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Preparation of poly(L-lactic acid) submicron particles in aerosol solvent extraction system using supercritical carbon dioxide

Mi Yeong Kim, Ki-Pung Yoo* and Jong Sung Lim*,†

Clean Technology Research Center, Korea Institute of Science and Technology,
39-1 Hawolgok-dong, Sungbuk-gu, Seoul 136-791, Korea
*Department of Chemical and Biomolecular Engineering, Sogang University,
1 Sinsu-dong, Mapo-gu, Seoul 121-742, Korea

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Abstract−The aerosol solvent extraction system process (ASES), which is one of the supercritical anti solvent processes (SAS), was used to produce poly(L-lactic acid) (PLLA) into the submicron particles. Dichloromethane (DCM, CH_2Cl_2) and carbon dioxide were selected as a solvent and as an antisolvent for PLLA, respectively. The objective of this study was to investigate the effect of the various process parameters such as temperature, pressure, and solution concentration on PLLA particles. With increasing temperature and pressure, particle size was increased. Also, higher PLLA concentration led to larger particle size and broader particle size distribution. A scanning electron microscope (SEM) was used to observe the morphology and size of PLLA particles recrystallized by ASES process. The mean particle size and its distribution of processed particles were measured by using a laser diffraction particle size analyzer (PSA).

Key words: Poly(L-lactic acid), ASES Process, Supercritical Carbon Dioxide, SAS Processes, Nano-particles, Recrystallization

INTRODUCTION

The supercritical antisolvent (SAS) process is used when a solute produced into fine particles is not soluble in the supercritical fluid. The fine particles are prepared by sudden reduction of the solubility of the solvent when solution containing the issued materials and appropriate solvent is dissolved in supercritical solvent. It is effective in the preparation of submicron particles of thermally sensitive medicine or protein without residual solvent and needs no spray drying process. Conventional techniques such as milling, spray drying and solvent evaporation are not always suitable for producing fine and pure particles. Spray drying can thermally denature compounds, milling produces broad size distribution and solvent/emulsion evaporation techniques often leave residual solvents that are difficult to remove [1]. The aerosol solvent extraction system process (ASES) is one of the supercritical anti solvent processes (SAS). The core of the ASES process is to spray a solution in the antisolvent environment throughout a fine nozzle. Through this action, fine droplets are generated in the precipitator. This is called atomization and is expressed by dimensionless Weber number defined as the ratio of the deformation force and the reformation force [2,3]:

$$N_{we}=\frac{\rho_A \mathbf{v}^2 \mathbf{d}}{\sigma} \tag{1}$$

Where ρ_A is the density of the antisolvent, v is the relative velocity, d is the diameter of the droplets by spraying the solution, which depends on the relative antisolvent-drop velocity and the antisolvent density. The term σ is the surface tension [4]. The surface tension also affects on droplet size. The numerator of Eq. (1) means the deformation force, and the denominator means the reformation force. In general, the higher N_{we} it has, the smaller the droplets are as the result of atomization. Mukhopadhyay explained that the drop dynamics could be illustrated briefly by the following steps. As soon as the drop comes in contact with surrounding supercritical fluid, the supercritical fluid is rapidly diffused into the drop. The drop is swollen by continuous 2-way mass transfer that is diffusion of supercritical fluid into drop and evaporation of solvent from drop surface to flow of supercritical fluid. When the number of nuclei in a droplet becomes abundant by continuous 2-way mass transfer, the swollen drop is shrunk by back diffusion of supercritical fluid. They clarified that substantial drop dynamics is more complex than the above explanation [5]. The energy for solvent evaporation from the droplet surface was supplied from the surrounding antisolvent by conduction and convection. The evaporated solvent is incorporated into the flow of antisolvent by convection and back diffusion. The overall rate of evaporation is affected by pressure, temperature, droplet diameter, and the velocity difference between the droplet and the surrounding gas [2]. After going through the 2-way mass transfer, the fine particles are collected on a filter at the bottom of the precipitator [5]. The two-way mass transfer is very important factor for micronization. Because the ASES is a semi-continuous process, this process can obtain a higher supersaturation than that of the GAS process in an instant. As a result, the particles produced by this process have a very small size and narrow particle distribution.

In this study, we produced submicron particles of PLLA to apply to the DDS (Drug Delivery System) in the form of microparticle/microsphere by using the ASES process. Supercritical carbon dioxide was used as an antisolvent and dichloromethane was selected as a solvent for PLLA. We investigated the effect of process parameters such as temperature, pressure, and concentration of PLLA on the particle size and morphology of PLLA. In other words, the effect of process parameters on PLLA particles was investigated.

[†] To whom correspondence should be addressed.
E-mail: limjs@sogang.ac.kr

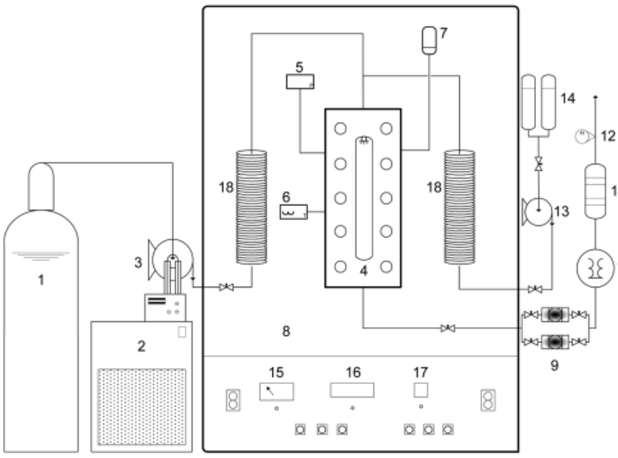


Fig. 1. Schematic diagram of apparatus for the aerosol solvent extraction system (ASES).

1. CO_2 cylinder
2. Cooling circulator
3. High pressure pump
4. Vessel
5. Pressure transducer
6. Thermocouple
7. Rupture
8. Air bath
9. Filter
10. Back-pressure regulator
11. Depressurizing tank
12. Rotameter
13. Solution pump
14. Solution tank
15. Temperature controller
16. Pressure indicator
17. Temperature indicator
18. Heat exchanger

EXPERIMENTAL SECTION

1. Materials

PLLA (M_w 85,000-160,000) was purchased from Sigma Aldrich Korea LTD. It was a long rod shape having average length of 350 μm and width of 100 μm. Carbon dioxide (purity 99.9%), used as an antisolvent for PLLA, was obtained from Sinyang Oxygen. Dichloromethane (99.9%, Sigma-Aldrich) was used as a solvent for PLLA. Methanol (98%, J. T. Baker) was selected for dispersion of the PLLA particles. They were used without further purification.

2. Experimental Apparatus

A schematic diagram of the ASES apparatus is shown in Fig. 1. It was composed of an antisolvent supplying system, a solution feeding system, a precipitation vessel (KISTEC Co, Korea), two filters (0.5 μm, Swagelok), a back pressure regulator (Tescom Corp.), and a gas vent system. A precipitator is placed on the center of a thermostat air chamber. Its pressure was controlled by a back pressure regulator located between the filters and depressurizing tank. Pure CO_2 was cooled by refrigeration bath circulator (Jeio tech) and continuously fed into a precipitator from the top of vessel by using a high pressure pump (Oriental Motors). It is continuously vented through passing a back pressure regulator and dry gas meter (Taekwang Energy S/T-3). The solution containing PLLA was sprayed into the precipitator by a high pressure liquid pump (Oriental Motors) through a fine nozzle (0.63 mm internal diameter) located on the top of vessel. It remained in a depressurizing tank (SUS 316) or vented with CO_2 as passing a dry gas meter.

3. Experimental Procedure

The precipitation vessel was filled with CO_2 until desired pressure was reached and was heated to the desired operating temperature. After the flow rate of CO_2 was maintained constantly at a designated value, liquid solution containing PLLA was injected into the precipitator, and was broken up into droplets by a fine nozzle. As the atomized droplet came in contact with the antisolvent CO_2, the latter diffused into the solution and the solvent evaporated from the droplet surface [5]. At this time, the solution became cloudy and nucleation followed. Consequently, polymers were crystallized to fine particles and particles were collected on a metal filter by continuous flow of CO_2. This continued until the liquid solution in the solution feed tank was injected completely into the precipitator while CO_2 continued to pump into the precipitator to remove the residual liquid content, which could remain on the particles for several minutes and make particles staying in the vessel leave for a filter. To obtain the collected particles, the valve between the vessel and filter was closed and then the pressure in the filter was gradually depressurized by using a back pressure regulator. Solvent separated with the PLLA by CO_2 during the spraying process remained in the depressurizing tank or was vented with CO_2 passing through a dry gas meter.

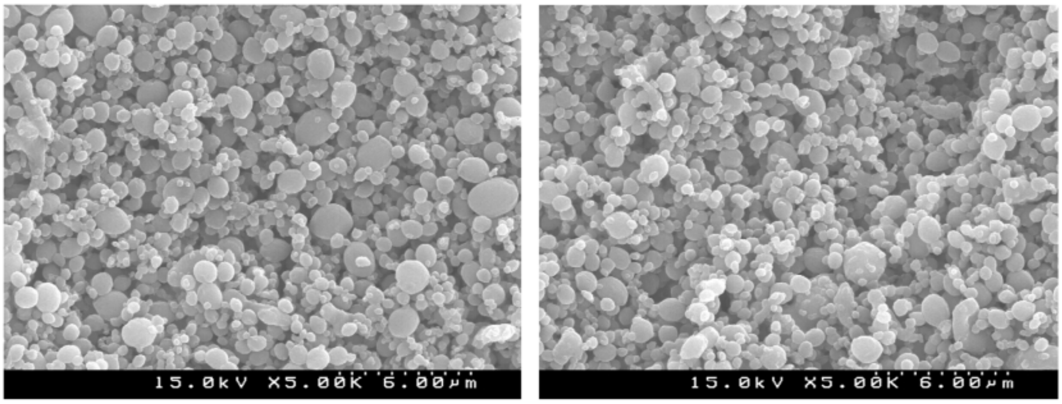
4. Particle Characterization

The morphology of the collected particles was analyzed by FE-SEM (Field emission scanning electron microscopy; HETACHI). The samples for SEM were attached by using double-coated adhesive tape and coated with gold by a sputter coater. PSA (Laser diffraction particle size analyzer; LS 230, Coulter Electronics) was used to measure the mean particle size and particle size distribution. It uses interaction between a laser and particles, such as diffraction, refraction, reflection and absorbance. Before particles were analyzed, they were dispersed in methanol for 1 min by using a sonicator (Power Sonic 510, Hwa Shin Technology Co.).

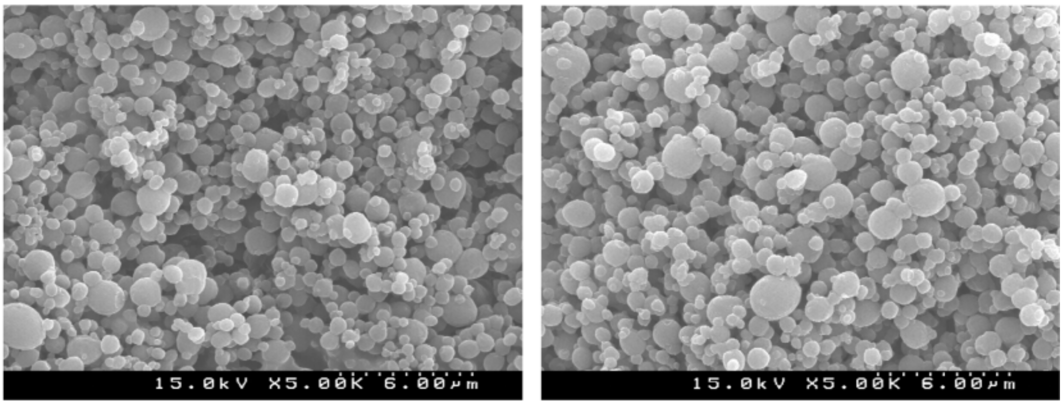
RESULTS AND DISCUSSION

1. The Effect of Temperature on Particles

The SEM images of Fig. 2(a)-2(d) show the effect of temperature on PLLA particle size and morphology. The system temperatures ranged from 35 °C to 60 °C, as shown in Table 1 and Fig. 2. Fresh CO_2 of 0.53 kg/hr was continuously fed into the precipitator by using the high pressure pump. The other conditions were constant at 100 bar, 1.0 wt% solution concentration, 0.2 ml/min solution injection rate. The morphology of the particles was not affected heavily by temperature through the range of experimental temperatures. As shown in Table 1, however, the mean particle size remarkably increased from 707.85 nm to 1326.61 nm with increasing temperature because relatively small drops were produced with decreasing the temperature due to high gas density which increases aerodynamic forces and break up. Especially, when the temperature was changed from 50 °C to 60 °C, considerable change in PLLA mean particle size was observed compared to the other experimental conditions. During the temperature rise from 35 °C to 40 °C, the particle size was not heavily changed as shown in Fig. 2(a)-2(b). Fig. 3 shows particle sizes and their distribution measured by a laser diffraction particle size analyzer (PSA) which sizes and counts the particles by measuring changes in electrical resistance produced by the nonconductive particles suspended in an electrolyte. A horizontal axis indicates particle size (nm) and a vertical axis means particle number (%) equivalent to the horizontal axis. Particle size distribution was also larger with increasing the temperature. The particle size



(a) 35°C (b) 40 °C



(c) 50 °C (d) 60 °C

Fig. 2. Effect of temperature on PLLA particles at 100 bar, 1.0 wt%, 0.2 ml/min solution injection rate and 5.0 *l*/min CO_2 feed.

Table 1. Experimental conditions at 0.2 ml/min solution injection rate and 5.0 *l*/min CO_2 feed rate

Temperature [°C]	Pressure [bar]	CO_2 density [g/cm^3]	Concentration in dichloromethane [wt%]	Mean particle size [nm]
35	100	0.719	1.0	708
40		0.641		709
50		0.397		793
60		0.297		1,327
35	76.3	0.397	1.0	630
	100	0.719		708
	150	0.820		1,476
	200	0.870		1,428
35	100	0.719	0.5	616
			1.0	708
			2.0	1,103
			3.0	1,226

distribution at 40 °C is similar to that of 50 °C.

CO_2 density was decreased from 0.719 g/cm^3 to 0.297 g/cm^3 while the temperature was increased from 35 °C to 60 °C. Because increasing temperature caused viscosity to decrease and diffusivity to increase, mass transfer between the droplet generated by atomization and the surrounding CO_2 has effective influence on PLLA particles. In other words, finer PLLA particles could be obtained by increasing CO_2 density because of the enhanced mass transfer between the droplet and the surrounding CO_2. But, from Eq. (1), the drop size increases with decreasing CO_2 density by jet breakup and hydrodynamics related to atomization. Both atomization and mass transfer are important in preparing fine particles. However, it is difficult to find and explain the tendency of particles since atomization and mass transfer have contrary effects on particles.

2. The Effect of Pressure on Particles

Fig. 4 shows the SEM images at pressure ranging from 76.3 bar

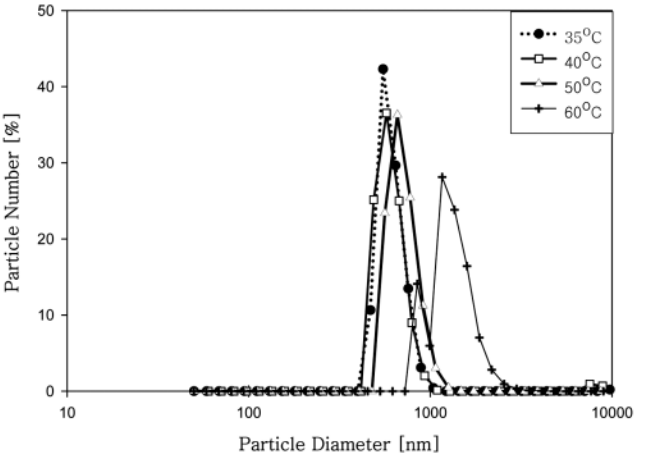


Fig. 3. Effect of temperature on particle size distribution of PLLA prepared at 100 bar, 1.0 wt%, 0.2 ml/min solution injection rate and 5.0 *l*/min CO_2 feed.

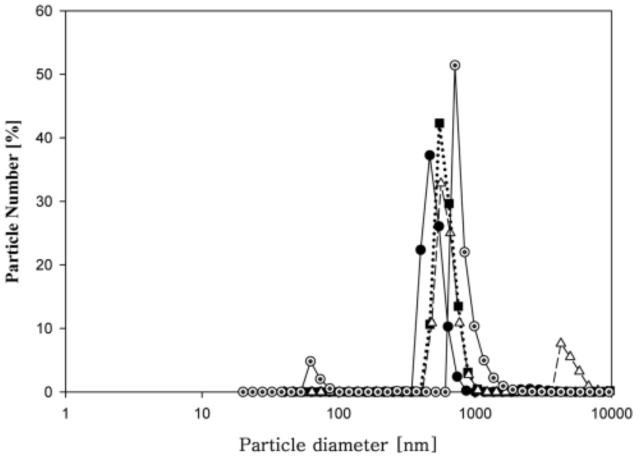
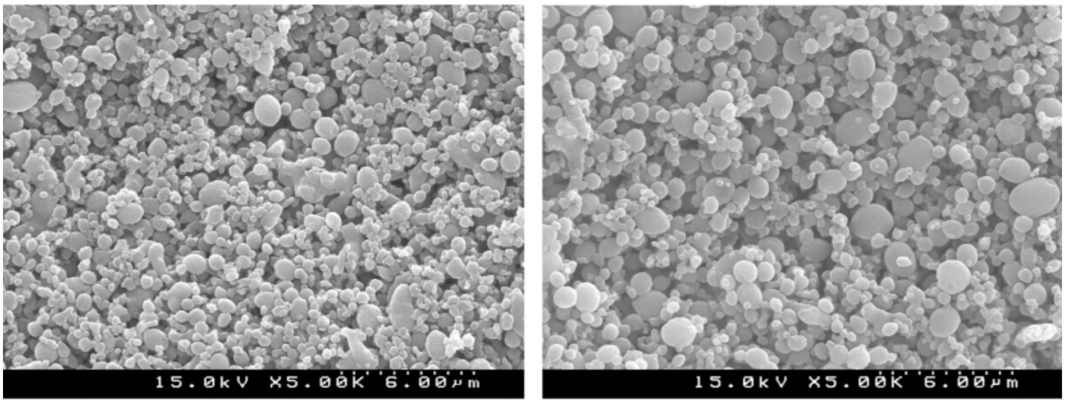
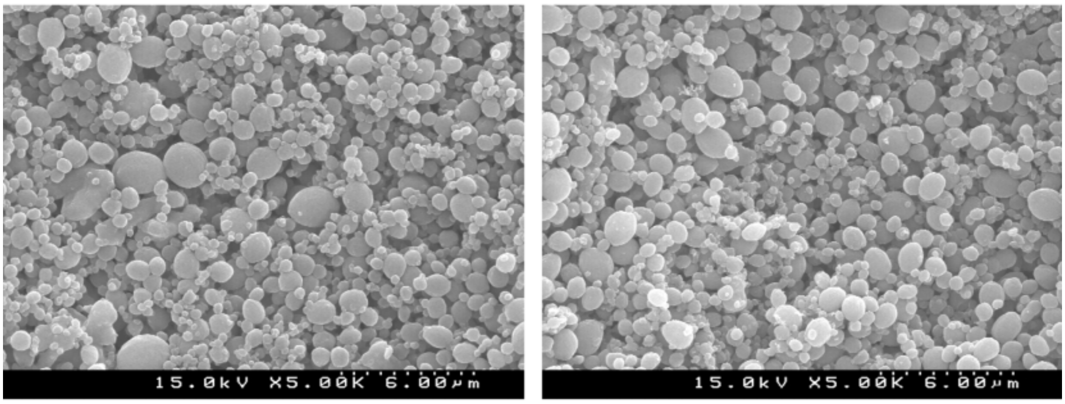


Fig. 5. Effect of pressure on particle size distribution of PLLA prepared at 35 °C, 1.0 wt% solution concentration, 0.2 ml/min solution injection rate and 5.0 *l*/min CO_2 feed.



(a) 76.3bar **(b) 100bar**



(c) 150bar **(d) 200bar**

Fig. 4. Effect of pressure on PLLA particles at 35 °C, 1.0 wt%, 0.2 ml/min solution injection rate and 5.0 *l*/min CO_2 feed.

to 200 bar with about 50 bar increment. Experimental conditions and mean particle size measured by PSA are presented in Table 1. All the morphology of the particles is spherical shape in spite of increasing pressure. The mean particle size was significantly increased from 630.22 nm to 1.476 μm with increasing pressure from 76.3 bar to 150 bar. Especially, when pressure increased from 100 bar to 150 bar, a remarkable change in mean particle size was observed as shown in Table 1. But, during increasing pressure from 150 bar to 200 bar, mean particle size was slightly reduced from 1.476 μm to 1.427 μm. Fig. 5 shows the particle size distribution measured by PSA. The narrowest particle size distribution was observed at 100 bar while the largest particle size distribution was observed at 150 bar. There was no uniform tendency with changing pressure in particle size distribution. We just found that relatively low pressure

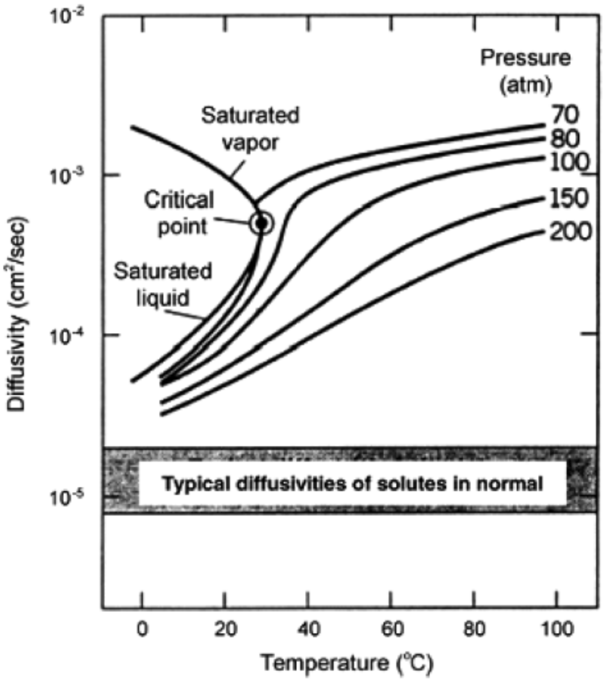


Fig. 6. Variation of the diffusivity in CO_2 as a function of temperature at several pressures [6].

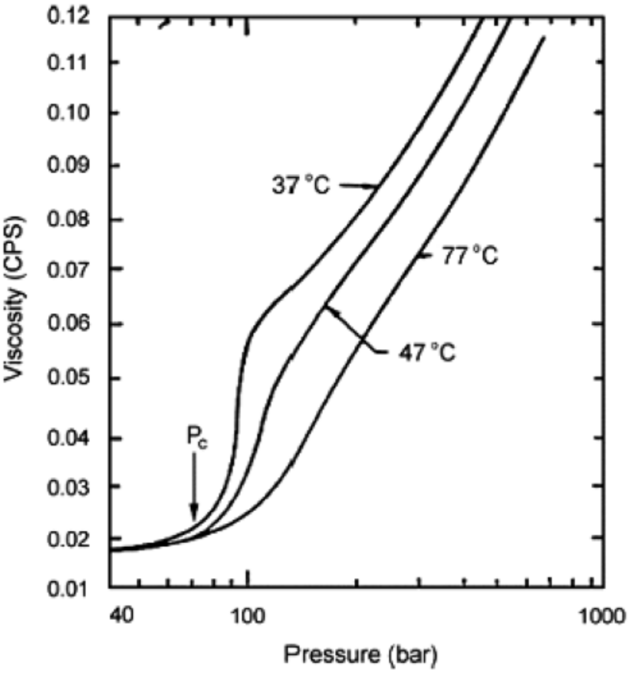
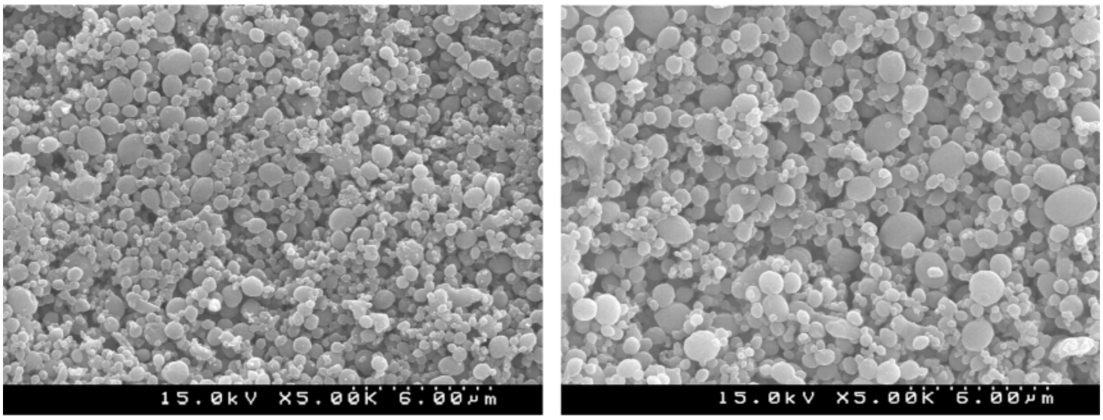
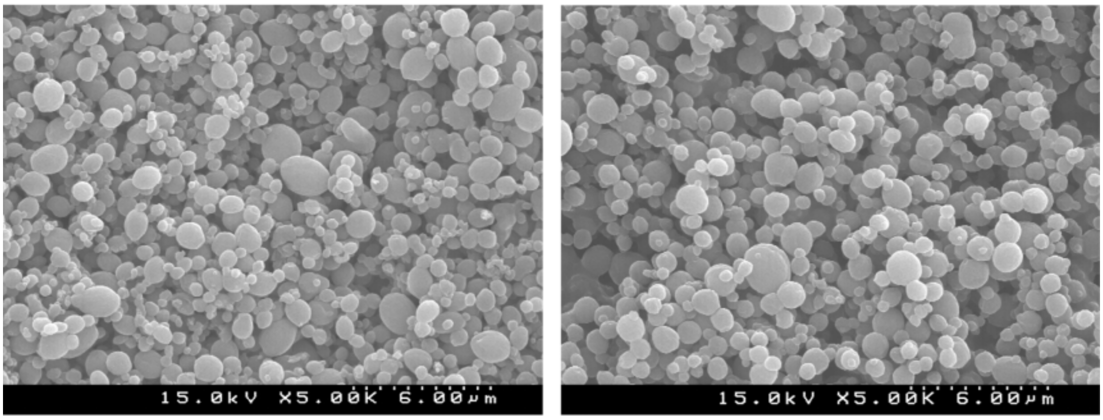


Fig. 7. Variation of the viscosity of CO_2 with pressure at three different temperatures [7].



(a) 0.5wt% **(b) 1.0wt%**



(c) 2.0 wt% **(d) 3.0wt%**

Fig. 8. Effect of concentration on PLLA particles at 35 °C, 100 bar, 0.2 ml/min solution injection rate and 5.0 *l*/min CO_2 feed.

led to narrow particle size distribution.

Variation of the diffusivity in CO_2 and viscosity of CO_2 was presented as functions of temperature and pressure in Fig. 6 [6] and Fig. 7 [7], respectively. At 35 °C in Fig. 6, diffusivity of CO_2 decreases considerably as the pressure increases from 76.3 bar to 100 bar and from 100 bar to 150 bar. But, when the pressure goes up from 150 bar to 200 bar, diffusivity of CO_2 is slightly reduced compared with the other pressure ranges. In Fig. 7, viscosity of CO_2 increases with pressure at the same temperature. Because, in general, reduced diffusivity and increased viscosity hinder mass transfer between the droplets and the surrounding CO_2, particle size must be increased with increasing pressure. But, increasing pressure led to fine droplets due to increasing aerodynamic force and breakup. Thus, various particle sizes were obtained with every pressure increment due to the contrary effect of mass transfer and atomization on particles.

These results agreed well with previous ones such as Rantakyla [1], Jarmer [8] and Song [9]. But Reverchon [10] obtained different results from us in that it had no effect on PLLA particles size and its distribution and they admitted that different results were obtainable. Also, they paid attention to the fact that all the results converged in indicating a limited range of particle size variation when the various process parameters were modified.

3. The Effect of PLLA Concentration on Particles

In Fig. 8, the SEM images show the effect of weight percent of PLLA in DCM on particle size and their morphology. Concentration of PLLA in DCM varied from 0.5 wt% to 2.0 wt% with 0.5 wt% increment. As can be seen in Fig. 8, the particle size was sensitive to the solute concentration in the liquid and particle size was increased remarkably with increasing concentration while only spherical particles were measured without aggregation. The finest particles were prepared by spraying 0.5 wt% PLLA in DCM solution into CO_2 at 35 °C, 100 bar, 0.2 ml/min solution injection rate and 5.0 *l*/min CO_2 feed rate.

As shown in Fig. 9, the smallest particle size and the narrowest particle size distribution were observed at 0.5 wt% concentration of PLLA, that is, at the lowest solute concentration. Particle size could be easily controlled from 615 nm to 1.2 μm with the concentration ranging from 0.5 wt% to 3.0 wt% of PLLA in DCM. It could be explained from the aspect of nucleation and growth of particles. As the solution became deeper, saturation was reached at an early stage of the process and growth process superimposed on nucleation [11]. In short, larger particles and broader particle size distribution were obtained.

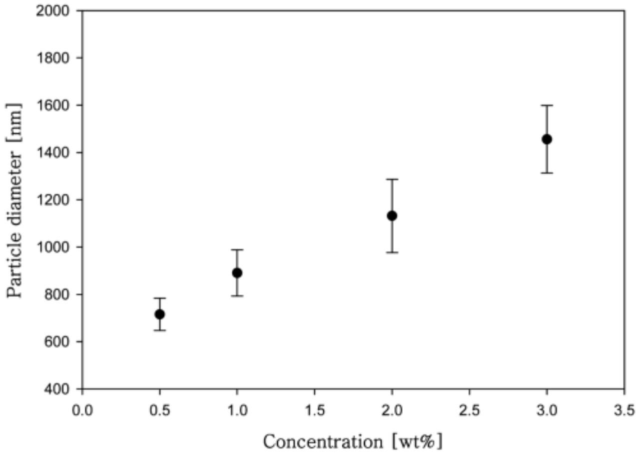


Fig. 9. Effect of concentration on particle size distribution of PLLA prepared at 35 °C, 100 bar, 0.2 ml/min solution injection rate and 5.0 *l*/min CO_2 feed.

CONCLUSIONS

PLLA submicron particles were successfully produced by ASES process. The atomization and mass transfer which affect the particle size and its distributions were also easily adjusted by controlling the temperature and pressure of CO_2. The particle size was increased with increasing temperature from 707 nm to 1.3 μm because of the predominant effect of atomization by jet breakup and hydrodynamics than enhancing the mass transfer which occurred between the droplets and the surrounding CO_2. The particle size was also increased with increasing pressure due to the predominant effect of reducing mass transfer rather than enhancing atomization. Increasing PLLA concentration also led to large particles by obstructing the mass transfer between the droplets and the surrounding CO_2 due to the increased viscosity and the early reaching to saturation. Thus the particle size and its distributions of PLLA can be easily adjusted by using the ASES process by controlling the temperature, pressure and solute concentration.

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