Chapter 17

Antimicrobial Dressings for Improving Wound Healing

Omar Sarheed, Asif Ahmed, Douha Shouqair and Joshua Boateng

Additional information is available at the end of the chapter

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Abstract

Wound healing occurs by a series of interrelated molecular events which work together to restore tissue integrity and cellular function. These physiological events occur smoothly in normal healthy individual and/or under normal conditions. However, in certain cases, these molecular events are retarded resulting in hard-to-heal or chronic wounds arising from several factors such as poor venous return, underlying physiological or metabolic conditions such as diabetes as well as external factors such as poor nutrition. In most cases, such wounds are infected and infection also presents as another complicating phenomenon which triggers inflammatory reactions, therefore delaying wound healing. There has therefore been recent interests and significant efforts in preventing and actively treating wound infections by directly targeting infection causative agents through direct application of antimicrobial agents either alone or loaded into dressings (medicated). These have the advantage of overcoming challenges such as poor circulation in diabetic and leg ulcers when administered systemically and also require lower amounts to be applied compared to that required via oral or iv administration. This chapter will review and evaluate various antimicrobial agents used to target infected wounds, the means of delivery, and current state of the art, including commercially available dressings. Data sources will include mainly peer-reviewed literature, clinical trials and reports, patents as well as government reports where available.

Keywords: antimicrobial, bioburden, dressings, infection, wounds, wound healing, bacterial resistance

1. Introduction

A wound may be defined as a disruption to the physiological arrangement of the skin cells and a disturbance to its function in connecting and protecting underlying tissues and organs. It may be primary caused by accidental cut, tear, scratch, pressure, extreme temperatures, chemicals, and electrical current, or secondary to surgical intervention or disease (i.e., diabetes, ulcers, or carcinomas) [1]. It ranges from superficial (affecting the epidermis) to partial-thickness (affecting both epidermis and parts of the dermis) and full-thickness (including subcutaneous fat and bones) wounds [2]. Wound healing is a physiological process, by which the living body repairs tissue damages, restores its anatomical integrity, and regains the functionality of the injured parts. A wound can be closed by primary intention or left to heal by secondary intention, and in both ways the healing process occurs through a series of overlapping events and is influenced by a number of intrinsic and extrinsic factors [3].

1.1. Acute wounds

Acute wounds can heal within a limited amount of time, usually show no complications, and are characterized by the loss of skin integrity (injury) that occurs suddenly. The injured tissue heals in a predictable manner where platelets, keratinocytes, immune surveillance cells, microvascular cells, and fibroblasts play major roles in the restoration of tissue integrity [4]. These wounds are either surgical or traumatic [5].

1.2. Chronic wounds

Chronic wounds are wounds that do not heal within normal period and are associated with predisposing factors that weaken the integrity of dermal and epidermal tissues. Those factors either disrupt the balance between wound bioburden and the patient's immune system or impair the wound healing cycle. In terms of duration, if the wound fails to heal or shows no sign of recovery within 12 weeks, it is considered a chronic wound. Predisposing factors may affect the tissue perfusion causing chronic wounds such as vascular ulcers, associated with metabolic disorders such as diabetes causing diabetic foot ulcers [6]. They can be identified by criteria such as delayed healing and friable granulation tissue, prolonged inflammatory phase, persistent infection, and presence of resistant microorganisms [7–10].

1.3. Wound healing

The repair (wound healing) process involves four overlapping biochemical, physiological, and molecular phases.

I. Hemostasis

> This stage is characterized by microvascular injury and release of blood components at the wound site. Platelets come into contact with and adhere to the wall of the injured blood vessels. This adherence activates the platelets to release cytokines, growth factors, and numerous pro-inflammatory mediators, resulting in platelet aggregation and triggering the intrinsic and extrinsic coagulation path-

ways to form a fibrin clot which limits further blood loss. Growth factors produced by the platelets initiate the healing cascade [11, 12].

II. Inflammatory phase

The inflammatory phase starts at the same time as hemostasis sometime between a few minutes after injury up to 24 h and lasts for about 3 days. Aggregated platelets store vasoactive amines such as prostaglandins and histamine while other amines from granules released by mast cells, in response to injury, result in increased microvascular permeability and vasodilation, leading to exudation of fluid into the extravascular space [13]. This allows the migration of monocytes and protein-rich exudate into the wound and surrounding tissue, resulting in edema. These are typical signs of the inflammation process, and patients start complaining about pain at the site of injury within 24 h.

III. Proliferative phase

This phase commences after the inflammatory phase wanes. The remaining inflammatory cells produce growth factors to initiate angiogenesis, which is important to keep adequate blood supply within the wound bed [14]. Newly formed blood vessels will contribute to granulation tissue (composed of collagen and extracellular matrix) formation and provide the required nutrients.

IV. Maturation phase

This commences when the wound is superficially sealed. It involves the re-epithelialization and remodeling of newly formed tissues in the proliferative phase and restoration of epidermal integrity [15]. It also involves transferring collagen III to collagen I.

1.4. Factors affecting wound healing

Multiple factors affect wound healing and lead to the impairment of healing classified into local and systemic factors [16].

1.4.1. Oxygenation

Oxygen is crucial to wound healing and for resistance to infection, and used for cellular energy production by adenosine triphosphate [17]. It acts on different levels of wound healing by inducing angiogenesis, keratinocytes differentiation, migration, re-epithelialization, fibroblast proliferation, and collagen synthesis, and promotes wound contraction [18]. When injury occurs, temporary hypoxia and oxygen are useful to trigger wound healing by inducing the production of cytokines and growth factors from macrophages, keratinocytes, and fibroblasts [16]. Chronic wounds are generally hypoxic with oxygen tissue tension of 5–20 mm Hg compared to normal levels of 30–50 mm Hg [19]. Factors predisposing chronic wounds such as advancing age and diabetes can induce poor oxygenation through impaired vascular flow. Interventional revascularization therapies have been used to reverse hypoxic conditions in diabetic foot ulcers [20]. However, it has also been reported that such procedures can cause

adverse effects to diabetic patients [21]. Recently, some topical foam dressings containing dissolved oxygen were developed to increase oxygen perfusion into the chronic wound area [22]. Results showed that dissolved oxygen from topical foam dressing penetrates into skin layers compared to topical gaseous oxygen.

1.4.2. Wound bioburden and infection

1.4.2.1. Bioburden

The intact skin acts to control the microbial population on the skin surface itself [23]. Once the integrity is lost through injury, the subcutaneous tissue becomes exposed, providing an environment for colonization and growth of microbes. However, this does not necessarily lead to an infection as there is a balance between the wound bioburden and the immune system [24].

1.4.2.2. Wound infection

Skin microflora is present to about 10^5 colonies without any clinical problems [25]. However, if the balance is disrupted, microorganisms will proliferate and start a microbiological chain of events by invading tissues resulting in an inflammatory response which may lead to tissue damage and delayed healing [7]. Once it causes damage to the host tissue, infection will arise. One of the consequences of infection is the prolonged inflammation due to prolonged elevation of pro-inflammatory cytokines, which causes the wound to enter the chronic stage and fail to heal within the expected 8–12 weeks [26]. This prolonged inflammation is also associated with increased levels of matrix metalloproteases which are capable of degrading the extracellular matrix which is the key component of proliferative phase of wound healing [9]. This increase in protease levels happens at the expense of the naturally occurring protease inhibitor levels that are decreased. From a microbiological perspective, wound infection is described as the presence of replicating microorganisms at the wound site overwhelming the host's immune system. It delays wound healing due to the release of toxins and exhibits active signs and symptoms of infections.

1.4.2.3. Common bacterial species present in chronic wounds

Generally, most infected wounds are polymicrobial and are commonly contaminated by pathogens found in the immediate environment, the endogenous microbes living in the mucous membranes, and the microflora on adjacent skin. Bacteria are the main cause of wound infection among other microorganisms present in the skin, though other microorganisms such as fungi have been implicated in certain mixed infections. In the initial stages of chronic wound formation, Gram-positive organisms such as *Staphylococcus aureus* and *Escherichia coli* are predominant [9]. In the later stages, Gram-negative *Pseudomonas* species are common and tend to invade deeper layers in the wound causing significant tissue damage [27]. Other aerobes implicated include *Staphylococci* and *Streptococci* species as well as anaerobic bacteria and are estimated in 50% of chronic wounds [28, 29].

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1.4.3. Chronic wounds and biofilm

Biofilm is defined as "a microbially derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are embedded in a secreted matrix of extracellular polymeric substances (EPSs), and exhibit an altered phenotype with respect to growth rate and gene transcription" [30]. Firstly, conditioning film forms and is composed of proteins and polysaccharide molecules adsorbed onto the solid surface. This makes the surface ready to receive the first cells of the insipient biofilm. Secondly, bacteria will start to approach and attach onto the surface by forces such as van der Waals forces and the negative electrostatic charges of bacterial surface [31]. The attached bacteria become encased in a polymeric matrix called extracellular polymeric substance (EPS). This bacterial attachment induces a phenomenon called quorum sensing, which is responsible for "the regulation of gene expression in response to fluctuations in cell population density" [32]. This causes the bacteria within biofilm to alter their phenotypes resulting in the production of more virulent factors in response to signals from other bacteria within biofilm. These factors with barrier made from EPS contribute to the increased resistance to antibiotics. It has been suggested that EPS can interact with antibiotics spontaneously thereby preventing them reaching the bacteria to exert their antimicrobial activity [33]. The biofilm also protects the bacteria from host defenses by the covering of glycocalyx while bacteria secrete products within the film which makes phagocytic penetration poor [34].

This understanding is of great importance for intervention modalities in chronic wounds especially the use of antimicrobial wound dressing. For example macrolides can have inhibitory effect on the film formation or induce phagocytic invasion into biofilms [35]. Furthermore, in clinical wound management, it is always essential to promptly clean the wound and remove necrotic tissue and foreign material (e.g. bacteria and biofilms) from areas around the wound to improve the chances of enhanced wound healing, and this is known as debridement [1]. This is important because the presence of necrotic tissue increases the risk of infection and sepsis, which prolongs the inflammatory phase. Several approaches are employed including surgical removal, wound irrigation (e.g. saline and antiseptics such as chlorhexidine), autolytic rehydration using hydrogel dressings, applying enzymes such as collagenases or streptokinase preparations as well as using maggots to selectively dissolve necrotic and infected tissue (including biofilms) without destroying healthy or newly formed tissue [1].

2. Wound dressings

Wound dressings can maintain a moist environment in the wound which helps in proliferation and migration of fibroblast and keratinocytes. Moisture in the wound serves as a transporter for enzymes, growth factors, and hormones, thus inducing cell growth. Moist wound dressings promote collagen synthesis and decrease scar formation [36] which help wounds to heal faster [37]. Modern moist wound dressings can be classified depending on their materials (synthetic and natural polymers) and physical forms (hydrogels, hydrocolloids, films, and wafers).

Hydrogels consist of hydrated polymers which make them hydrophilic in nature. Water content is higher than 95%, and as a result they cannot absorb much exudate and cause maceration. But, this dressing is very useful in dry wound which can maintain moisture within wounds [36]. A Cochrane Review [38] of hydrogel dressings for healing diabetic foot ulcers suggests that hydrogel dressings are more effective than basic wound contact dressing. Hydrogels have advantages of autolytic debridement of slough and necrotic tissue and do not support bacterial growth [39, 40]. Hydrocolloid dressings are occlusive and can absorb wound exudate into the matrix to help improve healing. It can work for a sustained period of time, thus reducing the frequency of dressing changes. It also assists autolysis of necrotic materials [40]. Due to its extra absorbent nature, it is widely used in the treatment of cavity wounds [41]. A Cochrane Review [42] reported that any type of hydrocolloid and other dressings have no difference in efficacy. Foam dressings are highly absorptive, protective, and comfortable to the body surface. They promote thermal insulation, angiogenesis, and autolysis [43]. Film dressings are adhesive, transparent, durable, comfortable, and cost effective. Due to their transparency, the wound bed can be monitored without removing the dressing. However, films are suitable for superficial pressure wounds. The disadvantage of film dressing is maceration of wound exudate [36]. Lyophilized wafers are one of the most recent moist dressings proposed for wound care. Due to their highly porous nature, they can absorb high amounts of exudate rapidly which improves wound healing. Wafers can carry both antibacterial and anti-inflammatory drugs at the same time which give dual effects of inhibiting bacteria and reducing inflammation [44]. Wafers have good adhesion and diffusion properties [45] while Labovitiadi et al. [46] reported that wafers are a compatible delivery system for both insoluble and soluble antimicrobial drugs that exhibit better antimicrobial activity.

3. Antimicrobial wound dressings

3.1. Need for antimicrobial wound dressing

The major need for antimicrobial dressing is drug resistance to bacteria. Zubair et al. [47] isolated bacteria from diabetic foot ulcer patients and their resistance to different classes of drugs with the penicillins showing highest susceptibility to resistance followed by cephalosporins (54%), quinolones and fluoroquinolones (52.8%), aminoglycosides (38.5%), beta lactams (32.2%), and carbapenems (18.4%). Further, most chronic wound sufferers such as older patients and diabetics with leg and foot ulcers suffer from complications of poor circulation at the lower extremities, which makes oral and IV antibiotics ineffective. In addition, topical dressings are able to avoid the adverse effects of systemic administration (oral and IV) of high antibiotic doses including nausea, vomiting, diarrhea, allergic reactions, leukocyturia, insomnia, headache, and vaginosis, when only small doses above the minimum inhibitory concentration are required at the infected wound site. Finally, production costs of most dressings are less than those of IV or oral products.

3.2. Advanced medicated antimicrobial wound dressings

Antimicrobial dressings can be broadly classified into two groups as antiseptic or antibiotic dressings. Antiseptic dressings have broad spectrum activity which can kill or inhibit bacteria, fungus, protozoa, viruses, and prions [48]; however, some antiseptic dressings often show dose-dependent cytotoxicity to the host cells including keratinocytes, fibroblasts, and leukocytes [49, 50]. The concentration of povidone iodine greater than 0.004 and 0.05% is completely toxic to keratinocytes and fibroblasts, respectively [51]. Cadexomer iodine is reported to be nontoxic to fibroblasts *in vitro* at concentrations of up to 0.45% [52]. Chlorhexidine also shows dose-dependent toxicity to fibroblasts at concentrations between 0.2 and 0.001% [53, 54]. Moreover, silver-impregnated dressings have been reported to be more cytotoxic to epidermal keratinocytes and dermal fibroblasts than honey-based dressings [55]. On the other hand,

Dressing type	Polymers	Drug	Reference
Pads	Bovine serum albumin	Ciprofloxacin	[58]
Nanofibers patch	PVA/sodium alginate	Ciprofloxacin	[59]
Hydrogel	Polyethylene glycol	Ciprofloxacin	[60]
Sponges	Alginate/chitosan	Ciprofloxacin	[61]
Films	Chitosan/gelatin	Ciprofloxacin	[62]
Nanofibers	PVA/regenerated silk fibroin	Ciprofloxacin	[63]
Nanofiber mats	Polyurethane/dextran	Ciprofloxacin	[64]
Nanofiber mats	PVA/poly(vinyl acetate)	Ciprofloxacin	[65]
Films	Poly (2-hydroxymethacrylate)	Ciprofloxacin	[66]
Films	PVA/aminophenylboronic acid	Ciprofloxacin	[67]
Collagen dressing	Collagen	Ciprofloxacin	[68]
Hydrogels	Keratin	Ciprofloxacin	[69]
Films	Sodium carboxymethyl cellulose/gelatin	Ciprofloxacin	[70]
Scaffolds	Chitosan/polyethylene glycol	Ciprofloxacin	[71]
Hydrogel films	Carboxymethyl chitin	Chlorhexidine gluconate	[72]
Gel	Chitosan	Ofloxacin	[73]
Wafers and films	Polyox/carrageenan	Streptomycin	[74–76]
Films	PVA/sodium alginate	Clindamycin and nitrofurazone	[77, 78]
Films	PVA/dextran	Gentamicin	[79]
Scaffolds	Collagen	Doxycycline	[80]
Microspheres	Gelatin	Doxycycline	[81]
Microspheres	Chitosan	Levofloxacin	[82]
Nanofibrous scaffolds	Chitosan/poly(e-caprolactone)	Levofloxacin	[82]
Hydrogels	Polyvinylalcohol	Nitric oxide	[83]
Hydrogels	poly(2-hydroxyethyl methacrylate)	Nitric oxide	[84]
Hydrogels	*S*-Nitrosothiol	Nitric acid	[85]

Table 1. Summary of antibiotic dressings reported in the literature.

antibiotic dressings (**Table 1**) are nontoxic and can work effectively on the target sites without damaging host tissues [49]. The ideal antimicrobial dressing should have broad spectrum activity against all major microorganisms, be nonallergic and nontoxic to host cells, have the ability to drain exudate and maintain a moist wound environment, should release drugs rapidly in a sustained manner, should reduce malodor, and be cost effective [56, 57].

3.3. Silver-based dressings

Silver is a natural broad spectrum antibiotic, and its dressings have not yet shown any bacterial resistance. Silver exists in different forms such as silver oxide, silver nitrate, silver sulfate, silver salt, silver zeolite, silver sulfadiazine (SSD), and silver nanoparticles (AgNPs). Before the eighteenth century, silver nitrate was used for leg ulcers, epilepsy, acne, and venereal infections [86]. Currently different forms of silver are widely used in acute wound (burns, partial-thickness burns, freshly grafted burns, second-degree burns, surgical/traumatic wounds, colorectal surgical wounds, pilonidal sinus, and donor site), and chronic wound (pressure ulcers, leg ulcers, and diabetic foot ulcers) healing [87].

3.3.1. Antimicrobial activity of silver dressings

Antimicrobial activity of silver dressings depends on the amount and rate of silver release and its toxicity to bacterial, fungal, and algal cells. Silver works by interacting with thiol groups present in bacterial cells thus stop their respiration process. In the case of *E. coli*, silver prevents phosphate uptake and catalysation of disulfide bonds with silver tending to change the nature of protein structure in *E. coli.* The degenerative changes in cytosolic protein cause cell death [86, 88]. Feng et al. [89] reported antibacterial mechanism of action of silver ions on *E. coli* and *S. aureus* and showed that silver ions penetrate into bacterial cells and condense DNA molecules which inhibit their replication capabilities leading to cell death. Matsumura et al. [90] introduced two bactericidal mechanism actions of silver zeolite on *E. coli*. Firstly, silver ions released from silver zeolite come into contact with cells and penetrate into cells, altering the cellular functions that cause cell death. Secondly, silver ions inhibit respiration process through the generation of reactive oxygen molecules. Silver zeolite has also been reported against oral microorganisms (*Streptococcus mutans, Lactobacillus casei, Candida albicans, and S. aureus*) [91].

Silver nanoparticles show the most efficient antimicrobial activity amongst all forms of silver. The bactericidal effects of AgNPs depend on the size, shape, surface characteristics, and their dose [88, 92–101]. It has been reported that 75 μg ml^{-1} of AgNPs having 1–100 nm particle size inhibits all bacterial strains (specifically, *E. coli, Vibrio cholerae, Salmonella typhi, and Pseudomonas aeruginosa).* It has also been reported nanoparticles having particle size ~1–10 nm have higher affinity of attaching to the surface of the cell membrane as compared to larger nanoparticles. Because of this nature, AgNPs can attach to the larger surface area of bacterial cell membrane and cause native membrane porations which cause cell damage [92]. Ivask et al. [93] examined toxicity of silver nanoparticles to bacteria (*E. coli*), yeast (*Saccharomyces cerevisiae*), algae (*Pseudokirchneriella subcapitata*), crustacean (*Daphnia magna*), and mammalian cells (murine fibroblast) according to their particle sizes ranging from 10 to 80 nm. They confirmed that the smaller-sized nanoparticles showed highly toxic effect. The review of Rai et al. [88] and Rizzello

et al. [92] explained that truncated triangular nanoparticles are the strongest biocidal active products compared to spherical- and rod-shaped nanoparticles. 1 μg of truncated triangular nanoparticles shows greater activity than 12.5 μg of spherical-shaped nanoparticles and 50–100 μg of rod-shaped nanoparticles due to the enhancement of electrostatic interaction with bacterial cells (**Table 2**).

Dressing type	Brand name	Silver form
Contact layer dressings	Restore contact layer	Silver sulfate
	Acticoat Flex 3; Acticoat Flex 7	Elemental silver
	KerraContact Ag	Silver salt
	SilverDerm 7	Ionic silver
	Silverlon Wound & Burn Contact Dressings	Ionic silver
	Therabond 3D with Silvertrak™ Technology	Silver
Foams	RTD	Silver zirconium phosphate
	Acticoat Moisture Control	Elemental silver
	Allevyn Ag	Silver sulfadiazine
	Aquacel Ag	Ionic silver
	Biatain Ag Adhesive	Silver
	HydraFoam/Ag	Silver
	MediPlus Comfort Border Foam Ag+	Silver
	Mepilex Ag	Silver
	Optifoam Ag Adhesive	Ionic silver
	PolyMem MAX Silver Non-Adhesive Dressing	Silver
	Silverlon Negative Pressure	Ionic silver
	UrgoCell Silver/Cellosorb Ag	Silver salts
	V.A.C GranuFoam Silver	Silver
	Silverlon Acute Burn Glove	Silver
	Silvercel	Elemental silver
Fibers/clothes/mats /pads/others	Tegaderm Ag Mesh Dressing	Silver sulfate
	Absorbent Dermanet Ag+ Border	Silver
	Acticoat	Elemental silver
	Allevyn Ag Non-Adhesive	Silver sulfadiazine
	Durafiber Ag	Ionic silver
	Exsalt SD7	Silver

Dressing type	Brand name	Silver form
	Gentell Calcium Alginate Ag	Silver
	Silverlon Calcium Alginate	Silver
	Simpurity Silver Alginate Pads	Silver particles
	Urgotul SSD	Silver sulfadiazine
	Vliwaktiv Ag	Silver
	Acticoat 7	Elemental silver
	Arglaes film	Silver
Films/meshes	Avance	Silver
	Acticoat Absorbent	Elemental silver
	Algicell Ag	Silver
Alginate based	Algidex Ag	Ionic silver
	Biatain Alginate Ag	Silver
	CalciCare	Silver zirconium
	DermaGinate/Ag	Silver
	Dermanet Ag+	Silver
	Maxorb ES Ag+	Silver
	Maxorb Extra Ag+	Silver zirconium phosphate
	McKesson Calcium Alginate with Antimicrobial Silver	Silver
	Opticell Ag+	Ionic silver
	Restore Calcium Alginate Dressing with Silver	Ionic silver
	Sofsorb Ag	Silver
	Sorbalgon Ag	Ionic silver
	Suprasorb A + Ag Calcium Alginate	Silver
	Askina Calgitrol Ag	Silver alginate
	Invacare Silver Alginate	Silver sodium hydrogen zirconium phosphate
	Melgisorb Ag	Silver
	SeaSorb Ag	Ionic silver
	Silvasorb	Ionic silver
	Sorbsan Silver	Silver Sorbsan
	Algidex Ag	Ionic silver
	Urgotul SSD/S.Ag	Silver sulfadiazine

Dressing type	Brand name	Silver form
Gauze	Aquacel Ag	Ionic silver
	Arglaes Powder	Silver
Hydrofiber	Cardinal Health Hydrogel +Ag	Silver
Powder	DermaSyn/Ag	Ionic silver
Hydrogel	Elta Silver Gel	Silver
	ExcelGinate Ag	Silver
	Gentell Hydrogel Ag	Silver sulfadiazine
	SilvaSorb Antimicrobial Silver Dressing	Ionic silver
	Silver-Sept Silver Antimicrobial Skin & Wound Gel	Silver
	SilverMed Amorphous Hydrogel	Silver
	Silverseal	Silver
	SilvrSTAT Gel	Silver nanoparticles
	Viniferamine Hydrogel Ag	Silver
	Silverseal	Silver oxide
	Silver-Sept Antimicrobial Gel	Silver salt
	DermaCol Ag Collagen Matrix	Silver
	Puracol Plus Ag+ MicroScaffold Collagen	Silver
Collagen based	SilvaKollagen Gel	Silver
	Silverlon Adhesive Strips	Silver
	Contreet Hydrocolloid	Silver
Adhesive strips	Silverseal Hydrocolloid	Silver
Hydrocolloid	SilverMed Antimicrobial Wound Cleanser	Silver microparticles

Table 2. List of selected commercially available antimicrobial silver-containing dressings [22, 102, 103].

3.3.2. Silver dressings in wound healing

AgNPs (~11 to ~12 nm) containing gelatin fiber mats were prepared by electrospinning process and inhibited major microorganisms present in wounds [104]. Lin et al. [105] compared silver-containing carbon-activated fibers with commercially available silver-containing dressings and showed the silver-containing carbon-activated fibers to exhibit antibacterial activity and biocompatibility and promoting granulation and collagen deposition. A novel chitosan–hyaluronic acid composite with nanosilver was reported as a potential antimicrobial wound healing dressing for diabetic foot ulcers possessing high porosity, swelling, water uptake abilities, and biodegradable and potential blood clotting ability. The authors proved the inhibitory effects on *S. aureus*, *E. coli*, MRSA, *P. aeruginosa,* and *Klebsiella pneumoniae* [106].

In a related study, chitosan incorporated with polyphosphate and AgNPs was studied. The polyphosphate acts as a procoagulant which boosts blood clotting, platelet adhesion, and thrombin generation [107]. A similar scaffold dressing was developed by incorporating silver nanoparticles with chitin and showed antibacterial and blood clotting activity [108]. In another study, AgNPs containing hydrogel without any cytotoxicity but with antibacterial activity were reported [109]. Various inorganic forms of silver including silver zeolite, silver zirconium phosphate silicate, and silver zirconium phosphate demonstrate antimicrobial activity against oral microorganisms [91]. Pant et al. [110] stated AgNPs containing nylon-6 nanofibers prepared by one-step electrospinning process could be an effective antimicrobial wound dressing to kill both Gram-negative *E. coli* and Gram-positive *S. aureus*. Archana et al. [111] evaluated chitosan-blended polyvinyl pyrrolidone (PVP)–nano silver oxide (CPS) as an effective wound dressing *in vitro* and *in vivo*.

Lansdown et al. [112] investigated two forms of silver-containing dressings (Contreet foam and Contreet hydrocolloid) and found these promoted healing in chronic venous leg ulcers and diabetic foot ulcers. Polyvinylpyrolidone and alginate-based hydrogel-containing nanosilver has been functionally evaluated for efficient fluid handling capacity and strong antimicrobial activity against all major microorganisms such as *Pseudomonas, Staphylococcus, Escherichia, and Candida* [113]. Jodar et al. [114] demonstrated silver sulfadiazine-impregnated hydrogel for antimicrobial topical application for wound healing. Silver sulfadiazine (SSD)-impregnated hydrogel was prepared by polyvinyl alcohol (PVA) and dextran blending. Boateng et al. [115] formulated an ideal lyophilized wafer dressing composed of alginate and gelatin containing silver sulfadiazine for wound healing and showed the controlled release of SSD over 7 h and expected to diminish microbial load in the wound area. A novel SSD-loaded bilayer chitosan membrane was prepared with sustained release of silver which inhibits the growth of *P. aeruginosa and S. aureus* [116]. Shanmugasundaram et al. [117] formulated SSD-impregnated collagen-based scaffold with strong antibacterial activity *in vitro.* Ammons et al. [118] formulated dressings by combining commercial silver dressings (Acticoat™ Absorbent, Aquacel® Ag, and Tegaderm™Ag) with lactoferrin and xylitol and demonstrated greater efficacy against MRSA and *P. aeruginosa*.

There are several clinical studies with silver-containing dressings in the treatment of infected wounds to enhance wound healing, and the reader is referred to these [119–125].

3.4. Iodine and other antiseptics

Iodine is an old agent used in the treatment of chronic wounds and was used by soldiers during wars. The antibacterial activity of iodine was first investigated by Davaine in 1880 [126]. Iodine penetrates into the cell wall of microorganisms and damages the cell membrane by blocking hydrogen bond. This phenomenon alters the structure and function of cell proteins and enzymes, leading to cell death [127]. Iodine is active against a broad spectrum of microorganisms including *S. aureus, E. coli, Pseudomonas, Streptococcus, Salmonella, Candida, Enterobacter, Klebsiella, Clostridium, Corynebacterium, and Mycobacterium* [126]. Iodine dressings can be found in two preparations as povidone iodine and cadexomer iodine, and the various commercial formulations are summarized in **Table 3**.

Polyhexamethylene biguanide (PHMB) is an another antiseptic and widely used as antimicrobial dressing in wound healing. PHMB is known to be effective against *E. coli. S. aureus* and *S. epidermidis.* PHMB also works like iodine as it attaches to the bacterial cells and disrupts cell membrane resulting in leakage of potassium ions and cytosolic components that lead to cell death [128]. A study by Eberlein et al. [129] confirmed that PHMB containing biocellulose wound dressings were more effective than silver-containing dressing in retarding microbial loads present in locally infected wounds. Loke et al. [130] developed a two-layer dressing with sustained release of chlorhexidine which showed activity against *S. aureus* and *P. aeruginosa in vitro*.

Dressing type	Product name	Antiseptic
Pad	Iodoflex 0.9% Cadexomer Iodine Pad	Cadexomer iodine
Foam	IodoFoam	Iodine
Fibers	**Inadine**	Povidone iodine
Colloidal ointment base	Braunovidon ointment/ointment gauze	Povidone
Hydrogel dressing	Iodozym	Iodine
Liposome hydrogel	Repithel	Povidone
Foam	Kerlix AMD	PHMB
Sponges	Telfa AMD	PHMB
Foam	Kendall AMD	PHMB
Gauzes sponges	Curity AMD Antimicrobial Gauze Sponges	PHMB

Table 3. List of other commercially available antiseptics [36, 127].

3.5. Honey dressings

Honey has been used as wound dressing over centuries [131]. Honey has been reported in several clinical studies for treating chronic diabetic foot ulcers [132–135] and has antimicrobial and anti-inflammatory activity [136–138]. It is reported that honey can inhibit around 60 species of bacteria including *Alcaligenes faecalis, Citrobacter freundii, E. coli, Enterobacter aerogenes, Klebsiella pneumoniae, Mycobacterium phlei, Salmonella california, Salmonella enteritidis, Salmonella typhimurium, Shigella sonnei, S. aureus, and Staphylococcus epidermidis* [139]. In addition, it is reported Manuka honey and Cameroonian honey have an effect on *Pseudomonas aeruginosa*, methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant *Enterococcus* species [137, 140]. The antimicrobial properties of honey are ascribed to its low pH, hygroscopic nature, and peroxide-containing compounds [141]. The rich contents of sugar in honey generate high osmotic pressure and present an unsuitable environment to bacterial growth and cell proliferation [139]. Van den Berg et al. [142] investigated the anti-inflammatory properties of different types of honey *in vitro* by testing reactive oxygen species (ROS) inhibition capability

and found American buckwheat honey exhibits high ROS inhibition ability. Many clinical studies have been performed on the basis of the antimicrobial effect of honey [143–145]. Clinical studies and bioactivity demonstrate the efficiency of honey in wound healing, maintaining a moist environment, promoting drainage of wound exudate and autolytic debridement [144]. It has been reported in minimizing malodour and scar formation of the wound [145] as well as angiogenic activity [146].

Sasikala et al. [147] developed a chitosan-based film dressing loaded with Manuka honey. They identified chitosan–lactic acid with 6% honey showed ideal dressing properties in terms of water vapor transmission rate, water absorption, tensile strength, elongation, and antibacterial activity against *E. coli* and *S. aureus.* **Table 4** summarizes the commercially available honey-based dressings currently sold on the market.

Dressing type	Product Name	Honey type
Hydrocolloid	MediHoney	Leptospermum honey
Alginate-based	MediHoney	Leptospermum honey
Fibers	MANUKAhd	Manuka honey
Pure honey	Surgihoney	Bioengineered honey
Foam	Ligasano	Honeycomb
Pure honey	MGO Manuka Honey	Manuka honey
Sterile Manuka honey	ManukaFill	Manuka honey
Honey-impregnated gauze	Manuka IG	Manuka honey
Sheets, ribbon, gel	TheraHoney	Manuka honey
Knitted viscose mesh dressing, pure honey	Activon	Manuka honey
Alginate ribbon and dressing	Algivon	Manuka honey
Composite, foam/silicone dressings	Actilite	Manuka honey
Nonadherent gauze fibers	MelDra	Buckwheat honey

Table 4. List of selected commercially available honey dressings used in wound healing [22, 148, 149].

3.6. Polymer-based antimicrobial dressings

Natural and synthetic polymers are widely used in acute and chronic wound healing due to their biodegradability, biocompatibility, and wound exudate handling capacity. However, some polymers themselves have an antimicrobial activity [150]. The combination of polymers and antimicrobial drugs provides effective dressings to improve wound healing. Biazar et al.

[151] evaluated a synthetic polymer-based hydrogel dressing that exhibits biocompatible and antimicrobials activity. In another study, synthetic polyvinyl alcohol was blended with calcium alginate to produce nano fiber matrix by electrospinning technique. *In vitro* antibacterial test showed the rate of inhibition of *S. aureus* depends on the concentration of calcium alginate [152]. Chitosan is a cationic polymer whose positive charge interacts with a negative charge of the microbial cell membrane, resulting in disruption and agglutination [153]. Carboxymethyl chitosan has been reported as a broad spectrum antibiofilm agent which can prevent biofilm formation for *E. coli and S. aureus* by 81.6 and 74.6%, respectively [154].

4. Summary

In this chapter, wound healing processes and types of dressings incorporating antimicrobial agents have been briefly discussed. Antimicrobials loaded into dressings for direct application to infected wound sites are becoming more popular worldwide in terms of safety, efficacy, cost effective, and convenience. The key antimicrobial agents ranging from antiseptics such as iodine, metals such as silver, antibiotics such as cephalosporins and aminoglycosides as well as natural products such as honey have been covered. In addition, the driving forces behind the developing of advanced therapeutic dressings have been reviewed. Furthermore, this review has demonstrated different and wide range of antimicrobial-loaded dressings, and a few clinical studies and commercially available antimicrobial dressings have been highlighted. Given the wide range of scientific studies and commercial products publicly available, it is evident that more evidence-based clinical trials are required to select appropriate dressings for the patients. It is also important to note the interdisciplinary fields (including formulation technology, biopharmaceutics, microbiology, materials and polymer chemistry and molecular biology) required for developing an effective antimicrobial dressing able to treat infection and also contribute towards enhanced wound healing.

Author details

Omar Sarheed[1*], Asif Ahmed[2], Douha Shouqair[1] and Joshua Boateng[2*]

*Address all correspondence to: sarheed@rakmhsu.ac.ae and j.s.boateng@gre.ac.uk

1 RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, Ras Al Khaiamah, United Arab Emirates

2 Department of Pharmaceutical, Chemical and Environmental Sciences, Faculty of Engineering and Science, University of Greenwich, Kent, UK

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