received recent attention in the particle formation of biodegradable polymers, which can be used as controlled drug delivery systems of bioactive agents and drugs in the pharmaceutical industry.[2−4] When producing the polymer particles, it is important to know the location of the phase boundaries for polymer−solvent mixtures.

The selection of supercritical fluid solvents to dissolve polymers is often challenging for processing applications because it is difficult to find a good solvent that will dissolve the polymer at relatively moderate conditions. Carbon dioxide (CO_2) is the favorite solvent in supercritical fluid processes because it has a relatively low critical temperature and pressure and because it is inexpensive, nonflammable, nontoxic, and readily available. However, it is not a good solvent for dissolving polar biodegradable polymers, and thus it has been used as an antisolvent when forming polymer particles by using a supercritical fluid process such as the supercritical antisolvent precipitation method.[5,6] On the other hand, polar solvents such as dichloromethane, chloroform, acetone, chlorodifluoromethane, and hydrofluorocarbons have been known to be good solvents for biodegradable polymers.

Lee et al.[7,8] observed that poly(L-lactide), a biodegradable polymer, was not soluble in nonpolar CO_2 at pressures as high as 80 MPa but was readily soluble in polar chlorodifluoromethane (saturated liquid) at room temperature. They also reported the phase behavior of poly(L-lactide) in supercritical mixtures of chlorodifluoromethane and CO_2. Conway et al.[9] investigated the phase behavior of poly(D,L-lactide) and poly(D,L-lactide-*co*-glycolide) polymers in supercritical CO_2, trifluoromethane, and chlorodifluoromethane. They reported that poly(D,L-lactide) dissolved in CO_2 at pressures near 140 MPa, in trifluoromethane at pressures of 50 to 70 MPa, and in chlorodifluoromethane at pressures of 2 to 10 MPa. It was also reported that as glycolide was added to the backbone of poly(D,L-lactide-*co*-glycolide), the cloud point pressure increased by 5 MPa per mole of glycolide in CO_2, by 2.5 MPa per mole of glycolide in trifluoromethane, and by only 0.25 MPa per mole of glycolide in chlorodifluoromethane.

Since the biodegradable polymers are used in biological applications, the solvents used to process these polymers should be pharmacologically acceptable. In this work, we tested several hydrofluorocarbon solvents in order to find a solvent to dissolve poly(D,L-lactide), as an alternative to organic liquid solvents. The cloud point pressures of poly(D,L-lactide) in chlorodifluoromethane, trifluoromethane, difluoromethane, and 1,1,1,2-tetrafluoroethane were measured by using a high-pressure variable-volume view cell apparatus and were characterized as functions of temperature, polymer concentration, and polymer molecular weight.

The physical properties of the solvents studied in this work are shown in Table 1, where μ is the permanent dipole moment and α is the molecular polarizability. The solvent names in parentheses in Table 1 are designations for halocarbons used by the refrigeration industry. Hydrofluorocarbon solvents are highly volatile and nontoxic[13,14] and typically have lower critical temperatures than the organic liquid solvents mentioned above. A solvent will dissolve a polymer if it can interact favorably with the

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10.1021/je010222s CCC: $22.00

Table 1. Physical Properties of the Solvents Used in This Work[a]

name	formula	MW	T_c/K	P_c/MPa	μ/D	$10^{24}\alpha$/cm^3
chlorodifluoromethane (HCFC-22)	$CHClF_2$	86.469	369.30	4.990	1.458	6.38[b]
trifluoromethane (HFC-23)	CHF_3	70.013	299.07	4.836	1.649	3.52[b]
difluoromethane (HFC-32)	CH_2F_2	52.023	351.26	5.782	1.978	2.48[c]
1,1,1,2-tetrafluoroethane (HFC-134a)	CF_3CH_2F	102.031	374.21	4.059	2.058	4.38[c]

[a] T_c, P_c, and μ are obtained from the REFPROP database.[10] [b] The values are obtained from the CRC handbook.[11] [c] The values are estimated from the Miller and Savchik method.[12]

polymer through intermolecular forces, such as hydrogen bonding and dipole−dipole interactions.[1] The solvents listed in Table 1 are polar solvents with high dipole moments. Their polar dipole moments are expected to interact favorably with the polar moment of the ester group in the poly(D,L-lactide) polymer. In this work, the effect of the dipole moment contribution of the solvents on the cloud point behavior was seen by comparing the cloud point curves for the solvents with different dipole moments. The phase behavior data produced in this work will be useful for establishing operating conditions in the particle formation of the poly(D,L-lactide) polymer by supercritical fluid processing.

Experimental Section

Materials. Poly(D,L-lactide) is a biodegradable amorphous polymer that is currently being used as a reservoir device for controlled drug delivery in pharmaceutical industries. The poly(D,L-lactides) (Resomer R104, MW = 2000; Resomer R203, MW = 30 000) were purchased from Boehringer Ingelheim Chemicals, Inc. (Ingelheim, Germany). The molecular weights, provided by the suppliers, are the viscosity average molecular weights derived from the intrinsic viscosity and the Mark−Houwink equation.

The solvents studied in this work are listed in Table 1. HCFC-22 (99.99% purity) was purchased from Solvay Fluorides Inc. (Greenwich, CT), HFC-134a (99.95% purity) was purchased from Allied Signal (Baton Rouge, LA), and HFC-32 (99.9% purity) and HFC-23 (99.9% purity) were purchased from Ulsan Chemical Co. (Ulsan, Korea). They were used as received without further purification.

Apparatus and Procedure. The cloud point behavior of poly(D,L-lactide) in four different solvents was measured using a high-pressure apparatus equipped with a variable-volume view cell. A detailed description of the experimental apparatus and procedure is given in our previous publications.[7,8] 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 video monitor, and a magnetic stirring system. The view cell has the dimensions 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 high-precision pressure gauge (Dresser Heise model CC-12-G−A-02B, ±0.05 MPa accuracy, ±0.01 MPa resolution) and a piezoresistive pressure transmitter (Keller Druckmesstechnik, type PA-25HTC/8585-1000). The system temperature is measured to within ±0.1 °C with an RTD (Pt-100 Ω) probe inserted into the cell.

The experiment for measuring a cloud point was performed by the following procedure. To remove any entrapped air present in the cell, the cell was purged with the solvent gas used in the experiment. A certain amount of the polymer was loaded into the cell. The amount of the polymer loaded into the cell was determined using a sensitive balance (AND model HM-300) to within ±0.1 mg. A solvent was then charged into the cell using a high-pressure sample cylinder. The amount of the solvent charged into the cell was determined by weighing the sample cylinder of the solvent before and after charging it into the cell using a balance (Precisa model 1212 M SCS) with an accuracy of ±1 mg. Approximately 7 to 9 g of the solvent was charged into the cell for each run.

The solution in the cell was compressed by moving the piston located within the cell using the pressure generator, and it was agitated with the magnetic stirrer until it became a single phase. The cell was then heated to the desired temperature. Once the system reached thermal equilibrium and the solution was maintained as a single phase, the pressure was then slowly reduced until the solution became cloudy. Enough time was allowed to ensure thermal equilibrium during the pressure reduction. The pressure was reduced very slowly when approaching the cloud point pressure. At a fixed temperature, the cloud point was defined as the pressure at which it was no longer possible to visually observe the stirring bar. For obtaining consistent measurements, every measurement was repeated at least twice at each temperature. The reproducibility of the cloud point pressures was within ±0.2 MPa. The system temperature was raised in about 10 K increments, and the above procedure was repeated, thus creating a pressure−temperature cloud point curve at a fixed polymer concentration.

Table 2. Experimental Data of Cloud Points of Poly(D,L-lactide) (1) in HCFC-22 (2)

MW of poly(D,L-lactide)	$100w_1$	T/K	P/MPa
30 000	0.50	343.05	4.23
		352.85	7.13
		362.85	9.81
		373.05	12.45
		382.55	14.85
30 000	2.87	338.25	3.35
		343.65	5.03
		352.75	7.71
		362.75	10.55
		372.95	13.13
		382.75	15.55
30 000	4.77	338.15	3.25
		343.25	4.81
		352.95	7.68
		362.85	10.53
		372.95	13.25
		382.25	15.63
30 000	7.84	338.15	3.09
		342.75	4.50
		352.85	7.45
		363.35	10.55
		372.85	13.17
		382.05	15.45
30 000	14.68	339.95	3.26
		343.25	4.29
		352.85	7.20
		363.35	10.25
		373.15	12.84
		382.75	15.30
2 000	2.74	342.85	3.61
		353.15	6.43
		362.35	8.89
		372.95	11.50
		383.05	13.84

Table 3. Experimental Data of Cloud Points of Poly(D,L-lactide) (1) in HFC-23 (2)

MW of poly(D,L-lactide)	$100w_1$	T/K	P/MPa
30 000	0.55	303.75	49.05
		313.25	53.75
		323.65	58.25
		333.15	63.25
		342.85	67.45
		353.15	71.85
		363.25	75.35
		372.85	78.25
30 000	3.10	303.95	53.75
		313.25	58.55
		323.25	63.35
		333.15	67.95
		343.15	72.35
		353.55	76.55
		363.35	80.25
		372.85	83.45
30 000	7.93	304.05	55.45
		313.25	60.05
		323.55	64.95
		333.35	69.45
		343.55	73.95
		353.25	77.75
		363.15	81.35
		373.35	84.75
30 000	13.17	303.65	54.15
		313.55	59.15
		323.75	64.05
		333.15	68.25
		343.45	72.65
		353.05	76.55
		363.15	80.15
		372.95	83.45
2 000	3.06	306.05	46.05
		313.25	48.75
		323.35	52.35
		332.75	55.75
		342.65	59.05
		352.55	62.05
		363.05	64.85
		373.85	67.35

Table 4. Experimental Data of Cloud Points of Poly(D,L-lactide) (1) in HFC-32 (2)

MW of poly(D,L-lactide)	$100w_1$	T/K	P/MPa
30 000	0.47	305.05	49.65
		311.95	48.25
		323.85	47.35
		333.75	48.05
		343.55	48.55
		352.85	49.25
		362.95	49.95
		372.95	50.75
30 000	1.64	303.55	54.75
		313.15	52.55
		323.25	51.65
		333.55	51.55
		342.65	52.05
		353.15	52.95
		363.05	53.85
		372.95	54.75
30 000	2.78	304.85	55.05
		313.55	53.15
		323.85	52.05
		334.45	52.15
		343.35	52.55
		352.95	53.45
		363.45	54.55
		373.05	55.45
30 000	4.80	304.15	55.55
		313.25	53.05
		323.75	52.05
		333.95	52.05
		343.35	52.55
		353.35	53.55
		363.05	54.45
		373.05	55.35
30 000	9.08	304.35	52.85
		312.85	50.85
		323.15	50.05
		334.75	50.25
		342.85	50.75
		352.85	51.65
		363.35	52.85
		375.55	54.25
30 000	15.00	303.45	49.35
		313.45	47.65
		323.15	47.25
		333.45	47.75
		342.85	48.55
		352.85	49.65
		362.95	50.95
		372.75	52.15
2 000	3.22	304.45	33.00
		315.55	33.00
		322.75	33.45
		333.25	34.55
		342.95	36.00
		353.15	37.65
		362.85	39.25
		372.75	40.90

Results and Discussion

The cloud point pressures of poly(D,L-lactide) in HCFC-22, HFC-23, HFC-32, and HFC-134a were investigated as functions of temperature, polymer concentration, and polymer molecular weight. All the experimental cloud point data are given in Tables 2−5, where w_1 is the mass fraction of poly(D,L-lactide) in solution. Figure 1 shows the $P-T$ isopleths of the cloud points of poly(D,L-lactide) (MW = 30 000) in HCFC-22 at various polymer concentrations up to about 15 mass %. The saturation curve of HCFC-22, which is obtained from Daubert and Danner,[15] is also shown along with the cloud point data. Above each cloud point is the single-phase region, and below the point is the two-phase region. This system exhibited the characteristics of a typical lower critical solution temperature (LCST) phase behavior. The cloud point curves had similar slopes for all the polymer concentrations.

The cloud point pressure was as low as about 15 MPa, even at 383 K, indicating that HCFC-22 was an excellent solvent to dissolve the poly(D,L-lactide). HCFC-22 can form hydrogen bonds with base molecules, but it does not self-associate.[1,9] Thus, the enhanced solvent power of HCFC-22 is attributed to the hydrogen bonding of the hydrogen atom in HCFC-22 with the ester group in the poly(D,L-lactide). The effect of the hydrogen bonding is evident with the HCFC-22 cloud point curves, which are situated at very low pressures. Several other studies[16−18] have also shown that HCFC-22 is an excellent solvent for polar polymers that can cross-associate with the acidic hydrogen in this solvent.

The cloud point curves intersected the HCFC-22 saturation curve at the lower critical end points (LCEPs), at which the fluid to liquid−liquid phase transition ended. The fluid to liquid−vapor phase transitions occurred on the HCFC-22 saturation curve at temperatures below the LCEP. The LCEPs for the poly(D,L-lactide) (MW = 30 000) + HCFC-22 system were observed around 337 K and 2.5 MPa, as shown in Figure 1.

The $P-T$ isopleths of the cloud points given in Figure 1 were further characterized by drawing a pressure−polymer concentration ($P-w_1$) diagram, which was obtained by fitting the cloud point curves at different polymer concentrations with polynomial equations and then by determin-

Table 5. Experimental Data of Cloud Points of Poly(D,L-lactide) (1) in HFC-134a (2)

MW of poly(D,L-lactide)	$100w_1$	T/K	P/MPa
30 000	0.54	302.95	21.75
		313.45	24.45
		324.25	26.95
		333.85	29.35
		343.15	31.55
		352.85	33.35
		362.75	34.95
		372.95	36.85
30 000	3.04	304.05	24.95
		314.75	27.37
		323.75	29.55
		333.25	31.75
		343.15	34.03
		353.25	36.15
		363.35	38.38
		372.95	40.15
30 000	5.26	303.65	25.24
		313.25	27.30
		323.85	29.70
		333.35	31.95
		342.95	34.15
		352.85	36.25
		363.05	38.35
		373.05	40.12
30 000	8.55	304.95	23.85
		313.35	25.80
		323.75	28.23
		333.35	30.50
		343.35	32.85
		352.75	34.95
		363.15	37.09
		373.05	38.91
30 000	15.05	303.75	21.63
		313.85	24.25
		323.85	26.81
		333.45	29.13
		343.15	31.41
		352.95	33.60
		363.25	35.71
		373.25	37.60
2 000	2.92	306.75	19.18
		315.05	20.43
		325.05	21.95
		334.65	23.65
		346.15	25.60
		353.65	26.90
		363.85	28.50
		373.45	30.05

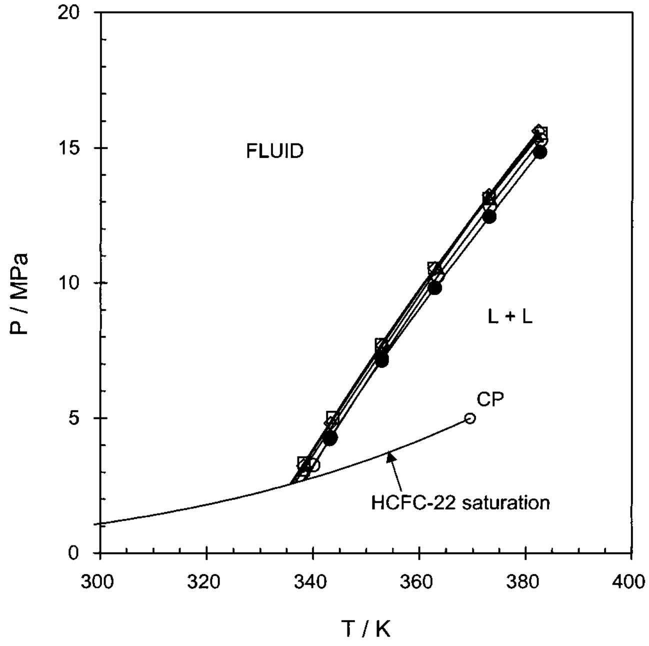

Figure 1. $P-T$ isopleths of cloud points of poly(D,L-lactide) (MW = 30 000) in HCFC-22 at various polymer concentrations: ●, 0.50 mass %; □, 2.87 mass %; ◇, 4.77 mass %; △, 7.84 mass %; ○, 14.68 mass %.

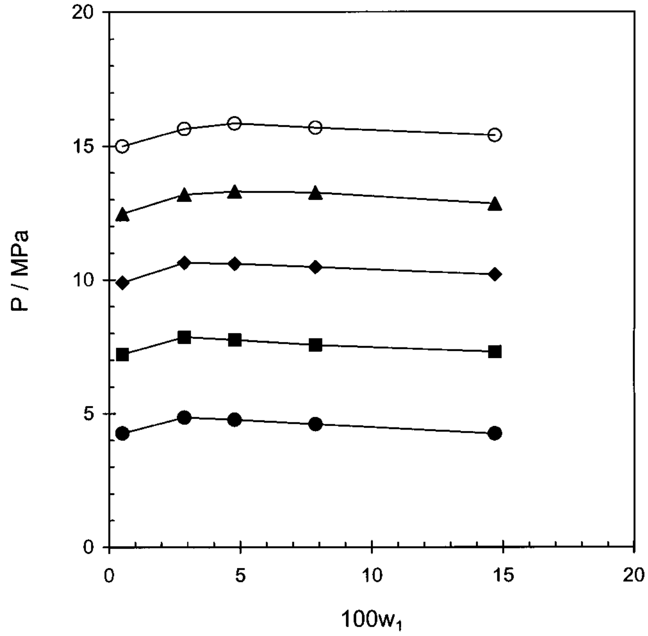

Figure 2. Pressure−polymer concentration isotherms for poly(D,L-lactide) (MW = 30 000) in HCFC-22 at various temperatures: ●, 343.15 K; ■, 353.15 K; ◆, 363.15 K; ▲, 373.15 K; ○, 383.15 K.

ing the pressures corresponding to the desired temperatures from the curve fits. Figure 2 shows the $P-w_1$ isotherms for the poly(D,L-lactide) (MW = 30 000) + HCFC-22 system. The cloud point pressures did not vary much with the polymer concentration; the isotherms were almost flat. As shown in each isotherm, the maximum cloud point pressure, that corresponds to an upper critical solution pressure, was observed at the polymer concentration around 3 or 5 mass %.

The cloud point data of poly(D,L-lactide) in HFC-23 and HFC-134a are given in Tables 3 and 4, respectively. The cloud point pressure increased with increasing temperature, indicating that these systems also exhibited the characteristics of an LCST phase behavior. Figures 3 and 4 show the $P-w_1$ isotherms of the poly(D,L-lactide) (MW = 30 000) in HFC-23 and HFC-134a, respectively. These figures were obtained by analyzing the $P-T$ data as a function of polymer concentration at various temperatures. The maximum cloud point pressures were observed at the polymer concentration around 8 mass % for the poly(D,L-lactide) + HFC-23 system, while they were observed at the polymer concentration between 3 and 5 mass % for the poly(D,L-lactide) + HFC-134a system. Although a lower cloud point pressure was obtained at a higher polymer concentration, a longer time was required to dissolve the polymer in the solvent.

Figure 5 shows the $P-T$ isopleths of the cloud points of poly(D,L-lactide) (MW = 30 000) in HFC-32 at various polymer concentrations up to 15 mass %. The cloud point curves can be interpreted as a combination of LCST-type transitions at higher temperatures and upper critical solution temperature (UCST)-type transitions at lower temperatures. The slopes of the cloud point curves were negative at temperatures below about 320 K. A minimum

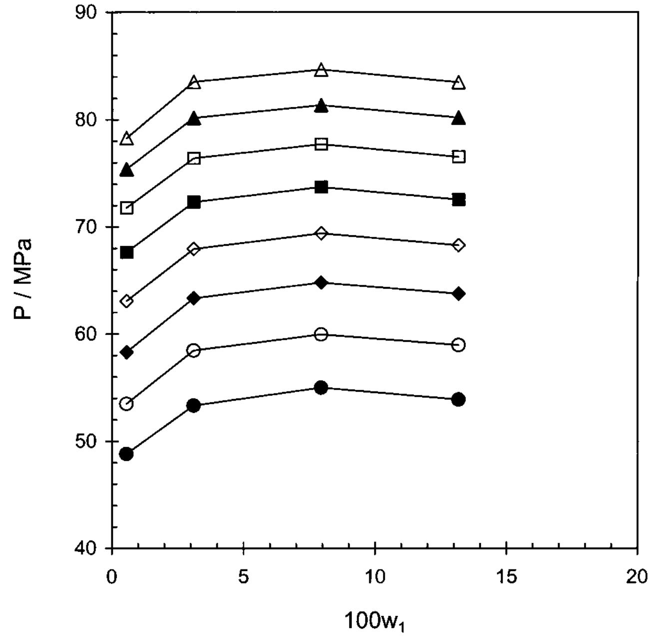

Figure 3. Pressure–polymer concentration isotherms for poly(D,L-lactide) (MW = 30 000) in HFC-23 at various temperatures: ●, 303.15 K; ○, 313.15 K; ◆, 323.15 K; ◇, 333.15 K; ■, 343.15 K; □, 353.15 K; ▲, 363.15 K; △, 373.15 K.

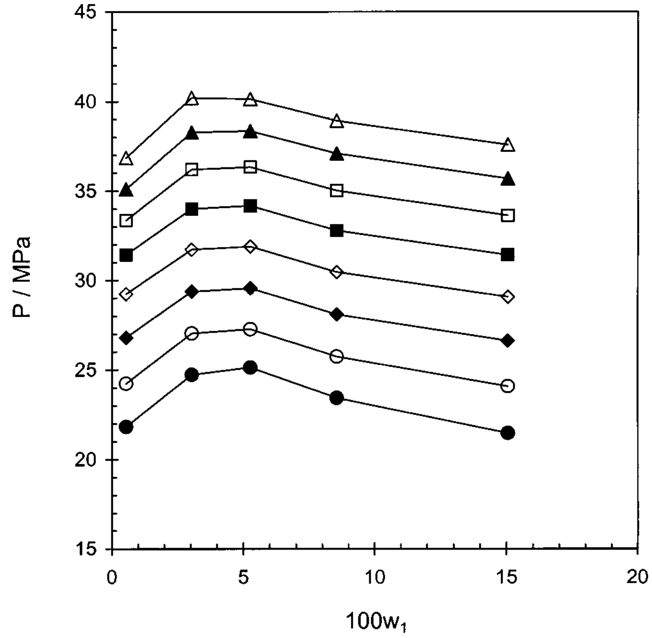

Figure 4. Pressure–polymer concentration isotherms for poly(D,L-lactide) (MW = 30 000) in HFC-134a at various temperatures: ●, 303.15 K; ○, 313.15 K; ◆, 323.15 K; ◇, 333.15 K; ■, 343.15 K; □, 353.15 K; ▲, 363.15 K; △, 373.15 K.

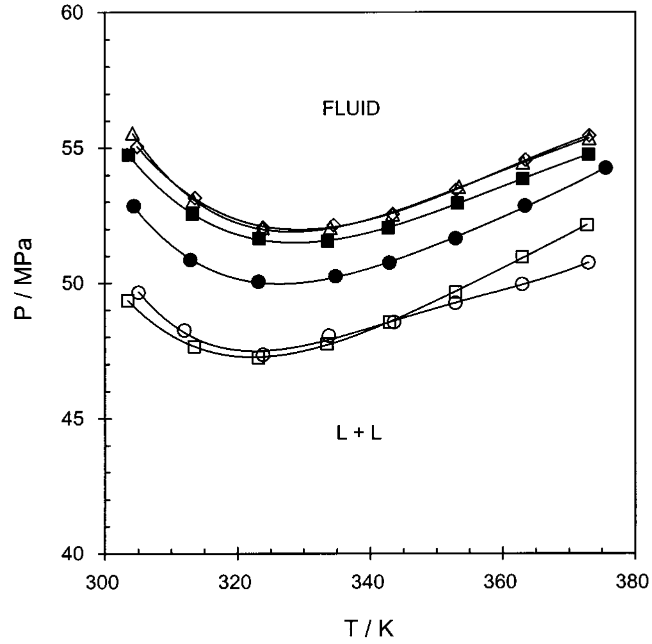

Figure 5. $P-T$ isopleths of cloud points of poly(D,L-lactide) (MW = 30 000) in HCFC-32 at various polymer concentrations: ○, 0.47 mass %; ■, 1.64 mass %; ◇, 2.78 mass %; △, 4.80 mass %; ●, 9.08 mass %; □, 15.00 mass %.

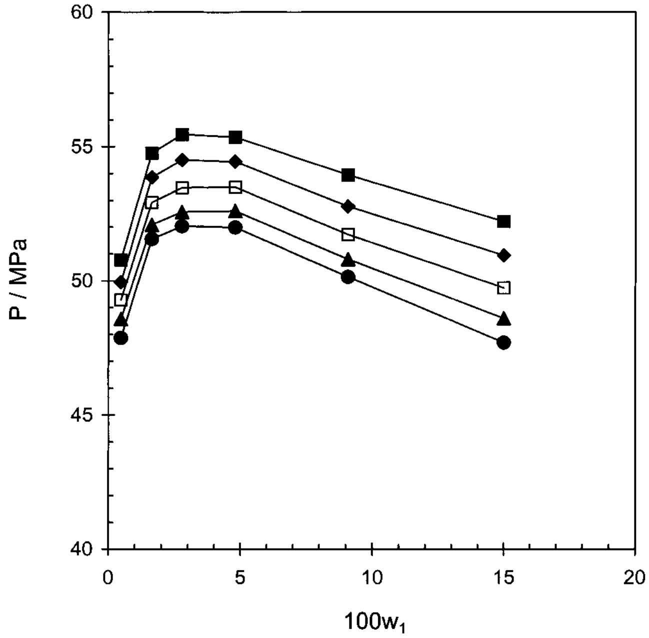

Figure 6. Pressure–polymer concentration isotherms for poly(D,L-lactide) (MW = 30 000) in HFC-32 at various temperatures: ●, 333.15 K; ▲, 343.15 K; □, 353.15 K; ◆, 363.15 K; ■, 373.15 K.

value of the cloud point pressure was measured at a temperature between 320 K and 330 K, depending upon the polymer concentration in solution. The switch from a positive to a negative slope suggests that the interchange energy, which is a measure of polymer–solvent interactions relative to polymer–polymer and solvent–solvent interactions, is weighted more toward polymer–polymer interactions rather than cross interactions.[9] A cloud point curve with a negative slope also clearly shows that increasing the system pressure does not help in obtaining a single phase as the system temperature is lowered. Figure 6 illustrates the $P-w_1$ isotherms for the poly(D,L-lactide) (MW = 30 000) + HFC-32 system, obtained from the $P-T$ curves in Figure 5. As the polymer concentration increased, the cloud point pressure increased sharply, reached a maximum at the polymer concentration of 3 to 5 mass %, and then decreased gradually.

Tables 2–5 also show the effect of polymer molecular weight on the cloud points of poly(D,L-lactide) in four different solvents studied in this work. As the polymer molecular weight increased, the cloud point pressure increased. In other words, increasing the polymer molecular weight reduced the single-phase region. This indicates that poly(D,L-lactide) becomes less soluble in solvents as its molecular weight increases, which is consistent with the

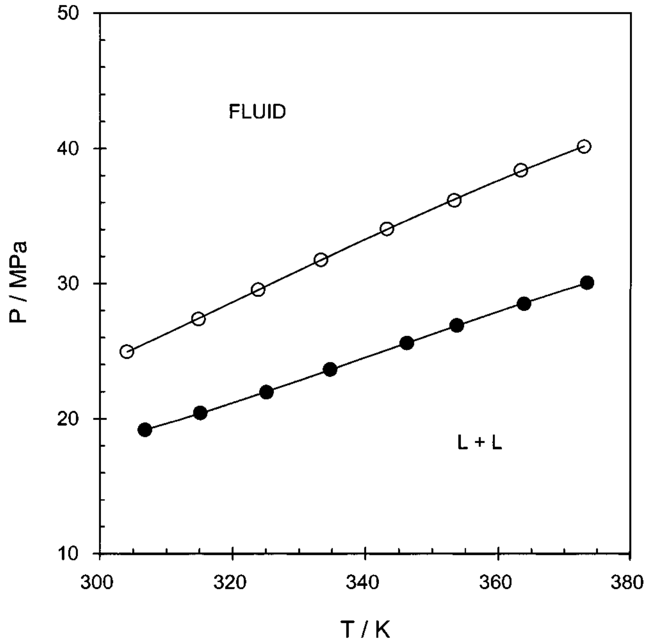

Figure 7. Effect of polymer molecular weight on cloud points of poly(D,L-lactide) in HFC-134a: ●, MW = 2000; ○, MW = 30 000.

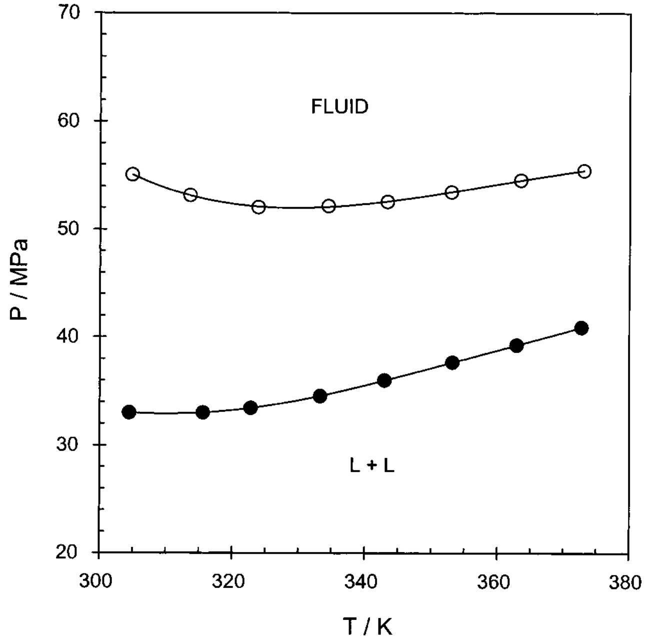

Figure 8. Effect of polymer molecular weight on cloud points of poly(D,L-lactide) in HFC-32: ●, MW = 2000; ○, MW = 30 000.

results of other polymer−solvent systems.[1,7,9] The difference between the cloud point pressures of the poly(D,L-lactides) of two different molecular weights in HCFC-22 was not as big as that in the other three HFC solvents. HCFC-22 was such a good solvent for the poly(D,L-lactide) that the increase of the polymer molecular weight did not have a big influence on the cloud point pressures. As graphical illustrations, Figures 7 and 8 show the effect of the polymer molecular weight on the cloud points for the poly(D,L-lactide) + HFC-134a and poly(D,L-lactide) + HFC-32 systems, respectively. Particularly, as shown in Figure 8, the cloud point curve for the poly(D,L-lactide) + HFC-32 system was shifted from LCST to U-LCST phase behavior with increasing polymer molecular weight in the given temperature range.

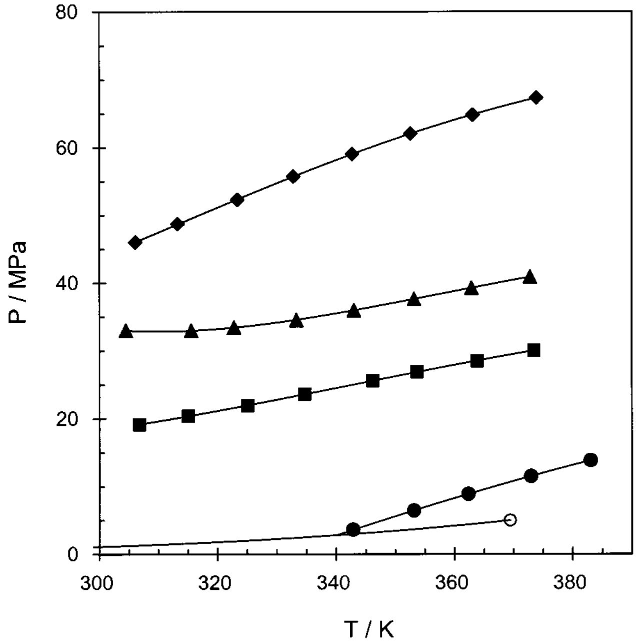

Figure 9. Comparison of solvent power of dissolving poly(D,L-lactide) (MW = 2000): ●, HCFC-22; ■, HFC-134a; ▲, HFC-32; ◆, HFC-23.

A solvent will dissolve a polymer when it can interact favorably with the polymer through intermolecular forces, such as hydrogen bonding and dipole−dipole interactions. The difference in the phase behavior depends on the strength of the intermolecular interactions between the components in the solution. The cloud point curves in Figure 9 show the differences between the solvent power of HCFC-22, HFC-32, HFC-23, and HFC-134a for the poly(D,L-lactide) (MW = 2000). The cloud point curves for each system show that HCFC-22 has the highest solvent power, while HFC-23 has the lowest solvent power. The enhanced solvent power of HCFC-22 relative to HFC solvents can be attributed to the stronger hydrogen bonding between HCFC-22 and poly(D,L-lactide). Because hydrogen bonding between HCFC-22 and poly(D,L-lactide) is very strong even at 383 K, HCFC-22 is indeed a good solvent for the poly(D,L-lactide) even at modest pressures of less than 14 MPa. HCFC-22 has the largest molecular polarizability among the solvents studied in this work, as shown in Table 1. This can probably make the hydrogen atom in HCFC-22 more acidic than that in other solvents and thus make HCFC-22 a better solvent.

The polar dipole moment of the HFC solvents is expected to interact favorably with the polar moment of the ester group in poly(D,L-lactide). The effect of the dipole moment contribution of the solvent on the cloud point behavior can be seen by comparing the cloud point curves for solvents of different dipole moments. As given in Table 1, the dipole moments of the HFC solvents increase in the order HFC-23, HFC-32, and HFC-134a. Figure 9 shows that the cloud point pressure decreases as the dipole moment of the HFC solvent increases, when compared at the same temperature. In other words, the solvent power of the HFC solvents of dissolving the poly(D,L-lactide) polymer increased in proportion to their dipole moments.

Conclusions

The cloud point experiments for the poly(D,L-lactide) polymer exhibited LCST phase behavior in HCFC-22, HFC-23, and HFC-134a, and U-LCST phase behavior in HFC-

32. The pressure–polymer concentration isotherm for each system showed that the maximum pressure was observed at a polymer concentration between 3 and 8 mass %, depending upon the system. The cloud point pressure increased with increasing molecular weight of the poly(D,L-lactide). It was observed that HCFC-22 had the highest solvent power, while HFC-23 had the lowest solvent power. The solvent power of the HFC solvents of dissolving the poly(D,L-lactide) increased in the order HFC-23, HFC-32, and HFC-134a in proportion to their dipole moments.

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Received for review August 2, 2001. Accepted February 24, 2002. This work was supported by Korea Research Foundation Grant KRF-99-003-E00438.

JE010222S