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Inhalation Therapy for Lung Diseases: A Comprehensive Review of Pulmonary Drug Delivery Systems

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ABSTRACT

Inhalation therapy has become a popular method for treating respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). The lungs are the primary organs responsible for gas exchange, and inhalation therapy provides a direct route for drug delivery. Various pulmonary drug delivery systems, including metered-dose inhalers, dry powder inhalers, and nebulizers, have been developed to improve the efficacy of inhalation therapy. These systems utilize various carriers, such as liposomes, nanoparticles, and microspheres, to deliver drugs directly to the lungs, enhancing efficacy and reducing systemic side effects. This review provides a comprehensive overview of the different types of pulmonary drug delivery systems, their advantages and disadvantages, and their applications in treating various lung diseases. The article also discusses the role of nanotechnology in pulmonary drug delivery and the potential benefits of using nanoparticles for targeted drug delivery.

Keywords: Inhalation therapy, Pulmonary drug delivery, Lung diseases, Nanotechnology, Respiratory diseases

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INTRODUCTION

The use of inhalation treatment has grown in popularity in recent years. Nowadays, the preferred method of administering medications to treat respiratory conditions like asthma and chronic obstructive pulmonary disease (COPD) is inhalation [(1)]. Respiratorydiseasesare common, have a high incidence rate around the globe, and cause almost 4 million deaths annually, making them a serious public health concern [(2)]. respiratory disorders contribute to a high disease burden. However, those who live in crowded locations, filthy environments, or poverty may be more susceptible to infections [(3)]. Furthermore, according to the World Health Organisation (WHO), more than 2.09 million people died from lung cancer in 2018 as a result ofoccu-patic carcinogens and the growing number of smokers [(4)].Since ancient times, traditional plants have developed into a wealth of therapeutic ingredients that are essential to preserving human health. Several Indian herbal plants are recognised to have good anti-oxidant, anti-bacterial, antidiabetic, immunomodulatory, and anti-cancer properties [(6)].Brazil was found to be the most affected of the 70 nations the WHO examined, with 12.6% of women and 11.5% of males confirmed to be sick [6].In the years to come, the prevalence of COPD is predicted to increase. Risk factors such as smoke, dust, chemicals, biomass fuel, and other air pollutants are the primary causes [(7)].Research on medicinal plants for the treatment of tuberculosis is being published on a regular basis [(8)]. According to the World Health Organisation (WHO), lung cancer, also known as lung carcinoma, is one of the leading causes of mortality worldwide [(9)].

Human Respiratory System

In the human respiratory system, the lungs are the fundamental organs that help move gases fromthe outside world into the bloodstream. In general, the conducting section and the respiratory portion are the two main parts of the human respiratory system. The respiratory portion of the respiratory system starts with the respiratory bronchiole, whereas the conducting section, which includes the nose, nasopharynx, larynx, trachea, bronchi, and bronchioles, directs air to the site of respiration [(4)].Together with the circulatory system, the respiratory system transports oxygen from the lungs to the cells and extracts carbon dioxide, which is then returned to the lungs for exhalation. Respiration is the process by which oxygen and carbon dioxide are exchanged between the air, blood, and bodily tissues. One pint of air is inhaled by healthy lungs 12 to 15 times each minute. Every minute, all of the body's blood

passes through the lungs. The respiratory tract is separated into two primary sections: the lower respiratory tract, which includes the lungs, larynx, trachea, and bronchi, and the upper respiratory tract, which includes the nose, nasal cavity, and pharynx [10].

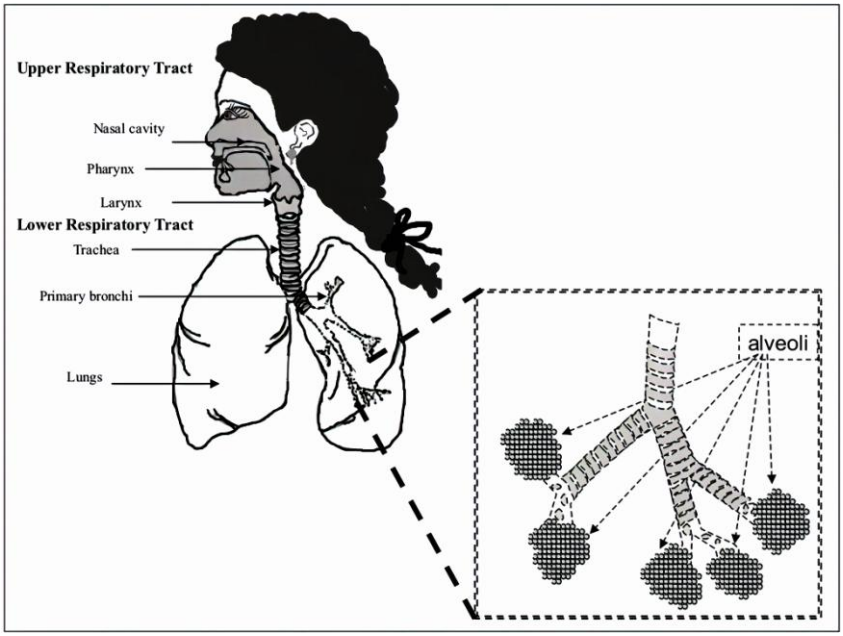

Figure 1: Upper respiratory tract and lower respiratory tract from [10].

Drug delivery device

Metered dose inhalers, dry powder inhalers, and nebulisers are the three main devices available for pulmonary medication delivery.

Metered-dose inhalers under pressure (pMDI):

Furthermore, because they produce chlorofluorocarbons (CFCs), which build up in the Earth's atmosphere's stratosphere and deplete the protective ozone layer, metered dose inhalers are not environmentally friendly [11].The first popular multi-dose portable inhalation device was the pMDI.Almost all patients with asthma and COPD use or have used a pMDI, usually ipratropium and/or albuterol. Every inhaled medication class for obstructive lung illnesses is offered as a single or combination product in a pMDI. However, one of the hardest devices for patients to use properly is the pMDI. The transition from CFC to hydrofluoroalkane (HFA) as the propellant was one of the most notable alterations to the pMDI over the years [12].

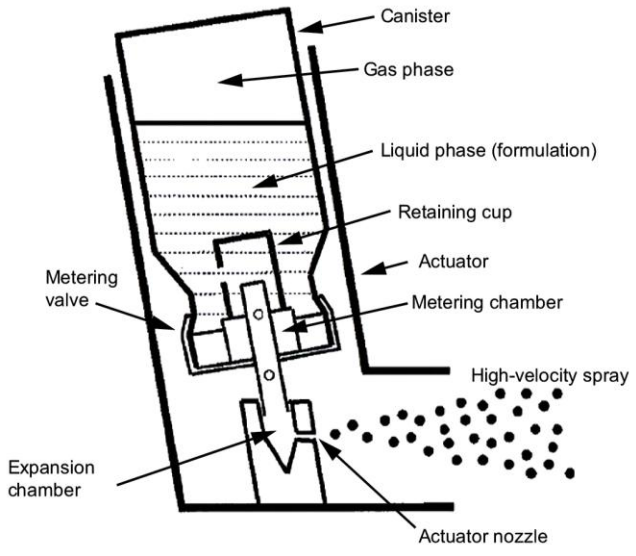

Figure 2: Components of a pressurized metered-dose inhaler. [12].

Metered-dose inhalers under pressure technological advancements Breath-actuated or coordination devices are two categories for new pMDIs. The Easibreathe® and other breath-actuated pMDIs were created to solve the issue of inadequate coordination between the patient's breath and the inhaler's actuation. When the mechanical device detects the patient's breathing and responds by emitting the dose, it is enabled. The patient has time to reliably actuate the pMDI during inhalation, and the actuator coordinates the inhalation flow rate [13].

Nebulizer

One of the earliest inhalation tools is a nebulizer. These turn liquid formulations into 1–5 μm droplets. One benefit of using a nebulizer is that it eliminates the need for patient coordination between inhalation and activation, which makes it easier for ventilated, elderly, and pediatric patients. Additionally, these can administer higher dosages of medication than traditional breathing devices. Jet nebulizers, ultrasonic nebulizers, and mesh nebulizers are the three other categories into which nebulizers fall. The Bernoulli principle to produce aerosols is the basis for jet nebulizers, sometimes known as "pneumatic nebulizers." The main structural elements of jet nebulizers are facemasks, mouthpieces, nebulizer chambers, and compressors. Any kind of liquid, solution, suspension, oil can be nebulized with these. On the other hand, high-frequency (1–3 MHz) vibrations of piezoelectric crystals are used by ultrasonic nebulizers to generate aerosol. High-viscosity liquids are not nebulized with these [14]. Although this device might be helpful in weaning patients with COPD off of ventilators, there aren't many studies demonstrating its efficacy in mechanically ventilated patients [15].

Nebulizers come in two varieties on the market:

- Jet Nebulizers: These devices, which are frequently used in clinical settings, create aerosol droplets within the respiratory range by using compressed gases.
- Ultrasonic Nebulizers: These devices create aerosols from liquid by using ultrasonic energy [16].

For those with asthma and COPD who are unable or unwilling to utilize inhaler devices, nebulizers may be a suitable substitute for inhalers. More recent formulations may provide a pertinent advancement for more effective medication nebulization [17].

Dry Powder Inhalers

DPIs are delivery devices that use the pulmonary route to administer a dry powder formulation of an active medication for either local or systemic effects. To collect powder from a container and deliver it into the lungs within the same airstream, DPIs use air that is pulled through the device. Because DPIs are activated during inhalation rather than using propellants, they are thought to be superior to pMDIs in this regard. This allows for the resolution of patient coordination concerns. Certain DPIs are single-dose devices that need drug capsules to be inserted and perforated to release all the powdered material into the airstream. Other DPIs include several doses extracted from a reservoir or several prefilled medication powder blisters or cartridges [18].

Passive Technology

In passive devices, the primary energy source for aerosolizing the medication powder is the patient's inspiration. These are the most common DPI device types available right now. Mostof the passive inhalers have a mouthpiece, dispersion chamber, and air inlet; however, the dispersion process varies greatly. Powders are entrained into the dispersion chamber of conventional passive inhalers, and airflow disperses the powder bed into inhalable aerosols that the patient can inhale [19].

Nasal vaccination

Nasal vaccination is a vaccination delivery method that uses the nasal mucosa to deliver the vaccine. Due to its potential benefits, such as ease of administration, increased patient compliance, and the nasal mucosa's abundant network of blood vessels that can promote quick vaccination absorption, this approach has drawn interest. Nasal vaccination is regarded as a non-invasive respiratory delivery method in the context of pulmonary medication delivery. Effective and quick systemic administration is made possible by the respiratory system's enormous surface area for drug absorption, which includes the nasal mucosa [20].

1. Inhalation therapy for lung diseases

When compared to other methods, inhalation medicine administration is a potential non-invasive approach and might be the best course of action for individuals with lung disorders. The market's interest in inhaled drugs These benefits could be confirmed in the treatment of pulmonary illnesses. Drugs delivered by inhalation to the lungs would act quickly and have fewer side effects, particularly in cases of COPD and asthma [21].

2. Pulmonary drug carrier

a) Liposomes

Liposomes are commonly used as drug delivery vehicles to encapsulate and deliver both hydrophobic and hydrophilic drugs [22]. Liposomes have proven to be efficient medicine carriers for respiratory conditions because of their safety and propensity to deliver drug release in the pulmonary tissues in a regulated manner. These nanocarriers can entangle a variety of medicinal molecules for delivery in large capacities to the peripheral airways using medical nebulizers (Elhissi 2017). These are synthetic spherical structures made of lipid bilayers that can be used to transport hydrophilic and hydrophobic materials while keeping the enclosed components from breaking down and releasing them at the intended location [23].

b) Lipid-based nanomaterials

Fatty acids and waxes are examples of suitable and biodegradable lipid components used in their preparation. To stabilise the combination, stabilisers, cosurfactants, and surfactants are added. SLNs are modified to create NLCs by combining liquid and solid lipids.[24].

c) Solid-lipid nanoparticles

Solid-lipid nanoparticles (SLN) are colloidal lipidic nanocarriers with a solid core composed of physiological lipids that degrade naturally and are stabilised by surfactants. They range in size from 40 to 1000 nm. There are two primary methods for obtaining SLNs: micro-emulsion technique and high-pressure homogenisation. Solid-lipid nanoparticles have recently been developed as a pulmonary delivery option to conventional nanocarrier systems. because, in contrast to liposomes, it demonstrated substantial drug assimilation and prolonged physical stability. Additionally, their toxicity profile is thought to be safer than that of polymeric nanoparticles because, among other things, their synthesis processes need a tiny quantity of organic solvent, and their core is composed of physiological lipids, which have higher tolerance and lower cytotoxicity [25].

Classification of Pulmonary Diseases

a) Asthma

A long-lasting inflammatory disease of the airways is what asthma is known as. Due to certain triggers, such as certain infections, allergies, and physical activity, the airways exhibit hyperresponsiveness in this syndrome. These lead to chronic inflammation, which in turn causes recurring episodes of chest tightness, wheezing, dyspnoea, and/or cough-like symptoms. Extensive, though diverse, blockage of air in the lungs is often the cause of symptom episodes. This blockage can be reversed naturally or with the aid of a fast-acting bronchodilator, an appropriate antiasthmatic medication [26].Asthma patients are treated with a variety of medications, including oral and inhaled corticosteroids, β2-agonists (short or long acting), leukotriene receptor antagonists, leukotriene synthesis inhibitors, and muscarinic antagonists (short or long acting) in varying dosages [27].

b) Chronic Obstructive Pulmonary Disorder (COPD)

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 report, COPD is a heterogeneous lung condition that is characterised by persistent, frequently progressive airflow obstruction caused by abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema). These abnormalities cause chronic respiratory symptoms (dyspnoea, cough, expectoration, and exacerbations). A startling 90% of these deaths take place in low- and middle-income countries (LMIC), making COPD one of the top three causes of death globally, according to the GOLD 2023 report [28].

c) Acute respiratory infections (ARIs)

The primary cause of death for children under five is acute respiratory syndromes (ARIs), also referred to as ARSs. ARIs are among the world's leading causes of death, accounting for approximately 4 million deaths per year.Two common colds, pharyngitis, laryngitis, bronchitis, pneumonia, and tuberculosis are among the lower respiratory tract illnesses chiefly caused by viruses and bacteria. As new virus-related illnesses like COVID-19, or the new coronavirus, arise, the severity of ARIs rises annually. Since the middle of the 1960s, seven distinct human coronaviruses have been identified; these viruses account for 15% of cases of the common cold [29].

d) Other inflammatory disorders

Airflow blockage, chronic bronchitis, and destruction to the alveolar sacs are the hallmarks of COPD, a progressive and irreversible inflammatory disease of the lower respiratory tract. A similar disorder called emphysema is caused by rupture of the alveolar sacs, which widens the air gaps and gradually damages the alveolar walls. The third most common cause of death in the US and the sixth most common cause globally is COPD. During COPD, the number of macrophages in the sputum, BAL fluid, and airways increases, and this increase is positively connected with the severity of the illness [30].

e) Lung cancer

Lung cancer, which has been and still is the leading cause of cancer-related death for many years, is predisposed to developing when exposed to respiratory toxicants. Male and female smokers have a 25-fold increased chance of dying from lung cancer compared to those who never smoke, and CS is responsible for a significant percentage of lung cancer deaths. When long-term exposure to respiratory toxins damages cells and subsequently disrupts DNA repair and cell cycle regulation, lung cancer develops. This effect is made worse by inflammation brought on by respiratory toxicants. Tumour growth is influenced by both tissuesremodelling and neoangiogenesis in addition to unchecked cell proliferation [31].

f) Pneumonia

During a pneumonia infection, the bacteria produce a lot of mucus and secretions. Gas exchanges between O2 and CO2 are impeded when air sacs are filled with fluid, which results in a decrease in O2 and an increase in CO2. Pneumophila Legionella. After Complement C3b is deposited on the alveolar surface, it enters alveolar macrophages and uses the host's protein as a ligand to attach to the macrophage surface, causing pneumonia to enter. Although they live inside the vacuoles, bacteria do not merge with the lysosomes and continue to exist. The polysaccharide capsules that enclose Streptococcus pneumoniae act as an anti-phagocytic agent to prolong its survival inside macrophages [32].

Polymeric microspheres

a) Sodium Alginate

B-1,4 D-Mannuronic acid and α-L-Guluronic acid monomer copolymerise to create sodium alginate, which can have a homogeneous or heterogeneous block pattern. Alginate polymers have the benefits of being non-toxic, biodegradable, biocompatible, and reasonably priced. In order to create microspheres, Al-Gates can be crosslinked in an aqueous solution with divalent Cations, such as Ca2+, Ba2+, and Sr2+ [33].

b) Chitosan

Because of its cationic charge, chitosan has mucoadhesive qualities that increase its likelihood of adhering to the lungs and extending the duration of medication release. Additionally, chitosan particles can engage with macrophages' mannose receptors, increasing phagocytosis. A number of anti-TB medications, such as rifampicin, rifabutin, isoniazid, ofloxacin, and ethionamide, have been combined with chitosan microparticles for pulmonary administration [34].

CONCLUSION

In conclusion, inhalation therapy is a highly effective method for treating respiratory diseases, and the development of various pulmonary drug delivery systems has improved the efficacy of this therapy. The growing prevalence of respiratory diseases such as asthma, COPD, and lung cancer necessitates continued innovation in drug delivery technologies. Inhalation therapy, supported by advanced delivery devices and nanotechnology, holds significant potential for improving treatment outcomes in these conditions. By delivering medication directly to the

lungs, inhalation therapies can provide faster relief with fewer systemic side effects, making them a valuable tool in modern respiratory care.

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