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Brief communication

Novel composite fiber structures to provide drug/protein delivery for medical implants and tissue regeneration

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Abstract

A novel class of bioresorbable composite (core/shell) fiber structures loaded with bioactive agents was developed and studied. These unique polymeric structures are designed to combine good mechanical properties with a desired controlled release profile, in order to serve as scaffolds for tissue regeneration applications and as basic elements of medical implants. These core/shell fiber structures were formed by "coating" core polymer fibers with drug/protein-containing poly(DL-lactic-co-glycolic acid) porous structures. The shell preparation ("coating") was performed by the freeze-drying of water-in-oil emulsions. Both water soluble and water insoluble agents can be incorporated in these structures and their activity is preserved, since the fiber fabrication requires neither high temperatures nor harsh solvents in the vicinity of the bioactive agents. Examples for release profiles of protein (horseradish peroxidase) and drug (paclitaxel) are presented. We have demonstrated that appropriate selection of the emulsion's parameters can yield a variety of new core/shell fiber structures with desirable drug/protein release behavior. This will lead to the engineering of new implants and scaffolds, and will advance the field of tissue regeneration and medical implants.

Keywords: Drug release; Horseradish peroxidase (HRP); Paclitaxel; Tissue regeneration; Medical implants

1. Introduction

The loss or failure of critical tissues is one of the most frequent and devastating problems in human health care. Tissue regeneration involves the preparation of polymeric structures that serve as degradable scaffolding for bioactive molecules or cells as well as the study of their structure and properties [1]. However, the key problem of how to incorporate bioactive molecules into thin delicate structures that construct devices and scaffolds remains, since they must be incorporated into dense polymeric structures without adversely affecting either the scaffold's properties or the agent's activity. Conventional scaffolds for tissue regeneration are usually composed of bioresorbable fibers that build bulky porous structures. Biologically active molecules are located in the pores, between adjacent fibers. We have developed and studied special implants, made of bioresorbable fibers, in which the biologically active molecules are incorporated within the fibers. Such unique scaffolds are ideal when thin, delicate structures are needed, but they are beneficial also as basic elements of conventional bulky structures, due to better release profile control. They can also be used to build implants that combine drug release with other functions, such as mechanical support.

Few controlled-release fiber systems based on bioresorbable polymers have been investigated to date [2–9]. The two basic types of drug-loaded fibers that have been reported are monolithic fibers and reservoir fibers. In systems that use monolithic fibers the drug is dissolved or dispersed throughout the polymer fiber. For example, curcumin, paclitaxel and dexamethasone have been melt spun with poly(L-lactic acid) (PLLA) to generate drug-loaded fibers [2] and aqueous drugs have been solution spun with PLLA

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[3]. Various steroid-loaded fiber systems have demonstrated the expected first order release kinetics [4–6]. In systems that use hollow reservoir fibers, drugs such as dexamethasone and methotrexane have been added to the internal section of the fiber [7–9]. Advantages of drug-loaded fibers include their ease of fabrication, high surface area for controlled release, wide range of possible physical structures including monolithic and reservoir devices, and localized delivery of bioactive agents to their target. Their disadvantages include poor mechanical properties due to drug incorporation and limitations in drug loading. Furthermore, many drugs and all proteins do not tolerate melt processing and organic solvents.

In the current study we present a new concept of core/shell fiber structures which successfully meets these challenges. In these fibers the drug or protein is located in a separate compartment (a "shell") around a melt spun "core" fiber. The shell is prepared using the "water-in-oil" emulsion freeze-drying technique [10]. This results in good mechanical properties as well as in the desired drug release profile. Two types of systems were investigated, fibers loaded with the water soluble model enzyme horseradish peroxidase (HRP) and fibers loaded with the water insoluble drug paclitaxel. The effects of the emulsion's composition on the release profile of the two active agents are presented in this study, as well as microstructure and tensile mechanical properties.

2. Materials and methods

2.1. Materials

2.1.1. Polymers

Bioresorbable fibers were made of relatively high molecular weight poly(L-lactic acid) (PLLA), RESOMER L210 (inherent viscosity = 3.6 dl/g in $CHCl_3$ at 30 °C), Boehringer Ingelheim, Germany. Ethilon™ W597 nylon sutures were purchased from Johnson & Johnson.

Bioresorbable porous structures (coatings for the fibers) were made of 75/25 poly(DL-lactic-co-glycolic acid) (PDLGA) (inherent viscosity = 0.65 dl/g in $CHCl_3$ at 30 °C, approximately 118,000 g/mole), obtained from Absorbable Polymer Technologies, Inc., USA.

2.1.2. Bioactive agents

Horseradish peroxidase (HRP) with an initial enzymatic activity of 500 U/mg, Aldrich, served as a protein model. Paclitaxel (Genexol™) was purchased from Sam Yang Corp, Seoul, Korea.

2.1.3. Others

A BCA™ Protein Assay Kit was used for measuring the protein content of solutions with a relatively high (20–2000 μg/ml) protein content, and a Micro BCA™ Protein Assay Kit was used for measuring the protein content of solutions with a relatively low (0.5–40 μg/ml) protein content.

2.2. Preparation of core/shell fiber structures

2.2.1. Core fibers

PLLA fibers were melt spun at 190 °C in a batch mode (Alex James, Greer, SC) and then drawn at 70 °C to a draw ratio of approximately 4:1 and used as core fibers for HRP-eluting fibers. Nylon (Ethilon™) sutures were used as core fibers for paclitaxel-eluting fibers. The diameters of both fibers were approximately 200 μm.

2.2.2. Emulsions

PDLGA was dissolved in chloroform to form an organic solution. Double distilled water was poured into the organic solution (in a test tube) and homogenization of the emulsion was performed using a hand-held homogenizer (OMNI TH, 7 mm rotor) operated at 5000 rpm for 3 min. We have previously found that these processing conditions are optimal [11]. For HRP-eluting fibers HRP was incorporated in the water to give an aqueous solution, while for paclitaxel-eluting fibers paclitaxel was incorporated in the organic solution. It should be mentioned that the HRP-containing emulsions are different from paclitaxel-containing emulsions. This is attributed mainly to the fact that HRP is a big molecule and actually acts as a surfactant which stabilizes the emulsion. Also, HRP is a water soluble agent, while paclitaxel is practically water insoluble. Hence, in order to get stable emulsions and also desirable release profiles of both active agents, we had to use different ranges of emulsion formulations (components). For example, relatively high organic:aqueous (O:A) ratios are relevant for HRP-release with relatively small burst effects, while relatively low O:A ratios are relevant for paclitaxel release with feasible rates of release.

2.2.3. Core/shell fiber structures

The core fibers were slightly stretched on special holders and then dip-coated in fresh emulsions and frozen immediately in a liquid nitrogen bath. The holders + samples were then placed in a pre-cooled freeze dryer (Virtis 101 equipped with a liquid nitrogen trap) capable of working with organic solvents (freezing temperature of the condenser, approximately −105 °C), and freeze-dried in order to preserve the microstructure of the emulsion-based core/shell fiber structures. The samples were stored in desiccators until use. The nylon fibers were dipped in 75/25 (v/v) formic acid/ethanol solution for 15 s prior to their coating process, in order to remove their original coat and enable a high quality interface with the shell.

2.3. Morphological characterization

The morphology of the composite core/shell fiber structures (cryogenically fractured surfaces) was observed using a JEOL JSM-6300 scanning electron microscope (SEM) at an accelerating voltage of 5 kV. The SEM samples were Au sputtered prior to observation.

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