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Design, Synthesis, and Characterization of Nanoparticles for Effective Treatment of Biofilm–Associated Lung Infection

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ABSTRACT

Biofilm-associated lung infections, particularly those caused by Pseudomonas aeruginosa in cystic fibrosis and bronchiectasis patients, represent a major therapeutic challenge. The extracellular polymeric substance (EPS) matrix, metabolic heterogeneity, and microenvironmental gradients within biofilms drastically reduce antibiotic penetration and efficacy. Nanoparticle (NP)-based therapeutics offer unique advantages, such as enhanced biofilm penetration, controlled release, and localized delivery via inhalation. This review summarizes the latest developments in the design, synthesis, and characterization of nanoparticles intended for treating biofilm-associated pulmonary infections. The discussion emphasizes materials selection, fabrication routes, and physicochemical parameters influencing antibiofilm performance, with critical perspectives on translational challenges, safety, and future directions.

Keywords: Nanoparticles, Biofilm, Lung infection, Pulmonary drug delivery, Antimicrobial resistance, Nanomedicine

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INTRODUCTION

Chronic pulmonary infections associated with bacterial biofilms are a persistent cause of morbidity and mortality in patients with cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and non-CF bronchiectasis. Biofilms are complex microbial communities encased within an extracellular polymeric substance (EPS) matrix composed of polysaccharides, proteins, lipids, and extracellular DNA (eDNA). This matrix serves as both a physical and biochemical barrier against host immune defenses and antibiotic therapy[1,2]. Within the lung environment, biofilms contribute to persistent infection, antibiotic tolerance, and inflammation.

Traditional antibiotic therapy often fails to eradicate biofilm-associated bacteria because biofilms limit diffusion and create metabolic heterogeneity, rendering subpopulations of bacteria in dormant or persister states. Nanoparticle-based delivery systems have emerged as promising tools to overcome these barriers. By tailoring size, surface chemistry, and composition, nanoparticles can improve drug retention, promote biofilm penetration, and enable targeted delivery to the infected airways[3,4]. This review highlights current advances in nanoparticle design, synthesis, and characterization with particular emphasis on their physicochemical optimization for effective antibiofilm action in lung infections.

DESIGN PRINCIPLES FOR ANTIBIOFILM NANOPARTICLES

The design of nanoparticles for antibiofilm lung therapy requires a multidisciplinary approach integrating materials science, microbiology, and pulmonary drug delivery. Several physicochemical parameters—size, charge, surface functionality, and shape—determine nanoparticle interaction with mucus, biofilm matrix, and airway epithelia[5,6].

Size: Nanoparticle size critically affects penetration through both the mucus layer and biofilm matrix. Particles smaller than 200 nm can diffuse more effectively, though excessively small particles (<20 nm) may be rapidly cleared from the lungs. Optimal sizes typically range from 80 to 150 nm[7].

Surface charge:

Biofilms are negatively charged due to eDNA and polysaccharides. Cationic nanoparticles (e.g., chitosan-based) can interact electrostatically with the EPS, enhancing retention, but excessive charge can lead to cytotoxicity. Neutral or zwitterionic coatings (PEG, polysarcosine) reduce mucoadhesion and improve penetration[8].

Surface chemistry and functionalization:

Functional groups or ligands such as lectins, peptides, and antibodies can enhance targeting to bacterial or EPS components. Surface PEGylation improves stability and reduces nonspecific interactions[9].

Shape and flexibility:

While spherical nanoparticles are the most common, rod-like or flexible structures may navigate complex biofilm channels more efficiently[10].

SYNTHESIS OF NANOPARTICLES FOR PULMONARY ANTIBIOFILM THERAPY

Synthesis techniques depend on the nanoparticle type—polymeric, lipidic, inorganic, or hybrid—and the physicochemical properties required. Reproducibility, scalability, and control over drug loading are critical for clinical translation.

Polymeric nanoparticles:

Common biodegradable polymers include poly (lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and chitosan. Solvent evaporation and nanoprecipitation techniques allow fine control of particle size and encapsulation efficiency[11,12]. Ionic gelation, often used for chitosan nanoparticles, provides a mild, aqueous synthesis suitable for sensitive biomolecules[13].

Lipid-based nanoparticles:

Liposomes and solid lipid nanoparticles (SLNs) offer high biocompatibility and efficient encapsulation of hydrophilic and hydrophobic drugs. Thin-film hydration and microemulsion techniques are common. Surface PEGylation and targeting ligand conjugation further improve biofilm targeting[14,15].

Inorganic and hybrid nanoparticles:

Metal and metal oxide nanoparticles (e.g., Ag, ZnO, TiO_2) possess inherent antimicrobial properties but require stabilization to minimize toxicity[16]. Green synthesis using plant extracts or biopolymers has gained attention as an eco-friendly alternative[17].

Hybrid nanostructures:

Combining organic and inorganic components yields hybrid nanoparticles with synergistic effects, such as polymer-coated silver NPs or mesoporous silica NPs loaded with antibiotics[18].

PHYSICOCHEMICAL AND BIOLOGICAL CHARACTERIZATION

Thorough physicochemical and biological characterization is essential for understanding nanoparticle behavior in pulmonary and biofilm environments.

Physicochemical characterization:

Dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA) determine size and polydispersity; transmission electron microscopy (TEM) reveals morphology and surface structure.

Zeta potential analysis quantifies surface charge and stability in physiological media[19,20]. Drug encapsulation efficiency, loading capacity, and release kinetics are quantified via HPLC or UV–VIS spectroscopy[21]. For inhalation formulations, aerosol performance is assessed through cascade impaction to measure the mass median aerodynamic diameter (MMAD)[22].

Biofilm-relevant assays:

Penetration studies employ fluorescent labeling and confocal laser scanning microscopy (CLSM) to visualize NP distribution within biofilms. Antibiofilm activity is assessed through minimum biofilm eradication concentration (MBEC) tests and biomass quantification[23,24]. EPS degradation can be evaluated using enzyme-linked assays, while cytotoxicity is tested in airway epithelial cell lines (A549, Calu-3) and macrophages[25].

IN VITRO AND IN VIVO EVALUATION MODELS

Preclinical testing of antibiofilm nanoparticles requires robust models to mimic the complex lung environment.

In vitro models:

Static biofilm assays, flow-cell systems, and co-culture airway epithelial-biofilm models provide insight into penetration and efficacy. Artificial sputum medium (ASM) replicates the viscosity and biochemical composition of CF sputum, allowing realistic diffusion studies[26,27].

In vivo models:

Rodent inhalation and intratracheal infection models enable evaluation of lung deposition, bacterial clearance, and inflammation. These models use pathogens such as Pseudomonas aeruginosa or Staphylococcus aureus to simulate chronic infection[28].

CHALLENGES AND FUTURE DIRECTIONS

Despite promising results, several challenges hinder clinical translation. Balancing biofilm adhesion with mucus penetration remains a major optimization problem[29]. Scalability and batch-to-batch reproducibility must be ensured for regulatory approval. Chronic exposure toxicity, especially for metal-based systems, requires long-term investigation[30].

Emerging directions include stimuli-responsive nanoparticles that release drugs in response to pH or enzymatic cues, and hybrid formulations combining antibiotics with EPS-degrading enzymes or quorum-sensing inhibitors[31,32]. Integration of computational modeling and machine learning may further optimize NP design for specific infection microenvironments[33].

CONCLUSION

Nanoparticle-based systems represent a promising frontier for treating biofilm-associated lung infections. Rational design incorporating optimized size, charge, and surface functionality can

overcome the physical and biological barriers imposed by biofilms. Continued progress in scalable synthesis, comprehensive characterization, and rigorous preclinical evaluation will pave the way for clinically translatable nanotherapeutics. Multimodal systems combining antibiotics, dispersive enzymes, and stimuli-responsive carriers hold the potential to redefine the therapeutic landscape of chronic pulmonary infections.

REFERENCES

1. Borisova D, et al. Biofilm formation of Pseudomonas aeruginosa in cystic fibrosis. J Clin Microbiol. 2025;63(4):e00234-25.
2. Flemming HC, et al. Biofilms: an emergent form of bacterial life. Nat Rev Microbiol. 2023;21(5):305–318.
3. Cojocaru E, et al. Nanoparticle-based drug delivery systems in inhaled applications. Pharmaceutics. 2024;16(2):277.
4. Sedighi O, et al. Nanoparticle strategies for managing biofilm infections. ACS Omega. 2024;9(12):10543–10560.
5. Zhang H, et al. Design considerations for nanocarriers targeting pulmonary infections. Adv Drug Deliv Rev. 2024;205:115456.
6. Patel R, et al. Nanoparticle physicochemical properties and mucosal transport. J Control Release. 2023;355:654–667.
7. Sabuj MZR, et al. Inhaled antibiotic-loaded polymeric nanoparticles for respiratory infections. Nanoscale Adv. 2021;3:2847–2866.
8. Thomas N, et al. PEGylation in mucosal nanocarriers. Int J Pharm. 2023;637:122965.
9. Lee JH, et al. Targeting biofilms using surface-functionalized nanoparticles. Nanomedicine. 2025;48:102782.
10. Wu M, et al. Effect of particle shape on biofilm penetration. ACS Nano. 2022;16(8):13056–13068.
11. Parra-Ruiz J, et al. Advances in polymeric nanoparticles for drug delivery. Int J Pharm. 2023; 622:121816.
12. Singh N, et al. Nanoprecipitation synthesis of PLGA nanoparticles. Mater Sci Eng C. 2024; 140:113247.
13. Luo Y, et al. Ionic gelation of chitosan nanoparticles. Carbohydr Polym. 2023; 313:120826.
14. Kim JS, et al. Liposomal systems for pulmonary drug delivery. Pharmaceutics. 2024;16(9):1453.

15. Das S, et al. Solid lipid nanoparticles in infection therapy. Front Pharmacol. 2025; 16:1148921.
16. Khalifa HO, et al. Silver nanoparticles as antimicrobial agents. Front Cell Infect Microbiol. 2025;15(3):334.
17. Park SY, et al. Green synthesis of metal nanoparticles. J Clean Prod. 2023; 421:138565.
18. Costa C, et al. Hybrid nanoparticles for antibiofilm applications. Mater Today Bio. 2025; 23:100578.
19. Patel M, et al. Characterization techniques for nanomedicines. Adv Drug Deliv Rev. 2024; 195:114692.
20. Zhao L, et al. Surface charge analysis in nanoparticle dispersions. Langmuir. 2022;38(32):9802–9811.
21. Rabea AM, et al. Quantification of drug encapsulation and release. J Pharm Sci. 2024;113(5):1431–1445.
22. Huang Q, et al. Aerosol delivery of nanoparticles: challenges and opportunities. Eur J Pharm Biopharm. 2025; 196:132–144.
23. Zhang Y, et al. Confocal imaging of nanoparticle penetration. Anal Methods. 2022;14(6):648–657.
24. Thomas N, et al. In vitro biofilm eradication assays. Microorganisms. 2024;12(4):875.
25. Jain P, et al. Cytotoxicity assessment of inhaled nanoparticles. Nanotoxicology. 2024;18(1):54–70.
26. Batra R, et al. Artificial sputum media for cystic fibrosis models. J Microbiol Methods. 2024;215:106789.
27. Singh PK, et al. Co-culture airway biofilm models. Front Microbiol. 2025; 16:223.
28. Chen X, et al. Rodent models for pulmonary biofilm infection. Front Pharmacol. 2023; 14:1178291.
29. Ullah S, et al. Mechanistic insights into biofilm disruption. Bioeng Transl Med. 2025;10(2):e1045.
30. Rabea AM, et al. Long-term toxicity of metal nanoparticles. Toxicol Lett. 2025;384:45–57.
31. Wang D, et al. Stimuli-responsive nanoparticles in infection therapy. J Nanobiotechnol. 2023;21(1):98.
32. Zhao F, et al. Enzyme-functionalized hybrid nanoparticles. ACS Appl Mater Interfaces. 2024;16(32):41573–41585.

33. Sun H, et al. Computational modeling of nanoparticle–biofilm interactions. Comput Biol Med. 2025;176:108199.