

Advances in Inhalable Nanoparticle-Based Drug Delivery Systems for Respiratory Disorders

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Abstract: *Respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary infections, tuberculosis, pulmonary fibrosis, and lung cancer remain major therapeutic challenges because conventional systemic drug administration may produce inadequate drug concentrations at the pulmonary site while increasing systemic adverse effects. Inhalation provides a direct and non-invasive route for transporting therapeutic agents to the respiratory tract, and advances in nanotechnology have created opportunities to improve pulmonary drug deposition, drug solubility, controlled release, cellular uptake, and disease-specific targeting. Inhalable nanoparticle-based drug delivery systems include polymeric nanoparticles, lipid nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, Nano emulsions, nanosuspensions, dendrimers, inorganic nanoparticles, and biomimetic nanocarriers. These systems can encapsulate small molecules, proteins, nucleic acids, antimicrobial agents, anti-inflammatory drugs, and anticancer compounds.*

Keywords: Inhalable Nanoparticles, Pulmonary Drug Delivery, Nano medicine, Respiratory Disorders, Targeted Delivery

I. INTRODUCTION

The respiratory system provides an attractive route for drug administration because the lungs possess a large surface area, extensive vascularization, and relatively thin epithelial barriers. Inhaled administration can deliver therapeutic compounds directly to the respiratory tract, potentially producing high local concentrations while reducing systemic exposure. Nevertheless, conventional inhaled medicines can suffer from rapid mucociliary clearance, poor aqueous solubility, short residence time, inefficient deposition, and limited penetration into pathological regions. Nanotechnology has therefore emerged as a strategy for modifying the physicochemical and pharmacological behavior of therapeutic compounds and improving their delivery to specific pulmonary regions.

Nanoparticles can act as carriers for poorly soluble drugs, peptides, proteins, nucleic acids, and other therapeutic molecules while enabling controlled or sustained release. Earlier investigations established the potential of polymeric nanoparticles, liposomes, solid lipid nanoparticles, and other colloidal systems for pulmonary administration, while more recent research has focused on rational particle engineering and overcoming biological barriers within diseased lungs (Patil et al., 2012; Mansour et al., 2015; Makwana et al., 2019).

RATIONALE FOR INHALABLE NANOPARTICLE-BASED DRUG DELIVERY

The major rationale for inhalable nanoparticle delivery is the possibility of combining the advantages of pulmonary administration with the functional characteristics of nanoscale carriers. Direct delivery to the lung can reduce the distance between a drug and its target site and may decrease the dose required to achieve a local pharmacological response. Nanoparticles can protect encapsulated drugs from degradation, improve apparent solubility, modify release kinetics, and facilitate cellular uptake. In addition, surface modification can potentially alter interactions with mucus, epithelial cells, macrophages, or specific receptors. The effectiveness of these systems, however, depends not only on

nanoparticle size but also on aerodynamic diameter, particle density, morphology, surface properties, formulation composition, and inhaler performance. Reviews published through 2023 emphasize that successful pulmonary nanomedicine requires simultaneous consideration of nanocarrier characteristics and aerosol-generation technology rather than treating nanoparticles and inhalation devices as independent components (Mansour et al., 2015; Yadav et al., 2022; Kole et al., 2023).

MAJOR TYPES OF INHALABLE NANOPARTICLE SYSTEMS

Polymeric nanoparticles are among the extensively investigated systems for pulmonary drug delivery. Materials such as poly(lactic-co-glycolic acid) (PLGA), chitosan, alginate, and polyethylene glycol-containing polymers can be engineered to provide controlled release and protection of therapeutic molecules. PLGA nanoparticles have demonstrated sustained release and pulmonary cellular uptake in experimental studies, supporting their potential for local delivery of proteins and nucleic acids. Liposomes represent another important category because their lipid bilayer can accommodate hydrophilic and hydrophobic therapeutic compounds and can be modified to alter stability and cellular interactions. Solid lipid nanoparticles and nanostructured lipid carriers provide lipid-based alternatives that can enhance drug solubilization and controlled release. Dendrimers, nanoemulsions, nanosuspensions, inorganic nanoparticles, and newer biomimetic carriers have also been investigated for respiratory applications. The selection of a carrier depends on the drug's physicochemical properties, target cell or tissue, required release profile, route of aerosolization, and safety requirements (Patil et al., 2012; Makwana et al., 2019; Gulati et al., 2021).

Table 1. Major Inhalable Nanoparticle-Based Drug Delivery Systems

Nanoparticle system	Major characteristics	Potential respiratory applications	Important advantages	Major limitations
Polymeric nanoparticles	Biodegradable polymeric matrix	Asthma, COPD, infections, cancer	Controlled release and drug protection	Manufacturing complexity and possible polymer-related concerns
Liposomes	Phospholipid bilayer vesicles	Asthma, infections, cancer, inflammation	Can carry hydrophilic and lipophilic drugs	Physical instability and leakage
Solid lipid nanoparticles	Solid lipid matrix	Anti-inflammatory and antimicrobial therapy	Improved stability and sustained release	Drug-loading limitations for some compounds
Nanostructured lipid carriers	Combination of solid and liquid lipids	Chronic respiratory disorders	Improved loading and release characteristics	Formulation optimization required
Nanoemulsions	Nanoscale dispersed oil/water systems	Anti-inflammatory and antimicrobial therapy	Improved dispersion of poorly soluble drugs	Physical stability may be problematic
Dendrimers	Highly branched nanoscale polymers	Gene and drug delivery	Surface functionalization and targeting potential	Toxicity and complex synthesis
Inorganic nanoparticles	Metal, silica or	Cancer,	Functional and	Long-term safety

	related materials	infection, imaging-assisted therapy	surface-engineering possibilities	and clearance concerns
Biomimetic/extracellular-vesicle systems	Biologically derived carriers	Inflammation, infection and regenerative applications	Biological compatibility and cellular communication potential	Production, characterization and standardization challenges

NANOPARTICLES FOR ASTHMA AND INFLAMMATORY RESPIRATORY DISORDERS

Asthma involves chronic airway inflammation, bronchial hyperresponsiveness, and structural changes in the respiratory tract. Conventional inhaled corticosteroids and bronchodilators remain important treatments, but nanoparticle systems are being explored to improve localization, residence time, and controlled release. Liposomes, polymeric nanoparticles, nanoemulsions, nanosuspensions, niosomes, and other nanoscale systems have been investigated for delivering anti-inflammatory compounds. Nanocarriers may protect drugs from rapid degradation and potentially prolong their presence at pulmonary sites. Experimental approaches have also investigated antioxidant and anti-inflammatory molecules whose therapeutic effectiveness may be limited by poor solubility or rapid clearance. Inhaled nano-based therapeutics therefore provide a platform for modifying drug distribution and release while potentially reducing unwanted systemic exposure (Gulati et al., 2021).

APPLICATIONS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is characterized by persistent airflow limitation and inflammatory and structural changes in the respiratory system. Effective treatment frequently requires prolonged drug administration, making controlled and targeted delivery particularly relevant. Nanoparticle systems may improve drug retention in the lungs and provide sustained release, potentially reducing dosing frequency. Polymeric nanoparticles, lipid-based carriers, and nanosuspensions have been studied for delivery of anti-inflammatory and other therapeutic agents. Their ability to modify pharmacokinetics and cellular uptake has generated interest in their application to chronic pulmonary conditions. However, COPD-associated mucus alterations, inflammation, airway obstruction, and heterogeneous regional deposition can influence the distribution of inhaled nanoparticles and must therefore be considered during formulation design (Paranjpe et al., 2021; Yadav et al., 2022).

NANOPARTICLE-BASED DELIVERY FOR PULMONARY INFECTIONS

Pulmonary infections present an important target for inhalable nanomedicine because the infection is frequently localized within the respiratory system. Direct inhalation may increase antimicrobial concentration at the infected site while potentially reducing systemic exposure. Nanoparticles can encapsulate antimicrobial drugs and protect them from premature degradation. They may also facilitate interaction with infected cells or pathogens. Research has examined nanocarriers for bacterial and viral respiratory infections, including tuberculosis and emerging viral infections. Liposomes, polymeric nanoparticles, solid lipid nanoparticles, and related systems have been investigated for pulmonary antimicrobial delivery. The 2023 literature particularly highlights the potential of inhaled nanocarriers for overcoming biological barriers and improving pulmonary bioavailability, although translation from experimental models to human clinical treatment remains a major requirement (Kole et al., 2023; Jin et al., 2023).

SAFETY AND TOXICOLOGICAL CONSIDERATIONS

Despite their therapeutic potential, inhalable nanoparticles require careful safety assessment. The same physicochemical properties that provide therapeutic functionality can also influence inflammatory responses, oxidative stress, cellular uptake, and clearance. Long-term accumulation is an important concern for certain non-biodegradable

materials, particularly inorganic nanoparticles. The safety assessment therefore needs to consider particle composition, concentration, surface properties, degradation products, repeated-dose exposure, and disease condition. In vitro cytotoxicity testing alone is insufficient because pulmonary deposition, clearance, immune responses, and systemic translocation can influence overall safety. Comprehensive preclinical assessment should incorporate cellular, animal, pharmacokinetic, histopathological, and repeated-exposure studies before clinical translation (Yadav et al., 2022; Jin et al., 2023).

RECENT ADVANCES FROM 2010–2023

The period from 2010 to 2023 demonstrates a transition from basic exploration of nanoparticle carriers toward multifunctional inhalable nanomedicine. Earlier studies concentrated on demonstrating the feasibility of pulmonary administration of liposomes, polymeric nanoparticles, and lipid nanoparticles. During the subsequent decade, researchers increasingly focused on controlled release, cellular targeting, surface modification, improved aerosolization, and disease-specific delivery. By 2021–2023, reviews described increasingly sophisticated approaches involving nano-in-micro formulations, multifunctional carriers, antimicrobial nanomedicines, nucleic-acid delivery, biomimetic systems, and strategies designed specifically to overcome pulmonary barriers. This progression indicates that the field is moving toward integrated systems in which nanoparticle composition, drug loading, surface engineering, particle engineering, and inhalation-device performance are optimized together (Gulati et al., 2021; Yadav et al., 2022; Kole et al., 2023; Jin et al., 2023).

Table 2. Research Advances in Inhalable Nanoparticle Drug Delivery

Period	Major research emphasis	Representative development
2010–2013	Establishment of pulmonary nanocarriers	Liposomes, polymeric nanoparticles and lipid nanoparticles for local lung delivery
2014–2016	Characterization and biological evaluation	Greater emphasis on aerosolization, cellular uptake and sustained release
2017–2019	Disease-specific applications	Development for asthma, COPD, tuberculosis and lung cancer
2020–2021	Multifunctional and anti-inflammatory systems	Increased interest in nano-based therapeutics for inflammatory and chronic pulmonary diseases
2022	Advanced inhalation and particle engineering	Improved dry-powder, nebulized and nano-in-micro approaches
2023	Barrier-oriented and targeted nanomedicine	Rational design for mucus, cellular and pulmonary barriers; improved targeting and controlled release

FUTURE PERSPECTIVES

Future research in inhalable nanoparticle-based drug delivery is likely to focus on precision pulmonary nanomedicine, disease-responsive carriers, biomimetic nanoparticles, nucleic-acid delivery, and personalized inhalation therapy. One important direction is the development of nanoparticles capable of responding to local pathological conditions such as altered pH, oxidative stress, enzymes, inflammatory mediators, or specific cellular receptors. Another direction is the integration of nanoparticles with advanced inhalation devices capable of improving regional lung deposition. Artificial intelligence and computational modelling may also support formulation optimization and prediction of aerosol behavior. The development of physiologically relevant lung models and improved in vitro–in vivo correlation will be particularly important for reducing uncertainty during translation. At the same time, regulatory standardization, scalable manufacturing, batch-to-batch reproducibility, long-term toxicity evaluation, and clinical evidence must progress alongside technological innovation. Recent reviews emphasize that although inhaled nanomedicine has considerable potential, pulmonary barriers, aerodynamic limitations, safety issues, and clinical translation remain significant challenges (Vaughan et al., 2022; Kole et al., 2023; Jin et al., 2023).

II. CONCLUSION

Inhalable nanoparticle-based drug delivery has developed considerably between 2010 and 2023 and represents an important approach for improving the treatment of respiratory disorders. Polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, dendrimers, inorganic nanoparticles, and emerging biomimetic systems offer different mechanisms for improving drug solubility, protecting therapeutic molecules, controlling release, and modifying pulmonary distribution. Their applications have been investigated in asthma, COPD, tuberculosis, pulmonary infections, inflammatory diseases, pulmonary fibrosis, and lung cancer. However, successful pulmonary delivery depends on more than nanoparticle size; aerodynamic properties, particle engineering, inhaler compatibility, pulmonary barriers, disease-specific physiology, toxicity, and manufacturing reproducibility must all be considered. Research published through 2023 indicates a shift toward multifunctional, targeted, controlled-release, and barrier-aware nanomedicines. The future clinical success of these technologies will depend on translating promising experimental findings into reproducible, safe, scalable, and clinically validated inhalable formulations.

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