FABRICATION OF BIODEGRADABLE POLYESTER MICROSPHERES BY ELECTROSPRAYING METHODS FOR DRUG CARRIER APPLICATION

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ABSTRACT

This research investigated the effects of polymer concentration, molecular weight polymer and type of polymer on the morphology of electrosprayed microparticles by Scanning Electron Microscopy. Electrospraying process has been studied to produce nano- and micro-particles for drug carrier application because of high loading capacity and high encapsulation efficiency. Controlling morphology and structure of electrosprayed particles can decide the release of drug from these particles. Particles were hollow and wrinkled semi-spheres as using low polymer concentration while wrinkled spheres as using higher polymer concentration. The electrosprayed particles obtained spherical morphology when the polymer concentration is high enough to generate significant chain entanglements. The results also indicated that high molecular weight polymer could produce spherical microspheres, even with low polymer concentration. The electrospraying process fabricated the microspheres from biodegradable PLA and PCL for drug carrier application.

Keywords: electrospray, microparticle, morphology, microsphere.

1. INTRODUCTION

The biodegradable polyesters, such as Polylactic acid (PLA) and Polycaprolactone (PCL), were used to produce drug loaded microparticles by several methods like micro-emulsion, solvent evaporation, spray drying, ionic gelation, etc. [1]. Electrospraying is an effective process to fabricate the polymeric microparticles for drug delivery systems because of the high loading capacity (LC) and the high encapsulation efficiency (EE) [2 - 17]. Bovine serum albumin (BSA) was encapsulated by PLA particle with high EE (81 %) and LC (91 %) [2]. Valo et al. investigated that the hydrophobic drug - Beclothemasone dipropionate (BDP) and the
hydrophilic drug Salbutamol sulfate (SS) were loaded by PLLA microparticles with EE = 54% and 56% [3]. The mechanism of drug release of the polymeric microparticles is as follows: the burst release of drug which occurs on the surface of particles while the slow and balance release of drug which is inside of the particles [4]. Morphology and structure of electroprayed particles influenced on the release of drugs. Therefore, controlling the size and morphology of microparticles was able to control the release of drugs [2, 5 – 7]. In addition, the polymeric intermolecular entanglement is a key factor to produce microparticles during the electrospaying process. The polymer concentration and molecular weight are responsible for forming the chain entanglements which leads to solid and reproducible microparticles when the significant degree of entanglement is obtained [8 – 10]. At low polymer concentration, there is no or a few chain entanglements, thus electrospayed particle is a film or a semi-sphere. In case, polymer concentration is so high that chain entanglements increase rapidly, beaded fibers and event fibers will be created. The electrospayed particles obtain spherical morphology when the polymer concentration is high enough to generate significant chain entanglements [12, 13]. The research of Meng et al. has shown that although PLGA concentration was low, the high molecular weight could also produce spherical particles. That demonstrates that high molecular weight could supply the deficiency of a low polymer concentration [9]. A high molecular weight increases the formation of the entanglements because the polymer chains are longer and overlap easier. With high molecular weight or high concentration, the polymer solution occurs with highly density of polymeric entanglements and this caused the undesirable morphologies like as tapered particles, fibers, etc. [14]. The polymer entanglements into the electrospayed droplets have time to arrange and shrink during solvent evaporation, leading to solid particles in the collector.

This research determined the effects of polymer concentration, molecular weight polymer on the morphology of electrospayed microparticles by Scanning Electron Microscopy. The electrospaying microspheres were established when the number of chain entanglements was obtained at a suitable value. The size and morphology of particles can be controlled by carefully changing electrospaying parameters, especially the nature of polymer solution. In future work, the influence of morphology and structure of microparticles on drug release was investigated.

2. MATERIALS AND METHODS

2.1. Materials

Polyactic Acid (PLA) (Mw = 180 kDa and Mw = 80 kDa) and Polycaprolactone (PCL) (Mw = 75 kDa), were purchased from Sigma-Aldrich.

Chloroform was purchased from Prolabo—France, HPLC grade.

Acetone was purchased from Merck—Germany, HPLC grade.

2.2. Solution preparation

Sprayed solutions were prepared by adding polymer to solvent with predetermined quantities (w/w) as described in Table 1. The polymeric solutions were stirred using a magnetic stirrer for 2-3 hours at room temperature.
Fabrication biodegradable polyester microspheres by electrospraying methods for drug carrier...

Table 1. Composition of electrosprayed solutions (w/w).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>PLA Mw = 180 kDa</th>
<th>PLA Mw = 80 kDa</th>
<th>PCL Mw = 75 kDa</th>
<th>Acetone</th>
<th>Chloroform</th>
</tr>
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<tr>
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<td>0 %</td>
<td>0 %</td>
<td>99 %</td>
</tr>
<tr>
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<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
<td>98 %</td>
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<tr>
<td>F4</td>
<td>0 %</td>
<td>0 %</td>
<td>1 %</td>
<td>0 %</td>
<td>99 %</td>
</tr>
<tr>
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<td>0 %</td>
<td>0 %</td>
<td>3 %</td>
<td>0 %</td>
<td>97 %</td>
</tr>
<tr>
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<td>0 %</td>
<td>0 %</td>
<td>5 %</td>
<td>0 %</td>
<td>95 %</td>
</tr>
<tr>
<td>F7</td>
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<td>3 %</td>
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</tr>
<tr>
<td>F8</td>
<td>3 %</td>
<td>0 %</td>
<td>0 %</td>
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<td>72.8 %</td>
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<tr>
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<td>0 %</td>
<td>5 %</td>
<td>0 %</td>
<td>0 %</td>
<td>95 %</td>
</tr>
</tbody>
</table>

2.3. Microparticle production

Figure 1. Setup for electrospraying process.

The electrospraying setup was illustrated as shown in Figure 1. The polymer solutions were first added into a syringe pump with stainless steel needle on top, then the needle was positive charged by the high voltage supplier. The negative electrode was attached to the collector plate covered with aluminum foil. The electrospraying process was executed by changing the needle gauge, flow rate, applying a voltage and collecting distance. As the droplet accelerated toward the collector, the solvent evaporated and polymer micro-particles were collected in aluminum...
foil. All electrospraying were carried out at room temperature. After electrospraying, the products were collected with an aluminum foil and were dried in vacuum for 1 - 2 days to remove solvent completely.

2.4. Morphology of particle

Morphology of microparticles was investigated by Hitachi S-4800 Scanning Electron Microscopy (SEM) – Japan at Nanotechnology Laboratory, R&D Center, Saigon Hi-tech Park Vietnam. Samples analysed by SEM were prepared with carbon tape. The accelerating voltage ranged 3-5 kV during scanning.

3. RESULT AND DISCUSSION

3.1. Effect of solution concentration

When electrospraying polymer solutions, solvent evaporation and polymer diffusion happened contemporaneously in the electrosprayed droplets. Chain entanglements occurred and were responsible for the morphology of microparticles.

The results indicated that chloroform solution with different polymer concentrations fabricated different morphologies of electrosprayed particles.

*Figure 2.* SEM images of micro particles from PLA (Mw= 180kDa) solution with chloroform. (a) 1 % PLA, (b) 2 % PLA, (c) 3 % PLA. Electrospraying parameters: needle gauge 18G, collecting distance = 20 cm, flow rate = 1 ml/h, voltage = 24 kV.

*Figure 3.* SEM images of micro particles from PCL solution with chloroform in different concentrations: (a) 1 %, (b) 3 %, (c) 5 %, voltage = 12 kV, collecting distance = 10 cm, and flow rate: 1 ml/h, needle gauge 20 G.
In Figure 2, the particle morphology was a hollow semi-sphere with low PLA concentration (1 % PLA) and a wrinkle sphere with higher PLA concentration (2 % and 3 %). At low PLA concentrations, there were fewer of chain entanglements thus the particle morphology was hollow semi-spherical shape. The higher PLA concentration could produce electrosprayed microspheres because of increasing the polymer chain entanglements. In the case of PCL, the microspheres was obtained only when the PCL solution was 1 % (Fig. 3b). A low concentration (1 % PCL) formed wrinkled semi-spherical shape, whereas the particle morphology was beaded fiber at 5 % PCL concentration (Fig. 3a and c).

SEM micrographs showed that all electrosprayed particles had wrinkle surfaces, this phenomenon was related to the evaporation of solvent. During flying to the collector, the skin of droplets was solidified because of solvent evaporation. Then, solidified skin moved to the droplet center and caused the surface particles wrinkled (Fig. 2 and 3).

### 3.2. Effect of polymer molecular weight

![Figure 4. SEM images of PLA electrosprayed particles with (a) Formation F7, (b) Formation F8. (voltage: 24 kV, collecting distance: 20 cm, flow rate: 1 ml/h, needle gauge 20 G).](image)

Despite of using the same electrospraying parameters, including applied voltage, needle gauge, flow rate, distance collector, and especially PLA concentration, the morphology of particles from high and low molecular weight PLA (Mw = 180 kDa and 80 kDa) was different. The particles from Formation F8 were wrinkled and distorted microspheres (Fig. 4b) while the morphology of particles from Formation F8 were discs and hollow semispheres in shape (Fig. 4a). This was explained that the length of PLA chain of high molecular weight polymer was higher, leading to increasing of intermolecular entanglements formation.

### 3.3. Effect of Polymer type

SEM pictures indicated that when the chloroform was used to dissolve different polyester, the electrosprayed microspheres could be fabricated (Fig. 5). Type of polymer was not an important factor to effect on the morphology and size of particles. Choosing polymer type depends on the desirable degradation of polymer on biomedical applications. For instance, PCL microsphere is suitable for drug delivery which needs long time to release drug, whereas PCL
microsphere is useful for shorter drug delivery. The reason is that it was take more time to degrade PCL than PLA, so that the release of drug from inside PCL particles was longer.

![Figure 5. SEM images of electrosprayed particles from chloroform solution with (a) 5 % PLA (Mw = 80 kDa), (b) 4 % PCL (Mw = 75 kDa), voltage: 15 kV, collecting distance: 15 cm, flow rate: 1 ml/h, needle gauge 20G.](image)

### 4. CONCLUSION

Polymer chain entanglements were responsible for the final morphology of electrosprayed particles. High polymer concentration and high molecular weight polymer produced chain entanglements easier because of the increasing of chain overlap. At low concentration, the morphology was a hollow and wrinkled semi-sphere because chain entanglement was limited. At high concentration, chain entanglements are easily obtained the spherical morphology. However, the surface of electrosprayed particles was wrinkle due to high solvent evaporation.

The result indicated that the biodegradable polyester microspheres such as PCL and PLA could be produced by electrospraying and the morphology of them could be controlled by adjusting fabrication parameter.

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*Từ khóa:* electrospray, vi hạt, hình thái, vi cầu.