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Review Article

Nanotechnology Interventions in Chronic Respiratory Diseases: Focus on COPD- A Review

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Abstract

Chronic obstructive pulmonary disease (COPD) refers to a progressive respiratory disease associated with airflow obstruction, chronic inflammation, oxidative stress, and irreversible damage to lung tissue. While conventional treatment regimens offer symptomatic relief, they are hampered by poor targeting of the lungs, systemic side effects, and low efficacy. Nanotechnology offers great potential in the enhancement of drug delivery, improvement of efficacy, and diagnosis of COPD. This paper discusses the current progress in nanotechnology-based interventions for COPD through novel carriers, targeted drug delivery, diagnosis, regenerative therapy, and translational barriers. Literature Review A literature review was carried out by collecting relevant scholarly literature from the PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar databases. Studies discussing nanotechnology-based therapeutic and diagnostic strategies for COPD were selected and critically analyzed. Present literature proves that nanotechnology-based drug delivery methods increase efficiency of pulmonary drug delivery, increase therapeutic efficiency, control drug delivery, and minimize toxicity. Newer applications of nanotechnology in molecular diagnostics, genetic delivery, and nanoregenerative medicine are some more areas where application of nanotechnology could revolutionize management of patients with COPD, but not much research has been done yet in this area. It is clear that nanotechnology holds great promise in making COPD treatment more effective and personalized. But further research is needed on safety aspects, manufacturing, regulations, etc.

Keywords: Chronic obstructive pulmonary disease (COPD); Nanotechnology; Nanocarriers; Pulmonary drug delivery; Targeted therapy.

1. INTRODUCTION

CRDs have been identified as one of the most significant public health issues of our times. In fact, CRDs are responsible for an important amount of morbidity, mortality, and health care costs globally. Chronic obstructive pulmonary disease (COPD) has been found to be one of the major reasons of chronic disability and early death in millions of patients around the world in both developed and developing nations. COPD is characterized by airflow limitation, lung inflammation, degradation of lung tissues, and flare ups. The condition puts a tremendous load on patients as well as health care delivery system and societies. Although a number of pharmacological interventions are available, none of them can prevent the disease from advancing or regenerating lung tissue1-2. On top of that, traditional inhaled or systemic drugs are known to deposit poorly into distal regions, have low availability, pose some systemic toxicities, and are unable to target the inflamed lungs tissues. The use of nanotechnology in drug delivery systems presents certain physiochemical properties such as small size at nanometer scale, large surface area, controllable surface chemistry, controlled drug release, and improved ability to target the diseased lung tissues. In addition to increased lung retention, enhanced effectiveness, low systemic toxicity, and combination of various drugs, nanotechnology has opened up the field of theranostics by creating multifunctional nano delivery systems that can be used for diagnostics and therapeutic purposes.

1.1 Global Burden of Chronic Respiratory Diseases

Chronic respiratory diseases (CRDs) comprise a heterogeneous group of long-term pulmonary disorders, including chronic obstructive pulmonary disease (COPD), asthma, interstitial lung diseases, bronchiectasis, pulmonary hypertension, occupational lung diseases, and cystic fibrosis. These conditions collectively affect hundreds of millions of individuals worldwide and constitute a major contributor to global disability, healthcare utilization, and premature mortality. Population aging, urbanization, environmental pollution, tobacco smoking, occupational exposure to harmful particles and gases, biomass fuel combustion, and recurrent respiratory infections

continue to increase the global incidence and prevalence of CRDs. Beyond their direct clinical consequences, chronic respiratory diseases impose substantial socioeconomic burdens by reducing quality of life, impairing productivity, increasing hospital admissions, and generating significant healthcare costs. Consequently, improving prevention, early diagnosis, and innovative therapeutic strategies has become a global public health priority[2].

1.2 Epidemiology and Clinical Burden of COPD

COPD is the most prevalent chronic respiratory disease and one of the leading causes of mortality worldwide. It is characterized by persistent respiratory symptoms, irreversible or partially reversible airflow obstruction, chronic airway inflammation, emphysematous destruction of alveolar structures, mucus hypersecretion, and progressive decline in pulmonary function. Cigarette smoking remains the principal risk factor; however, exposure to biomass smoke, occupational dust, air pollution, genetic susceptibility, recurrent respiratory infections, and aging also contribute significantly to disease development. Clinically, patients experience chronic cough, sputum production, dyspnea, exercise intolerance, fatigue, and recurrent exacerbations that progressively worsen lung function. Frequent exacerbations accelerate disease progression, increase hospitalization rates, diminish health-related quality of life, and substantially elevate mortality risk. The presence of comorbidities such as cardiovascular disease, diabetes mellitus, osteoporosis, anxiety, depression, and lung cancer further complicates disease management and adversely affects long-term outcomes[3-4].

1.3 Emergence of Nanotechnology in Respiratory Medicine

Nanotechnology has emerged as a transformative platform in respiratory medicine by enabling the design of nanoscale carriers capable of improving drug delivery, disease targeting, and therapeutic precision. Nanoparticles-including liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, micelles, nanoemulsions, and inorganic nanoparticles-can encapsulate a wide range of therapeutic agents, including small-molecule drugs, nucleic acids, proteins, peptides, antioxidants, and biologics. Their unique physicochemical characteristics facilitate enhanced pulmonary deposition, prolonged drug residence time, controlled and stimuli-responsive release, improved cellular uptake, and selective accumulation within inflamed lung tissues. Surface functionalization with targeting ligands further enhances site-specific delivery while reducing off-target toxicity. In addition to therapeutic applications, nanotechnology supports advanced diagnostic imaging, biomarker detection, biosensing, and theranostic platforms for personalized respiratory care[4-5].

This review article highlights the growing significance of nanotechnology as an innovative therapeutic strategy for chronic respiratory diseases, particularly COPD. It critically examines the pathophysiological basis for nanotechnology-based interventions, summarizes the major nanocarrier systems and pulmonary drug delivery approaches currently under investigation, and discusses their applications in targeted drug delivery, controlled drug release, anti-inflammatory and antioxidant therapy, gene delivery, and regenerative medicine. Furthermore, the review evaluates recent preclinical and clinical evidence, addresses safety, regulatory, and translational challenges, and outlines future perspectives for integrating nanotechnology into precision respiratory medicine. By consolidating current knowledge and identifying emerging research opportunities, this review aims to provide a comprehensive resource for researchers, clinicians, and pharmaceutical scientists engaged in the development of next-generation nanomedicine for COPD.

2. PATHOPHYSIOLOGY OF COPD AND THERAPEUTIC TARGETS

Chronic obstructive pulmonary disease (COPD) is a progressive, heterogeneous respiratory disorder characterized by persistent airflow limitation resulting from chronic inflammation, structural remodeling of the airways, emphysematous destruction of alveolar tissues, and impaired pulmonary repair mechanisms. The disease develops through a complex interplay between environmental exposures and host susceptibility, leading to chronic activation of innate and adaptive immune responses, oxidative stress, protease-antiprotease imbalance, mitochondrial dysfunction, cellular senescence, and abnormal tissue remodeling. These pathological processes culminate in irreversible airflow obstruction, impaired gas exchange, recurrent exacerbations, and progressive decline in lung function. Understanding the molecular and cellular mechanisms underlying COPD is essential for identifying novel therapeutic targets that can improve disease management beyond symptomatic relief. Recent advances have highlighted multiple therapeutic targets, including inflammatory cytokines, oxidative stress pathways (**Fig. 1**), proteolytic enzymes, growth factor signaling, epigenetic regulators, and gene-based interventions, many of which are being explored using nanotechnology-enabled drug delivery systems[6-7].

2.1 Etiology and Risk Factors

COPD develops as a consequence of prolonged exposure to harmful environmental agents in genetically susceptible individuals. Cigarette smoking remains the predominant risk factor, accounting for the majority of COPD cases worldwide. Tobacco smoke contains thousands of toxic chemicals and reactive oxidants that directly injure airway epithelial cells, activate inflammatory pathways, impair mucociliary clearance, and induce progressive destruction of lung tissue. However, a significant proportion of COPD patients are non-smokers, particularly in low- and middle-income countries where exposure to biomass fuel smoke from cooking and heating is common. Long-term exposure to ambient air pollution, occupational dust, silica particles, chemical fumes, heavy metals, and industrial pollutants also contributes significantly to disease development. Occupational exposure in miners, construction workers,

agricultural laborers, and manufacturing industries increases the risk of chronic airway injury and pulmonary inflammation. Recurrent lower respiratory tract infections during childhood, pulmonary tuberculosis, poor lung development, and chronic asthma further predispose individuals to COPD later in life[8].

Genetic susceptibility plays an important role in determining disease risk. Alpha-1 antitrypsin (AAT) deficiency is the best-characterized inherited cause of early-onset emphysema due to inadequate inhibition of neutrophil elastase-mediated alveolar destruction. Genome-wide association studies have also identified susceptibility genes, including HHIP, CHRNA3/5, FAM13A, MMP12, IREB2, TGFB2, and GST family genes, which influence inflammation, oxidative stress, extracellular matrix remodeling, and lung development. Aging, impaired immune responses, nutritional deficiencies, metabolic syndrome, and socioeconomic factors further contribute to disease susceptibility and progression[9-10].

2.2 Molecular Mechanisms of COPD Progression

The progression of COPD results from persistent activation of multiple interconnected molecular pathways that sustain chronic inflammation and tissue destruction. Airway epithelial injury caused by inhaled toxins activates pattern recognition receptors such as Toll-like receptors (TLRs), initiating intracellular signaling through nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways. These signaling cascades stimulate the production of pro-inflammatory cytokines and chemokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-8, IL-17, granulocyte-macrophage colony-stimulating factor (GM-CSF), and transforming growth factor-beta (TGF-β), which recruit neutrophils, macrophages, dendritic cells, and $CD8^+$ T lymphocytes into the lungs. Activated inflammatory cells release matrix metalloproteinases (MMP-9, MMP-12), neutrophil elastase, cathepsins, and other proteolytic enzymes that degrade elastin, collagen, and extracellular matrix proteins, resulting in alveolar wall destruction and emphysema. Simultaneously, oxidative stress impairs endogenous antiprotease activity, exacerbating protease-mediated tissue damage. Persistent inflammation also induces mitochondrial dysfunction, DNA damage, telomere shortening, autophagy dysregulation, apoptosis, ferroptosis, and cellular senescence, thereby limiting tissue repair and regeneration[11-12].

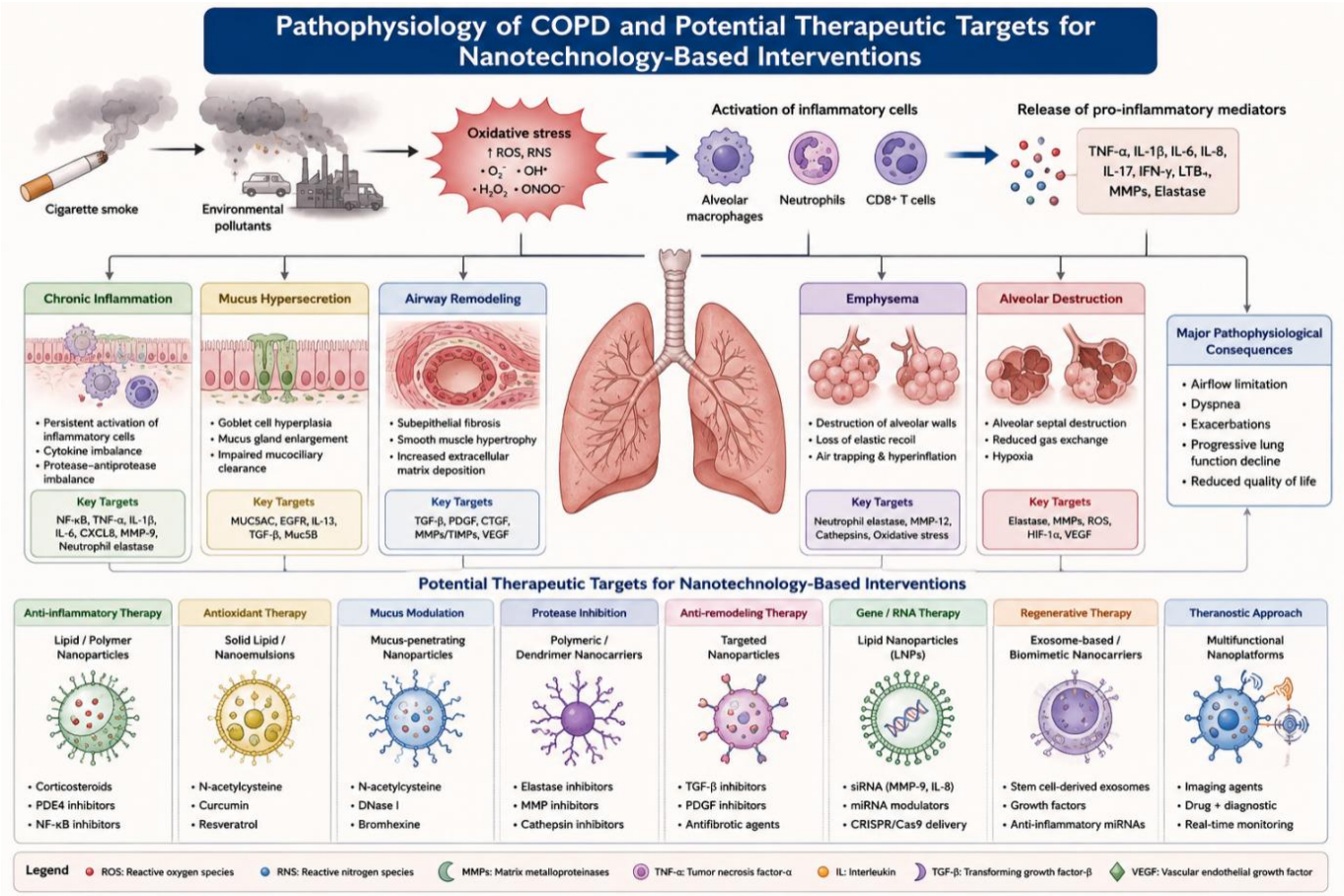

Figure 1. Pathophysiology of COPD and potential therapeutic targets for nanotechnology-based interventions. Schematic illustration depicting cigarette smoke and environmental pollutants inducing oxidative stress, chronic inflammation, mucus hypersecretion, airway remodeling, emphysema, and alveolar destruction, highlighting potential molecular targets for nanoparticle-mediated therapy.

Epigenetic alterations, including abnormal DNA methylation, histone modifications, and dysregulated microRNAs (miRNAs), further amplify inflammatory signaling and contribute to corticosteroid resistance. The nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant pathway is frequently impaired in COPD, reducing cellular defense against oxidative injury. Collectively, these molecular abnormalities promote irreversible airway remodeling, progressive airflow limitation, and declining pulmonary function[13-14].

2.3 Airway Inflammation and Oxidative Stress

Chronic airway inflammation is the hallmark pathological feature of COPD and involves persistent activation of both innate and adaptive immune responses. Cigarette smoke and environmental pollutants stimulate airway epithelial cells and alveolar macrophages to release inflammatory mediators that recruit neutrophils, monocytes, eosinophils in selected phenotypes, and cytotoxic $CD8^+$ T cells. Activated immune cells produce cytokines, chemokines, proteases, and reactive oxygen species (ROS), creating a self-perpetuating inflammatory microenvironment. Oxidative stress arises from an imbalance between excessive ROS generation and impaired antioxidant defense systems. Major endogenous sources of ROS include activated neutrophils, macrophages, mitochondrial dysfunction, and NADPH oxidase enzymes, whereas exogenous sources include cigarette smoke, biomass combustion, and atmospheric pollutants. Excessive ROS oxidize lipids, proteins, nucleic acids, and mitochondrial DNA, leading to epithelial cell injury, apoptosis, endothelial dysfunction, mucus hypersecretion, and impaired ciliary function[15].

Oxidative stress activates NF-κB and activator protein-1 (AP-1), enhancing transcription of inflammatory cytokines and perpetuating chronic inflammation. Furthermore, oxidative modifications reduce histone deacetylase-2 (HDAC2) activity, contributing to corticosteroid resistance commonly observed in COPD patients. The impaired Nrf2-mediated antioxidant response diminishes the production of protective enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase, and heme oxygenase-1 (HO-1), thereby exacerbating oxidative lung injury. These inflammatory and oxidative pathways represent attractive therapeutic targets for nanoparticle-mediated antioxidant and anti-inflammatory drug delivery[16-17].

2.4 Structural Remodeling and Emphysema

Chronic inflammation and repeated epithelial injury drive extensive structural remodeling of both the large and small airways in COPD. Airway remodeling is characterized by goblet cell hyperplasia, mucus gland hypertrophy, epithelial metaplasia, smooth muscle hypertrophy, collagen deposition, peribronchial fibrosis, and narrowing of small airways. Increased mucus production and impaired mucociliary clearance contribute to chronic cough, sputum retention, recurrent infections, and airflow obstruction. Emphysema represents irreversible destruction of alveolar walls accompanied by enlargement of distal airspaces and loss of pulmonary elastic recoil. This pathological process results primarily from protease-antiprotease imbalance, excessive oxidative stress, chronic inflammation, and defective tissue repair mechanisms. Neutrophil elastase, MMP-9, and MMP-12 degrade extracellular matrix proteins, while insufficient alpha-1 antitrypsin activity fails to neutralize proteolytic injury. The destruction of alveolar septa reduces the surface area available for gas exchange, leading to hypoxemia, hyperinflation, reduced exercise capacity, and respiratory failure in advanced disease[18-19].

2.5 Current Pharmacological Management and Challenges

The primary goals of COPD treatment are to relieve symptoms, improve exercise tolerance, reduce exacerbation frequency, preserve lung function, and enhance quality of life. Current pharmacological management includes bronchodilators, inhaled corticosteroids (ICS), long-acting β_2-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), phosphodiesterase-4 inhibitors, methylxanthines, mucolytic agents, antibiotics for infectious exacerbations, and supplemental oxygen therapy for advanced disease. Combination therapies such as LABA/LAMA and LABA/ICS are widely recommended for patients with moderate-to-severe COPD, while triple therapy (LABA/LAMA/ICS) is increasingly used in patients with persistent symptoms and frequent exacerbations. Despite these therapeutic advances, current treatments primarily provide symptomatic relief without reversing airway remodeling, emphysema, or chronic inflammation. Many inhaled drugs exhibit suboptimal deposition in the peripheral airways due to particle-size limitations, mucociliary clearance, poor inhaler technique, and reduced patient adherence. Systemically administered drugs often require higher doses to achieve therapeutic pulmonary concentrations, increasing the risk of cardiovascular, metabolic, gastrointestinal, and immunological adverse effects[20-21].

Another major challenge is corticosteroid resistance, largely driven by oxidative stress-induced HDAC2 dysfunction and persistent neutrophilic inflammation. Disease heterogeneity further complicates treatment, as distinct inflammatory phenotypes and molecular endotypes respond differently to available therapies. Additionally, conventional medications fail to adequately target oxidative stress, mitochondrial dysfunction, epithelial regeneration, and extracellular matrix repair. These limitations have stimulated growing interest in nanotechnology-based therapeutic strategies capable of improving pulmonary drug delivery, targeted cellular uptake, sustained drug release, reduced systemic toxicity, and personalized treatment approaches. Nanocarrier systems also provide promising platforms for delivering biologics, nucleic acids, antioxidants, and regenerative agents that directly modulate the molecular mechanisms driving COPD progression[22].

3. NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS FOR COPD

Nanotechnology has revolutionized pulmonary drug delivery by enabling the development of nanoscale delivery systems capable of overcoming many of the limitations associated with conventional COPD therapies. Nanocarriers, typically ranging from 1 to 1000 nm in diameter, possess unique physicochemical properties that enhance drug solubility, stability, controlled release, pulmonary deposition, and cellular uptake. Unlike conventional inhaled formulations, nanomedicine platforms can penetrate mucus barriers, target inflamed pulmonary tissues, protect encapsulated therapeutics from degradation, and minimize systemic adverse effects. In COPD, where chronic inflammation, oxidative stress, mucus hypersecretion, and structural remodeling hinder effective drug delivery, nanotechnology offers an attractive strategy to improve therapeutic efficacy and enable precision medicine. The design of pulmonary nanomedicines requires careful consideration of nanoparticle composition, size, surface characteristics, aerodynamic behavior, biocompatibility, and interaction with the respiratory microenvironment.

3.1 Principles of Pulmonary Nanomedicine

Pulmonary nanomedicine utilizes engineered nanocarriers to deliver therapeutic agents directly to the respiratory tract through inhalation or systemic administration. The lungs provide an ideal route for nanoparticle delivery due to their extensive alveolar surface area (approximately 70–140 m^2), thin alveolar-capillary membrane, rich vascular network, and relatively low enzymatic activity compared with the gastrointestinal tract. These characteristics facilitate rapid drug absorption while allowing localized treatment with reduced systemic exposure. The primary objective of pulmonary nanomedicine is to maximize drug concentration at diseased sites while minimizing off-target toxicity. Nanoparticles can encapsulate hydrophilic and hydrophobic drugs, peptides, proteins, nucleic acids, antioxidants, anti-inflammatory agents, and gene-editing molecules. Surface engineering with polyethylene glycol (PEG), antibodies, aptamers, peptides, carbohydrates, or receptor-specific ligands enhances mucus penetration and selective targeting of airway epithelial cells, alveolar macrophages, dendritic cells, or fibroblasts[23-24].

3.2 Types of Nanocarriers

Numerous nanocarrier systems have been investigated for COPD therapy, each possessing distinct structural characteristics, drug-loading capacities, release kinetics, and targeting capabilities. Selection of an appropriate nanocarrier depends on the physicochemical properties of the therapeutic agent, disease pathology, desired release profile, and administration route.

Liposomes

Liposomes are spherical phospholipid vesicles composed of one or more lipid bilayers surrounding an aqueous core. Their amphiphilic architecture allows simultaneous encapsulation of hydrophilic drugs within the aqueous compartment and lipophilic drugs within the lipid membrane. Liposomes exhibit excellent biocompatibility, biodegradability, low immunogenicity, and prolonged pulmonary retention. PEGylated liposomes further improve circulation time and reduce macrophage-mediated clearance. In COPD, liposomal formulations have been extensively explored for delivering corticosteroids, bronchodilators, antibiotics, antioxidants, and anti-inflammatory agents directly to inflamed lung tissues while minimizing systemic toxicity[25].

Polymeric Nanoparticles

Polymeric nanoparticles are fabricated from biodegradable natural or synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), chitosan, alginate, gelatin, and polycaprolactone (PCL). These nanoparticles provide high drug-loading efficiency, excellent structural stability, controlled drug release, and customizable surface functionalization. Polymeric nanocarriers protect encapsulated therapeutics from enzymatic degradation and facilitate targeted delivery of corticosteroids, siRNA, microRNA, proteins, peptides, and gene-editing systems. Their versatility makes them among the most widely investigated nanoplatforms for chronic inflammatory lung diseases.

Metallic and Inorganic Nanoparticles

Metallic and inorganic nanoparticles include gold nanoparticles, silver nanoparticles, iron oxide nanoparticles, silica nanoparticles, zinc oxide nanoparticles, cerium oxide nanoparticles, and mesoporous silica nanocarriers. These materials possess unique optical, magnetic, catalytic, and antioxidant properties that support both therapeutic and diagnostic applications. Cerium oxide nanoparticles exhibit potent ROS-scavenging activity, whereas gold nanoparticles serve as versatile drug carriers and imaging agents. Iron oxide nanoparticles enable magnetic targeting and image-guided therapy. Nevertheless, concerns regarding long-term pulmonary toxicity, oxidative stress, biodegradation, and biopersistence require careful evaluation before widespread clinical application[26-27].

Extracellular Vesicles and Biomimetic Nanocarriers

Extracellular vesicles (EVs), including exosomes and microvesicles, are naturally secreted nanoscale membrane vesicles that mediate intercellular communication by transporting proteins, lipids, messenger RNA, microRNA, and other bioactive molecules. Their intrinsic biocompatibility, low immunogenicity, and natural targeting capabilities make them attractive drug delivery vehicles for pulmonary diseases. Biomimetic nanocarriers, such as cell membrane-coated nanoparticles derived from macrophages, neutrophils, platelets, or stem cells, combine synthetic nanoparticle stability with biological functionality. These systems exhibit prolonged circulation, immune evasion, enhanced inflammation targeting, and improved compatibility with pulmonary

tissues, making them promising candidates for next-generation COPD therapeutics.

3.3 Physicochemical Characteristics Influencing Pulmonary Delivery

The therapeutic performance of pulmonary nanomedicines is strongly influenced by their physicochemical characteristics. Particle size is one of the most critical determinants of aerosol deposition, mucus penetration, macrophage clearance, and intracellular uptake. Nanoparticles with aerodynamic diameters between 1 and 5 μm are generally optimal for deep lung deposition when formulated as inhalable aerosols, whereas primary nanoparticles typically range between 50 and 300 nm to facilitate efficient cellular internalization. Particle shape influences airflow dynamics, diffusion, cellular interactions, and biodistribution. Spherical nanoparticles are most commonly employed due to ease of fabrication and predictable behavior, although rod-shaped and elongated nanoparticles may exhibit enhanced mucus penetration and prolonged retention under certain conditions. Surface charge significantly affects interactions with pulmonary mucus and cellular membranes. Positively charged nanoparticles often demonstrate enhanced cellular uptake but may interact strongly with negatively charged mucus, potentially limiting penetration and increasing cytotoxicity. Neutral or slightly negative nanoparticles generally exhibit improved mucus diffusion and greater pulmonary biocompatibility.

Other important parameters include surface hydrophobicity, porosity, elasticity, drug-loading efficiency, encapsulation stability, biodegradability, and release kinetics. Surface PEGylation and ligand conjugation improve colloidal stability, prolong pulmonary residence time, reduce immune recognition, and facilitate receptor-mediated targeting of inflamed pulmonary tissues[28-29].

3.4 Pulmonary Administration Routes and Aerosolized Nanomedicines

Pulmonary drug delivery is the preferred route for COPD therapy because it enables direct deposition of therapeutic agents within the respiratory tract while minimizing systemic exposure. Inhalation-based administration delivers nanomedicines directly to diseased airways, improving therapeutic efficacy and reducing adverse effects associated with oral or intravenous administration. Common inhalation devices include nebulizers, pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and soft mist inhalers (SMIs). Nebulizers are particularly suitable for nanoparticle suspensions because they generate fine aerosol droplets capable of reaching distal airways. Dry powder inhalers provide improved stability and portability but require optimized particle engineering to achieve efficient aerosolization.

3.5 Cellular Uptake and Intracellular Drug Transport

Following pulmonary deposition, nanoparticles interact with airway mucus, epithelial cells, alveolar macrophages, dendritic cells, fibroblasts, endothelial cells, and immune cells. Successful therapeutic delivery depends on efficient mucus penetration, avoidance of premature clearance, cellular internalization, intracellular trafficking, and controlled drug release. Nanoparticles enter pulmonary cells through multiple endocytic pathways, including clathrin-mediated endocytosis, caveolae-mediated endocytosis, macropinocytosis, phagocytosis, and receptor-mediated internalization. The predominant uptake mechanism depends on nanoparticle size, surface chemistry, shape, and ligand modification. Smaller nanoparticles generally undergo clathrin- or caveolae-mediated uptake, whereas larger particles are preferentially internalized through phagocytosis by alveolar macrophages. Following endocytosis, nanoparticles traffic through early endosomes, late endosomes, and lysosomes before releasing their therapeutic cargo into the cytoplasm or specific intracellular organelles. Advanced nanocarriers are engineered to escape lysosomal degradation through proton sponge effects, membrane fusion, pH-responsive polymers, or biodegradable linkers. Such intracellular delivery strategies are particularly important for nucleic acid therapeutics, gene-editing systems, proteins, peptides, and antioxidants that require cytoplasmic or nuclear localization to achieve maximal therapeutic efficacy[30-31].

Optimizing cellular uptake and intracellular transport remains central to the successful clinical translation of pulmonary nanomedicine, particularly for precision treatment of COPD, where effective modulation of inflammatory signaling, oxidative stress, and tissue remodeling requires efficient delivery to specific pulmonary cell populations[32].

4. THERAPEUTIC APPLICATIONS OF NANOTECHNOLOGY IN COPD

The multifactorial pathogenesis of chronic obstructive pulmonary disease (COPD), involving persistent inflammation, oxidative stress, excessive mucus production, airway remodeling, emphysema, and impaired tissue repair, necessitates therapeutic approaches that extend beyond conventional pharmacological management. Recent advances in nanotechnology have enabled the development of sophisticated drug delivery systems capable of enhancing pulmonary deposition, improving drug stability, facilitating targeted delivery, and providing controlled or stimuli-responsive drug release. Nanocarriers can transport a wide range of therapeutic agents—including corticosteroids, bronchodilators, antioxidants, nucleic acids, peptides, proteins, biologics, and regenerative molecules-directly to diseased lung tissues while minimizing systemic toxicity. In addition, multifunctional nanoplatforms integrating diagnostic imaging and therapeutic functions have accelerated the emergence of precision medicine in respiratory diseases. These advances position nanotechnology as a transformative strategy for improving COPD

management and addressing the limitations of conventional therapies[34-35].

4.1 Nanoformulations for Anti-inflammatory Drug Delivery

Chronic airway inflammation is the central pathological feature of COPD and is characterized by persistent activation of neutrophils, macrophages, dendritic cells, and $CD8^+$ T lymphocytes. These inflammatory cells release cytokines, chemokines, proteases, and reactive oxygen species (ROS) that progressively damage airway tissues and contribute to irreversible airflow limitation. Conventional anti-inflammatory therapies, particularly inhaled corticosteroids (ICS), reduce exacerbations in selected patient populations but often exhibit limited efficacy in neutrophil-dominant COPD, poor deposition in peripheral airways, and significant systemic adverse effects with prolonged use. Nanotechnology-based formulations have significantly improved anti-inflammatory drug delivery by enhancing pulmonary retention, increasing intracellular drug accumulation, and enabling sustained release. Liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), dendrimers, and polymeric micelles have been extensively investigated for encapsulating corticosteroids such as budesonide, fluticasone propionate, dexamethasone, and beclomethasone, as well as phosphodiesterase-4 inhibitors and novel anti-inflammatory compounds. Encapsulation protects drugs from premature degradation, prolongs drug residence time within the lungs, and reduces systemic absorption[36-39].

Surface-functionalized nanoparticles targeting alveolar macrophages, activated epithelial cells, or inflammatory receptors further improve therapeutic specificity. Ligands such as mannose, folic acid, antibodies, peptides, and hyaluronic acid facilitate receptor-mediated uptake into inflammatory cells, thereby reducing cytokine production and suppressing NF-κB, MAPK, and JAK/STAT signaling pathways. Stimuli-responsive nanocarriers capable of releasing drugs in response to acidic pH, elevated ROS levels, or inflammatory enzymes have demonstrated enhanced site-specific drug delivery within inflamed pulmonary tissues. Collectively, nanoformulations represent a promising approach for overcoming corticosteroid resistance, reducing chronic inflammation, and improving long-term disease control[40].

4.2 Antioxidant Nanotherapeutics

Oxidative stress plays a pivotal role in COPD pathogenesis by promoting epithelial injury, mitochondrial dysfunction, protease activation, cellular senescence, and corticosteroid resistance. Cigarette smoke, biomass combustion, environmental pollutants, activated neutrophils, and dysfunctional mitochondria generate excessive ROS that overwhelm endogenous antioxidant defenses, leading to progressive lung tissue damage. Consequently, restoring redox balance has emerged as an important therapeutic objective. Nanotechnology has enabled the development of antioxidant nanotherapeutics that improve the stability, bioavailability, and targeted delivery of antioxidant molecules. Lipid nanoparticles, polymeric nanocarriers, mesoporous silica nanoparticles, and nanomicelles have been employed to deliver antioxidants such as N-acetylcysteine, curcumin, resveratrol, quercetin, vitamin E, coenzyme Q10, and melatonin directly to inflamed lung tissues. These formulations protect antioxidant compounds from degradation while enabling sustained intracellular release.

4.3 Nanotechnology for Mucus Penetration and Targeted Drug Delivery

One of the difficulties in COPD therapy is the presence of excess mucus production along with reduced mucociliary clearance, which significantly hinders drug entry into the distal airways. Hyperviscous mucus becomes a physical obstruction to entrap inhaled drug particles in the airways, thus not permitting any sufficient access of drugs to inflamed epithelial cells and alveoli. Nanotechnology has provided an innovative solution to overcome these physiological barriers. Mucus-penetrating nanoparticles are designed with optimum particle size, hydrophilic surface coating, and neutral or negative surface charge in order to reduce interaction with mucin glycoproteins. Nanoparticles coated with polyethylene glycol show improved diffusion through airway mucus, resulting in increased distribution of the drug particles in the small airways and alveoli.

Targeted drug delivery further enhances therapeutic precision through ligand-mediated recognition of disease-associated receptors. Nanoparticles functionalized with antibodies, aptamers, peptides, transferrin, mannose, folate, or hyaluronic acid selectively bind receptors overexpressed on airway epithelial cells, activated macrophages, endothelial cells, or inflammatory leukocytes. Such receptor-mediated targeting increases intracellular drug accumulation while reducing off-target exposure and systemic toxicity. Emerging biomimetic nanocarriers coated with macrophage or platelet membranes exhibit prolonged circulation, immune evasion, and preferential accumulation within inflamed pulmonary tissues, representing a promising strategy for precision treatment of COPD[41-42].

4.4 Gene Therapy and RNA-Based Nanomedicine

Gene-based therapeutics have emerged as promising approaches for modifying the molecular mechanisms underlying COPD rather than merely controlling symptoms. Dysregulation of inflammatory cytokines, oxidative stress pathways, protease-antiprotease balance, mitochondrial function, and tissue repair involves numerous genes and non-coding RNAs that can potentially be targeted using nucleic acid therapeutics. However, naked nucleic acids are highly susceptible to enzymatic degradation and exhibit poor cellular uptake, necessitating efficient delivery systems. Nanocarriers provide effective platforms for delivering small interfering RNA (siRNA), microRNA (miRNA), messenger RNA (mRNA), antisense oligonucleotides, plasmid DNA, and CRISPR-Cas gene-editing components

into pulmonary tissues. Lipid nanoparticles remain the most clinically advanced nucleic acid delivery system because of their high encapsulation efficiency, biocompatibility, and ability to facilitate endosomal escape. Polymeric nanoparticles, dendrimers, lipid-polymer hybrid nanoparticles, and extracellular vesicles have also demonstrated efficient pulmonary gene delivery.

4.5 Stem Cell and Regenerative Nanomedicine

The irreversible destruction of alveolar structures and impaired regenerative capacity remain major obstacles in COPD therapy. Current pharmacological treatments alleviate symptoms but do not restore damaged lung architecture or regenerate functional pulmonary tissue. Regenerative nanomedicine seeks to overcome these limitations by combining stem cell therapy with advanced nanomaterial-based delivery platforms. Mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and lung progenitor cells exhibit anti-inflammatory, immunomodulatory, anti-fibrotic, and regenerative properties that may promote pulmonary repair. Nanomaterials improve stem cell therapy by enhancing cell survival, protecting transplanted cells from oxidative injury, improving pulmonary retention, and facilitating targeted delivery to damaged tissues. Biodegradable hydrogels, nanoparticle-loaded scaffolds, and injectable nanocomposite matrices provide supportive microenvironments that enhance stem cell engraftment and differentiation.

Exosome-based therapy has emerged as an attractive cell-free regenerative strategy. Stem cell-derived extracellular vesicles contain growth factors, cytokines, proteins, messenger RNA, and regulatory microRNAs that modulate immune responses, suppress inflammation, stimulate angiogenesis, and promote alveolar epithelial regeneration. Nanotechnology further enhances exosome stability, cargo loading, targeting efficiency, and controlled release. Although regenerative nanomedicine remains largely in the preclinical stage, it offers substantial potential for restoring pulmonary structure and function in patients with advanced COPD[43].

4.6 Nanotheranostics for Diagnosis and Treatment Monitoring

The integration of diagnostic imaging and targeted therapy within a single nanoplatform has given rise to the field of nanotheranostics. This approach enables simultaneous disease detection, therapeutic delivery, treatment monitoring, and personalized clinical decision-making. In COPD, where disease progression is highly heterogeneous and difficult to predict, nanotheranostic systems offer opportunities for early diagnosis and real-time assessment of therapeutic response. Functionalized nanoparticles can be engineered to carry imaging agents alongside therapeutic cargo. Gold nanoparticles enhance computed tomography (CT) imaging owing to their high X-ray attenuation, whereas superparamagnetic iron oxide nanoparticles improve magnetic resonance imaging (MRI) contrast. Quantum dots, fluorescent silica nanoparticles, and near-infrared probes facilitate molecular imaging of inflammatory activity, oxidative stress, and cellular interactions within pulmonary tissues. Biosensing nanoplatforms capable of detecting inflammatory biomarkers, oxidative stress mediators, exhaled volatile organic compounds, circulating microRNAs, and disease-specific proteins are also being developed for non-invasive COPD diagnosis. Smart nanoparticles responsive to ROS, pH changes, or inflammatory enzymes can simultaneously detect pathological alterations and release therapeutic agents, thereby enabling image-guided and personalized treatment. Integration of nanotheranostics with artificial intelligence, molecular imaging, wearable biosensors, and digital health technologies may further improve disease monitoring, optimize therapeutic interventions, and advance precision medicine for COPD.

5. RECENT ADVANCES IN NANOTECHNOLOGY FOR COPD MANAGEMENT

Recent years have witnessed remarkable progress in nanotechnology for the management of chronic obstructive pulmonary disease (COPD). Advances in material science, nanofabrication, molecular biology, and artificial intelligence have facilitated the development of next-generation nanomedicines with enhanced targeting capability, controlled drug release, improved biocompatibility, and multifunctional therapeutic properties. Unlike conventional nanoparticle formulations that primarily serve as passive drug carriers, modern nanoplatforms are designed to respond to the pathological microenvironment of diseased lungs, selectively deliver therapeutics to inflammatory cells, integrate diagnostic and therapeutic functions, and support personalized treatment strategies (**Table 1**). These innovations have significantly expanded the potential of nanomedicine to address the complex pathophysiology of COPD while improving therapeutic efficacy and minimizing systemic toxicity[44-45].

Table 1. Nanotechnology-Based Therapeutic Applications for COPD Management

Nanotechnology Strategy	Nanocarrier Type	Therapeutic Cargo	Mechanism of Action	Current Research Status	Ref.
Anti-inflammatory drug delivery	Liposomes	Budesonide, Dexamethasone, Fluticasone, Beclomethasone	Sustained pulmonary drug release; inhibition of NF-κB-mediated cytokine production	Preclinical; selected formulations in early clinical evaluation	[45-46]
Targeted anti-inflammatory therapy	Polymeric nanoparticles (PLGA, Chitosan, PLA)	Corticosteroids, PDE-4 inhibitors, Curcumin	Controlled drug release with receptor-mediated targeting of inflammatory cells	Extensive preclinical studies	
Antioxidant therapy	Solid lipid nanoparticles (SLNs)	N-acetylcysteine, Curcumin, Vitamin E	Reduction of ROS, protection against oxidative lung injury	Preclinical	
Targeted pulmonary delivery	Ligand-functionalized nanoparticles	Corticosteroids, Antibiotics, Biologics	Receptor-mediated uptake by alveolar macrophages and airway epithelial cells	Preclinical	[46]
RNA interference therapy	Lipid nanoparticles	siRNA, miRNA, Antisense oligonucleotides	Silencing inflammatory cytokines and protease-related genes	Experimental/ Preclinical	
Gene editing	Polymeric nanoparticles, Lipid nanoparticles	CRISPR-Cas9, Plasmid DNA, mRNA	Correction or modulation of disease-associated genes	Early experimental stage	[47]
Regenerative therapy	Extracellular vesicles (Exosomes)	miRNAs, Growth factors, Regulatory proteins	Tissue regeneration, immune modulation, epithelial repair	Preclinical	
Smart stimuli-responsive nanomedicine	ROS-responsive and pH-responsive nanoparticles	Anti-inflammatory drugs, Antioxidants	Site-specific drug release triggered by inflammatory microenvironment	Emerging preclinical research	

5.1 Stimuli-Responsive and Smart Nanocarriers

Stimuli-responsive nanocarriers represent one of the most significant advances in pulmonary nanomedicine. These "smart" delivery systems are engineered to release their therapeutic payload only when exposed to specific physiological or pathological stimuli present within diseased lung tissues. Since COPD lungs exhibit elevated oxidative stress, chronic inflammation, altered pH, increased enzymatic activity, and excessive reactive oxygen species (ROS), these pathological characteristics can be exploited to achieve site-specific drug delivery. ROS-responsive nanoparticles are among the most extensively investigated systems because oxidative stress is a hallmark of COPD. These nanocarriers contain oxidation-sensitive linkers that degrade in ROS-rich environments, enabling localized release of corticosteroids, antioxidants, or anti-inflammatory agents directly at inflamed pulmonary sites. Similarly, pH-responsive nanoparticles exploit the mildly acidic inflammatory microenvironment to trigger drug release, whereas enzyme-responsive systems utilize inflammatory enzymes such as matrix metalloproteinases (MMPs) or elastases for controlled drug activation.

Advanced multifunctional nanocarriers combine multiple responsive mechanisms within a single platform, enabling sequential drug release and enhanced therapeutic precision. Some systems also incorporate imaging agents, allowing simultaneous disease visualization and treatment monitoring. Such intelligent nanomedicines reduce premature drug leakage, improve pulmonary retention, minimize systemic toxicity, and increase therapeutic efficiency, making them promising candidates for precision COPD therapy.

5.2 Surface-Modified and Ligand-Targeted Nanoparticles

Surface engineering has become a fundamental strategy for enhancing nanoparticle performance in pulmonary drug delivery. Modification of nanoparticle surfaces improves physicochemical stability, prolongs circulation time, reduces immune recognition, facilitates mucus penetration, and enhances selective accumulation within diseased lung tissues. Polyethylene glycol (PEG)

remains the most widely used surface modification because PEGylation reduces protein adsorption, minimizes macrophage-mediated clearance, and prolongs nanoparticle residence within the respiratory tract. Improved mucus penetration achieved through PEG coating enables nanoparticles to reach distal bronchioles and alveolar regions that are often inaccessible to conventional inhaled drugs. Targeted nanomedicine further improves delivery specificity through conjugation of targeting ligands such as antibodies, peptides, aptamers, folic acid, mannose, transferrin, hyaluronic acid, or receptor-specific carbohydrates. These ligands recognize receptors overexpressed on airway epithelial cells, activated alveolar macrophages, dendritic cells, endothelial cells, or inflammatory leukocytes. Receptor-mediated endocytosis significantly enhances intracellular drug accumulation while reducing off-target exposure[48].

5.3 Biomimetic and Cell Membrane-Coated Nanoparticles

Biomimetic nanotechnology has emerged as an innovative approach that integrates synthetic nanomaterials with biological membranes to replicate the properties of natural cells. Unlike conventional nanoparticles, biomimetic systems possess enhanced biocompatibility, prolonged circulation, immune evasion, and improved targeting of inflamed tissues. Cell membrane-coated nanoparticles are generated by enveloping synthetic nanoparticle cores with plasma membranes derived from macrophages, neutrophils, erythrocytes, platelets, stem cells, or epithelial cells. These membrane coatings preserve membrane proteins and cell-surface receptors that enable natural interactions with inflammatory microenvironments. Macrophage membrane-coated nanoparticles exhibit preferential accumulation within inflamed pulmonary tissues because macrophages naturally migrate toward inflammatory cytokines and chemokines abundant in COPD lungs. Neutrophil membrane-coated nanoparticles similarly target inflamed endothelium, whereas platelet membrane-coated systems facilitate adhesion to damaged vascular surfaces and inflammatory lesions.

Extracellular vesicles (EVs), particularly exosomes, represent another important biomimetic platform. These naturally secreted nanoscale vesicles transport proteins, lipids, messenger RNA, microRNA, and signaling molecules between cells. Stem cell-derived exosomes possess potent immunomodulatory, anti-inflammatory, anti-fibrotic, and regenerative properties that promote epithelial repair and suppress chronic pulmonary inflammation. Owing to their intrinsic biological compatibility and low immunogenicity, biomimetic nanocarriers are increasingly regarded as promising candidates for next-generation COPD therapeutics[49].

5.4 Inhalable Nanoformulations and Dry Powder Nanocarriers

Direct pulmonary administration remains the preferred route for COPD therapy because it delivers therapeutic agents directly to diseased airways while minimizing systemic adverse effects. Recent advances in aerosol engineering have enabled the development of inhalable nanoformulations with improved aerodynamic performance, enhanced lung deposition, and prolonged pulmonary retention. Nanoparticle suspensions can be administered using nebulizers, pressurized metered-dose inhalers (pMDIs), and soft mist inhalers (SMIs), allowing efficient deposition throughout the bronchial tree and peripheral alveolar regions. These formulations improve dissolution of poorly water-soluble drugs, increase local bioavailability, and reduce dosing frequency. Particular attention has been directed toward dry powder nanocarriers because of their superior physicochemical stability, portability, and patient convenience. Nanocomposite microparticles are commonly produced through spray drying or spray freeze-drying techniques, in which nanoparticles are incorporated into inhalable microparticles possessing optimal aerodynamic diameters between 1 and 5 μm. Following inhalation, these microparticles rapidly disintegrate within the respiratory tract to release the encapsulated nanoparticles.

5.5 Artificial Intelligence and Precision Nanomedicine

Artificial intelligence (AI) is increasingly transforming nanomedicine development by accelerating nanoparticle design, optimizing formulation characteristics, and supporting personalized therapeutic strategies. Machine learning algorithms can analyze extensive physicochemical, biological, and pharmacokinetic datasets to predict nanoparticle behavior, including particle size, stability, encapsulation efficiency, drug release kinetics, biodistribution, toxicity, and therapeutic efficacy. AI-assisted formulation development substantially reduces experimental workload while improving reproducibility and formulation optimization. Computational models can identify optimal polymer compositions, lipid mixtures, surfactant concentrations, and targeting ligands that maximize pulmonary drug delivery and minimize toxicity. Precision nanomedicine further integrates AI with patient-specific clinical information, molecular biomarkers, genomic profiles, imaging data, pulmonary function measurements, and inflammatory phenotypes to develop individualized treatment strategies. Such personalized approaches are particularly valuable in COPD because the disease exhibits marked heterogeneity in terms of inflammatory pathways, disease severity, progression rate, and therapeutic response.

Digital health technologies, wearable respiratory sensors, remote patient monitoring, and AI-driven predictive analytics are expected to complement nanomedicine by enabling continuous disease monitoring, early detection of exacerbations, individualized dose adjustment, and improved long-term disease management. Together, AI and nanotechnology represent a powerful combination that is expected to redefine precision respiratory medicine.

5.6 Preclinical and Clinical Progress of Nanotherapeutics

Over the past decade, substantial progress has been achieved in the preclinical evaluation of nanotherapeutics for COPD. Numerous studies using cigarette smoke-induced, elastase-induced, lipopolysaccharide-induced, and genetically modified animal models have demonstrated that nanoparticle-based drug delivery significantly improves pulmonary drug retention, suppresses chronic inflammation, reduces oxidative stress, attenuates airway remodeling, and enhances lung function compared with conventional formulations. Preclinical investigations have successfully evaluated liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, micelles, exosome-based systems, and biomimetic nanoparticles for delivering corticosteroids, bronchodilators, antioxidants, antibiotics, nucleic acids, and regenerative agents. These studies consistently report enhanced therapeutic efficacy, reduced systemic toxicity, prolonged drug release, and improved pharmacokinetic profiles. Despite encouraging experimental findings, clinical translation remains limited. Several inhalable liposomal formulations and nanoparticle-based respiratory therapies have entered early-phase clinical trials, demonstrating acceptable safety profiles and improved pulmonary drug delivery. However, relatively few nanomedicines have progressed to large-scale Phase III clinical studies specifically for COPD. Key barriers include manufacturing scalability, batch-to-batch reproducibility, long-term biosafety, pulmonary immunotoxicity, regulatory approval, and cost-effective production[50-51].

6. CURRENT CHALLENGES, LIMITATIONS, AND FUTURE PERSPECTIVES

In spite of the great strides made in the field of nanotechnological drug delivery systems, the clinical implementation of nanomedicine in the management of chronic obstructive pulmonary disease (COPD) poses a formidable challenge. While there are a number of preclinical experiments which have shown improvement in drug delivery to the lungs, increased efficacy of treatment, and reduction in systemic toxicity, there is a very small number of nanoformulations which have been evaluated in clinical settings. The complexity of COPD, the peculiarities of the anatomy and physiology of the respiratory system, manufacturing issues, regulatory concerns, and safety concerns continue to pose challenges to the wide implementation of nanotherapeutics. Future developments should focus on designing safer, more effective, and patient-specific nanomedicines capable of meeting the diverse therapeutic needs of COPD patients[52-53].

6.1 Biological and Therapeutic Challenges

Pulmonary Mucus and Airway Barriers

One of the primary biological barriers to successful pulmonary nanomedicine is the abnormal mucus layer present in COPD. Chronic inflammation stimulates goblet cell hyperplasia and submucosal gland enlargement, resulting in excessive production of highly viscous mucus. This mucus acts as a physical barrier that traps inhaled nanoparticles, limiting their diffusion toward airway epithelial cells and distal alveolar regions. Furthermore, impaired mucociliary clearance leads to irregular nanoparticle distribution and variable therapeutic outcomes. The thickened airway epithelium, altered extracellular matrix composition, and disrupted epithelial integrity further reduce drug penetration into inflamed tissues. Consequently, considerable research is focused on developing mucus-penetrating nanoparticles with optimized size, hydrophilic surface coatings, and neutral surface charge to improve pulmonary transport.

Long-Term Pulmonary Toxicity

Long-term biosafety remains one of the most important concerns limiting clinical translation of pulmonary nanomedicine. Although many nanomaterials demonstrate excellent short-term biocompatibility, their chronic effects following repeated inhalation are not yet fully understood. Persistent nanoparticle accumulation may induce oxidative stress, chronic inflammation, epithelial injury, fibrosis, mitochondrial dysfunction, DNA damage, and altered immune responses. Metallic and inorganic nanoparticles may exhibit prolonged pulmonary persistence because of slower biodegradation, increasing the possibility of cumulative toxicity. Comprehensive long-term toxicological studies evaluating biodistribution, biodegradation, clearance, immunogenicity, reproductive toxicity, and carcinogenic potential are essential before routine clinical application.

Disease Heterogeneity and Patient Variability

COPD is a highly heterogeneous disorder characterized by substantial variation in disease severity, inflammatory phenotype, genetic susceptibility, environmental exposure, comorbidities, and treatment response. Patients exhibit diverse molecular endotypes involving neutrophilic, eosinophilic, mixed inflammatory, or emphysema-dominant phenotypes, each responding differently to available therapies. Differences in airway anatomy, mucus production, pulmonary function, smoking history, age, and immune status further influence nanoparticle deposition and therapeutic outcomes. Consequently, universal nanomedicine formulations may not provide optimal efficacy for all patient populations. Future therapeutic strategies should incorporate molecular biomarkers and personalized treatment approaches to address this clinical heterogeneity.

6.2 Manufacturing, Regulatory, and Clinical Translation Challenges

Large-Scale Manufacturing

Although laboratory-scale synthesis of nanoparticles is well established, translating these formulations into industrial-scale production remains technically demanding. Manufacturing processes must consistently produce nanoparticles with uniform size distribution, drug loading, encapsulation efficiency, and surface characteristics while maintaining high production

yields. Scale-up frequently alters critical physicochemical properties, potentially affecting therapeutic performance. Development of robust, reproducible, and Good Manufacturing Practice (GMP)-compliant production methods is therefore essential for commercial manufacturing[54-55].

6.3 Future Perspectives

Personalized Nanomedicine

Personalized nanomedicine is expected to become a major direction for future COPD management. Advances in genomics, transcriptomics, proteomics, metabolomics, and biomarker discovery will enable identification of disease-specific molecular signatures that guide individualized therapeutic strategies. Nanocarriers may be specifically engineered according to each patient's inflammatory phenotype, genetic profile, oxidative stress status, and disease severity, thereby maximizing therapeutic efficacy while minimizing adverse effects. Such individualized treatment approaches align closely with the principles of precision respiratory medicine[56-57].

AI-Assisted Nanocarrier Design

Artificial intelligence (AI) and machine learning are expected to accelerate the development of next-generation pulmonary nanomedicines. Computational algorithms can predict nanoparticle behavior, optimize formulation parameters, identify ideal drug–carrier combinations, and estimate pharmacokinetic and toxicological profiles before experimental validation. AI-assisted design may substantially reduce development time, lower research costs, improve reproducibility, and facilitate rational optimization of multifunctional nanocarriers. Integration of computational modeling with experimental nanotechnology is likely to become increasingly important in future pharmaceutical research.

Multifunctional Theranostic Nanoplatforms

Future nanomedicine will increasingly integrate therapeutic and diagnostic capabilities within single multifunctional platforms. Theranostic nanoparticles capable of simultaneously delivering drugs, monitoring inflammatory biomarkers, providing molecular imaging, and assessing treatment response offer substantial opportunities for precision medicine. Incorporation of magnetic nanoparticles, fluorescent probes, biosensors, and responsive imaging agents will enable clinicians to monitor disease progression and therapeutic efficacy in real time, allowing timely modification of treatment strategies[58-60].

Combination Therapies

Combination nanotherapeutics represent another promising strategy for improving COPD treatment. Multifunctional nanocarriers can simultaneously deliver bronchodilators, corticosteroids, antioxidants, anti-inflammatory agents, antibiotics, growth factors, and nucleic acid therapeutics within a single delivery platform. Such combination approaches target multiple pathological pathways involved in COPD progression, potentially producing synergistic therapeutic effects while reducing drug resistance and minimizing dosing frequency. Continued development of co-delivery systems will likely expand treatment options for complex respiratory diseases[61-62].

Clinical Translation and Precision Respiratory Medicine

The ultimate objective of nanotechnology research is successful clinical implementation. Achieving this goal will require well-designed multicenter clinical trials, standardized manufacturing protocols, harmonized regulatory guidelines, long-term safety evaluation, and cost-effective production methods [63-64]. Collaboration among academic researchers, clinicians, pharmaceutical industries, regulatory authorities, and healthcare policymakers will be essential for overcoming existing translational barriers. As advances in nanotechnology continue to converge with molecular medicine, artificial intelligence, biomarker-guided therapy, and digital healthcare, precision respiratory medicine is expected to transform COPD management by enabling highly targeted, individualized, and disease-modifying therapeutic interventions that improve both clinical outcomes and patient quality of life[65].

CONCLUSION

The chronic obstructive pulmonary disease is still one of the significant challenges in the sphere of health care, which is represented by a gradual development of airflow limitation, chronic inflammation, oxidative stress, and irreversible damage of the respiratory system structure. Even though the existing drugs allow decreasing symptoms and exacerbations, they cannot stop the disease process and recover the destroyed tissues. Such facts indicate that there is a need for finding new treatment methods. Nanotechnology can be considered as one of the promising directions that can help in better treatment of this problem due to such advantages as better drug delivery to the pulmonary organs, precise and targeted drug delivery, increased bioavailability and decreased systemic toxicity. Recent breakthroughs in smart nanocarriers, inhaled nano-drug delivery systems, and artificial intelligence-guided nanomedicine provide additional evidence to facilitate the creation of precise respiratory therapy. Although there have been some promising results in pre-clinical trials, there are still some problems related to safety, large-scale production, regulatory clearance, and clinical testing that need to be addressed. Further research needs to concentrate on improving the design of nanocarriers, safety evaluation via carefully conducted clinical trials, and the integration of nanotechnology into precision medicine.

LIST OF ABBREVIATIONS

AAT, alpha-1 antitrypsin; AI, artificial intelligence; AP-1, activator protein-1; CD8, cluster of differentiation 8; COPD, chronic obstructive pulmonary disease; CRDs, chronic respiratory diseases; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats–CRISPR-associated protein 9; CT, computed tomography; DNA, deoxyribonucleic acid; DPIs, dry

powder inhalers; EVs, extracellular vesicles; GM-CSF, granulocyte-macrophage colony-stimulating factor; GMP, Good Manufacturing Practice; HDAC2, histone deacetylase-2; HO-1, heme oxygenase-1; ICS, inhaled corticosteroids; IL, interleukin; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-8, interleukin-8; IL-17, interleukin-17; iPSCs, induced pluripotent stem cells; JAK/STAT, Janus kinase/signal transducer and activator of transcription; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MAPK, mitogen-activated protein kinase; miRNA, microRNA; MMPs, matrix metalloproteinases; MRI, magnetic resonance imaging; MSCs, mesenchymal stem cells; mRNA, messenger RNA; NLCs, nanostructured lipid carriers; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; PCL, polycaprolactone; PDE-4, phosphodiesterase-4; PEG, polyethylene glycol; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); pMDIs, pressurized metered-dose inhalers; RNA, ribonucleic acid; ROS, reactive oxygen species; siRNA, small interfering RNA; SLNs, solid lipid nanoparticles; SMIs, soft mist inhalers; SOD, superoxide dismutase; TGF-β, transforming growth factor-beta; TLRs, Toll-like receptors; TNF-α, tumor necrosis factor-alpha.

ETHICAL APPROVAL

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HUMAN AND ANIMAL ETHICAL RIGHT

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, and no funding was required to conduct these review data.

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AVAILABILITY OF DATA AND MATERIALS

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