THESIS INFORMATION

Title: The fabrication of the diabetics medicine delivery system based on the insulin-loaded PCL microparticles and the temperature/pH sensitive hydrogel OS-PCL-PEG-PCL-OS

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Abstract

Microparticles of polycaprolactone (PCL) and insulin-loaded PCL (In-PCL) were fabricated by the electrospray method. The effects of processing parameters such as solvent, polymer concentration, PCL types, applied voltage, collecting distance, and flow rate on the morphology and size of microparticles. Besides, the morphology and size of PCL microparticles (MPs) influenced the degradation of PCL in-vitro test (phosphate buffer saline (PBS)). The degradation of MPs PCL was determined by gel permeation chromatography (GPC), fourier transform infrared spectroscopy (FTIR) and SEM methods. After 70 days, the number average molecular weight (M_n) of PCL reduced from 45.000 g/mol to 6.432 g/mol. The cytotoxicity of the electrosprayed PCL MPs was investigated by 2 methods: the gas chromatography-mass spectrometry (GC-MS) and MTT assay by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazoliumbromid. The GC-MS results exhibited the PCL MPs were not contained toxic DCM solvent. Also, the A549 cell viability from MTT assay of PCL MPs supernatant was over 80% (based on ISO 10993-5). the MTT assay result indicated that the PCL MPs were non-toxic with cells.

Moreover, the OS-PCL-PEG-PCL-OS structure of pentablock was determined by Proton nuclear magnetic resonance (H^1NMR) and GPC methods. The results indicated that the pentablock was synthesized successfully and increased the reaction efficiency to 45%. The sensitive temperature/pH hydrogel (28%wt pentablock) showed the sol-gel transition in-

vitro test when the temperature and pH changed, the gel was formed under mouse skin after injecting. Then, this hydrogel was combined with the In-PCL MPs to produce the insulin delivery system for diabetes treatment. The complex of PCL MPs and hydrogel 28%wt pentablock was sol state at pH >8.5, room temperature, and changed to gel at pH 7.4, 37^{o}C. The complex was form gel under mouse' skin after 2 hours injection and this gel was degraded absolutely after 30 days.

Investigating the efficiency encapsulation and release profile of In-PCL MPs and complex gel which based on the combination of In-PCL MPs and temperature/pH sensitive hydrogel OS-PCL-PEG-PCL-OS in-vitro test, with the processing parameters following: DCM solvent, 9%wt PCL (M_n = 45,000 g/mol), applied voltage of 18 kV, collecting distance of 22.5 - 25 cm. Insulin was encapsulated in PCL MPs with different concentration: 25% insulin (wt/wt) (25In-PCL) and 20% insulin (wt/wt) (20In-PCL). The insulin efficiency encapsulation of PCL MPs was high, in detailed, 25In-PCL MPs was 80% and 20In-PCL MPs was 90%. After the first 8 hours, the insulin released from 25In-PCL MPs were 42.77% and 20In-PCL MPs were 32.45%. Then, the insulin concentration was maintained 2 - 4% after 16 hours. While, the insulin release was limited (reduced to 25.83% of the insulin release from the complex gel of 25In-PCL MPs/ hydrogel and 18.14% from the complex gel of 20In-PCL/hydrogel after 8 hours) and prolonged the release time compared to In-PCL MPs. The release of insulin amount remained stable after 1 - 16 days.

The main contribution of thesis

• Study the degradation of PCL MPs in-vitro test, M_n of PCL (type 45,000 g/mol) was degraded more than 80% after 70 days testing. The PCL MPs were non-toxic and biocompatible with A549 cells.

• Fabricating the In-PCL MPs with 20% - 25%wt of insulin with high efficiency encapsulation of PCL MPs, reaching 80-90%.

• Fabricating the drug delivery system combining electrospray In-PCL and temperature/pH sensitive hydrogel OS-PCL-PEG-PCL-OS successfully. The system had sol-gel transition in in-vitro test and could be injected on mouse' s skin. The gel was formed after 1 hour

injection and biodegradable after 30 days. The system could carry high concentration of insulin, prevent the burst release in the first 8 hours, and maintained a stable concentration of insulin release from 1-16 days.

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