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Preparation of Polymer/Drug Nano- and Micro-Particles by Electrospraying

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Summary: The surface energy control capability of electrohydrodynamic force provides electrospraying with various potential advantages such as simple particle size control, mono-dispersity, high recovery, and mild processing conditions. Herein, particle fabrication of biodegradable polymers using electrospraying was developed. The major processing parameters such as the conductivity of spraying liquids, flow rate, etc., were examined to obtain the successful apparatus configuration of electrospraying. The choice of a consolidation medium was critical in obtaining well-dispersed nanoparticles. When triphenylphosphate aqueous solution was employed as a consolidation medium, its concentration was not an effective parameter to control the aggregation of primary particles. When organic solvents were employed, the processing windows of electrospraying were relatively narrow than water-based systems.

Keywords: electrospraying; nanoparticles

Introduction

Particle formation via spraying has been an effective process in the pharmaceutical and food industries for decades. The importance of spraying technology can be presumed by the widely spread use of spray drying. Spray drying is indeed the cheapest method producing pharmaceutical particles, but the size of spray-dried particles is often limited by the surface tension of solvents employed. To prepare nanoparticles using the spraying technology, the surface tension penalty should be compensated by a form of external energy.[1,2] Electrical energy can be one of them.

Electrical energy enables the production of protein nanoparticles without deteriorating their activity which can easily be destroyed by organic solvents, salts, thermal or mechanical energy. Electrospraying using a co-axial nozzle having starch/bovine serum albumin (BSA) in inner nozzle and polydimethylsiloxane (PDMA) in an outer nozzle produced encapsulated 'microparticles' ($\Phi > 2$ μm).[3,4] However, no experiment on the successful preparation of well-dispersed particles below 1 μm has never been reported to the extent of our knowledge.

In electrospraying, particle size and its distribution depend on the surface electrical charge of particles. Thus, electrical energy can serve as a convenient control parameter. In addition to the advantages of the use of electrical energy, it is possible that this method can be combined with the conventional spraying technology. Various materials can be electrosprayed into nanoparticles while liquid-based preparation methods of nanoparticles are rather material specific.[5–9]

In this study, the applicability of electrohydrodynamic force to prepare micro- and

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nanoparticles of biodegradable polymers was assessed. How to obtain appropriate pharmaceutical nanoparticles through electrospraying is the major interest.

Experimental Part

Materials

Chitosan (Sigma Aldrich), polymethyl methacrylate (PMMA, Aldrich, 360 k), polycaprolactone (PCL, Aldrich, Mw 65 k), polyethylene glycol (PEG, Mw 5 k), and triphenylphosphate (TPP, Sigma Aldrich) were used without purification. As a medium, distilled water was used. Methanol, methylene chloride and cyclohexane were purchased from Duksan (South Korea, >99%).

Methods

As the source of electricity, a ConverTech model SHV300-RD and a NanoNC model NNC-30k-2mA were used. Electrospraying was performed in various configurations to find out their effects on the size and morphology of solidified particles. The operating mode was always inside the window of the 'Taylor cone' mode. Liquids were injected into a nozzle by a KdScientific model 100 (Holliston, MA, USA). An Eyela MP-1000 pump was used for liquid circulation.

Characterizations

Particle size was measured by using a Horiba Laser Light Scattering Particle Size Analyzer LA-910 (refractive index = 1.06, ultrasonic chamber power = 40 W, 39 kHz, 340 mL/min stirring flow (level 3), 95 ~ 100 mL water medium). Particle concentration in the particle size analyzer chamber was ca. 0.02 wt%, and repeated measurements of at least 3 times produced the error ranges of volume averaged mean size. Particle morphology was investigated by a Hitachi (Japan) scanning electron microscope S-4700 at 4 kV and 0.5 Hz. Samples were prepared by drying suspension drops on SEM sample stages previously cleaned, and they were coated with Pt-Pd at a coating speed of 6.7 nm/min for 2 min.

Results and Discussion

Electrosprayed particles were obtained by controlling the viscosity of solution, feed rate, applied voltage, and conductivity, etc. The formation of 'Taylor cone'[5,6] and spraying phenomenon were confirmed by the scattering of laser light as shown in Figure 1. The illumination of laser light was conveniently employed throughout the configuration development of electrospraying apparatus. Without the aid of laser light, no mist was visible. A voltage above several thousands volt was enough to produce the 'Taylor cone' mode, although the detailed conditions significantly rely on the characteristics of solutions.

The applied electrohydrodynamic force was enough to drag polymer solutions. At the nozzle, both the spinning and spraying can result depending on mainly their viscosity. It was found in most cases that the concentration of polymer solution should be below 1 wt% to produce nanoparticles. The relatively low concentration of polymer restricts the rapid removal of solvent during electrospraying, resulting in difficulty in solidification.

The electrosprayed liquid drops should be stably dispersed or consolidated for further pharmaceutical particle unit operations. Drying or precipitation steps were developed for complementing this problem. A consolidation medium such as a TPP aqueous solution or a nonsolvent was employed in our trials. Polymer solutions were electrosprayed into a consolidation medium in various conditions, i.e., without or with local stirring or with whole circulation, etc. As shown in Figure 2, when a PCL solution of 0.5 wt% was electrosprayed into water without any stirring, a thin film of PCL was generated on the surface of water (Figure 2(a)). However, when a PMMA solution of 0.5 wt% (Figure 2(b)) was electrosprayed in the same condition, particles of about 2 μm were obtained.

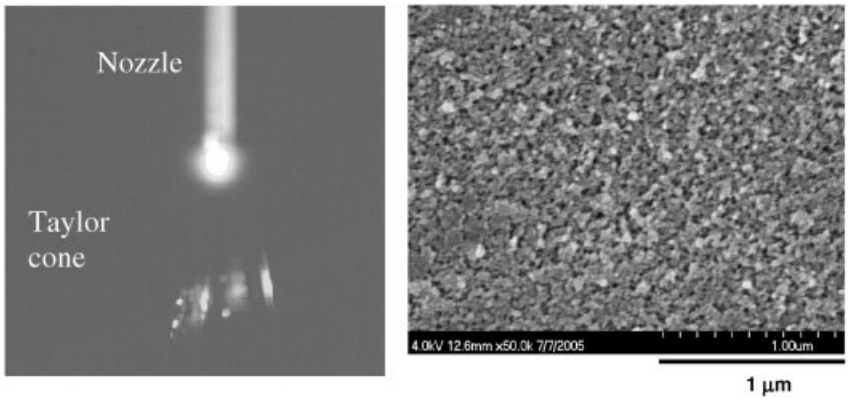

Figure 1.
Taylor cone illuminated by laser beam (left, PCL solution of 1 wt% in MC at 10 kV) and scanning electron micrograph of electrosprayed chitosan particles (right).

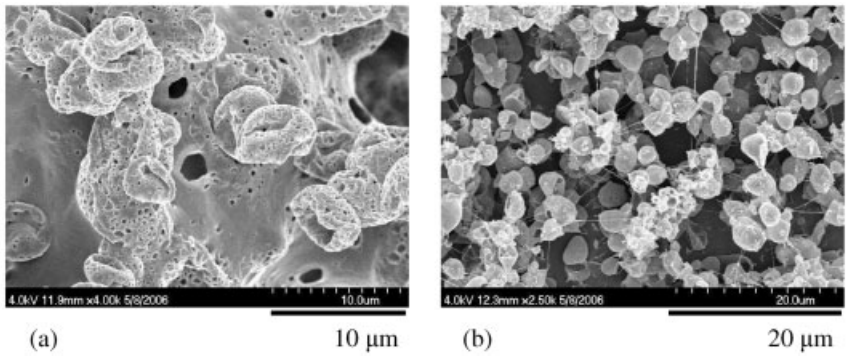

Figure 2.
Scanning electron micrographs of PCL (a) and PMMA (b) particles electrosprayed in methylene chloride at −12 kV.

Using a TPP aqueous solution (1 wt%) as a consolidation medium, chitosan (1 wt%) in acetic acid solution was solidified into nanoparticles less than 100 nm (12 kV and 1 mL/hr feed rate) (Figure 1). However, the primary particles tended to aggregate in the consolidation medium afterward. The concentration of TPP solution was not an effective variable to control the aggregation tendency.

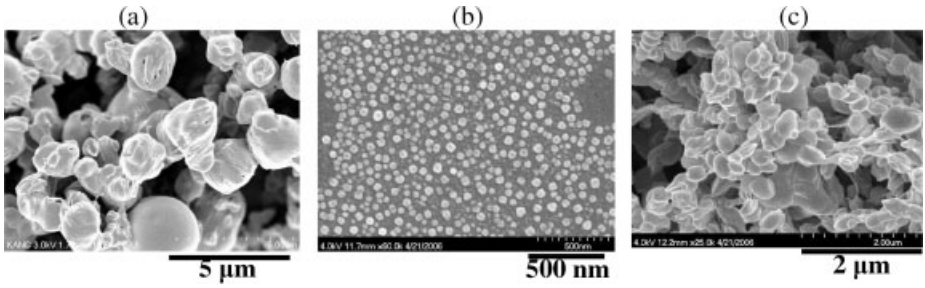

Figure 3.
SEM micrographs: (a) at 0 kV, (b) at −10 kV, electrosprayed in air with using a cyclohexane-collecting bath, and (c) at −10 kV, particles on the surface of collecting bath.

Lower conductivity in organic solvent-based systems generally ended up with larger particles if the same conditions were used. Figure 3 shows the morphologies of polycaprolactone (PCL) particles electrosprayed in air with using a cyclohexane-collecting bath. In the case of zero voltage, shriveled particles of about 3 μm (Figure 3(a)) were generated because the time for solidification of PCL might be longer than that for evaporation of solvent. At a −10 kV condition, particles of about 50 nm (Figure 3(b)) were fabricated in the collecting medium, while most PCL particles of about 250 nm were found on the surface of the collecting bath as shown in Figure 3(c). From these data, voltage control produces various particle sizes.

Conclusions

Various configurations to collect particles, i.e., water systems containing solidification medium, or organic medium-based systems, were tried and configurations to successful produce polymer nanoparticles were identified. Physical properties of each material used for electrospraying directly affect the mean size and the morphology of the particles. Important factors in the fabrication of micro-/nano-particles were found to be conductivity, concentration, collecting solvent, voltage, etc.

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