Microsphere Fabrication of Polycaprolactone via Electrospray: Effect of Different Parameters

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Abstract: In controlled drug release systems, biodegradable and biocompatible polymer microspheres are good candidates as drug carrier due to their large surface area. Here, we used the electrospraying technique to fabricate polycaprolactone microspheres. By exploring the process parameters systematically, microspheres with different morphology were produced. The increase of feed rate increased the particle size and collapse of the particle, a feed rate of 0.2 μL/min was found to produce narrow size distributed microspheres with the average size of ~4 μm. Our study shows that electrospray is a promising technique to fabricate microspheres applied in controlled drug delivery systems.

1 INTRODUCTION

Biodegradable microspheres have been applied in modern medical science for years. The drug delivery at targeted site can increase local drug concentration once the drugs are injected, which minimizes side effects like degradation of active therapeutic ingredient during its travel to the targeted site (Sinha et al., 2004; Xie et al., 2007). There are several common methods to make microspheres, like the emulsion method, freeze-drying, precipitation and spray drying. Among these methods, emulsion method has achieved commercial application. However, this method has its limitation since during fabrication, it has tedious separation process.

Electrospray is a convenient, one step technique that can fabricate microspheres via electric force. Under high electrical voltage, the liquid is charged and a Taylor cone is formed at the tip of a needle. When the electric force overcomes the surface tension, the liquid is dispersed into small charged droplets and travels from nozzle to the collector. This process involves the solidification of droplets and evaporation of solvent from the surface of droplets. The diameters and morphology of final microspheres vary according to the electrospray parameters (Kanani et al., 2011; Park et al., 2009). The factors include solution properties like concentration, solvent, conductivity and viscosity, processing factors like feed rate, applied voltage, nozzle to substrate distance and collector, ambient conditions like humidity and temperature (Guarino et al., 2015). Drug release rate is greatly influenced by microsphere size and morphology, thus controlling the electrospray parameters is important for microsphere applications as drug carrier.

The liquid is diverse in its composition and form, like natural polymer solution, synthetic polymer solution, mixed solution, emulsion, and even solid particle dispersed solution (Jafari-Nodoushan et al., 2015;Wang et al., 2018; Ding et al., 2005; Guo et al., 2017; Li et al., 2017). With the encapsulation of low solubility drug celecoxib in poly(D,L-lactide-co-glycolide) (PLGA 50:50), Bohr et al. successfully prepared 1-4 μm, nearly monodispersed microspheres at different composition ratios of polymer and drug (Bohr et al., 2011). Lai et. al. used carboxymethylcellulose (CMC) to prepare homogeneous core-shell hydrogel microspheres and tuned the drug release sustainability by the manipulation of processing parameters and hydrogel composition (Lai et al., 2017). Recently Huang et al. reported controllable preparation of porous polycaprolactone (PCL) microspheres, via the change of solvent composition for PCL solution (Huang et al., 2017). In this study, we also used PCL to fabricate microspheres since PCL is

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biodegradable and biocompatible. We prepared PCL solution with acetic acid and systemically studied the effect of solution properties and processing parameter. Our result lays the basis for future microsphere studies with different materials and shows that electrospray is a promising technique to fabricate micro or nano particles applied in drug delivery and controlled release system.

2 MATERIALS AND METHODS

2.1 Materials

The PCL pellets with an average molecular weight of 80 kDa were purchased from Sigma-Aldrich (Shanghai, China). Glacial acetic acid (99.7%) was purchased from Aladdin Industrial Corporation (Shanghai, China). Ethanol (99%) was purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China).

2.2 Characterization of Solution Viscosity

The viscosity of polymer solution was determined using Brookfield DV2T viscometer, equipped with LV spindle set. Briefly, 40 mL polymer solution was prepared and LV-63 spindle was placed into the solution until reaching the guradleg level. To measure the viscosity (η), the experiments were performed at room temperature 25 °C, the rotation speed of the spindle was set to 200 rpm and through torque calculation of a built-in calibrated spring, viscosity could be read directly from the viscometer.

2.3 Fabrication of Microspheres by Electrospray

The polymer solution was prepared by dissolving white PCL pellets (e.g. 1 g for 10 wt.%) in 10mL acetic acid and treated by ultra-sonication, shake the mixture time by time until the formation of a homogeneous colorless solution. The freshly prepared solution was transferred to a 10 mL syringe with a 26G stainless steel needle, which is the nozzle for electrospray. A syringe pump (NE-4000, New Era Pump System Inc., USA) was used to control the feed rate (FR) of the solution and drive the liquid to the nozzle. High electrostatic field is applied between the substrate and the nozzle, making the liquid in the nozzle charged and a Taylor cone is formed under the interaction of electric force, gravity and surface tension. An ejection of spray formed when the electric force exceeds the surface tension.

2.4 Characterization of Microsphere Morphology

Surface morphology of the microspheres was observed by scanning electron microscope (SEM, JSM-6510, JEOL, Japan). Samples were coated with platinum at 20 mA for 30 s before observation. Microsphere diameter was analyzed with Image J software.

3 RESULTS AND DISCUSSION

3.1 Solution Properties Effect

PCL is soluble in many organic solvents and there have been reports using dichloromethane (DCM)(Samsudin et al., 2017), chloroform (CFM), N,N-dimethylformamide (DMF) (Huang et al., 2017), etc. as the electrospray solvents. We chose acetic acid (AA) as the main solvent and ethanol (EtOH) as the auxiliary solvent for environmental considerations. When the concentration of PCL solution used was the same (10 wt%), microspheres covered with fine fibres were observed in Figure 1a using AA as solvent, while only microspheres were observed in Figure 1b using mixed solvents.

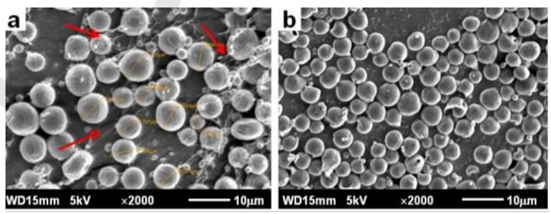

Figure 1: SEM images a) of 10 wt% PCL in AA, b) of 10wt% PCL in AA : EtOH = 8 : 2, temperature 21 °C, humidity 50%. Red arrow was eye guide for tiny fibres.

When the polymer solution has sufficient entanglement among chains, electrospin will happen (Gupta et al., 2005). A critical chain overlap concentration (c*) was proposed which was the crossover of concentration from semidilute unentanglement to semidilute entanglement regime. At the same PCL concentration, by the change of solvent composition, the morphology changed from microspheres with fiber (Figure 1a) to microspheres only (Figure 1b). We measured the viscosity of the two PCL solutions and η was nearly the same as shown in Table 1. Non-solvent assisted electrospray can produce more regular microspheres (Gao et al., 2014), and as a non-solvent for PCL, the addition of ethanol had the advantage to facilitated the formation of microspheres.

From Table 1, we can find that though the nozzle to substrate distance increased, the feed rate decreased, the voltage applied for the mixed solvent system decreased significantly. On the one hand, the surface tension for acetic acid and ethanol are 31.9 dyne/cm and 22.0 dyne/cm respectively(Bae et al., 2017). With the decrease of surface tension for the mixed solvent system, the required electrostatic force to start the spray is decreased. On the other hand, the dielectric constant for acetic acid and ethanol are 6.2 and 24.5 respectively at 25 °C(Dean, 2010), higher dielectric constant for the mixed solvent system also attributed to the decrease in the requisite voltage. Therefore, the addition of non-solvent ethanol for PCL solution improved the electrospray performance greatly.

Table 1: Comparison of electrospray parameters for the two solutions.

Parameters	AA	AA : EtOH = 8 : 2
PCL concentration (wt%)	10	10
Voltage (kV)	20	12
Distance (cm)	20	24
Feed rate (μL/min)	0.5	0.2
Viscosity (cP)	264.6	261.0

3.2 Processing Parameters Effect

3.2.1 Jetting Mode

Taylor cone forms when the electric force equals surface tension of the liquid. There is a critical applied voltage for the starting of electrospray, and when the feed rate of the polymer solution increases, the surface tension changed and the critical voltage alter accordingly. As Figure 2 showed, the applied voltage increased as feed rate increased.

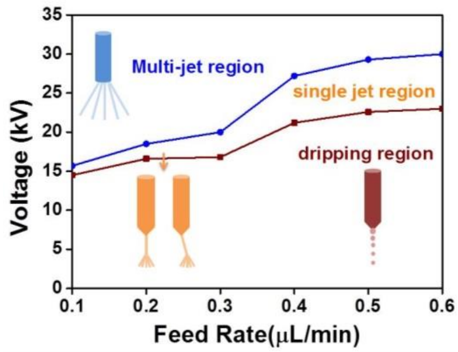

Figure 2: Critical voltage as a function of feed rate and spray mode classification according to the jetting: dripping region below the wine line, single jet region between wine and blue line, and multi-jet region above the blue line. The polymer concentration was 10wt% in mixed solvent AA : EtOH = 8 : 2, nozzle to substrate distance 20 cm, temperature 21°C, humidity 50%.

In Figure 2, the wine line is the critical voltage for electrospray. When voltage lower than the critical voltage was applied, the liquid at the nozzle tip accumulated and under the electric force and gravity, quick drops formed, namely dripping region. When voltage higher than blue line was applied, Taylor cone disappeared due to larger electrostatic force and multiple streams were observed, i.e. multi-jet region. The single jet region is narrow but important in the fabrication of microspheres. In this region, the applied voltage was the critical voltage or slightly higher, which produced Taylor cone with stable single stream of spray. When the Taylor cone was not stable, the droplets sprayed were unstable and broke up into primary or main large droplets and secondary or satellite small droplets. Consistent with previous studies(Park et al., 2009; Ioan et al., 2004; Enayati et al., 2010), our experimental results also showed that microspheres produced in single jet region were more mono-dispersed, and less satellite spheres were produced.

3.2.2 Feed Rate

Feed rate is one important parameter that affect the diameter of the microspheres. There has been many studies on the particle size and feed rate relationship (Park et al., 2009; Jafari-Nodoushan et al., 2015; Xie et al., 2007), and all were based on Ganan-Calvo et al.'s theoretical formulation (Equation 1), where α is a constant related to permittivity, Q is the solution feed rate, ε is dielectric constant in a vacuum, ρ, σ, γ are the density, surface tension, conductivity of the solution respectively (Ganan-Calvo et al., 1999).

$$d = \alpha\left(\frac{Q^3 \varepsilon \rho}{\pi^4 \sigma \gamma}\right)^{1/6} \quad (1)$$

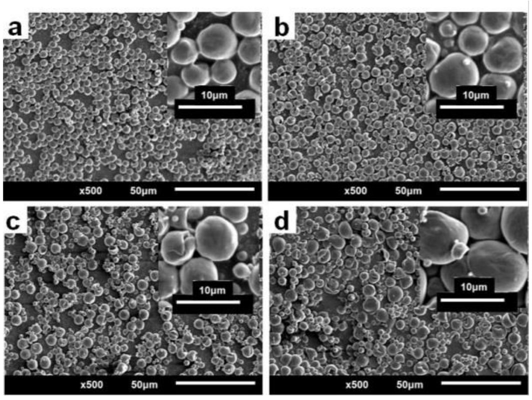

Figure 3: SEM images of 10wt% PCL in AA : EtOH = 8 : 2, at feed rate a) 0.2 μL/min, b) 0.4 μL/min, c) 0.6 μL/min, d) 0.8 μL/min, distance 24 cm, temperature 20 °C, humidity 50%.

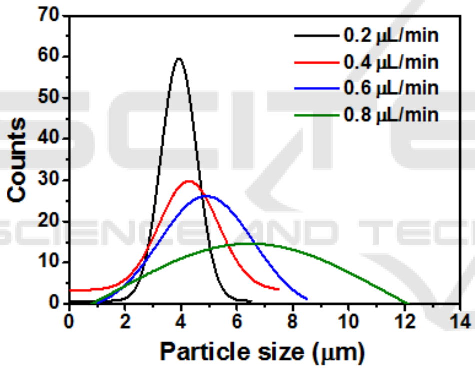

Figure 4: Gaussian fitted curves of size distribution histograms of 100 PCL particles at different feed rate.

Ganan-Calvo demonstrated that the diameter of microspheres is proportional to the square root of the solution feed rate, and as shown in Figure 3, the size of microspheres increases approximately 2 times when the feed rate increases from 0.2 μL/min to 0.8 μL/min, consistent with Ganan-Calvo's theory. Figure 4 shows the Gaussian curve of PCL microspheres for each feed rate. As the feed rate increases, the full width at half maximum (FWHM) become wider indicating heterogeneous size distribution. As the feed rate increased, more satellite microspheres were fabricated as shown in the insert SEM images, and the standard derivation of particle size increased greatly. Our research shows that when feed rate was 0.2 μL/min, the microsphere diameter was 3.92 ± 0.64 μm, indicating mono-dispersed microspheres.

3.2.3 Nozzle to Substrate Distance

Nozzle to substrate distance (D) is also call working distance, which is the distance from the tip of nozzle to the collector. D affects the applied voltage (V): E = V / D, where E is the electrostatic force generated. Table 2 shows that as D decreases from 24 cm to 15 cm, lower voltage was applied, and the size change of microsphere was negligible (within 0.1 μm), however, the standard derivation increases indicating that heterogeneous microspheres were fabricated. Figure 5 shows that more collapsed microspheres were produced when D decreased. This morphology was attributed to insufficient solvent evaporation within the microspheres when D decreased.

Table 2: Applied voltage and microsphere diameters for different working distance.

Distance (cm)	Voltage (kV)	Diameter (μm)	Standard derivation
24	12.5	5.04	0.54
20	11.5	4.98	0.67
15	9.5	5.01	0.96

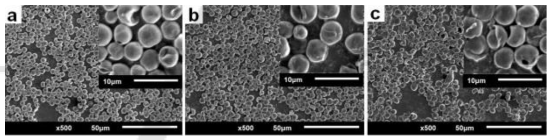

Figure 5: SEM images of 10wt% PCL in AA : EtOH = 8 : 2, at nozzle to substrate distance a) 24 cm, b) 20 cm, c) 15 cm, feed rate 0.2 μL/min, temperature 21°C, humidity 50%.

4 CONCLUSIONS

Choice of solvent for microsphere fabrication is important and the addition of non-solvent for PCL solution facilitate microsphere formation. We studied the processing parameters and showed the importance of using single jet mode for electrospray. The optimization of feed rate, applied voltage and nozzle to substrate distance is important for the fabrication of mono-dispersed microspheres. The microsphere diameter around 4 μm with low standard derivation could be produced and our study shows that electrospray is a facile and effective method to produce monodispersed microspheres and in the future we will fabricate drug loaded microspheres for drug delivery and controlled release studies.

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