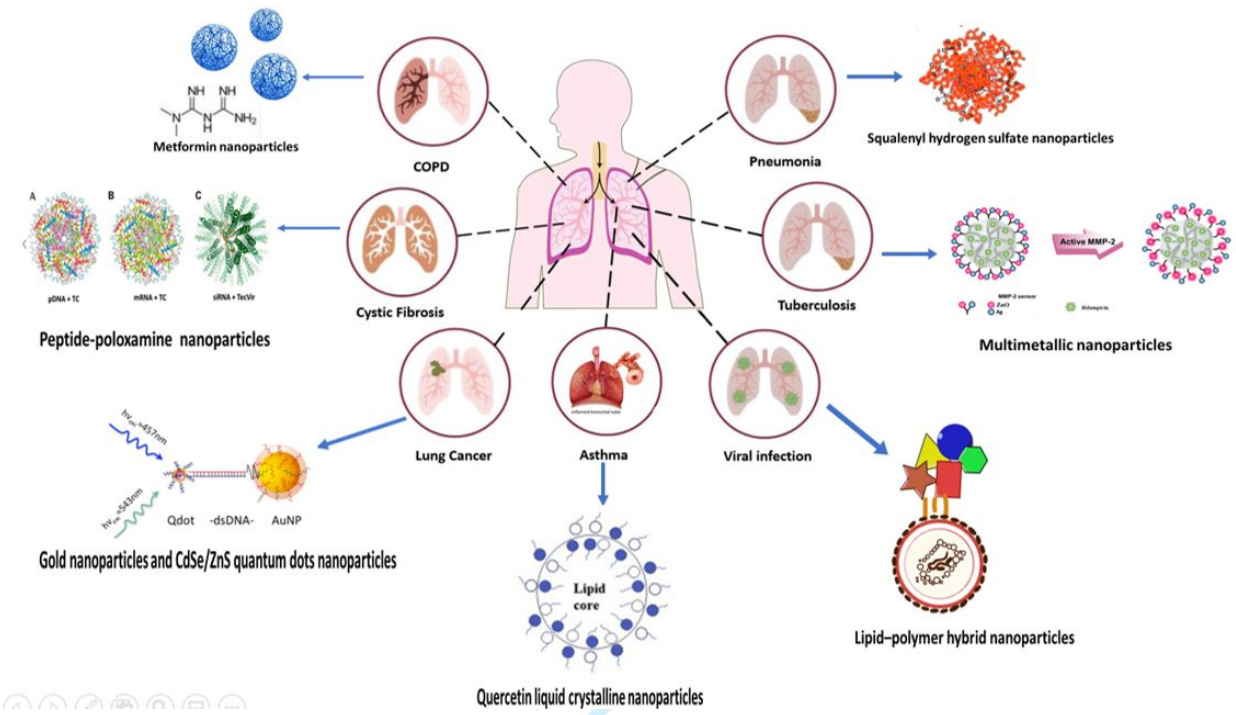
Exploring the advances in cellular and molecular targeted nanomedicines in managing acute and chronic inflammatory lung diseases: A state of art

Abstract

Lung diseases including lung cancers are the major threat to mankind health. Their treatments and diagnosis are still very challenging. The treatment and diagnostic methods that are available today shows poor reactions towards drug-resistant bacteria, chemotherapy, also show some side effects that result in toxicity in body and also show nonspecific delivery of drugs. This demands for the expansion of more and more advance methods for the cure of lung related diseases. Pneumonia, pulmonary tuberculosis, lung cancer as well as asthma require advance treatment with ease of more bioavailability of drugs through the narrow nasal passage especially during the conditions of mucosa formation. Mucosa layers causes the major challenges for drug penetration in the targeted sites. Nanotechnology provides many advantages in the field of medical science. Different nanoparticles (NPs) like lipid, carbon-based, liposome, magnetic, polymeric, metallic, protein, oxide as well as their combinations are used now to increase the targeting of drug delivery. Nanoparticles when combined with therapeutic agents called nanomedicine can provide delivery of drug at specific site with the aim of more bioavailability of drugs at the target sites. This technology overcomes many of the challenges faced by conventional chemotherapeutic strategies. This review presents the latest advancement, opportunities and challenges faced by nanomedicine drug delivery method in treatment, prevention, and diagnosis of acute and chronic lung disease.

Keywords: nanocarriers. nanomedicines. lung diseases. bio-pharmacokinetic. fluorodeoxyglucose PET. ROS. RNS. therapeutic

Graphical Abstract



Introduction

Respiratory illness is rising day by day globally. The morbidity and mortality rate continues to remain high due to lung diseases (i.e., ARDS and CRDS). While seeing the report of World Health Organization (WHO) 2016 scenario, over nine million people's deaths were reported related to lung diseases and about fifteen percent of deaths were reported through the world. Lung cancer, Chronic obstructive pulmonary disease (COPD), tuberculosis as well as infections of the lower respiratory tract are types of lung injuries that comes under the top ten major causes of death globally [1]. In past few years, although we understand the cellular and molecular pathology of acute and chronic lung diseases, but a major lag in new therapy development particularly drug delivery system still exists [2]. In accordance with the cellular and molecular understanding about lung diseases, researchers have found few advanced sites that are potential candidates for the cure of lung disease. However, in many cases translation to human therapies is limited owing to the drug delivery systems, this creates an urgent need to explore and develop new methods to cure lung diseases [3].

Nanoscience is the field where we study about nano size substances, procedures, and tools of size less than 10^-9. Nanomedicines is becoming an alluring method for targeting drug delivery of therapeutic and diagnostic compounds to cure lung diseases. It also increases the half-life of drugs, improve the bioavailability and pharmacology of drugs. Also, biodistribution of therapeutic agents increases to target organs which enhances the effectiveness of drug and minimize its toxicity [4].

Depending on the pathology of ARDS and CRDS drug delivery methods, the purpose of the article is to understand the development in nanomedicines used for the diagnosis as well as cure of lung injury in past few years and to introduce the principle value of nanocarrier drug delivery systems in future for different lung disease treatment.

Acute Lung Diseases

Acute Lung Diseases (ALD) occurs when water gets filled in the alveoli sacs of the lungs and air doesn't get space in it which cause pulmonary infiltrates, hypoxemia, and oedema [5]. ALD is the major reason of death globally and accounts for about 4 million deaths per year. Not only this, but it is the biggest reason of death for children below five years of age [6]. The most common cause of ALD are viruses and bacteria that mainly cause infection in the lower respiratory tract of lungs, which shows symptoms like common cold, laryngitis, tuberculosis, bronchitis, pharyngitis, and pneumonia [7]. The danger of ALDs is increasing in upcoming years because of the exposure of new disease related to viruses, like novel coronavirus, also known as COVID-19. Sometime, other, or previous health problems also cause acute respiratory distress syndrome (ARDS) of which COVID-19 is one of the best examples [8]. In the search of its cure recently lots of studies are in progress to understand the advancement in the epidemiology, pathogenesis, and treatment of this disease.

Factors that cause ALD/ARDS

Lung injuries which lead to ALD/ARDS are of two types, which can be either direct or remote to the lungs and also some environmental factors associated with it, which is illustrated in table 1.

Table 1. Types of risk factors that cause Acute lung injury [9].

Direct lung-injury risk factors	Indirect lung-injury risk factors	Environment related risk factors
• Pneumonia (bacterial, fungal, viral, or opportunistic) • Pulmonary contusion • Near drowning • Swine flu • Gastric content aspiration • Post lung transplantation • Injury while Inhalation	• Nonthoracic trauma or hemorrhagic shock • Major burn injury • Cardiopulmonary bypass • Reperfusion edema after lung transplantation or embolectomy • Pancreatitis • Blood product Transfusion • Sepsis (non-pulmonary source) • Overdose of drugs	• Smoking • Crowding • Cooking fuel • House make and size • Ethnicity

Treatments

Drugs that are used for the cure of lung injury, initially enters in human body via 3 ways, first through oral administration, second through inhalation and last through intravenous injections so that it can achieve the therapeutic effects. Although using these three methods of drug delivery to lungs is a good approach of therapeutic strategy, but still all these ways have several disadvantages, the reason behind it is the unique physical structure of the lungs i.e., alveolar region's large surface area, lack of preliminary metabolism etc. [3]. This forces scientist to find newer ways for delivering drug to cure lung injury. In recent years due to advancement in science and technology, Nanotechnology is becoming promising and useful platform for the identification and cure of diseases.

Nanocarriers drug delivery system is more advantageous when compared with traditional methods. They sustain for long time in blood, can load high drug, show less cytotoxicity, and also have limited immunogenicity. Nano drug delivery system (NDDS) also increase the drug's half-life and improve bio pharmacokinetic property as well as therapeutic outcome of drugs. Because of its adjustable size and surface properties, nano particles can easily deposit in the inflammatory sites of lungs through passive pathway and active pathway, or physicochemical

targeting methods. This boosts the medicine's potential as well as reduce the harmful effects of drugs [10]. Besides that, nanocarriers can also load multiple drugs at one time and thus this linkage can be developed through the pleiotropic pharmaceutical mechanisms.

Chronic Lung Diseases

Chronic disease of various parts of the lung along with the respiratory tract constitute the Chronic respiratory diseases (CRDs) which involves cystic fibrosis, asthma and respiratory allergies, chronic obstructive pulmonary disease (COPD), Pulmonary tuberculosis, occupational lung diseases, pulmonary hypertension, sleep apnea syndrome as well as lung cancer. These diseases account for 7% deaths worldwide and continue to impose considerable socioeconomic burden on societies [11]. CRDs including lung cancer are considered complex diseases whose prevention costs are less than treatment costs. To reduce CRD burden, apart from eliminating risk factors newer nanomaterial systems are being designed for improved diagnosis as well as the treatment of these diseases [12].

1. Chronic Obstructive pulmonary disease and asthma

WHO predictions say that in upcoming ten years, COPD is going to be 3rd major reason for people's death globally [13]. It has been characterized as a heterogeneous disease constituting airway and parenchymal abnormalities leading to decline in lung function [14]. This lung disease with a high mortality rate has a long refractory period and chronic cough, mucus hypersecretion and asthma are its primary clinical symptoms. COPD are of two types: chronic bronchitis and emphysema where the former is characterized by swelling, mucus overproduction and inflammation within in the secondary bronchioles. Whereas loss of function as well as structure of the lung alveoli is noticed in emphysema [15]. Commonly observed phenomenon during COPD includes heightened oxidative stress, enhanced autophagy, chronic inflammation as well as cellular senescence. The excessive mucus secretion caused by abnormal pulmonary inflammation work as a barrier to block the effective delivery of drugs. On bacterial infection this mucus barrier turns to a dense biofilm which can't be removed by any drug and results in drug resistance. Conventional therapeutic strategies targeting COPD involved the use of anti-inflammatory and antioxidant drugs that target OS such as Nrf2 activators (Figure 2), NAC (N-acetyl-L-cysteine), enzyme mimetics as well as spin traps. However, these antioxidant pharmacological strategies do not efficiently treat chronic lung disease owing to their low

diffusion rates and disrupted drug pharmacokinetics. This can be solved by the fabrication of nanocarriers with enhanced pharmacokinetics to target this chronic disease [16]. These nanocarriers ensure targeted delivery minimizing drug related toxicity by conjugation with diseased cells receptor specific ligands [17]. These nanocarriers have also been applied in stem cell-based therapies and gene therapies as efficient vectors. Asthma is another most common currently incurable CRD characterized by excess mucus production, breathlessness, aerobic function loss along with upper airway inflammation [18]. Asthma is not as lethal as COPD; however, it has deleterious effects and greater morbidity [19]. Both the above-mentioned conditions effect a person's breathing ability, turning to long-term disability which significantly impairs the patient's quality of life.

2. Lung cancer

It is the major reason of mortality among men across the globe. Majorly this chronic disease is caused owing to excessive smoking, use of tobacco products, air pollution exposures, radon gas, asbestos etc. Lung cancer are majorly of two types small-cell lung carcinomas (SCLC) and non-small cell lung carcinomas (NSCLC) [20]. Lung cancer is most often treated by conventional methods such as surgery, radiation, chemodrugs based therapy, and targeted treatment. Type as well as stage of cancer are the main determining factors in deciding on the therapeutic strategy. Despite several advances in the field of cancer, prognosis for lung cancer patients remains challenging. The response to current treatment regime remains poor except for the frequently localized cancers. The chemotherapy-based strategies and histology have helped manage advanced lung cancers. With the discovery of novel biomarkers newer opportunities have opened in the field of targeted therapy and immune based therapy. Proper staging of the disease is majorly required to investigate lung cancer and choose the adequate therapy strategy. Imaging methods such as fluorodeoxyglucose PET (FDG-PET) scans and MRI have been employed to distinguish the patients for curative treatment [21]. However, a substantial challenge faced by cancer patients is accessing them at affordable amounts due to the high cost of the drugs.

1. Cystic fibrosis

Cystic fibrosis is caused by an aberrant change in the coding of the gene for protein cystic fibrosis transmembrane conductance regulator (CFTR) which leads to cystic fibrosis [22]. It affects several organs such as the lungs, pancreas, intestine, upper airways, liver, and

reproductive organs. It is a life-threatening disorder having an autosomal recessive inheritance pattern. The aberrant function of the chloride channels presents in exocrine glands, specifically of the CFTR protein is a major cause for cystic fibrosis [23]. In individual cases the disease sensitivity depends upon variable organ sensitivity as well as on the residual function of the CFTR protein which is genetically determined. Pancreatic insufficiency a symptom of cystic fibrosis is majorly characterized by abdominal symptoms, large, fat content, shiny, unpleasant smell, pulpy stools, and deficiency of fat-soluble vitamins. Treatment strategy involves improvement in mucociliary clearance along with active treatment of lungs, exercise and facilitate expectoration therapies to prevent the chronic infections within the body.

2. Pulmonary tuberculosis

It is another class of CRDS which primarily affects the lungs. This disease condition develops at a very slow rate almost without any symptoms at initial stages. It is one of the harmful airborne diseases, which is caused by Mycobacterium tuberculosis and the major health concerns in worldwide. Patients with pulmonary tuberculosis additionally with sputum bacterial infection can become a primary source of infection and transmit the disease through droplets that passes in the air [94]. Low grade fever at the onset which gradually becomes prominent as the diseases progresses is the major constitutional symptom associated with pulmonary tuberculosis. The only existing study that suggests the diagnosis of tuberculosis is the chest radiograph which is different in primary compared to reactivation tuberculosis. The development of pneumothorax condition might require severe attention to the disease condition [24] where the cavity connecting the tracheobronchial tree with the pleural space gets ruptured creating a bronchopleural fistula. Another complication involves the development of bleb owing to the air trapping in the acinus segment leading to a submucosal bronchiolar lesion development causing major problems such as tuberculosis infection along with secondary invaders [25].

Design of Nanocarriers

The formulation and deposition difficulties in developing inhalable drugs are addressed using nanoparticles which penetrate the alveolar regions deep into the lungs. Owing to their minimized size and maximized surface area to volume ratio, improved biocompatibility, along with

biodegradability, nanoparticles offer efficient drug and gene delivery [26]. Development of nanocarriers carrying drugs efficiently treat chronic lung diseases by overcoming airway defenses along with targeted and controlled drug release. At the same time, Nanoparticles can also be used to deliver a combination of two drugs resulting in longer and enhanced drug effects. Nanodrug delivery pose several advantages including reduced loss of drug due to degradation, evade macrophage clearance, enhanced accumulation of drug at diseased site, possibility of developing inhalable formulations: and ease of delivery as well as specific cell targeted delivery [27].

1. Size:

Various drugs can be captured within the nanoparticles depending on their size, ranging between 10 nm to 200 nm, through different covalent and electrostatic interactions. Both charge and size of the nanoparticle determine their mucociliary clearance. Particles smaller than 10 nm get eliminated by the reticuloendothelial system (RES) while particles larger than 100 nm are targeted by the alveolar macrophages. Hence for developing an effective delivery system nanoparticle size is crucial. Nanoparticles face a major challenge of penetrating the thick viscoelastic mucus layer [28]. Studies have reported an inverse correlation between size and mobility of the nanoparticle [29]. Several nanoparticle types have been developed such as soft organic particles like liposomes and polymeric nanoparticles and more recently hard inorganic-based nanocarriers such as carbon nanotubes, dendrimers, micelles etc., in order to match compatibility of the drug to the nanoparticle. The surface modifications and the material used to make the nanoparticles determine nanoparticle properties and drug release characteristics [30].

2. Shape and surface charge:

It has also been observed that particle geometry also influences cellular uptake and particle fate. The discoidal particles exhibit better vessel wall interaction and migration dynamics compared to spherical particles [31]. Another study reported nanoparticle shape to play essential role in initiating phagocytosis effecting its circulation half-life [32]. The aspect ratio and nanoparticle curvature has been found to impact the nanoparticle uptake and hence particles with minimal curvature areas such as cylindrical, ellipsoidal, and discoid particles show enhanced therapeutic accumulation [33]. Various studies have proven that the nanoparticle accumulation and the circulation time can be enhanced by changing the surface charge. Neutral and negatively charged

nanoparticles do not get absorbed by serum proteins hence having an elongated circulation half-life while nanoparticles with a positive charge exhibit proton sponge effect facilitating endosomal release that hinders degradation of drugs, though are taken up non-specifically by all cells. Hence it is important to develop nanoparticles that can switch from negative to positive once they arrive at the target site for efficient drug delivery [34].

3. Surface Modifications:

The biodistribution is also affected by nanoparticles surface modifications for instance it has been observed that hydrophobic nanoparticles undergo rapid clearance without surface modifications [35]. Hence coating the nanoparticles with polyethylene glycol (PEG) and other hydrophilic polymers the circulation time of the particles in the blood as well as mucous penetration can be increased. Stealth coating to increase bioavailability of nanoparticles can help reduce their phagocytosis [36]. Moreover, certain biological fluids also result in altered nanoparticle properties by forming a protein corona [37]. It has been demonstrated that surfactant lipids and proteins play essential role in determining nanoparticle clearance by macrophages and hence lung surfactant phospholipid coating on inhalable nanoparticles increase their cellular uptake while decreasing the toxicity [38]. It is now possible to prepare liposomes from lung surfactants and hence have been widely used for delivery to the lungs.

Diagnosis and imaging based on nanotechnology

Nanoparticles improve pulmonary MR and x-ray diagnostics along with good biocompatibility, without effecting cell cycle, cell viability, cell morphology, and apoptosis. In COPD research studies CT and MRI have been used to provide complementary visual quantitative information of the disease providing considerable insights of COPD pathophysiology. Though CT provide high spatial resolution measurements of the lung structure they pose long-term risks for the patients. MRI proved to be an excellent alternating providing COPD lung structure insights without radiation exposure [14]. Therapies are becoming more individualized hence the need to develop better imaging techniques to quantify the treatment response. Recently theranostic advancements have been applied to treat chronic inflammatory lung diseases which involve combining diagnostic and therapeutic procedures in a single system. Nano-based theranostics involve

developing multifunctional nanocarriers which offer lung inflammation real-time diagnosis minimizing drug side effects. Multifunctional core-shell such as the magnetic iron oxide nanoparticle has been used to deliver MRI contrast agent as well as the hydrophobic drug enabling lung diseases theranostic treatment [39]. However, they lead to chronic inflammation and toxicity and are limited applications in chronic airway diseases. Liposomes have been used to develop theranostic hybrids encapsulating quantum dots and multiple drugs [40]. Moreover, various amphiphilic copolymers can form nano-assemblies like vesicles and micelle in aqueous solution that can deliver curative agents offering advantage of controllable biological, physical, and chemical properties. For COPD theranostic treatment drug encapsulating nanocarriers are attached with various probes. For instance, the PLGA-PEG polymeric vesicles have been applied theranostically in obstructive lung diseases for delivering COPD drugs with molecular probes. real-time imaging technologies are cheaper than clinical procedures like biopsy and bronchoscopy etc. Single photon emission computed tomography (SPECT) along with positron emission tomography (PET) help in the real time assessment of the disease by detection of radiolabeled tracers like FDG which accumulates at the site of inflammation. Thus, work on developing molecular probes may help us understand the pathogenesis of the disease better making targeted therapy possible [41]. A characteristic symptom associated with CF is high sweat chloride content hence its quantification is crucial for cystic fibrosis screening. Therefore, during preliminary screening of cystic fibrosis chloride ion concentration can be detected with silver nanoparticle modified electrodes. Another method used for tuberculosis diagnosis and detection is the conventional gold standard method which is disadvantageous as it is expensive with low sensitivity. To solve this problem researchers have developed the advance methods for high-throughput diagnosis that involves nanotechnology-based ideas to diagnose tuberculosis. One such method is nanodisk mass spectroscopy. Biomarkers play a key role in diagnosis of chronic diseases. Few such markers for tuberculosis are Culture filtrate protein 10 kDa (CFP-10) and 6 kDa early secretory antigenic target (ESAT-6) are one of the key biomarkers to diagnose chronic tuberculosis. Nanodisk mass spectrometry assay uses the silica NPs and merges the ESAT-6 and CFP-10 antibodies which can provide sensitive multiple quantitative analysis of ESAT-6 and CFP-10 biomarkers on patients with chronic tuberculosis cases. Sensitive and specific classification of Mtb is required for its rapid determination. CFP-10 and ESAT-6

biomarkers even at low concentration can be quantified. This test method can not only assess the severity of an active tuberculosis infection, but also the therapeutic effect [93].

Nanoparticle based therapy for acute lung disease

There are many types of nanocarriers which shows different features in delivering the drug to human body especially for enhancing stability, solubility and activity of peptides, enzymes, hydrophobic agent and nucleic acids. Phosphodiesterase 4 (PDE4) inhibitor, chemokines receptor 2 antagonist neutrophil elastase inhibitor and IKK-2 inhibitor, inhibit the inflammatory pathways during ARDS treatment. Some of these shows undesirable characteristics like low stability, poor solubility, and short half-life in In-vivo experiments which leads to undesirable clinical outcomes [42]. Talking about Src tyrosine kinase inhibitor (PP2) which is used for the cure of ALD, has poor solubility which restrict its use for the same. In the place of Src tyrosine kinase inhibitor (PP2), a toxic organic solvent, dimethyl sulfoxide, is used which increases the solubility for injection. This nanoform increased the solubility of drug which is employed with self-assembled peptides (EAK16-II) in combination of 83 amino acids. This combination increases the biocompatibility of drug and shows less infiltrate of inflammatory cells and secrete TNF-a in pretreatment for ARDS [43].

While administering drugs to the patients its bio-distribution is one of the most important parameters, one should consider. Studies shows that drug bio-distribution is greatly varied using nanocarriers. Nanoparticles without accounting for target modification show varied bio-distribution of drugs in healthy in comparison to ARDS patients. For instance, Cationic liposomes accumulate 1.54-fold times in inflamed lungs in comparison to healthy ones and β-cyclodextrin nanoparticles accumulation mounted to about 1.3-fold (**Figure 1**). Also, DOTAP was observed to generate up to double accumulation in inflamed lung tissues [44].

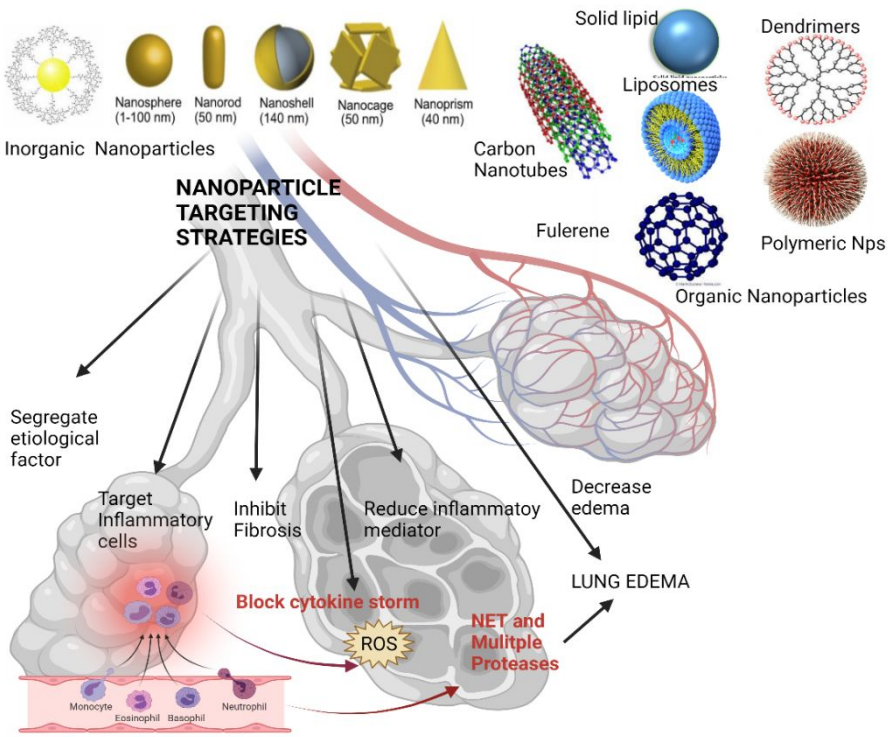


Figure 1. **Nanoparticle based therapy for acute lung disease**: Nanoparticles can be used to target inflammation because of lung injury by inhibition of inflammatory cells, decreasing inflammatory mediators, blocking cytokines and recovering the air–blood barrier.

Innovative methods for delivering drugs in ARDS treatment

In addition to common strategy of drug delivery of nanoparticles, several additional new approaches have emerged, including cell-hitchhiking technology, particle allosteric strategy, bio-inspired technology, pulmonary surfactant-based strategy as well as nanovaccines.

1. Cell-hitchhiking drug delivery system

Several circulating cells, such as red blood cells (RBCs), monocytes, neutrophils, and platelets, can travel into lung tissue during pathological as well as physiological processes like inflammation and blood circulation [45]. By exploiting these features, many advanced methods for delivering drugs are extensively utilized, that resolve the limitation of nanocarriers because of which mostly drugs will be eradicated in the circulation and possibly will not reach to the extent of the affected part [46]. RBCs, due to their excellent fluidity in circulation, can aid like a

convenient platform for hitch-hiking the nanoparticles to the affected area. For instance, using the surface of erythrocytes (RBC), the nanoparticles can be adsorbed on it by electrostatic interactions or non-covalent adsorption, hitch-hiking into the lungs after intravascular injection, and transferred to the lung endothelial cells in narrow lung tubes by mechanical extrusion, thereby the concentration of the nanocarriers has been increased in the lungs while decreasing the possible side effects [47]. One study used RBC hitchhiking strategies for curing lung cancer, which increased the release of non-targeted particles into the lungs by w120-times, as compared to the traditional ones [46]. Cell hitchhiking strategies based on neutrophils or macrophages have been used for acute as well as chronic inflammation to treat several syndromes such as myocardial ischemia-reperfusion damage, neuro-inflammation, inflammation of skeletal muscle, and post-operative recurrence of malignant gliomas [42]. Hitchhiking cells could also use nanoparticles as a tool to detect the delivery into the pulmonary. In another study, Dual polymer layered (UCNP-PEG-PEI) nanoparticles were tagged on human-amniotic fluid stem cells for in vivo up conversion luminescence imaging. Imaging has shown the human amniotic fluid-stem cells achieved well than mouse bone marrow-mesenchymal stem cells for repairing lung, emphasizing a favorable skill for imaging-guided treatment in ARDS [48].

2. Bio-mimetic method for delivering drugs

Cell membrane or Extra-cellular vehicles - based drug delivering approaches embrace high strength for combating inflammation with several advantages in refining biocompatibility, counteracting endotoxins / viruses, or inflammatory products, applying targeting properties, and controlling the immune system.

2.1. Membrane-based nano-formulations:

In recent years, instead of an additional adornment of targeting agents, a more innovative bio-mimetic strategy based on cell membranes has emerged, which is very promising in combating various diseases. Bio-mimetic strategies based on macrophage membranes are attractive for anti-inflammatory treatment [42]. Nano-iron oxide clusters camouflaged by the macrophage membrane can preserve the TLR4 as well as CD14 receptors inherited from the mother membrane and can arrest and deactivate the LPS, which might initiate the inflammation [49]. The magnetic iron-oxide core having positive charge can stabilize the tissue covering structure, adsorb, and detach the negatively charged LPS and nullify various pro-inflammatory cytokines.

Hence, this bio-mimetic nanoparticle apparently enhanced the lung morphology, comprising alveolar hemorrhage and pulmonary edema, upturned inflammation induced infiltration, and decreased mortality [42].

2.2. EV-based nano-formulations:

Extra-cellular vehicles (EVs) are nano-sized vesicles surrounded through a lipid membrane, which are secreted by various cells, and which can facilitate inter-cellular communication by releasing biological components like proteins, mRNA, lipids, and miRNA [50]. EVs contribute to several serious pathological and physiological processes by controlling the immune system in addition with mediating tissue regeneration. Numerous kinds of EVs are used as bio-active drug carriage for treating ARDS due to their precise aiming and transmission of various biological charges [51].

2.2.1. Mesenchymal stem cells-derived EVs:

Owing to the non-cellular structure with compact size and inherited functional properties, MSCs-derived EVs has shown beneficial characteristics over MSC in numerous cases, like reducing the chance of iatrogenic tumor development and improving pharmaco-kinetics in circulation. MSCs-EVs have been obtained from various stem cells from human/mouse tissues like umbilical cord blood, bone marrow, and adipose tissue and their healing properties have been investigated in pre-clinical as well as in clinical studies for ARDS. In addition to targeting the immune cells to apply immune-regulatory results, MSCs-EVs can connect with several lung cells, comprising endothelial cells or pulmonary epithelial to regulate lung permeability and repair damaged tissue [52].

1.1.1. Platelet-EVs:

Although activated platelets can aid as pro-inflammatory cells to worsen pneumonia and damage in ARDS development, it has been illustrated that platelet-derived extra-cellular vesicles (PEVs) do not intensify the inflammation in the inflamed areas. The bio-engineered PEVs enhanced the pulmonary release of TPCA-1, expressively inhibit the lung inflammatory cells infiltration, and block cytokines. The PEVs showed a 3.6-times increase in the lung buildup in ARDS mice as compared to the control mice, probably because of platelets intrinsic affinity for inflammation sites via receptor patterns like glycoproteins, P-selectin, and CD40L [53].

2. Pulmonary surfactant-associated drug delivery approaches

While drug delivery deep down into the lungs, it is difficult for breaking the natural barrier made up of respiratory surfactants, a skinny, thin layer that covers the respirational surface of the lungs. Lung surfactants can be produced by the AEC and their dys-functioning has been recognized in ARDS [54]. Technical problems have been encountered with direct intrapulmonary administration because pulmonary surfactant tends to foam during the compression process when an outsized dosage is required. Various attempts have been used by integrating pulmonary surfactant proteins and lipids to solve these complications based on nanotechnology [42].

2.1. Phospholipids-based nanocarriers:

Phospholipids, the chief constituents of pulmonary surfactants consider phosphatidylcholine (PC) to be its main lipid which has been used to mediate the transfer of nanoparticles into the alveoli. PEGylated PC-rich nano-vesicles can targets the pulmonary areas and remain in circulation movement for extended time [55]. The directing mechanism could be because of the richness of PC constituents that could interrelate intensely with dipalmitoyl phosphatidylcholine (DPPC), the main constituent of pulmonary surfactants [56].

2.2. Surfactant protein-based nanocarriers:

The surfactant proteins could be exploited for alveolar-epithelial directing alteration. SP-A is strongly and precisely expressed in AECII. This allows SP-A antibody-functionalized immune-liposomes to be used for specifically lung targeting [57]. As a result, the concentration and habitation period of dexamethasone enhanced significantly in the lungs. Though, the whole antibody can lead to speedy clearing from the circulation. Therefore, rSPANb (anti-rat SP-A nanobody) with less immunogenicity and low molecular weight was additionally investigated [58].

3. Particle allosteric strategies

For delivering nanoparticles in the lungs, an aerodynamic unit size of 1–5µm is necessary for breathing to transport the substances into the inferior airways, while particles with 1–5µm size are simply phagocytized by macrophages [59]. Most of the nano-sized particles are outside of

this dimension range and may aggregate into large-sized particles or get to be breathe out. Though, small-sized particles can attain more efficient intra-cellular delivery [60]. These paradoxical limitations on the size of the particle can hinder the operative therapy for pulmonary diseases, and the allosteric approach of particle size shows promise to meet the specific needs of pulmonary delivery. For example, PLGA nanoparticles were inserted in degradable micro-gels that were crosslinked by neutrophil elastase-sensitive peptides. With 3.9µm diameter, the micro-gels attained an adequate aerodynamic dimension for deep down lung deposition. The micro-gels were degraded by NE, where upon the PLGA nanoparticles caused the release of Nexinhib20 into the airways and were affected by polymorpho-nuclear neutrophils, resulting in a significant reduction in systemic and lung inflammation signaling [61].

4. Nanovaccines

In recent times, nanovaccines have received a lot of attention. Several nano-formulations such as lipid nanoparticles, liposomes, virus-like particles, and protein nanoparticles can be potentially used for nanovaccine formulation [42]. With higher surface energy and a size distribution alike to that of viruses, the nanoparticles can mimic the viruses to penetrate into the targeted cells and can trigger anti-viral immune responses. Nano-formulations could offer benefits to vaccines like, increasing antigen stabilization, enabling continuous antigen release, and the targeted release by surface engineering [62]. In addition, nanovaccines could attain the co-delivery of several adjuvants and antigens, advance targeting efficiency on APC, thus assisting the stimulation of the innate as well as adaptive immune system and triggering efficient vaccine reactions [63, 64].

Conventional therapeutic strategies for CRDS

Therapies based on conventional methods for the treatment of CRDs are based on antioxidant and anti-inflammatory drugs. The exposure to cigarette smoke and air pollutant causes the stimulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) endogenously which contribute to the oxidative stress (OS) in lungs, inflammation, and cancer. The major cause for lung cancer through reactive oxidative mechanism are often respirable hazardous matter, dust particles and ozone [65]. Anti-oxidative agents such as N-acetyl-L-cysteine (NAC), Nrf2 activators, enzyme mimetics and spin traps have been proposed to act against the oxidative

stress. These majorly controls the level of glutathione production (GSH) and NFK-B thereby affecting the redox system, chromatin remodeling machinery, activation of pro-inflammatory genes, thereby reducing the oxidative stress. NAC is an antioxidant drug that increases the GSH levels and majorly affects the pathways participating in inflammation. NAC has been reported to reduce cysteine levels and modulates the redox system in cells thereby influencing the canonical inflammatory signaling pathways [66]. NAC has additionally been reported to act as a mucus dissolving agent by breaking the crosslinking activity of mucus gel which affects the overall mucus secretion, viscosity, and elasticity. It also has been reported to prevent the mucin released by bacteria and over secretion of mucus by clearing the airway. The alternatives used for NAC are N-acystelynn (NAL) and N-isobutyrylcysteine (NIC) [67]. Two of them have the function in reducing the oxidative stress mediated inflammatory response by acting as mucolytic agents as well as an antioxidant thiol compound. S-carboxymethyl cysteine (S-CMC) are used as oral medicines for chronic bronchitis patients which enhances the mucocilliary transport and reduced mucus viscosity. Many clinical studies have showed the anti-inflammatory and Decreased ROS effects in lung cancer cells. It has also reported to activate or inhibit several signaling pathways such as PI3-AKT, MAP-ERK1/2 which prevent the lung cancer cells from H2O2 induced cell injury [68]. Carbocysteine prevents the attachment of bacteria to the cell membrane and thus has a role in inhibiting the progression of bacterial infections in CRDS. Erdosteine has multifunctional properties such as mucolytic agent which reduces the viscosity and Elasticity of sputum. It also inhibits the attachment of bacteria to the cell wall by acting as an antibacterial agent [69]. It also has antioxidant and anti-inflammatory properties. Many clinical studies have shown the effectiveness of carbocysteine against severe CRDS exacerbations. A propionic acid based fudosteine acquires both mucolytic and antioxidant properties and is majorly used for the treatment of pulmonary Emphysema, bronchial asthma and COPD[70] .Studies showed the down-regulation of MUC5ACgene by inhibiting major signaling molecules such as ERK, MAPK and thus reduce hypersecretion of mucus. Procysteineis another cysteine donating compound which has higher bioavailability than NAC. Sculforaphaneis a phytochemical that potentially detoxifies the free radicals, ROS in the body. Many other phytochemicals such as curcumin, resveratrol, catechin, terpenoids, quercetin has been clinically studies for their anti-ROS and anti-inflammatory studies [71].

Nanoparticle based therapy for chronic lung disease

Nanocarriers are capable of controlled release of the drug increasing its efficiency essential for therapeutic success. The polymeric nanoparticles and liposomes do so either by slowly degrading releasing the drug or by diffusing the drug outside the particle. Sometimes a stimulus leads to controlled drug release for instance in response to pH changes certain polymeric nanoparticles containing pH sensitive linkers change their conformation triggering the release of drugs[72]. The PEG-Peptide-Lipid conjugates are pH-responsive nanoparticles that release the drug when cleaved by the matrix metalloproteinases (MMPs) overexpressed in tumors[73]. Certain external physical stimuli like light, heat, magnetic field, and electric field can be used to control therapeutic cargo release such as physical stimuli magnetic field attracts super-paramagnetic iron oxide nanoparticles towards it.

Organic as well as inorganic nanocarriers have been fabricated for chronic lung disease targeting and have been classified based on their characteristic dimensionalities and components into liposomes, polymeric nanoparticles, lipid and protein nanoparticles, dendrimers, micelles, and inorganic nanoparticles. Targeting of alveolar macrophages can be an effective approach in **COPD** patients as they play essential role in COPD pathogenesis. This is achieved by negatively charged anionic liposomes that are readily taken up by macrophages [17]. A study showed the use of multifunctional polymeric vesicle formed by mixing PLGA and polyethylene glycol efficient in delivering COPD drugs prednisolone and theophylline[74]. Another study reported AuNP nanocarriers to be capable of successfully delivering drugs to the alveolar epithelial cells and the macrophages in COPD. Despite the advantage using metallic inorganic nanoparticles poses toxicity concerns due to their low excretion rates[75]. Carbon black nanoparticles and Titanium dioxide nanoparticles have been demonstrated to be a promising approach for COPD treatment[76] as well as antibody coated superparamagnetic iron oxide nanoparticles (SPIONs) could be used for macrophage MRI [77]. In a recent study researchers studied aerosol delivery of nano and micro particles for pulmonary disease treatment and found that inhalable solid-state metformin nanoparticles can be successfully designed and used for targeting COPD by AMPK and Nrf2 activation (Figure 2) [113].

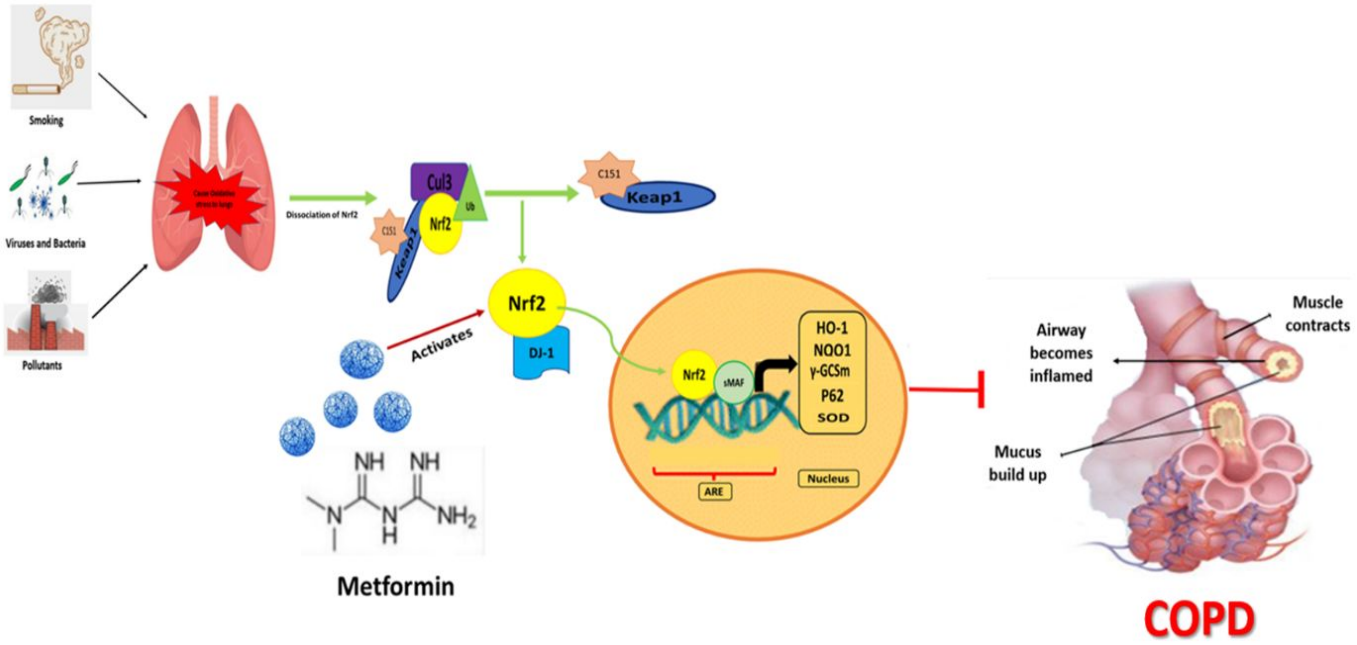


Figure 2. **Inhalable solid-state metformin nanoparticles activate Nrf2 and hence able to target COPD:** Smoke, pollutants and attack of bacteria and viruses cause Oxidative stress in lungs result in dissociation of Keap 1 from Nrf2, this stabilize and translocate Nrf2 to nucleus, where Nrf2 increase the expression of various antioxidant genes who protects the human body. Production of excessive mucus act as a barrier to block drug effect. To overcome this problem metformin nanoparticle is used to enhance the effect of Nrf2 by activating it and hence able to treat COPD.

A study on **Cystic Fibrosis** Subjects reported DNA nanoparticles administration to the patient's nasal mucosa, for effective vector gene transfer as well as partial Nasal Potential Difference correction, to be safe [78]. Curcumin has been found to have better therapeutic effects on CF mice when delivered encapsulated in PLGA nanoparticles [79]. Peptide-poloxamine nanoparticles have been found to boost both plasmid DNA and messenger RNA expression with negligible toxicity both *in vitro* and also in the cystic fibrosis lungs of mice [80]. Magnetic nanoparticles (MNPs) with their magnetic and heat-mediated characteristics have been proven to be favorable drug carriers owing to their high biocompatibility and biodegradability. MNPS enhance Drug delivery in CF treatment by cutting through the thick bacterial mucus layer in an

external magnetic force [81]. Several multifunctional metal and metal oxide nanoparticles have been applied in lung cancer treatment such as gold nanoparticles, liposome coupled multifunctional CdSe/ZnS quantum dots, for the delivery of chemotherapeutic drugs along with fluorescence imaging [82].

Flt1 peptide-hyaluronic acid conjugated nanoparticles (Flt1-HA NPs) have been used to treat neutrophilic pulmonary inflammation which indicates steroid resistance in **Asthma** patients [83] in which biodegradable HA interfaces with lung HA receptors and Flt1 peptide regulates neutrophilic inflammation. In eosinophilic and neutrophilic asthma mice models, Dexa-loaded Flt1-HA NPs show improved therapeutic effects with enhanced uptake into the lung tissue with prolonged accumulation time hence can be effective in treating steroid-resistant asthma [83]. Researchers have also demonstrated the possibility of prolonging the effect of broncho dilating drugs such as salbutamol sulfate (SBS) using soybean phosphatidylcholine (PC) liposomes forming vesicular phospholipid gel (VPG) shown in table 2 [84]. These liposomes increase the SBS concentration and retention time within the lungs thereby resulting in prolonged therapeutic effects alleviating CRD associated bronchoconstriction [85]. To control angiogenic inflammation of CPDs it is essential to develop methods to counter microvascular expansion and airway hyperresponsiveness. Sn2 lipase-labile prodrug αVβ3-micelles which are Inhalable antiangiogenic drugs have been developed to enhance selectivity minimizing premature drug release [86]. αVβ3-peptidomimetic homing ligand (αVβ3-PEG2000-PE) attached to the micelles are used to target the αVβ3 integrins receptors overexpressed on the lung epithelial cell membranes in asthma patients resulting in ameliorated asthma symptoms.

The medicine use for the treatment of **pulmonary tuberculosis** is called antituberculosis drugs have long medication cycle as well as show several side effects too. This disease is too harmful that if it is not cure at the right time, it will not only affect the patient health but also harm the public health. Seeing the severity of the situation, latest research focused on the development of ZnO and Ag containing multimetallic nanoparticles (MMP) which are biodegradable and deliver antituberculosis drug to Mycobacterium infected macrophages. Not only this, but the release of the nanoparticles (i.e., Ag and ZnO) in macrophages endosomal system increase the efficacy of rifampicin shown in table 2 [92].

Table 2. Nanomedicines for treatment of lung disease in the different stages of Clinical Trials

S. No.	Nanoparticle	Drug	Target Disease	Development stage	References
1.	Liposome	AM	Pneumonia	Market	[95]
		Salbutamol	Asthma	phase I	[101]
		MUC1	Lung cancer	phase III	[106]
		Aerosolized PGM169 plasmid DNA encoding the cystic fibrosis transmembrane conductance regulator gene	Cystic Fibrosis	phase IIb	[108]
		AM	Cystic Fibrosis	Market	[109]
		Ciprofloxacin	Cystic Fibrosis	Phase II	[110]
		miR-146a	Chronic obstructive pulmonary disease	Pre-clinical	[112]
2.	Synthesized squalenyl hydrogen sulfate Nano Particles	Tobramycin	Pneumonia	Pre-clinical	[96]
3.	Polymeric nanoparticles	Moxifloxacin (MXF)	Pneumonia	Pre-clinical	[97]
		Isoniazid	TB	Pre-clinical	[100]
		Nucleic acid	Asthma	Pre-clinical	[102]
		Gene encoding cystic fibrosis transmembrane conductance regulator	Cystic Fibrosis	Pre-clinical	[107]
		Ibuprofen	Chronic obstructive pulmonary disease	Pre-clinical	[111]

4.	Ag nanoparticles	Inactivated influenza vaccine	Pneumonia	Pre-clinical	[98]
5.	ZnO and Ag NPs	Rifampicin	Tuberculosis	Pre-clinical	[99]
6.	Nano-SBS	Salbutamol	Asthma	Pre-clinical	[103]
7.	Gold Nano Particles/ Polymeric NPs	Small interfering RNA	Lung cancer	Pre-clinical	[104]
8.	Non-viable minicells	Micro RNA	Lung cancer	phase I	[105]

Gene therapy and Stem cell therapy

To treat chronic lung diseases which are progressive in nature, gene therapy has proven to be a very promising strategy. The process includes identification of the defective gene followed by vector design and then delivery. Nanoparticle vectors have been observed to significantly increase the transgene expression in the lungs. On conjugating liposomes with cell penetrating peptides an increased cellular uptake to airway cells has been documented. Another attractive approach to treat COPD is the development of cationic liposomes for pulmonary gene delivery. Adenoviral vector-based gene therapy has proven to be successful therapeutic strategies for various lung diseases such as CF shown in clinical trials demonstrated in table 2 [86]. Delivery of CFTR cystic fibrosis transmembrane conductance regulator, gene therapy has been applied to CF patients. Other promising vectors applied to lung disease include AAVs (adeno-associated vectors) which deliver AAT transgene with minimum toxicity. LNP-cmRNA-based systems have been employed successfully for correction of cystic fibrosis long with other monogenic disorders [87]. Moreover, DNA-thymulin polymeric particles have been applied for the development of inhalable long-lasting gene therapy that induces anti-inflammatory effects in Asthma [88]. CK30PEG-DNA NPs are made of highly biocompatible poly-L-lysine and polyethylene glycol (CK30PEG) and plasmid DNA and have been found to prevent lung inflammation in the lungs of the allergic asthma murine model.

Advances in the stem cell research have led to the development of a promising COPD treatment strategy involving modulation of protease/anti-protease balance, inflammation, apoptosis, and

oxidative stress. However, clinical applications of MSCs faces challenges such as the long-term safety concerns in COPD patients [89]. Moreover, therapeutic schedule in MSC therapy remains unclear and additional studies need to be performed to specify the appropriate dosage, route of administration as well as the infusion rate. The difficulty of engraftment in host organs and their poor survival is another challenge associated with MSCs [90]. Nevertheless, MSC therapy has been proven to be a promising approach for COPD therapy despite all challenges.

Challenges in NP drug delivery methods in investigation and cure of lung diseases:

Despite the recent progress in development of multifunctional nano systems for COPD, monitoring and accessing drug activity using nanocarriers are time consuming and costly. A major concern in pulmonary medicine associated with nanoparticle use is the toxicity exerted by ultrafine low solubility synthesized nanoparticles as well as natural dusts particles. Nanoparticles exert toxicity through several mechanisms: for instance, interaction with the immune system, oxidative stress generation, as well as toxic effects on the genome. Genotoxicity can be quantified by performing comet assay, that detects DNA strand breaks using electrophoresis. A recent study showed that even low doses Printex 90 carbon black nanoparticles induced genotoxicity in mice[91] also in the absence of inflammation. Moreover, CF patients undergoing gene therapy trials are at a risk of bacterial dissemination by colonization with bacteria worsening infection. In addition, the latest Ad vectors have been found to elicit attenuated adaptive humoral responses due to which re-administration become difficult.

Conclusion

The advances in nanotechnology open improved newer treatment strategies for various lung diseases. The use of nanocarriers to deliver drugs targeting lung disorders has improved their efficiency while decreasing toxicity. To evaluate the state of chronic lung diseases and monitor the drug development in a cost-effective manner, effective non-invasive imaging techniques need to be developed. For fibrosis, inflammatory cell chemotaxis, chronic emphysema and lung obstruction associated with COPD and other lung diseases to be in control, it is essential to deliver drugs, loaded onto targeted nanoparticles, in a sustained manner. Nanoparticle

incorporation into liposomal nanostructures help overcome a few nanoparticle shortcomings and have been clinically applied in both diagnostic as well as therapeutic combinations. Also, better effective strategies can be developed by combining gene and stem cell therapy for treatment of various pulmonary chronic and acute disease therapeutics.

Future Perspectives

Nanotechnology advancement helped develop smart multifunctional drug nanocarriers with surface modifications capable of targeted delivery as well as diagnosis. However, there is a need to address the challenges faced with the application of these nanoparticles through clinical trials. Never nanomaterials which get cleared from the lungs after deposition need to be developed keeping cost/benefit ratio in mind. Even though inhalable nanomaterials are advantageous in treating respiratory illnesses, there is still a need to test the nanoparticle therapeutic systems in clinical trials. Moreover, most studies for understanding lung clearance kinetics and mechanisms, do not consider carrier compounds but only entrapped drugs, however they may be different for the nanomaterial and need to be taken into consideration to assess tissue accumulation, permeation, as well as adverse side effects. Also, to improve repeatability and patient compliance there is a need to improve aerosolization technologies to enhance control overdosing.

Executive summary:

- Nano drug delivery system (NDDS) increase the half-life and therapeutic outcome of drugs., Nano particles accumulate easily in the inflammatory sites of the lungs via passive pathway, active pathway, or physicochemical targeting strategies significantly reducing the drug side effects.
- Cystic fibrosis, Pulmonary tuberculosis, chronic obstructive pulmonary disease (COPD), breathing allergies and asthma, sleep apnea syndrome, occupational lung diseases, and pulmonary hypertension and lung cancer have been characterized as Chronic respiratory diseases (CRDs).
- Surface characteristics of nanoparticles such as size and shape impact nanoparticle biodistribution.

- PLGA-PEG polymeric vesicles deliver COPD drugs with molecular probes aiding theranostically in obstructive lung diseases.
- Novel molecular probes need to be developed for Single photon emission computed tomography (SPECT/CT) and positron emission tomography (PET/CT) that can be used for real time assessment of lung diseases.
- ALD are mainly cause by viruses and bacteria in lower respiratory tract of lungs, which shows symptoms like common cold, pharyngitis, laryngitis, bronchitis, pneumonia and tuberculosis.
- First lung injury (such as pneumonia, swine flu) that cause ALD/ARDS, Second Indirect Lung injury (such as sepsis, drug overdose) and environment factors like cooking fuel, smoking etc.
- Traditionally 3 ways are used to treat ALD which shows several disadvantages.
- To overcome the disadvantages of traditional methods, Nanocarriers drug delivery system is use which shows promising result.
- Cell hitchhiking technology, bio-inspired technology, pulmonary surfactant-based strategy, particle allosteric strategy, and nano-vaccines drug delivery approaches hold great potential for effective treatment of ARDS.
- Nanocarriers has improved the drug distribution in the lungs and the cellular uptake and has lowered the toxicity and side effects. In conclusion, nanoparticle-based drug delivery approaches to prevent, diagnose and prognosis of ARDS have exceptional clinical claim prospects that are likely to represent a new example for ARDS drug therapy.
- Conventional CRDs therapies include antioxidants such as N-acetyl-L-cysteine (NAC), Nrf2 activators, enzyme mimetics and spin traps as well as Carbocysteine like anti-inflammatory drugs.
- Negatively charged anionic liposome nanocarriers can be used to target the alveolar macrophages which play important role in COPD pathogenesis.
- Antibody coated superparamagnetic iron oxide nanoparticles (SPIONs) have been reported to work effectively for COPD diagnosis whereas Carbon black nanoparticles and Titanium dioxide nanoparticles have proven promising for COPD treatment.
- Magnetic nanoparticles and Peptide-poloxamine nanoparticles are preferred drug carriers for CF patients.

- Dexa-loaded Flt1-HA NPs show enhanced therapeutic effects in asthma patients by regulating neutrophilic inflammation.
- Sn2 lipase-labile prodrug αVβ3-micelles are inhalable antiangiogenic that enhance the selectivity by minimizing premature drug release and have been found to ameliorated asthma symptoms.
- successful therapeutic strategies include Cationic liposomes that have been used for pulmonary gene delivery to treat COPD and Adenoviral vector-based gene therapy and cystic fibrosis transmembrane conductance regulator (CFTR), gene therapy for CF patients.
- DNA thymulin polymeric particles induce anti-inflammatory effects in Asthma patients.
- CK30PEG-DNA NPs have also been found to prevent lung inflammation in the allergic asthma murine model.
- Toxicity is the major challenge that remains with the use of nanoparticles for the treatment of lung diseases.

Abbreviations

AAVs- Adeno-associated vectors

AEC- Alveolar epithelial cells

ALD- Acute Lung Diseases

APC- Antigen-presenting cells

ARDS- Acute Respiratory diseases

CFTR- Cystic fibrosis transmembrane conductance regulator

COPD- Chronic obstructive pulmonary disease

COVID- Corona Virus disease

CRDS- Chronic respiratory diseases

CT- Computed tomography

DOTAP- 1-diolefin-3-trimethylaminopropane

DPPC- Dipalmitoylphosphatidylcholine

EVs- Extracellular vehicles

GSH- Glutathione production

HA- Hyaluronic acid

IV- Intravenous

kDa- Kilo Dalton

LPS- Lipopolysaccharide

MMPs- Matrix metalloproteinases

MRI- Magnetic resonance imaging

MSC- Mesenchymal stem cells

NAC- N-acetyl-L-cysteine

NAL- N-acystelynn

NDDS- Nano drug delivery system

NE- Neutrophil elastase

NIC- N-isobutyrylcysteine

NSCLC- Non-small cell lung carcinomas

PC- Phosphatidylcholine

PDE4- Phosphodiesterase 4

PEG- Polyethylene glycol

PEI- Polyethylenimine

PET- Positron emission tomography scan

PEVs- Platelet-derived extracellular vesicles

PLGA- Poly(lactic-co-glycolic acid)

PP2- Src tyrosine kinase inhibitor

RBCs- Red blood cells

RES- Reticuloendothelial system

rSPANb- Anti-rat SP-A nanobody

SCLC- Small-cell lung carcinomas

S-CMC- S-carboxymethyl cysteine

SP-A- Surfactant protein A

SPECT- Single photon emission computed tomography

SPIONS- Superparamagnetic iron oxide nanoparticles

TB- Tuberculosis

TLR4- Toll-like receptor 4

UCNPs- Upconversion nanoparticles

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