Review

Nanotechnology-based approaches for targeted drug delivery for the treatment of respiratory tract infections

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Abstract

Background: Nanotechnology has emerged as a promising field for the diagnosis, monitoring, and treatment of respiratory tract infections (RTIs). By leveraging the unique properties of nanoscale delivery systems, nanotechnology can significantly enhance the selectivity and efficacy of antimicrobials, thereby reducing off-target effects. **Objective:** This review explores the development and application of targeted nanosystems in combating viral, bacterial, and fungal RTIs. Nanotechnology-based systems, including biological and non-biological nanoparticles, offer innovative solutions for overcoming antimicrobial resistance, improving drug bioavailability, and minimizing systemic side effects. RTIs are a leading cause of morbidity and mortality globally, particularly affecting vulnerable populations such as children, the elderly, and immunocompromised individuals. Traditional drug delivery methods face numerous challenges, such as rapid clearance, poor tissue penetration, and drug degradation. Nanoparticle-based delivery systems address these issues by enhancing tissue penetration, providing sustained drug release, and enabling targeted delivery to infection sites. These systems include liposomal delivery, polymeric nanoparticles, dendrimers, and metal-based nanoparticles, each offering unique advantages in treating RTIs. Nanotechnology also plays a crucial role in vaccine development by offering new strategies to enhance immune responses and improve antigen delivery. Furthermore, the review discusses the clinical translation and regulatory considerations for nanotechnology-based drug delivery, emphasizing the need for rigorous testing and quality control to ensure safety and efficacy. **Conclusion:** Nanotechnology offers promising advancements in the treatment, and prevention of RTIs by enhancing drug delivery and efficacy. By addressing challenges such as antimicrobial resistance and poor tissue penetration, nanotechnology-based systems have the potential to significantly improve patient outcomes.

Keywords: Nanotechnology, Targeted drug delivery, Respiratory tract infections, Nanoparticles, Antimicrobial resistance

1. INTRODUCTION

According to the World Health Organization, lower respiratory tract infections (RTIs) are the fourth leading cause of death globally. RTIs encompass a wide range of conditions, ranging from mild infections such as the common cold to severe diseases such as pneumonia, bronchitis, and tuberculosis (TB). Symptoms often include coughing, fever, sore throat, and difficulty breathing, with complications potentially leading to chronic respiratory diseases, sepsis, and respiratory failure [1].

Recurrent or severe RTIs can lead to chronic conditions such as chronic obstructive pulmonary disease (COPD) and asthma [2], both of which significantly impair quality of life and contribute to long-term healthcare costs. The economic impact of RTIs is substantial, involving both direct costs (hospitalizations and medications) and indirect costs (lost productivity and long-term care). In high-income countries, RTIs account for a significant portion of healthcare expenditures, while in low- and middle-income countries, they contribute to the cycle of poverty by posing a financial burden on affected families [3]. Certain groups,

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including young children, the elderly, immunocompromised individuals, and those with pre-existing health conditions, are particularly susceptible to severe RTIs. These populations often experience higher rates of complications and mortality [4].

Conventional drug delivery methods often result in the widespread distribution of the drug throughout the body, rather than targeted delivery to the infection site. This lack of specificity can reduce the drug's efficacy at the site of infection while increasing the risk of side effects in non-target tissues. Medications administered through conventional routes, such as oral or intravenous delivery, typically lack the precision to specifically target infected tissues or cells. As a result, suboptimal drug concentrations at the infection site may fail to eradicate the pathogen effectively [5].

Furthermore, many drugs, particularly those given orally, confront challenges such as degradation in the gastrointestinal tract or first-pass metabolism in the liver, which significantly reduces the amount of active drug reaching systemic circulation and, ultimately, the site of infection. In addition, conventional drugs often have a short half-life in the body, necessitating frequent dosing to maintain therapeutic levels. This frequent dosing can lead to poor patient adherence, especially in chronic conditions or infections requiring long-term treatment [6].

Nanotechnology is the science and engineering of manipulating matter on the nanoscale, typically between 1 and 100 nm. At this scale, materials exhibit unique physical, chemical, and biological properties that differ significantly from those of their bulk counterparts. Nanotechnology intersects with multiple scientific disciplines, including physics, chemistry, biology, and engineering, enabling the design and fabrication of nanomaterials and nanodevices with specific functionalities tailored to various applications, particularly in medicine [7].

The concept of nanotechnology was first introduced by physicist Richard Feynman in 1959. However, it was not until the late 20th and early 21st centuries that advancements in material science and molecular biology allowed for the practical application of nanotechnology in medicine, leading to the emergence of nanomedicine. Significant progress has been made in the development of nanoparticles, nanocarriers, and other nanostructures designed for diagnostic, therapeutic, and preventive purposes in medicine. The approval of the first nanomedicine, Doxil (a liposomal formulation of the chemotherapy drug doxorubicin), marked a turning point in the clinical application of nanotechnology [8,9].

The objective of the review is to explore nanotechnology-based approaches for targeted drug delivery in RTIs.

2. OVERVIEW OF NANOTECHNOLOGY

2.1. Definition and basic principles of nanotechnology

Nanotechnology involves the manipulation and control of matter on atomic, molecular, and supramolecular scales, typically ranging from 1 to 100 nm. [10].

At the nanoscale, quantum mechanical effects become significant, influencing the optical, electrical, and magnetic properties of materials. These effects enable the creation of nanoparticles with specific behaviors tailored to medical applications. Nanoparticles possess a high surface area-to-volume ratio, which enhances their reactivity and allows for the attachment of functional molecules, such as drugs, targeting ligands, or imaging agents. This feature is critical for the development of effective drug delivery systems. In addition, nanotechnology often employs the principle of self-assembly, where molecules spontaneously organize into well-defined structures due to intermolecular forces. This principle allows for the fabrication of complex nanostructures with precise functionalities [11].

2.2. Types of nanoparticles used in drug delivery

Liposomes are spherical vesicles composed of one or more phospholipid bilayers. They can encapsulate both hydrophilic and hydrophobic drugs, protecting them from degradation and enhancing their delivery to target sites. Liposomes are widely used in drug delivery for cancer treatment, gene therapy, and vaccines. They can be engineered to release their payload in response to specific stimuli, such as pH changes or enzymatic activity [12].

Dendrimers are highly branched, tree-like polymers with a central core, an inner branching layer, and multi-functional surface groups. This architecture allows for the conjugation of multiple drug molecules and targeting agents. Dendrimers are used in targeted drug delivery, gene delivery, and imaging. Their multivalency permits a high drug-loading capacity and facilitates targeted delivery to specific cells or tissues [13].

Polymeric nanoparticles are composed of biodegradable polymers, such as poly (lactic-co-glycolic acid) (PLGA). They can be designed as nanospheres or nanocapsules, depending on whether the drug is dispersed throughout the polymer matrix or encapsulated within a core. These nanoparticles are used for the sustained release of drugs, targeted delivery, and as carriers for vaccines. Their biodegradability and biocompatibility make them suitable for a wide range of therapeutic applications [14].

Solid lipid nanoparticles (SLNs) consist of a solid lipid core stabilized by surfactants. SLNs combine the advantages of both liposomes and polymeric nanoparticles, offering high stability and controlled drug release. They are used in

drug delivery systems for poorly soluble drugs, enhancing bioavailability and providing controlled release. SLNs are also employed in the delivery of lipophilic drugs [15].

Gold nanoparticles (AuNPs) are small gold particles with diameters in the nanoscale range. They exhibit unique optical properties due to surface plasmon resonance, which can be exploited in both imaging and therapeutic applications. AuNPs are used in drug delivery, photothermal therapy, and as contrast agents in imaging. Their surface can be easily functionalized with targeting ligands, drugs, or diagnostic agents [16].

2.3. Advantages of nanotechnology in drug delivery

Nanoparticles can enhance the solubility of poorly water-soluble drugs, leading to improved absorption and bioavailability. This is particularly important for drugs with limited clinical use due to poor solubility. Encapsulation within nanoparticles protects drugs from degradation caused by enzymes, pH changes, or other environmental factors, ensuring that a higher proportion of the drug reaches the target site in its active form [17].

Nanoparticles can exploit the enhanced permeability and retention (EPR) effect, allowing them to accumulate in tumor tissues or inflamed areas due to leaky vasculature. The EPR effect provides passive targeting of the drug to diseased sites. In addition, nanoparticles can be functionalized with ligands, such as antibodies, peptides, or small molecules, that bind specifically to receptors on target cells, enabling active targeting. This approach enhances drug accumulation at the target site while reducing systemic exposure and side effects [18].

Nanoparticles can also be engineered to release their drug payload in a controlled manner over time, reducing the frequency of dosing and minimizing fluctuations in drug concentration. Controlled release helps reduce peak drug concentrations that can cause toxic side effects. By delivering drugs specifically to diseased tissues or cells, nanoparticles reduce the exposure of healthy tissues to potentially toxic drugs. This targeted approach lowers the incidence of off-target effects, thus improving the overall safety profile of the treatment [19].

3. MECHANISMS OF RTI AND IMMUNE RESPONSE

3.1. Viral infections

Viruses such as influenza and severe acute respiratory syndrome coronavirus 2 enter the respiratory tract through inhalation, binding to specific receptors on the surface of epithelial cells. Once inside, they hijack the host cell's machinery to replicate and produce viral progeny. The innate immune system recognizes viral components through pattern recognition receptors (PRRs), such as Toll-like receptors, triggering an inflammatory response. Cytokines and interferons are released to limit viral replication and recruit immune cells, such as macrophages and T-cells, to the infection site. The adaptive immune response involves the activation of B-cells, which produce neutralizing antibodies, and T-cells, which target and destroy infected cells. In addition, memory cells are generated to provide long-term immunity [20].

3.2. Bacterial infections

Bacteria such as *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* colonize the respiratory tract and employ various mechanisms, such as capsule formation and intracellular survival, to evade the immune system. In response, the immune system recruits neutrophils, which phagocytose bacteria and release antimicrobial peptides. Macrophages and dendritic cells present bacterial antigens to T-cells, thus activating the adaptive immune response. In TB, this immune response leads to the formation of granulomas, that is, collections of immune cells that attempt to contain the bacteria, but can also result in tissue damage [21,22].

3.3. Fungal infections

Fungi such as *Aspergillus* and *Cryptococcus* are inhaled into the lungs, where they can establish infection, especially in immunocompromised individuals. The immune system recognizes fungal components through PRRs, leading to phagocytosis by macrophages and the activation of adaptive immunity. In the cases of severe immunosuppression, the immune response may be insufficient to control the infection, leading to invasive disease [23].

4. CHALLENGES IN TREATING RTIs

4.1. Drug resistance

The overuse and misuse of antibiotics have led to the emergence of antibiotic-resistant bacteria, such as multidrug-resistant *M. tuberculosis* and methicillin-resistant *Staphylococcus aureus*. The emergence of antibiotic-resistant bacteria complicates the treatment of bacterial RTIs and necessitates the development of new antibiotics or alternative therapies. Resistance to antiviral drugs, such as those used to treat influenza, can also arise due to mutations in viral genomes. The development of resistance to antiviral drugs limits the effectiveness of existing treatments and requires continuous surveillance as well as the development of new antiviral agents [24].

4.2. Bacterial biofilms and their role in chronic respiratory infections

Bacterial biofilms are complex, structured communities of bacteria that adhere to surfaces and are encased in a self-produced extracellular matrix composed of polysaccharides, proteins, and nucleic acids. In respiratory infections, biofilms are a major cause of chronic and persistent infections, enabling bacteria to evade the immune system and resist antibiotic treatment. Biofilms are a common feature of severe respiratory diseases such as cystic fibrosis, COPD, and bronchiectasis, where they contribute to long-term airway colonization by pathogens such as *Pseudomonas aeruginosa*, *S. aureus*, and *Haemophilus influenzae* [25].

A critical aspect of biofilms is their unique metabolic behaviors, which differ significantly from those of free-floating (planktonic) bacteria. Biofilm-associated bacteria exhibit reduced metabolic activity and slower growth rates due to the limited diffusion of nutrients and oxygen into the deeper layers of the biofilm. This metabolic heterogeneity creates a microenvironment within the biofilm, where aerobic bacteria reside at the surface and anaerobic bacteria thrive in deeper layers. These gradients influence the expression of various enzymes and biochemical pathways, making biofilms highly resistant to conventional antibiotics that typically target actively dividing cells [26].

One of the key aspects of biofilms is their ability to produce enzymes that degrade host tissues and promote bacterial survival, such as matrix metalloproteinases and proteases. In addition, biofilms can produce β-lactamase enzymes that break down β-lactam antibiotics, further contributing to antibiotic resistance. The extracellular polymeric substance matrix of the biofilm also acts as a physical barrier, limiting the penetration of antimicrobial agents and immune cells [27].

Quorum sensing, a cell-to-cell communication mechanism, plays a significant role in biofilm formation and maintenance. This process regulates the expression of genes related to virulence, motility, and biofilm stability. Disrupting quorum sensing is an emerging strategy for combating biofilm-associated infections, as interfering with this signaling system can reduce biofilm formation and increase bacterial susceptibility to treatment. Furthermore, the metabolism of biofilms can shift to alternative energy production pathways. For instance, bacteria in biofilms often switch to anaerobic respiration or fermentation, leading to the accumulation of metabolic byproducts such as lactate and acetate. These metabolic shifts can create an acidic microenvironment within the biofilm, further complicating treatment as certain antibiotics are less effective in low-pH environments [28].

4.3. Immune evasion

Respiratory pathogens have evolved various mechanisms to evade the host immune system. For example, *M. tuberculosis* can survive within macrophages, while influenza viruses can undergo antigenic drift, allowing them to escape immunosurveillance. These immune evasion strategies complicate treatment by enabling pathogens to persist in the host, leading to chronic or recurrent infections. This highlights the need for the development of therapies that can effectively overcome these evasion mechanisms [29].

4.4. Vaccine development

Developing vaccines for respiratory pathogens is challenging due to the high variability of some viruses, such as influenza, and the complexity of the immune responses they elicit. In addition, vaccine development for bacterial RTIs, such as TB, is compounded by the need for long-lasting immunity and protection against different strains. Innovative approaches, such as nanotechnology-based vaccines and adjuvants, are being explored to enhance both the effectiveness and durability of vaccines against respiratory pathogens [30].

5. NANOPARTICLES FOR TARGETED DRUG DELIVERY

5.1. Characteristics of ideal nanoparticles for respiratory drug delivery

Ideal nanoparticles for respiratory drug delivery are designed to possess specific properties that allow for efficient lung penetration, targeted delivery to infected tissues, and controlled release of therapeutic agents. These properties may vary, depending on the therapeutic goal, such as delivering antibiotics, antivirals, or anti-inflammatory agents directly to lung tissues while minimizing systemic exposure. For respiratory infections, nanoparticles typically range from 10 to 200 nm, have slightly negative or neutral surface charges to avoid rapid clearance by the immune system, and are often biodegradable to reduce long-term toxicity [31]. This size range allows for efficient circulation in the bloodstream, avoidance of rapid clearance by the reticuloendothelial system, and penetration of biological barriers. While spherical nanoparticles are the most common, non-spherical shapes (*e.g.*, rod-shaped or disk-shaped ones) can also be used, depending on the desired interaction with cells and tissues. The shape of nanoparticles influences cellular uptake, biodistribution, and circulation time. The surface charge of nanoparticles, usually described by their zeta potential, plays a critical role in their stability and interaction with biological systems. Slightly negative or neutral nanoparticles are often preferred to minimize non-specific interactions

with cells and reduce opsonization (marking for clearance by the immune system). Nanoparticles can also be surface-modified with various functional groups, ligands, or polymers *(e.g*., polyethylene glycol [PEG]) to improve biocompatibility, reduce immunogenicity, and enhance targeted delivery. These modifications can also provide attachment sites for drugs, targeting molecules, or imaging agents [31].

Ideal nanoparticles should be non-toxic, non-immunogenic, and compatible with biological systems, avoiding significant adverse immune responses or damage to healthy tissues. Biodegradable nanoparticles are particularly preferred for drug delivery, as they break down into non-toxic components that are easily eliminated from the body, thus reducing long-term accumulation and potential toxicity [32].

Nanoparticles should be able to carry sufficient therapeutic payloads to ensure that an effective dose can be delivered to the target site, which is particularly important for potent drugs that require only small quantities or those with low bioavailability. Ideal nanoparticles should allow for controlled and sustained drug release, maintaining therapeutic levels over an extended period. This can be achieved through various mechanisms, such as pH-sensitive release, temperature-sensitive release, or enzymatic degradation [33].

Stability in biological fluids is crucial for nanoparticles, as they must avoid aggregation or premature release of the drug to maintain efficacy and prevent rapid clearance from the bloodstream. Furthermore, ideal nanoparticles should have a long shelf life without losing their functionality, drug-loading capacity, or stability, which is critical for the practical application of nanoparticle-based drug delivery systems in clinical settings [34].

5.2. Mechanisms of nanoparticle-mediated drug delivery

Passive targeting fully utilizes the enhanced EPR effect, which is characteristic of many pathological conditions, such as tumors and tissue inflammation. In these conditions, the vasculature is often leaky, allowing nanoparticles to pass through blood vessel walls and accumulate in affected tissues. This passive accumulation is especially useful for targeting solid tumors or inflamed regions in RTIs. Passive targeting also relies on the ability of nanoparticles to remain in circulation long enough to reach the target site. Surface modifications, such as PEGylation, can help them evade immune recognition and prolong circulation time, thereby increasing the likelihood of accumulation at the diseased site [35].

Active targeting involves functionalizing the surface of nanoparticles with ligands (*e.g*., antibodies, peptides, and small molecules) that specifically bind to receptors overexpressed on the surface of target cells, such as infected or cancerous cells. This ensures that nanoparticles are directed precisely to the site of infection or disease. Once bound to target cells, the nanoparticles are internalized through receptor-mediated endocytosis, enhancing the intracellular delivery of the drug and ensuring that it reaches the subcellular compartments where it is most effective. In some cases, nanoparticles can be designed with dual targeting mechanisms, combining passive and active targeting. This dual approach improves the specificity and efficiency of drug delivery, particularly in complex environments such as the respiratory system [36]. Table 1 compares various types of nanoparticles used for respiratory drug delivery, detailing their drug delivery methods, advantages, and limitations.

6. NANOPARTICLES USED IN RTIS

The field of nano/microtechnology for drug delivery, particularly through inhalable particles, is undergoing rapid advancements. Initially, nano/microtechnologies utilized dosing methods to produce micron-sized particles composed of nanoparticles. Techniques such as spray drying, controlled precipitation, and grinding have been employed to generate dried particles from the drug's composite polymer. Recent innovations have led to the development of a new class of porous nanoparticles, constructed from polymers based on supramolecular structures. These particles, characterized by their optimal size range of 0.5–5 μm, exhibit excellent aerosolization properties. Their high porosity and drug-loading capacity offer significant advantages, including the potential for slow-release or stimulus-responsive drug delivery. These nanoparticles have shown promise in carrying anti-HIV RNA molecules, protecting them from degradation within lung tissue following *in vivo* administration [37].

Inhalable nano/micro-sized particles represent a promising drug delivery system, with various preparation methods such as dry powders, aqueous suspensions, and structured advanced nanoparticles. These particles exhibit a range of characteristics – such as surface charge, porosity, and solubility – tailored to optimize their performance in the lungs and their interaction with pathogens. For example, aqueous solutions can deliver drugs through the respiratory tract using surfactants for non-viral infections, resulting in relatively smaller, lower-density particles. Conversely, dry powders offer the advantage of maintaining drug stability without the need for cold storage, which is particularly crucial for biological products [38].

Interferon and cytokine inhalation therapies are promising therapeutic approaches, especially in treating viral respiratory infections, asthma, and other inflammatory lung conditions. Interferons, particularly interferon-α, are cytokines that play a critical role in the antiviral immune response. They can inhibit viral replication and modulate the immune system to

Table 1. Comparison of nanoparticle types used for respiratory drug delivery

Nanoparticle type	Examples of drugs delivered	Drug loading method	Advantages	Limitations
Liposomes	Amikacin, antivirals, antibiotics	Encapsulation within lipid bilayer	Biocompatibility, protection of drugs, targeted delivery	Low stability, short half-life
SLNs	Tuberculostatic drugs, antifungals	Drug dissolved in lipid core	High stability, controlled drug release	Potential drug expulsion during storage
Nanostructured lipid carriers	Antitubercular drugs, antivirals	Drug solubilized in mixed solid/liquid lipids	Increased drug loading, improved stability	More complex formulation than SLNs
Polymeric nanoparticles	Poly (lactic-co-glycolic acid) for antibiotics, RNA-based drugs	Encapsulation or surface attachment	Biodegradable, sustained release, versatile	Limited drug loading capacity, potential toxicity
Gold nanoparticles	Chemotherapeutics, photothermal agents	Surface functionalization	Unique optical properties, imaging capabilities	High cost, potential toxicity
Dendrimers	Antibacterial, gene therapy agents	Surface functionalization	High drug loading capacity, multivalency	Complex synthesis, potential toxicity

SLNs: Solid lipid nanoparticles.

enhance the body's defense against pathogens. Inhalation of interferons delivers the cytokine directly to the respiratory tract, allowing for localized activation of antiviral responses while minimizing systemic side effects. This method has been studied for treating conditions such as COPD, asthma exacerbations, and severe viral infections like Coronavirus disease 2019 (COVID-19) [39].

Similarly, the inhalation of other cytokines, such as interleukins and tumor necrosis factor, is being explored to modulate the immune response in the lungs. These cytokines can either promote an anti-inflammatory environment or stimulate the immune system to clear infections. Delivering these cytokines directly to the lungs through aerosolization enhances therapeutic effects at the site of infection or inflammation, offering a targeted approach that reduces the risks of systemic cytokine toxicity. However, despite the promise of cytokine inhalation therapy, its clinical application requires more extensive research, particularly regarding optimal dosing strategies, delivery systems, and long-term safety [40].

The primary methods for generating respiratory aerosols include nebulizers, pressurized metered-dose inhalers (pMDIs), and dry powder inhalers (DPIs), each utilizing different mechanisms to produce aerosols suitable for inhalation. Nebulizers convert liquid medications into a fine mist using ultrasonic vibrations or compressed air. These devices are effective for patients who require high doses of medication over extended periods, though they are generally bulky and require an external power source. Nebulizers are widely used in hospitals and home care settings for patients with severe respiratory conditions, such as asthma or COPD [41].

pMDIs use a propellant to release a pre-measured dose of medication in the form of an aerosol spray. They are more portable than nebulizers, making them convenient for regular use, but they require coordination between actuation and inhalation. In contrast, DPIs rely on the patient's inhalation effort to disperse a fine powder into the lungs. DPIs are compact and efficient for medication delivery, but their effectiveness depends on the patient's ability to generate sufficient inhalation force. Each of these methods provides unique advantages, depending on the drug formulation and the patient's needs [42].

Liquid aerosol delivery, typically administered through nebulizers or pMDIs, offers significant advantages in terms of dose flexibility and suitability for patients with varying respiratory capacities. This method is ideal for drugs that need to remain in a solubilized form, rendering them effective for patients with acute conditions requiring tailored dosing. However, liquid formulations often face stability challenges, especially with water-based drugs, which may degrade over time and require preservatives that could lead to side effects. Despite these limitations, nebulizers are better tolerated in populations such as children or patients with severe respiratory limitations due to the gentle delivery mechanism. In contrast, DPIs provide a more stable and portable alternative, often preferred for long-term treatments. The stability of dry powders allows for improved drug preservation, particularly for biologics, and eliminates the need for preservatives. In addition, DPIs are compact, making them convenient for on-the-go use. However, their effectiveness relies on the patient's ability to inhale the powder deeply, making them less suitable for individuals with severe lung impairment. Dry formulations are also sensitive to humidity, which may affect drug efficacy in high-moisture environments [43,44].

Dry inhalers, including devices like Spinhalers, have become a cornerstone in the management of bronchial asthma. These devices deliver medications in the form of dry powder, which is inhaled directly into the lungs. Spinhalers and other DPIs rely on the patient's breath to disperse the powdered drug, offering a highly targeted and effective treatment for asthma. DPIs are especially useful for delivering corticosteroids and bronchodilators, which are critical in reducing inflammation

and opening the airways, thereby relieving symptoms such as shortness of breath, wheezing, and coughing [45].

One of the main advantages of using dry inhalers like Spinhalers for asthma management is their portability and ease of use. Unlike nebulizers, DPIs do not require an external power source or complex preparation, making them particularly convenient for patients to use on-the-go or during sudden asthma attacks. However, the effectiveness of DPIs depends on the patient's ability to generate sufficient inhalation force to disperse the powder properly. This factor is critical when prescribing DPIs for children or patients with severe respiratory conditions, where lung function may be compromised [46].

Liposomes are used to deliver antibiotics, antiviral agents, and anti-inflammatory drugs directly to the lungs in RTIs. For example, liposomal formulations of antibiotics, such as amikacin, are used to treat severe bacterial lung infections, including those caused by drug-resistant pathogens. Liposomes can also be inhaled as aerosols, providing direct delivery to the lungs [47].

SLNs combine the benefits of liposomes and polymeric nanoparticles, offering high stability, controlled drug release, and protection of sensitive drugs. SLNs have been explored for delivering drugs to treat respiratory infections such as TB and fungal infections. Their ability to provide sustained drug release and protect active ingredients from degradation makes them suitable for treating chronic respiratory conditions, where protracted drug exposure is necessary [48]. However, SLNs also have notable limitations, including the potential for drug expulsion during storage due to the high crystallinity of the solid lipid matrix, which can reduce drug loading capacity and entrapment efficiency [48].

To overcome these drawbacks, nanostructured lipid carriers (NLCs) were developed as a second-generation lipid-based nanocarrier system. NLCs are composed of a blend of solid and liquid lipids, creating a less ordered lipid matrix that reduces the crystallization of the lipid core. This modification increases drug-loading capacity, enhances drug entrapment efficiency, and reduces the risk of drug expulsion over time. In addition, the more flexible structure of NLCs allows for enhanced control over the release kinetics of encapsulated drugs, making them a more versatile and efficient system for drug delivery [49].

The combination of solid and liquid lipids in NLCs also improves drug stability and prolongs its release, making it particularly advantageous for the sustained delivery of therapeutics in chronic respiratory conditions such as TB, cystic fibrosis, and COPD. Moreover, NLCs are highly biocompatible and can be used to deliver a wide range of drugs, including both lipophilic and hydrophilic molecules, thereby broadening their applications compared to SLNs. This advancement in lipid nanoparticle design addresses many of the limitations associated with SLN systems and highlights the growing importance of NLCs in nanotechnology-based drug delivery strategies for RTIs [50].

Polymeric nanoparticles are also used to deliver a wide array of drugs, including antibiotics, antivirals, and anti-inflammatory agents, to the lungs. For example, PLGA nanoparticles have been studied for the delivery of antitubercular drugs, enhancing drug stability and enabling targeted delivery to infected lung tissues. They are also being investigated for delivering RNA-based therapeutics for viral infections like COVID-19 [51].

6.1. Plasmid deoxyribonucleic acid (pDNA) nanoparticles for lung endothelial cell transformation and TB treatment

The aerosol delivery of pDNA nanoparticles offers a novel approach for transforming lung endothelial cells, presenting potential applications in gene therapy for various respiratory diseases. By encapsulating and protecting pDNA within nanoparticles, aerosolized formulations can be efficiently delivered to the lungs, where they are absorbed by the respiratory epithelium and endothelial cells. This method has shown promise in animal studies for promoting gene expression directly in the lungs. The ability to deliver genetic material through aerosol, combined with targeted nanoparticle systems, opens new avenues for treating lung-related diseases through gene therapy [52].

In the context of TB, gene therapy holds potential for addressing drug-resistant strains and enhancing immune responses to the *M. tuberculosis* infection. Aerosolized pDNA nanoparticles could be used to modify lung cells to express specific genes that boost the host's immune response or inhibit bacterial survival mechanisms. In addition, nanoparticle-based genetic therapies may contribute to the development of more effective TB vaccines by enhancing the delivery of genetic material that encodes antigens capable of eliciting stronger and longer-lasting immune responses. While genetic therapy for TB is still in its early stages, the use of aerosolized pDNA nanoparticles represents a promising future direction for overcoming the limitations of current treatments, particularly in tackling multidrug-resistant TB [53].

6.2. Aerosol halotherapy and its therapeutic applications

Aerosol halotherapy, commonly referred to as salt therapy, involves the inhalation of dry aerosolized salt particles in controlled environments, such as salt rooms or model salt caves. The principle behind halotherapy is that aerosolized sodium chloride (salt) particles, typically ranging in size

from 1 to 5 μm, can be inhaled deep into the respiratory tract. These particles are believed to help clear mucus, reduce inflammation, and improve respiratory function. The therapeutic effects are thought to stem from the hygroscopic properties of salt, which draws moisture from the airway linings, potentially thinning mucus secretions and aiding in the clearance of pathogens and allergens [54].

Halotherapy has been used as a complementary treatment for various respiratory conditions, including asthma, COPD, bronchitis, and sinusitis. Studies suggest that exposure to dry salt aerosol may enhance airway hydration, reduce airway resistance, and improve pulmonary function in some individuals. However, while anecdotal evidence supports its use, more rigorous clinical trials are warranted to fully establish the efficacy and safety of halotherapy for respiratory conditions. It is considered a non-invasive therapy with minimal side effects, making it an attractive option for patients seeking alternative or supplementary treatments for respiratory ailments [55].

6.3. Comparison of efficacy and safety with conventional therapies

Comparing the efficacy and safety of nanotechnology-based therapies with conventional treatments is a crucial research area, as nanomedicine offers the potential to enhance therapeutic outcomes while reducing adverse effects. One of the key advantages of nanotechnology is its ability to achieve targeted drug delivery, allowing for precise targeting of specific cells or tissues. This precision increases the concentration of the drug at the site of action while minimizing systemic exposure, leading to improved outcomes in treating conditions such as cancer, infectious diseases, and chronic inflammatory conditions. In addition, nanotechnology enhances drug solubility and bioavailability, particularly for poorly soluble drugs, rendering treatments more effective at lower doses. Nanocarriers can also be engineered for controlled or sustained drug release, maintaining therapeutic levels over extended periods and reducing the frequency of dosing, thereby improving patient adherence [56].

In terms of safety, nanotechnology-based therapies can significantly reduce side effects by delivering drugs specifically to the diseased site, thereby minimizing off-target effects. This is especially beneficial in chemotherapy and other treatments with high toxicity. Many nanomaterials are designed to be biocompatible and biodegradable, reducing the risk of long-term toxicity. However, the safety of certain nanomaterials, particularly concerning their long-term effects and potential accumulation in the body, remains under investigation. Nanoparticles can be engineered to evade the immune system, lowering the risk of immune responses, although unintended immune interactions remain a concern. Comparatively, nanotechnology has demonstrated superior outcomes in cancer treatment compared to conventional chemotherapies, offering improved targeting, reduced side effects, and enhanced drug efficacy. In treating infectious diseases, nanoformulations of antibiotics and antiviral drugs have demonstrated better efficacy against resistant strains and lower toxicity than traditional drugs. For chronic diseases such as diabetes and cardiovascular conditions, nanotechnology helps attain more precise management with fewer side effects than conventional therapies, highlighting its potential to revolutionize treatment across a spectrum of conditions [57].

6.4. Nanotechnology-based vaccines for RTIs

Nanoparticle-based vaccine designs represent a significant advancement in vaccine technology, offering the dual benefits of antigen delivery and immune stimulation. These nanoparticles have the potential to enhance cellular responses, as well as both innate and adaptive immune functions, including mucosal immunity, on immunization. By mimicking viruses, nanoparticles leverage their small size, viral-like structure, and biocompatibility. Their molecular composition allows them to be recognized as foreign bodies, thereby enhancing cross-presentation and increasing the production of inflammatory factors, which, in turn, stimulates a robust adaptive immune response. These characteristics make virus-mimicking nanoparticles (V-NPs) an excellent tool for developing vaccines against infectious diseases. V-NPs activate dendritic cells and facilitate antigen presentation, a critical step in innovative vaccine development, leading to bactericidal responses and the establishment of immune memory. Despite the progress made in vaccine development for respiratory infections, nanoparticle-based vaccines offer flexible and advantageous technological strategies for creating more effective and versatile vaccines. Respiratory infections, which are major causes of morbidity and mortality, can be triggered by viruses, bacteria, and occasionally fungi. Nanomaterials-based vaccines encompass various classes of nanoparticles with diverse shapes and compositions, designed not only to protect and deliver antigens to elicit immune responses but also to deliver specific antigens directly to target cells [58].

6.5. Immune adjuvant action of antigens and aerosol particle characteristics

The immune adjuvant effect of antigens in inhalation therapy is significantly influenced by both the size and chemical nature of the aerosol particles used for delivery. The size of aerosol particles affects their deposition within the respiratory tract, which, in turn, influences the immune response. Particles in the range of 1–5 μm are considered optimal for deep lung deposition, reaching the alveolar regions

where immune cells such as macrophages and dendritic cells are abundant. Smaller particles (below 1 μm) may be exhaled, while larger particles tend to deposit in the upper respiratory tract and are less effective in triggering a robust immune response in the lungs. The optimal particle size allows for better interaction with immune cells, enhancing antigen uptake and processing, which is critical for developing an effective immune response [59].

The chemical nature of aerosol particles also plays a key role in modulating immune responses. The surface chemistry, charge, and composition of particles can affect their interaction with biological membranes and immune cells. For example, nanoparticles functionalized with ligands or polymers that enhance cellular uptake can promote stronger antigen presentation, leading to a more effective activation of the adaptive immune system. In addition, biodegradable materials, such as liposomes or polymeric nanoparticles, are favored for their ability to deliver antigens while minimizing toxicity and enhancing sustained release. The choice of chemical composition can also influence the adjuvant properties of the antigen, as certain materials may stimulate the innate immune system more effectively, acting as both a delivery vehicle and an immune stimulator [60]. As follows, Table 2 summarizes the literature on nanoparticles as carriers of respiratory disease treatment.

7. CHALLENGES AND LIMITATIONS

7.1. Technical challenges in nanoparticle synthesis and stability

The synthesis and stability of nanoparticles present several technical challenges that can impact their efficacy in various applications, particularly in drug delivery and biomedical fields. Key challenges include controlling particle size and distribution, surface functionalization, maintaining stability under physiological conditions, and scalability of production.

Achieving a uniform particle size and narrow size distribution is crucial, as nanoparticle size affects biological behaviors, including cellular uptake, biodistribution, and clearance. Inconsistent sizes can lead to unpredictable performance and reduced efficacy. Variations in temperature, pH, and reactant concentrations during synthesis can affect nucleation and growth rates, resulting in heterogeneous particle sizes. The choice of solvents and surfactants also plays a significant role in influencing particle size and distribution. Improper selection can cause aggregation or lead to a broad size distribution [61].

Developing and optimizing reproducible protocols that control reaction kinetics can help achieve consistent particle sizes. Techniques such as microfluidics and flow synthesis can accomplish precise control over reaction parameters, enabling more uniform particle size distribution. Surface functionalization plays a crucial role in stabilizing nanoparticles, enhancing biocompatibility, and targeting specific cells or tissues. However, achieving stable and reproducible functionalization without altering the core properties of nanoparticles presents significant challenges. The complexity of the chemistry involved in attaching functional groups or ligands to the nanoparticle surface must be carefully managed to avoid cross-reactivity or incomplete coverage, which can affect nanoparticle functionality and stability. In addition, high surface energy can lead to nanoparticle aggregation if not adequately passivated. Potential solutions include layer-by-layer assembly for controlled deposition of functional molecules and surface coatings such as PEG or silica to stabilize the surface and prevent unwanted interactions [62].

Nanoparticles must also maintain their stability under physiological conditions, which is challenging due to the

Table 2. Summary of literature on nanoparticles as carriers for respiratory disease treatment

Nanoparticle type	Drug (s) delivered	Target disease	Study findings
Liposomes	Amikacin	TB, non-tuberculous mycobacterial infections	Liposomal amikacin showed enhanced lung penetration and sustained drug release, reducing dosing frequency.
SLNs	Rifampicin, isoniazid	TB	SLNs provided prolonged drug release and improved bioavailability in TB treatment models.
NLCs	Antitubercular drugs, antivirals	TB, viral infections	NLCs improved drug loading and provided a controlled release system, overcoming limitations of SLNs.
Polymeric nanoparticles (PLGA)	Antibacterial agents, RNA-based therapeutics	Bacterial pneumonia, COVID-19	PLGA nanoparticles enhanced drug stability and targeted delivery to lung tissues, improving therapeutic efficacy.
Gold nanoparticles (AuNPs)	Photothermal agents, antimicrobial peptides	Respiratory infections, lung cancer	AuNPs demonstrated photothermal effects in cancer therapy and effective drug delivery in treating lung infections.
Dendrimers	Antimicrobials, gene therapy agents	Cystic fibrosis, asthma	Dendrimers improved cellular uptake and drug delivery to infected lung tissues, enhancing anti-inflammatory effects.
Inorganic nanoparticles	Silver, zinc oxide nanoparticles	COPD	Inorganic nanoparticles provided antimicrobial and anti-inflammatory properties, reducing bacterial growth in COPD.

COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; NLCs: Nanostructured lipid carriers; PLGA: Poly (lactic-co-glycolic acid); SLN: Solid lipid nanoparticle; TB: Tuberculosis.

complex and dynamic environment within the human body. Factors such as pH variations, ionic strength, and protein corona formation – where proteins from biological fluids adsorb onto the nanoparticle surface – can alter nanoparticle stability and behavior. This can lead to aggregation, reduced targeting efficacy, or increased clearance by the immune system. Solutions to enhance stability include surface engineering with hydrophilic coatings, like PEGylation, to reduce protein adsorption, and the use of stabilizing agents during synthesis. In addition, ensuring long-term stability and storage of nanoparticles is critical, with solutions such as lyophilization (freeze-drying) and inert atmosphere packaging to prevent degradation over time. Addressing these technical challenges is essential for the successful development and application of nanoparticle-based systems in nanomedicine and other fields [63].

7.2. Potential toxicity and biocompatibility issues

Nanoparticles hold significant promise in biomedical applications such as drug delivery, imaging, and diagnostics, but their small size and high reactivity also pose potential toxicity and biocompatibility challenges that must be carefully tackled. One of the primary concerns is the generation of reactive oxygen species, particularly with metal-based nanoparticles such as silver and zinc oxide, which can lead to oxidative stress, cellular damage, and inflammation. In addition, nanoparticles can cause cytotoxicity by disrupting cellular membranes and triggering apoptosis, and their ability to activate the immune system may result in harmful inflammatory responses. There is also a risk of genotoxicity if nanoparticles interact with genetic materials, potentially leading to mutations and cancer. Another significant concern is the biodistribution and accumulation of nanoparticles in organs such as the liver and lungs, where non-biodegradable particles may cause chronic toxicity over time [64].

Biocompatibility issues further complicate the safe use of nanoparticles in clinical settings. The material composition of nanoparticles is critical – while materials such as gold and silica are generally biocompatible, others, such as certain metal oxides, may pose higher toxicity risks. Surface chemistry also plays a key role; inappropriate surface properties can lead to adverse interactions with biological systems, reducing the efficacy of therapeutic nanoparticles. Long-term effects are a major concern, particularly for nanoparticles that are not readily biodegradable, as their persistence in the body could lead to chronic health issues. In addition, the ability of nanoparticles to cross biological barriers, such as the blood-brain barrier or the gastrointestinal barrier, introduces the risk of unintended toxicity in sensitive tissues. Overcoming these challenges requires the development of new safety testing standards tailored to the unique properties of nanoparticles, along with careful design and thorough preclinical testing to ensure their safe application in medicine [65].

Nanoparticles hold significant potential for respiratory drug delivery, but their interaction with pulmonary surfactant – a lipid-protein complex that reduces surface tension in the alveoli – is a crucial consideration when evaluating their safety and biocompatibility. Pulmonary surfactant plays an essential role in maintaining alveolar stability, preventing collapse during exhalation, and facilitating efficient gas exchange. The introduction of nanoparticles into the lungs can disrupt the surfactant layer, impairing its ability to maintain alveolar surface tension and potentially leading to potential respiratory complications [66].

Nanoparticles may adsorb onto or penetrate through the pulmonary surfactant layer, depending on their size, shape, surface charge, and chemical composition. Studies have shown that surface-active nanoparticles can disrupt the organization of surfactant molecules, impairing their ability to reduce surface tension. This disruption can result in reduced lung compliance, alveolar collapse (atelectasis), and impaired gas exchange, which could exacerbate existing respiratory conditions or induce acute respiratory distress in vulnerable individuals [67].

The chemical nature of nanoparticles also influences their interaction with pulmonary surfactants. Hydrophobic nanoparticles tend to integrate more readily into the lipid components of the surfactant, potentially altering its biophysical properties. On the other hand, hydrophilic nanoparticles may interfere with the protein components of the surfactant, affecting its ability to spread uniformly across the alveolar surface. In addition, the aggregation of nanoparticles within the surfactant layer can provoke an inflammatory response, triggering the release of cytokines and the recruitment of immune cells to the lungs [66].

7.3. Regulatory hurdles and approval processes

The development and commercialization of nanoparticle-based therapies face significant regulatory challenges and complex approval processes due to the unique properties of nanomaterials. One of the primary hurdles is the lack of standardization in testing and characterizing nanoparticles, which vary widely in size, shape, and composition. This diversity complicates the assessment of safety, efficacy, and quality, leading to inconsistent results in regulatory evaluations. In addition, the complex physicochemical properties of nanomaterials – such as their ability to cross biological barriers and their unpredictable interactions with biological systems – make it difficult to assess their long-term safety and efficacy. As a result, existing regulatory frameworks, originally designed for small molecules and

biologics, are evolving to accommodate nanotechnology, leading to potential delays in approval processes. Furthermore, safety concerns regarding the long-term effects and potential environmental impact of nanoparticles necessitate more stringent testing and comprehensive evaluations, further complicating the regulatory landscape [68].

The approval processes for nanomedicines also involve navigating the specific requirements of major regulatory bodies, such as the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In the US, nanomedicines may follow the New Drug Application or Abbreviated New Drug Application pathways, with additional considerations for nanoparticle characterization and safety assessments. The FDA has issued specific guidance for products involving nanotechnology, emphasizing the need for detailed studies on nanoparticle behaviors in biological systems. Similarly, in Europe, the EMA offers a centralized procedure for the approval of nanomedicines, with scientific advice available to help developers meet regulatory requirements. Despite efforts toward global harmonization of regulatory standards, companies must still navigate varying requirements across different regions, further complicating the approval process. Case studies, such as the approval of Doxil and Abraxane, highlight the unique challenges of demonstrating bioequivalence and altered pharmacokinetics in nanoparticle formulations, underscoring the complexity of bringing nanomedicines to market [69,70].

7.4. Economic and manufacturing considerations

The development and commercialization of nanoparticle-based therapies in nanotechnology involve unique economic and manufacturing challenges that significantly impact their feasibility and market success. High research and development costs, extended development timelines, and the complexity of scaling up nanoparticle production are major hurdles. These factors drive up costs and delay time-to-market, making it difficult for smaller companies to compete and secure funding. Addressing these challenges requires strategic collaborations, the adoption of advanced manufacturing technologies such as continuous production processes, and the implementation of rigorous quality control measures to ensure consistency and regulatory compliance [71].

From an economic standpoint, market competition, pricing strategies, intellectual property issues, and regulatory compliance costs present additional challenges. Nanomedicines often face competition from cheaper, established therapies, and securing broad patent protection can be difficult due to the complex nature of nanotechnology. Moreover, the need for specialized testing and extensive documentation increases regulatory costs, which can further reduce profit margins. Successful commercialization depends on effective market adoption strategies, including educating healthcare providers and patients, ensuring proper infrastructure for storage and distribution, and securing favorable reimbursement terms from insurance providers. Overcoming these obstacles through innovation, strategic planning, and effective communication is crucial for the widespread adoption and success of nanotechnology in medicine [72].

8. FUTURE CONSIDERATIONS

Nanotechnology is rapidly advancing the treatment of RTIs with emerging trends such as nanoparticle-based antiviral therapies, inhalable nanomedicines, and targeted drug delivery systems. These innovations allow for precise delivery of therapeutic agents directly to the lungs or infected tissues, enhancing efficacy while minimizing side effects and overcoming challenges like antimicrobial resistance. In addition, nanotechnology is improving diagnostic tools, facilitating earlier detection and personalized treatment of RTIs. The integration of therapeutic and diagnostic functions within a single nanoparticle, known as theranostics, offers a personalized approach to treatment, allowing for real-time monitoring and adjustment of therapies based on patient response.

Looking ahead, nanotechnology is poised to play a central role in personalized medicine and precision drug delivery, especially when integrated with other technologies such as CRISPR and artificial intelligence. These integrations could lead to breakthroughs in gene editing, drug discovery, and diagnostics, offering more effective, safer, and tailored treatments. Future research is likely to focus on enhancing nanoparticle targeting, overcoming biological barriers, and developing sustainable manufacturing processes, all of which will be crucial for translating these advancements into clinical practice and making personalized nanomedicine widely accessible.

9. CONCLUSION

Nanotechnology-based approaches for targeted drug delivery in RTIs offer significant potential to improve treatment outcomes by enhancing drug efficacy, reducing systemic side effects, and overcoming challenges associated with traditional drug delivery methods. The unique properties of nanoparticles, such as their ability to penetrate biological barriers, provide controlled release, and enable targeted delivery, make them promising candidates for addressing the limitations of conventional therapies, particularly in the face of antimicrobial resistance and the immune evasion strategies employed by pathogens. However, the successful clinical translation of these technologies requires addressing technical challenges related to nanoparticle synthesis and stability, ensuring biocompatibility and safety, and navigating complex

regulatory hurdles. Continued research and development, alongside advancements in manufacturing and regulatory frameworks, will be crucial to realizing the full potential of nanotechnology in the treatment of RTIs, ultimately leading to more effective and personalized healthcare solutions.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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FURTHER DISCLOSURE

During the preparation of this work, the AI tool ChatGPT was used to improve the readability and language of the manuscript. The authors subsequently revised and edited the AI-generated content as necessary, taking full responsibility for the final version of the manuscript.

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