DOI 10.5012/bkcs.2009.30.12.3066

Notes

Preparation of Polymeric Microparticles by Horizontal Rotating

Jae-ryang Joo, Min Ju Shon, Yunseong Jeong, and Jong-Sang Park*

School of Chemistry & Molecular Engineering, Seoul National University, Seoul 151-747, Korea
**E-mail: pfjspark@plaza.snu.ac.kr*
Received September 4, 2009, Accepted October 12, 2009

Key Words: Microparticles, PLGA, Horizontal rotating, Solvent evaporation method

Drug delivery systems using degradable polymeric carriers are widely studied.[1-7] Recently, polymeric microspheres were developed for subcutaneous administration of drugs.[8-9] In general, the solvent evaporation method with an oil-in-water (o/w) emulsion has been used for fabricating of polymeric microparticles.[10] The emulsion is stirred to be dispersed, and the sizes of the microparticles show a wide distribution. Generally, microparticles which have a wide size distribution are thought to be produced because of inequal emulsifying. In this article, we report that microparticles which have a narrow distribution of sizes could be prepared by the oil-in-water emulsion solvent evaporation method with horizontal rotating. Thus, horizontal rotating seems to play a key role in generating the polymeric microparticles which have a narrow size distribution.

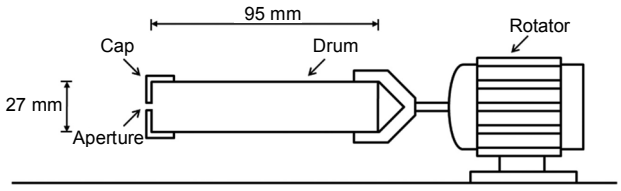

Figure 1. Schematic drowing of drum.

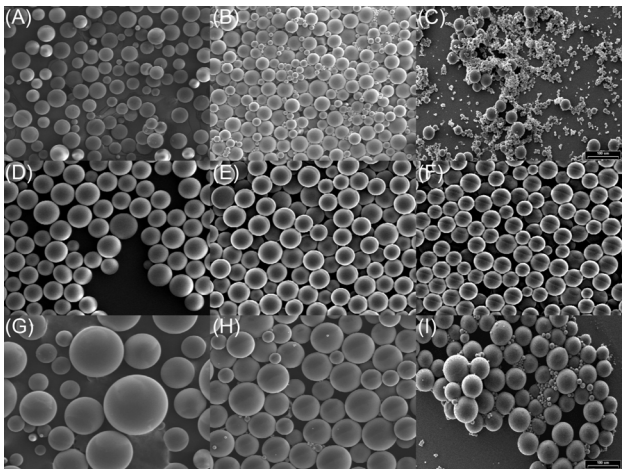

Figure 2. SEM images of PLGA microparticles. (A) PLGA 25 mg/mL, VF = 20%; (B) PLGA 25 mg/mL, VF = 30%; (C) PLGA 25 mg/mL, VF = 40%; (D) PLGA 50 mg/mL, VF = 20%; (E) PLGA 50 mg/mL, VF = 30%; (F) PLGA 50 mg/mL, VF = 40%; (G) PLGA 100 mg/mL, VF = 20%; (H) PLGA 100 mg/mL, VF = 30%; (I) PLGA 100 mg/mL, VF = 40% (scale bar = 100 μm).

Horizontal rotating is one of the widely used methods in engineering processes, including milling of particulate solids in similar sizes and mixing granular homogeneously.[11-13] Rotating drums agitate and make collisions between granular, particles or powders in the spaces of themselves by angular momentum through the rotating axis. The momentum equally produces energy to the granular, particles or powders throughout the axis. This equal energy can induce equal emulsifying.

Poly (D,L-lactic-co-glycolic acid) (PLGA) microparticles were fabricated by horizontal rotation and organic solvent evaporation. A solution of PLGA in methylene chloride (MC) was slowly added into an aqueous polyvinyl alcohol (PVA) solution during a cylinderic drum was rotating which contained the PVA solution (Figure 1). The droplets of the PLGA solution were submerged and separated from the PVA solution in the initial stage of rotating, then dispersed in the later stage. The microparticles were obtained as spherical shapes after methylene chloride evaporation (Figure 2). The rotating rate is one of the important factors of this horizontal rotating method.[14-15] Rates which are too low could not disperse the methylene chloride droplets, and rates which are too high generated centrifugal force that squashed up the emulsion so microparticles could not be fabricated. Several tests confirmed that the rotating rates between 500 rpm and 1000 rpm were appropriate to emulsify the methylene chloride droplets and the rates did not affect to the sizes of the PLGA microparticles. The concentration of PVA in aqueous solution and the duration of rotating also didn't have influences on the sizes of the microparticles (data not shown).

Table 1 represents that the average size of the microparticles was decreased as the concentration of PLGA in methylene chloride was decreased. PLGA which was used in this research has above 40,000 g/mol as its molecular weight and 0.40 ~ 0.60 dl/g as its inherent viscosity (0.1% in chloroform, 25 ^{o}C). The viscosity of the PLGA solution is linearly correlated with the concentration of itself. This fact influenced to the dispersion of the PLGA solution during horizontal rotating, controlling the sizes of the PLGA microparticles.

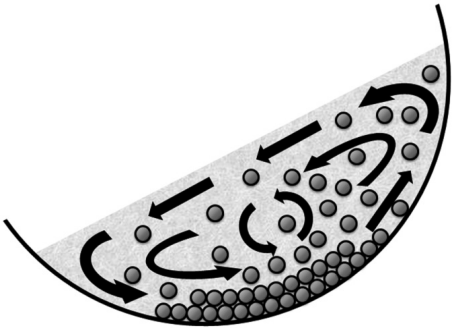

Figure 3. Velocity field from simulation (vectors indicate the direction of the local flow).

The volume of the emulsion (V_e) in the rotating drum (volume of drum, V_d) also determined the sizes of the microparitlces. Volume fraction (VF) was calculated as a follow.

$$VF\,(\%) = (V_e / V_d) \times 100$$

The rotating drum cannot contain the emulsion more than half of the volume of itself because of the aperture on the center of its cap to evaporate methylene chloride. Several tests confirmed that the volume fraction was appropriate between 20% and 40% to emulsify the methylene chloride droplets. The volume fractions which are under 20% could not disperse the methylene chloride droplets sufficiently, and the volume fractions which are over 40% overflowed through the aperture. The average size of the microparticles was decreased as the volume fraction was increased (Table 1). It is speculated that the agitation of the emulsion was influenced with the volume of the emulsion. The high volume fraction can support more extended space and energy to agitate, so the droplets will be dispersed in more tiny sizes.

Figure 3 illustrates the expected momentum of the droplets in the emulsion during horizontal rotating. The rotating drum induces the circular flow of the emulsion. This flow agitates and disperses the droplets of PLGA solution. Two factors participate the size and distribution control of the microparticles. The concentration of the PLGA solution is the first important factor that determine the size and the distribution of the microparticles. The concentration of the PLGA solution is directly related with the viscosity of the droplets. A more viscous PLGA solution is more resistible against the agitation and dispersion by horizontal rotating. This leads to the larger sizes of the microparticles. The size distribution of the microparticles also related with the PLGA concentration although it does not show a linear correlation between them. A specified PLGA concentration (50.0 mg/mL) could fabricate the regular microparticles which have the narrow size distribution. It is speculated that the viscosity of the droplets is the critical condition of the horizontal rotating method due to decrease the size distribution of the microparticles.

The volume fraction is the second factor due to determine the size. According to the results, the higher volume fraction fabricated the smaller microparticles among the same PLGA concentrations, respectively. A larger volume of the emulsion filled in the rotating drum is agitated with higher energy when the drum horizontally rotates, and the droplets in this emulsion are dispersed more tiny sizes. If the rotating drum gets larger and the volume of the emulsion increased markedly, the drum will induce higher dispersing energy enough to fabricate polymeric nanoparticles. Researches for the application of the horizontal rotating method aimed at nanoparticles should be followed.

In conclusion, horizontal rotating fabricates polymeric microparticles which have a narrow size distribution. The size and the distribution of the microparticles can be controlled by the concentration of the PLGA solution and the volume fraction of the emulsion. This method can be widely applicable to make large-scale production of polymeric microparticles for pharmaceutical and biotech machinery and to fabricate polymeric nanoparticles for several applications.

Experimental Section

PLGA Microparticle Preparation by Horizontal Rotating. PLGA microparticles were fabricated through a modified oil-in-water (o/w) single-emulsion solvent evaporation technique. Various amounts of PLGA (Resomer® RG 504H, lactide : glycolide = 50 : 50, Boehringer Ingelheim, Germany) were dissolved in methylene chloride. This PLGA solution was added into a PVA (polyvinyl alcohol, Mw 30,000 ~ 70,000, Sigma Chemical Co., USA) solution contained in a 50 mL-cylinderic drum of 27 mm diameter. The volume ratio of the PLGA solution and the PVA aqeuous solution was fixed at 1 : 10. The drum was laid horizontally and rotated with the rotation axis being parallel to the axis of the tube. An aperture of 5 mm diameter was made on the center of the cap to let the methylene chloride evaporate. After several hours of rotation under reduced air pressure, the solution was centrifuged and the supernatant was discarded. The remaining particles were washed with distilled water three times, and then lyophilized.

Morphology Observation and Particle Characteristics Analysis. The shape and morphological examinations of the PLGA microparticles were performed by scanning electron microscope (JSM 840-A, Jeol Ltd, Tokyo, Japan). A droplet of the PLGA microparticle colloid placed on a slide glass (35 × 25 mm) and dried at room temperature under reduced air pressure to get a uniform layer of the particles. The samples of above were coated with platinum using a sputter coater (Cressington 108, Jeol Ltd, Tokyo, Japan).

The sizes and distributions of the microparticles were cal-

Table 1. Sizes and distributions of microparticles

PLGA (mg/mL)	Volume fraction (%)	Average size (μm)	Standard deviation
25.0	20	53.49	8.90
25.0	30	41.31	12.03
25.0	40	39.50	28.41
50.0	20	67.68	9.91
50.0	30	63.14	5.39
50.0	40	54.91	7.78
100.0	20	134.07	50.04
100.0	30	90.15	33.48
100.0	40	62.21	37.97

culated by counting and sizing the particles in their SEM images. Three SEM images which magnified the object 100 times of the different areas were taken at each sample, respectively. All of the particles in the SEM images were counted and measured the sizes compared with the scale bar. The average size is the averaging value of the measured sizes and the distribution is calculated by the standard deviation value.

Acknowledgments. This study was supported by a grant of the Korea Healthcare technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A084285).

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