Morphology of Polymers Precipitated from the Mixtures of Carbon Dioxide and Cosolvent

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ABSTRACT

L-poly(lactic acid)(PLA) microspheres have been produced by particles from gas saturated solutions(PGSS). A CO2 saturated polymer solution containing ethanol is sprayed through a nozzle to air and/or aqueous solution. In this work, to control the particle morphology, the gas saturated polymer solution is expanded through the nozzle to water. After sprayed through a nozzle to air, polymeric fibers and coalescence particles were obtained. On the other hand, polymeric microspheres were obtained after sprayed through a nozzle to water. The particles were smaller than those produced by PGSS into air. Dispersion of polymeric particles in water impedes particles growth and agglomeration. The particles do not tend to agglomerate after expansion, since the ethanol used as cosolvent on the surface of particles diffuse through the water. The changing the pre-expansion pressure, nozzle diameter, and injection distance between the nozzle and water interface, controls the particle size distribution and morphology of microparticles.

KEYWORDS

supercritical carbon dioxide, PGSS, polymeric microspheres

INTRODUCTION

Recently, supercritical CO2 based production of micro- and nanoparticles is attracting much attention in the pharmaceutical, nutraceutical, cosmetic and specialty chemistry industry(Jung and Perrut, 2001). A considerable number of studies have been made on the preparation of microparticles and/or microcapsules of bridgeable polymer for pharmaceutical applications. To obtain the polymer
particles, several techniques have been reported (Biswas et al., 2001). Current techniques include spray drying, emulsion, and processes based on the high shear. However, there are several drawbacks, such as broad particles size distribution, in these techniques. And the solvent impurities and surfactants are often toxic and also degrade medicines within polymer matrix.

Therefore, we have challenged to develop a formation method of polymer microspheres that emits no such chemicals into our environment and controls the particles size using the supercritical fluids (SCF), especially CO₂. CO₂ may be utilized as an environmentally benign solvent substitute, because CO₂ is non-toxic, non-flammable, and has easily accessible critical conditions, i.e., $T_c=304$ K and $p_c=7.37$ MPa. Recently, several principles based on the supercritical CO₂ are used as the formation method of polymeric microspheres. Supercritical CO₂ have been used in a process called rapid expansion from supercritical solution (RESS) to produce a variety of powders and fibers (Jung and Perrut, 2001). In RESS, a supercritical fluid solution is expanded through the nozzle with formation of solid particles. However, RESS of polymer solutions in CO₂ has been scarcely reported (Mawson et al., 1995, Shim et al., 1999), because the low polymer solubility. In general, solubility of high molecular weight of polymer in CO₂ is very low at the temperature below 80°C (Sarbu et al., 2000). To accelerate the solubility of polymer in CO₂, the cosolvent is added in CO₂. Because the cosolvent is good solvent for polymer in general, agglomerated polymer particles or films were obtained after RESS with cosolvent.

On the other hands, particles from gas saturated solutions and/or suspensions (PGSS) technique is the effective method of the formation of polymer microparticles (Mandel et al., 1999). The solubilities of supercritical CO₂ in liquids and solids like polymer are usually high. In PGSS, the melted or liquid-suspended polymer solution, so called gas saturated solutions and/or suspensions, was expanded through the nozzle with formation of solid particles and/or films. The UNICARB process is typical approach for formation of polymer films (Donohue et al., 1996). In the UNICARB process, the formulation consists of a polymeric resin, an organic solvent, and CO₂ as a dissolved solute to serve as a diluent. The organic solvent is a good solvent in the UNICARB process, such that expansion produces highly swollen particles that coalesce to produce a film.

The objective of this study is to develop the production method of non-agglomerated micron sized polymeric microspheres using CO₂-based spray technique. We try the formation of the polymeric microparticles by the rapid expansion of CO₂ saturated polymer suspensions with a cosolvent to water. The process is shown in Figure 1, compared with routine PGSS and/or RESS with a cosolvent. Because the cosolvent is good solvent for polymer in routine PGSS and RESS with a cosolvent, the coalescence particles and/or films are obtained after expansion. Residual cosolvent on the particles accelerates the coalescence and flocculate of the particles. On the other hands, because the residual cosolvents diffuse into the water, polymeric microparticles were obtained by the rapid expansion of gas saturated suspensions to water. Young et al.(2000) have been reported the rapid expansion from supercritical to aqueous solution(RESAS) to produce submicron suspensions of water-insoluble drugs.
To impede particle agglomeration and growth, supercritical solutions were expanded to aqueous solution. The purpose of our study is the control of the polymer particle morphology by rapid expansion of gas saturated polymer suspensions to water. As shown in Figure 1, to control the particle morphology, the interfacial tension of the polymer solution droplets (suspensions) and diffusion of the cosolvent to water phase are the key novel feature of this work.

Figure 1. Principle of forming polymeric microspheres using the rapid expansion of the CO2 saturated polymer suspensions.

MATERIALS AND METHODS

Materials

Carbon dioxide (CO2), with 99.9 % minimum purity, was purchased from Fukuoka Sanso Co., Ltd. Methanol, ethanol, 1-propanol and toluene were obtained from Wako Pure Chemical Industry Co. Ltd. with purities of more than 99.5, 99.8, 99.5 and 99.8 %, respectively. L-poly(lactic acid) (PLA, M.W.=10,000) and poly(lactic acid)-poly(glycol acid) copolymer (PLGA, M.W.=10,000) were purchased from Wako Pure Chemical Industry Co. Ltd.

Procedure

Details of experimental apparatus and procedures were described in our previous paper (Mishima et al., 2000, Matsuyama et al., 2001). A schematic diagram of the experimental apparatus for making polymeric microspheres is presented in Figure 2. A high pressure cell (AKICO Co., SCV500A),
about 500 cm$^3$ in volume, was equipped with a sapphire window (10 mm in diameter). The system pressure was controlled by a back pressure regulator (V-1)(Tescom Co., model 26-1721-24, accurate to 0.1 MPa) and monitored by a digital pressure gauge. Temperature was controlled to within ±0.1 K with a water bath. Known amounts of the polymer and cosolvent were placed in the high pressure cell. SC-CO$_2$ was pumped through a 3 min length x 1/8 inch stainless steel tube pre-heater and then into the high pressure cell. The pre-expansion pressure was raised at 5 MPa intervals from 10 to 25 MPa. This mixture was stirred by an agitator rotating at 1000 rpm for about 1 hour and then kept for more than one hour without agitation. Prior to the expansion of the polymer solution, it was confirmed visually the phase condition.

The polymer suspension was sprayed toward a target plate (30 x 60 x 1 mm, aluminum plate) through a stainless steel capillary nozzle (Tungsten Carbide Co., model 500017-TC), for a short time (less than 3 seconds) by opening a valve (V-5) placed before the nozzle. The capillary nozzle has 50 mm length, 0.1–2.2 mm diameter ($L/D=23–500$). The nozzle was maintained at 313.15 K with an electric heater. The target plate was placed in a chamber (70cm x 80cm x 80cm) under atmospheric pressure. The distance from the tip of the nozzle to water interface in the water bath (19) was varied from 0 to 140 cm. After sedimentation of the microspheres, they were collected through out the entire chamber.

The polymeric microspheres were mounted on a small glass plate, covered with a small piece of double-sided carbon-conductive tape (E.F. Fullam Co., carbon conductive double sticky tape). The sample was sputter-coated with silver-palladium and imaged with a SEM (Shimadzu Co. Ltd., SSX-550). In order to evaluate effects of operating factors, the particle size and particle size distribution were determined by SEM and a laser diffraction particle size analyzer (Shimadzu Co. Ltd., SALD-2000). To analyze the particle size and distribution by SALD, the product microspheres were dispersed in ethanol or water with surfactant (sodium hexametaphosphate), and sonicated before the analysis. The reproducibility’s of primary particle diameter and geometric standard deviation of particle diameter of polymeric microspheres were within ±5 %. Physical properties of polymeric microparticles were investigated by high performance liquid chromatography (HPLC; column; TSKEL G4000, detector; refractive index detector (Tosoh Co. Ltd., RI 8012). For HPLC tetrahydrofurane was employed as the eluent. The residual solvent in the polymeric microspheres was measured by recording the weight loss after heating a 5 g sample at 413 K for 2 hours.

RESULTS AND DISCUSSION

Particle morphology

Prior to the expansion, phase behavior of the CO$_2$ + L-PLA + ethanol system at 20 MPa and 313 K was confirmed visually by high pressure cell equipped with sapphire windows. The system forms
the polymer phase and CO₂ phase. The polymer is glassy condition for the CO₂ + L-PLA binary system at 20 MPa and 313 K. However, with the addition about 10 wt. % ethanol, L-PLA melts in CO₂. Therefore, we try the formation of L-PLA particles by rapid expansion of the mixtures of CO₂, L-PLA and ethanol. The mixture was not agitated and two phases (polymer rich and CO₂ rich phase) were formed. Polymer products were not obtained, because the solubility of L-PLA in the mixtures of CO₂ and ethanol is very low and polymer phase is formed. On the other hands, polymer particles were obtained by rapid expansion of the polymer suspensions in the mixtures of the CO₂ and ethanol. This mixture was stirred by an agitator rotating at 1000 rpm for about 5 min and then polymer suspensions were obtained. Without the cosolvent, polymer products were not obtain after expansion with agitation. After the rapid expansion of the gas saturated polymer suspensions to water, we can obtain the L-PLA microspheres as in Figure 3(a). The pre-expansion pressure was 20 MPa and the temperature was 308 K. The temperature of the water bath is 308 K. Ethanol was used as a cosolvent at a concentration of 15 wt. %. The polymer microspheres are very small, on the order of only several microns and are spherical. Similar morphologies were observed for other cosolvents including methanol and 1-propanol. In the rapid expansion of the gas saturated polymer suspensions with cosolvent to water, diffusion of cosolvent to the water (nonsolvent for polymer), and the interfacial tension between the polymer droplet and water phase make it possible to produce polymeric
microspheres without agglomeration.

On the other hands, after the rapid expansion of the gas saturated polymer suspensions with ethanol to air, we can obtained the coalescence and flocculate particles as shown in Figure 3(b). Because the cosolvent is good solvent for polymer in our system, microparticles adhere to each other. Although the adhesion of polymer particles decrease with the decreasing the cosolvent feed composition, recovery ratio of polymer products were dramatically decrease with the decreasing the cosolvent feed composition. Furthermore, to discuss the effect of the nozzle configuration on the particle morphology, orifice was used as a nozzle. However, after expansion to air, polymer fibers were obtained as shown in Figure 3(c). It may be considered that the shear stress takes polymer suspensions in the orifice through the expansion process. To obtain the polymer droplets after expansion, the utilization of capillary nozzle is effective compared with orifice.

Figure 3. SEM photographs of a L-PLA microparticles by rapid expansion of the CO2 saturated polymer suspension. (a)expansion to water(capillary nozzle with 0.2 mm i.d.), (b)expansion to air(capillary nozzle with 0.2 mm i.d.), (c)expansion to air(orifice nozzle with 0.2 mm i.d.).

Effect of operating conditions

The effects of experimental parameters including the pre-expansion pressure, injection distance between a nozzle and water phase, feed compositions, and nozzle diameter on the mean particle diameter and standard deviation of particle diameter are discussed in this study. The Weber number ($N_{we}$) may be used to describe the size of droplets formed in the sprayed based technique. This dimensionless number is the ratio of interfacial forces to surface tension forces and is given by $N_{we}=\rho_A V^2 D/\sigma$ where $\rho_A$ is the anisotensolvent density, $V$ is the relative velocity, $D$ is the solution jet diameter, and $\sigma$ is the interfacial tension. Jet breakup by atomization is favored when $N_{we}$ is large. The $N_{we}$ is strongly depended on the pre-expansion pressure, and nozzle diameter. Furthermore the control of injection distance between the nozzle and water interface is possible through adjustment the particles size and morphology, because the residual cosolvent in the polymer droplet is strongly depend on the particle morphology. The polymer droplets containing cosolvent were formed and adhere to each
other after expansion. After the polymer droplets are reached in the water phase, residual cosolvent in polymer droplets is diffused to water phase. It may be considered that control the injection distance cause the adjustment the particles size and morphology.

The mean particle diameter and standard deviation of particle diameter decreases with an increase in the pre-expansion pressure, as shown in Figures 4 and 5. At 20 MPa the uniform polymer microspheres were obtained as shown Figure 4(a). On the other hands, at 10 MPa polymer microspheres have a fairly mono-dispersed distribution as shown in Figure 4(b). The larger spheres were made by the decrease the pre-expansion pressure. The velocity of fluids in the nozzle is increased with the increase the pre-expansion pressure, and causes the large $N_{we}$ number. A large $N_{we}$ number indicates that the deforming forces are large compared to the reforming surface forces, thus leading to drop breakup into smaller droplets.

![Figure 4](image-url)  
**Figure 4.** Effect of pre-expansion pressure on the particle morphology. Pre-expansion pressure; (a)20 MPa, (b)10 MPa

![Figure 5](image-url)  
**Figure 5.** Effect of pre-expansion pressure on the mean particle diameter and standard deviation of the particle distribution.
Furthermore, we discuss the effects of the injection distance between the nozzle and water phase on the particles morphology. The mean particle diameter and standard deviation of particle diameter increase with an increase in the injection distance, as shown in Figures 6 and 7. Because polymer droplets tend to agglomerate and growth after the expansion to air, the particle size increases with the increase of the injection distance. And particle agglomeration and growth were impeded in water phase.

![Figure 6](image)

**Figure 6.** Effect of injection distance between the nozzle and water phase on the particle morphology. Injection distance: (a)35 cm, (b)70 cm, (c)140 cm, injection distance 0 cm: see the Figure 3(a).

![Figure 7](image)

**Figure 7.** Effect of injection distance between the nozzle and water phase on the mean particle diameter and standard deviation of the particle distribution.

**CONCLUSIONS**

The rapid expansion of CO₂ saturated suspensions to water has been utilized to produce
polymeric microspheres without agglomeration. To impede particle agglomeration and growth, polymer suspensions were expanded to water. The products were analyzed by SEM and particle size analyzer. The microspheres have globular form and fairly monodispersed distribution of particle size. The particle size and particle size distribution of the microspheres could be controlled by changing the pre-expansion pressure, and injection distance. The particle size varied much more with the feed composition. To control the particle morphology, the interfacial tension of the polymer suspensions and diffusion of the cosolvent to water phase are the key novel feature of this work.

REFERENCES


