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Phase Behavior of Poly(lactic acid)/Poly(ethylene glycol)/Poly(lactic acid) (PLA-PEG-PLA) in Different Supercritical Systems of CO_2 + Dichloromethane and CO_2 + C_2H_5OH + Dichloromethane

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The supercritical phase behavior of the poly(lactic acid)/poly(ethylene glycol)/poly(lactic acid) (PLA-PEG-PLA) + CO_2 + dichloromethane (DCM) system and the PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH system was investigated using a supercritical phase monitor. The phase behavior data were measured at temperatures from (313.1 to 338.1) K and pressures up to 35 MPa. The results show that the systems exhibit the characteristics of lower critical solution temperature phase behaviors. The effects of temperature, the mass fraction of DCM (or DCM + C_2H_5OH), the PEG mass fraction in PLA-PEG-PLA, and the molar ratio of DCM/C_2H_5OH on cloud-point pressure were discussed in detail.

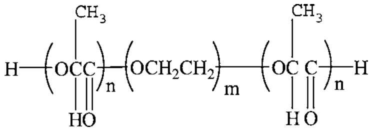
Introduction

In recent years, supercritical antisolvent processes have attracted considerable attention from many scientists and engineers because of the unique properties of supercritical fluids and their applications, such as new polymeric materials,[1,2] micro- and nanoparticulate power for pharmaceutical, biomedical, cosmetic, alimentary or electronic applications,[3−5] and particularly the microparticle formation of biodegradable polymers.[6]

During the formation of biodegradable particles in supercritical antisolvent process, supercritical CO_2 is usually employed as the antisolvent due to its properties such as a relatively low critical point, nontoxicity, nonflammability, and being inexpensive.[7] Organic solvents, such as dichloromethane (DCM) and acetone, are generally chosen to dissolve polymers. In pharmaceutical industry, polymers with biodegradable and biocompatible properties are potential drug carriers, such as poly(L-lactic acid) (PLA),[8] poly(D,L-lactide-co-glycolide) (PLGA),[9] and poly(lactic acid)/poly(ethylene glycol)/poly(lactic acid) (PLA-PEG-PLA).[10,11] Especially PLA-PEG-PLA, which has a core−shell structure formed by self-assembling in aqueous environment, is considered to be a promising delivery system for many hydrophobic drugs. Its hydrophobic core can catch the drug, and the hydrophilic shell can increase blood circulation time.

It is crucial to understand the phase behavior of systems containing supercritical CO_2, polymer, solvent, and cosolvent, because the particle morphology and size distribution are strongly affected by the phase behavior,[12,13] but there is still a lack of equilibrium data. Phase behaviors of PLA and PLGA in supercritical fluid have been investigated,[14,15] but to the best our knowledge, the phase behavior data of PLA-PEG-PLA in supercritical conditions have never been reported up to date, although these data are crucial.

The supercritical CO_2 + DCM system is full of interest for many polymers and pharmaceutical processes. In this work, the phase behavior data of the PLA-PEG-PLA + CO_2 + DCM system were first measured using a high-pressure phase equilibrium apparatus equipped with a variable-volume view cell. Then C_2H_5OH, based on its nontoxicity and good solvency for the poly(ethylene glycol) (PEG) component of PLA-PEG-PLA, was selected to substitute part of DCM according to the correlation and interaction among CO_2, PEG, C_2H_5OH, and DCM.[15−18] The molar ratio of DCM/C_2H_5OH was selected for clear observation of experimental phenomenon after preliminary experiments. The phase behavior data obtained in this work will be useful for efficient operation and particle quality control of PLA-PEG-PLA in a supercritical antisolvent process that utilizes DCM (or DCM + C_2H_5OH) as the solvent and CO_2 as the antisolvent.



$$H-\left(O\overset{CH_3}{\underset{H}{C}}\underset{\|\,O}{C}\right)_n-\left(OCH_2CH_2\right)_m-\left(O\overset{CH_3}{\underset{H}{C}}\underset{\|\,O}{C}\right)_n-H$$

Figure 1. Chemical structure of PLA-PEG-PLA.

Experimental Section

Materials. PLA-PEG-PLA with different PEG mass fractions (f) (f = 0.05, 0.10, 0.15, 0.20) and PLA (molar mass = 50 $kg \cdot mol^{-1}$) were supplied by Ji-Nan Dai Gang Biological Technology Co., Ltd. The structural formula of PLA-PEG-PLA is described in Figure 1. Analytical grade C_2H_5OH (mass fraction > 0.997) and DCM (mass fraction > 0.995) were purchased from Guangdong Guanghua Chemical Reagents Co. CO_2 (mass fraction > 0.999) was from Guangzhou Shengying Gas Co., Ltd. All of them were used directly without further purification.

Apparatus. The schematic diagram of the experimental apparatus for measuring phase behavior data of different systems is similar to that in Gong and Cao.[19] The supercritical phase monitor (SPM20, Thar Technology Co., Ltd.) contains several main parts, that is, (i) a PLC control panel; (ii) a high-pressure variable-volume view cell with a pressure transmitter and an internal working volume of about 20 mL; (iii) a movable piston inside the cell to change its volume by a hydraulic hand pump

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and thus change the pressure of the system; (iv) electric heater pads along with high-precision thermocouples for temperature measurement in the cell; (v) a sapphire window coupled with a charge-coupled device (CCD) camera which is connected to a computer for observing and recording experimental phenomenon; and (vi) a stirring system equipped on the top of the cell for agitating the solution in high pressure and sealing the cell. Its maximum operating pressure and temperature are 40.00 MPa and 423.1 K when stirring. The pressure and temperature of the monitor were measured with a resolution of 0.01 MPa and 0.1 K, respectively.

Experimental Procedure. To obtain detailed phase behavior data of PLA-PEG-PLA in the supercritical system, experiments were carried out for supercritical systems of CO_2 + DCM and CO_2 + DCM + C_2H_5OH as the following procedure, which is similar to Lee et al.[20] A main feature of using the monitor is that the concentration of the system is kept constant during the experiment. First, the piston was located to adjust the volume of the cell equal to that of the solution, so the entrapped air in the cell can be removed. Then the solution with a desired composition of PLA-PEG-PLA and DCM (or DCM + C_2H_5OH) was loaded into the cell and sealed the cell with the stirring system. After these processes, the piston loosened, and CO_2 was injected into the cell; its quantity was 12.0 g which was determined by mass flowmeter (MASS 6000, Siemens) with a precision of 0.1 g. For the PLA-PEG-PLA + CO_2 + DCM system, the quantity of DCM was about (5 to 10) g, depending on the desired mass fraction of DCM from 0.25 to 0.45. Meanwhile, for the PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH system, a different molar ratio of DCM/C_2H_5OH was explored, and the molar ratio of DCM/C_2H_5OH fixed at 9:1 was studied in detail. The total quantity of DCM + C_2H_5OH was about (4 to 8) g, which depends on their desired mass fraction from 0.25 to 0.40. All of them were measured by an electronic balance (AL104, Mettler Toledo) with an uncertainty of 0.1 mg.

The mixture in the cell was compressed and heated to a desired temperature. Simultaneously, the water in the hydraulic hand pump was compressed to displace the piston to the window side to decrease the cell volume and thus to raise the pressure in the cell. As the pressure increased and the system was well-agitated by the stirring system, the mixture of PLA-PEG-PLA + CO_2 + DCM or PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH became a homogeneous solution. After the system reached thermal equilibrium and its temperature was stable enough, the pressure was slowly reduced by about 0.5 $\text{MPa}\cdot\text{min}^{-1}$ until the single-phase solution became cloudy.[20] The cloud point indicates that the solute begins to precipitate and is defined as the pressure at which the stirrer is no longer to be visually observed.[20] Each point was repeated three times for its mean value and reliable result. The system temperature was from (313.1 to 338.1) K with each point increment of about 5 K. As the above procedure repeated, the pressure−temperature ($p-T$) cloud-point curves for the two systems were obtained.

Verification. Cloud-point pressures of PLA (molar mass = 50 $\text{kg}\cdot\text{mol}^{-1}$) in supercritical mixtures of DCM and CO_2 were measured to verify the reliability of the experimental apparatus and procedure. With a similar solvent composition and temperature range, experimental cloud-point pressures were compared with data reported by Lee and Kuk,[21] as shown in Figure 2. The obtained data were in reasonable agreement with an average absolute relative deviation of 2.39 %, which indicates the reliability of the apparatus and procedure.

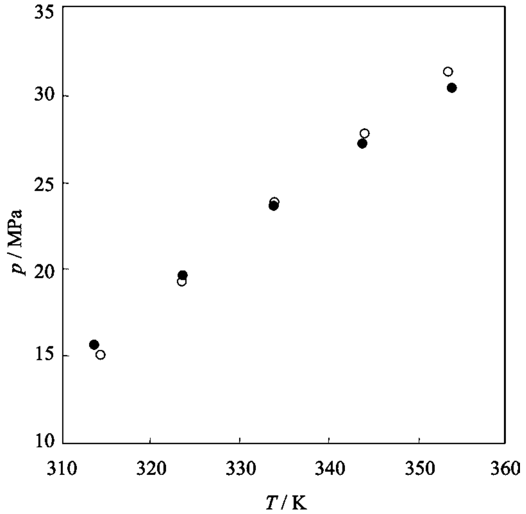

Figure 2. Cloud-point measurement reliability test of PLA (molar mass = 50 $\text{kg}\cdot\text{mol}^{-1}$). ○, this work; ●, Lee and Kuk.[21]

Results and Discussion

Cloud-point pressures (p) for different supercritical systems of PLA-PEG-PLA + CO_2 + DCM and PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH were investigated as functions of temperature (T), the mass fraction of DCM (or DCM + C_2H_5OH) in the system (w), the PEG mass fraction (f) in PLA-PEG-PLA, and the molar ratio of DCM/C_2H_5OH in solvent mixture (R). Experimental data of PLA-PEG-PLA + CO_2 + DCM system are given in Table 1. Table 2 shows the data of PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH system with different molar ratios of DCM/C_2H_5OH, and Table 3 is the data of PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH system with the molar ratio of DCM/C_2H_5OH fixed at $R = 9{:}1$. As shown in the three tables, the mass of PLA-PEG-PLA (m) is kept as a constant of ≈ 0.2240 g in all systems, which can be completely dissolved before CO_2 is injected.

Figures 3 and 4 show the $p-T$ isopleths of the PLA-PEG-PLA + CO_2 + DCM system and PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH system with different mass fractions of DCM (or DCM + C_2H_5OH), respectively. In these representative figures, the PLA-PEG-PLA with 0.15 PEG mass fraction was used as a sample, and the molar ratio of DCM/C_2H_5OH was fixed at 9:1. The cloud point indicates the change of the system from a single phase to double phases and is defined as the phase boundary as the pressure reduces. The bubble point is the pressure at which the single phase changes to gas−liquid phases directly without any solute separate out. The addition of C_2H_5OH makes the bubble point of the PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH system higher than the PLA-PEG-PLA + CO_2 + DCM system; these data show some similarities with those reported by Tsivintzelis et al.[16] It is obviously found that cloud-point curves have a typical lower critical solution temperature (LCST) phase behavior with a similar positive slope at pressures up to 35 MPa and temperatures between (313.1 and 338.1) K.

An increase of temperature results in the expansion of the system. In this case, supercritical CO_2 tends to swell and dissolves DCM (or DCM + C_2H_5OH), which makes the DCM (or DCM + C_2H_5OH) a worse solvent for PLA-PEG-PLA. Thus, it requires higher pressure to keep the system homogeneous. As the mass fraction of DCM (or DCM + C_2H_5OH) increases, the solvent polarity increases, which enlarges the solvency of DCM (or DCM + C_2H_5OH) and leads to lower pressure phase transition values. Comparing the two figures, it can be found

Table 1. Experimental Data of the PLA-PEG-PLA (with Different PEG Mass Fraction *f*) + CO_2 + DCM System (B: Bubble Point)

		p/MPa					
m/g	*w*	313.1 K	318.1 K	323.1 K	328.1 K	333.1 K	338.1 K
0.2240 (*f* = 0.05)	0.3000	24.46	26.57	28.54	30.40	32.54	34.44
	0.3460	16.63	18.24	19.85	21.73	23.38	25.36
	0.3642	13.01	14.82	16.90	19.20	20.75	23.00
	0.3839	10.83	12.51	14.29	16.44	18.36	20.10
	0.4280	7.22	9.43	11.29	13.44	15.36	16.94
0.2240 (*f* = 0.10)	0.3025	21.82	24.24	26.30	28.26	30.21	32.25
	0.3504	13.62	15.35	17.42	19.19	20.99	22.45
	0.3756	10.97	12.62	14.45	16.15	18.06	20.02
	0.4004	6.80	8.89	10.98	13.03	14.91	16.69
	0.4452	4.42^{B}	4.91^{B}	6.52	8.49	10.51	12.40
0.2240 (*f* = 0.15)	0.3051	19.51	21.46	23.34	25.40	27.38	29.40
	0.3195	18.03	19.92	21.86	23.87	25.90	27.70
	0.3534	12.62	14.41	16.28	18.30	20.10	22.10
	0.3819	8.51	10.35	12.13	14.15	15.96	17.81
	0.4437	4.15^{B}	4.50^{B}	6.04	7.64	9.59	11.31
0.2240 (*f* = 0.20)	0.2633	23.46	25.25	27.17	29.02	31.20	32.98
	0.2910	17.71	19.60	21.50	23.64	25.51	27.34
	0.3214	12.66	14.56	16.49	18.48	20.41	22.35
	0.3657	9.84	11.70	13.78	15.92	17.80	19.84
	0.4110	3.91^{B}	4.37^{B}	7.10	9.23	11.30	13.39

Table 2. Experimental Data of the PLA-PEG-PLA (with PEG Mass Fraction 0.10) + CO_2 + DCM + C_2H_5OH System with Different Molar Ratios of DCM/C_2H_5OH (B: Bubble Point)

			p/MPa					
m/g	*w*	*R*	313.1 K	318.1 K	323.1 K	328.1 K	333.1 K	338.1 K
0.2240 (*f* = 0.10)	0.3025	10:0	21.82	24.24	26.30	28.26	30.21	32.25
		9:1	14.10	15.98	17.91	19.99	22.13	24.01
		7:3	6.45^{B}	8.62	10.45	12.56	14.42	16.40

Table 3. Experimental Data of the PLA-PEG-PLA (with Different PEG Mass Fraction *f*) + CO_2 + DCM + C_2H_5OH System with a Fixed Molar Ratio of DCM/C_2H_5OH (*R* = 9:1) (B: Bubble Point)

		p/MPa					
m/g	*w*	313.1 K	318.1 K	323.1 K	328.1 K	333.1 K	338.1 K
0.2240 (*f* = 0.05)	0.2601	17.88	19.73	21.67	23.74	25.60	27.20
	0.2897	14.88	16.71	18.70	20.89	23.11	25.01
	0.3350	11.12	13.02	14.89	16.70	18.92	21.34
	0.3640	8.08	9.90	11.81	13.62	15.93	17.74
	0.3820	5.78^{B}	7.84	9.70	11.99	14.21	15.95
0.2240 (*f* = 0.10)	0.2601	15.79	17.71	19.61	21.35	23.56	25.13
	0.2967	14.10	15.98	17.91	19.99	22.13	24.01
	0.3235	8.57	10.45	12.38	14.52	16.62	18.25
	0.3640	5.89^{B}	8.29	10.17	12.35	14.29	16.20
	0.3820	5.28^{B}	5.75^{B}	8.01	10.31	12.42	14.02
0.2240 (*f* = 0.15)	0.2601	14.40	16.28	18.19	20.21	22.42	24.12
	0.2897	12.30	14.17	16.01	18.25	20.13	22.03
	0.3235	7.40	9.21	11.08	13.41	15.35	17.26
	0.3640	5.50^{B}	7.31	9.08	11.28	13.35	15.15
	0.3820	5.15^{B}	5.64^{B}	7.25	9.36	11.28	13.14
0.2240 (*f* = 0.20)	0.2601	12.60	14.62	16.51	18.72	20.58	22.31
	0.2897	10.75	12.70	14.55	16.35	18.45	20.14
	0.3235	5.23^{B}	7.88	9.72	11.62	13.50	15.40
	0.3640	4.89^{B}	5.58^{B}	8.15	10.02	12.01	13.89
	0.3820	4.62^{B}	5.01^{B}	6.41	8.56	10.41	12.23

that the cloud point of the PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH system is lower than that of the PLA-PEG-PLA + CO_2 + DCM system at given experimental factors. It suggests that the addition of C_2H_5OH causes some complex interaction among CO_2, C_2H_5OH, DCM, and PLA-PEG-PLA in supercritical conditions, especially the interaction of hydrogen bonding between CO_2 and C_2H_5OH and the interaction between DCM + C_2H_5OH and PLA-PEG-PLA.

Figures 5 and 6 show the $p-T$ isopleths of the PLA-PEG-PLA + CO_2 + DCM system and the PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH system with different PEG mass fractions in PLA-PEG-PLA at a given mass fraction of DCM (or DCM + C_2H_5OH) ≈ 0.3000. As the PEG mass fraction in the PLA-PEG-PLA increases, the $p-T$ isopleths shift to lower pressure with a similar slope. In other words, the larger PEG mass fraction in the copolymer, the higher its solubility in the supercritical systems.

Figure 7 shows the effect of the molar ratio of DCM/C_2H_5OH on the cloud-point pressure for the PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH system at a given total mass fraction of DCM + C_2H_5OH ≈ 0.3025. As shown in Figure 7, the PLA-PEG-PLA with 0.10 PEG mass fraction was used as sample, and the phase boundary shifted to lower pressure with the same slope as the molar ratio of DCM/C_2H_5OH decreased from 10:0 to 7:3. These experimental data show some similarities with those reported by Matsuyama and Mishima.[13] C_2H_5OH is a good solvent for PEG. As the quantity of C_2H_5OH increases, there may be two possibilities. First, the increase of C_2H_5OH causes a stronger cosolvent effect which increases the solvency of DCM + C_2H_5OH; second, the addition of C_2H_5OH reduces the antisolvent effect of supercritical CO_2, which results in the more difficult precipitation of the solute. This possibility can be concluded from the data reported by Tsivintzelis et al.[16] With the same temperature, the bubble-point pressure of the

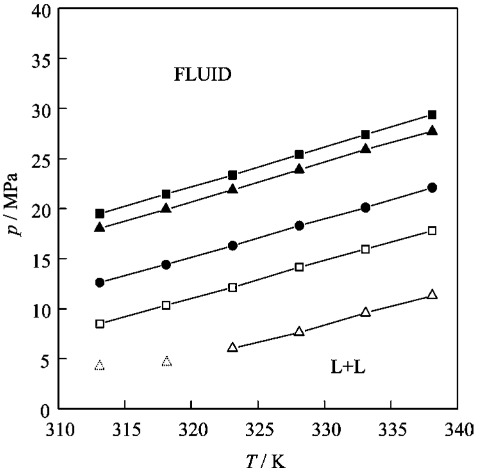

Figure 3. $p-T$ isopleths of the PLA-PEG-PLA ($f = 0.15$) + CO_2 + DCM system with different mass fractions of DCM. w = ■, 0.3051; ▲, 0.3195; ●, 0.3534; □, 0.3819; black △, 0.4437; gray △, 0.4437^B.

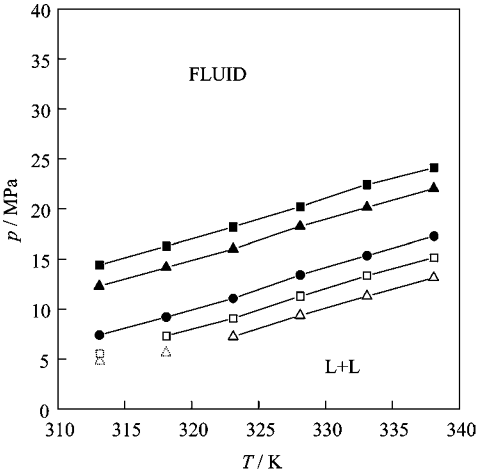

Figure 4. $p-T$ isopleths of the PLA-PEG-PLA ($f = 0.15$) + CO_2 + DCM + C_2H_5OH system (R = 9:1) with different mass fractions of DCM + C_2H_5OH. w = ■, 0.2601; ▲, 0.2897; ●, 0.3235; black □, 0.3640; black △, 0.3820; gray □, 0.3640^B; gray △, 0.3820^B.

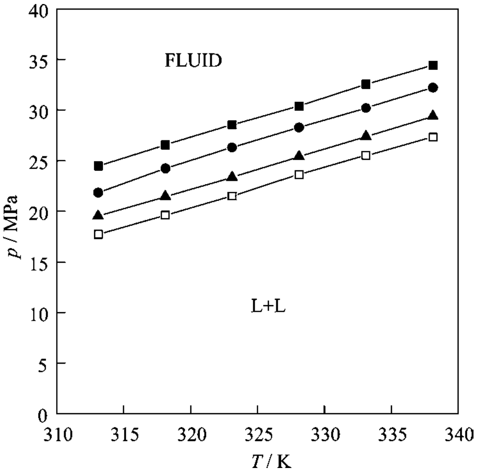

Figure 5. $p-T$ isopleths of the PLA-PEG-PLA (with different PEG mass fractions f) + CO_2 + DCM system ($w = 0.3$). f = ■, 0.05; ●, 0.10; ▲, 0.15; □, 0.20.

$CO_2-C_2H_5OH$ system is higher than that of the CO_2-DCM system. That is to say, the miscibility of CO_2-DCM is higher than that of $CO_2-C_2H_5OH$; thus, the antisolvent effect of supercritical CO_2 may be reduced because of the increase of C_2H_5OH in the system.

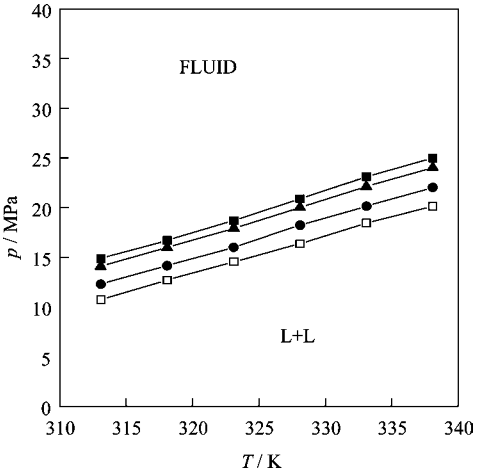

Figure 6. $p-T$ isopleths of the PLA-PEG- PLA + CO_2 + DCM + C_2H_5OH system (R = 9:1) with different PEG mass fractions f ($w = 0.3$). f = ■, 0.05; ▲, 0.10; ●, 0.15; □, 0.20.

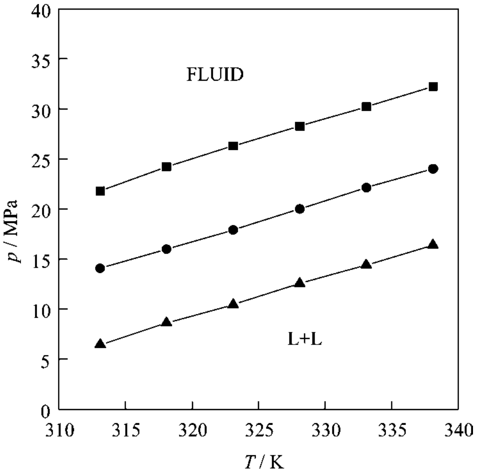

Figure 7. $p-T$ isopleths of the PLA-PEG-PLA ($f = 0.10$) + CO_2 + DCM + C_2H_5OH system with different R ($w = 0.3025$). R = ■, 10:0; ●, 9:1; ▲,7:3.

As discussed above, except for the molar ratio of DCM/C_2H_5OH in the solvent mixture, the phase behavior of the experimental systems is greatly affected by temperature, the mass fraction of DCM (or DCM + C_2H_5OH), and the PEG mass fraction in PLA-PEG-PLA. To explain the effects of them on the cloud-point pressure more vividly, three space diagrams are selected to illustrate the effect of temperature and the mass fraction of DCM (or DCM + C_2H_5OH) on cloud-point pressure with PEG mass fractions of 0.05, 0.10, 0.15, and 0.20. Figures 8 and 9 are the three space diagrams for the PLA-PEG-PLA + CO_2 + DCM system and the PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH system, respectively, where the top part was the single-phase region and the bottom part was the two-phase region.

Conclusion

The cloud point experiments indicate LCST phase behavior for both the PLA-PEG-PLA + CO_2 + DCM system and the PLA-PEG-PLA + CO_2 + DCM + C_2H_5OH system; that is, an increase of temperature leads to a reduction of the solvency of DCM (or DCM + C_2H_5OH) for PLA-PEG-PLA. The increase of the mass fraction of DCM (or DCM + C_2H_5OH) causes the increase of solvent polarity, which enlarges the solvency of DCM (or DCM + C_2H_5OH) and leads to lower cloud-point pressure values. At given experimental factors, the more PEG

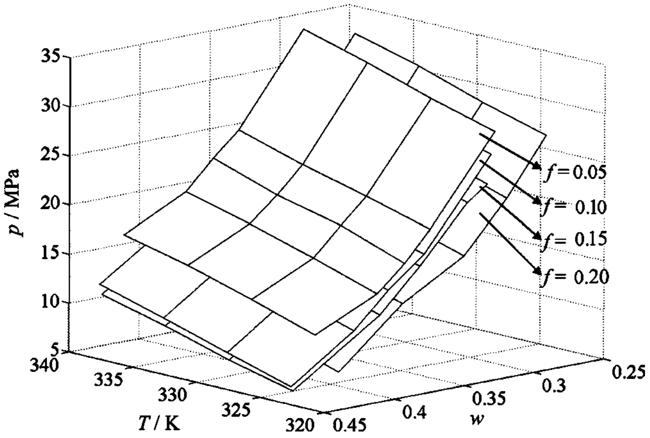

Figure 8. Cloud points in the $p-T-w$ space diagram of the PLA-PEG-PLA (with different PEG mass fractions f) + CO_2 + DCM system.

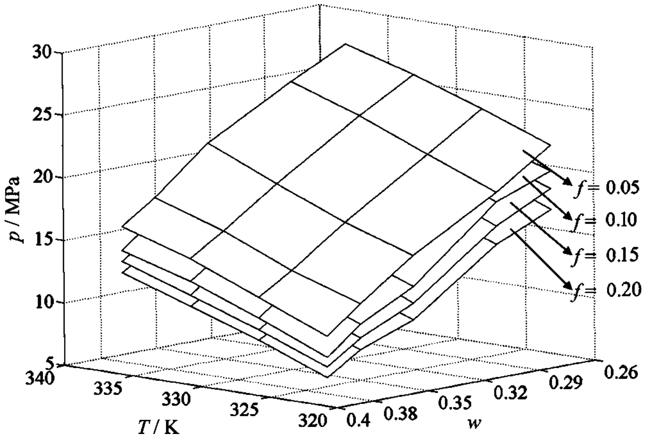

Figure 9. Cloud points in the $p-T-w$ space diagram of the PLA-PEG-PLA (with different PEG mass fractions f) + CO_2 + DCM + C_2H_5OH system.

in the copolymer, the higher its solubility in the chosen supercritical systems. Also, the addition of C_2H_5OH in the PLA-PEG-PLA + CO_2 + DCM system causes the decrease of cloud-point pressure and the increase of bubble-point pressure.

List of Symbols for Abbreviation

B	bubble point, MPa
f	the PEG mass fraction in PLA-PEG-PLA
m	the mass of PLA-PEG-PLA, g
p	the pressure of cloud point (or bubble point), MPa
R	the molar ratio of DCM/C_2H_5OH
T	temperature, K
w	the mass fraction of DCM (or DCM + C_2H_5OH) in the system

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