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Nanomedicine Approaches to Overcome Barriers in Pulmonary Drug Delivery for Respiratory Diseases

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Keywords

Nanomedicine, Pulmonary Drug Delivery, Respiratory Diseases, Nanocarriers, Targeted Therapy, Mucociliary Clearance

Abstract

Delivering drugs through the lungs is a promising method for treating respiratory conditions, offering quick absorption into the bloodstream and targeted therapeutic effects due to the lungs' distinct structure. However, obstacles like mucociliary clearance, activity of alveolar macrophages, and variations among patients can limit the success of traditional treatments. Nanomedicine has become a cutting-edge solution to these challenges, using diverse nanocarriers such as liposomes, polymeric nanoparticles, and hybrid systems to improve drug stability, availability, and precision in delivery. These systems enable controlled release, enhanced solubility, and reduced side effects on the rest of the body. Moreover, multifunctional nanocarriers combine diagnostic and therapeutic roles, paving the way for personalized treatments for diseases like asthma, COPD, pulmonary fibrosis, and lung infections. Despite its potential, issues like large-scale production, regulatory hurdles, and ensuring compatibility with the body remain challenges. This review explores how nanomedicine addresses barriers in lung drug delivery, highlights its role in treating respiratory diseases, and looks at opportunities for clinical advancement.

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1. Introduction

Drug delivery through the lungs has emerged as a key treatment option for a number of respiratory disorders, such as lung infections, pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease (COPD). Because of their huge surface area, abundant blood flow, and thin alveolar epithelium, the lungs provide a unique route for drug delivery that allows for rapid bloodstream absorption and targeted therapeutic effects [1]. By avoiding the gastrointestinal system and first-pass metabolism, this method may increase the bioavailability of drugs. Nevertheless, despite these benefits, there are still several obstacles in the way of successful pulmonary medication administration, which limits its wider use. The respiratory system's intricate architecture and physiology present a significant difficulty. The alveolar regions, conducting airways, and upper airways make up the respiratory tract. To protect the lungs against foreign objects, infections, and environmental irritants, each of these areas has defensive systems in place [2]. Despite being essential for lung health, these defenses pose serious challenges to effective medication delivery. The mucociliary clearance mechanism, for instance, can swiftly remove inhaled medications, lowering their duration of action and therapeutic efficacy. This occurs when cilia in the conducting airways transport mucus. Furthermore, particle drug carriers can be engulfed by alveolar macrophages, the lungs' immunological sentinels, which limits their capacity to reach their targeted destinations [3].

The drug's physicochemical characteristics present yet another major obstacle. The poor water solubility of many medications used to treat respiratory disorders makes it challenging to synthesize them into inhaled aerosols or particles. Additionally, for lung delivery to be successful, the proper particle size must be achieved [4]. Particles typically need to be 1–5 micrometers in size in order to settle in the lower respiratory tract. While tiny particles may be expelled before landing in the lungs, bigger particles have a tendency to gather in the upper airways. These specifications make the creation of medication formulations and delivery systems more difficult [5]. Some medications can be broken down by the presence of enzymes like esterases and proteases before they can start to work as intended. For instance, proteins and medications based on peptides are more susceptible to enzymatic breakdown in the lungs. Additionally, because of the dynamic nature of the respiratory process—which is defined by inhalation and exhalation—drugs may be distributed unevenly throughout the lungs, which might lead to less than ideal therapeutic results [6].

Moreover, patient-specific characteristics and environmental conditions make pulmonary medication administration even more challenging. Smoking, allergies, and environmental contaminants can change the lungs' structural and functional integrity, which can affect how drugs are deposited and absorbed. The effectiveness of pulmonary medication administration is also significantly influenced by patient-related characteristics, including age, lung function, and proficiency with inhalation devices [7]. For example, it may be difficult to provide adequate medication administration in youngsters with undeveloped respiratory systems or older patients with reduced lung capacity. Innovative strategies are needed to address these issues, and nanomedicine has shown promise as a potential remedy. Using materials and tools at the nanoscale to identify, cure, and prevent illnesses is known as nanomedicine [8]. Nanomedicine has various benefits when it comes to pulmonary medication delivery, such as the capacity to get past physiological and biochemical barriers, enhance drug stability and solubility, and accomplish tailored administration to certain lung areas. Because of these benefits, nanomedicine is a particularly attractive treatment option for respiratory conditions and a way to improve the effectiveness of pulmonary drug delivery systems [9].

One of the most researched nanocarriers, nanoparticles, has shown great promise for pulmonary medication delivery. To get desired characteristics including regulated drug release, prolonged retention, and enhanced mucus penetration, these particles may be made from a variety of materials, such as lipids, polymers, and inorganic substances [10]. For instance, phospholipid bilayer-based liposomal nanoparticles can encapsulate both water-soluble and water-insoluble medications, protecting them from enzymatic breakdown and increasing their bioavailability. In contrast, polymeric nanoparticles provide individualized drug release patterns that allow therapeutic medicines to be delivered continuously over an extended period of time. Another interesting type of nanocarriers for pulmonary medication administration are nanoemulsions and micelles [11]. Drugs that are poorly soluble in water can be dissolved and their absorption in the lungs increased by using nanoemulsions, which are thermodynamically stable blends of oil, water, and surfactants. Similarly, hydrophobic medications can be precisely delivered to specific areas using micelles, which are self-assembled structures made of amphiphilic molecules. To improve these systems' selectivity for lungs' sick tissues or cells, they can also be functionalized using targeting ligands. For pulmonary medication delivery, inorganic nanocarriers such carbon-based nanomaterials, silica nanoparticles, and gold nanoparticles have also been studied [12]. High surface area, tunable porosity, and the ability to functionalize with a variety of biomolecules are some of these materials' distinctive features. Gold nanoparticles, for example, can be used for imaging-guided drug administration, which allows for real-time monitoring of medication distribution and therapeutic results. Because of their porous architectures, silica nanoparticles can serve as reservoirs for prolonged medication release, while carbon-based nanomaterials like graphene oxide have the potential to carry genetic material to the lungs [13].

Even though nanomedicine has great potential for pulmonary medication delivery, a number of obstacles and restrictions need to be removed before it can be successfully implemented in clinical settings. Since the long-term impacts of nanoparticles on lung health are still poorly known, safety and biocompatibility are major concerns [14]. Inhaled nanoparticles may cause oxidative stress, cytotoxic consequences, or inflammatory reactions that might damage the lungs. Therefore, in order to fully evaluate the safety of therapies based on nanomedicine, extensive preclinical and clinical investigations are necessary. Scaling up manufacturing and production is another big obstacle that prevents nanomedicine from being used more widely for pulmonary treatments. On an industrial

scale, manufacturing nanocarriers with exact size, consistent quality, and dependable performance is still a challenging and resource-intensive process. Facilitating their acceptance and commercialization also requires resolving ethical issues and managing regulatory obstacles related to the use of nanomaterials in medicine. The use of nanomedicine in pulmonary medication delivery has a bright future despite these challenges. Many of the present problems should be resolved by developments in nanotechnology, such as the creation of biodegradable and stimuli-responsive nanocarriers. Additionally, the design and functionality of nanocarriers may be improved by incorporating AI and machine learning into nanomedicine research, opening the door to patient-specific customized medicine. There are also intriguing opportunities for treating complicated respiratory disorders when nanomedicine is combined with other treatment modalities like gene therapy and immunotherapy [15].

2. Barriers in Pulmonary Drug Delivery

For the treatment of a number of respiratory conditions, such as asthma, COPD, pulmonary fibrosis, and lung infections, pulmonary medication administration has become a crucial strategy. Because of their huge surface area, considerable vascularization, and thin alveolar epithelium, the lungs offer a unique route for drug delivery that enables both localized therapeutic effects and fast systemic absorption [16]. Bypassing the gastrointestinal system and first-pass metabolism, this method may increase a drug's bioavailability. Effective pulmonary medication delivery, however, has some drawbacks that prevent its widespread use despite its many benefits [17].

2.1. Anatomical and Physiological Barriers

The complex architecture and physiology of the respiratory system are one of the main obstacles to pulmonary medication administration. The alveolar area, conducting airways, and upper airways make up the respiratory tract's structural components. To shield the lungs from foreign objects, infections, and environmental assaults, these areas are outfitted with a variety of defense systems [18]. These processes provide major obstacles to efficient medication delivery, despite the fact that they are necessary for preserving lung health. For example, inhaled medications can be quickly cleared via the mucociliary clearance system, which includes the movement of mucus by cilia in the conducting airways, decreasing their residence duration and therapeutic efficacy [19]. In addition to efficiently clearing the airways of foreign objects, this clearance mechanism also reduces the amount of time that medications may have an impact. Drug deposition is complicated by the respiratory tract's structural complexity. Uneven medication distribution might result from turbulent airflow caused by airway branching and bifurcations in the conducting zone. As a result, instead of reaching the target spot in the lower respiratory tract, a sizable amount of the medication may deposit in unexpected places, such the upper airways [20]. Additionally, despite its thinness, the alveolar epithelium has tight junctions that restrict the paracellular transport of medications, especially those that are hydrophilic or big molecules. Drug delivery methods that may avoid these tight junctions or promote transcellular transport are thus required. Additionally, the respiratory system has a high surface area-to-volume ratio, which is good for gas exchange but makes it difficult for medications to be deposited uniformly. For instance, inflammation and airway blockage in conditions like asthma or COPD can further change airflow patterns, making medicine administration more challenging. In some respiratory disorders, an excess of mucus can serve as an extra physical barrier that prevents medications from penetrating the deeper layers of the airway epithelium [21].

2.2. Biochemical Barriers

For pulmonary medication administration, the metabolic milieu of the lungs poses additional difficulties. Proteases, esterases, and oxidases are among the many enzymes found in the lungs that can break down certain medications before they can reach their intended destinations. Since peptide and protein-based treatments are extremely prone to degradation, this enzymatic activity is especially troublesome for them [22]. For instance, proteases found in the lung lining fluid may turn therapeutic peptides that are utilized to modify inflammatory pathways in asthma ineffective. Although the lungs' synthesis of surfactants is necessary for lowering surface tension and averting alveolar collapse, it can also interfere with medication compositions and change their stability. The surfactant layer may selectively partition some lipophilic medications, reducing their availability for therapeutic activity [23]. Likewise, surfactant proteins' physicochemical characteristics may be impacted by interactions with nanoparticles or other drug carriers, which may result in aggregation or decreased bioactivity. The lung's immunological milieu is dynamic, which creates another biochemical barrier. Foreign particles, including drug transporters, are easily phagocytosed by alveolar macrophages, an essential aspect of the innate immune system. This

immune response lowers the bioavailability of medications given to the lungs, even though it is necessary for eliminating infections. Although they have been investigated, methods to avoid macrophage absorption, such as altering the surface of nanoparticles or applying covert coatings like polyethylene glycol (PEG), are still being studied [24].

Drug stability and effectiveness may be impacted by oxidative stress, which is frequently increased in respiratory conditions such cystic fibrosis or COPD. The lungs' production of reactive oxygen species (ROS) can break down some medications, especially those that are oxidation-sensitive, which lowers their potential as a treatment. Drug delivery methods must be designed to withstand enzymatic breakdown, evade immune clearance, and remain stable in the oxidative lung environment due to these biochemical obstacles [25].

2.3. Environmental and Patient-Specific Factors

The effectiveness of pulmonary medication administration is largely dependent on environmental conditions as well as patient-specific characteristics. The anatomical and functional integrity of the lungs can be changed by smoking, environmental contaminants, or allergies, which can affect medicine absorption and deposition. For example, long-term exposure to cigarette smoke can cause ciliary dysfunction, increased mucus production, and airway remodeling, all of which make it more difficult for medications to be breathed effectively [26]. Drug delivery can also be made more difficult by exposure to particulate matter and other environmental contaminants, which can worsen oxidative stress and inflammation. The effectiveness of pulmonary medication administration is also affected by patient-specific variables, including age, lung function, and proficiency with inhalation devices. Drug distribution and deposition in older patients may be impacted by age-related changes in lung architecture and physiology, such as decreased elastic recoil and airway constriction [27]. On the other hand, compared to adults, children may have immature lung development, which might result in variations in airway shape and deposition patterns. The necessity of age-appropriate medication compositions and delivery systems is highlighted by these variances. Another crucial element is using inhalation devices correctly. Many patients find it difficult to utilize equipment like nebulizers, dry powder inhalers, or metered-dose inhalers (MDIs) correctly. Inappropriate use can drastically lower medication delivery to the lungs, such as inadequate inspiratory flow or a failure to synchronize inhalation with actuation. To solve this issue, patient education and the creation of inhalation devices that are easy to use are crucial [28]. Variability in pulmonary medication delivery is also influenced by hereditary variables and co-morbid disorders. For instance, people with cystic fibrosis frequently have thicker mucus layers that prevent drugs from penetrating their lungs, whereas those with diabetes may have changed lung permeability. The pharmacokinetics and pharmacodynamics of inhaled medications can also be impacted by genetic variations in drug-metabolizing enzymes or transporters, requiring individualized treatment plans [29].

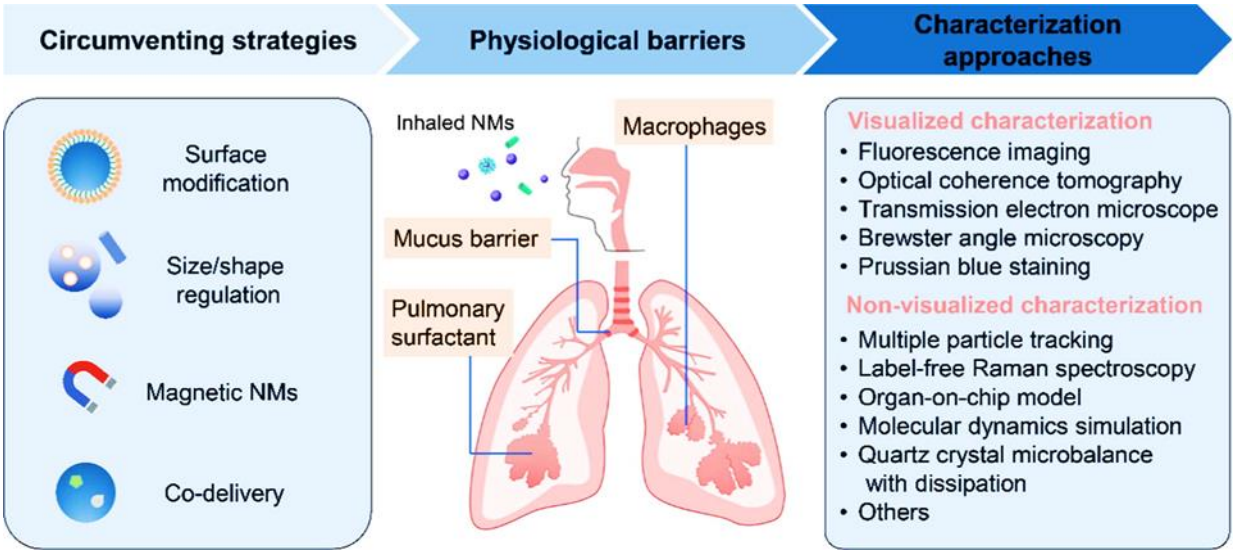

Figure 1: Physiological barriers affecting the in vivo fate of inhaled nanomedicines for lung local diseases.

3. Overview of Nanomedicine

The innovative discipline of nanomedicine uses the special properties of materials at the nanoscale to improve illness detection, management, and prevention. Fundamentally, nanomedicine uses tools and materials that are usually between 1 and 100 nanometers in size, enabling molecular and cellular interactions with biological structures. These nanoscale technologies provide unmatched potential to get beyond the drawbacks of traditional treatments since they can be precisely built to allow regulated drug delivery, targeting, and release [30]. High surface-area-to-volume ratios, adaptable surface chemistries, and the ability to encapsulate a wide variety of therapeutic agents—from proteins and nucleic acids to small-molecule medications—are among the salient features of nanomedicine systems. Additionally, nanocarriers may be engineered to react to particular physiological stimuli, including oxidative stress, pH variations, or enzyme activity, allowing for targeted medication release with the least number of off-target effects. Nanomedicine has clear benefits over conventional drug delivery techniques in pulmonary applications. The lungs provide an excellent route for therapies based on nanomedicine because of their large surface area, thin alveolar membrane, and abundant blood flow [31]. Drugs that are poorly soluble in water can be made more soluble and stable by using nanocarriers, which makes it easier to distribute them to certain locations in the respiratory system. To improve their bioavailability and therapeutic efficacy, medications with limited water solubility that are difficult to manufacture into inhalable aerosols might be added to nanoparticles or nanoemulsions. Targeted medication delivery is a major advantage of nanomedicine in pulmonary treatment. Targeting ligands that are made to identify certain cell surface receptors or disease indicators in the lungs, such as aptamers, peptides, or antibodies, can be added to nanocarriers to functionalize them. This focused strategy minimizes systemic adverse effects, preserves healthy cells, and guarantees the tailored delivery of therapeutic medicines to sick areas. For instance, preclinical research has demonstrated enhanced therapeutic results for nanoparticles functionalized with ligands that target overexpressed receptors in inflammatory or malignant lung tissues [32].

Rapid drug clearance processes, such the mucociliary system and alveolar macrophages, provide difficulties that nanomedicine successfully overcomes. By altering their surface, for as by coating them with PEG, nanocarriers can gain "stealth" characteristics that reduce their ability to be recognized by macrophages. This facilitates longer-lasting therapeutic benefits by extending the drug's residence period in the lungs [33]. Furthermore, it is possible to create nanocarriers that can cross the mucous barrier and deliver the medication to the deeper layers of the respiratory epithelium. Another significant benefit of nanomedicine for pulmonary medication delivery is controlled and sustained drug release. Drugs can have longer release profiles by being incorporated into polymeric nanoparticles, liposomes, or mesoporous silica nanoparticles. This eliminates the need for frequent dosage and improves patient adherence to treatment plans. This method works especially well for treating long-term respiratory diseases like asthma and COPD, when medication is necessary [34].

Nanomedicine has a lot of promise for pulmonary medicine diagnostic applications in addition to improving medication administration. In order to assess medication distribution, illness development, or therapy efficacy in real time, nanoparticles can be designed to contain imaging agents. This feature is particularly helpful for tracking diseases like lung cancer, where patient outcomes can be significantly impacted by early discovery and precise assessment of tumor response to treatment [35]. An important development in the management of respiratory disorders is the application of nanomedicine in pulmonary medication delivery. Nanomedicine provides answers to several problems with conventional medicines by utilizing the unique qualities of nanoscale materials, opening the door to more efficient, focused, and patient-friendly therapy alternatives [36].

4.Nanomedicine-Based Strategies for Pulmonary Drug Delivery Nanoparticles

Because of their capacity to encapsulate and preserve medications, improve solubility, and facilitate targeted distribution, nanoparticles have emerged as a flexible platform for pulmonary drug delivery. Drugs that are hydrophilic or hydrophobic are frequently delivered via liposomes, which are made of lipid bilayers. Drug release is regulated and sustained using polymeric nanoparticles, which are composed of biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA). Deeper lung penetration and less systemic adverse effects are made possible

by their tiny size and the potential for surface changes [37].

4.2. Nanoemulsions and Micelles

Micelles and nanoemulsions are colloidal systems created to increase the stability and solubility of medications that are not very soluble in water. A stable emulsion with droplet sizes in the nanoscale range is produced by combining oil, water, and surfactants to form nanoemulsions. Due to their ease of aerosolization, these methods are particularly advantageous for pulmonary administration. Amphiphilic molecules self-assemble to create micelles, which are nanosized carriers that can encapsulate hydrophobic medications, increasing their bioavailability and permitting controlled release inside lung tissue [38].

4.3. Inorganic Nanocarriers

Gold nanoparticles (AuNPs) and silica nanoparticles are two examples of inorganic nanocarriers that are attracting a lot of interest because of their special qualities, which include a large surface area, size flexibility, and ease of functionalization. The biocompatibility, drug-delivery capabilities, and potential for imaging and diagnostic applications make gold nanoparticles highly valued. Mesoporous silica nanoparticles in particular provide a high pore capacity for controlled release and drug loading. It is possible to modify both kinds of inorganic nanocarriers to target certain lung cells, increasing the effectiveness of treatment [39].

4.4. Hybrid Nanocarriers

The advantages of several nanomaterials are combined in hybrid nanocarriers to provide multifunctional pulmonary medication delivery. These systems might combine inorganic and organic components, including liposome-inorganic particle hybrids or silica nanoparticles covered with polymers. Better drug loading, increased stability, and the possibility of co-delivering many therapeutic agents are all benefits of hybrid nanocarriers. They are also potential options for treating complicated pulmonary conditions including lung cancer, COPD, and asthma because of their structural adaptability, which enables them to target certain lung areas [40].

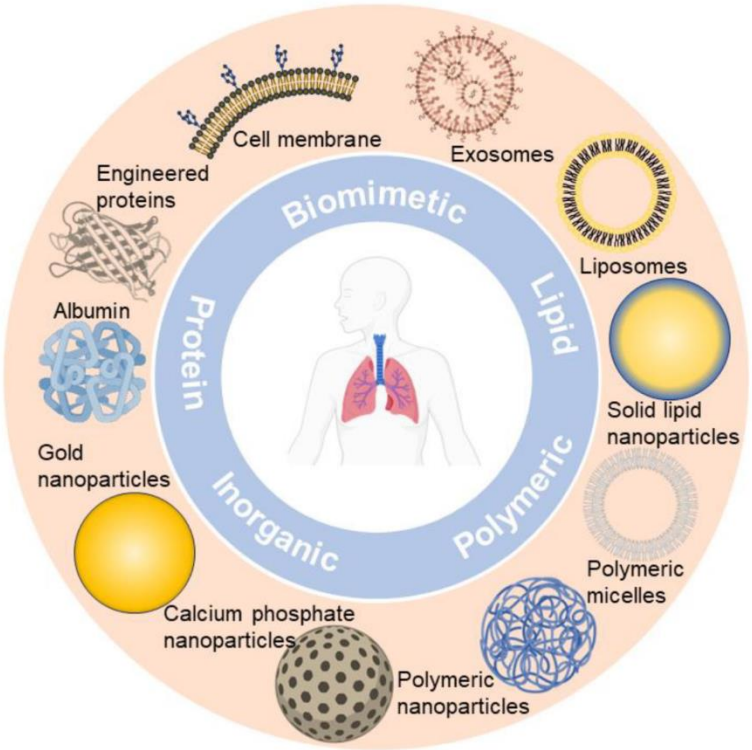

Figure 2: Key nano-formulations used in pulmonary drug delivery

Table 1: Comparison of Nanomedicine Strategies for Pulmonary Drug Delivery

S. No.	Type of Nanocarrier	Composition	Mechanism of Action	Applications	Advantages	Limitations	References
1.	Liposomes	Phospholipid bilayers	Encapsulation and release of drugs	Asthma, COPD, lung cancer	Biocompatible, enhances solubility	Limited stability, high production cost	[41]
2.	Polymeric Nanoparticles	PLGA, PLA, chitosan	Controlled drug release	Tuberculosis, cystic fibrosis	Biodegradable, tunable drug release	Risk of aggregation, possible immune response	[42]
3.	Nanoemulsions	Oil, water, surfactants	Enhanced solubility and delivery	Antimicrobial therapy	High drug loading, aerosolizable	Requires surfactants, potential toxicity	[43]
4.	Micelles	Amphiphilic polymers	Encapsulation of hydrophobic drugs	Anti-inflammatory treatments	Self-assembly, high solubilization	Stability issues in biological fluids	[44]
5.	Gold Nanoparticles	Gold core	Drug delivery and imaging	Lung cancer, diagnostics	Biocompatible, multifunctional	Potential toxicity at high doses	[45]
6.	Silica Nanoparticles	Mesoporous silica	Sustained drug release	Lung infections, cancer	High drug loading, customizable structure	Biodegradability concerns	[46]
7.	Hybrid Nanocarriers	Lipid-polymer hybrids	Targeted and controlled delivery	Multidrug-resistant infections	Combines benefits of multiple materials	Complex synthesis	[47]
8.	Solid Lipid Nanoparticles	Solid lipids	Controlled drug release	Antiviral therapy	Stable, scalable production	Limited drug loading capacity	[48]
9.	Nanocrystals	Pure drug particles	Enhanced dissolution	Antifungal therapy	High drug loading, improves solubility	Requires size reduction process	[49]
10.	Carbon Nanotubes	Carbon cylinders	Drug adsorption and release	Lung cancer	High surface area, multifunctional	Potential pulmonary toxicity	[50]
11.	Dendrimers	Branched	Encapsulation	Gene delivery, anti-	High drug loading,	Complex	[51]

		polymers	and targeting	inflammatory therapy	tunable surface	synthesis, cost	
12.	Albumin Nanoparticles	Albumin protein	Passive targeting and drug release	Lung fibrosis, cancer	Biocompatible, natural origin	Limited drug stability in vivo	[52]
13.	Chitosan Nanoparticles	Chitosan polymer	Mucoadhesion and sustained release	Cystic fibrosis	Biodegradable, enhances bioavailability	Solubility limitations in neutral pH	[53]
14.	PLGA Nanoparticles	Poly(lactic-co-glycolic acid)	Biodegradable controlled release	Tuberculosis	Long circulation, FDA approved	Limited loading of hydrophilic drugs	[54]
15.	Lipid-Based Nanoemulsions	Lipid surfactants	Enhanced drug solubility and dispersion	Antibacterial therapy	High bioavailability, scalable	Instability during storage	[55]
16.	Polymeric Micelles	Block copolymers	Drug encapsulation and release	Lung cancer	High stability, reduces toxicity	Limited encapsulation for some drugs	[56]
17.	Calcium Phosphate Nanoparticles	Calcium phosphate	Biodegradable targeted delivery	Gene therapy	Biocompatible, natural components	Limited drug encapsulation	[57]
18.	Iron Oxide Nanoparticles	Iron oxide core	Drug delivery and imaging	Pulmonary fibrosis	Magnetic properties, imaging capabilities	Potential oxidative stress	[58]
19.	Graphene Oxide Nanocarriers	Graphene oxide	Drug adsorption and release	Antibacterial therapy	High surface area, multifunctional	Cytotoxicity concerns	[59]
20.	Polysaccharide Nanoparticles	Polysaccharides	Mucoadhesion and sustained release	Antiviral therapy	Biodegradable, enhances bioavailability	Stability issues in vivo	[60]
21.	Nanosponges	Cyclodextrins	Encapsulation of small molecules	Antioxidant delivery	Prolongs drug stability, high loading	Complex synthesis	[61]
22.	Nanogels	Cross-linked hydrogels	Responsive drug release	Anti-inflammatory treatments	Biocompatible, stimuli-responsive	Limited mechanical strength	[62]
23.	Quantum Dots	Semiconductor nanocrystal	Imaging and drug delivery	Lung cancer diagnostics	Multifunctional, fluorescent	Potential toxicity	[63]

		s			properties		
24.	Ceramic Nanoparticles	Metal oxides	Sustained and targeted drug delivery	Pulmonary fibrosis	High stability, tunable properties	Biocompatibility concerns	[64]
25.	Peptide-Based Nanocarriers	Peptides	Targeted delivery	Antimicrobial therapy	Biodegradable, high specificity	Limited stability	[65]
26.	Protein Nanoparticles	Silk fibroin, albumin	Drug loading and release	Asthma, COPD	Natural materials, high biocompatibility	High susceptibility to enzymatic degradation	[52]
27.	Viral Nanoparticles	Viral capsids	Gene and drug delivery	Gene therapy	Efficient cell targeting, natural vectors	Immunogenicity concerns	[66]
28.	DNA Nanostructures	DNA origami	Gene and drug delivery	Genetic disorders	High precision, customizable	Stability issues in biological environments	[67]
29.	Magnetic Nanoparticles	Iron oxide, cobalt	Magnetically targeted drug delivery	Lung cancer	Magnetic targeting, imaging capabilities	Potential for oxidative damage	[68]
30.	Lipid-Coated Nanoparticles	Lipid coating over inorganic core	Enhanced stability and targeted delivery	Antifungal therapy	Improved biocompatibility	Complex manufacturing	[69]

5. Mechanisms of Action of Nanomedicine in Overcoming Barriers

Innovative approaches to the problems of pulmonary medication administration for respiratory disorders are provided by nanomedicine. Making medications more stable and soluble is one such approach. Effective transport of many therapeutic drugs to the lungs is hampered by their limits in watery settings, especially those with hydrophobic qualities. By encapsulating these medications, nanoparticles can improve their solubility and shield them from chemical instability or enzymatic breakdown, boosting their bioavailability. The efficiency with which nanomedicine may cross the mucous barrier is another important factor. Conventional medication formulations are frequently trapped by the respiratory tract's thick and sticky mucus coating, which limits their ability to reach the underlying epithelial cells [70]. PEG coatings and other surface changes can be used to create nanoparticles to lessen their interactions with mucus components, allowing them to diffuse through the barrier and more effectively reach their target areas. Nanomedicine also offers the benefits of regulated release and long-term retention of therapeutic substances. Drug release can be prolonged by using nanoparticles that are made to stick to lung tissues or stay in the respiratory system for long periods of time [71]. This characteristic improves patient compliance and treatment effectiveness by lowering the frequency of medication administration and sustaining therapeutic concentrations over time. Another crucial technique is targeted medication delivery. Ligands, antibodies, or peptides that selectively bind to receptors or biomarkers expressed on pulmonary sick cells can be used to functionalize nanoparticles. By reducing off-target effects and improving treatment results, this targeting capacity guarantees that the therapeutic

drugs are administered preferentially to the afflicted regions. Nanomedicine has enormous promise to transform the treatment of respiratory disorders by utilizing these processes to get beyond the inherent obstacles in pulmonary medication delivery [72].

6.Applications of Nanomedicine in Respiratory Diseases

Numerous respiratory disorders can be effectively treated and managed with the help of nanomedicine. By delivering bronchodilators, antioxidants, or anti-inflammatory medications straight to the lungs, nanoparticles can help treat COPD by lowering systemic adverse effects and decreasing oxidative stress and airway inflammation. Similar to this, nanomedicine makes it possible to precisely distribute corticosteroids or β-agonists for asthma, guaranteeing quick and localized therapeutic benefits while reducing side effects that are frequently linked to long-term usage of these drugs. Nanomedicine makes it easier to distribute antifibrotic medications to fibrotic lung tissues in pulmonary fibrosis [73]. Additionally, medications that alter the immune system or prevent the growth of fibrosis can be encapsulated in nanoparticles, which may enhance lung function and delay the course of the illness. By guaranteeing their continuous release and focused distribution to affected tissues, nanomedicine improves the effectiveness of antibiotics and antimicrobial medicines for lung diseases like pneumonia or TB. Through the maintenance of ideal medication concentrations at the infection site, this strategy not only improves therapeutic impact but also aids in the fight against drug resistance [74].

Nanomedicine offers cutting-edge treatment options for lung cancer by precisely delivering immunotherapeutic medicines, chemotherapeutic medications, or gene treatments to tumor cells. By improving medication accumulation in tumors while preserving healthy lung tissues, functionalized nanoparticles can lower toxicity and increase therapy results. The co-delivery of many therapeutic agents, including RNA-based treatments and chemotherapeutic medications, is also made possible by nanocarriers, providing a synergistic strategy to address the complexity of lung cancer. Nanomedicine is opening the door to more efficient and patient-friendly therapies by catering to the unique requirements of each respiratory ailment [75].

7. Challenges and Limitations of Nanomedicine in Pulmonary Drug Delivery

Notwithstanding its potential, there are a number of obstacles and restrictions with nanomedicine in pulmonary medication delivery. Because nanoparticles might cause toxicity, inflammation, or immunological reactions, especially after extended exposure or buildup in lung tissues, safety and biocompatibility are critical considerations. To reduce side effects and preserve therapeutic efficiency, nanoparticles' physicochemical characteristics—such as size, shape, and surface charge—must be carefully adjusted [76]. Furthermore, research into the long-term impacts of nanomaterials on the respiratory system is also underway. A major obstacle to bringing nanomedicine from the lab to the clinic is scale-up and manufacturing. It may be expensive and technically challenging to produce nanoparticles on an industrial scale with reliable quality, stability, and repeatability. The development process is complicated by elements like batch-to-batch variability and difficulties preserving the functionalization of nanoparticles throughout production. Moreover, another level of complication is added by making sure that inhalable nanoparticle formulations are sterile and scalable [77].

Adoption of nanomedicine for pulmonary applications is also heavily influenced by ethical and regulatory factors. Since nanoparticles' special qualities frequently defy established regulatory frameworks, new standards for their assessment and certification must be established. It may take a lot of preclinical and clinical research to prove these materials' safety, effectiveness, and environmental impact, which would delay their release onto the market. The broad application of nanotechnology is made more difficult by ethical issues, such as possible abuse and fair access to cutting-edge medicines based on nanomedicine. To fully realize the potential of nanomedicine in pulmonary medication delivery, these issues must be resolved [78].

8. Future Perspectives and Opportunities

Nanomedicine's role in pulmonary medication delivery has a bright future because to ongoing developments and new prospects. More sophisticated and adaptable nanocarriers with increased targeting, biocompatibility, and control over drug release patterns are anticipated as a result of advancements in nanotechnology. There is a lot of promise for improving medication delivery and therapeutic results with innovations like stimuli-responsive nanoparticles, which release therapeutic compounds in response to certain environmental triggers like pH or temperature [79]. The use of nanomedicine to the

treatment of respiratory disorders is about to undergo a revolution thanks to personalized medicine. Nanomedicine can offer highly targeted and efficient therapies by tailoring treatments according to each patient's unique profile, taking into account genetic, molecular, and environmental variables. More individualized methods are made possible by the capacity to create nanoparticles that target distinct biomarkers connected to certain subtypes of respiratory disorders, enhancing therapy results and reducing side effects. Research, development, and clinical application can be accelerated by the exciting prospects presented by the integration of artificial intelligence (AI) into nanomedicine. AI can help with creating nanoparticles with the best possible qualities, forecasting how they will behave in biological systems, and sifting through massive data sets to find novel treatment targets. Furthermore, by determining the right patient demographics and refining dosage techniques, AI-powered solutions can expedite clinical studies. These developments are anticipated to greatly solve present issues and increase the therapeutic potential of nanomedicine for respiratory disorders, in conjunction with interdisciplinary partnerships [80].

Conclusion

Nanomedicine has the potential to revolutionize pulmonary medication delivery by resolving significant issues with conventional treatments. Effective medication delivery is frequently hampered by the lungs' intricate structure and strong defenses, such as mucociliary clearance and immunological surveillance by alveolar macrophages. However, novel approaches are made possible by developments in nanotechnology, which allow for the exact, targeted, and prolonged release of medications for conditions such lung infections, pulmonary fibrosis, asthma, and COPD. Numerous nanocarriers have shown promise in improving medication stability, solubility, and bioavailability while reducing systemic adverse effects. These include liposomes, polymeric nanoparticles, nanoemulsions, and hybrid systems. These carriers get beyond the respiratory tract's physiological, biochemical, and anatomical obstacles by using strategies including mucoadhesion, targeted administration, and controlled drug release. Additionally, multifunctional nanocarriers that combine therapeutic and imaging properties, such magnetic nanoparticles and quantum dots, open the door to more sophisticated theranostic applications. Even with these developments, a number of obstacles still exist. The broad clinical use of nanomedicine is constrained by problems with production scalability, biocompatibility, possible toxicity, and regulatory compliance. Furthermore, to maximize therapy results, patient-specific variables such environmental impacts and variations in lung physiology necessitate customized methods. Future studies must concentrate on enhancing the safety profiles, simplifying the manufacturing process, and guaranteeing the economic viability of solutions based on nanomedicine. Innovation will be fueled by interdisciplinary collaboration that combines respiratory medicine, pharmacology, and nanotechnology. Nanomedicine has the potential to completely transform the treatment of respiratory conditions as the area develops, providing new avenues for individualized, efficient, and non-invasive therapies. These innovative technologies have the potential to greatly improve patient care and meet unmet medical needs in respiratory healthcare if they continue to advance.

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Author Contributions

T.A. conceptualized the review, conducted the literature search, and wrote the manuscript. All sections were critically reviewed and edited by T.A.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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