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Natural and synthetic polymers for wounds and burns dressing

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ABSTRACT

In the last years, health care professionals faced with an increasing number of patients suffering from wounds and burns difficult to treat and heal. During the wound healing process, the dressing protects the injury and contributes to the recovery of dermal and epidermal tissues. Because their biocompatibility, biodegradability and similarity to macromolecules recognized by the human body, some natural polymers such as polysaccharides (alginates, chitin, chitosan, heparin, chondroitin), proteoglycans and proteins (collagen, gelatin, fibrin, keratin, silk fibroin, eggshell membrane) are extensively used in wounds and burns management. Obtained by electrospinning technique, some synthetic polymers like biomimetic extracellular matrix micro/nanoscale fibers based on polyglycolic acid, polylactic acid, polyacrylic acid, poly-ε-caprolactone, polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol, exhibit *in vivo* and *in vitro* wound healing properties and enhance re-epithelialization. They provide an optimal microenvironment for cell proliferation, migration and differentiation, due to their biocompatibility, biodegradability, peculiar structure and good mechanical properties. Thus, synthetic polymers are used also in regenerative medicine for cartilage, bone, vascular, nerve and ligament repair and restoration. Biocompatible with fibroblasts and keratinocytes, tissue engineered skin is indicated for regeneration and remodeling of human epidermis and wound healing improving the treatment of severe skin defects or partial-thickness burn injuries.

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1. Introduction

During the wound healing process, dressings are used for the regeneration and repairing of dermal and epidermal tissues. Wound dressing materials, as physical barriers permeable for moisture and oxygen, protect the wound mainly against microorganisms (Adamian et al., 2004).

For the stimulation of wound healing, a passive dressing is essential for maintaining an optimally moisture. Several products such as gauzes, hydrogels, foams, hydrocolloids (carboxymethylcellulose), alginate, collagen, cellulose, cotton/rayon, transparent films (polyurethane) are recommended as passive dressings for wounds and burns, because of their influence on local cellular response (Livshits, 1988; Cornelius et al., 2007). Thus, they are distinguished by some useful properties: protect peri-wound skin, maintain a suitable moisture at the wound level, prevent and keep under control microbial biofilms, cleanse the injured tissues, eliminate/minimize pain, remove dead spaces and nonviable tissues, control the odors (Seaman, 2002; Boateng et al., 2008; Sawant et al., 2012).

Some natural products having emollient, demulcent, epithelializing, astringent, antimicrobial, anti-inflammatory and antioxidant properties can improve the wound healing process (Mogoşanu et al., 2012).

Active wound dressings are impregnated with antimicrobials (topical antibiotic and antifungal products), collagen or enzyme debriding agents. Silver sulfadiazine, methylene blue, crystal violet, honey, polyhexamethylene biguanide (PHMB) and cadexomer iodine are commonly used as antimicrobials, for the prevention of local infection, especially in chronic wounds (Zilberman and Elsner, 2008).

For the peri-wound skin protection, skin sealants, moisture barriers or pastes, solid skin barriers and skin barrier powders are the most used (Yudanova and Reshetov, 2006a).

Certain factors such as the presence of infection, the accumulation of fluid and debris, the cleanliness and integrity of bandage influence the frequency of dressing change (Stojadinovic et al., 2008).

Acting as molecular absorptive filters or traps, odor-controlling dressings are recommended for the management of wounds and burns odor. For this purpose, activated charcoal is the most used

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deodorizing agent because its large surface absorption area. In a recent randomized clinical trial, silver-impregnated activated charcoal dressing was better tolerated than the control, for the management of chronic venous leg ulcers, even at the debridement stage. Thus, this dressing may be used to remove fluids and toxins which delay the wound healing process (Kerihuel, 2010). Honey dressings are used for healing and reducing odor of abscesses, diabetic foot ulcers, leg ulcers because of their *in vitro* and *in vivo* antibacterial activity against anaerobic *Bacteroides* spp., *Peptostreptococcus* spp., *Prevotella* spp. (Moura et al., 2013).

By means of growth factors and natural or synthetic polymers (*e.g.*, alginate, collagen, acrylates, polyvinyl alcohol derivatives), the modern concept of interactive dressing envisages the changes in the wound environment for a better healing (Atiyeh et al., 2005). Consequently, the influence on local cellular response is revalued by improving the retention of moisture and wound collagen matrix, inhibiting microbial biofilm, decreasing of exudates and stimulating the epithelialization process (Singh et al., 2013).

Local delivery of growth factors and the application of tissue engineered skin (biosynthetic dressings) are up-to-date wound healing therapies. By using the so-called “artificial dermal layer”, in which natural or synthetic polymers are used as three-dimensional scaffolds for the adhesion and integration of dermal fibroblasts, the re-epithelialization process is enhanced especially for full thickness wounds (Sefton and Woodhouse, 1998). Sustained by a biocompatible polymer layer, skin substitutes are made mainly of collagen and seeded cells or reconstituted collagen and chondroitin sulfate (Bala and Thangeswaran, 2005; Nair and Laurencin, 2006).

Nanofibrous matrices, microspheres or hydrogels solid foams obtained from biodegradable and biocompatible polymeric scaffolds, containing cellular and molecular modulators that stimulates wound healing are used for tissue engineering. Because of their open porous structure and good mechanical strength, they provide an optimal microenvironment for cell proliferation, migration, and differentiation. In addition, for the complete regeneration of damaged tissues, natural or synthetic polymeric scaffolds can be surface engineered to provide a biocompatible extracellular matrix (ECM) (Chung and Park, 2007; Ma, 2008; Garg et al., 2012).

For the regeneration of full-thickness wounds, polysaccharides and proteins are the most common natural polymers used in the field of tissue engineering, because of their biocompatibility, biodegradability and similarity with ECM (Malafaya et al., 2007; Wiegand and Hipler, 2010).

Natural polymers such as collagen, chitosan, elastin, fibrinogen are biocompatible substrates similar to macromolecules recognized by the human body. They are also used in regenerative medicine for human epithelial stem cells culture or *in vitro* reconstituted epithelia, respectively (Guerra et al., 2009; Natesan et al., 2012).

In the last years, starting from natural or synthetic polymers, the production of biomimetic ECM micro/nanoscale fibers (80 nm–1.5 μm) through electrospinning process was found to be effective for tissue engineering. Thus, for wound healing or cartilage, bone, vascular, nerve and ligament repair and also for regeneration different non-woven structures of natural (*e.g.*, collagen, fibrinogen, elastin) or synthetic (*e.g.*, polyglycolic acid, polylactic acid, polydioxanone, poly-ε-caprolactone, polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol) origin are used (Sell et al., 2007, 2010; Naghibzadeh, 2012).

Natural macromolecules show a relatively low mechanical strength compared to synthetic polymers. By cross-linking or blending with synthetic polymers, the mechanical properties of natural polymers are improved; however, their biocompatibility is somewhat affected. Modern bandage materials, such as electrospun nanofibrous polymeric bandages are also used for active wound dressings. In addition, nanofibrous membranes may be used as carriers for local active principles (antimicrobial and anti-inflammatory drugs) and wound dressing materials that speed up the wound healing process (Zahedi et al., 2010; Zhong et al., 2010).

2. Natural polymers for wounds and burns healing

Natural polymers are widely used in the regenerative medicine field, for wounds and burns dressing because of their biocompatibility, biodegradability and similarity to the ECM. Inducing and stimulating the wound healing process, natural polymers are involved in the repair of damaged tissues and consequently in skin regeneration (Huang and Fu, 2010). Due to their three dimensional cross-linked polymeric networks that are soaked with water or biological fluids, biomaterial hydrogels are employed in the pharmaceutical and biomedical area, especially for wound management, tissue engineering, drug delivery, and organ transplant (Das et al., 2012). In addition, novel biomaterials based on renewable, non-toxic, and biodegradable natural polymers are obtained through radiation processing. Therefore, hydrogels containing cross-linked natural polymers can be used for wounds and burns dressing (Haji-Saeid et al., 2010).

2.1. Polysaccharides

Administered in the form of hydrogels, some polysaccharides are extensively used for the management of wounds and burns: neutral (β-glucans, dextrans, cellulose), acidic (alginic acid, hyaluronic acid), basic (chitin, chitosan) or sulfated polysaccharides (heparin, chondroitin, dermatan sulfate, keratan sulfate) (Kennedy et al., 2011).

2.1.1. Homoglycans

Homoglycans are naturally occurring biocompatible materials used as locally modulators of the cellular response actively participating in the wound healing process (Lloyd et al., 1998). In the field of regenerative medicine (tissue engineering, wound dressing), electrospun dextran, starch or cellulose are potentially useful materials for the obtaining of nanofiber matrices (Lee et al., 2009).

2.1.1.1. α-Glucans. Pullulan is a $\alpha(1\rightarrow4)$,$\alpha(1\rightarrow6)$-D-glucan biosynthesized from starch by the ubiquitous yeast-like fungus *Aureobasidium pullulans* (*Dothioraceae*). A superabsorbent polysaccharide hydrogel based on pullulan derivate as antibacterial release wound dressing was prepared by chemical cross-linking. The hydrogel is not cytotoxic and it has a remarkable water absorption property (swelling ratio up to 4000%), which means a quick haemostatic ability and prevention of the wound bed dehydration and accumulation of exudates. In addition, antibacterial or antimycotic drugs can be loaded into the hydrogel protecting the wounds and burns from microbial biofilm invasion (Li et al., 2011a).

2.1.1.2. β-Glucans. Different types of $\beta(1\rightarrow3)$-D-glucans isolated from yeast, grain, and fungi were investigated for their immunological and pharmacological properties because of their ability to form single- and triple-helical resilient gel structures. Recent studies highlight that highly purified yeast-derived insoluble $\beta(1\rightarrow3)$-D-glucan (Glucan #300) strongly inhibited adipogenic differentiation, supported wound healing and significantly lowered skin irritation (Lehtovaara and Gu, 2011; Vetvicka and Vetvickova, 2011).

2.1.1.3. Dextrans. Carboxymethyl benzylamide sulfonate dextran (CMDBS) is a functionalized dextran with heparin-like properties and different biomedical applications, including wounds and burns dressing. CMDBS, a soluble polymer structurally similar to glycosaminoglycan heparin, stimulates wound healing in various *in vivo* experimental models, controls the proliferation

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