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

Yijia Xie,†[a] Huanhuan Liu,†[a] Zihao Teng,†[b] Jiaxin Ma*[a] and Gang Liu *[a]

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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.

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.[1,2] 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.[3] 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.[4] 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.[5] 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.[6] 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.[7] 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.[8,9] 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-

[a]*State Key Laboratory of Vaccines for Infectious Diseases, Center for Molecular Imaging and Translational Medicine, Xiang An Biomedicine Laboratory, National Innovation Platform for Industry-Education Integration in Vaccine Research, School of Public Health, Xiamen University, Xiamen, 361102, China.*
E-mail: jiaxinma@xmu.edu.cn, gangliu.cmitm@xmu.edu.cn
[b]*School of Pharmaceutical Sciences, Xiamen University, Xiamen, 361102, China*
†These authors have contributed equally to this work.

ing delivery efficiency. Additionally, nano-delivery systems can be designed as smart responsive platforms that react to changes in the infection microenvironment (*e.g.*, pH, enzymes, and hydrogen peroxide) or to physical stimuli (*e.g.*, light, ultrasound, and magnetic field). These systems can also be combined with photothermal therapy (PTT), photodynamic therapy (PDT), and gas therapy to effectively eradicate bacteria and biofilms.[10] Nano-delivery systems offer a novel therapeutic approach to biofilm-related infections by overcoming drug resistance and minimizing side effects.

Nano-delivery systems show great potential in the treatment of biofilm infections due to their unique physicochemical properties, especially when antibiotic efficacy is limited. This review aims to provide a comprehensive overview of the design strategies and recent advancements in commonly used nano-delivery systems for biofilm treatment, including liposomes, 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.

2. Overview of biofilms

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.[11,12] These EPS protect the bacteria within the biofilm (Fig. 1A). A mature

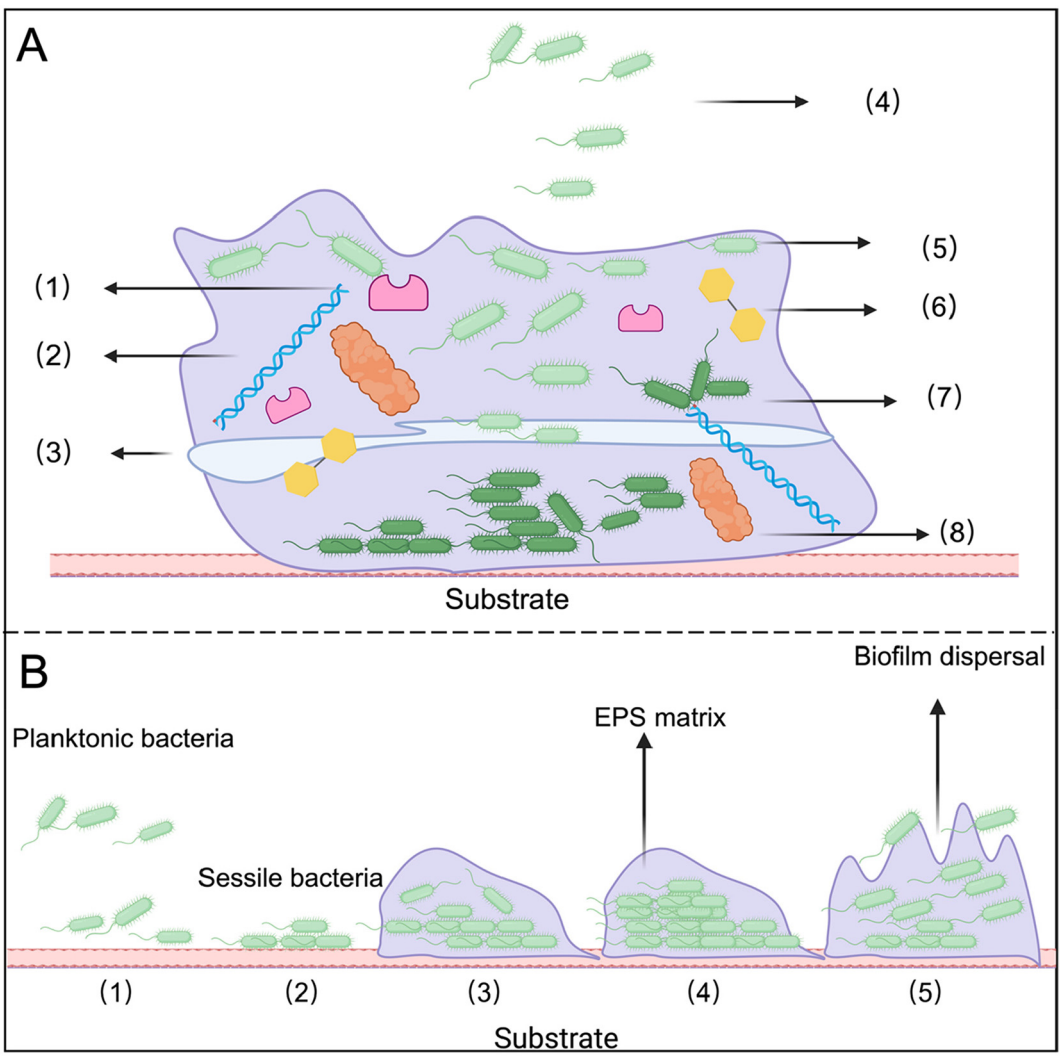

Fig. 1 (A) Composition of biofilm. (1) Exopolysaccharides; (2) Deoxyribonucleic acid (DNA); (3) Water channels; (4) Planktonic bacteria; (5) Surface bacteria; (6) Protein; (7) Nutrient deficient bacteria; (8) Enzymes. (B) Schematic diagram of biofilm formation. (1) Reversible attachment stage; (2) Irreversible attachment stage; (3) Microbial colony formation stage; (4) Biofilm maturation stage; (5) Bacterial shedding/diffusion stage. Created with BioRender.com.

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.[13]

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.[14]

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.[15]

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).[16] 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.[17] 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.[3,18] 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.[19] 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.[20] 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.[21] 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).[22,23] Moreover, differences in antimicrobial delivery are not solely related to liposome adsorption.[24] 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.[25] This lack of targeting limits the

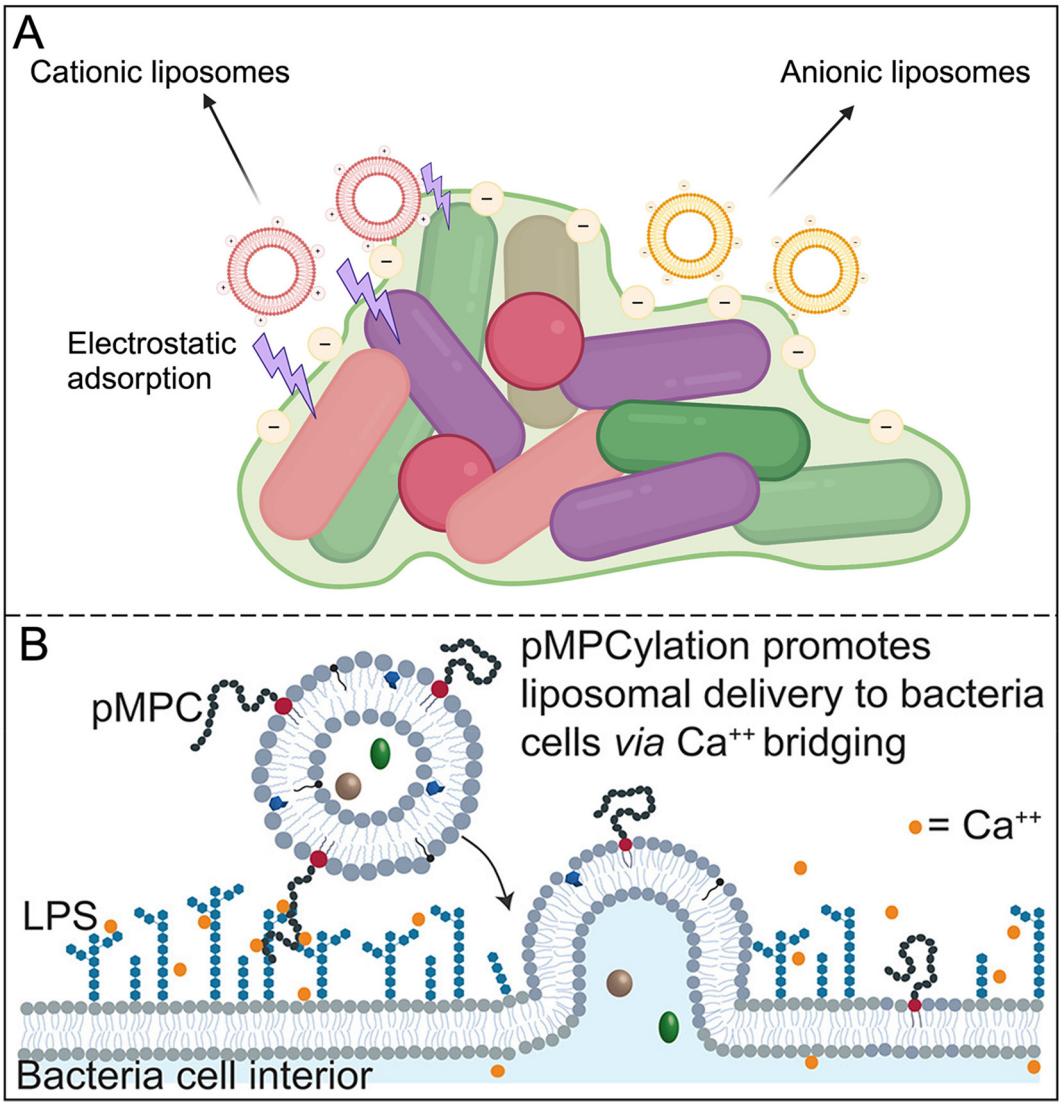

Fig. 2 (A) Different effects of surface charges of traditional liposomes on biofilms. Created with BioRender.com. (B) Schematic of proposed two-stage mechanism for calcium-mediated adhesion and fusion between pMPC-LUVs and *P. aeruginosa* membrane. Reproduced from ref. 27 with permission from *Monika 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.[26] 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).[27]

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 microenvironments 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).[25] 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.[28] 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).

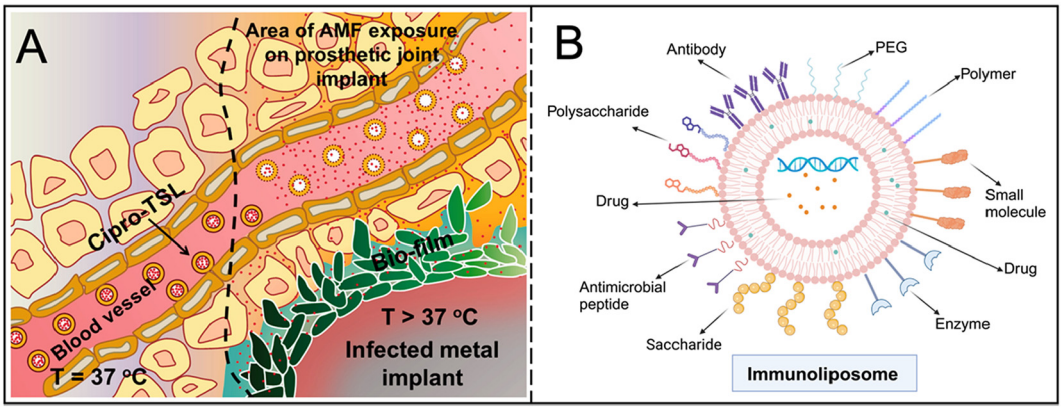

Fig. 3 (A) Schematic of ciprofloxacin release from temperature-sensitive liposomes in the vicinity of an infected metal implant heated by exposure to an alternating magnetic field. Reproduced from ref. 25 with permission from *Int J Hyperthermia*, copyright 2018. (B) Multiple antibody modifications of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

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).[29,30] Liposomes can also act as oxygen carriers to alleviate the anoxic microenvironment, thereby improving antibiotic efficacy and reducing drug resistance.[31] 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).[32]

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

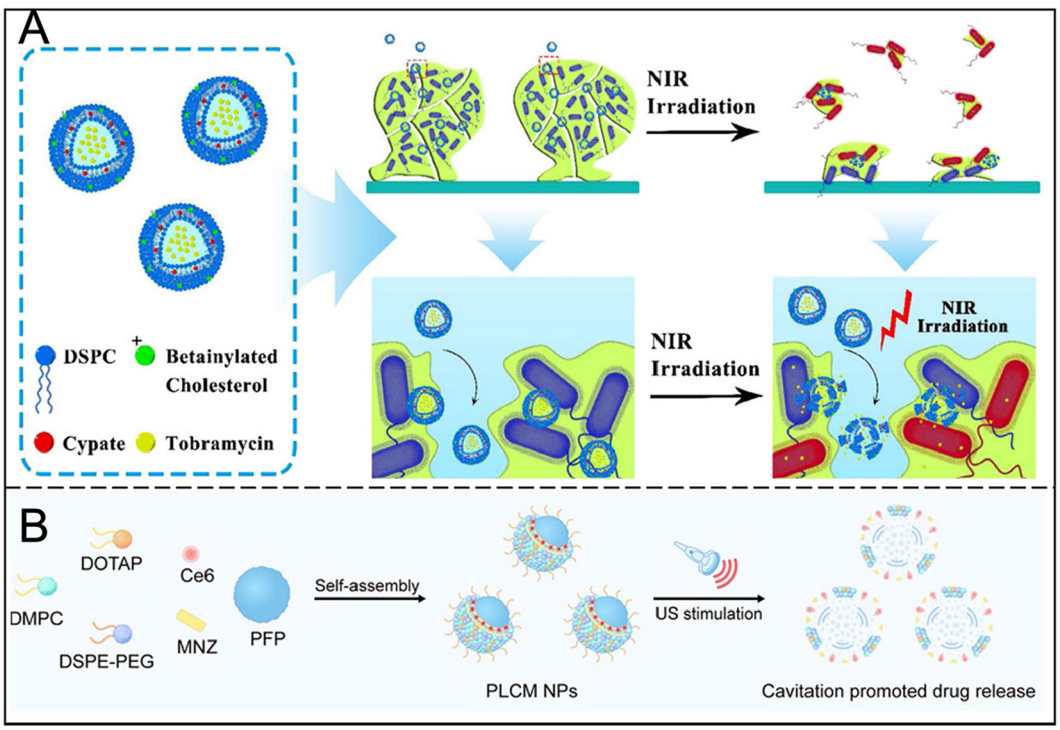

Fig. 4 (A) Structure and function of nanoparticles and mechanism of near-infrared light-activated thermosensitive liposomes for the treatment of biofilms. Reproduced from ref. 29 with permission from *ACS Appl Mater Interfaces*, copyright 2018. (B) Schematic illustration of the preparation and US-stimulated 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.[33]

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.[34] 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.[35]

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.[36] 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).[43] 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.[44,45] 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.[45] 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 *N*-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

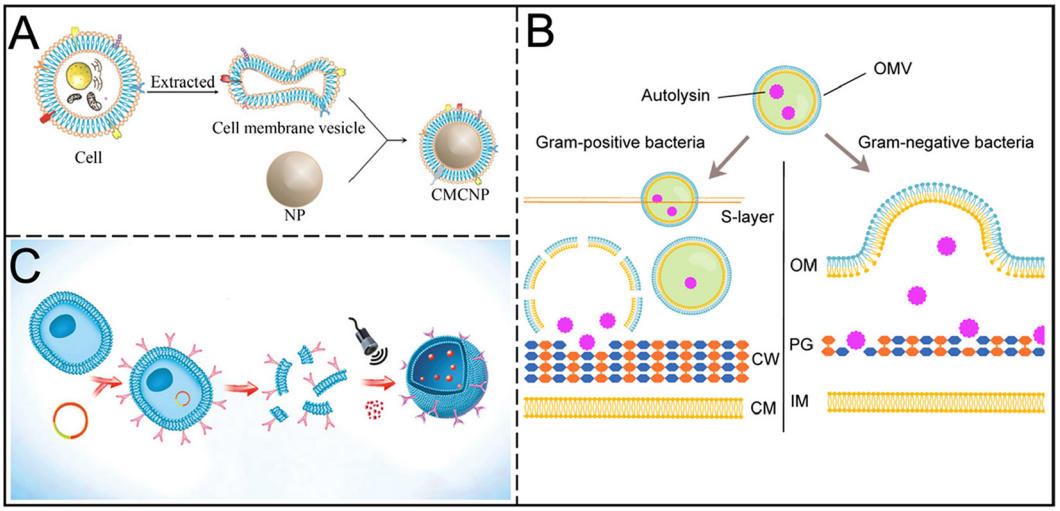

Fig. 5 (A) Structural representation of CMCNPs. Reproduced from ref. 43 with permission from *Journal of Shanghai Jiao Tong University (Medical Science)*, copyright 2021. (B) Schematic illustration of the antibacterial mechanisms of autolysin-loaded OMVs against Gram-positive and Gram-negative bacteria. 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.[46] 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.[47]

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 α-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).[48] 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.[49] 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.[50]

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 (HMV)-coated biocompatible lipid nanoparticles (LNP@HMVs) aimed at specifically delivering antibiotics to bacterial cells at infection sites. HMVs 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@HMVs on both planktonic bacteria and biofilms.[51] 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).[52]

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.[49] 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,[55] and their surfactant properties prevent phase separation.[56,57]

The natural antibacterial nanoemulsions include water-in-oil (W/O), oil-in-water (O/W) and double continuous types (Fig. 6A).[56] 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,[58] with peppermint nanoemulsions also showing inhibition of biofilm formation.[59] The phenolic hydroxyl groups of thyme and clove also enhanced their hydrophilicity and improved mem-

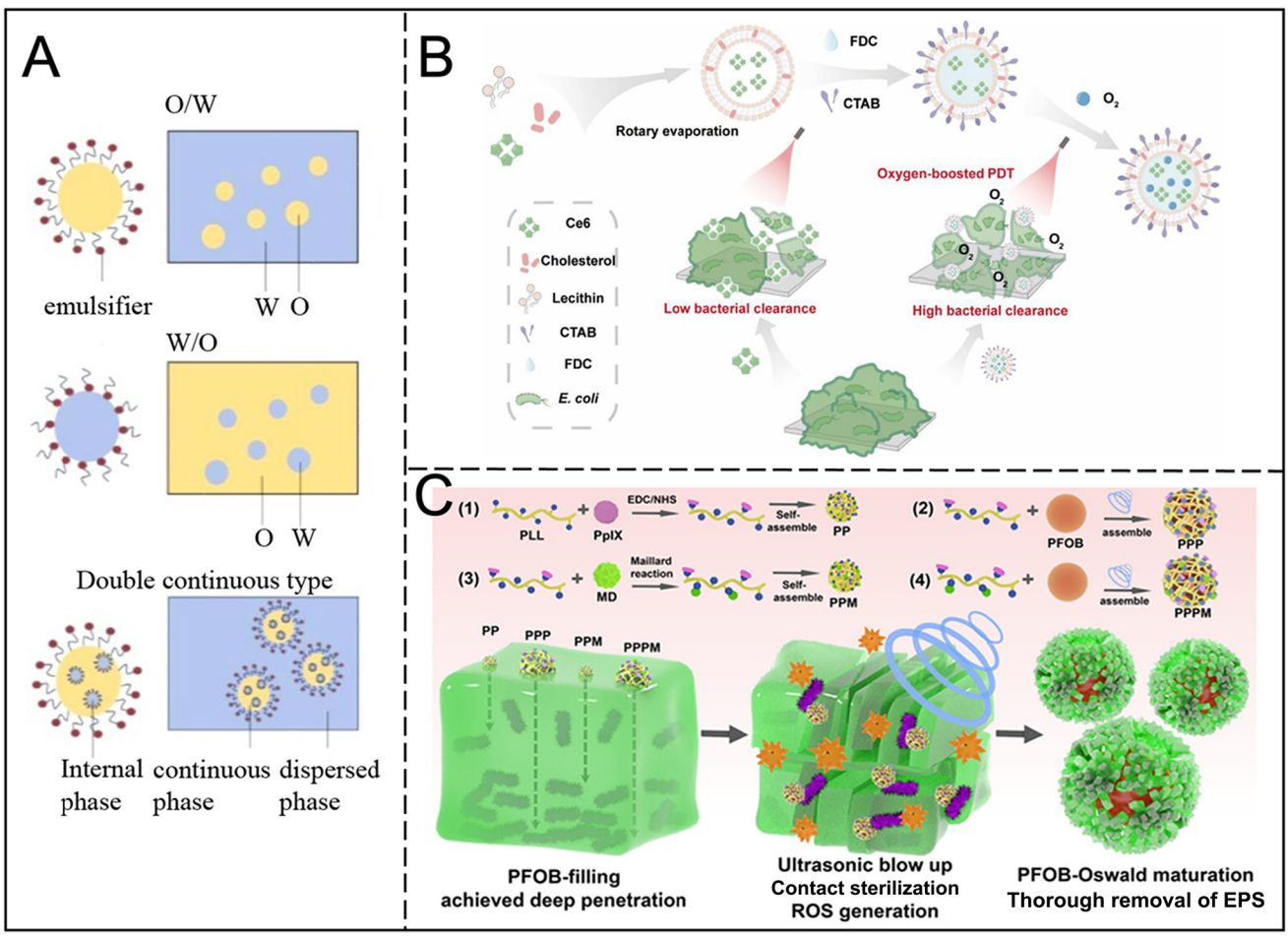

Fig. 6 (A) O/W, W/O, and double continuous type nanoemulsions. Reproduced from ref. 56 with permission from *Meat Research*, copyright 2022. (B) Schematic illustration of the fabrication process of Ce6@FDC nanoemulsion and its oxygen delivery for enhanced photodynamic antibacterial efficiency. Reproduced 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.

brane permeability.[60] Nanoemulsions combined with cashew gum and clove essential oil showed antioxidant and antibiofilm activity.[61]

Nanoemulsions can also achieve synergistic treatment, by encapsulating essential oils and antibiotics, improving the efficacy. For example, the combination of levofloxacin with clove oil can effectively remove biofilms.[62] In addition, porphyrin-based nanoemulsions have a good photosensitizer loading capacity, can directly target microbial cells, and enhance sensitivity to Gram-negative bacteria.[63] Oxygen, crucial to PDT, enhances the sensitivity of Gram-negative bacteria to treatment. Niu *et al.* synthesized a photodynamic perfluorocarbon nanoemulsion (Ce6@FDC) with oxygen transport capabilities, achieving a five-log reduction in planktonic bacteria and biofilm removal compared to free Ce6 treatment (Fig. 6B).[64] Combined with ultrasound, the biofilm can be further damaged. Low-intensity ultrasound is used to enhance the penetration of nanoemulsions and improve the destruction ability of biofilms (Fig. 6C).[65]

Nanoemulsions can encapsulate drugs or imaging probes and achieve precise delivery through targeted modifications, making them suitable for multiple drug delivery routes.[59,66] They exhibit low biotoxicity, do not promote resistant strains, and have a storage life of up to two years, facilitating transportation and clinical use.[67] However, the synthetic surfactants used in the preparation may present a risk of toxicity, so research into natural alternatives is particularly important. Scaling up the continuous production of nanoemulsions remains a challenge.

6. Polymers

Polymers, due to their modifiability, provide great flexibility in biofilm treatment. They can be classified as natural or artificial based on their composition source.

6.1 Natural polymers

Natural polymers have the advantages of diverse structure, extensibility and biocompatibility, and are effective drug carriers for inhibiting or eliminating bacterial biofilms. Among them, CS has good biocompatibility and antibacterial activity; through its positive charge interaction with bacterial cells, it effectively destroys the bacterial cell membrane and inhibits the formation of biofilm and bacterial growth. Although CS has mild bactericidal action and limited solubility,[68] studies have shown that improving the structure of CS can enhance its water solubility and antibacterial effect.[69] For example, CS nanoparticles (CSNPs) improve antibacterial potency by increasing the surface charge density and volume ratio. Combined with antibiotics (such as gentamicin)[70] or metal salts (such as silver, zinc, and copper),[71] the anti-biofilm effect of CS is significantly enhanced.

CSNPs can be used in different forms to achieve targeted antimicrobial therapy: nanospheres are used to adsorb or encapsulate drugs on the surface (Fig. 7A),[72] while nanocapsules encapsulate antimicrobials through core–shell structures (Fig. 7B).[73] Nanofibers, due to their needle-like physical structure, can penetrate the EPS matrix, delivering drugs into bacterial cells and eliminating biofilms (Fig. 7C).[74,75] It has been found that the combination of positively charged CSNPs with DNA enzymes or antimicrobial peptides has a highly efficient cleaning effect on Gram-positive and Gram-negative bacterial biofilms.[73] Core–shell nanocapsules and penetrating nanofibers can further enhance therapeutic effectiveness through deep delivery of effective drugs and are suitable for local infection control. In addition, sheet- and rod-like nanostructures have a "nanoknife" effect that can pierce bacterial membranes and increase antibacterial action.

6.2 Artificial polymers

Compared to natural polymers, synthetic polymers offer greater consistency and repeatability, and can be chemically modified to introduce specific functional groups for more precise drug release and targeting. Examples include polylactic acid-glycolic acid (PLGA) and micelles.

PLGA is an FDA-approved medicinal carrier material whose degradation products are safe for humans. PLGA nanoparticles can effectively encapsulate hydrophobic and hydrophilic drugs for sustained release and have been shown to be effective in removing *S. aureus* biofilms.[76] Xylitol in PLGA nanoparticles can enhance penetration into the biofilm matrix and overcome antibiotic resistance associated with biofilms.[77] The cationic PLGA nanopolymer can inhibit the growth of *Streptococcus mutans* within 24 hours, and can significantly destroy the biofilm at high concentrations.[78] In addition, polymers that respond to internal and external stimuli can increase antibacterial activity, such as pH-activated micelles that release drugs on demand (Fig. 8).[79] Polymers combined with PTT and PDT enhance the ability to eliminate biofilms under near-infrared irradiation. This multi-treatment strategy not only improves the antibacterial effect, but also provides a new idea for the treatment of biofilm-associated infections. Huang *et al.* have improved the loading efficiency of antibiotics by designing carbon quantum dots mixed with PLGA nanoparticles to effectively fight bacterial biofilms.[80] These results show that PLGA and its derived materials have broad application prospects in the field of antibacterial therapy.

Table 3 summarizes the types and characteristics of polymers. However, the preparation process for polymers is relatively complex, and quality control and economic feasibility must be further considered. The characteristics of polymer nanoparticles can be significantly influenced by changes in polymer monomers' properties, especially *in vivo*, which can result in performance variations, including circulation time, biological distribution, metabolic behavior, and other pharmacological effects. Improving drug loading capacity, achieving precise and controllable drug release, and developing polymers capable of tracking infections in the body are crucial development directions.

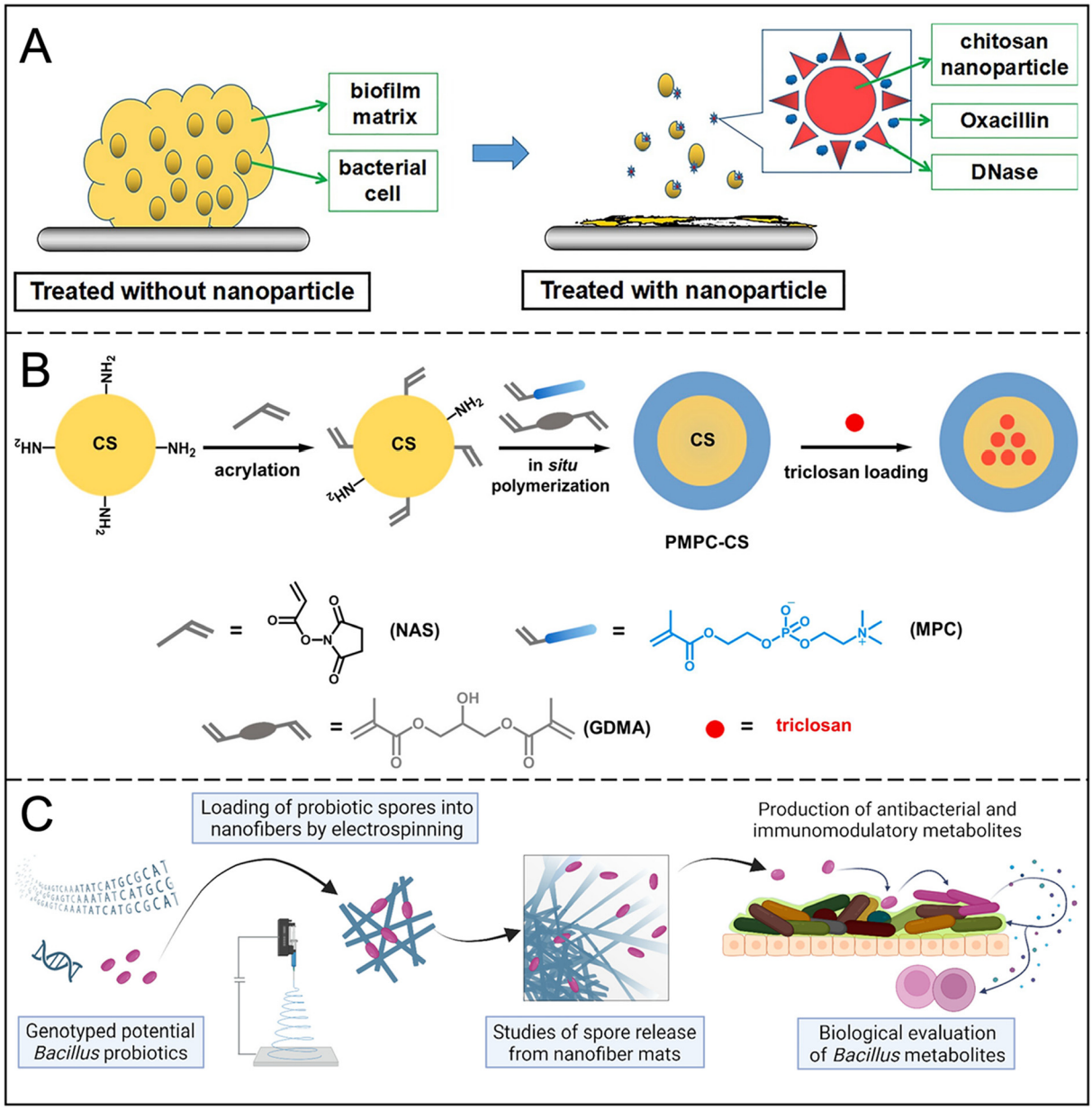

Fig. 7 (A) Schematic diagram of the composition and therapeutic mechanism of CSNP DNase Oxa. Reproduced from ref. 72 with permission from *Carbohydrate Polymers*, copyright 2018. (B) Sequential steps for the preparation of triclosan-loaded nanocapsules. Reproduced from ref. 73 with permission from *ACS 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.[81] 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.[82,83]

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.[84] 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-

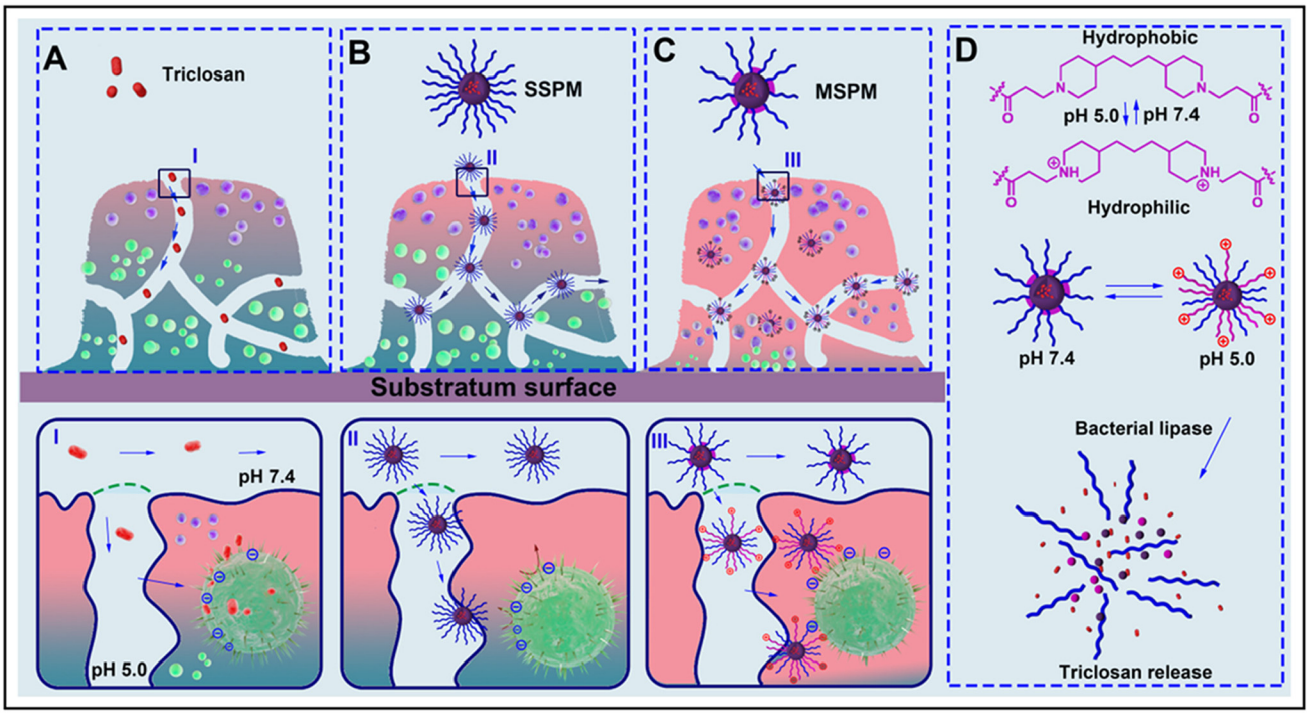

Fig. 8 Schematic diagram of the mechanism of action of MSPM. (A) Nonencapsulated antimicrobials penetrate to a limited degree into a biofilm and kill only bacteria on the outside of the biofilm. (B) Antimicrobials encapsulated in an SSPM nanocarrier with stealth properties will show better penetration 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).[85] Pamukçu *et al.* enhanced the bactericidal effect of curcumin and successfully inhibited the formation of MRSA biofilms by grafting mesoporous silica nanoparticles onto hyperbranched polyethyleneimine.[86] 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.[87] 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.[88,89] 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.[90] Yang *et al.* grafted Fe_3O_4@PDA as a photoconverter and core, with PAMAM and NO donors on the surface to obtain a multifunctional Fe_3O_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).[91]

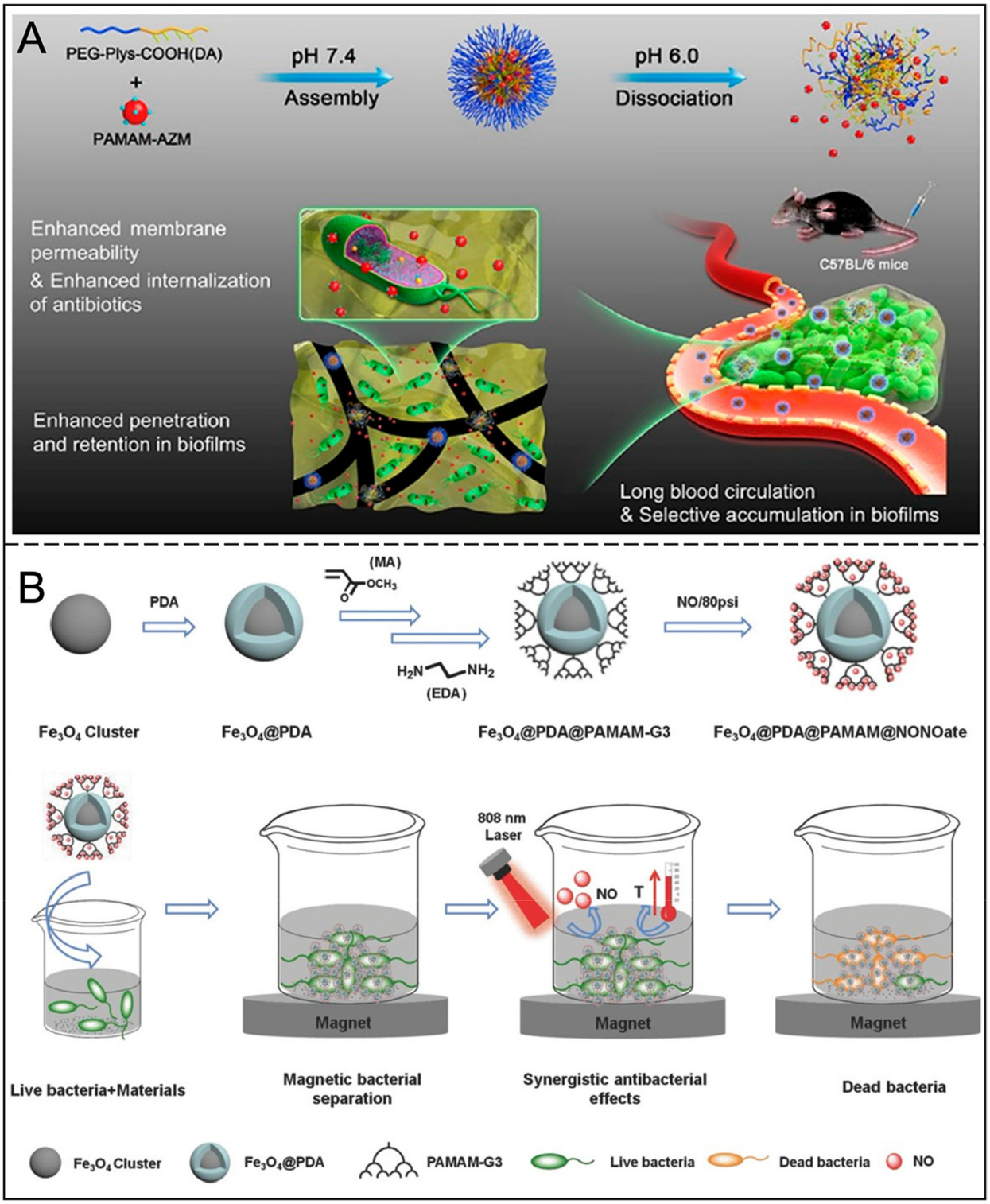

Fig. 9 (A) Illustration of the self-assembly of AZM-DA NPs at pH 7.4 and release of secondary PAMAM-AZM NPs in an acidic biofilm microenvironment and the accumulation of AZM-DA NPs in biofilms and subsequent release of PAMAM-AZM NPs for enhanced biofilm penetration, permeabilization of the bacterial membrane, and increased AZM internalization. Reproduced from ref. 85 with permission from *ACS Nano*, copyright 2020. (B) Fe_3O_4@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,[92] such as the gene transfection reagents Superfect® (Qiagen)and Priostar™ (Starpharma),[93] and the vaginal microbicide Vivagel® (SPL7013).[94] However, dendrimer-based nanomedicines still face challenges, including the need for expanded production, improved analytical characterization methods, and more promising clinical trial results.[95]

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.[95] 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.[99] 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.[99]

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).[100] 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.[101] 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.[102]

7.2 Combination treatment strategy

Nanogels have shown great potential as drug carriers in antibiofilm 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,[103] 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).[104] By co-delivering antibiotics and biofilm dispersants, nanogels effectively accelerate wound healing.[105] 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.[106] 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.[107,108] 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

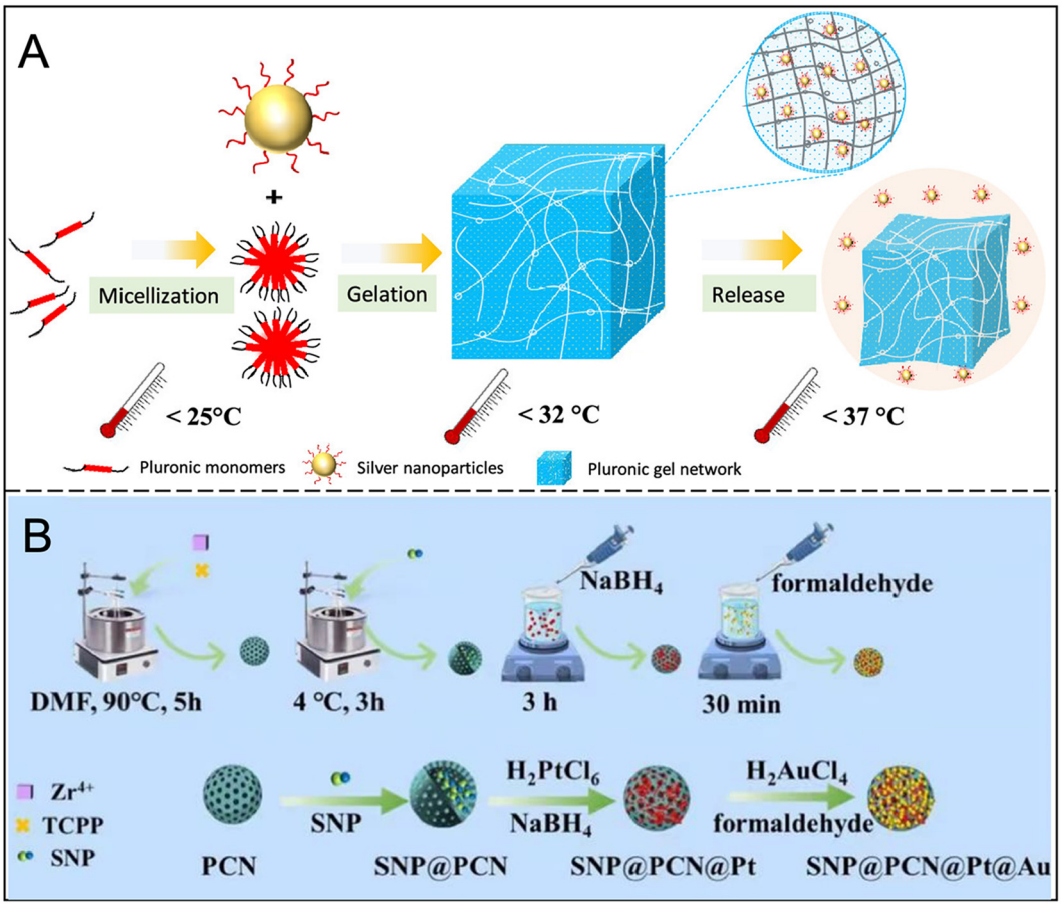

Fig. 10 (A) Schematic illustration of AgNPs@MSA-loaded pluronic hydrogel preparation. Reproduced from ref. 100 with permission from *ACS Appl. Mater. Interfaces*, copyright 2020. (B) Schematic diagram of the synthetic procedure for SNP@PCN@Pt@Au. Reproduced from ref. 104 with permission from *Acta Biomater*, 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.[109] Studies have shown that the combination of AuNPs with antibiotics significantly improves antibacterial efficacy;[110] for instance, Hasoon *et al.* found that the combination of AuNPs with ciprofloxacin effectively prevents the formation of bacterial biofilms (Fig. 11A).[111] Furthermore, Zhang *et al.* developed a glyconjugate-based imaging and therapeutic strategy that integrates PDT and PTT, successfully eradicating biofilms caused by *P. aeruginosa*.[112]

On the other hand, AgNPs can effectively penetrate bacterial biofilms and release a substantial amount of silver ions to enhance antibacterial activity.[113] By forming chelates with antibiotics, AgNPs can selectively target and eliminate biofilms that are resistant to traditional single antibiotics.[114] Metal nanoparticles can be endowed with various shapes, such as nanospheres,[115–117] nanorods,[118–121] nanostars,[122,123] nanoshells,[124] and nanocages.[125,126] 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 ultrasmall AgNPs, which significantly increased intracellular ROS levels and completely eradicated multidrug-resistant biofilms. Additionally, metal oxides such as ZnO,[127] TiO_2, and 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.

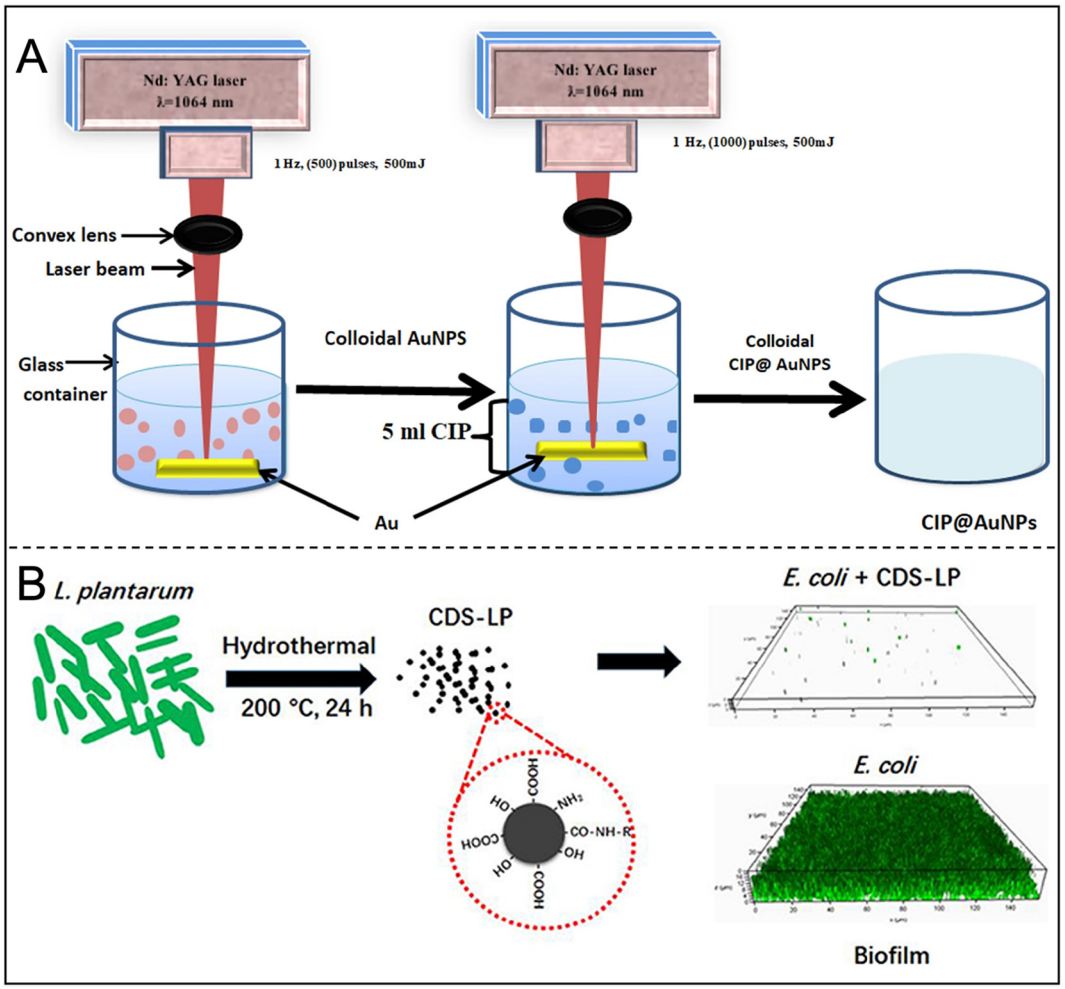

Fig. 11 (A) Synthesis of ciprofloxacin-conjugated gold nanoparticles and their study antibacterial effects on growth and biofilm formation through nebulizer mask against respiratory infections. Reproduced from ref. 111 with permission from *Plasmonics*, copyright 2023. (B) Schematic of the synthetic 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).[128] 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.[129] Barros *et al.* synthesized antibacterial Cur-conjugated silica nanoparticles that improved Cur solubility and disrupted mature biofilms by reducing biofilm adhesion protein production.[130] 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.[131]

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.[132] Addressing the toxic effects of carriers on delivery targets is crucial for advancing the clinical application of inorganic nano-delivery systems.

Table 4 Effect and characteristics of different types of representative inorganic nanoparticles and MOFs

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 MOFs	Enzyme	Cutting eDNA and hydrolyzing DNA	142
PCN-224	PDT and enzyme	Bactericidal and anti-inflammatory synchronous treatment mode	150

9. MOFs

MOFs are crystalline porous materials characterized by periodic network structures formed through the self-assembly of metal ions or clusters with organic ligands *via* coordination bonds. MOFs can inhibit the formation and development of biofilms through several mechanisms: (i) increased membrane permeability and leakage of cellular contents, (ii) deficiency in proton motive force, (iii) ROS generation, and (iv) metabolic dysregulation (Fig. 12A).[133,134] By rationally designing the structure and composition of MOFs, precise control over the release of antibacterial agents can be achieved, enhancing antibacterial efficacy while minimizing side effects.

9.1 Metal antibacterial properties

MOFs inherently contain antibacterial components, with many metal ions and organic ligands shown to possess antibacterial properties. These frameworks can release metal ions (such as Ag^{+}, Zn^{2+}, Co^{2+}, Cu^{2+}), organic ligands, or other antibacterial agents that interact with bacterial cell membranes, disrupt metabolic activity, cause leakage of cellular components, and ultimately lead to bacterial death.[135] For instance, the Zn-MOF synthesized by Akbarzadeh *et al.* demonstrates controlled ligand release and inhibits biofilm formation in various bacteria, including *E. coli*, *Bacillus subtilis*, *S. aureus*, and *Klebsiella pneumoniae*.[136] The Ag-MOF developed by Arenas-Vivo *et al.* utilizes multiple mechanisms to inhibit biofilms, including the intrinsic bactericidal activity of the MOFs, the biological killing ability of silver nanoparticles, and photoactivity following ultraviolet A irradiation.[137] The antibacterial effectiveness of Ni-MOFs likely stems from the synergistic release of Ni^{2+} and organic linkers; positively charged Ni^{2+} ions attract to the negatively charged bacterial cell envelope, resulting in ROS production and bacterial cell death.[138] Compared to traditional antibiotics, the release of metal ions may mitigate the development of bacterial resistance due to differing mechanisms of action. Furthermore, the antibacterial performance of these MOFs often surpasses that of conventional antibiotics.

9.2 Small molecule antibacterial properties

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

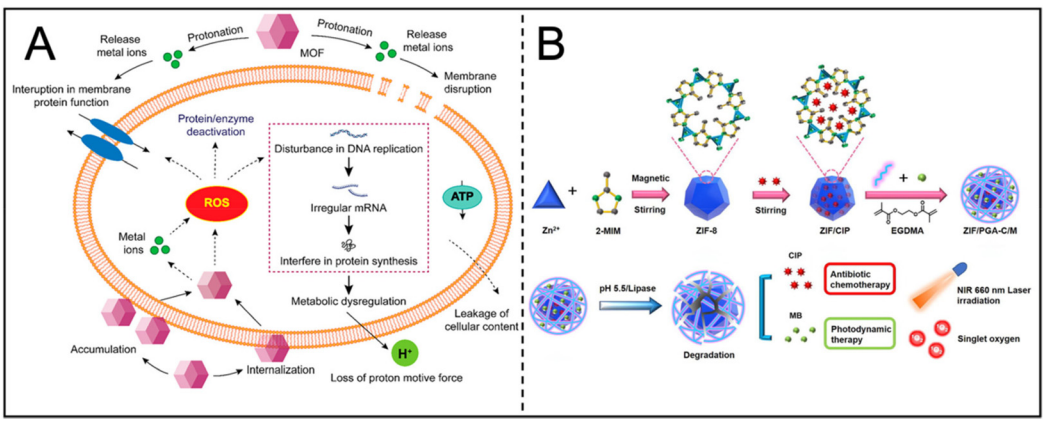

Fig. 12 (A) Proposed model illustrating the antimicrobial mode of action by MOF. Reproduced from ref. 134 with permission from *ACS Appl. Bio Mater*, copyright 2021. (B) Schematic illustration of the preparation of ZIF/PGA-C/M hybrid nanocomposite. Reproduced from ref. 139 with permission from *Materials & Design*, copyright 2023.

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).[139] 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.[140] Through charge conversion and pH response mechanisms, MOFs further enhance the permeability of nanocomposites to biofilms, facilitating drug delivery to the infection core.[141] 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 (HMUiO-66 (Zr/Ce)) effectively promote DNA hydrolysis and weaken biofilms through the synergistic interaction of Zr-OH and Ce-OH sites.[142,143] 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_2O_2.[144] 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.[145] 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.[146] In response to natural enzyme instability and the complexity of artificial enzyme synthesis, Qiu *et al.* developed CeO_2 modified porphyrin MOFs that synergistically inhibit biofilm formation through ATP deprivation and ROS production.[147] 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.[148] 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 *in vivo* 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.

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	*Methicillin-resistant Staphylococcus aureus*
NIR	Near-infrared
ILs	Immunoliposomes
S. aureus	*Staphylococcus aureus*
SLNs	Solid lipid nanoparticles
MVs	Membrane vesicles
BMVs	Bacterial membrane vesicles
OMVs	Outer membrane vesicles
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	*Lactobacillus plantarum*
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
P. aeruginosa	*Pseudomonas aeruginosa*
Am	α-Amylase
Cef	Cefepime
E. coli	*Escherichia coli*
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

DA	Dopamine
ATP	Adenosine triphosphate

Author contributions

Yijia Xie: writing – original draft & editing. Jiaxin Ma: writing – review & editing, formal analysis. Huanhuan Liu: writing – review & editing, formal analysis. Zihao Teng: writing – formal analysis. Gang Liu: writing – review & editing, supervision, conceptualization.

Conflicts of interest

The authors declare no competing financial interest.

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