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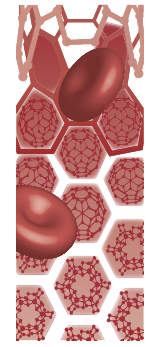

Exploring state-of-the-art advances in targeted nanomedicines for managing acute and chronic inflammatory lung diseases

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Diagnosis and treatment of lung diseases pose serious challenges. Currently, diagnostic as well as therapeutic methods show poor efficacy toward drug-resistant bacterial infections, while chemotherapy causes toxicity and nonspecific delivery of drugs. Advanced treatment methods that cure lung-related diseases, by enabling drug bioavailability via nasal passages during mucosal formation, which interferes with drug penetration to targeted sites, are in demand. Nanotechnology confers several advantages. Currently, different nanoparticles, or their combinations, are being used to enhance targeted drug delivery. Nanomedicine, a combination of nanoparticles and therapeutic agents, that delivers drugs to targeted sites increases the bioavailability of drugs at these sites. Thus, nanotechnology is superior to conventional chemotherapeutic strategies. Here, the authors review the latest advancements in nanomedicine-based drug-delivery methods for managing acute and chronic inflammatory lung diseases.

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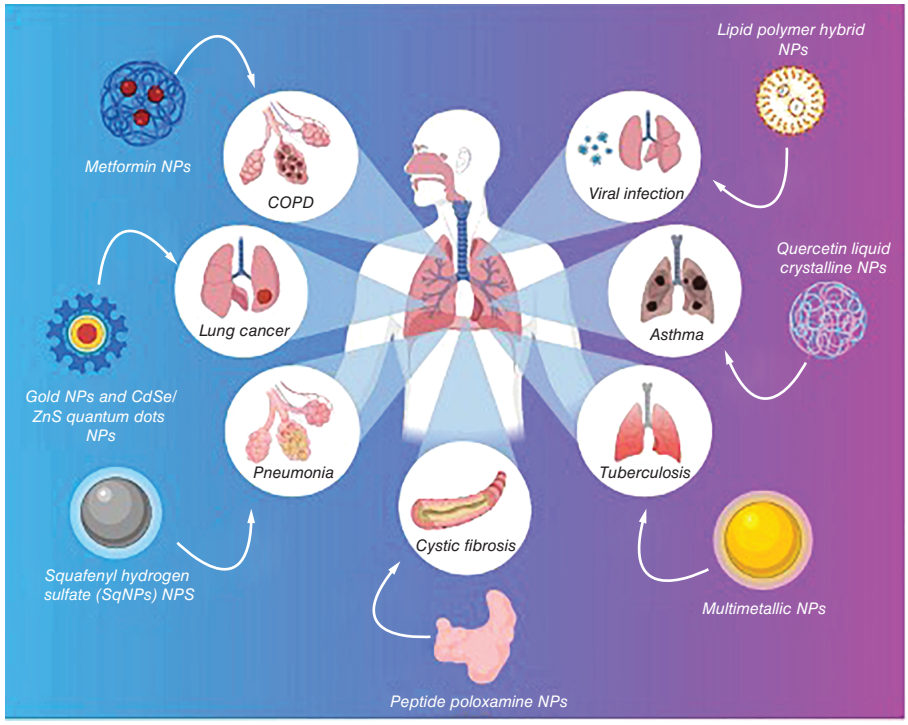

Global incidence of respiratory illnesses is rising. Morbidity and mortality rates due to lung diseases, categorized as acute respiratory distress syndrome (ARDS) and chronic respiratory diseases (CRDs), remain high. According to WHO, lung diseases fall under the top ten major causes of death globally [1]. Although the cellular and molecular pathologies of acute and chronic lung diseases have been largely clarified, the development of new therapies, particularly drug-delivery systems, is lagging behind [2]. Researchers exploring cellular and molecular aspects of lung diseases have found few advanced sites that might help treat the disease. However, translation to human therapies is limited owing to a lack of drug-delivery systems, emphasizing the need to develop new methods against lung diseases [3].

Nanoscience involves the study of nanosized substances, procedures and tools of sizes less than 10^{-9} meter. Nanomedicine enables targeted delivery of therapeutic and diagnostic compounds that counter lung diseases. It also increases the half-life of therapeutic agents, enhances their bioavailability and improves biodistribution in target organs, thereby improving drug effectiveness and minimizing drug toxicity [4].

Depending on the pathology of ARDS- and CRD-related drug-delivery methods, the purposes of this article are to review the latest developments in nanomedicine aimed at diagnosing and treating lung injuries and to introduce the principles governing nanocarrier drug-delivery systems used to treat lung diseases.

Acute lung diseases

Acute lung diseases (ALDs) manifest when water fills the alveoli, preventing air from entering alveolar spaces, causing pulmonary infiltration, hypoxemia and edema, among others [5]. ALDs account for approximately 4 million deaths annually and are considered the biggest cause of death in children below 5 years of age [6]. The most common causes of ALD are viruses and bacteria that infect the lower respiratory tract and lungs, leading to symptoms such as the common cold, laryngitis, tuberculosis, bronchitis, pharyngitis and pneumonia [7]. Exposure to new viral diseases, such as COVID-19, increases the danger of ALDs. Previous health problems may cause ARDS, COVID-19 being a fine example [8]. Many studies aimed at understanding the epidemiology, pathogenesis and treatment of this disease have been initiated.

Table 1. Types of risk factors that cause acute lung injury.

Direct lung injury risk factors	Indirect lung injury risk factors	Environment-related risk factors
• Pneumonia (bacterial, fungal, viral or opportunistic) • Pulmonary contusion • Near-drowning • Gastric content aspiration • Post-lung transplantation • Injury during inhalation	• Nonthoracic trauma or hemorrhagic shock • Major burn injury • Cardiopulmonary bypass • Reperfusion edema after lung transplantation or embolectomy • Pancreatitis • Blood product transfusion • Sepsis (nonpulmonary source) • Overdose of drugs • Pulmonary embolism	• Smoking • Crowding • Cooking fuel • House make and size • Ethnicity • Air pollution • Irritant gas • Occupation

Data taken from [9].

Factors causing ALD/ARDS

Two types of lung injuries can cause ALD/ARDS: direct or remote injuries. Some environmental factors may also be involved (Table 1) [9]. The epidemiology of ALD is influenced by community immunity, the amount of contact between individuals and age. ALDs can be categorized into upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs) [10]. URTIs include upper respiratory tract infections starting at the nose and ending in the larynx and large airways. Microbes invade the mucosal layer of the sinus and pharynx. Common ALDs include the common cold, pharyngeal syndrome, influenza, herpangina and croup [11]. Parts of the lungs below the larynx are affected by LRTIs, leading to diseases such as acute bronchitis, chronic obstructive pulmonary disease/chronic bronchitis and acute exacerbation of bronchiectasis [12]. URTIs are often caused by pathogenic microorganisms, which enter the respiratory tract and take up residence in the mucosa, as evidenced by various symptoms indicating epithelial destruction. These cells and cilia are lost due to the introduction of inflammatory molecules such as cytokines and immunoglobulins. LRTIs are caused by the entry of microorganisms through hematogenous seeding accompanied by inhalation. These damage the epithelial layer, specifically the bronchial region, via secretion of mucus, inhibition of mucociliary functions and necrosis [13]. Pulmonary embolism caused by vascular thromboses entering the pulmonary artery affects those with cardiorespiratory diseases, irrespective of the stage of the latter, paraplegia, surgery, trauma, cancer, thrombocytopenia, estrogen therapy, injury to vessel walls or increased coagulation and stasis. Consequently, prevention involves anticoagulant therapy, adjunctive therapy, thrombolytic therapy and antiplatelet therapy [14–16]. Protein-rich edema in the alveoli indicates acute lung edema, an advanced stage of ARDS. Increased permeability of alveoli due to epithelial damage lowers oxygen levels, causing hypoxemia. Such permeability is followed by an adverse accumulation of macromolecules, causing fluid accumulation in alveoli. Immune cells, leukocytes, activated procoagulant processes, disruption of tight junction complexes, attenuated exchange of compounds and ions between epithelial cells and the extracellular matrix and apoptosis play key roles in acute lung edema [17]. A study revealed that sepsis causes acute lung edema, with an alarming mortality rate. Of the 12 patients with pneumonia, multiple traumas and pancreatitis in that study, only five survived. All patients showed symptoms of pulmonary issues and refractory hypoxemia. Further autopsies confirmed hemorrhage and edema in alveoli accompanied by inflammation, fibrosis etc. [18].

Chronic lung diseases

Chronic diseases of various areas of the lung and the respiratory tract constitute CRDs, including cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis and lung cancer, among others. These diseases account for 7% of deaths worldwide and impose a socioeconomic burden on societies [19]. The prevention costs of CRDs, such as lung cancer, are lower than their treatment costs. Newer nanomaterial systems are being designed for improved diagnosis and treatment of these diseases [20].

COPD & asthma

WHO predicts that in the next decade, COPD will be the third major cause of death globally [21]. COPD involves airway and parenchymal abnormalities, leading to declined lung function [22]. Lung diseases have high mortality rates and long refractory periods, and they show primary clinical symptoms such as chronic cough, mucus hypersecretion and asthma. COPD is of two types: chronic bronchitis and emphysema. The former is characterized by swelling, mucus overproduction and inflammation within the secondary bronchioles. Loss of function and structure of lung alveoli is seen in emphysema [23]. Heightened oxidative stress, enhanced autophagy, chronic inflammation and

cellular senescence are common in COPD. Excessive mucus secretion caused by abnormal pulmonary inflammation acts as a barrier that blocks the effective delivery of drugs. During bacterial infection, this mucus barrier becomes a dense biofilm that cannot be removed by any drug, resulting in drug resistance. Conventional therapeutic strategies targeting COPD involve the use of anti-inflammatory and antioxidant drugs that target the overlap syndrome, such as nuclear factor erythroid 2-related factor 2 (NRF2) activators, N-acetyl-L-cysteine (NAC), enzyme mimetics and spin traps. However, these antioxidant pharmacological strategies do not treat chronic lung disease effectively, owing to low diffusion rates and disrupted drug pharmacokinetics. This may be solved by fabricating nanocarriers with enhanced pharmacokinetics that target this disease [24]. These nanocarriers, which ensure targeted delivery and minimize drug-related toxicity by conjugating with diseased cell receptor-specific ligands [25], have been applied as vectors in stem cell-based and gene therapies. Asthma is a currently incurable CRD characterized by excess mucus production, breathlessness, aerobic function loss and upper airway inflammation [26]. Although not as lethal as COPD, asthma exerts deleterious effects and greater morbidity [27]. Both these conditions affect breathing ability, leading to long-term disability and impairment of quality of life.

Lung cancer

This chronic disease, mainly caused by excessive smoking, tobacco product use, air pollution exposure, radon and asbestos, is a major cause of mortality in men worldwide. Lung cancer is of two types: small-cell lung carcinoma and non-small-cell lung carcinoma [28]. Lung cancer is mostly treated via conventional methods, such as surgery, radiation, chemo drug-based therapy and targeted treatment. The type and stage of cancer act as determining factors in therapeutic strategy. Despite several therapeutic advances, the prognoses for lung cancer patients remain challenging. Except for frequently localized cancers, the response to current treatment regimens remains poor. Chemotherapy-based strategies and histology help manage advanced lung cancer. Newly discovered biomarkers have enhanced targeted and immune-based therapies. Proper staging is required to investigate lung cancer and choose proper therapeutic strategies. Imaging methods, such as fluorodeoxyglucose-PET and MRI, help identify patients [29]. However, access to these treatments is associated with high costs, which is a substantial challenge faced by patients with cancer.

Cystic fibrosis

CF is a life-threatening disorder caused by an aberrant change in the coding of the *CFTR* gene [30]. It shows an autosomal recessive pattern of inheritance and affects the lungs, pancreas, intestine, upper airways, liver and reproductive organs. Aberrant function of chloride channels, including the CFTR protein, in exocrine glands leads to CF [31]. Individually, disease sensitivity depends upon organ sensitivity and the residual function of CFTR, which is genetically determined. Pancreatic insufficiency, a symptom of CF, is mainly characterized by abdominal symptoms; high-fat-content, shiny, unpleasant-smelling, pulpy stools and a deficiency of fat-soluble vitamins. Treatment involves improving mucociliary clearance, actively treating lungs, exercise and facilitating expectoration therapies to prevent chronic infections.

Pulmonary tuberculosis

Pulmonary tuberculosis develops slowly with almost no initial symptoms. It is a worldwide airborne disease caused by *Mycobacterium tuberculosis*. Pulmonary tuberculosis patients with sputum bacterial infection are a primary source of infection and transmit the disease through airborne droplets [32]. Low-grade fever at the onset, which gradually becomes prominent as the disease progresses, is a major symptom of pulmonary tuberculosis. Diagnosis of tuberculosis is based on chest radiography, which differs in primary tuberculosis compared with reactivation tuberculosis. Development of pneumothorax, wherein the cavity connecting the tracheobronchial tree with the pleural space is ruptured, creating a bronchopleural fistula, may require immediate attention [33]. Another complication involves the development of blebs due to air trapped in the acinus, leading to a submucosal bronchiolar lesion, causing major issues such as tuberculosis infection along with secondary invaders [34].

Design of nanocarriers targeting pulmonary epithelium

Difficulties in developing inhalable drugs are addressed using nanoparticles (NPs) that penetrate the alveolar regions deep in the lungs. Minimized size, maximized surface area-to-volume ratio and improved biocompatibility and biodegradability make NPs efficient drug and gene delivery agents (Figure 1) [35]. Nanocarriers that carry drugs ameliorate chronic lung diseases by overcoming airway defenses, followed by targeted and controlled drug release.

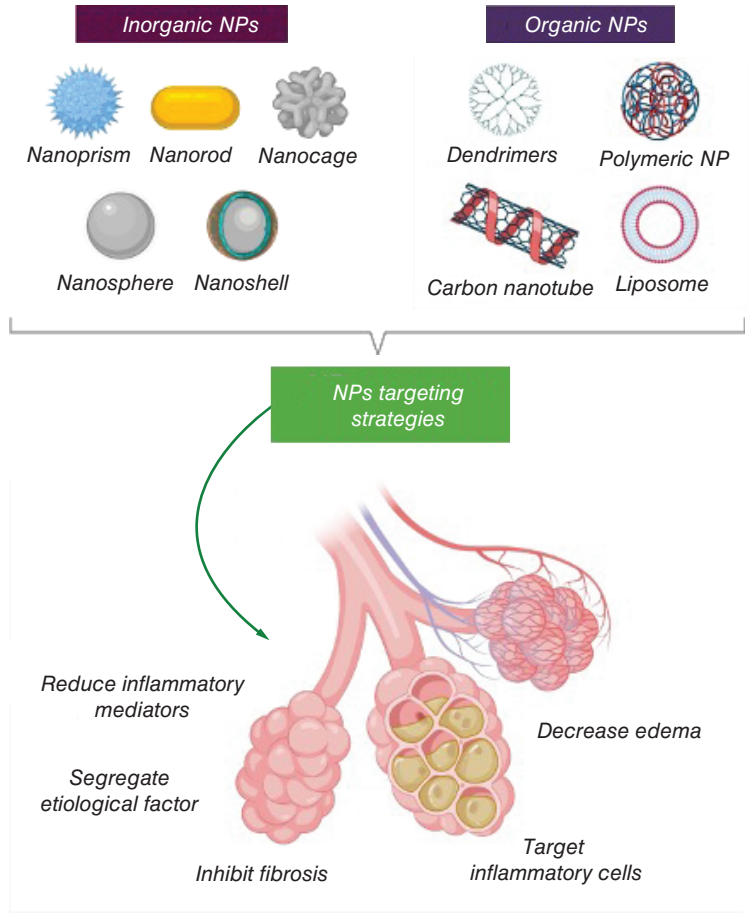

Figure 1. Nanoparticle-based therapy for acute lung diseases. Nanoparticles can be used to target inflammation because of lung injury by inhibiting inflammatory cells, decreasing inflammatory mediators, blocking cytokines and recovering the air–blood barrier.
NP: Nanoparticle.

NPs can be used to deliver a combination of two drugs simultaneously, resulting in longer and enhanced drug effects. Nanodrug delivery reduces drug loss due to degradation and evasion of macrophage clearance, and it enhances drug accumulation at the diseased site, the possibility of developing inhalable formulations, ease of delivery and specific cell-targeted delivery [36].

Size

Various drugs can be carried within NPs depending on their size (ranging from 10 to 200 nm) via different covalent and electrostatic interactions. The charge and size of NPs determine their mucociliary clearance. Particles smaller than 10 nm are eliminated by the reticuloendothelial system, whereas particles larger than 100 nm are targeted by alveolar macrophages. Hence, NP size is crucial for developing an effective delivery system. NPs face major challenges in penetrating the thick viscoelastic mucus layers [37]. NP size is inversely correlated to its mobility [38]. Several NP types, including soft organic NPs (e.g., liposomes) and hard inorganic-based nanocarriers (e.g., carbon nanotubes, dendrimers and micelles) have been used to ensure the compatibility between a drug and an NP. The material used to fabricate the NP and its surface modifications determine its properties and drug-release characteristics [39]. *In vivo* experiments, involving superoxide dismutase (SOD) and catalase and antibodies targeting PECAM, showed that binding (3.5–8.5%) and uptake (4.5–16%) increased with increasing size. Maximum specificity was achieved at 300 nm, indicating that size was important [40].

Shape & surface charge

Particle geometry also influences cellular uptake and particle fate. Homo-difunctional crosslinking, which affects the shape of targeted and untargeted nanogels, comprising lysozyme and dextran, showed variable binding depending upon the linker. The latter was obtained by crosslinking via a short hydrophilic cross-linker, 2,2′-(ethylenedioxy)bis(ethylamine) [41,42]. Deformation properties of nanogels allowed passage through caveolae into plasmalemma vesicle-associated protein (PLVAP) in the lungs of a rodent model [43]. This route is effective

for the delivery of SOD to inhibit inflammation [44]. Discoidal particles exhibit better vessel wall interactions and migration dynamics than spherical particles [45]. NP shape, which affects its circulation half-life, is essential for initiating phagocytosis [46]. Aspect ratio and NP curvature impact NP uptake, where particles with minimal curvature areas, such as cylindrical, ellipsoidal and discoid, show enhanced therapeutic accumulation [47,48]. NP accumulation and circulation time is enhanced by altering the surface charge. Although drugs are nonspecifically taken up by all cells, neutral or negatively charged NPs are not absorbed by serum proteins and hence display lengthier circulation half-lives, while positively charged NPs facilitate endosomal release that hinders drug degradation. Hence, fabricating NPs that can switch from negative to positive after arriving at the target site may enhance drug delivery [49].

Surface modifications

Biodistribution is affected by NP surface modifications; for instance, hydrophobic NPs undergo rapid clearance without surface modifications [50]. Hence, coating NPs with PEG and other hydrophilic polymers will increase the circulation time of particles in the blood and mucus penetration. Stealth coating, which increases the bioavailability of NPs, reduces their phagocytosis [51]. Certain biological fluids alter NP properties by forming a protein corona [52]. Surfactant lipids and proteins determine NP clearance by macrophages, and thus lung surfactant phospholipid coating on inhalable NPs increases cellular uptake while decreasing toxicity [53]. Liposomes prepared using lung surfactants have been widely used for delivery to lungs.

Nanocarrier drug-delivery systems are more advantageous than traditional methods. They remain in the blood longer, load higher amounts of drugs, show less cytotoxicity and limit immunogenicity. Nano drug-delivery systems increase the half-life of drugs and improve their pharmacokinetic properties and therapeutic effects. Adjustable size and surface properties enable NPs to easily deposit at inflammatory sites of lungs via passive and active pathways or physicochemical targeting, thereby boosting the potential of drugs and reducing their harmful effects [54]. Nanocarriers can load multiple drugs simultaneously, and such linkages, which are developed via availability inside the tissue, may affect delivery [55].

Diagnosis & imaging of pulmonary diseases based on nanotechnology

NPs improve pulmonary magnetic resonance and x-ray diagnostics along with the bioavailibility of the encapsulated drug, without affecting the cell cycle, cell viability, cell morphology and apoptosis. Computed tomography and MRI provide complementary visual, quantitative information and insight into COPD pathophysiology. Although computed tomography provides high spatial-resolution measurements of lung structure, it poses long-term risks. MRI is an excellent alternative that provides insights into COPD lung structure without radiation exposure [22]. As therapies become individualized, better imaging techniques that quantify treatment response become necessary. Theranostic advancements, involving a combination of diagnostic and therapeutic procedures in a single system, are being applied to treat chronic inflammatory lung diseases. Nano-based theranostic involve the development of multifunctional nanocarriers that diagnose a disease such as lung inflammation in real time and provide a therapeutic platform against the disease. Magnetic iron oxide NPs have been used to deliver MRI contrast agents and hydrophobic drugs, enabling theranostic treatment of lung diseases [56]. However, they lead to chronic inflammation and toxicity and have limited applications in chronic airway diseases. Liposomes have been used to develop theranostic hybrids that encapsulate quantum dots and multiple drugs [57]. Moreover, various nanoassemblies, such as vesicles and micelles, can deliver curative agents, offering controllable biological, physical and chemical advantages. Drug-encapsulating nanocarriers are attached to various probes for COPD theranostic treatment. For instance, poly(lactic-co-glycolic acid) (PLGA)-PEG polymeric vesicles have been applied theranostically in obstructive lung diseases to deliver COPD drugs using molecular probes. Real-time imaging technologies are cheaper than clinical procedures such as biopsies and bronchoscopies. Single-photon emission computed tomography and PET help detect radiolabeled tracers, such as fluorodeoxyglucose, which accumulate at inflamed sites. Molecular probes may help explain the pathogenesis of the disease, making targeted therapy possible [58]. High sweat chloride content, a symptom that is crucial for CF screening, can be quantified using silver NP-modified electrodes during preliminary screening. The conventional, 'gold-standard' method for diagnosing tuberculosis is expensive and has low sensitivity. Therefore, researchers have developed high-throughput-based diagnoses involving nanotechnology-based approaches, such as nanodisk mass spectroscopy, to diagnose tuberculosis. Biomarkers, such as CFP-10 and ESAT-6, play key roles in the diagnosis of chronic diseases, including chronic tuberculosis. Nanodisk mass spectrometric assays use silica NPs and merge ESAT-6 and CFP-10 antibodies, enabling sensitive multiple quantitative analysis of ESAT-6 and CFP-10

biomarkers in chronic tuberculosis patients. Sensitive and specific classification of *M. tuberculosis* is required for its rapid detection. CFP-10 and ESAT-6 biomarkers can be quantified even at low concentrations. This method can assess the severity of an active tuberculosis infection and help determine therapeutic effects [59].

NP-based therapy for ALD

Drugs that exert therapeutic effects on lung injury can be administered via oral administration, inhalation or intravenous injection. Although such methods of delivering drugs to lungs constitute a beneficial therapeutic strategy, there are several disadvantages associated with the unique physical structure of the lungs (i.e., large surface area of alveolar regions) and the lack of preliminary metabolism [3]. Thus, new techniques that deliver drugs to cure lung injury were researched, resulting in nanotechnology being accepted as a promising and useful platform for identifying and curing diseases.

Theranostic approaches that ensure efficient distribution of nanocarriers within an organ show a better therapeutic and diagnostic approach than the traditional therapies [60]. Their superior performance being attributed to their affinity, precision and accessibility to targeted epitopes, cellular organelles and controlled drug release into the endothelial lining of the lungs. The effect is mostly visible in antioxidative and anti-inflammatory properties [61–63].

Different types of nanocarriers show different capabilities for delivering drugs, especially in enhancing the stability, solubility and activity of peptides, enzymes, hydrophobic agents and nucleic acids. Phosphodiesterase 4 inhibitor, chemokine receptor 2 antagonist, neutrophil elastase inhibitor and IKK-2 inhibitor inhibit inflammatory pathways during ARDS treatment. Some show undesirable characteristics *in vivo*, such as low stability, poor solubility and short half-life, leading to undesirable clinical outcomes [64]. Src tyrosine kinase inhibitor PP2, which is used to cure ALD, has poor solubility, which restricts its use. Dimethyl sulfoxide is used in place of the Src tyrosine kinase inhibitor PP2 to increase solubility when injecting. This nanoform increases the solubility of the drug, which has been used with self-assembled peptides (EAK16-II) in combination with 83 amino acids. This combination increases the biocompatibility of the drug, resulting in less infiltration of inflammatory cells and secretion of TNF-α, during pretreatment of ARDS [65].

Biodistribution is a vital factor during drug administration. When target modification is disregarded, NPs exhibit variable biodistribution of drugs in healthy patients compared with ARDS patients. For instance, tropism toward neutrophils makes uptake possible via opsonization. Tropism can be differentiated based on the structure of pulmonary action [66]. Murciano demonstrated the potential of a conjugated antibody and plasminogen activator to deliver the drug to the pulmonary vascular lumen [67]. Anti-PECAM/SOD and anti-ICAM/catalase nanocarriers reduced antioxidative stress and abnormal permeation of endothelial cells and increased retention time and gaseous exchange and circulation [68–73]. Enhanced mutual binding via paired antibodies fused with nanocarriers yielded more promising results [74]. Coupling polymeric filomicelles with antibodies helps retain their structure and express specific binding during targeting [75]. Ding *et al.* generated a plasminogen activator targeting PECAM-1, which exhibited specific targeting, accumulation, lysis of emboli and ease of clearance from blood [76]. The mode of interaction involved tyrosine 686 in the cytoplasmic tail of PECAM-1, which induces binding and endocytosis of nanocarriers [77].

Nucleoside-modified mRNA lipid NPs combined with antibodies, designed to interact with PECAM-1, showed potential for delivering drugs to pulmonary vesicles [78]. Kiseleva discussed the role of conformational changes during ligand binding in mechanisms underlying efficient and enhanced interaction [79]. Combining antibodies with SOD [80,81] and catalase [82] enhances binding between antibodies and cell adhesion molecules depending on size and shape [80]. Permeable membranes of porous polymersomes enable them to be used as carriers of SOD, the efficiency of which has been validated in *in vivo* models that treat neuropathic pain [83]. Filamentous, spherical and polymer nanocarriers can be used to deliver catalases and peroxidases [84–87]. Metal NPs (i.e., ferritin NPs), with a size range of 20 nm to 80 nm, enhanced targeted binding, yielding better results for ICAM-1 and PLVAP rather than for PECAM-1 via efficient internalization and reduced inflammation [44,88]. Magnetically responsive magnetite NPs delivered into endothelial cells were unharmed by protease and hydrogen peroxide [89]. Vascular immune targeting may utilize receptors, such as ACE and Thy 1.1 along with ICAM-1 and PECAM-1, as targets for antibodies, providing 20- to 50-times higher accumulation in lungs than untargeted drugs [90,91]. Anti-PECAM/SOD inhibits VCAM-1 expression as well as reactive oxygen species (ROS), such as superoxide anions, thereby exhibiting anti-inflammatory effects [92,93]. Targeting PECAM-1 with liposomes containing the SOD/catalase mimetic EUK reduces inflammation in acute disorders [94]. A study indicated that the PECAM-1 epitope determines the fate of nanocarriers fused with antibodies [91,95]. Activated carriers, such as thrombomodulin or thrombin, which promote

regulated release of drugs, are promising therapies against thrombosis and inflammation [96–98]. Oxidant-resistant thrombomodulin and thrombomodulin fused with SCFV, used to target ICAM-1, were successful in binding to its key cofactor, EPCR, which cleaved protein C, inducing anti-inflammatory and antithrombotic activities [99,100].

Hood *et al.* discussed the use of protective antioxidant carriers for endothelial targeting carriers (PACkET) to simultaneously deliver the antioxidant enzymes catalase and SOD to endothelial targets [101]. Other combinations of NPs active against oxidation and inflammation have been coupled with anti-PECAM antibodies. Tocopherol phosphate, an anti-inflammatory molecule and Mn(III) tetrakis (1-methyl-4-pyridyl) porphyrin reduced oxidative stress [102]. NADPH oxidase combined with an antibody that targeted PECM-1 successfully decreased ROS by interfering with VEGF movement and inhibiting VCAM [103].

Innovative methods for delivering drugs in ARDS treatment

In addition to drug delivery using NPs, several new approaches, including cell-hitchhiking, particle allosteric strategy, bio-inspired technology, pulmonary surfactant-based strategy and nanovaccines, have emerged.

Cell-hitchhiking drug delivery

Red blood cells (RBCs), monocytes, neutrophils and platelets travel into lung tissues during inflammation and blood circulation [104]. Limitations affecting nanocarriers, such as drugs not reaching affected parts due to being eradicated while in circulation, may be avoided by using these advanced methods to deliver drugs [105]. The excellent fluidity of RBCs in circulation enables NPs to hitchhike on RBCs to reach affected areas. NPs adsorbed on the surface of RBCs via electrostatic interactions or noncovalent adsorption, may hitchhike into lungs following intravascular injection and travel to lung endothelial cells in narrow lung tubes via mechanical extrusion, thereby increasing nanocarrier concentrations in the lungs while decreasing their side effects [106]. In one study, RBC hitchhiking increased the release of nontargeted particles into the lungs of lung cancer patients by 120-times, in comparison with traditional methods [105]. Cell-hitchhiking strategies based on neutrophils or macrophages have been used to treat acute and chronic inflammation syndromes, such as myocardial ischemia-reperfusion damage, neuroinflammation, inflammation of skeletal muscles and postoperative recurrence of malignant gliomas [64]. NPs hitchhiking on cells may be used as tools that detect delivery into lungs. Another study tagged dual polymer-layered (upconversion-PEG-polyethylenimine) NPs on human amniotic fluid stem cells for *in vivo* upconversion luminescence imaging. Imaging indicated that human amniotic fluid stem cells are better than mouse bone marrow mesenchymal stem cells (MSCs) for repairing the lung, emphasizing the usefulness of imaging-guided treatment in ARDS [107].

Pulmonary surfactant-associated drug-delivery approaches

Drug delivery deep down into the lungs is obstructed by a natural barrier composed of respiratory surfactants, a thin layer that covers the respiratory surface of lungs. Lung surfactants produced by alveolar epithelial cells become dysfunctional in ARDS [108]. Direct intrapulmonary administration encounters technical issues, caused by foaming of pulmonary surfactants during the compression process, requiring an outsized dosage. Therefore, attempts are being made to integrate pulmonary surfactant proteins with lipids, using nanotechnology [64].

Phospholipid-based nanocarriers

Phosphatidylcholine (PC), the main phospholipid in pulmonary surfactants, is used to mediate the transfer of NPs into alveoli. PEGylated PC-rich nanovesicles that target pulmonary areas remain in circulation for an extended time [109]. Abundant PC constituents combining with dipalmitoyl PC, the main constituent of pulmonary surfactants, may be the mechanism underlying this process [110].

Surfactant protein-based nanocarriers

Surfactant proteins can be used to regulate alveolar-epithelial alterations. Surfactant protein A is strongly expressed in AECII, allowing surfactant protein A antibody-functionalized immuno-liposomes to be used for lung targeting [111]. The concentration and habitation of dexamethasone in lungs were significantly enhanced. However, whole antibodies are rapidly cleared from circulation. Therefore, anti-rat surfactant protein A nanobodies with low immunogenicity and low molecular weight were investigated [112].

Particle allosteric strategies

Aerodynamics linked to the transporting of substances into the inferior airways of lungs via breathing requires the unit size of NPs to be 1–5 μm, but particles of this size are simply phagocytized by macrophages [113]. Most nanosized particles are outside this range and aggregate into large particles or are breathed out. However, small particles can achieve more efficient intracellular delivery [114]. Such paradoxical limitations on particle size hinders operative therapy for pulmonary diseases, while an allosteric approach to particle size may satisfy the specific needs of pulmonary delivery. For example, PLGA NPs that were inserted into degradable microgels with a 3.9 μm diameter and crosslinked with neutrophil elastase-sensitive peptides satisfied the aerodynamic dimensions required for deposition deep down in the lungs. Microgels were degraded by neutrophil elastase, allowing PLGA NPs to release Nexinhib20 into the airways, where they were affected by polymorphonuclear neutrophils, resulting in a significant reduction in systemic and lung inflammation signaling [115].

Nanovaccines

Nanovaccines have received considerable attention. Several nanoformulations, such as lipid NPs, liposomes, virus-like particles and protein NPs, can be used as nanovaccines [64]. With a higher surface energy and a size distribution similar to that of viruses, NPs can mimic viruses and penetrate targeted cells and trigger antiviral immune responses. Nanoformulations benefit vaccines by increasing antigen stabilization, enabling continuous antigen release via surface engineering of the nanoformulations [116]. In addition, nanovaccines enable codelivery of several adjuvants and antigens and advance targeting efficiency on antigen-presenting cells, thus stimulating the immune system and triggering vaccine reactions [117,118].

Conventional therapeutic strategies for CRDs

Conventional therapies against CRDs include antioxidant and anti-inflammatory drugs. Exposure to cigarette smoke and air pollutants stimulate ROS and reactive nitrogen species, which increase oxidative stress (OS) in the lungs, inflammation and cancer. Respirable hazardous matter, dust particles and ozone may cause cancer via a reactive oxidative mechanism [119]. Antioxidative agents, such as NAC, NRF2 activators, enzyme mimetics and spin traps, may act against OS, by regulating glutathione and NF-κB levels, which affects redox systems, chromatin remodeling machineries and proinflammatory genes, thereby reducing OS. NAC, an antioxidant drug, increases glutathione levels and significantly affects inflammatory pathways. NAC reduces cysteine levels and modulates the cellular redox system, thereby influencing canonical inflammatory signaling pathways [120]. NAC acts as a mucus-dissolving agent by disrupting crosslinking in the mucus gel, which affects overall mucus secretion, viscosity and elasticity. It prevents mucin release by bacteria and mucus oversecretion by clearing the airways. N-acystelyn and N-isobutyrylcysteine are alternatives to NAC [121]. These two, as well as the antioxidant thiol compound, reduce OS-mediated inflammatory response by acting as mucolytic agents. S-carboxymethyl cysteine, which enhances mucociliary transport and reduces mucus viscosity, is used as an oral medication against chronic bronchitis. In many clinical studies, decreasing ROS levels in lung cancer cells induced anti-inflammatory effects. It also activates, or inhibits, several signaling pathways, such as PI3-AKT and MAP-ERK1/2, which protect lung cancer cells from H_2O_2-induced cell injury [122]. Carbocysteine prevents the attachment of bacteria to the cell membrane and inhibits the progression of bacterial infections in CRDs. Erdosteine shows multifunctional properties as a mucolytic agent that reduces the viscosity and elasticity of sputum while inhibiting the attachment of bacteria to the cell wall by acting as an antibacterial agent as well [123]. It also possesses antioxidant and anti-inflammatory properties. Carbocysteine has been clinically effective against severe CRD exacerbation. Propionic acid-based fudosteine shows both mucolytic and antioxidant properties and is used against pulmonary emphysema, bronchial asthma and COPD [124]. Downregulating *MUC5AC* by inhibiting major signaling molecules, such as ERK and MAPK, has reduced mucus hypersecretion. Procysteine, another cysteine-donating compound, displays higher bioavailability than NAC. Sculforaphane is a phytochemical that detoxifies free radicals and ROS in the body. Anti-ROS and anti-inflammatory effects of phytochemicals, such as curcumin, resveratrol, catechin, terpenoids and quercetin, have been clinically studied [125].

NP-based therapy for chronic lung disease

The therapeutic success and efficacy of nanocarriers depend on their capability to control drug release. Polymeric NPs and liposomes regulate the release of a drug by slowly degrading its release or diffusing it outside the particle. A stimulus, such as a pH change, may be associated with controlled drug release, where certain polymeric NPs

containing pH-sensitive linkers may change their conformation, triggering drug release [126]. PEG-peptide-lipid conjugates are pH-responsive NPs that release drugs when cleaved by matrix metalloproteinases overexpressed in tumors [127]. External physical stimuli, such as light, heat, magnetic fields (which attract superparamagnetic iron oxide NPs) and electric fields, can be used to regulate therapeutic cargo release.

Organic and inorganic nanocarriers that target chronic lung disease have been fabricated and classified based on their characteristic dimensionalities and components into liposomes, polymeric NPs, lipid and protein NPs, dendrimers, micelles and inorganic NPs. Targeting alveolar macrophages that play an essential role in COPD pathogenesis is effective against COPD. This is achieved via negatively charged anionic liposomes that are readily taken up by macrophages [25]. Multifunctional polymeric vesicles formed by mixing PLGA and PEG can be used to deliver the COPD drugs prednisolone and theophylline [128]. Gold NP nanocarriers have successfully delivered drugs to AECs and macrophages in COPD. However, low excretion rates of metallic inorganic NPs have raised toxicity concerns [129]. Carbon black and titanium dioxide NPs have shown promise against COPD [130], and antibody-coated superparamagnetic iron oxide NPs can be used for macrophage MRI [131]. Exploring aerosol-based delivery of nano- and micro-particles for pulmonary disease treatment indicated that inhalable solid-state metformin NPs can be successfully designed and used to target COPD via AMPK and NRF2 activation (Figure 2) [132]. Administering DNA NPs to the nasal mucosa of CF patients for effective vector gene transfer for partial nasal potential difference correction was safe [133]. Delivering curcumin encapsulated in PLGA NPs exerted better therapeutic effects on CF mice [134]. Peptide-poloxamine NPs boosted both pDNA and mRNA expression *in vitro* and in CF lungs of mice, with negligible toxicity [135]. Magnetic NPs with magnetic and heat-mediated characteristics are effective as drug carriers owing to high biocompatibility and biodegradability. Magnetic NPs enhance drug delivery for CF treatment by cutting through the thick bacterial mucus layer under an external magnetic force [136]. Several multifunctional metal and metal oxide NPs, such as gold NPs and liposome-coupled multifunctional CdSe/ZnS quantum dots, have been used to deliver chemotherapeutic drugs along with fluorescence imaging in lung cancer treatment [137].

Flt1 peptide-hyaluronic acid-conjugated NPs (Flt1-HA NPs) are used to treat neutrophilic pulmonary inflammation caused by steroid resistance in asthma patients [138]. Dexa-loaded Flt1-HA NPs improved therapeutic effects in mouse eosinophilic and neutrophilic asthma models, by increasing uptake into lung tissue with prolonged accumulation time, showing potential against steroid-resistant asthma [139]. Use of soybean PC liposome-based vesicular phospholipid gel, prolonged the effect of bronchodilating drugs, such as salbutamol sulfate (Table 2) [139]. These liposomes increased salbutamol sulfate concentration and retention time within the lungs, thereby prolonging therapeutic effects that alleviated CRD-associated bronchoconstriction [140]. Methods that counter microvascular expansion and airway hyperresponsiveness are essential for controlling angiogenic inflammation in CPDs. Sn2 lipase-labile prodrug αVβ3-micelles, which are inhalable antiangiogenic drugs, enhance selectivity and minimize premature drug release [141].

Antituberculosis drugs used against pulmonary tuberculosis have a long medication cycle and display several side effects. If not cured in time, this disease will not only affect the patient but also harm public health. Realizing its severity, studies have focused on developing biodegradable zinc oxide- and silver-containing matrix metalloproteinasess, which deliver antituberculosis drugs to *Mycobacterium*-infected macrophages. Release of the NPs (i.e., silver and zinc oxide) in the macrophage endosomal system increases the efficacy of rifampicin (Table 2) [159].

Gene therapy & stem cell therapy

Gene therapy, which shows promise against chronic lung diseases that are progressive, involves identification of the defective gene, followed by vector design and delivery. Conjugating liposomes with cell-penetrating peptides increases cellular uptake by airway cells. Cationic liposomes developed for pulmonary gene delivery were effective against COPD. Adenoviral vector-based gene therapy was clinically successful against lung diseases, such as CF (Table 2) [141]. *CFTR* gene therapy has been applied against CF. Other vectors used against lung diseases include adeno-associated vectors that deliver the alpha-1 antitrypsin transgene with minimal toxicity. Lipid NP-cmRNA-based systems have been used to correct CF along with other monogenic disorders [160]. DNA-thymulin polymeric particles have been used to develop inhalable and long-lasting gene therapy that induces anti-inflammatory effects in asthma [161]. CK30PEG-DNA NPs, made of highly biocompatible poly-L-lysine and PEG and plasmid DNA, prevented lung inflammation in murine allergic asthma models [161].

Advances in stem cell research have helped develop promising COPD treatments aimed at regulating protease/antiprotease balance, inflammation, apoptosis and OS. However, the clinical application of MSCs encounters challenges, such as long-term safety concerns for COPD patients [162]. Schedules for MSC therapy remain

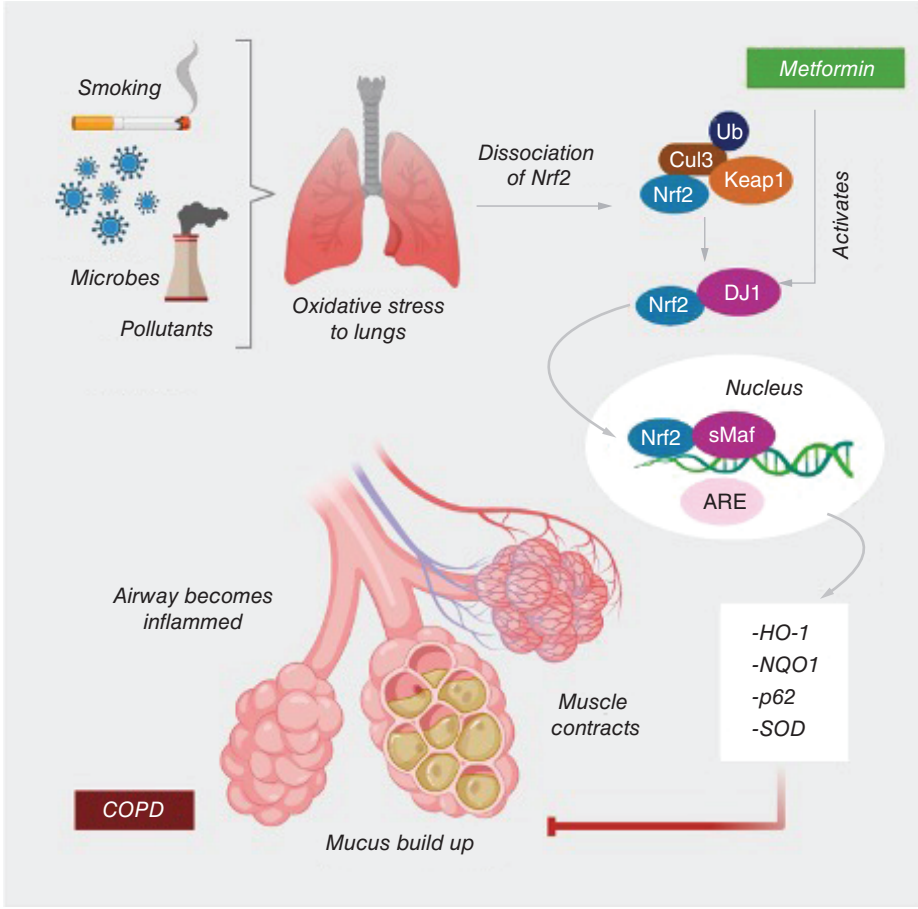

Figure 2. Inhalable solid-state metformin nanoparticles activate NRF2 and hence are able to target chronic obstructive pulmonary disease. Smoke which contains harmful chemicals, pollutants cause oxidative stress in lungs. This oxidative stress translocate NRF2 to nucleus, where NRF2 increase the expression of various antioxidant genes who protects the human body. Production of excessive mucus acts as a barrier to block the drug effect. To overcome this problem, metformin nanoparticles are used to enhance the effect of NRF2 by activating it and hence are able to treat chronic obstructive pulmonary disease.
COPD: Chronic obstructive pulmonary disease.

unclear and require additional studies to determine the appropriate dosage, route of administration and infusion rates. The grafting of the host organs and their poor survival is another challenge associated with MSCs [163]. Nevertheless, MSC therapy has shown potential against COPD, despite challenges.

Challenges in NP drug-delivery methods in investigation & cure of lung diseases

Despite recent progress in the development of multifunctional nanosystems for COPD, monitoring and assessing drug activity using nanocarriers are time consuming and costly. Major concerns in pulmonary medicine associated with NP use are toxicity, absence of high specificity and efficacy [164] and inflammation due to immune attack exerted by ultrafine low-solubility synthesized NPs and dust particles [165]. NPs exert toxicity via interaction with immune systems, OS generation and toxic effects on genomes. Genotoxicity can be quantified by performing a comet assay that detects DNA strand breaks. Even low doses of Printex 90 carbon black NPs induced genotoxicity in mice in the absence of inflammation [166]. CF patients undergoing gene therapy trials pose a risk of bacterial dissemination via bacterial colonization, which worsens infection. The latest adenovirus vectors elicited attenuated adaptive humoral responses, making readministering difficult. Recognition of features and suitable binding sites remains a challenging factor requiring further studies [61]. Other drawbacks are the labeling system that accompanies changes in pharmacokinetic properties, issues with background signals due to blood components and validation dyes, which add complexity to the drug-delivery system [167].

Table 2. Nanomedicines for the treatment of lung disease in different stages of clinical trials.

Serial number	Nanoparticle	Drug	Target disease	Development stage	Ref.
1	Liposome	Ethionamide	Pneumonia	Market	[142]
		Salbutamol	Asthma	Phase I	[143]
		MUC1	Lung cancer	Phase III	[144]
		Aerosolized PGM169 plasmid DNA encoding the *CFTR* gene	Cystic fibrosis	Phase IIb	[145]
		AM	Cystic fibrosis	Market	[146]
		Ciprofloxacin	Cystic fibrosis	Phase II	[147]
		miR-146a	Chronic obstructive pulmonary disease	Preclinical	[148]
2	Synthesized squalenyl hydrogen sulfate nanoparticles	Tobramycin	Pneumonia	Preclinical	[149]
3	Polymeric nanoparticles	Moxifloxacin	Pneumonia	Preclinical	[150]
		Isoniazid	Tuberculosis	Preclinical	[151]
		Nucleic acid	Asthma	Preclinical	[152]
		CFTR gene	Cystic fibrosis	Preclinical	[153]
		Ibuprofen	Chronic obstructive pulmonary disease	Preclinical	[145]
4	Silver nanoparticles	Inactivated influenza vaccine	Pneumonia	Preclinical	[154]
5	Zinc oxide and gold nanoparticles	Rifampicin	Tuberculosis	Preclinical	[155]
6	Nano-salbutamol sulfate	Salbutamol	Asthma	Preclinical	[156]
7	Gold nanoparticles/polymeric nanoparticles	siRNA	Lung cancer	Preclinical	[157]
8	Nonviable minicells	miRNA	Lung cancer	Phase I	[158]

Conclusion

Advances in nanotechnology have enhanced various treatment strategies aimed at lung diseases. The use of nanocarriers to deliver drugs that target lung disorders improves drug efficiency while decreasing toxicity. Effective noninvasive imaging techniques are needed to evaluate the state of chronic lung diseases and monitor drug efficacy in a cost-effective manner. Sustained delivery of drugs loaded on targeted NPs is required to control most lung diseases. NP incorporation into liposomal nanostructures has been clinically applied in both diagnostic and therapeutic combinations. More effective strategies for the treatment of various chronic and acute pulmonary diseases may be developed by combining gene and stem cell therapies.

Future perspective

Advances in nanotechnology have helped develop smart, multifunctional drug nanocarriers with surface modifications capable of targeted delivery and diagnosis. However, challenges that surface during the application of these NPs in clinical trials must be addressed. Newer nanomaterials that are rapidly cleared from lungs after deposition need to be developed while paying attention to cost/benefit ratios. Although inhalable nanomaterials are advantageous in treating respiratory illnesses, these NP therapeutic systems need to be tested via clinical trials. Most studies investigating lung clearance kinetics and mechanisms do not consider carrier compounds but only entrapped drugs. However, they may differ for different nanomaterials, which must be considered when assessing tissue accumulation, permeation and adverse side effects. To improve repeatability and patient compliance, aerosolization technologies that regulate overdosing must be improved.

Executive summary

Background

- According to WHO, lung diseases fall under the top ten major causes of death globally.
- Nanoscience involves the study of nanosized substances, procedures and tools of sizes less than 10^{-9} meter.
- Nano drug-delivery systems increase the half-life and therapeutic outcome of drugs. Nanoparticles (NPs) accumulate easily in the inflammatory sites of lungs via passive, active or physicochemical targeting strategies, significantly reducing drug side effects.

Acute lung diseases
- Acute lung diseases (ALDs) account for approximately 4 million deaths annually and are considered the biggest cause of death in children below 5 years of age.

Factors causing ALD/acute respiratory distress syndrome
- The epidemiology of ALD is influenced by community immunity, the amount of contact between individuals and age.

Chronic lung diseases
- WHO predicts that in the next decade, chronic obstructive pulmonary disease (COPD) will be the third major cause of death globally.
- Lung cancer is mostly treated via conventional methods, such as surgery, radiation, chemo drug-based therapy and targeted treatment.
- Cystic fibrosis is a life-threatening disorder caused by an aberrant change in the coding of the protein *CFTR* gene.
- Pulmonary tuberculosis patients with sputum bacterial infection are a primary source of infection and transmit the disease through airborne droplets.
- Cystic fibrosis, pulmonary tuberculosis, COPD, breathing allergies, asthma, sleep apnea syndrome, occupational lung diseases, pulmonary hypertension and lung cancer have been characterized as chronic respiratory diseases.

Design of nanocarriers targeting pulmonary epithelium
- Minimized size, maximized surface area-to-volume ratio and improved biocompatibility and biodegradability make NPs efficient drug- and gene-delivery agents.
- NP size is crucial for developing an effective delivery system.
- NP size is inversely correlated to its mobility.
- NP shape, which affects its circulation half-life, is essential for initiating phagocytosis.
- NP accumulation and circulation time is enhanced by altering the surface charge.
- Biodistribution is affected by NP surface modifications.
- Surface characteristics of NPs, such as size and shape, impact NP biodistribution.

Diagnosis & imaging of pulmonary diseases based on nanotechnology
- Nano-based theranostics involve the development of multifunctional nanocarriers that diagnose lung inflammation in real time and minimize drug side effects.
- Drug-encapsulating nanocarriers are attached to various probes for COPD theranostic treatment.

NP-based therapy for ALD
- Drugs that exert therapeutic effects on lung injury can be administered via oral administration, inhalation or intravenous injection.
- Biodistribution is a vital factor during drug administration.

Innovative methods for delivering drugs in acute respiratory distress syndrome treatment
- Cell-hitchhiking technology, bio-inspired technology, pulmonary surfactant-based strategy, particle allosteric strategy and nanovaccine drug-delivery approaches hold great potential for the effective treatment of acute respiratory distress syndrome.

Conventional therapeutic strategies for chronic respiratory diseases
- Conventional therapies against chronic respiratory diseases include antioxidant and anti-inflammatory drugs.

NP-based therapy for chronic lung disease
- Therapeutic success and efficacy of nanocarriers depend on their capability to control drug release.
- Magnetic NPs with magnetic and heat-mediated characteristics are effective as drug carriers owing to high biocompatibility and biodegradability.

Gene therapy & stem cell therapy
- Gene therapy, which shows promise against chronic lung diseases that are progressive, involves identification of the defective gene, followed by vector design and delivery.

Challenges in NP drug-delivery methods in investigation & cure of lung diseases
- Despite recent progress in the development of multifunctional nanosystems for COPD, monitoring and assessing drug activity using nanocarriers is time consuming and costly.
- NPs exert toxicity via interaction with immune systems, oxidative stress generation and toxic effects on genomes.

Conclusion
- Advances in nanotechnology have enhanced various treatment strategies aimed at lung diseases.
- Sustained delivery of drugs loaded on targeted NPs is required to control most lung diseases.

Future perspective
- Advances in nanotechnology have helped develop smart, multifunctional drug nanocarriers with surface modifications capable of targeted delivery and diagnosis.
- Most studies investigating lung clearance kinetics and mechanisms do not consider carrier compounds but only entrapped drugs.

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