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

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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 way of producing pharmaceutical particles, but the size of spray dried particles is often limited by the surface tension of solvent employed. To prepare nanoparticles using spraying technology, the surface tension penalty should be compensated by a form of external energy. Electrical energy can be one of them [1,2]

Electrical energy enables the production of protein drug nanoparticles without deteriorating their activity which can easily be destroyed by organic solvent, thermal or mechanical energy. In electrospraying, particle size and its distribution depend on the electrical charge on the surface 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 easily electrosprayed into nanoparticles while liquid-based preparation methods of nanoparticles are rather material specific.

In spite of the advantages expected for protein and other drug deliveries, electrosprayed protein nanoparticles have never been successfully prepared and tested *in-vivo* or *in-vitro*, mainly due to the difficulty involved in the preparation of actual formulation.

In this study, the applicability of surface energy control by electrical energy input to prepare micro- and nanoparticles useful for final protein formulation was assessed. How to obtain appropriate pharmaceutical particles through electrospraying is the major interest in here.

Experimental

Materials. Chitosan (Sigma Aldrich), polycaprolactone (Aldrich, Mw 65k), polyethylene glycol (PEG, Mw 5k), triphenylphosphate (TPP, Sigma Aldrich), bovine serium albumin (BSA, Sigma, 98%) 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, ConverTech model SHV300-RD and NanoNC model NNC-30k-2mA were used. Electrospraying was performed in various configurations to find out the relationship between them and the size and morphology of resulting 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 = 40W, 39 kHz, 340 mL/min stirring flow (level 3), 95 – 100 mL water medium). Drug 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

Spraying Systems. Electrosprayed aerosol particles were easily obtained by controlling the viscosity of solution, feed rate, applied voltage, and conductivity. The formation of 'Taylor cone' was confirmed by the scattering of laser light. A voltage above several thousands was enough to produce the 'Taylor cone' mode, although the detailed conditions significantly rely on the characteristics of solutions.

After particle formation, the liquid mist should be stably dispersed or consolidated for pharmaceutical formulation. Drying or precipitation steps were developed for the purpose. A consolidation medium such as TPP aqueous solution was employed. Polymer/drug solution was electrosprayed into the medium in various conditions, i.e., without stirring, with stirring, or with circulation.

The preparation of core-shell particles were possible using a coaxial nozzle. The encapsulation of the inner solution was confirmed using BSA/PEG solution as the inner stream and PCL solution as the outer stream and the subsequent BCA assay.

Water-based Systems. As can be seen in Figure 1, when chitosan was injected into water, nanoparticles less than 100 nm were obtained at an applied voltage of 12 kV and 1 mL/hr feed rate. Compared to the organic solvent based systems, the size of primary particles was rather smaller, although they tend to aggregate.

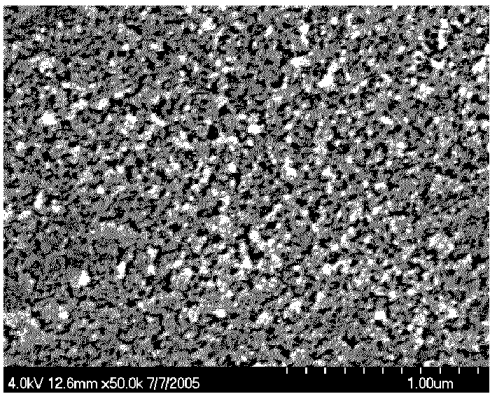

Figure 1. SEM micrographs of electrosprayed chitosan particles.

Organic-Solvent-based System. Lower conductivity in organic-solvent systems generally ended up with larger particles if the same conditions were used. Furthermore, electrospinning instead of electrospraying occurred more easily in certain conditions. Careful adjusting the variables of electrospraying allowed us to prepare particles such as Figure 2.

Conclusions

The micro- and nanoparticles of drugs and polymers were successfully prepared using electrospraying. The conductivity and viscosity of sprayed solution were found to be important factors.

References

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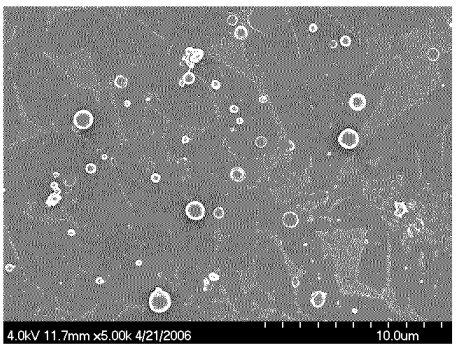

Figure 2. SEM micrographs of electrosprayed polycaprolactone particles.