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Cloud-point measurement of the biodegradable poly(d,l-lactide-co-glycolide) solution in supercritical fluid solvents

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Abstract−Experimental data of high pressure phase behavior between 35 °C and 105 °C and pressures up to 2,200 bar is presented for poly(d,l-lactic acid)(d,l-PLA) and poly(lactide-co-glycolide)$_{15}$ ($PLGA_{15}$), $PLGA_{25}$, and $PLGA_{50}$ in supercritical carbon dioxide, trifluoromethane (CHF_3), chlorodifluoromethane ($CHClF_2$), dichloromethane (CH_2Cl_2), and chloroform ($CHCl_3$). d,l-PLA dissolves in carbon dioxide at pressures of 1,250 bar, in CHF_3 at pressures of 500 to 750 bar, and in $CHClF_2$ at pressures of 30-145 bar. As glycolic acid (glycolide) is added to the backbone of PLGA, the cloud point pressure increases by 36 bar/(mol GA) in carbon dioxide, 27 bar/(mol GA) in CHF_3, and by only 3.9 bar/(mol GA) in $CHClF_2$. $PLGA_{50}$ does not dissolve in carbon dioxide at pressures of 2,800 bar, whereas it is readily soluble in $CHClF_2$ at pressures as low as 95 bar at 40 °C. Cloud point behavior of d,l-PLA, $PLGA_{15}$, and $PLGA_{25}$ in supercritical carbon dioxide shows the effect of glycolide content between 35 °C and 108 °C. Also, the phase behavior for poly(lactic acid) - carbon dioxide-$CHClF_2$ mixture shows the changes of pressure-temperature slope, and with $CHClF_2$ concentration of 6 wt%, 19 wt%, 36 wt% and 65 wt%. The cloud-point behavior shows the impact of glycolide content on the phase behavior of PLA, $PLGA_{15}$, $PLGA_{25}$ and $PLGA_{50}$ in supercritical $CHClF_2$. A comparison was made between the phase behaviors of d,l-PLA and poly(l-lactide)(l-PLA) in supercritical CHF_3. The phase behavior of CHF_3 as a cosolvent for 5 wt% d,l-PLA-supercritical carbon dioxide system is presented for the effect being added 10 wt% and 29 wt% to CHF_3 content.

Key words: Poly(l-lactide), Poly(lactide-co-glycolide), Cloud Point Data, Supercritical CO_2, $CHClF_2$, CHF_3, Phase Behavior, $CHCl_3$, CH_2Cl_2

INTRODUCTION

Supercritical fluids are an attractive alternative to incompressible liquid solvents, since they can have liquid-like dissolving power while exhibiting the transport properties of a gas. They have been used in a variety of polymer processes such as polymerization process, extraction, separation, and industrial application [McHugh and Krukonis, 1994; Benedetti et al., 1997; Lee, 2003; Lee et al., 2006].

Poly(d,l-lactide-co-glycolide) (PLGA) has been utilized in the medical industry such as in biodegradable sutures [Middleton and Tipton, 1998; Park et al., 2004]. PLGA has been tested for numerous biological applications including polymeric drug delivery devices, synthetic bone scaffolding and dental prosthetic devices [Mandel and Wang, 1999; Kim et al., 1996; Bodmeier et al., 1995]. Since PLGA is used in biological applications, the solvents used to process these copolymers should be pharmacologically acceptable. Recently, supercritical CO_2 has been investigated as a viable solvent for processing PLGA copolymers. To thermodynamic knowledge, the phase behavior of PLGA copolymers in CO_2 has been reported [Kuk et al., 2002; Conway et al., 2001]. Kuk et al. have performed experimental phase behavior studies for poly(d,l-lactide)-HCFC-22, HFC-23 and HFC-32 system at temperature 40 °C to 100 °C using a high pressure equilibrium apparatus equipped with a variable volume view cell. The phase behavior experimental data for poly(lactide-coglycolide) solution in supercritical CO_2, CHF_3 and $CHClF_2$ were reported by Conway et al. [2001]. Conway et al. studied the phase behavior and mixture density data between 20 and 100 °C and pressures to 3,000 bar.

The purpose of this work is to present the determination of the impact of glycolic acid content in PLGA on the temperatures and pressures. We measured the cloud-point of l-PLA, d,l-PLA, $PLGA_{15}$, $PLGA_{25}$ and $PLGA_{50}$ in solvent mixtures of compressed liquid ($CHCl_3$ and CH_2Cl_2) and supercritical CO_2, CHF_3 and $CHClF_2$. The cloud-point behavior measuring technique has been used to determine the location of the phase boundary between fluid (single) phase and two-phase regions [Kirby and McHugh, 1999]. We measured the phase behavior by using a high pressure phase equilibria apparatus with a variable-volume view cell. The cloud-point pressures of the biodegradable polymers in supercritical CO_2, CHF_3 and $CHClF_2$ were characterized as functions of pressure, temperature and glycolide concentration. The cloud-point data presented in this work would be useful for establishing operating conditions in the biopolymer particle formation using supercritical fluid solvent processing.

EXPERIMENTAL SECTION

Fig. 1 shows a schematic diagram of the experimental high-pressure apparatus. A detailed description of the experimental apparatus and procedure is given in the previous paper reported [Byun and McHugh, 2000]. The high-pressure variable-volume view cell used in this study is to obtain phase behavior data. The main body

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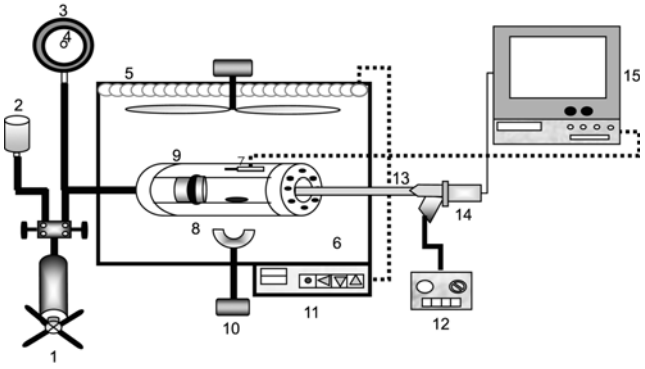

Fig. 1. Schematic diagram of the experimental high-pressure apparatus for biopolymer-supercritical fluid solvents mixture.

1. Pressure generator	9. Variable cell
2. Water	10. Motor
3. Pressure gauge	11. Temp. controller
4. Fan	12. Light source
5. Heater	13. Borescope
6. Air bath	14. Camera
7. Temperature indicator	15. TV monitor
8. Magnetic stirrer	

of the variable-volume cell apparatus is a high nickel content steel (7.0 cm O.D. and 1.59 cm I.D.) with ~28 cm^3 working volume. A sapphire window (1.9 cm O.D.×1.9 cm thick) is fitted to one end of the cell so that the cloud point can be determined visually. The view cell is compressed to the desired operating pressure by displacing a movable piston fitted within the cell using water pressurized with a high-pressure generator (HIP, Inc., Model 37-5.75-60). The system pressure is measured on the water side of the piston with a Heise gauge (Dresser Ind., model CM-108952, 0-3450 bar, accurate to within ±3.5 bar). A small correction of one bar is added to the pressure to compensate for the pressure needed to move the piston. The temperature of the view cell is measured to within ±0.2 °C with a platinum-resistance thermometer (Thermometrics Corp., Class A) and connected to a digital multimeter (Yokogawa, model 7563, accurate to within ±0.005%). The mixture inside the cell is viewed on a video monitor using a CCD camera (Watec Co., model WAT-202B) coupled to a borescope (Olympus Corp., model F100-038-000-50) placed against the outside of the sapphire window. Light is transmitted into the cell with a fiber optic cable connected at one end to a high-density illuminator (Olympus Optical Co., model ILK-5) and at the other end to the borescope.

While being maintained at room temperature, the cell is purged first with nitrogen at pressures of 3 to 5 bar and then with the CO_2 solvent at 3 to 6 bar to remove any entrapped air and organic matter. Approximately 1.0 to 8.0±0.004 g of CO_2 are transferred into the cell, which had been previously loaded with 0.1 to 7.0±0.002 g of polymer and copolymer, depending on the desired about 5 wt% polymer or copolymer in solution.

Cloud points are measured for binary and ternary solutions with a fixed biodegradable copolymer or polymer concentration of ~5 wt%. Cloud points are measured and reproduced at least twice to within ±2.8 bar and ±0.2 °C. The cloud point pressure is defined as the point at which the solution becomes so opaque that it is no longer possible to see the stir bar in the mixture.

1. Materials

Table 1. The properties of PLGA copolymers and d,l-PLA polymer used in this work

Polymers	i.v.*	M_w	M_w/M_n	T_g (°C)
d,l-PLA	0.35-0.45	20,000-30,000	1.8	55
$PLGA_{15}$	0.50-0.65	~20,000	1.8	50-55
$PLGA_{25}$	0.50-0.65	~20,000	1.8	50-55
$PLGA_{50}$	0.50-0.65	~12,000-16,000	1.8	45-50

*i.v. is an inherent viscosity (dl/g)

The biodegradable polymers used in this study were obtained from Polysciences, Inc. (Cincinnati, OH). The detailed content of polymer and copolymers presented the Table 1. The poly(l-lactic acid) [l-PLA; M_w=200,000] was obtained from Honam Petroleum Chemical Co.

CHF_3 (98% minimum purity), $CHCl_3$ (99.9% purity, HPLC grade) and CH_2Cl_2 (99.9% purity, HPLC grade) was obtained from Aldrich Chemical Company. CO_2 (99.9% minimum purity) was obtained from Daesung Industrial Gases Co., and $CHClF_2$ (99.8% minimum purity) from Dongil Gas (Yeosu, Korea). All of the solvents and biodegradable polymers were used as received without further purification.

RESULTS AND DISCUSSION

Table 2 shows the physicochemical properties of CO_2, CHF_3, $CHClF_2$, $CHCl_3$ and CH_2Cl_2 [Reid et al., 1987; Daubert and Danner, 1989; Prausnitz et al., 1986; Meyer et al., 1980; Benson et al., 1969]. Notice that the polarizability of CO_2 and CHF_3 is identical, which implies that the impact of the quadrupole moment of CO_2 can be contrasted to the impact of the dipole moment of CHF_3 on the phase behavior. The dipole moments of CHF_3 and $CHClF_2$ are 1.6 and 1.5 Debye, respectively, and the cloud-point behavior of the d,l-PLA in CHF_3 and $CHClF_2$ can be compared to determine the impact of polarizability on the phase behavior. Also, the dipole moments of $CHCl_3$ and CH_2Cl_2 show a big difference (1.1 and 1.8 Debye). We compared the phase behaviors of $PLGA_{15}$ in different supercritical $CHCl_3$ and CH_2Cl_2.

Fig. 2 shows the impact of glycolic acid content on phase behavior of d,l-PLA, $PLGA_{15}$ and $PLGA_{25}$ in supercritical CO_2. The phase behavior for $PLGA_{15}$-CO_2 and $PLGA_{25}$-CO_2 system exhibits UCST region curve with negative slope in –0.6 bar/°C ($PLGA_{15}$) and –2.6 bar/°C ($PLGA_{25}$), respectively. The cloud-point curve for d,l-PLA-supecritical CO_2 system exhibits an LCST curve with positive slope in 1.4 bar/°C (d,l-PLA). The switch from a positive to a negative

Table 2. Critical temperature Tc, critical pressure Pc, polarizability α, and dipole moment μ of the five solvents used in this study

Solvents	T_c (°C)	P_c (bar)	α ($cm^3 \times 10^{25}$)	μ (Debye)
CO_2	31.0	73.8	26.5	0.0
CHF_3	26.2	48.6	26.5	1.6
$CHClF_2$	96.2	49.7	44.4	1.5
$CHCl_3$	263.25	53.7	82.6	1.1
CH_2Cl_2	236.85	63.0	64.8	1.8

CO_2 possesses a quadrupole moment of -4.3×10^{-26} $erg^{1/2}$ $cm^{5/2}$.

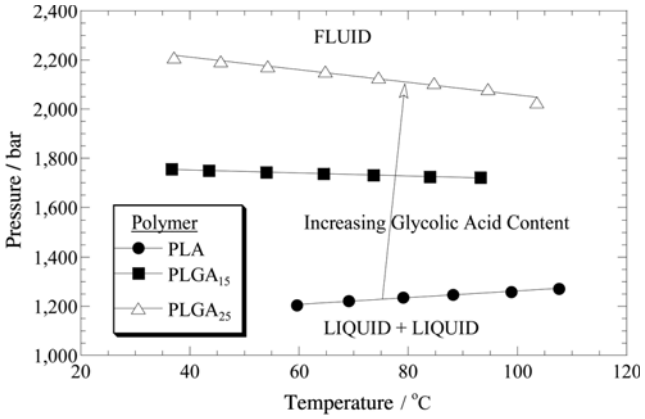

Fig. 2. Impact of glycolic acid (glycolide) content on the phase behavior of PLA, $PLGA_{15}$ and $PLGA_{25}$ in pure supercritical CO_2.

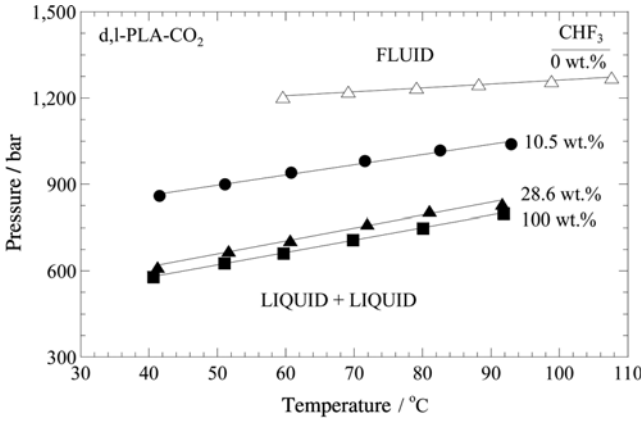

Fig. 4. Effect of CHF_3 as a cosolvent for poly(d,l-lactic acid) in supercritical CO_2. The polymer concentration is ~5.0 wt% for each solution.

slope suggests that the interchange energy, which is a measure of copolymer-CO_2 interactions relative to copolymer-copolymer and CO_2-CO_2 interactions, is weighted more toward copolymer-copolymer interactions rather than cross-interactions. A cloud point curve with a negative slope also clearly shows that increasing the system pressure, or conversely, does not help in obtaining a single phase as the system temperature is lowered.

It is apparent that the pressures needed to obtain a single phase are fixed more by the glycolic acid content in the backbone of the copolymer rather than the copolymer weight average molecular weight (M_w). As shown in Fig. 2, if M_w governed the location of the cloud point curve, the $PLGA_{15}$ and $PLGA_{25}$ curves would be at pressures below which needed to dissolve PLA_H rather than at higher pressures. The $PLGA_{50}$ does dissolve in pure CO_2 to a temperature of 120 °C and pressure of 2,800 bar.

Fig. 3 shows the effect of $CHClF_2$ as a cosolvent for poly(d,l-lactic acid) in supercritical CO_2. In Fig. 4, the phase behavior of the d,l-PLA-CO_2-DME mixture was shown. The d,l-PLA-CO_2 mixture was obtained in the range of temperature of 60-107 °C and at pressures of 1,204-1,270 bar, and for d,l-PLA-chlorodifluoromethane ($CHClF_2$) mixture at the range of temperature of 65-105 °C and pressures of 28-143 bar. The pressure difference between two systems is due to whether or not a dipole moment in $CHClF_2$ (1.3 Debye) [Reid et al., 1987] and CO_2 (0.0 Debye) [Reid et al., 1987].

As shown in Fig. 3, the d,l-PLA-CO_2-6.3 wt% $CHClF_2$ mixture shows LCST-type behavior of the positive slope, and then the pressure increases slightly at 70-98 °C. With 18.7 wt% $CHClF_2$ added to the solution, the cloud-point curve exhibits LCST region phase behavior of a positive slope in 4.1 bar/°C. When 35.8 and 64.9 wt% $CHClF_2$ is added in the d,l-PLA-CO_2 mixture, which shows the LCST-type of the positive slope in 4.6 bar/°C and 3.9 bar/°C, respectively. At 80 °C, the pressure difference of the d,l-PLA-CO_2-35.8 and 64.9 wt% $CHClF_2$ system shows about 300 bar, which is caused by the impact of free volume as $CHClF_2$ concentration increases.

Fig. 4 shows the effect of CHF_3 as a cosolvent for d,l-PLA in supercritical CO_2. The d,l-PLA-CO_2 mixture was obtained in the range of temperature of 60-108 °C and at pressures of 1,200-1,270 bar, and for d,l-PLA-CHF_3 mixture from 40-90 °C and pressures of 580-800 bar. The pressure difference between two systems is due to whether or not a dipole moment in CHF_3 (1.6 D) and CO_2 (0.0 D),

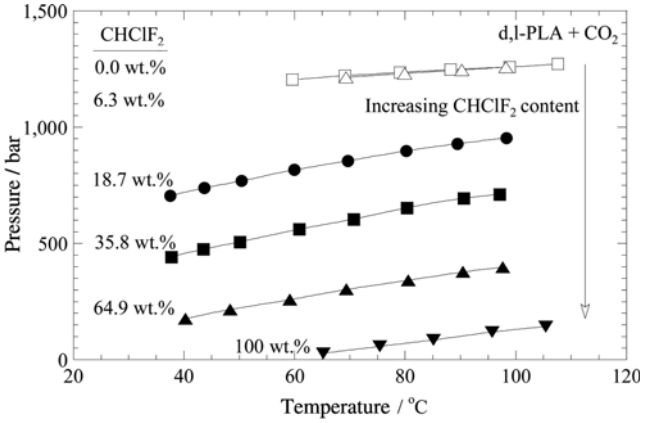

Fig. 3. Effect of $CHClF_2$ as a cosolvent for poly(d,l-lactic acid) [d,l-PLA] in supercritical CO_2. The polymer concentration is ~5.0 wt% for each solution.

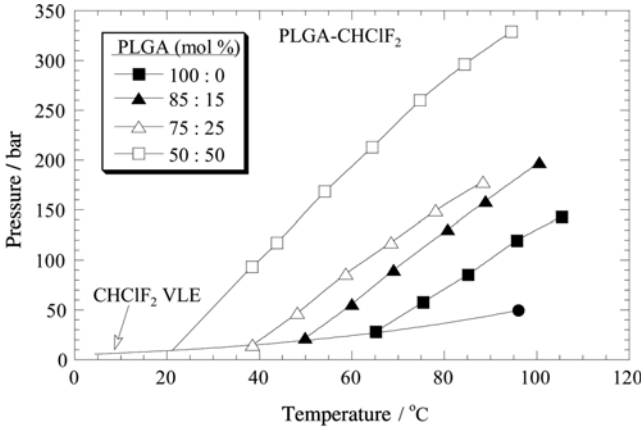

Fig. 5. Impact of glycolide content on the phase behavior of PLA, $PLGA_{15}$, $PLGA_{25}$ and $PLGA_{50}$ in supercritical $CHClF_2$. The solid circle is the critical point of $CHClF_2$. The seven cloud point curves terminate on the vapor pressure curve of $CHClF_2$.

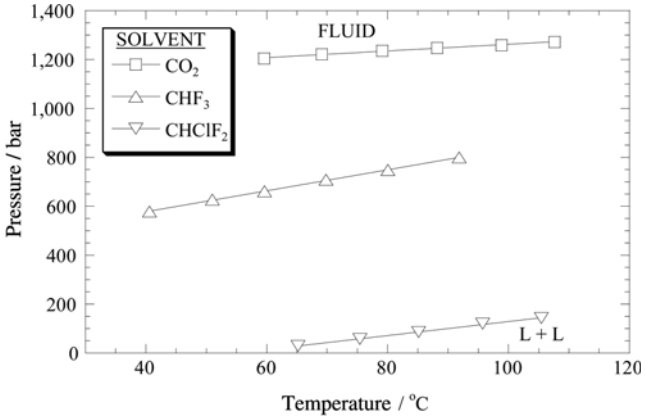

Fig. 6. Comparison of different supercritical fluid solvents for dissolving poly(d,l-lactic acid).

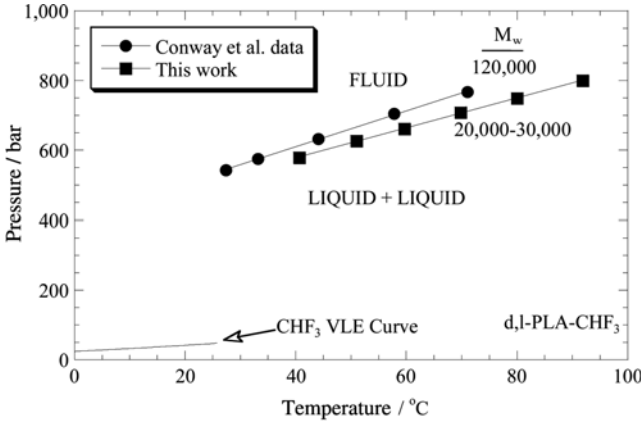

Fig. 7. Effect of weight average molecular weight for experiment data and Conway et al. data [2001] on the phase behavior of poly(d,l-lactic acid) in supercritical CHF_3.

as shown in Table 2. The d,l-PLA-CO_2-10.5 wt% CHF_3 system exhibits LCST type phase behavior to positive slope in 3.6 bar/°C. The cloud-point pressure decreases as the temperature decreases in the range from 42 to 94 °C. With 28.6 wt% CHF_3 in solution, the cloud-point pressure curve shows the LCST behavior of positive slope (4.5 bar/°C) at pressures from 610 bar to 830 bar and at temperature range of 40 to 90 °C.

Fig. 5 shows a pressure-temperature diagram of phase behavior for d,l-PLA, $PLGA_{15}$, $PLGA_{25}$ and $PLGA_{50}$ in $CHClF_2$. Although it is not possible to dissolve $PLGA_{50}$ in pure CO_2, this $PLGA_{50}$ copolymer readily dissolves in $CHClF_2$ even at temperatures as low as 20 °C. This means that LCST behavior is sensitive to the glycolic acid concentration in PLGA. As the glycolide content in PLGA increases, the two-phase region expands. The slope of the curve reported by Lele and Shine [1994] is approximately 3.0 bar/°C and here the positive slopes of the cloud point curves are 2.9, 3.5, 3.3, and 4.3 bar/°C for d,l-PLA, $PLGA_{15}$, $PLGA_{25}$, and $PLGA_{50}$, respectively.

Fig. 6 shows the phase behavior curve of d,l-PLA dissolved in supercritical CO_2, CHF_3 and $CHClF_2$. The cloud-point behavior for d,l-PLA-CO_2 (1.4 bar/°C), -CHF_3 (4.3 bar/°C) and -$CHClF_2$ (2.9 bar/°C) system exhibits lower critical solution temperature (LCST) curves with a positive slope. The d,l-PLA-CO_2 system is presented at the temperature range of 59-107 °C and pressure up to 1,270 bar. The d,l-PLA-CHF_3 mixture shows at the temperature from 59 to 107 and the pressure range of 579-800 bar. Also, the d,l-PLA-$CHClF_2$ system is presented at the temperature range of 65-105 °C and the pressure from 28 to 143 bar. At 90 °C, the phase behavior boundary has shifted at ~1,250 bar (CO_2), ~800 bar (CHF_3) and ~100 bar ($CHClF_2$), and it is due to the polarizability difference of CO_2 (26.5×10^{-25} cm^3) and $CHClF_2$ (44.4×10^{-25} cm^3). Also, the CHF_3 system shows at 1,250 bar (CO_2) and 800 bar (CHF_3), and it is due to the dipole moment difference of CO_2 (0.0 Debye) and CHF_3 (1.6 Debye). As shown in Table 2, it seems to be due to polarizability and dipole moment difference for the CO_2, CHF_3 and $CHClF_2$. The pressure difference for d,l-PLA-CO_2, d,l-PLA-CHF_3 and d,l-PLA-$CHClF_2$ mixture is considered by means of polarity factor. Very low pressures are needed to dissolve the PLGA copolymers in contrast to the kilobar pressures needed with CO_2 and near-kilobar pressures needed with CHF_3, even though both $CHClF_2$ and CHF_3 have similar dipole moments. However, $CHClF_2$ is a better solvent for PLGA than CHF_3 since it has a larger polarizability than the other two SCF solvents and also it has hydrogen that is probably more acidic than the hydrogen in CHF_3.

Fig. 7 shows the effect of weight average molecular weight on the phase behavior of d,l-PLA in supercritical CHF_3. The cloud-point curve exhibits LCST type behavior of the positive slope in 5.2 bar/°C (Conway et al.) and 4.3 bar/°C (this work). As shown in Fig. 7, the pressure difference of two curves is presented at about 50 bar and at temperature of 60 °C. This difference seems to be due to weight average molecular weight (M_w) difference.

Fig. 8 shows the impact of glycolic acid content on the phase behavior of d,l-PLA and $PLGA_{25}$ in pure supercritical CHF_3. It is clear that adding 25 mol% glycolide to the backbone of PLA shifts the CHF_3 cloud point pressures by as much as ~700 bar at 40 °C. The cloud-point curves of PLGA-CHF_3 system show similarly the phase behavior for PLGA-CO_2 mixture in Fig. 2. The pressure curve of $PLGA_{25}$-CHF_3 system increases as a glycolic acid (25 mol%) concentration increase. The $PLGA_{25}$-CHF_3 curve exhibits LCST type with a positive slope (2.5 bar/°C) at pressures from 1,300 bar to 1,430 bar and a temperature range of 40-92 °C.

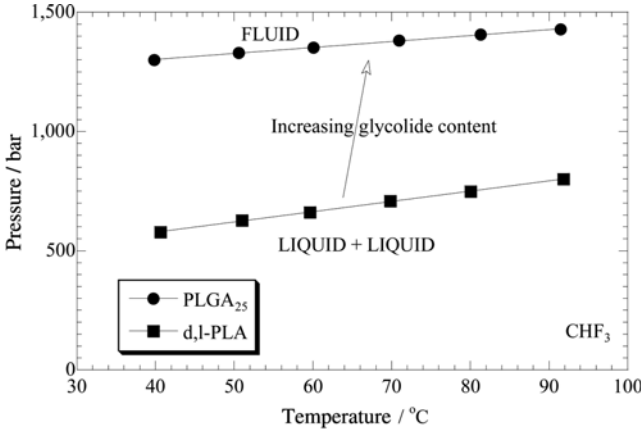

Fig. 8. Impact of glycolide content on the phase behavior of d,l-PLA and $PLGA_{25}$ in pure supercritical CHF_3.

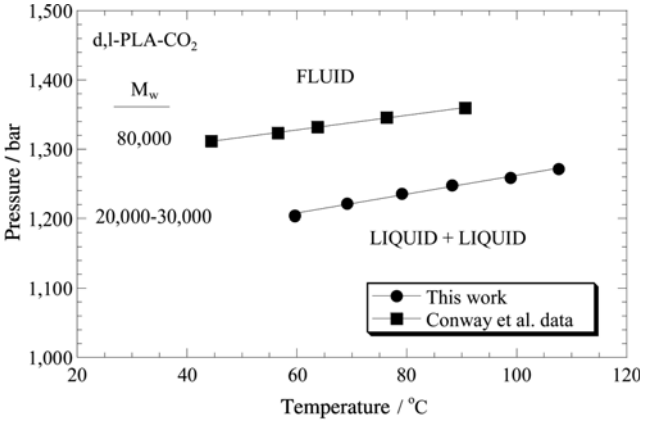

Fig. 9. Comparison of weight average molecular weight for experiment data and Conway et al. data [12] on the phase behavior of poly(d,l-lactide) in supercritical CO_2.

This shift is not quite as large as that observed with CO_2 as shown in Fig. 2. Both CO_2 and CHF_3 have approximately the same polarizability, and also both of them have some polarity, that is, CHF_3 has a dipole moment of 1.6 Debye and CO_2 does a quadrupole moment of -4.3×10^{-26} erg$^{1/2}$ cm$^{5/2}$. However, CHF_3 has an acidic proton that is capable of hydrogen bonding with the ester groups in PLGA, whereas CO_2 is not expected to form any type of complex with PLGA. More than likely, the ability of CHF_3 to form a complex with PLGA makes it a better solvent than CO_2 especially since any change in favorable energetic interactions is magnified in these dense SCF solvents.

Fig. 9 shows the impact of M_w for experimental data and Conway et al. data [9] on the phase behavior of the d,l-PLA-CO_2 system. These cloud point curves exhibit an LCST type of slight positive slope in 1.1 bar/°C (M_w=80,000) and 1.4 bar/°C (M_w=20,000-30,000). The two cloud point curves in Fig. 9 are separated by approximately 110 bar for the molecular weight difference of ~55,000 as compared to the pressure difference of 900 bar between the d,l-PLA and $PLGA_{25}$ curves in Fig. 2.

Fig. 10 shows the impact of Mw and polymers on cloud-point behavior of d,l-PLA and poly(l-lactide)[l-PLA] in supercritical

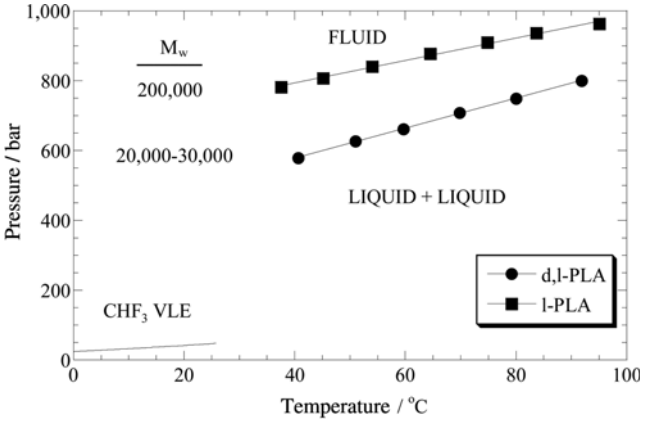

Fig. 10. Impact of weight average molecular weight on the phase behavior of poly(d,l-lactide) [d,l-PLA] and poly(l-lactide) [l-PLA] in supercritical CHF_3.

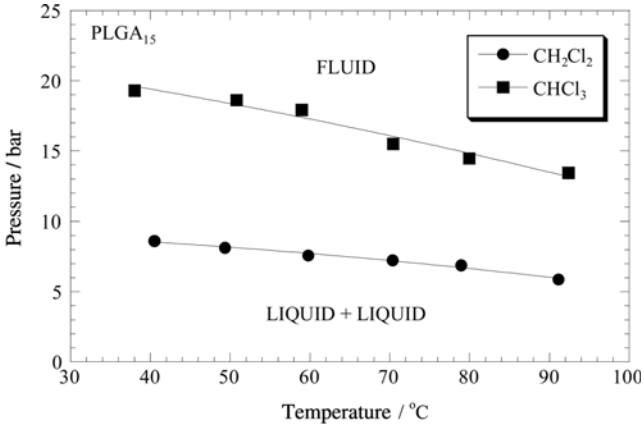

Fig. 11. Comparison of different supercritical fluid solvents (CH_2Cl_2 and $CHCl_3$) for dissolving $PLGA_{15}$.

CHF_3. The pressure difference shows approximately 200 bar for a molecular weight difference of about 175,000 between the d,l-PLA-CHF_3 and l-PLA-CHF_3 mixture. Also, The two phase behavior curves exhibit the LCST type of positive slope in 3.2 bar/°C (l-PLA) and 4.3 bar/°C (d,l-PLA).

Fig. 11 shows the impact of cloud-point for the $PLGA_{15}$-CH_2Cl_2 and $PLGA_{15}$-$CHCl_3$ mixture at temperature range of ~40-90 °C and at lower pressure below ~20 bar.

The phase behavior difference is due to dipole moment 1.1 D ($CHCl_3$) and 1.8 D (CH_2Cl_2). These two cloud-point curves exhibit UCST type behavior of a negative slope in −0.05 bar/°C (CH_2Cl_2) and −0.12 bar/°C ($CHCl_3$) at lower pressure.

CONCLUSIONS

CO_2 is a poor quality solvent for PLGA (glycolide=0.0, 15, 25 and 50 wt%) copolymers. Particularly, it is impossible for the $PLGA_{50}$-CO_2 mixture to dissolve at temperature to 120 °C and pressures up to 2,800 bar. The phase behavior for d,l-PLA-CO_2, $PLGA_{15}$-CO_2 and $PLGA_{25}$-CO_2 system exhibits UCST region curve with negative slope in −0.6 bar/°C ($PLGA_{15}$) and −2.6 bar/°C ($PLGA_{25}$), and LCST curve with positive slope in 1.4 bar/°C (d,l-PLA). As the glycolide concentration in the backbone increases, the phase behavior pressure increases substantially to obtain a single phase. The effect of glycolide and weight average molecular weight on the cloud point pressure is significant of the effect with supercritical CO_2, $CHClF_2$, CHF_3, $CHCl_3$ and CH_2Cl_2. The differences in the phase behavior exhibited by the d,l-PLA-, $PLGA_{15}$-, $PLGA_{25}$- and $PLGL_{50}$-SCF solvent systems are related to those in intermolecular interactions between the components in the solution. The $CHClF_2$ data strongly suggest that a polar cosolvent capable of hydrogen bonding to the ester linkage in PLGA (0.0-50 mol%) is needed if low pressure, single-phase processing of this copolymer is desired.

However, d,l-PLA, $PLGA_{15}$, $PLGA_{25}$ and $PLGL_{50}$ polymers can be intimately mixed with a variety of insoluble materials at low pressures in pure CO_2 since the glass transition temperature of the biodegradable polymer is significantly lowered by the plasticization effect of supercritical CO_2.

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