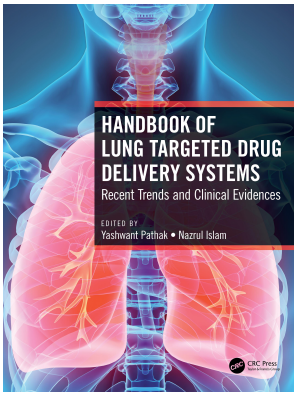

Handbook of Lung Targeted Drug Delivery Systems Recent Trends and Clinical Evidences

Yashwant Pathak, Nazrul Islam

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Aparoop Das, Riya Saikia, Kalyani Pathak, Urvashee Gogoi, Surovi Saikia
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Chronic Lung Diseases: Treatment, Challenges, and Solutions

Aparoop Das[1], Riya Saikia[1], Kalyani Pathak[1], Urvashee Gogoi[1], and Surovi Saikia[2]
[1]Department of Pharmaceutical Sciences, Dibrugarh University, Assam, India
[2]Natural Products Chemistry Group, CSIR North East Institute of Science & Technology, Jorhat, Assam, India

6.1 Introduction

Lung diseases over the years have become one of the leading causes of death and disability across the world. Chronic obstructive pulmonary disease (COPD) affects about 65 million people and kills 3 million annually, making it the third leading cause of death worldwide. Around 334 million people suffer from asthma, the most common chronic disease amongst children, affecting 14% of them globally. Respiratory ailments alone account for substantial morbidity and mortality, but factors like poverty, environmental exposures, crowding and generally poor living conditions increase vulnerability to such ailments. The highest mortality due to chronic respiratory diseases comes from Asia while the lowest is from sub-Saharan Africa (1).

Chronic lung disease (CLD) is the term for a wide variety of persistent lung disorders. It usually develops slowly and may get worse over time. CLDs may be caused by smoking tobacco or by breathing in second-hand tobacco smoke, chemical fumes, dust or other forms of air pollution and frequent lower respiratory infections during childhood. CLDs are generally not curable, but the symptoms can be managed by use of certain medications that help dilate major air passages and improve shortness of breath.

6.1.1 Types of Chronic Lung Diseases

CLDs impose an immense worldwide health burden. The following constitute the majority of the global cases of severe illness and death.

6.1.1.1 Asthma

Asthma affects both children and adults, and is one of the most common chronic ailments encountered in any clinical setting. Asthma is a chronic inflammatory disorder of the airways, usually associated with airway hyper-responsiveness and variable airflow obstruction, that is often reversible spontaneously or under treatment (2). Asthma sets in quite early and can attack all age groups of people. It is often characterized by repeated attacks of breathlessness and wheezing, which differ in severity and frequency from person to person. This happens due to airway inflammation in the lungs and affects the sensitivity of the nerve endings of the airways, making them easily irritated. In an attack, the lining of the passages swell, causing broncho spasm and reducing the flow of air across the lungs. A combination of factors encompassing specific genes, prenatal maternal smoking, diet, and environmental pollution are found to increase the risk of asthma in individuals (3).

6.1.1.1.1 Pathophysiology

Cellular inflammation: A characteristic feature of asthma is congestion of the airway lumen by a tenacious mucus plug which is composed of exuded plasma proteins and mucus glycoproteins secreted from surface epithelial cells (4). Multiple cellular mediators are involved in the inflammatory process, viz. T lymphocytes, mast cells, macrophages, eosinophils, neutrophils, and epithelial cells (5).

Tissue remodeling: Structural airway changes occur chiefly in the mucosal and submucosal tissues of the airways. Pathological changes in the mucosa include epithelial hyperplasia and goblet cell metaplasia with increase in mucus production. Submucosal changes include smooth muscle hypertrophy, collagen deposition, and enlarged mucous glands, causing the airways to narrow and increasing mucus production during an asthma attack (6).

Bronchoconstriction and airway hyper-responsiveness: Seen during acute exacerbations of asthma, a bronchoconstrictor stimulus occurs rapidly to constrict the airways in response to inhalation of an allergen or exposure to occupational sensitizers and irritants (7). Multiple mechanisms, including inflammation, dysfunctional neuroregulation, and structural changes, influence airway hyper-responsiveness.

6.1.1.2 Chronic Bronchitis

Clinically, chronic bronchitis (CB) is defined as production of cough and sputum for at least 3 months a year for two consecutive years (8). About one third of patients with COPD suffer from CB, however it has also been seen in individuals who are otherwise healthy, with prevalence estimates ranging widely both in population-based studies (2.6–16%) (9) and

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among COPD patients (7.4–53%) (10). Chronic bronchitis results from an array of insults to the lung over time. These predominantly include cigarette smoking, respiratory infections, and environmental pollutants and irritants. Viruses cause upto 50% of acute exacerbations of chronic bronchitis and several causative agents have been implicated so far, viz. influenza virus, RSV, rhinovirus, and parainfluenza virus. The other 50% of acute exacerbations are bacterial in nature, with the most common pathogens being *Haemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis*(11).

6.1.1.2.1 Pathophysiology

The pathological hallmark of chronic bronchitis is mucous metaplasia, a process where mucus is overproduced following an inflammatory signal. The dominant mechanisms responsible for copious amounts of mucus in CB are overproduction and hypersecretion of mucus by goblet cells and decreased elimination of mucus. The heightened mucus secretion may develop as a result of a variety of factors that include cigarette smoke exposure (12), acute and chronic viral infections (13), bacterial infections (14), or activation of inflammatory mediators for mucin gene transcription via activation of the epidermal growth factor receptor. This instigates overproduction and hypersecretion of mucus from increased degranulation by neutrophil-mediated elastase. All of these factors team up to cause difficulty in clearing secretions because of poor ciliary function, distal airway occlusion, and ineffective cough secondary to respiratory muscle weakness and reduced peak expiratory flow (15).

6.1.1.3 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a leading cause of death globally. Apart from increasing healthcare expenditures (16), it imposes a significant burden with respect to disability and impaired life quality (17). COPD is an umbrella term for several conditions that block the flow of air in the bronchi and trachea. COPD has been defined as "a diseased state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases" (18),(19). The technical definition of COPD by the Global Initiative for Obstructive Lung Diseases (GOLD) is based on spiromeric criteria and uses the post-bronchodilator forced expiratory volume in one second (FEV1) and its ratio tothe forced vital capacity (FVC). COPD is characterized by a FEV1/FVC ratio <70% (20). Due to its heterogeneity, a variety of different definitions of COPD have become popular that include limitation of airflow, components of destruction of the lung parenchyma (emphysema), development of hypoxemia, and chronic sputum production (bronchitis). However, the terms *chronic bronchitis* and *emphysema* have now been omitted from the formal COPD definition (21).

6.1.1.3.1 Risk Factors

Tobacco smoke remains the prime determining factor leading to the development of COPD. Tobacco smoke causes destruction of lung tissue (emphysema) and obstruction of the small airways with inflammation and mucus (chronic bronchitis), producing the cardinal symptoms of COPD, namely shortness of breath and cough. Other environmental and occupational exposures, air pollution (both indoor and outdoor), genetic abnormalities (such as 1-antitrypsin deficiency), childhood respiratory infections (such as TB, pneumonia, or chronic asthma) may also contribute to the development of COPD. Any factor that affects the lung growth during gestation and childhood has also been found to have the potential of increasing an individual's risk of developing COPD (22). Pulmonary hypertension is a common sequel of chronic airflow obstruction (23). Diet and nutrition may not directly lead to chronic respiratory diseases, however, obesity has been found to coordinate with dyspnea and thus aid in producing symptoms of chronic respiratory diseases. Age-induced physiological lung-function decline can also predispose individuals to COPD.

6.1.1.3.2 Pathophysiology

Mucus hypersecretion and ciliary dysfunction: Airway mucus hypersecretion causes chronic productive cough. This hypersecretion is as a result of squamous metaplasia, increase in the number of goblet cells, and increased size of submucosal glands of the bronchi in response to chronic irritation by harmful particles and gases. Metaplasia of the squamous epithelial cells leads to ciliary dysfunction which is seen in the form of an abnormal mucociliary escalation and difficulty in expectorating (24).

Airflow obstruction and hyperinflation or air trapping: The primary sites of airflow obstruction are the small conducting airways that are < 2 mm in diameter. This is due to inflammation together with narrowing (airway remodeling) and presence of inflammatory exudates in the small airways. In addition, loss of lung elastic recoil and destruction of alveolar support also contribute to airflow obstruction.

Gas exchange abnormalities: Such abnormalities are seen in the advanced stages and can be identified in the form of arterial hypoxemia with or without hypercapnia.

Pulmonary hypertension: This also develops in the later stages of COPD together with severe gas exchange abnormalities. Pulmonary arterial constriction (as a result of hypoxia), endothelial dysfunction, remodeling of the pulmonary arteries (smooth muscle hypertrophy and hyperplasia), and destruction of the pulmonary capillary bed can trigger this condition.

Systemic effects: Systemic manifestations in the form of inflammation and skeletal muscle wasting restricts the exercise capacity of patients and worsens the prognosis, regardless of the degree of airflow obstruction.

6.2 Different Treatment Strategies of Chronic Lung Diseases along with Their Pharmacology

CLD is a group of disorders that affect the lungs and other parts of the respiratory system. CLD may be caused by smoking tobacco or by breathing in second-hand tobacco smoke, chemical fumes, dust, or other forms of air pollution.

CLDs include asthma, chronic bronchitis, pulmonary fibrosis, COPD, asbestosis, pneumonitis, and other lung conditions. These types of lung diseases may affect the airways, lung tissues, or circulation of blood in and out of the lungs (25).

6.2.1 Current Treatment Strategy for Lung Diseases

6.2.1.1 Treatment of Chronic Asthma (26–28)

Asthma is a CLD that inflames and narrows airways in the lungs and causes difficulties in breathing. Asthma occurs in people of all ages and generally progresses during childhood. It may cause wheezing or coughing, or a feeling of tightness in the chest. Treatment can only ease symptoms and prevent the complications. Long-term control medications are the only treatment for severe asthma. They help in preventing asthma symptoms and complications. These include:

a. Inhaled corticosteroids (ICS): ICSs are one of the effective controllers of asthma. They reduce inflammation by inhibiting multiple activated inflammatory genes through reversing histone acetylation (HDAC2), e.g. fluticasone, budesonid, mometasone, beclomethasone, and ciclesonide.
b. Inhaled long-acting beta agonists: Inhaled long-acting beta agonists open the airways by relaxing the smooth muscles around the airways, e.g. salmeterol, formoterol.
c. Inhaled long-acting anticholinergics: These relax the airways in the lungs, making breathing easier for the patients, e.g. aclidinium, umeclidinium, glycopyrronium, iIpratropium, tiotropium.
d. Leukotriene modifiers: Leukotriene modifiers are also used to prevent asthma. Leukotriene modifiers decrease the body's production of the leukotrienes that worsen both asthma and allergic reactions, e.g. montelukast sodium, zafirlukast, and zileuton.
e. Cromolyn sodium: Cromolyn sodium prevents the bronchial hyper-reactivity induced by chronic allergen exposure. Cromolyn is found to be effective in treatment of mild to moderate symptoms of chronic asthma in 60% of patients.
f. Theophylline: Theophylline is mainly used for treatment of lung diseases like asthma, bronchitis, emphysema, etc. It should be used on regular basis to prevent wheezing and breathing problems. It acts by relaxing the smooth muscles around the airways of lung.
g. Oral corticosteroids (OCS): OCS are commonly used for treatment of asthma symptoms and complications. It reduces inflammation and swelling in the airways and relaxes the airways. OCS has been shown to reduce emergency room visits and hospitalizations for asthma. Some examples are cortisone, prednisone, dexamethasone, prednisolone, betamethasone, and hydrocortisone.
h. Quick-relief medications: They can also relieve asthma attacks. These include:
    i. Inhaled short-acting beta-agonists: They provide quick relief of asthma symptoms, albuterol and levalbuterol.
    ii. Inhaled short-acting anticholinergics: They act by widening the airways by blocking the cholinergic nerves which release chemicals that can cause the muscles lining the airways to tighten. They can be used for patients with moderate symptomatic asthma, e.g. tiotropium and ipratropium.
    iii. Combination of an inhaled short-acting anticholinergic and inhaled short-acting beta agonist: This therapy is the most effective treatment of asthma in adults who are treated in emergency departments. It is very effective in controlling symptoms and complications compared with beta agonists alone.

i. Biologics
Biologic drugs improve the immune system to treat asthma. They inhibit the activity of chemicals that swell up the airways. These drugs can prevent asthma attacks or make the attacks much milder. Four monoclonal antibodies are currently approved to treat severe asthma:

1. Reslizumab (Cinqair): Used to treat severe asthma which is a specific type of white blood cell present in blood.
2. Mepolizumab (Nucala): Also used to treat severe asthma caused by eosinophil (eosinophilic asthma).
3. Omalizumab (Xolair): Used to treat severe asthma that is triggered by allergies.
4. Benralizumab (Fasenra): Used to treat severe asthma caused eosinophil (eosinophilic asthma).

6.2.1.2 Current Treatment Strategy of Bronchitis (29,30)

The treatment for bronchitis based on its types whether is acute or chronic. In general, acute bronchitis does not need any treatment. Over-the-counter drugs can break up mucus and treat fever or pain. Treatment of chronic bronchitis is different than acute bronchitis. Chronic bronchitis is often considered as not curable. Only Symptoms can be treated by using drugs, oxygen therapy, pulmonary rehabilitation, combination therapy, and surgery.

Medications used to treat chronic bronchitis

a. Antibiotics: They are used to treat worsening coughs, breathlessness, and mucus production caused by infections in chronic bronchitis. For example, Amoxicillin, Augmentin.
b. Anti-inflammatory drugs: They are used for reducing swelling and mucus output, such as corticosteroids (also called steroids). Steroids help in relieve from symptoms in upper respiratory tract infections. They reduce the inflammation of the lining of the nose and throat. They also help in improving the symptoms of the bronchitis. Steroids can have several side effects like swelling in feet and hands, mood changes, increased appetite and weight gain, etc. Some important corticosteroids are cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, etc.
c. Bronchodilators: They relax the smooth muscles around the airways to make the airways stay open. There are

long-acting and short-acting bronchodilators. Short-acting drugs are most commonly known as rescue drugs as they act quickly. The three most widely used bronchodilators are:

1. Beta-2 agonists, such as salbutamol, vilanterol, salmeterol, and formoterol.
2. Anticholinergics like ipratropium, aclidinium,tiotropium, and glycopyrronium.

d. Combination drugs: They contain a mix of steroids and long or short-acting bronchodilators. This therapy is combined with an inhaled corticosteroid and two long-acting bronchodilators. It may be used for severe bronchitis to overcome the breathing problem. Combinations of two long-acting bronchodilators such as aclidinium/formoterol (Duaklir) and glycopyrrolate/formoterol (Bevespi Aerosphere)

6.2.1.3 Current Treatment Strategy of COPD (31–34)

COPD is characterized by trouble breathing, cough, wheezing, and pain in the chest. COPD is often caused by smoking but is also caused by inhaling toxins from the environment. There is no cure for COPD. The damage caused in the lungs and airways is often permanent. Several drugs can help in reducing the inflammation and open the airways to help make breathing easier. These include:

a. Short-acting bronchodilators
   Bronchodilators open the airways to make breathing easier. Short-acting bronchodilators are often used for emergency condition for quick relief. It can be taken by using an inhaler or nebulizer. Examples of short-acting bronchodilators are mainly-albuterol, levalbuterol, ipratropium, etc.
b. Corticosteroids
   In COPD, airways of lungs can be inflamed, swollen and irritated. Corticosteroids are the drugs which reduce inflammation in the body, making the air flow easier to lungs. They are usually prescribed in combination with a long-acting COPD drug. These forms can be used on a short-term basis when COPD suddenly gets worse. The corticosteroids often prescribe for COPD are:

   1. Fluticasone (Flovent): This is used as an inhaler twice daily. Side effects may occur, like headache, sore throat, voice changes, nausea, cold-like symptoms, and thrush.
   2. Budesonide (Pulmicort): This drug is used as a handheld inhaler or in a nebulizer.
   3. Prednisolone: This drug comes in form of a pill and liquid. It is only given for urgent rescue treatment. Side effects may be headache, muscle weakness, upset stomach, and weight gain.

c. Methylxanthines
   This drug is given to those patients who have severe COPD and whom the typical first-line treatments, such as fast-acting bronchodilators and corticosteroids, cannot help. When this happens, a drug called theophylline, along with a bronchodilator, can be used. Theophylline is a anti-inflammatory drug and it works by relaxing the muscles in the airways.
d. Long-acting bronchodilators
   Long-acting bronchodilators are used to treat COPD for a longer period of time. They are taken once or twice daily using inhalers or nebulizers. They gradually help to ease breathing. The long-acting bronchodilators available today are aclidinium, arformoterol, formoterol, glycopyrrolate, etc.
e. Combination drugs
   Several COPD drugs come as combination medications. These are the combinations of two long-acting bronchodilators or an inhaled corticosteroid and a long-acting bronchodilator. Triple therapy is also recommended, which is a combination of an inhaled corticosteroid and two long-acting bronchodilators for treatment of severe COPD. Combinations of two long-acting bronchodilators include aclidinium, glycopyrrolate, etc. Combinations of an inhaled corticosteroid and a long-acting bronchodilator include budesonide, fluticasone etc.
f. Roflumilast
   Roflumilast (Daliresp) is a drug that falls under the class of a phosphodiesterase-4 inhibitor. It can be orally administered as a pill. Roflumilast helps relieve inflammation, which can improve air flow to the lungs.
g. Mucoactive drugs
   COPD complications can cause increased levels of mucus in the lungs. Mucoactive drugs reduce mucus secretion and help in easy breathing. They often come in form of pill and include drugs like carbocysteine, erdosteine, and N-acetylcysteine.
h. Vaccines
   It is important for patients with COPD to get a yearly flu vaccine. Pneumococcal vaccine is usually recommended for COPD patients. Vaccines can reduce the risk of severe sickness and can help to avoid infections and other complications related to COPD.

6.2.2 Bioactive Compounds

Plants have played an important role in the drug discovery process. The lead or bioactive compounds isolated from herbs can be used for treatment of chronic asthma, chronic bronchitis, and COPD (35). They have fewerside effects than modern allopathic medicines.

6.2.2.1 Bioactive Compounds for Treatment of Asthma (36,37)

Several bioactive compounds derived from plant sources are currently used in the treatment of chronic asthma. Some of the important compounds are

1. Flavonoids

Flavonoids are natural bioactive compounds obtained from leaves, nuts, and fruits. Some of the important flavonoids used in treatment of asthma are

a. Chrysin: A flavone found in *Passiflora caerulea* and *Passiflora incarnate* flowers. It is able to suppress the proliferation of airway around smooth muscles cells to promote a reduction in the levels of pro-inflammatory cytokines which is a key factor in asthma treatment.
b. Baicalin: A bio-metabolite mainly found in leaves and bark of several species of the *Scutellaria* genus. Studies performed on baicalin confirmed that it possesses anti-inflammatory properties, decreasing the inflammatory cell infiltration and the levels of TNF-α in the broncho alveolar lavage fluids (BALF).
c. Luteolin: A flavonoid compound which had also been demonstrated for anti-asthmatic activity. It is widely distributed in aromatic flowering plants and green vegetables.
d. Oroxylin: A flavone obtained from the extracts of *Scutellaria baicalensis Georgi* and *Oroxylum indicum* trees was found to be effective in lowering the airway hyperactivity in an OVA-induced asthma murine model and decreasing the levels of IL-4, IL-5, IL-13, and OVA-specific IgE in BALF.
e. Quercetin: It is a flavonol compound mainly found in citrus fruits, onions, apples, broccoli, cereals, grapes, tea, and wine, and has been known as the main active compound of plants known for their widespread use in traditional medicine for the treatment of inflammatory, allergic, and viral diseases. The studies using this compound as an anti-asthmatic show its high efficacy in reducing inflammatory processes. The anti-inflammatory mechanism of quercetin is attributed to the lipoxygenase and PDE4 inhibition, which promote a reduction in the pro-inflammatory cytokine formation.

2. Resveratrol

Resveratrol is a natural stilbenoid compound obtained from the bark of red fruits. Scientific reports demonstrated that resveratrol was found to be effective against the asthmatic mouse model by significantly lowering the activity of pro-inflammatory cytokines and reducing the airway hyper-responsiveness.

6.2.2.2 Bioactive Compounds for Treatment of Chronic Bronchitis (38, 39)

Several bioactive compounds originating from plants had been reported to be very useful in curing the complications of chronic bronchitis. Some of the reported potent bioactive compounds used against chronic bronchitis are

a. Terpenoid compounds
   Sesquiterpenoid compounds such as farnesol and caryophyllene; flavonoids like apigenin; monoterpenes like linalool, cineole, and fenchone; and triterpenoids such as ursolic acid have been reported to inhibit various viral infections of DNA and RNA viruses. They can be effectively used against viral pathogens involved in bronchitis.
b. Phenolic compounds
   Bioactive components isolated from *Plantago major* contain biologically active compounds like aucubin, baicalein, baicalin luteolin, caffeic acid, chlorogenic acid, ferulic acid, *p*-coumaric acid, etc. In vitro antiviral activity of these compounds has been sucessfully demonstrated against three types of human adenovirus at different concentrations. They are found to be effective in treatment of chronic bronchitis infection.
c. Bioactive compounds of *Zingiber officinale*
   The active compounds isolated from *Z. officinale*, such as β-sesquiphellandrene, α-zingiberene, and β-bisabolene and some flavonoids have been investigated for their antiviral activity. All these compounds showed 50% inhibition against viral pathogens at different concentrations.

6.2.2.3 Bioactive Compounds for Treatment of COPD (40, 41)

COPD is a disease characterized by progressive airflow limitation associated with abnormal inflammatory response of the lung to noxious particles. The inhibition of inflammation by lowering the levels of inflammatory mediators in the COPD pathology such as TNFα, LTB4, and IL-8 by some active compounds from natural sources were investigated and found to be effective in treatment of COPD. They include

1. Austrasulfone, an important bioactive compound obtained from the soft coral *Cladiellaaustralis* has been successfully used for treatment of COPD. It mediated the regulation of the Akt and heme oxygenase (HO)-1 signaling pathways.
2. 1-O-(Myristoyl) glycerol (MG), obtained from the head of the fish *Ilishaelongate*, induces 42% of the neurite outgrowth of rat PC12 cells through the activation of element-binding protein (CREB) and PI3K signaling pathways.
3. Sargaquinoic acid, isolated from a marine alga, *Sargassum macrocarpum*, enhances neuritere generation and protected rat PC12D cells from oxidative stress through PI3K signaling pathways.
4. Bafilomycin(s), a family of toxic macrolide antibiotics obtained from marine *Streptomyces griseus*, can inhibit autophagy by preventing fusion of autophagosomes with lysosomes.
5. Austrasulfone, an important bioactive compound isolated from the soft coral *Cladiella australis*, has shown potent anti-apoptotic activity on neuronal cells SH-SY5Y mediated through the regulation of the Akt and heme oxygenase (HO)-1 signaling pathways.

6.3 Conventional Drug Delivery Systems for Mitigating Chronic Lung Diseases

The drug delivery mechanism for treating lung diseases has increased due to the potential for localized therapeutic options. Some CLDs are irreversible and fatal and there exist few effective treatments for reversing the lung function (42). Pharmacotherapy traditionally available for CLD is recently classified into types based on the forms of therapeutic agents used. These include a variety of antibodies, peptides, chemical drugs, and genetic molecules like SiRNA, shRNA, and miRNA (43–45). The following sections show the different types of therapeutics used as CLD therapeutics.

6.3.1 Material Based

6.3.1.1 Multifunctional Nanocarriers

A wide range of materials are used in the preparation of multifunctional nanocarriers which have the benefit of acting as carriers providing specific effects with improved efficacies and performances, either in the bound or adsorbed state. These varieties currently meet the recent challenges and address the various needs of diseases which are discussed in the following sections.

Delivery of protein and related materials:

Advances in biotechnological research recently saw a huge surge in protein-based drugs. Oral delivery of such drugs is difficult due to the degrading effect of proteases. As a result they are solely injection-based with much therapeutic noncompliance (46). These protein-based drugs also have applications in treatment of local lung diseases, as the first candidate to reach market as an inhalable protein was recombinant human DNase (rhDnase) for treating cystic fibrosis. Nanoparticles with aerodynamic properties suitable to reach the alveolar zone of the lungs was made in the form of a nano micro-system using spray drying (to encapsulate the particles with mannitol). This helps the microspheres of nanoparticles to be released post dissolving in the lining fluid of the lungs (47). Solid lipid nanoparticles (SLN) also provide homogenous distribution on lungs upon nebulization, as found from studies carried out on diabetic rats (48). However, it has been shown that the contact of nanoparticles with the surfactant of the alveolar region promotes coating of nanocarriers via a corona (bimolecular) mainly composed of lipids and proteins (49). Hydrophobicity of nanoparticles is affected by this corona and thereby enhances the biorecognition, showing interactions with other cells and biological entities with no effect on therapeutic levels.

Antibiotic materials:

Antibiotic delivery to the lungs is a very reasonable therapeutic approach in combating lung infections and the most common routes for its administration remain parenternal and oral. Some inhaled antibiotics are available in the market, like colistin, tobramycin, and aztreonan, which are used in cystic fibrosis (50). Other applications of such aerosolized antibiotics are in pneumonia (hospital acquired) (51). All the above formulations are based on nanoparticles as many published works in the literature show that nanoparticles can improve the efficacy of the drugs including side effects and improved kinetic profiles.

6.3.1.2 Hydrogels

Based on the polymeric source used, hydrogels may be homopolymer or copolymer, which have the ability to swell in contact with water (52). They are nontoxic, biodegradable, and biocompatible with high absorption capacity; due to this they have a wide range of therapeutic applications in tissue engineering, drug delivery, and wound healing. Further, temperature sensitive and pH responsive smart hydrogels also help in site-specific targeted drug delivery.

6.3.1.3 Micelle

They are formed through self assembly, due to dispersion of amphiphilic molecules comprising both hydrophobic and hydrophilic components in solution. Due to their minimal toxicity and high stability they are of high importance for sustained and controlled drug delivery (53).

6.3.1.4 Dendrimer

These are hyperbranched macromolecules with many functional groups which have emerged has an ideal drug delivery vehicle. Drugs conjugated to such vehicles are of high stability, increased bioavailability, and long self-life (54).

6.3.1.5 Liposomes

Biodegradable, biocompatible drug delivery vehicles with low toxicity used for site specific drug delivery. They can encapsulate both hydrophobic and hydrophilic drug molecules, preventing the rapid decomposition of the drug released at the specific site (55).

6.4.2 Administration Based

6.4.2.1 Pulmonary Drug Administration

Alveolar ducts, respiratory bronchioles, and alveolar sacs comprise the respiratory region of humans. Methods of transporting drugs along the respiratory transepithelial layer differ a lot and are limited to the upper airways. The administration of drugs via the pulmonary route is mainly by two methods: intranasal and oral inhalation. The former has anatomical limitations, such as narrow lumen, and the later stands to be a better therapeutic option for delivering drugs of very small particles, and loss of concentration is 20% as compared to that of 85% via the nasal route. Oral administration is divided into intra-tracheal instillation and intra-tracheal inhalation (56).

6.4.2.2 Inhalation Delivery

This procedure is non-invasive, and easy to carry and use with improved pharmacokinetics (57). The required doses needed for enhanced treatment of lung diseases are fewer and off-target effects are avoided (58). Lymphatic circulation redistributes drugs into the peripheral airways and prevents first pass metabolism with low enzymatic activity on lungs (59).

6.4.2.3 Systematic Delivery

A quick administration procedure in lung diseases with immediate dissolution to blood stream via IV injection. It is also easily controlled with adjustable drug dosage and patients are more compliant with injections and oral administration. However, higher doses are required for therapeutic implications and molecules have shorter life in bloodstreams (57).

6.4.3 Different Drug Delivery Systems for Different Categories of Patients

6.4.3.1 Elderly Patients

Local tissues and compartments which are not accessible in elderly patients through oral administration are done via the parenteral route (58). It is considered the emerging route for delivery of peptides and proteins with optimal drug release (59). The intravenous (IV) route is commonly used in hospitalized old patients avoiding fast mass metabolism of the drug and remains to be the first choice during emergencies (60). Intramuscular injection (IM), on the other hand, has the potential advatnages of self-administration and earlier hospital discharge (61). Subcutaneous (SC) delivery is preferred for supplying fluid therapy in elderly patients (dehydrated) and is also considered cost effective, can be made for self-injection, and is less invasive with few side effects as compared to the IV route (62, 63). The oral route is the generally preferred route for drug delivery in elderly patients, including oral films, sublingual tablets, medicated gums, orally disintegrating tablets, buccal patches, and sprays that deliver the drug via the mucosal surfaces of the mouth (64, 65).

6.4.3.2 Pregnant Patients

The use of nanomedicine during pregnancy has shown increased bioavailability in the target tissues and minimized concerns regarding side effects to fetus and the transplacental passage (66). An increase in molecular size for restricting transplacental movement can be achieved by attaching the drug to macromolecular carriers like cyclodextrins, or using liposomes or dendrimers (67,68). Fetal growth restriction can be cured by selective drug delivery to a poor-functioning placenta (69).

6.4.3.3 Obese Patients

Oral administration is the most commonly used route for administering drugs, and obesity causes some important metabolic changes which include higher cardiac output, increased gastrointestinal perfusion of blood and splanchnic blood flow, high gastric emptying, and disturbances in enterohepatic recirculation. These change the rate and extent of drug absorption (70). Highly obese individuals may need a higher dosage of drug due to higher plasma volume and delayed gastrointestinal absorption (71). Other administration routes such as transdermal, subcutaneous, and intramuscular administration are affected due to the deposition of subcutaneous fat (70). Also, the intrinsic physiological properties of a drug influence its distribution preferences in obese individuals (72).

6.4 Recent Development in Targeted Drug Delivery Systems for Mitigating Chronic Lung Diseases

Developments in this area include delivery devices and drug formulations which include microspheres, liposomes, and nanoformulations for intranasal delivery. AERx pulmonary technology developed Aradigm, which helps in transferring morphine and insulin to the pulmonary route. Improved inhalation of patients on ventilators are now in the form of a baby mask (42). An advanced strategy for targeted drug delivery in CLD is nanocarriers, which can improve the pharmacokinetics of loaded drugs based on their individual physical properties. Adverse effects of drugs can be minimized based on the current progress in nanoparticles, to target diverse motifs for selective delivery (73). Gene delivery attempts using nanoparticles also are promising therapeutics for CLD, as most of them are related to the chronic failure of defense mechanisms (pulmonary) due to genetic disorders (74). A new class of drug such as mepolizumab (75), (CXCR)-2 antagonist (76), and phosphoinositide 3-kinase (PI3K) inhibitors has (77) gained prominence as a new class of therapeutics for the efficient treatment of CLD.

6.5 Challenges and Solutions

6.5.1 Asthma

Any condition in which an individual's airway becomes inflammed, resulting in a narrow passage that produces extra mucus and causes difficulty in breathing, is termed *asthma*. The effects of asthma can be observed both in children and adults, and it has a variable course in children younger than 5 years of age. And it is this variability that produces challenges in the treatment of asthma. For many years, the SABA bronchodilator was considered the primary treatment for asthma instead of the use of anti-inflammatory agents like ICS (78–80). However, when treatment with a Short Acting Beta Agonist (SABA) was unable to control the effects associated with asthma, and there were occurrences of asthma exacerbation, then ICS was introduced.

Now, the use of ICS has created other challenges, because it was recommended as a maintenance therapy, and the dosage set by physicians was to be adjusted with the clinical response. But the dose often remained unchanged over long time periods. Moreover, the shift to regular therapy of ICS along with SABA was not adopted very well by parents, young patients, adult patients, and caregivers. Later on, to overcome the problems of ICS therapy combined with SABA, Long Acting Beta Agonist (LABA) therapy combined with ICS was introduced (81, 82), which led to further confusion and safety concerns. The Treating Children to Prevent Exacerbations of Asthma (TREXA) trial found that low doses of beclomethasone combined with albuterol decreased the exacerbation frequency to a great extent as compared to albuterol alone. Hence, ICS along with albuterol was used as a stepdown rescue therapy for children who have controlled asthma (83). The same therapy

was also found to be effective in adults in that it could lower the frequency of exacerbations. Use of the drug budesonide in combination with formoterol was also an effective maintenance and reliever therapy that could control exacerbations in adults as compared to the combined therapy of budesonide, formoterol, and SABA (84, 85). Further investigation by the researchers revealed that, taking into account the needs of patients, the combined use of ICS along with a specific dose of fast-acting β2-agonist could potentially overcome the difficulties related to the continuous and dependent use of ICS and SABA monotherapy (86–88).

6.5.2 Bronchial Disorders

The diseased state that causes inflammation of the bronchial tube linings that are responsible for carrying the air from and into the lungs can be termed *bronchial disorders*. Because of the characteristic structure exhibited by the airways, there can be subtle changes in the physiology and clinical aspects related to bronchiolitis (89). The diagnosis of bronchiolitis becomes challenging only when there are greater abnormalities indicated in the physiologic test results of the patient (90). The test patterns of patients with bronchiolitis include trapping of air, and obstructive and mixed obstructive patterns (91). Bronchiolitis may also be evident in those patients who have normal PFTs. Most of the time, the results obtained from chest radiograph reports are normal and hence the small airways need to be subjected to a High Resolution Computed Tomography (HRCT) scan. HRCT cannot scan the normal bronchioles but can identify the diseased bronchioles, either by indirect or direct signs. Ways of managing bronchiolitis may differ depending upon the clinical features and the severity of the diseased state. But the general therapies include treatment of already existing infections in airways and lungs, gastroesophageal reflux, and omitting potential exposures. Use of macrolide antibiotics will not only help to cure different forms of bronchiolitis but will also impact the remodeling of airways in an effective manner (92–94).

6.5.3 COPD

A diseased state whereby various lung diseases block the flow of air and cause difficulty in breathing can be termed *COPD*. The reports of qualitative findings have stated the ways people suffering from severe COPD fight with the various changes in their condition (95). However, in a wide-ranging sense, self-care serves as the primary motivator for all those individuals who have been facing the long term effects of COPD (96). Recognizing and responding to various credences like inappropriate symptom attribution, perceptions related to emotion and low sense of control, should be considered the central basis of the support of self-care and self-management. Self-management cannot be defined as a single phenomenon; rather, to maintain the changes in behavior, continuous support is of utmost importance. Thus, it can be defined as a continuous process. The main challenge with self-management of COPD is that half of the patients have multiple morbidities and most of them have comorbidity. Common morbidities include anxiety, depression, coronary diseases, and pain (97). However, there are no specific self-management guidelines for patients with multiple morbidities.

There is no clear guidance on self-management appropriate for patients with multiple morbidities. Therefore, to help patients with multiple morbidities, counseling and advice from professionals are highly advised. This will help the patients analyse, interpret, and positively respond to the worsening status so that they can survive without undue suffering. Hence, a an effective implementation of a whole system approach is required that can support self-management (98). The approach aims ato address patients with multiple morbidities, ensuring easy and flexible access to the advice of professionals and a continuous care process (99, 100). Currently, self-management is aided within pulmonary rehabilitation programs, but it is expected that in the coming days it will be supported with primary care systems that would facilitate and improve the ongoing support enhancing the efficiency of the complete process (101).

6.6 Future Prospects

The main aim of the respiratory care unit is to look after the coronary care, respiratory failure, and stroke care units. Along with various developments, the medicines used for the intensive care of these patients have given rise to new challenges for the physicians associated with respiratory systems (102). Therefore, it is important to employ various educational programs that can address the problems related to rising requirements and growing challenges. Even though the connection between intensive care and respiratory medicine is not yet clear, they hold certain connections in the domiciliary ventilation area. Respiratory medicine is only utilized in weaning centers, respiratory intermediate units, and home ventilation management in some countries. In the same manner, the subject of respiratory medicine is not even incorporated into the curriculum of respiratory physicians in many countries across the world. Also, it can be seen that conventional intensive care units inadequately represent respiratory medicine. Patient-centered acute care training is initiated by the European Society of Intensive Care Medicine (ESICM) for carrying out an up-to-date intensive care curriculum. The objective behind bringing out such a program is to achieve a harmonized and advanced medicine practice and training that can enhance the quality of acute and critical care. The Pain and Intensive Care Curriculum of the Medicine and Anesthesiology branch was developed by the European Board of Anesthesiology. Further, a diploma course in Anesthesiology and Intensive Care was also introduced by the European Society of Anesthesiology. Also the European Diploma in Intensive Care was developed by ESICM. The physicians of respiratory units should look after respiratory intermediate units, home ventilation units, intensive care units, and weaning centers. Respiratory medicine should also set standards for all other professional units that are associated with intensive care medicine. They should also hold the potential to define the educational standards of weaning units, intermediate respiratory care units, and units of home ventilation (103–108).

6.7 Conclusion

Treatment of patients with CLDs have become a major challenge over the past few decades. Due to a combination of various factors, both past and present, include smoking habits and an ageing population; it is the only major chronic disease that is still associated with rising mortality. However, the last decade has witnessed the rise of technology in almost all fields of healthcare. New advances in the field of treatment strategies and technologies were also introduced and accordingly adapted to overcome various obstacles and challenges in the treatment of CLDs. The data on recent treatment strategies have shown that surgery to reduce lung volume is a promising intervention for COPD; leukotriene blocking agents have gained much attention for treatment of chronic asthma as they have both bronchodilator and anti-inflammatory properties in asthma. Further, positron emission tomography is proved to be a highly sensitive and specific diagnostic tool for diagnosis of CLDs. The monoclonal antibody against immunoglobulin E plays a pivotal role in atopic disease and also has putative immunomodulatory properties, because of which it seems to be very close to being marketed. Lowering the doses of inhaled steroids have resulted in improvements in symptoms. Also, the interleukin 4 receptor antagonist can inactivate naturally occurring interleukin 4 and is considered to be an important pro-inflammatory mediator in asthma. Even though there are some additional obstacles in the treatment of CLDs and controlling the mortality rate, further research must still be carried out so that the mortality rate associated with different CLDs can be controlled to a great extent utilizing various aspects of technology.

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Conflicts of Interest

There are no conflicts of interest among the authors to report with respect to this chapter.

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