博 士 論 文 の 内 容 の 要 旨

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論文題目	Fabrication of biodegradable PHBH-based composite nanofibers and monofilament for wound healing application (創傷治癒のための生分解性 PHBH 複合ナノファイバーとモノフィラメントの作製)

（博士論文の内容の要旨）

This research covered the fabrication and characterization of biodegradable Poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate) (PHBH) nanofibers and monofilament by electrospinning and melt-spinning, respectively.

PHBH is a copolymer, developed from poly[(*R*)-3-hydroxybutyrate] (PHB), the basic homopolymer in PHA, which is a family of polyesters produced by bacterial fermentation. Recently, these materials have attracted much attention for material as medical applications such as skin scaffold, tissue engineering, suture, etc. The use of PHBH polymer has been desirable from the advantages of biodegradable, biocompatibility, and a non-toxic polymer for the human body. Furthermore, the improvement of polymer characteristics is needed, such as mechanical properties, degradation rate, effective acceleration of the wound healing process, etc. In this research, biodegradable PHBH was used as the primary material for producing nanofibers as an artificial extracellular matrix (ECM) and monofilament suture for wound healing and closure applications.

Firstly, PHBH nanofibers was blended with PVA polymer for improving its characteristic as brittle polymer and controlling hydrophobic surface. PVA was chosen due to water-soluble, biocompatible, flexible polymer, and it is also used in a wide range of industrial and medical applications. Then, the characteristics of blend ratio of PHBH/PVA nanofibers (90/10, 70/30, 50/50, 30/70, 10/90) were analyzed. PHBH/PVA blend nanofibers were immiscibility in the crystalline phase and indicated the intermolecular interaction in the amorphous phase. This blending system was also influencing of the stability of the surface nanofiber against water in the ratio of more 50% PHBH content. These nanofibers of pure PHBH and ratio PHBH/PVA of 90/10, 70/30, and 50/50 will expect to be useful material to have the biocompatibility with cell attachment. However, blend nanofibers with PVA-rich content inhibited the growth of the NIH3T3 cells.

In the same way, composite nanofibers are an effective strategy for the delivery of antibacterial reagents or anti-inflammatory drugs. Currently, the conventional synthetic antiseptic (iodine and silver) have combined with materials as wound healing and closure. However, to diminish the risk of sensitization and wound infection due to synthetic antiseptic, I am focusing on developing antibacterial PHBH biodegradable composite nanofibers with natural products such as *centella*, propolis, and hinokitiol. The loading of *centella*, propolis, and hinokitiol have influenced on the surface morphology and fiber diameter of PHBH composite nanofibers. The loading of propolis to PHBH composite nanofibers showed good mechanical properties, increased in crystallinity of PHBH, proved the antibacterial effect, and long release period. The use of hinokitiol in PHBH composite nanofibers demonstrated effective zone inhibition (*E. coli* and *S. aureus*) and a rapid release period. In the case of *centella* incorporated in PHBH composite, it might be necessary to increase the concentration of *centella* if it is used as an antibacterial reagent.

PHBH monofilament was fabricated by the melt-spinning process followed one-step-drawing after isothermal crystallization (IC) near T_g for 24, 48, and 72 h. A feasible way to improve the functionality of suture is the incorporation of natural compounds as antibacterial reagents such as propolis. Various solvents were used to evaluate the penetration of propolis into PHBH monofilaments. The effect of heat treatment by various organic solvent such as acetone, ethanol, hexane, propanol, as well as water and air in physical change of fibers have been studied. The change in shrinkage and diameter fibers was found to be highly dependent on the temperature set up of each solvent.

Ethanol and acetone were chosen as a solvent to prepare propolis solutions as antibacterial reagents. Several important aspects of this study were investigated by the propolis solution penetration, characteristic change in PHBH IC monofilaments by dip-coating in propolis solutions, as well as antibacterial activity. Acetone-propolis (AP) showed excellent penetration into monofilament. However, the dip-coating method at 50℃ affected the physical properties, mechanical properties, and inner structure of PHBH IC monofilaments. From the antibacterial test, PHBH IC monofilaments containing propolis resulted in the inhibitory effect against the growth of *S. aureus.*

As a consequence, in this research, I am successfully developed PHBH-based composites as materials for wound healing application. These promising characteristics of composites were mainly obtained by blend system or loading with natural antibacterial products such as water resistance, high mechanical properties, and delivery of antibacterial reagents of PHBH composite nanofibers. Besides, I also studied PHBH IC monofilaments, which targeted to delivery of an antibacterial reagent to reduce infection on the fast-growing microorganism. Based on my results, the PHBH nanofiber with natural products may be considered to be a better candidate for future *in vivo* or *in vitro* investigation and resolve biocompatibility issues in wound healing application. Furthermore, the information of characteristic change in PHBH IC monofilaments can be the reference for the next research regarding drug delivery or the dyeing process by various using solvent in other fibers.