ELECTROSPRAY: NOVEL FABRICATION METHOD FOR BIODEGRADABLE POLYMERIC
NANOPARTICLES FOR FURTHER APPLICATIONS IN DRUG DELIVERY SYSTEMS

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Abstract

Electrospray is an old processing technique that has recently been rediscovered. This technology is revolutionizing the biomaterials and nanotechnology fields by opening up new areas of research in fabricating drug delivery nano-devices. Due to their size, nanoparticles have the advantage of reaching less accessible sites in the body by escaping phagocytosis and entering tiny capillaries. Nanoparticles also have the unique property to accumulate at the site of inflammation and therefore, are very suitable for targeted drug delivery. The feasibility of fabricating relatively monodispersed polymeric nanoparticles by electrospray method in a modified electrospray setup is demonstrated in this study. The process comprises of dissolving desired polymer, in this study PLGA and PEG, in a volatile solvent, here acetonitril. The solution is then electrosprayed in the single cone-jet regime through a nozzle. After solvent evaporation during the path of which particles pave from the nozzle to collector, the fabricated nanoparticles can be collected in DI water which plays the role of surfactant for particles not letting them to aggregate. The results of SEM analysis clearly confirm the fabrication of monodispersed spherical polymeric nanoparticles with diameter range from 80 to 120 nm with smooth surface. The optimum processing variables of polymer concentration, voltage difference, and flow rate are 0.04 %w/v, 10 kV, and 0.01 ml/h for PLGA nanoparticles fabrication and 0.3 %w/v, 8 kV, and 0.01 ml/h for PEG nanoparticles fabrication.

1. INTRODUCTION

Different fabrication methods such as solvent evaporation, single emulsion, and double emulsion are commonly employed to fabricate polymeric nanoparticles [1]. However, the size distribution is broad and the process is hard to scale up. Most importantly, biofunctionalities of drugs, especially for biomacromolecules were lost due to exposure to harsh chemicals such as organic solvents, high shear stress, aqueous organic interfaces, or extreme conditions such as elevated temperature [2].

On the other hand, a technique has successfully demonstrated its ability to disperse masses of liquids into very fine mists. This technique is Electro-hydrodynamic atomization in the cone-jet mode commonly referred to as Electrospray. The electrospray technique has proved to be soft [3] and powerful technique that can be either scale up easily for mass production through the use of multiplexed spray sources, or miniaturized to portable devices for encapsulation and delivery of drugs for patient specific needs [4]. The application of this method ranges from the celebrated ionization method for analyzing biomolecules, by which John B. Fenn shared the Nobel Prize in chemistry in 2002, to space propulsion, production of thin films and microparticles.
coating, pesticides dispersion, and microparticles fabrication [5]. However, electrospray in cone-jet mode has not been reported to fabricate polymeric nanoparticles so far.

In the most general sense, electrospray is a method of generating a very fine liquid aerosol through electrostatic charging, rather than the more familiar gas (pneumatic) method. Electrospray, as the name implies, uses electricity instead of gas to form the droplets. In electrospray, a liquid is passing through the nozzle. The plume of droplets is generated by electrically charging the liquid to a very high voltage. The charged liquid in the nozzle becomes unstable as it is forced to hold more and more charges. Soon, the liquid reaches a critical point, at which it can hold no more electrical charge and at the tip of the nozzle it blows apart into a cloud of tiny, highly charged droplets. These tiny droplets are less than 10 µm in size and fly about searching for a potential surface to land on that is opposite in charge to their own. As they fly about, they rapidly shrink as solvent molecules evaporate from their surface. Since it is difficult for charge to evaporate, the distance between electrical charges in the droplet dramatically decreases. If the droplet cannot find a home in which to dissipate its charge in time, the electrical charges reaches a critical state and the droplet will violently blow apart again [6].

In this study, we will present the electrospray as a novel method of nanoparticle fabrication in order to yield nanoparticles in diameter less than 200 nm with narrow size distribution. We fabricated biodegradable PLGA and biocompatible PEG nanoparticles as two applicable polymers in drug delivery systems. The mean size and morphology of generated nanoparticles at optimized parameters such as solution flow rate, solution concentration, and voltage difference between two electrodes were evaluated by using Scanning Electron Microscope (SEM) analysis.

2. EXPERIMENTS AND RESULTS

2.1. Spray modes

Different spray modes can be achieved by adjusting the potential difference between two electrodes in the electrospray process [7]. These modes are characterized by the shape of the surface from which the liquid jet originates [8]. These modes have significant effects on droplet size distribution. The three distinct spray modes are single spray cone mode, multiple spray cone mode, and dripping mode, which are shown in Figure 1.

![Fig. 1: Three distinct electrospray modes. (a) Single spray cone mode, (b) Multiple spray cone mode, and (c) Dripping mode](image-url)

In the single spray cone mode, only one steady spray cone was observed with the cone axis slightly rotating around the spray nozzle axis; in the multiple spray cone mode, several unstable thin cones were observed revolving around the rim of the spray nozzle; there was no spray cone observed in the dripping mode with
liquid dripping down at a speed higher than that of natural dripping [7]. Observations in this study show that in constant process variables of flow rate, spray solution concentration, and system geometry, the applied voltage differences between two electrodes play key roles in determining the spraying pattern. This phenomenon has already been investigated in the literature [9].

Observations showed that single spray cone mode is the most desired operating regime for particle fabrication [3] owing to the fact that the single spray cone mode is able to fabricate particles with the most narrow size distribution.

2.2. Possible mechanisms of particle formation

Three different mechanisms exist for particle formation depending on the surface charge density and the droplet surface tension. First of all, when the surface charge density is very low, the Rayleigh limit is never reached even though the diameter of the droplets keeps shrinking due to solvent evaporation; therefore, no coulomb fission occurs. The second possible mechanism is that the surface charge density is very high, which causes the particles to disintegrate rapidly and form nanoparticles. The third suggested mechanism of particle formation is that the surface charge density is not very high first, but will reach the Rayleigh limit after solvent evaporation due to shrinking of the droplets. This coulomb fission causes the disintegration of particles to form nanoparticles.

When coulomb fission occurs, the particle size distribution will change. Thus, the main possible mechanism for nanoparticle formation in this study could be the first mechanism because of the uniformity of particle size observed.

2.3. Processing variables

Different processing variables such as solution flow rate, polymer concentration, and conductivity of the solution have been investigated to evaluate their effects on the nanoparticle fabrication [10]. It is found that increasing solution flow rate from 0.01 to 10 ml/h will increase the particle size as shown in Figure 2. Our observations showed that solution flow rate is the predominant factor for determining the particle size, and we can fabricate smaller particles simply by decreasing the solution flow rate. Moreover, solution concentrations between 0.01 to 0.1% w/v for PLGA, and 0.1 to 1% w/v for PEG resulted in more spherical particles with better morphology and smoother surface, which is confirmed by images in Figures 3 and 4. Rounder particles with smooth surface would have a relatively lower surface to volume ratio and hence a slower degradation rate.

It is concluded that high polymer concentration causes premature drying of the droplets at the orifice tip, whereas too low concentration causes solvent saturation at the collector. Furthermore, it is observed that higher polymer concentration results in larger particles possibly because there is more polymer mass in each droplet and thus after the solvent evaporation, more solid is left in each particle. Our experiments indicated that, for a given voltage and liquid flow rate, an optimal concentration exists that optimizes both the size and the structure of the resulting polymeric nanoparticles. Another important process variable is solution conductivity. It has been observed that particle size increases with decreasing solution conductivity [10].
Fig. 2: Particle size changes versus solution flow rate at constant processing variables of solution concentration: 0.01 %w/v for PLGA and 0.1 %w/v for PEG, voltage difference: 10 kV for PLGA and 9 kV for PEG

2.4. Morphology

The morphology of nanoparticles was observed by SEM. Nanoparticles fabricated by electrospray generally have a smooth surface and uniform morphology. Through the principle of mass conservation, the relation between final spherical particle size \( d_p \), initial droplet size \( d \), and weight fraction of solid materials \( w \) is given by following equation [11]:

\[
\frac{d_p}{d} = \left( \frac{\rho_s w}{\rho_s + \rho_p (1 - w)} \right)^\frac{1}{3}
\]

Where \( \rho_s \) and \( \rho_p \) are the densities of the solvent and the solid material, respectively. Figures 5 and 6 represent the comparison between calculated and experimental values of particle size for PLGA and PEG. The well conformity of these two curves could be attributed to the spherical shape of nanoparticles.
**Fig. 3:** Effect of solution flow rate and solution concentration on fabricated PLGA nanoparticles.

SEM images (a) to (c) show the results of decreasing flow rate from 3 ml/h (a) to 1.5 ml/h (b) and to 0.05 ml/h (c) at constant solution concentration of 0.02 %w/v on particle size.

SEM images (d) to (f) show the results of decreasing solution concentration from 0.1 %w/v (d) to 0.07 %w/v (e) and to 0.03 %w/v (f) at constant flow rate of 0.5 ml/h on particle morphology.
Fig. 4: Effect of solution flow rate and solution concentration on fabricated PEG nanoparticles

SEM images (a) to (c) show the results of decreasing flow rate from 3 ml/h (a) to 2 ml/h (b) and to 1 ml/h (c) at constant solution concentration of 0.3 %w/v on particle size.

SEM images (d) to (f) show the results of decreasing solution concentration from 1 %w/v (d) to 0.5 %w/v (e) and to 0.1 %w/v (f) at constant flow rate of 0.5 ml/h on particle morphology.

Therefore, controllable morphology of particles could be achieved by electrospray. These results suggest that uniformly round polymeric nanoparticles could be obtained by electrospray in the single spray cone-jet mode.
2.5. Nanoparticle size analysis

The size of the fabricated nanoparticles can be evaluated by a comparison of the shrinking rate of droplets and the diffusion of the polymer molecule in the droplets. The diffusion rate of PLGA and PEG molecules in liquid solvent would be very slow on the ground that polymers are large macromolecules. Due to surface evaporation of solvent, the droplet shrinks and consequently there would be an increasingly higher concentration of polymer near the surface of the droplets. As solvent evaporated from the surface, the polymer concentration increased and a shell of solid polymer would be formed on the surface of the droplets. In our investigations, we found that when the concentration of PLGA and PEG inside the droplets was less than 0.04 and 0.3 %w/v, the formation of fragmented particles was observed. This phenomenon is explained by considering the fact that when the solvent has evaporated, a thin shell of polymer macromolecules was formed. Because the polymer concentration is very low, the core of the particle would be structurally weak, and therefore the shell would collapse and the thin shell would fragment into individual pieces. When the concentration of polymer is within the range of 0.04 to 0.1 %w/v for PLGA and 0.3 to 1 %w/v for PEG, spherical nanoparticles of similar size with thicker surface polymer shell were obtained. In this case, the
polymeric shell would not collapse after solvent evaporation owing to the fact that the cores of the particles were structurally stronger due to presence of more solutes. Within this concentration range, the higher the polymer concentration, the better mechanical strength of particle would reach. For concentrations larger than 0.1 %w/v for PLGA and 1 %w/v for PEG, it was observed that by increasing the polymer solution concentration, the size of the fabricated particles is increased due to high concentration of polymer established on the surface of the droplets.

3. CONCLUSION

We have demonstrated the capability of the electrospray as a viable, attractive and promising method to produce size predictable nanoparticles with monodispersity in comparison with conventional fabrication techniques. Particle size analysis obtained from SEM images showed that quasi-monodispersed nanoparticles with average diameter of approximately 100 nm can be produced by operating the electrospray in the single spray cone-jet mode. It was investigated that smaller particles can be fabricated by decreasing the polymer solution concentration and/or by spraying the solution in lower flow rates. Morphology and particle size analysis illustrated that fabricated nanoparticles are clearly spherical with smooth surface. The optimum values of the electrospray parameters were applied in this study, though the process was not fully optimized. For PLGA nanoparticle fabrication, the preferred parameters were 0.04 %w/v polymer concentration, 10 kV voltage difference, and 0.01 ml/h flow rate. These values were 0.3 %w/v polymer concentration, 8 kV voltage difference, and 0.01 ml/h flow rate for PEG.

LITERATURE REFERENCES