

## Solvent Power Dependence of Phase Behavior of Biodegradable Polymers in High-Pressure Hydrofluorocarbons

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**Abstract**—Phase behavior data at temperatures from 30 °C to 100 °C and at pressures from 30 bar to 850 bar are presented for poly(D,L-lactide) in hydrofluorocarbon solvents: difluoromethane (HFC-32), trifluoromethane (HFC-23), and 1,1,1,2-tetrafluoroethane (HFC-134a). The cloud point pressures were measured by 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. The solvent power of hydrofluorocarbon 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.

Key words: Cloud Point, Biodegradable Polymer, Poly(D,L-lactide), Difluoromethane (HFC-32), Trifluoromethane (HFC-23), 1,1,1,2-Tetrafluoroethane (HFC-134a)

### 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 [McHugh and Krukoni, 1994]. 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 [Bodmeier et al., 1995; Kim et al., 1996; Benedetti, 1997]. 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<sub>2</sub>) 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 [Reverchon, 1999; Reverchon et al., 2000; Song et al., 2002]. On the other hand, polar solvents such as dichloromethane, chloroform, acetone, and chlorodifluoromethane have been known to be good solvents for biodegradable polymers.

Lee et al. [2000a, b] observed that poly(L-lactide), a biodegradable polymer, was not soluble in nonpolar CO<sub>2</sub> at pressures as high as 800 bar 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<sub>2</sub>. Conway et al. [2001] investigated the phase behavior of poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) polymers in supercritical CO<sub>2</sub>, trifluoromethane, and chlorodifluoromethane. They reported that poly(D,L-lactide) dissolved in CO<sub>2</sub> at pressures near 1,400 bar, in trifluoromethane at pressures of 500 to 700 bar, and in chlorodifluoromethane at pressures of 20 to 100 bar. 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 50 bar per mole of glycolide in CO<sub>2</sub>, by 25 bar per mole of glycolide in trifluoromethane, and by only 2.5 bar 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 three hydrofluorocarbon (HFC) 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 the poly(D,L-lactide) in trifluoromethane (HFC-23), difluoromethane (HFC-32), and 1,1,1,2-tetrafluoroethane (HFC-134a) 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  $\mu$  is the permanent dipole moment and  $\alpha$  is the molecular polarizability. HFC solvents are highly volatile and nontoxic, 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 polymer through intermolecular forces, such as hydrogen bonding and dipole-dipole interactions [McHugh and Krukoni, 1994]. 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 con-

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<sup>‡</sup>Dedicated to Dr. Youn Yong Lee on the occasion of his retirement from Korea Institute of Science and Technology.

**Table 1. Physical properties of the hydrofluorocarbon solvents used in this work\***

Name	Formula	M.W.	T <sub>c</sub> (°C)	P <sub>c</sub> (bar)	ρ <sub>c</sub> (kg/m <sup>3</sup> )	μ (debye)	α × 10 <sup>24</sup> (cm <sup>3</sup> )
Trifluoromethane (HFC-23)	CHF <sub>3</sub>	70.01	25.92	48.36	525.0	1.649	3.52**
Difluoromethane (HFC-32)	CH <sub>2</sub> F <sub>2</sub>	52.02	78.11	57.82	424.0	1.978	2.48***
1,1,1,2-Tetrafluoroethane (HFC-134a)	CF <sub>3</sub> CH <sub>2</sub> F	102.03	101.06	40.59	511.9	2.058	4.38***

\*T<sub>c</sub>, P<sub>c</sub>, ρ<sub>c</sub>, and μ are obtained from the REFPROP database [McLinden et al., 1998].

\*\*Obtained from the CRC handbook [Lide, 1995].

\*\*\*Estimated from the method by Miller and Savchik [1979].

**Table 2. Experimental data of cloud points of poly(D,L-lactide) ( $\bar{M}_n=30,000$ ) in HFC solvents**

Polymer concentration (wt%)	Temperature (°C)	Pressure (bar)	Polymer concentration (wt%)	Temperature (°C)	Pressure (bar)
HFC-23					
0.55	30.6	490.5	7.93	30.9	554.5
	40.1	537.5		40.1	600.5
	50.5	582.5		50.4	649.5
	60.0	632.5		60.2	694.5
	69.7	674.5		70.4	739.5
	80.0	718.5		80.1	777.5
	90.1	753.5		90.0	813.5
3.10	99.7	782.5	13.17	100.2	847.5
	30.8	537.5		30.5	541.5
	40.1	585.5		40.4	591.5
	50.1	633.5		50.6	640.5
	60.0	679.5		60.0	682.5
	70.0	723.5		70.3	726.5
	80.4	765.5		79.9	765.5
	90.2	802.5		90.0	801.5
	99.7	834.5		99.8	834.5
	HFC-32				
0.47	31.9	496.5	4.80	31.0	555.5
	38.8	482.5		40.1	530.5
	50.7	473.5		50.6	520.5
	60.6	480.5		60.8	520.5
	70.4	485.5		70.2	525.5
	79.7	492.5		80.2	535.5
	89.8	499.5		89.9	544.5
	99.8	507.5		99.9	553.5
1.64	30.4	547.5	9.08	31.2	528.5
	40.0	525.5		39.7	508.5
	50.1	516.5		50.0	500.5
	60.4	515.5		61.6	502.5
	69.5	520.5		69.7	507.5
	80.0	529.5		79.7	516.5
	89.9	538.5		90.2	528.5
	99.8	547.5		102.4	542.5
2.78	31.7	550.5	15.00	30.3	493.5
	40.4	531.5		40.3	476.5
	50.7	520.5		50.0	472.5
	61.3	521.5		60.3	477.5
	70.2	525.5		69.7	485.5
	79.8	534.5		79.7	496.5
	90.3	545.5		89.8	509.5
	99.9	554.5		99.6	521.5

ditions in the particle formation of the poly(D,L-lactide) polymer by supercritical fluid processing.

## EXPERIMENTAL

### 1. Materials

The polymer sample used in this work is poly(D,L-lactide), an amorphous biodegradable polymer that is currently being used as a reservoir device for controlled drug delivery in pharmaceutical industries. The poly(D,L-lactide) is a racemic mixture of poly(L-lactide) and poly(D-lactide). The poly(D,L-lactide)s (Resomer R104,  $\bar{M}_v=2,000$ ; Resomer R203,  $\bar{M}_v=30,000$ ) were purchased from Boehringer Ingelheim Chemicals, Inc. (Ingelheim, Germany).  $\bar{M}_v$ , provided by the supplier, is the viscosity-average molecular weight of the polymer derived from the intrinsic viscosity and the Mark-Houwink equation.

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

### 2. Apparatus and Procedure

The cloud point behavior of poly(D,L-lactide) in three different solvents was measured by using a high-pressure apparatus equipped with a variable-volume view cell. A detailed description of the experimental apparatus and procedure is given elsewhere [Lee et al., 2000a, b; Byun and Park, 2002; Lee and Kim, 2002; Lee and McHugh, 2002]. 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<sup>3</sup>. The system pressure is measured with a high-precision pressure gauge (Dresser Heise model CC-12-G-A-02B,  $\pm 0.5$  bar accuracy,  $\pm 0.1$  bar resolution) and a piezoresistive pressure transmitter (Keller Druckmesstechnik, type PA-25HTC/8585-1000). The system temperature is measured to within  $\pm 0.1$  °C with an RTD (Pt-100  $\Omega$ ) 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 with a sensitive balance (AND model HM-300) to within  $\pm 0.1$  mg. A solvent was then charged into the cell by means of 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 with a balance (Precisa model 1212 M SCS) with an accuracy of  $\pm 1$  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 by 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

Table 2. Continued

Polymer concentration (wt%)	Temperature (°C)	Pressure (bar)	Polymer concentration (wt%)	Temperature (°C)	Pressure (bar)
HFC-134a					
0.54	29.8	217.5	8.55	31.8	238.5
	40.3	244.5		40.2	258.0
	51.1	269.5		50.6	282.3
	60.7	293.5		60.2	305.0
	70.0	315.5		70.2	328.5
	79.7	333.5		79.6	349.5
	89.6	349.5		90.0	370.9
	99.8	368.5		99.9	389.1
3.04	30.9	249.5	15.05	30.6	216.3
	41.6	273.7		40.7	242.5
	50.6	295.5		50.7	268.1
	60.1	317.5		60.3	291.3
	70.0	340.3		70.0	314.1
	80.1	361.5		79.8	336.0
	90.2	383.8		90.1	357.1
	99.8	401.5		100.1	376.0
5.26	30.5	252.4			
	40.1	273.0			
	50.7	297.0			
	60.2	319.5			
	69.8	341.5			
	79.7	362.5			
	89.9	383.5			
	99.9	401.2			

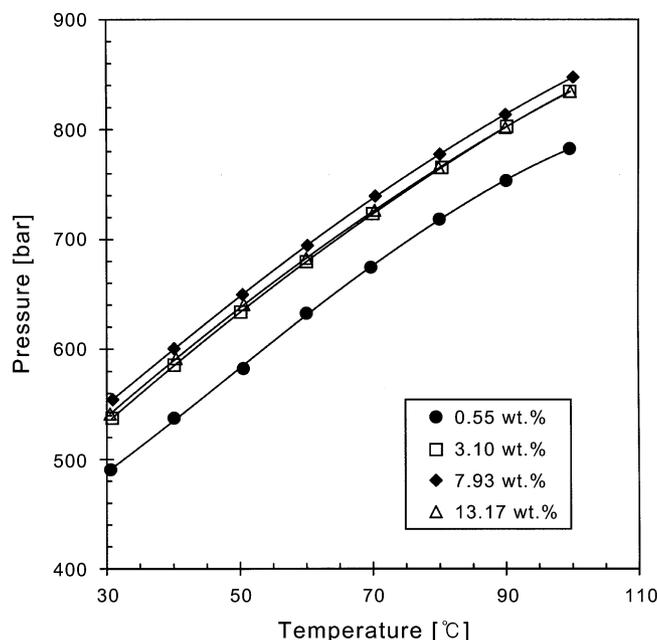
single phase, the pressure was then slowly reduced until the solution became cloudy. Enough time was allowed to ensure thermal equilibrium during the pressure reduction. The pressure was reduced very slowly when approaching the cloud point pressure. At a fixed temperature, the cloud point was defined 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  $\pm 2$  bar. The system temperature was raised in about  $10^\circ\text{C}$  increments, and the above procedure was repeated, thus creating a pressure-temperature cloud point curve at a fixed polymer concentration.

## RESULTS AND DISCUSSION

The cloud point pressures of poly(D,L-lactide) in 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 and 3. Fig. 1 shows the P-T isopleths of the cloud points of poly(D,L-lactide) ( $\bar{M}_v=30,000$ ) in HFC-23 at various polymer concentrations up to about 13 wt%. Above each cloud point is the single-phase region, and below the point is the two-phase region. The cloud point pressure increased with increasing temperature, indicating that 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.

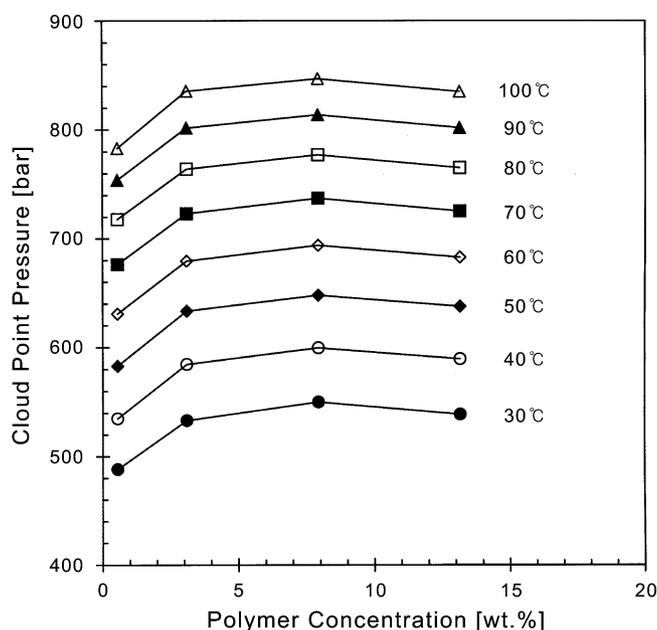
**Table 3. Experimental data of cloud points of poly(D,L-lactide) ( $\bar{M}_v=2,000$ ) in HFC solvents**

HFC solvent	Polymer concentration (wt%)	Temperature ( $^\circ\text{C}$ )	Pressure (bar)		
HFC-23	3.06	32.9	460.5		
		40.1	487.5		
		50.2	523.5		
		59.6	557.5		
		69.5	590.5		
		79.4	620.5		
		89.9	648.5		
		100.7	673.5		
		HFC-32	3.22	31.3	330.0
				42.4	330.0
49.6	334.5				
60.1	345.5				
69.8	360.0				
80.0	376.5				
89.7	392.5				
99.6	409.0				
HFC-134a	2.92			33.6	191.8
				41.9	204.3
		51.9	219.5		
		61.5	236.5		
		73.0	256.0		
		80.5	269.0		
		90.7	285.0		
		100.3	300.5		



**Fig. 1. P-T isopleths of cloud points of poly(D,L-lactide) ( $\bar{M}_v=30,000$ ) in HFC-23 at various polymer concentrations.**

The P-T isopleths of the cloud points given in Fig. 1 were further characterized by drawing a pressure-polymer concentration diagram, which was obtained by fitting the cloud point curves at different polymer concentrations with polynomial equations, and then by determining the pressures corresponding to the desired temperatures from the curve fits. Fig. 2 shows the pressure-polymer concentration isotherms for the poly(D,L-lactide) ( $\bar{M}_v=30,000$ )+HFC-23 system. As shown in each isotherm, the maximum cloud point pressure, that corresponds to an upper critical solution pressure, was



**Fig. 2. Pressure-polymer concentration isotherms for poly(D,L-lactide) ( $\bar{M}_v=30,000$ ) in HFC-23 at various temperatures.**

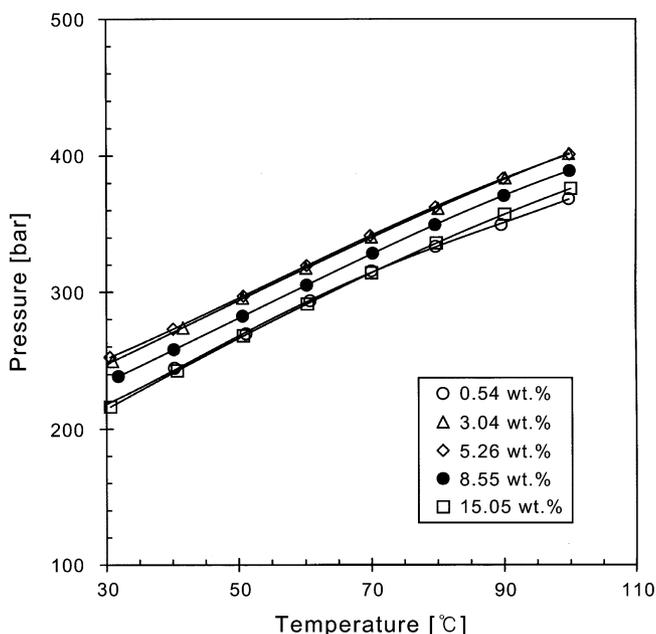


Fig. 3. P-T isopleths of cloud points of poly(D,L-lactide) ( $\bar{M}_n=30,000$ ) in HFC-134a at various polymer concentrations.

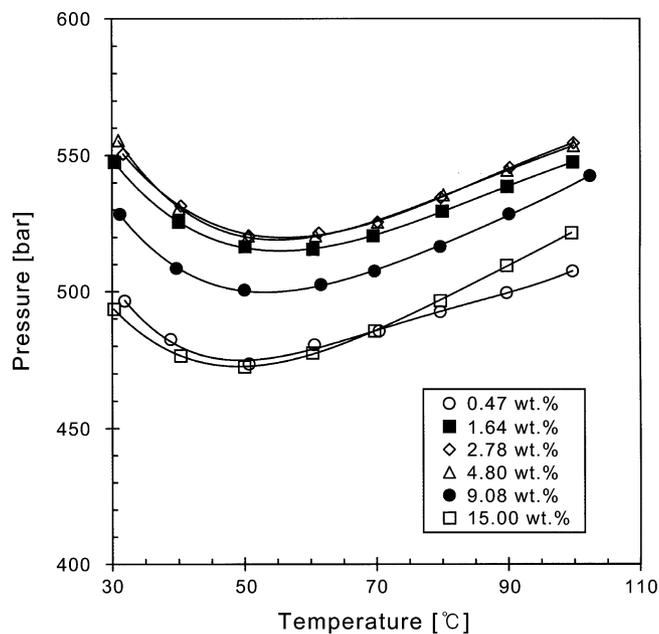


Fig. 5. P-T isopleths of cloud points of poly(D,L-lactide) ( $\bar{M}_n=30,000$ ) in HFC-32 at various polymer concentrations.

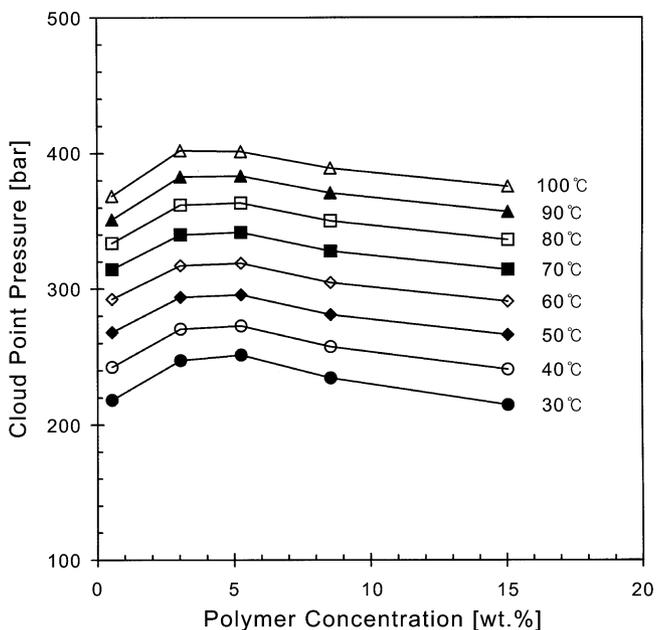


Fig. 4. Pressure-polymer concentration isotherms for poly(D,L-lactide) ( $\bar{M}_n=30,000$ ) in HFC-134a at various temperatures.

observed at the polymer concentration around 8 wt%.

The P-T isopleths of the cloud points of poly(D,L-lactide) in HFC-134a are given in Fig. 3. This system also exhibited the characteristics of an LCST phase behavior. Fig. 4, obtained by analyzing the P-T data of Fig. 3 as a function of polymer concentration at various temperatures, shows the pressure-polymer concentration isotherms of the poly(D,L-lactide) ( $\bar{M}_n=30,000$ ) in HFC-134a. The maximum cloud point pressures were observed at the polymer concentration between 3 and 5 wt%. Although a lower cloud point pressure was obtained at a higher polymer concentration, a longer time was re-

quired to dissolve the polymer in the solvent.

Fig. 5 shows the P-T isopleths of the cloud points of poly(D,L-lactide) ( $\bar{M}_n=30,000$ ) in HFC-32 at various polymer concentrations up to 15 wt%. 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 50 °C. A minimum value of the cloud point pressure was measured at a temperature between 50 °C and 60 °C, 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 [Conway et al., 2001]. 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. Fig. 6 illustrates the pressure-polymer concentration isotherms for the poly(D,L-lactide) ( $\bar{M}_n=30,000$ )+HFC-32 system, obtained from the P-T curves in Fig. 5. As the polymer concentration increased, the cloud point pressure increased sharply, reached a maximum at the polymer concentration of 3 to 5 wt%, and then decreased gradually.

Tables 2 and 3 also show the effect of polymer molecular weight on the cloud points of poly(D,L-lactide) in three 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 results of other polymer-solvent systems [McHugh and Krukonic, 1994; Lee et al., 2000a].

A solvent will dissolve a polymer when it can interact favorably

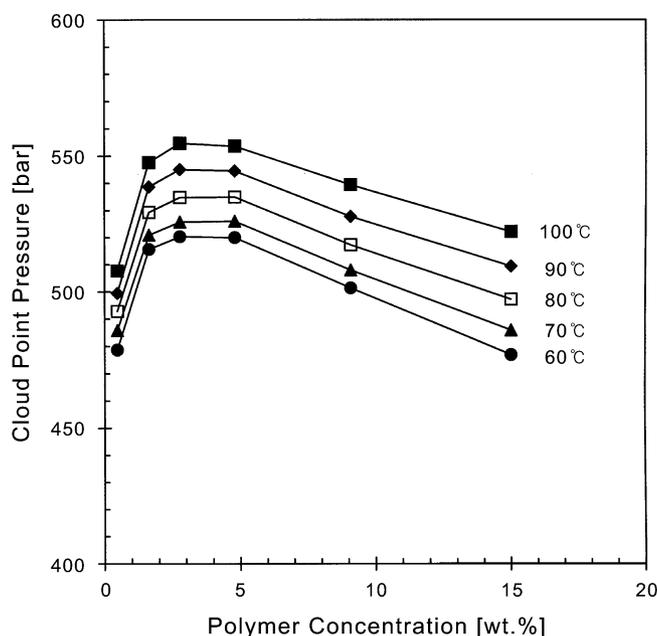


Fig. 6. Pressure-polymer concentration isotherms for poly(D,L-lactide) ( $\bar{M}_n=30,000$ ) in HFC-32 at various temperatures.

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 Fig. 7 show the differences between the solvent power of HFC-32, HFC-23, and HFC-134a for the poly(D,L-lactide) ( $\bar{M}_n=30,000$ ) at the polymer concentration of about 3 wt%. The cloud point curves for each system show that HFC-134a has the highest solvent power, while HFC-23 has the lowest solvent power.

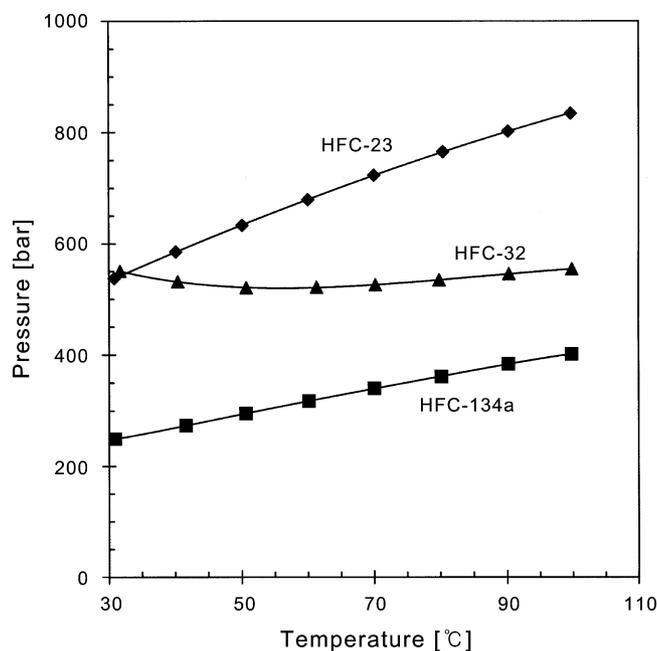


Fig. 7. Comparison of solvent power of dissolving poly(D,L-lactide) ( $\bar{M}_n=30,000$ ).

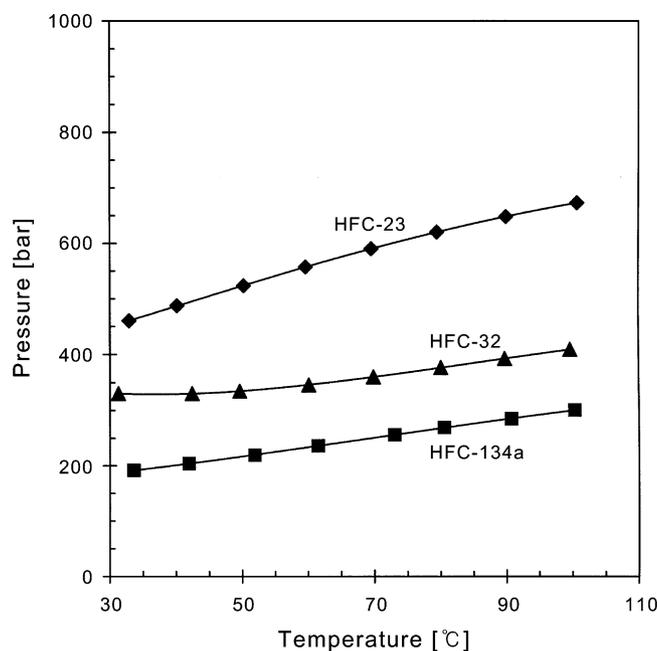


Fig. 8. Comparison of solvent power of dissolving poly(D,L-lactide) ( $\bar{M}_n=2,000$ ).

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. Fig. 8 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. The enhanced solvent power of HFC-134a relative to HFC-23 and HFC-32 can be attributed to the stronger hydrogen bonding between HFC-134a and poly(D,L-lactide) due to its larger dipole moment. This behavior is shown similarly for the poly(D,L-lactide) of  $\bar{M}_n=2,000$ , as given in Fig. 8.

## CONCLUSIONS

The cloud point experiments for the poly(D,L-lactide) polymer exhibited LCST phase behavior in 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 wt%, depending upon the system. The cloud point pressure increased with increasing molecular weight of the poly(D,L-lactide). 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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