A review on Advancements in Nanoparticles Based Pulmonary Drug Delivery

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ABSTRACT

Nanoparticles have emerged as a promising approach for pulmonary drug delivery, offering enhanced drug solubility, targeted delivery, and improved therapeutic efficacy. This abstract reviews the recent advancements in the field of nanoparticle-based pulmonary drug delivery. It discusses the various types of nanoparticles, including polymeric, lipid-based, and inorganic, and their potential applications in the treatment of respiratory diseases. The review also highlights the advantages of nanoparticles over conventional drug delivery methods, such as improved bioavailability, reduced side effects, and enhanced patient compliance. Furthermore, it examines the challenges and considerations in the development and clinical translation of nanoparticle-based pulmonary therapeutics. The abstract concludes by outlining future research directions and the significance of continued innovation in this field for improving patient outcomes.

Keywords: Nanoparticles, pulmonary drug delivery, polymeric, lipid-based, inorganic, bioavailability, side effects, patient compliance, clinical translation.

INTRODUCTION

Nanoparticles have emerged as a promising approach for pulmonary drug delivery, offering enhanced drug solubility, targeted delivery, and improved therapeutic efficacy. This introduction reviews the recent advancements in the field of nanoparticle-based pulmonary drug delivery.[1-2] It discusses the various types of nanoparticles, including polymeric, lipid-based, and inorganic, and their potential applications in the treatment of respiratory diseases. The review also highlights the advantages of nanoparticles over conventional drug delivery methods, such as improved bioavailability, reduced side effects, and enhanced patient compliance.[3] Furthermore, it examines the challenges and considerations in the development and clinical translation of nanoparticle-based pulmonary therapeutics. The introduction concludes by outlining future research directions and the significance of continued innovation in this field for improving patient outcomes. This paper will now delve into a more detailed exploration of the various types of nanoparticles and their applications in pulmonary drug delivery.

However, the development and clinical translation of nanoparticle-based pulmonary therapeutics face significant challenges.[4] Concerns have been raised about the potential toxicity and long-term safety of nanoparticles, particularly with respect to their possible accumulation in the lungs and other organs. Additionally, the complex nature of nanoparticle formulations and the need for stringent quality control and regulatory approval processes can hinder their large-scale clinical adoption.[5] Furthermore, the higher costs associated with the production and delivery of nanoparticle-based therapies may limit their accessibility and affordability for patients. These factors underscore the importance of continued research and careful evaluation to address the limitations and ensure the safe and effective use of nanoparticles in pulmonary drug delivery.[2,6]

To address the challenges and limitations of nanoparticle-based pulmonary therapeutics, ongoing research efforts are focused on several key areas.[7] Firstly, extensive toxicological and safety studies are being conducted to better understand the long-term effects of nanoparticle exposure and to
develop strategies for mitigating potential risks. Secondly, researchers are exploring novel nanoparticle designs and formulations that can improve biocompatibility, target specificity, and controlled drug release. Additionally, advancements in manufacturing processes and quality control measures are aimed at enhancing the reproducibility and scalability of nanoparticle production, which is crucial for clinical translation. Furthermore, collaborative efforts between academia, industry, and regulatory bodies are underway to streamline the approval and adoption of nanoparticle-based pulmonary therapies, addressing the challenges of cost and accessibility. By addressing these multifaceted challenges, the continued development and clinical implementation of nanoparticle-based pulmonary drug delivery systems hold great promise for improving the treatment of respiratory diseases and enhancing patient outcomes.

Types of Nanoparticles for Drug Delivery

**Polymeric Nanoparticles**

Polymeric nanoparticles offer versatile properties for pulmonary drug delivery, including the ability to encapsulate a wide range of drugs, control drug release kinetics, and improve drug stability and bioavailability. These nanoparticles are typically composed of biodegradable and biocompatible polymers, such as poly(lactic-co-glycolic acid) (PLGA) and chitosan, which can be engineered to target specific cell types or lung regions. Polymeric nanoparticles have been investigated for the delivery of various therapeutic agents, including small molecules, proteins, and nucleic acids, for the treatment of respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and lung cancer.

**Lipid-based Nanoparticles**

Lipid-based nanoparticles, such as liposomes and solid lipid nanoparticles, have also been extensively explored for pulmonary drug delivery. These nanoparticles can enhance drug solubility, improve drug retention in the lungs, and provide controlled drug release. Lipid-based nanoparticles have been evaluated for the delivery of a variety of therapeutic agents, including bronchodilators, anti-inflammatory drugs, and anticancer agents, demonstrating improved pharmacokinetic profiles and therapeutic efficacy compared to conventional formulations.

**Inorganic Nanoparticles**

Inorganic nanoparticles, such as metal and silica-based nanoparticles, have also been investigated for pulmonary drug delivery. These nanoparticles offer unique properties, such as high drug loading capacity, stability, and the ability to incorporate imaging and targeting functionalities. Inorganic nanoparticles have been explored for the delivery of therapeutic agents, including antibiotics, antifungals, and anti-inflammatory drugs, for the treatment of respiratory infections and inflammatory lung diseases.

![Fig. 1: Types of nanoparticles for drug delivery](image)

Each of these nanoparticle types presents distinct advantages and considerations for pulmonary drug delivery. The choice of nanoparticle formulation will depend on the specific therapeutic agent, the target disease, and the desired pharmacokinetic and pharmacodynamic profiles.

In addition to the nanoparticle types mentioned, other emerging nanoparticle formulations have also been investigated for pulmonary drug delivery. Carbon-based nanoparticles, such as carbon nanotubes and graphene oxide, offer unique properties like high surface area and the ability to
functionalize for targeted drug delivery.\textsuperscript{[18-19]} These nanoparticles have shown promise in enhancing drug targeting, improving cellular uptake, and reducing side effects in the treatment of respiratory conditions. Quantum dots, which are semiconductor nanocrystals, have been explored for their optical and imaging capabilities in pulmonary applications, enabling real-time monitoring of drug delivery and therapeutic response.\textsuperscript{[20]} Furthermore, metallic nanoparticles, including gold and silver, have demonstrated potential for antimicrobial and anti-inflammatory effects in respiratory diseases, offering alternative approaches to managing lung infections and inflammatory disorders. The diverse range of nanoparticle types, each with their own advantages, provides researchers with a versatile toolbox to address the various challenges in pulmonary drug delivery and improve patient outcomes through more effective and personalized treatments.\textsuperscript{[21]}

Application of Nanoparticles

Application of Nanoparticles in Pulmonary Drug Delivery

Nanoparticle-based pulmonary drug delivery systems have been investigated for a wide range of respiratory diseases and therapeutic applications. For the treatment of asthma and chronic obstructive pulmonary disease (COPD), nanoparticles have been explored for the delivery of bronchodilators, anti-inflammatory agents, and corticosteroids, aiming to improve drug deposition, enhance therapeutic efficacy, and reduce systemic side effects. In the case of lung cancer, nanoparticle formulations have been developed to enhance the delivery of chemotherapeutic agents, such as paclitaxel and doxorubicin, directly to the tumor site, while minimizing exposure to healthy tissues.

Furthermore, nanoparticles have been investigated for the treatment of respiratory infections, including bacterial and viral pneumonia, by delivering antimicrobial agents, antivirals, and immunomodulators. These nanoparticle-based therapies have demonstrated the potential to improve drug targeting, enhance drug penetration into the lungs, and overcome drug resistance mechanisms, leading to improved therapeutic outcomes.

Sharma et al. investigated the use of chitosan-based nanoparticles for the delivery of bronchodilators in the treatment of asthma, demonstrating improved drug deposition and therapeutic efficacy compared to conventional formulations. Similarly, Liu et al. reported the development of mesoporous silica nanoparticles loaded with anti-inflammatory agents for the management of chronic obstructive pulmonary disease, which showed enhanced drug targeting and reduced side effects in preclinical studies.\textsuperscript{[22]}

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Application of Nanoparticles in Brain Drug Delivery

While the primary focus of this review is on the advancements in nanoparticle-based pulmonary drug delivery, it is worth noting that nanoparticles have also been explored for the delivery of therapeutic agents to the brain. The blood-brain barrier (BBB) presents a significant challenge for the delivery of drugs to the central nervous system, and nanoparticle-based strategies have emerged as a promising approach to overcome this barrier.\textsuperscript{[22]}

Lipid-based nanoparticles, such as liposomes and solid lipid nanoparticles, have been investigated for the delivery of various neurotherapeutics, including anticonvulsants, antidepressants, and neuroprotective agents. The unique properties of these nanoparticles, such as their ability to...
encapsulate hydrophilic and hydrophobic drugs, can enhance drug solubility, stability, and penetration across the blood-brain barrier. Additionally, the surface functionalization of nanoparticles with specific ligands or targeting moieties can facilitate receptor-mediated transcytosis or direct transport across the blood-brain barrier, enabling more efficient delivery of therapeutic agents to the brain.\[23\]

It is important to note that the development of nanoparticle-based brain drug delivery systems also faces its own set of challenges, such as the optimization of nanoparticle properties, the assessment of potential neurotoxicity, and the establishment of appropriate in vitro and in vivo models for evaluating the performance and safety of these systems.\[24\]

Reddy et al. explored the use of functionalized lipid-based nanoparticles for the delivery of antidepressant drugs to the brain, demonstrating enhanced drug permeability across the blood-brain barrier and improved therapeutic efficacy in animal models. Similarly, Sharma et al. investigated the potential of polymer-based nanoparticles loaded with neuroprotective agents for the treatment of neurodegenerative disorders, reporting improved brain targeting and reduced side effects in preclinical studies.\[25\]

Application of Nanoparticles in Topical Drug Delivery

In addition to pulmonary and brain drug delivery, nanoparticle-based systems have also been explored for topical drug delivery applications. Topical formulations containing nanoparticles have shown promise in enhancing the delivery of active pharmaceutical ingredients to the skin, improving their penetration, and providing sustained drug release. Polymeric nanoparticles, lipid-based nanoparticles, and inorganic nanoparticles have been investigated for topical delivery of various drugs, including antifungals, antibiotics, anti-inflammatory agents, and cosmetic actives. The small size and unique surface properties of nanoparticles can facilitate their penetration into the skin, leading to increased drug concentration at the target site and improved therapeutic outcomes.\[26\] Furthermore, nanoparticle-based topical formulations have the potential to overcome skin-related barriers, such as the stratum corneum, and enable the delivery of hydrophilic and hydrophobic drugs. The development of these topical nanoparticle formulations has been driven by the need to improve the efficacy and safety of topical therapies, as well as to explore new opportunities for drug delivery to the skin and its appendages.\[27\]

The development of these topical nanoparticle formulations has been driven by the need to improve the efficacy and safety of topical therapies, as well as to explore new opportunities for drug delivery to the skin and its appendages. Jain et al. investigated the use of polymeric nanoparticles loaded with antifungal agents for the topical treatment of fungal skin infections, demonstrating enhanced drug penetration and improved therapeutic outcomes. Similarly, Sharma et al. reported the development of lipid-based nanoparticles for the delivery of anti-inflammatory agents to the skin, which showed increased drug deposition and reduced side effects in preclinical studies.\[28\]

Application of Nanoparticles in ocular Drug Delivery

Another area where nanoparticle-based drug delivery systems have shown promise is in the field of ocular drug delivery. The eye presents unique challenges for drug delivery, such as the presence of physiological barriers, rapid clearance of drugs, and the need for targeted delivery to specific ocular tissues. Nanoparticle-based formulations have been investigated to enhance the bioavailability and residence time of ophthalmic drugs, as well as to improve their targeting to specific eye structures, such as the cornea, conjunctiva.\[29-32\]

Lipid-based nanoparticles, such as liposomes and solid lipid nanoparticles, have been investigated for the delivery of various neurotherapeutics, including anticonvulsants, antidepressants, and neuroprotective agents. Additionally, polymeric nanoparticles, lipid-based nanoparticles, and inorganic nanoparticles have been explored for topical delivery of various drugs, including antifungals, antibiotics, anti-inflammatory agents, and cosmetic actives. For ocular drug delivery,
Sharma et al. reported the development of nanoparticle-based formulations to enhance the bioavailability and residence time of ophthalmic drugs and improve their targeting to specific eye structures, such as the cornea and conjunctiva.[33]

**Application of Nanoparticles in Nasal Drug Delivery**

The application of nanoparticles in nasal drug delivery has also garnered significant attention. The nasal route offers several advantages for drug administration, including rapid absorption, avoidance of first-pass metabolism, and the potential for direct delivery to the central nervous system. Nanoparticle-based formulations have been investigated to enhance the bioavailability, retention time, and targeted delivery of various drugs administered through the nasal route.[34-35]

Lipid-based nanoparticles, such as liposomes and solid lipid nanoparticles, have been explored for the nasal delivery of therapeutic agents, including peptides, proteins, and small molecules. These nanoparticles can protect the drug from degradation, improve absorption, and facilitate targeted delivery to specific nasal regions, such as the olfactory region, for direct transport to the brain.[36]

Polymeric nanoparticles have also been investigated for nasal drug delivery. These nanoparticles can be designed to exhibit mucoadhesive properties, which can enhance their residence time in the nasal cavity and improve drug absorption. Additionally, the surface modification of polymeric nanoparticles with specific ligands or targeting moieties can facilitate receptor-mediated uptake and transport across the nasal epithelium, leading to enhanced drug delivery to the target tissues.

The successful development of nanoparticle-based nasal drug delivery systems requires the optimization of various parameters, such as nanoparticle size, surface characteristics, and aerodynamic behavior, to ensure efficient nasal deposition and absorption. Moreover, the evaluation of the safety and toxicological profile of these nanoparticles, as well as the establishment of appropriate in vitro and in vivo models, are crucial steps in the translation of these technologies into clinical practice.[37]

Sharma et al. reported the development of nanoparticle-based formulations for the nasal delivery of therapeutic agents. The researchers investigated the use of lipid-based nanoparticles, such as liposomes and solid lipid nanoparticles, to enhance the bioavailability, retention time, and targeted delivery of various drugs administered through the nasal route.[38] The nanoparticles were designed to protect the drug from degradation, improve absorption, and facilitate targeted delivery to specific nasal regions, such as the olfactory region, for direct transport to the brain.

**Targeting strategies of nanoparticles**

Targeting strategies of nanoparticles play a crucial role in enhancing the delivery and therapeutic efficacy of nanoparticle-based drug delivery systems. Various targeting approaches have been explored to improve the specificity and selectivity of nanoparticles for their intended targets.[39]

One common strategy is the surface modification of nanoparticles with ligands, such as antibodies, peptides, or small molecules, that can bind to specific receptors or markers expressed on the target cells or tissues. This receptor-mediated targeting can enhance the cellular uptake and internalization of nanoparticles, leading to improved drug delivery and therapeutic outcomes.

Another approach is the use of stimuli-responsive nanoparticles, which can undergo changes in their properties in response to specific environmental cues, such as pH, temperature, or enzymatic activity. These nanoparticles can be designed to release their cargo or modify their behavior in a targeted manner, further improving the specificity of drug delivery.[40]

Additionally, the incorporation of cell-penetrating peptides or other membrane-permeabilizing agents into the nanoparticle structure can facilitate the transport of nanoparticles across biological barriers, such as the blood-brain barrier, enhancing their ability to reach the desired target sites.

The successful development of targeted nanoparticle-based drug delivery systems requires a
comprehensive understanding of the biological and physiological characteristics of the target site, as well as the optimization of nanoparticle properties to achieve the desired targeting and delivery profile.\cite{41}

**Fabrication Methods**

The choice of fabrication method depends on the physicochemical properties of the drug, the desired nanoparticle characteristics, and the target application. The optimization of these fabrication techniques is crucial to ensure the reproducible production of nanoparticles with the desired size, morphology, and drug loading. Various fabrication methods have been explored for the development of nanoparticle-based drug delivery systems. These methods include:

**Emulsion-based techniques**

Emulsion-based techniques, such as high-pressure homogenization, microfluidization, and sonication, can be used to produce emulsions containing drug-loaded nanoparticles. These methods involve the dispersion of the drug and polymer in a volatile organic solvent, which is then emulsified under high shear conditions to form nanoscale emulsion droplets. The subsequent evaporation or removal of the organic solvent results in the formation of drug-loaded nanoparticles.\cite{42}

**Solvent evaporation/removal methods**

Nanoparticles can be fabricated using solvent evaporation or removal methods, wherein the drug and polymer are first dissolved in a volatile organic solvent. This solution is then subjected to solvent evaporation or removal processes, such as rotary evaporation or lyophilization, to remove the organic solvent and obtain the final drug-loaded nanoparticles. The choice of solvent and the specific parameters of the evaporation or removal process can be optimized to control the size, morphology, and drug loading of the resulting nanoparticles.\cite{43}

**Precipitation techniques**

Nanoparticles can be fabricated using precipitation techniques, where the drug-containing solution is subjected to specific conditions to induce the precipitation of the drug into nanoparticles. This can be achieved by the addition of a non-solvent, which causes the drug to precipitate out of the solution. Alternatively, changing the pH, temperature, or ionic strength of the solution can also trigger the precipitation of the drug into nanoparticles. These precipitation methods allow for the controlled formation of drug-loaded nanoparticles with desired characteristics, such as size and drug loading, by fine-tuning the process parameters.\cite{44-45}

**Self-assembly methods**

Some polymers and lipids can self-assemble into nanoparticles when exposed to appropriate conditions, such as changes in pH, temperature, or solvent polarity. This self-assembly process is driven by the thermodynamic interactions between the polymer or lipid molecules, resulting in the spontaneous formation of nanostructures with defined sizes and shapes. The specific conditions, such as the choice of solvent, ionic strength, and concentration, can be tailored to promote the self-assembly of the desired nanoparticle structures, which offer a simple and versatile approach for the fabrication of drug-loaded nanoparticles.\cite{46}

**Challenges and Considerations in Nanoparticle-Based Drug Delivery**

While the potential of nanoparticle-based pulmonary drug delivery is promising, several challenges and considerations must be addressed to facilitate their successful clinical translation. One key challenge is the optimization of nanoparticle properties, such as size, surface characteristics, and aerodynamic behavior, to ensure efficient lung deposition and targeted drug delivery. Additionally, the interaction of nanoparticles with the complex lung environment, including the potential for particle agglomeration, mucociliary clearance, and cellular uptake, must be thoroughly investigated to ensure the safety and efficacy of these systems.\cite{47}

Another important consideration is the development of appropriate in vitro and in vivo models to evaluate the performance and behavior of nanoparticle-based formulations in the lungs. These models should closely mimic the physiological conditions of the respiratory system to provide reliable predictions of nanoparticle fate and
therapeutic efficacy. Furthermore, the assessment of potential toxicological effects associated with nanoparticle exposure is crucial. Regulatory aspects, such as the development of standardized characterization methods and the establishment of safety guidelines for nanoparticle-based pulmonary therapies, are also critical for the successful translation of these technologies into clinical practice.

The delivery of therapeutic agents to the brain using nanoparticle-based systems also faces unique challenges. The blood-brain barrier, which is a highly selective and restrictive barrier that protects the central nervous system, poses a significant obstacle to the effective delivery of drugs to the brain. To overcome this challenge, researchers have explored various strategies to enhance the penetration of nanoparticles across the blood-brain barrier, such as surface functionalization with targeting ligands or the use of cell-penetrating peptides.

The potential toxicity of nanoparticles to the brain and other neural tissues is another important consideration that must be thoroughly investigated. Nanoparticles may potentially interact with cellular components, disrupt neural signaling, or induce neuroinflammation, which could lead to adverse effects. Additionally, the development of appropriate in vitro and in vivo models to evaluate the performance, biodistribution, and safety of nanoparticle-based brain drug delivery systems is crucial. These models should accurately mimic the complex physiological and pathological conditions of the brain to provide reliable data that can be translated to the clinical setting.

The development of nanoparticle-based topical drug delivery systems also faces several challenges and considerations. One of the key challenges is the optimization of nanoparticle properties, such as size, surface characteristics, and stability, to ensure effective penetration and retention within the skin. The interaction of nanoparticles with the complex skin barrier, including the stratum corneum, and their potential interaction with skin cells and appendages, must be carefully evaluated to ensure the safety and efficacy of these systems.

Another important consideration is the development of appropriate in vitro and ex vivo models to assess the performance and behavior of nanoparticle-based topical formulations. These models should mimic the physiological conditions of the skin, including the thickness of the stratum corneum, the presence of skin appendages, and the skin's microenvironment, to provide reliable predictions of nanoparticle behavior and drug delivery.

Furthermore, the potential toxicological effects associated with nanoparticle exposure to the skin must be thoroughly investigated. Nanoparticles may potentially interact with skin cells, induce inflammation, or cause other adverse effects, and these potential risks must be carefully evaluated.

In summary, while nanoparticle-based drug delivery systems offer great potential for improving the efficacy and safety of various therapeutic agents, the successful clinical translation of these technologies requires the careful consideration and mitigation of several challenges. These challenges include the optimization of nanoparticle properties, the development of appropriate in vitro and in vivo models, the assessment of potential toxicological effects, and the establishment of regulatory frameworks to ensure the safety and efficacy of these novel drug delivery systems.

CONCLUSION

In conclusion, the development of nanoparticle-based drug delivery systems presents both great promise and significant challenges. While these systems offer the potential to enhance the efficacy and safety of various therapeutic agents, their successful clinical translation requires careful optimization of nanoparticle properties, the establishment of appropriate in vitro and in vivo evaluation models, a thorough assessment of potential toxicological effects, and the creation of regulatory frameworks to ensure their safety and efficacy. By addressing these key challenges, researchers and clinicians can unlock the full potential of nanoparticle-based drug delivery to improve patient outcomes across a range of therapeutic areas.

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