Effect of Solvent Composition and Polymer Molecular Weight on Cloud Points of Poly(L-lactide) in Chlorodifluoromethane + Carbon Dioxide[†]

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Phase behavior data are presented for poly(L-lactide) in supercritical solvent mixtures of chlorodifluoromethane and carbon dioxide. Experimental 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, solvent composition, and polymer molecular weight. The carbon dioxide composition in the solvent mixture was varied up to ~0.82 mass fraction on a polymer-free basis at temperatures to 373.15 K. Poly(L-lactides) of three different molecular weights (2000, 50 000, 100 000) were examined, and the polymer concentration was kept constant at ~0.03 mass fraction of total in solution. This system exhibited the characteristics of a lower critical solution temperature phase behavior. As the carbon dioxide composition in the mixed solvent increased, the cloud-point pressure at a fixed temperature increased significantly. Addition of carbon dioxide to chlorodifluoromethane caused a lowering of the dissolving power of the mixed solvent due to the decrease of the solvent polarity. The cloud-point pressure increased linearly with a logarithmic increase of the poly(L-lactide) molecular weight.

Introduction

Supercritical fluid (SCF) solvents are an attractive alternative to incompressible organic liquid solvents because they can have liquidlike dissolving power while exhibiting transport properties of a gas.[1] They have been used in a variety of polymer processes such as extractions and separations, fractionations, and reactions. Particularly, SCF technology has recently gained attention in the particle formation of biodegradable polymers, which can be used as controlled drug delivery systems of bioactive agents and drugs in pharmaceutical industries.[2,3] In the production of the polymer particles, it is important to know the location of the phase boundaries for polymer−solvent mixtures.

The selection of SCF solvents to dissolve polymers is often challenging for processing applications because it is difficult to find a good SCF solvent that will dissolve the polymer at relatively moderate conditions. Carbon dioxide (CO_2) is the favorite solvent in SCF 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 polymer particles have been formed using SCF processes such as a supercritical antisolvent precipitation method.[4,5] For example, Lee et al.[6] reported that poly(L-lactide) was not completely soluble in pure CO_2 at pressures as high as 80 MPa and at temperatures up to 373.15 K. On the other hand, chlorodifluoromethane is an excellent solvent of dissolving poly(L-lactide). It has a dipole moment of 1.4 D,[7] and its polar moment interacts favorably with the polar moment of the ester group in the poly(L-lactide). Poly(L-lactide) is readily soluble even in saturated liquid chlorodifluoromethane at a room temperature.[8]

In this work, we measured the cloud points of poly(L-lactide) in solvent mixtures of chlorodifluoromethane and CO_2 by using a high-pressure phase equilibrium apparatus equipped with a variable-volume view cell. Cloud-point pressures were characterized as functions of temperature, solvent composition, and polymer molecular weight. The phase behavior data produced in this work would be useful for establishing operating conditions in the particle formation of poly(L-lactide) by the supercritical antisolvent precipitation process that utilizes chlorodifluoromethane as a solvent and CO_2 as an antisolvent.

Experimental Section

Materials. Poly(L-lactides) of three different molecular weights (MW = 2000, 50 000, 100 000) were purchased from Polysciences, Inc. (Warrington, PA). The polymer molecular weights, provided by the suppliers, are the viscosity-average molecular weights derived from the intrinsic viscosity and Mark−Houwink equation. Chlorodifluoromethane and CO_2 were obtained from Solvay Fluorides Inc. (Greenwich, CT) and Myung-Sin General Gas Co. (Yangsan, Kyungnam, Korea), respectively, and their certified purities were 99.99 mass %. They were used as received without further purification.

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Table 1. Experimental Data of Cloud Points of Poly(L-lactide) (1) in CO_2 (2) + Chlorodifluoromethane (3)

w_1[a]	w_2[b]	T/K	P/MPa	w_1[a]	w_2[b]	T/K	P/MPa	w_1[a]	w_2[b]	T/K	P/MPa	w_1[a]	w_2[b]	T/K	P/MPa
Poly(L-lactide) (MW = 2000)															
0.0288	0.0000	344.35	3.60	0.0316	0.3159	309.75	5.07	0.0281	0.5159	302.45	12.62	0.0282	0.8228	323.95	56.55
		353.05	5.95			316.75	8.10			315.85	18.22			334.35	60.65
		363.35	8.72			324.05	10.93			325.05	22.55			343.45	63.75
		372.75	10.90			333.95	14.50			333.75	25.72			353.25	66.55
0.0278	0.0743	333.85	3.98			344.75	18.05			342.55	28.90			363.35	69.15
		342.45	6.53			353.85	21.07			354.05	33.02			372.05	71.45
		352.95	9.70			362.25	23.50			363.65	35.87				
		362.85	12.53			372.85	26.42			373.35	38.65				
		373.35	15.20	0.0326	0.4400	305.05	9.25	0.0260	0.6643	315.35	30.25				
0.0310	0.1517	325.35	3.97			315.35	13.90			324.55	34.42				
		333.75	9.70			324.35	17.40			335.15	38.18				
		344.45	10.03			328.05	18.95			343.85	41.50				
		355.45	13.20			338.15	22.40			352.95	44.45				
		364.55	16.10			350.85	26.97			362.95	47.75				
		372.65	18.10			362.45	30.70			372.85	50.65				
						372.85	33.60								
Poly(L-lactide) (MW = 50 000)															
0.0303	0.0000	336.95	4.08	0.0266	0.3059	303.55	6.70	0.0281	0.5250	323.45	32.80				
		350.95	8.60			313.25	11.30			333.55	37.65				
		360.35	11.38			323.75	16.00			343.05	41.90				
		373.85	15.03			333.45	20.20			353.15	46.15				
0.0276	0.1199	323.85	5.75			343.45	24.20			363.15	50.10				
		333.55	9.45			353.05	27.90			373.15	53.50				
		343.15	12.85			363.15	31.55	0.0254	0.6044	323.65	43.20				
		353.05	16.30			373.25	34.95			333.75	48.15				
		363.25	19.65	0.0278	0.3891	303.15	11.50			343.05	52.30				
		373.05	22.70			313.35	16.50			353.15	56.65				
0.0307	0.1912	313.55	5.50			323.95	21.60			363.25	60.65				
		323.45	9.65			333.35	25.80			373.25	64.05				
		333.55	13.60			343.35	30.05								
		343.35	17.30			353.05	33.95								
		353.55	21.00			362.95	37.70								
		363.05	24.25			372.95	41.15								
		373.25	27.57												
Poly(L-lactide) (MW = 100 000)															
0.0291	0.0000	334.25	3.60	0.0296	0.2078	312.85	6.95	0.0311	0.3854	303.15	12.55	0.0289	0.6238	323.85	47.85
		342.55	6.30			323.95	11.50			313.15	17.65			333.95	52.68
		353.15	9.63			333.65	15.55			323.65	22.60			343.15	56.90
		364.45	12.86			343.65	19.35			333.25	26.95			353.05	61.00
		373.95	15.76			353.65	23.15			343.05	31.20			363.25	65.00
0.0284	0.1035	323.85	5.57			362.95	26.45			353.25	35.35			373.25	68.50
		333.85	9.40			372.85	29.70			362.95	39.12				
		343.25	12.70	0.0302	0.2944	303.15	6.85			373.35	42.85				
		352.95	16.05			313.55	11.65	0.0310	0.5004	313.15	27.70				
		362.75	19.30			323.95	16.30			323.75	33.15				
		373.35	22.58			333.55	20.50			333.25	37.75				
						343.65	24.70			343.15	42.28				
						353.15	28.35			353.05	46.45				
						363.25	32.05			363.15	50.55				
						373.85	35.75			373.15	54.15				

[a] Poly(L-lactide) mass fraction of the total. [b] CO_2 mass fraction in CO_2 + chlorodifluoromethane on a polymer-free basis.

Apparatus and Procedure. The cloud-point behavior of poly(L-lactide) in the mixtures of chlorodifluoromethane and CO_2 was measured using a high-pressure apparatus equipped with a variable-volume view cell. A main feature of using the variable-volume cell apparatus is that the concentration of the system is kept constant during the experiment. A detailed description of the experimental apparatus and procedure is given in our previous publications.[6,8−10] 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 dimensions of 16 mm i.d. by 70 mm o.d. and an internal working volume of ~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). The system temperature is measured to within ±0.1 °C by an RTD (Pt-100 Ω) probe inserted into the cell.

The experiment for measuring a cloud point was performed by the following procedure. The cell was purged with enough chlorodifluoromethane gas to remove any entrapped air present in the cell. A certain amount of poly(L-lactide) was loaded into the cell along with a stirring bar. The amount of the poly(L-lactide) loaded into the cell was determined using a sensitive balance (AND, model HM-300) measurable to ±0.1 mg. Chlorodifluoromethane and CO_2 were charged into the cell using high-pressure sample cylinders. Chlorodifluoromethane was first charged because its vapor pressure was lower than that of CO_2. The composition of each component in the solvent mixture was determined by weighing the chlorodifluoromethane and CO_2 sample cylinders before and after they had been charged into the cell using a balance (Precisa, model 1212 M SCS) with an accuracy of ±1 mg. To minimize the

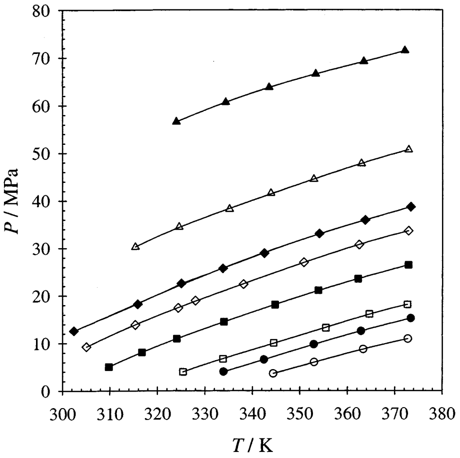

Figure 1. $P-T$ isopleths of cloud points of poly(L-lactide) (MW = 2000) in CO_2 + chlorodifluoromethane: ○, 0.0000; ●, 0.0743; □, 0.1517; ■, 0.3159; ◇, 0.4400; ♦, 0.5159; △, 0.6643; ▲, 0.8228.

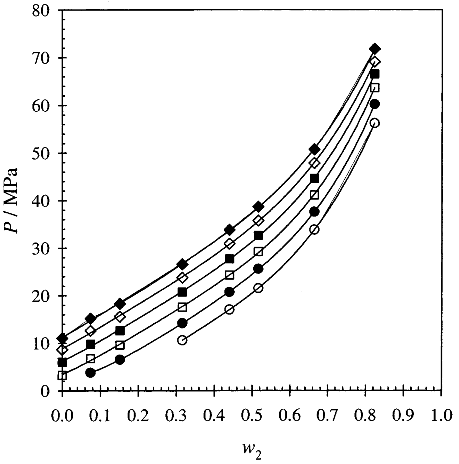

Figure 2. Effect of CO_2 composition in a mixed solvent on cloud-point pressures of poly(L-lactide) (MW = 2000) at various temperatures: ○, 323.15 K; ●, 333.15 K; □, 343.15 K; ■, 353.15 K; ◇, 363.15 K; ♦, 373.15 K.

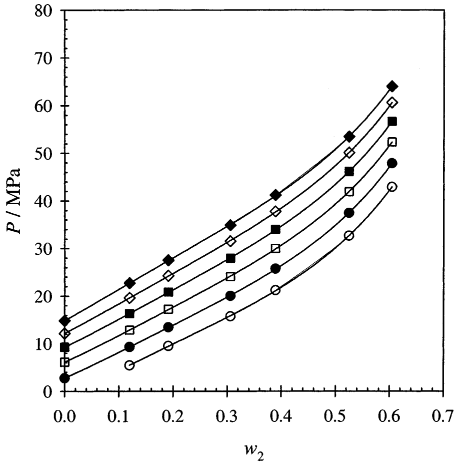

Figure 3. Effect of CO_2 composition in a mixed solvent on cloud-point pressures of poly(L-lactide) (MW = 50 000) at various temperatures: ○, 323.15 K; ●, 333.15 K; □, 343.15 K; ■, 353.15 K; ◇, 363.15 K; ♦, 373.15 K.

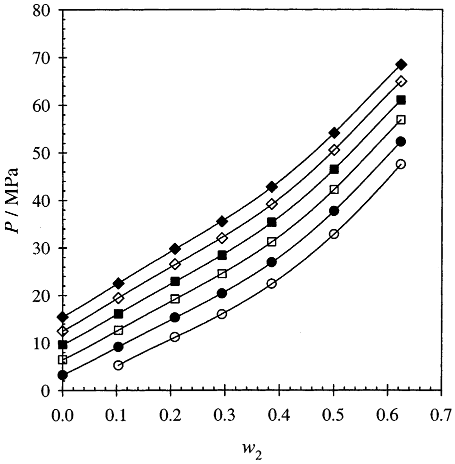

Figure 4. Effect of CO_2 composition in a mixed solvent on cloud-point pressures of poly(L-lactide) (MW = 100 000) at various temperatures: ○, 323.15 K; ●, 333.15 K; □, 343.15 K; ■, 353.15 K; ◇, 363.15 K; ♦, 373.15 K.

amount of components lost when charging them into the cell, we used a fine and short inlet line (0.03 in. i.d., 10 cm long) and heated it by a heat gun. The uncertainty in solvent composition measurement was $<2 \times 10^{-4}$ in mass fraction.

The solution in the cell was compressed by moving the piston located within the cell using the pressure generator and agitated by the magnetic stirrer until it became a single phase. The cell was then heated to a desired temperature. Once the system reached thermal equilibrium and the solution was maintained at 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 as the cloud-point pressure was approached. At fixed polymer and solvent concentrations and 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. Reproducibility of the cloud-point pressures was within ±0.2 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.

Results and Discussion

Cloud-point pressures of poly(L-lactide) in solvent mixtures of chlorodifluoromethane and CO_2 were investigated as functions of temperature, solvent composition, and polymer molecular weight. Experimental cloud-point data are given in Table 1. The cloud-point data for the poly(L-lactide) (MW = 2000) have already been reported in our previous publication.[6] In this work, the cloud points for the poly(L-lactides) of MW = 50 000 and 100 000 were additionally measured to observe the effect of the polymer molecular weight on the cloud points. The polymer concentration in the solution was fixed at (0.0290 ± 0.0015) mass fraction of the total, to eliminate the effect of the polymer concentration on the cloud points.

Figure 1 shows the $P-T$ isopleths of the cloud points of poly(L-lactide) (MW = 2000) in mixed solvents of CO_2 and chlorodifluoromethane for various CO_2 compositions up to ∼0.82 mass fraction on a polymer-free basis. Above each cloud point is the single-phase region, and below the point is the two-phase region. The cloud-point curves in Figure 1 exhibited the characteristics of a typical lower critical solution temperature (LCST) phase behavior; the pressure necessary to maintain the polymer solution in the single-phase region increased with the temperature. The cloud-

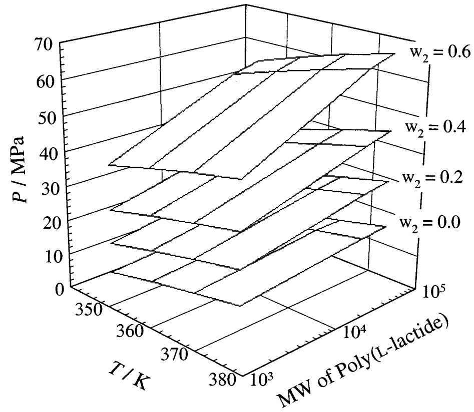

Figure 5. Cloud points in $P-T-$MW space of poly(L-lactide) in chlorodifluoromethane + CO_2.

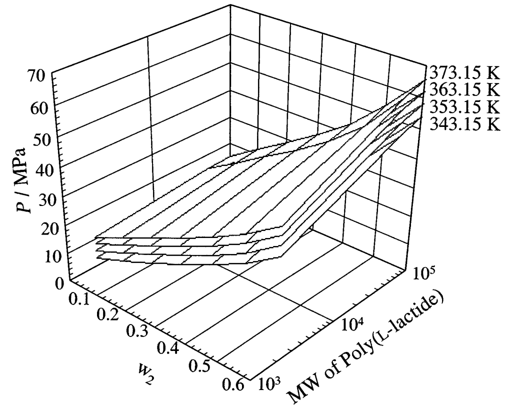

Figure 6. Cloud points in $P-w_2-$MW space of poly(L-lactide) in chlorodifluoromethane + CO_2.

point curves had similar slopes for all of the CO_2 compositions.

As the CO_2 composition in the solvent increased at a given temperature, the cloud-point curve was shifted to higher pressures so that the two-phase region of polymer−solvent miscibility enlarged. CO_2 is not a good solvent to dissolve the poly(L-lactide) polymer. Therefore, addition of CO_2 to chlorodifluoromethane caused a decrease of the dissolving power of the mixed solvent. This can be attributed to the decrease of the solvent polarity by the increase of CO_2 composition in the solvent. Consequently, chlorodifluoromethane acted as a solvent and CO_2 acted as an antisolvent.[6]

The effect of solvent composition on cloud points is more easily seen by examining a pressure-solvent composition ($P-w_2$) diagram. Figure 2 shows the effect of CO_2 composition in the mixed solvent on the cloud-point pressures at several temperatures for the poly(L-lactide) (MW = 2000). This $P-w_2$ diagram was obtained by fitting the cloud-point curves of Figure 1 with polynomial equations and then by determining the pressures corresponding to desired temperatures from the curve fits. The correlation coefficients of the curve fits, which expressed the goodness of the fits, were >0.999 for all cases. Similarly, the $P-w_2$ diagrams for the poly(L-lactides) of MW = 50 000 and 100 000 were obtained, as shown in Figures 3 and 4. The cloud-point pressures increased sharply with increasing the CO_2 composition in the mixed solvent.

In this work, the factors, which affect the cloud-point pressure of poly(L-lactide) in chlorodifluoromethane + CO_2, are temperature (T), CO_2 composition in a mixed solvent (w_2), and polymer molecular weight (MW). To examine more vividly the dependence of cloud-point pressure on these three factors, the cloud-point pressures were shown in three-dimensional diagrams. The cloud-point pressures at w_2 of 0.0 to 0.6 at 0.1 intervals were obtained from the curve fits of the isotherms (Figures 2−4). The effect of temperature and polymer molecular weight on cloud-point pressures at w_2 of 0.0, 0.2, 0.4, and 0.6 is shown in Figure 5 in $P-T-$MW space. Figure 6 shows the effect of CO_2 composition and polymer molecular weight at 343.15, 353.15, 363.15, and 373.15 K in $P-w_2-$MW space. The cloud-point pressure increased linearly with a logarithmic increase of the poly(L-lactide) molecular weight. In Figures 5 and 6, the upper part is the single-phase region and the lower part is the two-phase region.

Conclusions

The cloud-point experiments indicated LCST phase behavior for poly(L-lactide) in chlorodifluoromethane + CO_2 mixtures. At a given temperature, the cloud-point pressure increased with increasing the CO_2 composition in the solvent mixture. Addition of CO_2 to chlorodifluoromethane caused a decrease of the dissolving power of the mixed solvent due to the decrease of the solvent polarity and reduced the area of miscibility by shifting the cloud-point curve to lower temperatures and higher pressures. As the poly(L-lactide) molecular weight increased logarithmically, the cloud-point pressure increased linearly.

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