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Controlled heparin conjugation on electrospun poly(ε-caprolactone)/gelatin fibers for morphology-dependent protein delivery and enhanced cellular affinity

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ABSTRACT

Electrospun fibrous scaffolds have now been shown to possess great potential for tissue engineering applications, owing to their unique mimicry of natural extracellular matrix structure. In this study, poly(ε-caprolactone) and gelatin were electrospun to fabricate tissue-engineered scaffolds with three different fiber morphologies (1.0 μm, 3.0 μm and co-electrospun containing both 1.0 and 3.0 μm diameter fibers). Subsequently, these scaffolds were conjugated with heparin to immobilize a bioactive molecule by electrostatic interactions. This study determined the quantity of heparin conjugation on the scaffolds and that the crosslinking time and the fiber morphologies govern the extent of heparin conjugation on the fibers. In order to evaluate the release capacity of the heparin-conjugated scaffolds, lysozyme was used as a model protein for conjugation. The heparin-conjugated scaffolds provided high loading efficiency and cumulative release of lysozyme with a relatively linear relationship. In addition, the release kinetics was significantly dependent on heparin conjugation and fiber morphology. This fundamental investigation into how fiber morphology and crosslinking protocols can affect the heparin binding ability of electrospun fibers is crucial for predicting the delivery of many different types of bioactive molecules from an electrospun scaffold for tissue engineering applications.

1. Introduction

Electrospinning technology provides the production of either randomly oriented or aligned fibers with dimensions on the scale of nanometers to micrometers from natural and/or synthetic polymers, and has gained much attention as a potential method for generating scaffolds for tissue engineering and drug delivery [1]. Electrospun scaffolds with a high surface-area-to-volume ratio are well suited for tissue engineering applications because their fibrous structure is very similar to the structure of native extracellular matrix (ECM) [2]. Electrospun scaffolds have been used in a number of different applications, including the engineering of blood vessels [3], tendons and ligaments [4], bone [5] and cartilage [6]. Currently, there has been increasing interest in developing a "smart biomaterial", which would be able to provide not only physical templates for cell accommodation, but also microenvironments that could control cell fate [7]. Such scaffolds would be expected to encourage proliferation and differentiation of cells seeded onto them in vitro as well as enhance the physiological responses needed for tissue regeneration in vivo [1].

Recent research has presented numerous techniques for preparing electrospun fibers and functionalizing them by incorporating diverse bioactive molecules such as growth factors and cytokines. These methods include physical adsorption of bioactive molecules, emulsion electrospinning, coaxial electrospinning and surface modification of the electrospun fibers, followed by chemical conjugation (formation of a covalent bond) of the desired molecule onto the surface of the fibers [1,8]. Physical adsorption is the simplest way to load bioactive molecules onto electrospun fibers and can be achieved by dipping a scaffold into an aqueous, protein-containing solution. However, this method is of limited use, because it often results in uncontrolled release patterns, including an intense initial burst release of the adsorbed moiety [9]. In emulsion electrospinning, bioactive molecules are blended with polymers dissolved in organic solvents prior to electrospinning. The resultant fibers obtained from this method may provide more sustained release kinetics than physical adsorption, because the bioactive molecules are randomly dispersed within emulsion electrospun fibers rather than exposed on the surface of the fibers. However, the bioactivity of these molecules can easily be lost during the preparation of the polymer–protein solution and/or during the electrospinning process, both of which can cause conformational changes to proteins that damage their function. Coaxial electrospinning is a modified version of traditional electrospinning techniques. In this method, two different solutions are fed into the system and are electrospun coaxially and simultaneously to generate a composite "core–shell" structure in which the desired bioactive molecules are entrapped in the core

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