Review Article

A Technical Overview: Polymers for Wounds and Burns Dressing as Hydrogel Drug Delivery System

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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 fibres 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 remodelling of human epidermis and wound healing improving the treatment of severe skin defects or partial-thickness burn injuries. This article offers an insight into several different types of polymeric materials clinically used in wound dressings and the events taking place at cellular level, which aid the process of healing, while the biomaterial dressing interacts with the body tissue.

Keywords: Polymeric biomaterials · Wound healing · Bio-engineering skin substitutes · Hydrogels · Hydrocolloid.

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INTRODUCTION

From ancient years till now, wound assessment is a challenge beyond medical society. In most cases, wounds are associated with increased morbidity as well as substantial mortality [1-2]. As wounds are any disruptions or injuries of anatomical structure and function due to severe breakage in organs such as skin. This break can extend further to other tissues and structures such as subcutaneous tissue, muscles, tendons, nerves, vessels as well as bone. It can be said that the skin, the largest human organ is mostly exposed to damage since can be easily burned or injured either by trauma or surgery. Wounds are mainly classified as acute or chronic; acute wounds processed through the normal phases of wound healing as well as exhibit well-defined signs of healing within four weeks, whereas chronic wounds do not show normal progress through the healing stages and healing is not obvious within four weeks. Wound healing is one of the most complex processes in multicellular organisms, involving multi phases during process which include haemostasis/inflammation phase, proliferation phase, and remodelling phase [3]. Unbalancing one or more of these phases could lead to two distinct damaging outcomes: either chronic wound development or the formation of a hypertrophic scar/keloid [4]. It can be said that the healing process relies upon local wound factors, systemic mediators, any underlying disease as well as the injury type [5]. Clinicians recommend that the primary intention of wound healing associates with the closure of wound edges via sutures, clips or skin adhesive. The secondary intention arises, when the edges cannot be approached so the wound remains open and the defected area slowly being filled with connective tissue. These wounds healed slowly and are susceptible to infections. Commonly, this happens to patients with underlying conditions such as vascular, diabetic or pressure ulcers as well as in patients with post-surgical wound infections, haematomas or mechanical tension. Finally, tertiary intention, or delayed primary intention, includes wound to left open until the removal of

non-viable tissue due to any infection or contamination, then the wound edges are approached. Finally, the healing carries on similarly to primary intention [6].

Factors Affecting Wound Healing

Numerous factors which influence wound healing can impair the whole process. In general, these factors are classified as local and systemic (Guo and Dipietro 2010). Local factors, oxygenation and infection, directly affect wound healing. Oxygen is critical for cell metabolism, energy production, and for all phases of wound healing. Superoxide, for oxidative killing of pathogens, produced by leukocytes is dependent on oxygen levels. In wounded region, vascular disruption causes depletion of oxygen leading to hypoxia. In wounds, where oxygenation is not restored, healing is impaired. Temporary hypoxia stimulates wound healing, while chronic hypoxia delays the process. Hypoxia induces macrophages, fibroblasts, and keratinocytes to produce cytokines and growth factors crucial for cell proliferation migration and chemotaxis, and angiogenesis in wound healing. Reactive oxygen species, during normal oxygenation, induce wound healing. However, in case of hypoxia, as their levels increase in cell, their beneficial effects are thwarted by their harmful effects of tissue damage (Bishop 2008). Once skin is injured, the barrier it provides against foreign invasion is breached. Instead of being sequestered at skin surface, microorganisms enter the wound and contaminate or colonize it. Inflammation is an important part of wound healing. However, improper removal of bacteria from wound leads to prolonged elevation of pro-inflammatory cytokines and matrix metalloproteinases. Enhanced production of proteases can recede the production of naturally occurring proteases. Imbalanced production of protease degrades growth factors allowing bacteria to form a biofilm. Infected wounds are teeming with Staphylococcus aureus (S. aureus), Pseudomonas aeruginosa (P. aeruginosa), and β-haemolytic streptococci (Guo and Dipietro 2010). Systemic factors are essential in determining the overall well-being of an individual on wound healing. Increased age is a risk factor for impaired wound healing. It hampers the process by altering inflammatory responses, re-epithelialization, collagen synthesis, and angiogenesis in aged mice as compared to young ones. Female estrogen and male androgens play an important role in wound healing. Estrogen is known to regulate genes involved in regeneration, matrix production, protease inhibition, epidermal functions, and inflammation (Guo and Dipietro 2010). Stress causes substantial delay in wound healing. Glucocorticoids are up-regulated in stress, reducing the levels of pro-inflammatory cytokines and chemo-attractants, necessary for inflammatory phase of wound healing. Glucocorticoids induce reduced differentiation and proliferation of immune cells, cell adhesion molecules, and expression of gene-regulating transcription (Godbout and Glaser 2006). Diabetic individuals show delayed and impaired wound healing. Such individuals are prone to diabetic foot ulcer (DFU) which subsequently causes lower limb amputation in 80% of cases. DFU is accompanied by hypoxia which causes insufficient angiogenesis and amplifies early inflammatory response and enhanced levels of oxygen radicals. Hyperglycaemia boosts ROS level, adding oxidative stress. High levels of MMP in DFU, 60 times higher than acute wounds, distort tissues, and impede wound healing (Brem and Tomic-Canic 2007). Neuropeptides, important for cell chemotaxis, growth, and proliferation, recede substantially, thus affecting the process of wound healing. Obesity, being a leading risk factor for myriad diseases and health conditions, affects wound healing process. High infection rates are reported in obese individuals undergoing bariatric and non-bariatric surgeries. Hypo-vascularity in wounded area also contributes towards impaired healing. Adipose tissues and macrophages within contain bioactive adipokines. Negative influence of adipokines impairs wound-healing process (Wilson and Clark 2004). Clinical evidence and experimental studies suggest alcohol consumption as a risk factor for impaired wound healing. Exposure to alcohol interferes with defines mechanism rendering wound vulnerable to further infection. Most significant impairment is due to reduced angiogenesis (Radek et al. 2005). Like alcohol consumption, smoking has deleterious effects on wound healing. Compounds of cigarette smoke interfere with the process. Nicotine causes vasoconstriction and reduces blood perfusion. Carbon monoxide compromises oxygen consumption. Despite overall negative outcomes, recent studies put forth low dose of nicotine to stimulate angiogenesis (Ahn et al. 2008).

Types of Wound Dressings

Traditional dressing

These are still the most commonly used materials for wound and burn dressings15. The traditional dressings, which are generally used during the first intervention in wound treatment, prevent wound's contact with outer environment and bleeding [7-8]. The best sample of this group is gauze and gauze cotton composites which have very high absorption capacity. As they cause rapid dehydration whereas they are being removed from the wound surface, they can cause bleeding and damage of newly formed epithelium [9-10]. Therefore, gauze composites with a non-adhesive inner surface are prepared to reduce the pain and trauma which can occur when removing traditional wound dressings from the wound surface. Some of the dressings used are Paraffin gauze dressing containing0.5% chlorhexidine acetate, Paraffin gauze dressing, petrolatum gauze, petrolatum gauze containing 3% bismuth tribromo phenate, scarlet red dressing, sterile hydrogel dressing, highly absorbent cotton wool pad, highly absorbent rayon/cellulose blend sandwiched with a layer of anti-shear, high density polyethylene, and absorbent cotton pad. Exudates leaking from traditional dressing materials usually increases the risk of infection is one of the most significant problems of these type dressings. Antibacterial agents are added into the

dressings to eliminate the infection. In addition, one of the most significant problems encountered in this material is a foreign body reaction in the wound caused by cotton fibres. The biggest advantage of these materials is their low cost [11-12-13].

Biomaterial-based dressings

Biological dressings are natural dressings with collagen-type structures, generally including elastin and lipid. Such dressings can mainly be categorised under the following groups [14-15-16].

1. Allografts - (Scalp tissue, Amniotic) , 2. Tissue derivatives- (Highly purified bovine collagen, Formalin fixed skin), 3. Xenografts- (Porcine tissue, Silver impregnated porcine Tissue). The most common source for allograft dressing is fresh or freeze-dried skin fragments taken from the patient's relatives or cadavers. Immune reaction as a result of the use of allograft can be seen and the body may reject the tissue. Infection risk also increases with suppression of the immune system to prevent the body's rejection of transplanted tissue. The other disadvantages of these dressings include the difficulty of preparation, lack of donors, high cost and limited shelf life [17-18]. Amniotic membrane {AM), which is separated from chorion, generally uses in superficial partial thickness burns as a dressing material for many years. AM has been routinely used in several clinical studies for the treatment of burns on the skin, ulcers and, pre-dominantly in ophthalmology, for the treatment of eye piece surface disorders. Its use is based on its ability to improve the process of epithelisation, as well as reducing the inflammatory processes, angiogenesis and scarring alopecia. Though it has advantages such as ease of preparation and use, it has disadvantages like causing cross infection and dehydration of the wound [19-20-21]. Xenografts are commercially available materials contrary to autografts and allografts. The most common of xenografts is the ones derived from pig skin [22,23], which have a long shelf-life and can be sterilized easily. Although pig skin is not microscopically similar to human skin, it shows close similarity in terms of adhesion and collagen content. Its disadvantage is the risk of triggering an immune response due to the foreign tissue. Tissue derivatives materials, derived from different forms of collagen, have the advantages like ease of preparation, low contamination risk and weak antigenic features. The greatest disadvantage of these materials is the risk of infection, particularly in long term usage [24-25].

Artificial dressing

These are used in the form of film/membrane, foam, gel, composite, spray. Two types of polymers are used for artificial dressings: 1. Natural polymers Collagen, alginic acid & salts, hyaluronic acid derivatives, fucoidan, chitosan, poly N acetyl glucosamine. 2. Synthetic polymers Polyurethane & derivatives, Teflon, methyl methacrylate, silicon.

Natural Polymers

Natural polymers are widely used in the regenerative medicine field, for wounds dressing because of their biocompatibility, biodegradability and similarity to the ECM. Natural polymers are involved in the repair of damaged tissues and consequently in skin regeneration by inducing and stimulating the wound healing process [26-27]. These are typically composed of a polymeric network that can contain up to 99 per cent or higher water content. As a result, they are referred to as 'hydrogels', and their swelling capability in water allows them to exhibit an environment that resembles the highly hydrated state of natural tissues [28-29]. Although naturally derived polymers are characterized by having batchto-batch variations and poor mechanical properties, they are also readily available, inexpensive and easy to fabricate into hydrogels, which makes them appealing choices for scaffolds. 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 trans plant [30-31]. Creams has been formulated with honey and plant extract which can enhance wound healing. 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 [32-33].

Chitin and Chitosan

Chitosan is derived from chitin, which is found in the exoskeleton of marine crustaceans such as shrimps and crabs, as well as insects and the cell walls of fungi [34-35]. It is derived from chitin through a deacetylation process to obtain a linear structure of glucosamine and N-acetyl glucosamine linked in a b-1,4 manners [36-37]. Chitin is the most abundant natural amino polysaccharide (poly-N-acetylglucosamine). Chitosan is soluble at pH lower than 5.5, thus solvents such as acetic acid and hydrochloric acid are often used so as to dissolve chitosan. Chitosan forms gels either by raising the pH to 6 or higher61, or by interacting with a variety of divalent and polyvalent anions and is biocompatible, biodegradable, non-toxic and bifunctional [38-39-40]. The applications of chitosan include drug delivery, growth factor encapsulation and gene delivery by forming complexes between the cationic chitosan and negatively charged DNA [41-42]. This cationic natural polymer, has been widely used as a topical dressing in wound management owing to its haemostatic, stimulation of healing, antimicrobial, nontoxic, biocompatible and biodegradable properties. Chitosan preparations are classified into native chitosan, chitosan formulations, complexes and derivatives with other substances [43-44]. Chitosan possesses properties of binding with red blood cells allow it to rapidly clot blood, and it has recently gained regulatory approval in the USA for use in bandages and other haemostatic agents [45-46]. In addition,

chitosan modulates the functions of inflammatory cells and promotes granulation. As a semi permeable biological dressing, it maintains a sterile wound exudate beneath a dry scab, which prevents dehydration and contamination of the wound, thus helps to optimize conditions for healing [47-48]. The antimicrobial effects of chitosan are due to destabilization of the outer membrane of Gram-negative bacteria and permeabilization of the microbial plasma membrane [49-50]. Apart from this many factors present in the chitosan molecule or its environment can influence the antimicrobial properties, such as the molecular weight, DDA and the ionic strength and pH of the dissolving medium, the physical state of the chitosan, such as whether the it is present in the form of films, hydrogels, coatings, in solutions or in combinations with other materials. Its use in the treatment of wounds and burns is due to its haemostatics effect [51-52-53]. It is thought that chitosan accelerates the formation of fibroblasts and increases early phase reactions related to healing [54-55]. The applications of chitosan in commercial and biomedical fields have increased due to its low toxicity and biodegradation products, and its biocompatibility with blood and tissues [56-57-58]. Chitosan can be prepared in a variety of forms, namely films, hydrogels, fibres, powders and micro-nanoparticles. Chitosan was evaluated to determine the efficacy to act as a wound healing accelerator. Open skin wounds were made on the dorsal side of 3 beagles and cotton fibre chitosan was applied for 15 days. Wound healing process was evaluated histologically and immunochemically [59-60-61]. Results showed that the chitosan treated wounds had a severe infiltration of polymorphonuclear cells and increase in effusion compared with that in control. Granulation was more pronounced by the chitosan treatment on day 9 and15 post wounding[62-63]. Composite nanofibrous membrane of chitosan/collagen is known for their beneficial effects on wound healing. The membrane was found to promote wound healing and induce cell migration and proliferation. Animal studies have proved that nanofibrous membranes are better than gauze and commercial collagen sponge in wound healing [64-65-66]. The chitin powder was found to be more efficient than chitin or chitosan as a wound healing accelerator: wounds treated with chitin hydrogel were completely reepithelialized, granulation tissues were nearly replaced by fibrosis and hair follicles were almost healed in 7 days after initial wounding [67-68-69]. Also, the chitin hydrogel treated skin had the highest tensile strength and the arrangement of collagen fibres in the skin was similar to normal skins [70-71]. Dibutyrylchitin (DBC) is a water-soluble chitin derivative. DBC fibrous materials were used for wound healing applications. In a study done on 9 patients with different indications satisfactory results were obtained especially in case of burn wounds and post operative/ post traumatic wounds and various other conditions causing skin/epidermis loss [72-73]. Treatment of full thickness cutaneous wounds in a diabetic mouse model with chitin-containing membranes results in a increased wound closure rate correlated with the impressive rise of angiogenesis. Serum starved endothelial cells were treated with either VEGF or different concentration of chitin. The results obtained after 48 hrs and compared with the control plate. In control plates a two-fold reduction in cells occurred whereas this effect is compensated by VEGF and different concentration of chitin in the test plates. Chitin treated plated does not show any increase in cell number indicating no proliferation occurred but chitin helped to rescue the cells from dying due to serum deprivation [74], developed a non-adherent wound dressing with sustained antimicrobial capability to treat mustard burns. It contains two layers: upper layer is a carboxymethyl chitin hydrogel material, and lower layer is an antimicrobial impregnated biomaterial. Carboxymethyl chitin hydrogel provides mechanical and microbial barrier along with the capability of adsorbing wound exudates. This property makes it ideal for use in second degree burns as hydrogels can swell considerably holding up to 4 times its own weight of water thus preventing accumulation of fluids in highly exudating wounds [75]. Chitosan acetate foam impregnated with chlorhexin gluconate forms the lower layer. In the in vitro release studies, to obtain sustained antimicrobial activity for 24 h loading concentrations were optimized which in turn provide sufficient anti-microbial drug into the wound area. For treatment of full thickness burn injuries a bio-inspired bilayer physical hydrogel only constituted of chitosan and water were processed and applied. To ensure good mechanical properties and gas exchange first layer is made of rigid protective gel and a soft and flexible second layer allow the material to follow the geometry of the wound and ensure good superficial contact. In order to compare highly viscous solutions of chitosan were also considered. Only one chitosan material is used for each time [76]. Studies were done to determine effects of sterilization methods on morphology, mechanical properties, and cytotoxicity of chitosan membranes used as wound dressing. In the study effects induced by two different sterilization methods (exposed to gamma radiation and ethylene oxide) and an antiseptic technique (immersion in 70% ethanol aqueous solution) on the morphology, tensile strength, percentage of strain at break, and in vitro cytotoxicity to Vero cells on chitosan membranes designed for wound healing was done. With chitosan, glycerol, and chitin as components four different membrane compositions were evaluated. Gamma radiation, in spite of being one of the most commonly employed sterilizing agent, negatively affected the morphology of membranes composed solely by chitosan as well as the percentage of strain break of the chitosan-membranes containing glycerol on their composition. Its use also affected the colour of chitosan membranes[77-78]. The use of 70% ethanol aqueous solution does not change the chitosan membrane characteristics significantly, but its use has limitation concerning process scale up. With ethylene oxide (EtO), chitosan morphology, percentage of strain break, and in vitro cytotoxicity to Vero cells were not significantly affected. The tensile strength of membranes containing chitin were reduced after the treatment with

ethylene oxide; however, the obtained values were comprised in the range verified for normal human skin. Therefore, when considering their use as a wound healing device, and because this sterilization process is easily adjusted to use as an industrial scale, EtO can be considered the most adequate sterilization agent for chitosan membranes. However, it should be considered that this chemical is associated with toxicity, flammability, and environmental risks, as well as with possible material contamination with ethylene oxide residues[83]. Effect of chitosan and linear polyvinyl amine were studied to explore and compare its antibacterial properties of the prepared dressing based on cotton. Using butane tetracarboxylic acid biopolymer molecules were covalently fixed on the cotton. They are characterised using amine groups created on the surface of the fabric. Escherichia coli (E. coli) DSMZ 498 was used to evaluate bacteriostatic effect. From the results obtained it showed a synergistic bacteriostatic effect of treated cotton samples by using chitosan/polyvinyl amine finishing system. Thus, produced cotton can be used to treat wounds, ulcers as well as diabetic ulcers in addition to some kind of burns. Using Tegaderm as backing a novel wound dressing was made with chitosan (CH) and minocycline hydrochloride (MH). CHs with different deacetylation degrees were used. CH with 67% and 83% showed sustained release of minocycline in vitro. During in vivo studies a negative effect was shown in wounds applied with 10mg minocycline and sealed completely with Tegaderm. CH83 with 2mg minocycline showed an excellent effect along with CH 83 alone. Pus removal was better for CH83 with minocycline thus it is considered as better than CH83 alone[79]. In recent years, new forms of chemically modified chitosan have been developed in order to improve the properties of chitosan for various biological activities, and these substances have gained increasing attention. Representative members of these novel polymers include ammonium chitosan, carboxymethyl chitosan and derivatives.

Alginate

Alginate, a predominantly brown alga sourced polysaccharide, is comprised of (1-4)-linked β-D-mannonate and α-L-guluronate monomers. Alginate is quite effective in absorbing the wound excretion and preventing undesired odor and pain. Alginate dressings turn into gels through absorbing wound excretions via ionic exchange of alginate calcium and wound, or blood, sodium[80]. As expected, alginate also provides necessities for a proper wound treatment such as moist environment, limiting infection and external interference, and stimulating tissue regeneration. Also, monocytes were shown to produce elevated levels of IL-6 and TNF-α, which are important cytokines for wound healing, following alginate introduction. Cell adhesiveness to the alginate is the main drawback of alginate use in wound treatment. This lack of scaffolding support for new ECM formation was overcome through the addition of peptide sequences in order to obtain cell-interactive alginates. Cell-interactive alginates were observed to mimic ECM features to accelerate the wound healing process by stimulated cellular response to alginate. In addition, modifications on alginate were regarded to be more attainable compared to some other polymers which leaded to development of alginate-based combined wound treatment agents. Improved wound healing results were achieved by blending alginate with curcumin or silver, silk fibroin, and chitosan [81]. Hydrogen films formed by sodium alginate blended with Aloe vera prior to UV-crosslinking showed favourable wound protection along protection from UV and light-induced damages. Promising results were observed on wounds of healing-impaired mice when a hydrogel blend of alginate, chitosan, and fucoidan was applied. In another study by Xie et al., chitosan-colla gen-alginate composite dressing expressed increased fibroblast migration, and upregulated expression of bFGF, EGF. Rats treated with composite dressing showed accelerated and smooth wound healing compared to rats treated with gauze or chitosan-only dressings. Alginate-chitosan composite dressings were also tested for their ability to be carriers for beneficial molecules. Hu et al. reported that amorphous hydrogels based on chitosan/alginate composite impregnated by EGF showed significantly better healing outcomes on rat wounds. Likewise, alginate was also shown to be feasible for mineral crosslink, particularly zinc. Crosslinked zinc-sodium alginate polyacrylamide hydrogels showed superior antibacterial and wound care properties.

Collagen

Collagen is the most abundant protein in mammals as it is the dominant component of the connective tissue. It is formed by repeating amino acids bound by peptide bonds and constitute the substantial part of ECM. Although there are more than 20 types of collagens, human body consists of mainly type I collagen followed by type II and III which comprise less than 10% of total collagen [82]. Collagen is degraded into small fragments, particularly gelatin, during the inflammatory response to an injury. Collagen degradation is followed by macrophage migration to injured area and fibroblast proliferation in order to form the new tissue. These processes are initiated by the specific cleaved parts (Arg-GlyAsp) of the collagen; hence, collagen degradation is one of the most important parts of the wound healing [83]. In a similar fashion, presence of gelatin induces keratinocytes to lose cell adhesion and gain their mobility, therefore stimulating migration for tissue regeneration. However, deteriorated regulation of collagen production versus the collagen cleavage results in unsuccessful healing, undesired outcomes, or chronic wounds. When the collagen degradation is not coupled with sufficient collagen synthesis due to dysregulated enzymatic activity (especially MMPs), newly formed collagens are steadily cleaved keeping wound healing process in the inflammatory step[84]. This problem was shown to be eliminated via external collagen supplement. Collagen based wound dressings play important role in this context, providing the excess collagen by means of inert

collagen and gelatin which in turn hinder the MMP activity and further the wound healing process from inflammatory step to proliferation. Structural modification (cross-linking, blen ng, loading, etc.) of collagen supplied by wound dressings can help to maintain the degradation rates, hence, accelerating the wound healing. Studies exhibited that wound healing action of collagen can be significantly improved by modifications such as depolymerization, binding with anti-inflammatory and antibacterial molecules, etc. Use of exogenous collagen for skin repair by remodelling the collagen fibrils with electrospinning and crosslinking with bioactive ingredients showed improved wound healing benefits[85]. Rho et al. suggested that mimicking the ECM collagen could be achieved by electro spinning collagen nanofibers coated with laminin. Using electro spun collagen-laminin composite expressed improvements in cell adhesion and proliferation during tissue repair. Diabetic wounds improved when collagen linked with quercetin was introduced, due to remarkable reactive oxygen species scavenging. A similar study also suggested that curcumin loaded collagen matrix showed healing properties on diabetic wounds with improved reepithelization. Electrospinning collagen fibrils in a similar way to that of natural skin also showed increased wound healing efficiency for collagen-based wound treatment products. Sun et al. reported that producing nanofibrous collagen scaffolds electro spun in a basket weave pattern which resembles the collagen in native skin, enhanced wound healing in diabetic wounds of rats.

Hyaluronan

Hyaluronan is a biopolymer found in human body commonly throughout connective, epithelial, and neural tissues. It is made of disaccharide repeats; D-glucuronic acid and N-acetyl-D-glucosamine linked by alternating glycosidic bonds of β-1,4 and β-1,3. Present in epithelial tissue, the role of hyaluronan in efficient wound healing is critical. Migration/proliferation and remodelling stages of wound healing are stimulated by the presence of hyaluronan. When degraded, the cleaved parts of hyaluronan were showed to exhibit angiogenesis enhancing properties[86]. Also, proliferation of keratinocytes was enhanced following degradation of hyaluronan as the degradation products bound to CD44 receptors. In the same way to collagen supplement, providing exogenous hyaluronan during the healing process of an injury expressed beneficial effects, although hyaluronan is natively present in skin tissue. Following post-injury hyaluronan introduction, reduced scarring was observed with heal sue repair. Hu et al. developed a hyaluronan scaffold which downregulated the TGF-β1 expression and provided an environment for promoted wound healing. Huang et al. suggested that treating non-healing wounds with hyaluronan-chitosan hydrogels loaded with vancomycin carrying poly (lactic-co-glycolic acid) microspheres significantly reduced microbial load of the injured area and stimulated the proliferation of endothelial cells. Likewise, hyaluronan pullulan composite wound films improved wound healing by means of stimulated haemostasis and improved non-enzymatic debridement [87]. Similar results were reported with wound healing studies using hyaluronan linked with active molecules or other polymers. Hyaluronan conjugated with chitosan and edaravone exhibited anti-inflammatory effects during wound healing both in vitro and in vivo while hyaluronic acid, bisphosphonate and silver conjugation resulted in promoted healing with minimal microbial load in vivo. Also, a randomized clinical trial conducted by Yildirim et al. reported that topically applied hyaluronan presented improved palatal epithelial wound healing with reduced pain.

Cellulose

Cellulose is a biopolymer containing repeating β-d-glucose monomers linked with β-1, 4-glycosidic bonds and present in cell walls of plant and bacteria. The porous structure of cellulose resembles the ECM of human skin and is suggested to be beneficial as a scaffold for tissue generation [88]. Due to its chemical structure, cellulose is mainly used to keep the wounds moist and remove the wound excretions via absorbing the dead tissue molecules and fibres. Keeping wound moist is of high importance to wound healing, as the moist environment is needed for supplying growth factors, migrating macrophages and proliferating fibroblasts. Other than wound protection activities cellulose does not exhibit any beneficial effects in healing process. However, modification of cellulose by linking bioactive agents and therapeutic molecules or conjugating with other polymers generated promising results for cellulose to be used as base for wound treatment products. Blending cellulose with antimicrobials such as silver nanoparticles and myostatin resulted in wound dressing materials that show notable antibacterial effects against E. coli and S. aureus when applied on open wounds. Reepithelization of burn wounds was achieved by wound dressing hydrogels produced from cellulose UV cross-linked with acrylic acid. Similar results were observed with bacteria-derived cellulose membrane conjugated with chitosan. Wound dressings with antibacterial and anti-inflammatory activities that can accelerate tissue regeneration were obtained by conjugating cellulose with tungsten oxide and polydopamine. Some cellulose modifications such as creating nanoscale fibrillary, oxidized, and methylated cellulose produced promising results. Nano-fibrillar cellulose showed improved healing on skin graft donor wounds[87]. while methylated and oxidized cellulose stimulated critical cellular responses such as cell migration and proliferation in injured area with improved haemostasis. Cellulose provides perfect environment for keeping wound moist and protected and with efficiently modifiable structure cellulose-based wound treatment agents and tissue repair applications can be developed with improved benefits.

Synthetic Polymers

Synthetic polymers (composite nano biomaterials with small pores and very high specific surface area) used for wounds and burns dressing are made by various techniques but mainly by electrospinning: wound-dressing materials with antibacterial activity from electrospun polyurethane-dextran nanofiber mats containing ciprofloxacin hydrochloride, water soluble polymer–carrageenan hydrogels, cellulose acetate, poly-l-lactide and poly(lactideco-glycolide) impregnated with shikonin for wound healing, antimicrobial, anti-inflammatory, antioxidant and antitumor activity, novel chitosan–poly(N,N-diethyl-acrylamide) interactive and thermos responsive interpenetrating polymer network films for potential wound dressing and biomedical applications, ciprofloxacin hydrochloride loaded poly(ethylene glycol)/chitosan scaffold as wound dressing, bactericidal films based on chitin derivatives (carboxymethylchitin) and silver nanoparticles for wound dressing applications, polyethylene glycol functionalized with low molecular weight heparin, poly(ethylene glycol)–protein conjugates was evaluated as an occlusive wound dressing material, polyethylene glycol–gelatin based semi-interpenetrating networks for use in wound healing, gelatin sponges prepared with different cross-linking agents such as glutaraldehyde (GA), 1-ethyl-3-(3- dimethylaminopropyl)-carbodiimide hydrochloride (EDAC), and d-fructose, polyvinyl alcohol–gelatin esterified hydrogel membrane for wound dressing compatible with the L929 fibroblast cell line and mice splenocytes, polyvinyl alcohol–sodium carboxymethylcellulose membranes loaded with fucidic acid, novel porous cryo-foam for potential wound healing application starting from polyvinyl alcohol and polyacrylic acid based hydrogels, polyvinyl alcohol/polyethylene Q3 glycol–tannin based hydrogel, curcumin loaded polylactic acid nanofibers for wound healing, collagen–poly-l-lactic acid composite material for wound dressing, polylactic acid based polymers and copolymers which are emerging as the candidate biodegradable materials, novel absorptive and antibacterial polyurethane membranes as wound dressing, polyurethane foam combined with pH-sensitive alginate/bentonite hydrogel for wound, polyvinylpyrrolidone–alginate hydrogel containing nano silver as wound dressing, resveratrol in immobilization on polyvinylpyrrolidone hydrogel dressing for dermatological use, electrospun emodin polyvinylpyrrolidone blended nanofibrous membrane for drug delivery and accelerated wound healing, fatty acid-based polyurethane films for wound dressing applications, poly-3-hydroxybutyrate–polyε-caprolactone biodegradable porous films/membranes, non-woven matrices from poly ε-caprolactone homopolymers and poly-l-lactide–ε-caprolactone, silicone-coated non-woven polyester dressing enhances re-epithelialization in a sheep model of dermal wounds. A recent study revealed that carboxymethyl-chitosan exhibits in vivo and in vitro wound healing properties through the activation of macrophages, stimulation of fibroblasts growth and secretion of different cytokines. While irrigating with Ringer's solution, polyacrylates dressing absorbs proteins, bacteria and necrotic tissue (with cca. 38% wound debriding rate just as well as collagenase), creating a "rinsing effect".

Skin Substitutes and Tissue Engineered

Skin substitutes are developed starting from biocompatible and bioresorbable polymeric dermal scaffolds such as chitosan–gelatin composite films, poly(d,l-lactic acid), poly–polyethylene glycol–poly(d,l-lactic acid), poly(lacticco-glycolic acid) membranes containing (1→3),(1→6)-˘-d-glucans, porous scaffolds composed of gelatin, hyaluronic acid and (1→3),(1→6)-˘d-glucans cross-linked with 1-ethyl-(3-3-dimethylaminopropyl) carbodiimide hydrochloride for artificial dermis. Compatible with fibroblasts and keratinocytes cultures, skin substitutes are recommended for regeneration and remodelling of human epidermis and for enhancing wound healing in the treatment of severe skin defects or partial-thickness burn injuries[87]. Tissue engineered skin is usually made of a matrix of bioabsorbable natural polymers such as collagen or fibronectin impregnated with human fibroblasts and/or keratinocytes. It promotes wound healing process for venous ulcerations and full thickness diabetic neuropathic foot ulcers. Tissue engineered skin is contraindicated in infected wounds and bovine collagen allergy. [88]

CONCLUSION

This review has considered many classes of wound dressings that can be used for wound healing purpose. The use of three-dimensional polymeric scaffolds for cell targeting is a common strategy for tissue engineering. Recent studies about biocompatible and biodegradable natural/synthetic polymers led to a substantial development of novel types of wound dressings and to outstanding applications in the biomedical area particularly for regenerative medicine. The effectiveness of these can be improved further by incorporating wound healing accelerating molecules like growth factors, peptides or various natural substances like honey, aloe vera and various plants and peel extracts. Various polysaccharides have been used either alone or in combination or in derivative forms for wound healing applications. Most of these are biodegradable in human body which makes it more attractive. Effective dressings should have properties and delivery characteristics that are optimised for specific wound types with minimum or no inconvenience to the patient and at reasonable cost. To achieve such objectives, manipulation of the physical characteristics of the identified systems is necessary so the use of composite dressings which combine the different characteristics of various polymers is good. This will be helpful for targeting many aspects of the complex wound healing process, and to ensure effective, complete wound healing and shorter healing times for chronic wounds and other difficult to heal wounds.

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SUMMARY

The use of three-dimensional polymeric scaffolds for cell targeting is already a common strategy for tissue engineering. Recent studies of biocompatible and biodegradable natural/synthetic polymers will lead to a substantial development of novel types of wound dressings and to outstanding applications in the biomedical area and especially for regenerative medicine. In this respect, the most promising materials for wounds and burns dressing are still based on natural polymers such as polysaccharides (alginates, chitin, chitosan, heparin, chondroitin), proteoglycans and proteins (collagen, gelatin, fibrin, keratin, silk fibroin, eggshell membrane.

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