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# Biodegradable, spun nanocomposite polymeric fibrous dressings loaded with bioactive biomolecules for an effective wound healing: A review

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**Abstract.** In recent years, spinning techniques have been highlighted for their capability of producing complex, fibrous and reticulated constructs with great potential for biomedicine. Indeed, biodegradable constructs based on polymeric fibers are desirable in wound healing due to their large surface area, interconnectivity, open pore structure, and controlled mechanical strength. Modern dressings made of spun biopolymers can incorporate active compounds within their matrix, which can be delivered topically, very beneficial to the healing process. In the present work, we explore the spinning techniques used to process polymers in the form of fibers, assess the properties of some of the most common biodegradable polymers used in wound dressing production, and highlight the potentialities of important biomolecules used in the production of new generation of bioactive wound dressings.

## 1. Introduction

For many years, the use of artificial fibrous structures was restricted to applications in clothing and decoration. In the past century though, fiber constructs made breakthroughs in engineering with applications in filtration, composite fabrication, energy systems, microfluids and even medicine [1]. In fact, fibers manufactured as mono- or multi-filaments quickly became very useful in medicine regenerative, particularly in skin management and treatment.

Biotextiles based on natural and synthetic fibers are highly desirable in tissue engineering. They are defined as ‘‘structures composed of textile fibers and designed for uses in a specific biological environment, where their performance depends on their interactions with cells and biological fluids as measured in terms of biocompatibility and biostability’’ [2]. Depending on their production and arrangement processes, fibers can be knitted, braided, woven and nonwoven, in aligned or random way, to produce complex structures with tuned flexibility, surface area, porosity and mechanical performance [3]. Wound dressing design and production follows these same principles. However, aside from protecting the wound, an effective and functional wound dressing should also take into consideration the wound type and the healing time, so the highest healing rate and the best aesthetic repair is attained in the shortest period possible [4]. In recent years, known spinning techniques have been highly sought to produce fibrous dressings with large surface area for wound healing. Indeed, polymeric constructs in the form of films, mats or even scaffolds have been spun and functionalized with active biomolecules, giving rise to a new generation of wound dressings, the bioactive [5,6].

In the present work, we highlight the most important spinning techniques and polymers (natural and synthetic) applied to the production of wound dressings and offer some examples of the many

potentialities of these constructs. Surface functionalization methods and the most desirable biomolecules in wound healing are also analyzed. This work focuses on the use of biodegradable polymer nanocomposites. Contrary to non-biodegradable polymers, which are formed of long chains of C and H atoms that form inter-atomic bonds very difficult to break, biodegradable polymers get decomposed under aerobic or anaerobic conditions, in result of microorganism and enzymes actions.

## 2. Production of fibrous dressings via spinning techniques

For many years, man-made fibers have been part of our quotidian. Yet, it was only in the last 50 years that efforts have been devoted to the understanding of the fundamental theories behind fiber production, required for the development of complex fibrous systems for biomedical uses. Between the many spinning techniques used to produce polymeric fibers, the following four can be highlighted. Melt spinning is perhaps the preferred method due to the simplicity of polymer processing, as it does not require any solvents. Yet, the electrospinning technique has gained more attention in wound healing due to the structural similarities between the electrospun mats and the extracellular matrix [7].

### *2.1. Melt spinning*

This spinning technique allows the production of customized fibrous constructions, including mono- and multi-filaments, by melting polymer granules at high temperatures and then by drawing the extruded polymer through the spinneret, followed by fiber solidification via rapid quenching or gradual cooling. Mel spinning can only be applied to polymers that resist thermal degradation, i.e. polyethylene terephtalate (PET), starch–polycaprolactone (PCL), poly (L-lactic acid) (PLLA) and poly(lactic acid) (PLA), for instance. Melt spinning is an efficient method to combine two or more polymers to produce fibers without concerns with polymer solubility or solvent miscibility. The polymers' molecules interact via collision during movement and establish interactions via secondary forces such as hydrogen bonding, dipole, ionic or van-der Waals forces. By varying the processing parameters, it is possible to fabricate fibers in the range of few micrometers with tailored morphology, diameter, cross-section and texture. Also, the mechanical properties can be improved at the spin-line by heat treatment or at the drawing and winding station [8-11].

### *2.2. Wet spinning*

Wet spinning is based on the principle of precipitation, in which mass transfer of both solvent and polymer must be considered. It produces fibers of diameters between 30 and 600 μm by extruding the polymeric solution through the spinneret directly into a liquid bath of a poor or non-solvent. This triggers polymerization while drawing off to form long fibers. The coagulation bath removes the solvent as the filaments solidify (from the surface to the core). A diffusional interchange between the newly formed filaments and the coagulation bath causes the bath components to diffuse into the polymeric filament, rendering it insoluble by chemical reaction, and the solvent to diffuse out of the fiber. Alginate, collagen, chitosan, PCL and many of their composites have been processed in the form of fibers using wet spinning, for a variety of tissue engineering uses. Because of the fibers relatively larger diameters (in the micrometer range), fibrous constructs are fashioned with intrinsically high porosity (larger pore size) and interconnected open pore structure, which are desirable for cell penetration, adhesion and proliferation [12-14].

### *2.3. Dry spinning*

In dry spinning, a bi-component system of polymer and solvent is employed. Here, production of filaments is function of both gas temperature and polymer concentration and is coupled to the mass transfer mechanisms of solvent evaporation. The solution containing the polymer (the also known spin dope) is processed and filtered to achieve the right consistency and viscosity, and then is forced at a controlled rate through a fine jet (spinneret). The polymeric solution solidifies as the highly volatile solvent evaporates. As a binary system, mass transport must be considered inside the filament, as a molecular diffusion process, and at the boundary, as the interphase mass transfer of solvent vapor.

Conventional and less conventional polymers like cellulose acetate, polymers and co-polymers of vinyl chloride, PLLA, and dibutyrylchitin have been processed by extrusion into a hot gas stream. Dry spinning is a common alternative for polymers vulnerable to thermal degradation [15-17].

*2.4. Electrospinning*

Electrospinning is extensively used for fiber production of thinner diameters, 2 nm to several micrometers, and large surface area. In electrospinning, fibers are produced from a polymeric solution pumped at constant rate through a syringe or capillary tube that is subjected to an electrical field, which once reached a critical value surpasses the surface tension and extrudes the solution in the direction of the collecting plate. As the fibers are extruded, they assume a conical shape, known as the Taylor cone. It elongates, subdividing into nanofiber jets that are collected at an optimal distance, while the volatile organic solvent evaporates. The electrospinning technique allows for fibers to be formed in the submicron range with extremely high surface-to-volume ratio, tunable porosity and malleability, interconnected open pore structure, and desirable composition. This is perhaps the most important spinning technique in wound dressing production. Its reticulated network of fibers allows for a breathable dressing to be formed, with a structure that resembles closely the extracellular matrix, this way facilitating tissue regeneration [5,6].

## 3. Biodegradable polymers

For many years now, biodegradable polymers (hydrolytically and enzymatically degraded) have been used for biomedical applications. In wound healing, biodegradable polymers are required to exhibit specific properties: do not instigate or induce a toxic response upon use; present an acceptable shelf life; degrade at a rate that matches the regeneration process; possess appropriated mechanical properties that vary with degradation in a proportion compatible with regeneration; do not produce toxic degradation by-products; and are permeable and easily processed [18].

**Table 1.** Biodegradable synthetic polymers: physical and mechanical properties [20-23].

| Polymer | Melting Point (ºC) | Glass Transition Temperature (ºC) | Tensile Modulus (GPa) | Elongation (%) | Degradation time (months) |
|---|---|---|---|---|---|
| Polycaprolactone (PCL) | 58 - 63 | (-65) - (-60) | 0.2–0.4 | 300–1000 | > 24 |
| Poly(glycolic acid) (PGA) | 220 - 233 | 35 - 40 | 6.0 - 7.0 | 1.5 - 20 | 6 - 12 |
| Poly(lactic-co-glycolic acid) (PLGA) | Amorphous | 45 - 55 | 1.4 - 2.8 | 3 - 10 | 1 - 12 (adjustable) |
| Poly(lactic acid) (PLA) | 150 - 162 | 45 - 60 | 0.4 - 3.5 | 2.5 - 6 | > 24 |
| Poly (L/D-lactide) (PLLA or PDLA) | 170 - 200 | 55 - 65 | 2.7 - 4.1 | 3 - 10 | > 24 |
| Poly (DL-lactide) (PDLLA) | Amorphous | 50 - 60 | 1 - 3.5 | 2 - 10 | 12 - 16 |

Degradation of synthetic and natural polymers requires cleavage of bonds sensitive to hydrolytic or enzymatic action. Synthetic polymers are characterized by predictable properties and a certain uniformity in site-to-site and patient-to-patient outcomes. They can be processed with specific properties that respond to specific demands or application requirements and are most of the time hydrolytically degraded. Compared to polymers susceptible to enzymatic degradation, those hydrolytically degraded are preferred due to the predictability in body response. Table 1 provides a list of some of the most common synthetic biodegradable polymers used in wound dressing production and their inherent properties, including average degradation rates (time to complete resorption) [19].

PCL is a hydrophobic, semi-crystalline, linear resorbable aliphatic polyester, obtained by either ring-opening polymerization of -caprolactone or via free radical ring-opening polymerization of 2-methylene-1-3-dioxepane. Its biodegradation is associated with its aliphatic ester linkage susceptibility to hydrolysis. Poly(glycolic acid) (PGA) is a highly crystalline, biocompatible polyester with good mechanical features and degradation profile, and low solubility in organic solvents. PGA has been used for a variety of purposes including bone fixation devices, drug carriers and scaffolds. PLA is a biodegradable, aliphatic polyester derived from lactic acid. It is a versatile polymer made of renewable materials, i.e. corn starch or sugar cane, that can be fermented into lactic acid and prepared via cyclic dilactone, lactide, ring-opening polymerization. By varying the ratios between its copolymers PGA and PLA, the poly (lactic-co-glycolic acid) (PLGA) co-polymer offers a wide range of degradation rates. Its degradation kinetics is governed by both the hydrophobic/hydrophilic balance and crystallinity, which makes PLGA particularly desirable for medicine regenerative. PLA exists in two stereoisomeric forms giving rise to PDLA and PLLA, two stereoregular polymers, and PDLLA, a racemic polymer obtained from the mixture of D- and L-lactic acid. PDLLA is an amorphous polymer commonly used for drug delivery due to its ability to disperse homogeneously the active species within a monophasic matrix [20-23].

Regarding natural polymers, the majority degrades via enzymatic degradation. The rate of degradation dependents on the application site, accessibility to and concentration of enzymes, and possible chemical alterations made to their structure. They are also susceptible to cell-triggered proteolytic degradation. Natural polymers are classified as polysaccharides, such as alginate, cellulose and chitosan, and as polypeptides, that include collagen and gelatin. Alginate is a polyanion, typically obtained from brown seaweed, that possesses solubility in water, great biocompatibility, low toxicity and is of relatively low cost. Its physical and mechanical properties are dependent on the length, molecular weight and proportion of the guluronate block within the polymeric chain. Cellulose is an abundant polysaccharide based on glucose, that is present in plants, bacteria, fungi, algae and animals. Cellulose can also be biosynthesized by bacteria in the form of bacterial cellulose. It exhibits a unique nanostructure, remarkable physical-chemical properties and biocompatibility and is resistant to hydrolysis, strong alkali and oxidizing agents. Chitosan, derived from partially deacetylated chitin, is composed of D-glucosamine and N-acetylglucosamine repeat units, forming the only pseudonatural cationic polymer. By varying the degree of deacetylation, viscosity and molecular weight, a series of chitosan polymers may be generated. Chitosan is known for its biocompatibility, biodegradability, antimicrobial activity, and wound healing abilities. Collagen is the most abundant mammalian protein, accounting for around 30% of all body proteins, and a major component of ligaments, tendons, skin and bone. It is a good surface-active agent and is capable of penetrating within lipid-free interfaces. It is desirable in many biomedical applications because of its biodegradability, weak antigenicity and superior biocompatibility compared with other natural polymers, i.e. gelatin. Gelatin is a natural polymer derived from the controlled structural and chemical degradation of collagen. Gelatin contains many functional groups and cell binding sites in its structure, increasing its cell binging ability. It is very common in the production of biocompatible and biodegradable drug delivery systems [24-28].

## 4. Functionalized biomolecules and their effect in wound healing

Skin is the largest organ in the body, formed mainly of two layers, the epidermis and the dermis, and primarily serving as a protective barrier against the environment. Skin wounds normally heal in the predictable amount of time by forming an epithelialized scar tissue. However, whenever burns, trauma, irreversible damaged skin or chronic wounds occur, the need for substitutes or more efficient protective barriers is raised. Engineered skin tissue and high-performance wound dressings are an excellent solution. Although allografts and autografts have been the most recurrent choice in the past, temporary 3D constructs mimicking the skin architecture and loaded with fibroblasts, keratinocytes and endothelial cells or bioactive biomolecules have gained more attention [5,6].

Biodegradable fiber-based structures have been proposed for the healing of dermal and epidermal injuries. In fact, PLGA fibrous dressings have been already successfully used in clinical patients

diagnosed with diabetic foot ulcers (i.e. Dermagraft and Dermagraft-TC) [3]. Thin biodegradable hybrid meshes of PLGA and collagen have also been produced for culture of human skin fibroblasts. Results indicated the web-like collagen formations distributed along the PLGA knitted fibers increased the fibroblasts seeding and distribution and facilitated rapid formation of dermal tissue with uniform thickness [29]. Recently, Norouzi *et al* produced nanofibers of PLGA and gelatin via electrospinning and demonstrated desirable bioactivity and hemostasis of the fibrous scaffolds with controlled release of the protein [30]. Electrospun PLGA nanofibers have also been encapsulated with epidermal growth factors (EGF) resulting in desirable biocompatible and bioactive scaffolds with EGF controlled release [31]. Collagen-based scaffolds have been the most popular for skin regeneration both alone or in combination with other polymeric matrices or molecules (growth factors, proteins, etc.). For instance, dermal substitutes composed of type I collagen and elastin hydrolysate, applied in combination with split-skin mesh grafts contributed to the healing of full-thickness wounds [32] and improved dermal regeneration [33]. It has also been shown that preparations of collagen type I and PCL result in optimal degradation kinetics and mechanical performance while supporting dermal fibroblasts attachment and proliferation. Developing a porous structured expedited the healing process, assisted in re-epithelialization and follicle regeneration, and promoted the formation of dermal tissue with a matrix architecture resembling normal, unwounded skin [34]. Additionally, they revealed these microporous electrospun constructs pre-seeded with fibroblasts to promote greater wound healing than acellular scaffolds [35].

Synthetic biodegradable polymers have been used as matrices for skin regeneration both individually and in combination with other natural origin polymers, and more recently have served as base substrates for the incorporation of bioactive molecules. Kenawy *et al* were the first to report the incorporation of antibiotics within nanofiber meshes produced via electrospinning [36]. Since then, more reports on the antibacterial performance of immobilized antibiotics onto PLA, PCL or PLGA nanofibers have been published [37,38]. As the incorporation of bioactive molecules affects the polymer spinnability, more complex systems have been developed; for instance, two stream electrospinning setups have been engineered so the influence of the antibiotic was only seen in one layer of the composite mat and, hence, the elasticity and tensile strength were maintained while the antibacterial performance was enhanced [39]. Biocides, such as QACs, triclosan and chlorhexidine, have also been applied to conventional fibers and textiles for antibacterial purposes. Even though they are not recommended for skin care, they are quite useful in hospital environments [40]. Metal oxide nanoparticles (NPs) have long been known as effective antibacterial agents for medical applications. Silver (Ag), zinc oxide (ZnO) and titanium dioxide ($TiO_2$) NPs are perhaps the most common and widely studied. AgNPs have attracted interest in wound healing for their large surface area and strong and broad-spectrum of antimicrobial action. They have been loaded onto PCL, PVA, PLGA, chitosan or gelatin for topical and systemic administration with successful results against both Gram-positive and Gram-negative bacteria [41-43]. However, with the rising of antibiotic resistant pathogens and the increasing concern over the impact of NPs in the environment, new alternatives have been researched.

Antimicrobial peptides (AMPs) form an integral part of the innate immune system, working as a defense mechanism in multicellular organisms to control microbial proliferation and modulate the host's response. AMPs are low molecular weight molecules, often cationic, composed of 5-100 amino. Because of their amino acids-based composition, they can be easily surface immobilized and structurally modified, being possible to obtain new AMPs with improved stability and greater targets range. AMPs have also been seen to display synergistic effects with antibiotics, increasing their overall antimicrobial action. Contrary to antibiotics which act selectively against bacteria, AMPs act at multiple sites within microbial cells reducing their resistance [5,6,44]. They play a key role as endogenous mediators of wound healing making their inclusion in active wound dressings, with the goal of both fighting infections and aiding with the skin regeneration, highly demanded. Incorporation of AMPs by simple co-electrospinning or physical binding has been recently explored. The release kinetics of fluorescein labelled inverse-Crabrolin AMP incorporated into PCL nanofibers was examined against *Escherichia coli* and *Bacillus subtilis* with very promising results [45]. In another

study, the AMP motif Cys-KR12 originated from the human cathelicidin peptide LL37 was immobilized onto electrospun silk fibroin nanofiber membranes via click chemistry. Data revealed great antimicrobial action against four pathogenic bacterial strains (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, and *Pseudomonas aeruginosa*) without biofilm formation, and functionalized mats were seen to facilitate the proliferation of keratinocytes and fibroblasts and to promote the differentiation of keratinocytes with enhanced cell-cell attachment [46]. Lysozyme and nisin AMPs were functionalized onto poly(acrylic acid) (PAA) and PVA electrospun mats and their antibacterial activity assessed against *Staphylococcus aureus*, the most commonly isolated bacterium in infected wounds. Results showed the ability of the functionalized mats to eliminate bacteria colonies, being able to free the affected area of microbial growth within 14 days [47]. There is still much to explore about the incorporation of AMPs within fibrous constructs; however, as research evolves quickly, we expect progress in this area to arrive very soon.

## 5. Conclusions and future perspectives

Since the early 20$^{th}$ century that great advances have been introduced and achieve in the area of fibrous constructs, namely bioactive wound dressings. As a result, it is now possible to produce uniform nanofibrous systems with the most complex architectures and features mimicking the extracellular matrix. Natural and synthetic polymeric matrices functionalized with small but highly effective biomolecules have revolutionize and continue to revolutionize the way we treat wounds and protect our skin. Even though significant advances have been made, several issues still need to be further addressed, particularly the biomolecules functionalization process. The inefficient immobilization of metal nanoparticles has caused significant impact in the environment. The activity of many AMPs cannot reach optimal values since, in many instances, is lost when in contact with physiological media and instead of being topically delivered is systemically, putting our immune system at risk. Additionally, the slow and controlled release of the antibacterial agents *in vitro* is not entirely mimicked *in vivo*, with the initial antimicrobial burst being less easy to predict.

In conclusion, great advances have been achieved in wound healing with the use of spinning techniques, particularly those capable of producing fibers at the nanoscale. Nevertheless, more research is required to fully realize the potential of this new generation of bioactive dressings.

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