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Biodegradable nanoparticles for intracellular delivery of antimicrobial agents

Shuyu Xie [a,b], Yanfei Tao [a,b], Yuanhu Pan [c], Wei Qu [c], Guyue Cheng [a,b], Lingli Huang [c], Dongmei Chen [c], Xu Wang [c], Zhenli Liu [a,b], Zonghui Yuan [a,b,c,*]

[a] National Reference Laboratory of Veterinary Drug Residues (HZAU), Huazhong Agricultural University, Wuhan, Hubei 430070, China
[b] MAO Key Laboratory for Detection of Veterinary Drug Residues, Huazhong Agricultural University, Wuhan, Hubei 430070, China
[c] MOA Laboratory for Risk Assessment of Quality and Safety of Livestock and Poultry Products, Huazhong Agricultural University, Wuhan, Hubei 430070, China

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ABSTRACT

Biodegradable nanoparticles have emerged as a promising strategy for ferrying antimicrobial agents into specific cells due to their unique properties. This review discusses the current progress and challenges of biodegradable nanoparticles for intracellular antimicrobial delivery to understand design principles for the development of ideal nanocarriers. The intracellular delivery performances of biodegradable nanoparticles for diverse antimicrobial agents are first summarized. Second, the cellular internalization and intracellular trafficking, degradation and release kinetics of nanoparticles as well as their relation with intracellular delivery of encapsulated antimicrobial agents are provided. Third, the influences of nanoparticle properties on the cellular internalization and intracellular fate of nanoparticles and their payload antimicrobial agents are discussed. Finally, the challenges and perspectives of nanoparticles for intracellular delivery of antimicrobial agents are addressed. The review will be helpful to the scientists who are interested in searching for more efficient nanosystem strategies for intracellular delivery of antimicrobial agents.

Contents

Abbreviations: CME, Clathrin-mediated endocytosis; CvME, Caveolae-mediated endocytosis; DMPC, Dimyristoylphosphatidylcholine; DOPE, Dioleoylphosphatidylethanolamine; DPPC, Dipalmitoylphosphatidylcholine; DPPG, Dipalmitoylphosphatidylglycerol; DSPC, Distearoylphosphatidylcholine; EPC, L-Ac-phosphatidylcholine type III-E; EPR, Enhanced permeation and retention; MAC, *Mycobacterium avium* complex; Man-C4-Chol, Cholesten-5-yloxy-N-(4-((1-imino-2-D-thiomannosylethyl)amino)alkyl)formamide; MAI, *Mycobacterium avium–Mycobacterium intracellulare*; MICs, Minimum inhibitory concentrations; MLV, Multilamellar large vesicle; MPS, Mononuclear phagocytic system; *MRSA*, Methicillin-resistant *Staphylococcus aureus*; PBCA, Poly(butyl cyanoacrylate); PC, Phosphatidylcholine; PDPA, Poly[2-(disopropylamino) ethylmethacrylate]; PECA, Polyethylcyanoacrylate; PEG, Polyethylene glycol; PEI, Poly(ethyleneimine); PEO-b-PPO-b-PEO, Poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) triblock; PIHCA, Polyisohexylcyanoacrylate; PIBCA, Poly(isobutylcyanoacrylate); PLA, Poly(D,L-polylactide); PLGA, Poly(lactide-co-glycolide) acid; PMPC, Poly(2-methacryloyloxyethyl phosphorylcholine); PG, Phosphatidylglycerol; PS, Phosphatidylserine; SLN, Solid lipid nanoparticles; SM, Sphingomyelin; T_{max}, The time to reach the maximum concentration.

* Corresponding author at: National Reference Laboratory of Veterinary Drug Residues (HZAU), MOA Laboratory for Risk Assessment of Quality and Safety of Livestock and Poultry Products and MAO Key Laboratory for Detection of Veterinary Drug Residues, Huazhong Agricultural University, Wuhan, Hubei 430070, China. Tel.: +86 27 87287186; fax: +86 27 87672232.
E-mail address: yuan5802@mail.hzau.edu.cn (Z. Yuan).

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1. Introduction

Intracellular bacteria, e.g., *Mycobacterium* spp., *Brucella* spp., *Listeria monocytogenes*, are notorious as causative agents of a number of serious diseases worldwide [1]. These bacteria evolve a number of ingenious mechanisms to exploit host processes to multiply and spread without damaging the host cells to maintain their intracellular lifestyle [2,3], resulting in persistent, severe and latent infections. The entry of antimicrobial agents into the infected cells and intracellular niches where pathogens reside with sufficiently high therapeutic concentrations is a necessity to achieve effective treatment of intracellular infections. However, most antimicrobial agents have poor cellular penetration, limited intracellular retention, unsatisfactory subcellular distribution and decreased intracellular activity. Therefore, intracellular infection treatment is a great challenge [1,4].

Over the decades, diverse biodegradable nanoparticles including liposomes, polymeric nanosystems, e.g., polymeric nanoparticles, polymer micelles, dendrimers and niosomes, and solid lipid nanoparticles (SLN) have been explored for intracellular delivery of antimicrobial agents that exhibit a high bactericidal activity *in vitro* [1,5,6]. These biodegradable nanoparticles can load antimicrobial agents through physical encapsulation, adsorption, or chemical conjugation and deliver their payloads into host cells through different pathways, e.g., contact release, adsorption and endocytosis [1,5,6]. The enhanced cellular uptake and subsequent sustained release of nanoparticle adsorbed/entrapped antimicrobial agents could effectively improve their antibacterial effects due to both the direct action by contact of nanoparticles with bacteria [7] and diffusion of the released antimicrobial agents to bacteria located sites [1,3]. The intracellular delivery, distribution, sustained release and antibacterial effects of encapsulated antimicrobial agents can be controlled via modulation of nanoparticle compositions and properties. The nanocarriers armed with antimicrobial agents have the ability to passively accumulate in infection foci in the body via the recognition and transport by the phagocytic cells of the mononuclear phagocytic system (MPS) [5,8], and the enhanced permeation and retention (EPR) effect due to the locally increased microvascular capillary permeability and impaired lymphatic drainage by inflammatory reactions [3,9]. The *in vivo* behavior of nanocarriers and consequently their therapeutic potential for intracellular infections are determined by their routes of administration. When administered intravenously, nanoparticles and their payload antimicrobial agents rapidly accumulate in the cells of MPS, and hence intravenous administration is the most common way for the treatment of infections involving the MPS, particularly in the liver and spleen [3,10]. Oral administration is effective in treating intestinal tract infections and appears to have no abnormal *in vivo* toxicity, although it is less effective in reducing the intracellular bacteria from liver and spleen compared with intravenous administration. Pulmonary administration is commonly studied for the treatment of respiratory infections such as tuberculosis [10]. The role of nanoparticles as a potential vehicle for antimicrobial agents in the treatment of intracellular bacterial infections has been reviewed elsewhere [1,3,5,11], which mainly focused on the enhanced antimicrobial activity of nanoparticles encapsulating antimicrobial agents *in vitro* and *in vivo*. This review systematically discusses the efficacy, mechanisms, influence factors, challenges and perspectives of biodegradable nanoparticles for intracellular delivery of antimicrobial agents to explore strategies in development of more efficient nanosystems to overcome the difficulty in the treatment of intracellular infections.

2. Intracellular delivery performances of biodegradable nanoparticles for antimicrobial agents

It is reported that biodegradable nanoparticles can effectively improve the cellular penetration, intracellular retention and specific subcellular distribution of antimicrobial agents, and even evade intracellular inactivation of antimicrobial agents. This section summarizes biodegradable nanoparticles for intracellular delivery of various antimicrobial agents.

2.1. Aminoglycosides

Because of high polarity, aminoglycosides like gentamicin penetrate across cell membranes very slowly and, once inside, remain confined in the endolysosomal compartments, where their activity is reduced by the acidic endosomal pH [12–14]. A growing number of biodegradable nanoparticles have been explored to solve these hurdles (summarized in Table 1).

The earliest liposomes formed with a mixture of egg phosphatidylcholine (PC), cholesterol, and phosphatidic acid for the intracellular delivery of aminoglycosides were developed in 1978, which enhanced the activity of dihydrostreptomycin against *Staphylococcus aureus* within phagocytic vacuoles by 10- and 40-fold after incubation for 6 and 16 h, respectively [15]. Afterwards, extensive liposomes were explored to achieve effective intracellular delivery and specific subcellular distribution of aminoglycosides, especially for gentamicin [16,17]. These liposomes were mostly reported to yield effective therapeutic drug