Polymeric Particle Formation Through Electrospraying at Low Atmospheric Pressure

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Abstract: Electrospraying is a simple and versatile technique capable of producing polymeric particles. However, most investigations carried out thus far have been performed at ambient atmospheric pressure without studying the influences of pressure on the formation of polymeric particles. Here, we report our investigation on the effects of varying the pressure and the solution concentration on the microstructures of electrosprayed polymeric particles. Pressures are varied from ambient atmospheric pressure to 380 mmHg below ambient pressure, and solution concentrations are varied over a range of 3–7 w/v%. By varying these parameters, we manipulated the rate of solvent evaporation and the solidification of the electrosprayed particles. The results show that changes to the pressure had significant effects on the microstructure and morphology of poly(ε-caprolactone) (PCL) particles. The average particle size became larger as the chamber pressure decreased. At a solution concentration of 5 w/v% and a pressure 150 mmHg below ambient pressure, uniform and spherical PCL particles were generated. Electrospun fibers were formed when a solution concentration of 7 w/v% was used. The developed technique can be applied to prepare polymeric drug delivery carriers though a low-pressure-assisted spray-drying method, and is particularly suitable for fabricating delivery microspheres encapsulated with temperature-sensitive drugs and biomolecules. © 2008 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 90B: 381–387, 2009

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INTRODUCTION

Polymeric particles have been found to be useful in biomedical applications. They are widely used as drug delivery carriers that can prolong and control the delivery of therapeutic agents. Control is achieved by tailoring the structure, size, and the specific polymeric matrix of the particles.1,2 Additionally, polymeric particles with unique mechanical, magnetic, and optical properties can be used in the fields of physics, chemistry, and biology.3–5 Traditionally, polymeric particles have been produced by solvent extraction/evaporation, spray drying, and suspension/emulsion polymerization.6–8 Recently, a simple and cost-effective electrospraying technique has been used to prepare polymeric particles with the capability to generate size-controlled, near-monodisperse particles by optimizing the processing parameters and the properties of the solution.9,10 This technique for producing monodisperse polymeric particles of nanometer scales is easier than any other aerosol generating method.11

The enabling principle behind electrospraying is that a charged droplet becomes unstable as solvent evaporates and the particle becomes smaller. The liquid droplet undergoes Coulomb fission and breaks into smaller jets when the electrohydrodynamic forces overcome the surface tension forces.12 So far, most investigations of electrospraying have been performed in open atmosphere. However, it is known that the evaporation rate of solvents and the associated solidification of electrosprayed jets are important factors that affect the morphology and microstructure of polymeric particles generated via electrospraying.13 In this article, the effects of pressure on the morphologies of polymeric particles were investigated. A low atmospheric pressure was used as a driving force to promote the evaporation of the solvent from the electrosprayed polymeric particles. In this way, the evaporation rate of the solvent was adjusted by controlling the pressure in an electrospraying chamber.
trospraying would occur under an appropriate electric field and the working distance were selected to ensure that electrospraying occurred between the nozzle and the collector. The applied voltage was applied to the aluminum disk to collect the polymeric PCL particles. The working distance was set at 30 cm from the nozzle relative to ambient pressure. The syringe pump (Cole-Parmer) and syringe (BD company) were positioned on one end of the electrospraying chamber. The syringe was equipped with a stainless steel nozzle (McMaster) that was connected to a high-voltage power supply (Acopian) capable of generating voltages up to 30 kV. On the other end of the chamber, the power supply was connected to a circular aluminum disc that served as the collector. A circular shape was used to maximize the uniformity and symmetry of the electric field.

Preparation of PCL Polymeric Particles
To prepare electrosprayed PCL particles, solutions with concentrations of 3, 5, and 7 w/v % were prepared by dissolving PCL polymer into DCM solvent. The reagent was analytical grade and used as received.

MATERIALS AND METHODS

Materials
Poly(ε-caprolactone) (PCL; $M_w = 80,000$) and dichloromethane (DCM) were purchased from Sigma-Aldrich (USA). The reagent was analytical grade and used as received.

Experimental Setup
A schematic illustration of the electrospraying setup is shown in Figure 1. A custom electrospraying chamber was built in-house using a cast acrylic tube (Spartech Townsend). The chamber pressure was controlled using a vacuum pump (GAST); pressure measurements were made relative to ambient pressure. The syringe pump (Cole-Parmer) and syringe (BD company) were positioned on one end of the electrospraying chamber. The syringe was equipped with a stainless steel nozzle (McMaster) that was connected to a high-voltage power supply (Acopian) capable of generating voltages up to 30 kV. On the other end of the chamber, the power supply was connected to a circular aluminum disk that served as the collector. A circular shape was used to maximize the uniformity and symmetry of the electric field.

Characterization of Electrosprayed Particles
The microstructures and morphologies of electrosprayed PCL polymeric particles were characterized using a field-emission scanning electron microscope (FE-SEM, Philips XL 30 SEM, Netherlands) operated at an accelerating voltage of 5 kV and a working distance of 5 mm. To obtain SEM images, the PCL particles were collected on an aluminum disk and coated with gold before FE-SEM analysis. The diameter size of particles and size distribution were measured using Image J analysis software (NIH).

RESULTS

The Process Pressure Effects
Figures 2 and 3 show low- and high-magnification SEM images of the morphologies of PCL particles prepared under different pressures between 0 and −380 mmHg using a solution concentration of 5 w/v %. At 0 mmHg, a mixture of particles and fibers was produced, as shown in Figures 2(a) and 3(a). The average particle size was 2.0 ± 0.3 μm. The particle size distribution and standard deviation are shown in Figure 4(a), which shows that most of the particles sizes were distributed in a range of 0.7–3.2 μm. The average fiber diameter was 0.8 ± 0.5 μm, and there were some smaller nanometer-scale fibers connecting particles to each other. At a pressure of −150 mmHg, the fibers completely disappeared and uniform spherical PCL particles were generated as shown in Figures 2(b) and 3(b). These PCL polymeric particles were separated and covered a narrow size distribution as shown in Figure 4(b). The diameters of most particles were within a range of 3.0–4.0 μm, reaching a fraction >70%. The average particle size increased from 2.0 ± 0.3 μm at 0 mmHg to 3.5 ± 0.4 μm at −150 mmHg. When the pressure was further decreased to −250 mmHg, a significant increase in the average particle diameter was observed from SEM images as shown in Figures 2(c) and 3(c). Large PCL particles with rough surfaces were formed, and the particle size distribution increased as shown in Figure 4(c). The morphologies of PCL polymeric particles were in shapes ranging from elongated to spherical as shown in Figure 3(c). The average particle size increased to 8.5 ± 0.2 μm at −250 mmHg. The distribution of particles between 0.5 and 6.0 μm made up 70 ± 0.8% of the sample. A detailed size distribution within 0.5–6.5 μm and standard deviation is shown in Figure 5. When the pressure was decreased to −380 mmHg, larger PCL particles with a wider size distribution were formed. These electrosprayed particles had rough surfaces and an aggregate and irregular morphology, as shown in
Figures 2(d) and 3(d). The average particle size was 26 ± 3.0 μm. The particle size distribution is shown in Figure 4(d).

**The Solution Concentration Effects**

To investigate the influences of solution concentration on the formation of PCL polymeric particles at low pressure, two additional solution concentrations of 7 and 3 w/v% were electrosprayed at pressures of 0, −150 and −250 mmHg using the same experimental setup. Figure 6 shows SEM images of the polymeric PCL products that illustrate that the solution concentration had a significant influence on their microstructure. As shown in Figure 6(a), uniform PCL fibers with an average diameter of 600 ± 40 nm were generated at ambient atmospheric conditions using a 7 w/v% solution. Figures 6(b-c) show that a 7 w/v% solution electrosprayed at pressures of −150 and −250 mmHg resulted in microstructures consisting of spherical PCL particles and fibers, indicating that a higher concentration favored the formation of fibers. Additionally, when the pressure was at −250 mmHg, particles with a collapsed surface were produced. The average diameter of fibers obtained at a pressure of −150 mmHg was approximately 220 ± 60 nm, which is smaller than those obtained at a pressure of −250 mmHg, which had an average diameter of 580 ± 30 nm. The average particle sizes were 10 and 13 μm for pressures of −150 and −250 mmHg, respectively. When the solution concentration was decreased to 3 w/v%, fibers disappeared, and aggregated particles were obtained, as shown in Figure 6(d-f). Using a solution concentration of 3 w/v%, different morphology particles were obtained under different pressures ranging from −250 to 0 mmHg. At pressures of 0 and −150 mmHg, smooth particles were generated, but they were stuck together. When the pressure was pumped down to −250 mmHg, the particles were slightly separated and had a more spherical morphology. The average sizes of the particles increased from 7 to 9 μm when the pressure was changed from 0 to −250 mmHg.

**DISCUSSION**

The process of generating monodisperse particles through electrospraying is believed to be more stable under low
pressure than under atmospheric pressure. The electrospraying of a solution at atmospheric pressure results in a corona discharge near the nozzle tip. The high voltages create a charged jet instability that forms poly-disperse droplets. The experimental results showed that the resulting microstructure of the electrosprayed PCL polymeric particles had a great dependence on the pressure and solution concentration. By reducing the pressure to \(2150\) mmHg, uniform, spherical PCL polymeric particles were obtained from a \(5\) w/v % solution. However, a further decrease of pressure resulted in the aggregation of large particles with a wide size distribution. There was a decrease in the number of polymeric particles and an increase of the average diameter size. The formation of large particles under lower pressure was attributed to the solvent evaporating more quickly. As the charged jets dried, the jets had less time to break up into smaller polymeric particles. Meanwhile, the electrostatic forces on the jets deformed the morphologies of particles and generated irregular shapes. The experiments demonstrated that an appropriate pressure promoted the formation of separated, spherical, uniform polymeric particles; however, when the pressure was too low, it would form large, aggregate PCL particles with irregular morphologies and a wide size distribution. The semi-dry or dry charged jets had a relatively high viscosity that inhibited the breakup of the jets and resulted in the formation of large polymeric particles.

The formation of fibers was attributed to a bending instability created by the electrostatic field before the charged jets were fully solidified. Particle-on-fiber microstructure is a phenomenon between the particulate and fibrous microstructures. When the solution concentration was increased, uniform fibers or a hybrid structure of fibers with particles could be produced because the increased intermolecular chain entanglements stabilized the electrospun jets, inhibiting their breakup. The particle size and the ratio of fibers to particles could be adjusted by varying the solution concentration and the processing parameters. SEM images in Figure 6 revealed that a significant fraction of the electrosprayed PCL particles adhered together. For low concentration solutions, when the electrostatic forces break up the jets into droplets, the polymeric particles need more time for the solvents to evaporate completely. This increases the chance of subsequent coalescence of electrospayed particles. The experimental results demonstrated that the solution concentration did not change the average

![Figure 3. High-magnification SEM images of PCL polymeric particles generated at the following pressures: (a) 0 mmHg, (b) –150 mmHg, (c) –250 mmHg, and (d) –380 mmHg.](image-url)
particle size dramatically, but it did affect the microstructure of the electrosprayed products and the morphologies of the polymeric particles significantly. The surface of the PCL particles changed from rough and porous to smooth when the solution concentration was decreased from 7 to 3 w/v % solution aggregated significantly. The formation of porous structures could result from the phase separation of the charged jets during electrospraying. Adjusting the pressure and the solution concentration can provide additional control over the solvent evaporation during electrospraying, which is a simple and cost-effective technique for preparing polymeric particles with spherical morphologies and narrow size distributions. Compared with conventional spray-drying methods such as those using hot gases to dry polymeric drug delivery microspheres, this mild processing condition could improve the stability of drugs and biomolecules encapsulated within the polymeric microspheres. The microparticles formed through this technique have great potential for applications ranging from drug delivery carriers, microencapsulation of biomolecules for protection, and drug delivery coatings.

Figure 4. Histogram of the size distribution of PCL polymeric particles generated at the following pressures: (a) 0 mmHg, (b) -150 mmHg, (c) -250 mmHg, and (d) -380 mmHg.

Figure 5. Partial histogram of the size distribution of PCL particles generated at a pressure of -250 mmHg (details for the particles in the range of 0.5-6.5 μm under a pressure of -250 mmHg).
CONCLUSION

A novel low-pressure electrospraying technique for atomizing and drying droplets of polymer solution was investigated. It was concluded that the pressure was an effective electrospraying parameter that influenced the formation and morphology of polymeric particles. When the pressure was reduced from 0 to −250 mmHg relative to ambient pressure, the average diameter of the solidified particles increased from 2.0 ± 0.3 to 8.5 ± 0.2 μm. At a pressure of −150 mmHg, uniform and separate PCL particles were obtained through electrospraying. These polymeric particles had a spherical morphology with an average particle size of 3.5 ± 0.4 μm. The size distribution under these conditions was narrower than at atmospheric conditions. It was also shown that the solution concentration affected the microstructures of the electrosprayed products, dramatically. Using a solution concentration of 7 w/v %, a hybrid
structure of particles and fibers was formed. This shows that charged jets of high concentration, high viscosity solution were created that developed bending instabilities and formed fibers. When a concentration of 3 w/v % was used, an aggregated particulate microstructure was generated due to the coalescence of wet electrosprayed particles caused by the increased amount of solvent within the jets.

The developed spray-drying technique is a mild process that has the potential to enable more control in preparing polymeric microspheres to serve as drug delivery carriers or to serve as reservoirs for the controlled release of functional substances. We anticipate further study into the development of low-pressure-assisted spray-drying methods as versatile and cost-efficient processes for encapsulating drugs and biomolecules into microparticles and microcapsules.

REFERENCES