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Review article

Recent advances on antimicrobial wound dressing: A review

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ABSTRACT

Skin and soft tissue infections (SSTIs) have high rates of morbidity and mortality associated. Despite the successful treatment of some SSTIs, those affecting the subcutaneous tissue, fascia, or muscle delay the healing process and can lead to life-threatening conditions. Therefore, more effective treatments are required to deal with such pathological situations. Recently, wound dressings loaded with antimicrobial agents emerged as viable options to reduce wound bacterial colonization and infection, in order to improve the healing process. In this review, an overview of the most prominent antibacterial agents incorporated in wound dressings along with their mode of action is provided. Furthermore, the recent advances in the therapeutic approaches used in the clinic and some future perspectives regarding antibacterial wound dressings are also discussed.

1. Introduction

Skin is the largest and outermost organ that covers the entire body. Therefore, above all, skiń s primary function is to protect underlying muscles, bones, ligaments and internal organs from external biological, chemical, mechanical and physical agents [1,2]. Furthermore, skin is also involved in sensation, temperature regulation, immunological surveillance, prevention of water loss (dehydration) and synthesis of vitamin D3 [3]. However, the structure and functions performed by this organ can be affected by cuts, burns, surgical incisions or illnesses, such as diabetes [4]. After skin structure be compromised, its structure and functions must be re-established, as soon as possible to ensure the body homeostasis. To accomplish that, the wound healing process begins almost immediately after a skin injury occurs, in order to avoid the risk of bacterial contamination [5]. Non-healing wounds usually appear after this type of contamination occur [4].

Skin and soft tissue infections (SSTIs) are the most common types of infections and they affect approximately 14 million people every year in the United States [6,7]. Depending on the etiology and severity of the microbial invasion, SSTIs can range from minor superficial to life-threatening infections [8]. In the initial stage of the infectious process, gram-positive organisms such as *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pyogenes* (*S. pyogenes*) are the dominant organisms involved, while gram-negative organisms like *Escherichia coli (E. coli)* and *Pseudomonas aeruginosa (P. aeruginosa)* are only found in later stages of the process, i.e. when a chronic wound is developed [7].

In a healthy human being, infection is avoided, by activating the immune system for abolishing the invading pathogens. In this process, macrophages initiate the migration to the wound site and subsequently perform phagocytosis of the pathogens (which are destroyed in a phagolysosome or by nitric oxide production). In a later stage of infection, the immune response is performed by the activation of lymphocytes T helper which secrete interferon-γ and CD40 ligand to coordinate the immune adaptive and humoral response to kill and remove the invading

Abbreviations: A. iwoffii, *Acinetobacter iwoffii*; AMPS-Na$^+$, 2-acrylamido-2-methylpropane sulfonic acid sodium salt; *B. cereus*, *Bacillus cereus*; *B. subtilis*, *Bacillus subtilis*; BC, Bacterial cellulose; CA, Cellulose Acetate; *C. freundii*, Citrobacter freundii; CMCS, Carboxymethyl Chitosan; CMGG, Carboxymethyl Guar Gum; CS, Chitosan; DHBA, 2,3-dihydroxybenzoic acid; *E.aerogenes*, *Enterobacter aerogenes*; *E.coli*, *Escherichia coli*; EDA, Ethylenediamine; *E. faecalis*, *Enterococcusi faecalis*; GMs, Gelatin Microspheres; HNTs, Halloysite Nanotubes; HA, Hyaluronic acid; *K. pneumoniae*, *Klebsiella pneumoniae*; MMSA, Methicillin susceptible *Staphylococcus aureus*; MRSA, Methicillin resistant *Staphylococcus aureus*; nAg, nano silver; NIPAAm, N-isopropyl acrylamide; OAlg, Oxidized Alginate; *P. aeruginosa*, *Pseudomonas aeruginosa*; PCD, β-cyclodextrin polymer; PCL, Polycaprolactone; PEI, Polyethyleneimine; PEO, Polyethylene oxide; PHEA, Poly(2-hydroxyethylacrylate); PLA, Poly(lactic acid); PLGA, Polylactic-co-glycolic acid; Plur, Pluronic F127; *P. mendocina*, *Pseudomonas mendocina*; PP, Polypropylene; PRP, Platelet rich-plasma; PSSA-MA, Poly(styrene sulfonic acid-co-maleic acid); PU, Polyurethane; PVA, Polyvinyl alcohol; PVP, Polyvinylpyrrolidone; *P. vulgaris*, *Proteus vulgaris*; SA, Sodium Alginate; *S. aureus*, *Staphylococcus aureus*; *S. epidermidis*, *Staphylococcus epidermidis*; *S. haemolyticus*, *Staphylococcus haemolyticus*; *S. pyogenes*, *Streptococcus pyogenes*; *S. typhi*, *Salmonella typhi*; *S. typhimurium*, *Salmonella typhimurium*; SF, Silk Fibroin; *V. vulnificus*, *Vibrio vulnificus*; ZN, Zein

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bacteria [9]. However, if the immune system is not able to remove the pathogen, infection occurs and causes the deterioration of granulation tissue, growth factors and extracellular matrix components (collagen, elastin and fibrin), thus compromising the normal wound healing process [10,11]. Therefore, it is fundamental to develop wound dressings that are capable of preventing bacteria penetration into the wound or avoid microorganisms' growth. To accomplish that, different approaches involving materials with intrinsic bactericidal activity, modified surface or incorporating antimicrobial agents, are being used to produce wound dressings displaying bactericidal activity [12].

Herein, an overview of the most prominent antibacterial agents incorporated in wound dressings along with their mode of action is provided. Furthermore, the recent advances in the therapeutic approaches used in the clinic and some future perspectives regarding antibacterial wound dressings are also discussed. Due to the higher prevalence of bacterial infections, this review does not provide any data concerning SSTIs caused by viral, fungal or parasites (protozoa, helminths, and ectoparasites).

2. Wound pathophysiology and the wound healing process

Wounds occur when a tissue is disrupted or the cellular integrity is compromised due to mechanical, physical or metabolism-related issues [13]. According to the duration and nature of the healing process, skin wounds can be classified as acute or chronic. An acute wound occurs suddenly, as a consequence of abrasions, avulsions, burns, incisions, lacerations and punctures, and have associated an healing time that is dependent on the size and number of layers of skin that have been affected [12,14]. Under normal physiological conditions, the restoration of the epidermal structure is highly efficient, however when a chronic wound occur, it is characterized by displaying a defective healing process, that do not allow skin to be repaired in an orderly and timely manner [15]. Based on etiology, the Wound Healing Society classifies chronic wounds into four categories: pressure, diabetic, venous and arterial insufficiency ulcers [16]. Bacterial colonization usually occurs in chronic wounds and it is considered as a primary cause of chronic inflammation [17].

The healing process comprises a cascade of precisely synchronized events in which are involved both resident and migratory cell populations, extracellular matrix components and soluble mediators [18]. This process includes five distinct phases: hemostasis, inflammation, migration, proliferation and remodeling [19]. In the first phase, hemostasis, a fibrin clot is formed to prevent blood loss through vasoconstriction as well as to avoid microbial contamination [20]. The inflammatory phase begins almost simultaneously with hemostasis and it involves the recruitment of neutrophils (that engulf bacteria and decontaminate the wound through proteases and antimicrobial peptides secretion and by producing reactive oxygen intermediates), monocytes/macrophages (monocytes differentiate into macrophages to remove apoptotic neutrophils and other cells and secrete cytokines and multiple growth factors), and lymphocytes that exert a specific response against microbes (B–lymphocytes produce antibodies, while T–lymphocytes secrete cytokines involved in cytolytic activity) [20–22]. The migration and proliferative phases begin with fibroblast migration to the wound site and differentiation into myofibroblasts to produce extracellular matrix components like fibronectin, hyaluronic acid, collagen and proteoglycan, that are involved in the production of extracellular matrix (ECM), new blood vessels and re-epithelization [20]. Maturation, or remodeling, is the last stage of the wound healing process and in this phase all processes that were activated after injury are ceased [19].

In order to ensure an effective wound healing process, it is fundamental to maintain a controlled set conditions at the wound site (i.e. oxygenation, temperature and high availability of vitamins, minerals, and trace elements) that sustain the complex cellular activity during this process [23]. However, chronic wounds, burns, diabetic ulcers and post-surgical wounds have extended healing times and, in some cases, even fail. For example, burn wounds usually display high levels of exudate, which provides a moist and nutrient-rich environment that promotes bacterial growth, namely *Pseudomonas* species [24]. These bacteria produce virulence factors that mediate a number of processes like adhesion, nutrient acquisition, leucocyte killing and bloodstream invasion. Furthermore, these microorganisms are also able to produce endotoxins that promote pro-inflammatory cytokines expression, such as interleukin-1 and tumor necrosis factor-α, that ultimately lead to wound inflammation [25–27]. Wounds exhibiting an extended inflammation, show a high content of metalloproteinases (MMPs) that are involved in the degradation of ECM components, thus avoiding the formation of the granulation tissue and consequently delaying the healing [11,28].

On the other hand, patients suffering from Diabetes mellitus (DM) have an impaired protective sensation and altered pain response, which makes them vulnerable to trauma and extrinsic forces. Diabetic wounds are characterized by their dry and keratinized aspect, that usually crack or suffer fissures more easily, leading to an extended healing time [29]. Therefore, patients with DM are predisposed to cutaneous infections occur, namely those caused by *S. pyogenes* and *S. aureus* [30].

3. Wound dressings displaying antimicrobial activity

In 1987, Gristina came up with the expression "race for the surface" to describe the competition that occurs between cells and bacteria for colonize a surface. Bacteria are inherently favored in this event, due to is natural ability to colonize both biological and non-biological surfaces [31]. An open wound is a favorable niche for microbial colonization [32]. Generally, the majority of infected wounds present polymicrobial and are usually contaminated by pathogens found in the surrounding environment, i.e. endogenous microbes living in the mucous membranes, and by the microflora available on the adjacent skin [33]. In the initial stages of chronic wound formation, gram-positive organisms, specifically *S. aureus*, are predominant. In the later stages, gram-negative *E. coli* and *Pseudomonas* species are observed and tend to invade deeper layers of skin causing significant tissue damage. Furthermore, *Staphylococci* and *Streptococci* species are also found in 50% of chronic wounds [7].

Nowadays, bacterial contamination of skin wounds are responsible for the high rates of morbidity and mortality [34]. To address this health issue, different labs around the world started to develop antimicrobial wound dressings to prevent wound contamination [35]. The wound dressings develop up to now have been produced with different materials (synthetic or natural) and with various physical forms (sponges, hydrogels, hydrocolloids, films, membranes). These different formulations have distinct properties that make them suitable for the treatment of a particular type of wound. For example, sponges exhibit a huge porosity, provide thermal insulation and sustain a moist environment at the wound site. Nonetheless, the sponges are mechanically weak, may provoke skin maceration and are unsuitable for the treatment of third-degree burns or wounds with dry eschar [36,37]. On the other hand, hydrogels are characterized by their capacity to store high amounts of water within their 3D polymeric network, which allow them to provide a moist environment to the wound. However, hydrogels display weak mechanical properties, thus demanding a secondary dressing [38,39]. Furthermore, hydrocolloids are easily removed by saline or sterilized water, non-adherent, present high density and are painless dressings. Nevertheless, hydrocolloids display some disadvantages that may limit their use, i.e. they may be cytotoxic, display an unpleasant odor, present a low mechanically stability and maintain an acid pH at the wound site [40,41]. Films used as wound dressings are impermeable to bacteria, allow healing monitorization and are painless. However, this type of dressing are hard to handle, adhere to the wound bed and cause exudate accumulation [14,40]. In turn, membranes (specially electrospun membranes) are known to act as physical barriers