We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

5,400
Open access books available

133,000
International authors and editors

165M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the top 1% most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
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].
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-hydroxyethyl methacrylate)    | 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 catalysis 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/Ap                                    | Silver                |
|                              | MediPlus Comfort Border Foam Ag+                | Silver                |
|                              | Meplex 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                 |
|               | Argaes film                                     | Silver                           |
| Films/meshes  | Avarce                                          | 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                      | Silver                           |
|               | with Antimicrobial Silver                       |                                 |
|               | Opticell Ag+                                    | Ionic silver                     |
|               | **Restore Calcium Alginate Dressing with 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                     |
|               | Urgotol SSD/S.Ag                                | Silver sulfadiazine              |
Table 2. List of selected commercially available antimicrobial silver-containing dressings [22, 102, 103].

| 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  |

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. Polyvinylpyrrolidone 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, Aquacell® 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 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.
evaluated a synthetic polymer-based hydrogel dressing that exhibits biocompatible and antimicrobial 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.
References

[1] Boateng JS, Matthews KH, Stevens HN, Eccleston GM. Wound healing dressings and drug delivery systems: a review. J Pharm Sci. 2008;97(8):2892–2923.

[2] Flanagan M. Wound care. Assessment criteria. Nurs Times. 1994;90(35):76–88.

[3] Hutchinson J. The Wound Programme. Centre for Medical Education: Dundee; 1992.

[4] Singer AJ, Clark RA. 1999. Cutaneous wound healing. N Engl J Med. 1999;341:738–746.

[5] Gottrup F, Melling A, Hollander DA. An overview of surgical site infections: aetiology, incidence and risk factors. EWMA J. 2005;5(2):11–15.

[6] Alavi A, Sibbald RG, Phillips TJ, Miller OF, Margolis DJ, Marston W, Woo K, Romanelli M, Kirsner RS. What's new: management of venous leg ulcers: approach to venous leg ulcers. J Am Acad Dermatol. 2016;74(4):627–640.

[7] Moffatt C. Identifying criteria for wound infection. EWMA Position document: 1–5 [Internet]. 2005. http://ewma.org/fileadmin/user_upload/EWMA/pdf/Position_Documents/2005__Wound_Infection_/English_pos_doc_final.pdf. [Accessed 17 Mar 2016].

[8] Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. J Invest Dermatol. 2007;127(3):514–525.

[9] Edwards R, Harding KG. Bacteria and wound healing. Curr Opin Infect Dis. 2004;17:91–96.

[10] Wolcott RD, Rhoads DD, Dowd SE. Biofilms and chronic wound inflammation. J Wound Care. 2008;17(8):333–341.

[11] Weyerich AS, Zimmerman GA. Platelets: signaling cells in the immune continuum. Trends Immunol. 2004;25(9):489–495.

[12] Reinke JM, Sorg H. Wound repair and regeneration. Eur Surg Res. 2012;49(1):35–43.

[13] Singer AJ, Clark RA. Cutaneous wound healing. N Engl J Med. 1999;341:738–746.

[14] Li J, Zhang YP, Kirsner RS. Angiogenesis in wound repair: angiogenic growth factors and the extracellular matrix. Microsc Res Tech. 2003;60(1):107–114.

[15] Steed, DL. The role of growth factors in wound healing. Surg Clin North Am. 1997;77(3):575–586.

[16] Guo S, Dipietro LA. Factors affecting wound healing. J Dent Res. 2010;89(3):219–229.

[17] Gottrup F. Oxygen in wound healing and infection. World J Surg. 2004;28(3):312–315.

[18] Rodriguez PG, Felix FN, Woodley DT, Shim EK. The role of oxygen in wound healing: a review of the literature. Dermatol Surg. 2008;34(9):1159–1169.
[19] Tandara AA, Mustoe TA. Oxygen in wound healing—ore than a nutrient. World J Surg. 2004;28(3):294–300.

[20] Faries PL, Teodorescu VJ, Morrissey NJ, Hollier LH, Marin ML. The role of surgical revascularization in the management of diabetic foot wounds. Am J Surg. 2004;187(5):S34–S37.

[21] Smith SC, Faxon D, Cascio W, Schaff H, Gardner T, Jacobs A, et al. Prevention conference VI: diabetes and cardiovascular disease: writing group VI: revascularization in diabetic patients. In: Proceeding of the American Heart Association; 18–20 January 2001; Circulation. 2002;105(18). p. 165–169.

[22] Boateng JS, Catanzano O. Advanced therapeutic dressings for effective wound healing—a review. J Pharm Sci. 2015;104(11):3653–3680.

[23] Bowler PG, Duerden BI, Armstrong DG. Wound microbiology and associated approaches to wound management. Clin Microbiol Rev. 2011;14(2):244–269.

[24] Sue E. Gardner, Rita A. Frantz. Wound bioburden and infection-related complications in diabetic foot ulcers. Biol Res Nurs. 2008;10(1): 44–53.

[25] Noble WC. Ecology and Host Resistance in Relation to Skin Disease. 5th ed. New York: McGraw-Hill; 1999. p. 184–191.

[26] Menke NB, Ward KR, Witten TM, Bonchev DG, Diegelmann RF. Impaired wound healing. Clin Dermatol. 2007;25(1):19–25.

[27] Dow G, Browne A, Sibbald RG. Infection in chronic wounds: controversies in diagnosis and treatment. Ostomy Wound Manage. 1999;45(8):23–7, 29–40; quiz 41–2.

[28] Sun Y, Smith E, Wolcott R, Dowd SE. Propagation of anaerobic bacteria within an aerobic multi-species chronic wound biofilm model. J Wound Care. 2009;18(10):426–431.

[29] Stephens P, Wall IB, Wilson MJ, Hill KE, Davies CE, Hill CM, Harding KG, Thomas DW. Anaerobic cocci populating the deep tissues of chronic wounds impair cellular wound healing responses in vitro. Br J Dermatol. 2003;148(3):456–66.

[30] Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev. 2002;15(2):167–193.

[31] Garrett TR, Bhakoo M, Zhang Z. Bacterial adhesion and biofilms on surfaces. Prog Natl Sci. 2008;18(9):1049–1056.

[32] Miller MB, Bassler BL. Quorum sensing in bacteria. Annu Rev Microbiol. 2001;55:165–199.

[33] Song C, Sun XF, Xing SF, Xia PF, Shi YJ, Wang SG. Characterization of the interactions between tetracycline antibiotics and microbial extracellular polymeric
substances with spectroscopic approaches. Environ Sci Pollut Res Int. 2014;21(3):1786–1795.

[34] Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science. 1999;284(5418):1318–1322.

[35] Yamasaki O, Akiyama H, Toi Y, Arata J. A combination of roxithromycin and imipenem as an antimicrobial strategy against biofilms formed by *Staphylococcus aureus*. J Antimicrob Chemother. 2001;48(4):573–577.

[36] Moura LI, Dias AM, Carvalho E, de Sousa HC. Recent advances on the development of wound dressings for diabetic foot ulcer treatment—a review. Acta Biomater. 2013;9(7):7093–7114.

[37] Harding KG, Jones V, Price P. Topical treatment: which dressing to choose. Diabetes Metab Res Rev. 2000;16: S47–S50.

[38] Dumville JC, O’Meara S, Deshpande S, Speak K. Hydrogel dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2011;9:CD009101.

[39] Fonder M., Lazarus G, Cowan D, Aronson-Cook B, Kohli A, Mamelak A. Treating the chronic wound: a practical approach to the care of nonhealing wounds and wound care dressings. J Am Acad Dermatol. 2008;58(2):185–206.

[40] Hilton JR, Williams DT, Beuker B, Miller DR, Harding KG. Wound dressings in diabetic foot disease. Clin Infect Dis. 2004;39(Suppl 2):S100–S103.

[41] Lloyd LL, Kennedy JF, Methacanon P, Paterson M, Knill CJ. Carbohydrate polymers as wound management aids. Carbohydr Polym. 1998;37(3):315–322.

[42] Dumville JC, Deshpande S, O’Meara S, Speak K. Hydrocolloid dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2013;8:CD009099.

[43] Skórkowska-Telichowska K, Czemplik M, Kulma A, Szopa J. The local treatment and available dressings designed for chronic wounds. J Am Acad Dermatol. 2013;68(4):117–126.

[44] Pawar HV, Boateng JS, Ayensu I, Tetteh J. Multifunctional medicated lyophilised wafer dressing for effective chronic wound healing. J Pharm Sci. 2014;103(6):1720–1733.

[45] Boateng JS, Pawar HV, Tetteh J. Evaluation of in vitro wound adhesion characteristics of composite film and wafer based dressings using texture analysis and FTIR spectroscopy: a chemometrics factor analysis approach. RSC Adv. 2015;5(129):107064–107075.

[46] Labovitiadi O, Lamb AJ, Matthews KH. In vitro efficacy of antimicrobial wafers against methicillin-resistant *Staphylococcus aureus*. Ther Deliv. 2012;3(4):443–55.
Antimicrobial Dressings for Improving Wound Healing
http://dx.doi.org/10.5772/63961

[47] Zubair M, Malik A, Ahmad J. Clinico-microbiological study and antimicrobial drug resistance profile of diabetic foot infections in North India. Foot (Edinburgh, Scotland). 2011;21(1):6–14.

[48] Gethin G. Role of topical antimicrobials in wound management. J Wound Care. 2009;Nov:4–8.

[49] Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. Clin Infect Dis. 2009;49(10):1541–1549.

[50] Drosou A, Falabella A, Kirsner RS. Antiseptics on wounds: an area of controversy. Wounds Compend Clin Res Pract. 2003;15(5):149–166.

[51] Burks RI. Povidone-iodine solution in wound treatment. Phys Ther. 1998;78(2):212–218.

[52] Zhou LH, Nahm WK, Badiavas E, Yufit T, Falanga V. Slow release iodine preparation and wound healing: in vitro effects consistent with lack of in vivo toxicity in human chronic wounds. Br J Dermatol. 2002;146(3):365–374.

[53] Mirhadi H, Azar MR, Abbazadegan A, Geramizadeh B, Torabi S, Rahsaz M. Cytotoxicity of chlorhexidine-hydrogen peroxide combination in different concentrations on cultured human periodontal ligament fibroblasts. Dent Res J. 2014;11(6):645–648.

[54] Severyns AM, Lejeune A, Rocoux G, Lejeune G. Non-toxic antiseptic irrigation with chlorhexidine in experimental revascularization in the rat. J Hosp Infect. 1991;17(3):197–206.

[55] Du Toit, DF, Page BJ. An in vitro evaluation of the cell toxicity of honey and silver dressings. J Wound Care. 2009;18:383–389.

[56] Vowden K, Vowden K, Carville K. Antimicrobials made easy. Wounds Int. 2011;2(1):1–6.

[57] Cutting K. Wound dressings: 21st century performance requirements. J Wound Care. 2010;19(Suppl 1):4–9.

[58] Phoudee W, Wattanakaroon W. Development of protein-based hydrogel wound dressing impregnated with bioactive compounds. Nat Sci. 2015;49(1):92–102.

[59] Kataria K, Gupta A, Rath G, Mathur RB, Dhakate SR. In vivo wound healing performance of drug loaded electrospun composite nanofibers transdermal patch. J Pharm Sci. 2014;469(1):102–110.

[60] Shi Y, Truong V, Kulkarni K, Qu Y, Simon G, Boyd R. Light-triggered release of ciprofloxacin from an in situ forming click hydrogel for antibacterial wound dressings. J Mater Chem B. 2015;3(45):8771–8774.
[61] Öztürk E, Ağalar C, Keçeci K, Denkba E. Preparation and characterization of ciprofloxacin-loaded alginate/chitosan sponge as a wound dressing material. J Appl Polym Sci. 2006;101(3):1602–1609.

[62] Hima Bindu, TVL, Vidyavathi M, Kavitha K, Sastry T P, Kumar RVS. Preparation and evaluation of chitosan-gelatin composite films for wound healing activity. Trends Biomater Artif Organs. 2010;24(3):122–130.

[63] El-Shanshory A, Chen W, Mei M. Preparation of antibacterial electrospun PVA/ regenerated silk fibroin nanofibrous composite containing ciprofloxacin hydrochloride as a wound dressing. J Donghua Univ. 2014;31(5):566–571.

[64] Unnithan AR, Barakat NA, Pichiah PB, Gnanasekaran C, Nirmala R, Cha YS, Jung CH, El-Newehy M, Kim HY. Wound-dressing materials with antibacterial activity from electrospun polyurethane–dextran nanofiber mats containing ciprofloxacin HCl. Carbohydr Polym. 2012;90(4):1786–1793.

[65] Jannesari M, Varshosaz J, Morshed M, Zamani M. Composite poly(vinyl alcohol)/ poly(vinyl acetate) electrospun nanofibrous mats as a novel wound dressing matrix for controlled release of drugs. Int J Nanomed. 2011;6:993–1003.

[66] Tsou TL, Tang ST, Huang YC, Wu JR, Young JJ, Wang HJ. Poly(2-hydroxyethyl methacrylate) wound dressing containing ciprofloxacin and its drug release studies. J Mater Sci Mater Med. 2005;16(2):95–100.

[67] Manju S, Antony M, Sreenivasan K. Synthesis and evaluation of a hydrogel that binds glucose and releases ciprofloxacin. J Mater Sci. 2010;45(15):4006–4012.

[68] Puoci F, Piangiolino C, Givigliano F, Parisi OL, Cassano R, Trombino S, Curcio M. Ciprofloxacin–collagen conjugate in the wound healing treatment. J Funct Biomater. 2012;3(2):361–371.

[69] Roy DC, Tomblyn S, Burmeister DM, Wrice NL, Becerra SC, Burnett LR, Saul J. Ciprofloxacin-loaded keratin hydrogels prevent infection and support healing in a porcine full-thickness excisional wound. Adv Wound Care. 2015;4(8):457–468.

[70] Okoye EI, Okolie TA. Development and in vitro characterization of ciprofloxacin loaded polymeric films for wound dressing. Int J Health Allied Sci. 2015;4(4):234–42.

[71] Sinha M, Banik RM, Haldar C, Maiti P. Development of ciprofloxacin hydrochloride loaded poly(ethylene glycol)/chitosan scaffold as wound dressing. J Porous Mater. 2013;20:799–807.

[72] Loke WK, Lau SK, Yong LL, Khor E, Sum CK. Wound dressing with sustained antimicrobial capability. J Biomed Mater Res. 2000;53(1):8–17.
[73] Kota S, Jahangir M, Ahmed M, Kazmi I, Bhavani P, Muheem A, Saleem M. Development and evaluation of ofloxacin topical gel containing wound healing modifiers from natural sources. Sch Res Library. 2015;7(10):226–233.

[74] Boateng JS, Pawar HV, Tetteh J. Polyox and carrageenan based composite film dressing containing anti-microbial and anti-inflammatory drugs for effective wound healing. Int J Pharm. 2013;1–2(441):181–191.

[75] Pawar HV, Boateng JS, Ayensu I, Tetteh, J. Multifunctional medicated lyophilised wafer dressing for effective chronic wound healing. J Pharm Sci. 2014;103(6):1720–1733.

[76] Pawar HV, Tetteh J, Boateng JS. Preparation, optimisation and characterisation of novel wound healing film dressings loaded with streptomycin and diclofenac. Colloid Surf B: Biointerfaces. 2013;102:102–110.

[77] Kim JO, Choi JY, Park JK, Kim JH, Jin SG, Chang SW, Li DX. Development of clindamycin-loaded wound dressing with polyvinyl alcohol and sodium alginate. Biol Pharm Bull. 2008;December(31):2277–2282.

[78] Kim JO, Park JK, Kim JH, Jin SG, Yong CS, Li DX, Choi JY. Development of polyvinyl alcohol–sodium alginate gel-matrix-based wound dressing system containing nitrofurazone. Int J Pharm. 2008;1–2(359): 79–86.

[79] Hwang MR, Kim JO, Lee JH, Kim YI, Kim JH, Chang SW, Jin SG. Gentamicin-loaded wound dressing with polyvinyl alcohol/dextran hydrogel: gel characterization and in vivo healing evaluation. AAPS PharmSciTech. 2010;11(3):1092–103.

[80] Adhirajan N, Shanmugasundaram N, Shanmuganathan S, Babu M. Collagen-based wound dressing for doxycycline delivery: in-vivo evaluation in an infected excisional wound model in rats. J Pharm Pharmacol. 2009; 61(12):1617–23.

[81] Adhirajan N, Shanmugasundaram N, Shanmuganathan S, Babu M. Functionally modified gelatin microspheres impregnated collagen scaffold as novel wound dressing to attenuate the proteases and bacterial growth. Eur J Pharm Sci. 2009;36(2–3):235–245.

[82] Guan J, Dong LZ, Huang SJ, Jing ML. Characterization of wound dressing with microspheres containing levofloxacin. In: Proceedings of the International Conference on Information Technology and Scientific Management; 20 December 2010; Tianjin, China: 2010;1–2. p. 344–348.

[83] Bohl MKS, Leibovich SJ, Belem P, West JL, Poole WLA. Effects of nitric oxide releasing poly(vinyl alcohol) hydrogel dressings on dermal wound healing in diabetic mice. Wound Repair Regen. 2002;10(5):286–294.

[84] Halpenny GM, Steinhardt RC, Okialda KA, Mascharak, PK. Characterization of pHEMA-based hydrogels that exhibit light-induced bactericidal effect via release of NO. J Mater Sci Mater Med. 2009;20(11):2353–2360.
[85] Li Y, Lee PI. Controlled nitric oxide delivery platform based on S-nitrosothiol conjugated interpolymer complexes for diabetic wound healing. Mol Pharm. 2010;7(1):254–266.

[86] Lansdown AB. Silver. I: its antibacterial properties and mechanism of action. J Wound Care. 2002;11(4):125–130.

[87] Leaper D. Appropriate use of silver dressings in wounds: international consensus document. Int Wound J. 2012;9(5):461–464.

[88] Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. Biotechnol Adv. 2009;27(1):76–83.

[89] Feng QL, Wu J, Chen GQ, Cui FZ, Kim TN, Kim JO. A mechanistic study of the antibacterial effect of silver ions on *Escherichia coli* and *Staphylococcus aureus*. J Biomed Mater. 2000;52(4):662–668.

[90] Matsumura Y, Yoshikata K, Kunisaki SI, Tsuchido T. Mode of bactericidal action of silver zeolite and its comparison with that of silver nitrate. Appl Environ Microbiol. 2003;69(7):4278–4281.

[91] Saengmee-anupharb S, Sirkhirin T, Thaweboon B, Thaweboon S, Amornsakchai T, Dechkunakorn S, Suddhasthira T. Antimicrobial effects of silver zeolite, silver zirconium phosphate silicate and silver zirconium phosphate against oral microorganisms. Asian Pac J Trop Biomed. 2013;3(1):47–52.

[92] Rizzello L, Pompa PP. Nanosilver-based antibacterial drugs and devices: mechanisms, methodological drawbacks, and guidelines. Chem Soc Rev. 2014;43(5):1501–18.

[93] Ivask A, Kurvet I, Kasemets K, Blinova I, Aruoja V, Suppi S, Vija H. Size-dependent toxicity of silver nanoparticles to bacteria, yeast, algae, crustaceans and mammalian cells in vitro. PLoS One. 2014;9(7):e1–14.

[94] Sondi I, Salopek-Sondi B. Silver nanoparticles as antimicrobial agent: a case study on *E. coli* as a model for Gram-negative bacteria. J Colloid Interface Sci. 2004;275(1):177–182.

[95] Shrivastava S, Bera T, Roy A, Singh G, Ramachandrarao P, Dash D. Characterization of enhanced antibacterial effects of novel silver nanoparticles. Nanotechnology. 2010;18(22):1–9.

[96] Kazachenko A, Legler A, Per’yanova O, Vstavskaya Y. Synthesis and antimicrobial activity of silver complexes with histidine and tryptophan. Pharm Chem J. 2000;34(5):257–258.

[97] Baker C, Pradhan A, Pakstis L, Pochan DJ, Shah SI. Synthesis and antibacterial properties of silver nanoparticles. J Nanosci Nanotechnol. 2005;5(2):244–249.

[98] Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ram JT, Yacaman MJ. The bactericidal effect of silver nanoparticles. Nanotechnology. 2005;16(10):2346–53.
Antimicrobial Dressings for Improving Wound Healing

Panacek A, Kvitk L, Prucek R, Kolar M, Vecerova R, Pizurova N, Sharma VK. Silver colloid nanoparticles: synthesis, characterization, and their antibacterial activity. J Phys Chem B. 2006;110(33):16248–16253.

Kim JS, Kuk E, Yu KN, Kim JH, Park SJ, Lee HJ, Kim SH. Antimicrobial effects of silver nanoparticles. Nanomed Nanotechnol Biol Med. 2007;3(1):95–101.

Gade AK, Bonde P, Ingle AP, Marcato PD, Duran N, Rai MK. Exploitation of Aspergillus niger for synthesis of silver nanoparticles. J Biobased Mater Bioenergy. 2008;2(3):1–5.

Lindsay S. Silver white paper—everything you ever wanted to know about the use of silver in wound therapy [Internet]. 2011. http://www.systagenix.co.uk/cms/uploads/1458_Silver_WhitePaperA4_LP3_060.pdf. [Accessed 10 Mar 2016].

Wound Source [Internet]. http://www.woundsource.com/product-category/dressings/antimicrobial-dressings. [Accessed 10 Mar 2016].

Rujitanaroj PO, Pimpha N, Supaphol P. Wound-dressing materials with antibacterial activity from electrospun gelatin fiber mats containing silver nanoparticles. Polymer. 2008;49(21):4723–4732.

Lin YH, Hsu WS, Chung WY, Ko TH, Lin JH. Evaluation of various silver-containing dressing on infected excision wound healing study. J Mater Sci Mater Med. 2014;25(5):1375–1386.

Anisha BS, Biswas R, Chennazhi KP, Jayakumar R. Chitosan–hyaluronic acid/nano silver composite sponges for drug resistant bacteria infected diabetic wounds. Int J Biol Macromol. 2013;62:310–320.

Ong SY, Wu J, Moochhala SM, Tan MH, Lu J. Development of a chitosan-based wound dressing with improved hemostatic and antimicrobial properties. Biomaterials. 2008;29(32):4323–4332.

Madhumathi K, Sudheesh Kumar PT, Abhilash S, Sreeja V, Tamura H, Manzoor K, Nair SV. Development of novel chitin/nanosilver composite scaffolds for wound dressing applications. J Mater Sci Mater Med. 2010;21(2):807–813.

Boonkaew B, Suwanpreuksa P, Cuttle L, Barber PM, Supaphol P. Hydrogels containing silver nanoparticles for burn wounds show antimicrobial activity without cytotoxicity. J Appl Polym Sci. 2014;131(9):40215.

Pant B, Pant HR, Pandeya DR, Panthi G, Nam KT, Hong ST, Kim CS. Characterization and antibacterial properties of Ag NPs loaded nylon-6 nanocomposite prepared by one-step electrospinning process. Colloid Surf A: Physicochem Eng Aspects. 2012;395:94–99.

Archana D, Singh BK, Dutta J, Dutta PK. Chitosan-PVP-nano silver oxide wound dressing: in vitro and in vivo evaluation. Int J Biol Macromol. 2015;73(1):49–57.
[112] Lansdown BG, Jensen K, Jensen MQ. Contreet foam and contreet hydrocolloid: an insight into two new silver-containing dressings. J Wound Care. 2003;12(6):205–210.

[113] Singh R., Singh D. Radiation synthesis of PVP/alginate hydrogel containing nanosilver as wound dressing. J Mater Sci Mater Med. 2012;23(11):2649–2658.

[114] Jodar KSP, Balcão VM, Chaud MV, Tubino M, Yoshida VMH, Oliveira JM, Vila MMDC. Development and characterization of a hydrogel containing silver sulfadiazine for antimicrobial topical applications. J Pharm Sci. 2015;104(7):2241–2254.

[115] Boateng JS, Burgos AR, Okeke O, Pawar H. Composite alginate and gelatin based biopolymeric wafers containing silver sulfadiazine for wound healing. Int J Biol Macromol. 2015;79:63–71.

[116] Mi FL, Wu YB, Shyu SS, Schoung JY, Huang YB, Tsai YH, Hao JY. Control of wound infections using a bilayer chitosan wound dressing with sustainable antibiotic delivery. J Biomed Mater Res. 2002;59(3):438–449.

[117] Shanmugasundaram N, Sundaraseelan J, Uma S, Selvaraj D, Babu M. Design and delivery of silver sulfadiazine from alginate microspheres-impregnated collagen scaffold. J Biomed Mater Res B: Appl Biomater. 2006;77(2):378–388.

[118] Ammons M, Ward L, James G. Anti-biofilm efficacy of a lactoferrin/xylitol wound hydrogel used in combination with silver dressings. Int Wound J. 2011;8(3):268–273.

[119] Rayman G, Rayman A, Baker NR, Jurgeviciene N, Dargis V, Sulcaite R., Pantelejeva O. Sustained silver-releasing dressing in the treatment of diabetic foot ulcers. Br J Nurs (Mark Allen Publishing). 2005;14(2):109–114.

[120] Jude EB, Apelqvist J, Spraul M, Martini J, Jones G, Harding K, Benbow S. Prospective randomized controlled study of Hydrofiber® dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers. Diabet Med. 2007;24(3):280–288.

[121] Gago M, Garcia F, Gaztelu V, Verdu J, Lopez P, Nolasco A. A comparison of three silver-containing dressings in the treatment of infected, chronic wounds. Wound Res. 2008;20(10):273–278.

[122] Hiro ME, Pierpont YN, Ko F, Wright TE, Robson MC, Payne WG. Comparative evaluation of silver-containing antimicrobial dressings in vitro and in vivo processes of wound healing. Eplasty. 2012;12:48.

[123] Thomas S, McCubbin P. A comparison of the antimicrobial effects of four silver-containing dressings on three organisms. J Wound Care. 2003;12(3):101–107.

[124] Thomas S, McCubbin P. An in vitro analysis of the antimicrobial properties of 10 silver-containing dressings. J Wound Care. 2003;12(8):305–308.
[125] Gaisford S, Beezer AE, Bishop AH, Walker M, Parsons D. An in vitro method for the quantitative determination of the antimicrobial efficacy of silver-containing wound dressings. Int J Pharm. 2009;1–2(366):111–116.

[126] Sunil KP, Raja BP, Jagadish RG, Uttam A. Povidone iodine—revisited. Indian J Dent Adv. 2011;3(3):617–620.

[127] Sibbald R, Leaper D, Queen D. Iodine made easy. Wounds Int. 2011;2(2):1–6.

[128] Gilliver S. PHMB: a well-tolerated antiseptic with no reported toxic effects. J Wound Care. 2009; Active Health Care Suppl:9–14.

[129] Eberlein T, Haemmerle G, Signer M, Gruber MU, Traber J, Mittlboeck M, Abel M. Comparison of PHMB-containing dressing and silver dressings in patients with critically colonised or locally infected wounds. J Wound Care. 2012;21(1):13–19.

[130] Loke WK, Lau SK, Yong LL, Khor E, Sum CK. Wound dressing with sustained antimicrobial capability. J Biomed Mater Res. 2000;53(1):8–17.

[131] Forrest RD. Early history of wound treatment. J R Soc Med. 1982;75(3):198–205.

[132] Hammouri S. The role of honey in the management of diabetic foot ulcers. JRMS. 2004;11(2):20–22.

[133] Schumacher HH. Use of medical honey in patients with chronic venous leg ulcers after split-skin grafting. J Wound Care. 2004;13(10):451–452.

[134] Molan P, Betts J. Using honey to heal diabetic foot ulcers. Adv Skin Wound Care. 2008;21(7):313–316.

[135] Mclennan ASV, Henshaw FR, Twigg SM. What’s the buzz: bee products and their potential value in diabetic wound healing. J Diabet Foot Complic. 2014;6(2):24–39.

[136] Boateng JS, Diunase K. Comparing the antibacterial and functional properties of Cameroonian and Manuka honeys for potential wound healing—have we come full cycle in dealing with antibiotic resistance? Molecules. 2015;20(9):16068–16084.

[137] Subrahmanyam M. A prospective randomised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. Burns J Int Soc Burn Inj. 1998;24(2):157–161.

[138] Cooper RA, Halas E, Molan, PC. The efficacy of honey in inhibiting strains of Pseudomonas aeruginosa from infected burns. J Burn Care Rehabil. 2002;23(6):366–370.

[139] Aggad H, Guemour D. Honey antibacterial activity. Med Aromat Plants. 2014;2(3):1–2.

[140] Song JJ, Salcido R. Use of honey in wound care: an update. Adv Skin Wound Care. 2011;24(1):40–4; quiz 45–6.
[141] Karayil S, Deshpande SD, Koppikar GV. Effect of honey on multidrug resistant organisms and its synergistic action with three common antibiotics. J Postgrad Med. 1998;44(4):93–96.

[142] Van den Berg AJ, Van den Worm E, Van Ufford HC, Halges SB, Hoekstra MJ, Beukelman CJ. An in vitro examination of the antioxidant and anti-inflammatory properties of buckwheat honey. J Wound Care. 2008;17(4):172–174, 176–178.

[143] Gethin G, Cowman S. Bacteriological changes in sloughy venous leg ulcers treated with Manuka honey or hydrogel: an RCT. J Wound Care. 2008;17(6):241–244, 246–247.

[144] Molan P, Betts J. Clinical usage of honey as a wound dressing: an update. J Wound Care. 2004;13(9):353–356.

[145] Alam F, Islam M, Gan S, Khalil M. Honey: a potential therapeutic agent for managing diabetic wounds. Evidence Based Complement Altern Med. 2014;2014:Article ID 169130.

[146] Rossiter K, Cooper AJ, Voegeli D, Lwaleed BA. Honey promotes angiogenic activity in the rat aortic ring assay. J Wound Care. 2010;19(10):440, 442–446.

[147] Sasiakala L, Durai B, Rathinamoorthy R. Manuka honey loaded chitosan hydrogel films for wound dressing applications. Int J PharmTech Res. 2013;5(4):1774–1785.

[148] Halstead F, Webber M, Rauf M, Burt R, Dryden M, Oppenheim B. In vitro activity of an engineered honey, medical-grade honeys, and antimicrobial wound dressings against biofilm-producing clinical bacterial isolates. J Wound Care. 2016;25(2):93–102.

[149] Molan PC. The evidence and the rationale for the use of honey as a wound dressing. Wound Practice Res. 2011;19(4):204–220.

[150] Mogosanu GD, Grumezescu AM. Natural and synthetic polymers for wounds and burns dressing. Int J Pharm. 2014;463(2):127–136.

[151] Biazar E, Roveimia Z, Shahhosseini G, Khataminezhad M, Zafari M, Majdi A. Biocompatibility evaluation of a new hydrogel dressing based on polyvinylpyrrolidone/polyethylene glycol. J Biomed Biotechnol. 2012;2012:Article ID 343989.

[152] Tarun K, Gobi N. Calcium alginate/PVA blended nano fibre matrix for wound dressing. Indian J Fibre Textile Res. 2012;37(2):127–132.

[153] Dai T, Tanaka M, Huang YY, Hamblin MR. Chitosan preparations for wounds and burns: antimicrobial and wound-healing effects. Exp Rev Anti-infect Ther. 2011;9(7):857–879.

[154] Tan Y, Han F, Ma S, Yu W. Carboxymethyl chitosan prevents formation of broad-spectrum biofilm. Carbohydr Polym. 2011;84(4):1365–1370.