Antimicrobial hydrogels: promising materials for medical application

Abstract: The rapid emergence of antibiotic resistance in pathogenic microbes is becoming an imminent global public health problem. Local application of antibiotics might be a solution. In local application, materials need to act as the drug delivery system. The drug delivery system should be biodegradable and prolonged antibacterial effect should be provided to satisfy clinical demand. Hydrogel is a promising material for local antibacterial application. Hydrogel refers to a kind of biomaterial synthesized by a water-soluble natural polymer or a synthesized polymer, which turns into gel according to the change in different signals such as temperature, ionic strength, pH, ultraviolet exposure etc. Because of its high hydrophilicity, unique three-dimensional network, fine biocompatibility and cell adhesion, hydrogel is one of the suitable biomaterials for drug delivery in antimicrobial areas. In this review, studies from the past 5 years were reviewed, and several types of antimicrobial hydrogels according to different ingredients, different preparations, different antimicrobial mechanisms, different antimicrobial agents they contained and different applications, were summarized. The hydrogels loaded with metal nanoparticles as a potential method to solve antibiotic resistance were highlighted. Finally, future prospects of development and application of antimicrobial hydrogels are suggested.

Keywords: nanomaterials, hydrogels, nanoparticles, antibiotics, drug delivery, infection

Introduction

Nowadays, with the rapid development of biomaterials and medical devices, health care-associated infections (HAIs) have posed severe problems on clinicians. For example, in the US, the annual costs associated with HAIs are estimated to be up to $33 billion.¹ The rapid emergence of antibiotic resistance in pathogenic microbes is becoming an imminent global public health problem.² According to a report in Lancet, most acute sequelae and global mortality were caused predominantly by infectious diseases.³ Medical devices may bring HAIs to patients in hospital. These biomaterials and medical devices including joint implants, wound dressings, catheters, cardiac pacemakers and contact lenses bring implant-associated infection, calling for an urgent need of inherent antimicrobial biomaterials and medical devices. Among all antimicrobial materials, heavy metals and natural extracts have been used for a long time since first discovered. However, these materials still have inherent disadvantages that restrict their application and efficacy. They fight against microbes as well as normal cells which cause damage to normal organs and tissues of patients.⁴ Antibiotics emerged in antimicrobial history 80 years ago when penicillin was discovered by Sir Alexander Fleming.² For all these decades, antibiotics have brought us consolation until the existence of drug-resistant bacterium was discovered. At the beginning of antibiotic resistance development, conventional antibiotics such as penicillin and methicillin were...
noneffective to resistant strains. Now, vancomycin-resistant and linezolid-resistant strains have emerged. This has led to ceaseless demands for novel antibiotics, putting clinicians in a dilemma whether to test a novel multi-resistant strain with another antibiotic. Synthetic antimicrobial agents such as salicylate, chlorhexidine, isothiazolinones, thiosemicarbazones, octenidine and even quaternary ammonium compounds also faced progressive threats with the development of drug resistance. According to the Darwinian view of the role of antibiotics, it is widely accepted that antibiotics and antibiotic-resistant genes act as weapons and shields in shaping the structures of microbial communities. Nowadays, antibiotic resistance is considered as bacteria’s specific response to an injury caused by antibiotics, which means it cannot be totally avoided even if we create a new antibiotic agent. Increasing rates of antibiotic resistance, drug allergies and antibiotic shortages further complicate the choice of antibacterial agents. Problems that the traditional antimicrobial agents faced include drug resistance, overdose and cytotoxicity. These problems urgently call for an efficient and safe delivery system of drug release, which can delay the release of toxic antimicrobial agents and reduce the risk of bacterial drug resistance. Apart from antibiotics, other antimicrobial materials also have their own problems in clinical application. In recent years, antimicrobial peptides (AMPs) have been reported to have antimicrobial properties (especially short sequences) because of their ionic structure; so, it is difficult to induce resistance of bacterium or formation of biofilm. However, AMPs are also hemolytic, toxic and easy to lose efficacy and hence, AMPs need an effective drug delivery system to avoid these side effects. Besides, antimicrobial amylolytic polymers, antimicrobial polysaccharides and other antimicrobial components have also been reported, which can be frameworks of biomedical polymers. Current drug delivery systems need an effective drug delivery system to avoid these side effects. Yet, how to make these biomaterials play the greatest role in fighting against HAIs remains a problem.

In these cases, a novel drug delivery system with absorbability and delayed release performance is needed. The nanocarrier system or nano-drug delivery systems (DDS) can carry the antibiotic as well as protect it. Nanomaterials with inherent antimicrobial activity or nanomaterials that can improve the efficacy and safety of antimicrobial drugs are called nanoantimicrobials (NAMs). They could be an effective alternative to conventional antibiotics by the provision of improved bioavailability, protection, mucoadhesion, absorption, controlled release and target delivery for the encapsulated or surface-adsorbed drugs. A set of organic, inorganic and hybrid materials can be identified in the NAM family. Among all the NAMs, hydrogel is a three-dimensional cross-linked polymeric network that can swell dramatically in an aqueous medium such as body fluids, while maintaining its structure and controlling drug release. Hydrogels can also be triggered by stimulations such as changes in pH, temperature, enzyme catalysis, ultraviolet gamma irradiation and even inflammation. Hydrogel can be coated on urinary catheters, central venous catheters, contact lenses, joint and dental implants and local injection for drug release and wound healing. Moreover, some types of hydrogels also have inherent antimicrobial properties. Combined with nanomaterials such as hydrogel, the antibacterial agent may be used at a lower dose than when administered systemically, thus overcoming the problem of resistance and diminishing other undesirable side effects to some extent. These characteristics have drawn remarkable attention in the pharmaceutical and medical fields especially for antimicrobial application (Figure 1). According

Figure 1 The different applications of hydrogels.
to the development of antimicrobial agents, the progresses of antimicrobial hydrogels in recent years are shown in the following section.

**Hydrogel loaded with metal nanoparticles**

Heavy metals have been used to fight against microbes for a long time. Silver, gold, copper and zinc were all reported to be used in this area. Among these metals, silver is most widely used due to its good antibacterial property and relatively low toxicity. However, other metals, such as gold, copper and zinc, have their own advantages and antibacterial spectrums.

**Sliver nanoparticles (Ag NPs)**

Silver have been regarded as an antimicrobial agent for thousands of years, before people knew about the word “microorganisms”. Silver bowls, water vessels, spoons and other containers were used to preserve water, food and wine in their condition. Silver powder was applied in wound healing and treatment of ulcers, which was first documented in medical history by Hippocrates. Silver still plays an important role in biomedical areas such as wound dressings, textiles, bone implants etc. Thanks to the development of nanoscience and technology, nowadays silver is mainly applied in the form of nanoparticles. Ag NPs have antimicrobial activity against a wide spectrum of microbes (probably due to their multiple mechanisms of antimicrobial action), including activity against drug-resistant bacteria, fungi (such as Candida albicans) and viruses. Ag NPs are emerging as efficient antimicrobial agents because of their different mechanisms of sterilization, although no final conclusion about mechanisms has been made. Recent studies suggest that the primary mechanism of the antibacterial action of Ag NPs is to release silver ion (Ag⁺). Particle-specific activity of Ag NPs cannot be ignored, which indicates that the mechanism of antibacterial action differs between Ag⁺ and AgNPs. The most universally accepted hypothesis is that the Ag⁺ released from Ag NPs interact with cysteine in certain regions of proteins on bacterial membranes, causing K⁺ loss from inside and the disruption of cellular transport systems, which finally leads to bacterial cell death (Figure 2). Other studies show that Ag⁺ interact with proteins of the cell wall and plasma membrane of bacteria. Combination of Ag⁺ with negatively charged membrane perforates the membrane, thus allowing cytoplasmic contents to flow out of the cell, dissipating the H⁺ gradient across the membrane and sometimes causing cell death. If the bacteria have not been killed yet, these contacts allow Ag⁺ to move through the cell wall and the plasma membrane. Finally, Ag⁺ functions as an extra antimicrobial agent in the cytoplasm of the bacterial cell. Despite widespread use of Ag⁺, bacterial resistance to Ag⁺ has been found rare and developed slowly, especially compared to resistance to antibiotics, which makes it a potential antimicrobial agent to solve the problem of antibiotic resistance. Again, this is presumably due to the multiple mechanisms of antimicrobial action of Ag described earlier, whereas antibiotics usually have only one mechanism of action. As is known to all, Ag NP-based hydrogels have so many merits that they performed better on Gram-negative bacteria than Gram-positive bacteria because Gram-negative bacteria have low resistance of the cellular membranes compared with the peptidoglycan cellular walls of Gram-positive bacteria. But, it has also been argued that Gram-negative bacteria are less sensitive than Gram-positive bacteria to Ag⁺, because Ag⁺ binds to the negatively charged lipopolysaccharide (LPS) of the outer membrane of Gram-negative bacteria more strongly than to the peptidoglycan layer of Gram-positive bacteria. By this argument, Ag⁺ is trapped in the LPS and is less likely to enter a Gram-negative cell than a Gram-positive cell.

In this review, we concentrate on the hydrogels that are loaded with Ag NPs. There are mainly two types of hydrogel matrices: one is the natural polymer (including modified natural polymer) and the other is the synthetic polymer. The most common natural polymers are polysaccharides. Polysaccharides mainly include alginate, chitin, chitosan (CS) and carboxymethyl cellulose (CMC). Alginate is a natural derivative linear copolymer that can form...
hydrogel via methods such as Ca\textsuperscript{2+} ionic interaction. Ag NPs were incorporated into alginate microbeads through electrochemical synthesis by Stojkovska et al.,\textsuperscript{43,44} which showed antibacterial activity against \textit{Staphylococcus aureus} and \textit{Escherichia coli}. Although alginate has been already commercially in use for wound dressings, Ag NPs on alginate have high tendency to aggregate. Obradovic et al\textsuperscript{45} optimized the technique for the production of Ag/alginate microbeads by freezing–thawing based on alginate, poly(vinyl alcohol) (PVA) and poly(N-vinylpyrrolidone) (PVP) to reduce the aggregation. Ghasemzadeh et al\textsuperscript{46} also attempted to use alginate/PVA as a hydrogel matrix with sodium borohydride as a reducing agent. Madhusudana Rao et al\textsuperscript{47} went one step further by fabricating sodium alginate-based semi-interpenetrating polymer network (IPN) hydrogels for delivery of Ag NPs, and the hydrogel exhibited good antibacterial activity. The degree of cross-linking and nature of semi-IPN polymer chains are key factors in regulating the size, shape and release of nanoparticles.\textsuperscript{48} Neibert et al\textsuperscript{49} described a method to enhance mechanical strength of alginate hydrogel loaded with Ag NPs by chemical cross-linking, which is more favorable for epidermal regeneration while maintaining antibacterial properties.\textsuperscript{50} Many animal experiments on alginate hydrogel loaded with Ag NPs have been conducted, which means this kind of antimicrobial hydrogel has been studied thoroughly.

Other important polysaccharides used as antimicrobial hydrogels are chitin and CS. It is notable that both chitin and CS have antimicrobial and metal-binding properties. Chitin- or CS-based hydrogels such as CS/2-glycerophosphate/nanosilver hydrogel and silver molybdate nanoparticle/chitin matrix (Ag\textsubscript{3}Mo\textsubscript{2}O\textsubscript{5}/chitin) hydrogel also provide green synthetic process and excellent antibacterial performance against \textit{E. coli}.\textsuperscript{51,52} The other polysaccharide hydrogels include iota-carrageenan-based Ag NP hydrogel and Ag NP-loaded PVA/gum acacia (GA) hydrogel,\textsuperscript{53,54} both iota-carrageenan and GA are well-known polysaccharides with rich production in nature. Both the hydrogels showed good antibacterial activity against Gram-negative bacterium \textit{E. coli}. Sodium CMC is another kind of biocompatible and biodegradable polysaccharide polymer which can effectively work as both reducing and stabilizing agents. It has been reported that CMC can be cross-linked by epichlorohydrin as an antimicrobial hydrogel matrix, and it can also be added into CMC and starch-composed hydrogel network as a component,\textsuperscript{55,56} both systems work well as antimicrobial hydrogels. Ranga Reddy et al\textsuperscript{57} demonstrated that the natural polysaccharide gelatin has contributed an excellent property for anchoring and stabilizing the Ag NPs and formulating poly (gelatin–acrylamide) silver nanocomposite hydrogels for inactivation of bacteria. The natural hydrogels have weak antimicrobial properties, but they can be good carriers for Ag NPs, and other antibiotic agents. Moreover, they can be extracted from natural materials easily.

As for a synthetic matrix for Ag NP hydrogels, there is a large diversity, but most of them are poly(acrylamide) (PAM), acrylic acid, poly(ethylene glycol) (PEG), PVA, pyrrolidone and their derivatives. The main advantage of using this template is that the morphology and size of the nanoparticles can be easily controlled by changing the amount of cross-linker and monomer of the hydrogel network.\textsuperscript{48,58,59} For example, PAM/PVA hydrogel–Ag NPs fabricated by Varaprasad et al\textsuperscript{60} can obtain Ag NPs of 2–3 nm size in gel networks, which exhibit higher antibacterial activity on \textit{E. coli} compared with Ag NPs alone and Ag\textsuperscript{2+}-bonded hydrogels. Styrene sulfonic acid sodium salt was incorporated into hydrogels to form poly(acrylamide-styrene sulfonic acid sodium salt) Ag NP hydrogel, and the most sensitive strain it can deal with was \textit{Bacillus subtilis}.\textsuperscript{58} PAM is also used to form semi-interpenetrating network hydrogels composed of pluronic and PAM by simultaneous free-radical cross-linking polymerization and served as nanoreactors for the synthesis of Ag NPs.\textsuperscript{59} PAM mixed with itaconic acid (IA) or starch to form Ag NP-loaded hydrogels was also reported to have good antibacterial properties while providing a green process of synthesis.\textsuperscript{61,62} Poly(N-isopropylacrylamide) (PNIPAM) is the second commonly used matrix in Ag NP hydrogels. James et al.\textsuperscript{63} Manjula et al\textsuperscript{64} and Zafar et al\textsuperscript{65} used PNIPAM as a main component to synthesize Ag NP hydrogels. James et al\textsuperscript{63} synthesized PNIPAM-co-allylamine nanogels and grafted them onto non-woven polypropylene. Hydrogels made by Manjula et al\textsuperscript{64} were reduced with neem leaf (\textit{Azadirachta indica}) extracts, providing another green process. During the fabrication, emphasis was placed on green techniques, in order to make it environmentally friendly. Zafar et al\textsuperscript{65} mixed Ag NPs with N-isopropylacrylamide-based nanogels which had a peak of lower critical solution temperature (LCST) that is close to the human body temperature. This increases the possibility in practical medical application. All these three hydrogels demonstrated conspicuous antibacterial properties. Hydrogels of 2-acrylamido-2-methylpropane sulfonic acid sodium salt containing Ag NPs have been proved to have no cytotoxicity while exhibiting better antimicrobial ability than commercial Acticoat\textsuperscript{TM} (Smith & Nephew, London, UK) and PolyMem Silver\textsuperscript{®} (Ferris Mfg. Corp., Fort Worth, TX, US),\textsuperscript{66,67} which can give us more confidence in exploitation of Ag NP hydrogels. However, some researchers would like to try some new
ways, such as cross-linking fumaric acid (FA) and CMC. These hydrogel-based silver nanocomposites were coated on cotton fabric for antibacterial property, and the result was promising.68 Paladini et al69 used in situ photochemical reaction to coat Ag NPs on the fibers of hydrogel and demonstrated their antibacterial capabilities by any hydrogel blend on E. coli and S. aureus.

As for other Ag NP hydrogels, different matrices bring different characteristics and different processes of synthesis, all these creative points offered us a unique view on the way to more advanced antimicrobial biomaterials. Poly(acrylic acid co-poly(ethylene glycol)methyl ether acrylate)/Ag NP composite hydrogels were developed by Lee et al,70 offering a novel promising bioadhesive patch or wound dressing materials with their inherent good electrical conductivity. Thermoplastic PEG-polyhedral oligosilsesquioxane (POSS) hydrogels were synthesized from multiblock PEG-POSS polyurethanes by Wu et al,71 and their antimicrobial property lasts over 10 days. PVA/PVP-based hydrogels containing Ag NPs fabricated by Eid et al72 were reported to be high, uniformly distributed, and stable. Poly(methacrylic acid) (PMAA) hydrogel reduced with borohydride by Bajpai et al73 and poly(2-hydroxyethyl methacrylate/IA)/Ag NP hydrogels synthesized with gamma irradiation by Micic et al74 showed antimicrobial activity against E. coli. The pH-sensitive poly(methyl methacrylate-methacrylic acid)/Ag NP hydrogels synthesized with free radical cross-linking by Wei et al75 can be potentially smart antimicrobial biomaterials. All the abovementioned hydrogels displayed enhanced antimicrobial ability against E. coli, S. aureus, Pseudomonas aeruginosa and even B. subtilis. Some of them even acquired longer antimicrobial duration than antibiotics.76 The antimicrobial ability and cytotoxicity can be regulated by diverting the amount of components, which may turn out to be potentially smart antimicrobial biomaterials.

A novel antibacterial coating made of poly(L-lysine)/hyaluronic acid multilayer films and liposomes loaded with Ag+ was designed in 2008.77 The strong antibacterial effect was attributed to the diffusion of silver ions from the AgNO3 coating, which resulted in a bactericidal concentration of silver ions aggregated around the membrane of the bacteria. Similarly, other small antimicrobial chemicals such as antibiotics can be loaded in liposomes in hydrogels to reach the aim of delayed drug delivery. Malcher et al opened a new route to modify surfaces with small chemicals which cannot permeate phospholipid membranes.78

The most interesting Ag NP hydrogels are hydrogels synthesized with water-soluble PEG polymers, which contain reactive catechol moieties. Synthesis of this hydrogel was inspired by mussel adhesive proteins. This biomimetic material has a strong potential for antibacterial tissue adhesives and biomaterial coatings because of the material-independent adhesive properties of catechols.79 Another new hydrogel with Ag NPs was called reduced graphene oxide (GO)-based Ag NP-containing hydrogel. This composite was fabricated in situ through the simultaneous reduction of GO and noble metal precursors within the GO gel matrix.80 This new kind of hydrogel has already been used in waste water cleansing due to its antimicrobial and antifouling properties inspiring the idea of clinical application. For example, this hydrogel can be used to deal with a polluted wound as a wound dressing.

However, serum albumin also reduces the antibacterial effects of Ag NP-embedded hydrogels.81 The gene toxicity of Ag NPs has also been reported, and balances between anti-reactive oxygen species (ROS) response and DNA damage; and mitosis inhibition and chromosome instability, might play significant roles in silver-induced toxicity.82 Therefore, the vital issues are: improvement of the antimicrobial ability against Gram-positive bacteria, minimization of gene toxicity, and reduction of serum albumin when designing Ag NP-based hydrogels. More non-toxic and environmentally friendly synthetic processes such as the idea of size-controllable synthesis of Ag NPs with tobacco mosaic virus (TMV) as a biomediator without external reducing agents83 should be developed. In recent studies, more hydrogels loaded with Ag NPs have been discovered. Researchers have improved their properties, such as strong antimicrobial properties and prolonged release. All these developments and improvements ensure the clinical potential of the hydrogels. To provide clarity, all the hydrogels with Ag NPs are recorded in Table 1.

Gold nanoparticles (Au NPs)

Gold is universally considered as biologically inert but Au NPs have a diversity of biological functions.84 Au NPs can be designed into different sizes and be functionalized with desired polymers, thus they are realized as biocompatible materials.84 Au NPs can be attached to the bacterial membrane, which leads to the leakage of bacterial contents or penetration of the outer membrane and the peptidoglycan layer, resulting in bacterial death.85 However, compared with Ag NPs, studies on antimicrobial Au NP hydrogels alone are rare. In a recent study by Brown et al,86 Au NPs lack antibacterial activity alone. However, Au NP with ampicillin bound to the surface (Au NP-AMP) killed multiple drug-resistant
Table 1 Information of hydrogels with Ag NPs

<table>
<thead>
<tr>
<th>Species of hydrogels</th>
<th>Synthesis of hydrogels</th>
<th>Highlights of hydrogels</th>
<th>Antimicrobial agents delivered</th>
<th>Content of antimicrobial agents</th>
<th>Rate of release</th>
<th>Diameter of nanoparticles</th>
<th>Antimicrobial capability</th>
<th>Application</th>
<th>References</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alginate hydrogel</td>
<td>Electrochemical synthesis</td>
<td>Uniform hydrogel microbeads</td>
<td>Ag NPs</td>
<td>0.5–3.9 mM/mL</td>
<td>–</td>
<td>10–30 nm</td>
<td>–32 µg/mL Stop/lyococcus aureus (95.8%)</td>
<td>Biocompatible carriers</td>
<td>43</td>
<td>2012</td>
</tr>
<tr>
<td>Alginate-based nanocomposite hydrogel</td>
<td>Synthesis by aggregative mechanism and Ostwald ripening, then grown in alginate solutions</td>
<td>Colloid solutions can be stable for 30 days</td>
<td>Ag NPs</td>
<td>0.2–4.5 mM/mL</td>
<td>–</td>
<td>–30 nm</td>
<td>–112 µg/mL Escherichia coli 97.5% for 1 h and 99.9% over 24 h</td>
<td>Biomimetic bioreactor</td>
<td>45</td>
<td>2012</td>
</tr>
<tr>
<td>Alginate nanocomposite hydrogels</td>
<td>Electrochemical synthesis and rehydration</td>
<td>Composition and mechanical properties of Ag/ hydrogel disks based on alginate, PVA and PVP can be adjusted</td>
<td>Ag NPs</td>
<td>0.3–5 mM/mL</td>
<td>35%-53% silver released for 48 h</td>
<td>10–30 nm</td>
<td>–10 µg/mL S. aureus (99.8% 24 h) and E. coli (over 99.99% 24 h)</td>
<td>Potential wound dressings</td>
<td>44</td>
<td>2014</td>
</tr>
<tr>
<td>Alginate/ PVA silver nanocomposite hydrogel</td>
<td>Free radical polymerization and green process</td>
<td>Appropriate rate parameter for swelling</td>
<td>Ag NPs</td>
<td>1–15 mM/mL</td>
<td>–</td>
<td>4–10 nm</td>
<td>MBC/MIC ratio of E. coli and S. aureus both achieved 4</td>
<td>Wound dressings, catalysis and water purification</td>
<td>46</td>
<td>2014</td>
</tr>
<tr>
<td>Sodium alginate-based semi-IPN hydrogels</td>
<td>Cross-linked via radical redox polymerization</td>
<td>Well dispersed Ag NPs, cytocompatible and biodegradable hydrogel networks</td>
<td>Ag NPs</td>
<td>1 mM/mL</td>
<td>–</td>
<td>–5 nm</td>
<td>E. coli and S. aureus. E. coli is better than S. aureus</td>
<td>Drug delivery applications</td>
<td>47</td>
<td>2013</td>
</tr>
<tr>
<td>PAM hydrogels and its mixtures</td>
<td>Facile synthetic strategy of cross-linking</td>
<td>Hydrogels as templates to obtain metal nanostructures of different sizes and morphologies</td>
<td>Ag NPs</td>
<td>–</td>
<td>–</td>
<td>1–10 nm</td>
<td>Clear inhibition in growth of E. coli and Bacillus on solid agar medium</td>
<td>Desired nanoproduct tailor made for particular applications</td>
<td>48</td>
<td>2010</td>
</tr>
<tr>
<td>Hydrogel fibers loaded with Ag NPs</td>
<td>Wet spinning in a CaCl₂ precipitation bath and chemical cross-linking</td>
<td>Mechanically robust and biodegradable</td>
<td>Ag NPs</td>
<td>0.383 wt% in 0.05 mM AgNO₃ solution and 0.013 wt% in 0.005 mM AgNO₃ solution</td>
<td>–</td>
<td>11 nm</td>
<td>–</td>
<td>Wound dressings for improving the overall quality and speed of healing</td>
<td>49</td>
<td>2012</td>
</tr>
<tr>
<td>Semi-IPN hydrogel of PVP and PAM</td>
<td>Free radical polymerization</td>
<td>Excellent nanoreactors for producing and stabilizing metal nanoparticles</td>
<td>Ag NPs</td>
<td>3.71 wt%</td>
<td>–</td>
<td>3–5 nm</td>
<td>Significant inhibition of E. coli on solid agar medium</td>
<td>Preliminary antibacterial applications</td>
<td>50</td>
<td>2008</td>
</tr>
<tr>
<td>Thermosensitive CS/2-glycerophosphate/nanosilver hydrogels</td>
<td>Synthesized in low temperature</td>
<td>Similar antibacterial activity, lower MW CS, lower concentration of Ag NPs and lower cytotoxicity</td>
<td>Ag NPs</td>
<td>DD80 and DD88 CS hydrogels were 3.82 kg/cm² (14.8%) and 4.99 kg/cm² (19.4%)</td>
<td>21.8 nm and 20.22 ppm</td>
<td>Inhibition of Pseudomonas aeruginosa and S. aureus on solid agar medium</td>
<td>Thermosensitive in situ formed wound dressings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iota-carrageenan-based Ag NP hydrogels</td>
<td>Green process using acrylamide with iota-carrageenan</td>
<td>Biodegradable, reducing AgNO₃ with leaf extracts of Azadirachta indica</td>
<td>Ag NPs</td>
<td>100.07 mM (5.1 g/300 mL)</td>
<td>3 ± 2 nm</td>
<td>Only weight loss of the composite hydrogels</td>
<td>Inactivation of bacteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ag NP-loaded PVA/GA hydrogel</td>
<td>One-pot method by gamma radiation-induced cross-linking</td>
<td>GA improves the biocompatibility and swelling properties of the hydrogel</td>
<td>Ag NPs</td>
<td>1 mM</td>
<td>Increase with content of GA fraction</td>
<td>Inhibition of E. coli on solid agar medium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMC-based hydrogels</td>
<td>Prepared using epichlorohydrin in alkaline medium, silver nitrate</td>
<td>Ag NPs prepared using two different processes: in situ process and postloaded technique</td>
<td>Ag NPs</td>
<td>18.99 wt% for in situ process and 9.51 wt% for postloaded method</td>
<td>10–38 nm</td>
<td>Only TEM about distribution of Ag NPs using two processes</td>
<td>Inhibition of E. coli, P. aeruginosa, S. aureus and Bacillus subtilis on solid agar medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semi-hydrogel networks of PAM and carbohydrates</td>
<td>An optimized rapid redox solution polymerization</td>
<td>Highly stable and uniformly distributed Ag NPs</td>
<td>Ag NPs</td>
<td>—</td>
<td>2–5 nm</td>
<td>Mild inhibition of E. coli on solid agar medium</td>
<td>Potential candidates for medical field with high antibacterial activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelatin-based inorganic nanocomposite hydrogels</td>
<td>Incorporating Ag⁺ and treatment with sodium borohydride</td>
<td>Using acrylamide and biodegradable gelatin</td>
<td>Ag NPs</td>
<td>9.38%</td>
<td>—</td>
<td>Inhibition in growth of B. cereus on solid agar medium</td>
<td>Preliminary antibacterial activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogels composed of acrylamide, ionic monomer and CS</td>
<td>Ag NPs were synthesized and stabilized using the hydrogel template method</td>
<td>Template nanoreactors</td>
<td>Ag NPs</td>
<td>12.5 μg for spherical nanoparticles, 50–100 μg for rod-shaped particles</td>
<td>70 nm</td>
<td>Inhibition zone Bacteria: B. cereus B. subtilis S. aureus E. coli Yeast: Candida albicans Candida pseudotropicalis and the other five fungi</td>
<td>An antimicrobial agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogels composed of pluronic and PAM</td>
<td>Free radical polymerization with a redox initiator system</td>
<td>Semi-interpenetrating network to produce highly stable and uniformly distributed Ag NPs</td>
<td>Ag NPs</td>
<td>35%</td>
<td>5–10 nm</td>
<td>Inhibition of E. coli on solid agar medium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
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<th>Antimicrobial capability</th>
<th>Application</th>
<th>References</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAM/poly(vinyl alcohol) hydrogel</td>
<td>An aqueous redox copolymerization</td>
<td>PVA acts as an highly efficient stabilizer for Ag NPs in the hydrogels</td>
<td>Ag NPs</td>
<td>–</td>
<td>2–3 nm</td>
<td>Inhibition of E. coli on solid agar medium</td>
<td>Antibacterial and wound dressing applications</td>
<td></td>
<td></td>
<td>2010</td>
</tr>
<tr>
<td>PAM/itaconic acid–Ag NP hydrogels</td>
<td>Gamma irradiation</td>
<td>Different sizes and morphologies depend on different irradiation doses</td>
<td>Ag NPs</td>
<td>100 µL/mL</td>
<td>10–100 nm</td>
<td>Promising activity against P. aeruginosa and slightly active against E. coli, MRSA and Klebsiella pneumoniae</td>
<td>Antibacterial coatings on different material surfaces for various biomedical applications</td>
<td></td>
<td></td>
<td>2013</td>
</tr>
<tr>
<td>Silver/starch/PAM nanocomposite hydrogels</td>
<td>By grafting/crosslinking reaction</td>
<td>Starch components are capable of arresting the agglomerated Ag NPs</td>
<td>Ag NPs</td>
<td>Changed from 0 to 50 ppm</td>
<td>60% 10 nm</td>
<td>Inhibition zone began from 5 ppm Fungi: Aspergillus flavus and C. albicans Bacteria: S. aureus and E. coli</td>
<td>–</td>
<td></td>
<td>62</td>
<td>2014</td>
</tr>
<tr>
<td>NIPAM-based nanogels</td>
<td>Free radical polymerization</td>
<td>Thermoresponsive nanogels which have an LCST close to the human body temperature</td>
<td>Ag NPs</td>
<td>–</td>
<td>5–100 nm</td>
<td>Inhibition of Staphylococcus epidermidis and E. coli on solid agar medium</td>
<td>Biomedical applications such as wound dressings</td>
<td></td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>PNIPAM-co-allylamine nanogels</td>
<td>Nanogels were synthesized and grafted onto non-woven polypropylene</td>
<td>Thermally responsive</td>
<td>Ag NPs</td>
<td>50 mmol dm$^{-3}$ silver nitrate solution</td>
<td>220 ± 10 nm below 34 s and 72 ± 12 nm at 37°C</td>
<td>Bacteria: S. aureus and P. aeruginosa below the LCST, bacteria grew, above the LCST bacterial growth was prevented or retarded</td>
<td>Utility in designing infection responsive wound dressings</td>
<td></td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>Hydrogels composed of gelatin and NIPAM</td>
<td>Green process Ag NPs reduced with neem leaf (A. indica) extracts</td>
<td>Gelatin, biodegradable hydrogels</td>
<td>Ag NPs</td>
<td>–</td>
<td>9.83%</td>
<td>5–10 nm</td>
<td>Inhibition of Bacillus on solid agar medium</td>
<td>Applications in wound and burn dressings</td>
<td></td>
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<tr>
<td>Hydrogels</td>
<td>Process</td>
<td>Property</td>
<td>Ag NPs</td>
<td>Silver Concentration</td>
<td>Aggregation</td>
<td>Pathogen</td>
<td>Test Condition</td>
<td>Result</td>
<td></td>
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<tr>
<td>2-Acrylamido-2-methylpropane sulfonic acid sodium salt hydrogels</td>
<td>Gamma irradiation at 25 kGy to form Ag NP-infused hydrogels</td>
<td>Comparison to two common silver burn wound dressings: Acticoat and PolyMem Silver</td>
<td>Ag NPs</td>
<td>--</td>
<td>5 mM initial concentration</td>
<td>2.1–15.6 nm</td>
<td>Burn wound pathogens (P. aeruginosa, MSSA, Acinetobacter baumannii and C. albicans) and antibiotic-resistant strains (MRSA and VRE)</td>
<td>94%–99% viability after 24 h exposure</td>
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<td></td>
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<tr>
<td>2-Acrylamido-2-methylpropane sulfonic acid sodium salt hydrogels</td>
<td>Ultraviolet radiation</td>
<td>No cytotoxicity</td>
<td>Ag NPs</td>
<td>70%–82% of silver was released within 72 h and 88.0%–94.5% after 10 days of immersion</td>
<td>1, 2.5 and 5 mM</td>
<td>2–16 nm</td>
<td>5 mM silver hydrogel had the greatest inhibitory activity against MRSA and P. aeruginosa, S. aureus</td>
<td>A perfect antibacterial efficiency against E. coli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogels prepared from acrylic acid, PEG methyl ether acrylate</td>
<td>In situ polymerization by UV irradiation</td>
<td>A good electrical conductivity</td>
<td>Ag NPs</td>
<td>--</td>
<td>1.39 ppm</td>
<td>233 nm</td>
<td>56–139 ppm</td>
<td>A potential burn wound dressing</td>
<td></td>
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<tr>
<td>Hydrogel composed of multiblock PEG-POSS polyurethanes</td>
<td>A one-step method synthesized and electrospun into nanofibrous webs</td>
<td>Thermoplastic and unusual shrinkage during water uptake</td>
<td>Ag NPs</td>
<td>--</td>
<td>1.0 wt% AgNO$_3$</td>
<td>Nanofiber (diameter ~150 nm)</td>
<td>No E. coli cells on the surface of electrospun nanofibrous mat for 10 days incubation</td>
<td>Promising bioadhesive patch or wound dressing material or electrical massage patch</td>
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<td>Hydrogels of PVA/PVP</td>
<td>Gamma irradiation</td>
<td>Highly stable and uniformly distributed</td>
<td>Ag NPs</td>
<td>--</td>
<td>0.01 g of polymer powder contain 12 mmol AgNO$_3$</td>
<td>Mean size 2 nm by TEM</td>
<td>--</td>
<td>Wound dressings</td>
<td></td>
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<tr>
<td>PMAA hydrogel</td>
<td>Novel approach involving equilibration of PMAAc hydrogels and reduction with borohydride</td>
<td>In situ formation of Ag NPs</td>
<td>Ag NPs</td>
<td>--</td>
<td>50 mg AgNO$_3$ per 50 mL water</td>
<td>Average size is 10–20 nm</td>
<td>Fair antibacterial action against E. coli</td>
<td>A good candidate as wound dressing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Species of hydrogels</th>
<th>Synthesis of hydrogels</th>
<th>Highlights of hydrogels</th>
<th>Antimicrobial agents delivered</th>
<th>Content of antimicrobial agents</th>
<th>Rate of release</th>
<th>Diameter of nanoparticles</th>
<th>Antimicrobial capability</th>
<th>Application</th>
<th>References</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(2-hydroxyethyl methacrylate/itaconic acid) nanocomposite hydrogels</td>
<td>In situ reduction of silver nitrate and gamma radiolysis method</td>
<td>IA used as a carrier and a stabilizing agent</td>
<td>Ag NPs</td>
<td>0.68 wt% Ag in Ag(c1):P(HEMA/IA3.5), 1.27 wt% Ag in Ag(c2):P(HEMA/IA3.5) and 6.3 wt% Ag in Ag(c3):P(HEMA/IA3.5)</td>
<td>&lt;30 nm</td>
<td>Inhibition of S. aureus, E. coli and C. albicans was proved by measuring the colony-forming unit</td>
<td>Wound dressing</td>
<td>74</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>P(MMA-co-MAA)/silver nanocomposite hydrogels</td>
<td>Free radical cross-linking polymerization and follow-up reduction of silver nitrate</td>
<td>pH-responsive</td>
<td>Ag NPs</td>
<td>13.7 wt%</td>
<td>–</td>
<td>Significant antibacterial properties against both S. aureus and B. subtilis by inhibition zone</td>
<td>A potentially smart material in the range of applications of antibacterial activity</td>
<td>75</td>
<td>2014</td>
<td></td>
</tr>
<tr>
<td>Hydrogel synthesized with PEG containing reactive catechol moieties</td>
<td>Utilizing silver nitrate to oxidize polymer catechols, leading to covalent cross-linking and hydrogel formation with simultaneous reduction of Ag(I)</td>
<td>No significantly affecting mammalian cell viability</td>
<td>Ag NPs</td>
<td>Sustained for at least 2 weeks in PBS solution with total amount 1 µg</td>
<td>100 µg in one hydrogel disk</td>
<td>~50 nm</td>
<td>Inhibition zones of S. epidermidis and P. aeruginosa</td>
<td>Antibacterial biomaterial coatings and tissue adhesives</td>
<td>78</td>
<td>2012</td>
</tr>
<tr>
<td>An agar hydrogel model with Ag NPs immobilized</td>
<td>Produced ligand-free Ag NPs laser ablation in water</td>
<td>A significant reduction of antibacterial activity in the presence of BSA</td>
<td>Ag NPs</td>
<td>–</td>
<td>Ag NP concentrations is 0.5–7.1 wt%</td>
<td>–</td>
<td>All P. aeruginosa, E. coli, Streptococcus salivarius and S. aureus should be inhibited completely by any of the applied Ag NP concentrations in the presence of BSA except S. aureus</td>
<td>The presence of a major blood serum protein significantly decreases the antimicrobial effects of Ag NPs</td>
<td>80</td>
<td>2012</td>
</tr>
<tr>
<td>TMV as a biomediator</td>
<td>TMV as a biomediator</td>
<td>Simple, robust and size-tunable synthesis of Ag NPs with TMV as a biomediator under mild aqueous conditions</td>
<td>Ag NPs</td>
<td>–</td>
<td>1, 5, 10 and 20 mM initial concentration</td>
<td>Average diameter of 2, 4 and 9 nm</td>
<td>MIC of 2.3 and 2.5 ppm for 2 and 9 nm Ag NPs, respectively, against E. coli</td>
<td>Improved functionalities such as high catalytic and antibacterial activity</td>
<td>82</td>
<td>2014</td>
</tr>
<tr>
<td>Hydrogel Type</td>
<td>Processing Method</td>
<td>CS chains easily bind to the Ag⁺ cations. Not requiring heat or any other tools for nanoparticle in situ synthesis</td>
<td>Ag NPs</td>
<td>1 g of CS and desired amount of AgNO₃ (0.5, 1.0 and 1.5 mmol)</td>
<td>In vitro drug release was performed in pH 7.4 PBS for 24 h</td>
<td>They showed antibacterial activity toward S. aureus and E. coli for &gt;1 week</td>
<td>Potential drug delivery carrier</td>
<td>296</td>
<td>2015</td>
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<tr>
<td>CS hydrogel beads</td>
<td>Physically cross-linked in sodium tripolyphosphate as the cross-linker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>98</td>
<td>2016</td>
<td></td>
</tr>
<tr>
<td>FA cross-linked CMC hydrogel</td>
<td>NaCMC was dissolved in distilled water. FA was added to solution and stirred until FA was dissolved</td>
<td>Silver ions were dispersed in hydrogel coating on cotton fabric which can sustain antimicrobial ability after being washed</td>
<td>Ag NPs</td>
<td>5 × 10⁻⁴, 1 × 10⁻³ and 2 × 10⁻³ mol/L</td>
<td>–</td>
<td>–</td>
<td>Showed 99.999% reduction for S. aureus and K. pneumonia</td>
<td>68</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>Cross-linking copolymers</td>
<td>The wet spray-coated fibers were exposed to UV irradiation</td>
<td>Silver antibacterial coating was deposited for the first time on hydrogel fibers through an in situ photochemical reaction</td>
<td>Ag NPs</td>
<td>4 g of Ag solution per each gram of hydrogel fibers</td>
<td>After 168 h (7 days), silver release calculated per gram was 6 ppm (g/mL)</td>
<td>They exhibited an excellent capability in inhibiting the growth of S. aureus and E. coli</td>
<td>A novel silver antibacterial coating hydrogel fibers</td>
<td>69</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>QPV A hydrogel</td>
<td>Freeze–thaw method</td>
<td>The effect of QAS-grafted PVA hydrogel on selected microbes and its synergetic effect in combination with Ag NPs</td>
<td>Ag NPs</td>
<td>Solubilizing 10 g QPV A in 100 mL Ag NPs solution (7.8 μg/mL)</td>
<td>Major release mechanism of Ag NPs release follows Fickian diffusion</td>
<td>100–600 nm&lt;100 nm</td>
<td>They showed promising antimicrobial property after 96 h against E. coli, S. aureus and P. aeruginosa</td>
<td>A promising antimicrobial dressing</td>
<td>76</td>
<td>2016</td>
</tr>
<tr>
<td>RGO-based composite hydrogel</td>
<td>In situ reduction of GO using vitamin C in the presence of heat (90°C)</td>
<td>The facile preparation and dye degradation capacity of RGO/PEI/Ag hydrogels</td>
<td>Ag NPs</td>
<td>50 μL of aqueous solution of CH₃COOAg (8 mg/mL) added to 1.2 mL mixture</td>
<td>The amount of released silver ions was 4.696 × 10⁻³ and 2.348 × 10⁻⁴ g/L/g after 20 days</td>
<td>–</td>
<td>Highly efficient catalyst for wastewater treatment</td>
<td>79</td>
<td>2015</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** Ag⁺, silver ions; Ag NPs, silver nanoparticles; CMC, carboxymethyl cellulose; CS, chitosan; FA, fumaric acid; GA, gum acacia; HEMA, 2-hydroxyethyl methacrylate; IA, itaconic acid; IPN, interpenetrating polymer network; LCST, lower critical solution temperature; MIC, minimal inhibition concentration; MRSA, methicillin-resistant S. aureus; MW, molecular weight; NaCMC, CMC sodium salt; NIPAM, N-isopropylacrylamide; PAM, poly(acrylamide); PBS, phosphate buffered saline; PEG, polyethylene glycol; PMAA, Poly(methacrylic acid); PNPAM, poly(N-isopropylacrylamide); POSS, polyhedral oligosilsesquioxane; PVA, poly(vinyl alcohol); PVP, poly(N-vinylpyrrolidone); QPVA, quaternized PVA; RGO, reduced graphene oxide; TEM, transmission electron microscope; TMV, tobacco mosaic virus; UV, ultraviolet; VRE, vancomycin-resistant Enterococcus.
bacteria, including methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa*, Enterobacter aerogenes and *E. coli* K-12 substrain DH5-alpha (pPCR-Script AMP SK+). Though N-isopropylacrylamide-based hydrogels containing Au NPs and pH-responsive PMAA hydrogel microcapsules carrying Au NPs had already been reported, their antimicrobial property had not been studied until Gao et al demonstrated that hydrogel containing Au NP-stabilized liposomes for antimicrobial application displayed excellent antibacterial properties on *S. aureus* without skin toxicity in a mouse model. In the research of Ribeiro et al, silk fibroin/nanohydroxyapatite hydrogel modified with in situ-synthesized Au NPs showed antimicrobial activity. Compared with Ag NPs, no toxicity against osteoblastic cells was found, which means Au NPs could be used for bone regeneration. Moreover, Jayaramudu et al used acrylamide (AM) and wheat protein isolate (WPI) to develop biodegradable gold nanocomposite hydrogels. The results indicated that these biodegradable gold nanocomposite hydrogels can be used as potential candidates for antibacterial applications. Through combination of bimetallic (Ag, Au) hydrogel nanocomposites, Ranga Reddy et al took it one step further to enhance their antimicrobial activity. Varaprasad et al even prepared dual-metallic (Ag0–Au0) nanoparticles via a green process with mint leaf extract, which exhibited significant antibacterial activity against Bacillus and *E. coli* (Figure 3). Although the antimicrobial ability of Au NPs is weaker than that of Ag NPs, the Au NPs have their own advantages. The antibacterial spectrum of Ag NPs is broad, including MRSA. Moreover, the hydrogels with Au NPs showed negligible interference to bone regeneration. These properties of hydrogels with Au NPs make them promising materials in clinical orthopedic surgery.

**Zinc oxide nanoparticles (ZnO NPs)**

There are also many other metal nanoparticles with antimicrobial activities besides silver and gold, but only a few are embedded into hydrogels. Among these, zinc is the most popular antimicrobial agent. ZnO NPs are used in many cosmetic materials because of their well-known antibacterial activity and non-cytotoxicity at an appropriate concentration. ZnO NPs combat microbes through multiple mechanisms. Resistance to ZnO NPs is rarely reported.

Some of the mechanisms are as follows: 1) ZnO NPs bind to bacterial cell membranes tightly and destroy both the lipids and proteins of the membrane causing increased membrane permeability and cell lysis; and 2) ZnO NPs also cause the formation of Zn2+ ions and ROS, including hydrogen peroxide (H2O2), which damage the bacterial cell.

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**Figure 3** Gao et al synthesized hydrogel containing Au NP-stabilized liposomes for antimicrobial application (A) illustrations of hydrogel containing nanoparticle-stabilized liposomes for topical antimicrobial delivery; (B) bacteria incubated with AuC–liposome hydrogel (PEGDMA 0.8 vol%) at pH = 4.5; (C) a zoomed-in image of (B).

ZnO NPs are effective against both Gram-positive and Gram-negative bacteria because of their antibacterial activity against high temperature-resistant and high pressure-resistant bacterial spores.99 Similar to Ag NPs, ZnO NPs were incorporated into PNIPAM as antimicrobial hydrogel coatings, which was demonstrated to be a promising candidate for novel biomedical device coatings.100,101 Yadollahi et al102 synthesized CMC/ZnO nanocomposite hydrogel through the in situ formation of ZnO NPs within swollen CMC hydrogels which demonstrated their antibacterial effects against E. coli and S. aureus bacteria. Nanocomposite hydrogels with IPN structure based on PEG methyl ether methacrylate-modified ZnO (ZnO-PEGMA) and 4-azidobenzoic agarose (AG-N3) exhibited an increasing anti-adhesive property and bactericidal activity toward Gram-negative E. coli and Gram-positive S. aureus.103 Moreover, the ZnO hydrogels showed great potential in drug carrying and wound healing in some recent studies.103-105 CMC and CS hydrogels were also reported to be used as a hydrogel matrix for ZnO NPs.99,99,106 CMC hydrogels exhibited antibacterial activity against both Gram-positive and Gram-negative bacteria, and CS hydrogels were confirmed eligible wound dressing materials.103,107,108 Although the antibacterial ability of ZnO NPs is relatively weak, the low cytotoxicity still indicated that ZnO NPs have potential in clinical use. Moreover, ZnO NPs have a positive effect on bone regeneration,109 which means ZnO NPs are promising materials in orthopedic surgery.

Other metal nanoparticle-based antimicrobial hydrogels
There are many other metal nanoparticles combined with hydrogels, which have been studied in recent years. Their antibacterial mechanisms are shown in Figure 4.11 Apart from these commonly used metal nanoparticles, cytocompatible nickel nanoparticle-loaded chitin hydrogels were developed against S. aureus,110 and antibacterial cobalt-exchanged natural zeolite/PVA hydrogel was proved to have antibacterial activity against E. coli.111 Although copper-containing NPs (Cu NPs/CuO NPs) have weaker antibacterial effects than Ag NPs, they have a greater range of microbialic activities against both fungi, especially Saccharomyces cerevisiae, and bacteria, including E. coli, S. aureus and Listeria monocytogenes.112-114 CMC/CuO nanocomposite hydrogels and CS hydrogel loaded with copper particles demonstrated excellent antibacterial effects against E. coli and S. aureus without causing any toxicity in recent studies.115,116 It was reported recently that magnesium-containing nanoparticles, including magnesium halogen-containing nanoparticles (MgX, NPs) and magnesium oxide-containing nanoparticles (MgO NPs), also combat microbes through multiple mechanisms.117-119 Hezaveh and Muhama120 loaded MgO NPs to hydrogels prepared from hydroxyalkyl κ-carrageenan derivatives, thus controlling the drug delivery in gastrointestinal tract studies. This may enlighten us with the idea that we can load hydrogels with metal nanoparticles or other ingredients to adjust the release of other drugs in the same system. Different from Ag NPs and Au NPs, other metal nanoparticles might need further exploitation as many of these kinds of metals or their alloys appear more in designing and fabricating modern medical biomaterials. The hydrogels with other metal nanoparticles are recorded in Table 2.

Hydrogel with metal nanoparticles might be a way to solve antibiotic resistance. There are several advantages of these antimicrobial materials. First, metal nanoparticles could be good substitutes for antibiotics. Despite widespread use of metal nanoparticles, bacterial resistance has been rarely reported. This is presumably due to the multiple mechanisms of antimicrobial action (Table 3), while antibiotics usually have only one mechanism of action. Second, the small size of particles allows them to pass through peptidoglycan cell walls and cell membranes, getting into the cytoplasm of bacterial cells easily. Third, metal nanoparticles are stable in quality, which means they could go on to kill other microbial cells after being released from dead cells. Metal nanoparticles could bring sustainable antimicrobial effect in this way. Finally, hydrogels can offer delivery system for local application. Antibacterial property improves with increasing concentration of nanoparticles. The concentration of metal nanoparticles could be high at the infection zone. All the abovementioned advantages indicate that hydrogels with nanoparticles can help to solve the present-day challenges of antimicrobial medicine.

Hydrogel loaded with micromolecular drugs
Micromolecular drugs include various antibiotic agents, such as antibiotics, biological extracts and synthetic antimicrobial drugs. All these drugs have been used for their great antimicrobial properties clinically. Usually, they are systematically used in the hospital. Once carried by hydrogels, they can be used locally around the focus, and are a good way to reduce the dosage and the appearance of resistance.

Antibiotics
Though antibiotics were discovered later than metal antimicrobial agents in human history, they are undoubtedly the most
commonly used, and the most effective antimicrobial agents until now. The drug-resistant effect of antibiotics becomes the biggest obstacle on the development and application of antibiotics. In recent years, there have been several new antibiotic approvals as well as renewed interest in second- and third-line antibiotics because of the concerns mentioned earlier. Almost all recent antibiotic resistance appeared in the year when the resistant bacterium were discovered (Figure 5). In recent studies, only one antibiotic, teixobactin, has no resistant bacteria strains. It is very effective to Gram-positive bacteria. However, the antibacterial spectrum of teixobactin does not include Gram-negative bacteria. Moreover, the lack of selection of resistance to teixobactin in vitro should be viewed with great caution before large scale of clinical use. Although the Governments of US and European Union tried to make it attractive, most pharmaceutical companies have stopped, or severely limited, investments to discover or develop new antibiotics to treat the increasing prevalence of infections caused by multidrug-resistant bacteria.
| Species of hydrogels       | Synthesis of hydrogels                                                                 | Highlights of hydrogels                                                                 | Antimicrobial agents delivered      | Content of antimicrobial agents                                                                 | Rate of release | Diameter of nanoparticles | Antimicrobial capability                                                                 | Application                                                                 | References Year |
|---------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------|-----------------------------------------------------------------------------------------------|----------------|--------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|----------------|-------------------|
| Alginate hydrogel         | CS pellet was mixed with alginate solution as a cross-linker to strengthen the alginate hydrogel through freeze-dry process | Alginate hydrogel/nano-zinc oxide composite showed controlled degradation profile, faster blood clotting ability and excellent cytocompatibility | ZnO NPs                            | The suspension of ZnO NPs was added into the alginate hydrogel at different concentrations (0.05%-1% w/w) | --             | 70–120 nm                | Excellent antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and MRSA | Alginate hydrogel/nano-zinc oxide composite bandages for infected wounds | 101 2015       |
| HT CS–metal composite hydrogel | Copper sulfate and/or zinc nitrate at room temperature mixed with HT CS                | Hydrothermal treatment of CS results in increased functional groups availability for loading high amounts of antimicrobial copper and similar metals | Cu/CuO NPs Zn/ZnO NPs             | Copper sulfate (10 mg/mL) and zinc nitrate (100 mg/mL) were added to the CS dissolved in 1% HCl at 10 mg/mL | --             | < 5 nm                   | Growth inhibitory effect on both the “fermenters” group of gastric flora and the “opportunistic pathogen” group | Animal feed in industrial scale livestock farms | 116 2015       |
| SF/nano-HA hydrogel       | Incorporated nanosized HA particles (nanoHA) into porous SF hydrogels                  | Hydrogels showed promising physicochemical performance with improved osteoblastic induction characteristics | Ag NPs Au NPs                      | Solutions were mixed with the SF solution with Au NP/Ag NP concentrations of 0%, 0.1%, 0.5% and 1% | 12.7–69.1 nm | 9.3–54.7 nm              | Hydrogels with Ag NPs/Au NPs presented antimicrobial activity against MRSA, MSSA and *E. coli* (not effective against *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*) | Bone tissue engineering with antimicrobial properties | 90 2017         |
| AG with IPN structure     | IPN hydrogel nanocomposites based on ZnO-PEGMA and AG-N3 were prepared under UV irradiation | The IPN hydrogels exhibited excellent mechanical strength, light transmittance, bactericidal activity and negligible cytotoxicity pH sensitive, allow controlling and adjusting of the final release properties of the formulation | ZnO NPs                            | --                                                                                              | --             | --                       | IPN hydrogel has shown antibacterial activity against Gram-positive and Gram-negative bactericides | A potential material for wound dressing | 103 2016       |
| CMC/ZnO nanocomposite hydrogels | Cross-linked with Fe³⁺ in solution of CMC and ZnO NPs                                  | Cross-linked with CMC and ZnO NPs                                                     | ZnO NPs                            | --                                                                                              | < 70 nm        | --                       | An oral drug delivery system for the controlled delivery of drugs                         | --                                                                           | 104 2016       |

(Continued)
<table>
<thead>
<tr>
<th>Species of hydrogels</th>
<th>Synthesis of hydrogels</th>
<th>Highlights of hydrogels</th>
<th>Antimicrobial agents delivered</th>
<th>Content of antimicrobial agents</th>
<th>Rate of release</th>
<th>Diameter of nanoparticles</th>
<th>Antimicrobial capability</th>
<th>Application</th>
<th>References</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMCh hydrogel</td>
<td>CMCh solution cross-linked with epichlorohydrin at 80°C</td>
<td>CMCh has several advantages over CS, such as increased water solubility, better biocompatibility, high moisture retention ability, etc</td>
<td>ZnO NPs</td>
<td>0.6 g of dry CMCh hydrogel was immersed in different concentrations of Zn(NO₃)₂ solutions (0.005, 0.010, 0.020, 0.030 and 0.050 M) for 24 h</td>
<td>–</td>
<td>190–600 nm</td>
<td>The CMCh/ZnO nanocomposite hydrogel has shown antibacterial activity against Gram-positive and Gram-negative bacteriodes</td>
<td>Applications in biomedical fields</td>
<td>106</td>
<td>2016</td>
</tr>
<tr>
<td>CS hydrogel</td>
<td>CS hydrogel beads were physically cross-linked using sodium tripolyphosphate as the cross-linker</td>
<td>Prolonged and controlled drug releases were observed for ZnO NPs containing CS beads</td>
<td>ZnO NPs</td>
<td>Zn(NO₃)₂ · 6H₂O (0.5, 1.0 and 1.5 mmol) was added to 437.5 mL mixture system</td>
<td>10–25 nm</td>
<td>–</td>
<td>Hopeful candidates for the controlled delivery of drugs</td>
<td>105</td>
<td>2016</td>
<td></td>
</tr>
<tr>
<td>CMC/ZnO nanocomposite hydrogels</td>
<td>CMC solution cross-linked with epichlorohydrin at 80°C</td>
<td>Novel CMC/ZnO nanocomposite hydrogels were synthesized by in situ oxidation of the Zn²⁺ ions in the CMC hydrogel matrix</td>
<td>ZnO NPs</td>
<td>0.6 g of dried CMC hydrogel was immersed in zinc nitrate solutions with different concentrations (0.005, 0.010, 0.020 and 0.030 M) for 24 h</td>
<td>30–40 nm</td>
<td>The CMC/ZnO nanocomposite hydrogel has shown antibacterial activity against Gram-positive and Gram-negative bacteriodes</td>
<td>Applications in biomedical fields</td>
<td>102</td>
<td>2015</td>
<td></td>
</tr>
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<td>Modified κC hydrogel</td>
<td>κC was blended with NaCMC dissolved in distilled water</td>
<td>The release ability of carrageenan hydrogels was increased under pH of gastrointestinal conditions</td>
<td>MgO NPs</td>
<td></td>
<td>&lt; 50 nm</td>
<td>–</td>
<td>A potential strategy to develop controlled drug delivery especially in gastrointestinal tract studies</td>
<td>120</td>
<td>2012</td>
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<tr>
<td>Agarose hydrogels</td>
<td>An agarose gel is loaded with Au salt by immersion for 24 h</td>
<td>Approximate size of the particles increases with increasing Au loading</td>
<td>Au NPs</td>
<td>–</td>
<td>20 mM</td>
<td>0.5–4 nm</td>
<td>–</td>
<td>Application of these nanocomposites as carriers in remotely controlled light-triggered drug release</td>
<td>–</td>
<td>83</td>
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<tr>
<td>Gelatin hydrogels</td>
<td>Genipin cross-linked</td>
<td>Thermoresponsive</td>
<td>Au NPs</td>
<td>–</td>
<td>52, 104 and 156 ppm</td>
<td>10 ± 2 nm</td>
<td>–</td>
<td>–</td>
<td>84</td>
<td>2013</td>
</tr>
<tr>
<td>Reference</td>
<td>Year</td>
<td>Hydrogel/CS Hydrogel/AM and 2-acrylamido-2-methyl-1-propanesulfonic acid-based hydrogels</td>
<td>pH-responsive</td>
<td>Bi-metalled (Ag, Au) hydrogel nanocomposites</td>
<td>Au NPs</td>
<td>–</td>
<td>(PMAA) 10 average size of 16 ± 3 nm</td>
<td>Potential use for fabrication of hybrid organic-Au NPs for biomedical sensing and delivery applications</td>
<td>Hold great promise for topical applications against various microbial infections</td>
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<td>China 88 2009</td>
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<td>Hydrogel PMAA capsules</td>
<td>—</td>
<td>pH-responsive multilayer precursor through cross-linking with EDA</td>
<td>Au NPs</td>
<td>–</td>
<td>–</td>
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<td>China 88 2009</td>
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<tr>
<td>AuC–liposome hydrogel</td>
<td>—</td>
<td>pH-responsive Au NP-stabilized liposomes and no observable skin toxicity</td>
<td>Au NPs</td>
<td>0.7 and 0.8 vol%, within the first 24 h, only 25% and 17% liposomes were released</td>
<td>Mixing with AuC at a liposome-to-AuC molar ratio of 1:200</td>
<td>AuC liposomes 97.1 ± 1.0 nm, Au NPs 4 nm</td>
<td>Inhibition zone against S. aureus on solid agar medium</td>
<td>China 88 2009</td>
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</tr>
<tr>
<td>AM and 2-acrylamido-2-methyl-1-propanesulfonic acid-based hydrogels</td>
<td>—</td>
<td>Free radical polymerization of AM monomer with the addition of hydrophilic vinyl monomer</td>
<td>Au NPs and Ag NPs</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>— China 88 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogels of Carbopol® 980 NF and AM</td>
<td>—</td>
<td>A green process by the nucleation of silver and gold salts with mint leaf extract to form a hydrogel network</td>
<td>Biomaterial (Ag, Au) hydrogel nanocomposites</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>— China 88 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogel of acrylic acid Zn(Bipy-(AMOE))2</td>
<td>—</td>
<td>pH responsive to give a new cross-linked polymer system</td>
<td>Zn(Bipy(AMOE))2</td>
<td>4%–10%</td>
<td>From 3.47 ± 0.43 to 5.78 ± 0.45 ppm/h according to different pH values</td>
<td>—</td>
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<td>— China 88 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS hydrogel</td>
<td>—</td>
<td>Flexible and microporous</td>
<td>Nano ZnO composite</td>
<td>0.005%–0.01% ZnO NPs</td>
<td>—</td>
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<td></td>
</tr>
<tr>
<td>(Continued)</td>
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<td>— China 88 2009</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2 (Continued)

<table>
<thead>
<tr>
<th>Antimicrobial capability</th>
<th>Application</th>
<th>Species of hydrogels</th>
<th>Antimicrobial agents</th>
<th>Antimicrobial agents delivered</th>
<th>Diameter of nanoparticles (RAM)</th>
<th>Rate of release (µg/cm²)</th>
<th>Co-zeolite content</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficient antimicrobial activity</td>
<td>Various in biomedical applications</td>
<td>Chitin nanogels</td>
<td>ZnO NPs</td>
<td>Spin coating and photocross-linking method</td>
<td>23 ± 6 nm</td>
<td>0.59–2.5 mg/µL cm²</td>
<td>&lt; 0.02 µg/cm² after 12 h</td>
<td>111</td>
</tr>
<tr>
<td>Efficient antimicrobial activity</td>
<td>Various in biomedical applications</td>
<td>Natural zeolite</td>
<td>Ag NPs</td>
<td>Physical cross-linking method</td>
<td>20 ± 6 nm</td>
<td>0.36–3.6 mg/mL cm²</td>
<td>&lt; 0.02 µg/cm² after 12 h</td>
<td>111</td>
</tr>
<tr>
<td>Efficient antimicrobial activity</td>
<td>Various in biomedical applications</td>
<td>Natural zeolite</td>
<td>Au NPs</td>
<td>Physical cross-linking method</td>
<td>20 ± 6 nm</td>
<td>0.63–3.6 mg/mL cm²</td>
<td>&lt; 0.02 µg/cm² after 24 h</td>
<td>111</td>
</tr>
<tr>
<td>Efficient antimicrobial activity</td>
<td>Various in biomedical applications</td>
<td>Natural zeolite</td>
<td>Co-zeolite</td>
<td>Physical cross-linking method</td>
<td>20 ± 6 nm</td>
<td>800–8000 kDa/mL cm²</td>
<td>&lt; 0.02 µg/cm² after 12 h</td>
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<tr>
<td>Efficient antimicrobial activity</td>
<td>Various in biomedical applications</td>
<td>Natural zeolite</td>
<td>Co-zeolite</td>
<td>Physical cross-linking method</td>
<td>20 ± 6 nm</td>
<td>0.36–3.6 mg/mL cm²</td>
<td>&lt; 0.02 µg/cm² after 24 h</td>
<td>111</td>
</tr>
</tbody>
</table>

**Highlights of hydrogels**

- Quite a uniform spin coating and photocross-linking distribution.
- Quite a uniform spin coating and photocross-linking distribution.
- Quite a uniform spin coating and photocross-linking distribution.
- Quite a uniform spin coating and photocross-linking distribution.
- Quite a uniform spin coating and photocross-linking distribution.

**References**

23, 111

**Co-zeolite content**

- Higher than 0.48 wt%.
- Higher than 0.48 wt%.
- Higher than 0.48 wt%.
- Higher than 0.48 wt%.
- Higher than 0.48 wt%.

**Application**

- Hydrogels, as a kind of local administration matrix, offer high surface area to volume ratio and the capacity to design their physical properties such as porosity to match natural tissue. Recent studies have shown that a combination of synthetic antimicrobial polymers and antibiotics could potentially evade problems of drug resistance by taking advantages of the polymer’s membrane-lytic mechanism. Meanwhile, polymer toxicity is mitigated as the co-usage of antibiotics allows for a smaller amount of polymer in use. So, it is easy for hydrogels to selectively load drug molecules with controlled release at the desirable site and to offer accurate prolonged release.31,129–131

The antibiotics in common use for antimicrobial hydrogels are as follows.

**Ciprofloxacin**

Ciprofloxacin is a fluoroquinolone antibacterial agent, which is active against a broad spectrum of Gram-positive and Gram-negative bacteria.136 It is the gold standard for various topical applications, such as eye and skin infections.137

Ciprofloxacin is also a recommended treatment for Shigella infections. However, ciprofloxacin-resistant *Shigella sonnei* are being increasingly isolated in Asia and sporadically reported on other continents.138,139 The mechanism of ciprofloxacin depends upon blockage of bacterial DNA duplication by binding itself to DNA gyrase, thereby causing double-stranded ruptures in the bacterial chromosomes, so resistance to this drug develops slowly.140 Minimal toxicity of ciprofloxacin is related to dosage, and excessive doses can cause damages to tissues, whereas hydrogels can solve this problem as a local delivery system.

Ciprofloxacin can be self-assembled with a tripeptide into an antimicrobial nanostructured hydrogel to enable abundant drug to be carried along with prolonged release.129,137 Modified hydrogel coatings were reported to prevent titanium implant-associated infections.128 A hydrogel generated by polymerizing aminophenyl boronic acid in PVA with ciprofloxacin was reported to treat wound healing in diabetes patients.141

It has been reported that diseases associated with the colon
1. ZnO NPs bind to bacterial cell membranes and destroy the lipids and proteins on them.

2. Inside the microbial cell, Ag NPs exert several antimicrobial effects: 1) inhibiting cytochromes of the electron transport chain of microbes; 2) causing damage to DNA and RNA of microbes; 3) inducing formation of ROS, which are also toxic to host cells; and 4) inhibiting cell wall synthesis in Gram-positive bacteria.

3. After the Ag NPs are leaked from the dead microbes, Ag NPs could go on to kill other microbial cells.

4. Unlike any other metal, the antimicrobial activity of MgO works by adsorbing halogen molecules onto the surface of the MgO.

such as constipation may be treated with hydrogels containing laxative psyllium and ciprofloxacin. Hosny demonstrated that a liposomal hydrogel containing ciprofloxacin improved maximum ocular availability through albino rabbit cornea.

In the research of Zhou et al, porous scaffolds of PVA were prepared by quenching in liquid nitrogen and the freeze drying method, from different concentration aqueous solutions loaded with ciprofloxacin were fabricated. Complete inhibition of

Table 3 Antimicrobial mechanism of nanoparticles

<table>
<thead>
<tr>
<th>Nanoparticles</th>
<th>Antimicrobial mechanisms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag NPs</td>
<td>1. Ag⁺ dissolved from Ag NPs interact with sulfur-containing and phosphorus-containing groups of proteins of the cell wall and plasma membrane of bacteria. Binding to negatively charged parts of the membrane creates holes in the membrane, allowing plasma contents (including K⁺) to flow out of the cell, dissipating the H⁺ gradient across the membrane.</td>
<td>34, 36, 39–42</td>
</tr>
<tr>
<td>Au NPs</td>
<td>First, the presence of multiple Amp molecules on the surface of Au NP allows the Au NP-Amp to overwhelm the outer membrane and peptidoglycan layer, resulting in bacterial death. Second, Au NP-Amp inhibits the transmembrane pump that catalyzes drug efflux from the bacterial cell.</td>
<td>85</td>
</tr>
<tr>
<td>ZnO NPs</td>
<td>1. ZnO NPs bind to bacterial cell membranes and destroy the lipids and proteins on them. 2. ZnO NPs could cause formation of Zn²⁺ ions and ROS, which damage the bacterial cell. 3. When coated with PVA, ZnO NPs increase membrane permeability and enter the cytoplasm of the bacterial cell.</td>
<td>31, 33, 35, 95, 98</td>
</tr>
<tr>
<td>CuO/Cu NPs</td>
<td>1. Cu interacts with amine and carboxyl groups on the surfaces of microbial cells. Therefore, microbes with higher density of the two groups have higher sensitivity to CuO/Cu NPs. 2. ZnO NPs could cause formation of ROS. 3. When coated with PVA, ZnO NPs increase membrane permeability and enter the cytoplasm of the bacterial cell.</td>
<td>112–114</td>
</tr>
<tr>
<td>MgO/MgX NPs</td>
<td>1. MgO/MgX NPs inhibit certain enzymes of microbial cells. 2. MgX⁺ NPs may induce formation of ROS. 3. MgX₂⁻ NPs inhibit growth and biofilm formation. 4. Unlike any other metal, the antimicrobial activity of MgO works by adsorbing halogen molecules onto the surface of the MgO.</td>
<td>117–120</td>
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</table>

Abbreviations: Ag NPs, silver nanoparticles; Amp, ampicillin; Au NPs, gold nanoparticles; CuO/Cu NPs, copper-containing NPs; MgO NPs, magnesium oxide-containing nanoparticles; MgX NPs, magnesium halogen-containing nanoparticles; PVA, polyvinyl alcohol; ROS, reactive oxygen species; ZnO NPs, zinc oxide nanoparticles.

Figure 5 Development of antibiotics and appearance of drug resistance are summarized chronologically referring to Huh and Kwon, Andersson and Hughes, Rodriguez-Rojas et al, van Hoek et al, Molton et al. Abbreviations: E. coli, Escherichia coli; K. pneumoniae, Klebsiella pneumoniae; MRSA, meticillin resistant S. aureus; S. aureus, Staphylococcus aureus; VISA, vancomycin intermediate resistant S. aureus; VRE, vancomycin-resistant Enterococcus; VRSA, vancomycin-resistant S. aureus.
microorganism growth revealed the sustaining release of ciprofloxacin. Other researchers used dextrin and poly-based hydrogel as a carrier for ciprofloxacin, and the results suggest that hydrogel was a promising candidate for controlled release of ciprofloxacin.\textsuperscript{144,145} These studies indicate that the hydrogels loaded with ciprofloxacin have great potential of clinical administration, especially for infectious diseases due to their excellent antimicrobial properties and prolonged effect.

**Gentamicin**

Gentamicin is a traditional broad spectrum antibiotic used for the treatment of skin and soft tissue infections. However, systemic toxicity, especially for kidney, and low plasma concentration hinder its application.\textsuperscript{146} To avoid the side effects, gentamicin is often used locally nowadays.\textsuperscript{147,148} Local administration of functional gentamicin hydrogels offers an efficient solution. Gentamicin-loaded PVA and PVA-AAm hydrogels cross-linked by sterculia have many biomedical properties such as blood compatibility, tensile strength, burst strength, water vapor permeability and oxygen diffusion. It can be a kind of potent antimicrobial wound dressings.\textsuperscript{149,150} Superabsorbent polysaccharide gentamicin hydrogels based on pullulan derivatives also brought a broadened view about antimicrobial hydrogels. It may become one of the important applications in the future with the ability to expand to 4,000\% of its volume.\textsuperscript{151} Phospholipid-modified solid lipid microencapsites encapsulating gentamicin were loaded into three polymeric hydrogels. Poloxamer 407 microgels were proved to have the most desirable properties in terms of fast antibacterial activity, in vitro diffusion-dependent permeation, spread ability, pH and viscosity.\textsuperscript{152} This implied that the same drug can reach different diffusion speeds on hydrogels of different matrices. Hydrogel based on the copolymer poly(N-isopropylacrylamide-co-dimethyl-\textgamma-butyrolactoneacrylate-co-Jeffamine\textsuperscript{8} M-1000 acryl amide) (PNDJ) with delivery in \textgtr\textless 6 weeks was loaded with gentamicin. This hydrogel might decrease treatment failure for orthopedic infection.\textsuperscript{153} Inspiringly, Wu et al\textsuperscript{154} found that gentamicin sulfate (GS)-loaded carboxymethyl-chitosan (CMCh) hydrogel cross-linked by genipin was an effective and simple approach to achieve genipin was an effective and simple approach to achieve

The hydrogels have broken the limit of gentamicin application since the effective dosage can be decreased. Other antibiotics with serious side effects can also be used with hydrogels.

**Vancomycin**

Vancomycin, a macromolecular glycopeptide antibiotic, is considered as the last defense of infection clinically, especially for methicillin-resistant \textit{Staphylococcus}.\textsuperscript{155,156} But now even vancomycin-resistant \textit{Enterococcus} (VRE) has been found in different regions.\textsuperscript{157–160} As mentioned earlier, hydrogels as a delivery system are able to protect and enhance the validity of vancomycin. Syringeable pluronic-\textalpha-cyclodextrin (CD) supramolecular gels,\textsuperscript{161} hydrogel of thiolated CS cross-linked with maleic acid-grafted dextrin,\textsuperscript{162} thermosensitive hydrogel of CS/gelatin/\textbeta-glycerol phosphate,\textsuperscript{163} hydrogel of oligo(PEG fumarate)/sodium methacrylate (OPF/ SMA) charged copolymers as biocompatible matrices,\textsuperscript{164} poly(\textbeta-amino ester) (PBAE) hydrogels mixed with PEG (MW = 400) diacrylate (PEGDA) and diethylene glycol diacrylate (DEGDA)\textsuperscript{165} and hydrogels achieved by photo cross-linking of methacrylated dextran and poly(\textgama-glutamic acid)-g-hydroxyethyl methacrylate are all studied, and they exhibited excellent antimicrobial properties and desirable release capacity.\textsuperscript{166} The most common pathogen of osteomyelitis is \textit{S. aureus}, especially MRSA. Vancomycin is always used in the treatment of osteomyelitis because it is the most effective antibiotic against MRSA. The combination of hydrogels and vancomycin is a good material, which can prevent osteomyelitis clinically.

**Synthetic antimicrobial drugs**

Here, synthetic antimicrobial drugs refer to the nitroimidazoles, sulfanilamide groups and other frequently used antibiotics through de novo synthesis, not including semi-synthetic antibiotics or biological extract. Synthetic drugs have many advantages because of their special chemical structures, but they bring risks and damage to normal tissue for the same reason too. So, stable and safe delivery systems become necessary.\textsuperscript{167} Nitroimidazoles can have an effect on anaerobic bacteria and amoeba, so they are often used for the digestive system.\textsuperscript{168} Ornidazole has been loaded on hydrogels composed of CMCh for colon-targeted delivery, and its release can be controlled by a change in pH.\textsuperscript{163,166} Das et al\textsuperscript{130,144,170} used dextrin and poly-based hydrogel as a carrier for ornidazole, and the result suggests that the hydrogel was a promising vehicle. Hydrogels based on dextrin grafted with poly(2-hydroxyethyl methacrylate) by embedding N,N-methylene bisacrylamide as a cross-linker can also be a good candidate for an orally administered drug delivery system for the colon region.\textsuperscript{130} Metronidazole (MTZ) containing PMAA nanogel
as an oral dosage form for gastrointestinal infection and tinidazole containing hydrogels based on CS have also been studied. Moreover, floating pH-sensitive CS hydrogels containing MTZ were more effective against *Helicobacter pylori* than the commercially available oral MTZ tablets. CS/gelatin/β-glycerol phosphate hydrogels could maintain sustained release of MTZ in concentrations that are effective for eliminating pathogenic bacteria over time. Chlorhexidine is considered a promising antimicrobial agent and possesses a broad spectrum of activity against bacteria. Chlorhexidine thermosensitive hydrogel and chlorhexidine diacetate containing thermoresponsive hydrogel copolymers exhibit novel application of this traditional sterilization agent. In recent research studies, the micrometer-sized β-CD-based hydrogel (bCD-Jef-MPs) system also achieved sustained release of chlorhexidine digluconate, thus treating periodontitis lesions became effective. The prolonged release has made it possible to decrease its dosage. Therefore, its side effects were reduced. Octenidine, as an external application, has become active wound dressings with minimized side effects after being loaded on bacterial nanocellulose. Thiosemicarbazone, an antimicrobial drug used in ophthalmic diseases, was loaded on poly(2-hydroxyethyl methacrylate)-conjugated beta-CD or directly cross-linked hydroxypropyl-beta-CD to explore novel materials for fabrication of soft contact lenses. In the study by Sittiwong et al, the drug release rate of sulfanilamide-loaded PVA hydrogels could be controlled through the drug size, matrix pore size, electrode polarity and applied electric field. As for wound therapy, immobilization of cetylpyridinium chloride to PVA hydrogels offers suppressed release; chloramine-T and sulfadiazine sodium salt-loaded hydrogels composed of PVA, PVP and glycerin showed an excellent swelling capacity; a novel polyvinyl–pyrrolidone–iodine hydrogel in wound therapy was found to be able to enhance epithelialization and reduce loss of skin grafts; poly(N-hydroxyethyl acrylamide)/salicylate hydrogels provide both antimicrobial and antifouling functions; and isothiazolinones delivered in alginate and enhancement of drug bioavailability. A hydrogel based on (−)-menthol, which is a traditional cooling compound tailored by an amino acid derivate through an alkyl chain, can provide innomxious environment to living cells and deliver lincomycin to the local infection site. O-Carboxymethyl CS (CS-MCMS) hydrogels synthesized from CS and monochloroacetic acid were reported as a promising carrier for antibiotics, which showed significant antibacterial activities against *E. coli* and *S. aureus* while loaded with lincomycin. Doxycycline was also loaded on an in situ thermally sensitive hydroxypropyl-β-CD hydrogel for ophthalmic delivery. Controlled release of doxycycline from CS-gelatin hydrogels cross-linked with transglutaminase was observed in other research, indicating that it is a potential carrier for cell delivery. Mupirocin appears to be one of the promising antimicrobials, as it is well tolerated in topical administration with very few side effects. Liposomes-in-hydrogel delivery system for mupirocin solved the problem of controlled and its own antibacterial spectrum and advantages. Amoxicillin trihydrate, a common treatment for peptic or gastric ulcers caused by *H. pylori* infection, loaded in κ-carrageenan hydrogels containing CaCO₃ and NaHCO₃ or CS/poly-gamma-glutamic acid nanoparticle pH-sensitive hydrogels was well protected from the gastric juice, thus facilitating drug effects specifically at the site of infection. The similar results of in vivo studies by Moogooee et al showed that the amoxicillin-loaded hydrogels enhance drug concentration at the topical site than powder amoxicillin, meaning that therapeutic concentration can be achieved at a much lower dose which may reduce the adverse effects of amoxicillin in high doses. Ampicillin sodium-loaded PVA–alginate physically cross-linked hydrogel exhibited both Gram-positive and Gram-negative antimicrobial properties and improved hemolysis. Cefalosporin belongs to beta-lactamase, and it is a widely used β-lactamase-resistant and broad spectrum antibiotic. Cefixime (CFX)-loaded CS/PEG hydrogel exhibited controlled release of drug and antibacterial activity against Gram-negative bacteria (*E. coli*) and Gram-positive bacteria (*S. aureus*). Cefditoren pivoxil hydrogels with gastrotretentive effect were achieved, and cefazolin containing methoxy PEG-co-poly(lactic acid-co- aromatic anhydride) hydrogels offered a stable release without initial burst. Levofloxacin-loaded hyaluronic acid hydrogels were reported to be able to chase bacteria within the cells for both *S. aureus* and *P. aeruginosa* strains. In order to eradicate bacterial biofilm and avoid possible intestinal obstructions, Islan et al reported a smart auto-degradable hydrogel containing alginate lyase (AL) and levofloxacin, which induced the reduction of drug toxicity and enhancement of drug bioavailability. A hydrogel based on Bacillus subtilis, which is a traditional cooling compound coated by an amino acid derived through an alkyl chain, can provide innocent environment to living cells and deliver lincomycin to the local infection site. O-Carboxymethyl CS (CS-MCMS) hydrogels synthesized from CS and monochloroacetic acid were reported as a promising carrier for antibiotics, which showed significant antibacterial activities against *E. coli* and *S. aureus* while loaded with lincomycin. Doxycycline was also loaded on an in situ thermally sensitive hydroxypropyl-β-CD hydrogel for ophthalmic delivery. Controlled release of doxycycline from CS-gelatin hydrogels cross-linked with transglutaminase was observed in other research, indicating that it is a potential carrier for cell delivery. Mupirocin appears to be one of the promising antimicrobials, as it is well tolerated in topical administration with very few side effects. Liposomes-in-hydrogel delivery system for mupirocin solved the problem of controlled and
prolonged release of mupirocin, which offered an improved burn therapy, and substantial efforts have been devoted in the literature to prove its antibiofilm activity against \textit{S. aureus} biofilms and non-toxicity against keratinocytes.\textsuperscript{200,201} The methoxypoly(ethylene glycol)-co-poly(lactic-co-glycolic acid) (mPEG-PLGA) hydrogel containing teicoplanin was reported effective for treating osteomyelitis in rabbits.\textsuperscript{202} There are a plenty of reports about different antibiotics loaded in hydrogels, but the three mentioned earlier are the mostly used ones. However, other antibiotics and hydrogel offered us with more choices when facing different bacterial infections. Meanwhile, it decreases the risk of antibiotic resistance. The controlled release of antibiotics is another advantage of hydrogels. The stable and continuous release without initial burst would ensure prolonged antimicrobial effect which can satisfy clinical demand. To offer an easier query, most of the hydrogels with antibiotics are recorded in this review (Table 4).

### Biological extracts

Biological extracts include extracts from vegetations and animals, some of these extracts have a long history of application, and others were discovered in recent years.\textsuperscript{203} For example, the therapeutic efficiency of herbal extracts and ingredients has been limited by various factors, including the lack of targeting capacity and poor bioavailability. Hydrogel is a promising carrier for the extracts of herbal medicine in recent studies.\textsuperscript{204} Following are reports of hydrogels loaded with various natural extracts. Seaweed extract-based hydrogel was reported as a novel antimicrobial wound dressing, and no seaweed-derived antimicrobials have been used in wound dressings ever before.\textsuperscript{205} Combinations of agar and carrageenan-PVA hydrogel wound dressing have been proved to be useful in treating burns, other external wounds and non-healing ulcers of diabetes.\textsuperscript{206} Hydrogels extracted and assembled from dermis samples containing basement membrane proteins vital to skin regeneration, including laminin \( \beta 3 \), collagen IV and collagen VII, were applied as a barrier against bacteria in wound healing.\textsuperscript{207} Though according to some research studies alginates do not display antimicrobial properties, it can be an ideal wound dressing due to its morphology, fiber size, porosity, degradation and swelling ratio.\textsuperscript{205-208} Allicin-CS complexes were proved to have antibacterial activity against spoilage bacteria, and they may be used as an antimicrobial agent in foods.\textsuperscript{209} CS-based hydrogel film loaded with ethyl acetate Salix alba leaves extract showed no cytotoxicity and excellent antibacterial ability against \textit{Salmonella typhi} and \textit{Candida guilliermondii}.\textsuperscript{210} Achyrocline satureioides is a medicinal plant widely used in South America, which exhibits a well-documented antioxidant activity against Gram-positive and Gram-negative bacteria, as well as a set of yeast molds.\textsuperscript{211} Curcumin is non-toxic and bioactive agent with multifunction; it is found in turmeric and has been applied for centuries as a remedy to various ailments.\textsuperscript{212} However, low aqueous solubility and poor bioavailability limit the application of curcumin, and thus curcumin nanoparticles and hydrogels were developed. Ag NPs-curcumin hydrogels for wound dressing were also reported, exhibiting good antibacterial properties and sustained release, which indicate enormous prolonged therapeutic value.\textsuperscript{213,214} A polysaccharide extracted from Aloe vera, Asecmannan, has various medical properties, such as antibacterial property, and it can accelerate healing of lesions.\textsuperscript{215} Some studies demonstrated its antibacterial activity against both susceptible and resistant \textit{H. pylori} strains.\textsuperscript{216} Alginate hydrogels containing Aloe vera were applied in clinical wound care treatment due to their antimicrobial and anti-inflammation capacity.\textsuperscript{217} Essential oils, such as lavender, thyme oil, peppermint, tea tree, rosemary, cinnamon eucalyptus, lemongrass and others, have been found to possess particular antimicrobial properties, mainly in response to the overwhelming concern of consumers over the safety of synthetic food additives.\textsuperscript{218,219} Essential oils encapsulated in sodium alginate were reported to be qualified as disposable wound dressings.\textsuperscript{220} For those extracts from animals, honey was the most easily acquired; a Malaysian honey, Gelam honey, was incorporated into a hydrogel system to produce a functional wound dressing.\textsuperscript{221} Besides honey, bee propolis loaded into hydrogels has good antibacterial ability, making it a good wound dressing for skin wound healing.\textsuperscript{222} Another bee derivative is bee venom peptide, namely melittin, and its copolymer interactions on thermosensitive PLGA-PEG-PLGA hydrogel can be used as delivery systems for peptide drugs.\textsuperscript{222} Lysozymes, derived from normal tears with their inherent antibiotic properties, were deposited on hydrogel contact lenses that exhibit marked activity.\textsuperscript{223} Vitamin E is also an important antioxidant, biodegradable hydrogel from vitamin E-functionalized polycarbonates for antimicrobial applications; it displayed excellent compatibility with human dermal fibroblast loaded with cationic polymers and/or fluconazole at minimum biocidal concentrations.\textsuperscript{224} Lignins and lignin-derived compound model polymer, dehydrogenate polymer (DHP) in alginate hydrogel, have shown strong antimicrobial and wound healing activity.\textsuperscript{225} These biological extracts are easier to get and more readily accepted. Excellent biocompatibility and good antibacterial properties also make them promising antimicrobial biomaterials in the future. However, with the studies ongoing,
<table>
<thead>
<tr>
<th>Species of hydrogels</th>
<th>Synthesis of hydrogels</th>
<th>Highlights of hydrogels</th>
<th>Antimicrobial agents delivered</th>
<th>Content of antimicrobial agents</th>
<th>Rate of release</th>
<th>Antimicrobial capability</th>
<th>Application</th>
<th>References</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphiphilic mono-mPEG-PLGA copolymers</td>
<td>Ring-opening polymerization of monomers and mPEG in the presence of stannous 2-ethyl hexanoate</td>
<td>Easy preparation, 100% encapsulated rate, near-linear sustained release of drugs, injectable design and in situ gelling at the target tissue</td>
<td>Teicoplanin</td>
<td>840 mg/mL</td>
<td>At day 31, teicoplanin releases 73%, 70% and 60%, respectively (in different groups)</td>
<td>Antimicrobial activity against Staphylococcus aureus</td>
<td>A therapeutic strategy for infected diseases, such as osteomyelitis</td>
<td>202</td>
<td>2010</td>
</tr>
<tr>
<td>Gentamicin-loaded thermosteting composite hydrogels</td>
<td>Combined CS with bovine bone substitutes (Orthoss® granules), beta-glycerophosphate as cross-linker and lyophilized</td>
<td>Porosity (80%-86%), scaffold water uptake and retention capability</td>
<td>Gentamicin</td>
<td>4 mg in 1 mL thermosteting composite hydrogel starting solution</td>
<td>Release was completed in 4 h</td>
<td>Antimicrobial effect on Escherichia coli</td>
<td>Drug delivery for reducing infection risk during bone open surgeries</td>
<td>155</td>
<td>2017</td>
</tr>
<tr>
<td>OPF/SMA charged</td>
<td>UV cross-linking</td>
<td>Negatively charged, non-toxic and is able to be cross-linked into several known copolymer formulations</td>
<td>Vancomycin</td>
<td>500 µg/mg</td>
<td>33.7% in the first 6 h &lt;80% in the first 24 h</td>
<td>Antimicrobial activity against MRSA</td>
<td>Appropriate candidates to deliver local antibiotic therapy for prophylaxis of surgical site infection</td>
<td>164</td>
<td>2016</td>
</tr>
<tr>
<td>Micrometer-sized β-cyclodextrin-based hydrogel (bCD-Jef-MPs)</td>
<td>Introduced Jeffamine segments in the polymeric network</td>
<td>1) Appropriate stiffness, 2) adaptability to the pocket geometrical structure and 3) ease of application by minimally invasive approach</td>
<td>CHX-dg</td>
<td>–</td>
<td>CHX-dg was released in a time-dependent fashion and by following a quasi-constant rate of 10%/day</td>
<td>–</td>
<td>Effectively treating periodontitis lesions</td>
<td>177</td>
<td>2017</td>
</tr>
<tr>
<td>O-CMCS hydrogels</td>
<td>O-CMCS hydrogel was prepared by CS, monochloroacetic acid EDC and NHS</td>
<td>The hydrogels performed good swelling capacities and obvious pH-sensitive properties</td>
<td>Lincomycin</td>
<td>–</td>
<td>–</td>
<td>Significant antibacterial activities against Gram-negative E. coli and Gram-positive S. aureus</td>
<td>Antibacterial material</td>
<td>197</td>
<td>2016</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Species of hydrogels</th>
<th>Synthesis of hydrogels</th>
<th>Highlights of hydrogels</th>
<th>Antimicrobial agents delivered</th>
<th>Content of antimicrobial agents</th>
<th>Rate of release</th>
<th>Antimicrobial capability</th>
<th>Application</th>
<th>References</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS/Gβ-Gp hydrogel</td>
<td>Added gelatin molecules to the thermosensitive CS/Gβ-Gp hydrogels to form CS/Gβ-Gp hydrogels</td>
<td>The gel strength increased at body temperature over the results from the CS/Gβ-Gp hydrogel</td>
<td>MTZ vancomycin hydrochloride</td>
<td>–</td>
<td>The initial burst and total in vitro drug release for MTZ was 13% and 67%, while vancomycin hydrochloride 3% and 23%</td>
<td>Inhibition of anaerobic Gram-positive <em>Clostridium sporogenes</em></td>
<td>Drug carrier with no cytotoxic effects</td>
<td>163</td>
<td>2016</td>
</tr>
<tr>
<td>PBAE hydrogel</td>
<td>Through the free radical polymerization of PBAE macromers using redox initiators</td>
<td>May reduce the potential for bacterial colonization of this biomaterial as antibiotic was found to be released until the hydrogel loses structural integrity</td>
<td>Vancomycin</td>
<td>1.5 wt%</td>
<td>One group finished vancomycin release after 11 days The other 21 days</td>
<td>Against <em>S. aureus</em></td>
<td>An important step in degradative-based drug delivery for local antibiotic treatment</td>
<td>165</td>
<td>2014</td>
</tr>
<tr>
<td>Calcium–alginate–gelatin hydrogels with CS/ poly-γ-glutamic acid nanoparticles</td>
<td>Dropping aqueous alginate–gelatin into an aqueous solution of calcium chloride</td>
<td>Hydrogels are pH-sensitive, leading to protection of the nanoparticles from destruction by gastric acid</td>
<td>Amoxicillin</td>
<td>–</td>
<td>At pH 6.0, only a very small amount of amoxicillin was released, whereas, at pH 7.0, the amoxicillin was released rapidly</td>
<td>Effective for <em>Helicobacter pylori</em></td>
<td>An efficient carrier for antibiotic drug (amoxicillin) delivery</td>
<td>188</td>
<td>2010</td>
</tr>
<tr>
<td>c-Dxt/PAA hydrogel</td>
<td>The c-Dxt/PAA hydrogel was synthesized via free radical polymerization in the presence of KPS initiator</td>
<td>Non-cytotoxic toward human mesenchymal stem cells, degradable in nature</td>
<td>Ornidazole and ciprofloxacin</td>
<td>–</td>
<td>Controlled release behavior remains stable in the tablet formulations for up to 3 months</td>
<td>Controlled release of ornidazole and ciprofloxacin</td>
<td>Open a new platform as matrix for controlled release of ornidazole and ciprofloxacin</td>
<td>144</td>
<td>2015</td>
</tr>
<tr>
<td>Cross-linked hydrogel derived from Dxt, N-isopropylacrylamide and N,N'-methylene bis(acrylamide) (c-Dxt/ pNIPAm)</td>
<td>Dxt as biopolymer, NIPAm as monomer, MBA as cross-linker and KPS as initiator</td>
<td>The pH and temperature responsiveness, non-cytotoxicity, biodegradability and good compatibility between the drugs and the matrix along with the controlled release behavior</td>
<td>Ornidazole and ciprofloxacin</td>
<td>–</td>
<td>Controlled release behavior ~97% ornidazole and ~98% ciprofloxacin remain stable in the tablet formulations for up to 3 months</td>
<td>Controlled release of ornidazole and ciprofloxacin</td>
<td>An excellent alternative for controlled release of ornidazole and ciprofloxacin</td>
<td>170</td>
<td>2015</td>
</tr>
<tr>
<td>Hydrogel Type</td>
<td>Description</td>
<td>Drug</td>
<td>Release/Effectiveness</td>
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<td>P (NIPAM-AA-HEM) hydrogel</td>
<td>Poly(NIPAM-AA-HEM) was cross-linked by free radical copolymerization of monomers in 1,4-dioxane under ( \text{N}_2 ) atmosphere with TEGDM (0.1 wt%) as a cross-linking agent</td>
<td>Amoxicillin</td>
<td>1%, 2% and 5% 88.5% of amoxicillin in the hydrogels was released in 4 h in the pH 1.0 medium, whereas at pH 7.4 not &gt;45% at 37°C Effective for <em>H. pylori</em> A novel therapeutic modality for the treatment of <em>H. pylori</em>-mediated infections</td>
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<tr>
<td>Floating pH-sensitive CS hydrogels</td>
<td>Cross-linking high molecular weight CS in lyophilized solutions containing MTZ using either citrate or tri-polyphosphate salts at 1% or 2% concentration</td>
<td>MTZ</td>
<td>Ranged from 246 ± 4.24 to 249.5 ± 10.60 mg/500 mg formula More than 70% of the loaded drug was released in SGF (pH 1.2) within 24 h, while none of the prepared formulas released &gt;70% within the 24 h in phosphate buffer (pH 7.4) More effective against <em>H. pylori</em> than the commercially available oral MTZ tablets</td>
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<tr>
<td>PVA hydrogel</td>
<td>Glutaraldehyde was used as the cross-linking agent for PVA hydrogels</td>
<td>Sulfanilamide</td>
<td>– Drug release was effected by different factors – Drug delivery system</td>
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<tr>
<td>CG injectable hydrogels</td>
<td>Solution of 2% (w/v) CS, 4% (w/v) gelatin, 2% (w/v) powdered low glucose DMEM and 0.003%, (w/v) transglutaminase were prepared in 0.1 N HCl</td>
<td>DOX</td>
<td>90% of DOX released from cross-linked CG hydrogels after 4 days Significant potential as a carrier for cell delivery</td>
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<th>References</th>
<th>Year</th>
</tr>
</thead>
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<tr>
<td>PNDJ</td>
<td>Free radical polymerization in a blend of dioxane/tetrahydrofuran</td>
<td>Gentamicin is delivered from PNDJ hydrogel with low systemic exposure and decreased treatment failure for orthopedic infection</td>
<td>Gentamicin</td>
<td>1.61%</td>
<td>96% of the contained gentamicin load was recovered by 72 h for the lower-dose formulation, whereas the higher dose delivered 75% and took 7 days to release 100%</td>
<td>Sustained antimicrobial activity against S. aureus</td>
<td>Resorbable viscosous hydrogels for local antimicrobial delivery may improve outcomes for one-stage management of implant infections</td>
<td>Injectable depot gel for drug delivery</td>
<td>153</td>
</tr>
<tr>
<td>mPEG-PLCPHA thermosensitive hydrogels</td>
<td>mPEG-PLCPHA was synthesized by polymerization of aromatic polyanhydrides, mPEG and polyesters</td>
<td>mPEG-PLCPHA copolymer could form gel at body temperature with excellent biocompatibility and a stable release for 30 days</td>
<td>Cefazolin</td>
<td>20 mg/mL</td>
<td>The steady release of cefazolin lasted up to 4 weeks and no significant burst effect was shown in the release profiles</td>
<td>Sustained antimicrobial activity against E. coli</td>
<td>Injectable depot gel for drug delivery</td>
<td>194</td>
<td>2014</td>
</tr>
<tr>
<td>PVA</td>
<td>The scaffolds of PVA were fabricated by quenching in liquid nitrogen and freezing–drying and resoaking method from different original concentration aqueous solutions</td>
<td>Excellent release capability of ciprofloxacin, non-cytotoxicity and induction of cell growth</td>
<td>Ciprofloxacin</td>
<td>10 wt% of corresponding PVA weight</td>
<td>86.0%, 76.6% and 54.5% for 10 wt%, 14 wt% and 18 wt% scaffolds, respectively, at 128 h</td>
<td>Completely inhibited the growth of E. coli</td>
<td>A good potential application in tissue engineering, demanding high strength and well drug release capability</td>
<td>143</td>
<td>2016</td>
</tr>
<tr>
<td>PMAA nanogels</td>
<td>Ethylene glycol dimethacrylate is used as the cross-linker of PMAA nanogels</td>
<td>MTZ/PMAA nanogels sustained the release of MTZ in the simulated gastrointestinal medium and exhibited less cytotoxicity than MTZ alone</td>
<td>MTZ</td>
<td>23.2–69.1 g/mg</td>
<td>&lt;12.7% (pH = 1.2), 33.3% (pH = 6.8) and 58.9% (pH = 7.2)</td>
<td>Excellent antibacterial activity against Bacteroides fragilis</td>
<td>MTZ/PMAA nanogel would be a more useful dosage form than MTZ for mild-to-moderate Clostridium difficile infections</td>
<td>Injectable depot gel for drug delivery</td>
<td>171</td>
</tr>
<tr>
<td>Dxt and poly (2-hydroxyethyl methacrylate)-based cross-linked hydrogel (c-Dxt/pHEMA)</td>
<td>c-Dxt/pHEMA was synthesized by free radical polymerization technique</td>
<td>Non-toxic against HaCaT cells, excellent drug stability and released ciprofloxacin</td>
<td>Ciprofloxacin</td>
<td>1 wt%</td>
<td>Sustainable release of ciprofloxacin (33.75% release after 18 h)</td>
<td>–</td>
<td>A potential candidate for ciprofloxacin carrier</td>
<td>Injectable depot gel for drug delivery</td>
<td>145</td>
</tr>
<tr>
<td>CS with PEG pH-sensitive hydrogels</td>
<td>CS and PEG cross-linked with tetraethyl orthosilicate as cross-linker</td>
<td>The pH sensitivity and non-cytotoxicity made these hydrogels an appropriate candidate for injectable drug delivery</td>
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<tr>
<td>Hyaluronic acid nanohydrogels</td>
<td>Self-assembling of the hyaluronic acid-cholesterol amphiphilic chains in aqueous environment</td>
<td>Polysaccharide nanohydrogel</td>
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<tr>
<td>Polysaccharide hydrogel</td>
<td>In situ cross-linking and Michael addition reaction</td>
<td>Closely mimic the nature extracellular matrix glycosaminoglycans</td>
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<tr>
<td>Hydrogelator containing an L-lysine</td>
<td>Synthesized by linking with amino acid or carboxylic acid derivatives</td>
<td>(−)-Menthol-based thixotropic hydrogels</td>
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<tr>
<td>CS-based composite hydrogels</td>
<td>Free radical cross-link copolymerization</td>
<td>wt% of CS and MBA and pH of the medium strongly influence the drug release</td>
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<tr>
<td>Bacterial nanocellulose hydrogels</td>
<td>Octenidine was incorporated in bacterial nanocellulose with the intention</td>
<td>Biocompatible, stable, releasable and biologically active over a period of 6 months</td>
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</table>

Hydrogels exhibited antibacterial activity against Gram-negative bacteria E. coli and Gram-positive bacteria S. aureus

| CFX (25 mg/25 mL of methanol) was loaded into blend of CS (0.75 g) and PEG (0.1 g, MW = 6,000) | Sustained amount of drug (CFX) is released (85%) during 80 min |
| Levofloxacin | 5.0% ± 0.5% w/w |
| Vancomycin | 0.9 mg/mL |
| Zn²⁺ or lincomycin | Zn²⁺ 0.01 M lincomycin 0.001 M |
| Tinidazole | 15–20 wt% |
| Octenidine | 0.1 mg/mL |

Mean MIC values of S. aureus is 0.104 ± 0.058 mg/L and Pseudomonas aeruginosa is 0.557 ± 0.078 mg/L

Inhibition against E. coli and S. aureus

A promising carrier have potential application for wound healing

Optimum swelling, drug entrapment and drug release profiles at pH 7.5

Ready-to-use system for wound treatment

(Continued)
<table>
<thead>
<tr>
<th>Species of hydrogels</th>
<th>Synthesis of hydrogels</th>
<th>Highlights of hydrogels</th>
<th>Antimicrobial agents delivered</th>
<th>Content of antimicrobial agents</th>
<th>Rate of release</th>
<th>Antimicrobial capability</th>
<th>Application</th>
<th>References</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVA hydrogels</td>
<td>Prepared from PVA in a saline solution by γ-irradiation</td>
<td>Easy and inexpensive synthesis, suppressed release</td>
<td>Cetylpyridinium chloride</td>
<td>0.08%–0.24%</td>
<td>&lt;1.08 mg/mL for 0.08% CPC, &lt;1.35 mg/mL for 0.16% CPC and &lt;2.44 mg/mL for 0.24% CPC</td>
<td>Inhibition zone against E. coli</td>
<td>Achieving the suppressed release of antibacterial agents</td>
<td>181</td>
<td>2014</td>
</tr>
<tr>
<td>Hydrogel based on Dxt grafted with poly(2-hydroxyethyl methacrylate)</td>
<td>Synthesized via free radical polymerization technique</td>
<td>Good biocompatibility and drug release in a controlled and sustained way</td>
<td>Ciprofloxacin</td>
<td>30 µg/mL for 0.1% w/v CIP and 51 µg/mL for 0.2% w/v CIP</td>
<td>0.1% w/v or 0.2% w/v 2 mg/mL⁻¹</td>
<td>Inhibition zones of S. aureus, E. coli, Klebsiella pneumoniae</td>
<td>Cost-effective wound dressings and novel antimicrobial formulations</td>
<td>129</td>
<td>2013</td>
</tr>
<tr>
<td>Gelatin/genipin hydrogel</td>
<td>Gelatin/genipin solution firstly absorbed by TCP cements via vacuum treatment, then cross-linked</td>
<td>Gentamicin-doped beta-TCP scaffold reinforced with a gelatin/genipin hydrogel</td>
<td>Gentamicin</td>
<td>–</td>
<td>17% initial release on the first day and 2–4 µg after that</td>
<td>Antimicrobial ability against S. aureus by spread plate method</td>
<td>Promising gentamicin releasing bone scaffolds in treating osteomyelitis</td>
<td>146</td>
<td>2013</td>
</tr>
<tr>
<td>Acacia gum and carbopol hydrogels</td>
<td>Solution casting method</td>
<td>Blood compatibility, antioxidant activity, mucoadhesion, oxygen/water vapor permeability, microbial penetration</td>
<td>Gentamicin</td>
<td>Diffusion coefficients 3.095 × 10⁴ mm²/min</td>
<td>Fickian diffusion mechanism</td>
<td>Inhibition zones against Gram-negative bacteria than Gram-positive</td>
<td>Wound dressings</td>
<td>150</td>
<td>2013</td>
</tr>
<tr>
<td>Hydrogels of Poloxamer 407 and polyacrylic acids (Carbopol 971P and 974P)</td>
<td>Commercial acquired</td>
<td>Comparison of three transdermal microgels</td>
<td>Gentamicin</td>
<td>P90H-based C971P gave the best drug content of 95.66%</td>
<td>Fast antimicrobial activity</td>
<td>P90H-based microgels of P07 had the highest IZD value against E. coli</td>
<td>Transdermal system</td>
<td>152</td>
<td>2013</td>
</tr>
<tr>
<td>Hydrogels based on dextran and poly(L-glutamic acid)</td>
<td>Photo cross-linking</td>
<td>Higher swelling ratio and quicker degradation</td>
<td>Vancomycin</td>
<td>Higher vancomycin loading content</td>
<td>Sustained release up to 72 h</td>
<td>Efficient MRSA inhibition to 7 days</td>
<td>Scaffolds or coatings for local antibacterial drug release in tissue engineering</td>
<td>166</td>
<td>2013</td>
</tr>
<tr>
<td>Hydrogel Type</td>
<td>Preparation Method</td>
<td>Properties</td>
<td>Antibiotics/Compounds</td>
<td>Applications</td>
<td></td>
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<tr>
<td>PVA–alginate hydrogel</td>
<td>Physically cross-linked and freezing–thawing method</td>
<td>No riskiness of chemical reagents and cross-linkers</td>
<td>Sodium ampicillin</td>
<td>38%–45% burst release of ampicillin and no significant distinctions after 6 h of release, Inhibition zones against Streptococcus pyogenes, <em>S. aureus</em>, <em>P. aeruginosa</em> and <em>Proteus vulgaris</em></td>
<td>Wound dressing applications</td>
<td></td>
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</tr>
<tr>
<td>Hydrogel tablets of carbopel and sodium alginate</td>
<td>Direct compression of the tablets</td>
<td>Successful gastroretentative effect, Biodegradable and excellent compatibility, vitamin E-functionalized polycarbonates</td>
<td>Cefditoren and pivoxil</td>
<td>Release of 95.012% at 24th hour</td>
<td>Achieve gastroretentive effect, Prevention and treatment of skin infections</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hydrogel of polycarbonate and PEG triblock copolymers</td>
<td>Incorporating polycarbonates with vitamin E moiety into physically cross-linked network</td>
<td></td>
<td>Fluconazole</td>
<td>Most drug molecules at 2 h</td>
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<tr>
<td>β-cyclodextrin hydrogels</td>
<td>Directly cross-linked hydroxypropyl-cyclodextrin</td>
<td>Superhydrophilic, Thiosemicarbazones</td>
<td>Up to 4,000 µg/g dry hydrogel</td>
<td>A controlled TSC release for at least 2 weeks</td>
<td>Treatment of ocular infections</td>
<td></td>
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<tr>
<td>Poly(N-hydroxyethylacrylamide)/SA hydrogels</td>
<td>Prepared by adding “monomer solution” and MBAA as cross-linker</td>
<td>High surface resistance to protein adsorption, cell adhesion and bacteria attachment</td>
<td>SA</td>
<td>82% SA rapidly released within 15–20 min, reached a limit (98%) after 240 min</td>
<td>Antifouling and antimicrobial properties</td>
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<tr>
<td>Alginate hydrogel sphere</td>
<td>Two-step approach</td>
<td>Improved alkaline and heat resistances</td>
<td>Isothiazolinones</td>
<td>Released MCI/MI in a sustained manner</td>
<td>Easily added antibacterial hydrogel sphere for a wide range of products</td>
<td></td>
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</tr>
<tr>
<td>PVA and PVA-poly(AAm) hydrogel</td>
<td>Solution casting method</td>
<td>Permeable for oxygen and water vapor, blood compatibility</td>
<td>Gentamicin</td>
<td>Non-Fickian and Case II diffusion mechanism</td>
<td>Wound dressings for the slow release of antibiotic drug to the wound</td>
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</tr>
<tr>
<td>Pluronics-α-cyclodextrin supramolecular gels</td>
<td>Cold method</td>
<td>A cyclodextrin concentration acts on the tuning of the rheological features and drug release</td>
<td>Vancomycin</td>
<td>Completely impermeable of microorganism and inhibition zone against microorganisms</td>
<td>Sustained delivery of vancomycin</td>
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</tr>
<tr>
<td>CS hydrogel</td>
<td>Conventional film method for liposomes</td>
<td>Liposomes-in-hydrogel and prolonged retention time of this delivery system on the skin surface</td>
<td>Mupirocin</td>
<td>Inhibition zones against <em>S. aureus</em></td>
<td>Burn therapy</td>
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<th>References</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alginate hydrogel</td>
<td>By three-dimensional plotting system</td>
<td>Changes in fiber size and porosity altered the performance of the dressings</td>
<td>Tetracycline</td>
<td>–</td>
<td>65%–75% of TCH for the fibrous samples after 6 h and 94%–99% for films after 6 h</td>
<td>Inhibition zone against E. coli</td>
<td>Wound dressings</td>
<td>208</td>
<td>2012</td>
</tr>
<tr>
<td>Hydrogel of carboxymethyl CS</td>
<td>Prepared from CS, cross-linked with glutaraldehyde</td>
<td>Excellent pH-sensitivity</td>
<td>Ornidazole</td>
<td>&gt;74% drug loading</td>
<td>Where 0.5 &lt; n &lt; 1.0 non-Fickian transport and for n approaches 1 zero order, release is approaching zero order</td>
<td>–</td>
<td>Colon-targeted drug delivery</td>
<td>169</td>
<td>2012</td>
</tr>
<tr>
<td>Hydrogels of poly(2-hydroxyethyl methacrylate) or poly(ethylene–glycol dactrylate) or acrylic acid</td>
<td>Electrosynthesized directly on titanium substrates and loaded with ciprofloxacin</td>
<td>In situ sustained release system</td>
<td>Ciprofloxacin</td>
<td>100 µg/mL</td>
<td>0.45 ± 0.05, 1.25 ± 0.02, 3.38 ± 0.16 µg/mL⁻¹ after 48 h</td>
<td>Inhibition zones of MRSA</td>
<td>Prevention of titanium implant-associated infections</td>
<td>128</td>
<td>2011</td>
</tr>
<tr>
<td>Polysaccharide hydrogels</td>
<td>Chemical cross-linking</td>
<td>Superabsorbent</td>
<td>Gentamicin</td>
<td>400,000 U/mL</td>
<td>60%–90% release according to different cross-linking hydrogels after 72 h</td>
<td>Inhibition zones against both S. aureus and E. coli</td>
<td>New ideal wound-dressing materials</td>
<td>151</td>
<td>2011</td>
</tr>
<tr>
<td>Poloxamer hydrogels</td>
<td>Dox by a mechanism involving poloxamer corrosion</td>
<td>Chemically and physically stable formulation and thermal sensitive</td>
<td>DOX</td>
<td>0.1 wt%–0.3 wt%</td>
<td>Release follows a zero-order equation</td>
<td>–</td>
<td>Ophthalmic delivery</td>
<td>198</td>
<td>2011</td>
</tr>
<tr>
<td>Liposomal hydrogels</td>
<td>Reverse-phase evaporation for the preparation of liposomes</td>
<td>Prolonged-release liposomal hydrogel formulation</td>
<td>Ciprofloxacin</td>
<td>0.3% ciprofloxacin aqueous solution</td>
<td>75% release of ciprofloxacin for 10 h</td>
<td>–</td>
<td>Maximum in vitro ocular availability</td>
<td>136</td>
<td>2010</td>
</tr>
<tr>
<td>Hydrogel of PVA and polyaminophenyl boronic acid</td>
<td>Generated by polymerizing aminophenylboronic acid in PVA</td>
<td>Extended swelling</td>
<td>Ciprofloxacin</td>
<td>–</td>
<td>95% was diffused out of the system in 5 h</td>
<td>Inhibition zone against S. aureus, E. coli, K. pneumoniae, Acinetobacter coloaceticus anitratns and Klebsiella sap</td>
<td>Tuning a new dressing for wounds particularly in diabetic patients</td>
<td>141</td>
<td>2010</td>
</tr>
<tr>
<td>Hydrogels of PVA and poly(acrylamide)</td>
<td>Free radical polymerization</td>
<td>Containing laxative psyllium</td>
<td>Ciprofloxacin</td>
<td>–</td>
<td>Rickian diffusion mechanism in pH 2.2 and pH 7.4 buffer non-Fickian diffusion mechanism in distilled water</td>
<td>–</td>
<td>Constipation caused by diverticulitis</td>
<td>142</td>
<td>2010</td>
</tr>
</tbody>
</table>
Hydrogels with inherent antimicrobial activity

Antimicrobial polymers

Hydrogels as antimicrobial biomaterials

Here, hydrogels with inherent antimicrobial activity refer to polymers or hydrogels that exhibit antimicrobial activity by themselves, without the need for external agents such as free radicals or light. The hydrogels can incorporate antimicrobial compounds such as silver sulfadiazine, silver nitrate, and sulfadiazine sodium, or can be modified to release antimicrobial agents such as chlorhexidine digluconate. These hydrogels can exhibit high inhibition zones and MIC values against various bacteria, including Porphyromonas gingivalis, Prevotella intermedia, and Aggregatibacter actinomycetemcomitans.

The multiple mechanisms of these hydrogels provide not only novel antimicrobial materials but also novel delivery and release methods. Hydrogels developed in recent years can be regarded as novel antimicrobial agents without traditional defects. The main types of these hydrogels are as follows:

- **Antimicrobial polymers**: Non-stimulated or potential antimicrobials. Some of the antimicrobial polymers can form hydrogels. For non-stimulated polymers, most commonly there are certain components in the chemical structures which can play a role in antimicrobial activity. These polymers could have great potential for biomedical applications, especially for skin treatment and wound dressings.

- **Novel hydrogels**: Composed of thermostressive PNIPAM and relax-responsive poly(ferrocenylsilane) (PFS) macromolecules exhibited strong antimicrobial activity while maintaining a high biorocompatibility with cells. These hydrogels can also incorporate light-responsive systems to release antimicrobial agents.

- **Active inorganic systems**: These hydrogels incorporate chemical modification or release antimicrobial compounds without traditional defects. The main types of these hydrogels are as follows:


Abbreviations: c-Dxt/PAA, dextrin and poly(acrylic acid); CFX, cefixime; CG, chitosan–gelatin; CHX-dg, chlorhexidine digluconate; CS, chitosan; CS/G/β-Gp, chitosan/gelatin/β-glycerol phosphate; DOX, doxycycline; Dxt, dextrin; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; KPS, potassium persulfate; mPeG, methoxy poly(ethylene glycol); mPeG-PLGA, methoxypoly(ethylene glycol)-co-poly(lactic-co-glycolic acid); mPeG-PLCPHA, methoxy poly(ethylene glycol)-co-poly(lactic acid-co-aromatic anhydride); N-hydroxysuccinimide; O-CMCS, O-carboxymethyl CS; OPF/SMA, oligo(poly(ethylene glycol)fumarate)/sodium methacrylate; PBAe, poly(β-amino ester); PNDJ, poly(N-isopropylacrylamide-co-dimethyl-c-butyrolactone acrylate-co-Jeffamine® M-1000 acrylamide); PEG, poly(ethylene glycol); P (NIPAM-AA-HEM), N-isopropylacrylamide-acrylic acid-hydroxyethyl methacrylate; PMAA, poly(methacrylic acid); PNDJ, poly(N-isopropylacrylamide-co-dimethyl-c-butyrolactone acrylate-co-Jeffamine® M-1000 acrylamide); PEG, poly(ethylene glycol); P (NIPAM-AA-HEM), N-isopropylacrylamide-acrylic acid-hydroxyethyl methacrylate; PMAA, poly(methacrylic acid); PVA, poly(vinyl alcohol); SA, salicylate; TCP, tricalcium phosphate; UV, ultraviolet; GP, glycerophosphate; IZD, inhibition zone diameter.
which can be a turn on–off switch. Although not all the ingredients can be used as antibacterial agents, they provide us with the reference. In further research studies, we may design the antimicrobial hydrogels with some functional structures or ingredients that are able to function with bacteria. As for the other parts, we shall keep them for some other properties, such as anti-inflammation or antifouling.

### Antimicrobial Polypeptides

AMPs are an abundant and diverse group of molecules produced by multicellular organisms as a defense mechanism against competing pathogenic microbes.\(^{234}\) They are recognized as a possible source of panacea for the treatment of antibiotic-resistant bacterial infections,\(^{13,235}\) because AMPs have strong antimicrobial activity against a very broad spectrum of microorganisms, including Gram-positive and Gram-negative bacteria, fungi and virus.\(^ {5,236}\) Although agreement about the specific mechanism of AMPs has not been reached until now, it is known that AMPs work with membranes and finally lead to bacteria killing (Figure 6).\(^ {235}\) However, AMPs have their own disadvantages. They are not stable and easy to degrade. Moreover, antimicrobial properties of natural AMPs are not as good as antibiotics. To overcome all these disadvantages, researchers have designed some recombinant AMPs with short chains, which have improved antibacterial property. The hydrogels can also be good media for AMPs to prevent self-degradation.

At first, relatively simple AMPs were loaded on hydrogels, and then AMPs with certain structures or even self-assembled AMPs were developed. Mitra et al developed dipeptide-based amphiphile hydrogel with good antibacterial activities and greater cell specificities.\(^ {14}\) Peptide-based hairpin hydrogels were reported, respectively, by Salick et al with MAX1 peptides and Veiga et al with arginine-rich peptides; both of them are self-assembly peptides exhibiting potent antibacterial activity.\(^ {237,238}\) A Gram-positive antibacterial activity possessing peptide (KIGAKI)\(_3\)-NH\(_2\) with hairpin and self-assembly structure was incorporated with hydrogels by Liu et al.\(^ {239}\) Highly active AMP CKRWKWIRW-NH\(_2\) was immobilized to the surface of poly(ethylene terephthalate) hydrogel, thus establishing bactericidal activity against *S. aureus* and *S. epidermidis*.\(^ {240}\) Poly-lysine, a popular AMP that has been reported by Zhou et al, was applied in photopolymerized antimicrobial hydrogels, which can be promising coatings for medical devices and implants (Figure 7).\(^ {241,242}\) In the research

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**Figure 6** Mode of action for intracellular antimicrobial peptide activity. In this figure *Escherichia coli* was shown as the target microorganism from Brogden.

studies conducted by Jiang et al., cationic multidomain peptides (MDPs) demonstrated a better antimicrobial activity in hydrogels than in solution. AMP maximin-4-loaded poly (2-hydroxyethyl methacrylate) hydrogels, L-cysteine- and silver nitrate-loaded hydrogels were proved to have qualified antibacterial activity.

Although AMPs still have disadvantages, such as tissue toxicity and hemolysis, they also exhibited a higher antimicrobial biocompatibility index value compared with synthetic drugs with similar structures, and a lot of studies have attempted to improve the biocompatibility. A cell adhesive polypeptide and PEG hydrogel with inherent antibacterial activity was developed by Song et al as a potential scaffold for cutaneous wound healing. Moreover, a protein anchor developed to immobilize functional protein to PEGDA microspheres by Buhrman et al demonstrated a novel method to maintain therapeutic efficacy without toxicity. In the study of Xie et al, in situ forming biodegradable hydrogel (iFBH) system conjugated and functionalized with AMPs offered excellent bacteria inhibition and promoted wound healing without cytotoxicity. Interestingly, nanostructured hydrogels with D-amino acids for peptide self-assembling demonstrated better antimicrobial activity without cytotoxicity. These studies have brought us the possibility of applying the AMPs as antibiotic agents in the hospital. However, there is still a long way to go due to the fact that AMPs are not stable and they degrade easily. Whether AMPs can be kept in the hydrogels for a long time still needs further studies.

Amphoteric ion hydrogels

Amphoteric ion hydrogels work in the similar way to AMPs. They are synthetic mimics (polymers) of AMPs; the feature of the mechanisms includes electrostatic interactions that facilitate binding of polymers with anionic bacterial membrane. The resulting amphiphilic interactions physically destroy the membrane structure, leading to cell death. This is also the mechanism of some types of drugs. However, we concentrate on novel amphoteric hydrogels functioning in the same way. A plethora of antimicrobial synthetic cationic polymers have been reported, including poly(acrylate) and poly(norbornene) systems, poly(arylamide) poly-β-lactams and polycarbonates. Jiang and Cao are the frontrunners in this area and have published several works and reviews on zwitterionic polymers such as poly(carboxybetaine) (pCB) and poly(sulfobetaine) (pSB) in the construction of antimicrobial hydrogels. Mi and Jiang reported a new antimicrobial and non-fouling zwitterionic hydrogel through using the antibacterial salicylate.

Figure 7 Morphological observation of various microorganisms seeded on hydrogels by scanning electron microscope. Left columns (control), right columns (antimicrobial hydrogels).


Abbreviations: C. albicans, Candida albicans; E. coli, Escherichia coli; F. solani, Fusarium solani; P. aeruginosa, Pseudomonas aeruginosa; S. aureus, Staphylococcus aureus; S. marcescens, Serratia marcescens.
anion with the negative charge to initialize its zwitterionic state. Quaternary ammonium group was one of the most famous antimicrobial materials; an in situ antimicrobial and antifouling hydrogel was fabricated from polycarbonate and PEG through Michael addition by Liu et al.266 When combined with hydrogels, amphiphiles work as effectively as AMPs. Polymampholytic hydrogels with high antibacterial activity exhibited water absorbency, making them a good carrier for water-soluble agents.267 Potent antimicrobial hydrogels were formed with anti-inflammatory N-fluorenyl-9-methoxy carbonyl (Fmoc) amino acid/peptide-functionalized cationic amphiphiles and exhibited efficient antibacterial activity against both Gram-positive and Gram-negative bacteria.268 To achieve the bifunctional aim of antibacteria and antifouling, a zwitterionic hydrogel is conjugated with an antimicrobial agent salicylate. This hydrogel can reach one-salicylate-per-monomer drug delivery while still maintaining non-fouling property at protein and bacteria levels.265 For amphiphiles, biocompatibilities may be an obstacle to overcome. Dutta et al269 developed cholesterol-based amino acid containing hydrogels with the aim to improve the biocompatibility of these amphiphilic molecules. In their studies, Ag NPs were synthesized in situ. The amphiphile—Ag NP soft nanocomposite exhibited notable antimicrobial property. Apart from disinfection of normal Gram-positive and Gram-negative bacteria, an antimycobacterial supramolecular hydrogel based on amphiphiles was developed by Bernet et al,270 which retains specific, chain length-dependent antimicrobial and antimycobacterial activity, while showing practically negligible antiproliferative cytotoxic effects. With good antibacterial properties and negligible cytotoxicity, the clinical application of amphoteric ion hydrogel still needs to be developed. These hydrogels may be a promising material to solve the problem of antibiotic resistance.

Antimicrobial polysaccharides
Antimicrobial polysaccharides are usually natural polymer or its derivatives such as starch and CS, which are being recently used for the preparation of hydrogels because of their nontoxicity, biodegradability, biocompatibility and abundance in nature.271,272 Some of these polysaccharides have inherent antimicrobial activity, the most popular one is CS. CS has wide antibacterial spectrum of activity and high killing rate against Gram-positive and Gram-negative bacteria and low toxicity toward mammalian cells.16 As for bacteria, polysaccharide capsule plays a key role in dampening the effects of environment on bacteria. In particular, the capsule protects bacteria from osmotic stress, ensuring the cells maintain viable cytoplasmic turgor.273 CS can be dissolved in weakly acidic solution and release NH$_2^+$, which could bind with negative charge to achieve bacteria stasis.274 As for the polymers composed mainly of CS, semi-interpenetrating CMCh/poly(acrylonitrile) hydrogels were reported to have clearly better antibacterial activity with more CMCh, and hydrogel coating by electrophoretic co-deposition of CS/alkynyl CS exhibited better antibacterial activities than pure CS hydrogel.19,275 In the study by Straccia et al,276 alginate hydrogels coated with CS hydrochloride showed intrinsic antimicrobial activity against E. coli. Quaternary ammonium CS/PVA/polyethylene oxide (PEO) hydrogels were reported to exhibit a pronounced inhibitory effect against S. aureus and E. coli.277 As for the polymers containing CS which is just an antibacterial modification, PNIPAM/polyurethane copolymer hydrogel after CS modification exhibited good antibacterial activity.278 CS-grafted hydrogels containing mica nanocomposite produced a rougher surface while maintaining antibacterial activity.279 The CS hydrogels have already been used clinically as wound dressings due to their good antihemorrhagic properties. The antibacterial ability suggests that the clinical usage of CS hydrogels can be further developed in the future.

Peptide-based hydrogels
Several notable peptide-based antimicrobial hydrogels have also been reported in recent years. Different from hydrogels loaded with AMPs, peptide-based hydrogels refer to those hydrogels that were synthesized with amino acid or peptides as ingredients in their structure. For example, Salick et al237 designed a β-hairpin hydrogel scaffold based on the self-assembling 20-residue peptide for tissue regeneration purposes, whereby the hydrogel itself possessed intrinsic broad-spectrum antibacterial activity. Two years after the development of the β-hairpin hydrogel, the same group reported another injectable β-hairpin hydrogel based on a different 20-residue peptide, which is capable of killing MRSA on contact.240 In the work of Schneider et al,238 the role of arginine in the structure of antibacterial peptide was highlighted which worked as instructions for the following research studies. Moreover, recently, Liu et al239 also designed a Gram-positive antibacterial peptide-containing hydrogel material which can self-assemble in response to external stimuli such as pH, ionic strength and heat. Debnath et al248 reported a class of Fmoc-protected peptide hydrogelators that contained terminal pyridinium moieties, known as possessing antibacterial properties due to their propensity for penetrating cell membranes. All of the peptide hydrogels tested were effective at killing both Gram-positive and Gram-negative bacteria.268
A related AMP hydrogel was designed by Hughes et al. They exploited enzymatic hydrolysis mechanisms inside E. coli cells to trigger an intracellular molecular self-assembly of amphiphilic peptide hydrogelators. Song et al developed all-synthetic polypeptide hydrogels with antibacterial activity by cross-linking poly(Lys)x(Ala)y copolymers with six-armed N-hydroxysuccinimide (NHS)-terminated PEG. Zhou et al modified epsilon-poly-L-lysine (EPL), an AMP produced by Streptomyces albulus, with methacrylamide moieties, and it was then cross-linked with PEGDA to form antibacterial hydrogels. Besides their antibacterial applications, these peptide-based hydrogels have offered inspiration of hydrogel design for us in the future. We can design antimicrobial hydrogels according to the different active structures of antimicrobial drugs. Therefore, the hydrogels would have excellent antimicrobial capacity. The hydrogels with inherent antibacterial activity are in Table 5.

Hydrogels with synergistic effect

Hydrogels with synergistic effect refer to hydrogels containing two or more antimicrobial agents combined to reach more powerful antimicrobial effect. There are two main types of antimicrobial biomaterials that are commonly reported to be incorporated into hydrogels with synergistic effect: metal nanoparticles group and antibiotics group. Those containing both metal nanoparticles and antibiotics are assigned to the antibiotics group because antibiotics feature prominently in clinical practice.

Synergistic effective hydrogels containing metal nanoparticles

Metal nanoparticles in synergistic effective hydrogels were mainly Ag NPs. Ag NPs can be loaded on synthetic amphiphilic or amino acid-based hydrogels, and they can also be loaded with biological extracts. Reithofer et al synthesized size-controlled, stable Ag NPs within ultrashort peptide hydrogels with great potential for applications in wound healing due to their low silver content, sustained Ag NP release and biocompatibility. Novel Ag NP composite systems are more suitable for biomedical applications because of their good biocompatibility with biological molecules, cells, tissues and so on. In situ-synthesized Ag NPs on amphiphilic hydrogels by Dutta et al exhibited improved biocompatibility and antimicrobial efficacy, which has promising applications in biomedicine and tissue engineering. The same laboratory also reported in situ-synthesized Ag NP in self-assemblies of amino acid-based amphiphilic hydrogel in the same year, exhibiting normal growth of mammalian cells on its surface while being lethal toward both Gram-positive and Gram-negative bacteria. Some researchers synthesized antimicrobial Ag NPs and impregnated them into antifouling zwitterionic hydrogels, thus getting mussel-inspired, antifouling, antibacterial hydrogels with great potential in wound healing applications (Figure 8). Both bactericidal hydrogels based on L-cysteine and silver nitrate and Ag(I)-glutathione hydrogel which exhibited improved cytocompatibility were reported in 2011, offering more possibilities on potential application in biomedical field such as burn wound dressings. For other combinations, Ag NP–curcumin composite hydrogels demonstrated that incorporation of curcumin into these hydrogel nanocomposites would further enhance their antibacterial efficacy. The entrapped Ag NPs and curcumin molecules proved sustained release, which could be exerted in enormous prolonged therapeutic values. Anjum et al reported a composite hydrogel for wound dressing containing nanosilver along with aloe vera and curcumin. It showed better antimicrobial nature, wound healing and infection control compared with the control group. Synergistic effective hydrogels containing metal nanoparticles show great antibacterial ability and large antibacterial spectrum. According to distinct antimicrobial pathways, it is impossible to develop antimicrobial resistance. These materials are promising for hospital application in the future.

Synergetic effective hydrogels containing antibiotics

Hydrogels containing antibiotics exhibit more potent antimicrobial properties and biocompatibility when combined with other antimicrobial materials. As for traditional gentamicin, a novel controlled release zinc oxide/gentamicin–CS composite gel with potential application in wounds care was reported. ZnO, gentamicin and CS are all antimicrobial agents, but the composite gel can significantly improve minimal inhibition concentrations (MICs) of Gram-positive and Gram-negative bacteria compared with only gentamicin (Figure 9). Bacterial cellulose polymers functionalized by RGDC (R: arginine; G: glycine; D: aspartic acid; C: cysteine)-grafting groups and gentamicin offer a creative method for novel antimicrobial composite though it was not hydrogel. To cure keratitis, and disinfectant, Paradozo et al added levofloxacin and chlorhexidine to vitamin E-loaded silicone hydrogel contact lenses and found that drug loaded in the lenses can be controlled to achieve a daily release in vivo. Ciprofloxacin is one of the most effective antibiotics used clinically, and it has become the gold standard for various topical applications such as skin and eye infections. It was reported to be able to be combined with different materials...
<table>
<thead>
<tr>
<th>Species of hydrogels</th>
<th>Synthesis of hydrogels</th>
<th>Highlights of hydrogels</th>
<th>Antimicrobial mechanism or agents</th>
<th>Antimicrobial capability</th>
<th>Applications</th>
<th>References</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(2-hydroxyethyl methacrylate/itaconic acid) hydrogels</td>
<td>Prepared by γ-irradiation</td>
<td>pH and temperature sensitive</td>
<td>A good barrier against the microbes</td>
<td>Microbe penetration test: neither Staphylococcus aureus nor Escherichia coli passed through the hydrogel dressing</td>
<td>Great potential for biomedical applications, especially for skin treatment and wound dressings</td>
<td>230</td>
<td>2010</td>
</tr>
<tr>
<td>Hydrogels of PEGDA and containing ammonium salt (RNH3Cl)</td>
<td>Photopolymerization</td>
<td>Extremely high water uptake and permeability</td>
<td>Containing quaternary ammonium moieties</td>
<td>Excellent anti-fouling efficiency in cross-flow filtration test and antibacterial activity against E. coli</td>
<td>Coatings for water purification membrane</td>
<td>231</td>
<td>2011</td>
</tr>
<tr>
<td>Anionic hydrogel copolymers</td>
<td>Binding a cationic porphyrin through electrostatic interactions as a thin surface layer</td>
<td>Photodynamic</td>
<td>Anionic</td>
<td>Staphylococcus epidermidis adherence reduced by up to 99.02% ± 0.42%</td>
<td>Prevention of intraocular lens-associated infectious endophthalmitis</td>
<td>232</td>
<td>2009</td>
</tr>
<tr>
<td>Hydrogels of self-assembling β-hairpin peptides</td>
<td>Designed to self-assemble into a mechanically rigid antibacterial hydrogel</td>
<td>Arginine content largely influences the antibacterial activity</td>
<td>Arginine-rich self-assembling peptides</td>
<td>Extremely effective to Gram-positive, Gram-negative bacteria and multi-drug resistant Pseudomonas aeruginosa</td>
<td>Directly treat accessible wounds to prevent or kill existing infection</td>
<td>238</td>
<td>2012</td>
</tr>
<tr>
<td>A novel designed peptide for hydrogels</td>
<td>Electrostatic repulsion and hydrophobic attraction determines the molecular state</td>
<td>Stimuli-responsive self-assembling</td>
<td>Peptide sequences (KIGAKI)3-NH2</td>
<td>Antibacterial assay against E. coli</td>
<td>Applications in drug delivery, tissue engineering and regenerative medicine</td>
<td>239</td>
<td>2013</td>
</tr>
<tr>
<td>Poly(2-hydroxyethyl methacrylate) hydrogels</td>
<td>Matrix loaded and immersion loaded</td>
<td>Antiadherent properties</td>
<td>Ultrasht short peptide H-Orn-Orn-Trp-Trp-NH2 and lipopeptide C12-Orn-Orn-Trp-Trp-NH2</td>
<td>Antibacterial activity against S. epidermidis</td>
<td>Serve as an important weapon against biomaterial associated infections</td>
<td>244</td>
<td>2012</td>
</tr>
<tr>
<td>Polypeptide and poly(ethylene glycol) hydrogel</td>
<td>Metal-free ring-opening polymerization</td>
<td>Cell-adhesive</td>
<td>Poly(Lys)x(Ala)y</td>
<td>Significant antibacterial activity against E. coli and S. aureus</td>
<td>A potential scaffold for cutaneous wound healing</td>
<td>250</td>
<td>2012</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>Description</td>
<td>Method</td>
<td>Result</td>
<td>Year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
<td>--------</td>
<td>--------</td>
<td>------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(ethylene glycol) diacrylate hydrogel</td>
<td>GST to anchor melittin to the surface of hydrogel microspheres</td>
<td></td>
<td>The anchored protein is enzymatically released</td>
<td>Novo</td>
<td>2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycarbonate and poly(ethylene glycol) hydrogels</td>
<td>Antimicrobial polycarbonate chemically incorporated into PEG hydrogel networks via Michael addition chemistry</td>
<td></td>
<td>Polycarbonate</td>
<td>&gt;99.9% killing efficiency against multidrug-resistant Gram-positive, Gram-negative bacteria and fungi</td>
<td>2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyampholytic hydrogels</td>
<td>Synthesized by inverse suspension polymerization</td>
<td>Can be separated by filtration after contacting with bacterial suspensions</td>
<td>Polyampholytic</td>
<td>Antibacterial activity against E. coli and Staphylococcus hyicus</td>
<td>2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogelators of Fmoc amino acid/peptide-functionalized cationic amphiphiles Zwitterionic hydrogel</td>
<td>Incorporation of a pyridinium moiety and self-assembly of functionalized amphiphiles Conjugated with an antimicrobial agent as a leaving group</td>
<td>Cell membrane penetration Switchable polymer and one-salicylate-per-monomer drug loading</td>
<td>Salicylate anion</td>
<td>Inhibition of growth against S. epidermidis</td>
<td>2010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol-based hydrogels</td>
<td>Synthesized in situ within the hydrogels using sunlight</td>
<td>Better water gelation efficiency</td>
<td>Amphiphile Ag NPs soft nanocomposite</td>
<td>Notable bactericidal property against both Gram-positive and Gram-negative bacteria</td>
<td>2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supramolecular hydrogels</td>
<td>Synthetically modify antimycobacterial 4-alkoxyanilines by amidation with diglycolic acid anhydride yielding amphiphilic hydrogelators</td>
<td>Thermoreversible</td>
<td>Antimycobacterial amphiphiles</td>
<td>Mycobacterium leprae Mycobacterium bovis and Mycobacterium tuberculosis</td>
<td>2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boron/starch/polyvinyl alcohol hydrogels</td>
<td>Synthesized using glutaraldehyde as a cross-linking agent</td>
<td>Moderate antibacterial activity and antifungal activity</td>
<td>Boron complexes</td>
<td>Antibacterial activity against five different bacterial cultures and one fungus proved by disk diffusion susceptibility tests</td>
<td>2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogel coating of chitosan/alkynyl chitosan</td>
<td>Electrophoretic co-deposition</td>
<td>Alkynyl chitosan derived from chitosan</td>
<td>Chitosan/alkynyl chitosan</td>
<td>MIC against E. coli and S. aureus were tested</td>
<td>2013</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5 (Continued)

<table>
<thead>
<tr>
<th>Species of hydrogels</th>
<th>Synthesis of hydrogels</th>
<th>Applications</th>
<th>Antimicrobial capability</th>
<th>Highlights of hydrogels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(N-isopropylacrylamide)/polyurethane copolymer hydrogel</td>
<td>Synthesized by using ammonium persulfate as initiator and N,N,N,N-tetramethyl-ethane-1,2-diamine as accelerator</td>
<td>Smart non-woven fabric potentially applicable in medical and cosmetic fields</td>
<td>Temperature sensitive</td>
<td>Chitosan</td>
</tr>
<tr>
<td>Chitosan-grafted mica-containing nanocomposite hydrogels</td>
<td>Radical copolymerization with mica provides a rougher surface</td>
<td>Antiproliferative activity against S. aureus</td>
<td>Chitosan</td>
<td>Chitosan</td>
</tr>
<tr>
<td>Citric acid-functionalized silver nanoparticles</td>
<td>Synthesized by using sodium citrate, glutathione, and silver nitrate.</td>
<td>Citric acid binding to silver nanoparticles increases their stability and antimicrobial activity</td>
<td>Silver nanoparticles</td>
<td>Silver nanoparticles</td>
</tr>
<tr>
<td>Ciprofloxacin loaded into an antimicrobial nanostructured self-assembly tripeptide hydrogel</td>
<td>Synthesized by using metal nanoparticles to amphiphiles.</td>
<td>Graphical representation of MICs obtained after growing S. aureus and P. aeruginosa in the presence of different concentrations of gentamicin and ZnO/gentamicin–chitosan.</td>
<td>Gentamicin</td>
<td>ZnO/gentamicin–chitosan</td>
</tr>
</tbody>
</table>

Notes: On the top is the schematic illustration of the combination of AgNPs and antifouling hydrogel. In the middle, photographs show the changes in color of hydrogels by changing the pH because of reaction that converts the Ag+ into solid AgNPs. The bottom section shows the surface structure and the morphology of hydrogel via scanning electron microscopy. Reprinted with permission from GhavamiNejad A, Park CH, Kim CS. In situ synthesis of antimicrobial silver nanoparticles within antifouling zwitterionic hydrogels by catecholic redox chemistry for wound healing application. Biomacromolecules. 2016;17(3):1213–1223. Copyright (2016), American Chemical Society.

Abbreviations: MICs, minimal inhibition concentrations; S. aureus, Staphylococcus aureus; P. aeruginosa, Pseudomonas aeruginosa.
In their design, drug incorporation in the delivery could lead to prolonged release and novel antimicrobial formulations. Release of ciprofloxacin loaded on PVA-based super paramagnetic nanocomposites can be magnetically mediated, which provides novel approach of release though no hydrogel formation was studied in this article. In vivo studies, dextrin polymer hydrogels impregnated with amikacin and clindamycin were applied in dogs whose tibial plateau leveling osteotomy implants were removed due to suspected surgical site infection, and no signs of inflammation or infection in any dog were found at the 12th week. Quaternized gellan gum-based particles for controlled release of ciprofloxacin demonstrated another potential dermal application. Besides, tetracycline hydrochloride Ag NP composite hydrogels were developed to inhibit bacteria in simulated colon environment. All these synergetic effective composite hydrogels offer possible approaches for minimum of antibiotics dosage. Combination with other antibacterial ingredients can be a good way to solve the antibiotic resistance and side effects. Meanwhile, the antibacterial spectrum is enlarged, indicating that synergetic effective composite hydrogels have great potential clinically. However, synergetic effects occur when two or more drugs work together to form a stronger response than individually, known as 1+1>2 effect. In most of the abovementioned studies, researchers were more likely to describe additive effect. When the different antimicrobial ingredients were put together in hydrogel, the antibacterial spectrum was boarder and the antimicrobial effect became better compared with hydrogels loaded with one agent separately, whereas we could not tell if the overall effect was synergistic. We would like to see whether the two antimicrobial ingredients would exhibit synergetic effect or only additive effect in further study.

Summary and prospect

Recent advances in natural and synthetic hydrogels have either intrinsic antimicrobial properties or act as carriers for antibiotics. Hydrogels as antimicrobial biomaterials can be an alternative and amendable solution other than the traditional antibiotic treatment since too many drug-resistant bacteria were developed due to misuse of antibiotics and other antimicrobial drugs. Controlled and prolonged release, local administration, stimulated switch on--off release, enhanced mechanical strength and improved biocompatibility are important advantages which a broad diversity of hydrogels can bring. Antimicrobial hydrogels can be applied to a broad spectrum such as wound dressings, urinary tract coatings, contact lens, treatment of osteomyelitis, catheter-associated infections, gastrointestinal infections and so on, finally conquer formidable problems in traditional therapy. Novel antimicrobial biomaterials, novel combination of these materials and novel approaches will bring us brand new prospects and promising further in anti-infection treatment.

For treating microbial infections, it is crucial that antimicrobial components can be released from gels to enter immune cells and kill the pathogenic microbes from inside. Hydrogels loaded with antibiotics, metal nanoparticles, antimicrobial polymers and peptides can release the antimicrobial agents in a sustained manner, which is important to treat infections effectively and prevent biofilm formation. Biodegradable antimicrobial polymer-loaded or peptide-loaded gels are more attractive than gels encapsulated with antibiotics or metal nanoparticles because antibiotics easily develop drug resistance, and it is relatively more difficult to mitigate toxicity of metal nanoparticles due to their non-degradability.

Antimicrobial hydrogels could help to solve the present-day challenges of antimicrobial medicine, including antibiotic resistance. The mechanisms are as follows: 1) the antimicrobial hydrogels could be used locally, which would avoid the side effect of systemic application; 2) the hydrogels, as a novel drug delivery system providing sustainable release of antimicrobial drugs, could offer prolonged antimicrobial effect and avoid screening of resistant bacteria; 3) according to the multiple mechanisms of nanoparticles and other antibacterial ingredients, it is difficult for bacteria to develop resistance aiming at only one target; and 4) different ingredients might exhibit synergetic effect. This would bring broader antibacterial spectrum and better antimicrobial effect.

Hydrogels have offered us a new way to fight against antibiotic resistance in clinical application. However, the controlled release of drugs cannot be accurate in the existing hydrogels. Some of the hydrogels degrade too fast to prolong the effect. Moreover, the antibacterial property of hydrogels is usually weak. Most of them cannot be used as antimicrobial materials alone. Some hydrogels would react with drugs they load, thus limiting their practical application. In the future, these problems still call for more research studies to be solved.

As for the antimicrobial spectrum of antimicrobial hydrogels, lots of them were determined by the antimicrobial ingredients they carried. Some of the materials were only tested with specific bacteria. Some of the hydrogels were examined with both Gram-positive (usually S. aureus) and Gram-negative bacteria (E. coli). The result indicated that the antimicrobial properties of the materials was different against various bacteria. Rarely, researchers have reported the entire antimicrobial spectrum of antibacterial hydrogels in their articles. We hope that researchers could carry out more
studies about the antibacterial properties of materials against different bacteria. This will help us to find out if activity against one particular bacterium is limited in scope or that nanomaterial might have broader utility.

For future clinical applications, it is critical to test antimicrobial hydrogels against clinically isolated microbes, especially multidrug-resistant strains and evaluate the in vitro and in vivo biocompatibility of hydrogels and encapsulated cargo. With rational design, synthetic polymer chemistry and comprehensive in vitro and in vivo evaluation, hydrogel systems with broad-spectrum antimicrobial activity against multidrug-resistant microbes, high selectivity and negligible toxicity would find great potential in the prevention and treatment of infections.

Disclosure
The authors report no conflicts of interest in this work.

References


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