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Phase Behavior of Poly(L-lactide) in Supercritical Mixtures of Dichloromethane and Carbon Dioxide

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Phase behavior data are presented for poly(L-lactide) in supercritical mixtures of dichloromethane and carbon dioxide. Cloud point pressures were measured using a variable-volume view cell apparatus as functions of temperature, dichloromethane composition in a mixed solvent, and molecular weight of poly(L-lactide) at the polymer concentration of ≈0.05 mass fraction in solution. This system exhibited the characteristics of lower critical solution temperature phase behavior. As the dichloromethane composition in the mixed solvent increased, the cloud point pressure at a fixed temperature decreased significantly. 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 liquid-like 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 great 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.[2−4] 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.[5,6] For example, Lee et al.[7] 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, dichloromethane is an excellent solvent of dissolving poly(L-lactide). It has a dipole moment of 1.8 D,[8] and its polar moment interacts favorably with the polar moment of the ester group in the poly(L-lactide).

In this work we measured the cloud points of poly(L-lactide) in solvent mixtures of dichloromethane 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 dichloromethane as a solvent and CO_2 as an antisolvent.

Experimental Section

Materials. Poly(L-lactides) of three different molecular weights (MW = 2000, 50000, 100000) 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. Anhydrous dichloromethane of 99.8% purity was obtained from Aldrich Chemical Co. (Milwaukee, WI) and CO_2 of 99.99% purity from Myung-Sin General Gas Co. (Yangsan, Kyungnam, Korea). They were used as received without further purification.

Apparatus and Procedure. The cloud point behavior of poly(L-lactide) in the mixtures of dichloromethane 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.[7,9,10] 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. × 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 CO_2 gas to remove any entrapped air present

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in the cell. A known mass of poly(L-lactide) was loaded into the cell along with a stirring bar. Dichloromethane was injected into the cell using a gastight syringe that was weighed before and after injection, and then the piston was positioned immediately. The amounts of the polymer and dichloromethane loaded into the cell were measured using a sensitive balance (AND, model HM-300) measurable to ±0.1 mg. CO_2 was charged into the cell using a high-pressure sample cylinder. The amount of CO_2 charged was determined by weighing the sample cylinder before and after CO_2 had been charged into the cell using a balance (Precisa, model 1212 M SCS) with an accuracy of ±1 mg. To minimize the amount of CO_2 lost when charging it 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 dichloromethane and CO_2 were investigated as functions of temperature, solvent composition, and polymer molecular weight. Experimental cloud point data are given in Table 1. Cloud points were measured at a fixed poly(L-lactide) concentration of ≈0.05 mass fraction of the total, which is typical of the concentration used for polymer−solvent studies.[1] Figure 1 shows the $P-T$ isopleths of the cloud points of poly(L-lactide) (MW = 2000) in mixed solvents of dichloromethane and CO_2 for various dichloromethane compositions up to ≈0.53 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 point curves had similar slopes for all of the dichloromethane compositions.

As the dichloromethane 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 polymer−solvent miscibility enlarged. Dichloromethane is an excellent solvent for the poly(L-lactide) polymer. Therefore, addition of dichloromethane to CO_2 caused an increase of the dissolving power of the mixed solvent. This can be attributed to the increase of the solvent polarity by the increase of dichloromethane composition in the solvent. Consequently, dichloromethane acted as a solvent and CO_2 acted as an antisolvent.

For the solution of high dichloromethane composition, cloud point behavior was not measured in a low-temperature region. As an illustration, for the poly(L-lactide)

Table 1. Experimental Data of Cloud Points of Poly(L-lactide) (1) in w_2Dichloromethane + $(1-w_2)CO_2$

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)							
0.0506	0.0802	322.65	76.65	0.0492	0.2927	323.25	29.75
		333.45	78.45			333.35	33.65
		343.15	80.45			343.35	37.15
		353.15	82.05			353.15	40.35
		363.15	83.35			362.75	43.05
		373.35	84.75			373.15	45.95
0.0477	0.1215	324.55	66.05	0.0498	0.4012	323.75	14.85
		333.65	68.25			333.25	18.55
		343.45	70.35			343.15	22.25
		353.55	72.15			353.15	25.55
		363.25	74.15			363.45	28.75
		372.95	75.65			373.15	31.25
0.0495	0.1527	323.65	56.75	0.0522	0.5307	304.05	4.82^c
		333.35	59.65			313.95	5.65^c
		343.25	62.35			323.75	6.55^c
		353.25	64.75			333.85	7.58^c
		363.55	67.05			343.25	8.60^c
		375.15	69.35			353.25	11.37
0.0515	0.2152	323.15	42.55			363.25	14.45
		333.25	46.05			372.65	17.05
		343.25	49.25				
		353.15	52.05				
		363.25	54.65				
		373.25	57.05				
Poly(L-lactide) (MW = 50000)							
0.0508	0.2206	318.15	52.75	0.0508	0.5356	312.35	5.26^c
		326.15	55.93			322.35	6.14^c
		334.35	58.78			333.55	8.67
		343.25	62.00			342.45	12.29
		352.75	65.07			353.15	16.23
		362.95	68.14			362.55	19.50
		372.85	70.85			372.45	22.75
0.0484	0.2995	318.05	35.30	0.0509	0.5928	311.65	4.82^c
		322.65	37.28			322.75	5.75^c
		333.25	41.78			332.45	6.76^c
		343.55	45.82			345.05	7.97
		352.45	49.06			352.35	10.73
		363.35	52.75			361.75	13.55
		373.25	55.67			373.15	17.43
0.0507	0.4050	313.95	15.07				
		323.05	19.30				
		333.35	23.87				
		343.45	27.84				
		352.75	31.44				
		363.75	35.27				
		372.65	38.15				
Poly(L-lactide) (MW = 100000)							
0.0509	0.2120	318.45	58.20	0.0499	0.3661	317.95	20.47
		324.75	60.55			324.15	23.40
		333.45	63.67			334.75	27.95
		343.25	67.05			345.75	32.55
		352.75	69.97			352.05	34.85
		362.35	72.85			362.75	38.70
		372.25	75.52			372.65	42.05
0.0531	0.3084	316.85	34.94	0.0513	0.5162	314.35	5.45^c
		324.45	38.55			322.85	7.37
		333.75	42.37			333.15	11.72
		343.55	46.18			343.55	15.94
		352.85	49.64			352.95	19.50
		363.05	53.07			364.25	23.56
		373.05	56.15			372.95	26.05

[a] Poly(L-lactide) mass fraction of the total. [b] Dichloromethane mass fraction in dichloromethane + CO_2 on a polymer-free basis. [c] Fluid− to liquid−vapor-phase transitions.

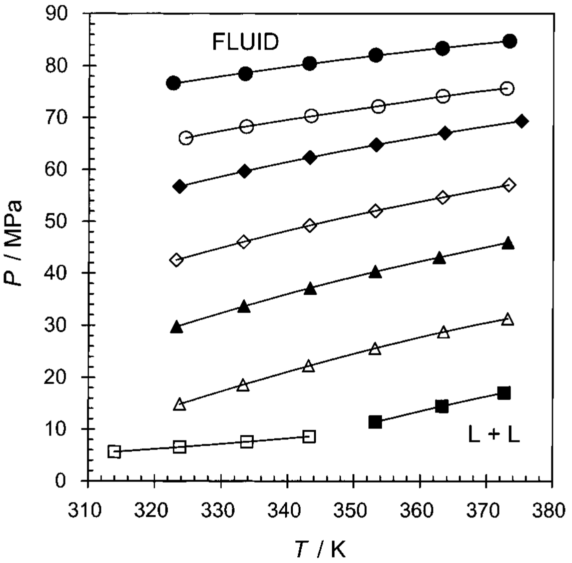

Figure 1. $P-T$ isopleths of cloud points of poly(L-lactide) (MW = 2000) in dichloromethane + CO_2. Mass fractions of dichloromethane in the mixed solvent on a polymer-free basis (w_2): ●, 0.0802; ○, 0.1215; ♦, 0.1527; ◇, 0.2152; ▲, 0.2927; △, 0.4012; ■, 0.5307; □, 0.5307 (fluid− to liquid−vapor-phase transitions).

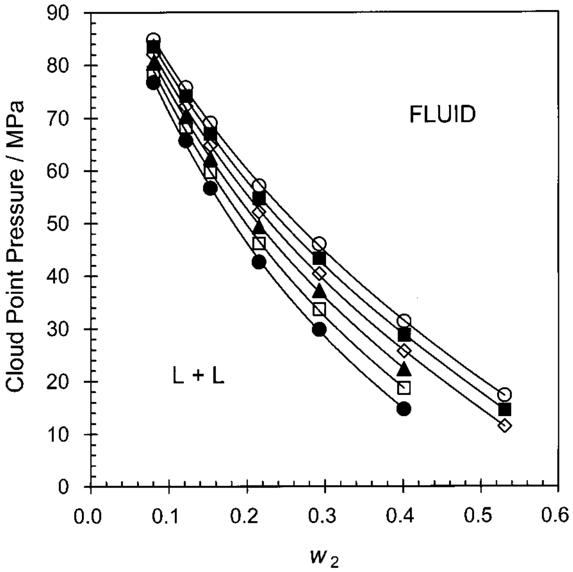

Figure 2. Effect of dichloromethane composition in a mixed solvent on cloud point pressures of poly(L-lactide) (MW = 2000) at various temperatures: ●, 323.15 K; □, 333.15 K; ▲, 343.15 K; ◇, 353.15 K; ■, 363.15 K; ○, 373.15 K.

(MW = 2000) in the solvent mixture with the dichloromethane mass fraction of 0.5307, the fluid− to liquid−vapor-phase transitions (open squares) instead of the cloud point transition were observed at temperatures below ≈345 K, as shown in Figure 1. This type of phase transition was also observed for the poly(L-lactides) of MW = 50000 and 100000 when the dichloromethane mass fraction was greater than ≈0.5, as indicated in Table 1. The fluid− to liquid−vapor-phase transitions actually occurred on the bubble points of the dichloromethane + CO_2 mixture.

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 dichloromethane 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. The cloud point pressures decreased sharply with increasing dichloromethane composition in the mixed solvent.

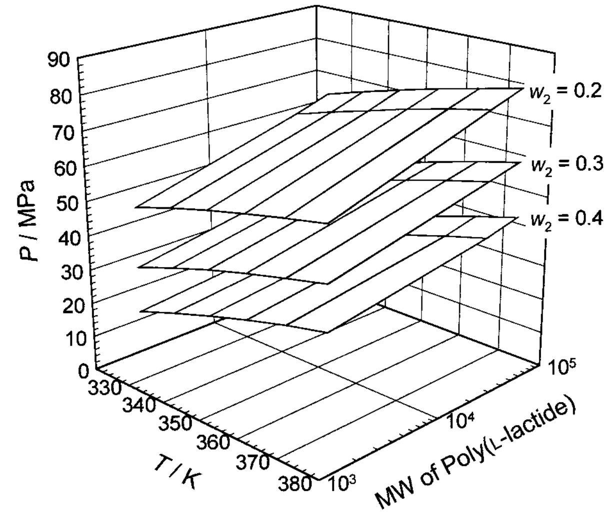

Figure 3. Cloud points in $P-T-$MW space of poly(L-lactide) in dichloromethane + CO_2.

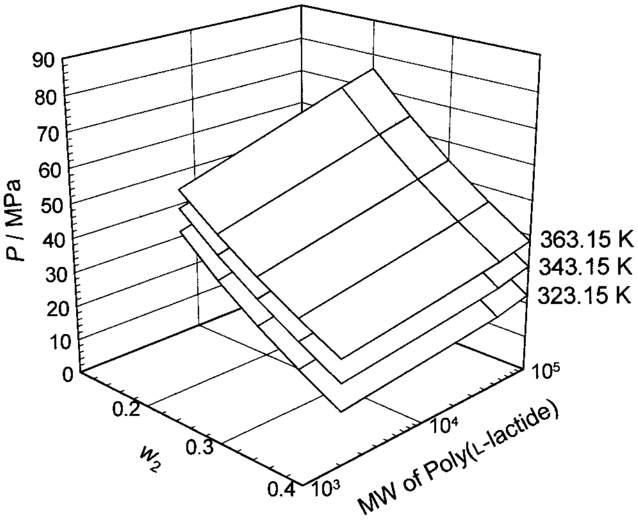

Figure 4. Cloud points in $P-w_2-$MW space of poly(L-lactide) in dichloromethane + CO_2

In this work, the factors, which affect the cloud point pressure of poly(L-lactide) in dichloromethane + CO_2, are temperature, dichloromethane composition in a mixed solvent, and polymer molecular weight. 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 0.2 to 0.4 at 0.05 intervals were obtained from the curve fits of the isotherms. The effect of temperature and polymer molecular weight on cloud point pressures at w_2 of 0.2, 0.3, and 0.4 is shown in Figure 3 in $P-T-$MW space. Figure 4 shows the effect of dichloromethane composition and polymer molecular weight at 323.15 K, 343.15 K, and 363.15 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 3 and 4, 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 dichloromethane + CO_2 mixtures. At a given temperature, the cloud point pressure decreased with increasing the dichloromethane composition in the solvent mixture. Addition of dichloromethane to CO_2 caused an increase of the dissolving power of the mixed solvent 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. As the poly(L-lactide) molecular weight increased logarithmically, the cloud point pressure increased linearly.

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