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Abstract

Development of a novel coaxial wet-spinning method to produce AAPV-loaded fibers for chronic wound care †

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Abstract: Chronic wounds (CW) are a worldwide concern, causing serious strives on the health and quality of patients' life. In CW, human neutrophil elastase (HNE) enzyme gets highly expressed during inflammation, reaching abnormally elevated concentrations. Additionally, prevalence of Staphylococcus aureus-induced infections remains very high and difficult to treat. Considering these phenomena, a drug delivery system made of co-axial wet-spun fibers, loaded with the tetrapeptide Ala-Ala-Pro-Val (AAPV, a known inhibitor of HNE activity) and N-carboxymethyl chitosan (NCMC, responsive to neutral-basic pH's, characteristic of CW and endowed with antibacterial features), was proposed.

AAPV was synthesized by solid-phase peptide synthesis, whereas NCMC was synthesized from low molecular weight chitosan in a chloroacetic acid mixture. HNE inhibition tests were conducted to establish the AAPV IC50 in 1.50 μg/mL and the NCMC minimum bactericidal concentration (MBC) against S. aureus in 6.40 mg/mL. These determinations were used to establish fiber loading amounts. Core-shell structures were produced with 10% w/v polycaprolactone (PCL) at the core and 2% w/v sodium alginate (SA) solutions at the shell. NCMC was mixed with SA at 2xMBC so neutral-basic pH-triggered solubility (characteristic of CW) would allow pores to be opened in the outer layer for accessing the core, where AAPV was combined with PCL.

Fourier-transform infrared spectroscopy and brightfield microscopy were used to confirm the presence of the four components on the fibers and the co-axial architecture, respectively. Fibers presented maximum elongations of over 100%. Release kinetics studies conducted via UV-visible absorption spectroscopy mapped NCMC liberation overtime but were uncapable of detecting AAPV, since polymer degradation masked AAPV absorption peaks. Time-kill kinetics studies against S. aureus demonstrated the effectiveness of NCMC in eliminating this bacterium, particularly after 6 h of incubation. On its turn, AAPV guaranteed HNE inhibition. Data demonstrated the potential of SA-NCMC-PCL-AAPV co-axial systems to work as stepwise, pH-triggered delivery platforms.

Keywords: wound healing; drug delivery; therapeutic tetrapeptides