J. Chem. Eng. Data **2006,** *51,* 107−111

Bubble and Cloud Points of the Systems Poly(ϵ-caprolactone) + Carbon Dioxide + Dichloromethane or Chloroform

Constantinos G. Kalogiannis and Constantinos G. Panayiotou*

Department of Chemical Engineering, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece

Experimental data for the phase behavior of poly(ϵ-caprolactone) (PCL) in mixtures of carbon dioxide with dichloromethane or chloroform over a range of external conditions are presented. Cloud point pressures were measured using a variable-volume view cell as functions of temperature, carbon dioxide-to-organic solvent ratio, and concentration of PCL. A high-molecular weight (M_w = 124 200) PCL was used in all studies and at mass fractions of 0.01, 0.02, and 0.03. For the adequate control of the carbon dioxide-to-organic solvent ratio, a new experimental procedure was employed that allows for a good control of the composition.

Introduction

Processes involving supercritical fluids have attracted particular attention over the last few decades. Their applications have a wide scope such as extraction, separation, fractionation, reaction, processing of drugs and polymers, micronization, and foam formation. Supercritical fluids may be employed as solvents or nonsolvents and are environmentally friendly, less hazardous and more versatile than the common organic solvents, and comply with modern standards of the drug and food industry.[1]

In the past few years, attempts have been made to produce microparticles of biodegradable polymers and to encapsulate drugs in such polymers so that they be used as agents for the administration of drugs to the human body.[2,3] Carbon dioxide is the number-one fluid employed as a supercritical nonsolvent in such cases because of its availability, because of its low critical pressure and temperature, and because it is environmentally friendly.[4] Microparticles of PCL have been produced, and encapsulation of drugs in this polymer has been attempted successfully.[5] However, the phase equilibrium of the treated system (PCL + CO_2 + organic solvent) has not been studied systematically so far.

Dichloromethane and chloroform are both good solvents for PCL, whereas carbon dioxide is not a good solvent of PCL leading to the sedimentation of its organic solutions upon mixing. Knowledge of the phase behavior of the system polymer + organic solvent + supercritical antisolvent is important for the determination of the best-operating conditions for the production of microparticles of biodegradable polymers and for the encapsulation of drugs in such polymers.

In this work, the borders where phase separation occurs were determined for the systems: PCL + carbon dioxide + dichloromethane and PCL + carbon dioxide + chloroform. For this purpose, a high-pressure phase equilibrium apparatus with a variable-volume view cell was used. As will be shown, both liquid−vapor (L−V) and liquid−liquid (L−L) transitions occur in these systems, depending on the temperature and the composition of the mixtures. To our knowledge these systems have not been studied previously.

Experimental Section

Materials. Poly(ϵ-caprolactone) (PCL) (M_w = 122 400; polydispersity index, I = 2.06) was supplied by Union Carbide Benelux under the trade name Tone 787 and used without further purification. Instrument-grade carbon dioxide (purity 99.99 %) was supplied by Air Liquide Mediterranée (Vitrolles, France). Analytical-grade dichloromethane and chloroform (99.9 % purity) were purchased from Riedel-de Haen (Germany).

Apparatus and Procedure. Both the apparatus and the experimental procedure have been described in detail elsewhere.[6] Briefly, the experimental procedure is as follows. Initially, a known mass of polymer with an uncertainty of 10^{-4} was inserted into the cell along with a stirring magnet bar. The uncertainty of the polymer mass is far too small to affect the values of the points received, which may be observed from Tables 1 and 2, that follow the effect that the polymer mass has on bubble and cloud points. Afterward, the cell was purged several times with CO_2 to ensure that there is no entrapped air left. The cell was then filled with CO_2 at a specific pressure and temperature. Precise knowledge of the pressure and temperature of CO_2, with uncertainties of 0.05 bar and 0.05 K, respectively, allow for the calculation of its density with the recommended IUPAC equation of state.[7] A Milton Roy HPLC minipump was used for the addition of the organic solvent into the cell. The exact volume of the added organic solvent was measured with a calibrated pipet placed at the inlet of the pump. In this way, the amounts of all three components may be specified, allowing for the precise control of the composition of the mixture and for reproducibility. The cell was heated to the desired temperature with a silicon heating tape wrapped around it and insulated to ensure temperature stability. A second Milton Roy minipump compressed the mixture.

Depending on the conditions, either a bubble is formed or a cloud, corresponding to L−V and L−L transitions, respectively. The pressures measured in each case are the pressure at which the first bubble is formed and the pressure at which the magnetic bar is no longer visible.[6,8] The temperature of the system was increased in 5 K increments to a maximum of 373.15 K for each mixture. The uncertainties for pressure and temperature were 0.05 bar and 0.05 K, respectively.

---

* Corresponding author e-mail: cpanayio@auth.gr.

10.1021/je0502602 CCC: $33.50

Table 1. Experimental Data of Bubble and Cloud Points of PCL (1) in CH_2CL_2 (2) and CO_2 (3)[a]

	P/bar at $w_1 = 1$ %				
T/K	w_2: 0.2520 w_3: 0.7480	w_2: 0.2910 w_3: 0.7090	w_2: 0.3442 w_3: 0.6558	w_2: 0.4001 w_3: 0.5999	w_2: 0.4383 w_3: 0.5617
308.15	**34.62**	**37.93**	**41.75**	**45.96**	**47.77**
313.15	**37.73**	**41.45**	**45.36**	**49.98**	**52.78**
318.15	**40.74**	**44.86**	**49.27**	**54.09**	73.5
323.15	**43.85**	**48.37**	**53.09**	**58.3**	97.94
328.15	**46.97**	**51.88**	**57**	77.87	121.1
333.15	**50.03**	**55.39**	**61.01**	101.35	142.49
338.15	**54.29**	**59.2**	**65.33**	121.82	164.96
343.15	**57.58**	**63.12**	**69.64**	143.59	185.84
348.15	**60.92**	**67.13**	82.59	164.26	
353.15	**64.42**	**70.95**	103.06	184.53	
358.15	**67.9**	**74.86**	123.22		
363.15	**71.45**	**78.87**	142.29		
368.15	**75.26**	**83.19**	160.95		
373.15	**78.87**	96.23			

	P/bar at $w_1 = 2$ %				
T/K	w_2: 0.2517 w_3: 0.7483	w_2: 0.2911 w_3: 0.7089	w_2: 0.3442 w_3: 0.6558	w_2: 0.4009 w_3: 0.5991	w_2: 0.4384 w_3: 0.5616
308.15	**34.82**	**38.13**	**42.35**	**46.46**	**48.17**
313.15	**37.94**	**41.65**	**46.26**	**50.48**	63.82
318.15	**41.05**	**44.96**	**50.08**	**55.58**	86.8
323.15	**44.05**	**48.57**	**54.09**	68.94	110.48
328.15	**47.37**	**52.05**	**58.2**	91.41	133.86
333.15	**50.68**	**55.6**	**62.32**	113.09	155.43
338.15	**54.19**	**59.4**	**66.73**	134.96	177.11
343.15	**57.7**	**63.35**	80.28	156.24	
348.15	**61.32**	**67.35**	100.25	177.1	
353.15	**64.83**	**71.2**	121.12	197.07	
358.15	**68.44**	**75.1**	140.99		
363.15	**72.05**	**79.1**	160.05		
368.15	**75.86**	**83.4**	178.81		
373.15	**79.48**	102.2			

	P/bar *at* $w_1 = 3$ %				
T/K	w_2: 0.2511 w_3: 0.7489	w_2: 0.2910 w_3: 0.7090	w_2: 0.3441 w_3: 0.6559	w_2: 0.4027 w_3: 0.5973	w_2: 0.4384 w_3: 0.5616
308.15	**35.3**	**38.54**	**42.85**	**47.37**	85.1
313.15	**38.44**	**41.95**	**46.46**	59.41	109.18
318.15	**41.45**	**45.36**	**50.38**	83.59	133.16
323.15	**44.76**	**48.97**	**54.39**	105.87	156.43
328.15	**47.97**	**52.59**	**58.51**	128.24	178.91
333.15	**51.38**	**56.3**	**62.72**	149.31	
338.15	**55**	**60.1**	**67.03**	171.38	
343.15	**58.51**	**64.12**	83.29	192.46	
348.15	**62.12**	**68.04**	103.56		
353.15	**65.83**	**71.95**	123.63		
358.15	**69.64**	**76.16**	143.23		
363.15	**73.46**	83.49	162.76		
368.15	**77.27**	101.75			
373.15	**80.98**	120.01			

[a] w_1, w_2, and w_3 are mass fractions. w_2 and w_3 are calculated on a polymer-free basis. Bold data are L−V transitions; the rest are cloud points.

Table 2. Experimental Data of Cloud points of PCL (1) in $CHCl_3$ (2) and CO_2 (3)[a]

	P/bar at $w_1 = 1$ %				
T/K	w_2: 0.2520 w_3: 0.7480	w_2: 0.2910 w_3: 0.7090	w_2: 0.3444 w_3: 0.6556	w_2: 0.4002 w_3: 0.5998	w_2: 0.4383 w_3: 0.5617
308.15	**41.14**	**44.05**	**48.06**	55.19	91.62
313.15	**44.56**	**48.17**	**52.28**	75.06	112.58
318.15	**48.07**	**51.88**	**56.6**	97.24	133.1
323.15	**51.78**	**55.9**	**61**	115	152.83
328.15	**55.29**	**60.11**	**66.33**	132.25	171.19
333.15	**59**	**64.32**	76.97	149.21	191.25
338.15	**62.92**	**68.64**	96.83	166.97	208.11
343.15	**67.03**	**72.85**	115.5	186.74	
348.15	**70.75**	**77.37**	134.46		
353.15	**74.66**	**81.7**	153.22		
358.15	**78.67**	**85.9**	169.88		
363.15	**82.59**	97.3	187.24		
368.15	**86.4**	112.18	201.29		
373.15	**89.91**	124.93			

	P/bar at $w_1 = 2$ %				
T/K	w_2: 0.2520 w_3: 0.7480	w_2: 0.2911 w_3: 0.7089	w_2: 0.3444 w_3: 0.6556	w_2: 0.4005 w_3: 0.5995	w_2: 0.4378 w_3: 0.5622
308.15	**41.24**	**44.15**	**48.37**	70.24	118.91
313.15	**44.65**	**48.37**	**52.68**	93.22	138.68
318.15	**48.17**	**52.15**	**56.89**	115.7	158.34
323.15	**51.95**	**56.1**	**61.4**	137.57	178
328.15	**55.39**	**60.4**	**66.73**	159.55	197.5
333.15	**59.1**	**64.52**	77.6	179.82	
338.15	**63.02**	**68.85**	99.3	200.69	
343.15	**67.23**	**73.1**	117.1		
348.15	**70.84**	**77.6**	138.3		
353.15	**74.75**	**82**	157.13		
358.15	**78.75**	**86.4**	175.9		
363.15	**82.7**	103.75	194.63		
368.15	**86.6**	121.31			
373.15	**90.21**	138.3			

[a] w_1, w_2, and w_3 are mass fractions. w_2 and w_3 are calculated on a polymer-free basis. Bold data are L−V transitions; the rest are cloud points.

Results and Discussion

The experimental apparatus and procedure have been tested for validity and accuracy, and this series of experiments have been described in detail elsewhere.[6] This type of phase transition (L−V or L−L) depends on the type of the organic solvent, the polymer mass fraction, the carbon dioxide to organic solvent ratio, and the temperature. The first series of experiments reported here concern the phase transition behavior of the ternary system PCL + CO_2 + CH_2Cl_2. Following the procedure described previously, we obtained the experimental data for the cloud and bubble points of our ternary system, which are reported in Table 1.

Three different PCL compositions were investigated for temperatures ranging from 308.15 to 373.15 K and pressures up to 200 bar. In Figures 1 to 3, the $P-T$ isopleths are shown for 0.01, 0.02, and 0.03 mass fractions of PCL, respectively.

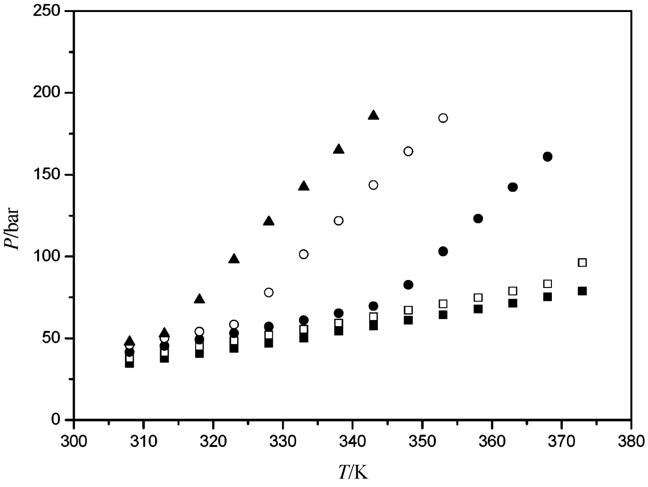

Figure 1. $P-T$ isopleths of cloud points of mass fraction PCL = 1 % in dichloromethane + CO_2. Mass fractions of CO_2 in the mixed solvent on a polymer-free basis: ■, 0.252; □, 0.291; ●, 0.3442; ○, 0.4001; ▲, 0.4383.

Each curve corresponds to a specific CO_2-to-dichloromethane ratio. In the low-temperature region a L−V transition occurs, leading to the formation of a bubble in the mixture during depressurization. However, as the temperature increases, a corresponding increase in the pressure where the L−V occurs is noted. Beyond a certain temperature, the L−V transition is replaced by a L−L transition, which is characterized by the formation of a cloud. The temperature region where the shift

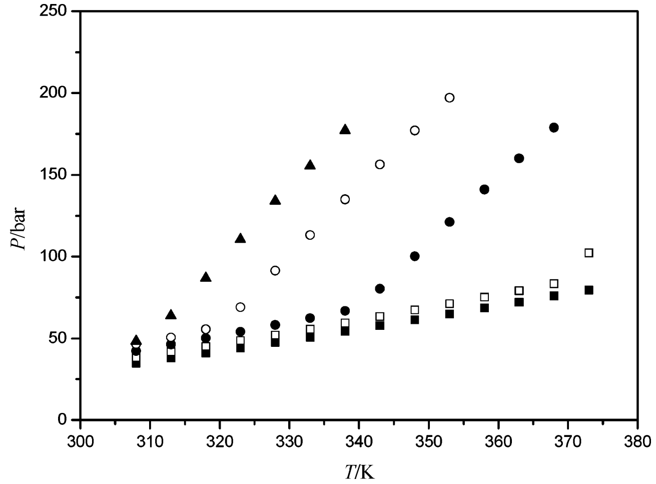

Figure 2. $P-T$ isopleths of cloud points of mass fraction PCL = 2 % in dichloromethane + CO_2. Mass fractions of CO_2 in the mixed solvent on a polymer-free basis: ■, 0.2517; □, 0.2911; ●, 0.3442; ○, 0.4009; ▲, 0.4384.

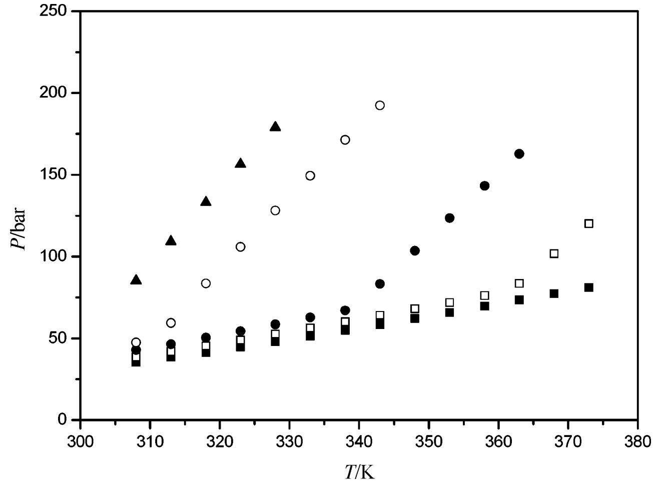

Figure 3. $P-T$ isopleths of cloud points of mass fraction PCL = 3 % in dichloromethane + CO_2. Mass fractions of CO_2 in the mixed solvent on a polymer-free basis: ■, 0.2511; □, 0.291; ●, 0.3441; ○, 0.4027; ▲, 0.4384.

from the L−L to the L−L transition occurs depends on the PCL mass fraction and the CO_2/CH_2Cl_2 loadings. The higher the CO_2/CH_2Cl_2 loading, the lower the temperature at which the L−L transition is first observed. Additionally, at L−V transitions, an increase in temperature leads to a relatively small increase in the bubble point. In L−L transitions the temperature increase has a significant effect on the cloud point, increasing it dramatically. Being polar, dichloromethane is a good solvent for PCL, whereas CO_2 is not. A decrease in dichloromethane composition causes a corresponding decrease in solvent polarity, and thus, the solvent power of the mixture is decreased, which leads to higher pressures necessary to maintain the single phase.

The above observations are characteristic of the LCST behavior of polymer−solvent−gas systems.[6,9] Such a LCST behavior for the system PLA + CH_2Cl_2 + CO_2 has been described previously.[6] As shown in Figures 1 to 3, the L−L transition is shifted to lower temperatures with increasing amounts of CO_2, a fact allowing for the manipulation of the system conditions in a way that is beneficial to the micronization process. Moreover, the mass fraction of PCL has a pronounced effect on the system: lowering the temperature where the first L−L transition is observed and raising the pressure of bubble and cloud points. Figure 4 presents the effect of the PCL mass fraction on the phase behavior.

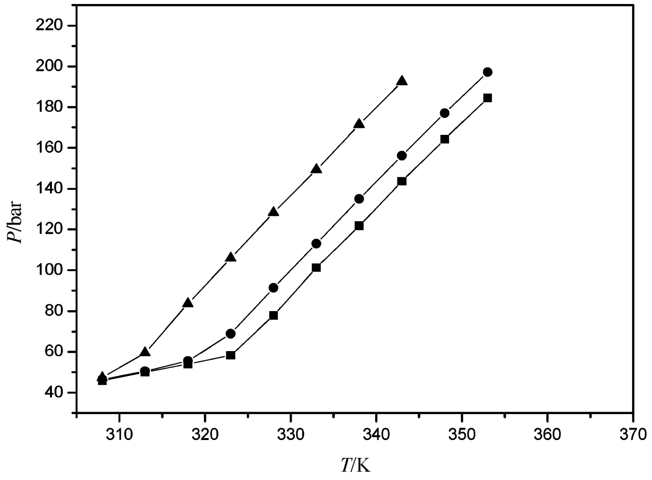

Figure 4. Effect of PCL composition in a mixed solvent of CO_2 (mass fraction = 0.401 on a polymer free basis) and dichloromethane (mass fraction = 0.599 on a polymer free basis); Mass fraction of PCL: ■, 1 %; ●, 2 %; ▲, 3 %.

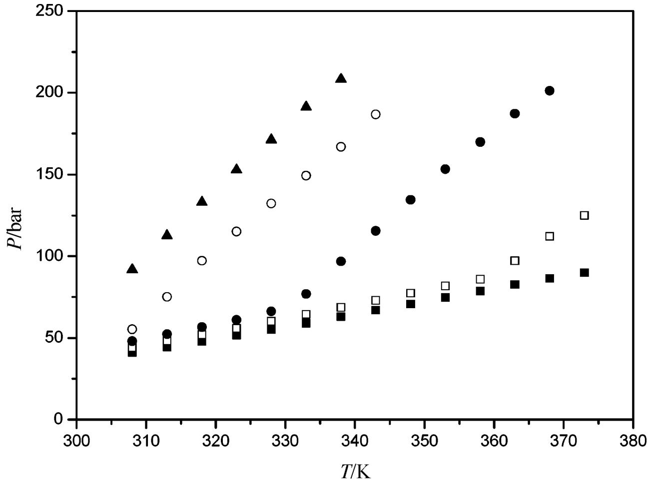

Figure 5. $P-T$ isopleths of cloud points of mass fraction PCL = 1 % in chloroform + CO_2. Mass fractions of CO_2 in the mixed solvent on a polymer-free basis: ■, 0.252; □, 0.291; ●, 0.3444; ○, 0.4002; ▲, 0.4383.

To study the effect of the organic solvent on the LCST behavior of the system and, thus, on the bubble and cloud points, the system PCL + $CHCl_3$ + CO_2 was investigated for polymer mass fractions 0.01 and 0.02; the corresponding data are presented in Table 2.

Again, the carbon dioxide acts as a nonsolvent in this system, lowering the temperature where the cloud point is first observed for a given composition of the system. Figures 5 and 6 present the $P-T$ isopleths for 0.01 and 0.02 mass fractions of PCL, respectively.

Comparing Figures 5 and 6 with Figures 1 and 2, respectively, it is obvious that the two systems exhibit a similar behavior. The LCST behavior is characteristic of both ternary systems, and the increase in temperature and CO_2/organic solvent loading has the same effects in both cases. However, due to the difference between dichloromethane and chloroform, the bubble and cloud points are observed at different pressures. It seems that the CO_2 + CH_2Cl_2 mixture is a better solvent for PCL as compared to the CO_2 + $CHCl_3$ mixture. In Figure 7, a comparison is made between the two ternary systems for polymer mass fraction 0.01 and mass fraction of 0.3442 for the CO_2 in the mixed solvent on a polymer-free basis.

The elevated bubble points of the ternary system PCL + CO_2 + $CHCl_3$ indicate the lower solvent strength of chloroform

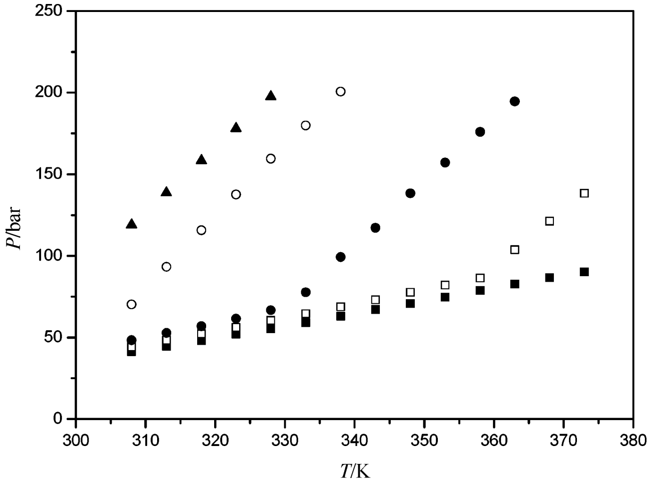

Figure 6. $P-T$ isopleths of cloud points of mass fraction PCL = 2 % in chloroform + CO_2. Mass fractions of CO_2 in the mixed solvent on a polymer-free basis: ■, 0.252; □, 0.2911; ●, 0.3444; ○, 0.4005; ▲, 0.4378.

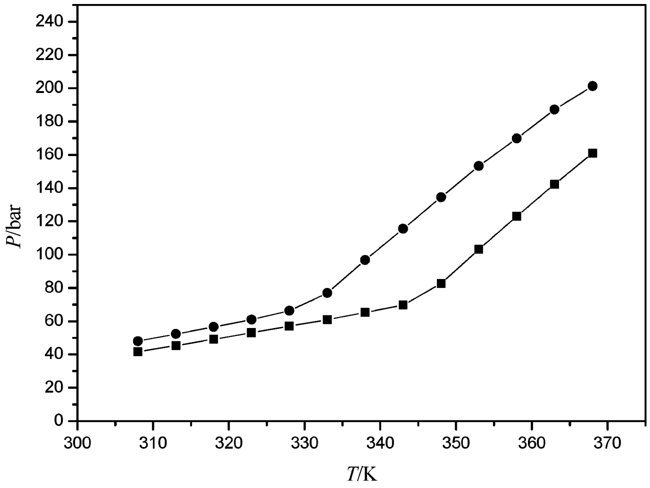

Figure 7. Effect of organic solvent on bubble and cloud points in a mixed solvent of CO_2 (mass fraction = 0.3443 on polymer free basis) and organic solvent (mass fraction = 0.6557 on a polymer free basis) for PCL mass fraction = 2 %. Solvents: ■, dichloromethane; ●, chloroform.

compared to dichloromethane. This ranking of the solvent strength of the two solvents is in agreement with their ranking on the basis of their solubility parameters. More specifically, the solubility parameters of chloroform, dichloromethane, and PCL are 18.92, 20.37, and 20.46 $(MPa)^{1/2}$, respectively.[10,11] It is well-known that the smaller the difference between the solubility parameters of two substances, the more miscible they are likely to be.[12] Thus, dichloromethane should be a much stronger solvent than chloroform for PCL. The effect of the difference in solvent strength is more pronounced in the cloud point region. The difference between the cloud points is about 45 to 50 bar, the cloud points of the PCL + CO_2 + CH_2Cl_2 system being lower than those of the PCL + CO_2 + $CHCl_3$. Moreover, the replacement of dichloromethane with chloroform results in the lowering of the temperature where the L−L transition is first observed, as is obvious from Figure 7.

Another important factor that must be taken into consideration in the case of ternary mixtures (and, thus, in applications of microparticle production) is the polymer mass fraction. The bubble points are slightly influenced for the system PCL + CO_2 + $CHCl_3$: an increase of the mass fraction of 1 to 2 % results in an elevation of the bubble points of 0.1 to 0.3 bar. The corresponding change in cloud points is much more pronounced (5 to 35 bar, depending on the CO_2 mass fraction of the mixture). CO_2-rich mixtures are more influenced since they are not strong solvents of the polymer, thus an increase of CO_2 mass fraction results in greater pressures necessary to maintain the mixture in a single phase.

Similar observations are made for the PCL + CO_2 + CH_2Cl_2 system. The bubble points are affected slightly more than the previous system (an increase in mass fraction of PCL of 1 to 2 % results in an elevation of the bubble points of 0.2 to 1.5 bar). However, in the cloud point region a corresponding increase in polymer mass fraction has a relatively less pronounced effect (12 to 18 bar). This is due to the higher solvent strength of dichloromethane and the difference that entails for the expansion of the ternary system. During a L−L transition, two liquid phases appear, one rich in carbon dioxide (thus, poor in polymer), and one rich in organic solvent (thus, rich in polymer). In a system exhibiting LCST behavior, an increase in carbon dioxide or temperature results in the expansion of the system.[9] In simple terms, the nonsolvent of the polymer, in this case carbon dioxide, tends to swell and dissolve the organic solvent, reducing its solvent strength. As a consequence, greater pressures are necessary to maintain the mixture in a single phase. In the case of a strong organic solvent, the increase in the polymer mass fraction has a less pronounced effect since a smaller amount of organic solvent is needed for the dissolution of the polymer in the liquid phase rich in organic solvent. Thus, the expansion of the system, either because of the increase of temperature or the increase of the carbon dioxide mass fraction, has a smaller effect as compared to the case where the organic solvent is not as strong a solvent for the polymer.

Conclusions

In this work the bubble and cloud points of the systems PCL + CO_2 + $CHCl_3$ and PCL + CO_2 + CH_2Cl_2 were determined. Depending on the temperature, the polymer concentration, and the CO_2/organic solvent mass ratio, L−V or L−L transitions may occur, each marked by the formation of a bubble or a cloud, respectively. An increase in temperature for a given mixture results in an increase in the necessary pressure to maintain the single phase. An increase in organic solvent mass fraction causes an increase in the polarity of the solvent, leading to a shift of the L−V and L−L transitions to higher temperatures and lower pressures. Moreover, the LCST behavior of the systems was observed, and the related effects of the increase in CO_2 mass fraction and temperature were investigated.

Finally, the effect of the polymer mass fraction was investigated. An increase in the polymer mass fraction led to an increase of the bubble and cloud point pressures. In the case of the bubble points, the observed increase in bubble pressure was more significant in systems rich in CO_2. Dichloromethane is a stronger solvent for PCL as compared to chloroform. Taking this parameter into account, the differences between the bubble and cloud points of the two systems were observed, and the effect that the organic solvent has on the behavior of the ternary systems was investigated. The above data, along with the study of the effects that temperature, polymer mass fraction, CO_2/organic solvent ratio, and nature of the organic solvent, especially its solvent strength for the polymer, have on the bubble and cloud points allows for a better understanding and therefore command of the supercritical antisolvent micronization process.

Literature Cited

(1) Subra, P.; Jestin, P. Powders elaboration in supercritical media: comparison with conventional routes. *Powder Technol.* **1999**, *103*, 2−9.

(2) Reverchon, E. Supercritical antisolvent precipitation of micro- and nano-particles. *J. Supercrit. Fluids* **1998**, *15*, 1−21.

(3) Sze, T. L.; Dehghani, F.; Foster, N. R. Micronisation and microencapsulation of pharmaceuticals using a carbon dioxide antisolvent. *Powder Technol.* **2002**, *126*, 134−149.

(4) York, P. Strategies for particle design using supercritical fluid technologies. *Pharm. Sci. Technol. Today* **1999**, *11*, 430−440.

(5) Ghaderi, R.; Artursson, P.; Carlfors, J. A new method for preparing biodegradable microparticles and entrapment of hydrocortisone in DL-PLG microparticles using supercritical fluids. *Eur. J. Pharm. Sci*. **2000**, *10*, 1−9.

(6) Kalogiannis, C.; Panayiotou, C. Bubble and cloud points of the system poly(L-lactic acid) + carbon dioxide + dichloromethane. *J. Chem. Eng. Data* **2005**, 50, 1442−1447.

(7) *International Thermodynamic Tables of the Fluid State*: *Carbon Dioxide*; Pergamon Press: Oxford, U.K., 1976.

(8) Meilchen, M. A.; Hasch, B. M.; McHugh, M. A. Effect of copolymer composition on the phase behavior of poly(ethylene-*co*-methyl acrylate) with propane and chlorodifluoromethane. *Macromolecules* **1991**, *24*, 4874−4882.

(9) Bungert, B.; Sadowski, G.; Arlt, W. Separations and material processing in solutions with dense gases. *Ind. Eng. Chem. Res*. **1998**, *37*, 3208−3220.

(10) Daubert, T. E.; Danner, R. P. *DIPPR*: *Physical and Thermodynamic Properties of Pure Compounds: Data Compilation*; Hemisphere: New York, 1989.

(11) Saraç, A.; Türe, A.; Cankurtaran, Ö.; Ylmaz, F. Determination of some thermodynamical interaction parameters of polycaprolactone with some solvents by inverse gas chromatography. *Polym. Int.* **2002**, *51*, 1285−1289.

(12) Krevelen, D. W. V. *Properties of Polymers*: *Their Estimation and Correlation with Chemical Structure*, 2nd ed.; Elsevier: Amsterdam, The Netherlands, 1976.

Received for review July 7, 2005. Accepted October 18, 2005. Financial support for this work has been provided by the Greek GSRT/PENED 2001.

JE0502602