Chapter 20

Progress and Perspectives in the Management of Wound Infections

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Abstract

The progress in nanotechnology and the medical application of novel generations of nanomaterials have opened new horizons in the definition of non-conventional approaches against multiple diseases. Biomaterials coated with antimicrobial metal nanoparticles, along with the topical applications of zinc, silver or copper-based formulations have demonstrated huge potential in prevention from infections associated with implantable medical devices and in biofilm eradication. In wound healing, in particular, the increasing healthcare costs and the antibiotic resistance demonstrated by several microorganisms have encouraged researchers and companies in the development of innovative wound dressings with antibacterial properties and capability to promote and enhance the healing process. Supported by scientific evidence, many formulations have been proposed and a large number of works involves the use of hybrid metal nanoparticles/polymer products, which have demonstrated encouraging results both *in vitro* and *in vivo*. In this chapter, recent progress in the development of novel wound dressings based on antibacterial metal nanoparticles is presented, along with the most interesting results achieved by the authors, mainly devoted to the application of silver nanocoatings in wound management.

Keywords: infection, antibacterial, wound dressings, metal nanoparticles

1. Introduction

The Wound Healing Society has defined the wound as the result of 'disruption of normal anatomic structure and function'. A wound can be also described as a defect or break in the skin, which results from physical or thermal damage, or from medical and physiological

conditions [1]. The wound healing is a dynamic process consisting of four continuous and precisely programmed phases, namely haemostasis, inflammation, proliferation and remodelling. Multiple factors, such as infections, stress, diabetes, smoking and obesity, can lead to impaired wound healing by interfering with one or more of these phases [2]. Once injured, the skin loses many of the protective defence mechanism of the intact skin and is colonized by the microorganisms on its surface. According to the replication status of the microorganisms, a wound can be classified as contaminated, colonized, locally infected and/or with spreading invasive infection [3]. The main bacterial mode of living in an infected wound is biofilm, which can be defined as a confluent community of adherent bacteria characterized by high cell densities and encased in an extracellular polymeric matrix that acts as physical barrier for biological and pharmaceutical antimicrobials [4, 5]. The presence of bacterial biofilm is associated with impaired epithelialization and granulation tissue formation and promotes a low-grade inflammatory response that interferes with wound healing [6]. The biofilm matrix plays an important role in the increased antibiotic resistance and has an enormous impact on medicine in terms of both therapeutic options and costs. Biofilm has been estimated to be associated with 65% of nosocomial infections, and the treatment costs associated with biofilm infection and chronic wounds have been estimated to be more than 1 billion USD annually in the United States [4, 7].

The increasing resistance of bacteria to antibiotics represents a huge concern, so that the World Health Organization recently has described the problem as 'so serious that it threatens the achievements of modern medicine' [8, 9]. Moreover, the large number of wound dressings and the limited guidelines available have induced an undesirable inconsistency in wound-care practice [10]. The local treatment of wounds is crucial for preventing infections, controlling exudates and providing the moist environment necessary for wound healing. At this purpose, efforts have been made by many research groups in the development of bioactive dressings, which can play an active role in wound protection and healing, and/or are able to release biomolecules and antimicrobials for prevention and treatment of wound infections [8, 11, 12]. A strategy for the treatment of infected wounds with increased resistance to traditional antibiotic therapy is the use of specific antibacterial agents immobilized on the surface of a material, thus providing a wide spectrum of activity in terms of bacterial toxicity and destructuration of the bacterial biofilm matrix [13].

This chapter aims to provide the reader with an overview of the most promising routes to develop advanced biomaterials with antimicrobial properties for the management of wound infections through nanotechnology approaches. The new generation and application of nanomaterials with novel properties are one of the century's key technology developments, which offer extraordinary opportunities in the pharmaceutical and medical field [14]. The great potential of nanometals such as zinc, copper and silver in wound dressing formulations and their use as antimicrobial agent in wound infections will be presented, along with the most recent efforts and results achieved by several research group in the definition of effective strategies for prevention of wound infection and for enhanced wound healing. Moreover, the most relevant results obtained by the authors of this chapter in the field of silver-based antibacterial treatments for wound-healing application will be presented and discussed.

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2. Wound infections

The skin represents a complex and effective barrier between the organism and the environment, preventing invasion of pathogens, chemical and physical insults and unregulated loss of water and solutes [15]. From a microbiological point of view, the primary function of normal and intact skin is to control the microbial populations that live on the skin surface and to prevent the underlying tissues from invasion and colonization by potential pathogens [16]. A wound, which represents the loss of skin integrity and following exposure of subcutaneous tissue, provides a moist, warm and nutritious environment for microbial colonization and proliferation. The abundance and diversity of microorganisms in any wound depend on different factors such as wound type, depth, location and quality, the level of tissue perfusion and the antimicrobial efficacy of the host immune response [16]. As all open wounds lack the protective covering of skin, microorganisms from endogenous or exogenous sources can be introduced onto the wound surface and can lead to colonization [17, 18]. Colonization is defined as the presence of proliferating bacteria on the surface of a wound, without a noticeable host response and without clinical signs and symptoms. Differently, wound infection depends on the pathogenicity of the microorganisms and on the immune competency of the host, and it is characterized by the presence of the clinical signs of infection such as erythema, pain, tenderness, heat, oedema, cellulites and abscess or pus [19, 20]. Within an infected wound, the main bacterial mode of living is a biofilm [4]. Bacterial biofilm consists of a complex microenvironment of single or mixed bacterial species encased within an extracellular polymeric substance (EPS) produced by bacteria. The moist, adhesive and proteinaceous wound surface represents the ideal environment for biofilm development [21]. If microbes attach to the wound surface and proliferate, the biofilm begins to develop and, when it is well established, it exhibits resistance to the host immune system and antimicrobials. At this stage, the biofilm is considered mature and difficult to eradicate, thus requiring specialized management practices and increasing the risk of non-healing and clinically infected wound (i.e. showing signs of inflammation or purulence) [17]. Biofilm infections compromise wound closure and contribute to wound chronicity. Persistent infections may arrest the growth of the repairing tissue and significantly [22] impairing the key healing processes such as the inflammatory immune response, granulation tissue formation and epithelialization. Although a moist environment is necessary for optimal wound healing, poor moisture/exudate control within a wound environment promotes the development of biofilm. Consequently, moisture balance is essential to optimize the wound environment for healing and minimize the opportunity for biofilms to develop [23–25]. Preventing biofilm is fundamental for faster and more effective treatment of chronic wounds [17]. However, despite the evidence for the presence of biofilm in wounds, research studies are required to detect biofilm and to determine the exact role played by multispecies biofilms in terms of delayed wound-healing process [26]. Different biofilms can be identified within a wound environment, such as aggregates of cells dispersed within the wound exudate, in slough or on necrotic tissue or on the wound dressing [27]. The microbial community presents multiple difficulties for clinicians in attempting to heal a chronic wound. Biofilms are resistant to many biocides, antibiotics and wound-care products. So, managing

biofilm often involves its physical removal from the wound surface with sharp or surgical debridement [28].

The control of biofilm is a key part of chronic wound management, but the use of antiseptic dressings for preventing and managing biofilm and infection still needs further research involving well-designed, randomized controlled trials [29]. The concept of a bacterial contamination, colonization and biofilm-related infection is now widely accepted in wound care, and the recognition of the biofilm and the evolution of topical antiseptics to control bioburden in wounds are considered strictly related to the concept of TIME (tissue, infection/inflammation, moisture balance and edge of wound) and to its relation with the current best practice [30]. In healthcare, infections lead to longer hospital stays for patients, specifically wound dressings and increased hospital costs [12]. Also worsened by an ageing population and the incidence of diabetes and obesity, the huge economic and social impact of wounds requires higher level of attention and resources to understand biological mechanisms underlying cutaneous wound complications [31].

Infections of the dermis, including burns, surgical site infections and non-healing diabetic foot ulcers affect over a million people. Individuals with diabetes represent a particularly vulnerable category because many of them develop foot ulceration during the course of their disease and undergo amputation. In addition to diabetics, several other groups of immune-compromised patient populations are plagued by slow-healing and non-healing wounds, such as trauma and burn victims, cancer patients and pressure ulcers in the elderly [32]. The incidence, morbidity, mortality and costs associated with non-healing of chronic skin wounds are dramatic. Chronic wounds cost millions of dollars annually in the healthcare industry of the United States, and biofilm significantly contributes many billions of dollars to the global cost of chronic wounds because of its role in delaying the wound-healing process and extending the inflammatory phase of repair [19, 33–35].

Along with the direct medical costs borne by the hospital or insurer, also indirect costs including lost patient productivity and diminished functional status should be considered [36]. The control of bioburden is recognized as an important aspect of wound management, which requires new solutions against microbes and their biofilms. Octenidine dihydrochloride and polyhexanide are effective and tolerated antiseptics used in wound management today, but antiseptics alone may not be able to achieve wound healing without addressing other factors such as the general health of patients or the wound's physical environment [37, 38]. Next generation of wound treatment strategies for non-healing chronic wounds can be achieved by adopting a biofilm-based management approach to wound care, in order to kill and prevent reattachment of microorganisms [26].

3. The antibacterial activities of metals

The antibiotic resistance of microorganisms determines serious complications like infection, and delayed wound healing and great concerns are related to the numbers and types of residing microorganisms and the ability of the host's immune system to control their prolif-

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eration [39–41]. Along with the emergence of microorganisms' resistance to multiple antibiotics, the increased healthcare costs and the huge social and economic impact of wound care have increased attention towards the biological mechanisms underlying cutaneous wound complications and have encouraged the researchers towards the development of new bactericide agents [31, 42]. The new frontier in clinical medicine and disease burden is represented by the medical applications of nanotechnology. Antimicrobial nanoparticles (NPs) offer an effective approach against numerous microorganisms where conventional antimicrobial agents fail [43, 44] and, compared with micron-sized particulate matter, have greater potential to enter cells and be more biologically active due to their small size and large surface area [X3]. Endowing ordinary products with new functionalities, consumer products containing engineered nanoparticles, are growing tremendously, and the global nanotechnology industry is becoming a major economic force of the twenty-first century [45, 46]. Some natural antibacterial materials such as zinc, silver and copper possess great antibacterial properties at nanometric size and their way of interaction with bacteria provides unique bactericidal mechanisms [43, 47].

Zinc is a transitional metal known since ancient time and widely distributed in the human environment. Today, many zinc-containing products are available for topical application in wound management due to the demonstrated improved re-epithelialization, reduced inflammation and bacterial growth. [48, 49]. ZnO has demonstrated to possess both antibacterial and anti-inflammatory properties and to accelerate the healing of both acute and chronic wounds. ZnO-NPs have exhibited antimicrobial capability and effectiveness against Gram-positive and Gram-negative bacteria, including pathogens such as *Escherichia coli*, *Salmonella*, *Listeria monocytogenes* and *Staphylococcus aureus* [49]. Several mechanisms have been reported for the antibacterial activity of ZnO-NPs. Some of them involve the interaction with membrane lipids and structure, leading to loss of membrane integrity, malfunction, and finally to bacterial death. ZnO-NPs may also penetrate into bacterial cells, thus resulting in the production of toxic oxygen radicals, which damage DNA, cell membranes or cell proteins [50–52]. The direct interaction between ZnO nanoparticles and cell surfaces affects the permeability of membranes and results in the inhibition of cell growth and cell death. Recent studies have also shown that these nanoparticles have selective toxicity to bacteria but exhibit minimal effects on human cells, thus suggesting their potential as nanomedicine-based antimicrobial agents [53, 54].

The bactericidal effect of metal nanoparticles has been attributed to their small size and high surface to volume ratio, and it is not merely due to the release of metal ions in solutions [55]. Copper ions released subsequently may bind with bacterial DNA molecules and disrupt biochemical processes inside bacterial cells. The exact mechanism behind bactericidal effect of copper nanoparticles is not fully elucidated; however, Cu-NPs were found to cause multiple toxic effects such as generation of reactive oxygen species, lipid peroxidation, protein oxidation and DNA degradation in *E. coli* [47, 56]. Although the potential use of copper-based nanomaterials in wound healing has recently emerged and also supported by the hypothesis that copper ions regulate the activity and expression of proteins involved in the wound repair process, however, the synthesis of stable metallic Cu-NPs still remains a challenge because of the rapid oxidation to $Cu2^{+}$ ions in air or aqueous media [47, 57].

In combination with silver, copper nanoparticles may give rise to more complete bactericidal effect against a mixed bacterial population [56]. The broad-spectrum antimicrobial activity of silver has been demonstrated against a wide range of microorganisms, including methicillin resistant bacteria, fungi and viruses [58]. Although the exact antimicrobial mechanism still represents a debated topic, many theories on the action of silver nanoparticles on microbes have been proposed. One of them involves the anchorage and penetration of the nanoparticles into the bacterial cell wall, which cause structural changes in the cell membrane such as permeability and respiration [59–62]. *E. coli* cells treated with silver nanoparticles appear damaged and show the formation of 'pits' in the cell wall of the bacteria, where the silver nanoparticles accumulate [59, 63]. Another antibacterial mechanism involves the release of silver ions and their interaction with the enzymes of the respiratory chain, the cell membrane and the DNA. The binding of silver to the membrane can inhibit the passage of nutrients through the membrane, interfering with normal concentration gradients between the cell and the surrounding environment, so leading to cell death [64, 65]. The formation of free radicals has also the ability to damage the cell membrane and makes it porous, thus causing the death of bacteria [66].

Nanosilver products safety data available in EPA's formal incident reporting database indicates that nanosilver products are safe. Silver nanoparticles can be easily incorporated into matrix materials and have demonstrated a great potential in applications of huge interest in nanotechnology [66]. When incorporated into wound treatment systems, silver nanoparticles can provide clinically relevance in the development of ideal environment for rapid and effective healing. These systems may significantly reduce the time required for the homeostatic equilibrium, while reducing the risk of complications and improving the physical appearance of the scar [67]. Silver nanoparticles induce rapid healing and improved cosmetic appearance in a dose-dependent manner and exert positive effects through their antimicrobial properties, reduction in wound inflammation and modulation of fibrogenic cytokines [68].

4. Metal nanoantimicrobials for wound dressing applications

Wound healing still represents a clinical challenge, which requires efficient wound management strategies [69]. Indeed, a crucial component of wound care is the choice of dressing. Many modern wound dressings have been developed to promote wound healing, such as dressings designed to absorb exudate, to provide an ideal moisture balance at the wound surface, to prevent maceration of surrounding tissue and infections and to reduce the bacterial load [70, 71]. Biomaterials, such as chitosan, alginate and collagen, play an important role as wound dressing materials by accelerating the healing of wounds and also because they can embed many nanoparticles for the development of metal nanoparticles-based wound dressings [69, 72]. Hydrogel-based wound dressings provide a cooling sensation and a moisture environment [73]. Several systems based on the combination of hydrogel and metal nanoparticles, such as zinc, copper and silver, have been recently proposed by many authors, aiming to develop wound dressings with antibacterial and enhanced wound-healing properties. For example, an alginate hydrogel/zinc oxide nanoparticles composite bandage was developed

by Mohandas *et al*. using a freeze-drying method. The results obtained demonstrated controlled degradation profile and faster blood clotting ability, along with excellent antimicrobial activity against different microorganisms such as *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and methicillin resistant *S. aureus* (MRSA) [74]. β-chitin hydrogel/nZnO composite bandages with interconnected micro-porous structure were also obtained by freeze-drying technique and proposed for infected wounds with large volume of exudate. Indeed, the wounds treated with the composite bandages promoted the healing and the re-epithelialization, enhanced collagen deposition and showed reduced number of bacterial colonies [75]. Other formulations involving the use of chitin hydrogel/nano ZnO composite bandages were proposed by Kumar *et al*. for burn, diabetic and chronic wound defects, because of the enhanced swelling, blood clotting and antibacterial properties achieved [76]. Kumar *et al*. have also developed a flexible and microporous chitosan hydrogel/nano zinc oxide composite bandages by incorporating the zinc oxide nanoparticles into chitosan hydrogel. *In vivo* wound-healing evaluations proved the enhanced healing ability of the materials without causing toxicity to cells [73]. Chitosan and copper nanoparticles co-introduced into an ointment preparation were investigated by Rakhmetova *et al*. and their combination at certain ratio of components, concentrations and physicochemical characteristics enhanced the antibacterial and wound-healing properties of the individual components [77]. Babushkina *et al*. demonstrated the efficacy of local application of a suspension of copper and zinc nanoparticles and of a drug based on chitosan and copper/zinc on bacterial contaminated purulent wound in rats [78]. Copper (II) cross-linked alginate hydrogels with body fluid absorption ability and haemostatic properties were developed and suggested by Klinkajon and Supaphol for the treatment of exudation/bleeding wounds and burns [79].

Among the recent trends against burn infections involving the use of noble metal antimicrobials, the most prevalent is represented by silver [80]. For nearly 50 years, silver-containing compounds have been the mainstay of burn wound care and silver sulfadiazine (SSD) has been the standard topical antimicrobial for burn wounds for decades [64, 81].

Silver has been used as an antimicrobial agent for a long time in the form of metal silver and silver sulfadiazine ointments [41], and today, there is scientific evidence supporting the use of silver-based wound dressings highlighting antimicrobial efficacy on biofilms within the *in vitro* and *in vivo* environments [40]. A number of wound dressings developed using silver have been approved by the US Food and Drug Administration (FDA) [82]. In addition to antimicrobial activity, silver dressings may modulate or reduce wound pain and limit the frequency of changes [83]. While topical silver creams and solutions require frequent application, the dressings can control the release of silver to the wound and require to be changed with less frequency [84]. Nanocrystalline silver dressings are considered as the gold standard in the conservative treatment of wounds and burns. It has been demonstrated that nanosilver has both anti-inflammatory effects and improves wound healing [85]. The healing response studied by Chowdhury *et al*. in laparotomy wounds after application of silver nanoparticles determined increased collagen expression from dermal fibroblasts, improved wound healing and reduced microbial load [86]. Rigo *et al*. have observed that the application of Ag NP-based dressing for prolonged time does not affect the proliferation of fibroblasts and keratinocytes,

leading to the restoration of the organized skin structure in previously unhealed parts of the wound [87]. Polyvinyl alcohol (PVA) hydrogels loaded with a controlled concentration of silver could combine the hydrogel property of keeping a moisturized environment, thus stimulating healing, with the effect of silver of inhibiting or killing the bacteria [88]. PVA-Ag NPs mats, fabricated by Nguyen *et al*. from a suspension of PVA and Ag NPs after microwave irradiation, possess high tensile stress and anti-bacterial activities at the same time and were proposed as a promoter of wound healing [89].

Hydrogels with polyvinyl pyrrolidone (PVP) and alginate were synthesized by Singh *et al*., and silver nanoparticles were incorporated in hydrogel network using gamma radiation. The hydrogel-containing nanosilver demonstrated strong antimicrobial effect and complete inhibition of microbial growth, absorption capacity, moisture permeability and the ability to prevent fluid accumulation in exudating wound [90]. Chitosan-PVP-nanosilver oxide wound dressings showed excellent results such as good swelling capability, good antibacterial activity and also transparency of the film, which helps to regularly monitor the condition of wound without removing it from the wound site [81]. The silver nanocrystalline chitosan dressing described by Lu *et al*. significantly increased the rate of wound healing and was associated with silver levels in blood and tissues well below those associated with the silver sulfadiazine dressing ($p < 0.01$) [91]. Silver released in a moist wound surface environment significantly increases the rate of re-epithelialization compared to a standard antibiotic solution, as demonstrated by Demling *et al*. [92].

The application of both silver dressings and antibiotic therapy can have a synergistic effect in improving wound healing, since the interaction of silver released from the dressings significantly increases the susceptibility of bacterial cells within biofilms to antibiotics. Moreover, the reduction of the silver particle size to nanoscale level provides better penetration and accumulation of silver within biofilms, thus contributing to the effectiveness of the silver based product [93]. As silver is the most widely used substance to obtain antimicrobial effects, different formulations involving the use of silver-containing solution or silver nanoparticles have been developed. Among the most widespread antimicrobial dressings, silver foam dressings and silver alginate dressings are applied to exuding wounds and demonstrate improved performances than the traditional gauze dressings [94]. Silver alginate wound dressings have demonstrated beneficial effects on wound healing, in terms of wound exudates levels and prevention from wound infections [95–97]. Silver alginate dressings are particularly known for the prolonged antimicrobial efficacy, which indicates sustained availability of ionic silver and suggests the necessity of reduced dressings changes [98]. Excellent and sustainable controllability of Ag^+ release were obtained by the AgNP-bacterial cellulose hybrid nanostructure developed by Wu *et al*., which offered promising results for antimicrobial wound dressing through the addition of silver nanoparticles. Indeed, bacterial cellulose has attracted great attention as novel wound dressing material, but it has no antimicrobial activity [99]. The silver nanoparticle/bacterial cellulose gel membranes developed by Wu *et al*. demonstrated *in vivo* excellent healing effects in a second-degree rat wound model and were proposed as promising antimicrobial wound dressing with good biocompatibility to promote scald wound healing [100].

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The use of cellulose/nanosilver sponge materials was strongly encouraged in case of serious wound infection and *in vivo* tests confirmed accelerate infected wound healing and absorbing capacity for wound exudate [101]. Other examples of composite scaffolds are biocomposite films containing alginate and sago starch impregnated with silver nanoparticles [102], chitin/nanosilver composite scaffolds and electrospun mats doped with nanosilver, zinc oxide, etc., as degradable and non-degradable polymers [103, 104]. For example, polymeric nanofilm-containing silver nanoparticles exhibit antimicrobial activity at loadings and release rates of silver lower than conventional dressings. When placed on a moist wound, the PVA dissolves and the silver-loaded nanofilm results immobilized on the wound bed, thus allowing the normal and complete wound closure by re-epithelialization [104]. A general overview of some relevant techniques adopted to incorporate nanometals into hydrogel network for wound dressing production is reported in **Table 1**.

Nanomaterial	Description of the technique	References
Zinc oxide (ZnO)	Hydrogel/zinc oxide nanoparticles (nZnO) composite wound dressings developed by freeze-dry method from the mixture of nZnO and alginate or chitosan hydrogels.	[73–76]
Copper oxide (CuO)	Cu^{2+} cross-linked alginate hydrogels by a two-step cross-linking technique. (i) Preparation of solid alginate films through solvent-casting method from soft gels of alginate solutions lightly cross-linked using a Cu^{2+} sulphate solution; (ii) further cross-linking of the films in Cu^{2+} sulphate solution using a dipping method.	[79]
Silver nanoparticles	Silver nanoparticles incorporated in hydrogels network using microwave/electro-spinning, gamma radiation, self-assembling. Composite sponges and films obtained by freeze drying and solvent casting.	[89–91, 101, 102]

Table 1. Overview of some relevant techniques for production of nanometal-based antimicrobial wound dressings.

The widespread use of silver-based dressings in surgery is promising, inexpensive and well tolerated. The placement of silver-nylon dressings over incision sites in colorectal, neurological, spinal, cardiovascular and orthopaedic procedures at the time of primary closure has been described by Abboud *et al*. as effective in reducing surgical site infection rates [105]. Commercial dressings impregnated by immersion in solutions of AgNPs using different concentrations of silver from 125 to 1000 ppm demonstrated anti-biofilm efficacy against *Pseudomonas aeruginosa* [70]. Conventional cotton gauzes were modified by Sannino *et al*. through the deposition of silver-based nanocoatings obtained by a patented photo-assisted deposition process, which allows the silver treatment of natural and synthetic materials for different applications [106–108]. Particularly, the technology adopted involves the preparation of a silver-based solution, and then the deposition of the silver solution onto the surface of the material through spray coating or dip coating and the following exposure of the wet material to ultraviolet light, in order to induce the photo-chemical deposition of silver nanoparticles on the surface of the product. Indeed, the synthesis and deposition of the silver nanoparticles

occur simultaneously onto the surface of the material because the photo-reduction reaction induced by UV irradiation determines the conversion from the silver precursor to metal silver nanoparticles. The silver coatings deposited are characterized by a strong adhesion to the substrate, good antimicrobial capability and biocompatibility and low silver release [109]. Cotton gauzes treated with low amounts of silver have demonstrated good antimicrobial activity against different bacterial strains and fungi, and the good antibacterial properties were further confirmed in simulated working conditions such as after incubation in artificial exudate inoculated with bacteria [110]. **Figure 1** reports the agar diffusion test performed on untreated gauze and gauze treated with silver by adopting the technology described using *Staphylococcus aureus* as tester microorganism.

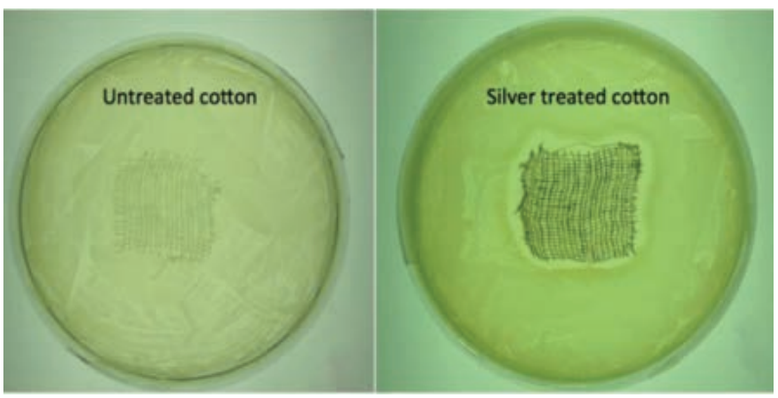

Figure 1. Agar diffusion tests on untreated gauze and cotton gauze treated by photo-reduction technology.

Description of the product	Application	References
Polyester textile mesh impregnated with hydrocolloid particles, vaseline and silver sulphate.	Low to moderate exuding acute and chronic wound at risk of infection.	[112, 113]
Sodium carboxymethylcellulose hydrofibres combined with ionic silver.	Acute and chronic wounds at risk of infection, with moderate and abundant exudate.	[112, 113]
Flexible polyethylene cloth coated with nanocrystalline Ag particles.	Infected ulcers, surgical wounds and burns.	[87, 112]
Silver nylon cloth/activated charcoal.	Most type of chronic wounds and infected wounds and ulcers.	[112, 114]

Table 2. Examples of commercial silver-containing dressings.

Although the impregnating silver solution was prepared by using a percentage of silver lower than 0.5 wt/v%, the antibacterial test clearly demonstrated that the presence of the silver coating successfully inhibited the bacterial growth beneath and around the sample, thus indicating a good potential of product as antibacterial wound dressing. Also flax substrates have been treated with silver by adopting the same technology and the microbiological activity was still confirmed after industrial washing, thus suggesting the excellent stability of the

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coating on the surface of the textile material [111, 112]. In order to provide flax substrates with a moist environment and antibacterial capability at same time, Paladini *et al*. has developed a wound dressing biomaterial based on silver-doped self-assembling di-phenylalanine hydrogels. These peptide-based hydrogels have some similarities to the extracellular matrix due to their high hydration and nanofibrous architecture, which make them suitable for wound dressing applications where the wound environment needs to be controlled to prevent microbial invasion and to favour tissue regeneration [113]. Along with research efforts, in recent years, many silver-based wound dressings have been marketed for medical problems such as wide-body burns, sepsis in traumatic wounds and chronic diabetic ulcers [114, 115]. Some examples are collected in **Table 2**.

5. Conclusion and future perspectives

Nanotechnology is gaining huge impetus in the present century due to the drastic changes of chemical, physical and optical properties of metals at nanoscale size [84]. The cutting-edge combination of nanotechnology with medicine offers unprecedented opportunities to revolutionize currently available macro-scale therapeutics. Nanoparticles-based delivery systems can be highly beneficial to improve the therapeutic power of biological and synthetic molecules [90]. Due to the knowledge of cellular and molecular processes underlying wound healing, the new therapeutic approaches act directly on cellular and subcellular events during the healing process [90].

In recent years, metal nanoparticles/polymer composites have created lot of attraction due to their wide range of applications [41]. The interest in broad-spectrum antimicrobial agents is particularly increasing for medicated wound dressings, in order to control colonization of wounds by opportunistic pathogens. Medicated wound dressings have demonstrated efficacy *in vitro* against planktonic microorganisms; however, *in vivo* bacteria are organized in biofilms, which is more challenging to control and eradicate [116]. Silver nanoparticles, in particular, have been identified as potent antimicrobial agent and are being evaluated in different medical applications ranging from silver based dressings to silver coated medical devices [117]. Silver in ionized form or nanoparticles exhibits excellent antimicrobial and antifungal properties and efficacy in preventing biofilm formation by pathogenic bacteria. Silver-based wound dressings are widely used in clinical practice and show promising results in healing of contaminated wounds [118].

Despite its recognized importance, there have not been systemic studies that probe the targeting efficiency of nanoparticles nor international standards on their toxicology and biocompatibility [119]. Despite their promise, further studies are needed to elucidate the pharmacokinetics of nanoparticles and potential for *in vivo* toxicity. However, to date, studies have found limited toxicity without evidence of systemic absorption [120].

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