

초임계이산화탄소를 이용한 PHB 나노 입자 제조

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Formation of PHB micro particles using supercritical carbon dioxide

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INTRODUCTION

Application of supercritical fluids, especially with supercritical carbon dioxide for processing of pharmaceuticals and sustainable plastic has been attracted considerable interests in recent years. Some of the most recent studies have involved the use of supercritical fluids technology for the micronizing biodegradable polymers such as Poly(3-hydroxybutyric acid) (PHB), L-poly(lactic acid) (L-PLA), and so on. All of which have been used extensively in medical and pharmaceutical applications including materials for tissue engineering and drug carriers.

The precipitation using supercritical CO₂ as an anti-solvent utilizes a similar concept to the use of the anti-solvent in solvent-based crystallization processes[1]. In the Supercritical Anti-Solvent (SAS) method, an organic solution including compounds like polymers and drugs is introduced to the bulk supercritical fluid[2]. A variety of the SAS process is the Aerosol Solvent Extraction System (ASES), in which a drug or polymer solution is sprayed into a high pressure chamber flowing supercritical fluid[3,4]. As detailed in a recent literature and patent review[5], particle design using supercritical fluid can be operated by many different processes.

EXPERIMENTAL

1. Materials

Poly(3-hydroxybutyric acid) (CAS#:26063-00-3) was supplied by ALDRICH. Carbon dioxide (99.0%) was purchased by a local gas company in Korea. Methylene chloride (analytical reagent for HPLC, J.T.Baker) was used as an organic solvent.

2. Apparatus

The apparatus which can be seen in Fig.1 is made up of CO₂ supplying part, PHB solution feeding part, a precipitator having injector, filters, a pressure regulator and gas-liquid separation part. A high-pressure metering pump (Milton Roy, USA) into the precipitator (Jerguson Gage, 34 ml) through a capillary tubing (stainless steel, 0.01" I.D., 1/16" O.D.) sprays methylene chloride solution containing PHB. A capillary tube as a nozzle is located on the top of the precipitator to atomize the PHB solution. After injection of solution into the precipitator vessel, PHB particles generated are collected on the

filter (Tee-Type, 0.5 μm) that is placed between the precipitator and the back pressure regulator. The

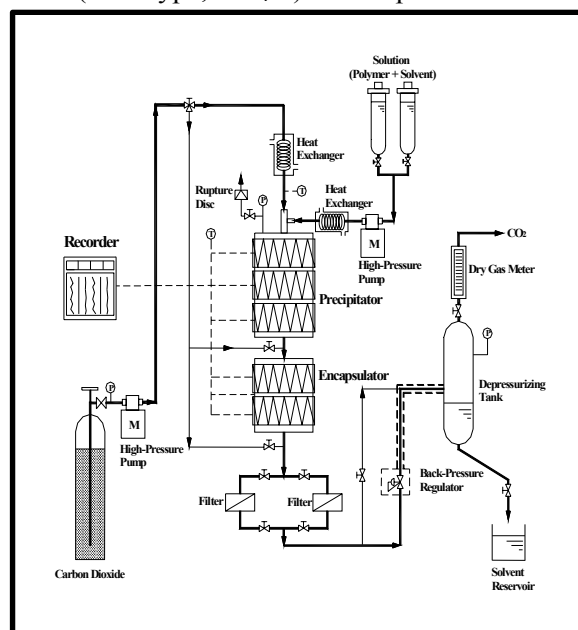


Fig. 1 Experimental apparatus

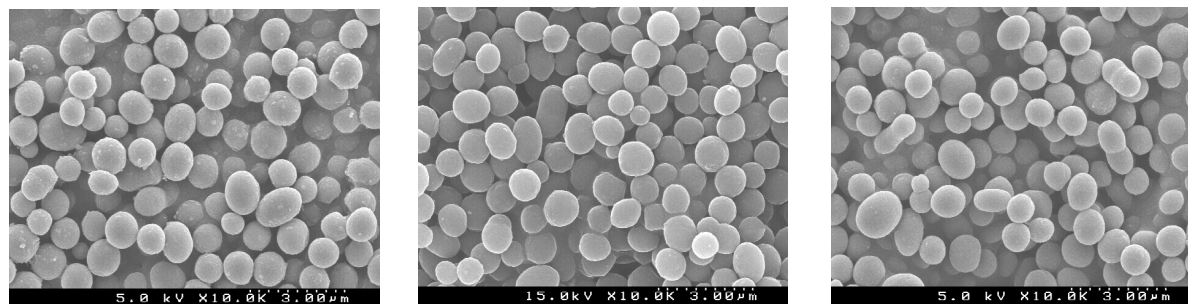
effluent mixture is depressurized and expanded to atmospheric pressure as it passing through a depressurizing tank (SUS 316; 300ml) which is from the back pressure regulator.

3. Micronization in the ASES process

Methylene chloride solution containing PHB was pumped into the precipitator through the capillary nozzle at a flow rate changing from 0.30 to 3.00 ml/min. Carbon dioxide was introduced using a high pressure pump up to a desired pressure (75-200 bar). The temperature was maintained from 31 to 60 °C. The concentration of PHB solution was changed from 0.3 to 4.0 wt%. The particles formed were collected in the filter. Upon stopping injection, CO₂ continued to flow for several minutes to wash out any residual solvent from the particles.

RESULTS AND DISCUSSTION

Fig. 1(a)-(c) show SEM micrographs of particles obtained during the ASES process which have variables of pressure. These particles are observed to be spherical shape and have narrow size distribution. Because of the miscibility between methylene chloride and supercritical CO₂ in the constant temperature of 35 °C, fast diffusion of CO₂ into the solution droplet causes the methylene chloride to evaporate out of droplet. CO₂ diffusion let PHB solubility within the droplet decrease. As it



(a) 75 bar

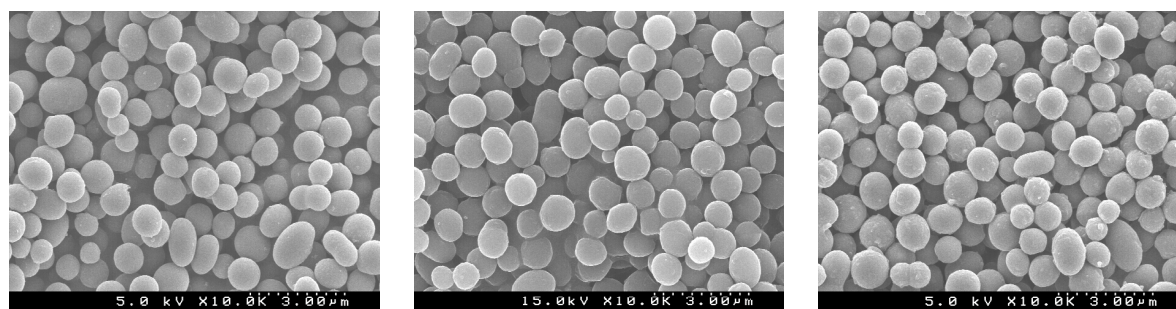
(b) 100 bar

(c) 200 bar

Fig. 2 SEM micrographs of PHB particles at 35 °C, 0.5 wt% of PHB in CH₂Cl₂, 0.01" nozzle diameter, 29.7g/hr PHB soln. flow rate, 642g/hr CO₂ flow rate.

can be seen from Fig. 1(a)-(c), the average diameter of PHB increased with pressure. It can be attributed to slow mass transfer rate between solvent and anti-solvent due to low diffusion coefficient at high pressure. As a result of slow supersaturation rate, larger particles are precipitated at higher pressure.

To investigate the effect of temperature on particle size, the pressure was kept constant at 100bar while the temperature was ranged from 31 °C to 60 °C. The particles formed also were spherical, as shown Fig. 2, having a narrow size distribution. The jet breakup length changed at different



temperature. That is, we makes an observation the jet breakup was not occurred at a CO₂ density

(a) 31 °C

(b) 35 °C

(c) 40 °C

Fig. 3 SEM micrographs of PHB particles at 100bar, 0.5wt%, 0.01"nozzle diameter, 29.7g/hrPHB soln.flow rate, 642g/hr CO₂ flow rate.

0.3g/ ml or below[6]. And also Fig. 2 shows that particle size decreased weakly from 31 to 60 °C. The particle size decreases with increasing the diffusion coefficient due to the low CO₂ density[7]. However, as mentioned above, the extremely low density raises a poor atomization so that no particles are formed.

The effect of solution concentration was investigated at five different initial concentrations from 0.3 wt% to 4.0 wt%. In our laboratory, a series of the particle size and distribution is shown in Fig. 3. It is observed that the particle size increases from 350 to 600nm and particle size distribution becomes wider as concentration increases at 35 °C and 100 bar.

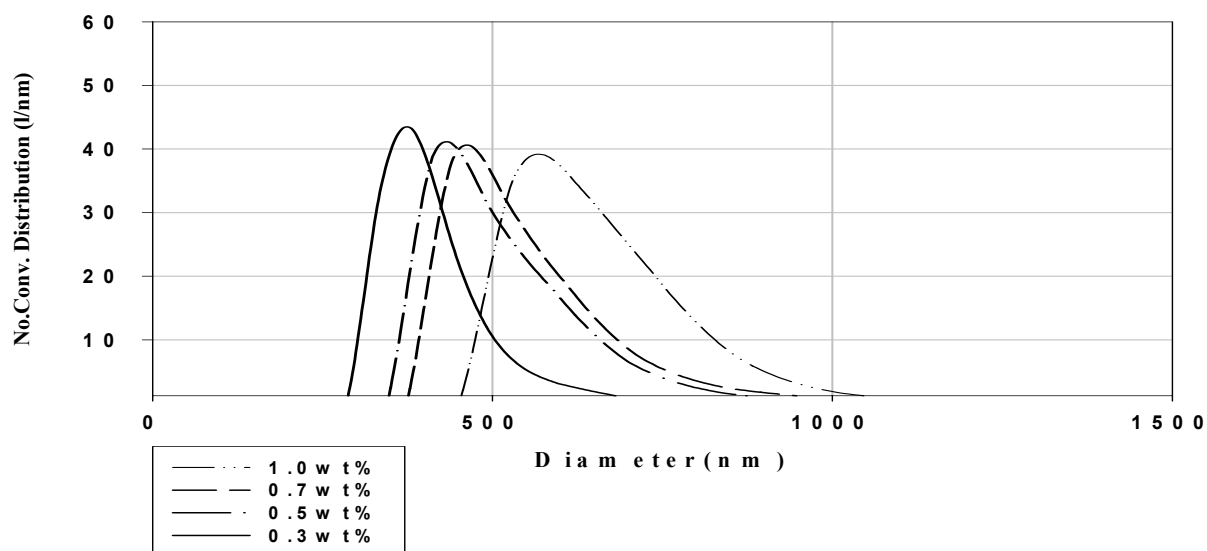


Fig. 4 The particle size and distribution with initial PHB concentration at 35? 100bar.

CONCLUSIONS

PHB nano-particles (300-600nm) were successfully precipitated by ASES process using supercritical carbon dioxide as an anti-solvent. It is demonstrated that the particles have spherical and oval form with non-agglomerated and free-flowing. The size of PHB particles can be adjusted by changing of CO₂ density. High pressure induces slow mass transfer rate and slow supersaturation rate between

solvent and anti-solvent, which leads to larger precipitated particles. An increase in temperature causes smaller particle size with increasing the diffusion coefficient. Nevertheless, excess high temperature at 100 bar raises a poor atomization because of low density of CO₂. We observe that the more concentrated solution let particle sizes increase and distribution broaden at a constant density of carbon dioxide.

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