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Research Paper

Protein-loaded emulsion electrospun fibers optimized for bioactivity retention and pH-controlled release for peroral delivery of biologic therapeutics

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ABSTRACT

Biologics are the most rapidly growing class of therapeutics, but commonly suffer from low stability. Peroral administration of these therapeutics is an attractive delivery route; however, this route introduces unique physiological challenges that increase the susceptibility of proteins to lose function. Formulation of proteins into biomaterials, such as electrospun fibers, is one strategy to overcome these barriers, but such platforms need to be optimized to ensure protein stability and maintenance of bioactivity during the formulation process. This work develops an emulsion electrospinning method to load proteins into Eudragit® L100 fibers for peroral delivery. Horseradish peroxidase and alkaline phosphatase are encapsulated with high efficiency into fibers and released with pH-specificity. Recovery of protein bioactivity is enhanced through reduction of the emulsion aqueous phase and the inclusion of a hydrophilic polymer excipient. Finally, we show that formulation of proteins in lyophilized electrospun fibers extends the therapeutic shelf life compared to aqueous storage. Thus, this platform shows promise as a novel dosage form for the peroral delivery of biotherapeutics.

1. Introduction

While the development of biological products has increased dramatically in the last three decades, the delivery of protein therapeutics remains particularly challenging (Mitragotri et al., 2014). Proteins are large macromolecules that require a precise 3D structure to carry out their function. Due to this structural complexity, loss of protein activity can occur in response to a variety of factors that cause protein stress and changes in conformation such as temperature, pH, ultraviolet light, and interaction with organic solvents. In the clinical application of such biopharmaceutics, the route of administration introduces a variety of these unique challenges. Peroral administration, through swallowing of a solution or pill, is one of the most attractive routes for therapeutic delivery, as patient comfort is increased, the use of needles is eliminated, and local delivery to the gastrointestinal tract can be achieved, reducing systemic side effects (Levine and Dougan, 1998). However, peroral delivery of proteins is difficult due to the inherent barrier of the acidic environment of the stomach, which can result in protein degradation, leading to low bioavailability and the need for multiple doses (Goldberg and Gomez-Orellana, 2003; Pawar et al., 2014). Recently, a variety of nanotechnology platforms utilizing biomaterials have been developed to overcome these challenges in biologic formulation and peroral delivery to the gut (Gupta et al., 2013; Yu et al., 2016).

Electrospinning is a technique that has been explored in the pharmaceutical nanotechnology field to develop materials as scaffolds for tissue engineering and for the delivery of small molecule therapeutics (Sill and von Recum, 2008). The electrospinning platform has many advantages compared to other formulations such as particulates, films, and tablets, including the versatility of polymers that can be employed to tailor release kinetics and therapeutic targeting for specific applications, high encapsulation efficiency, which is critical when loading high-cost therapeutics, high surface-area-to-volume ratio for enhanced interaction with the tissue of interest, and ease of production (Agarwal et al., 2008; Hu et al., 2014; Sill and von Recum, 2008). In the last 10 years, electrospun nanofibers have been investigated for the delivery of larger, less stable therapeutics such as protein biologics and have proven to be advantageous in terms of controlled delivery and enhancing protein stability (Ji et al., 2011). While protein encapsulation into nanofibers has been primarily developed for the production of bioactive scaffolds, we expect this platform holds promise for the targeted delivery of proteins to the gut with the proper design and optimization.

Proteins can be loaded into electrospun nanofibers by a method called emulsion electrospinning, which forms core-shell nanofibers

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