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Review article

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A Review of Some Significant Advances in Nano Fibers for Wound Dressings

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Abstract

The article comprehensively reviews the recent trends in use of nano fibers for wound dressings. Globally, chronic wounds impose a notable burden to patients and healthcare systems. Such skin wounds are readily subjected to bacteria that provoke inflammation and hence challenge the healing process. Furthermore, bacteria induce infection impeding re-epithelialization and collagen synthesis. With an estimated global market of $20.4 billion by 2021, appropriate wound dressing materials e.g. those composed of biopolymers originating from nature, are capable of alleviating the infection incidence and of accelerating the healing process. Particularly, biopolymeric nanofibrous dressings are biocompatible and mostly biodegradable and biomimic the extracellular matrix structure. Such nanofibrous dressings provide a high surface area and the ability to deliver antibiotics and antibacterial agents locally into the wound milieu to control infection. Skin and soft tissue infections are major concerns with respect to wound repair. Recently, anti-bacterial wound dressings have been emerging as promising candidates to reduce infection, thus accelerating the wound healing process. This paper presents our work to develop and characterize poly (vinyl alcohol) (PVA) chitosan (CS) silk sericin (SS) tetracycline (TCN) porous nanofibers, with diameters varying from 305 to 425 nm, both in vitro and in vivo for potential applications as wound dressings.

Keywords: Nano Fibre, Wound Dressing, Antimicrobial Agent, Sericin, Biocompatibility, In Vitro, In vivo.

Introduction

Globally, acute and chronic wounds, e.g. burns and diabetic ulcers, respectively, impose a notable burden to patients and the health-care systems. In Europe, there are more than 55 million patients suffering from diabetes, thereof 8 million ones are vulnerable to developing a diabetic foot ulcer. As a consequence of inefficient treatment of such ulcers, annually up to 450,0 0 0 lower limb amputations take place that can cost as much as €2–2.5 billion [1]. The statistic for the US indicates 6.5 million patients whose annual treatment cost is as much as $25 billion [2]. In the case of acute wounds, in the USA, trauma induced wounds that are the most incident one's result in nearly 41 million emergency department referrals and 2.3 million hospital stays. This situation imposes large relevant costs of $670 billion / year including those of health care as well as disability [3]. To alleviate such a costly burden, there is extensive research in progress to develop technologies able to treat wounds effectively in a short time. Appropriate treatment strategies include use of wound dressings with a high healing rate that can hinder infection, prevent the undesired outcomes and lead to reduction of costs.

Physical damage to the skin is a very common injury that occurs over the course of a human's lifespan. Developing novel wound dressing materials is an essential challenge in terms of current medical technological innovation [4, 5]. In new dressing materials manufactured in recent years, biocompatible hydrogels with water uptake absorption capacity are regarded as an appealing choice for functional applications in skin tissue engineering [6, 7]. An ideal wound dressing requires a number of properties, including an appropriate swelling ratio, oxygen permeability, wound exudate absorption, and preservation of moisture in the wound surroundings to enhance wound healing [8, 10].

Antibacterial Hybrid Nano Fibers

Skin wound dressings are a crucial segment of the wound care industry and trade worldwide. The global market of these products is estimated to surpass $20.4 billion by 2021 from $17.0 bil- lion in 2016, due to the rising aging population and increasing incidence of chronic diseases such as diabetes [11]. The wound dressings currently available in the market are typically in the form of hydrogels, films, sponges, and foams. As a relatively new class of wound dressing materials, nanofibers have emerged that offer distinct advantages. Nanofibrous meshes comprising many intersecting nanofibers as small as a few microns to a few hundred nano-

meters can provide a notably large exposed surface area and Nano porosity, thereby facilitating interaction with the cells avail- able in the wound bed through an extracellular matrix (ECM) mimicking structure [12]. While nanofibers can be produced via several methods such as drawing, template synthesis, phase separation or self-assembly, electrospinning is a superior technique due to its simplicity, cost efficiency, and versatility [13, 23]. The drawing method, fabricating individual long nanofibers, is restricted to viscoelastic materials able to tolerate large deformations while re- mining cohesive to resist against pulling stresses. Employing a Nano porous template, the template synthesis allows for production of solid/hollow yet discontinuous individual nanofibers. More- over, the time consuming phase separation method comprises stages of dissolution, gelation, extraction by another solvent, free-zing, and drying, leading to formation of a nanoporous foam. Self- assembly methods are also time consuming techniques wherein single, building blocks are arranged as particular configurations to offer desired functions [24]. In comparison to the golden benchmark for wound dressings including films, foams, and micro fibrous and mesh ones, nano fibrous dressings usually exhibit higher porosity thus allowing more efficient permeability for water and oxygen, and superior inter- change of nutrients as well as exclusion of metabolic wastes [25]. Also, nanoscale fibers, conferring the dressing small interstices and high surface area, can enhance hemostasis. Not only the small pore size of nanofibrous dressings protects the wound against bacterial infection and cell/tissue ingrowth, also advantageous over the micro fibrous and mesh commercial counterparts, nanofibrous dressings can provide excellent conformability, thus a better coverage and protection of the wounds from infection [26]. Most significantly, compared to commercial dressings, the expansive surface area of nanofibrous dressings enables efficient loading incorporation of drugs. Thus, they show a promising potential for development of advanced, biologically active dressings. Such capability of nanofibers has become highly attractive in the biomaterials sector leading to a vast research effort, as documented by several relevant reviews in recent years [27-38. Different to those publications, specifically, we focus here only on biohybrid nanofibrous wound dressings based on biopolymers combined with anti-bacterial agents in diverse modes. These advanced classes of anti-bacterial nanofibrous dressings can potentially replace their established counterparts, that are antibiotic delivery nanofibrous systems, given the expanding concern about the increase of antibiotic resistant bacteria. In this context, depending on the type of the antibacterial agent incorporated, being nanoparticles, organic macromolecules (peptides or amino acids), and nature (e.g. plant) derived compounds, nanocomposites, bio functionalized, and blend systems, respectively, are introduced. As a specific highlight, in this review we evaluate the most relevant studies published since 2015 and unravel the latest status of research in this area.

Electrospun nanofibers have shown promising potential for a diverse range of advanced applications in environmental remediation, energy, and biomedicine. This attractive potential stems from a number of advantages including interconnected tunable porosity, biomimicry, and large specific surface area enabling engineering of the surface to include a plethora of functional groups as well as immobilization of drug molecules. These features have drawn the attention of the scientific community for the purpose of developing nanofibrous biomedical devices such as wound dressings. Given the large incidence of acute and chronic wounds across the world, the necessity of production of nanofibrous wound dressings able to control infection by releasing bactericidal agents and to block invasion of microbes is felt nowadays more than ever. Despite promising wound healing outcomes in terms of re-epithelialization, angiogenesis and antibacterial activity, nanofibrous wound dressings should be still improved in the following different aspects: 1- Composition: In terms of chemistry and composition, biopolymers that are biocompatible and induce anti-inflammatory and antibacterial properties, thereby accelerating wound healing, are preferred for nanofiber synthesis. Despite favorable potential of interactive biopolymeric nanofibrous dressings for wound healing, verified through many related studies, to the best of the authors' knowledge, there is no commercial product of them in the market. This arises from possible com- plications of electrospinning of biopolymers in a large scale, and biocompatibility concerns due to the existence of impurities such as cross-linkers and residual solvents in the fibers and the likely immunogenic reactions induced by such com- pounds. Specifically, biopolymers like chitosan and gelatin are hardly water soluble, thus for electrospinning they need to be dissolved in toxic, highly acidic solvents including 1,1,1,3,3,3-hexafluoro-2-propanol and trifluoroacetic acid (TFA) [39]. To acquire antimicrobial effect, the nanofibers should be equipped with secondary agents (additives) such as AMPs, metallic ions and nanoparticles, antibiotics, or plant-derived compounds, as discussed in this article. Taking into consideration the rapid evolution of antibiotic resistant bacteria, research is being carried out to develop alternatives to conventional drug delivery nanofibers, for example considering AMP functionalized ones. Recalling the hazardous dissolution and release of metallic (e.g. Ag) ions, if exceeding the WHO limits, both AMP functionalized nanofibers and plant-derived biohybrid nanofibers appear to be suitable substitutes for conventional drug delivery de- vices. However, long term in vitro and in vivo investigations of such systems are still demanded to guarantee their efficiency within the course of the wound healing process. To promote the wound healing effect, supplementary compounds such as growth factors, metallic ion delivering materials, etc. could be also embedded into the nanofibers. Furthermore, it is known that acidification of the wound milieu can accelerate the healing process, thus inclusion of various agents that help acidify the wound bed is another helpful strategy. Also, from the com- position point of view, a state of the art class of smart nanofibrous wound dressings can be defined as those releasing anti-microbial agents and drugs when subjected to different stimuli including pH and temperature. This class of dressings has been rarely developed and studied and as prospective wound healing materials they should be further considered. Lastly, synthetic, industrial polymers could be also proposed for construction of wound dressings, provided that they show no toxicity effects. Such materials are promising due to their widely known processing methods, favorable physicochemical properties, the possibility of integration into engineered structures, and potential for scalability. These merits can be appealing for the development of wound dressing materials widely and economically. However, bio inertness is indeed a challenge that can complicate the removal process of the dressing upon healing of the wound. To address this bottleneck, a surface treatment involving biodegradable materials as a coating can be a solution. 2- Synthesis: With respect to antibacte-

rial nanofibrous wound dressings, many antibiotics and anticancer drugs as well as antimicrobial agents have been conveniently incorporated into electrospun polymeric nanofibers for local delivery [40, 41]. Traditionally, incorporation of such compounds into nanofibers is done via blending them into the polymer, followed by electrospinning of the blend or core-shell electrospinning wherein the drug/agent is located within a polymeric outer shell. In the former method, drugs or antimicrobial materials would loosely reside at the surface of the nanofibers, resulting in an unwanted burst release, thus imposing cytotoxicity toward tissue cells. In the latter one, involving high voltage and high shearing forces exerted at the interface between core and shell fluids, proteins could be rapidly dehydrated and delicate bioactive agents harmed. Thus, there is a need to develop alternative methods allowing for sustained delivery of antibacterial agents without damaging them. Despite versatility of electrospinning for production of nanofibers in different compositions and configurations, creation of an effective, reliable formulation for such bio hybrid nanofibers is intricate. In this regard, the technique must be widely, yet precisely understood and standardized, particularly in the sophisticated versions of emulsion and coaxial electrospinning. Additionally, the production level of any desired formulation must be largely developed up to industrial scale. Hence, the production cycle must be economical and scalable, particularly considering the relatively low price of many avail- able commercials wound dressings. 3- Design and engineering: Structurally, nanofibrous dressings need to be engineered so that either entrap bacteria or block their pathways into the wound. Moreover, coupled with nanoparticles, they can form a hierarchical nanostructure, whose nan- topography can potentially raise surface hydrophobicity thus lowering the chance of bacterial adhesion. As a result, biofilm formation and its adverse consequences can be drastically reduced. Moreover, nanofibrous dressings must hinder tissue in- growth into the structure, enabling its easy and painless removal while encouraging cells to adhere and proliferate. Moreover, the dressing must be sufficiently porous and permeable to allow exchange of air and water vapor as well as nutrients and waste. On the other hand, such extent of porosity should not lead to loss of mechanical stability and pliability of the dressing. Given the diverse stresses applied to the dressing de- pending on its location and intended use duration, mechanical fatigue could be a crucial consideration as well. The dressing needs to adequately remove exudates, thus in addition to porosity, surface chemistry could play a vital role. 4- Multifunctionality: As a further necessity, the real-time monitoring of the wound bed conditions in terms of pH or temperature is a sophisticated challenge. Such parameters potentially indicate the wound healing status and they need to be assessed precisely and in the point of care. For this purpose, various classes of biosensors should be integrated into nanofibrous wound dressings and an advanced generation of smart devices, that are able to real time sense and monitor the wound conditions, should be developed. Accordingly, as an all in one package, multifunctional dressings are required that can treat various classes of chronic wounds while notably declining the infection tendency and wound recurrence [42]. In fact, knowledge frontier should be pushed towards creation of dressings that merge three crucial functions, Fig. 11: (i) stimulating the healing process through the main, relevant physiological mechanisms and even by inclusion of further functionalities such as electrical responsiveness; (ii) monitoring the wound healing and infection indicators such as temperature, pH, and bacteria; and (iii) drug delivery in a controlled manner if wound in- fiction emerges. A nanofibrous wound dressing fulfilling these concerns guarantees not only fast healing of a wound but also avoids infection occurrence. Moreover, the treatment cycle and duration could be predicted and controlled over time by providing diverse readouts by the integrated biosensor concerning wound healing status, exudate amount, infection, and lifespan of the dressing. 5- Testing: Alongside production, advanced testing approaches for the developed nanofibrous systems must be designed and verified to enable reliable evaluation and prompt translation of these devices to clinical applications. For instance, to determine the clinical potential of such dressings, the in vitro interaction of the nanofibers with cells must be investigated in the presence of bacteria to simulate realistically the conditions of the wound beds. Surprisingly, almost no research in the literature has considered this important characterization involving bacteria and cell co-cultures. The achieved information can shed light on the adhesion and growth mechanisms of bacteria onto the nanofibers, thereby enabling physically or chemically adjustment of their characteristics to overcome microbial challenges. Consequently, the impact of nanofibrous dressings on dermal cells in the presence of bacteria should be largely investigated to assure applicability of the dressings in micro biological environments similar to those of real wounds. Certainly, depending on the type of wound, involving various specific biological factors, and its chronicity, in vitro tests need to be customized. In addition to the development of advanced biological testing, physicochemical characteristics must be investigated under realistic conditions in terms of pH, humidity, temperature, mechanical and thermal stress magnitude and frequency to simulate the practical situation. In this case, it is necessary to follow the designed standards for such kind of materials to enable comparison with the available benchmarks and to verify their modifications.

Use of PVA/CS Nanofibres with Sericin

This paper describes the development of wound dressings composed of silk sericin (SS), a natural protein biomaterial and bioactive compound that does not require extra functionalization [43, 47]. Silk sericin is a glycoprotein that comprises nearly 30% of the mass of silk cocoons and is generally a waste product of the textile industry [48]. Silk sericin has also been explored as a serum alternative on account of its bioactivity with respect to improving cell adhesion and promoting cell proliferation, biodegradability, and antibacterial activities [49,50]. However, neat sericin does not possess suitable properties due to its fragile nature [51]. Thus, it is crucial to improve the mechanical characteristics of sericin to broaden its potential applications. Blending with other polymers is one the best methods to enhance the mechanical characteristics of sericin [52]. Polyvinyl alcohol (PVA) is a synthetic polymer that possesses a variety of remarkable properties, such as biocompatibility, chemical stability, affordability, and outstanding film forming ability, and is often blended with natural polymers to increase their mechanical performance [53, 54]. Chitosan (CS) is another appealing polymer as it possesses structural likeness to extracellular matrix (ECM) and anti-bacterial activity, and thus can assist in enhancing the effectiveness of ECM in skin tissue engineering [55, 58]. Blending of sericin and PVA can improve the mechanical characteristics of sericin while preserving the swelling capacity of chitosan, hence expanding the utilization of sericin in biomedical

fields as a drug carrier, antibacterial agent, and wound dressing [59]. Gilotra designed biopolymer nanofibers composed of PVA and SS with a wide range of porous structures for wound dressing and demonstrated greater attachment and proliferation of PVA/SS mats than neat PVA mats. Shi et al. [60] reported that the water uptake capability and swelling ratios of poly (γ-glutamic acid) hydrogel containing SS increased with SS concentration. Likewise, incorporation of SS into the hydrogel improved the adhesion and growth of L929 cells. A number of studies [61, 62] demonstrate that nanofibers containing sericin have the ability to rebuild epidermal-dermal tissue, thus resulting in skin tissue regeneration and wound repair, and therefore the idea to prepare nano fibers containing sericin with enhanced biological properties, mechanical characteristics, and antibacterial performance for wound dressings is appealing. Drug incorporating biomaterials also provide a valuable opportunity to deliver medications to specific locations. Indeed, tetracycline (TCN) can be incorporated into nano fibers to impede bacterial infections and has the capacity to promote the body's protection mechanisms to eliminate the bacteria that might result in infection [63, 64]. Yang et al. proposed a sericin-based nanocomposite hydrogel with substantial antibacterial performance for wound dressing, revealing that the macromolecular sericin within the nano composite attracts bacteria through charge interaction. Chao et al. [65] studied the antibacterial performance of sericin/PVA-based fibers and showed that the incorporation of tigecycline into the fibers leads to increased inhibition zones and significant antibacterial performance toward Escherichia coli and Bacillus subtilis. Therefore, the fabrication of nano fibers containing sericin with good mechanical and swelling properties, biocompatibility, and antibacterial performance has attracted considerable attention for wound dressing. In this study, PVA/CS/SS-TCN nano fibers were fabricated via electrospinning and subsequently examined both in vitro and in vivo for their potential in wound healing with the topical delivery of an antibiotic.

In this study, sericin-tetracycline (SS-TCN) was successfully incorporated into poly(vinyl alcohol) chitosan (PVA/CS) nanofibers using electro spinning technology. The novel nano fibers containing sericin were continuous, with a uniform diameter distribution between 305 and 425 nm [66]. Furthermore, increased SS content led to an increase in the swelling capacity and flexibility but a decline in mechanical strength. In vitro cell investigations demonstrated that nano fibers with low sericin content display considerably greater adhesion and higher proliferation potential for L929 cells in comparison to nano fibers without sericin (PVA/CS). In addition, the nanofibers loaded with SS-TCN demonstrated excellent bactericidal performance toward both Gram positive and Gram-negative bacteria, with better reduction at more elevated concentrations. In vivo results indicated that the application of the PVA/CS/2SS-TCN nanofiber results in skin repair along with epithelialization and formation of compact collagen fibrils; this further confirms the benefits of employing the PVA/CS/2SS-TCN nano fiber over traditional clinical gauze for wound dressing applications.

Conclusion

In this regard, with the dangerous evolution of antibiotic resistant bacteria, antibiotic delivery systems are being gradually replaced with antibacterial biohybrid nanofibrous wound dressings. This emerging class of wound dressings comprises biopolymeric nanofibers containing antibacterial nanoparticles, nature-derived compounds and bio functional agents. Here, the most recent (since 2015) developments of antibacterial biopolymeric nanofibrous wound dressings, particularly those made of bio- hybrids, are reviewed and their antibacterial efficiency is evaluated based on a comprehensive literature analysis. Lastly, the prospects and challenges are discussed to draw a roadmap for further progresses and to open up future research avenues in this area. With a global market of $20.4 billion by 2021, skin wound dressings are a crucial segment of the wound care industry. As an advanced class of bioactive wound dressing materials, natural polymeric nanofibers loaded with antibacterial agents, e.g. antimicrobial nanoparticles/ions, nature-derived compounds and bio functional agents, have shown a remarkable potential for replacement of their classic counterparts. Also, given the expanding concern regarding antibiotic resistant bacteria, such biohybrid nanofibrous wound dressings can outperform classical drug delivery systems. Here, an updated overview of the most recent (since 2015) developments of antibacterial biopolymeric nanofibrous wound dressings is presented. In this review, while discussing about the antibacterial efficiency of such systems, the prospects and challenges are highlighted to draw a roadmap for further progresses in this area. The fabricated nanofibers possess a considerable capacity to take up water through swelling (325–650%). Sericin addition leads to increased hydrophilicity and elongation at break while decreasing fiber diameter and mechanical strength. Moreover, fibroblasts (L929) cultured on the nanofibers with lows ricin content (PVA/CS/1-2SS) displayed greater proliferation compared to those on nanofibers without sericin (PVA/CS). Nanofibers loaded with high sericin and tetracycline content significantly inhibited the growth of Escherichia coli and Staphylococcus aureus. In vivo examination revealed that PVA/CS/2SS-TCN nano fibers enhance wound healing, repithelialization, and collagen deposition compared to traditional gauze and nano fibers without sericin. The results of this study demonstrate that the PVA/CS/2SS-TCN nano fiber creates a promising alternative to traditional wound dressing materials.

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