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Fabrication Drug Loaded Polycaprolactone by Electrospaying Method

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Abstract. The drugs such as Insulin and Paclitaxel were encapsulated in Polycaprolactone (PCL) by electrospaying method. Some fabricated factors which influenced the morphology of PCL microparticles were investigated. Electrospaying is an effective and approachable method to produce considerable solid drug-loaded microparticles for drug delivery system. Using the Scanning electron microscopy to observe the morphology and size of particles and Thermal Analysis evaluated the compatibility of drug and polymer matrix. The toxicity of products was determined by checking the existence of solvent inside the electrospayed particles. The results showed that the drug-loaded microspheres were fabricated at 15-20% drug (w/w), 4.5% PCL in Dichloromethane. Besides, the hydrophobic drug (Paclitaxel) had a good compatibility with PCL matrix, therefore, the surface of particles was smoother. In case of Insulin, it and PCL created a suspension and consequently generated the undesirable morphology with holes and wrinkled surfaces. The drug-loaded microparticles didn't contain toxic solvent so that it can be applied in pharmacy.

Keywords: electrospaying, drug-loaded particles, Polycaprolactone, insulin, Paclitaxel.

1 Introduction

Electrospaying is an efficient method to fabricate solid drug-loaded microparticles in drug carrier system over the conventional treatment due to some advantages such as macromolecules high penetration, high loading capacity, simple process, and ability for encapsulating both hydrophobic and hydrophilic drug [1-3]. Besides some drug delivery systems such as liposome, micro-emulsion, solvent evaporation, hydrogel, spray drying, layer by layer, etc..., the electrospaying technique fabricated solid micro(nano)particles has been studying to lengthen the release time of drug or protein; increase safety and the patient compliances [4, 5]. Depend on the desirable degradation of the drug carrier and the release of drug from the polymer matrix, the sort of polymer would be chosen. Thank more ester groups on polymer backbone than

PCL, Poly(lactic-co-glycolic)acid (PLGA) and Polylactic acid (PLA) are suitable for short-term drug release while PCL microparticles are suitable for long-term release system [1, 2, 6]. In previous studies, PLGA and PLA encapsulated some hydrophilic drugs (Salbutamol sulfate, Bovine serum albumin, oestradiol, etc...) and hydrophobic drugs (Beclomethasone dipropionate, Paclitaxel, Celecoxib) [7-10]. In case of PCL, a hydrophobic polymer, it combined with Paclitaxel (PTX) to form the PTX-loaded PCL microparticles for the brain tumor treatment [9, 10]. Besides PTX, some kind of drug was encapsulated with PCL such as β - Oestradiol, Bovine serum albumin (BSA) [11, 12]. In this research, the insulin-loaded PCL microparticles were fabricated and compared with PTX-loaded PCL particles about the morphology, compatibility of polymer and drug.

2 Materials and Methodology

Materials.

Polycaprolactone (PCL) ($M_w = 75 - 90$ kDa), PTX and Insulin (Human recombinant) were purchased from Sigma-Aldrich, UK. Dichloromethane (DCM) was used as an organic solvent and supplied by Prolabo, France, 99% purified.

Fabrication drug-loaded polycaprolactone by electrospraying.

The polymer solution was prepared by dissolving PCL in DCM at room temperature for 1.5 hours. Then, the drug (insulin or PTX) was added to PCL solution and stir for 1 hour. Next, they were filled in a 10 ml glass syringe with a flat stainless steel needle on top (Gauge 20G). Next, this syringe was placed in a Micropump Top-5300 (Japan) with adjustable flow rate. Finally, the solid drug-loaded PCL particles were collected in aluminum foil thanks to the solvent evaporation and Coulomb fission when the electrospraying happened.

Methods.

Scanning Electron Microscopy (SEM), Hitachi S4800-Japan, was used to determine the morphology of drug-loaded microparticles. The accelerating voltage of SEM was set at 5 kV during scanning. The DCM solvent in the drug-loaded particles was detected by Gas Chromatography - Mass Spectrometry (GC-MS), GC 7890A/5975C MS detector (Agilent Technology, US) and equipped with a non-polar column DB-5 (Agilent Technology, US). The detector was operated in electron impact ionization mode (electron energy 70eV). The injection port was operated in split mode 1:10, Helium (99.99% purity) was used as a carrier gas, 280°C. The column temperature was kept at 50°C for 3 min, increasing at 10°C/min to 150°C.

The Differential scanning calorimetry (DSC) spectrum (NETZSCH DSC 204F1 Phoenix - Germany) evaluated the interaction of drug and PCL. The temperature was increased gradually from 30°C to 250°C, with step 5°C/ min, in the Nitrogen environment.

3 Results and discussion

Effect of PCL concentration and flow rate on the morphology of the PTX-loaded and insulin-loaded PCL particles.

Polymer concentration and flow rate are main factors influence the morphology of the PCL particles. The high number of chain entanglements can be created by high polymer concentration or low flow rate due to increasing the density of polymer chains in the electrospray droplets [1].

With high chain entanglements in solution, the heterogeneous morphology of PTX-loaded PCL particles such as tapered particles, beaded fibers and spheres were generated (fig. 1a). Whereas, lower PCL concentration (4.2%) and higher flow rate (1.3 mL/h) created homogeneous spheres (fig. 1b and c) although their size was different.

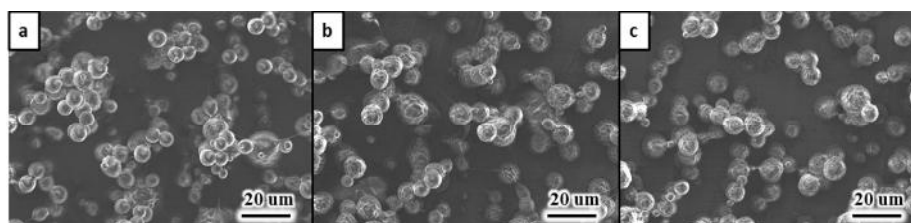


Fig. 1. SEM images of 15% PTX-loaded PCL particles; (a) 4.5% PCL, 1.2 mL/h; (b) 4.2 % PCL, 1.2 mL/h; (c) 4.2 % PCL, 1.3 mL/h (voltage 18 kV, collecting distance 21 cm)

In case the insulin-loaded particles, lower PCL concentration (4.5%) created the hollow and corrugated particles (fig. 2a and b) while 4.75% PCL generated microspheres (fig. 2c). Moreover, the microparticles were deformed and sticky on the collector due to the presence of the solvent in the particles at a high flow rate (fig. 1c and fig. 2b and c).

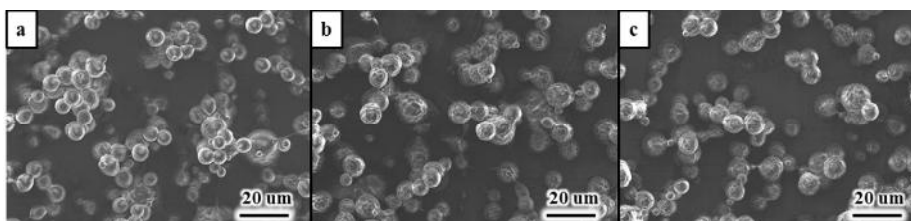


Fig. 2. SEM images of 20% insulin-loaded particles: (d) 4.5% PCL, 1 mL/h; (e) 4.5% PCL, 1.2 mL/h; (f) 4.75% PCL, 1.2 mL/h (voltage 18 kV, collecting distance 21 cm)

Fabrication drug-loaded PCL particles by electrospraying.

The results indicated that the nature of drug impact on the distribution of drug inside the polymer matrix and the particles' morphology. The hydrophobic drug (PTX) was compatible with PCL effectively therefore small molecule of PTX could fill the

hollow and pore inside the microparticles [9]. The PTX-loaded particles were dense microspheres with smoother surfaces (fig. 3b). In case of a hydrophilic drug, insulin was suspended in PCL solution due to insolubility and incompatibility with polymer. Therefore, the sedimentation and the migration of drug on and near the surface particles were formed during spraying. Fig. 3c showed that the morphology of the insulin-loaded particles was irregularly corrugated and aggregated.

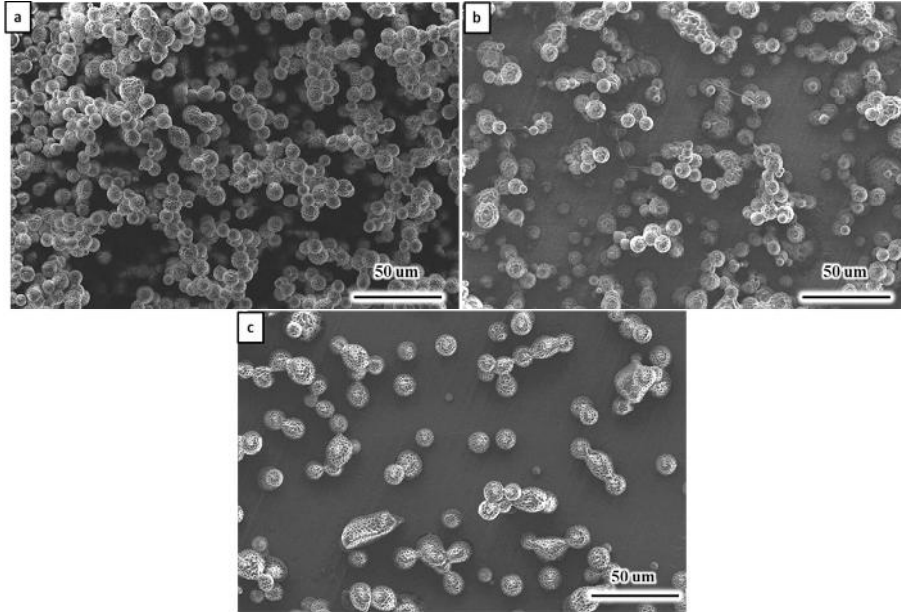


Fig. 3. SEM micrograph of drug-loaded PCL microparticles; 4.5% PCL in DCM, applied voltage 18 kV, gauge 20G, collecting distance 21 cm, flow rate 1.2 ml/h with (a) no drug, (b) 15% PTX in PCL particles and 15% insulin in PCL particles (w/w).

Evaluate the properties of electrosprayed drug-loaded PCL microparticles.

According to the results of GC-MS, the DCM solvent cannot be detected in the drug-loaded PCL microparticles due to the completed solvent evaporation (fig.4). Therefore, the drug-loaded particles are non-toxic and safe in drug delivery system application.

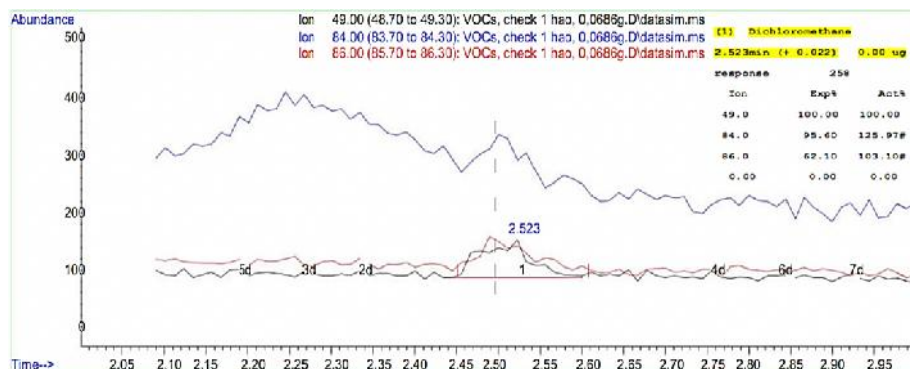


Fig. 3. The GC-MS spectrum of detecting DCM in PCL particles

The DSC Thermogram showed that the melting transition peak of Paclitaxel (180-250°C) [9] was indistinct, as a result of the PTX is well dispersed and compatible in the PCL matrix. While insulin wasn't integrated with Polymer, therefore, the melting transition peak of Insulin (200-220°C) was detected (fig.5).

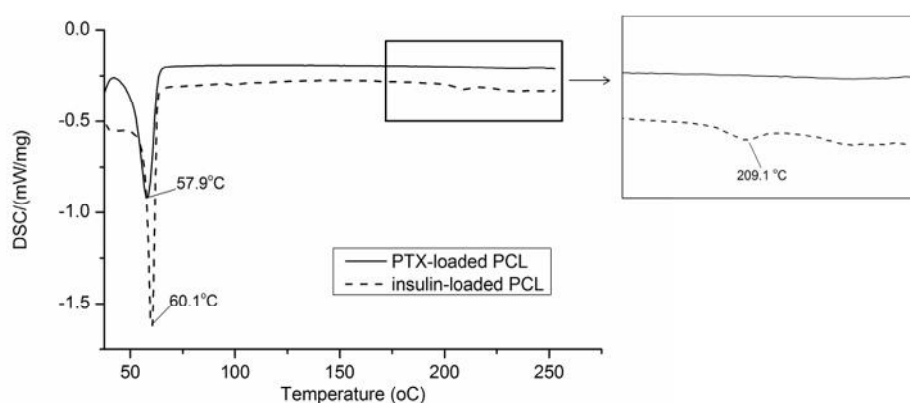


Fig. 4. DSC thermogram of electrosprayed drug-loaded PCL particles (drug: insulin and PTX)

4 CONCLUSION

The homogeneous drug-loaded microspheres can be generated by tailoring the electrosprayed parameters such as PCL concentration and flow rate. Besides, PCL can combine both hydrophobic drug (PTX) and hydrophilic drug (insulin) and create the drug-loaded particles. They don't contain the toxic solvent (DCM) after drying so that they can be applied to drug carrier system.

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Conflict of interest statement:

The authors declare that they have no conflict of interest.

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