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Research Paper

Modulation of the nano-tensile mechanical properties of co-blended amphiphilic alginate fibers as oradurable biomaterials for specialized biomedical application

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ABSTRACT

The modulation of the mechanical properties of monolithic fibers by plasticizing and crosslinking enables the dynamic control of the nano-tensile forces, thereby obtaining optimized Young's modulus and ultimate strain for specialized application in the treatment of periodontal disease. In this work, drug-loaded crosslinked and plasticized alginate fibers (*cl*-PAFs) were prepared by extrusion-gelification with the aim of designing oradurable biomaterials for placement within the periodontal pocket and provide prolonged drug delivery. Mechanical properties of drug-free *cl*-PAFs were determined using a nanoTensile™ 5000 instrument and subsequently optimized versus the quantity of plasticizer and crosslinker as formulation variables employing a Box–Behnken experimental design strategy. Mechanically optimized fibers obtained (Young's Modulus = 314.04 MPa, yield stress = 5.80 MPa, ultimate strength = 10.05 MPa, ultimate strain = 0.29 MPa and toughness = 2.39 J cm^{-3}) were loaded with the model drugs ciprofloxacin and diclofenac both individually and simultaneously. The Young's modulus of *cl*-PAFs loaded with either drug individually exhibited a steep decline. However, in the case of *cl*-PAFs loaded with both drugs simultaneously, Young's modulus regained the original value which may be attributed to the cohesive energy density, porosity and space filling. The effect of various formulation variables on the drug entrapment and release characteristics of the alginate fibers was elucidated at pH 4.0 and pH 6.8. Furthermore, a previously established atomistic computational model based on energy refinements was employed to mechanistically describe the fiber performance. The effect of varying the plasticizer and crosslinking ion concentration on Young's modulus and ultimate strain of the linear elastic polymer matrix and the performance of the ciprofloxacin and/or diclofenac loaded optimized fiber was elucidated and conceptualized using molecular mechanics energy relationships (MMER) via the geometrical conformation and positioning of the molecular architectures.

1. Introduction

Alginate, a well-known biocompatible and biodegradable natural polysaccharide used extensively in the food and pharmaceutical industry, is obtained from brown seaweed such as *Laminaria* sp. and *Ascophyllum* sp. Chemically, alginates are linear block copolymer of uronic acid residues, β-D-mannuronate (M) and α-L-guluronate (G) monomers, connected to each other by a

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1,4-glycosidic linkage (Watthanaphanit et al., 2009). These monomers join to form blocks finally disposing themselves in one of the following patterns: MMMMMM, GGGGGG or GMGMGMGM. This very arrangement of the monomers within these blocks determines the mechanical stability of the architectures formed from this polysaccharide with increased G monomers resulting in high mechanical strength while higher M monomers lead to increased flexibility (Smidsrød and Skjak-Bræk, 1990). Being a natural polymer, it is quite difficult to obtain a certain amount of G and M in a specific pattern and thus to generate an alginate architecture such as films, fibers or scaffolds with desirable mechanical properties for various biomedical applications. In the present study, we designed and evaluated alginate fibers with mechanical properties optimized for their application as an implant for periodontal disease.

A familiar approach for the improvement of rigidity of alginate fibers or films consists of crosslinking two adjacent alginate chains in the presence of multivalent ions. Conceptually, multivalent cations bind to the carboxylic groups on the G monomers on two adjacent chains forming a gelled network (Augst et al., 2006). Various such cations have been tested to date for the extent of their crosslinking ability. Haug and Smidsrød (1965), experimentally determined that the concentration of cations needed to induce gelation and precipitation of sodium alginate prepared from the *Laminaria digitata* and *Laminaria hyperborean* species performs in the following order: Ba < Pb < Cu < Sr < Cd < Ca < Zn < Ni < Co < Mn, Fe < Mg (Haug and Smidsrød, 1965). To describe this pattern and the interaction and placement of the cations in the alginate structure geometrically and conformationally, Grant et al. (1973) developed the "egg-box model" . The model described and simulated the alignment of the polymeric chains into a two-dimensional model in the presence of cations resembling the shape of a corrugated egg box which might be responsible for the rigidity of the alginate gels in the presence of these cations due to space filling phenomenon and various interaction parameters (Braccini and Pérez 2001; Choonara et al., 2008). Specifically, gels crosslinked with barium cations have a higher Young's modulus than the calcium crosslinked gels attributed to a higher crosslinker density (Jejurikar et al., 2011). In a recent study, Kuo and Ma, 2007, reported that for a given multivalent cation, crosslinker density and concentration as well as polymer concentration affected the mechanical properties of the matrix (Kuo and Ma, 2007). Crosslinked alginate matrices form a brittle structure however incorporation of a plasticizer can reduce the interaction between polymer chains resulting in a flexible structure (da Silva et al., 2009). Plasticization of a crosslinked alginate films are reported to cause a reduction in tensile strength with an increase in elongation of the matrix (da Silva et al., 2009; Olivas and Barbosa-Cànovas, 2008). Furthermore, the different molecular compositions of alginate interact with the plasticizer affects the tensile properties of the film. When glycerol was incorporated with alginates of higher G subunits entanglement of the plasticizer within the polymeric matrix occurred while glycerol incorporated with alginates of higher M monomer concentration resulted in more flexible films (Avella et al., 2007).

Periodontal disease (PD) is a worldwide prevalent disease with 10–15% of adults showing signs of advanced disease (periodontal pockets > 6 mm) (Petersen and Ogawa, 2005). PD is a chronic bacterial infection affecting gums and bone supporting the teeth is characterized with cascading inflammatory reactions that if left untreated may lead to the permanent tooth loss. Scaling and root planing (SRP) forms the keystone of periodontal therapy involving the removal of calculus and plaque (Pihlstrom et al., 2005; Ryan, 2005; Chapple, 2009). Multiple clinical trials have proved that SRP may lead to improved clinical outcomes however; it often leaves behind microorganisms leading to recolonization (Ryan, 2005). To counter the later problem, pharmacological therapy is often prescribed in combination with SRP delivering one or more pharmacological agent delivered either systemically or locally within the periodontal pocket.

Fiber composite systems are widely used for their inherent and modifiable mechanical properties which can be employed for specialized applications in the field of biomedical and dental sciences. In a preliminary study, Goodson et al. (1983), performed an extensive experimental study related to polymeric fibers for periodontal delivery of tetracycline using various biocompatible such as polyethylene, polypropylene, polycaprolactone, polyurethane and cellulose acetate propionate. The study proved that monolithic fibers have the potential and required characteristics of a tetracycline delivery system for the treatment of periodontal disease. Agren (1999) cross-linked alginate fibers with zinc ions for wound dressing application wherein the immunomodulatory and anti-microbial effects of zinc ions were also explored. In an another interesting study using metal ions and alginate fibers, Qin, 2005, incorporated fine particles of silver sodium hydrogen zirconium phosphate into alginate fibers to form a highly absorbant antimicrobial wound dressing capable of maintaining the physical structure and silver ion release for a very prolonged time. Furthering the biomedical applications of polymeric fibers, Zilberman et al. (2009), fabricated gentamicin-eluting core–shell bioresorbable composite fibers composed of a polyglyconate core and a porous poly(DL-lactic-*co*-glycolic acid) (PDLGA) shell for wound healing applications.

The present study aimed at the design, development, formulation and in vitro evaluation of a novel polymeric matrix system to deliver an antimicrobial and anti-inflammatory drug over a prolonged period of time for the treatment of PD. The crosslinked plasticized-alginate fibers (*cl*-PAFs) were designed to be placed in the periodontal pocket for site-specific delivery of an anti-inflammatory and antibacterial agent. The model drugs used in *cl*-PAFs were ciprofloxacin, as the model antimicrobial agent, and diclofenac sodium, as the model anti-inflammatory agent. The crosslinked plasticized alginate fibers were designed for placement within the periodontal pocket either around the tooth or overlapping on itself filling the pocket. The periodontal pocket is a narrow sulcus which is formed as free gingiva moves away from the tooth surface, which is approximately 3 mm deep in healthy gums and increases to 6 mm in the presence of PD (Nield-Gehrig, 2007). This relatively small area poses challenges for placement of a "fibre based implant", therefore rendering it necessary to formulate a strong, flexible fiber in the form of *cl*-PAFs, which can be easily handled and effectively and securely placed within the pocket.