HIGH PRESSURE MISCIBILITY AND VOLUMETRIC PROPERTIES OF POLY(LACTIDE-CO-GLYCOLIDE) SOLUTIONS IN ACETONE AND ACETONE + CO_2 FLUID MIXTURES

Heather E. Grandelli, Erdogan Kiran*

Department of Chemical Engineering
Virginia Tech
Randolph Hall, Blacksburg, VA 24061

Email: ekiran@vt.edu

Abstract. High pressure density, miscibility and compressibility of poly(lactide-co-glycolide) (PLGA) solutions in acetone and in acetone + CO_2 mixtures have been studied at temperatures from 75 - 150 ^{o}C and pressures up to 400 bar. At and above 125 C, these solutions display LCST-type liquid-liquid phase separation. At lower temperatures only liquid-vapor type phase separation is observed. Densities are lowered with increasing carbon dioxide content, or with increasing polymer concentration in the solution. Compressibilities show unexpected features that are interpreted in terms of association of carbon dioxide with acetone versus the carbonyl groups in the polymer.

Keywords : Poly(lactide-co-glycolide), CO_2, Acetone, Miscibility, Density

1. Introduction

Poly(DL-lactide-*co*-glycolide) (PLGA), $-[(CH_3)\text{-}CH\text{-}COO]_m\text{-}[CH_2\text{-}COO]_n\text{-}$, is a biomedical polymer that is of high interest in drug delivery and tissue engineering applications [1-7]. Processing of biomedical polymers in supercritical carbon dioxide is attractive due to the non-toxicity of CO_2; however, processing of PLGA in CO_2 alone is not practical since the solubility of the polymer in pure CO_2 is low even at very high pressures [5, 8, 9]. An approach to improve the solubility of polymers in CO_2 is to employ binary fluid mixtures that incorporate an organic solvent as a co-solvent. In this context, acetone-CO_2 mixtures are particularly interesting since CO_2 can interact with the carbonyl groups in both the acetone and the PLGA, thereby altering the miscibility pressures and influencing the overall volumetric properties of the solutions. As presented in our recent publication [16] and further emphasized in this paper, the extent of association of carbon dioxide with acetone versus the polymer chains influences not only the density but also the compressibility in these solutions.

The consequences of association have been possible to delineate by employing an experimental technique which permits determination of density in a continuous manner as pressure is altered at a given temperature. These $\rho = f(P)$ functions are then differentiated to generate the isothermal compressibilities $k_T = (1/\rho)(\partial\rho/\partial P)_T$.

2. Materials and Methods

2.1 Materials

Poly(DL-lactide-co-glycolide) (PLGA) with 50:50 lactide:glycolide ratio was purchased from Boehringer Ingelheim (Resomer RG 504 H). The weight average molecular weight and polydispersity index as determined by gel permeation chromatography analyses conducted in our laboratory were M_w = 65,000 with a PDI = 2.02. Acetone (99.5% purity, ACS reagent grade) was purchased from Sigma. Carbon dioxide (99.8% purity) was purchased from Airgas.

2.2 Experimental System Description and Operational Procedures

Experiments were carried out using a high pressure variable-volume view-cell [10], which is illustrated in a schematic diagram and photograph in Figure 1. It consists of two sapphire windows for observations or measurement of transmitted light intensities, and a movable piston, the position of which is altered with the action of a pressure generator using ethanol as pressurizing fluid. A long stroke-length LVDT (linear variable differential transformer) that is computer interfaced permits real-time continuous monitoring of the position of the piston as it is moved with the pressure generator to alter the pressure in the cell. The piston position information is then translated to cell volume at any given P/T condition, which permits density determination since the initial mass loading is known.

In a typical experiment, the view-cell is first loaded with PLGA powder and acetone. The vessel is then closed and CO_2 is charged from a pre-loaded transfer vessel. After loading, the cell temperature is adjusted using symmetrically positioned cartridge heaters. Pressure is then increased to bring about homogenous conditions, and further increased to about 400 bar. Pressure scans are generated by lowering the pressure while recording the pressure, temperature, piston position, and transmitted light intensity in real time with the dedicated computer at a desired sampling rate, typically 2 per second.

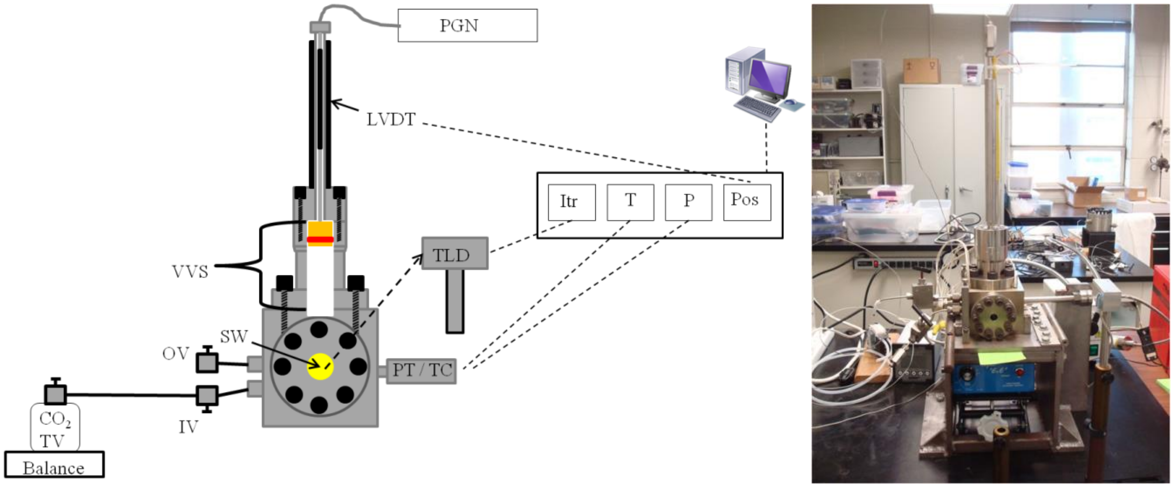

Figure 1. Schematic (left) and photograph (right) of the view-cell system in the upright position. PGN = pressure generator; LVDT = Linear variable differential transformer, VVS = variable volume section of the cell housing the piston; SW= sapphire window; TLD = transmitted light detector; PT/TC = pressure transducer and thermocouple; IV/OV = inlet and outlet vales; TV = carbon dioxide transfer vessel; Itr = transmitted light intensity; T/P= temperature and pressure; Pos = piston position.

Figures 2 is an example of the actual data generated for a 5 wt% PLGA solution in a binary fluid mixture composed of 89:11 wt% Acetone:CO_2 at 150 °C. Piston position, internal volume, cell pressure and normalized transmitted light intensity (I/I_0) are shown as functions of time during this experiment. The pressure was reduced from about 400 to 40 bar over 300 s. The plots represent nearly 600 data points. The cell volume had increased from about 17.5 to 23 cm^3. The data shows that pressure decreases with increasing internal volume up to a point and then remains unchanged with further increase in volume, as observed at around 170 s in the pressure vs time plot. This reflects the formation of a vapor phase in the system. In this particular system this is the liquid-liquid-vapor (LLV) phase separation condition as the solution undergoes liquid-liquid (LL) phase separation at a higher pressure which is displayed in the transmitted light intensity (I/I_0) which shows a sharp decrease at around 120 s (corresponding to about 100 bar). Figure 2 also shows a combined plot of the variation of density and transmitted light intensity with pressure which captures the LL and LLV phase separation conditions in this solution at 150 °C.

Figure 3 illustrates a second set of data generated for the same solution at 75 °C. At this temperature LL phase separation is not observed for this solution and only a liquid-vapor (LV) phase boundary is observed and is depicted by both the variation of density and transmitted light intensity with pressure at the same pressure. Upon entering the LV region, transmitted light intensity does not go to zero as was the case with LL transition at 150 °C, illustrated in Figure 2 above. If the solution first undergoes a LL phase separation, the transmitted light intensity essentially goes to zero and a further change in transmitted light intensity when LLV occurs cannot be discerned, as was the case at 150 °C. Here however at 75 °C, in the absence of LL phase separation, LV phase separation is reflected not only in the density but also in the transmittance data, even though the drop in transmitted light intensity is not as intense.

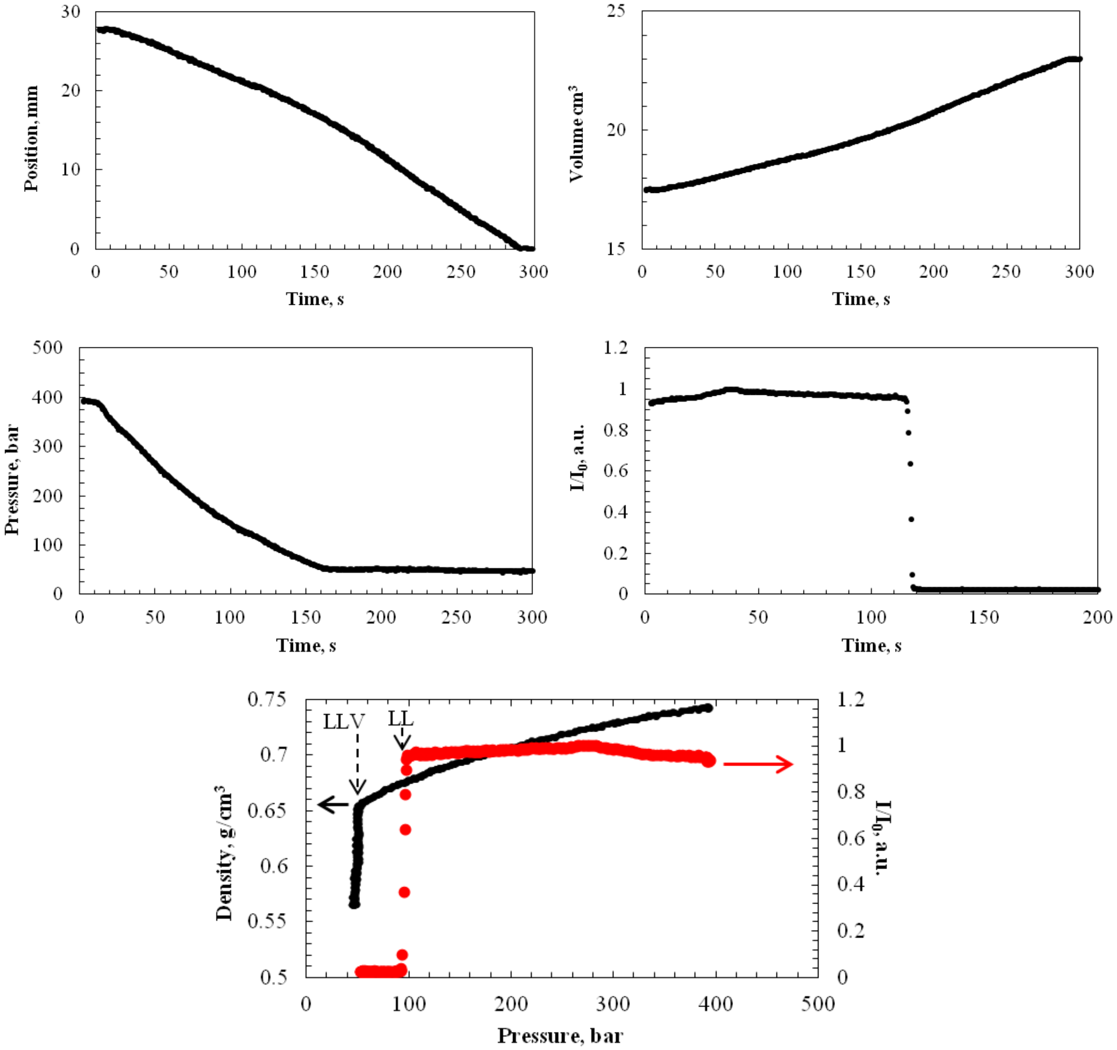

Figure 2. Typical position, volume, pressure, transmitted light intensity and density profiles in real time for a 5 wt% PLGA solution in the 89:11 wt% Acetone:CO_2 mixture at 150 °C, which undergoes LL and LLV phase separation.

3. Results

Phase boundaries, densities, and compressibilities have been determined for solution with mixture PLGA:Acetone:CO_2 mixture compositions of 10:90:0 (which is the solution of PLGA + acetone only), 10:85:5, 10:80:10, 5:84.5:10.5 and 0:89:11 (which is the solvent mixture acetone + CO_2 only).

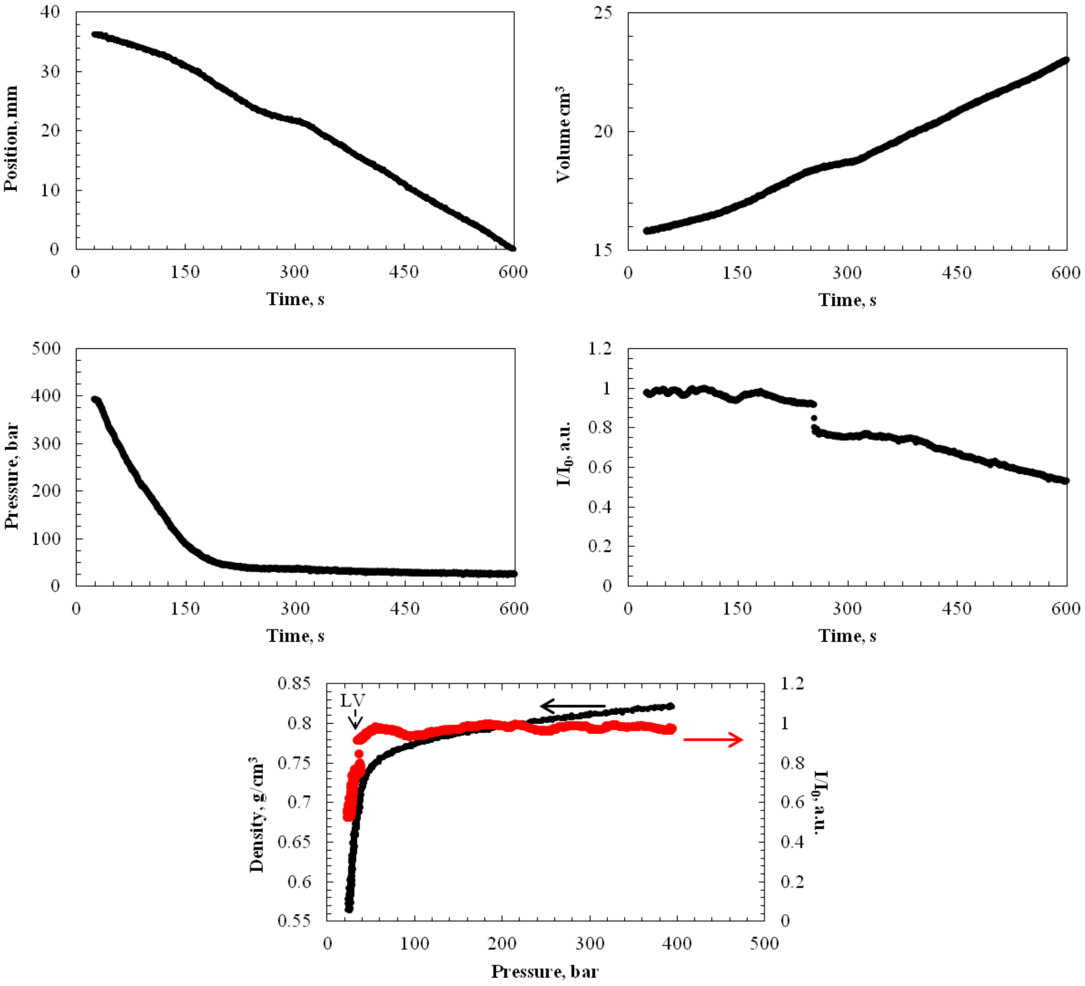

Figure 3. Typical position, volume, pressure, transmitted light intensity and density profiles in real time for a 5 wt% PLGA solution in the 89:11 wt% Acetone:CO_2 mixture at 75 ^oC, which displays only LV phase separation upon pressure reduction.

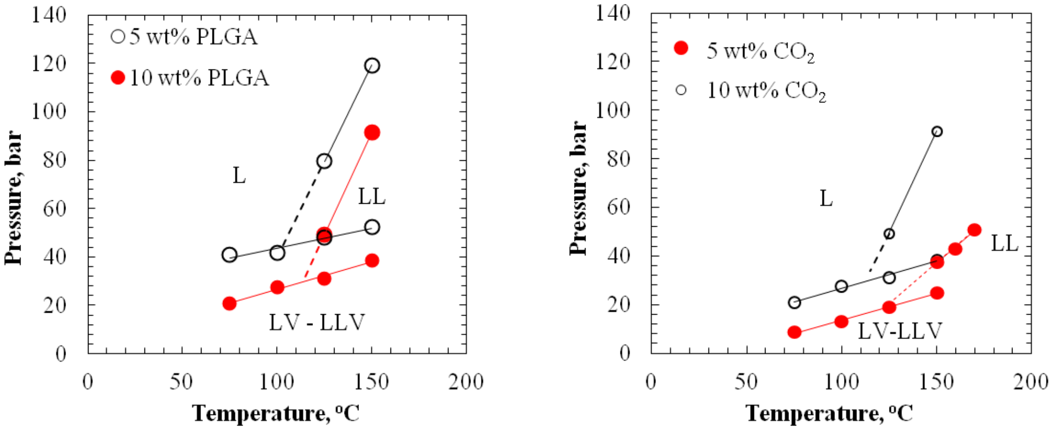

Figure 4. Phase boundaries for 5 and 10 wt% PLGA in an 89:11 wt% Acetone:CO_2 fluid mixture (left – dashed lines are extrapolations of the LL boundary) and for 10 wt% PLGA solutions in acetone-CO_2 mixtures with 5 and 10 wt% CO_2 content (right).

3.2 Density and Compressibility

Figure 5 shows comparative density and compressibility plots generated for solutions with PLGA:Acetone:CO_2 concentrations (in wt%) of 10:90:0, 10:85:5, 10:80:10, 5:84.5:10.5 and 0:89:11. These compositions allow the evaluation of *(i)* the effect of PLGA concentration while holding the acetone-to-CO_2 ratio in the solvent mixture the same at 89:11 wt% Acetone:CO_2 (curves c, d, e) and (*ii*) the effect of changing the amount of CO_2 in the solvent mixture while holding the PLGA concentration unchanged at 10 wt% (curves a, b, c).

For each solution, densities increase with pressure and decrease with temperature as would be expected. Data shows that increasing the CO_2 content (curves a, b, c) or decreasing PLGA concentration (curves c, d, e) result in a decrease in solution density.

The density data were correlated with second order polynomial function of the form $\rho = A + BP + CP^2$ at pressures above the LV or LLV phase boundary at each temperature. Isothermal compressibility profiles were then generated using the relationship, $k_T = (1/\rho)(d\rho/dP)_T$ [10]. As shown in the figure, compressibilities all decrease with pressure in all the solutions as would be expected. Also, while numerical values are small, the compressibilities appear to increase at higher temperatures, which, other things being equal, would also be expected. The data however shows an unexpected trend when compared with the densities. Generally, higher compressibilities would be expected in solutions of lower densities, which would, in the present case, point to the solutions with higher CO_2 content (i.e., in the direction of a, b, c, d). However, this trend is not observed at all the temperatures investigated as the trends appear to be in the opposite direction at $T < 125$ °C (where compressibilities decrease in the direction $a \rightarrow b \rightarrow c$) while at 125 and 150 °C they are as would be anticipated (as compressibilities basically increase in going from a to d). This unexpected behavior at lower temperatures can however be rationalized if one considers the intermolecular interactions in this ternary system in terms of the specific interactions of CO_2 with the carbonyl groups in acetone versus the carbonyl groups in the polymer backbone and the sensitivity of interactions to temperature. Even though associations in ternary systems have not been previously explored, association of CO_2 with acetone or with the carbonyl groups in polymer chains is well documented in the literature [11, 12].

Figure 6 is an illustration showing the consequences of association of CO_2 with the carbonyl groups in PLGA. Clearly, CO_2 would be acting like a spacer, and the end result would be an increased spacing between the polymer backbone chains in the solution. This picture would suggest a decrease in the density of the solution with carbon dioxide addition, which is in fact what is observed in Figure 5. Figure 6 also helps visualize that in the presence of increasing CO_2, greater fraction of the backbone carbonyl groups will undergo association. It can further be visualized that association will hinder chain backbone flexibility which will make the solution less compressible even though densities are lowered. This appears to be the prevailing factor at $T < 125$ °C. At 125 °C and higher temperatures, the compressibility trends conform to generally expected behavior. It appears that at higher temperatures the association of carbon dioxide with the carbonyl groups of polymer is weakened and the association with acetone becomes the more dominant interaction. There is prior literature evidence of potentially weakened CO_2 polymer interactions at higher temperatures in another polymer system with carbonyl groups, poly(ε-caprolactone) [13].

4. Conclusions

Continuous recording of the density as a function of pressure at a given temperature helps identify the LV or LLV phase boundaries, as well as development of density–pressure correlations from which compressibilities can be generated. Solutions of PLGA in CO_2-acetone mixtures display a LCST-type LL phase boundary. Miscibility pressures increase with increasing CO_2 content in the solvent mixture. Densities decrease with increasing CO_2 or PLGA content in the solutions. Compressibilities however also appear to decrease. This unexpected behavior is interpreted as arising from the association of carbon dioxide with the carbonyl groups in the polymer chain, which acts as spacers and reduce density, but also hinder chain flexibility and reduce the compressibility which appears to be more prevalent at lower temperatures.

Acknowledgements

This research was in part supported by the National Science Foundation (CBET Award # 0929978).

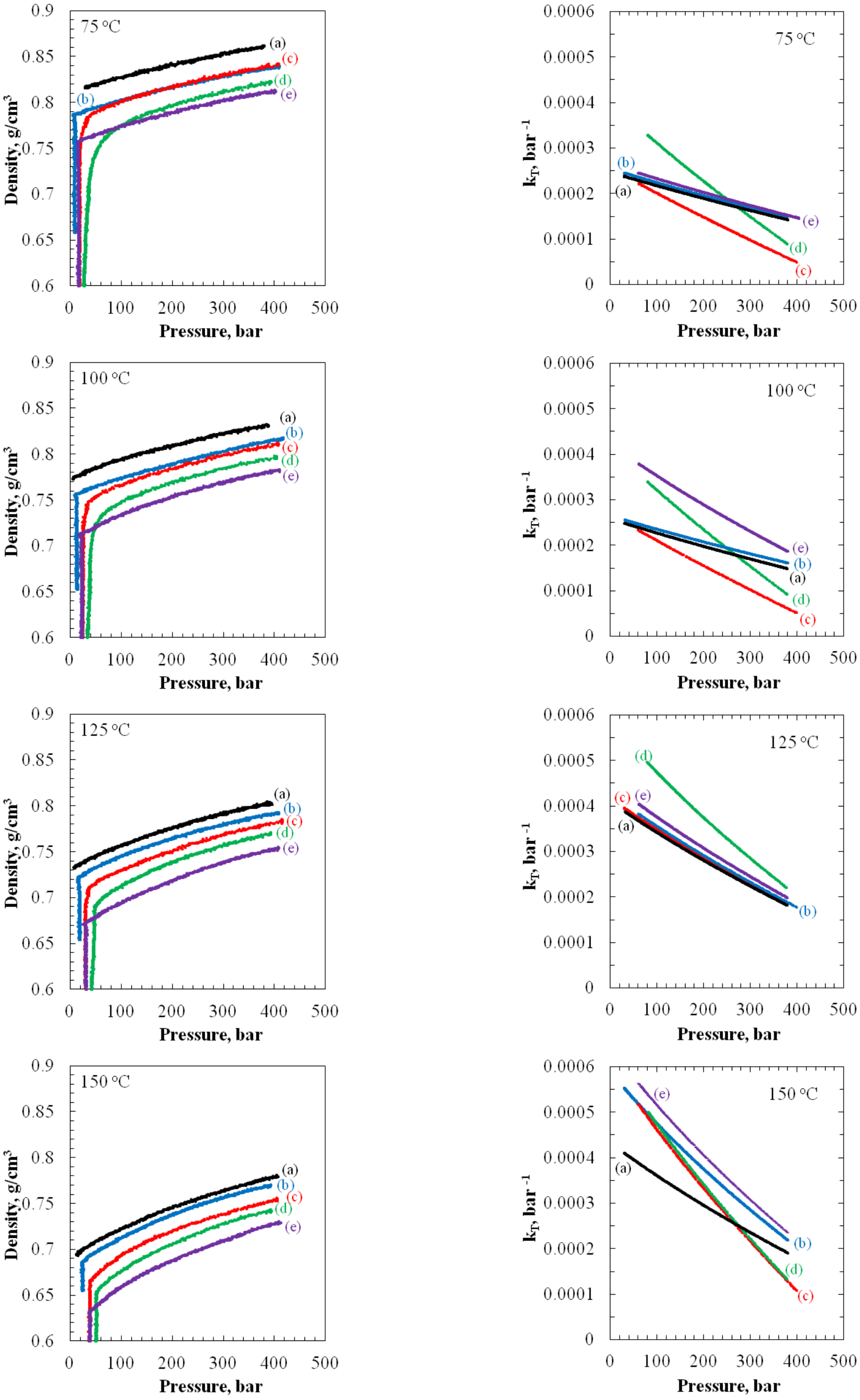

Figure 5. Comparison of density and compressibility profiles for mixture compositions of (a) 10:90:0, (b) 10:85:5, (c) 10:80:10, (d) 5:84.5:10.5 and (e) 0:89:11 wt% PLGA:Acetone:CO$_2$.

I

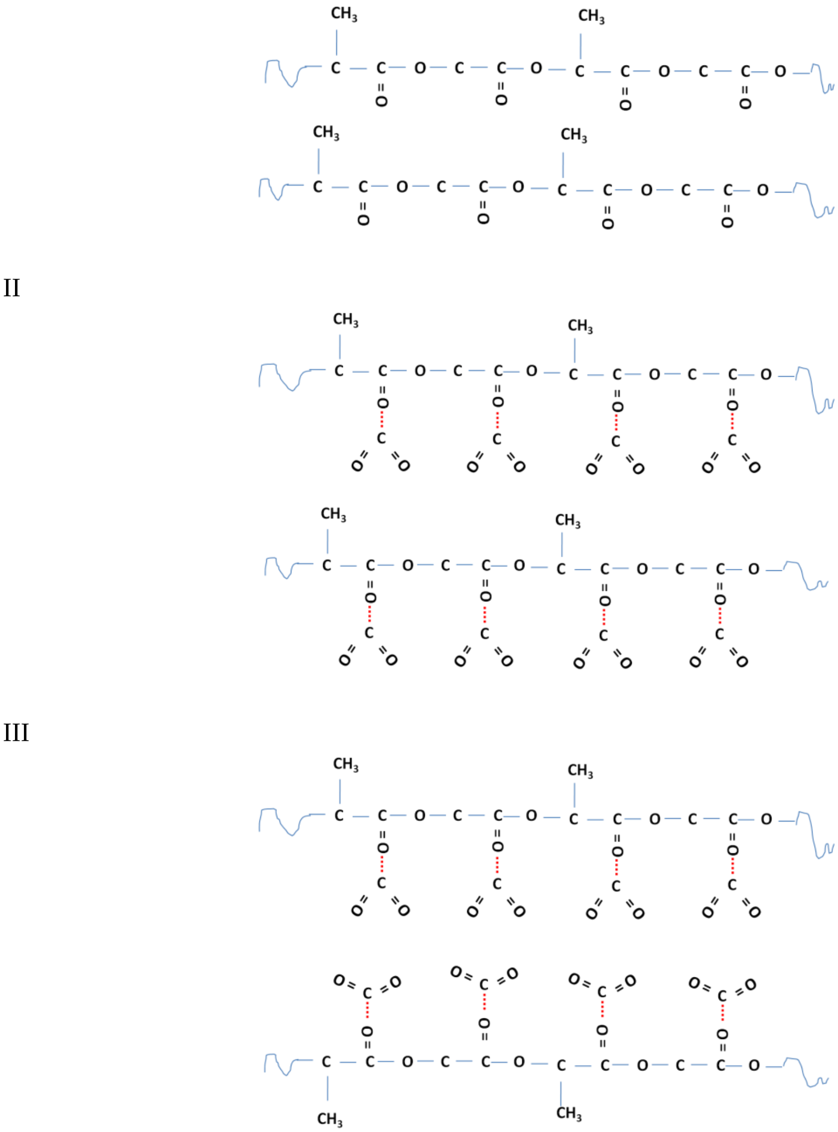

Figure 6. Schematic illustration of the association of CO_2 with the carbonyl groups of PLGA (I) leading to different degree of spacing between the chains (II, III) leading to lower densities, but reduced compressibility.

References

[1] R.A. Quirk, R.M. France, K.M. Shakesheff, S.M. Howdle, Supercritical fluid technologies and tissue engineering scaffolds, Current Opinion in Solid State & Materials Science 8 (2004) 313-321.

[2] O.R. Davies, A.L. Lewis, M.J. Whitaker, H.Y. Tai, K.M. Shakesheff, S.M. Howdle, Applications of supercritical CO(2) in the fabrication of polymer systems for drug delivery and tissue engineering, Advanced Drug Delivery Reviews 60 (2008) 373-387.

[3] G. Della Porta, N. Falco, E. Reverchon, NSAID drugs release from injectable microspheres produced by supercritical fluid emulsion extraction, Journal of Pharmaceutical Sciences 99 (2010) 1484-1499.

[4] E. Kiran, Modification of biomedical polymers in dense fluids. Miscibility and foaming of poly(p-dioxanone) in carbon dioxide plus acetone fluid mixtures, Journal of Supercritical Fluids 66 (2012) 372-379.

[5] H.-S. Byun, H.-Y. Lee, Cloud-point measurement of the biodegradable poly(d,l-lactide-co-glycolide) solution in supercritical fluid solvents, Korean Journal of Chemical Engineering 23 (2006) 1003-1008.

[6] D.J. Mooney, D.F. Baldwin, N.P. Suh, L.P. Vacanti, R. Langer, Novel approach to fabricate porous sponges of poly(D,L-lactic-co-glycolic acid) without the use of organic solvents, Biomaterials 17 (1996) 1417-1422.

[7] H.Y. Tai, M.L. Mather, D. Howard, W.X. Wang, L.J. White, J.A. Crowe, S.P. Morgan, A. Chandra, D.J. Williams,

S.M. Howdle, K.M. Shakesheff, Control of pore size and structure of tissue engineering scaffolds produced by supercritical fluid processing, European Cells & Materials 14 (2007) 64-76.

[8] P. Arce, M. Aznar, Modeling the thermodynamic behavior of poly (lactide-co-glycolide) plus supercritical fluid mixtures with equations of state, Fluid Phase Equilibria 244 (2006) 16-25.

[9] S.E. Conway, H.S. Byun, M.A. McHugh, J.D. Wang, F.S. Mandel, Poly(lactide-co-glycolide) solution behavior in supercritical CO2, CHF3, and CHClF2, Journal of Applied Polymer Science 80 (2001) 1155-1161.

[10] H.E. Grandelli, E. Kiran, High pressure density, miscibility and compressibility of poly(lactide-co-glycolide) solutions in acetone and acetone + CO2 binary fluid mixtures, The Journal of Supercritical Fluids 75 (2013) 159-171.

[11] S.G. Kazarian, M.F. Vincent, F.V. Bright, C.L. Liotta, C.A. Eckert, Specific Intermolecular Interaction of Carbon Dioxide with Polymers, Journal of the American Chemical Society 118 (1996) 1729-1736.

[12] J.Y. Wang, M.Y. Wang, J.M. Hao, S. Fujita, M. Arai, Z.J. Wu, F.Y. Zhao, Theoretical study on interaction between CO2 and carbonyl compounds: Influence of CO2 on infrared spectroscopy and activity of C = O, Journal of Supercritical Fluids 54 (2010) 9-15.

[13] K. Liu, E. Kiran, High-pressure solution blending of poly(epsilon-caprolactone) with poly(methyl methacrylate) in acetone plus carbon dioxide, Polymer 49 (2008) 1555-1561.