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# Nanomaterial-enabled anti-biofilm strategies: new opportunities for treatment of bacterial infections

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Biofilms play a pivotal role in bacterial pathogenicity and antibiotic resistance, representing a major challenge in the treatment of bacterial infections. The limited diffusion and inactivation efficacy of antibiotics within biofilms hinder their clearance, and while increasing dosage may enhance effectiveness, it also promotes antibiotic resistance. Nano-delivery systems that target antimicrobial agents directly to biofilms offer a promising strategy to overcome this challenge. This review summarizes the resistance mechanisms and therapeutic challenges associated with biofilms, with a focus on recent advances in nano-delivery systems such as liposomes, nanoemulsions, cell membrane vesicles (CMVs), polymers, dendrimers, nanogels, inorganic nanoparticles, and metal-organic frameworks (MOFs). Furthermore, the review explores the potential applications and challenges of nano-delivery systems in biofilm treatment and provides recommendations to guide future research and development in this field.

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## 1. Introduction

Biofilms are critical in bacterial pathogenicity and resistance, complicating the treatment of bacterial infections. Approximately 65–80% of microbial infections and 80% of chronic human infections are linked to biofilm formation.<sup>1,2</sup> Conditions such as endocarditis, osteomyelitis, sinusitis, urinary tract infections, chronic prostatitis, periodontitis, otitis media, chronic pneumonia, and cystic fibrosis of the lungs are all associated with biofilm development. Furthermore, biofilms can form on surgical implants, leading to device failure and, in severe cases, patient mortality.<sup>3</sup> Protected by the biofilm matrix, these infections exhibit remarkable resistance to antibiotics and evade the immune system, often resulting in persistent or recurrent infections that present significant therapeutic challenges.

Current strategies for biofilm removal include surgical debridement and antibiotic therapy. Surgical debridement typically utilizes ultrasound to disrupt the biofilm structure, followed by physical removal.<sup>4</sup> However, this method can cause patient discomfort, and residual bacteria may lead to reinfection. Antibiotic treatment is another common strategy, but the extracellular polymeric substances (EPS) of biofilms hinder

antibiotic penetration, rendering the bacteria 1000 to 1500 times more resistant than their planktonic counterparts.<sup>5</sup> While conventional antibiotics can eliminate planktonic bacteria released from biofilms, they fail to eradicate bacteria embedded within biofilms, resulting in suboptimal treatment outcomes. Moreover, traditional antibiotics lack specificity, and systemic administration often results in reduced drug concentrations at the infection site due to metabolic degradation. Although high-dose antibiotics may temporarily suppress biofilm infections, they can cause severe side effects.<sup>6</sup> The overuse and misuse of antibiotics have contributed to the emergence of multidrug-resistant bacteria, complicating infectious disease control. According to the World Health Organization, antimicrobial resistance accounts for approximately 7 million deaths annually, a figure projected to rise to 10 million by 2050.<sup>7</sup> Therefore, biofilm-associated infections have become one of the most pressing challenges in global healthcare, highlighting the urgent need for innovative treatment strategies.

Nano-delivery systems present significant advantages in addressing biofilm-related infections. While emerging strategies, such as novel antibiotics, biofilm disruption, quorum sensing inhibition, and biofilm dispersal, show some promise, they still face limitations. In contrast, nanomaterials, due to their small size, large surface area, and high reactivity, offer more effective treatment options.<sup>8,9</sup> Certain nano-delivery systems exhibit intrinsic antibacterial properties and enable precise drug delivery, optimizing drug concentration, minimizing adverse effects, and enhancing therapeutic efficacy. Their nanoscale size facilitates penetration into biofilms, increasing drug concentration and uniform distribution, thereby improv-

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nanoemulsions, CMVs, polymers, dendrimers, nanogels, inorganic nanoparticles, and MOFs. The mechanisms, features, and advantages of these systems in combating bacterial biofilms are discussed, along with current challenges in biofilm management, existing treatment strategies, and future directions for the development of nano-delivery systems.

Biofilms refer to the adhesion of extracellular viscous substances, such as polysaccharide matrices, fibrin, and lipoproteins secreted by microorganisms, to the surfaces of living or inanimate objects under external environmental stimuli, resulting in the formation of microbial aggregates.<sup>11,12</sup> These EPS protect the bacteria within the biofilm (Fig. 1A). A mature

**A**

Diagram illustrating the formation and development of a biofilm. The process is shown in eight numbered steps:

- (1) Initial attachment of planktonic bacteria to the substrate.
- (2) Bacteria begin to produce extracellular polymeric substances (EPS), represented by blue wavy lines.
- (3) EPS production continues, forming a matrix around the bacteria.
- (4) The biofilm matures, with bacteria embedded in the EPS matrix.
- (5) The biofilm becomes more complex, with bacteria and EPS matrix forming a structured community.
- (6) The biofilm continues to grow and expand.
- (7) The biofilm becomes more complex, with bacteria and EPS matrix forming a structured community.
- (8) The biofilm becomes more complex, with bacteria and EPS matrix forming a structured community.

**B**

Diagram illustrating the dispersal of a biofilm. The process is shown in five numbered steps:

- (1) Planktonic bacteria are present in the environment.
- (2) Bacteria attach to the substrate and begin to form a biofilm.
- (3) The biofilm grows and matures.
- (4) The biofilm becomes more complex, with bacteria and EPS matrix forming a structured community.
- (5) The biofilm disperses, releasing planktonic bacteria back into the environment.

Labels: Planktonic bacteria, Sessile bacteria, EPS matrix, Biofilm dispersal, Substrate.

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biofilm structure consists of a matrix layer, conditional layer, connecting layer, and biofilm layer, arranged from the innermost to the outermost.

## 2.1 Properties of bacterial biofilms

**1. Electronegativity:** most substances within bacterial biofilms are anionic, resulting in a negatively charged surface.<sup>13</sup>

**2. Hydrophobicity:** the outer layer of the biofilm typically contains lipids, methylated and acetylated polysaccharides, and proteins, contributing to its hydrophobic nature. This hydrophobic zone helps protect bacterial cells from external influences and the invasion of foreign molecules.<sup>14</sup>

**3. Acidity:** the biofilm creates an anoxic, malnourished, and acidic microenvironment. Bacteria at the surface rapidly consume oxygen, leading to relative hypoxia within the biofilm. Additionally, anaerobic processes produce numerous acidic metabolites, resulting in a low pH environment.<sup>15</sup>

**4. Abundant enzymes:** when bacteria colonize and form biofilms, they secrete various enzymes, including those capable of degrading or modifying antibiotics. These enzymes can alter the molecular structure of antibiotics before they reach bacterial cells, reducing or eliminating their effectiveness and contributing to antibiotic resistance.

**5. Variety of toxins:** toxins in bacterial biofilms primarily include exotoxins and endotoxins, both of which can harm the host. Exotoxins are proteins or peptides secreted by bacteria that can directly damage host cells or disrupt their normal functions. Endotoxins mainly refer to lipopolysaccharides (LPS) found in the cell walls of Gram-negative bacteria. When bacteria die and break down, LPS is released, triggering an immune response that can cause inflammation and fever. For example, *Pseudomonas aeruginosa* (*P. aeruginosa*) biofilms contain significant amounts of endotoxins, which can elicit strong inflammatory reactions upon release.

## 2.2 The process of bacterial biofilm formation

The formation of biofilms is a complex and dynamic process that can be divided into five distinct stages (Fig. 1B).<sup>16</sup> Notably, even dead biofilms can facilitate the adhesion of other microbial cells and promote biofilm regeneration.

The biofilm lifestyle begins with bacterial attachment to a surface, starting with the reversible attachment stage. In this phase, floating bacteria temporarily adhere to the substrate through electrostatic, van der Waals, and hydrophobic interactions. The second stage is the irreversible attachment stage, during which bacteria secrete EPS, promote colony growth, and form a nanogel layer that envelops the bacterial cells. The third stage involves the increment of microcolonies, characterized by the early formation and proliferation of small colonies. In the fourth stage, known as the full maturity stage, the biofilm develops a mature, three-dimensional structure. Finally, during the aging and diffusion stage, certain enzymes degrade the substrate, allowing bacteria to revert to their planktonic form. These planktonic bacteria can then seek out new nutrients and surfaces, perpetuating the biofilm cycle.

## 2.3 Challenges in treating bacterial biofilm infections

First, biofilms serve as physical barriers that restrict the penetration of antibiotics, making it challenging to achieve sufficient drug concentrations within the biofilm to effectively kill or inhibit bacteria.<sup>17</sup> Only a few antibiotics, such as gentamicin, cefotaxime, and certain fluoroquinolones, demonstrate effective activity against biofilms, as they can penetrate the EPS. However, in some cases, these antibiotics can still lead to clinical treatment failure, such as failure to treat intracellular bacterial infections, development of drug resistance, biological toxicity, and so on.<sup>3,18</sup> Second, the microenvironment within the biofilm promotes bacterial entry into dormant or slow-growing states, rendering these non-proliferating bacteria particularly tolerant to antibiotics, many of which target actively growing cells.<sup>19</sup> Third, biofilms facilitate the transfer of drug-resistant genes, resulting in the formation of highly resistant bacterial populations. Additionally, bacteria within biofilms can evade the host immune system, achieving immune escape, while toxins secreted by these bacteria can directly damage immune cells. Consequently, the protective nature of biofilms allows some bacteria to survive treatment and re-establish the biofilm, leading to recurrent infections.

## 3. Lipid-based nanoparticles

Lipid molecules are synthesized and self-assembled to form lipid-based nanoparticles, with liposomes being among the most widely studied and promising antimicrobial nanocarriers. Composed primarily of double-layer vesicles formed by phospholipids and cholesterol or other additives, liposomes feature one hydrophilic end and one hydrophobic end, resembling the structure of cell membranes. This amphiphilic property facilitates the fusion of liposomes with bacterial cell membranes, enhancing their encapsulation capacity for both water-soluble and lipophilic drugs. Liposomes offer advantages such as prolonged drug efficacy, reduced biological toxicity, and altered drug delivery pathways.<sup>20</sup> Based on their functions, liposomes can be categorized into conventional liposomes and functional liposomes.

### 3.1 Liposomes

Traditional liposomes are simple in structure, are usually unmodified, and have good carrying capacity and biocompatibility. However, they often lack targeting ability and are quickly cleared by the mononuclear phagocytic system (RES), making long circulation in the body difficult.<sup>21</sup> Although they can optimize their distribution in biofilms by regulating particle size and surface charge, they still have the problem of poor specificity (Fig. 2A).<sup>22,23</sup> Moreover, differences in antimicrobial delivery are not solely related to liposome adsorption.<sup>24</sup> For instance, uncharged liposomes can enhance their antibacterial effects by fusing with bacterial membranes, releasing drugs into the surrounding media to interact with bacteria and biofilms.<sup>25</sup> This lack of targeting limits the



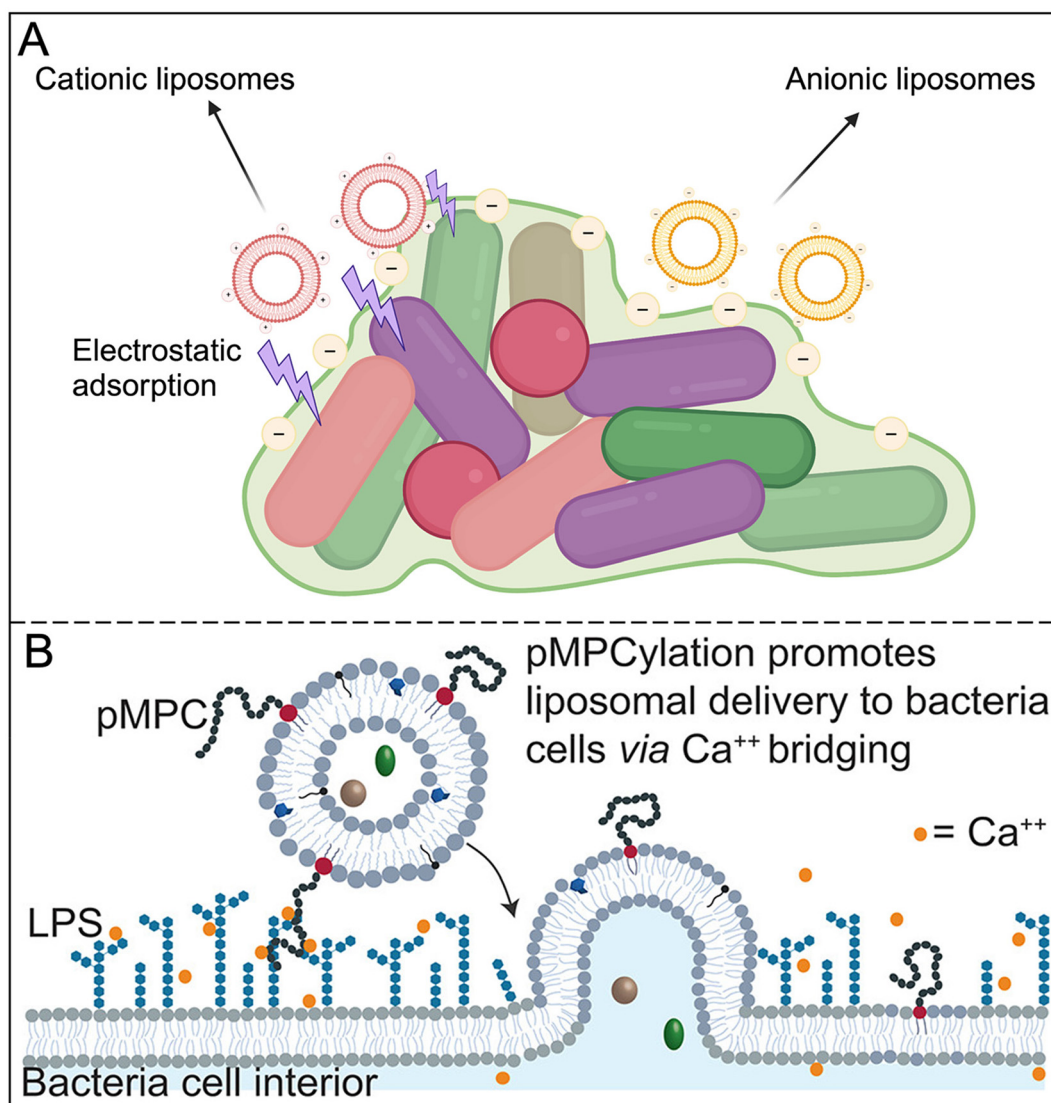


**Fig. 2** (A) Different effects of surface charges of traditional liposomes on biofilms. Created with [BioRender.com](https://www.biorender.com/). (B) Schematic of proposed two-stage mechanism for calcium-mediated adhesion and fusion between pMPC-LUVs and *P. aeruginosa* membrane. Reproduced from ref. 27 with permission from Monika Kluzek, copyright 2022.

efficacy of conventional liposomes in complex biofilm environments.

To overcome the limitations of traditional liposomes, researchers have developed engineered liposomes, covering a variety of types such as temperature-sensitive, pH-sensitive, targeting and immune liposomes. For example, PEG-modified liposomes significantly extend blood circulation time, but at the same time reduce interaction with target cells, thus weakening the targeting effect.<sup>26</sup> To solve this problem, some novel materials such as pMPC were introduced into the liposome membrane to enhance the adsorption of negatively charged bacteria, which significantly improved the biofilm ablation efficiency (Fig. 2B).<sup>27</sup>

Stimulus-responsive liposomes enable targeted drug release by modifying molecules on the surface of the liposome to respond to specific internal or exogenous stimuli (such

as temperature, pH, or magnetic field). This technique is particularly useful for antimicrobial therapy in complex micro-environments such as biofilms. For example, temperature-sensitive liposomes can release drugs at specific temperatures, further enhancing the effectiveness of treatment. Munaweera *et al.* explored the potential of temperature-sensitive liposomes to deliver ciprofloxacin to the site of infection for treating metal implant biofilms (Fig. 3A).<sup>25</sup> Zhou *et al.* effectively packaged doxorubicin into quaternary ammonium chitosan liposome nanoparticles with pH-triggered drug release, demonstrating higher anti-biofilm properties and high biosafety.<sup>28</sup> By binding to monoclonal antibodies, immune liposomes achieve efficient recognition and binding to target bacteria or cells, thereby reducing the distribution of drugs in healthy tissues and reducing side effects (Fig. 3B).



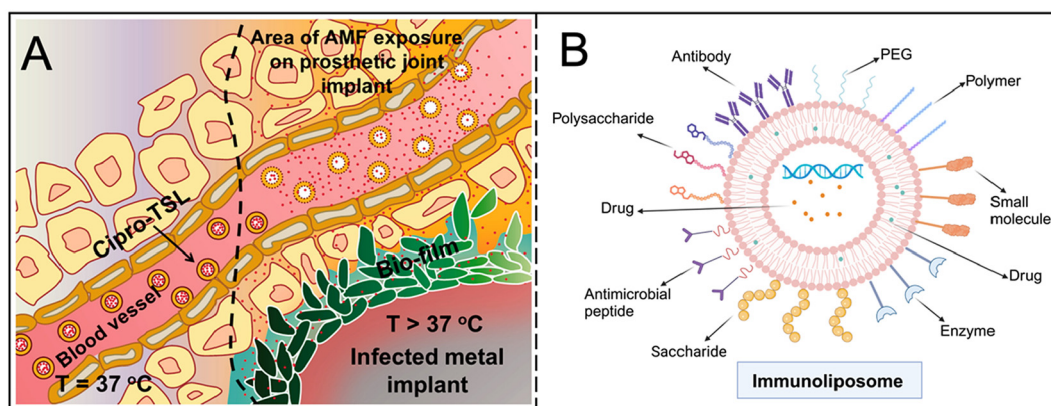


**Fig. 3** (A) Schematic of ciprofloxacin release from temperature-sensitive liposomes in the vicinity of an infected metal implant heated by exposure to an alternating magnetic field. Reproduced from ref. 25 with permission from *Int J Hyperthermia*, copyright 2018. (B) Multiple antibody modifications of immunoliposomes. Created with [BioRender.com](https://www.biorender.com).

In combination therapy, liposomes further demonstrated synergistic effects with techniques such as phototherapy and ultrasound. Through PTT and PDT, liposomes can accurately release antibacterial components in the biofilm, and use reactive oxygen species (ROS) or heat energy to destroy the extracellular matrix, enhancing the killing effect on the biofilm (Fig. 4A).<sup>29,30</sup> Liposomes can also act as oxygen carriers to alleviate the anoxic microenvironment, thereby improving antibiotic efficacy and reducing drug resistance.<sup>31</sup> In addition,

ultrasound stimulates liposomes to release ROS and drugs, improves the penetration of liposomes to bacteria and biofilms, and increases the efficacy of anti-biofilms (Fig. 4B).<sup>32</sup>

The development of liposomes has gradually evolved from simple drug carriers to multi-functional combination therapy systems. Although the traditional liposomes have strong biocompatibility, there are some problems such as insufficient targeting and short cycle time. Engineered and stimulus-responsive liposomes provide effective solutions in terms of

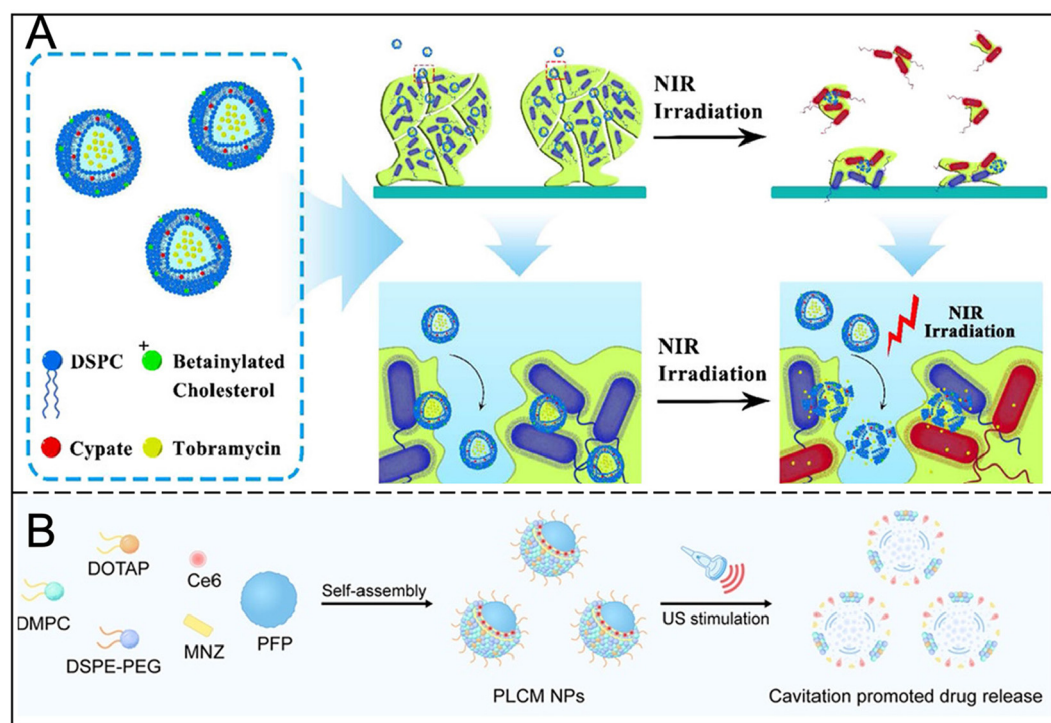


**Fig. 4** (A) Structure and function of nanoparticles and mechanism of near-infrared light-activated thermosensitive liposomes for the treatment of biofilms. Reproduced from ref. 29 with permission from *ACS Appl Mater Interfaces*, copyright 2018. (B) Schematic illustration of the preparation and US-stimulated cavitation of PFP@Lip-Ce6/MNZ nanoparticles. Reproduced from ref. 32 with permission from *ACS Nano*, copyright 2024.



specificity and controlled release. With advancements in technology, the application of liposomes is expected to achieve personalized and precise treatment by combining multiple stimulus-response functions and precise targeting, and ultimately improve the application value in anti-biofilm therapy.

### 3.2 Solid lipid nanoparticles (SLNs)

SLNs have been developed based on liposome technology. Unlike liposomes, SLNs do not possess a bilayer structure, but they offer higher loading capacity and bioavailability, as well as long-term stability; aquatic SLNs can be stored for up to three years. Typically composed of solid lipids with the addition of surfactants, SLNs are easy to mass-produce and do not require the use of organic solvents. Notably, even without encapsulated antibiotics, core-shell SLNs can effectively eradicate bacteria and reduce bacterial adhesion.<sup>33</sup>

SLNs present rich possibilities for intravenous, oral, and ocular drug therapy, achieving the best encapsulation rates for water-soluble antibiotics, prolonging drug action time, and enhancing penetration through biofilm matrices. For instance, tobramycin encapsulated in SLNs and nanostructured lipid carriers can remain in the body for up to 34 hours, maintaining antibacterial activity against planktonic bacteria while also preserving or enhancing the ability to eradicate pre-formed biofilms.<sup>34</sup> Similarly, various SLNs containing rifampicin have shown increased effectiveness in reducing the number of biofilms and live bacterial residues in *Staphylococcus epidermidis*. Additionally, some SLNs exhibit triple activity, for example, SLN-Nisin can significantly inhibit the growth of the oral pathogen *Treponema denticola*, disrupt oral biofilms, and reduce the viability of oral squamous cell carcinoma cells.<sup>35</sup>

While liposomes have stable physical properties, adjustable particle sizes, and good cellular compatibility, many liposomal formulations have entered clinical trials. Liposomes coated with antibiotics, such as amikacin, have been approved for use in biofilm-related lung infections.<sup>36</sup> Table 1 summarizes the types and characteristics of liposomes. In addition to treating biofilm infections, liposomes are utilized for various diseases, including cancer and ocular conditions. However, liposomes

also have disadvantages, such as high costs and complex production technologies.

## 4. CMVs

Although liposomes excel in drug encapsulation and protection, their synthetic nature can provoke immune responses in the host. In contrast, natural cell membranes derived from the host offer a gentler, more effective, and stable drug delivery route. CMVs possess a "core-shell" structure, consisting of membrane vesicles that encapsulate the nanoparticle core, thereby mimicking the properties of natural cell membranes (Fig. 5A).<sup>43</sup> This design retains the complexity of cell membranes and overcomes the limitations of traditional surface modifications in nano-delivery.

Both eukaryotic and prokaryotic cells can actively or passively generate membrane vesicles (MVs). These MVs inherit the membrane proteins and bioactivity of their parent cells, enabling them to perform similar biological functions and making them ideal platforms for drug delivery and gene therapy. Living bacteria can also produce MVs, which can passively accumulate at infection sites or actively target pathogens and macrophages, effectively inducing host immune responses and demonstrating unique advantages.<sup>44,45</sup> Further modifications through physical, chemical, or biological methods can reduce vesicle toxicity and enhance targeting capabilities.

### 4.1 Targeting bacteria

CMVs can be designed to target bacteria, carrying therapeutic agents within the vesicles or coating the surfaces of drug-loaded core nanoparticles.<sup>45</sup> Antibiotics encapsulated in cell membrane vesicles not only enhance specificity and binding but also facilitate direct delivery to biofilms, increasing drug concentration. Nanoparticles coated with bacterial membrane vesicles (BMVs) exhibit stability, uniformity, and enhanced antibacterial efficacy. Huang *et al.* demonstrated that *Bacillus subtilis*-derived outer membrane vesicles loaded with levofloxacin show superior antibacterial effects in mice infected with intestinal bacteria compared to free levofloxacin. Additionally,

**Table 1** Effect and characteristics of different types of representative liposomes

| Liposome types            | Antibacterial element                       | Characteristics                                                                          | Ref. |
|---------------------------|---------------------------------------------|------------------------------------------------------------------------------------------|------|
| Anionic liposomes         | Antibiotics                                 | Bind to cationic antibiotics                                                             | 37   |
| Cationic liposomes        | Electrostatic interaction                   | Combine with negatively charged biofilms                                                 | 37   |
| PEGylated liposomes       | Antibiotics                                 | Avoid nanoparticle aggregation and be engulfed by the body                               | 38   |
| pMPCylation liposomes     | Antibiotics                                 | Calcium-mediated adhesion for efficiently delivery of antibiotics                        | 27   |
| pH-sensitive liposomes    | Antibiotics                                 | pH-responsive drug release                                                               | 28   |
| Targeted liposome         | Antibiotics                                 | Attracted to <i>N</i> -acetylglucosamine residues in bacterial cell walls                | 39   |
| Thermosensitive liposomes | Antibiotics                                 | Heat-triggered drug release upon entering the microchannels of biofilms                  | 29   |
| Immunoliposomes           | Antibiotics                                 | Active targeting, increasing efficiency, reducing antibiotic usage and reducing toxicity | 40   |
| SLNs                      | Fatty acid                                  | Obstructing biofilm formation and reducing bacterial adhesion to tissues and surfaces    | 41   |
| SLNs                      | Quorum sensing inhibitor and alginate lyase | Site-specific biofilm-targeted interventional therapy                                    | 42   |



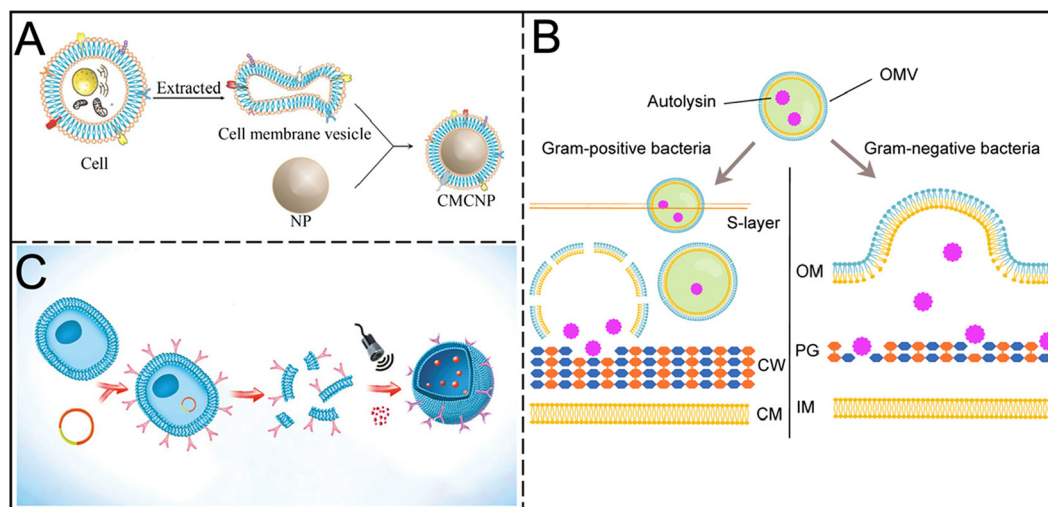


**Fig. 5** (A) Structural representation of CMCNPs. Reproduced from ref. 43 with permission from *Journal of Shanghai Jiao Tong University (Medical Science)*, copyright 2021. (B) Schematic illustration of the antibacterial mechanisms of autolysin-loaded OMVs against Gram-positive and Gram-negative bacteria. Reproduced from ref. 46 with permission from *Acta Biomaterialia*, copyright 2022. (C) Schematic illustration of the budding process of ANVs nanocapturer from antibody-overexpressed cells. Reproduced from ref. 48 with permission from *Adv Mater*, copyright 2019.

outer membrane vesicles (OMVs) secreted by Gram-negative bacteria can transport hydrolytic proteins, leading to the breakdown of peptidoglycan in both Gram-positive and Gram-negative bacteria (Fig. 5B). OMVs serve as effective carriers for delivering antibiotics such as fluoroquinolones, which easily fuse with Gram-negative bacteria.<sup>46</sup> Further studies employed a "toxin-for-toxin" strategy, enhancing biofilm disruption through the synergistic effects of membrane characteristics and antibiotics. Researchers encapsulated triclosan (TCS) in poly(lactic-co-glycolic acid) (PLGA) to significantly inhibit *S. aureus* biofilms.<sup>47</sup>

Targeted delivery of bacterial toxin monoclonal antibodies can be achieved by modifying the surface of cell membranes through genetic engineering. Liu *et al.* first demonstrated the combined application of antibacterial sonodynamic therapy and antitoxin immunotherapy using nanovesicles synthesized from engineered cell membranes. This method effectively neutralizes  $\alpha$ -toxin secreted by *Methicillin-resistant Staphylococcus aureus* (MRSA), while ultrasound activation generates ROS that disrupt bacterial cell membranes, leading to depolarization of the membrane potential and accelerated bacterial cell death, along with promoting toxin removal (Fig. 5C).<sup>48</sup> On this basis, cell membrane vesicles with mutated penicillin-binding protein PBP2a on the surface of MRSA were designed by genetic engineering to target the delivery of nano-antibiotics, showing better drug targeted delivery ability in MRSA-induced pneumonia, keratitis, muscle abscess models, and overcoming the alveolar barrier. This enhanced the accumulation of drugs at the MRSA infection site and helped inhibit the formation of MRSA biofilms.<sup>49</sup> Gong *et al.* developed nanoparticles combining naftifine, hemoglobin (Hb), and erythrocyte membrane coatings. Naftifine disrupts carotenoid biosynthesis, Hb reduces hydrogen sulfide levels in bacteria, and the erythrocyte

membrane alters bacterial lipid composition, collectively exerting destructive effects on *S. aureus* biofilms.<sup>50</sup>

## 4.2 Targeting the infection microenvironment

CMVs can be designed to target the infectious microenvironment, providing a carefully engineered approach for antibacterial treatment. Peng *et al.* developed neutrophil-bacteria hybrid membrane vesicle (HNV)-coated biocompatible lipid nanoparticles (LNP@HNVs) aimed at specifically delivering antibiotics to bacterial cells at infection sites. HNVs exhibit dual-targeting capabilities, accumulating in inflammatory endothelial cells and homologous Gram-negative bacterial cells, enhancing the *in vitro* inhibitory effects of levofloxacin-loaded LNP@HNVs on both planktonic bacteria and biofilms.<sup>51</sup> Gao *et al.* found that BMV-coated nanoparticles demonstrated significant targeting capabilities both *in vitro* and *in vivo*, with increased drug accumulation in *S. aureus* infected mice compared to healthy controls, particularly in macrophages and major organs (kidney, lung, spleen, and heart).<sup>52</sup>

By integrating the natural targeting mechanisms of cell membranes with the antibacterial properties of specific drugs, CMVs offer a promising strategy for targeted and effective antibacterial therapy. This approach has the potential to transform the fight against antibiotic-resistant bacterial infections. Attenuated vaccines can also be delivered by fusing cell membranes for antimicrobial treatment.<sup>49</sup> Table 2 summarizes the types and characteristics of MVs. However, it is crucial to consider the immunogenicity and pathogenicity of OMVs used for antibacterial treatment. Challenges remain in the large-scale production of uniform membrane vesicles, effective encapsulation of drugs with varying physicochemical properties, and ensuring safety, all of which require further investigation.



**Table 2** Effect and characteristics of different types of representative MVs

| Membrane vesicles types | Antibacterial element | Characteristics                                                            | Ref. |
|-------------------------|-----------------------|----------------------------------------------------------------------------|------|
| CMV                     | Sonosensitizer        | Sonodynamic therapy and antitoxin immunotherapy                            | 48   |
| OMV                     | Antibiotics           | Interference with biofilm formation and reduction of the virulence factors | 47   |
| OMV                     | Antibiotics           | Targeted delivery and immune regulation                                    | 53   |
| OMV                     | PDT and metal         | Targeted delivery                                                          | 54   |
| HMV                     | Antibiotics           | Targeting specific bacterial infection microenvironments                   | 51   |

## 5. Nanoemulsions

Nanoemulsions are systems that encapsulate active substances through nanodroplets of oil to stabilize and control drug release. Despite lacking the biocompatibility of cell membrane vesicles, nanoemulsions offer greater flexibility in drug encapsulation and release characteristics. They exhibit significant antibiofilm activity, exceeding that of commercially available antibiotics,<sup>55</sup> and their surfactant properties prevent phase separation.<sup>56,57</sup>

The natural antibacterial nanoemulsions include water-in-oil (W/O), oil-in-water (O/W) and double continuous types (Fig. 6A).<sup>56</sup> Essential oils, such as cloves, thyme and peppermint, have poor solubility and stability, but their conversion into nanoemulsions can improve their bioavailability and ability to inhibit biofilms. For example, clove oil nanoemulsions showed enhanced antimicrobial properties,<sup>58</sup> with peppermint nanoemulsions also showing inhibition of biofilm formation.<sup>59</sup> The phenolic hydroxyl groups of thyme and clove also enhanced their hydrophilicity and improved mem-

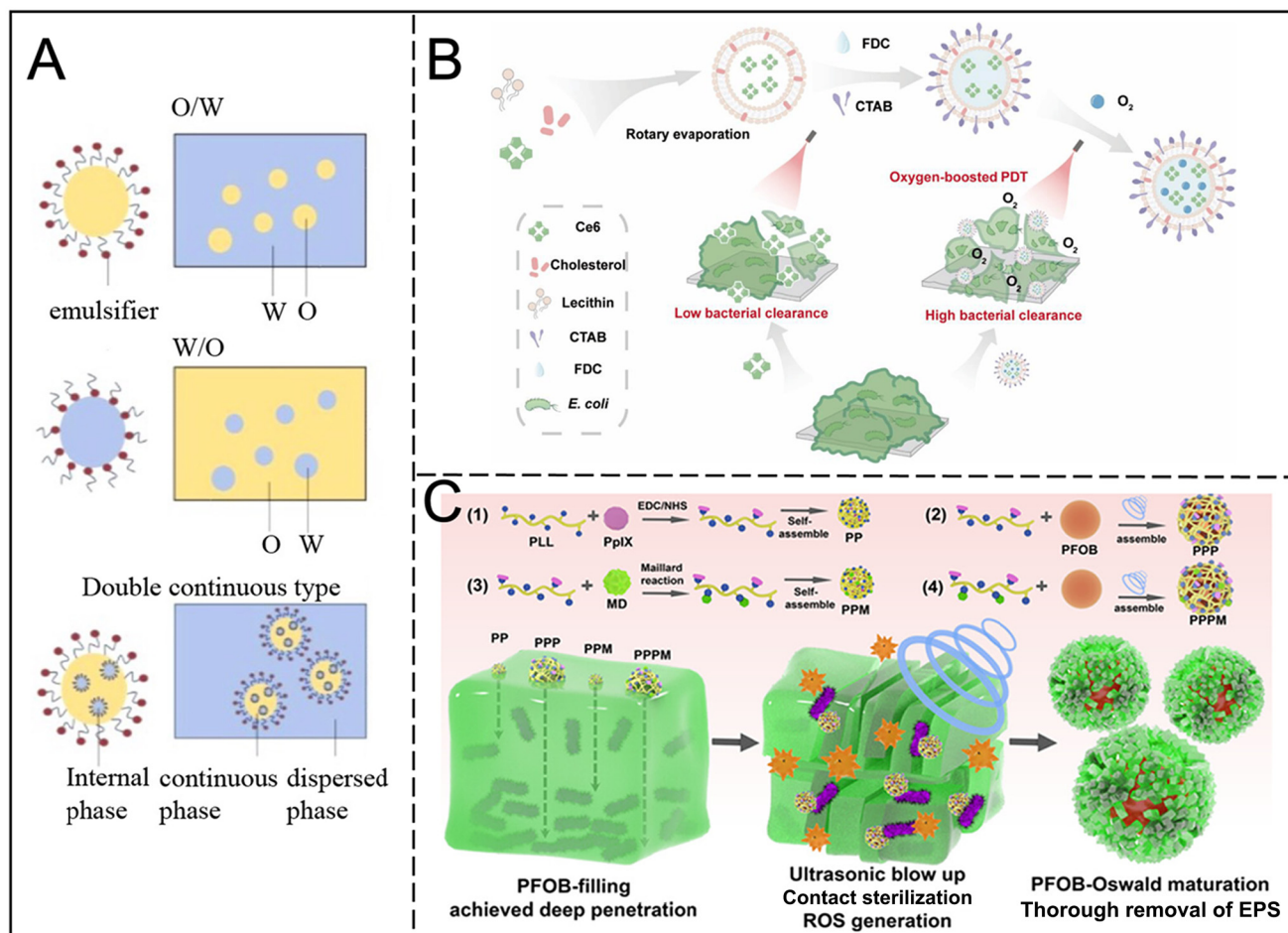


**Fig. 6** (A) O/W, W/O, and double continuous type nanoemulsions. Reproduced from ref. 56 with permission from *Meat Research*, copyright 2022. (B) Schematic illustration of the fabrication process of Ce6@FDC nanoemulsion and its oxygen delivery for enhanced photodynamic antibacterial efficiency. Reproduced from ref. 64 with permission from *Springer Nature*, copyright 2018. (C) Schematic illustration of fabricating various nanoagents and the potential advantages of PFOB in biofilm treatment. Reproduced from ref. 65 with permission from *ACS Appl. Mater. Interfaces*, copyright 2024.



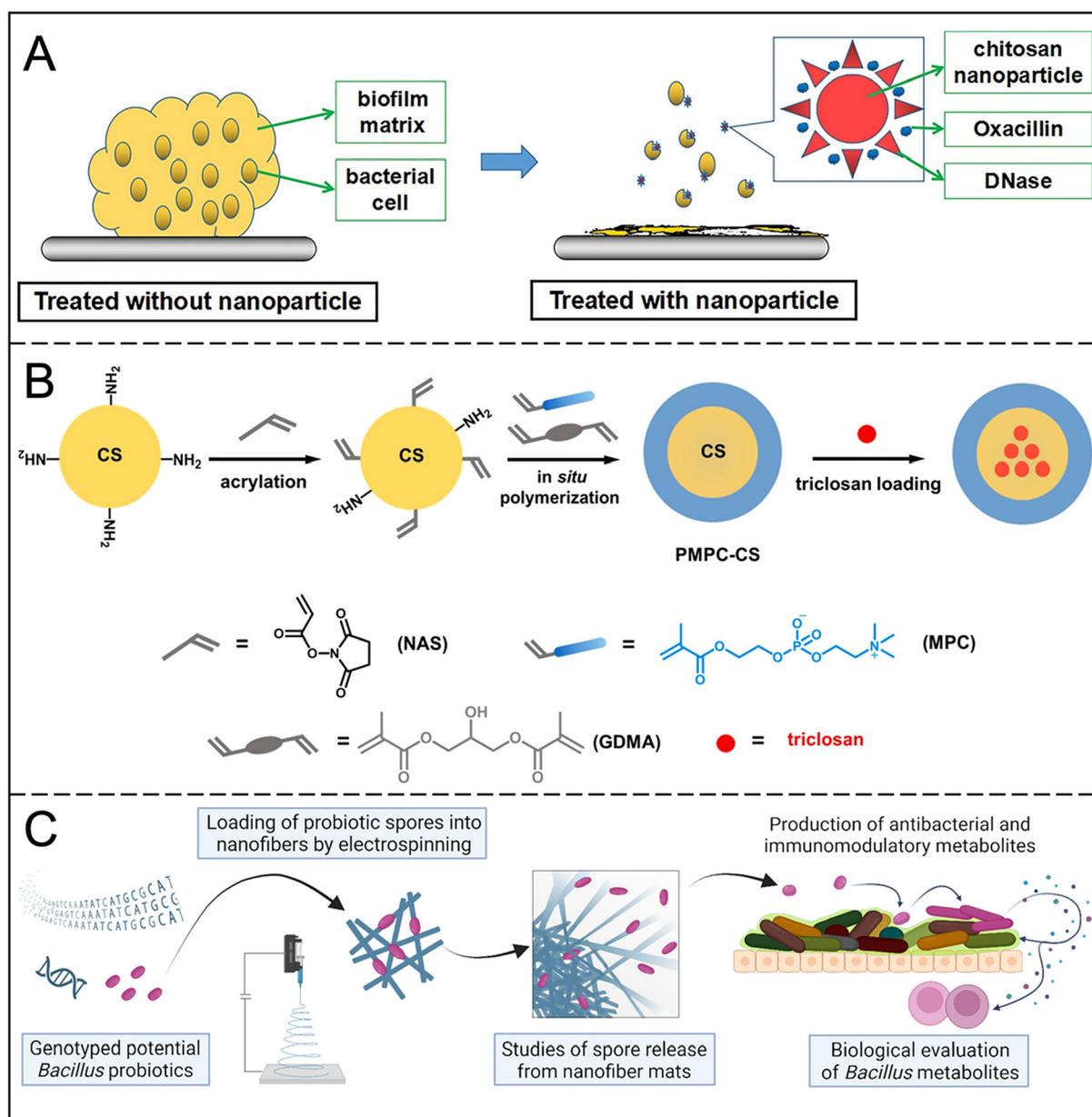


**Fig. 7** (A) Schematic diagram of the composition and therapeutic mechanism of CSNP DNase Oxa. Reproduced from ref. 72 with permission from *Carbohydrate Polymers*, copyright 2018. (B) Sequential steps for the preparation of triclosan-loaded nanocapsules. Reproduced from ref. 73 with permission from *ACS Macro Lett*, copyright 2019. (C) Schematic diagram of the composition and therapeutic mechanism of nanofibers. Reproduced from ref. 75 with permission from *J Control Release*, copyright 2023.

### 6.3 Dendrimers

Hyperbranched and dendritic macromolecules show great potential as delivery carriers of fungicides and nano-antimicrobials due to their highly branched properties, nanoscale size and abundant terminal functional groups. Dendritic macromolecules have significant advantages over conventional polymers, with their three-dimensional structure offering unique nanoscale spherical properties and internal hydrophobic or hydrophilic cavities.<sup>81</sup> This structure makes them highly responsive to microorganisms, and multiple surface functional

groups can be easily chemically modified for use in combination with chemotherapy drugs to regulate antimicrobial properties.<sup>82,83</sup>

Dendrimers can interfere with biofilm formation. For example, the glycopeptide dendritic macromolecules synthesized by Bergmann *et al.* can significantly inhibit the formation and dispersion of biofilms.<sup>84</sup> When used in combination with antibiotics, dendrimers can enhance the efficacy of antibiotics and reduce drug resistance. The AZM-DA nanoparticles developed by Gao *et al.* decomposed in an acidic microenvironment and released azithromycin, which signifi-



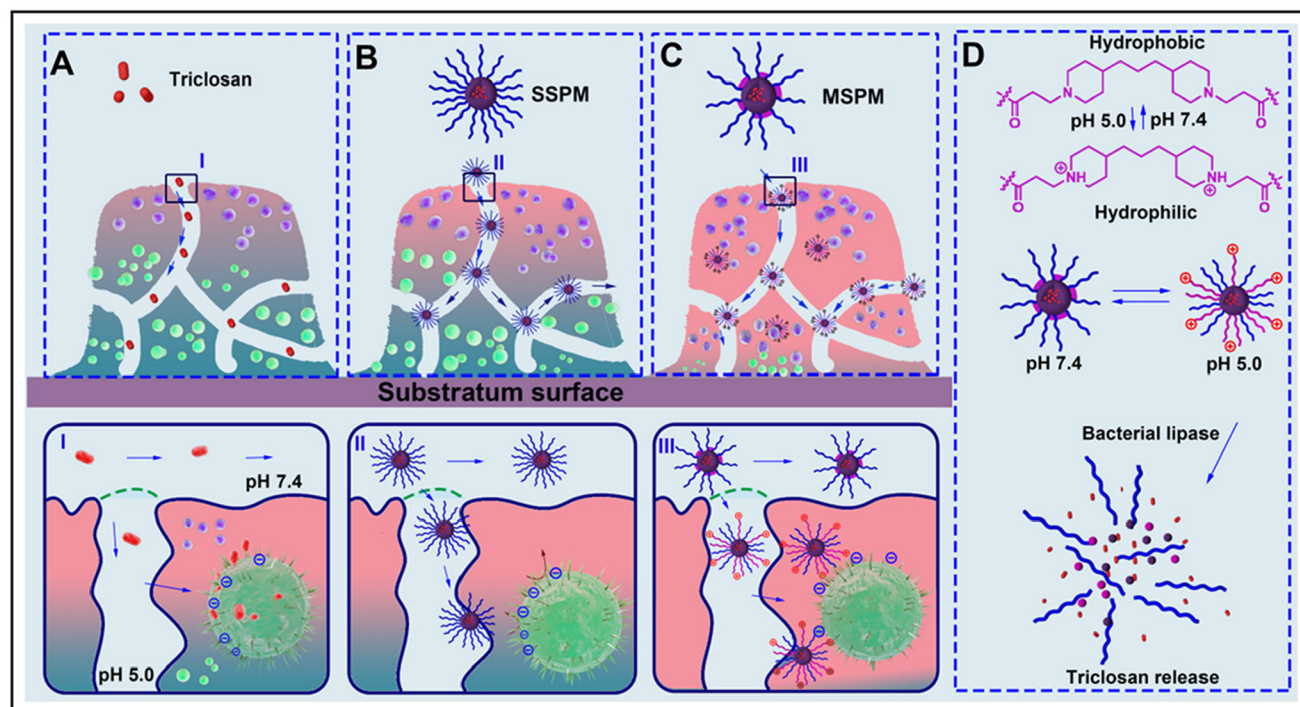


**Fig. 8** Schematic diagram of the mechanism of action of MSPM. (A) Nonencapsulated antimicrobials penetrate to a limited degree into a biofilm and kill only bacteria on the outside of the biofilm. (B) Antimicrobials encapsulated in an SSPM nanocarrier with stealth properties will show better penetration into a biofilm and thus kill bacteria in deeper layers of the biofilm, provided sufficient antimicrobial release. (C) MSPM target the bacterial cell surface and expose their micelle core, which subsequently becomes hydrolyzed by bacterial lipases to release its antimicrobial content. (D) Summary of the surface adaptability of MSPMs under the influence of pH changes and lipase degradation. Reproduced from ref. 79 with permission from ACS Nano, copyright 2016.

**Table 3** Effect and characteristics of different types of representative polymers and dendrimers

| Delivery types   | Antibacterial element                 | Characteristics                                      | Ref. |
|------------------|---------------------------------------|------------------------------------------------------|------|
| Natural CS       | CS                                    | Reduces the vitality of initially adhering bacteria  | 96   |
| CS derivatives   | DNase and CS and antibiotics          | Degradation of eDNA                                  | 72   |
| Engineering CS   | Natural polyphenol                    | Mucoadhesion profile                                 | 97   |
| PLGA             | Xylitol                               | Enhance penetration of biofilm matrix                | 77   |
| Micelle          | Enzymes and electrostatic interaction | pH-responsive drug release and charge reversal       | 79   |
| h-PAMAM, $D < 1$ | NO                                    | Enhance penetration of biofilm matrix and NO release | 90   |
| PAMAM, $D = 1$   | PTT and NO                            | Increased local temperature and the released NO      | 98   |

cantly improved the killing effect on biofilms (Fig. 9A).<sup>85</sup> Pamukcu *et al.* enhanced the bactericidal effect of curcumin and successfully inhibited the formation of MRSA biofilms by grafting mesoporous silica nanoparticles onto hyperbranched polyethyleneimine.<sup>86</sup> In addition, dendrimers also show advantages in targeted therapy. For example, the Cur-DA NPs prepared by Chen *et al.* using polyamide tree-like macromolecules enhance the targeting of infected tissues through interaction with biotin, thus improving the therapeutic effect of antibiotics.<sup>87</sup> Polyamides are dendritic macromolecules most widely studied in the field of biomedicine, which can be divided into hyperbranched polyamides (h-PAMAM,  $D < 1$ ) and dendritic polyamides (PAMAM,  $D = 1$ ) according to different synthesis methods and branching degrees ( $D$ ). h-PAMAM with different terminations has different effects on biofilms, and h-PAMAM

with amine termination has a better eradication effect.<sup>88,89</sup> In addition, dendritic macromolecules can further enhance their antibacterial properties through functionalization. For example, the introduction of NO into polyamides can significantly increase their bactericidal activity. h-PAMAM-PO-2/NO can not only reduce the metabolic activity of biofilms, but also kill the bacteria isolated from biofilms, and has good water solubility, which has broad application prospects in mouthwash, gel, ointment and other fields.<sup>90</sup> Yang *et al.* grafted  $\text{Fe}_3\text{O}_4$ @PDA as a photoconverter and core, with PAMAM and NO donors on the surface to obtain a multifunctional  $\text{Fe}_3\text{O}_4$ @PDA@PAMAM@NONOates nanocomposite, which can activate both photothermal and non-release properties after laser irradiation. This leads to more effective antimicrobial effects and eradication of bacterial biofilms (Fig. 9B).<sup>91</sup>

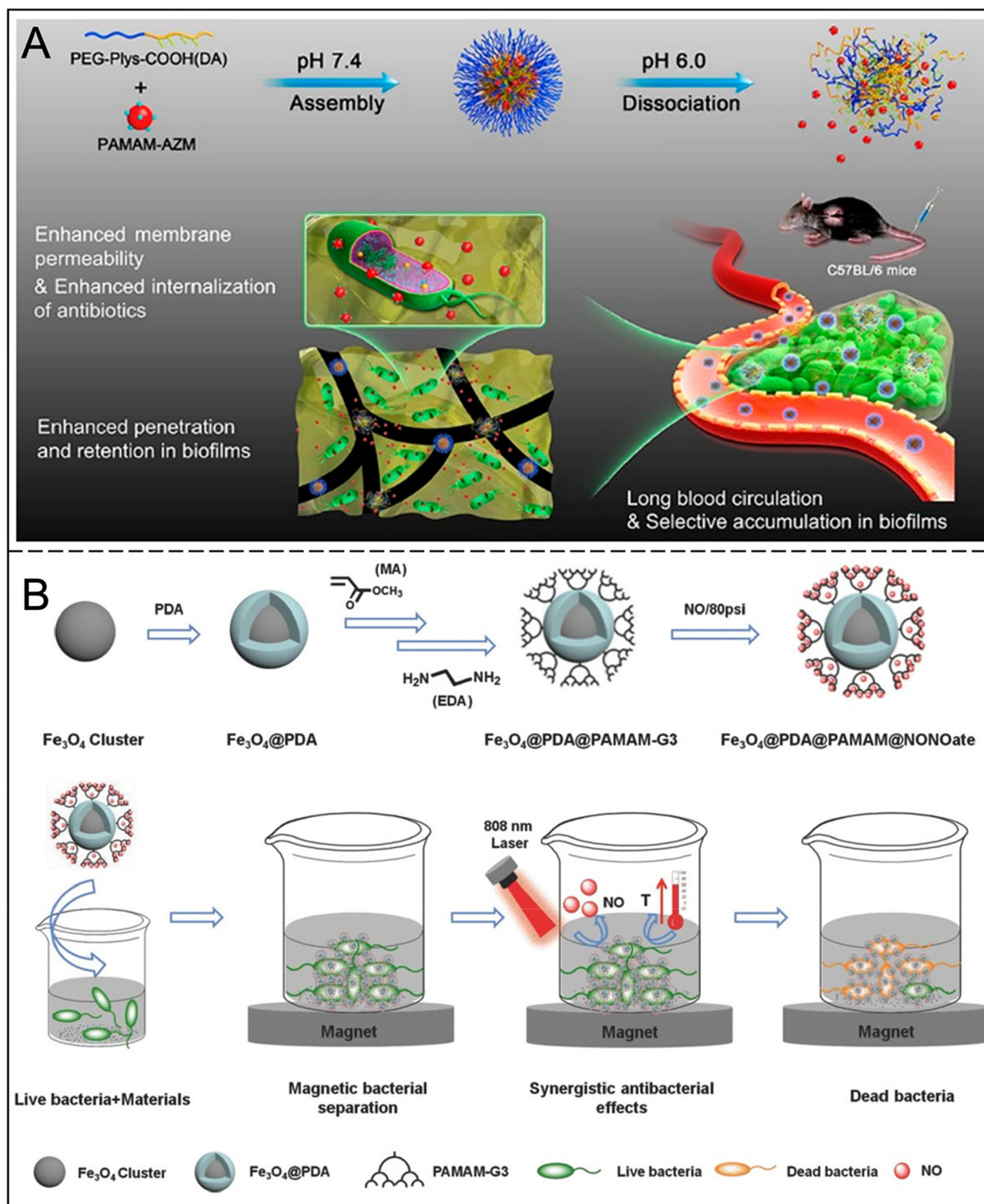


**Fig. 9** (A) Illustration of the self-assembly of AZM-DA NPs at pH 7.4 and release of secondary PAMAM-AZM NPs in an acidic biofilm microenvironment and the accumulation of AZM-DA NPs in biofilms and subsequent release of PAMAM-AZM NPs for enhanced biofilm penetration, permeabilization of the bacterial membrane, and increased AZM internalization. Reproduced from ref. 85 with permission from *ACS Nano*, copyright 2020. (B) Fe<sub>3</sub>O<sub>4</sub>@PDA@PAMAM@NONOate synthetic route for magnetic separation, synergistic photothermal and NO killing bacteria. Reproduced from ref. 91 with permission from *Advanced Functional Materials*, copyright 2018.



Dendrimers enhance bactericidal activity, reduce cell toxicity, and have a lower synthetic burden, providing a new platform for anti-biofilm therapies. Table 3 summarizes the types and characteristics of dendrimers. Some dendrimer-based nanodrugs have already been commercialized or are in clinical development,<sup>92</sup> such as the gene transfection reagents Superfect® (Qiagen) and Priostar™ (Stapharma),<sup>93</sup> and the vaginal microbicide Vivagel® (SPL7013).<sup>94</sup> However, dendrimer-based nanomedicines still face challenges, including the need for expanded production, improved analytical characterization methods, and more promising clinical trial results.<sup>95</sup>

## 7. Nanogels

Nanogels have gained considerable attention for applications in drug-controlled release, temperature sensing, and various sensing devices. Their porous three-dimensional mesh structure, excellent adhesion properties, and biodegradability make them promising materials for wound dressings.<sup>95</sup> These characteristics enable gas exchange, absorption of wound exudate, maintenance of a moist microenvironment, prevention of bacterial adhesion and biofilm formation, and promotion of wound healing. Consequently, they hold significant potential in anti-biofilm applications. Some antibacterial nanogels have inherent antibacterial properties. For instance, CS possesses intrinsic antibacterial properties due to its abundant amino groups.<sup>99</sup> Zhang *et al.* utilized the peptide QP5 in CS nanogels, leveraging the interaction between the positively charged CS and bacterial cell walls. This approach significantly impacted biofilm models, resulting in low colony-forming unit counts, reduced lactic acid production, and diminished metabolic activities after seven days of treatment.<sup>99</sup>

### 7.1 Loading antibacterial agents

Another design approach for nanogels is the incorporation of antibacterial agents, such as metal NPs and antimicrobial peptides. These nanogels typically comprise highly biocompatible materials, such as natural polysaccharides and collagen, minimizing adverse reactions and tissue damage *in vivo*.

Nanogels can achieve continuous release of antibacterial agents. Haidari *et al.* proposed a design that utilizes F-127 polymers as AgNPs carriers, facilitating targeted transport to infected wounds while maintaining safe concentrations to mitigate toxic effects on cells. The ultra-small size of AgNPs enables them to penetrate the dense extracellular matrix of the bacterial biofilm, while the hydrogel enables the continuous release of silver particles, enhancing interactions with the bacterial membrane and promoting the elimination of pathogens (Fig. 10A).<sup>100</sup> Nanogels can not only improve the sensitivity of bacteria to antibiotics, but also have a high drug loading capacity due to their large pores and surface area, improving the efficiency of drug loading and release. A smart hydrogel developed by Zhang *et al.* is able to release pectinase and antibiotics when an infection occurs, effectively eliminating biofilms.<sup>101</sup> A novel nanogel consists of cationic peptide pools

from curds that self-assemble into nanogels that are subsequently cross-linked with zinc ions to inhibit bacterial flagellar movement and exhibit antimicrobial and antibiofilm properties.<sup>102</sup>

### 7.2 Combination treatment strategy

Nanogels have shown great potential as drug carriers in anti-biofilm combination therapy. Their unique structure allows the loading and simultaneous delivery of multiple therapeutic ingredients, facilitating targeted drug release and synergies. For example, CS nanogels combined with antimicrobial peptides and hydrogen peroxide can significantly reduce biofilms,<sup>103</sup> while multifunctional nanogel devices based on PDT, PTT and NO gases can alleviate the hypoxic microenvironment of wound infection and further inhibit biofilm formation (Fig. 10B).<sup>104</sup> By co-delivering antibiotics and biofilm dispersants, nanogels effectively accelerate wound healing.<sup>105</sup> In addition, the precise tunability of nanogels makes them particularly effective in controlling drug release. For example, by adjusting crosslinking density and acid-sensitive bonds, on-demand responsive release of antibiotics can be achieved, reducing side effects on healthy tissues. pH-switched antibacterial nanogels release antimicrobials in acidic pathological environments, protecting healthy tissue from damage.<sup>106</sup> Local delivery capabilities further enhance therapeutic effectiveness: modified dextran bismuth selenide nanoparticles and iron-responsive antimicrobials both target biofilm removal while avoiding damage to normal tissue.<sup>107,108</sup> These properties make nanogels widely used in infection control and targeted drug delivery.

The high biocompatibility of nanogels minimizes adverse effects on normal cells and enhances drug penetration within biofilms. Their three-dimensional network structure protects encapsulated drugs from enzymatic degradation and allows for the adjustment of physical and chemical properties to meet drug delivery needs, achieving continuous and controlled release while reducing treatment frequency. Nonetheless, challenges remain, including potential immune responses, difficulty in controlling degradation rates, and limited loading capacity for hydrophobic drugs. However, the versatility of nanogels offers opportunities for integrating novel antibacterial strategies, such as magnetothermal therapy, immunotherapy, and metabolic interference therapy, to expand their applications and develop more diverse formulations.

## 8. Inorganic nanoparticles

Inorganic nanoparticle carriers are increasingly utilized for drug delivery due to their ability to disrupt biofilms and interfere with cellular processes. The positive charge of metal ions allows these nanoparticles to attract negatively charged biofilms, impairing their protective effects. They can bind to thiol groups on the surface of proteins, leading to protein coagulation and disruption of enzyme function, which hinders cell division and proliferation. Inorganic nanoparticles deliver



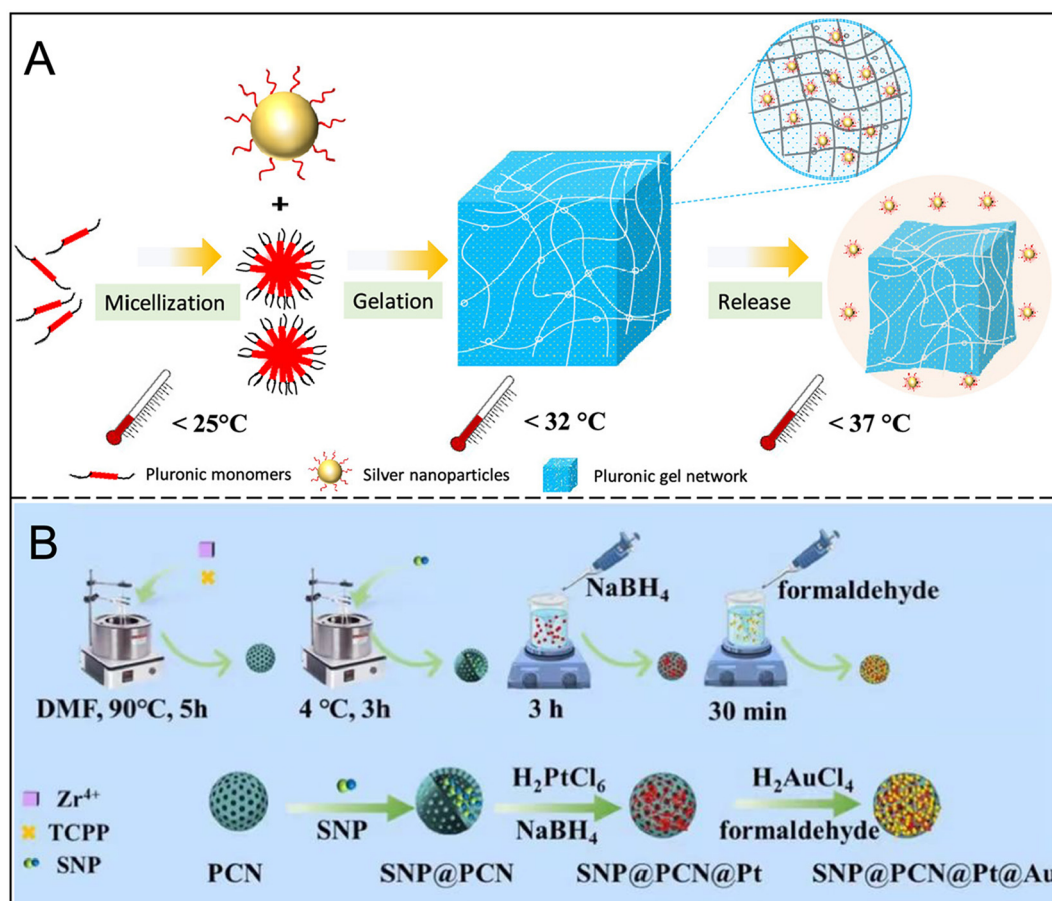


**Fig. 10** (A) Schematic illustration of AgNPs@MSA-loaded pluronic hydrogel preparation. Reproduced from ref. 100 with permission from ACS Appl. Mater. Interfaces, copyright 2020. (B) Schematic diagram of the synthetic procedure for SNP@PCN@Pt@Au. Reproduced from ref. 104 with permission from Acta Biomater, copyright 2023.

drugs through two main methods: encapsulation, where drugs are stored in the nanoparticle pores for controlled release, and surface modification, where drugs are attached to the nanoparticle surface *via* degradable chemical bonds.

### 8.1 Metal nanoparticles

Metal nanoparticles, particularly gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs), have demonstrated significant potential in the treatment of biofilms and drug delivery. AuNPs can inhibit the synthesis of intracellular adenosine triphosphate (ATP) and affect the binding of transfer RNA, thereby enhancing the permeability of antibiotics to bacterial cells.<sup>109</sup> Studies have shown that the combination of AuNPs with antibiotics significantly improves antibacterial efficacy;<sup>110</sup> for instance, Hasoon *et al.* found that the combination of AuNPs with ciprofloxacin effectively prevents the formation of bacterial biofilms (Fig. 11A).<sup>111</sup> Furthermore, Zhang *et al.* developed a glyconjugate-based imaging and therapeutic strategy that integrates PDT and PTT, successfully eradicating biofilms caused by *P. aeruginosa*.<sup>112</sup>

On the other hand, AgNPs can effectively penetrate bacterial biofilms and release a substantial amount of silver ions to

enhance antibacterial activity.<sup>113</sup> By forming chelates with antibiotics, AgNPs can selectively target and eliminate biofilms that are resistant to traditional single antibiotics.<sup>114</sup> Metal nanoparticles can be endowed with various shapes, such as nanospheres,<sup>115–117</sup> nanorods,<sup>118–121</sup> nanostars,<sup>122,123</sup> nanoshells,<sup>124</sup> and nanocages.<sup>125,126</sup> Among them, gold-silver nanocages (GSNCs) are regarded as effective drug delivery systems for near-infrared PTT; however, the limited silver release from these structures remains a challenge that needs to be addressed. Qin *et al.* synthesized GSNC-Cyh using cysteine hydrochloride, successfully enhancing bacterial adhesion to the nanoparticles and promoting the effective release of ultra-small AgNPs, which significantly increased intracellular ROS levels and completely eradicated multidrug-resistant biofilms. Additionally, metal oxides such as  $\text{ZnO}$ ,<sup>127</sup>  $\text{TiO}_2$ , and  $\text{SiO}_2$  also exhibit the ability to inhibit resistant bacterial strains and prevent biofilm formation.

### 8.2 Non-metal nanoparticles

Other inorganic nanoparticles, such as CQDs, calcium phosphate, and mesoporous silica nanoparticles, have been effectively employed for *in vitro* delivery of various molecules.



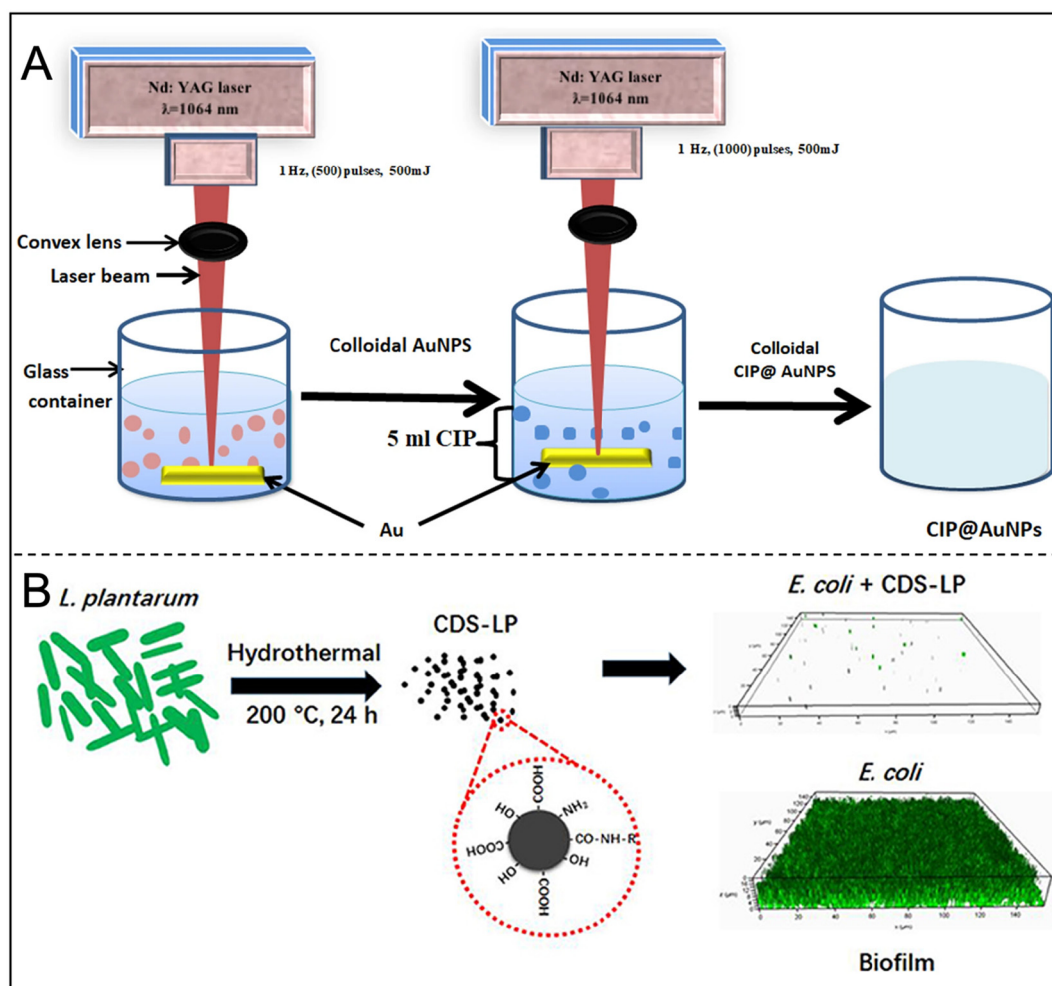


**Fig. 11** (A) Synthesis of ciprofloxacin-conjugated gold nanoparticles and their study antibacterial effects on growth and biofilm formation through nebulizer mask against respiratory infections. Reproduced from ref. 111 with permission from *Plasmonics*, copyright 2023. (B) Schematic of the synthetic route and anti-biofilm activity of CDs-LP. Reproduced from ref. 128 with permission from Lin, Li and Chen, copyright 2018.

CQDs, with sizes under 10 nm, are notable for their modifiable functional groups and ability to generate ROS *via* photodynamic mechanisms, making them effective against bacterial biofilms. Wan *et al.* designed CQD and PLGA mixed nanoparticles encapsulating azithromycin and tobramycin, utilizing a combination of chemotherapy and photothermal effects to combat biofilms. Lin *et al.* used CQDs synthesized by *Lactobacillus plantarum* (LP) to inhibit *E. coli* biofilm formation without cytotoxic effects (Fig. 11B).<sup>128</sup> Ching *et al.* functionalized curcumin (Cur) with calcium phosphate, finding that while the release of Cur was low, it effectively inhibited biofilm maturation. They proposed using pH-sensitive linkers to enhance Cur release from hydroxyapatite surfaces.<sup>129</sup> Barros *et al.* synthesized antibacterial Cur-conjugated silica nanoparticles that improved Cur solubility and disrupted mature biofilms by reducing biofilm adhesion protein production.<sup>130</sup> Hydrophilic antibiotics, such as vancomycin, can bind to amine-functionalized silica nanoparticles for tandem transport and bacterial killing. Mesoporous silica nanoparticles

encapsulated with chlorhexidine, averaging approximately 140 nm, demonstrated promising antimicrobial effects against planktonic *S. mutans*, as well as monospecies and multispecies bacterial biofilms.<sup>131</sup>

Most inorganic nanoparticles exhibit good biocompatibility and stability, addressing the decreased stability often associated with organic materials and macromolecules in drug delivery. Their low cost, ease of manufacturing, prolonged *in vivo* residence time, and improved pharmacokinetics make them attractive options. Table 4 summarizes the types and characteristics of inorganic nanoparticles. However, the potential toxicity of metal and inorganic particles and their distribution and metabolism within the body remain poorly understood, limiting their clinical applications. In research contexts, it is essential to consider the metabolic capacity of cells and the impact of the delivery carriers, especially those containing heavy metals.<sup>132</sup> Addressing the toxic effects of carriers on delivery targets is crucial for advancing the clinical application of inorganic nano-delivery systems.



| Delivery types            | Antibacterial element | Characteristics                                                                                    | Ref. |
|---------------------------|-----------------------|----------------------------------------------------------------------------------------------------|------|
| Metal nanoparticles       | Antibiotics and Au    | Strong antioxidant properties and synergistic enhancement of antibiotic efficacy                   | 111  |
| Metal oxide nanoparticles | Zn and ROS            | ROS and free radical production, synergistic CIP                                                   | 127  |
| CDs                       | Antibiotics and PTT   | Stimuli-responsive release of the cargos and chemo-photothermally synergistic anti-biofilm effects | 149  |
| Metal nanoparticles       | Antibiotics and Au    | Strong antioxidant properties and synergistic enhancement of antibiotic efficacy                   | 111  |
| MOFs                      | Zn and antibiotics    | Inhibition of biofilm formation and controlled release of Zn                                       | 136  |
| ZIF-8                     | Antibiotics and PDT   | pH-responsive drug release and PDT                                                                 | 139  |
| Simulation enzyme         | Enzyme                | Cutting eDNA and hydrolyzing DNA                                                                   | 142  |
| MOFs                      |                       |                                                                                                    |      |
| PCN-224                   | PDT and enzyme        | Bactericidal and anti-inflammatory synchronous treatment mode                                      | 150  |

With a diverse spatial structure and adjustable composition, MOFs can respond to the microenvironment of biofilms and dynamically release bioactive substances, including antibiotics and photosensitizers in addition to metal ions. Represented by Zeolitic Imidazolate Framework-8 (ZIF-8) nanoparticles, MOFs



can degrade in an acidic environment (pH 5.5–6.8), but remain stable under physiological conditions, providing a platform for controlled release of antibacterial drugs. Ciprofloxacin (CIP) and methylene blue (MB) were loaded into ZIF-8 nanocomposites to form a dual response system, which promoted the synergistic release of CIP and MB under low pH and high lipase conditions in the bacterial microenvironment, and enhanced the chemical-photodynamic therapeutic effect (Fig. 12B).<sup>139</sup> At the same time, MOFs can also improve the stability and solubility of small molecules, which is conducive to the effective release of ROS at the infected site.<sup>140</sup> Through charge conversion and pH response mechanisms, MOFs further enhance the permeability of nanocomposites to biofilms, facilitating drug delivery to the infection core.<sup>141</sup> Based on this function, MOFs show great application prospects in the rapid control of infection and improving the stability of antimicrobial agents.

### 9.3 Enzyme activity antibacterial properties

Some MOFs exhibit enzyme-like activity, capable of cutting extracellular DNA, disrupting biofilm stability and inhibiting bacterial growth. For example, bimetallic layered macroporous MOFs (HMO-66 (Zr/Ce)) effectively promote DNA hydrolysis and weaken biofilms through the synergistic interaction of Zr-OH and Ce-OH sites.<sup>142,143</sup> Ce-MOF nanoenzymes simulate the dual activity of DNase and peroxidase, using Ce(IV) complexes to hydrolyze eDNA to destroy mature biofilms, and peroxidase activity further removes dispersed bacteria in the presence of H<sub>2</sub>O<sub>2</sub>.<sup>144</sup> Due to their ultra-small size, Ce-MOF nanofibers have 3–15 times the hydrolytic activity of conventional MOFs, which make them excellent for biofilm prevention and removal.<sup>145</sup> In addition, the gold-cluster-modified Au@ZIF-8 showed enhanced peroxidase activity and photothermal responsiveness under near-infrared irradiation, and had a significant bactericidal effect on MRSA.<sup>146</sup> In response to natural enzyme instability and the complexity of artificial enzyme synthesis, Qiu *et al.* developed CeO<sub>2</sub> modified porphyrin MOFs that synergistically inhibit biofilm formation through ATP deprivation and ROS production.<sup>147</sup> These approaches demonstrate the innovative potential of MOFs in dynamic biofilm therapy.

Given these advantages, MOFs hold significant potential for applications in antibacterial therapy and medical devices. For instance, antibacterial coatings or membrane materials based on MOFs can be designed for surface modification of medical devices to inhibit bacterial adhesion and colonization. Zang *et al.* prepared an MOF polymer coating that effectively prevents bacterial attachment and colonization, significantly inhibiting biofilm formation.<sup>148</sup> Table 4 summarizes the types and characteristics of MOFs. However, despite the considerable promise of MOFs in anti-biofilm applications, practical implementation faces challenges. Key issues include ensuring the stability and biocompatibility of MOFs in complex biological environments and achieving precise regulation of MOF structure and composition to meet specific application requirements. Therefore, further in-depth research on the preparation, properties, and mechanisms of MOFs is essential

to advance their practical applications in the field of anti-biofilm strategies.

## 10. Future perspectives and conclusions

The complex structure and drug resistance of biofilms make the effective delivery of drugs within the membrane a major problem in the field of anti-biofilm therapy. The nano-delivery system not only has the advantages of nanosize and can penetrate the biofilm more easily, but also can increase solubility, stability, and blood circulation time, while reducing the dosage. Precision therapy can also be achieved through active or passive targeting to maximize the local effective concentration of the drug. In addition, through personalized design, intelligent responsive drug release can be achieved, ensuring drug release on demand. More importantly, nano-delivery systems can also achieve combined therapy, including PTT, PDT, *etc.*, which not only shows excellent results in inhibiting biofilm formation and accelerating the degradation of biofilm, but also reduces the risk of drug resistance. The versatility and adaptability of nano-delivery systems make them show great prospects in the field of anti-biofilm therapy, making targeted therapy, combination therapy and immunotherapy possible. We summarize the advantages and disadvantages of several types of nano-delivery systems for antimicrobial and anti-biofilm applications that have been mainly reported in the current literature (Table 5).

Although nano-delivery systems show significant advantages in anti-biofilm therapy, most research is still at the laboratory stage, and clinical applications have not been widely realized. In order to accelerate the development of this field, we suggest that future research should focus on the following areas:

**1. Clinical translation potential:** although many nano-delivery systems have shown promise at the laboratory stage, clinical translation remains challenging. More preclinical and clinical studies are needed to validate their safety and efficacy. Establishing *in vitro* and *in vivo* models that closely simulate real pathological environments could lay the groundwork for their application.

**2. Combination therapy:** given the complexity of biofilms, future studies could explore the co-administration of various agents (*e.g.*, antibiotics and anti-biofilm drugs) for synergistic treatment at multiple targets. Integrating multidisciplinary approaches may enhance therapeutic outcomes.

**3. Personalized treatment:** with advancements in precision medicine, nano-delivery systems customized according to patient characteristics (*e.g.*, infection type and immune status) may offer higher efficacy.

**4. Long-term efficacy and resistance:** investigating ways to mitigate antibiotic resistance through nano-delivery systems is crucial. For instance, modulating release rates to avoid peak drug concentrations may help reduce resistance pressure on bacteria.



**Table 5** Summary of various antibacterial nano-delivery systems: advantages and disadvantages

| Nano-delivery systems   | Advantages                                                                                          | Disadvantages                                                                         |
|-------------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Liposomes               | Enhance drug efficacy, reduce biological toxicity, alter delivery pathways                          | Rapid clearance affects drug concentration; need to extend retention time in biofilms |
| CMVs                    | Can evade immune clearance                                                                          | Production challenges; limited scalability for application                            |
| Nanoemulsions           | Multiple delivery routes; enhance penetration through biofilms                                      | Low drug encapsulation efficiency; complex preparation processes                      |
| Polymers                | Accommodate various drug types; numerous modification options suitable for controlled release       | Physiological stability and clearance efficiency <i>in vivo</i> need improvement      |
| Dendrimers              | Lower synthetic burden                                                                              | Often exhibit poorer biocompatibility                                                 |
| Nanogels                | Favorable biocompatibility and biodegradability; facilitate sustained release of antibiotics        | Stability challenges                                                                  |
| Inorganic nanoparticles | High drug loading capacity; low immunogenicity                                                      | Potential toxicity warrants careful consideration                                     |
| MOFs                    | High surface area; ease of functionalization; suitable for effective antibiotic storage and release | Frequently lack stability                                                             |

**5. Biocompatibility assessment:** although certain materials (e.g., nanogels and CMVs) have shown good biocompatibility, systematic evaluation of their potential side effects in long-term use remains essential.

**6. Development of new nano-delivery systems:** increasing the specificity and sensitivity of these delivery platforms could enable real-time monitoring, early intervention, and cost-effective treatment.

In conclusion, as a nanotechnology, nano-delivery systems enhance their function in treating biofilm diseases through specific modifications. This article provides a review of the application progress of nano-delivery systems in the treatment of biofilm diseases. In addition to developing new antibiotics, nano-delivery systems may be a new strategy for the future treatment of bacterial infections and biofilm diseases. Although there are still challenges in preparation, quality control, personalized application, and regulation, future research and development will help address these issues and promote the clinical application of nano-delivery systems.

|                      |                                                       |
|----------------------|-------------------------------------------------------|
| CMVs                 | Cell membrane vesicles                                |
| HMV                  | Hybrid membrane vesicle                               |
| O/W                  | Oil in water                                          |
| W/O                  | Water in oil                                          |
| CL                   | Clove oil                                             |
| Hb                   | Hemoglobin                                            |
| TCS                  | Triclosan                                             |
| LP                   | <i>Lactobacillus plantarum</i>                        |
| PLGA                 | Poly(lactic-co-glycolic acid)                         |
| NPs                  | Nanoparticles                                         |
| CS                   | Chitosan                                              |
| Oxa                  | Oxacillin                                             |
| CSNPs                | Chitosan nanoparticles                                |
| DNase                | Deoxyribonuclease                                     |
| PMPC                 | Poly(2-methacryloxyethyl phosphate choline) copolymer |
| ROS                  | Reactive oxygen species                               |
| CQDs                 | Carbon quantum dots                                   |
| h-PAMAM              | Hyperbranched polyamide                               |
| PAMAM                | Branched polyamide                                    |
| NO                   | Nitric oxide                                          |
| AZM                  | Azithromycin                                          |
| Cur                  | Curcumin                                              |
| DA                   | 2,3-Dimethyl maleic anhydride                         |
| MSN                  | Mesoporous silica nanoparticles                       |
| PEI                  | Polyethyleneimine                                     |
| <i>P. aeruginosa</i> | <i>Pseudomonas aeruginosa</i>                         |
| Am                   | $\alpha$ -Amylase                                     |
| Cef                  | Cefepime                                              |
| <i>E. coli</i>       | <i>Escherichia coli</i>                               |
| CDs                  | Carbon nanodots                                       |
| KCDs                 | Carbon nanodots derived from kanamycin                |
| GSNC                 | Gold and silver nanocages                             |
| Cyh                  | Cysteine hydrochloride                                |
| ZIF-8                | Zeolitic imidazolate framework-8                      |
| CIP                  | Ciprofloxacin                                         |
| MB                   | Methylene blue                                        |

## Abbreviations

|                  |                                                    |
|------------------|----------------------------------------------------|
| MOFs             | Metal-organic frameworks                           |
| DNA              | Deoxyribonucleic acid                              |
| EPS              | Extracellular polymeric substances                 |
| PTT              | Photothermal therapy                               |
| PDT              | Photodynamic therapy                               |
| PEG              | Polyethylene glycol                                |
| pMPC             | Poly[2-(methacryloyloxy)ethyl phosphorylcholine]   |
| MRSA             | <i>Methicillin-resistant Staphylococcus aureus</i> |
| NIR              | Near-infrared                                      |
| ILs              | Immunoliposomes                                    |
| <i>S. aureus</i> | <i>Staphylococcus aureus</i>                       |
| SLNs             | Solid lipid nanoparticles                          |
| MVs              | Membrane vesicles                                  |
| BMVs             | Bacterial membrane vesicles                        |
| OMVs             | Outer membrane vesicles                            |





- infections in cystic fibrosis patients, *J. Antimicrob. Chemother.*, 2015, **70**(3), 784–796.
- 24 H. Nsairat, W. Alshaer, F. Odeh, *et al.*, Recent advances in using liposomes for delivery of nucleic acid-based therapeutics, *OpenNano*, 2023, **11**, 100132.
  - 25 I. Munaweera, S. Shaikh, D. Maples, *et al.*, Temperature-sensitive liposomal ciprofloxacin for the treatment of biofilm on infected metal implants using alternating magnetic fields, *Int. J. Hyperthermia*, 2018, **34**(2), 189–200.
  - 26 J. J. Verhoef and T. J. Anchordoquy, Questioning the Use of PEGylation for Drug Delivery, *Drug Delivery Transl. Res.*, 2013, **3**(6), 499–503.
  - 27 M. Kluzek, Y. Oppenheimer-Shaanan, T. Dadosh, *et al.*, Designer Liposomal Nanocarriers Are Effective Biofilm Eradicators, *ACS Nano*, 2022, **16**(10), 15792–15804.
  - 28 Z. Zhou, F. Hu, S. Hu, *et al.*, pH-Activated nanoparticles with targeting for the treatment of oral plaque biofilm, *J. Mater. Chem. B*, 2018, **6**(4), 586–592.
  - 29 Y. Zhao, X. Dai, X. Wei, *et al.*, Near-Infrared Light-Activated Thermosensitive Liposomes as Efficient Agents for Photothermal and Antibiotic Synergistic Therapy of Bacterial Biofilm, *ACS Appl. Mater. Interfaces*, 2018, **10**(17), 14426–14437.
  - 30 S. Afrasiabi, A. Partoazar and N. Chiniforush, In vitro study of nanoliposomes containing curcumin and doxycycline for enhanced antimicrobial photodynamic therapy against *Aggregatibacter actinomycetemcomitans*, *Sci. Rep.*, 2023, **13**(1), 11552.
  - 31 P. Cressey, L. G. Bronstein, R. Benmahmoudi, *et al.*, Novel liposome-like assemblies composed of phospholipid-porphyrin conjugates with photothermal and photodynamic activities against bacterial biofilms, *Int. J. Pharm.*, 2022, **623**, 121915.
  - 32 W. Xiu, H. Dong, X. Chen, *et al.*, Metabolic Modulation-Mediated Antibiotic and Immune Activation for Treatment of Chronic Lung Infections, *ACS Nano*, 2024, **18**(23), 15204–15217.
  - 33 E. N. Taylor, K. M. Kummer, D. Dyondi, *et al.*, Multi-scale strategy to eradicate *Pseudomonas aeruginosa* on surfaces using solid lipid nanoparticles loaded with free fatty acids, *Nanoscale*, 2014, **6**(2), 825–832.
  - 34 R. Tenchov, R. Bird, A. E. Curtze, *et al.*, Lipid Nanoparticles—From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement, *ACS Nano*, 2021, **15**(11), 16982–17015.
  - 35 A. Radaic, E. Malone, P. Kamarajan, *et al.*, Solid Lipid Nanoparticles Loaded with Nisin (SLN-Nisin) are More Effective Than Free Nisin as Antimicrobial, Antibiofilm, and Anticancer Agents, *J. Biomed. Nanotechnol.*, 2022, **18**(4), 1227–1235.
  - 36 Z. Ehsan and J. P. Clancy, Management of *Pseudomonas aeruginosa* infection in cystic fibrosis patients using inhaled antibiotics with a focus on nebulized liposomal amikacin, *Future Microbiol.*, 2015, **10**(12), 1901–1912.
  - 37 M. Alhajlan, M. Alhariri and A. Omri, Efficacy and safety of liposomal clarithromycin and its effect on *Pseudomonas aeruginosa* virulence factors, *Antimicrob. Agents Chemother.*, 2013, **57**(6), 2694–2704.
  - 38 K. Ahmed, P. W. Muiruri, G. H. Jones, *et al.*, The effect of grafted poly(ethylene glycol) on the electrophoretic properties of phospholipid liposomes and their adsorption to bacterial biofilms, *Colloids Surf., A*, 2001, **194**, 287–296.
  - 39 Y. Meng, X. Hou, J. Lei, *et al.*, Multi-functional Liposomes Enhancing Target and Antibacterial Immunity for Antimicrobial and Anti-Biofilm Against Methicillin-Resistant *Staphylococcus aureus*, *Pharm. Res.*, 2016, **33**(3), 763–775.
  - 40 Y. Zhang, Y. Zhao, D. Dong, *et al.*, Effects of isosorbide mononitrate loaded nanoparticles conjugated with anti-*Staphylococcus aureus*  $\alpha$ -toxin on *Staphylococcus aureus* biofilms, *Exp. Ther. Med.*, 2020, **19**(2), 1267–1274.
  - 41 E. N. Taylor, K. M. Kummer, D. Dyondi, *et al.*, Multi-scale strategy to eradicate *Pseudomonas aeruginosa* on surfaces using solid lipid nanoparticles loaded with free fatty acids, *Nanoscale*, 2014, **6**(2), 825–832.
  - 42 N. Nafee, D. M. Gaber, A. Abouelfetouh, *et al.*, Enzyme-Linked Lipid Nanocarriers for Coping Pseudomonal Pulmonary Infection. Would Nanocarriers Complement Biofilm Disruption or Pave Its Road?, *Int. J. Nanomed.*, 2024, **19**, 3861–3890.
  - 43 T. Shi and Y. Chen, Preparation of cell membrane-coated nanoparticles and its application to antimicrobial, *J. Shanghai Jiaotong Univ., Med. Sci.*, 2021, **41**(7), 953–958.
  - 44 J. Xie, X. Liu and G. Liu, A new track for antibacterial treatment: Progress and challenges of using cytomembrane-based vesicles to combat bacteria, *Particuology*, 2023, **78**, 136–146.
  - 45 Q. V. Le, J. Lee, H. Lee, *et al.*, Cell membrane-derived vesicles for delivery of therapeutic agents, *Acta Pharm. Sin. B*, 2021, **11**(8), 2096–2113.
  - 46 W. Huang, L. Meng, Y. Chen, *et al.*, Bacterial outer membrane vesicles as potential biological nanomaterials for antibacterial therapy, *Acta Biomater.*, 2022, **140**, 102–115.
  - 47 L. Weng, L. Wu, R. Guo, *et al.*, *Lactobacillus* cell envelope-coated nanoparticles for antibiotic delivery against cariogenic biofilm and dental caries, *J. Nanobiotechnol.*, 2022, **20**(1), 356.
  - 48 X. Pang, X. Liu, Y. Cheng, *et al.*, Sono-Immunotherapeutic Nanocapturer to Combat Multidrug-Resistant Bacterial Infections, *Adv. Mater.*, 2019, **31**(35), e1902530.
  - 49 L. Ding, X. Liang, J. Ma, *et al.*, Sono-Triggered Biomimetically Nanoantibiotics Mediate Precise Sequential Therapy of MRSA-Induced Lung Infection, *Adv. Mater.*, 2024, e2403612.
  - 50 J. Zhu, R. Xie, R. Gao, *et al.*, Multimodal nanoimmunotherapy engages neutrophils to eliminate *Staphylococcus aureus* infections, *Nat. Nanotechnol.*, 2024, **19**(7), 1032–1043.
  - 51 X. Peng, J. Chen, Y. Gan, *et al.*, Biofunctional lipid nanoparticles for precision treatment and prophylaxis of bacterial infections, *Sci. Adv.*, 2024, **10**(14), eadk9754.
  - 52 F. Gao, L. Xu, B. Yang, *et al.*, Kill the real with the fake: eliminate intracellular *Staphylococcus aureus* using nano-



65 R. Yang, H. Zhang, Z. Marfavi, *et al.*, Infiltrating Perfluorocarbon Nanoemulsion and Sensitizing Ultrasound Cavitation to Eradicate Biofilms, *ACS Appl. Mater. Interfaces*, 2024, **16**(3), 3126–3138.

79 Y. Liu, H. J. Busscher, B. Zhao, *et al.*, Surface-Adaptive, Antimicrobially Loaded, Micellar Nanocarriers with Enhanced Penetration and Killing Efficiency in Staphylococcal Biofilms, *ACS Nano*, 2016, **10**(4), 4779–4789.

- 80 Z. Huang, T. Zhou, Y. Yuan, *et al.*, Synthesis of carbon quantum dot-poly lactic-co-glycolic acid hybrid nanoparticles for chemo-photothermal therapy against bacterial biofilms, *J. Colloid Interface Sci.*, 2020, **577**, 66–74.
- 81 V. Gajbhiye, V. K. Palanirajan, R. K. Tekade, *et al.*, Dendrimers as therapeutic agents: a systematic review, *J. Pharm. Pharmacol.*, 2009, **61**(8), 989–1003.
- 82 A. Santos, F. Veiga and A. Figueiras, Dendrimers as Pharmaceutical Excipients: Synthesis, Properties, Toxicity and Biomedical Applications, *Materials*, 2019, **13**(1), 65.
- 83 R. Kharwade, S. More, A. Warokar, *et al.*, Starburst pamam dendrimers: Synthetic approaches, surface modifications, and biomedical applications, *Arabian J. Chem.*, 2020, **13**(7), 6009–6039.
- 84 M. Bergmann, G. Michaud, R. Visini, *et al.*, Multivalency effects on *Pseudomonas aeruginosa* biofilm inhibition and dispersal by glycopeptide dendrimers targeting lectin LecA, *Org. Biomol. Chem.*, 2016, **14**(1), 138–148.
- 85 Y. Gao, J. Wang, M. Chai, *et al.*, Size and Charge Adaptive Clustered Nanoparticles Targeting the Biofilm Microenvironment for Chronic Lung Infection Management, *ACS Nano*, 2020, **14**(5), 5686–5699.
- 86 A. Pamukçu, N. Erdoğan and D. Şen Karaman, Polyethylenimine-grafted mesoporous silica nanocarriers markedly enhance the bactericidal effect of curcumin against *Staphylococcus aureus* biofilm, *J. Biomed. Mater. Res., Part B*, 2022, **110**(11), 2506–2520.
- 87 Y. Chen, Y. Gao, Y. Huang, *et al.*, Inhibiting Quorum Sensing by Active Targeted pH-Sensitive Nanoparticles for Enhanced Antibiotic Therapy of Biofilm-Associated Bacterial Infections, *ACS Nano*, 2023, **17**(11), 10019–10032.
- 88 Y. Zhou, W. Huang, J. Liu, *et al.*, Self-assembly of hyperbranched polymers and its biomedical applications, *Adv. Mater.*, 2010, **22**(41), 4567–4590.
- 89 A. Labena, K. I. Kabel and R. K. Farag, One-pot synthesis of dendritic hyperbranched PAMAM and assessment as a broad spectrum antimicrobial agent and anti-biofilm, *Mater. Sci. Eng., C*, 2016, **58**, 1150–1159.
- 90 L. Yang, F. Teles, W. Gong, *et al.*, Antibacterial action of nitric oxide-releasing hyperbranched polymers against ex vivo dental biofilms, *Dent. Mater.*, 2020, **36**(5), 635–644.
- 91 S. Yu, G. Li, R. Liu, *et al.*, Dendritic Fe<sub>3</sub>O<sub>4</sub>@Poly(dopamine) @PAMAM Nanocomposite as Controllable NO-Releasing Material: A Synergistic Photothermal and NO Antibacterial Study, *Adv. Funct. Mater.*, 2018, **28**(20), 1707440.
- 92 J. M. Caster, A. N. Patel, T. Zhang, *et al.*, Investigational nanomedicines in 2016: a review of nanotherapeutics currently undergoing clinical trials, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.*, 2017, **9**(1), 27312983.
- 93 S. Akhtar, B. Al-Zaid, A. Z. El-Hashim, *et al.*, Impact of PAMAM delivery systems on signal transduction pathways in vivo: Modulation of ERK1/2 and p38 MAP kinase signaling in the normal and diabetic kidney, *Int. J. Pharm.*, 2016, **514**(2), 353–363.
- 94 C. F. Price, D. Tyssen, S. Sonza, *et al.*, SPL7013 Gel (VivaGel®) retains potent HIV-1 and HSV-2 inhibitory activity following vaginal administration in humans, *PLoS One*, 2011, **6**(9), e24095.
- 95 Y. Kim, E. J. Park and D. H. Na, Recent progress in dendrimer-based nanomedicine development, *Arch. Pharmacol. Res.*, 2018, **41**(6), 571–582.
- 96 N. Hazime, Y. Belguesmia, A. Barras, *et al.*, Enhanced Antibacterial Activity of Dermaseptin through Its Immobilization on Alginate Nanoparticles-Effects of Menthol and Lactic Acid on Its Potentialization, *Antibiotics*, 2022, **11**(6), 787.
- 97 L. Spósito, D. Fonseca, S. Gonçalves Carvalho, *et al.*, Engineering resveratrol-loaded chitosan nanoparticles for potential use against *Helicobacter pylori* infection, *Eur. J. Pharm. Biopharm.*, 2024, **199**, 114280.
- 98 L. Yang, F. Teles, W. Gong, *et al.*, Antibacterial action of nitric oxide-releasing hyperbranched polymers against ex vivo dental biofilms, *Dent. Mater.*, 2020, **36**(5), 635–644.
- 99 M. C. Jennings, L. E. Ator, T. J. Paniak, *et al.*, Biofilm-eradicating properties of quaternary ammonium amphiphiles: simple mimics of antimicrobial peptides, *ChemBioChem*, 2014, **15**(15), 2211–2215.
- 100 H. Haidari, Z. Kopecki, R. Bright, *et al.*, Ultrasmall AgNP-Impregnated Biocompatible Hydrogel with Highly Effective Biofilm Elimination Properties, *ACS Appl. Mater. Interfaces*, 2020, **12**(37), 41011–41025.
- 101 J. Hu, C. Zhang, L. Zhou, *et al.*, A smart hydrogel for on-demand delivery of antibiotics and efficient eradication of biofilms, *Sci. China Mater.*, 2021, **64**(4), 1035–1046.
- 102 S. Manna, A. K. Ghosh and S. M. Mandal, Curd-Peptide Based Novel Hydrogel Inhibits Biofilm Formation, Quorum Sensing, Swimming Motility of Multi-Antibiotic Resistant Clinical Isolates and Accelerates Wound Healing Activity, *Front. Microbiol.*, 2019, **10**, 951.
- 103 V. O. Fasiku, C. A. Omolo, N. Devnarain, *et al.*, Chitosan-Based Hydrogel for the Dual Delivery of Antimicrobial Agents Against Bacterial Methicillin-Resistant *Staphylococcus aureus* Biofilm-Infected Wounds, *ACS Omega*, 2021, **6**(34), 21994–22010.
- 104 T. Du, Z. Xiao, G. Zhang, *et al.*, An injectable multifunctional hydrogel for eradication of bacterial biofilms and wound healing, *Acta Biomater.*, 2023, **161**, 112–133.
- 105 S. Liang, L. Xiao, Y. Fang, *et al.*, A nanocomposite hydrogel for co-delivery of multiple anti-biofilm therapeutics to enhance the treatment of bacterial biofilm-related infections, *Int. J. Pharm.*, 2024, **649**, 123638.
- 106 H. Chen, J. Cheng, X. Cai, *et al.*, pH-Switchable Antimicrobial Supramolecular Hydrogels for Synergistically Eliminating Biofilm and Promoting Wound Healing, *ACS Appl. Mater. Interfaces*, 2022, **14**(16), 18120–18132.
- 107 Z. Liu, K. Guo, L. Yan, *et al.*, Janus nanoparticles targeting extracellular polymeric substance achieve flexible elimination of drug-resistant biofilms, *Nat. Commun.*, 2023, **14**(1), 5132.
- 108 K. Richter, N. Thomas, J. Claeys, *et al.*, A Topical Hydrogel with Deferiprone and Gallium-Protoporphyrin Targets Bacterial Iron Metabolism and Has Antibiofilm Activity,



- Antimicrob. Agents Chemother.*, 2017, **61**(6), e00481–e00417.
- 109 S. M. Dizaj, F. Lotfipour, M. Barzegar-Jalali, *et al.*, Antimicrobial activity of the metals and metal oxide nanoparticles, *Mater. Sci. Eng., C*, 2014, **44**, 278–284.
  - 110 H. Motamedi, S. Khademi Mazdeh, A. Akbarzadeh Khiavi, *et al.*, Optimization of Gold Nanoparticle Biosynthesis by *Escherichia coli* DH5 $\alpha$  and its Conjugation with Gentamicin, *J. Nano Res.*, 2015, **32**, 105–193.
  - 111 B. A. Hasoon, K. H. Jawad and S. S. Abdulsahib, Synthesis of Ciprofloxacin-Conjugated Gold Nanoparticles and their Study Antibacterial Effects on Growth Biofilm Formation Through Nebulizer Mask Against Respiratory Infection, *Plasmonics*, 2023, 1–15.
  - 112 C. Zhang, D. T. Shi, K. C. Yan, *et al.*, A glycoconjugate-based gold nanoparticle approach for the targeted treatment of *Pseudomonas aeruginosa* biofilms, *Nanoscale*, 2020, **12**(45), 23234–23240.
  - 113 B. Le Ouay and F. Stellacci, Antibacterial activity of silver nanoparticles: A surface science insight, *Nano Today*, 2015, **10**(3), 339–354.
  - 114 K. Zheng, M. I. Setyawati, D. T. Leong, *et al.*, Antimicrobial silver nanomaterials, *Coord. Chem. Rev.*, 2018, **357**, 1–17.
  - 115 G. A. Pang, J. Laufer, R. Niessner, *et al.*, Photoacoustic Signal Generation in Gold Nanospheres in Aqueous Solution: Signal Generation Enhancement and Particle Diameter Effects, *J. Phys. Chem. C*, 2016, **120**, 27646–27656.
  - 116 Z. Wang, L. Chen, Z. Chu, *et al.*, Gemcitabine-loaded gold nanospheres mediated by albumin for enhanced anti-tumor activity combining with CT imaging, *Mater. Sci. Eng., C*, 2018, **89**, 106–118.
  - 117 W. Li, H. Zhang, X. Guo, *et al.*, Gold Nanospheres-Stabilized Indocyanine Green as a Synchronous Photodynamic-Photothermal Therapy Platform That Inhibits Tumor Growth and Metastasis, *ACS Appl. Mater. Interfaces*, 2017, **9**(4), 3354–3367.
  - 118 L. An, Y. Wang, Q. Tian, *et al.*, Small Gold Nanorods: Recent Advances in Synthesis, Biological Imaging, and Cancer Therapy, *Materials*, 2017, **10**(12), 1372.
  - 119 Y.-S. Chen, Y. Zhao, S. J. Yoon, *et al.*, Miniature gold nanorods for photoacoustic molecular imaging in the second near-infrared optical window, *Nat. Nanotechnol.*, 2019, **14**(5), 465–472.
  - 120 O. B. Knights, S. Ye, N. Ingram, *et al.*, Optimising gold nanorods for photoacoustic imaging in vitro, *Nanoscale Adv.*, 2019, **1**(4), 1472–1481.
  - 121 F. Ratto, S. Centi, C. Avigo, *et al.*, A Robust Design for Cellular Vehicles of Gold Nanorods for Multimodal Imaging, *Adv. Funct. Mater.*, 2016, **26**(39), 7178–7185.
  - 122 Y. Liu, H. Yuan, A. Fales, *et al.*, Multifunctional gold nanostars for molecular imaging and cancer therapy, *Front. Chem.*, 2015, **3**(3), 51.
  - 123 F. Xia, J. Niu, Y. Hong, *et al.*, Matrix metalloproteinase 2 targeted delivery of gold nanostars decorated with IR-780 iodide for dual-modal imaging and enhanced photothermal/photodynamic therapy, *Acta Biomater.*, 2019, **89**, 289–299.
  - 124 W. Shang, C. Zeng, Y. Du, *et al.*, Core-Shell Gold Nanorod@Metal-Organic Framework Nanoprobes for Multimodality Diagnosis of Glioma, *Adv. Mater.*, 2017, **29**(3), 1604381.
  - 125 Z. Qin, Y. Zheng, T. Du, *et al.*, Cysteamine: A key to trigger aggregation-induced NIR-II photothermal effect and silver release booming of gold-silver nanocages for synergetic treatment of multidrug-resistant bacteria infection, *Chem. Eng. J.*, 2021, **414**, 128779.
  - 126 B. Pang, X. Yang and Y. Xia, Putting gold nanocages to work for optical imaging, controlled release and cancer theranostics, *Nanomedicine*, 2016, **11**(13), 1715–1728.
  - 127 K. H. Jawad, Laser ablation mediated ZnO nanoparticles inhibit growth and biofilm forming potential of urinary tract bacterium *Proteus mirabilis*, *Adv. Nat. Sci.: Nanosci. Nanotechnol.*, 2023, **14**(1), 015002.
  - 128 F. Lin, C. Li and Z. Chen, Bacteria-Derived Carbon Dots Inhibit Biofilm Formation of *Escherichia coli* without Affecting Cell Growth, *Front. Microbiol.*, 2018, **9**, 259.
  - 129 W. H. Lee, R. Rohanizadeh and C. Y. Loo, In situ functionalizing calcium phosphate biomaterials with curcumin for the prevention of bacterial biofilm infections, *Colloids Surf., B*, 2021, **206**, 111938.
  - 130 C. H. N. Barros, H. Devlin, D. W. Hiebner, *et al.*, Enhancing curcumin's solubility and antibiofilm activity via silica surface modification, *Nanoscale Adv.*, 2020, **2**(4), 1694–1708.
  - 131 H. Yan, H. Yang, K. Li, *et al.*, Effects of Chlorhexidine-Encapsulated Mesoporous Silica Nanoparticles on the Anti-Biofilm and Mechanical Properties of Glass Ionomer Cement, *Molecules*, 2017, **22**(7), 1225.
  - 132 Y. Wang, Z. Wang, K. Xie, *et al.*, High-Efficiency Cellular Reprogramming by Nanoscale Puncturing, *Nano Lett.*, 2020, **20**(7), 5473–5481.
  - 133 R. Li, T. Chen and X. Pan, Metal-Organic-Framework-Based Materials for Antimicrobial Applications, *ACS Nano*, 2021, **15**(3), 3808–3848.
  - 134 S. A. Polash, T. Khare, V. Kumar, *et al.*, Prospects of Exploring the Metal–Organic Framework for Combating Antimicrobial Resistance, *ACS Appl. Bio Mater.*, 2021, **4**(12), 8060–8079.
  - 135 C. Pettinari, R. Pettinari, C. Di Nicola, *et al.*, Antimicrobial MOFs, *Coord. Chem. Rev.*, 2021, **446**, 214121.
  - 136 F. Akbarzadeh, M. Motaghi, N. P. S. Chauhan, *et al.*, A novel synthesis of new antibacterial nanostructures based on Zn-MOF compound: design, characterization and a high performance application, *Heliyon*, 2020, **6**(1), e03231.
  - 137 A. Arenas-Vivo, G. Amariei, S. Aguado, *et al.*, An Ag-loaded photoactive nano-metal organic framework as a promising biofilm treatment, *Acta Biomater.*, 2019, **97**, 490–500.
  - 138 P. Raju, T. Ramalingam, T. Nooruddin, *et al.*, In vitro assessment of antimicrobial, antibiofilm and larvicidal activities of bioactive nickel metal organic framework, *J. Drug Delivery Sci. Technol.*, 2020, **56**, 101560.



- 139 Y.-L. Xiang, S.-H. Huang, D.-Y. Tang, *et al.*, MOF/polypeptide hybrid nanocomposites with pH/lipase dual responsive drug release and photodynamic effect for combination treatment of drug-resistant bacterial infection, *Mater. Des.*, 2023, **232**, 112180.
- 140 M. Ding, W. Zhao, X. Zhang, *et al.*, Charge-switchable MOF nanocomplex for enhanced biofilm penetration and eradication, *J. Hazard. Mater.*, 2022, **439**, 129594.
- 141 Q. Deng, P. Sun, L. Zhang, *et al.*, Porphyrin MOF Dots-Based, Function-Adaptive Nanoplatfrom for Enhanced Penetration and Photodynamic Eradication of Bacterial Biofilms, *Adv. Funct. Mater.*, 2019, **29**(30), 1903018.
- 142 J. Yang, K. Li and J. Gu, Hierarchically Macro-Microporous Ce-Based MOFs for the Cleavage of DNA, *ACS Mater. Lett.*, 2022, **4**(2), 385–391.
- 143 F. Xia, K. Li, J. Yang, *et al.*, DNase-mimetics based on bi-metallic hierarchically macroporous MOFs for the efficient inhibition of bacterial biofilm, *Sci. China Mater.*, 2024, **67**(1), 343–354.
- 144 Z. Liu, F. Wang, J. Ren, *et al.*, A series of MOF/Ce-based nanozymes with dual enzyme-like activity disrupting biofilms and hindering recolonization of bacteria, *Biomaterials*, 2019, **208**, 21–31.
- 145 X. Yuan, J. Xiong, X. Wu, *et al.*, Ultrasmall Ce-based metal-organic frameworks nanozyme with hydrolytic activity for boosting antibiofilm therapy, *Chem. Eng. J.*, 2024, **480**, 148246.
- 146 X. Ren, L. Chang, Y. Hu, *et al.*, Au@MOFs used as peroxidase-like catalytic nanozyme for bacterial infected wound healing through bacterial membranes disruption and protein leakage promotion, *Mater. Des.*, 2023, **229**, 111890.
- 147 H. Qiu, F. Pu, Z. Liu, *et al.*, Depriving Bacterial Adhesion-Related Molecule to Inhibit Biofilm Formation Using CeO<sub>2</sub>-Decorated Metal-Organic Frameworks, *Small*, 2019, **15**(36), e1902522.
- 148 Y. Zang, T. R. Roberts, A. I. Batchinsky, *et al.*, Metal-Organic Framework Polymer Coating Inhibits Staphylococcus aureus Attachment on Medical Circulation Tubing under Static and Dynamic Flow Conditions, *ACS Appl. Bio Mater.*, 2020, **3**(6), 3535–3543.
- 149 Z. Wang, P. Zhang, C. Yin, *et al.*, Antibiotic-Derived Carbon-Nanodot-Decorated Hydrogel for Reactive Oxygen Species-Enhanced Anti-Infection Through Biofilm Damage, *Adv. Funct. Mater.*, 2023, **33**(29), 2300341.
- 150 Y. Peng, S. Pang, Y. Zeng, *et al.*, Antibiotic-free ocular sterilization while suppressing immune response to protect corneal transparency in infectious keratitis treatment, *J. Controlled Release*, 2024, **374**, 563–576.