学 位 論 文 審 査 の 要 旨

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学 位 論 文 題 名

On-chip Preparation of Size-controlled PLGA Nanoparticles for Drug Delivery
（薬物送達のためのサイズ制御された PLGA ナノ粒子のオンチップ調製）

Since the introduction of microfluidic devices, they have been widely used in various studies. In recent years, microfluidic devices have been regarded as the most powerful tools for preparing nanoparticles (NPs). By employing microfluidic devices, it is easy and fast to precisely modulate the fluid and thus the properties of the final prepared particles. Nonetheless, the transition from laboratory to clinical applications of poly (lactic-co-glycolic acid) nanoparticles (PLGA NPs) is gradual, partially due to the lack of precision control of each condition in the manufacturing process and the rich selectivity of nanoparticles with varied features. The use of PLGA NPs to create a wide range of size-controlled drug delivery systems and accomplish size-selective drug delivery targeting remains a problem in the development of therapeutics for several illnesses. In this study, a microfluidic device was employed to perform the preparation of PLGA polymer NPs and explored further precision: particle size modulation under the same polymer precursor. The broadened range of applications was achieved: greater particle size selectability for drug-loaded sub-200 nm particles, with greater solvent tolerance. In this context, relevant studies are presented, and the current status of the field is described in Chapter 1.

A microfluidic device was used in Chapter 2 to achieve extensive selectability for the size of PLGA NPs without alteration of polymer precursors. NPs of specific sizes were created from PLGA, poly (ethylene glycol)-methyl ether block poly (lactic-co-glycolide) (PEG-PLGA), and blended (PLGA finite element+ PEG-PLGA). By merely altering the flow rate parameters without modifying the precursor, blended NPs display the largest size range (40–114 nm) (polymer molecular weight, concentration, and chain segment composition). Paclitaxel (PTX), a model hydrophobic drug, was encapsulated in the NPs, and the PTX-loaded NPs had a wide range of adjustable NP sizes. In addition, size-controlled NPs were employed to evaluate the influence of particle size on tumor cell development in sub-200 nm NPs. The 52 nm NPs inhibited cell proliferation more effectively than the 109 nm NPs. This provides a way to achieve further refinement of particle size tailoring by using the desired polymer precursors for preparation. Moreover, this method expands the choice of diverse particle sizes for different needs in the suitable size range (below 200 nm) of NPs for drug delivery.

To improve PLGA NPs usability for drug delivery systems, it is necessary to expand the spectrum of preparation conditions for particle size controllable PLGA NP. This was accomplished utilizing a glass-based microfluidic device and a range of organic solvents in Chapter 3. Four solvents, acetonitrile (ACN), dimethyl sulfoxide (DMSO), dimethylformamide (DMF),

and tetrahydrofuran (THF) were employed as solvents to dissolve PLGA and to perform the preparation of NPs, respectively. Additionally, the effect of solvent properties on the particle size and size distribution of the prepared NPs in a non-simple capillary microfluidic device was compared and discussed. To confirm the ability of glass device to prepare NPs in a large size range, we compared the NPs obtained by the glass device with those prepared by the PDMS device. The glass device was able to maintain a good range of preparable particle sizes of sub-200 nm NPs , although the particle sizes obtained by preparation under the same flow rate conditions were different from those of the PDMS device. To further validate the encapsulation possibilities of different drugs, three distinct kinds of taxanes were used for encapsulation, and PLGA NPs of various sizes (sub-200 nm) were effectively produced. In cellular experiments, the drug-loaded NPs displayed size-dependent cytotoxicity, regardless of the taxane agent utilized. With this chapter, the selectivity is further expanded based on Chapter 2: Solvent Selectivity.

The last chapter concludes this study with the significance of this research in the field. In addition, some future research is proposed based on the current problems that still need to be solved in this study.

Based on the review and interview of the doctor thesis, this study can be judged to be very significant and valuable from the viewpoints of scientific research and application potential. Ph.D. degree in Engineering should be awarded to the candidate.