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Antimicrobial polymeric nanoparticles

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ABSTRACT

Currently, infections caused by multidrug-resistant bacteria have reached critical levels. Thus, various approaches are being explored for the development of new and effective antimicrobial agents, one of which lies in the form of polymeric nanoparticles. Driven by the significant advancements in controlled polymerization techniques over the last few decades, antimicrobial polymeric nanoparticles have recently been investigated as potential new antibiotics to combat the rise of infectious diseases. This review aims at presenting an overview of the history and state-of-the-art of antimicrobial polymeric nanoparticles including their available structure-activity relationship, and highlights the impact of controlled polymerization has on the antimicrobial field as well as some of the key challenges that still need to be overcome for potential clinical applications. Herein, potential new developments are suggested as well.

Contents

Abbreviations: AgNP, silver nanoparticle; AIE, aggregation-induced emission; ATRP, atom transfer radical polymerization; AuNP, gold nanoparticle; CAC, critical aggregation concentration; CEVE, 2-chloroethyl vinyl ether; CFU, colony forming units; CLSI, Clinical and Laboratory Standards Institute; CMC, critical micelle concentration; C-PVPS, catechol-conjugated poly(*N*-vinylpyrrolidone) sulfobetaine; CVC, critical vesiculation concentration; *D*h, hydrodynamic diameter; DPn, number-averaged degree of polymerization; FA, folic acid; HC10, concentration of a compound that cause 10% red blood cell lysis; HC50, concentration of a compound that cause 50% red blood cell lysis; MBC, minimum bactericical concentration; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; MRI, magnetic resonance imaging; MRSA, methicillin-resistant *S. aureus*; MTC-(CH2)3Br, 5-methyl-5-(3-bromopropyl) oxycarbonyl-1,3-dioxan-2-one; MTC-BnCl, 5-methyl-5-(4-(chloromethyl)benzyl) oxycarbonyl-1,3-dioxan-2-one; MTC-Et, 5-methyl-5-ethyloxycarbonyl-1,3-dioxan-2-one; NCA, *N*-carboxyanhydride; NIR, near-infrared; NMR, nuclear magnetic resonance; P4VMP, poly(4-vinyl-*N*-methylpyridinium iodide); P4VP, poly(4-vinylpyridine); PAA, poly(acrylic acid); PAH, polycyclic aromatic hydrocarbon; PAN, polyacrylonitrile; PBA, poly(butyl acrylate); PBMA, poly(butyl methacrylate); PCL, poly(ε-caprolactone); PDEA, poly[2-(diethylamino)ethyl methacrylate]; PDMAEMA, poly[2-(dimethylamino)ethyl methacrylate]; PDMC, poly(methacryloyloxy ethyl trimethylammonium chloride); PEB, poly(ethylene-*co*-butylene); PEDOT, poly(3,4-ethylenedioxythiophene); PEG, poly(ethylene glycol); PEGDMA, poly(ethylene glycol dimethacrylate); PEHA, poly(ethylhexyl acrylate); PEI, poly(ethylene imine); PEO, poly(ethylene oxide); PGA, poly(glutamic acid); PGSA, polyglucosamine; PHMG, poly(hexamethylene guanidine hydrochloride); PHNA, poly[2-hydroxy-3-(naphthalene-1-ylamino)propyl methacrylate]; PIC, polyion complex; PLA, polylactide; PLL, poly(L-lysine); PMA, poly(maleic anhydride); PMAG, poly[(2-methacrylamide) glucopyranose]; PMEO2MA, poly[2-(2-methoxyethoxy)ethyl methacrylate]; PMMA, poly(methyl methacrylate); PMTC-(CH2)3Cl, poly(5-methyl-5-(3-chloropropyl) oxycarbonyl-1,3-dioxan-2-one); PNETA, poly(*N*-ethylaniline); PNIPAM, poly(*N*-isopropylacrylamide); PPEG, poly[poly(ethylene glycol) methyl ether methacrylate; PPhe, polyphenylalanine; PPy, polypyrrole; PQA, poly(quaternary ammonium); PS, polystyrene; PSA, poly(sulfone amine); PTBAM, poly[(2-*tert*-butylaminoethyl) methacrylate]; PTEPM, poly[3-(triethoxysilyl)propyl methacrylate]; PTMC, poly(trimethylene carbonate); PZLL, poly(Z-L-lysine); qPDMAEMA, quaternized poly[2-(dimethylamino)ethyl methacrylate]; RBC, red blood cell; RNA, ribonucleic acid; ROMP, ring-opening metathesis polymerization; ROP, ring-opening polymerization; ROS, reactive oxygen species; SCPN, single-chain polymeric nanoparticle; SLS, static light scattering; SNAPP, structurally nanogineered antimicrobial peptide polymer; SPION, superparamagnetic iron oxide nanoparticle; TEM, transmission electron microscopy; TiO2, titanium(IV) oxide; TPE, tetraphenylethylene; UV, ultraviolet; VBC, vinylbenzyl chloride; VEAH, *N*-(4-vinylbenzyl)-*N*,*N*-diethylamine hydrochloride; VRE, vancomycin-resistant *Enterococci*; WHO, World Health Organization.

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1. Introduction

Recently, the World Health Organization (WHO) revealed that the threat of antibiotic resistance has reached critical levels worldwide [1]. Specifically, WHO has identified 12 emerging superbugs that are resistant to many antibiotics as priority targets to combat, grouping them into three categories: critical, high, and medium. For instance, carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were listed as critical, methicillin-resistant *Staphylococcus aureus* (MRSA) can be found in the high category, whereas ampicillin-resistant *Haemophilus influenza* was classified as medium [2]. Coupled with the lack of new product discovery due to the near-complete screening of available natural resources, the world is facing the risk of reverting back to the 'medical dark ages' (i.e., the pre-antibiotic era). Many world governments thus recognize the urgent need for new solutions to combat this global healthcare issue. Driven by the significant advancements in controlled polymerization techniques [3–14], that have enabled the production of nanomaterials with tailorable biological properties for a wide range of biomedical applications [15–23], synthetic polymers potentially represent a promising approach to curb the rise of antibiotic resistance. In fact, there are various examples in literature that describe the synthesis of linear polymers with antimicrobial properties [24–35], mostly by mimicking the chemical structure of antimicrobial peptides (AMPs), while others include the conjugation of synthetic polymers with conventional antibiotics (to improve pharmacokinetics for instance) [36–38].

However, there has been growing interest recently in the development of antimicrobial polymeric nanoparticles. This is because the formulation of polymers into nanoparticles (e.g., micelles, vesicles, star polymers, and inorganic-polymer hybrids) of various shapes and sizes has been shown to yield many advantages over linear polymers in other targeted applications such as drug/gene delivery [39–42]. For instance, a main advantage is the multivalency of polymeric nanoparticles, where the presentation of a cluster of (multiple) functional groups from a nanoparticle construct enables higher cell recognition and binding capabilities compared to linear polymers [43,44]. In addition, polymer nanoparticles like micelles, vesicles or star polymers allow for the efficient encapsulation of cargo molecules that can be released at targeted sites [45–48]. Furthermore, the fabrication of inorganic-polymer hybrid nanoparticles provides new avenues for synergistic therapy (e.g., photodynamic therapy) and/or diagnostic purposes (e.g., biosensing) [49–51].

In this review, we present an overview of the history and recent advances of polymeric nanoparticles that have been applied in the antimicrobial field where some of these nanoparticles have been demonstrated to be effective against the pathogens specified above by WHO. Specifically, the review focuses on the development of polymeric nanoparticles that demonstrate inherent antimicrobial properties (i.e., the nanoparticle acts as the active antimicrobial agent) and highlights any structural-activity relationship that will aid our understanding on the rational design of polymer-based antimicrobial agents.

2. Polymer nanoparticles as active antimicrobial agents

By mimicking the general chemical structure of naturally-occurring AMPs [52], synthetic polymers could be endowed with intrinsic antimicrobial activity by incorporating cationic and hydrophobic moieties into the polymer chains [27,53]. The overall cationic charge of the polymer enables interaction with bacterial cell walls that are typically negatively charged, while the hydrophobic counterparts facilitate microbial membrane penetration [27]. It should be noted, however, that antimicrobial polymers with differing chemical structures (*e.g.*, quaternary ammonium-containing polymers without any hydrophobic components [54,55]) have also been reported. The possible enhancement of antimicrobial activity through nanoparticle formation was inspired by multivalent interactions found ubiquitously throughout biology, where the simultaneous binding of multiple ligands from one entity to multiple receptors on another could lead to stronger effects than corresponding monovalent systems [56]. This hypothesis was substantiated by studies reported by Yang and co-workers in 2009 and 2010, where core-shell micellar nanoparticles based on the self-assembly of an amphiphilic peptide (prepared by solid phase peptide synthesis) showed superior efficacy against a range of Gram-positive bacteria and fungal species (Fig. 1) [57,58]. Improved antimicrobial properties in the assembled state were attributed to increased and more localized density of cationic charges and peptide mass, resulting in stronger electrostatic interactions with anionic microbial membranes.

Here, synthetic polymer-based nanoparticles (mainly made from controlled polymerization techniques) displaying direct antimicrobial activity will be reviewed. These polymer nanoparticles are categorized based on their complex macromolecular architecture, and the effects of these polymer architectures on the antimicrobial performance and biocompatibility of such nanoparticles will be discussed.

2.1. Self-assembled polymer nanoparticles

Self-assembly has been recognized as one of the most commonly used routes for the construction of nanostructured materials from small building blocks [59]. Inspired by nature, the formation of highly complex molecular and supramolecular structures in the most thermodynamically stable form, such as micelles and vesicles, is made possible by multiple weak and non-covalent interactions between the chemical building blocks [59–61]. In the field of therapeutics, self-assembly has been increasingly used for the synthesis of nano-sized biomaterials due to the relative ease, precision and versatility of the method, enabling the incorporation of functions such as stimuli-responsiveness, recognition and targeting [62]. More specifically, micelles and vesicles formed through the self-assembly of polymer building blocks have been explored for possible use as novel antimicrobial agents.

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