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REVIEW

Antimicrobial hydrogels: promising materials for medical application

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Kerong Yang
Qing Han
Bingpeng Chen
Yuhao Zheng
Kesong Zhang
Qiang Li
Jincheng Wang

Department of Orthopedics, The Second Hospital, Jilin University, Changchun, Jilin, People's Republic of China

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

Correspondence: Jincheng Wang
Department of Orthopedics, The Second Hospital, Jilin University, No 218 of Ziqiang Street, Changchun, Jilin 130041 People's Republic of China
Tel +86 431 8879 6747
Fax +86 431 8879 6747
Email jinchengwang@hotmail.com

Qing Han; Bingpeng Chen
Department of Orthopedics, The Second Hospital, Jilin University, No 218 of Ziqiang Street, Changchun, Jilin 130041, People's Republic of China
Email my.hanqing@163.com; 53495365@qq.com

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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.[5] 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.[6] 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.[7] 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.[8] Increasing rates of antibiotic resistance, drug allergies and antibiotic shortages further complicate the choice of antibacterial agents.[9] 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.[10–13] 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.[12,14] Besides, antimicrobial amylolytic polymers, antimicrobial polysaccharides and other antimicrobial components have also been reported, which can be frameworks of biomedical polymers.[15,16] 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.[17] A set of organic, inorganic and hybrid materials can be identified in the NAM family.[18] 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.[19,20] Hydrogels can also be triggered by stimulations such as changes in pH, temperature, enzyme catalysis, ultraviolet gamma irradiation and even inflammation.[21] Hydrogel can be coated on urinary catheters, central venous catheters,[22] contact lenses, joint and dental implants[23,24] and local injection for drug release and wound healing.[25] Moreover, some types of hydrogels also have inherent antimicrobial properties.[26,27] 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.[28] These characteristics have drawn remarkable attention in the pharmaceutical and medical fields especially for antimicrobial application (Figure 1). According

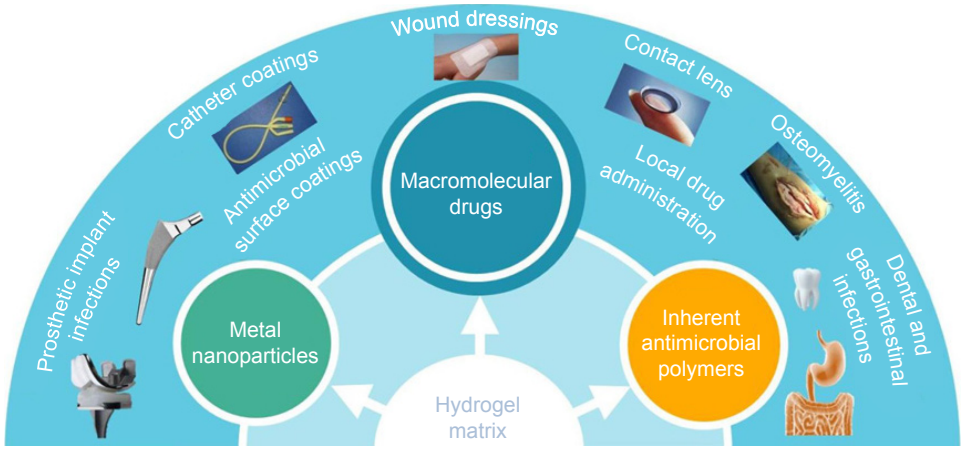

Figure 1 The different applications of hydrogels.

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.[4,29] Silver powder was applied in wound healing and treatment of ulcers, which was first documented in medical history by Hippocrates.[4] Silver still plays an important role in biomedical areas such as wound dressings, textiles, bone implants etc.[30] Thanks to the development of nanoscience and technology, nowadays silver is mainly applied in the form of nanoparticles.[31,32] 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.[33–36] Ag NPs are emerging as efficient antimicrobial agents because of their different mechanisms of sterilization,[32,37,38] 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.[39] 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).[40,41] Other studies show that Ag^+ interact with proteins of the cell wall and plasma membrane of bacteria.[31] 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.[42] If the bacteria have not been killed yet, these contacts allow Ag^+ to move through the cell wall and

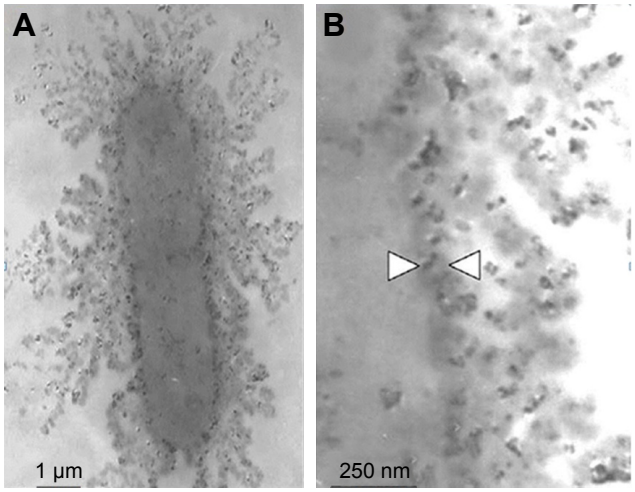

Figure 2 Transmission electron microscope image of *Escherichia coli* cells treated with silver nanoparticles in liquid Luria-Bertani medium: (**A**) membrane of *E. coli*; (**B**) nanoparticles accumulated in the membrane and penetrated the cell (arrows).
Note: Reprinted from *Adv Drug Deliv Rev*. 65(13–14). Pelgrift RY, Friedman AJ, Nanotechnology as a therapeutic tool to combat microbial resistance1803–1815, Copyright (2013), with permission from Elsevier.[31]

the plasma membrane. Finally, Ag^+ functions as an extra antimicrobial agent in the cytoplasm of the bacterial cell.[34] 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.[34,36,42] 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.[40] 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.[31,34]

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^{2+} ionic interaction. Ag NPs were incorporated into alginate microbeads through electrochemical synthesis by Stojkovska et al,[43,44] which showed antibacterial activity against *Staphylococcus aureus* and *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[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[46] also attempted to use alginate/PVA as a hydrogel matrix with sodium borohydride as a reducing agent. Madhusudana Rao et al[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.[48] Neibert et al[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.[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 ($Ag_2Mo_2O_7$/chitin) hydrogel also provide green synthetic process and excellent antibacterial performance against *E. coli*.[51,52] The other polysaccharide hydrogels include iota-carrageenan-based Ag NP hydrogel and Ag NP-loaded PVA/gum acacia (GA) hydrogel,[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 *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,[55,56] both systems work well as antimicrobial hydrogels. Ranga Reddy et al[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.[48,58,59] For example, PAM/PVA hydrogel–Ag NPs fabricated by Varaprasad et al[60] can obtain Ag NPs of 2–3 nm size in gel networks, which exhibit higher antibacterial activity on *E. coli* compared with Ag NPs alone and Ag^+-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 *Bacillus subtilis*.[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.[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.[61,62] Poly(N-isopropylacrylamide) (PNIPAM) is the second commonly used matrix in Ag NP hydrogels. James et al,[63] Manjula et al[64] and Zafar et al[65] used PNIPAM as a main component to synthesize Ag NP hydrogels. James et al[63] synthesized PNIPAM-co-allylamine nanogels and grafted them onto non-woven polypropylene. Hydrogels made by Manjula et al[64] were reduced with neem leaf (*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[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™ (Smith & Nephew, London, UK) and PolyMem Silver® (Ferris Mfg. Corp., Fort Worth, TX, US),[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 al[69] 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 al[72] were reported to be high, uniformly distributed, and stable. Poly(methacrylic acid) (PMAA) hydrogel reduced with borohydride by Bajpai et al[73] and poly(2-hydroxyethyl methacrylate/IA)/Ag NP hydrogels synthesized with gamma irradiation by Micic et al[74] 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 al[75] 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 $AgNO_3$ 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.[77]

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.[78] 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.[79] 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.[80] 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.[81] 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 agents[82] 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.[83] 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

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	Electrochemical synthesis	Uniform hydrogel microbeads	Ag NPs	0.5–3.9 mM/mL	–	10–30 nm	~32 μg/mL *Staphylococcus aureus* (95.8%)	Biocompatible carriers	43	2012
Alginate-based nanocomposite hydrogel	Synthesis by aggregative mechanism and Ostwald ripening, then grown in alginate solutions	Colloid solutions can be stable for 30 days	Ag NPs	0.2–4.5 mM/mL	–	~30 nm	~112 μg/mL *Escherichia coli* 97.5% for 1 h and 99.9% over 24 h	Biomimetic bioreactor	45	2012
Alginate nanocomposite hydrogels	Electrochemical synthesis and rehydration	Composition and mechanical properties of Ag/hydrogel disks based on alginate, PVA and PVP can be adjusted	Ag NPs	0.3–5 mM/mL	35%–53% silver released for 48 h	10–30 nm	~10 μg/mL *S. aureus* (99.8% 24 h) and *E. coli* (over 99.99% 24 h)	Potential wound dressings	44	2014
Alginate/PVA silver nanocomposite hydrogel	Free radical polymerization and green process	Appropriate rate parameter for swelling	Ag NPs	1–15 mM/mL	–	4–10 nm	MBC/MIC ratio of *E. coli* and *S. aureus* both achieved 4	Wound dressings, catalysis and water purification	46	2014
Sodium alginate-based semi-IPN hydrogels	Cross-linked via radical redox polymerization	Well dispersed Ag NPs, cytocompatible and biodegradable hydrogel networks	Ag NPs	1 mM/mL	–	~5 nm	*E. coli* and *S. aureus*. *E. coli* is better than *S. aureus*	Drug delivery applications	47	2013
PAM hydrogels and its mixtures	Facile synthetic strategy of cross-linking	Hydrogels as templates to obtain metal nanostructures of different sizes and morphologies	Ag NPs	–	–	1–10 nm	Clear inhibition in growth of *E. coli* and *Bacillus* on solid agar medium	Desired nanoproduct tailor made for particular applications	48	2010
Hydrogel fibers loaded with Ag NPs	Wet spinning in a $CaCl_2$ precipitation bath and chemical cross-linking	Mechanically robust and biodegradable	Ag NPs	0.383 wt% in 0.05 mM $AgNO_3$ solution and 0.033 wt% in 0.005 mM $AgNO_3$ solution	–	11 nm	–	Wound dressings for improving the overall quality and speed of healing	49	2012
Semi-IPN hydrogel of PVP and PAM	Free radical polymerization	Excellent nanoreactors for producing and stabilizing metal nanoparticles	Ag NPs	3.71 wt%	–	3–5 nm	Significant inhibition of *E. coli* on solid agar medium	Preliminary antibacterial applications	50	2008

Thermosensitive CS/2-glycerophosphate/nanosilver hydrogels	Synthesized in low temperature	Similar antibacterial activity, lower MW CS, lower concentration of Ag NPs and lower cytotoxicity	Ag NPs	DD80 and DD88 CS hydrogels were 3.82 kg/cm^2 (14.8%) and 4.99 kg/cm^2 (19.4%)	–	21.8 nm and 20.22 ppm	Inhibition of *Pseudomonas aeruginosa* and *S. aureus* on solid agar medium	Thermosensitive in situ formed wound dressings	51	2013
Iota-carrageenan-based Ag NP hydrogels	Green process using acrylamide with iota-carrageenan	Biodegradable, reducing $AgNO_3$ with leaf extracts of *Azadirachta indica*	Ag NPs	100.07 mM (5.1 g/300 mL)	Only weight loss of the composite hydrogels	3 ± 2 nm	Inhibition of *Bacillus* and *E. coli* on solid agar medium	Inactivation of bacteria	53	2013
Ag NP-loaded PVA/GA hydrogel	One-pot method by gamma radiation-induced cross-linking	GA improves the biocompatibility and swelling properties of the hydrogel	Ag NPs	1 mM	Increase with content of GA fraction	10–40 nm	Inhibition of *E. coli* on solid agar medium	–	54	2012
CMC-based hydrogels	Prepared using epichlorohydrin in alkaline medium, silver nitrate	Ag NPs prepared using two different processes: in situ process and postloaded technique	Ag NPs	18.99 wt% for in situ process and 9.51 wt% for postloaded method	Only TEM about distribution of Ag NPs using two processes	10–38 nm	Inhibition of *E. coli*, *P. aeruginosa*, *S. aureus* and *Bacillus subtilis* on solid agar medium	Potential candidates for medical field with high antibacterial activity	55	2013
Semi-hydrogel networks of PAM and carbohydrates	An optimized rapid redox solution polymerization	Highly stable and uniformly distributed Ag NPs	Ag NPs	–	–	2–5 nm	Mild inhibition of *E. coli* on solid agar medium	Preliminary antibacterial activity	56	2009
Gelatin-based inorganic nanocomposite hydrogels	Incorporating Ag^+ and treatment with sodium borohydride	Using acrylamide and biodegradable gelatin	Ag NPs	9.38%	–	~15 nm	Inhibition in growth of *Bacillus* on solid agar medium	Useful in medical applications, as antibacterial agents	57	2013
Hydrogels composed of acrylamide, ionic monomer and CS	Ag NPs were synthesized and stabilized using the hydrogel template method	Template nanoreactors	Ag NPs	12.5 μg for spherical nanoparticles, 50–100 μg for rod-shaped particles	–	70 nm	Inhibition zone Bacteria: *Bacillus cereus* *B. subtilis* *S. aureus* *E. coli* Yeast: *Candida albicans* *Candida pseudotropicalis* and the other five fungi	An antimicrobial agent	58	2011
Hydrogels composed of pluronic and PAM	Free radical polymerization with a redox initiator system	Semi-interpenetrating network to produce highly stable and uniformly distributed Ag NPs	Ag NPs	35%	–	5–10 nm	Inhibition of *E. coli* on solid agar medium	–	59	2011

(*Continued*)

Table 1 (*Continued*)

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
PAM/poly(vinyl alcohol) hydrogel	An aqueous redox copolymerization	PVA acts as an highly efficient stabilizer for Ag NPs in the hydrogels	Ag NPs	–	–	2–3 nm	Inhibition of *E. coli* on solid agar medium	Antibacterial and wound dressing applications	60	2010
PAM/itaconic acid–Ag NP hydrogels	Gamma irradiation	Different sizes and morphologies depend on different irradiation doses	Ag NPs	100 μL/mL	–	10–100 nm	Promising activity against *P. aeruginosa* and slightly active against *E. coli*, MRSA and *Klebsiella pneumoniae*	Antibacterial coatings on different material surfaces for various biomedical applications	61	2013
Silver/starch/PAM nanocomposite hydrogels	By grafting/cross-linking reaction	Starch components are capable of arresting the agglomerated Ag NPs	Ag NPs	Changed from 0 to 50 ppm	–	60% 10 nm 40% 13–30 nm	Inhibition zone began from 5 ppm Fungi: *Aspergillus flavus* and *C. albicans* Bacteria: *S. aureus* and *E. coli*	–	62	2014
NIPAM-based nanogels	Free radical polymerization	Thermoresponsive nanogels which have an LCST close to the human body temperature	Ag NPs	–	–	5–100 nm	Inhibition of *Staphylococcus epidermidis* and *E. coli* on solid agar medium	Biomedical applications such as wound dressings	65	2014
PNIPAM-co-allylamine nanogels	Nanogels were synthesized and grafted onto non-woven polypropylene	Thermally responsive	Ag NPs	50 mmol dm^{-3} silver nitrate solution	–	220 ± 10 nm below 34 s and 72 ± 12 nm at 37°C	Bacteria: *S. aureus* and *P. aeruginosa* below the LCST, bacteria grew, above the LCST bacterial growth was prevented or retarded	Utility in designing infection responsive wound dressings	63	2011
Hydrogels composed of gelatin and NIPAM	Green process Ag NPs reduced with neem leaf (*A. indica*) extracts	Gelatin, biodegradable hydrogels	Ag NPs	–	9.83%	5–10 nm	Inhibition of *Bacillus* on solid agar medium	Applications in wound and burn dressings	64	2014

Hydrogels composed of 2-acrylamido-2-methylpropane sulfonic acid sodium salt	Gamma irradiation at 25 kGy to form Ag NP-infused hydrogels	Comparison to two common silver burn wound dressings: Acticoat and PolyMem Silver	Ag NPs	–	5 mM initial concentration	2.1–15.6 nm	Burn wound pathogens (*P. aeruginosa*, MSSA, *Acinetobacter baumannii* and *C. albicans*) and antibiotic-resistant strains (MRSA and VRE) has 94%–99% viability after 24 h exposure	A novel burn wound hydrogel dressing	66	2014
2-Acrylamido-2-methylpropane sulfonic acid sodium salt hydrogels	Ultraviolet radiation	No cytotoxicity	Ag NPs	70%–82% of silver was released within 72 h and 88.0%–94.5% after 10 days of immersion	1, 2.5 and 5 mM	2–16 nm	5 mM silver hydrogel had the greatest inhibitory activity against MRSA and *P. aeruginosa*, *S. aureus*	A potential burn wound dressing	67	2014
Hydrogels prepared from acrylic acid, PEG methyl ether acrylate	In situ polymerization by UV irradiation	A good electrical conductivity	Ag NPs	–	56–139 ppm	233 nm	A perfect antibacterial efficiency against *E. coli*	Promising bioadhesive patch or wound dressing material or electrical massage patch	70	2009
Hydrogel composed of multiblock PEG-POSS polyurethanes	A one-step method synthesized and electrospun into nanofibrous webs	Thermoplastic and unusual shrinkage during water uptake	Ag NPs	–	1.0 wt% $AgNO_3$	Nanofiber (diameter ~150 nm)	No *E. coli* cells on the surface of electrospun nanofibrous mat for 10 days incubation	Wound dressings	71	2009
Hydrogels of PVA/PVP	Gamma irradiation	Highly stable and uniformly distributed	Ag NPs	–	0.01 g of polymer powder contain 12 mmol $AgNO_3$	Mean size 23 nm by TEM	–	A good candidate as wound dressing	72	2012
PMAA hydrogel	Novel approach involving equilibration of PMAAc hydrogels and reduction with borohydride	In situ formation of Ag NPs	Ag NPs	–	50 mg $AgNO_3$ per 50 mL water	Average size is 10–20 nm	Fair antibacterial action against *E. coli*	Wound dressing	73	2013

(*Continued*)

Table 1 (*Continued*)

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
Poly(2-hydroxyethyl methacrylate/itaconic acid) nanocomposite hydrogels	In situ reduction of silver nitrate and gamma radiolysis method	IA used as a carrier and a stabilizing agent	Ag NPs	–	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)	<30 nm	Inhibition of *S. aureus*, *E. coli* and *C. albicans* was proved by measuring the colony-forming unit	Wound dressing	74	2013
P(MMA-co-MAA)/silver nanocomposite hydrogels	Free radical cross-linking polymerization and follow-up reduction of silver nitrate	pH-responsive	Ag NPs	–	13.7 wt%	–	Significant antibacterial properties against both *S. aureus* and *B. subtilis* by inhibition zone	A potentially smart material in the range of applications of antibacterial activity	75	2014
Hydrogel synthesized with PEG containing reactive catechol moieties	Utilizing silver nitrate to oxidize polymer catechols, leading to covalent cross-linking and hydrogel formation with simultaneous reduction of Ag(I)	No significantly affecting mammalian cell viability	Ag NPs	Sustained for at least 2 weeks in PBS solution with total amount 1 μg	100 μg in one hydrogel disk	~50 nm	Inhibition zones of *S. epidermidis* and *P. aeruginosa*	Antibacterial biomaterial coatings and tissue adhesives	78	2012
An agar hydrogel model with Ag NPs immobilized	Produced ligand-free Ag NPs laser ablation in water	A significant reduction of antibacterial activity in the presence of BSA	Ag NPs	–	Ag NP concentrations is 0.5–7.1 wt%	10–60 nm	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*	The presence of a major blood serum protein significantly decreases the antimicrobial effects of Ag NPs	80	2012
TMV as a biomediator	TMV as a biomediator	Simple, robust and size-tunable synthesis of Ag NPs with TMV as a biomediator under mild aqueous conditions	Ag NPs	–	1, 5, 10 and 20 mM initial concentration	Average diameter of 2, 4 and 9 nm	MIC of 2.3 and 2.5 ppm for 2 and 9 nm Ag NPs, respectively, against *E. coli*	Improved functionalities such as high catalytic and antibacterial activity	82	2014

CS hydrogel beads	Physically cross-linked in sodium tripolyphosphate as the cross-linker	CS chains easily bind to the Ag^+ cations. Not requiring heat or any other tools for nanoparticle in situ synthesis	Ag NPs	1 g of CS and desired amount of $AgNO_3$ (0.5, 1.0 and 1.5 mmol)	In vitro drug release was performed in pH 7.4 PBS for 24 h	–	They showed antibacterial activity toward *S. aureus* and *E. coli* for >1 week	Potential drug delivery carrier	296	2015
FA cross-linked CMC hydrogel	NaCMC was dissolved in distilled water. FA was added to solution and stirred until FA was dissolved	Silver ions were dispersed in hydrogel coating on cotton fabric which can sustain antimicrobial ability after being washed	Ag NPs	5×10^{-4}, 1×10^{-3} and 2×10^{-3} mol/L	–	–	Showed 99.999% reduction for *S. aureus* and *K. pneumonia*	A green method which can apply to cotton fabric	68	2015
Cross-linking copolymers of acrylic acid (acrylic acid, methyl acrylate and a silicone nish)	The wet spray-coated fibers were exposed to UV irradiation	Silver antibacterial coating was deposited for the first time on hydrogel fibers through an in situ photochemical reaction	Ag NPs	4 g of Ag solution per each gram of hydrogel fibers	After 168 h (7 days), silver release calculated per gram was 6 ppm (g/mL)	100–600 nm<100 nm	They exhibited an excellent capability in inhibiting the growth of *S. aureus* and *E. coli*	A novel silver antibacterial coating hydrogel fibers	69	2015
QPVA hydrogel	Freeze–thaw method	The effect of QAS-grafted PVA hydrogel on selected microbes and its synergetic effect in combination with Ag NPs	Ag NPs	Solubilizing 10 g QPVA in 100 mL Ag NPs solution (7.8 μg/mL)	Major release mechanism of Ag NPs release follows Fickian diffusion	1.3–1.9 nm	They showed promising antimicrobial property after 96 h against *E. coli*, *S. aureus* and *P. aeruginosa*	A promising antimicrobial dressing	76	2016
RGO-based composite hydrogel	In situ reduction of GO using vitamin C in the presence of heat (90°C)	The facile preparation and dye degradation capacity of RGO/PEI/Ag hydrogels	Ag NPs	50 μL of aqueous solution of CH_3COOAg (8 mg/mL) added to 1.2 mL mixture	The amount of released silver ions was 4.696×10^{-5} and 2.348×10^{-4} g/L/g after 20 days	60–70 nm	–	Highly efficient catalyst for wastewater treatment	79	2015

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, poly(ethylene glycol); PMAA, Poly(methacrylic acid); PNIPAM, 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+).[86] Though N-isopropylacrylamide-based hydrogels containing Au NPs and pH-responsive PMAA hydrogel microcapsules carrying Au NPs had already been reported,[87,88] their antimicrobial property had not been studied until Gao et al[89] 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,[90] 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.[90] Moreover, Jayaramudu et al[91] 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.[91] Through combination of bimetallic (Ag, Au) hydrogel nanocomposites, Ranga Reddy et al[92] took it one step further to enhance their antimicrobial activity. Varaprasad et al[93] even prepared dual-metallic (Ag^0–Au^0) 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,[94,95] but only a few are embedded into hydrogels. Among these, zinc is the most popular antimicrobial agent.[96,97] ZnO NPs are used in many cosmetic materials because of their well-known antibacterial activity and non-cytotoxicity at an appropriate concentration.[98] ZnO NPs combat microbes through multiple mechanisms. Resistance to ZnO NPs is rarely reported.[31] 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[31,33,95] 2) ZnO NPs also cause the formation of Zn^{2+} ions and ROS, including hydrogen peroxide (H_2O_2), which damage the bacterial cell.[33,35]

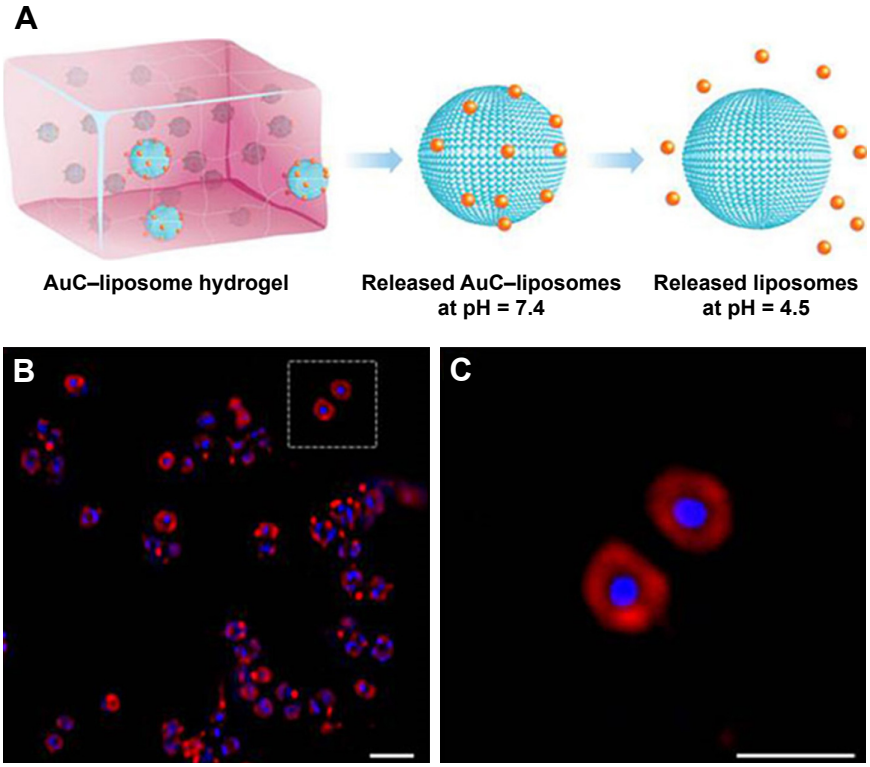

Figure 3 Gao et al synthesized hydrogel containing Au NP-stabilized liposomes for antimicrobial application (**A**) illustrations of hydrogel containing nanoparticle-stabilized liposomes for topical antimicrobial delivery; (**B**) bacteria incubated with AuC–liposome hydrogel (PEGDMA 0.8 vol%) at pH = 4.5; (**C**) a zoomed-in image of (**B**).
Note: The scale bars in (**B** and **C**) represent 1 μm. Reproduced from Gao W, Vecchio D, Li J, et al. Hydrogel containing nanoparticle-stabilized liposomes for topical antimicrobial delivery. *ACS Nano*. 2014;8(3):2900–2907.[89]

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 al[102] 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.[98,99,106] 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.[31] 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 microbicidal 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_2 NPs) and magnesium oxide-containing nanoparticles (MgO NPs), also combat microbes through multiple mechanisms.[117–119] Hezaveh and Muhamad[120] 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

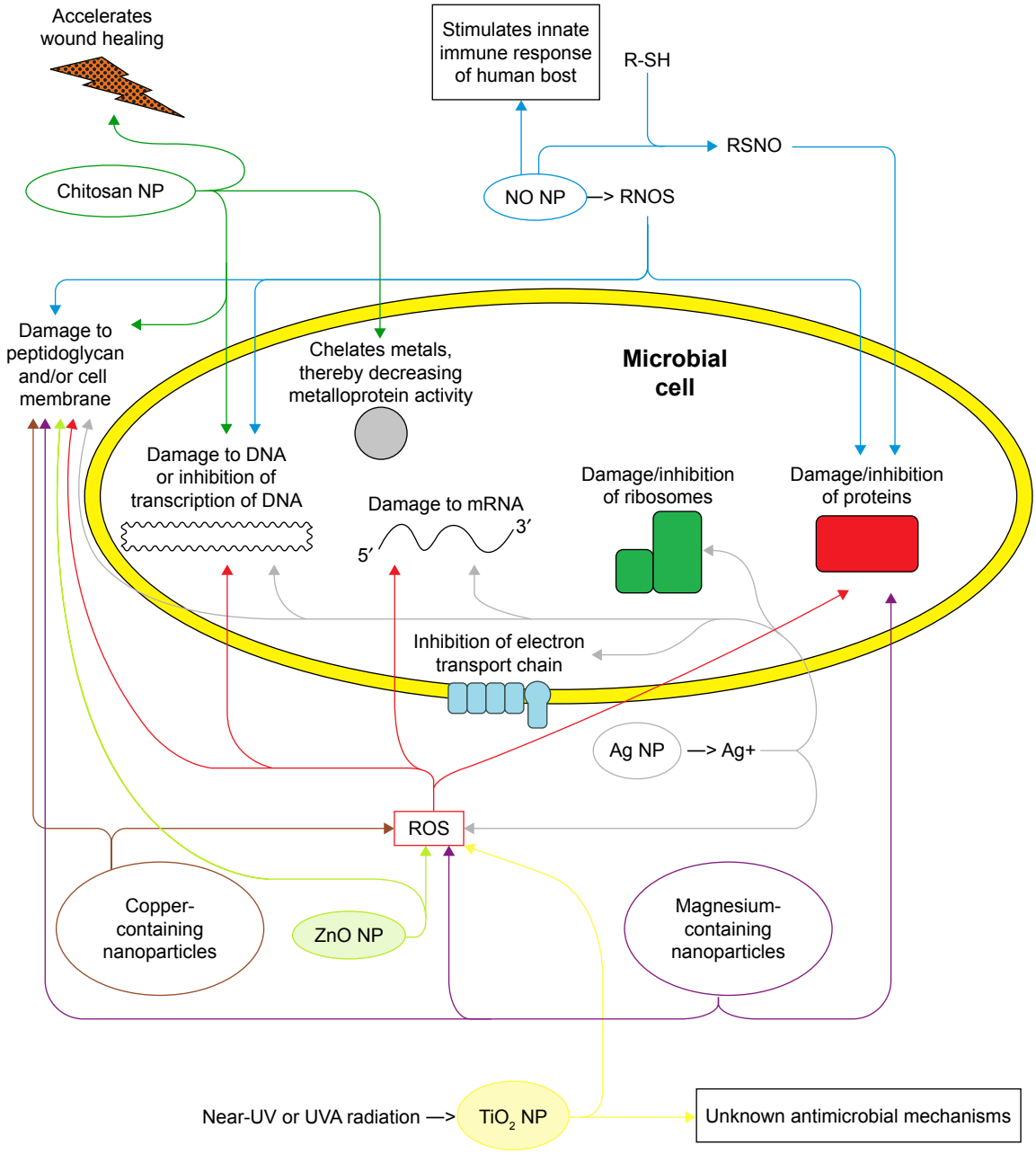

Figure 4 Multiple mechanisms of antimicrobial action of Ag NPs, ZnO NPs, copper-containing nanoparticles and Mg NPs are separately exhibited.
Note: Reprinted from *Adv Colloid Interface Sci.* 166(1–2). Dallas P, Sharma VK, Zboril R, Silver polymeric nanocomposites as advanced antimicrobial agents: classification, synthetic paths, applications, and perspectives, 119–135, Copyright 2011, with permission from Elsevier.[37]
Abbreviations: Ag NPs, silver nanoparticles; Mg NPs, magnesium-containing nanoparticles; NP, nanoparticle; ROS, reactive oxygen species; UV, ultraviolet; ZnO NPs, zinc oxide nanoparticles.

commonly used, and the most effective antimicrobial agents until now.[121] 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.[9] 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.[122] It is very effective to Gram-positive bacteria. However, the antibacterial spectrum of teixobactin does not include Gram-negative bacteria.[123] Moreover, the lack of selection of resistance to teixobactin in vitro should be viewed with great caution before large scale of clinical use.[124] 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.[125] The

Table 2 Information of hydrogels with other metal nanoparticles

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	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 Fe^{3+} in solution of CMC and ZnO NPs	pH sensitive, allow controlling and adjusting of the final release properties of the formulation	ZnO NPs	–	–	< 70 nm	–	An oral drug delivery system for the controlled delivery of drugs	104	2016

(*Continued*)

Table 2 (*Continued*)

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
CMCh hydrogel	CMCh solution cross-linked with epichlorohydrin at 80°C	CMCh has several advantages over CS, such as increased water solubility, better biocompatibility, high moisture retention ability, etc	ZnO NPs	0.6 g of dry CMCh hydrogel was immersed in different concentrations of $Zn(NO_3)_2$ solutions (0.005, 0.010, 0.020, 0.030 and 0.050 M) for 24 h	–	190–600 nm	The CMCh/ZnO nanocomposite hydrogel has shown antibacterial activity against Gram-positive and Gram-negative bactericides	Applications in biomedical fields	106	2016
CS hydrogel	CS hydrogel beads were physically cross-linked using sodium tripolyphosphate as the cross-linker	Prolonged and controlled drug releases were observed for ZnO NPs containing CS beads	ZnO NPs	$Zn(NO_3)_2{\cdot}6H_2O$ (0.5, 1.0 and 1.5 mmol) was added to 437.5 mL mixture system	–	10–25 nm	–	Hopeful candidates for the controlled delivery of drugs	105	2016
CMC/ZnO nanocomposite hydrogels	CMC solution cross-linked with epichlorohydrin at 80°C	Novel CMC/ZnO nanocomposite hydrogels were synthesized by in situ oxidation of the Zn^{2+} ions in the CMC hydrogel matrix	ZnO NPs	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	–	30–40 nm	The CMC/ZnO nanocomposite hydrogel has shown antibacterial activity against Gram-positive and Gram-negative bactericides	Applications in biomedical fields	102	2015
Modified κC hydrogel	κC was blended with NaCMC dissolved in distillated water	The release ability of carrageenan hydrogels was increased under pH of gastrointestinal conditions	MgO NPs	0.1, 0.15 and 0.2 g in the 30 mL system with 0.48 g κC and 0.12 g NaCMC	–	< 50 nm	–	A potential strategy to develop controlled drug delivery especially in gastrointestinal tract studies	120	2012
Agarose hydrogels	An agarose gel is loaded with Au salt by immersion for 24 h	Approximate size of the particles increases with increasing Au loading	Au NPs	–	20 mM	0.5–4 nm	–	–	83	2009
Gelatin hydrogels	Genipin cross-linked	Thermoresponsive	Au NPs	–	52, 104 and 156 ppm	10 ± 2 nm	–	Application of these nanocomposites as carriers in remotely controlled light-triggered drug release	84	2013

Hydrogel PMAA capsules	PMAA/PVPON multilayer precursors through cross-linking with EDA	pH-responsive layered hydrogel	Au NPs	–	–	(PMAA) 10 average size of 16 ± 3 nm	–	Potential use for fabrication of hybrid organic-Au NPs for biochemical sensing and delivery applications	88	2009
AuC–liposome hydrogel	Au NPs through sodium borohydride reduction method and liposomes through the standard extrusion method	pH-responsive Au NP-stabilized liposomes and no observable skin toxicity	Au NPs	0.7 and 0.8 vol%, within the first 24 h, only 25% and 17% liposomes were released	Mixing with AuC at a liposome-to-AuC molar ratio of 1:200	AuC liposomes 97.1 ± 1.0 nm, Au NPs 4 nm	Inhibition zone against *S. aureus* on solid agar medium	Hold great promise for topical applications against various microbial infections	89	2014
AM and 2-acrylamido-2-methyl-1-propanesulfonic acid-based hydrogels	Free radical polymerization of AM monomer with the addition of hydrophilic vinyl monomer	Bimetallic (Ag, Au) hydrogel nanocomposites	Au NPs and Ag NPs	–	–	–	Inhibition zone against Bacillus on solid agar medium	Promising antibacterial materials in biomedical field	92	2012
Hydrogels of Carbopol® 980 NF and AM	A green process by the nucleation of silver and gold salts with mint leaf extract to form a hydrogel network	Bimetallic (Ag, Au) hydrogel nanocomposites	Au NPs and Ag NPs	3.41 wt%	–	5 ± 3 nm	Inhibition zone against Bacillus and *E. coli* on solid agar medium	Effective pharmaceutical formulations for wound dressing	93	2014
Hydrogel of acrylic acid Zn(Bipy-(MMOES)2)	Free radical polymerization to give a new cross-linked polymer system	pH responsive	Zn(Bipy-(MMOES)2)	4%–10%	From 3.47 ± 0.43 to 5.78 ± 0.45 ppm/h according to different pH values	–	Inhibition zone against both MSSA 476 and *P. aeruginosa* (PA01) and MIC	–	97	2011
CS hydrogel	Incorporation of ZnO NPs into CS hydrogel	Flexible and microporous	Nano ZnO composite	0.005%–0.01% ZnO NPs	–	70–120 nm	Antibacterial ability exhibited by evaluation of *P. aeruginosa*, *Streptococcus intermedius*, *Staphylococcus hyicus* isolated from the rat wound	Bandages for burn wounds, chronic wounds, and diabetic foot ulcers	98	2012

(*Continued*)

Table 2 (*Continued*)

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
Poly(N-isopropylacrylamide) hydrogel	Spin coating and photocross-linking	Quite a uniform distribution	ZnO NPs	0.58–2.5 mmol cm^{-3} for the thin and 0.63–3.36 mmol cm^{-3} for the thick films	–	23 ± 6 nm	Efficient antimicrobial activity against *E. coli* at very low ZnO loadings	Promising candidates for novel biomedical device coatings	100	2012
Chitin nanogels	Nickel nanoparticles prepared by hydrothermal method	Cytocompatibility	Nickel nanoparticles	800 μg/mL support both cytocompatibility and antibacterial activity	–	120–150 nm	Antibacterial activity against *S. aureus*	Various applications in biomedical field	110	2013
Zeolite/poly(vinyl alcohol) hydrogel	Physically cross-linked by the freezing–thawing method	Natural zeolite powder loaded with cobalt(II) ions	Co-zeolite content	Co-zeolite content higher than 0.48–4.77 wt%	< 0.02 mg after 24 h immersion	–	Co-zeolite content higher than 0.48 wt% has antibacterial activity against *E. coli* by the disk-diffusion method	–	111	2013

Abbreviations: AG, agarose; Ag NPs, silver nanoparticles; AG-N3, 4-azidobenzoic agarose; AG-N3, 4-azidobenzoic agarose; AM, acrylamide; Au NPs, gold nanoparticles; CMC, carboxymethyl cellulose; CMCh, carboxymethyl chitosan; CS, chitosan; CuO/Cu NPs, copper-containing NPs; EDA, ethylenediamine; HA, hydroxyapatite; HT, hydrothermally treated; IPN, interpenetrating polymer network; κC, κ-carrageenan; MgO NPs, magnesium oxide-containing nanoparticles; MRSA, methicillin-resistant *S. aureus*; NaCMC, CMC sodium salt; PMAA, poly(methacrylic acid); SF, silk fibroin; UV, ultraviolet; ZnO NPs, zinc oxide nanoparticles; ZnO-PEGMA, poly(ethylene glycol) methyl ether methacrylate-modified ZnO.

reason is that return on investment has been mostly negligible for antibiotics with US Food and Drug Administration (FDA) certification in the last few decades.[126] There are two main ways to overcome antibiotic resistance, one is manufacture of novel antibiotics, and the other is minimizing the dosage to decrease antibiotic resistance.[127] To achieve the second aim, local antibiotic administration has drawn increasing attention in recent years to improve the treatment effects. Antibiotic-loaded systems can deliver an adequate local bactericidal dose directly to the infected site, without significantly overtaking the systemic toxicity level.[128] 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.[2] 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

Table 3 Antimicrobial mechanism of nanoparticles

Nanoparticles	Antimicrobial mechanisms	References
Ag NPs	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. 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.	34, 36, 39–42
Au NPs	Au NPs can be attached to bacterial membrane, which leads to leakage of bacterial contents or penetration of the outer membrane and peptidoglycan layer, resulting in bacterial death.	85
Au NP-Amp	First, the presence of multiple Amp molecules on the surface of Au NP allows the Au NP-Amp to overwhelm high concentrations of beta-lactamase expressed by these bacteria. Second, Au NP-Amp inhibits the transmembrane pump that catalyzes drug efflux from the bacterial cell.	86
ZnO NPs	1. ZnO NPs bind to bacterial cell membranes and destroy the lipids and proteins on them. 2. ZnO NPs could cause formation of Zn^{2+} 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.	31, 33, 35, 95, 98
CuO/Cu NPs	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. Cu++ ions induce formation of ROS.	112–114
MgO/MgX_2 NPs	1. MgO/MgX_2 NPs inhibit certain enzymes of microbial cells. 2. MgX_2 NPs may induce formation of ROS. 3. MgX_2 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.	117–120

Abbreviations: Ag NPs, silver nanoparticles; Amp, ampicillin; Au NPs, gold nanoparticles; CuO/Cu NPs, copper-containing NPs; MgO NPs, magnesium oxide-containing nanoparticles; MgX_2 NPs, magnesium halogen-containing nanoparticles; PVA, polyvinyl alcohol; ROS, reactive oxygen species; ZnO NPs, zinc oxide nanoparticles.

such as constipation may be treated with hydrogels containing laxative psyllium and ciprofloxacin.[142] Hosny[136] demonstrated that a liposomal hydrogel containing ciprofloxacin improved maximum ocular availability through albino rabbit cornea. In the research of Zhou et al,[143] 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

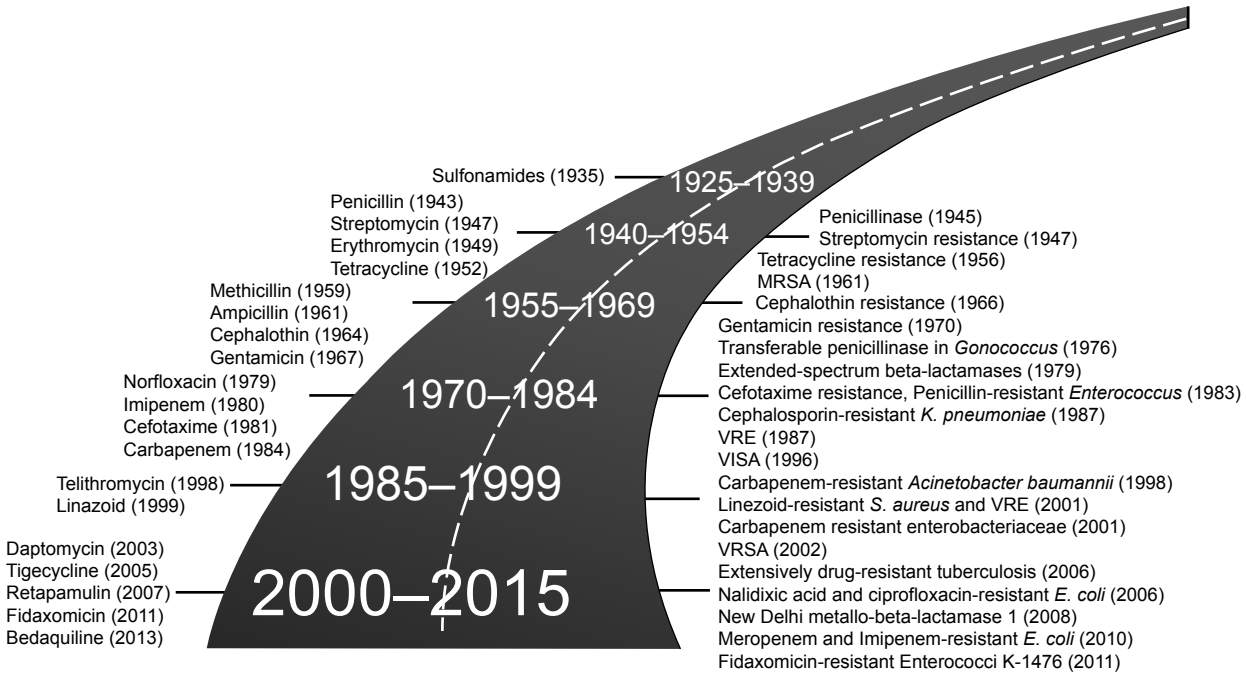

Figure 5 Development of antibiotics and appearance of drug resistance are summarized chronologically referring to Huh and Kwon,[35] Andersson and Hughes,[132] Rodriguez-Rojas et al,[133] van Hoek et al,[134] Molton et al.[135]

Abbreviations: *E. coli*, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*; MRSA, methicillin resistant *S. aureus*; *S. aureus*, *Staphylococcus aureus*; VISA, vancomycin intermedicate resistant *S. auereus*; 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.[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.[146] To avoid the side effects, gentamicin is often used locally nowadays.[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.[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.[151] Phospholipid-modified solid lipid microparticles 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.[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-γ-butyrolactoneacrylate-co-Jeffamine® M-1000 acryl amide) (PNDJ) with delivery in >6 weeks was loaded with gentamicin. This hydrogel might decrease treatment failure for orthopedic infection.[153] Inspiringly, Wu et al[154] found that gentamicin sulfate (GS)-loaded carboxymethyl-chitosan (CMCh) hydrogel cross-linked by genipin was an effective and simple approach to achieve combined antibacterial efficacy and excellent osteoblastic cell responses, which has great potential in orthopedic applications. In open orthopedic surgeries, gentamicin-loaded thermosetting composite hydrogels, which were prepared combining CS with bovine bone substitutes (Orthoss® granules, Orange, CA, USA), beta-glycerophosphate as a cross-linker and lyophilized to obtain moldable composite scaffolds (moldable composite scaffold loaded with gentamicin [mCSG]), were considered to reduce the infection risks.[155] 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 *Staphylococcus*.[156,157] But now even vancomycin-resistant *Enterococcus* (VRE) has been found in different regions.[158–160] As mentioned earlier, hydrogels as a delivery system are able to protect and enhance the validity of vancomycin. Syringeable pluronic-α-cyclodextrin (CD) supramolecular gels,[161] hydrogel of thiolated CS cross-linked with maleic acid-grafted dextrin,[162] thermosensitive hydrogel of CS/gelatin/β-glycerol phosphate,[163] hydrogel of oligo(PEG fumarate)/sodium methacrylate (OPF/SMA) charged copolymers as biocompatible matrices,[164] poly(β-amino ester) (PBAE) hydrogels mixed with PEG (MW = 400) diacrylate (PEGDA) and diethylene glycol diacrylate (DEGDA)[165] and hydrogels achieved by photo cross-linking of methacrylated dextran and poly(L-glutamic acid)-g-hydroxyethyl methacrylate are all studied, and they exhibited excellent antimicrobial properties and desirable release capacity.[166] The most common pathogen of osteomyelitis is *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.[167] Nitroimidazoles can have an effect on anaerobic bacteria and amoeba, so they are often used for the digestive system.[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.[163,169] Das et al[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.[130] Metronidazole (MTZ) containing PMAA nanogel

as an oral dosage form for gastrointestinal infection[171] and tinidazole containing hydrogels based on CS have also been studied.[172] Moreover, floating pH-sensitive CS hydrogels containing MTZ were more effective against *Helicobacter pylori* than the commercially available oral MTZ tablets.[173] CS/gelatin/β-glycerol phosphate hydrogels could maintain sustained release of MTZ in concentrations that are effective for eliminating pathogenic bacteria over time.[163] Chlorhexidine is considered a promising antimicrobial agent and possesses a broad spectrum of activity against bacteria.[174] Chlorhexidine thermosensitive hydrogel[175] and chlorhexidine diacetate containing thermoresponsive hydrogel copolymers exhibit novel application of this traditional sterilization agent.[176] 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.[177] 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.[178] 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.[179] In the study by Sittiwong et al,[180] 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;[181] chloramine-T and sulfadiazine sodium salt-loaded hydrogels composed of PVA, PVP and glycerin showed an excellent swelling capacity;[182] a novel polyvinyl–pyrrolidone–iodine hydrogel in wound therapy was found to be able to enhance epithelialization and reduce loss of skin grafts;[183] poly(N-hydroxyethyl acrylamide)/salicylate hydrogels provide both antimicrobial and antifouling functions;[184] and isothiazolinones delivered in alginate hydrogel sphere achieved long-term antibacterial activity by improvement of the alkali and heat resistances.[185] All these evidence showed that novel applications of synthetic drugs and hydrogels can avoid risks and side effects. The combination of synthetic drugs and hydrogels offers us a an effective clinical antimicrobial method.

Other antibiotics

Besides the aforementioned most commonly used antibiotics, there are many other antibiotics loaded in hydrogels, such as amoxicillin, ampicillin, cephalosporin etc. Each of them has its own antibacterial spectrum and advantages. Amoxicillin trihydrate, a common treatment for peptic or gastric ulcers caused by *H. pylori* infection,[186] loaded in κ-carrageenan hydrogels containing $CaCO_3$ and $NaHCO_3$ 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.[187,188] The similar results of in vivo studies by Moogooee et al[189] 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.[190] Cephalosporin belongs to beta-lactamase, and it is a widely used β-lactamase-resistant and broad spectrum antibiotic.[191] 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*).[192] Cefditoren pivoxil hydrogels with gastroretentive effect were achieved,[193] and cefazolin containing methoxy PEG-co-poly(lactic acid-co-aromatic anhydride) hydrogels offered a stable release without initial burst.[194] Levofloxacin-loaded hyaluronic acid hydrogels were reported to be able to chase bacteria within the cells for both *S. aureus* and *P. aeruginosa* strains.[127] In order to eradicate bacterial biofilm and avoid possible intestinal obstructions, Islan et al[195] 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 (−)-menthol, which is a traditional cooling compound tailed by an amino acid derivate through an alkyl chain, can provide innoxious environment to living cells and deliver lincomycin to the local infection site.[196] O-Carboxymethyl CS (O-CMCS) 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.[197] Doxycycline was also loaded on an in situ thermally sensitive hydroxypropyl-β-CD hydrogel for ophthalmic delivery.[198] 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.[199] 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 *S. aureus* biofilms and non-toxicity against keratinocytes.[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.[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.[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.[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.[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.[206] Hydrogels extracted and assembled from dermis samples containing basement membrane proteins vital to skin regeneration, including laminin β3, collagen IV and collagen VII, were applied as a barrier against bacteria in wound healing.[207] Though according to some research studies alginate does not display antimicrobial properties, it can be an ideal wound dressing due to its morphology, fiber size, porosity, degradation and swelling ratio.[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.[209] CS-based hydrogel film loaded with ethyl acetate Salix alba leaves extract showed no cytotoxicity and excellent antibacterial ability against *Salmonella typhi* and *Candida guilliermondii*.[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.[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.[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.[213,214] A polysaccharide extracted from Aloe vera, Acemannan, has various medical properties, such as antibacterial property, and it can accelerate healing of lesions.[215] Some studies demonstrated its antibacterial activity against both susceptible and resistant *H. pylori* strains.[216] Alginate hydrogels containing Aloe vera were applied in clinical wound care treatment due to their antimicrobial and anti-inflammation capacity.[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.[218,219] Essential oils encapsulated in sodium alginate were reported to be qualified as disposable wound dressings.[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.[221] Besides honey, bee propolis loaded into hydrogels has good antibacterial ability, making it a good wound dressing for skin wound healing.[217] 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.[222] Lysozymes, derived from normal tears with their inherent antibacterial properties, were deposited on hydrogel contact lenses that exhibit marked activity.[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.[224] Lignins and lignin-derived compound model polymer, dehydrogenate polymer (DHP) in alginate hydrogel, have shown strong antimicrobial and wound healing activity.[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 4 Information of hydrogels with antibiotic agents

Species of hydrogels	Synthesis of hydrogels	Highlights of hydrogels	Antimicrobial agents delivered	Content of antimicrobial agents	Rate of release	Antimicrobial capability	Application	References	Year
Amphiphilic mono-mPEG-PLGA copolymers	Ring-opening polymerization of monomers and mPEG in the presence of stannous 2-ethyl hexanoate	Easy preparation, 100% encapsulated rate, near-linear sustained release of drugs, injectable design and in situ gelling at the target tissue	Teicoplanin	840 mg/mL	At day 31, teicoplanin releases 73%, 70% and 60%, respectively (in different groups)	Antimicrobial activity against *Staphylococcus aureus*	A therapeutic strategy for infected diseases, such as osteomyelitis	202	2010
Gentamicin-loaded thermosetting composite hydrogels	Combined CS with bovine bone substitutes (Orthoss® granules), beta-glycerophosphate as cross-linker and lyophilized	Porosity (80%–86%), scaffold water uptake and retention capability	Gentamicin	4 mg in 1 mL thermosetting composite hydrogel starting solution	Release was completed in 4 h	Antimicrobial effect on *Escherichia coli*	Drug delivery for reducing infection risk during bone open surgeries	155	2017
OPF/SMA charged	UV cross-linking	Negatively charged, non-toxic and is able to be cross-linked into several known copolymer formulations	Vancomycin	500 μg/mg	33.7% in the first 6 h <80% in the first 24 h	Antimicrobial activity against MRSA	Appropriate candidates to deliver local antibiotic therapy for prophylaxis of surgical site infection	164	2016
Micrometer-sized β-cyclodextrin-based hydrogel (bCD-Jef-MPs)	Introduced Jeffamine segments in the polymeric network	1) Appropriate stiffness, 2) adaptability to the pocket geometrical structure and 3) ease of application by minimally invasive approach	CHX-dg	–	CHX-dg was released in a time-dependent fashion and by following a quasi-constant rate of 10%/day	–	Effectively treating periodontitis lesions	177	2017
O-CMCS hydrogels	O-CMCS hydrogel was prepared by CS, monochloroacetic acid EDC and NHS	The hydrogels performed good swelling capacities and obvious pH-sensitive properties	Lincomycin	–	–	Significant antibacterial activities against Gram-negative *E. coli* and Gram-positive *S. aureus*	Antibacterial material	197	2016

(*Continued*)

Table 4 (*Continued*)

Species of hydrogels	Synthesis of hydrogels	Highlights of hydrogels	Antimicrobial agents delivered	Content of antimicrobial agents	Rate of release	Antimicrobial capability	Application	References	Year
CS/G/β-Gp hydrogel	Added gelatin molecules to the thermosensitive CS/β-Gp hydrogels to form CS/G/β-Gp hydrogels	The gel strength increased at body temperature over the results from the CS/β-Gp hydrogel	MTZ vancomycin hydrochloride	–	The initial burst and total in vitro drug release for MTZ was 13% and 67%, while vancomycin hydrochloride 3% and 23%	Inhibition of anaerobic Gram-positive *Clostridium sporogenes*	Drug carrier with no cytotoxic effects	163	2016
PBAE hydrogel	Through the free radical polymerization of PBAE macromers using redox initiators	May reduce the potential for bacterial colonization of this biomaterial as antibiotic was found to be released until the hydrogel loses structural integrity	Vancomycin	1.5 wt%	One group finished vancomycin release after 11 days The other 21 days	Against *S. aureus*	An important step in degradative-based drug delivery for local antibiotic treatment	165	2014
Calcium–alginate–gelatin hydrogels with CS/poly-γ-glutamic acid nanoparticles	Dropping aqueous alginate–gelatin into an aqueous solution of calcium chloride	Hydrogels are pH-sensitive, leading to protection of the nanoparticles from destruction by gastric acid	Amoxicillin	–	At pH 6.0, only a very small amount of amoxicillin was released, whereas, at pH 7.0, the amoxicillin was released rapidly	Effective for *Helicobacter pylori*	An efficient carrier for antibiotic drug (amoxicillin) delivery	188	2010
c-Dxt/PAA hydrogel	The c-Dxt/pAA hydrogel was synthesized via free radical polymerization in the presence of KPS initiator	Non-cytotoxic toward human mesenchymal stem cells, degradable in nature	Ornidazole and ciprofloxacin	–	Controlled release behavior remains stable in the tablet formulations for up to 3 months	–	Open a new platform as matrix for controlled release of ornidazole and ciprofloxacin	144	2015
Cross-linked hydrogel derived from Dxt, N-isopropylacrylamide and N,N′-methylene bis(acrylamide) (c-Dxt/pNIPAm)	Dxt as biopolymer, NIPAm as monomer, MBA as cross-linker and KPS as initiator	The pH and temperature responsiveness, non-cytotoxicity, biodegradability and good compatibility between the drugs and the matrix along with the controlled release behavior	Ornidazole and ciprofloxacin	–	Controlled release behavior ~97% ornidazole and ~98% ciprofloxacin remain stable in the tablet formulations for up to 3 months	–	An excellent alternative for controlled release of ornidazole and ciprofloxacin	170	2015

P (NIPAM-AA-HEM) hydrogel	Poly(NIPAM-AA-HEM) was cross-linked by free radical copolymerization of monomers in 1,4-dioxane under N_2 atmosphere with TEGDM (0.1 wt%) as a cross-linking agent	The hydrogel enhanced drug concentration at the topical site than powder amoxicillin, thus reducing the adverse effects	Amoxicillin	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 >45% at 37°C	Effective for *H. pylori*	A novel therapeutic modality for the treatment of *H. pylori*-mediated infections	189	2011
Floating pH-sensitive CS hydrogels	Cross-linking high molecular weight CS in lyophilized solutions containing MTZ using either citrate or tripolyphosphate salts at 1% or 2% concentration	Hydrogel formula was retained in environment of stomach for at least 48 h	MTZ	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 >70% within the 24 h in phosphate buffer (pH 7.4)	More effective against *H. pylori* than the commercially available oral MTZ tablets	A promising site-specific delivery system for the treatment of peptic ulcer caused by *H. pylori*	173	2016
PVA hydrogel	Glutaraldehyde was used as the cross-linking agent for PVA hydrogels	The drug size, matrix pore size, drug–matrix interaction, electrode polarity and an applied electric field were shown to be important controlling factors for drug release	Sulfanilamide	–	Drug release was effected by different factors	–	Drug delivery system	180	2012
CG injectable hydrogels	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	Controlled release of DOX and improved mechanical stability	DOX	–	90% of DOX released from cross-linked CG hydrogels after 4 days	–	Significant potential as a carrier for cell delivery	199	2015

(*Continued*)

Table 4 (*Continued*)

Species of hydrogels	Synthesis of hydrogels	Highlights of hydrogels	Antimicrobial agents delivered	Content of antimicrobial agents	Rate of release	Antimicrobial capability	Application	References	Year
PNDJ	Free radical polymerization in a blend of dioxane/ tetrahydrofuran	Gentamicin is delivered from PNDJ hydrogel with low systemic exposure and decreased treatment failure for orthopedic infection	Gentamicin	1.61% 3.14%	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%	Sustained antimicrobial activity against *S. aureus*	Resorbable viscous hydrogels for local antimicrobial delivery may improve outcomes for one-stage management of implant infections	153	2015
mPEG-PLCPHA thermosensitive hydrogels	mPEG-PLCPHA was synthesized by polymerization of aromatic polyanhydrides, mPEG and polyesters	mPEG-PLCPHA copolymer could form gel at body temperature with excellent biocompatibility and a stable release for 30 days	Cefazolin	20 mg/mL	The steady release of cefazolin lasted up to 4 weeks and no significant burst effect was shown in the release profiles	Sustained antimicrobial activity against *E. coli*	Injectable depot gel for drug delivery	194	2014
PVA	The scaffolds of PVA were fabricated by quenching in liquid nitrogen and freezing–drying and resoaking method from different original concentration aqueous solutions	Excellent release capability of ciprofloxacin, non-cytotoxicity and induction of cell growth	Ciprofloxacin	10 wt% of corresponding PVA weight	86.0%, 76.6% and 54.5% for 10 wt%, 14 wt% and 18 wt% scaffolds, respectively, at 128 h	Completely inhibited the growth of *E. coli*	A good potential application in tissue engineering, demanding high strength and well drug release capability	143	2016
PMAA nanogels	Ethylene glycol dimethacrylate is used as the cross-linker of PMAA nanogels	MTZ/PMAA nanogels sustained the release of MTZ in the simulated gastrointestinal medium and exhibited less cytotoxicity than MTZ alone	MTZ	23.2–69.1 g/mg	$<$12.7% (pH =1.2), 33.3% (pH =6.8) and 58.9% (pH =7.2)	Excellent antibacterial activity against *Bacteroides fragilis*	MTZ/PMAA nanogel would be a more useful dosage form than MTZ for mild-to-moderate *Clostridium difficile* infections	171	2014
Dxt and poly (2-hydroxyethyl methacrylate)-based cross-linked hydrogel (c-Dxt/pHEMA)	c-Dxt/pHEMA was synthesized by free radical polymerization technique,	Non-toxic against HaCaT cells, excellent drug stability and released ciprofloxacin	Ciprofloxacin	1 wt%	Sustainable release of ciprofloxacin (33.75% release after 18 h)	–	A potential candidate for ciprofloxacin carrier	145	2015

	with MBA and KPS as cross-linker and initiator, respectively, in nitrogen atmosphere	hydrochloride in more sustained way than that of other hydrogels							
CS with PEG pH-sensitive hydrogels	CS and PEG cross-linked with tetraethyl orthosilicate as cross-linker	The pH sensitivity and non-cytotoxicity made these hydrogels an appropriate candidate for injectable drug delivery	CFX	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	Hydrogels exhibited antibacterial activity against Gram-negative bacteria *E. coli* and Gram-positive bacteria *S. aureus*	An attractive biomaterial for injectable drug delivery with physiological pH and other biomedical applications	192	2015
Hyaluronic acid nanohydrogels	Self-assembling of the hyaluronic acid-cholesterol amphiphilic chains in aqueous environment	Polysaccharide nanohydrogel	Levofloxacin	5.0% ± 0.5% w/w	–	Mean MIC values of *S. aureus* is 0.104 ± 0.058 mg/L and *Pseudomonas aeruginosa* is 0.557 ± 0.078 mg/L	Promising method for intracellular infection treatment	127	2014
Polysaccharide hydrogel	In situ cross-linking and Michael addition reaction	Closely mimic the nature extracellular matrix glycosaminoglycans	Vancomycin	0.9 mg/mL	6%, 30% and 48% in the initial 48 h	Inhibition against *E. coli* and *S. aureus*	A promising carrier have potential application for wound healing	162	2014
Hydrogelator containing an L-lysine	Synthesized by linking with amino acid or carboxylic acid derivatives	(–)-Menthol-based thixotropic hydrogels	Zn^{2+} or lincomycin	Zn^{2+} 0.01 M lincomycin 0.001 M	–	Oxford cups inhibition zone against *Staphylococcus epidermidis* and *E. coli*	A universal carrier for antibacterial agent	196	2014
CS-based composite hydrogels	Free radical cross-link copolymerization	wt% of CS and MBA and pH of the medium strongly influence the drug release	Tinidazole	15–20 wt%	Close to Korsmeyer–Peppas model	–	Optimum swelling, drug entrapment and drug release profiles at pH 7.5	172	2014
Bacterial nanocellulose hydrogels	Octenidine was incorporated in bacterial nanocellulose with the intension	Biocompatible, stable, releasable and biologically active over a period of 6 months	Octenidine	0.1 mg/mL	Rapid release in the first 8 h, followed by a slower release rate up to 96 h	Freshly prepared and 6 months both act effectively on *S. aureus*	Ready-to-use system for wound treatment	178	2014

(*Continued*)

Table 4 (*Continued*)

Species of hydrogels	Synthesis of hydrogels	Highlights of hydrogels	Antimicrobial agents delivered	Content of antimicrobial agents	Rate of release	Antimicrobial capability	Application	References	Year
PVA hydrogels	Prepared from PVA in a saline solution by γ-irradiation	Easy and inexpensive synthesis, suppressed release	Cetylpyridinium chloride	0.08%–0.24%	<1.08 mg/mL for 0.08% CPC, <1.35 mg/mL for 0.16% CPC and <2.44 mg/mL for 0.24% CPC	Inhibition zone against *E. coli*	Achieving the suppressed release of antibacterial agents	181	2014
Nanostructured hydrogel containing self-assembly of ciprofloxacin and a tripeptide	Modified morphology and rheological properties	Self-assembly of ciprofloxacin and a hydrophobic tripeptide	Ciprofloxacin	30 μg/mL for 0.1% w/v CIP, and 51 μg/mL for 0.2% w/v CIP	0.1% w/v or 0.2% w/v 2 mg/mL^{-1}	Inhibition zones of *S. aureus*, *E. coli*, *Klebsilla pneumoniae*	Cost-effective wound dressings and novel antimicrobial formulations	129	2013
Hydrogel based on Dxt grafted with poly(2-hydroxyethyl methacrylate)	Synthesized via free radical polymerization technique	Good biocompatibility and drug release in a controlled and sustained way	Ornidazole	0.36992–1.8496 × 10^{-6} mol	Ornidazole release follows first-order kinetics and non-Fickian diffusion mechanism	–	Colon-specific delivery of ornidazole	130	2013
Gelatin/genipin hydrogel	Gelatin/genipin solution firstly absorbed by TCP cements via vacuum treatment, then cross-linked	Gentamicin-doped beta-TCP scaffold reinforced with a gelatin/genipin hydrogel	Gentamicin	–	17% initial release on the first day and 2–4 μg after that	Antimicrobial ability against *S. aureus* by spread plate method	Promising gentamicin releasing bone scaffolds in treating osteomyelitis	146	2013
Acacia gum and carbopol hydrogels	Solution casting method	Blood compatibility, antioxidant activity, mucoadhesion, oxygen/water vapor permeability, microbial penetration	Gentamicin	Diffusion coefficients 3.095 × 104 mm^2/min	Fickian diffusion mechanism	Inhibition zones against Gram-negative bacteria than Gram-positive	Wound dressings	150	2013
Hydrogels of Poloxamer 407 and polyacrylic acids (Carbopols 971P and 974P)	Commercial acquired	Comparison of three transdermal microgels	Gentamicin	P90H-based C971P gave the best drug content of 95.66%	Fast antimicrobial activity	P90H-based microgels of P407 had the highest IZD value against *E. coli*	Transdermal system	152	2013
Hydrogels based on dextran and poly(L-glutamic acid)	Photo cross-linking	Higher swelling ratio and quicker degradation	Vancomycin	Higher vancomycin loading content	Sustained release up to 72 h	Efficient MRSA inhibition to 7 days	Scaffolds or coatings for local antibacterial drug release in tissue engineering	166	2013

PVA–alginate hydrogel	Physically cross-linked and freezing–thawing method	No riskiness of chemical reagents and cross-linkers	Sodium ampicillin	0.2–0.8 mg in 50 mL	38%–45% burst release of ampicillin and no significant distinctions after 6 h of release	Inhibition zones against *Streptococcus pyogenes*, *S. aureus*, *P. aeruginosa* and *Proteus vulgaris*	Wound dressing applications	190	2013
Hydrogel tablets of carbopol and sodium alginate	Direct compression of the tablets	Successful gastroretentive effect	Cefditoren and pivoxil	94.25%–97.88%	Release of 95.012% at 24th hour	–	Achieve gastroretentive effect	193	2013
Hydrogel of polycarbonate and PEG triblock copolymers	Incorporating polycarbonates with vitamin E moiety into physically cross-linked network	Biodegradable and excellent compatibility, vitamin E-functionalized polycarbonates	Fluconazole	4 mg/L	Most drug molecules at 2 h	MBC observed in *S. aureus*, *E. coli*, *Candida albicans*	Prevention and treatment of skin infections	224	2013
β-cyclodextrin hydrogels	Directly cross-linked hydroxypropyl-cyclodextrin	Superhydrophilic	Thiosemicarbazones	Up to 4,000 μg/g dry hydrogel	A controlled TSC release for at least 2 weeks	Against *P. aeruginosa* and *S. aureus*	Treatment of ocular infections	179	2013
Poly(N-hydroxyethylacrylamide)/SA hydrogels	Prepared by adding "monomer solution" and MBAA as cross-linker	High surface resistance to protein adsorption, cell adhesion and bacteria attachment	SA	SA was increased from 3.4% to 34% (w/v), the loading efficiency of SA incorporation was 20% and ~80% (w/w)	82% SA rapidly released within 15–20 min, reached a limit (98%) after 240 min	*E. coli* and *S. epidermidis*	Antifouling and antimicrobial properties	184	2013
Alginate hydrogel sphere	Two-step approach	Improved alkali and heat resistances	Isothiazolinones	Drug loading is 12.8 mg/g	Released MCI/MI in a sustained manner	Long-term antibacterial activity	Easily added antibacterial hydrogel sphere for a wide range of products	185	2013
PVA and PVA-poly(AAm) hydrogel	Solution casting method	Permeable for oxygen and water vapor, blood compatibility	Gentamicin	–	Non-Fickian and Case II diffusion mechanism	Completely impermeable of microorganism and inhibition zone against microorganisms	Wound dressings for the slow release of antibiotic drug to the wound	149	2012
Pluronic-α-cyclodextrin supramolecular gels	Cold method	A cyclodextrin concentration acts on the tuning of the rheological features and drug release	Vancomycin	5.5 mg/mL	The higher the cyclodextrin proportion, the slower the release was	Inhibition zones against *S. aureus*	Sustained delivery of vancomycin	161	2012
CS hydrogel	Conventional film method for liposomes	Liposomes-in-hydrogel and prolonged retention time of this delivery system on the skin surface	Mupirocin	10%, w/w	505 μg/mL	*S. aureus* and *Bacillus subtilis*	Burn therapy	200	2012

(*Continued*)

Table 4 (*Continued*)

Species of hydrogels	Synthesis of hydrogels	Highlights of hydrogels	Antimicrobial agents delivered	Content of antimicrobial agents	Rate of release	Antimicrobial capability	Application	References	Year
Alginate hydrogel	By three-dimensional plotting system	Changes in fiber size and porosity altered the performance of the dressings	Tetracycline	–	65%–75% of TCH for the fibrous samples after 6 h and 94%–99% for films after 6 h	Inhibition zone against *E. coli*	Wound dressings	208	2012
Hydrogel of carboxymethyl CS	Prepared from CS, cross-linked with glutaraldehyde	Excellent pH-sensitivity	Ornidazole	>74% drug loading	Where $0.5 < n < 1.0$ non-Fickian transport and for n approaches 1 zero order, release is approaching zero order	–	Colon-targeted drug delivery	169	2012
Hydrogels of poly(2-hydroxyethyl methacrylate) or poly(ethylene–glycol diacrylate) or acrylic acid	Electrosynthesized directly on titanium substrates and loaded with ciprofloxacin	In situ sustained release system	Ciprofloxacin	100 μg/mL	0.45 ± 0.05, 1.25 ± 0.02, 3.38 ± 0.16 μg/mL^{-1} after 48 h	Inhibition zones of MRSA	Prevention of titanium implant-associated infections	128	2011
Polysaccharide hydrogels	Chemical cross-linking	Superabsorbent	Gentamicin	400,000 U/mL	60%–90% release according to different cross-linking hydrogels after 72 h	Inhibition zones against both *S. aureus* and *E. coli*	New ideal wound-dressing materials	151	2011
Poloxamer hydrogels	Dox by a mechanism involving poloxamer corrosion	Chemically and physically stable formulation and thermal sensitive	DOX	0.1 wt%–0.3 wt%	Release follows a zero-order equation	–	Ophthalmic delivery	198	2011
Liposomal hydrogels	Reverse-phase evaporation for the preparation of liposomes	Prolonged-release liposomal hydrogel formulation	Ciprofloxacin	0.3% ciprofloxacin aqueous solution	75% release of ciprofloxacin for 10 h	–	Maximum in vitro ocular availability	136	2010
Hydrogel of PVA and polyaminophenyl boronic acid	Generated by polymerizing aminophenylboronic acid in PVA	Extended swelling	Ciprofloxacin	–	95% was diffused out of the system in 5 h	Inhibition zone against *S. aureus*, *E. coli*, *K. pneumoniae*, *Acinetobacter calcoaceticus anitratus* and *Klebsiella sap*	Tuning a new dressing for wounds particularly in diabetic patients	141	2010
Hydrogels of PVA and poly(acrylamide)	Free radical polymerization	Containing laxative psyllium	Ciprofloxacin	–	Fickian diffusion mechanism in pH 2.2 and pH 7.4 buffer non-Fickian diffusion mechanism in distilled water	–	Constipation caused by diverticulitis	142	2010

CS hydrogel	Free radical polymerization	Thermosensitive and injectable	Chlorhexidine	0.1%	68% release of CSHTCC/GP and 85% release from CS/GP at 18 h	Inhibition zones and MIC of *Porphyromonas gingivalis*, *Prevotella intermedia* and *Aggregatibacter actinomycetemcomitans*	A local drug delivery system for periodontal treatment	175	2010
PVA/PVP/glycerin hydrogels	γ-Irradiation and freezing–thawing	Excellent swelling capacity	Silver sulfadiazine, silver nitrate and sulfadiazine sodium salt	1 wt%	–	Inhibition zone against *E. coli*, *S. aureus* and *S. aeruginosa*	A wound dressing	182	2009

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 polyethylene glycol-co-poly(lactic acid-co-aromatic anhydride); MIC, minimal inhibition concentration; MRSA, methicillin-resistant *S. aureus*; MTZ, metronidazole; NHS, 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); PVA, poly(vinyl alcohol); SA, salicylate; TCP, tricalcium phosphate; UV, ultraviolet; GP, glycerophosphate; IZD, inhibition zone diameter.

we still need to test its properties once we find a new natural extract. We cannot evaluate it's antimicrobial properties and it's safety until we conduct some experiments about it as it is newly found.

Hydrogels with inherent antibacterial activity

Here, hydrogels with inherent antibacterial activity refer to polymers of these hydrogels that exhibit antimicrobial activity by themselves or those whose biocidal activity is conferred through their chemical modification, not including hydrogels that incorporate antimicrobial organic compounds or active inorganic systems.[6,15,226] These hydrogels developed in recent years can be regarded as novel antimicrobial agents without traditional defects.[7] The main types of these hydrogels are as follows.

Antimicrobial polymers

Antimicrobial polymers are 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 be prepared by several routes such as in situ synthesis within a hydrogel to obtain antimicrobial activities.[227] Novel hydrogels composed of thermoresponsive PNIPAM and redox-responsive poly(ferrocenylsilane) (PFS) macromolecules exhibited strong antimicrobial activity while maintaining a high biocompatibility with cells.[228] Jiang et al[229] synthesized the quaternary ammonium salt of gelatin using 2,3-epoxypropyl trimethylammonium chloride (EPTAC) as the antimicrobial polymer ingredient of the hydrogel. pH-sensitive and temperature-sensitive hydrogels based on 2-hydroxyethyl methacrylate (HEMA) and IA copolymers were proved to have great potential for biomedical applications, especially for skin treatment and wound dressings with excellent results of microbe penetration test.[230] Antimicrobial property of an antifouling hydrogel prepared by the photopolymerization of PEGDA and a monomer containing ammonium salt (RNH3Cl) in the presence of a photoinitiator was also demonstrated by a study employing *E. coli*.[231] As for potential antimicrobial polymers, light is one of the most important factors. Photodynamic porphyrin anionic hydrogel copolymers were reported and showed great promise to the prevention of intraocular lens-associated infectious endophthalmitis.[232] Another photodynamic pHEMA-based hydrogels exhibit light-induced bactericidal effect via release of NO.[233] All mechanisms of these antimicrobial polymers provide not only novel antimicrobial materials but also novel delivery and release methods,

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-NH2 with hairpin and self-assembly structure was incorporated with hydrogels by Liu et al.[239] Highly active AMP CKRWWKWIRW-NH2 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

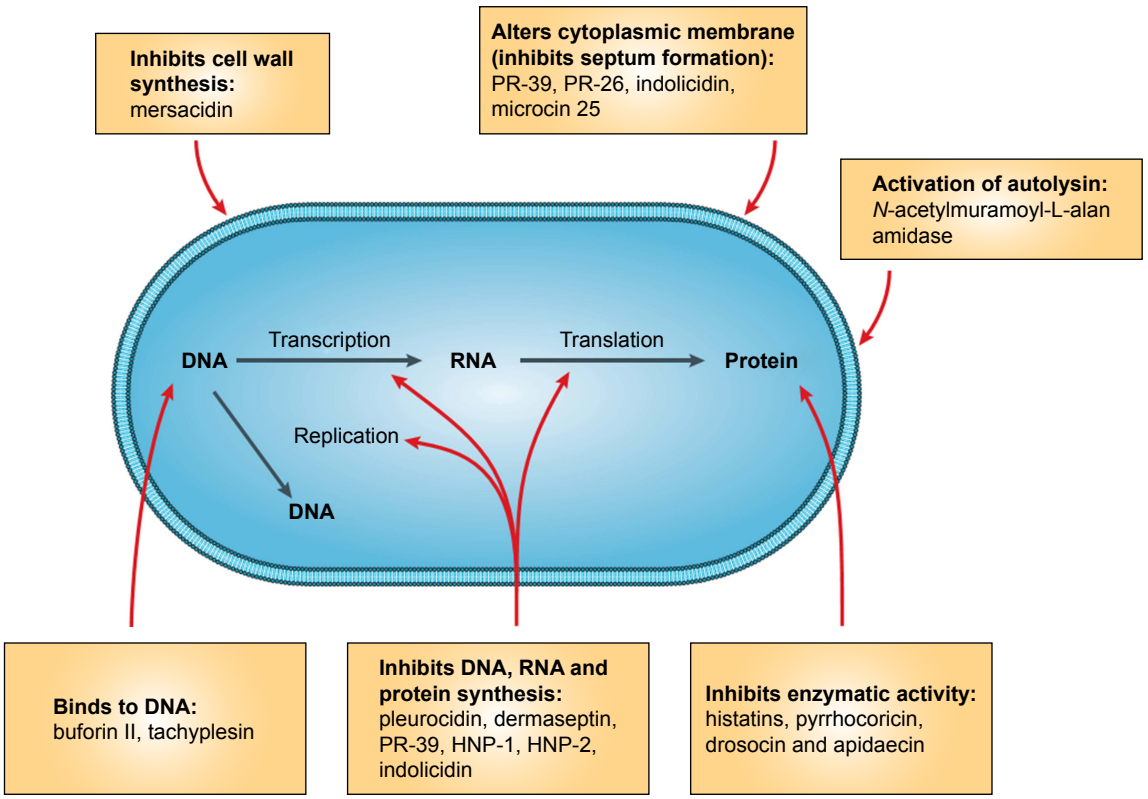

Figure 6 Mode of action for intracellular antimicrobial peptide activity. In this figure *Escherichia coli* was shown as the target microorganism from Brogden.
Note: Reprinted by permission from Springer Nature, *Nat Rev Microbiol*, Brogden KA, Antimicrobial peptides: pore formers or metabolic inhibitors in bacteria? 2005;3(3): 238–250, Copyright 2005.[235]

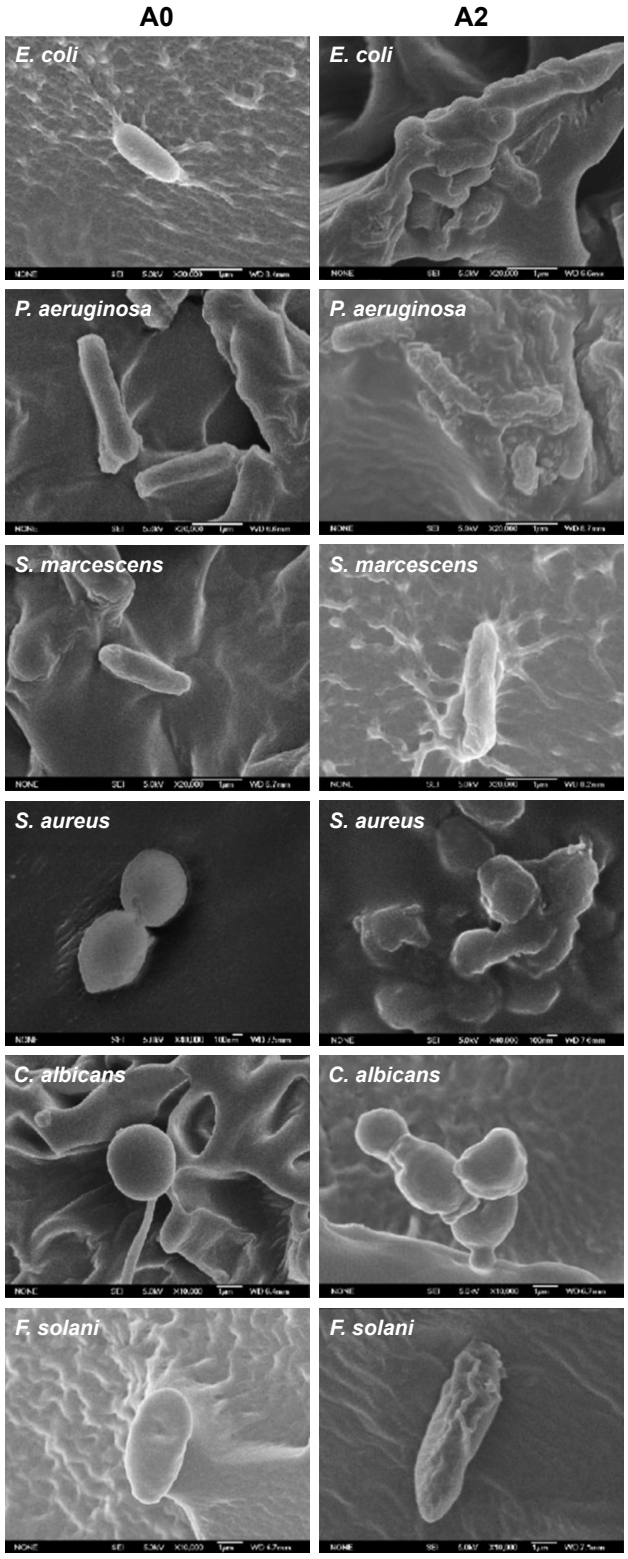

Figure 7 Morphological observation of various microorganisms seeded on hydrogels by scanning electron microscope. Left columns (control), right columns (antimicrobial hydrogels).

Note: Reprinted from *Biomaterials*. 32(11). Zhou C, Li P, Qi X, et al, A photopolymerized antimicrobial hydrogel coating derived from epsilon-poly-l-lysine, 2704–2712, Copyright 2011, with permission from Elsevier.[242]

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*.

studies conducted by Jiang et al,[243] cationic multidomain peptides (MDPs) demonstrated a better antimicrobial activity in hydrogels than in solution. AMP maximin-4-loaded poly (2-hydroxyethyl methacrylate) hydrogels,[244] L-cysteine- and silver nitrate-loaded hydrogels were proved to have qualified antibacterial activity.[245]

Although AMPs still have disadvantages, such as tissue toxicity and hemolysis,[246,247] they also exhibited a higher antimicrobial biocompatibility index value compared with synthetic drugs with similar structures,[248,249] and a lot of studies have attempted to improve the biocompatibility.[234–236] 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.[250] 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.[251] In the study of Xie et al,[252] 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.[253] 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.[254] 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)s poly-β-lactams and polycarbonates.[255–262] Jiang and Cao[263,264] 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[265] reported a new antimicrobial and non-fouling zwitterionic hydrogel through using the antibacterial salicylate

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. Polyampholytic 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-methoxycarbonyl (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 al[269] 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 non-toxicity, 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 al[237] 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.[280] 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 al[239] 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 al[268] 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.[281] They exploited enzymatic hydrolysis mechanisms inside *E. coli* cells to trigger an intracellular molecular self-assembly of amphiphilic peptide hydrogelators.[281] Song et al[250] 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[242] 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.[282] Reithofer et al[283] 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.[284] In situ-synthesized Ag NPs on amphiphilic hydrogels by Dutta et al[285] 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.[286] 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).[287] Both bactericidal hydrogels based on L-cysteine and silver nitrate and Ag(I)–glutathione hydrogel which exhibited improved cytocompatibility were reported in 2011,[245,288] 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.[213] Anjum et al[289] 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.[289] 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).[290] 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.[291] To cure keratitis, Paradiso et al[292] 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 5 Information of hydrogels with inherent antibacterial activity

Species of hydrogels	Synthesis of hydrogels	Highlights of hydrogels	Antimicrobial mechanism or agents	Antimicrobial capability	Applications	References	Year
Poly(2-hydroxyethyl methacrylate/itaconic acid) hydrogels	Prepared by γ-irradiation	pH and temperature sensitive	A good barrier against the microbes	Microbe penetration test: neither *Staphylococcus aureus* nor *Escherichia coli* passed through the hydrogel dressing	Great potential for biomedical applications, especially for skin treatment and wound dressings	230	2010
Hydrogels of PEGDA and containing ammonium salt (RNH3Cl)	Photopolymerization	Extremely high water uptake and permeability	Containing quaternary ammonium moieties	Excellent anti-fouling efficiency in cross-flow filtration test and antibacterial activity against *E. coli*	Coatings for water purification membrane	231	2011
Anionic hydrogel copolymers	Binding a cationic porphyrin through electrostatic interactions as a thin surface layer	Photodynamic	Anionic	*Staphylococcus epidermidis* adherence reduced by up to 99.02% ± 0.42%	Prevention of intraocular lens-associated infectious endophthalmitis	232	2009
Hydrogels of self-assembling β-hairpin peptides	Designed to self-assemble into a mechanically rigid antibacterial hydrogel	Arginine content largely influences the antibacterial activity	Arginine-rich self-assembling peptides	Extremely effective to Gram-positive, Gram-negative bacteria and multi-drug resistant *Pseudomonas aeruginosa*	Directly treat accessible wounds to prevent or kill existing infection	238	2012
A novel designed peptide for hydrogels	Electrostatic repulsion and hydrophobic attraction determines the molecular state	Stimuli-responsive self-assembling	Peptide sequences (KIGAKI)3-NH2	Antibacterial assay against *E. coli*	Applications in drug delivery, tissue engineering and regenerative medicine	239	2013
Hydrogels of epsilon-poly-L-lysine-graft-methacrylamide	Photopolymerization	Conveniently ultraviolet-immobilized onto plasma-treated plastic surfaces	Epsilon-poly-L-lysine	Wide spectrum antimicrobial activity against bacteria (*E. coli*, *P. aeruginosa*, *Serratia marcescens*, *S. aureus*, *Candida albicans*, *Fusarium solani*)	Hydrogel coatings for medical devices and implants	242	2011
Poly(2-hydroxyethyl methacrylate) hydrogels	Matrix loaded and immersion loaded	Antiadherent properties	Ultrashort peptide H-Orn-Orn-Trp-Trp-NH2 and lipopeptide C12-Orn-Orn-Trp-Trp-NH2	Antibacterial activity against *S. epidermidis*	Serve as an important weapon against biomaterial associated infections	244	2012
Polypeptide and poly(ethylene glycol) hydrogel	Metal-free ring-opening polymerization	Cell-adhesive	Poly(Lys)x(Ala)y	Significant antibacterial activity against *E. coli* and *S. aureus*	A potential scaffold for cutaneous wound healing	250	2012

Poly(ethylene glycol) diacrylate hydrogel	GST to anchor melittin to the surface of hydrogel microspheres	The anchored protein is enzymatically released	Bactericidal peptide, melittin	Efficiently inhibits growth of *Streptococcus pyogenes*	Novel way to load therapeutic proteins into a hydrogel-microsphere-based drug delivery system	251	2013
Polycarbonate and poly(ethylene glycol) hydrogels	Antimicrobial polycarbonate chemically incorporated into PEG hydrogel networks via Michael addition chemistry	No significant hemolytic activity or skin toxicity	Polycarbonate	>99.9% killing efficiency against multidrug-resistant Gram-positive, Gram-negative bacteria and fungi	A wide range of biomedical applications including catheter coating and wound dressing to prevent multidrug-resistant infections	266	2012
Polyampholytic hydrogels	Synthesized by inverse suspension polymerization	Can be separated by filtration after contacting with bacterial suspensions	Polyampholytic	Antibacterial activity against *E. coli* and *Staphylococcus hyicus*	–	267	2009
Hydrogelators of Fmoc amino acid/peptide-functionalized cationic amphiphiles	Incorporation of a pyridinium moiety and self-assembly of functionalized amphiphiles	Cell membrane penetration	Fmoc-peptide functionalized cationic amphiphiles	Efficient antibacterial activity against both Gram-positive and Gram-negative bacteria	Immense importance in the materials science	268	2010
Zwitterionic hydrogel	Conjugated with an antimicrobial agent as a leaving group	Switchable polymer and one-salicylate-per-monomer drug loading	Salicylate anion	Inhibition of growth against *S. epidermidis*	Open a door to the design and development of stealth materials and coatings with built-in biological functions	265	2012
Cholesterol-based hydrogelators	Synthesized in situ within the hydrogels using sunlight	Better water gelation efficiency	Amphiphile Ag NPs soft nanocomposite	Notable bactericidal property against both Gram-positive and Gram-negative bacteria	An effective step for designing smart biomaterials in future	269	2013
Supramolecular hydrogels	Synthetically modify antimycobacterial 4-alkoxyanilines by amidation with diglycolic acid anhydride yielding amphiphilic hydrogelators	Thermoreversible	Antimycobacterial amphiphiles	*Mycobacterium leprae Mycobacterium bovis and Mycobacterium tuberculosis*	–	270	2012
Boron/starch/polyvinyl alcohol hydrogels	Synthesized using glutaraldehyde as a cross-linking agent	Moderate antibacterial activity and antifungal activity	Boron complexes	Antibacterial activity against five different bacterial cultures and one fungus proved by disk diffusion susceptibility tests	–	271	2011
Hydrogel coating of chitosan/alkynyl chitosan	Electrophoretic co-deposition	Alkynyl chitosan derived from chitosan	Chitosan/alkynyl chitosan	MIC against *E. coli* and *S. aureus* were tested	Better antibacterial activities than pure chitosan hydrogel	275	2013

(*Continued*)

Table 5 (*Continued*)

Species of hydrogels	Synthesis of hydrogels	Highlights of hydrogels	Antimicrobial mechanism or agents	Antimicrobial capability	Applications	References	Year
Poly(N-isopropylacrylamide)/polyurethane copolymer hydrogel	Synthesized by using ammonium persulfate as initiator and N,N,N′,N′-tetramethyl-ethane-1,2-diamine as accelerator	Temperature sensitive	Chitosan	Antibacterial efficiency against *S. aureus* and *E. coli* is ~80%	Smart non-woven fabric potentially applicable in medical and cosmetics fields	278	2009
Chitosan-grafted mica-containing nanocomposite hydrogels	Radical copolymerization	Mica provides a rougher surface	Chitosan	Antiproliferative activity against *S. aureus*	–	279	2013

Abbreviations: Ag NPs, silver nanoparticles; Fmoc, N-fluorenyl-9-methoxycarbonyl; GST, glutathione S-transferase; PEG, poly(ethylene glycol); PEGDA, polyethylene glycol diacrylate; MIC, minimal inhibition concentration.

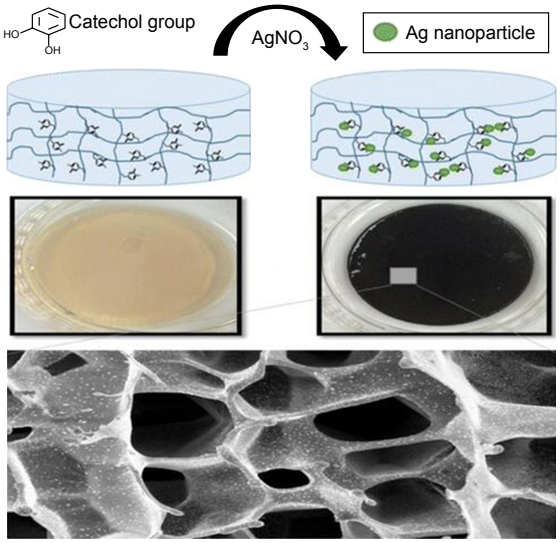

Figure 8 A new strategy that uses catecholic chemistry to synthesize antimicrobial silver nanoparticles impregnated into antifouling zwitterionic hydrogels.
Notes: On the top is the schematic illustration of the combination of AgNPs and antifouling hydrogel. In the middle, Photographs show the changes 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.[287]

from metal nanoparticles to amphiphiles.[137] Ciprofloxacin loaded into an antimicrobial nanostructured self-assembly tripeptide hydrogel was reported by Marchesan et al,[129] which is meaningful to the design of cost-effective nanomaterials.

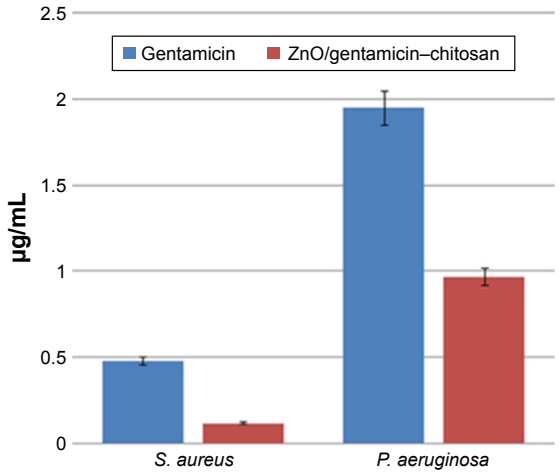

Figure 9 Graphical representation of MICs obtained after growing *S. aureus* and *P. aeruginosa* in the presence of different concentrations of gentamicin and ZnO/gentamicin–chitosan.
Note: Reprinted from *Int J Pharm*. 463(2). Vasile BS, Oprea O, Voicu G, et al, Synthesis and characterization of a novel controlled release zinc oxide/gentamicin-chitosan composite with potential applications in wounds care, 161–169, Copyright 2014, with permission from Elsevier.[290]
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.[129] 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.[140] In 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.[293] Quaternized gellan gum-based particles for controlled release of ciprofloxacin demonstrated another potential dermal application.[294] Besides, tetracycline hydrochloride Ag NP composite hydrogels were developed to inhibit bacteria in simulated colon environment.[295] 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, synergistic 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 synergistic 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 synergistic 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.

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