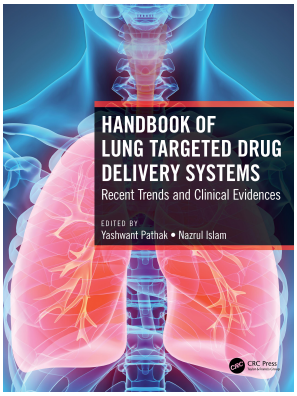

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Understanding of Lung Diseases with a Focus on Applications of Nano-particulate Drug Delivery Systems

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Abbreviations

IPF	Idiopathic pneumonic fibrosis
COPD	Chronic obstructive pulmonary disease
WHO	World Health Organization
TB	Tuberculosis
CF	Cystic fibrosis
EMT	Epithelial-mesenchymal transition
ACIF	Airway-centered interstitial fibrosis
LHCH	Langerhans cell histiocytosis
RB	Respiratory bronchiolitis
ARDS	Adult respiratory distress syndrome
BPD	Broncho pulmonary dysplasia
GOLD	Global initiative for chronic obstructive lung disease
GINA	Global initiative for asthma
SABA	Short-acting β2-agonists
MRA	Muscarinic receptor antagonist
SAMA	Short-acting muscarinic receptor antagonist
SDMI	Spring-driven mist inhaler
ICS	Inhaled corticosteroids
NAC	N-acetylcysteine
LAMA	Long-acting muscarinic antagonist
PDE4	Phosphodiesterase-4
NPPV	Non-invasive positive-pressure ventilation
RCT	Randomized controlled trial
CFC	Chlorofluorocarbon
MMAD	Mass median aerodynamic diameter
PNAPs	Porous nanoparticle aggregate particles
MALT	Mucosa-associated lymphoid tissue
SLN	Solid lipid nanoparticles
PLGA	Polylactic-co-glycolic acid
LVRS	Lung volume reduction surgery
FEV	Forced expiratory volume
HLA	Human leukocyte antigen

7.1 Introduction

Lungs are the key organ of the respiratory system and considered a vital and vulnerable part of the breathing system which plays an essential function in oxygen exchange in the body (1). Because of its daily exposure to pollutants, irritants, and infectious agents, the respiratory system is more susceptible to foreign invaders and thus inflammation of and damage to the whole system. It is estimated that 1 billion people inhale polluted outdoor air and are exposed to tobacco smoke. Moreover, poor living conditions and exposure to environmental toxins increases vulnerability leading to respiratory impairment causing disability and death in all regions of the world (2). Respiratory diseases impose an immense worldwide health burden with lung ailments as the main source of mortality, killing around 4,000,000 individuals every year on the planet (1,3).

Lung diseases range from acute conditions to chronic illness, genetic and congenital anomalies to acquired ailments, allergic to nonallergic, and curable to controllable disorders. Among them are asthma, chronic obstructive pulmonary disease (COPD), and bronchitis which have been extensively explored for understanding of their pathogenesis and treatment strategies; however, there are some, like interstitial lung diseases (ILD) which still needed deeper understanding and more research. Today, nanotechnology is playing a major role in addressing the challenges for treating lung diseases, especially in administration of drugs to the respiratory tissues with a special emphasis on lung tissue. Some of the nano-delivery methods such as nanoparticles, liposomes, micelles, dendrimers, etc. are designed to be delivered to the specific site, avoiding undesirable distribution. Moreover, degradation, elimination from lung tissue, and changes in the lung physiology on administering drugs through nano-systems is well studied and understood.

Advancement in science and medicine has justifiably addressed this area; however, there is still a lacuna in the area where scientists need to do more work. Therefore, this chapter

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highlights various lungs diseases, their pathologies, and the application of nano delivery systems in addressing those lung diseases or disorders.

7.2 Lung Diseases: A Brief Insight

Any health condition that prevents the lungs from working properly can be termed *lung disease* . Diseases of the lungs affect various regions of the organ that forms the basis of their classification (Figure 7.1), leading to difficulty in gaseous exchange and thus breathing. The diseases affecting the lungs differ in their origins, including the disorders hampering the airways, ailments of the interstitium and the pleural cavity, and defects in the vasculature of the pulmonary system. The four previously mentioned lung illnesses share qualities such as incessant, dynamic, diminished lung capacity, and irritation (1,4,5). On the other hand, smoking, air contamination, comorbid conditions, and hereditary parameters are among the hazard factors that influence the development of these illnesses (6,7). Moreover, cough, dyspnea, chest tightness, shortness of breath, and mucus production are known as some of the mutual clinical indications of disease conditions (5,7,8).

7.2.1 Obstructive Lung Disease (OLD)

Obstructive lung disease (OLD) is characterized by difficulty in exhaling the air present in the airways and alveoli, thus causing reduction in airflow and shortness of breath in exhalation. The primary cause for this type of pulmonary disease is inflammation that ultimately leads to constrictions of airways, disallowing ease in exchange of gases. Inflammatory

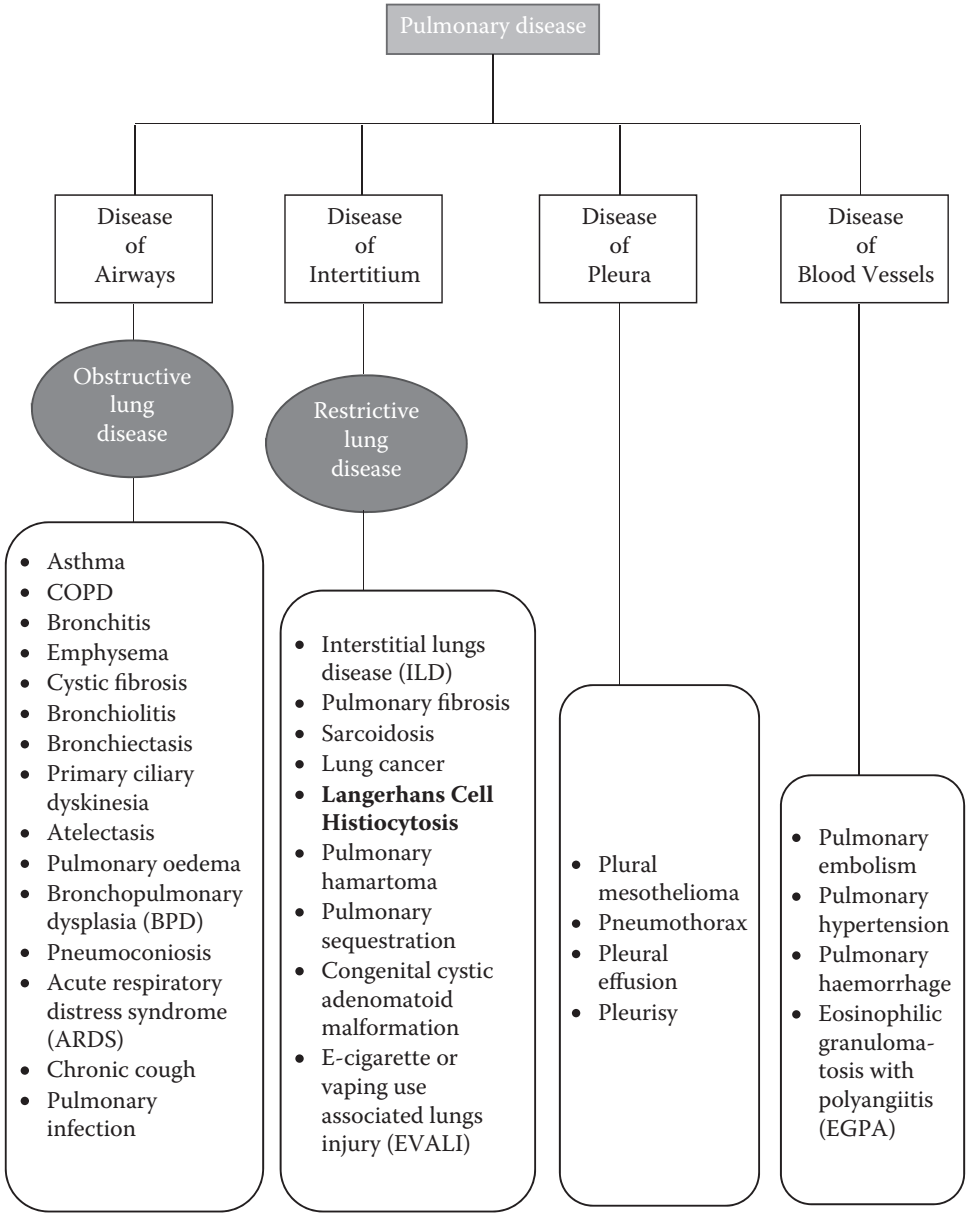

FIGURE 7.1 Classification of lung diseases

lung diseases can be divided into chronic and acute diseases. Acute inflammatory lung diseases are caused by environmental stimuli without the involvement of genetics. Airway disorders with chronic inflammation, such as asthma, COPD, and cystic fibrosis (CF), are categorized as chronic disorders which are affected by a combination of environmental, epigenetic, and genetic factors (9).

Asthma causes reversible constriction of airways (10) due to inflammation that leads to hyperactivity and tightness of the airway's smooth muscles with mucus accumulation in its lumen, making it narrower, thus difficult for air passage. Clinically it is characterized by shortness of breath, wheezing, and chest tightness. Asthma is a chronic inflammation caused by persistent infiltration of mast cells and eosinophils associated with the poor response of Th2 and associated cytokines. Th2 inflammatory mediators are all involved in airway hypersensitivity, increased mucus secretion, and high levels of IgE. The global incidence of asthma is reported to be 300 million people, constituting 21% of adults. Moreover, the incidence of asthma is increasing, mainly in children of less than 10 years (11). Both genetic and environmental factors play roles in the pathogenesis of the disease. Traditionally, asthma was divided into allergic (intrinsic) and nonallergic (extrinsic) asthma, but in recent years, within nonallergic asthma several so-called endotypes have been identified. Therefore, asthma is no longer regarded as a single disease but rather a syndrome (12). These endotypes differ concerning genetic susceptibility, environmental risk factors, age of onset, clinical presentation, prognosis, and response to treatment (13).

The next most common disease that causes deaths due to lung disorders is COPD, which has variable causes, from genetic alpha-1-antitrypsin deficiency to environmental factors such as dust and chemicals. Nearly 329 million people (approximately 5% of the world population) are struggling with COPD. The incidence rate from 1990 to 2015 has indicated an increase of 44.2% (1). Additionally, COPD is listed as the leading cause of morbidity by the World Health Organization (WHO) (6). In 2015, about 3.2 million people died of COPD and the death rate had increased by 11.6% compared to 1990 (1). Increased levels of inflammatory markers and neutrophils in blood circulation are characteristic features of COPD and are associated with oxidative stress (14). COPD is a chronic, uncurable condition which comprises two lung ailments: emphysema and chronic bronchitis. Emphysema is defined as an enlargement of alveolar spaces combined with the destruction and remodeling of the alveolar septa, usually resulting in the numerical loss of alveoli (15). Emphysema destroys the alveoli and hampers their function by making them stiff, thus preventing the air from getting out, whereas chronic bronchitis causes irritated, red, swollen airways with mucus overproduction due to inflammation causing cough with phlegm and shortness of breath (1,7).

Another deadly and fatal lung disease is *cystic fibrosis* (CF), a genetic disease that forms thick and sticky mucus that blocks the lung airways which precipitates into recurrent lung infections and breathing complications that ultimately damage lungs and cause patient death. Mutations in the CFTR gene are responsible for the disease having an autosomal recessive pattern (16). Cystic fibrosis mostly has its incidence in Caucasians where it was found to be 1:3600 in North America and Europe. Despite advances in treatment regimens, CF still has no cure and more than 90% of deaths occur as a result of lung failure (17).

Bronchiolitis is often associated with either bronchitis, such as in asthma, or with pneumonia, such as organizing pneumonia. However, there are two reasons to discuss bronchiolitis separately. Bronchiolitis is the underlying pathology of small airways disease, and furthermore, it does occur sometimes as an isolated disease. At present we best classify bronchiolitis into acute bronchiolitis, chronic bronchiolitis, COPD-associated bronchiolitis, and distinct forms of bronchiolitis, however there are several more types as shown in Table 7.1.

Bronchiectasis is a incurable disease that affects the cilia of the airways; moreover, it causes smooth muscle stretch in the airways creating a pocket that acts as a substratum of mucus and foreign particles. Since the ciliary functions are hampered, clearance of mucus and foreign particles is compromised, causing frequent pulmonary infections damaging to the airway.

TABLE 7.1

Types of Bronchiolitis

Sr. No.	Type of Bronchiolitis	Etiology
1	Bronchiolitis obliterans	Graft versus host disease, vascular collagen diseases, cardiac graft rejection, idiopathic disease
2	Organizing pneumonia	Unresolved bacterial pneumonia, inhalation of poisonous smoke, inhalation of insecticides / pesticides, inhalation of gastric juice, autoimmune disorders, toxicity of medications, idiopathic disease
3	Constrictive bronchiolitis	Graft versus host disease, vascular collagen disorders, cardiac transplantation rejection, drug reaction
4	Respiratory bronchiolitis and RB combined interstitial lung disease	Smoking cigarettes, rare idiopathic medication
5	Follicular bronchiolitis	Recurrent viral infection, immunodeficiency, autoimmune diseases, idiopathic immune defects (T cells or NK); HP / EAAA portion
6	Diffuse pan bronchiolitis	HLA system-related immune defect
7	Airway-centered interstitial fibrosis (ACIF)	Hypersensitivity pneumonia, vascular collagen infections, hazardous material inhalation, idiopathic

Primary ciliary dyskinesia is a genetic form of bronchiectasis affecting infants and children.

Atelectasis is defined as an alveolar collapse due to a lack of air filling. In newborns there exists a condition of primary atelectasis; however, normally the lung extends with the first inspiration and the alveoli are filled with air. In rare cases, this inspiration does not happen, mainly as the result of severe cerebral malformations. In other cases, primary lung injury, such as meconium aspiration, sepsis, or persistent pulmonary hypertension, can also cause severe or partial atelectasis (18). Secondary atelectasis can occur at any age after birth. The causes of atelectasis in childhood are infantile myofibromatosis (19), infantile bronchial obstruction or atresia (20,21), or compression by cysts, as in congenital adenomatoid pulmonary malformation (22).

Pulmonary edema happens due to the accumulation of fluid in the alveoli and its surrounding area due to the leakage of lung capillaries. Fluid enters the peripheral lung from the circulation via the interstitium into alveoli. Among the variable causes, the most common is congestion of the pulmonary circulation, most often caused by heart failure due to infarction, valvular diseases, and the like. In these cases, the venous flow into the left atrium is reduced, resistance in the venous part of the circulation increases, and leakage of the pulmonary veins increases. The gaps between the endothelial cells increase in size and serum gets into the interstitium and causes interstitial edema. Another important cause includes lung infections such as pneumonia and tuberculosis.

Bronchopulmonary dysplasia (BPD) is a chronic disease that occurs in newborns and infants causing scarring of the lungs, including alveoli and bronchi. It occurs in babies born prematurely when the lungs are underdeveloped, requiring the use of ventilators. Due to undeveloped lungs, the oxygen in the alveoli causes overstretching of the sac leading to damage of the airway lining; moreover, it affects the blood vessels surrounding them, leading to pulmonary hypertension. Infection and inflammation are major contributors to the pathogenesis of BPD, which is often initiated by a respiratory distress response, and exacerbated by mechanical ventilation and exposure to supplemental oxygen (23). Similar to Wilson-Mikity syndrome, infectious organisms such as cytomegalovirus (CMV) have been reported to cause BPD (24). Other risk factors include maternal smoking, preeclampsia, drug use, etc.

Pneumoconiosis, for example, asbestosis and coal worker disease, are lung disorders caused by the inhalation of a substance which damages the alveoli and causes scarring and stiffness, making it difficult to transport oxygen into systemic circulation.

Acute respiratory distress syndrome (ARDS) is a condition in whch the lungs suffer sudden depression and slow their function due to the existing condition, including severe lung infections like COVID-19 such that the person requires ventilators until recovery (25).

Chronic cough is more of a symptom than a disease that can last for more than 8 weeks due to underlying conditions such as tuberculosis, COPD, severe pneumonia, etc.

As far as *respiratory infections* are concerned, discussion of it is beyond the limit of this chapter, since they include a long list of bacterial, viral, and fungal diseases which includes COVID-19, aspergillosis, influenza, coccidioidomycosis, common cold, hantavirus, croup, pertussis, pneumonia, tuberculosis, respiratory syncytial virus, SARS, MERS, histoplasmosis, human metapneumovirus, Legionnaires' disease, mycobacterium avian complex (MAC) disease, and non-tuberculosis mycobacterium (NLM) lung disease.

7.2.2 Restrictive Lung Disease (RLD)

Restrictive lung disease (RLD) are characterized by the inability of the lungs to inhale, thus making the lungs unable to expand. The primary reason for this is the inflammation and fibrosis of the lung tissue, causing it to stiffen. One of the most prevalent RLDs is *interstitial lung disease* (ILD), a class of irreversible lung diseases causing lung scarring, thus preventing lungs from transporting oxygen into bloodstream. ILDs consist of various subclass of lung ailments such as idiopathic pulmonary fibrosis and sarcoidosis. ILDs are mostly due to inhalation of hazardous materials, like cigarette smoke, or through medications such as chemotherapy; the cause can also genetic. Shortness of breath is the most common symptom in addition to chest discomfort, dry cough, fatigue, and weight loss. Since the disease is progressive, the treatment involves managing the symptoms and improving quality of life.

Idiopathic pulmonary fibrosis (IPF) is a chronic disease characterized by excessive accumulation of extracellular proteins, such as collagen, in parenchymal tissue, fibroblast proliferation, and scarring of lung epithelial (26). The incidence of IPF is found to be approximately 23 in every 100,000 people. Parenchymal fibrosis is probably a product of activated alveolar epithelial cells that causes epithelial–mesenchymal transition (EMT), extracellular matrix construction, and accumulation of fibroblasts and myofibroblasts (10,27). Whereas *sarcoidosis* is an autoimmune inflammatory disorder causing granulomas in the lung and other body parts, which at its most severity causes heart failure.

Despite advances in diagnosis and treatment of *lung cancer*, this disease has the highest rate of cancer-related deaths worldwide. Though most lung cancer starts in the lungs, some cases start in other parts of the body and spread to the lungs. The two main types of lung cancer are small cell and non small cell, which grow and spread in different ways and hence each type may be treated differently. Like COPD, non small cell lung cancer (NSCLC) is thought to be generated due to long term exposure to cigarette smoke. Moreover, breathing secondhand smoke can also increase a person's chance of developing the disease.

Langerhans cell histiocytosis (LHCH, histiocytosis X, eosinophilic granuloma) is a very rare interstitial lung disease caused by excessive inhalation of tobacco smoke; tobacco plant antigens present within the tobacco smoke cause accumulation and proliferation of Langerhans cells (28,29). The continuous exposure of Langerhans cells (antigen presenting reticulum cell population) to plant proteins causes proliferation of these cells to keep up with the increasing number of antigens to be processed. Inhaled antigens are presented to LH cells, which are taken up and processed by specific mechanisms involving toll receptors and langerin, a molecule with a C-type lectin domain (30,31). Patients suffering from this disease experience acute respiratory failure and asphyxia.

Pulmonary hamartoma is a common benign tumor of lungs made up of connective tissue, cartilage, fat, muscle, and bone. *Pulmonary sequestration* is the outgrowth of tissues from lungs, also known as accessory lungs, but it is not connected with the bronchial tree or pulmonary artery. *Congenital cystic adenomatoid malformation* is a rare congenital form of pulmonary sequestration which appears before birth and hampers the normal breathing pattern of a fetus. *E-cigarette or vaping use associated lung injury (EVALI)* is a unique lung disorder identified in 2019 whereby the lung tissue is injured due to vitamin E acetate present in e-cigarettes.

7.2.3 Pleural Lung Disease

Disease of the pleura involves *pleural mesothelioma*, a rare form of pleural cancer that is usually due to inflammation of the pleural lining due to the inhalation of hazardous substances like asbestos fibres. Another common ailment is *pneumothorax* , also known as collapsed lungs, which occurs when there is an air leakage between the lungs and the chest wall cavity, making it impossible for the lungs to expand and work efficiently. *Pleural effusion* is a form of pneumothorax in which the cavity between lungs and chest wall is filled with fluid that can lead to heart failure. *Pleurisy*, also known as pleuritis, is an inflammation of both the pleural membranes, making them swollen and creating a gap between the two that leads to infection if filled with a fluid.

7.2.4 Vascular Lung Disease

Pulmonary embolism and *pulmonary hypertension* are the two most common diseases affecting the pulmonary blood vessels. Other important but less discussed diseases include *pulmonary hemorrhage* and *eosinophilic granulomatosis with polyangiitis* (EGPA), an inflammation of the tiny blood vessels of the lungs that damages the organ.

7.3 Management and Treatment of Lung Diseases

The treatment of pulmonary disease involves both pharmacological and non-pharmacological interventions since certain lung ailments are incurable and require supportive and lifelong interventions to improve the quality of life (Figure 7.2). Pharmacological measures involve the use of conventional and some newly approved therapies that include bronchodilators, corticosteroids, antimalarials, TNF inhibitors, etc., whereas non-pharmacological therapy includes oxygen support, ventilation, pulmonary rehabilitation, etc. Different lung diseases differ in their characteristic features, which means clinicians must make a wise selection of a particular therapy and a step-by-step strategy for disease management. This led to the formation the of Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the treatment of asthma and COPD, respectively, and other guidelines, too, for the management of other pulmonary ailments (32). Below is detailed information regarding the therapy used in different lung diseases with a special emphasis on asthma and COPD.

7.3.1 Pharmacological Approaches to Treating Lung Diseases

7.3.1.1 Bronchodilators

Bronchodilators are the mainstay agents for the management of lung disease associated with the airways, such as asthma, COPD,

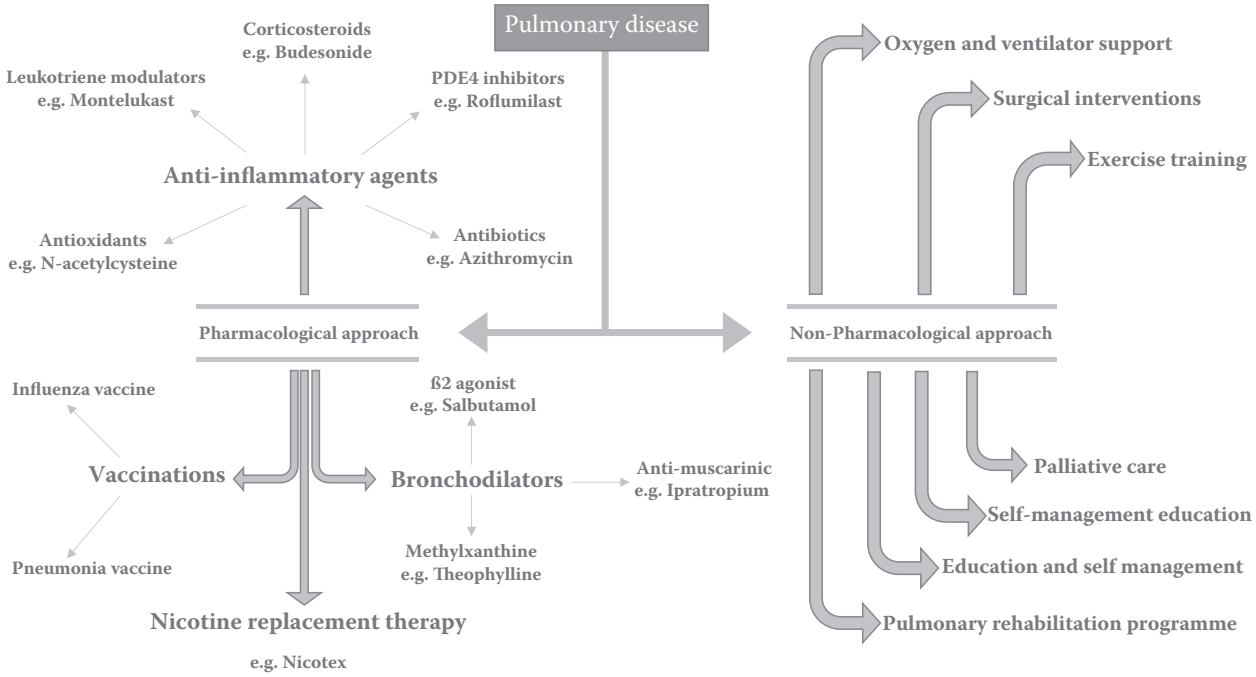

FIGURE 7.2 Treatment of lung diseases

bronchitis, atelectasis, emphysema, BPD, etc. Bronchodilators dilate, the airway smooth muscles thus increasing the force of the expiratory volume (FEV1), and reducing dynamic hyperinflation at rest and during exercise, thus improving exercise performance (33). These medications are usually given regularly to prevent or reduce the symptoms of bronchoconstriction associated with the underlying disease.

7.3.1.1.1 Beta-2 Agonists

Beta-2 agonists, including short-acting (SABA) and long-acting (LABA) agents, relax airway smooth muscle. The primary short-acting inhaled B2AR (beta-2 adrenergic receptor) agonist (SABA) used for bronchodilation is albuterol (known as salbutamol in Europe). Levalbuterol, the R-enantiomer of albuterol is also available for inhalation. The use of long-acting beta-2 agonists (LABA), includimg formoterol and salmeterol, has evolved over the last several years in the treatment of both asthma and COPD. Stimulation of beta-2 adrenergic receptors has been observed to produce resting sinus tachycardia and precipitate cardiac rhythm disturbances in susceptible patients. Moreover, exaggerated somatic tremor occurs in some patients treated with higher doses of beta-2 agonists.

7.3.1.1.2 Anti-muscarinic Drugs

Anticholinergic drugs, specifically anti-muscarinic agents, act on bronchi and inhibit the contraction of smooth muscle by acetylcholine. It was observed that the short-acting muscarinic antagonist (SAMA), provides small benefits over the short-acting beta-2 agonist in terms of lung function, health status, and the requirement for oral steroids. Ipratropium bromide is the major SAMA used in the US and Europe, and is available in nebulizer and spring-driven mist inhaler (SDMI) products. Unlike atropine, ipratropium bromide in the airway is poorly systemically absorbed and tends not to cross into the central nervous system, and as a result has limited systemic adverse effects. In addition to that, an unexpected small increase in cardiovascular events was reported in COPD patients regularly treated with ipratropium bromide. However, a large trial reported no differences in mortality, cardiovascular morbidity, or exacerbation rates when using tiotropium (34). As far as long-acting muscarinic antagonists (LAMA) such as tiotropium are concerned, clinical trials have shown a greater effect on exacerbation rates when compared to LABA treatment (35). Long-acting muscarinic antagonist (LAMA) treatment improves symptoms and health status (36), improves the effectiveness of pulmonary rehabilitation, and reduces exacerbations and related hospitalizations.

7.3.1.1.3 Methylxanthines

Theophylline exerts a modest bronchodilator effect in stable COPD, and improves FEV1 and breathlessness when added to salmeterol. There is limited and contradictory evidence regarding the effect of low-dose theophylline on exacerbation rates. Toxicity of theophylline is dose-related, which is a problem as most of the benefit occurs when near-toxic doses are given (37).

7.3.1.1.4 Combination Bronchodilator Therapy

Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation with a lower risk of side effects compared to increasing the dose of a single bronchodilator. There are numerous combinations of long-acting beta agonists (LABA) and long-acting muscarinic antagonists (LAMA) in a single inhaler available. These combinations improve lung function compared to placebo and have a greater impact on patient-reported outcomes compared to monotherapies. It was found that LABA plus LAMA improves symptoms and health status in COPD patients (38) and is more effective than long-acting bronchodilator monotherapy for preventing exacerbations. Moreover, it was found that this combination decreases exacerbations to a greater extent than an inhaled corticosteroid (ICS)/LABA combination (39). As far as Asthma–COPD Overlap Syndrome (ACOS) is concerned, a combination of inhaled products containing the SABA albuterol or salbutamol with the SAMA agent ipratropium can be used as a relief medication or as a maintenance medication if taken every 6 hours. These combined inhaled products are available by nebulization (NEB) or by spring-driven mist inhaler (SDMI).

7.3.1.2 Anti-Inflammatory Agents

Anti-inflammatory drugs are the first line therapy for the management and treatment of both obstructive lung disease and restrictive lung disease, since inflammation is the primary reason for the emergence of pulmonary disorder. The disorders where these agents are used include asthma, COPD, chronic bronchitis, BPD, cystic fibrosis, EVALI, emphysema, EGPA, IPF, ILD, sarcoidosis, pleurisy, etc. (40). These agents act on various targets, hence are classified accordingly, such as corticosteroids, phosphodiesterase-4-inhibitors, antibiotics, leukotriene modulators, and antioxidants, the details of which are discussed below.

7.3.1.2.1 Corticosteroids

Inhaled corticosteroids (ICS), for example, budesonide and fluticasone as initial maintenance therapy, is advocated for the treatment of both adult and childhood asthma (41). A recent set of trials (TRIMARIN and TRIGGER) in uncontrolled asthma patients found that the triple fixed dose combination (FDC) inhaler (ICS + LABA + LAMA) was superior to a double FDC inhaler (ICS + LABA) in reducing asthma exacerbations and improving lung function (42). Short courses of less than a week of systemic corticosteroids (oral or parenteral) remains the mainstay therapy for exacerbations of COPD (43,44). However, long term daily treatment of COPD with oral glucocorticoids lacks benefit due to a high rate of systemic complications. It was reported in clinics that an ICS combined with a LABA is more effective than the individual components in improving lung function and health status, and reduces exacerbations in patients with moderate to very severe COPD. Additionally, triple inhaled therapy of ICS/LAMA/LABA improves lung functions, symptoms and health status, and reduces exacerbations compared to ICS/LABA or LAMA monotherapy. Nevertheless, survival is not affected by combination therapy (45).

7.3.1.2.2 Phosphodiesterase-4-Inhibitors (PDE4 Inhibitors)

PDE4 inhibitors, such as roflumilast have been studied and proposed in asthma patients because of their anti-inflammatory mechanisms (46). Roflumilast, use in patients with asthma, is associated with reduced allergen-induced acute bronchoconstriction as measured by both forced expiratory volume (FEV) in asthma patients and modulation of inflammatory biomarkers (47). Roflumilast reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis and severe to very severe COPD. However, phosphodiesterase-4 (PDE4) inhibitors have more adverse effects than inhaled medications for COPD. The most frequent are diarrhea, nausea, reduced appetite, weight loss, abdominal pain, sleep disturbance, and headache. Furthermore, roflumilast should be avoided in underweight patients and used with caution in patients with depression (48,49).

7.3.1.2.3 Antibiotics

Azithromycin (250 mg/day or 500 mg three times per week) or erythromycin (500 mg two times per day) for 1 year reduces the risk of exacerbation in patients suffering from COPD. Since bacteria too resides in the patient airways causing purulent sputum that eventually causes pneumonia. Azithromycin also showed a reduction in exacerbation rate in former smokers but is associated with an increased incidence of bacterial resistance. However, pulse moxifloxacin therapy in patients with chronic bronchitis and frequent exacerbations does not reduce exacerbation rate.

7.3.1.2.4 Leukotriene Modulators

Leukotriene pathway modifiers, including both leukotriene synthesis inhibitors (e.g. meclofenamate sodium) and receptor antagonists (e.g. montelukast) are widely available and used in asthma and other atopic diseases, however, they have not been adequately tested in COPD (32,50).

7.3.1.2.5 Antioxidants

Inhaled carbocysteine and N-acetylcysteine (NAC) are classified as mucolytics since they reduce sputum viscosity and elasticity, improving mucociliary clearance. Additionally, they also possess anti-inflammatory properties and are considered antioxidants. Regular treatment with them reduces exacerbations and modestly improves health status in patients not receiving ICS (49). NAC is used orally and intravenously as a glutathione replacement in the prevention and treatment of acetaminophen-induced hepatitis. The innate antioxidant protection in airway tissue is thought to be in part from its glutathione-like characteristics such that a transformation of its thiol group from reduced to oxidize state provides a potent antioxidant effect (51). In addition to these, macrolide antibiotics such as azithromycin have an immuno-modulatory function in addition to their anti-bacterial effects (52).

7.3.1.3 Vaccinations

Influenza vaccination reduces serious illness, death, the risk of ischemic heart disease (53), and the total number of exacerbations (54). Influenza vaccination containing either killed or live inactivated viruses is recommended for all patients with COPD as they are more effective in elderly patients with COPD. Pneumococcal vaccinations, PCV13, and PPSV23 are recommended for all patients > 65 years of age. The PPSV23 is also recommended for younger COPD patients with significant comorbid conditions, including chronic heart or lung disease (55).

7.3.1.4 Nicotine Replacement Therapy

Nicotine replacement therapy involves the use of nicotine in a form (e.g. gums, sprays) other than tobacco, mainly for smoking cessation to combat the withdrawal symptoms so as to prevent and treat diseases associated with it. The therapy is more beneficial and better than the other placebo effects in treating smoking-related lung disease (56–58).

7.3.2 Non-pharmacological Approach

7.3.2.1 Oxygen Therapy and Ventilatory Support

7.3.2.1.1 Oxygen Therapy

The long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure increases survival in patients with severe resting hypoxemia. Long-term oxygen therapy provides sustained benefit for any of the measured outcomes in patients with stable COPD and resting or exercise-induced moderate arterial oxygen desaturation (59).

7.3.2.1.2 Ventilatory Support

Whether to use non-invasive positive-pressure ventilation (NPPV) chronically at home to treat patients with acute or chronic respiratory failure following hospitalization remains undetermined. Randomized controlled trials (RCTs) have yielded conflicting data on the use of home NPPV on survival and re-hospitalization in chronic hypercapnic COPD. In patients with both COPD and obstructive sleep apnea, continuous positive airway pressure improves survival and avoids hospitalization (60).

7.3.2.2 Surgical Interventions

7.3.2.2.1 Lung Volume Reduction Surgery

An RCT confirmed that COPD patients with upper lobe emphysema and low post-rehabilitation exercise capacity experienced improved survival when treated with lung volume reduction surgery (LVRS) compared to medical treatment. In patients with high post-pulmonary rehabilitation exercise capacity, no difference in survival was noted after LVRS, although health status and exercise capacity were improved. LVRS has been demonstrated to result in higher mortality than medical management in severe emphysema patients with a forced expiratory volume (FEV1) ≤ 20% (61)).

7.3.2.2.2 Bullectomy

In selected patients with relatively preserved underlying lung, bullectomy (surgical removal of lung parenchyma filled with

air with a size of more than 1 cm) is associated with decreased dyspnea, and improved lung function and exercise tolerance.

7.3.2.2.3 Lung Transplantation

In selected patients, lung transplantation has been shown to improve health status and functional capacity but not has been seen to prolong survival. However, bilateral lung transplantation has been reported to result in longer survival than single lung transplantation in COPD patients, especially those < 60 years of age (62). In selected patients with very severe COPD and without relevant contraindications, lung transplantation may be considered (63).

7.3.2.2.4 Bronchoscopic Interventions

Less invasive bronchoscopic approaches to lung reduction have been developed. In selected patients with heterogeneous or homogenous emphysema and significant hyperinflation refractory to optimized medical care, surgical or bronchoscopic modes of lung volume reduction (e.g. endobronchial one-way valves or lung coils) may be considered. Prospective studies have shown that the use of bronchial stents is not effective while the use of lung sealant caused significant morbidity and mortality (64).

7.3.2.3 Education and Self-Management

An individual patient's evaluation and risk assessment (e.g. exacerbations, patient's needs, preferences, and personal goals) should aid the design of personalized self-management.

7.3.2.4 Pulmonary Rehabilitation Programs

Patients with high symptom burden and risk of exacerbations should take part in a full rehabilitation program that considers the individual's characteristics and comorbidities (65).

7.3.2.5 Exercise Training

A combination of constant load or interval training with strength training provides better outcomes than either method alone. Adding strength training to aerobic training is effective in improving strength, but does not improve health status or exercise tolerance. Upper extremity exercise training improves arm strength and endurance, and improves capacity for upper extremity activities (66).

7.3.2.6 Self-Management Education

An educational program should include smoking cessation, basic information about COPD, aspects of medical treatment (respiratory medications and inhalation devices), strategies to minimize dyspnea, advice about when to seek help, and possibly a discussion of advance directives and end-of-life issues.

7.3.2.7 Palliative Care

Patients should be informed that should they become critically ill, they or their family members may need to decide whether a course of intensive care is likely to achieve their personal goals for care. Simple, structured conversations about these possible scenarios should be discussed while patients are in a stable state (67).

7.4 Application of Nano-Drug Delivery Systems in Lung Diseases

The use of nanocarriers in drug delivery has seen a growing interest in recent times for respiratory products (68). Nanocarriers are classified, in particular, as drug carriers for controlled release and guided distribution. After the NIH launch of the National Nano Initiative in 2000, work on nanocarriers in the field of drug distribution is growing. ISO describes *nanoscale* as a size range from approximately 1 to 100 nm, and *particles*, as described by the European Commission, are known to be a *minute piece of matter with specified physical limits* . A nanomaterial as described in this recommendation should consist of 50% or more of particles having a size between 1 nm and 100 nm. Nanoparticles may be characterized as particulate drug carrier networks that contain the drug and consist of excipient material—sometimes a polymer—to a significant degree that covers, protects, or functionalizes the particulate matter or a nanoscale substance consisting (mostly) of the drug, such as nanocrystals (69).

7.4.1 Characteristics of Pulmonary Nano-Drug Delivery

7.4.1.1 Pulmonary Distribution of Drug

Nanoparticles can achieve a fairly uniform drug delivery across alveoli. It is especially valid if nanoparticles may be distributed to produce an ultra-fine aerosol; it is well known that this results in the more peripheral deposition, hence reduce dosage will be required for therapeutic benefit. Specific deposition trends have been observed for pulmonary nanoparticles, whereby smaller particles enter the peripheral lung and larger specimens are preferentially deposited in the central region. Lung distribution usually needs particle sizes between 1 and 5 μm (aerodynamic size)—which ensures that nanoparticles will only be distributed and successfully stored in the lung if larger particles or droplets are transported inside (70).

7.4.1.2 Improved Solubility/Dissolution Rate

Drug nanocrystals (nanoscale active pharmaceutical ingredient, API) can exhibit improved solubility/dissolution rate of the product and thus increase diffusion and permeation. It has been shown to boost the bioavailability of improperly water-soluble medications delivered orally, which may theoretically even be used to enhance the potency of medication after administration to the lungs (71).

7.4.1.3 Sustained Release Properties

Nanocarriers may act as a medication reservoir and thus can be used to regulate the rate of drug release in the lungs continuously and in a controlled manner. This may also result in decreased dosing duration.

7.4.1.4 Delivery of Macromolecules

Nanocarriers may be used as a sensitive device for their API load, thus enabling the delivery of macromolecules which are highly susceptible to uncertainty without additional security.

7.4.1.5 Internalization by Cells

Due to their small size, nanocarriers can enter as untouched, undissolved particles (72) by phagocytosis/macro pinocytosis. This provides the capacity for transmission of intracellular drugs after cell internalization. Furthermore, if nanocarriers are functionalized with targeting moieties, this may allow for cell-specific targeting and delivery. There are mainly pulmonary macrophages and dendritic cells in the respiratory system which are part of the pulmonary mucosal immune system. Nanocarriers, especially nanoparticles, can therefore be an alternative for the supply of immune-active APIs (e.g. vaccination). Seeing that macrophages play a significant role in the development of lung tuberculosis disease, targeting macrophages for (sustained) intracellular antibiotic transmission is another fascinating application.

7.4.2 Fate of Nanocarriers in the Lungs

Once the nano formulation reaches the lung, deposits and nanocarriers are made available from the dosage form; they will be subjected to lung clearance processes such as mucociliary clearance and macrophage clearance (73). In the conducting airways, the lung epithelium is lined with ciliated cells and goblet cells that create a mucus coating which offers efficient mechanisms to remove contaminants from the lung. The pulmonary mucus could be outlined as a tightly packed network of highly heterogeneous pore sizes from 100 nm to several micrometers allowing multipurpose small-affinity interactions via negatively charged mucin and uncharged regions side chains of glycan. It also shows some size-filtering effect and electrostatic/hydrophobic interactions. Furthermore, phagocytose particulate content is found in macrophages and pulmonary dendritic cells (DCs). Because macrophages do not move to local lymph nodes, content that ends up there is often lost unless the target inside the macrophages is pathogens. Dendritic cells, on the other side, may absorb and present materials to the immune system via the lymphatic system, rendering this route important for an immune distribution (74). Clearance is much slower in the lung periphery (in the alveolar region), due to the absence of mucociliary clearance. The primary approach here is the incorporation of contaminants into the phagocytotic cells. Furthermore, alveolar dendritic cells are said to be more effective in the presentation of antigen relative to DCs found in the conducting airways (75).

7.4.3 Strategies to Overcome Clearance of Nanocarriers

Different strategies are addressed to prevent lung clearing processes. In addition to the scale and location-specific uptake or avoidance of uptake, mucoadhesive and extremely penetrative nanoparticles were investigated, respectively. Mucoadhesion was historically used as a way of reducing clearance. On the other hand, experiments have shown that tiny particles having an overall negative charge on the hydrophilic surface (virus-like particles) penetrate the mucus and thus prevent mucociliary clearance improving contact of particles with the underlying cells. PEG-coating is also used to allow further penetration, as it provides the particles with a clear, hydrophilic surface. Reports observe that particles of PEG-coated polystyrene had improved diffusion in human mucus in vitro relative to those that were COOH-modified. Moreover, Schneider et al. (76) showed that PEG-coated PLGA particles had enhanced lung retention in vivo in a mouse model compared to free poly (lactic-co-glycolic acid) (PLGA) particles.

7.4.4 Nano-Formulation for Drug Delivery to Lungs

Nanomedicine is emerging very rapidly in two areas where the impacts are likely to be most significant: the diagnostic field and the medicine and new treatment area (77). Indeed, various nanocarriers are in clinical use or under development to develop systems for imaging and drug delivery (Table 7.2). Nano vectors may allow overcoming several challenges in drug delivery including protect them from degradation, a controlled release of therapeutics enabling persistent drug delivery and treatments at diminished doses, targeted drug delivery which allows reducing administration doses and thus lowering side-effects, toxicity, and exposure of non-target organs. However, certain drugs are difficult to be efficiently transported through physiological barriers and are administered systemically, which results in possible metabolism and clearance in the liver. Moreover, higher dosing is necessary to achieve therapeutic effects with possible target and non-target organ toxicity. An important field of nanomedicine research is consequently the development of new treatment strategies for a controlled, selective and efficient transport of drugs through biological barriers such as the lungs. However, the safety of nanomedicine is a principal issue of concern as shown by in vivo and in vitro studies which demonstrated induction of toxicity in multiple organ systems and thus have adverse health effects that have been poorly studied so far (94).

7.4.4.1.1 Polymeric Nanoparticles

Sustained-release products with greater intrinsic durability are polymeric stable particles. Due to its biodegradability and nontoxicity, polylactic-co-glycolic acid (PLGA) nanoparticles are of prime importance. Particulate PLGA has a robust shape with a uniform particle size and morphology (75). Degradation times may be adjusted to match the option of polymer and processing method (95). In one of the reports prolonged-release inhaled PLGA nanoparticle was formulated for the cell-specific treatment of tuberculosis (96). Rifampicin is a common antibiotic in TB care, which is administered orally for months. The explanation behind this repetitive administration is mycobacterium tuberculosis which exists within the pulmonary macrophages where an appropriate antibiotic delivery

TABLE 7.2

Application of Nanocarriers for Diagnosis and Therapies of Pulmonary Diseases

Sr. No.	Nanocarriers	Route	Description	Use	Reference
1	Respirocytes	Hypodermal injection	Nanodevices which act as red blood cells, but with greater effectiveness	Oxygen supply to tissues	(78)
2	Quantum dots	Intra-abdominal organs space	Nanocrystals which are produced to fluoresce; Stimulated by illumination	Lung cancer imaging	(79)
3	Fullerenes	Intra-tracheal bolus	Water-soluble C60 fullerenes	Blocking allergic reaction	(80)
4	INGN401	Intravenous	Tumor suppression gene nano particulate formulation FUS1	Lung cancer	(81)
5	ABRAXANE®	Intravenous infusion	Taxane albumin-bound particles	Non small cell lung cancer	(81)
6	Liposomes	Intravenous	Uni-multilamellar spherical nanoparticles made of lipid bilayer membranes	Cancer chemotherapy/ gene therapy	(81)
7	Poly PLA homopolymers conjugated with PEG	Intravenous	Betamethasone encapsulated by poly PLA homopolymers	Asthma	(82)
8	PEG-PLGA	Subcutaneous injection	Nanoparticle compacted with NF-κB	Pulmonary arterial hypertension	(83)
9	PLGA and VS(72)-10		Salbutamol-loaded polymeric nanoparticle	Respiratory diseases	(84)
10	Gelatin nanoparticles	Oral	Natural polymer encapsulated with rifampicin	Tuberculosis	(85)
11	Poly(L-aspartic acidco-lactic acid)/DPPE co-polymer NPs	Intraperitoneal injection	Amphiphilic biodegradable poly(L-aspartic acid-co-lactic acid)/DPPE co-polymer NPs loaded with doxorubicin (DOX)	Lung cancer	(86)
12	PEG-dendritic block telodendrimer	Intravenous injection	Self-assembling nanoparticles containing Dex	Allergic Asthma	(87)
13	pDNA nanoparticles (NPs)	Intranasal	Chitosan/IFN-gamma pDNA NPs (CIN)	Allergic Asthma	(88)
14	poly (DL-lactidecoglycolide) NPs	Inhalation	poly (DL-lactideco-glycolide) loaded with ATDs	Tuberculosis	(89)
15	Polybutyl cyanoacrylate NPs	Intravenous injection	DOX-loaded NPs were incorporated into inhalable effervescent and non-effervescent carrier particles using a spray-freeze drying technique	Lung cancer	(90)
16	Poly (beta-amino ester) (PBAE) polymers	Intratumoral injection	Biodegradable PBAE polymers that self-assemble with DNA	Lung cancer	(91)
17	LPH (liposomepolycation-hyaluronic acid) nanoparticles	Intravenous injection	LPH nanoparticle formulation modified with tumor-targeting single-chain antibody fragment for systemic delivery of siRNA and micro RNA efficiently downregulated the target genes(c-Myc/MDM2/VEGF)	Cancer lung metastasis	(92)
18	Nanodiamond	Subcutaneously into the right flank area	The carbon nanomaterial nanodiamond (ND) is nontoxic and biocompatible because cytotoxicity is not caused in lung cells	Labeling and tracking of cancer cells and lung cancer therapy	(93)

is very challenging (97). However, when the medication is delivered through inhalation, local concentration rises, but rifampicin is quickly extracted from the lungs upon dissolution. But when rifampicin is manufactured in PLGA nanoparticles [e.g. as porous nanoparticle aggregate particles' (PNAPs)] and delivered by the inhaled pathway, particles are ingested in lung macrophages at the effector site substantially increasing local drug concentration (98).

7.4.4.1.2 Antigenic Nanoparticles

Nanoparticles are also tested for the transmission of macromolecules to the lungs (99), where they have proven viable for the distribution of siRNA (100) including micro RNA. A unique feature of macromolecule distribution throughout the process of mucosal vaccination is the transmission of antigens into the lungs. The goal here is to promote local antigen storage and presentation by the mucosal immune system (dendritic cells and also the mucosa-associated lymphoid tissue (MALT). This provides a special immune system that is distinguished by a very controlled humoral or cellular response and a specifically secreted antibody, sIgA (101). This form of immune response is particularly beneficial in defending against infectious diseases, intracellular bacteria, infections with parasites, etc. The availability of a particulate antigen is an essential requirement for local production, which may resemble a natural pathogen and therefore has an adjuvant operation. However, a soluble antigen migrates into the lymph nodes and does not cause immunity; therefore, it is a common goal for formulating nanoparticles that contains antigens. Moreover, compared to parenteral vaccines, vaccination via the respiratory tract further has the beauty of

non-invasiveness, which does not require medical personnel and is not associated with needle-stick injuries or infections (102). Besides, no sterile liquid formulations are required with this expanding formulation option (e.g. dry powder) which may further offer increased storage stability. As such, it is a perfect way of vaccination for remote areas of the world. Additionally, to further increase specificity in delivery, the size of nanoparticles can be used for the avoidance of macrophage phagocytosis or specific uptake into macrophages, respectively. It is known that dendritic cells take up particles from the low nanometer range up to the micrometer scale, whereas macrophages prefer particles larger than 500 nm. The latter will hardly get into the lung unless they are large porous particles' having a low density and thus small aerodynamic size despite a larger geometric diameter. In turn, macrophage targeting can be achieved with particles between 500 nm and 3 μm, whereas for preferential DC uptake in the course of mucosal vaccination, particles smaller than 500 nm should be used (103).

7.4.4.1.3 Solid Lipid Nanoparticles

The advantage of local delivery to the target site with the reduction of systemic side effects is especially attractive for the therapies with chemotherapeutics, therefore, lung cancer is a natural target for local respiratory therapy. However, so far chemotherapeutics are mostly administered systemically by intravenous infusion, possibly due to difficulties of water-insoluble materials to formulate them for respiratory delivery. This problem can be overcome by formulation of nanoparticles which not only increases the therapeutic index but also controls the release of a chemotherapeutic agents. This would allow the delivery of a chemotherapeutic to its site of action, which means efficient local doses and low side effects. Numerous attempts in different stages have been made to use nanoparticles for the treatment of lung cancer, and these are excellently reviewed elsewhere (104,105). Interestingly, systemic side effects were diminished, while local side effects (e.g. pharyngitis) remained pronounced, especially for liposome-based therapies with hydrophilic drugs in clinical studies indicating that this system might be too fluid to efficiently inhibit drug leakage and, with this, side effects in non-targeted areas of the respiratory tract. Delivery by nebulization, as mostly used in studies, will probably further increase liposomal membrane instabilities and add to the problem (106). To overcome these, solid nanocarriers for chemotherapeutics might be an alternative with a range of different polymeric, inorganic, and lipid-based systems. One promising lipid-based system showing increased stability compared to liposomes along with maintaining the physiologic-alike lipid composition, was described for paclitaxel by being incorporated in solid lipid nanoparticles (SLN). These are prone to very low side effects and showed remarkable retention times for the drug in vivo in rodents (twice weekly administration) which was attributed to increased cell uptake of those 100 nm SLNs. When nanocarriers are combined with targeting moieties such as ligands, antibodies, or antibody fragments, and are delivered locally to the lungs, preferential uptake into cancer cells was observed.

7.4.4.1.4 Depots

If nanoparticles are to be used for continuous release to prevent repeated dosing, the formulation must be capable of creating depots to remain at the release/action site (107). However, in this type of formulation, usually a greater dosage of the API is required to enable product delivery for a longer period. Moreover, due to their small size and large surface, nanoparticles cannot be deemed an ideal preparation for a depot, and fast diffusion speed and gradual dissolution remain other blocks. Therefore, to overcome these, suitable excipients (e.g. insoluble polymers or lipids forming a diffusion barrier or biodegradable polymers) are required to produce a nanoparticle with sustained-release properties, which often reduces the total mass of material to be applied for continued release (108).

7.4.4.1.5 Pressure Sensitive Metered Dose Inhalers (pMDIs)

With the reformulation of CFC-containing pMDIs after the 1987 prohibition on chlorofluorocarbon (CFC) propellants in the Montreal Agreement, it has been observed that the precipitation of API from pMDI formulations was altered due to the specific properties of hydrofluoroalkane (HFA) propellants (109). Many APIs which had been formulated in the old CFC-pMDIs as a suspension had a higher solubility in HFA which enabled them to be formulated as a solution rather than suspensions. Besides, the overall aerodynamic scale was calculated not by the particle size of micronized API in the formulation but by the droplet size and evaporation behavior Salinity at the exit of the nozzle is faster due to the higher vapor pressure, which contributes to smaller droplets and smaller solidified particles. Those, in effect, are retained in the oropharynx to a smaller degree and are dispersed more peripherally in the lung. Such formulations have a mass median aerodynamic diameter (MMAD) about 1 μm suggesting that the nanometer size is a large proportion of particles. Those drugs are potentially the first nano-particulate formulations for respiratory distribution. Beclomethasone propionate (QVAR®) is an indicator of a drug comprising such “ultrafine fragments” and it has been seen that lung deposition rises from 8% to 56% (110).

7.4.4.2 Vesicular Nano-Drug Delivery to Lungs

7.4.4.2.1 Liposomes

Throughout the years the FDA and other authorities have licensed growing amounts of nano-drug carriers (111), with Doxil® (liposomal doxorubicin) becoming the first nanopharmaceutical to be licensed in 1995 (112). Liposomes are auto-assembled vesicles in an aqueous media, formed from phospholipids and cholesterol. These consist of a lipid bilayer structure and have an inner aqueous nucleus (113,114). They can be used in parenteral supply to raise the therapeutic index and the same is applicable to the respiratory system. An indication of this is Curosurf®, a liposomal defensive alfa preparation for acute respiratory distress syndrome therapy. It is delivered by instillation and makes improved distribution with a limited amount, thus showing decreased toxicity relative to

non-liposomal preparation (115). Furthermore, the controlled release of drug can be obtained with antibiotic liposomal preparations for the local management of lung infections. An example of which includes a colloidal formulation composed of hydrogenated soy phosphatidylcholine (HSPC), unilamellar small liposomes, and 50 mg/ml cholesterol-containing ciprofloxacin (Lipoquin®) for nebulized delivery (116).

Due to the very limited size of the liposomes (50–100 nm), the formed droplets are dispersed very uniformly during nebulization and stay intact, while larger liposomes are considered to be (partially) disturbed when nebulized. Clinical research has demonstrated that this approach helps the dosage level to be decreased to one-day care while retaining a strong local concentration. A further illustration in this axis is liposomal amikacin (Insmed's Arikayce®) (117). This formulation was well received and demonstrated an improved concentration and clinical enhancement of intracellular products. A liposomal amphotericin B (Ambisome®) is being applied to the lung via nebulisation in phase 2 clinical trials to combat allergic bronchopulmonary aspergillosis. Nonetheless, liposomes as vesicles based on phospholipids exhibit some fluidity that make them inherently unstable. Furthermore, they are prepared from dispersion and thus colloidal stability (storage) is an essential parameter to be considered. To improve storage flexibility, liposomes might be converted either by freeze-drying or spray-drying to a dry powder composition. Spray-drying has the benefit of producing individual microparticles, the scale of which can be modified by modifying the surface features suited to the inhalation criteria (118).

7.4.4.2.2 Nanoemulsions

Nanoemulsions were also examined for the delivery of drugs by nebulisation to the lungs (119). They can be particularly useful when administering low melting point drugs (e.g. CoQ10) as a formulation technique. These can lead to improved therapies with decreased occurrence of side effects and better patient compliance with the above-mentioned benefits of nanoparticles.

7.4.4.3 Advantage of Particulate Drug Delivery to Lungs

Nanoparticles in aqueous dispersion will not be stable but tend to agglomerate, which ultimately results in non-redispersible aggregates. Thus, an important aspect of the formulation of nanoparticles is the physical stabilization of individual nanoparticles. This can be achieved by the embedding of nanoparticles into a solid matrix by spray drying. By this approach, microparticles can be used to tailor size and surface characteristics to optimize aerodynamic properties and ensure lung deposition at the desired target. Other approaches include the formation of "Trojan particles" in which nanoparticles form the shell of a hollow dry microparticle or the assembly of "porous nanoparticle aggregates particles" (PNAP). These approaches are especially feasible for "solid" polymeric or lipid nanoparticles, whereas fluidic vesicular systems such as liposomes and micelles are more difficult to transfer to a dry powder while maintaining their particulate nature (120,121).

7.5 Conclusion

Asthma, COPD, acute lower respiratory tract infections, TB, and lung cancer are the most severe cause of mortality in the world. Understanding the pathogenesis of pulmonary disease is essential for its proper management and treatment. The emergence of nanocarriers in the field of medicine has played a major role in addressing the challenges faced by current clinical therapy or diagnosis. Thus, understanding various aspects of nano-drug delivery from its preparation to its fate in vitro and in vivo is essential for the drug to reach the target site to render its efficacy while improving its safety. However, the intervention of nano-drug delivery in treating lung disorders in clinics is still lacking, although the demands for the same is very high, perhaps due to the high cost of its production. Some products in the market have shown success in treating lung diseases and many more are in the pipeline. Thus, further research in this field would be very much helpful in understanding both the pathogenesis and a nano-drug delivery system for the management and treatment of lung diseases.

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