

# Poly(lactide-co-glycolide) Solution Behavior in Supercritical CO<sub>2</sub>, CHF<sub>3</sub>, and CHClF<sub>2</sub>

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**ABSTRACT:** Cloud point and solution density data between 20 and 100°C and pressures to 3000 bar are presented for poly(lactide) (PLA) and poly(lactide-co-glycolide) (PLGA<sub>x</sub>), where the molar concentration of glycolide in the backbone  $x$  ranges from 0 to 50 mol % in supercritical CO<sub>2</sub>, CHClF<sub>2</sub>, and CHF<sub>3</sub>. PLA dissolves in CO<sub>2</sub> at pressures near 1400 bar, in CHF<sub>3</sub> at pressures of 500 to 750 bar, and in CHClF<sub>2</sub> at pressures of 20–100 bar. As glycolide (GA) is added to the backbone of PLGA, the cloud point pressure increases by 50 bar/(mol GA) in CO<sub>2</sub>, 25 bar/(mol GA) in CHF<sub>3</sub>, and by only 2.5 bar/(mol GA) in CHClF<sub>2</sub>. PLGA<sub>50</sub> does not dissolve in CO<sub>2</sub> to pressures of 3000 bar whereas it is readily soluble in CHClF<sub>2</sub> at pressures as low as 100 bar at 50°C. In comparison, the increases in cloud point pressure with increasing weight average molecular weight ( $M_w$ ) are only approximately 2.3 bar/(1000  $M_w$ ) for PLGA copolymers in CO<sub>2</sub>. The solution densities with all three SCF solvents range from 1.1 to 1.5 g/cm<sup>3</sup> and they vary only by a small amount over the 80°C range used to obtain cloud point data. More than likely, the ability of the acidic hydrogen in CHF<sub>3</sub> and CHClF<sub>2</sub> to complex with the ester linkage in PLGA makes these better solvents than CO<sub>2</sub> especially since any change in favorable energetic interactions is magnified due to the liquid-like densities exhibited by these SCF solvents. © 2001 John Wiley & Sons, Inc. *J Appl Polym Sci* 80: 1155–1161, 2001

**Key words:** poly(lactide); poly(lactide-co-glycolide); cloud point data; solution density data; supercritical; CO<sub>2</sub>; CHClF<sub>2</sub>; CHF<sub>3</sub>

## INTRODUCTION

Copolymers of glycolide, a dimer of glycolic acid, and lactide, a dimer of lactic acid, (PLGA<sub>x</sub>) have

been utilized in the medical industry, beginning with biodegradable sutures that were first approved in the 1960s.<sup>1</sup> Since that time PLGA has been tested for numerous biological applications including polymeric drug delivery devices, synthetic bone scaffolding, and even dental prosthetic devices. Since PLGA is used in biological applications, the solvents used to process these copolymers should be pharmacologically acceptable. Recently supercritical CO<sub>2</sub> has been investigated as a viable solvent for processing PLGA

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**Table I Critical Temperature  $T_c$ , Critical Pressure,  $P_c$ , Polarizability  $\alpha$ , and Dipole Moment  $\mu$  of the Three Solvents Used in this Study<sup>19,20a</sup>**

Solvent	$T_c$ (°C)	$P_c$ (bar)	$\alpha$ (Å <sup>3</sup> )	$\mu$ (Debye)
CO <sub>2</sub>	31.0	73.8	2.65	0.0
CHF <sub>3</sub>	26.2	48.6	2.65	1.6
CHClF <sub>2</sub>	96.2	49.7	4.44	1.5

<sup>a</sup> The polarizability,  $\alpha$ , of the fluorinated solvents is calculated using the method of Miller and Savchik.<sup>20</sup> CO<sub>2</sub> also possesses a quadrupole moment of  $-4.3 \times 10^{-26}$  erg<sup>1/2</sup> cm<sup>5/2</sup>.

copolymers.<sup>2</sup> Although, to the best of our knowledge, the phase behavior of PLGA copolymers in CO<sub>2</sub> has not been reported, this fact is not surprising since CO<sub>2</sub> at pressures well below 700 bar does not dissolve PLGA copolymers, but it does lower the glass transition of the copolymer sufficiently to make it processible near ambient temperatures.<sup>2</sup> The focus of the work presented here is the determination of the impact of glycolic acid content in PLGA on the temperatures and pressures needed to completely dissolve PLGA copolymers in pure CO<sub>2</sub> rather than to just plasticize it. In addition, the phase behavior of the same PLGA copolymers in CHF<sub>3</sub> and CHClF<sub>2</sub> are measured to provide insight into the solvent character of CO<sub>2</sub>.

Table I shows the physicochemical properties of CO<sub>2</sub>, CHF<sub>3</sub>, and CHClF<sub>2</sub>. Notice that the polarizability of CO<sub>2</sub> and CHF<sub>3</sub> are identical, which implies that the impact of the quadrupole moment of CO<sub>2</sub> can be contrasted to the impact of the dipole moment of CHF<sub>3</sub> on the phase behavior.

Since the dipole moments of CHF<sub>3</sub> and CHClF<sub>2</sub> are very close, the phase behavior of the PLGA copolymers in CHF<sub>3</sub> and CHClF<sub>2</sub> can be compared to determine the impact of polarizability on the phase behavior. However, the hydrogen bonding between the hydrogen on CHF<sub>3</sub> and CHClF<sub>2</sub> and ester linkage in PLGA makes this comparison more tenuous since hydrogen-bonding interactions are close to ten times stronger than non-polar dispersion interactions.<sup>3-8</sup> Several other studies have also shown that CHClF<sub>2</sub> is an excellent solvent for polar polymers that can cross-associate with the acidic hydrogen in this solvent.<sup>9-15</sup>

Table II shows the properties of the amorphous PLGA copolymers and the amorphous poly(lactic acid) used in this study. The cyclic dimer of lactic acid used to synthesize the copolymers and the PLA is a mixture of the d and l optical isomers. The influence of molecular weight will be compared to that of glycolide content for several of the PLGA copolymers and for PLA. The density of the solution at the cloud point is also reported in addition to pressure and temperature of the cloud point for mixtures of a fixed concentration of ~5 wt %. These density data clearly show that the conditions needed to obtain a single phase are a complex function of temperature, pressure, and density.

## EXPERIMENTAL

A high-pressure view cell is used in this study to obtain cloud point data. The body of the cell is a high nickel content steel (Nitronic 50) with a 5.7 cm OD by 1.59 cm ID, and with approximately 30

**Table II Properties of d,1-PLGA Copolymers and d,1-PLA Polymers Used in this Study<sup>a</sup>**

Polymer	Weight Average Molecular Weight	Number Average Molecular Weight	Glass Transition Temperature (°C)
PLA <sub>L</sub>	84,500	60,600	49.9
PLA <sub>H</sub>	128,450	80,900	52.2
PLGA <sub>15H</sub>	149,000	86,100	50.7
PLGA <sub>15L</sub>	95,000	61,650	47.4
PLGA <sub>25</sub>	130,100	77,650	46.9
PLGA <sub>35H</sub>	141,000	80,100	48.2
PLGA <sub>35L</sub>	82,950	57,900	44.5
PLGA <sub>50</sub>	69,600	50,800	47.2

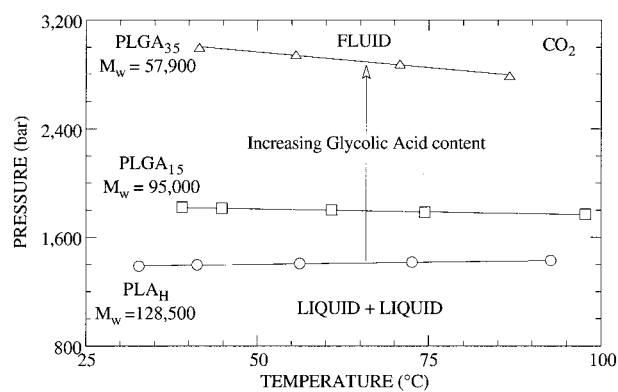
<sup>a</sup> The subscripts represent the percent glycolide in the backbone.

cm<sup>3</sup> working volume. A 1.9 cm OD × 1.9 cm thick sapphire window is fitted to one end of the cell so that the phase behavior can be determined visually. The cell contents are 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 accurate to within ±2.8 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 cell, measured to within ±0.2°C with a type-E thermocouple (Omega) connected to a digital multimeter, is also maintained to within ±0.2°C. The location of the piston is determined with a linear transducer coil (Lucas Schaevitz Company, 2000-HR Linear Variable Differential Transducer) that fits around a 9/16 in. high-pressure tube at the end of the cell. The transducer tracks the location of the magnetic tip of the rod that is connected to the piston. The volume of the cell as a function of piston location is known to within ±0.02 cm<sup>3</sup>.<sup>16</sup>

Cloud points are measured for solutions with a fixed copolymer or polymer concentration of ~5 wt % that is expected to be close to the maximum in the pressure-composition isotherm.<sup>15,16</sup> Cloud points are measured and reproduced at least twice to within ±2.8 bar and ±0.4°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 solution. Cloud points obtained in this manner are identical within reproducibility limits to those defined as the point at which there is a 90% drop in transmitted light through the solution. The pressure difference between the conditions when the solution just becomes hazy and totally opaque is less than 16 bar for 50 of the 54 data points presented here.

## MATERIALS

The polymers used in this study were obtained from Alkermes, Inc. (Cincinnati, OH). The molecular weights given in Table II are determined by Alkermes, Inc., using gel permeation chromatography calibrated relative to polystyrene standards. CHF<sub>3</sub> (98 % minimum purity) was obtained from Aldrich Chemical Company, Inc., CO<sub>2</sub> (bone dry grade, 99.8 % minimum purity) was obtained from Airgas, Inc., and CHClF<sub>2</sub>



**Figure 1** Impact of glycolic acid (glycolide) content on the phase behavior of PLGA<sub>x</sub> in pure supercritical CO<sub>2</sub>.

(99.8% minimum purity) was obtained from Matheson Gas Products. All of the solvents were used as received.

## RESULTS AND DISCUSSION

Figure 1 shows the effect of glycolide content in the backbone of the copolymer on the pressure needed to obtain a single phase in pure CO<sub>2</sub>. It is apparent that the pressures needed to obtain a single phase are fixed more by the glycolide content in the backbone of the copolymer rather than the copolymer weight average molecular weight ( $M_w$ ). In fact, if  $M_w$  governed the location of the cloud point curve, the PLGA<sub>15</sub> and PLGA<sub>35</sub> curves would be at pressures below that needed to dissolve PLA<sub>H</sub> rather than at higher pressures as shown in Figure 1. It is not possible to dissolve PLGA<sub>50</sub> in CO<sub>2</sub> to pressures of 3000 bar. Table III lists the solution density data for these mixtures at the cloud point. Notice that the solution density for each curve changes only a small amount over the pressure and temperature range of the cloud points, suggesting that density itself is not the dominant factor controlling solubility. Very high pressures and solution densities are needed to increase the cohesive energy density of CO<sub>2</sub> sufficiently to dissolve these polar polymers even though the polar quadrupole moment of CO<sub>2</sub> is expected to interact favorably with the polar moment of the ester linkage in PLGA.

Figure 2 shows the impact of  $M_w$  on the phase behavior of the PLA-CO<sub>2</sub> system. These cloud point curves exhibit a slight positive slope relative to the curves in Figure 1; however, the pressure axis is very expanded in Figure 2. The two

**Table III** Cloud Point and Density Data for PLA and PLGA in Supercritical CO<sub>2</sub> Obtained in this Study<sup>a</sup>

PLA <sub>L</sub>		
Temperature (°C)	Pressure (bar)	Density (g/cm <sup>3</sup> )
44.4	1312	1.213
56.5	1323	1.193
63.7	1332	1.182
76.3	1346	1.161
90.6	1360	1.137
PLA <sub>H</sub>		
Temperature (°C)	Pressure (bar)	Density (g/cm <sup>3</sup> )
32.7	1389	1.192
41.2	1398	1.179
56.2	1408	1.154
72.6	1418	1.130
92.7	1429	1.099
PLGA <sub>15L</sub>		
Temperature (°C)	Pressure (bar)	Density (g/cm <sup>3</sup> )
39.0	1822	1.243
44.8	1815	1.232
60.8	1801	1.207
74.4	1784	1.185
91.7	1770	1.158
PLGA <sub>15H</sub>		
Temperature (°C)	Pressure (bar)	Density (g/cm <sup>3</sup> )
36.7	1918	1.247
42.6	1901	1.237
56.3	1881	1.214
72.6	1860	1.188
85.5	1843	1.165
PLGA <sub>25</sub>		
Temperature (°C)	Pressure (bar)	Density (g/cm <sup>3</sup> )
38.9	2394	1.337
47.1	2373	1.323
62.2	2322	1.297
79.7	2249	1.266
79.8	2198	1.237

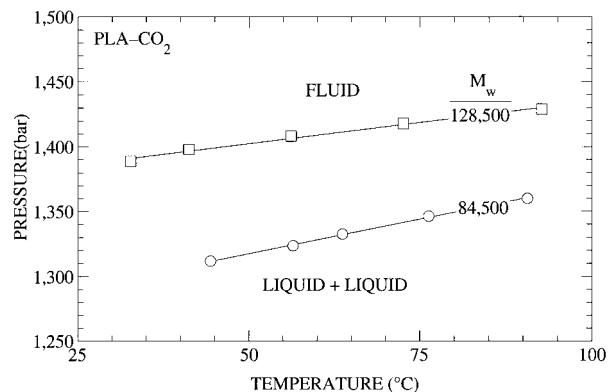
cloud point curves in Figure 2 are separated by approximately 70 bar for a molecular weight difference of 44,000 as compared to a pressure dif-

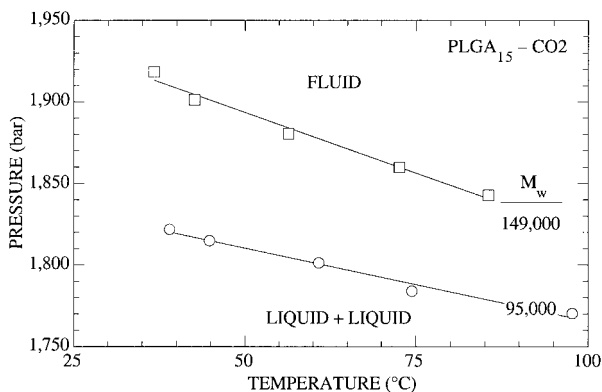
**Table III** *Continued*

PLGA <sub>35L</sub>		
Temperature (°C)	Pressure (bar)	Density (g/cm <sup>3</sup> )
41.5	2999	1.375
55.6	2946	1.352
70.8	2877	1.327
86.7	2791	1.299
PLGA <sub>35H</sub>		
Temperature (°C)	Pressure (bar)	Density (g/cm <sup>3</sup> )
43.4	3108	1.368
60.4	3022	1.339
79.9	2922	1.306
96.7	2822	1.269

<sup>a</sup> The subscripts L and H represent low and high molecular weights.

ference of 1500 bar between the PLA<sub>H</sub> and PLGA<sub>35</sub> curves. Figures 3 and 4 show that molecular weight also has only a minor effect on the location of the PLGA<sub>15</sub> and PLGA<sub>35</sub> curves similar to that observed for the PLA system. Also, the slopes of the PLGA<sub>15</sub> and PLGA<sub>35</sub> cloud point curves are now negative at approximately  $-1.2$  and  $-5.0$  bar/°C, respectively, compared to positive 0.9 bar/°C for the PLA curves. The switch from a positive to a negative slope suggests that the interchange energy, which is a measure of copolymer-CO<sub>2</sub> interactions relative to copolymer-copolymer and CO<sub>2</sub>-CO<sub>2</sub> interactions, is weighted more toward copolymer-copolymer interactions rather than cross-interactions. A cloud

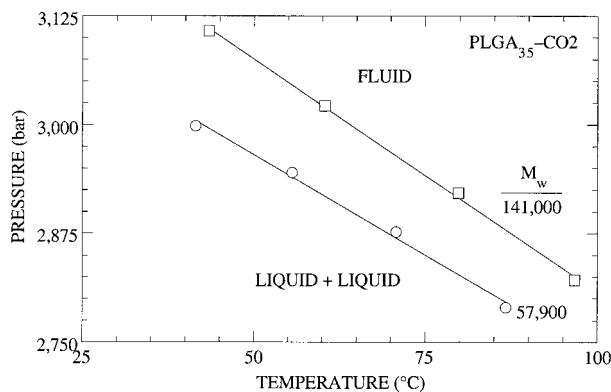
**Figure 2** Effect of weight average molecular weight on the phase behavior of PLA in supercritical CO<sub>2</sub>.



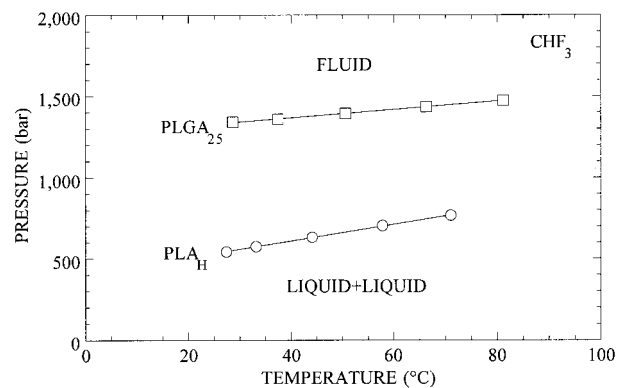
**Figure 3** Effect of weight average molecular weight on the phase behavior of PLGA<sub>15</sub> in supercritical CO<sub>2</sub>.

point curve with a negative slope also clearly shows that increasing the system pressure, or conversely, the solvent density, does not help in obtaining a single phase as the system temperature is lowered.

Figure 5 shows clearly that adding 25 mol % glycolide to the backbone of PLA shifts the CHF<sub>3</sub> cloud point pressures by as much as 800 bar at room temperature. This shift is not quite as large as that observed with CO<sub>2</sub> as shown in Figure 1. Both CO<sub>2</sub> and CHF<sub>3</sub> have approximately the same polarizability and both have some polarity since CHF<sub>3</sub> has a dipole moment of 1.6D and CO<sub>2</sub> has a quadrupole moment of  $-4.3 \times 10^{-26}$  erg<sup>1/2</sup> cm<sup>5/2</sup>. However, CHF<sub>3</sub> has an acidic proton that is capable of hydrogen bonding with the ester groups in PLGA whereas CO<sub>2</sub> is not expected to form any type of complex with PLGA. More than likely, the ability of CHF<sub>3</sub> to form a complex with PLGA makes it a better solvent than CO<sub>2</sub> especially since any change in favorable energetic in-



**Figure 4** Effect of weight average molecular weight on the phase behavior of PLGA<sub>35</sub> in supercritical CO<sub>2</sub>.



**Figure 5** Impact of glycolic acid (glycolide) content on the phase behavior of PLGA<sub>x</sub> in pure supercritical CHF<sub>3</sub>. Both polymers have approximately the same *M<sub>w</sub>*.

teractions is magnified in these dense SCF solvents. Once again, the change in solution density, given in Table IV, is very modest over the pressure and temperature range of the data shown in Figure 5.

Figure 6 shows a different type of phase behavior for PLGA in CHClF<sub>2</sub>. In this instance lower critical solution temperature (LCST) behavior is exhibited that is sensitive to the glycolide content in PLGA. As the glycolide content in PLGA increases, the two-phase region expands. Although it is not possible to dissolve PLGA<sub>50</sub> in pure CO<sub>2</sub>,

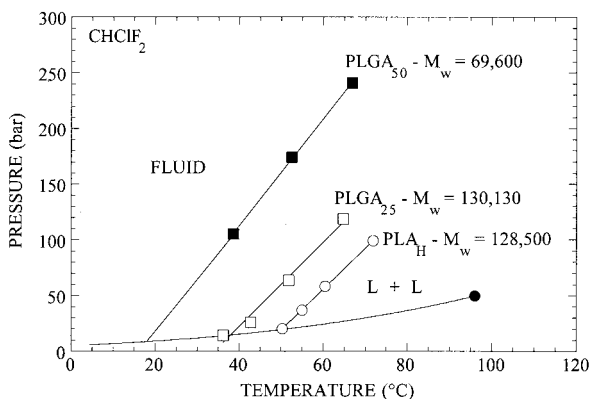
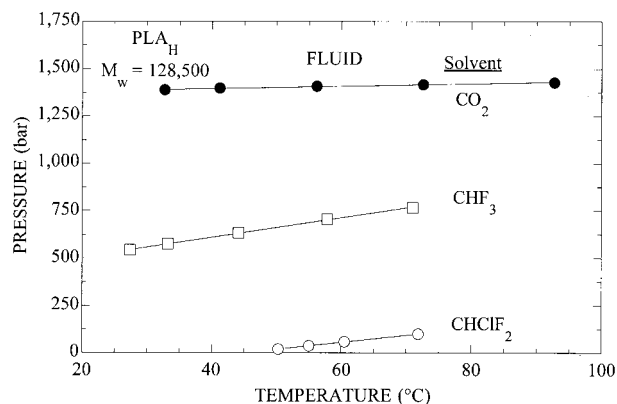
**Table IV** Cloud Point and Density Data for PLA<sub>H</sub> and PLGA<sub>25</sub> in Supercritical CHF<sub>3</sub> Obtained in this Study

PLA <sub>H</sub>		
Temperature (°C)	Pressure (bar)	Density (g/cm <sup>3</sup> )
27.4	543	1.334
33.2	575	1.332
44.1	633	1.321
57.8	705	1.311
71.0	767	1.302
PLGA <sub>25</sub>		
Temperature (°C)	Pressure (bar)	Density (g/cm <sup>3</sup> )
28.6	1341	1.535
37.4	1360	1.522
37.5	1394	1.505
66.3	1436	1.485
81.1	1474	1.464

**Table V** Cloud Point and Density Data for  $\text{PLA}_H$ ,  $\text{PLGA}_{25}$ , and  $\text{PLGA}_{50}$  in Supercritical  $\text{CHClF}_2$ 

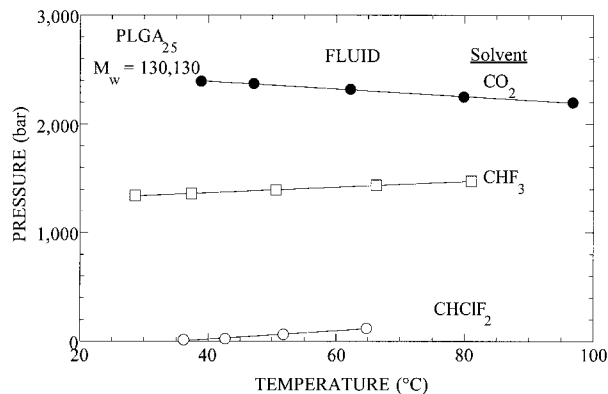
$\text{PLA}_H$		
Temperature ( $^{\circ}\text{C}$ )	Pressure (bar)	Density ( $\text{g}/\text{cm}^3$ )
50.3	20.3	1.106
55.0	36.9	1.101
60.5	58.3	1.096
71.9	99.3	1.084
$\text{PLGA}_{25}$		
Temperature ( $^{\circ}\text{C}$ )	Pressure (bar)	Density ( $\text{g}/\text{cm}^3$ )
36.2	14.5	1.193
42.7	25.8	1.177
51.8	63.8	1.167
64.8	118.9	1.154
$\text{PLGA}_{50}$		
Temperature ( $^{\circ}\text{C}$ )	Pressure (bar)	Density ( $\text{g}/\text{cm}^3$ )
38.6	105.1	1.298
52.5	174.1	1.286
66.9	241.0	1.274

this copolymer readily dissolves in  $\text{CHClF}_2$  even at temperatures as low as  $20^{\circ}\text{C}$ . Notice that  $\text{PLGA}_{50}$  has the lowest  $M_w$  but this copolymer is more difficult to dissolve than higher molecular weight copolymers with less glycolide—the same trend observed with  $\text{CO}_2$  and  $\text{CHF}_3$ . Very low

**Figure 6** Impact of glycolide content on the phase behavior of  $\text{PLGA}_x$  in  $\text{CHClF}_2$ . The solid circle is the critical point of  $\text{CHClF}_2$ . The three cloud point curves terminate on the vapor pressure curve of  $\text{CHClF}_2$ .**Figure 7** Comparison of different SCF solvents for dissolving  $\text{PLA}_H$ .

pressures are needed to dissolve the PLGA copolymers in contrast to the kilobar pressures needed with  $\text{CO}_2$  and near-kilobar pressures needed with  $\text{CHF}_3$  even though both  $\text{CHClF}_2$  and  $\text{CHF}_3$  have similar dipole moments.  $\text{CHClF}_2$  is a better solvent for PLGA since it has a larger polarizability than the other two SCF solvents and it has a hydrogen that is probably more acidic than the hydrogen in  $\text{CHF}_3$ . The cloud point curve for  $\text{PLA}_H$  is in good agreement with the results reported earlier for the d isomer  $\text{PLA}-\text{CHClF}_2$  system. The slope of the curve reported by Lele and Shine is approximately  $3.0 \text{ bar}/^{\circ}\text{C}$  and here the slopes of the cloud point curves are 3.7, 3.8, and  $4.8 \text{ bar}/^{\circ}\text{C}$  for  $\text{PLA}_H$ ,  $\text{PLGA}_{25}$ , and  $\text{PLGA}_{50}$ , respectively. As with the other polymer-SCF mixtures, there is only a very modest change in the solution densities for the polymer mixtures with  $\text{CHClF}_2$ .

The cloud point curves in Figures 7 and 8 demonstrate the vast differences between the solvent

**Figure 8** Comparison of different SCF solvents for dissolving  $\text{PLGA}_{25}$ .

power of supercritical CO<sub>2</sub>, CHF<sub>3</sub>, and CHClF<sub>2</sub> for PLGA copolymers as well as the significant impact of PLGA backbone architecture on the phase behavior. The cloud point curves in each figure show that CO<sub>2</sub> is the poorest quality solvent and that CHClF<sub>2</sub> is the highest quality solvent. And a comparison of the pressure axes of both graphs reveals that cloud point pressures increase substantially when glycolide is added to the backbone of PLGA.

## CONCLUSIONS

Supercritical CO<sub>2</sub> is a poor quality solvent for PLGA<sub>x</sub> copolymers. As the glycolide content in the backbone increases, the pressures needed to obtain a single phase also increase substantially and it is not possible to dissolve PLGA<sub>50</sub> to pressures of 3000 bar. The effect of molecular weight on the cloud point pressure is insignificant relative to the effect of glycolide content even with CHClF<sub>2</sub> as the solvent. The solution densities with all three SCF solvents are very high and they only vary by a small amount over the 80°C range used to obtain cloud point data. Hence, the differences in the phase behavior exhibited by the PLGA<sub>x</sub>-SCF solvent systems are related more to differences in intermolecular interactions between the components in the solution rather than simply to differences in solution density. The CHClF<sub>2</sub> data strongly suggest that a polar cosolvent capable of hydrogen bonding to the ester linkage in PLGA<sub>x</sub> is needed if low pressure, single-phase processing of this copolymer is desired. However, PLGA<sub>x</sub> copolymers can be intimately mixed with a variety of insoluble materials at low pressures in pure CO<sub>2</sub> since the glass transition temperature of the PLGA<sub>x</sub> is significantly lowered by the plasticization effect of supercritical CO<sub>2</sub>. Once an intimate mixture is formed, it is possible to recover the insoluble material as particles in a desired size range and with a fixed coating of PLGA<sub>2</sub>. It is now well established that fluorinating a polymer increases its solubility in supercritical CO<sub>2</sub> (see, for example, the review of Kirby and McHugh<sup>18</sup>). Further work is in progress to synthesize fluorinated methyl groups attached to the asymmetric site of the lactide to determine the impact of fluorine on CO<sub>2</sub> solubility.

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