

Antibacterial Hydrogel Dressings and their Applications in Wound Treatment

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Abstract

Antimicrobial hydrogels, both in semi-stiff sheets and amorphous form, have been extensively studied for wound management mainly owing to their high-water content, lower wound adherence, promoted autolysis debridement, epithelial migration, and granulation growth. Benefiting from the recent advances in materials science, biotechnology, and a growing understanding of wound microbiology, an extensive variety of antimicrobial hydrogels have been developed. These novel antimicrobial hydrogels can prevent and control microbial infection. In addition, they possess wound healing functions for improved wound management. This chapter will provide a comprehensive summary of the current studied antimicrobial hydrogels in literature and available hydrogel dressings in the market, including their design, fabrication method, and wound management efficacy *in vitro* or *in vivo*. The detailed and critical discussion of the advantages and disadvantages of each type of hydrogel dressing will provide insights into the future design of antimicrobial hydrogels for better management of wounds in clinical application.

Keywords: Nanomaterials, Hydrogels, Stimuli-responsive, Nanoparticles, Wound monitoring

1. Introduction

Open wound occurs from the traumatic damage to the skin, which could be resulted from cuts, lacerations, abrasions, avulsion, penetrations, surgery, bite, burns, or diseases (ulcers from diabetes, hypertension, rheumatoid arthritis, etc.) (Jeschke et al., 2020). The management of

open wounds remains a serious global challenge, resulting in severe morbidity, mortality, and a substantial economic burden (Falcone et al., 2021). Wound healing process often comprises a dynamic series of overlapping phases, namely inflammation, proliferation (including coagulation, granulation tissue formation, and re-epithelialization), and extracellular matrix (ECM) establishment (Song et al., 2021). Based on the healing time and progress, the open wound can be further categorized as acute and chronic wounds (Koehler et al., 2018). Acute wounds that are normally generated from common trauma or surgical operations are expected to progress through an orderly set of wound healing phases, usually lasting for 8 to 12 weeks depending on their size and depth (Ovais et al., 2018). If a prolonged period of the inflammation phase unfolds, then an acute wound may be classified as a chronic wound, which often experience a postponed and incomplete healing process (Jones et al., 2018, Maaz Arif et al., 2021). Wound healing can be delayed by the presence of intrinsic and extrinsic factors including the lack of nutrition, pathogenic infections, co-morbidities, medications, or inappropriate wound dressing selection or management (He et al., 2022, Nosrati et al., 2021). When the defensive skin integrity is compromised in an open wound, it allows the invasion of pathogenic microorganisms, causing local infections or even sepsis (Duan et al., 2022, Chelkeba and Melaku, 2021). Accurate wound assessment and appropriate wound management are necessary for the appropriate treatment of wounds to achieve an effective healing (Mai et al., 2020, Shi et al., 2019).

Advanced biomaterials have been developed to accelerate the healing process and reduce the risk of infection. These biomaterial wound dressings encompass cloths, foams, films, hydrofibers, hydrocolloids, hydrogels, among others (Zhang et al., 2020b, Ding et al., 2019, Ding et al., 2018). Hydrogels are defined as three-dimensional network structure gels of crosslinked hydrophilic polymers by physical interactions or covalent bonds, containing more than 70% of water. Hydrogels can be often found in semi-stiff sheets and amorphous forms (Fan et al., 2019, Wang et al., 2020c). Benefiting from their high water content, lower wound adherence, promoted autolysis debridement, epithelial migration, granulation growth, biocompatibility, biodegradability, and easy loading and release of bioactive agents, several hydrogels have been extensively, and successfully, employed as wound dressings (Zheng et al., 2022, Li et al., 2018). The advances in materials science and biotechnology, an extensive variety of antimicrobial hydrogels comprising a sensor, imaging, debridement, microbial infection control, and wound healing functions (including immunoregulation, angiogenesis, and ECM remodeling) have been developed for improved wound management (Liao et al., 2018, Tripodo et al., 2018, Moeini et al., 2020, Tavakoli and Klar, 2020). Antimicrobial hydrogels

can be divided into contact-killing-based and release-killing-based antimicrobial hydrogels according to their modes of action. In the case of contact-killing, pathogenic microorganisms can be eradicated only upon contact or close contact with the hydrogel (Tavakoli and Klar, 2020). Whereas in the release-killing, bioactive agents are leached into the wound site, acting against pathogens near the hydrogel contact area and in the wound-infected surrounding area (Fig. 8.1). It is worth pointing out that the contact-killing-based category comprises both inherently active and drug-loaded antimicrobial hydrogels (Wang et al., 2019c, Tavakoli and Klar, 2020). The inherently active antimicrobial hydrogels are generally fabricated by functional polymers, such as polypeptides, polysaccharides (e.g. chitosan, alginate, cellulose, gellan gum, dextran, hyaluronic acid, starch), and proteins (e.g. silk protein, fibrins, collagen) (Kirschning et al., 2018, Ahmad Raus et al., 2021). While drug-loaded antimicrobial hydrogels possess the versatility of the various active agents loaded in the hydrogels, including antimicrobial agents (e.g. antibiotics, silver nanoparticles, gold nanoparticles, antimicrobial peptides, essential oils), growth factors (e.g. vascular endothelial growth factor, epidermal growth factor, fibroblast growth factor, transforming growth factor β , platelet-derived growth factor), and anti-oxidant and anti-inflammatory agents (e.g. vitamin, trace elements, therapeutic gases, heparin, curcumin, capsaicin, cytokines) (Vijayan et al., 2019, Lee et al., 2021, Rousselle et al., 2019, Peng et al., 2020, Malone-Povolny et al., 2019, Xu et al., 2020). Moreover, multifunctional antimicrobial hydrogels with stimuli-responsive drug release features (pH, enzyme, temperature, light, magnetic, etc.) have attracted extensive attention as the new generation of wound dressings (Hu et al., 2022, Peers et al., 2022, Wang et al., 2019a, Zhao et al., 2017). Furthermore, antimicrobial hydrogels are being developed to integrate sensor and imaging functions. These functions may assist in the detection of real-time moisture, pH, temperature, or other infection biomarkers for accurate assessments of wound etiology and the current status (Francesko et al., 2019, Xiong et al., 2021).

Please insert Figure 8.1

Figure 8.1. Distinct antibacterial hydrogel modus operandi: (a) contact-killing-based antibacterial hydrogel; (b) release-killing based antibacterial hydrogel.

This chapter will provide a comprehensive summary of the advanced antimicrobial hydrogels in research and available hydrogel dressings in the market, including their design, fabrication method, and wound management efficacy in vitro or in vivo. The antimicrobial hydrogels were categorized based on their mode of action and mechanisms of drug versatility. Their modus

operandi details and critical discussion, encompassing their advantages and disadvantages, may provide insights into the future design of antimicrobial hydrogels for better management of wounds in clinical application.

2. Contact-killing-based hydrogels

Hydrogels may be applied as matrixes, emulsions, or as injectables. Matrixes are the most commonly used, being prepared and tailored *ex situ* from the wound site and are easily manipulated. Emulsion templates facilitate the simple production of porous polymeric networks. Whereas injectable hydrogels are favorable carriers, biocompatible, non-invasive, and adaptable to a variety of wound types (Wang et al., 2018). Independently of the type of hydrogel used as a wound dressing the active antibacterial agent may be designed to be firmly attached to the matrix. Therefore, no release of the antibacterial agent is expected. This strategy denotes two clear advantages and two disadvantages. Without release, the time span of the antibacterial activity may be considerably higher. Moreover, if the antibacterial agent displays remarkable bactericidal properties but unacceptable cytotoxicity (particularly systemic toxicity), this strategy may mitigate considerably this important issue. However, by being strongly entrapped in the hydrogel matrix, the active agent may not be effective in its vicinity. Unless it is able to perform an indirect antibacterial activity, such as the generation of reactive oxygen species, which will be released in the wound site and kill the invading bacteria (Rebelo et al., 2020). Furthermore, if the active agent requires an “unrestricted” interaction with the bacteria, its tight connection with the hydrogel matrix may seriously hinder its effectiveness. This issue was reported by Padrão et al., where the antibacterial agent, bovine lactoferrin, was covalently bounded to bacterial nanocellulose through periodate oxidation. This process not only restricted the mobility of bovine lactoferrin but also made the N-terminal of the protein, the most antimicrobial domain, bio-unavailable, hampering its antibacterial activity (Padrão et al., 2020). Baus et al. reported the use of copper and calcium ions as crosslinkers of cellulose nanofibrils and as an active antibacterial agent. It displayed a bacteriostatic and antifouling effect against *Staphylococcus epidermidis* (*S. epidermidis*) and *Pseudomonas aeruginosa* (*P. aeruginosa*), respectively (Basu et al., 2018). Want et al. developed a polyethylene glycol dimethacrylate, N,N-methylene-bis-acrylamide, methyl methacrylate, 1-vinyl-3-butylimidazolium, and acrylamide hydrogel using an ionic liquid as a crosslinker. It proved efficacy against *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*), and *Candida albicans* (*C. albicans*). Due to its prompt tackling of the wound infection, this hydrogel accelerated the

wound healing process (Wang et al., 2020b). Finally, it should be mentioned that some hydrogels possess inherent antimicrobial properties when their main matrix components possess biocidal activity. Chitosan is the most renowned, intrinsically antibacterial compound (Tang et al., 2020).

3. Release-killing-based hydrogels

Hydrogels that are envisioned to eliminate microorganisms within the entire wound site environment require the release of antimicrobial agents. This strategy is expected to manage the infections effectively and safely due to the administration of a high dose of the antimicrobial agents in its location and within its vicinity. However, antimicrobial agents are commonly released with or without the presence of infection, resulting in the fast depletion of their drug supply. This facilitates the development of resistant strains of pathogens due to the presence of sub-lethal doses. Furthermore, diffusional-release hydrogels are prone to burst releases, characterized as an abrupt release of a high concentration of antimicrobial agents due to being weakly absorbed or bonded to the hydrogels. Burst release may represent a serious risk for host cell viability, and may imply critical organ and tissue damage (Tallet et al., 2020). Thus, the development of hydrogels with controlled drug release systems or even with a stimuli response release has enormous potential. Drug release kinetics may be characterized using mathematical models that are generated based on experimental release data. Through the understanding of the different factors that govern the release rate and behavior, it is possible to design safer materials or adjust their use in specific clinical situations. The kinetics of drug release can be described through several mathematical models. The main mathematical models of drug release are the zero-order, first order, Higuchi, Hixson-Crowell, Ritger-Peppas, Korsmeyers-Peppas, Brazel-Peppas, Baker-Lonsdale, Hopfenberg, Weibull, and Peppas-Sahlin (Bruschi, 2015). The release values must be modeled according to their fitness to each of the referred models (or even others, such as modified Gompertz) (Padrão et al., 2016, Alves et al., 2022). Briefly, the zero-order model applies to materials where the drug is released at a fixed rate through time. The first-order model is used when the percentage of release depends on the concentration of active agent. The Higuchi model is applied to three-dimensional structures where release unfolds through diffusion. The Hixson-Crowell model is applied in drugs that change their diameter and surface area during their release. Finally, the Korsmeyer-Peppas and its derivative models are the most applied models to describe drug release systems, in particular in hydrogels (Vigata et al., 2020).

Relatively to the models: Ritger-Peppas, Korsmeyers-Peppas, Brazel-Peppas, and Peppas-Sahlin, the good of the fitness determines which model provides a more accurate representation of the release behavior. For these models, the release is described according to the diffusivity exponent (n). The model data provides information about the release mechanism, namely quasi-Fickian, Fickian diffusion, Anomalous transport (non-Fickian), and transport case II (non-Fickian). When the degree of swelling governs agent release it fits in a Fickian diffusion. Quasi-Fickian diffusion describes a rapid release of an agent due to its considerably smaller size in comparison to the hydrogel matrix. When diffusion and swelling are the main events influencing the release rate, the Anomalous transport model is applied. Transport II encompasses the cases where the diffusion is the prevalent mechanism (over swelling), and may be correlated to erosion of the hydrogel. Table 1 depicts the release mechanisms related to the diffusivity exponent (n) and the active agent structure shape.

Table 1. Diffusivity exponent (n) value according to the release mechanism of the models (Vigata et al., 2020, Ritger and Peppas, 1987, Siepmann, 2001).

Diffusivity exponent (n)			Release mechanism
Film	Cylinder	Spheres	
$n < 0.5$	$n < 0.45$	$n < 0.43$	Quasi-Fickian
$n = 0.5$	$n = 0.45$	$n = 0.43$	Fickian Diffusion
$0.5 < n < 1.0$	$0.45 < n < 0.89$	$0.43 < n < 0.85$	Anomalous transport (non-Fickian)
$n > 1.0$	$n > 0.89$	$n > 0.85$	Transport case II

In this section, the common strategies for the development of diffusional release of active antimicrobial agents from hydrogels are described, divided by the type of active ingredients: nanoparticles, antibiotics, and other antimicrobial agents (e.g. curcumin, quercetin, dopamine, matrine, and cordycepin). The mathematical model of drug release will be described when available.

3.1. Silver nanoparticles

Numerous studies reported functional hydrogels incorporating metal nanoparticles as biocompatible active antimicrobial agents. In contrast to the individual mechanism of conventional antimicrobial agents, metal nanoparticles present multiple mechanisms of action, often impeding microbial resistance. The antimicrobial mechanisms of the used metal nanoparticles are not entirely understood. Nevertheless, numerous metal nanoparticles modus

operandi have been proposed, such as: i) direct electrostatic interactions with the microorganism cell membrane and/or cell wall components; ii) homeostatic stress generation due to an abnormal imbalance of ions, which impair respiration, interrupt energy transduction, and lead to cell death; iii) interactions with sulfur-containing molecules such as proteins; iv) the production of reactive oxygen species and the release of metal ions that denature proteins and damage ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and lipids. Metal nanoparticles are also described as being able to prevent biofilm formation and hinder cell wall synthesis (Ribeiro et al., 2022, Baptista et al., 2018).

Silver nanoparticles have received particular attention as antimicrobial agents due to their excellent properties against a broad range of bacteria, fungi, and viruses, including some resistant strains (Dakal et al., 2016). Furthermore, silver nanoparticles cytotoxicity is under intensive analysis. Silver nanoparticles concentration of $0.5 \mu\text{g mL}^{-1}$ has been described as highly effective against bacteria. Moreover, $0.25 \mu\text{g mL}^{-1}$ of silver nanoparticles display absent cytotoxicity to various mammalian cells (Le Thi et al., 2018). For this reason, hydrogels, biomembranes, and scaffolds combining crosslinked polymers containing silver nanoparticles have emerged as a new class of multifunctional biomaterials for skin tissue engineering (Capanema et al., 2018). Silver nanoparticles-based wound dressings have been designed and are already commercially available as Aquacel Ag, Acticoat Flex, Tegader Ag, Silverce, among others (Zepon et al., 2018).

Different strategies have been used to prepare the hydrogels containing silver nanoparticles. The silver nanoparticles can be prepared in an individual step by chemical or biological synthesis and then embedded into hydrogel matrixes or directly synthesized by in situ processes during the hydrogel formation. In the reduction step, commonly highly reactive chemicals are used such as sodium borohydride, however, plant extracts or even the hydrogel components (without any additives) were also used. Accordingly, green solvents, eco-friendly reducing agents, and nontoxic hydrogels materials are the key issues that merit attention in synthesis protocols (Zhao et al., 2019).

A straightforward approach for producing hydrogels containing silver nanoparticles is the two-step method, comprising the separate production of the hydrogel and silver nanoparticles, followed by their combination. Several works report distinct strategies to delay/control the release of the silver nanoparticles or silver ions.

3.1.1. Two-step method hydrogel synthesis

Jiang et al. mixed commercial silver nanoparticles with oxidized konjac glucomannan and carboxymethyl chitosan using cavitation. The obtained hydrogels were able to mitigate the

burst release of silver ions and reduce the silver nanoparticles cytotoxicity. The concentration of diffused silver ions from the hydrogel was detected using inductively coupled plasma mass spectrometry in a weakly acidic solution, depicting gradual and slower release of silver ions release in comparison to pure silver nanoparticles. The achieved hydrogel did not compromise fibroblasts viability in vitro and displayed superior antibacterial effectiveness against *S. aureus* and *E. coli*, than the hydrogel without silver nanoparticles (Jiang et al., 2020a). Zhao et al. developed an injectable hydrogel containing polydopamine, polyaniline, polyvinyl alcohol, and silver nanoparticles. This hydrogel was produced using sodium borohydride as a reducing agent, and polyvinylpyrrolidone and trisodium citrate as stabilizing agents. The hydrogel denoted a significant inhibition of *E. coli* and *S. aureus* growth and exhibited good biocompatibility (Zhao et al., 2019). Kumar et al. reported the synthesis of silver nanoparticles using extracts from *Eucalyptus citriodora* leaves. The produced silver nanoparticles were added to a solution containing polyvinyl alcohol and chitosan. The hydrogel was obtained through spray using glutaraldehyde and boric acid as crosslinkers. The silver nanoparticles release profiles were monitored by atomic absorption spectroscopy, being observed a clear delay of the maximum cumulative release of silver ions in the different hydrogel formulations tested. The hydrogel exhibited hemocompatibility due to the hydrophilic and biocompatible nature of the polymers present in its formulation. Finally, the hydrogel exhibited weak and moderate activity against *S. aureus* and *E. coli*, respectively (Kumar and Kaur, 2020). Gou *et al.* developed an injectable gelatin-carboxylated cellulose hydrogel containing aminated-silver nanoparticles. The aminated-silver nanoparticles were obtained using polyvinyl pyrrolidone and a silver salt precursor at 120 °C, followed by silver nanoparticles reaction with 3-aminopropyltriethoxysilane. The negatively charged carboxylated cellulose interacted with the aminated silver nanoparticles through electrostatic forces. Additionally, van der Waals interactions and hydrogen bonds were also indicated to promote the formation of the ternary hydrogel with a homogeneous polymeric network. The referred chemical interactions controlled the release of the silver nanoparticles with prolonged activities, accelerated wound healing and displayed antibacterial activity against *E. coli* (Gou et al., 2020). Gupta *et al.* produced silver nanoparticles using a curcumin-hydroxypropyl- β -cyclodextrin complex as reducing and stabilizing agent. The microencapsulation of curcumin in cyclodextrins was performed to overcome the hydrophobicity of curcumin. Silver nanoparticles were loaded in bacterial nanocellulose hydrogels through pad-dry method. The suitable antimicrobial performance of the hydrogel against *S. aureus*, *P. aeruginosa*, and *Candida auris*, and the

absence of cytotoxicity suggested an adequate release of silver nanoparticles (Gupta et al., 2020).

3.1.2. One-step method hydrogel synthesis

3.1.2.1. Chemical based methodology

The one-step method comprises the synthesis of silver nanoparticles within the hydrogels matrix. This strategy intends to avoid unwanted agglomeration and the burst leakage of silver nanoparticles during hydrogel applications. Tan *et al.* produced boron-catechol and polyaspartamide hydrogel with in situ synthesized silver nanoparticles. After the immersion of the hydrogel in a silver solution, the silver nanoparticles were formed due to the catechol moieties that can coordinate with metal ions and induce the growth of metal nanoparticles without using an additional reducing agent. Release kinetic studies were performed in a cell culture medium, showing a slow release profile over a long period (40 days to release only 7.5%), mainly attributed to the hydrolysis of the carbonate ester linkages along the polyaspartamide chains. It was justified by the high hydrophobicity of the hydrogels, leading to poor water uptake and slow diffusion through the network. This profile indicated that this material could be used for long-term applications. However, cytotoxicity was observed at high concentrations (5 mg mL^{-1}). Antimicrobial tests showed a bacteriostatic and bactericidal effect against *S. aureus* and *E. coli*, respectively (Tan et al., 2018). Chalitangkoon et al. developed hydroxyethylacryl-chitosan and sodium alginate hydrogel with chemically synthesized in situ silver nanoparticles using sodium borohydride. The results showed that the presence of silver nanoparticles increased the swelling and enhanced mechanical properties. In vitro drug release profiles were examined using para-acetylamino phenol, as a soluble model drug. The increase in crosslinking density and silver concentration prolonged the drug release. The entire drug was released within 32 h. The film showed a good fit for the first-order model suggesting the dependence of para-acetylamino phenol concentration on drug release. The hydrogels exhibited antibacterial activity against *E. coli* and *S. aureus* without cytotoxicity (Chalitangkoon et al., 2020). Chen et al. also produced chemical synthesized silver nanoparticles with sodium alginate as reducing and stabilizing agents. The carboxymethyl chitosan and polyvinyl alcohol hydrogel were obtained by the freeze-thaw method and the calcium ion crosslinking method. The silver nanoparticles were uniformly distributed within the hydrogel and showed a synergistic antibacterial effect with chitosan against *E. coli* and *S. aureus*. A possible synergistic modus operandi may be described as on the one hand, the protonated ammonium on the chitosan chain promotes electrostatic interaction and tropism with the negatively charged cell membrane of

bacteria, disturbing the membranes stability and interfering with the metabolism. On the other hand, the present silver nanoparticles generate lethal reactive oxygen-catalyzed reactions. Furthermore, the hydrogel exhibited excellent biocompatibility within a 72 h period (Chen et al., 2020a).

3.1.2.2. Polymer-based methodology

Thi et al. mixed catechol-rich gelatin solution with a silver salt precursor to produce an injectable hydrogel. The silver nanoparticles were simultaneously synthesized in situ during hydrogel formation via catechol groups without additional reductants. The hydrogel was formed via 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide and N-hydroxysuccinimide coupling reaction. The silver was sustainably released over two weeks from the hydrogels and prolonged the degradation time of pure hydrogel scaffolds from 18 h to 70 h. The superior crosslinking density obtained in this hydrogel delayed silver nanoparticles diffusion. In fact, solely 8.7% (~4.5 µg) of the total silver incorporated inside the hydrogel was released. This dose, sustained by a slow release of silver, was maintained within effective bactericidal concentrations and absence of cytotoxicity. Thus, the composite had excellent antibacterial activities against both Gram-negative and Gram-positive bacteria, while not causing toxicity to mammalian cells (Le Thi et al., 2018). Capanema et al. formed hybrid membranes of carboxymethyl cellulose by the solvent casting method using citric acid as a crosslinker. The functional groups of carboxymethyl cellulose played a relevant role in the silver nanoparticles synthesis and the crosslinking process of the polymer network. The results demonstrated that superabsorbent hydrogels were produced with swelling and degradation behaviors dependent on the concentration of crosslinker, degree of carboxymethylation of carboxymethyl cellulose, and content of silver nanoparticles in the formulation. The hybrid nanocomposite displayed cytocompatibility and antibacterial activity against *S. aureus*, *E. coli*, and *P. aeruginosa* (Capanema et al., 2018). Wang et al. produced hydrogels mixing a chitosan solution with oxidized konjac glucomannan and silver nanoparticles. The self-adapting hydrogel wound dressings were constructed with Schiff-base linkages between the aldehyde groups of oxidized konjac glucomannan and amine groups in the backbone of protonated chitosan and protonated tranexamic acid. Histological analysis indicated that this self-adapting hydrogel provides a clear advantage over the commercial hydrogel dressing, namely Aquacel Ag, in the in vivo wound-healing process. The cytotoxicity results indicated that the cell viability in the case of the experimental group remained greater than 98% for at least 48 h. The biocompatibility of the natural polymers in the hydrogel formulation was defined as responsible for such a low cytotoxicity. An interesting antibacterial effect was observed in Aquacel Ag and in the prepared

hydrogel against *E. coli* and *S. aureus*. Nevertheless, a superior effectiveness was observed in the chitosan-konjac-silver nanoparticles hydrogel (Wang et al., 2020d).

Masood et al. described the production of a chitosan and polyethylene glycol hydrogel containing silver nanoparticles. The silver nanoparticles were obtained by the addition of the polyethylene glycol during the formation of the hydrogel. The incorporation of polyethylene glycol also assisted silver nanoparticles stabilization, a crucial feature for their prolonged biological activity. Furthermore, glutaraldehyde was added as a crosslinker. Silver nanoparticles release rate was monitored using ultraviolet-visible spectrophotometry. The hydrogel showed a slow and sustained release of silver nanoparticles for at least seven days manifesting the slow biodegradation of developed hydrogels (there was no burst release). This hydrogel showed activity against *P. aeruginosa*, *E. coli*, *S. aureus*, *Bacillus subtilis*, and *Bacillus pumilus* (Masood et al., 2019). Zepon et al. reported a simple and green method for producing κ -Carrageenan hydrogels by a sol (heating) - gel (cooling) process, which enabled the simultaneous synthesis of silver nanoparticles during the heating time. Based on ultraviolet analysis, silver nanoparticles synthesis showed to be faster with higher temperature reaction probably due to the expansion of the κ -Carrageenan, which facilitates the interaction between silver ions and the available functional groups on the polysaccharide. The introduction of silver nanoparticles changed the swelling properties of the hydrogel and reduced its viscosity and gelling temperature. In the release study, the silver nanoparticles were continuously released for up to 48 h in a concentration sufficient to prevent bacterial growth as confirmed by antimicrobial tests. The pH of pseudo-extracellular fluid did not significantly affect the amount of silver released from the hydrogel. The antimicrobial activity of the hydrogel was tested against *S. aureus* and *P. aeruginosa*, confirming the inhibitory effects of silver nanoparticles (Zepon et al., 2018).

3.1.2.3. Irradiation-based methodology

Several works describe the use of gamma irradiation to reduce silver ions present in a polymer matrix to simultaneously generate silver nanoparticles and hydrogels (Alcântara et al., 2020, Kumaraswamy et al., 2020, Khozemy et al., 2018, de Lima et al., 2018). For instance, Lima et al. produced a hydrogel containing polyvinylpyrrolidone, polyethylene glycol, agar, and carboxymethyl cellulose with silver nanoparticles using Cobalt 60 gamma irradiation under an inert atmosphere (nitrogen). Gamma irradiation was concomitantly performed for polymer crosslinking, reduction of silver ions, and sterilization of the obtained hydrogel. The release profiles for silver nanoparticles from the hydrogel exhibited an initial burst release up to 3 h. A

relative stability of release thereafter up to 40 h followed. No indications of in vitro toxicity were observed (de Lima et al., 2018).

Ultraviolet light was used to reduce silver ions and form the hydrogel (Xiao et al., 2020, Baukum et al., 2019, Yang et al., 2020a). Baukum et al. developed alginate-gelatin hydrogel with silver nanoparticles under ultraviolet radiation and crosslinked with glutaraldehyde and calcium chloride by solvent casting method. The amount of silver ions released from the hydrogel was measured by atomic absorbance spectroscopy. An initial burst release was observed, however the diffusion rate eventually slowed and stabilized. The hydrogel was non-toxic and showed antibacterial activity against *S. aureus*, *P. aeruginosa*, and *E. coli* (Baukum et al., 2019).

The work from Ounkaew et al. focused on the production of hydrogel membranes of carboxymethyl starch and polyvinyl alcohol-containing in situ synthesized silver nanoparticles. The conversion into a hydrogel crosslinking was achieved via chelation with polyvalent cations, namely citric acid, which established ester linkages. The silver ion release from the hydrogel was characterized through atomic absorbance spectroscopy. Rapid silver ion release was observed during the first 6 hours followed by a slower release. The initial release may prevent bacterial adhesion to the wound and consequent formation of biofilm, whereas the slower release stage provides wound site asepsis during prolonged treatment. Kormeyer-Peppas model fitted the profile release mechanism of silver nanoparticles, denoting a Fickian diffusion mechanism. Moreover, the hydrogel showed low toxicity to human fibroblast cells indicating good biocompatibility and antibacterial activity against *E. coli* and *S. aureus*. The antibacterial activity could be related to the acidity of citric acid and also to the release of silver ions from silver nanoparticles. The inhibition zones of *S. aureus* were larger than those of *E. coli* (Ounkaew et al., 2020, Masood et al., 2019, Zepon et al., 2018)

3.2. Additional nanoparticles

Most of the studies in the literature were performed using silver nanoparticles, however, also some different nanoparticles can be found, namely copper (Ponco and Helmiyati, 2020), gold (Mahmoud et al., 2019), zinc oxide (Kai and Xuesong, 2020), magnesium (Eivazzadeh-Keihan et al., 2020), cerium (de Lima et al., 2018), silver-titanium (Ahmed et al., 2020), and zinc oxide-silver (Li et al., 2019) nanoparticles. Ponco et al. produced carboxymethyl cellulose and polyvinyl alcohol with copper nanoparticles. First, copper ions were stabilized in the polymers matrixes electrostatically bonded with the hydroxyl and carboxyl groups. Then, the nanoparticles were obtained by chemical synthesis using hydrazine. The composite showed better activity for *E. coli* than *S. aureus* (Ponco and Helmiyati, 2020). Zinc oxide nanoparticles

were incorporated in hydrogels of bacterial cellulose/chitosan (Kai and Xuesong, 2020), xanthan/polyvinyl alcohol (Raafat et al., 2018), and carboxymethyl cellulose/ κ -Carrageenan/graphene oxide/konjac glucomannan (Li et al., 2019). Zinc oxide nanoparticles exhibited interesting antimicrobial properties against *S. aureus*, *E. coli*, and *C. albicans*. Ahmed et al. produced a hydrogel composed of polyvinyl alcohol and starch and crosslinked with glutaraldehyde. The authors also added graphitic carbon nitride as a filler and silver-titanium dioxide nanoparticles as an antibacterial agent. The kinetics of drug release was performed by using various mathematical models, where the Higuchi model was found to be the best fit. The non-Fickian diffusion mechanism prevailed and a sustained and slow release of nanoparticles was observed. Using the hydrogel, the complete healing was accomplished in seven days and good antibacterial properties were achieved against *S. aureus* and *E. coli* (Ahmed et al., 2020). The works using different nanoparticles from silver showed the potential for the development of novel antimicrobial hydrogels with similar or even better properties. The environmental and safety concerns about the use of silver nanoparticles make the development of novel materials an imperative issue.

3.3. Antibiotics

Antibiotics represent a cornerstone for the control of microbial infection. Antibiotics are usually administrated by injection or by oral administration, being necessary considerable dosages due to change/degradation or leakage between the tissues and organs until it reaches the target area (Polat et al., 2020). They can also be applied directly to the wounds through creams or gels, but they are not active for a prolonged period (Ahmed et al., 2017). Alongside metallic nanoparticles, antibiotics and their release from hydrogel materials are the most studied active pharmaceutical agents for wound dressing applications. Drug-loaded wound dressings can provide delivery of the drug molecules through the wound site for longer time without needing frequent replacement of the dressing material (Tamahkar et al., 2020).

Hydrogel dressings can be prepared by simple mixture/drying, or they can also be crosslinked, increasing the stability and porosity. Porous structures provide an adequate environment for transfer of nutrients and oxygen, cell growth and proliferation, evaporation of wound exudates, preventing fluid accumulation and subsequently reducing the risk of skin maceration and infections, and the release of drug molecules (Tao et al., 2019, Ahmed et al., 2017). In the work developed by Huang et al., an antimicrobial hydrogel film was prepared by crosslinking hyaluronic acid with carboxylated chitosan and gentamicin through intermolecular covalent bonds mediated by carbodiimide chemistry. Hyaluronic acid is an important molecule for connective tissue structuration and supports collagen formation and maintenance, while

carboxylated chitosan prevents bacterial growth. Both polymers present water solubility, biocompatibility, biodegradability, and easy modification. To improve the mechanical properties and control the degradation rate they were crosslinked, achieving the long-term antibacterial effect of the hydrogel film. The developed hydrogel presented good water absorption capacity, water vapor permeation rate, mechanical properties, resistance to enzymatic hydrolysis, and biocompatibility. Release tests showed that almost 40% of gentamicin was released in 24 h and after that was released at a slower rate for 9 days. This behavior indicates a simultaneous release of gentamicin through degradation and diffusion. Moreover, the hydrogel antibacterial activity against *P. aeruginosa* and *S. aureus* was found to be moderate whereas the commercial dressing Aquacel Ag displayed weak activity. In vivo wound healing test using a full-thickness skin defect in mice showed that both the hydrogel and Aquacel Ag led to a relatively intact skin within 16 days (Huang et al., 2020a). Picone et al. prepared a chemical crosslinked xyloglucan-polyvinyl alcohol hydrogel film using glutaraldehyde. Before drying, glycerol was added as plasticizer and provide adequate water retention properties. The obtained hydrogel exhibited a porous morphology (pore size of 20 μm), high gel fraction (93%), swelling of 350% in phosphate buffer saline, biocompatibility (viability of 90% for epithelial cells), hemocompatibility and immunogenicity, and partial adhesiveness. To study the ability to absorb and release molecules, the hydrogel was first swollen in water to the equilibrium state, and then a fluorescent hydrophilic dye was used for spectroscopic evaluation. The hydrogel absorbed 80% of the dye and released 98% of the load in 24 h, following a Fickian diffusion model. Furthermore, antibacterial tests showed that this hydrogel provides mechanical protection against bacterial infiltration, while the hydrogel loaded with ampicillin showed an inhibitory effect against *E. coli* (Picone et al., 2019). In the study carried out by Polat et al. nanocomposite hydrogels comprising agar, κ -Carrageenan, and montmorillonite crosslinked through free radicals were developed. These hydrogels were used as carriers for lidocaine hydrochloride, an analgesic, and chloramphenicol, a wide spectrum antibiotic. Montmorillonite contributed to increase the ultimate compressive stress (47.70 kPa) and reducing the amount of lidocaine hydrochloride and chloramphenicol released (90% within 3.5 h). The hydrogels presented a high swelling index in different physiological solutions, biocompatibility (osteosarcoma cells viability of 104%), and antibacterial activity against *E. coli* and *S. aureus* (strong inhibition zones) (Polat et al., 2020).

In several works, freeze-drying is performed in order to obtain stable crosslinked porous hydrogels. Erdagi et al. synthesized gelatin/diosgenin-carboxylated nanocellulose antibiotic-based hydrogels using the natural extract genipin as crosslinking agent. This strategy achieved

reduced cytotoxicity and anti-inflammatory properties when compared to other synthetic crosslinking agents. The hydrogels exhibited a porous morphology with interconnected porosity (pore sizes of 10 to 30 μm), good swelling capacity, high gel yield ($\sim 90\%$), and biocompatibility (fibroblast cells viability of $\sim 80\%$). The loading efficiency of neomycin in the hydrogels was found to be 95.5% and drug release tests showed a release of approximately one-fifth within 15 min and was complete after 24 h. The hydrogels presented weak and moderate antibacterial activity against *E. coli* and *S. aureus*, respectively (Ilkar Erdagi et al., 2020). Sadeghi et al. developed an antibacterial wound dressing using carboxymethyl cellulose (carboxymethyl cellulose-human hair keratin and clindamycin loaded halloysite nanotubes, using citric acid as a crosslinker and glycerol as plasticizer, through freeze-drying. The obtained hydrogel presented a distinctly interconnected porous structure (mean pore sizes of 98 μm), high compressive modulus (179 KPa), high water uptake (1.5 g g^{-1}), and adequate water vapor permeation rate ($1921 \text{ g m}^{-2} \text{ day}^{-1}$). Moreover, the hydrogel showed blood compatibility (protein adsorption of $\sim 37 \text{ mg g}^{-1}$, clotting time of 13 s) and cell viability ($>90\%$ of mouse fibroblasts viability). The in vitro release study indicated that the clindamycin release was controlled via a Fickian diffusion mechanism, with a release of nearly 13% in 4 h, reaching 50% in 7 days. Additionally, the fabricated hydrogel dressing displayed a weak activity against *S. aureus* (79%) (Sadeghi et al., 2020). Kaur et al. developed poly(vinyl alcohol)-sodium alginate hydrogels crosslinked via chemical/ionic method in order to obtain water insoluble membranes to be used in the treatment of burn wound infections. Bacteriophages were loaded to combat antibiotic-resistant pathogens and were co-incorporated along with minocycline to increase the efficacy of the phage treatment. The hydrogel presented self-adherence, high swelling index ($\sim 850\%$), high gel fraction ($\sim 52\%$), high protein absorption (0.1 mg cm^{-2}), good hemocompatibility, antibacterial activity against methicillin resistant *S. aureus*, *Klebsiella pneumoniae*, and *P. aeruginosa*, and biocompatibility (skin epithelial cells viability $>94.25\%$). Elution assay showed nearly all the antibiotic and phage particles were released within the first 15 min. In vivo tests using an induced murine burn wound model confirmed the potential of the combinational treatment with phage and antibiotic showing complete regeneration on the 14th day of treatment (Kaur et al., 2019). Tao et al. have prepared a sericin and polyvinyl alcohol hydrogel through repetitive freeze-thawing to obtain a stable drug carrier hydrogel. The hydrogel presented a porous morphology (pore size of 38.19 μm , porosity $>85\%$), high swelling index (1200%), good mechanical properties, and biocompatibility (mouse fibroblasts and human epithelial cells viability of 130 and 140%, respectively). The hydrogel has also the ability to load and release drugs (gentamicin release of approximately 80% within 10 h) and

antibacterial activity against *E. coli*, *S. aureus*, and *P. aeruginosa* (Tao et al., 2019). Ahmed et al. prepared calcium alginate hydrogels through several freeze-drying cycles to deliver ciprofloxacin directly to the wound site of infected diabetic foot ulcers. Dressings with 0.005–0.025% of ciprofloxacin presented high porosity (~98–95%), moisture content (~17%), equilibrium water content (~94–92%), swelling (~1520–1087%), water vapor transmission rate (~3446–3499 g m⁻² day⁻¹), and biocompatibility (human keratinocytes cell viability >85%). The hydrogel with 0.025% ciprofloxacin showed the fastest release rate (nearly 68% within 5 min), followed by sustained Fickian drug release. Furthermore, it exhibited very strong antibacterial activity against *E. coli*, *S. aureus*, and *P. aeruginosa*. Overall, the new hydrogel dressing presented better properties than the commercial dressing Algisite Ag (Ahmed et al., 2017).

A different approach for the development of hydrogels is using multilayers where the advantages of each constituent are integrated. Tamahkara et al. developed a multilayer wound dressing via layer-by-layer self-assembly through electrostatic interactions between polymeric layers, formed by four layers. The upper layers, carboxylated polyvinyl alcohol, and gelatin, were responsible for the moisture control and physical barrier for microorganisms. The hyaluronic acid was incorporated as an antibiotic-loaded layer, and the lower layer, also gelatin, was used to control the antibiotic release and to remove excess exudate from the wound site. The multilayer hydrogels presented swelling ratios of approximately 518% and 339% for pH 5.5 and 7.4, respectively. The hydrolytic degradation test showed complete degradation after 15 days, exhibiting a long-term degradation profile with good stability. Regarding drug release, ampicillin exhibited a burst release of 34.5% within 6 h followed by a 65% zero-order model release within 7 days. Moreover, multilayer hydrogels showed no toxicity (mouse fibroblast cells) and moderate antibacterial activity against oxacillin sensitive *S. aureus* (Tamahkar et al., 2020). In another work, an antibiotic-loaded carboxymethylcellulose hydrogel was incorporated into a crosslinked nano-electrospun fiber mat composed of nanofibers of enzymatic poly-3-caprolactone grafted with poly(gallic acid). Carboxymethylcellulose hydrogel was used as drug carrier, while the electrospun polymers provided mechanical support in a porous three-dimensional (3D) structure. The obtained composites showed to be hemocompatible and not cytotoxic (epithelial cells). The release of the antibiotic clindamycin followed a Fickian diffusion model and the antibacterial tests showed activity against *S. aureus* (moderate activity) (Romero-Montero et al., 2020). In addition to the mentioned properties of the hydrogels, injectable hydrogels have also the ability to fill wound sites. Qu et al. developed injectable hydrogel dressings by mixing oxidized hyaluronic acid-graft-aniline tetramer and N-carboxyethyl chitosan with the formation of the Schiff base bond at physiological conditions.

Aniline possesses conductivity and antioxidant properties, contributing to the proliferation of the electrical stimuli sensitive cells and free radical scavenging, accelerating the wound healing process. The addition of in situ encapsulated amoxicillin exhibited a Fickian diffusion model and showed strong antibacterial ability against *S. aureus* and *E. coli*. Moreover, in vivo experiments using a full-thickness skin defect model showed better therapeutic effect of the developed hydrogels than the commercial film dressing Tegaderm (Qu et al., 2019).

A summary of the antimicrobial hydrogel carriers is depicted in Table 2.

Table 2. Summary of hydrogel dressings for release of antibiotics by diffusion.

Hydrogel composition	Functionalization	Diffusion model	Results	Refs.
Hyaluronic acid/carboxylated chitosan	Gentamicin sulphate (antibiotic)	n.d.	Drug release (39.91%, 24 h); Biocompatibility (NIH-3T3 cells); Antibacterial activity against <i>P. aeruginosa</i> and <i>S. aureus</i> (inhibition zone: 12.5 mm and 14.8 mm).	(Huang et al., 2020a)
Xyloglucan/polyvinyl alcohol	Ampicillin (antibiotic)	Fickian	Biocompatibility (A549 epithelial cells viability of 90%); Hemocompatibility; Antibacterial activity against <i>E. coli</i> (inhibition zone: 40 mm).	(Picone et al., 2019)
Agar/κ-Carrageenan/montmorillonite	Lidocaine hydrochloride (analgesic) and chloramphenicol (antibiotic)	n.d.	Biocompatibility (M-63 cells viability of 104%); Drug release (91.66% and 86.46% (LDC, CLP), 210 min); Antibacterial activity against <i>E. coli</i> and <i>S. aureus</i> (inhibition zone: 29.7 mm and 29.3 mm, respectively).	(Polat et al., 2020)
Gelatin/diosgenin/carboxylated nanocellulose	Neomycin (antibiotic)	n.d.	Drug release (25% to 18%, pH 5.5 and pH 7.4, 15 min, 100% in 24 h); Biocompatibility (human dermal fibroblast cells viability of 80.1%); Antibacterial activity against <i>E. coli</i> and <i>S. aureus</i> (inhibition zone: 10.8 mm and 14.2 mm, respectively).	(Ilkar Erdagi et al., 2020)
Carboxymethyl cellulose/keratin	Clindamycin (antibiotic)	Fickian	Drug release (13.2% in 4 h and 50% in 7 days.); Hemocompatibility (protein adsorption, 36.85 mg g ⁻¹ , clotting time, 13 s); Biocompatibility (L929 mouse fibroblasts viability >90%); Antibacterial activity against <i>S. aureus</i> (78.66%).	(Sadeghi et al., 2020)
Poly(vinyl alcohol/sodium alginate	Minocycline (antibiotic) and phages	n.d.	Drug release (99.9%, 15 min); Hemocompatibility; Biocompatibility (SK-1 skin epithelial cells viability >94.25%);	(Kaur et al., 2019)

			Antibacterial activity against methicillin resistant <i>S. aureus</i> , <i>K. pneumoniae</i> , and <i>P. aeruginosa</i> .	
Silk sericin/poly(vinyl alcohol)	Gentamicin (antibiotic)	n.d.	Drug release (~80%, 10 h); Biocompatibility (NIH-3T3 and HEK-293 cells viability of 130 and 140%, respectively); Antibacterial activity against <i>E. coli</i> , <i>S. aureus</i> and <i>P. aeruginosa</i> .	(Tao et al., 2019)
Calcium alginate	Ciprofloxacin (antibiotic)	Fickian (0.005 and 0.025%), non Fickian (0.010%)	Drug release 0.025% ciprofloxacin with the fastest release rate (68.36%, 5 min) followed by sustained drug release; Biocompatibility (human adult keratinocytes cell viability >85%, 72 h); Antibacterial activity against <i>E. coli</i> , <i>S. aureus</i> , and <i>P. aeruginosa</i> (inhibition zone: 43.43, 34.67, and 40.00 mm, respectively).	(Ahmed et al., 2017)
Carboxylated poly(vinyl alcohol)/gelatin/hyaluronic acid/gelatin	Ampicillin (antibiotic)	Zero order	Drug release (34.5%, 6 h and 65%, 7 days); Biocompatibility (L929 cells viability); Antibacterial activity against oxacillin sensitive <i>S. aureus</i> (inhibition zone: ~14 mm).	(Tamahkar et al., 2020)
Nanofibers of enzymatic PCL grafted with poly(gallic acid) (PGAL)/sodium carboxymethylcellulose, and CMC	Clindamycin (antibiotic)	Fickian	Hemocompatibility; Biocompatibility (viability of epithelial cells); Antibacterial activity against <i>S. aureus</i> (inhibition zone: ~14 mm).	(Romero - Montero et al., 2020)
Oxidized hyaluronic acid-graft-aniline tetramer/N-carboxyethyl chitosan	Amoxicillin (antibiotic)	Fickian	Antibacterial activity against <i>E. coli</i> and <i>S. aureus</i> (inhibition zone: ~30 and 45 mm, respectively).	(Qu et al., 2019)

3.4. Other antimicrobial agents

Nanoparticles and antibiotics commonly display several problems such as: insolubility, systemic toxicity, and extend the healing process of a wound. Additionally, overconsumption of antibiotics is dangerously increasing the microorganism's resistance (Yu et al., 2020, Xuan et al., 2020, Song et al., 2019). Therefore, to overcome these disadvantages, new antimicrobial agents can be incorporated into composites for the treatment of wounds. The application of

antimicrobial hydrogels based on polysaccharides loaded with natural organic compounds, salts, or mixtures of these components, such as calcium alginate, modified starch, and hyaluronic acid derivatives, may be found in the literature (González et al., 2018, Zhang et al., 2020a, Chen et al., 2020b). Among all of them, chitosan is the most widely applied polysaccharide in the production of dressings due to its intrinsic antimicrobial activity. Ren et al. produced a hydrogel through crosslinking reactions between chitosan, genipin (crosslinker), and licorice polysaccharide. The presence of the crosslinker improved the stiffness of the composite and allowed it to obtain a slow degradation. On the other hand, the bacteriostatic effect against *S. aureus* and *E. coli* was achieved in the presence of licorice polysaccharide, while maintaining the biocompatibility of the composite, making it an excellent application in wound dressings (Ren et al., 2020a). Similarly, diazo resin crosslinked chitosan and cordycepin hydrogels, as well as chitosan or thiolated chitosan crosslinked with polyethylene glycol diacrylate and loaded with symmetric tryptophan-rich peptide produced biocompatible composites and showed an acceleration of wound healing in vivo between 14 to 21 days (Song et al., 2019, Gao et al., 2020, Huang et al., 2019). As an alternative to conventional wound dressing application processes, injectable, and emulsion hydrogels have been evaluated (Wang et al., 2018). According to this, Xuan and co-workers developed an injectable chitosan-silver hydrogel loaded with fibroblast growth factors (Xuan et al., 2020). After 17 days, the wound healing process ended due to the occurrence of a sustained release of growth factors and silver.

The application of natural compounds with biological properties to replace metallic nanoparticles has been one of the topics to be prioritized in the production of wound dressings. Curcumin, quercetin, dopamine, and matrine are some of the examples of compounds used (Zeighampour et al., 2018, di Luca et al., 2019, Zhou et al., 2020). For example, curcumin has been incorporated into hydrogels produced through esterification reactions between lignin, polyethylene glycol, Gantrez S-97, and a polyacid (poly(methylvinyl ether-co-maleic acid)) (Larrañeta et al., 2018). Overall, the developed composites exhibited antimicrobial activity against *S. aureus* and *Proteus mirabilis* (*P. mirabilis*). Curcumin was released for up to 4 days, depending on the type of hydrogel. In the case of the formulation with polyethylene glycol (molecular weight 14,000), a fit to the Korsmeyer-Peppas model was found. The release of curcumin unfolds through its diffusion along the polymeric matrix of the hydrogel (Fickian diffusion). Based on this release mechanism, a similar process was found to be present in the formulation of the antimicrobial peptide hydrogel loaded with glucose oxidase (Zhao et al., 2020b). This formulation successfully inhibited *S. aureus*. Furthermore, glucose oxidation catalysis of glucose into hydrogen peroxide depicts two important advantages when applied in

diabetics' wounds: i) it decreases the glucose concentration at the wound site; ii) it generates hydrogen peroxide that will act as antimicrobial agent. A bacterial nanocellulose-based hydrogel was impregnated with coniferyl alcohol to obtain a composite with healing properties (Zmejkoski et al., 2018). In this case, the coniferyl alcohol release fits the Korsmeyer-Peppas model, and this is classified as quasi-Fickian diffusion. Again, the swelling of bacterial nanocellulose (74–97%) determines the release profile, and no erosion of the hydrogel was detected. On the other hand, anomalous diffusion was observed during in vitro release of salicylic acid from a polyvinyl alcohol-fish gelatin-based hydrogel (Ren et al., 2020b). The diffusion of the solvent into the polymer matrix of the hydrogel is influenced by the swelling process (~60–85%). In general, diffusional-release hydrogels have mechanical, physicochemical, and biological properties that are advantageous for use in wound management. The main identified disadvantage was the initial burst release, which promotes an inadequate release in a short period.

Table 3. Summary of hydrogels dressings for release of other antimicrobial agents by diffusion.

Hydrogel composition	Functionalization	Diffusion model	Results	Ref.
Chitosan	Silver nitrate	Quasi-Fickian	Rapid release within the first 24 h, followed by controlled over 11 days; Antimicrobial activity against <i>E. coli</i> and <i>S. aureus</i> ; Anti-inflammatory.	(Xuan et al., 2020)
Chitosan	Cordycepin	n.d.	Initial burst release of 80% in 12 h; Biocompatibility; Antimicrobial activity against <i>E. coli</i> and <i>S. aureus</i> ; Wound-healing promoter.	(Song et al., 2019)
Starch	Graphene and salvia	n.d.	Weak antimicrobial activity against <i>E. coli</i> and <i>S. aureus</i> (inhibition zone: 7.0 mm 9.5 mm, respectively); Electrical conductivity.	(González et al., 2018)
Calcium alginate	Zinc ions	n.d.	Biocompatible; Antimicrobial activity against <i>S. aureus</i> and <i>E. coli</i> (96.2% and 95.7%, respectively).	(Zhang et al., 2020a)
N-halamine hydrogel from hyaluronic acid	Chloride ions	n.d.	Biocompatible (NIH-3T3 and C28/I2, 92% and 78%, respectively); Antimicrobial activity against <i>E. coli</i> and <i>S. aureus</i> (in vivo and in vitro); Wound healing promoter.	(Chen et al., 2020b)
Chitosan-genipin	Licorice	n.d.	Biocompatible (>74%); Bacteriostatic effect against <i>E. coli</i> and <i>S. aureus</i> (81% and 75%, respectively).	(Ren et al., 2020a)

Chitosan	Diazo-resin	n.d.	Biocompatible; Weak antimicrobial activity against <i>E. coli</i> and <i>S. aureus</i> (inhibition zone: 2.2 and 3.5 mm, respectively); Wound healing promoter.	(Gao et al., 2020)
Polyethylene glycol diacrylat and chitosan or thiolated chitosan	Symmetric Trp-rich peptide	n.d.	Initial burst release followed by a sustained release for 20 days; Biocompatibility; Weak antimicrobial activity against <i>S. aureus</i> and <i>E. coli</i> (inhibition zone: 4.5 and 4.7 mm, respectively); Anti-inflammatory.	(Huang et al., 2019)
Acrylamide and gelatin	Cinnamon oil	Fickian	Initial burst release in first 18 h, followed by a control release for over than 20 days (85%); Antimicrobial activity against <i>S. aureus</i> and <i>E. coli</i> .	(Wang et al., 2018)
Polyvinyl alcohol	Propolis	Fickian	Initial burst release of 45% in 3 h, followed by control release, continues for 96 h; Moderate antimicrobial activity against <i>S. aureus</i> .	(Zeigham pour et al., 2018)
Gelatin and Polyethylene glycol	Curcumin and quercetin	Second-order	Controlled release, 85% release; Antimicrobial activity against planktonic methicillin-resistant <i>S. aureus</i> (MRSA).	(di Luca et al., 2019)
Konjac and fish gelatin	Matrine	n.d.	Initial burst release of 90% 45 min; Hemocompatible; Moderate antimicrobial activity against <i>E. coli</i> and <i>S. aureus</i> (inhibition zone: 12.0 and 11.5 mm, respectively).	(Zhou et al., 2020)
Lignin-based hydrogel	Curcumin	Fickian	Controlled release for 4 days; Antimicrobial activity against <i>S. aureus</i> and <i>P. mirabilis</i> .	(Larrañeta et al., 2018)
Heptapeptide	Glucose oxidase	Fickian	Maximum release of 55% in 4 h; Biocompatible (>80%); Antimicrobial activity against <i>S. aureus</i> .	(Zhao et al., 2020b)
Bacterial nanocellulose	Coniferyl alcohol	Quasi-Fickian	Initial burst release of 24%, total release of 46.2% after 72 h; Antimicrobials against <i>S. aureus</i> , <i>Listeria monocytogenes</i> , and <i>Salmonella typhimurium</i> .	(Zmejkoški et al., 2018)
Polyvinyl alcohol and fish gelatin	Salicylic acid	Anomalous diffusion	Initial burst release of 34% and 72% after 3 h; Moderate antimicrobial activity <i>S. aureus</i> and <i>E. coli</i> (17 mm).	(Ren et al., 2020b)

4. Stimuli-responsive hydrogels

Diffusional-release hydrogels have been found to be the most frequently studied hydrogel application for wound management. However, uncontrolled diffusional release driven by the difference in drug concentrations may result in dangerous burst releases, usually resulting in adverse effects on patients at the initial stage and greatly dwindled drug efficacy (antimicrobials, growth factors, anti-oxidant, and anti-inflammatory agents) in the long run (Yi et al., 2015, Bhattarai et al., 2010). Therefore, the development of “smart” hydrogels possesses high demand. These “smart” textiles comprise one or several of the following features: i) drug release on-demand triggered by surrounding stimuli; ii) controllable “on/off” release; iii) tunable release kinetics (Wu et al., 2020, Vázquez-González and Willner, 2020). Stimuli-responsive hydrogels can be classified according to their stimuli (physical or chemical)-responsive mechanisms: light-responsive, temperature-responsive, magnetic-responsive, mechano-responsive, electric-responsive, pH-responsive, enzyme-responsive, redox-responsive, among others (Makvandi et al., 2019, Castelletto et al., 2019, Pawar et al., 2019, Wang et al., 2020a, Fang et al., 2020). When used in infected wounds, wound dressings composed of stimuli-responsive hydrogels can reversibly change their phases or stiffness, achieving functions such as injectability, sensing, controlled drug release, self-healing or shape memory (Deng et al., 2018, Amaral and Pasparakis, 2017, Rezaei et al., 2020). These stimuli-responsive hydrogels may be further categorized based on their responses to different physical and chemical signals that may unfold inside and outside the wound site: i) external stimuli-responsive hydrogels, which comprise triggers such as: light, temperature, electrical field, magnetic field, etc.; ii) internal stimuli-responsive hydrogels, include the following triggers: pH, enzymes, redox, etc. Light-responsive and pH-responsive hydrogels are the most extensively studied stimuli-responsive hydrogels and are depicted in Fig. 8.2. In the following sections, the composition, preparation methods, antimicrobial and other properties of light-responsive and pH-responsive hydrogels in the application of wound treatment are depicted.

Please insert Figure 8.2

Figure 8.2. Light or pH stimuli-responsive antibacterial hydrogel.

4.1. Light-responsive hydrogels

Light-responsive hydrogels contain in their formulation photo-responsive units such as: iron(III), zinc oxide, tungsten disulfide, gold nanorods, silver nanoparticles, trans-azobenzene, graphene oxide, carbon nanotubes, among others. These photo-responsive units can convert different light signals such as: near infrared light, ultraviolet or visible light into heat or reactive

oxygen. The heat or the reactive oxygen species will generate photo-thermal or photo-dynamic responses, respectively, namely: antimicrobial effects, reversible modification of the hydrogel phase (Takashima et al., 2012, Yang et al., 2020b). For example, graphene oxide-based nanomaterials can locally raise the temperature when irradiated with near infrared light leading to photo-thermal bactericidal effect (Zhang et al., 2021a, Huang et al., 2020b). Rosselle et al. fabricated a near infrared light-responsive and cefepime loaded hydrophilic cryogel, which is composed of butyl methacrylate and poly(ethylene glycol) methyl ether methacrylate incorporated with reduced graphene oxide to achieve an on-demand drug release (Rosselle et al., 2020). When exposed to near infrared light the reduced graphene oxide heated the cryogel leading to its swelling which releases the encapsulated antimicrobial drug. These cefepime loaded cryogels denoted significant reductions of pro-inflammatory responses in *ex vivo* human skin model wound explants infected with *S. aureus*. On the basis of the previous work, the research group has further covalently conjugated maleimide-modified antimicrobial peptides onto furan-based cryogels via the Diels–Alder cycloaddition to minimize passive and burst release of antimicrobial peptides, achieving an on-demand peptide release (Chambre et al., 2020). Their study has confirmed that the cryogel can effectively load either small molecular or biomacromolecular drugs for controlled near infrared light-responsive antimicrobial action in the treatment of infected wounds. Similarly, Zhang et al. have incorporated reduced graphene oxide, molybdenum disulfide, silver phosphate composites into a polyvinyl alcohol hydrogel to enhance the photo-thermal conversion ability of reduced graphene oxide, achieving synergistic antibacterial activities under dual visible and near infrared light irradiation (Zhang et al., 2019a). Also, with the developed composite, the hybrid hydrogels were endowed with improved mechanical property and swelling ratio, showing great potential as antibacterial wound dressing. In another study, graphene oxide sheets were modified with zinc oxide quantum dots to construct a chitosan-based hybrid hydrogel via electrostatic interaction. The composite hydrogel demonstrated synergistic photo-thermal and photo-dynamic antimicrobial effects when exposed to near infrared irradiation, promoting wound healing in the *in vivo* wound infection model (Liang et al., 2019a). Besides graphene oxide-based carbon material, other carbon material, such as hollow carbon nanoparticles, were also used as photosensitizer in the fabrication of light-responsive hydrogels. Polyethylene glycol modified hollow carbon nanoparticles were co-embedded with natural antibiotic aloe-emodin in poly-2-dimethylaminoethyl methacrylate-based hydrogel, exerting photo-dynamic and photo-thermal antimicrobial activity upon near infrared exposure. Furthermore, long-term therapeutic effects were exerted by the aloe-emodin release from the gel (Xi et al., 2018). Moreover, this aloe-

emodin and carbon material co-loaded polymer hydrogel exhibited the best anti-infection performance and promoted wound healing in comparison with the monotherapy, showing good clinical potential in wound management. Similarly, Liang et al. have employed carbon nanotubes as the photosensitizer in their construction of multifunctional hydrogels. In brief, chitosan, gelatin-grafted-dopamine and polydopamine-coated carbon nanotubes were used as building blocks to fabricate composite hydrogels. The crosslinking was established by the oxidative coupling of catechol groups using a hydrogen peroxide horseradish peroxidase catalytic system. Further, encapsulated doxycycline was added into the polymeric network for effective and prolonged antibacterial effects (Liang et al., 2019b). The combination of the above-mentioned materials has endowed the hydrogel with antibacterial properties (photo-thermally and chemical), adhesive, antioxidant, and conductive properties. This complex composite demonstrated good therapeutic effect both in vitro and in the infected full-thickness mouse skin defect wound model.

Photosensitizers, such as titanium dioxide, zinc oxide, copper(I) oxide, molybdenum disulfide, zinc phthalocyanine, silver nanoparticles, among others, can generate reactive oxygen species by exposure to visible light, hence, they are frequently employed in the construction of light-responsive hydrogels (Karimi and Khodadadi, 2016, Wang et al., 2019d). Wang et al. incorporated silver-doped titanium dioxide nanoparticles into a polyvinyl alcohol hydrogel. The reactive oxygen species generated by this hydrogel when exposed to visible light were intended to combat multidrug-resistant bacteria in wound management (Wang et al., 2019b). Both in the in vitro and in vivo rat model wounds infected with *S. aureus* by the hybrid hydrogel exhibited excellent antibacterial activity within a short period of time. It is worth mentioning that the hybrid hydrogels presented accelerated wound healing in rat model compared with a traditional 3M wound dressing. Similarly, in another work, silver phosphate and molybdenum disulfide photosensitizer composite were embedded in the polyvinyl alcohol-based hybrid hydrogel to exert synergistic photodynamic and photothermal bactericidal effects under co-irradiation of visible (660 nm) and near infrared (808 nm) light. Once irradiated the hydrogel accelerated wound healing in rat wound infection model in comparison to the pure hydrogel and a commercial medical gauze (Zhang et al., 2019b). In the study of Bayat et al., zinc phthalocyanine photosensitizer was employed and incorporated with the amphiphilic polypeptide colistin to fabricate chitosan-based hydrogel (Bayat and Karimi, 2019). The incorporation of colistin not only increased the bioavailability and solubility of zinc phthalocyanine but also enhanced the overall photo-bactericidal activity.

Overall, light-responsive hydrogels can unfold antimicrobial activity under specific light exposure, providing on-demand therapeutic effects in the treatment of wound infections. However, in such cases, additional devices are needed to trigger their activity. Moreover, the action period is highly dependent on the irradiation period. On one side, it can be considered as a safe by design strategy. On the other hand, it may be considered as a deficient antimicrobial wound dressing, which requires assistance from extra drug loading for sustained antimicrobial activity when dealing with infected wound management.

4.2. pH-responsive hydrogels

The pH of intact skin is commonly 4.5 to 5.0, and at the wound site it is slightly acidic (<7.0). The slightly acidic environment is attributed to the thriving metabolic activity of fibroblasts and keratinocytes during proliferation and angiogenesis (Percival et al., 2014). It would also be expected that the acidic substances commonly produced during aerobic bacteria metabolism would also contribute to a pH drop at the wound site. Nevertheless, the favored metabolism at the wound site may be anaerobic, which is known to promptly release polyamines and ammonia and that may increase environmental pH if they are not quickly swept by the immune system components (Metcalf et al., 2019). Therefore, alkaline pH may be an indicative not only of bacterial activity but also of a faulty immune response at the wound site. Despite the historically alkaline pH of infected and chronic wounds, several pH-responsive hydrogels were designed to respond to a pH drop, based on bacteria aerobic metabolism (Jiang et al., 2020b, Anh et al., 2019, Sakthivel et al., 2019). Khan et al. used arabinoxylan and chitosan, crosslinked using tetraethyl orthosilicate and anchored with reduced graphene oxide sheets to fabricate a series of composite hydrogels, which were further loaded silver sulfadiazine with antimicrobial agent. The envisaged objective was to achieve sustained and controlled wound disinfection (Khan et al., 2021). In acidic condition (pH~6.4), the protonation of the alcoholic and carboxylic acid functional groups of arabinoxylan and chitosan reduced anion-anion repulsion, resulting in swelling of the composite hydrogel. During swelling the release of silver sulfadiazine is promoted, thus displaying a pH-responsive drug delivery feature. The composite hydrogels exhibited good antibacterial activity against several skin disease-causing pathogens, namely: *S. aureus*, *E. coli*, and *P. aeruginosa* and *Enterococcus faecalis*. Furthermore, it displayed excellent biocompatibility when incubated with mouse pre-osteoblast cells. Similarly, in the study of Mohamed et al., the pH-responsive carboxymethyl chitosan and carboxymethyl pullulan were employed with temperature sensitive polymer poly (N-isopropylacrylamide) as the crosslinker and zinc oxide nanoparticles as the antimicrobial agent to fabricate a hybrid nanogel (Mohamed and Hassabo, 2018). Subsequently the nanogel was incorporated into a

cellulosic fabric to form a pH and thermosensitive wound dressing, showing good antimicrobial activity toward *S. aureus* and *E. coli*. Alginate may be also used as a pH-responsive biopolymer since it deforms or shrinks under acidic condition (Chuang et al., 2017). Based on that, Shahriari-Khalaji et al. efficiently incorporated sodium alginate into the bacterial nanocellulose matrix using a time-saving vacuum suction method followed by crosslinking through immersion in separate solutions of various cations. A pH-responsive antibacterial activity and promoted wound healing in the full-thickness skin defect rat model were achieved (Shahriari-Khalaji et al., 2020). In addition to utilizing different degradation behaviors of polysaccharides under different pH conditions, researchers also employed pH-sensitive chemical bonds (such as imine, acylhydrazone, or carboxyl bonds) in the construction of pH-responsive hydrogels. For example, in the study of Guan et al., aldehyde hyaluronic acid and adipic acid dihydrazide graft hyaluronic acid as the main polymer building blocks and sisomicin sulfate as the antimicrobial agent. Crosslinking occurred via imine and acylhydrazone bonds between each of the components generating a hydrogel (Guan et al., 2020). The composite hydrogel proceeded a rapid degradation rate under acid condition and released and sisomicin sulfate, exerting on-demand and sustained antibacterial activity, shortened inflammation period and promoted wound healing in the full-thickness mouse skin defect wound. Also, in another study, methacrylated gelatin was polymerized with methacrylic acid and crosslinked with ethylene glycol dimethacrylate. Gentamicin was added and covalently bonded through its primary amine group and the carboxylic acid group of the copolymer, forming a polymer-drug conjugate with pH sensitivity (Anirudhan and Mohan, 2018). This polymer-drug conjugate was further loaded with ampicillin and 2-amino guanidine to achieve synergistic antimicrobial effect and reactive oxygen species scavenging. Overall, the designed hydrogel demonstrated good anti-inflammatory properties and prolonged, controlled and synergistic antimicrobial activity in response to the pH shift.

In addition, researchers have combined several stimuli responsive mechanisms together, generating dual or multiple stimuli-responsive hydrogels for infected wound management (Cheng et al., 2018). In the study of Zhao et al., developed an injectable, anti-oxidative, near infrared and pH-responsive antimicrobial, tissue adhesive, and self-healing physical double-network hydrogel. This hydrogel was designed as removable wound dressing for multi-drug resistant bacterial infection control (Zhao et al., 2020a). In brief, the hydrogel was prepared by using poly(glycerol sebacate)-co-poly(ethylene glycol)-g-catechol prepolymer, UPy-hexamethylene diisocyanate synthon modified gelatin and iron(III) chloride, via catechol-iron(III) coordination between the pre-polymer, iron(III) and quadrupole hydrogen bonding of

synthon modified gelatin. It is worth mentioning that the coordination between prepolymer and iron(III) endowed the hydrogel with pH and near infrared responsiveness. In vivo experiments confirmed their excellent antimicrobial activity against MRSA and good hemostasis to skin trauma. Furthermore, in the full-thickness skin defect model, comparing to the biomedical glue and surgical suture, the designed hydrogel achieved better wound closure and wound healing. This was attributed to the regulation of inflammation, accelerated collagen deposition, promoting angiogenesis. While in another study of Ma et al., a thermo and pH-responsive hydrogel was prepared by simple assembly of reversible thermosensitive hydroxypropyl chitin polymer, tannic acid as crosslinker and iron(III) chloride. The obtained chitin-based hydrogel forms gel spontaneously under physiological temperature ($\sim 37^{\circ}\text{C}$) and the pyrogallol/catechol groups of tannic acid tended to deprotonate at physiological pH (~ 7.4), making the complexation stronger and leading to the slower release from the hydrogels (Ma et al., 2020). This composite hydrogel exhibited extended bacterial infection control and accelerated wound healing effects in the full-thickness mouse skin defect wound model, showing promise as future bioactive wound dressing in clinical wound management. Different from the previous study as thermo-sensitive for injectability and pH-sensitive for controlled drug release, in the study of Huang et al., the dual thermo and pH-responsive mechanisms were employed for controlled and prolonged release of silver ions in the presence of pathogens at the wound site. In brief, the hydrogel is fabricated via hydrogen bonding and supramolecular complexation between carboxymethyl agarose and the silver ions. Under acidic and higher temperature conditions, the ionic interaction is disrupted leading to the increased release of silver ions from the hydrogel (Huang et al., 2020c). This composite hydrogel exhibited enhanced antibacterial and anti-inflammatory properties with outstanding cytocompatibility and hemocompatibility. It markedly accelerated wound closure.

Independently of which trigger is envisaged, pH-responsive antimicrobial hydrogels can specifically release drugs at the wound infection site with switch on/off property, which significantly reduced toxicity of the uncontrolled drug release in general, lifting the therapeutic efficacy in infected wound treatment. In combination with other stimuli-responsive mechanisms, hydrogels can achieve multifunction of on-demand antimicrobial action, anti-oxidation, anti-inflammation, tissue adhesion, self-healing, injectability, and easy removability, etc. generating novel bioactive wound dressings for clinical wound management.

5. Sensor and imaging hydrogels for wound healing

Timely detection of wound infections is essential for an adequate and effective treatment. The presence of pathogenic bacteria is a major factor contributing to wound healing hinderance (Bowler et al., 2001, Falanga, 2005). Wound evaluation in the traditional clinical settings is however impracticable, lacks objective basis and may also increase the risk of wound infection (Collier and Hollinworth, 2000, Powers et al., 2016). Thus, a technology that allows real-time management of medical conditions that can interface with wounds, detect pathogenic bacteria, and wirelessly transmit data without impairing the treatment, enables a continuous and effective monitoring (Xiong et al., 2021, Pang et al., 2020). Furthermore, common components used in wound debridement are not entirely proven efficient in wound healing (Wilkins and Unverdorben, 2013). Zhang et al. designed an integrated smart dressing capable of monitoring the wound microenvironment without disturbing the healing process, providing a promising strategy for intelligent wound care (Zhang et al., 2021b). This three-layer integrated smart dressing, includes a biomimetic nanofiber membrane, microenvironment sensor and a hydrogel of β -cyclodextrin containing gelatin methacryloyl, crosslinked by ultraviolet light. The hydrogel displays a similar structure as the ECM, thus benefiting the expression of vascular endothelial growth factors promoting neovascularization and wound healing. The wound microenvironment data, obtained by the integrated sensor chip, were transmitted via a Bluetooth low energy 4.0 antennae, and displayed on a customized application for mobile devices (Fig. 8.3). A flexible and battery-free sensor developed by Xiong et al. is able to respond selectively to the enzyme deoxyribonuclease which is secreted by pathogenic bacteria such as *S. aureus*, *P. aeruginosa*, and *Streptococcus pyogenes* (Xiong et al., 2021). According to in vitro experiments, this engineered DNA hydrogel responds selectively to concentrations of *S. aureus* near the threshold of clinical infection (1×10^6 colony forming units gram⁻¹ of viable tissue), thus prior to visible manifestation of infection. The tunable dielectric changes activated in the presence of deoxyribonuclease are transduced into a wireless signal detectable by a smartphone. Moreover, in vivo studies demonstrated the detection of clinically relevant amounts of *S. aureus* for 24 hours. These results demonstrate the promising application of such strategy for continuous infection monitoring, thus improving the management of surgical or chronic wounds.

Please insert Figure 8.3

Figure 8.3. Sensor stimuli-responsive antibacterial hydrogel.

Other physicochemical markers for wound infection include temperature and pH. Increase of wound temperature may be an early indication of infection. According to this principle, Pang et al. developed a smart flexible electronics-integrated wound dressing for early infection diagnosis via real-time wound-temperature monitoring by means of an integrated sensor (Pang et al., 2020). Furthermore, on-demand infection treatment of the mentioned smart wound dressing was possible through the release of antibiotics from the hydrogel by in situ ultraviolet irradiation. This wound dressing is composed of a double-layer structure: an upper layer of polydimethylsiloxane-encapsulated flexible electronics integrated with a temperature sensor and ultraviolet light-emitting diodes, and the lower layer composed of an ultraviolet-responsive antibacterial hydrogel. The temperature was continuously monitored by the integrated sensor and transmitted via Bluetooth. Once the wound temperature increased above the pre-set threshold value, the integrated ultraviolet light-emitting diodes were turned on to trigger antibiotic release in situ. pH monitoring of wound infections based on electronic devices however, often imply the use of expensive and sophisticated technology (Omidi et al., 2017). The use of indicator dyes, in particular natural dyes due to the absence of potential toxic effect, are simple and cost-effective alternatives for pH monitoring (Dargaville et al., 2013, Wallace and Giusti, 2015, Zepon et al., 2019). Zepon et al. developed a pH-responsive hydrogel film as smart wound dressing based on κ -Carrageenan, locust bean gum, and cranberry extract for monitoring bacterial infections (Zepon et al., 2019). It exhibited a good response to the pH change caused by the basic compounds released from the digested proteins during the bacterial growth. The color changes of the hydrogel film were verified through in vitro studies using *S. aureus* and *P. aeruginosa*. The changes could be observed by naked eye, thus demonstrating the potential use of the obtained hydrogel film as a visual system for monitoring bacterial wound infections (Fig. 8.4). In addition, the presence of cranberry extract in the hydrogel film serves not only as a pH sensor, but also as inhibitor of bacteria adhesion on the hydrogel surface. The administration of antibacterial compounds as agents to promote wound healing by accelerating wound closure is still unregulated, independently if they are: drugs, peptides, or nanoparticles. To overcome this issue, Chekini et al. reported the use of cellulose nanocrystals decorated with carbon dots composite hydrogel with strong iron(III) ion sequestration capability (Chekini et al., 2020). Once the ionic iron adsorbed onto the hydrogel surface, the photoluminescence of the nanocolloidal hydrogel was quenched, indicating the removal of iron(III) ions and consequent growth arrest of *E. coli*, *P. aeruginosa*, and *S. aureus*. The wound dressings could be easily assembled through three-dimensional printing.

An injectable, self-healing, and conductive chitosan-based hydrogel with inherent antibacterial properties was developed via dynamic hydrogen and Schiff base crosslinking bonds (Fan et al., 2021). The reversible pH responsiveness allows sol-gel conversion of the hydrogel, thereby promoting its degradation. In vivo experiments confirmed the outstanding effect on wound healing. In addition, the conductive hydrogel could provide real-time analysis of the patient's healthcare information. A different conductive hydrogel based on a dual network of polyacrylamide and agarose, together with tannic acid-borax complexes, formed strain sensor with antibacterial properties (Lei et al., 2021). The hydrogel demonstrated an increase in compressive stress by 58.14% compared to hydrogel composed of polyacrylamide and agar, granting more accurate measurements. Its transparency and excellent light transmission allows wound assessment, thus avoiding the physical trauma and potential infection caused by the removal of conventional dressings. Furthermore, there is a reduced risk of infection due to the antibacterial properties of tannic acid-borax. Chai et al. developed an adhesive hydrogel with repeatable adhesion capacity up to seven times, with excellent stretchability and resilience (Chai et al., 2020). Based on poly(thioctic acid) and crosslinked using polydopamine, this hydrogel also exhibits anti-swelling behavior and self-healing properties. Experiments confirmed the hydrogel ability to accelerate the wound healing process, and an enhancement in conductivity through the introduction of iron(III) ions, making it viable as strain sensors. Inspired by the natural mussel adhesive mechanism, Jing et al. envisaged a hydrogel for various applications including electronic skin, wound dressings, and wearable devices (Jing et al., 2018). Polydopamine-coated talc nanoflakes were incorporated into a polyacrylamide hydrogel, with dopamine molecules intercalated into talc. After oxidation, the dispersion was enhanced and the catechol groups in the hydrogel preserved. The resulting hydrogel showed a remarkable stretchability, with over 1000% extension and a recovery rate over 99%. Strong adhesiveness to various substrates, including human skin, rapid self-heal and recovery of the mechanical properties without needing any external stimuli were also verified. Furthermore, the hydrogel showed high sensitivity, with a gauge factor of 0.693 at 1000% strain, and was able to monitor human motions such as the bending of a finger, knee, or elbow and taking a deep breath. By introducing negatively charged clay nanosheets, Zhu et al. developed a smart ionic gelatin based polyacrylamide and clay hydrogel with high conductivity of 10.87 mS cm^{-1} (Zhu et al., 2020). The gel exhibited excellent self-healing properties, robust adhesion (interfacial toughness of up to 485 J m^{-2} with pigskin), and multiple stimuli-responses driven by salt ions, pH, and stress. The applicability of the hydrogel includes muscle movement sensors, wound pH monitoring, oxygen delivery and drug delivery adjustment. A mechanically flexible,

electroactive, and self-healable hydrogel was engineered for the combinational function of electrically-stimulated accelerated wound healing and motion sensing. Zheng et al. developed a gelatin-based smart 3D-scaffold by incorporating the functional building blocks of water-dispersible conducting polymer complex, poly(3,4-ethylenedioxythiophene) polystyrene sulfonate, and multi-walled carbon nanotubes (Zheng et al., 2021). The obtained hydrogel considerably promotes wound healing through precise electrical stimulation and wearable motion sensing function at the wound injury area, with real-time monitoring of injury motion activities.

Please insert Figure 8.4

Figure 8.4. pH chromatic shift stimuli-responsive antibacterial hydrogel: (a) unfavourable pH shift – infected injury; (b) favorable pH variation – non-infected wound.

6. Concluding remarks and future perspectives

Hydrogels represent a relevant strategy to enhance or replace conventional woven and non-woven antibacterial textiles, due to their proficient antibacterial activity that use novel agents and strategies to overcome their alarming emergence resistance. Moreover, hydrogels, due to their structure and active ingredients effectively boost the wound healing process, further diminishing the probability of chronic wound development. Most of the developed hydrogels are focused on the release of their active agents which is controlled in its vast majority by the swelling. Different approaches have been applied to control this important feature and to attribute different triggers for the swelling to begin and to stop. Attributing a tunable on-demand drug release feature, integrated in a wound dressing can be used to control wound infections when they happen, and only if they happen. This greatly minimizes the occurrence of bacterial resistance and potentially unwanted side effects on the patients by the active agents. Finally, the remote control of the wound dressing may help not only the patient by minimizing the chance of wound infections, pain and complications; but also represents an important feature to maximize the efficacy of the treatment by the health care professionals.

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