Polymeric Microspheres Prepared by Spraying into Compressed Carbon Dioxide

Roland Bodmeier,[1,3] Hui Wang,[1] David J. Dixon,[2] Simon Mawson,[2] and Keith P. Johnston[2]

Received: January 6, 1995; accepted April 3, 1995

Purpose. The objective was to prepare polymeric microparticles by atomizing organic polymer solutions into a spray chamber containing compressed CO_2 (PCA-process) and to study the influence of various process parameters on their morphological characteristics. ***Method.*** The swelling of various pharmaceutically acceptable polymers [ethyl cellulose, poly(methyl methacrylate), poly(ϵ-caprolactone), poly(dl-lactide), poly(l-lactide) and poly(dl-lactide-glycolide) copolymers] in CO_2 was investigated in order to find polymers which did not agglomerate during the spraying process. Poly(l-lactide) (L-PLA) microparticles were prepared by spraying the organic polymer solution into CO_2 in a specially designed spraying apparatus. The effect of various process (pressure and temperature of the CO_2 phase, flow rate) and formulation (polymer concentration) variables on the morphology and particle size of L-PLA-microparticles was investigated. ***Results.*** Polymers with low glass transition temperatures agglomerated even at low temperatures. The formation of microparticles was favored at moderate temperatures, low polymer concentrations, high pressures and high flow rates of CO_2. High polymer concentrations and low flow rates resulted in the formation of polymeric fibers. Colloidal L-PLA particles could also be prepared with this technique in a surfactant-free environment. Initial studies on the microencapsulation of drugs resulted in low encapsulation efficiencies. ***Conclusions.*** The PCA method is a promising technique for the preparation of drug-containing microparticles. Potential advantages of this method include the flexibility of preparing microparticles of different size and morphology, the elimination of surfactants, the minimization of residual organic solvents, low to moderate processing temperatures and the potential for scale-up.

KEY WORDS: carbon dioxide; controlled drug release; microencapsulation; microspheres; supercritical fluids.

INTRODUCTION

Drug containing hydrophobic polymer particles with matrix (microsphere) or reservoir (microcapsule) structure can be prepared by various microencapsulation techniques including solvent evaporation-, spray drying- and organic phase separation techniques (1,2). Most of these methods suffer from drawbacks such as the use of organic solvents for the solubilization of polymers, the hazards and environmental concerns associated with these solvents, residual organic solvents, low encapsulation efficiencies because of drug partitioning between two immiscible phases, difficulties in the scale-up process and stability problems.

It is desirable to develop microencapsulation techniques which, at least partially, overcome these potential problems. Recently, hydrophobic microparticles have been prepared in a completely organic solvent-free medium by a novel technique. Drug-containing colloidal polymer dispersions were coalesced into polymeric microparticles with the aid of the ionotropic gelation of polysaccharides (3). In other developments, supercritical fluids have shown great promise in the preparation of polymeric microparticles. Supercritical CO_2 offers various advantages when contrasted with organic solvents widely used in microencapsulation processes. It is environmentally acceptable, non-flammable, relatively non-toxic, and inexpensive. The temperature and pressure conditions can be varied to control the solvent strength with a single compound (4-6).

Two techniques which minimize the use of organic solvents during microparticle preparation and the presence of residual solvents in the microparticles are based on the use of compressed or supercritical fluids such as CO_2. First, microparticles have been formed by spraying a solution of the polymer in a mixture of CO_2 and organic solvent into air (7-11). This process has been termed rapid expansion of supercritical solutions (RESS). The active ingredient and the polymer have to be soluble in the compressed gas/solvent mixture. Limitations of the RESS-process include the low solubility of most polymers in CO_2 and possibly problems seen with conventional spray drying techniques such as porous microparticles with rapid drug release and stability problems caused by crystallization or polymorphic transformations of encapsulated drug (12). The solubility of the biodegradable polymer, poly(l-lactide) with a low molecular weight of 5500 in supercritical CO_2 and 1 wt% (9).

In the second method, organic polymer solutions are atomized into a vessel containing compressed CO_2 (13-19). Microparticles are formed after precipitation of the polymer caused by extraction of the organic solvent into CO_2 and by CO_2 diffusion into the droplets. When compared with the RESS process, this technique allows the processing of more concentrated polymer solutions and also the use of drug suspensions. This process, which has been termed aerosol solvent extraction system (ASES) (13,19) or precipitation with a compressed fluid antisolvent (PCA) (14-17), has great versatility as the properties of CO_2 may be adjusted over a continuum throughout the gaseous, supercritical and liquid states by varying temperature and pressure. Polystyrene particles and fibers with a wide range in size and morphology have been prepared by simply varying the temperature and density of CO_2, which influenced the chemical potential and transport properties of the various components (14-17).

The objective of this study was to evaluate the PCA-process for the preparation of microparticles from pharmaceutically acceptable polymers and to study the influence of various process parameters on the morphological characteristics of the microparticles.

---

[1] College of Pharmacy, The University of Texas at Austin, Austin, Texas 78712.

[2] Department of Chemical Engineering, The University of Texas at Austin, Austin, Texas 78712.

[3] To whom correspondence should be addressed at Institut für Pharmazie, Freie Universität Berlin, Kelchstr. 31, 12169 Berlin, Germany.

0724-8741/95/0800-1211$07.50/0

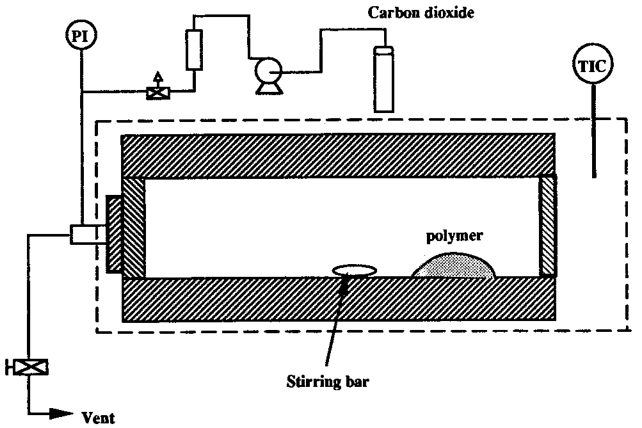


Fig. 1. Horizontal view cell used for the observation of the morphology of polymers in contact with carbon dioxide at different pressures and temperatures (see Table I for results).

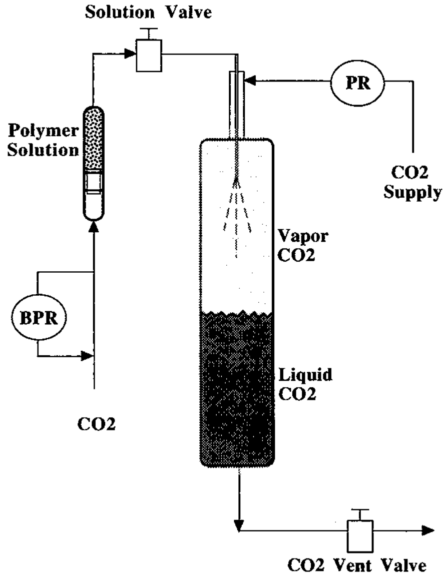


Fig. 2. Apparatus for the precipitation of polymers (preparation of microparticles) with compressed carbon dioxide (BPR = back pressure regulator; PR = pressure regulator).

MATERIALS AND METHODS

Materials

The following chemicals were used as received: ethyl cellulose (EC) (STD 10-premium grade, Dow Chemical Company, Midland, MI), poly(methyl methacrylate) (PMMA) (M.W. 100,000), poly(ϵ-caprolactone) (PCL) (Polysciences, Inc. Warrington, PA), poly(d,l-lactide) (DL-PLA) (M_w: 110,200, M_w/M_n: 1.95, Medisorb™ 100DL), poly(l-lactide) (L-PLA) (M_w: 94,100, M_w/M_n: 1.85, Medisorb™ 100DL), poly(dl-lactide-glycolide) (50/50) (Medisorb™ 5050 DL, Stolle-DuPont Co. Cincinnati, OH), chlorpheniramine maleate, indomethacin (Sigma Chemical Company, St. Louis, MO), methylene chloride (EM Science, Gibbstown, NJ), carbon dioxide (99.99%, Liquid Carbonics UHP).

Methods

Effect of Compressed CO_2 on the Polymers

The apparatus used to study the effect of compressed CO_2 on the morphology of the polymers is shown in Figure 1 and was described in detail elsewhere (19). The temperature was varied from room temperature to 40 °C (±0.1 °C) by immersing the cell into a thermostated water bath; the pressure was varied from 20.7 bar to 275.9 bar. If the polymer agglomerated at room temperature, the temperature was lowered to -10 °C using dry ice in an ethanol/water bath. The morphology of the polymers in CO_2 was then observed through the sapphire window and classified as either unchanged or swollen and agglomerated.

Experiments were performed to determine the extent to which carbon dioxide depresses the glass transition temperature (T_g) of L-PLA (20,21). The L-PLA was cast into 2.75″ × 1/4″ # 300 ×m films using methylene chloride as a solvent. The thickness was measured to five places with a micrometer, and an average thickness was calculated to ±.0001″. The films were dried in air for two days and evacuated in a dessicator. The swelling apparatus consisted of a high pressure Jerguson gauge view cell, containing a brass guide to hold the strip of L-PLA. At each pressure, the polymer strip was allowed to equilibrate for one to two hours, after which no further dilation was observed. The length of the L-PLA film was measured with a cathetometer to the nearest 0.01″.

Separate experiments were used to measure the creep compliance, which is the strain per time divided by the stress (21). The stress was produced with a total weight of 10.1 g, which was 14% of the L-PLA yield stress. The creep compliance was determined for a period of 15 minutes. An additional experiment was conducted at 70°C to determine if L-PLA would creep at a temperature far above the normal T_g. A film of L-PLA, 30 microns in thickness, was loaded

Table I. Morphology of Polymers in CO_2

Polymer	Temperature, °C	Pressure, bar	Morphology
Ethyl cellulose	23–40	69.0–275.7	unchanged
Poly(d,l-lactide) – 10–33	– 10–33	20.7–158.6	agglomeration
Poly(l-lactide)	23–40	69.0–275.7	unchanged
Poly(ϵ-caprolactone)	23–32,	69.0–275.7	unchanged
	40	106.2	agglomeration
Poly(d,l-lactide-glycolide) (50/50)	0–23	41.4–62.1	agglomeration
Poly(methyl methacrylate)	23	69.0–275.7	agglomeration

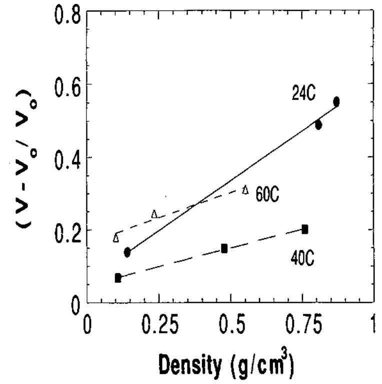


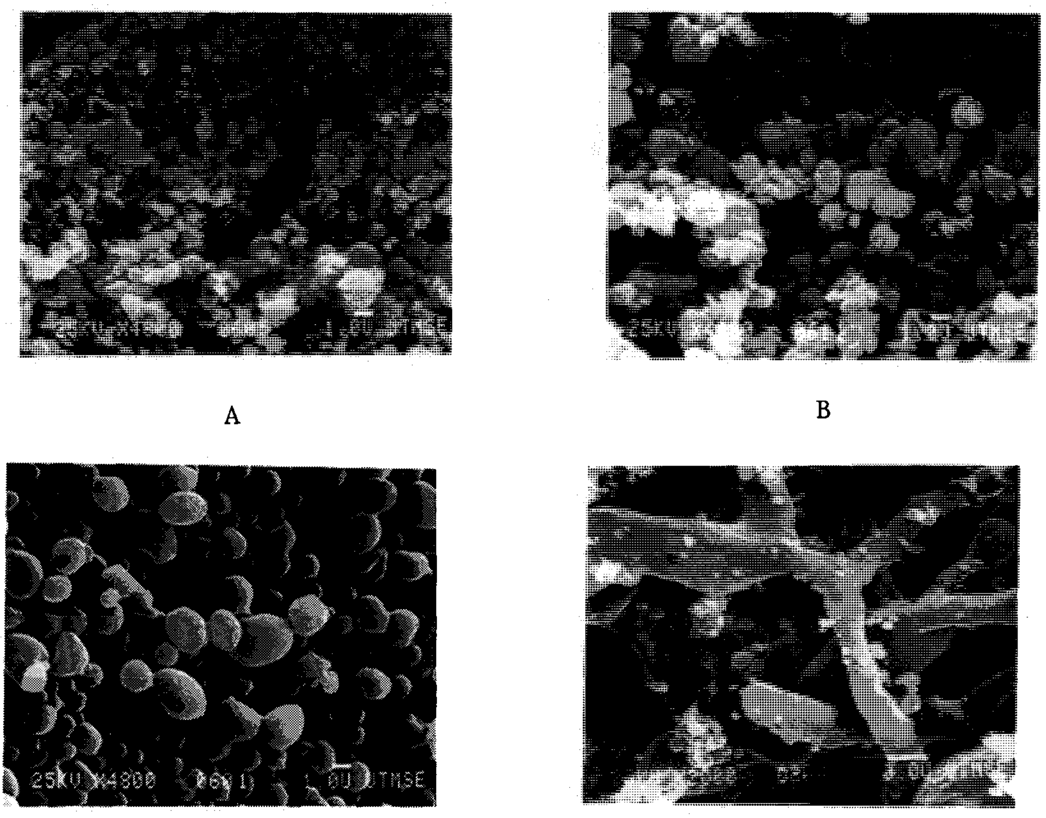
Fig. 3. Swelling of L-PLA as a function of carbon dioxide density at different temperatures.

with a weight of 6.7g or 84% of the yield stress. The total film length changed <0.05 cm in 2 hrs.

Preparation of the Polymeric Microspheres by the PCA-Method

For the preparation of the polymeric microspheres, an apparatus with a vertical spray chamber was built (Figure 2). Autoclave Engineers (AE) medium pressure nipples (1″ OD by 0.688″ ID by 8″ long, model CNLX 1608-316) rated up to 689 bar were used both for the polymer solution vessel, containing a piston, and the spray chamber. The nozzle consisted of a fused silica capillary tube with a polyimide coating (ID = 100 μm, length = 17.4 cm). To facilitate recovery of the precipitated polymer, a filter arrangement (0.2 μm cellulose filter paper held between two stainless steel screens) was fabricated to fit into the reducing union at the bottom of the cell. The bottom vent valve consisted of a stainless steel needle valve (Whitey, SS-31RS4). For CO_2 delivery, pressure was generated with a Haskel model AC-152 air driven gas booster and controlled with a Tescom pressure regulator (PR) (model 26-1021). The system was equilibrated for 10 - 20 minutes before the polymer solution was sprayed. The pressure in the polymer solution vessel was generated with a metering pump and back pressure regulator (BPR) as described previously (16). The polymer solution (L-PLA in methylene chloride, 1% - 6%w/v) was sprayed in the chamber for 10 to 15 s. The flow rate of the polymer solution was measured for a given Δ P across the capillary in a separate experiment prior to making the particles. After atomization of the polymer solution, CO_2 was swept through the chamber to remove the solvent and dry the microparticles for 30 min followed by depressurization over another 30 min period. The bottom coupling of the cell was then removed and the dried polymer particles were recovered.

This vertical cell was also used for experiments in which the antisolvent was a two phase mixture of vapor over liquid CO_2. At the saturation temperature, approximately 30 ml of CO_2 were metered into the vertical spray chamber with a HIP 60 ml manual syringe pump. The cell was filled approx-



A B

C D

Fig. 4. Scanning electron micrographs of L-PLA microparticles prepared from different polymer solution concentrations in methylene chloride: (a) 1% w/v, (b) 2 %w/v, (c) 3 %w/v, (d) 6 %w/v.

imately half with liquid CO_2, this phase being in equilibrium with the gas phase above it. The polymer solution was therefore first sprayed into the vapor phase with the atomized polymer droplets then contacting the liquid CO_2. The remaining process was the same as described above.

Scanning Electron Microscopy

Scanning electron microscopy (SEM) was used to characterize the morphological properties of the microspheres. The mounted microspheres were sputter-coated for 70 seconds under an argon atmosphere with gold-palladium (Pelco Model 3 Sputter Coater) and then observed with a scanning electron microscope (SEM) (Jeol JSM 35C).

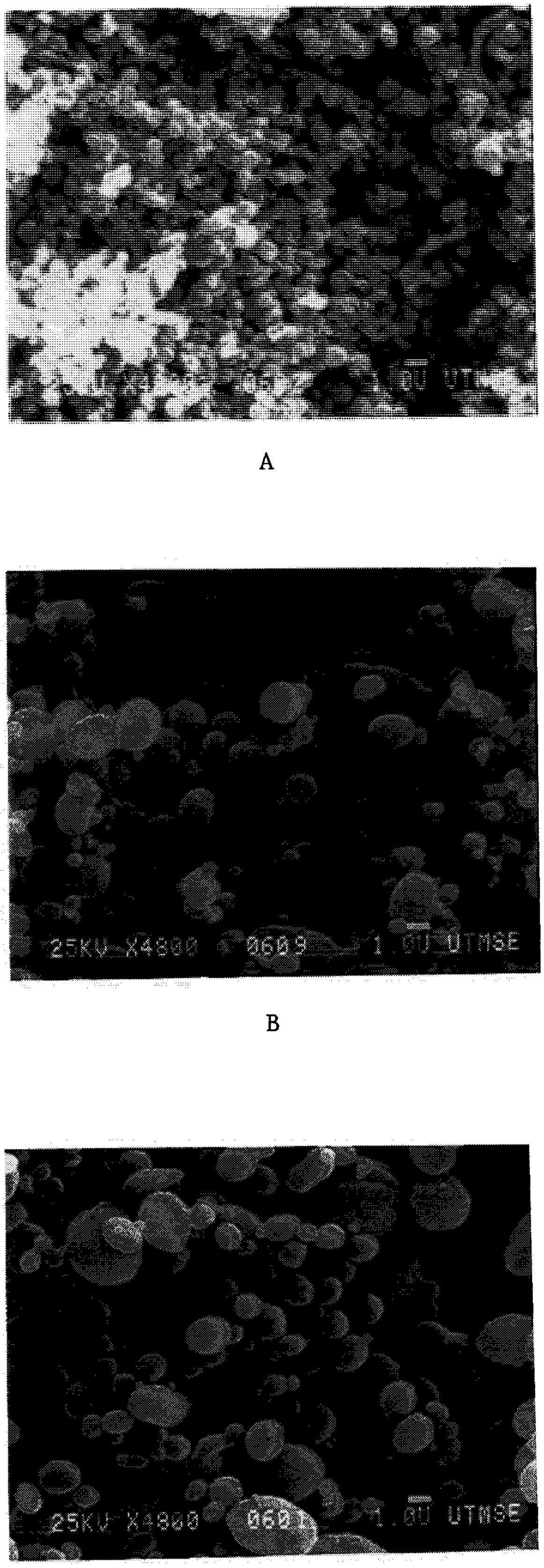
Determination of the Drug Content of the Microspheres

The drug content of the microspheres was obtained by extracting the microspheres (20 mg) with 20 ml of methanol for 24 hours. The samples were centrifuged, if necessary, and then assayed for drug content by UV-spectroscopy (U-1100 Spectrophotometer, Hitachi Instruments Inc., Danbury, CT) at the wavelength of maximum absorbence (chlorpeniramine maleate, $\lambda = 262$ nm; indomethacin, $\lambda = 258$ nm). The theoretical drug loading of the microspheres was 10%w/w.

RESULTS AND DISCUSSION

Effect of Compressed CO_2 on Different Polymers

A prerequisite for the successful preparation of polymeric microparticles by this method was the atomization of the polymer solution into droplets and the hardening of the droplets into microparticles. In initial studies, the amorphous biodegradable polymer, poly(dl-lactide) was sprayed from a solution in methylene chloride into compressed CO_2 to obtain microspheres. After depressurization, an agglomerated mass of polymer was retained on the filter. This indicated, that CO_2 acted as a plasticizer for the polymer, resulting in swelling and agglomeration of the polymer. In order to find polymers suitable for this process, pharmaceutically acceptable polymers including ethyl cellulose, poly(methyl methacrylate) and the biodegradable polymers, poly(ϵ-caprolactone), poly(dl-lactide), poly(l-lactide) and poly(dl-lactide-glycolide) copolymers were screened for morphological changes in compressed CO_2. The polymer and compressed CO_2 were fed into the pressure cell shown in Figure 1. The polymer was then observed through the sapphire window for morphological changes under various pressure and temperature conditions (Table I). Ethyl cellulose was not affected by carbon dioxide. The semi-crystalline poly(l-lactide) was unchanged, while the amorphous poly(dl-lactide) and poly(dl-lactide-glycolide) copolymers agglomerated even at low temperatures. The amorphous biodegradable polyesters have low glass transition temperatures in the range of 30 to 50 °C, which can easily be lowered below ambient temperatures by CO_2 based on similar studies (20,21). The semicrystalline poly(ϵ-caprolactone) swelled in CO_2 at higher temperatures and pressures. Poly(methyl methacrylate) swelled in CO_2 at room temperature and high pressure.


A

B

C

Fig. 5. Scanning electron micrographs of L-PLA microparticles prepared at different temperatures: (a) 0 °C, (b) 23 °C, (c) 32 °C.

From these morphological studies, ethyl cellulose and poly(l-lactide) were not affected by carbon dioxide and therefore suitable candidates for the preparation of the polymer microparticles. The biodegradable polymer, poly(l-lactide) (L-PLA), was further evaluated.

The results of the quantitative dilation experiments with L-PLA films are shown in Figure 3. From 24 to 40 °C, the swelling decreased with increasing temperature due to the increased activity of the diluent. At 60 °C, a reversal in the swelling was observed. This increase suggested a morphological change in the polymer, since the activity of CO_2 continues to increase with temperature at constant density. This increase in swelling is consistent with the normal T_g of L-PLA, which is 55-60 °C.

The creep compliance was extremely small in all of the experiments, even up to 70 °C, which is well-above the normal T_g. The change in length from 10 seconds after dropping the weight to 15 minutes was always less than 0.01″. This limits the creep compliance to $< 6.03 \times 10^{-8}$. In contrast, the creep compliance of polymethyl methacrylate changed from 10^{-8} in the glassy region to 10^{-6} in the rubbery region as the CO_2 pressure was increased. Thus, it appears that the crystalline domains in L-PLA limit the creep even when the amorphous regions are plasticized. This conclusion was consistent with the qualitative observation that the L-PLA particles did not become sticky at the conditions studied. However, the dilation experiments at 60 °C suggest that the amorphous regions may be plasticized. Therefore, other techniques would be required to determine the T_g depression more quantitatively.

Preparation of Polymeric Microspheres by the PCA-Method

In the PCA experiments, a solution of L-PLA in methylene chloride was sprayed through a nozzle (capillary tube) into a vessel containing compressed CO_2. Many similarities exist with classical spray-drying techniques, the major difference being the spraying of the polymer solution into a compressed gas instead of into air as the external phase. Compressed CO_2 is quite miscible with methylene chloride at the conditions studied; however, it is a nonsolvent for the polymer.

L-PLA microspheres prepared by the PCA method were spherical, free-flowing and non-agglomerated with a smooth surface structure. The particles were smaller than 5 μm with a narrow particle size distribution. Scanning electron micrographs of the cross-sections of the microspheres revealed a homogeneous and dense matrix structure (not shown).

The effect of various process (temperature, density of CO_2, and flow rate) and formulation (polymer concentration) variables on the morphology of the microparticles was investigated. As observed with many spray processes, polymer concentration and hence solution viscosity strongly affected the morphology of the polymer microparticles. Increasing the solution concentration from 1 to 6 w/v% resulted first in larger, less spherical microparticles and, at high polymer concentrations, in the formation of fibers (Figure 4). A prerequisite for the formation of individual microparticles was the breakup of the liquid jet of the polymer solution entering the spray chamber into individual droplets prior to the precipitation of the polymer. As the concentration of polymer solution increased, the viscosity of the sprayed polymer solution increased and acted as a stabilizing force on the jet. At a polymer concentration of 6 %w/v, the atomization forces were not sufficient to break up the liquid jet into droplets. The time scale for droplet formation was longer than the time scale for polymer precipitation, resulting in fibers rather than in microspheres (15,16). In addition, at higher polymer concentrations, less CO_2 was required to precipitate the polymer.

As discussed above, the break up of the liquid jet into droplets was also affected by the atomization conditions. Microparticles as well as fibers could be obtained by simply varying the flow rate of CO_2 through the spray chamber. At a slow flow rate of CO_2 (9.7 ml/sec), fibers were obtained. The atomization forces were not sufficient to break up the jet of the polymer solution prior to precipitation of the polymer. The polymer solution was broken up into droplets at fast flow rates and microparticles were obtained. The selection of suitable flow rates of CO_2 was therefore another factor, which could be used to control the morphology of the resulting polymer matrix.

In order to examine the effect of temperature on the morphology of the microparticles, experiments were performed at constant concentration of the polymer solution (3% L-PLA in CH_2Cl_2), pressure of CO_2 (81.6 bar) and nozzle diameter (100 μm). Scanning electron micrographs of L-PLA microparticles prepared at 0 °C, 23 °C (room temperature) and 32 °C (critical temperature of CO_2) are shown in Figure 5. The smallest microparticles were obtained at 0 °C (density of CO_2 = 0.9649 g/cc) (Figure 5a), with a particle size less than 1 μm and a narrow particle size distribution. The particle size increased with increasing temperature as reported by Randolph et al. (18). At 23 °C (density of CO_2 = 0.8069 g/cc) and 32 °C (density of CO_2 = 0.6850 g/cc), the particle size was in the range of 1 - 5 μm (Figure 5b and c). Irrespective of the temperature and size, the microparticles were all spherical and nonagglomerated. The differential in pressure across the capillary tube was constant for all cases. However, the flow rate varied with temperature. Increasing the temperature from 0 °C to 32 °C resulted in a decrease in the viscosity of the polymer solution and hence increased the flow rate accordingly. An increase in flow rate reduces the particle size, which is opposite of the actual results. However, the increase in particle size with temperature may be explained by several factors. The decrease in the density of CO_2 with an increase in temperature reduces the degree of atomization, although this effect does not appear to be important in the isothermal experiments described below. More significantly, both the temperature

Table II. Encapsulation of Drugs with Poly(l-lactide) by the PCA Technique

Drug	Drug loading, %	Particle size, μm
chlorpheniramine maleate	3.73	1–5
indomethacin	0.73	1–5

Processing condition: room temperature, CO_2 pressure: 69.0 bar, ΔP across the nozzle: 34.5 bar, nozzle size: 100 μm, 4% poly(l-lactide) in CH_2Cl_2, theoretical drug loading: 10%.

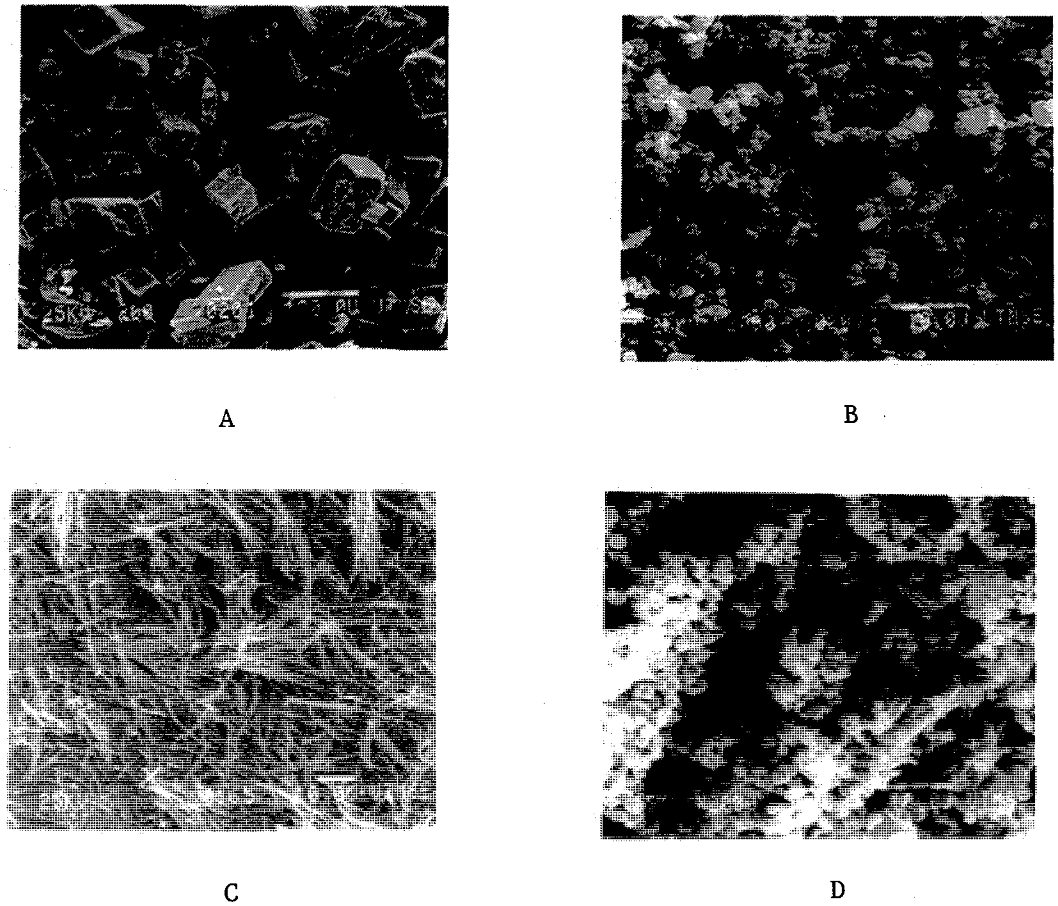


Fig. 6. Scanning electron micrographs of pure drug and drug-L-PLA microparticles prepared by precipitation in carbon dioxide: (a) chlorpheniramine maleate, (b) chlorpheniramine maleate - L-PLA microparticles, (c) indomethacin, (d) indomethacin - L-PLA microparticles.

increase and density decrease lower the sorption of CO_2 in the polymer. With less sorption, nucleation is slower, leading to fewer larger particles. The larger particles may also be produced by the higher growth rates at the higher temperatures (18).

Yet another factor that influences particle size is the depression of the T_g of the polymer. This factor played a major role for the polystyrene-toluene system. (15,16). The sorption of CO_2 into the L-PLA can depress the T_g causing the particles to become sticky, leading to coalescence. Residual methylene chloride will further contribute to plasticization. Unfortunately, the creep compliance experiments were not definitive concerning T_g due to complications from the crystalline domains. Although the swelling data at 60°C suggest the polymer was plasticized, it would be useful to verify this with other techniques in the future.

The density of CO_2 also affected the size and morphology of the microparticles. The density of CO_2 was varied isothermally between 0.170 g/cc and 0.964 g/cc by changing the pressure from 55.2 bar to 275.7 bar. The smallest particle size was obtained by spraying into low density CO_2. At a density of 0.170 g/cc, CO_2 is in the vapor state. The small increase in particle size with density from 0.170 to 0.964 g/cc is consistent with Randolph et al. (18). These results suggest that the initial forces were sufficiently strong to atomize the jet at 0.170 g/cc and a further increase in density had little effect on this atomization. The largest particles were produced by a vapor over liquid PCA method (CO_2 densities of 0.221/0.738 g/cc). The vapor over liquid PCA technique was designed to spray the polymer solution into the vapor phase to allow the jet to break up into droplets. The polymer droplets then fell into a pool of liquid CO_2 in order to solidify the droplets and to form the microparticles. The transfer of methylene chloride into the external CO_2 vapor phase was significantly lower when compared to spraying the polymer solution into liquid CO_2. The precipitation of the polymer was therefore retarded, allowing the polymer solution to break up into droplets prior to contacting the liquid CO_2 phase. Once the droplets fell into the liquid CO_2 phase, CH_2Cl_2 diffused rapidly into the external phase, resulting in polymer precipitation and microparticle formation.

The ultimate goal of this work is to entrap drugs within the polymeric microparticles. A water-soluble drug, chlorpheniramine maleate, and a water-insoluble drug, indomethacin, were selected as model drugs at a theoretical drug loading of 10%. The drugs were dissolved in the polymer solution prior to the spray process. The drug loading of the resulting microspheres was low, especially for the water-insoluble drug, indomethacin (Table II). This indicated, that both drugs partitioned into the external CO_2 phase. Lipophilic drugs have shown to be soluble in compressed gases (6,22). The partitioning of drugs into the external phase during microparticle formation is a problem commonly seen with techniques using immiscible phases (23). The solubility of the drugs in the external phase was further increased because of the presence of methylene chloride, which diffused into CO_2. In addition, the drug could have been extracted from the microspheres during the drying step. Scanning electron micrographs of the drug containing microspheres and pure drug particles prepared by this method are shown in Figure 6. Large cubic crystals of chlorpheniramine maleate were formed (Figure 6a, while indomethacin resulted in fiber-like agglomerates (Figure 6c). The microparticles were similar in appearance to the drug-free microparticles (Figures 6 b and d). Future studies will be directed towards improving the drug loading of the microparticles.

In summary, the PCA method appears to be a promising technique for the preparation of drug-containing microparticles. Potential advantages of this method include the flexibility of preparing microparticles of different size and morphology, the elimination of temperatures, the potential for scale-up and the possibility for aseptic preparation of the microparticles.

REFERENCES

1. P. B. Deasy. *Microencapsulation and Related Drug Processes.* Marcel Dekker, New York, 1984.
2. A. Kondo. *Microcapsule Processing and Technology,* Marcel Dekker, New York, 1979.
3. R. Bodmeier and J. Wang. Microencapsulation of drugs with aqueous colloidal polymer dispersions. *J. Pharm. Sci.* 82(2): 191-194 (1993).
4. M. A. McHugh and V. J. Krukonis. *Supercritical fluid extraction principles and practice,* Butterwirths, Stoneham, MA, 1986.
5. K. P. Johnston, S. Kim, and J. R. Combes. Spectroscopic determination of solvent strength and structure in supercritical fluid mixtures: A Review. In K. P. Johnston and J. M. L. Penninger (eds.), *Supercritical Fluid Science and Technology,* ACS Symposium series #406, American Chemical Society, Washington, DC, 1989.
6. E. Stahl, K. W. Quirin, and D. Gerard. *Dense Gases for Extraction and Refining,* Springer-Verlag, Berlin, 1987.
7. D. W. Matson, R. C. Petersen, and R. D. Smith. Production of powders and films by the rapid expansion of supercritical solutions. *J. Mater. Sci.,* 22:1919-1928 (1987).
8. J. W. Tom and P. Debenedetti. Particle formation with supercritical fluids: A review. *J. Aerosol Sci.* 22:555-584 (1991).
9. J. W. Tom and P. Debenedetti. Formation of bioerodible microspheres and microparticles by rapid expansion of supercritical solutions. *Biotechnol. Prog.* 7:403-411 (1991).
10. A. K. Lele and A. D. Shine. Morphology of polymers precipitated from a supercritical solvent. *AIChE J.* 38:7442-752 (1992).
11. E. M. Phillips and V. J. Stella. Rapid expansion from supercritical solutions: application to pharmaceutical processes. *Int. J. Pharm.* 94:1-10 (1993).
12. R. Bodmeier and H. Chen. Preparation of biodegradable poly(±)lactide microparticles using a spray-drying technique. *J. Pharm. Pharmacol.* 40:754-757 (1988).
13. B. W. Müller and W. Fischer. Verfahren zur Herstellung einer mindestens einen Wirkstoff und einen Träger umfassenden Zubereitung, *German Patent Appl. No. DE 3744329 AI,* 1989.
14. D. J. Dixon and K. P. Johnston. Molecular thermodynamics of solubilities in gas anti-solvent crystallization. *AICHE J.* 37:1441-1449 (1991).
15. D. J. Dixon. Ph.D. dissertation, The University of Texas at Austin, Austin, TX, 1992.
16. D. J. Dixon, R. Bodmeier, and K. P. Johnston. Polymeric materials formed by precipitation with a compressed fluid antisolvent. *AICHE J.,* 39:127-139 (1993).
17. D.J. Dixon and K.P. Johnston. Microporous polymer fibers and oriented fibrils by precipitation with a compressed fluid antisolvent. *J. Appl. Polym. Sci.,* in press.
18. T. W., Randolph, A. D. Randolph, M. Mebes, and S. Yeung. Sub-micron sized biodegradable particles of poly(l)lactic acid in the gas anti-solvent spray precipitation process. *Biotechnol. Progress* 9:429-435 (1993).
19. J. Bleich, B. W. Müller, and W. Waßmus. Aerosol solvent extraction system — a new microparticle production technique. *Int. J. Pharm.* 97:111-117 (1993).
20. P. D. Condo, I. C. Sanchez, C. G. Panayiotou, and K. P. Johnston. Glass transition behavior including retrograde vitrification of polymers with compressed fluid diluents. *Macromolecules* 25:6119-6127 (1992).
21. P. D. Condo and K. P. Johnston. In-situ measurements of the glass transition temperature of polymers with compressed fluid diluents. *J. Poly. Sci.: Part B: Polym. Phys.* in press.
22. K.A. Larson and M. L. King. Evaluation of supercritical fluid extraction in the pharmaceutical industry. *Biotech. Progress,* 2:73-82 (1986).
23. R. Bodmeier and J. W. McGinity. The preparation and evaluation of drug-containing poly(dl-lactide) microspheres formed by the solvent evaporation method. *Pharm. Res.* 4(6):465-471 (1987).