Cellulose Acetate in Wound Dressings Formulations: Potentialities and Electrospinning Capability

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Abstract. Any open wound is a potential site for microorganisms' invasion since their presence around us is inevitable. Skin wound healing relies on a series of complex physiochemical processes that remain a big challenge for healthcare professionals, particularly when the wounds are colonized by bacteria. Wound dressings play a major role in wound healing as they manage the wounded site, controlling the moisture balance and protecting the wound from repeated trauma, and by preventing possible infections from developing into more serious complications. Recently, bioactive dressings loaded with drugs and/or antimicrobial agents, allowing for a continuous and sustainable release of these molecules at the wounded site, have appeared in the market. Antimicrobial resistance is a growing health care problem, requiring more effective solutions than antibiotics. As such, nano- and microfibrous mats produced via electrospinning technique and loaded with natural-origin antimicrobial agents have attracted a lot of attention. Various polymers have been applied to engineer nanofibrous electrospun dressings. However, the environment impact of the synthesis and processing methods of synthetic polymers is undesirable. Therefore, the application of cellulose-derived materials (highly abundant polymer of natural-origin) becomes crucial as a green alternative to produce electrospun wound dressings with superior wettability, breathability and high capacity to promote cell proliferation, at relatively low costs. In this paper, different biomolecules loaded onto cellulose acetate (CA)-based polymeric nanofibers were investigated, and their antimicrobial properties were highlighted as alternatives to conventional antibiotics.

Keywords: Natural-origin polymers · Electrospinning · Biodegradable mats · Antimicrobial agents · Bioactive wound dressings

1 Introduction

Fighting wound infections is a major problem in the field of wound care. Infections delay wound healing and may even cause local exudates formation, systemic problems and, in serious cases, threaten the patient's life [1]. An ideal wound dressing must confer protection from external microorganisms and from chemical and physical aggressions,

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as well as to promote the healing process by stimulating cell adhesion, proliferation and differentiation [2]. Nowadays, it is imperative to search for efficient alternatives that reduce microbial resistance and offer a platform that allows for the wound to breath, maintain a moisture balance and absorb exudates. Electrospun nanofibrous dressings with incorporated biomolecules meet all these requirements. These dressings mimic the reticulated extracellular matrix, offering a large surface area with oxygen exchange capacity and exudates absorbency, and promoting connective tissue synthesis and angiogenesis for an enhanced epidermal cell migration and growth [3].

Electrospun dressings have been fashioned using a variety of natural and synthetic polymers. Among those, cellulose acetate (CA), which is the acetate ester of cellulose generated by acetylation of the hydroxyl groups, can be electrospun in the form of ultrafine fibers of sub-micrometer scale with desirable properties for wound healing. CA electrospun fibers have shown high capacity to promote cell proliferation due to their hydrophilicity and bioactivity. Also, CA nanofibers have been characterized as possessing good thermal and hydrolytic stability, chemical resistance and being of low cost [4]. In the following sections, we evaluate the impact of CA-based electrospun nanofibers, modified with active biomolecules, for prospective wound healing applications.

2 Antimicrobial Agents Combined with Cellulose Acetate-Based Dressings

Various biomolecules have been functionalized or incorporated within CA-based electrospun dressings for the treatment of skin wounds, including antibiotics, nanoparticles, plant extracts, proteins, antimicrobial peptides (AMPs), etc. For instance, CA/corn starch dressings have been treated with silver sulfadiazine to prevent a chronic inflammatory response and kill Gram-negative bacteria [5]. Thymoquinone (TQ), a natural antibacterial drug, has been used with CA to prevent common clinical infections and to accelerate the rate of wound closure and re-epithelialization [6]. Antibacterial electrospun nanofibers were also prepared by physically blending polyurethane (PU), CA, zein and streptomycin sulfate. This combination revealed desirable properties of hydrophilicity, excellent cell attachment, proliferation and blood clotting ability, together with good antimicrobial features [1]. Even though successful results have been achieved with antibiotics, in the fight against wound infections, their selective and slow action mode against microorganisms has become a disadvantage. In fact, many organisms are now able to resist their action, the currently known antibiotic-resistant pathogens. As such, new biomolecules have been developed and tested on electrospun polymeric dressings, including nanoparticles (NPs, i.e. silver nanoparticles) and natural extracts/polymers (e.g. honey, essential oils and chitosan) [2].

NPs such as silver (AgNPs), titanium dioxide (TiO_2), and zinc oxide (ZnO) are well known effective groups of antimicrobial agents. However, research has been a bit ambiguous regarding NPs advantages and disadvantages. Studies have shown that NPs display no cytotoxicity towards human cells in low concentrations and possess a lower tendency to induce microbial resistance compared with antibiotics. On the other hand, it has been shown that, based on their size alone, NPs can penetrate the circulatory system and even cross the blood-brain barrier in humans [7]. To prevent this from happening, AgNPs nanocomposite particles have been synthesized with dopamine hydrochloride on top of TiO_2 NPs to obtain an improved anchoring to electrospun CA. The composite nanofibers were found desirable for long-term antibacterial applications, demonstrating excellent infection fighting skills [8]. In fact, CA fibers incorporated only with AgNPs have demonstrated significant antimicrobial action against Gram-negative bacteria *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* and Gram-positive *Staphylococcus aureus* (*S. aureus*) [9].

Various plant-derived essential oils (EOs) have been incorporated in CA-based electrospun nanofibers for topical wound care. CA mats containing EOs have demonstrated high cell compatibility and no cytotoxicity. Low amount of EOs immobilized on CA dressings were seen to exert exceptional growth inhibition of *E. coli*. For instance, rosemary and oregano oils successfully immobilized onto CA-based fibers revealed high antimicrobial activity against both *E. coli* and *Candida albicans* [4]. Curcumin (Curc), a biologically active substance with remarkable antibacterial, antifungal, antioxidant, anti-inflammatory, anticoagulant and antitumor activity has also been encapsulated within CA and polyvinylpyrrolidone nanofibers. Curc-containing mats exhibited antibacterial activity against *S. aureus* and, due to an increase of surface hydrophilicity and programmed control release, were determined effective as wound dressings [10].

More recently, a major advance in the manufacture of wound dressings has been uncovered: the incorporation or functionalization of electrospun mats with AMPs [3]. AMPs are low molecular weight cationic molecules that provide a nonspecific defense against a broad spectrum of invaders, including bacteria, virus, and fungi, with low propensity to induce bacterial resistance. They have been used in different applications, including blood-contacting medical devices [11], and more recently have been identified as potent antimicrobial and regenerative agents for wound healing [3]. AMP coatings are characterized as the new, promising step in the manufacture of bioactive dressings for new generation of acute and chronic wound therapies.

3 Conclusion and Future Work

To prevent common clinical infections various antimicrobial biomolecules have been incorporated into nano- and microfibrous electrospun wound dressings. However, the rising of antibiotic-resistant infection agents has increased the need for more effective therapies, namely the AMPs. Little research has yet been presented regarding AMPs' contribution in wound healing when incorporated onto electrospun polymeric mats. In fact, to our best knowledge, dressings that combine CA-based electrospun mats and AMPs have not yet been explored. Currently, we are developing such tests, incorporating immunoregulatory AMPs within the polymeric matrices of composite electrospun scaffolds mats containing CA. Preliminary data revealed the symbiotic nature of these dressings in both accelerating clotting time and fighting bacterial colonization.

It was also demonstrated the thermal and physical stability of the porous mats and their biodegradability in physiological media. The proposed alternatives aim an accelerated healing but as well the development of clean, safer processing approaches to produce wound dressings with minimal environment impact.

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