Journal of Population Therapeutics & Clinical Pharmacology

REVIEW ARTICLE
Doi: 10.53555/hah9at91

INHALED NANOMEDICINE FOR LUNG CANCER: INNOVATIONS AND CHALLENGES IN TARGETED PULMONARY DELIVERY.

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Abstract
Lung cancer is the most common type of cancer worldwide and the leading cause of cancer-related mortality, accounting for around 18% of all cancer-related fatalities, according to the most recent data available on cancer surveillance. Lung cancer ranks among the top five most lethal cancers worldwide, with an overall 5-year survival rate of 20–26%. Inhaled delivery of chemotherapeutic nanomedicines has been proposed as a solution to this drawback of inhaled small molecule chemotherapeutics. These nanomedicines may serve as slow-release drug depots in the lungs or actively transport the packaged drug to lung cancer cells through cancer targeting ligands. Pulmonary drug delivery for lung cancer therapy has been only partly explored in recent decades even though it could represent an attractive alternative route of administration of drug-based therapies, including chemotherapy. In this article, we summarize the best results and limitations of these drug delivery systems and discuss the potential capacity of nanomedicine.

1. Introduction

Lung cancer is the most frequently found cancer in men and the second most common disease that is diagnosed globally. Furthermore, lung cancer accounts for 18% of all cancer fatalities, making it the cancer type with the greatest mortality rate. As a result, lung cancer is a serious issue due to its sharp rise in incidence and significant role in many cancer cases. Early detection of lung cancer is one of the biggest obstacles. Early on, the illness frequently shows no symptoms, and screening methods are insufficient for widespread early detection. As a result, the majority of lung cancer patients receive their diagnosis later, which lowers their chance of survival.[1]

Globally, the overall 5-year survival rate for lung cancer is around 20–26%, which places the disease in the top five most deadly cancers. The primary reason for this high mortality rate is the typically late stage of the disease at diagnosis as a result of the lack of notable symptoms in the early stages.[2,3]

Regional chemotherapy was first used for lung cancer 30 years ago. Since then, new methods of drug delivery and pharmaceuticals have been investigated in vitro, and in animals and humans. An extensive review of drug delivery systems, pharmaceuticals, patient monitoring, methods of enhancing inhaled drug deposition, safety and efficacy, and also additional applications of inhaled chemotherapy and its advantages and disadvantages are presented. Safety depends on the chemotherapy agent delivered to the lungs and is dose-dependent and time-dependent.[4]

Lung cancer is the second most diagnosed cancer worldwide, and it is the most frequently identified disease among men. Furthermore, lung cancer accounts for 18% of all cancer-related deaths, making it the cancer type with the greatest mortality rate. As a result, lung cancer is a serious issue due to its

sharp rise in incidence and significant role in many cancer cases. Early detection of lung cancer is one of the biggest obstacles. In its early stages, the disease frequently exhibits no discernible symptoms, and screening methods are insufficient for widespread early detection. As a result, the majority of lung cancer patients receive their diagnosis later in life, which lowers their chance of survival. This highlights the necessity of creative strategies to enhance early detection and treatment results.[5,6,7]

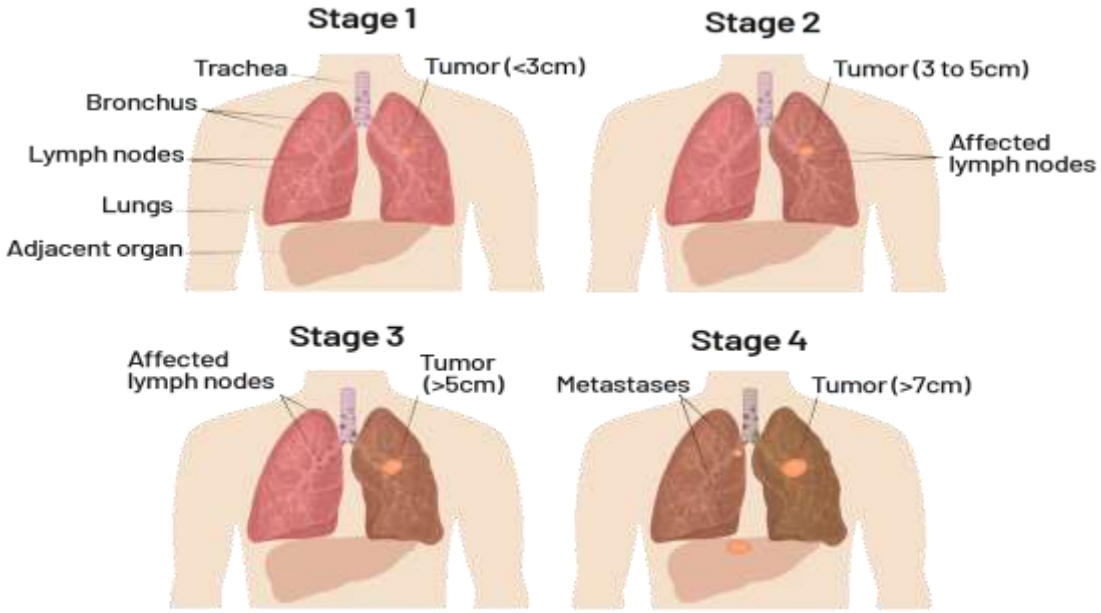

Figure 1 Lung Cancer Symptoms, Risk Factor, Diagnosis, and Treatment.

Lung cancers come in several forms. Small cell lung cancer (SCLC), which causes 15% of cases, and non-small cell lung cancer (NSCLC), which causes 85% of cases, are the two main histological subtypes of lung cancer. Adenocarcinoma (ADC), squamous cell carcinoma (SCC), neuroendocrine tumors, and large cell carcinoma (LCC) are further subtypes of non-small cell lung cancer (NSCLC). Despite being less frequent, small cell lung cancer is quite aggressive.[8,9,10,11]

There are numerous benefits of using nanocarrier technologies for pulmonary medication administration. Among these benefits are the following: 1) the potential to distribute the drug dose among the alveoli in a relatively uniform manner; 2) the achievement of improved drug solubility compared to its own aqueous solubility; 3) the drug's sustained-release, which subsequently lowers the frequency of dosing; 4) the drug's suitability for delivering macromolecules; 5) a lower incidence of side effects; 6) better patient compliance; and 7) the possibility of drug internalization by cells.[12,13] Overall survival rates are improved by early screening programs, particularly for "at-risk" populations. However, diagnosis is challenging and program implementation is complicated. Therefore, there is an urgent need for better treatment options for late-stage lung malignancies that can greatly increase long-term survival.[14,15]

The inhaled delivery of chemotherapeutic nanomedicines has been proposed as a solution to this drawback of inhaled small molecule chemotherapeutics. These nanomedicines may serve as slow-release drug depots in the lungs or may actively deliver the packaged drug to lung cancer cells through cancer targeting ligands. For this goal, a variety of nanocarriers, including lipid-based systems (mostly liposomes), polymers (such dendrimers), and inorganic nanoparticles, have been created and studied preclinically.[16,17]

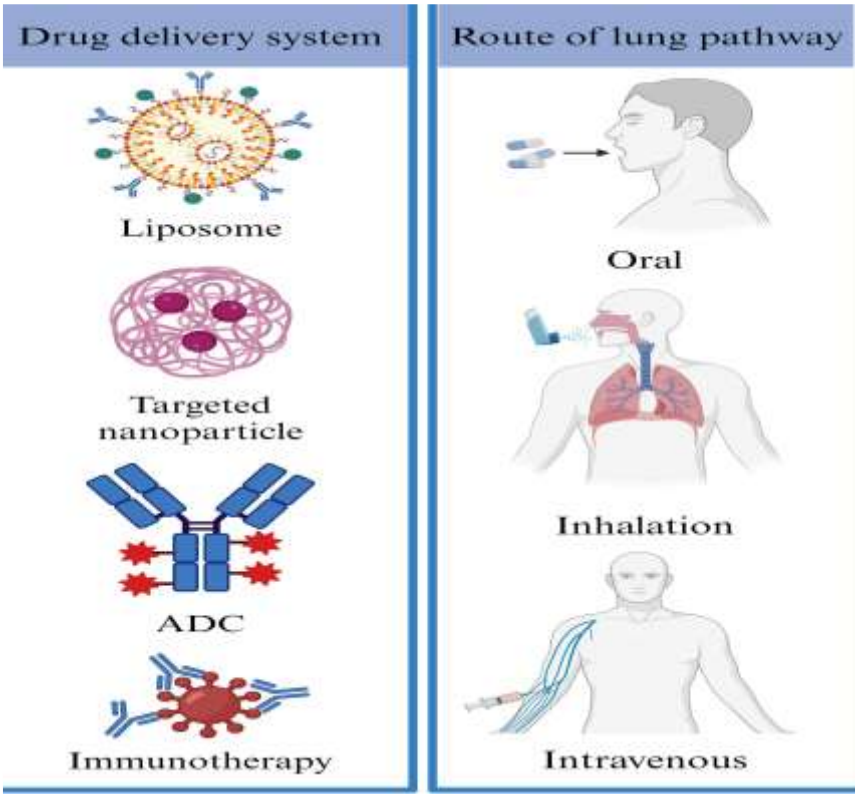

Figure 2 Schematic representation showing current status of clinical trials of lung cancer through delivery pathway

A strategy for delivering high medication concentrations to the intended location without exposing critical organs to harmful drug concentrations in the bloodstream is the idea of local drug delivery. Systemic side effects are reduced in this method. The respiratory system is the best way to administer drugs because of its enormous surface area, thin alveolar epithelium, quick absorption, high bioavailability, absence of first-pass metabolism, and ability to absorb large amounts of medication. Numerous medications have been studied in vitro, in animal models, and in human trials with regard to aerosol chemotherapy used for lung cancer.[18,19]

2. Lung Cancer, Etiology, and Current Practice

Lung cancer continues to be the leading cause of cancer-related deaths worldwide, accounting for almost one-fourth of these terrible deaths. Because cancer is complicated, its treatment depends on a number of variables, including the disease's stage, its precise location within the body, the patient's age and general health, and any underlying medical disorders. Chemotherapy sessions are typically administered after surgery for confined malignancies that have not spread outside of their original site. Adenocarcinoma, squamous cell, and large-cell undifferentiated carcinoma are among the lung cancer forms that fall under the umbrella of non-small-cell lung cancer (NSCLC).The most common type of NSCLC, adenocarcinoma, makes up 40–50% of cases, while bronchiolo-alveolar carcinoma makes up 10-15%. Large-cell undifferentiated carcinoma is distinguished by its fast proliferation and capacity to appear anywhere in the lung, whereas squamous cell carcinoma usually begins in the core parts of the lung. NSCLC accounts for over 85% of all lung cancer cases that are diagnosed, and the vast majority of patients are elderly. Approximately 70 years of age is the usual age at diagnosis. [20,21,22,23,24]

Tobacco smoking remains the main cause of NSCLC, being responsible for nearly 90% of all cases, yet there are other contributors like exposure to second-hand smoke, the presence of radon, environmental pollution, genetic predispositions towards lung cancer, and certain genetic markers like the CYP1A1 gene variant. External factors, such as exposure to harmful substances like asbestos, tar, and specific metals, also play a pivotal role . The probability of developing lung cancer is intrinsically tied to the frequency and longevity of smoking habits. Interestingly, individuals with

HIV present heightened risks of lung cancer as compared to the broader population, and a noticeable association has been established between pulmonary fibrosis and increased lung cancer susceptibility. [25,26,27,28]

For NSCLC, the range of therapeutic alternatives includes surgery, radiation, chemotherapy, and specialized medical interventions. Chemotherapy typically involves a combination of a platinum-based compound with other therapeutic agents. First-line treatments usually encompass a platinum-based compound, synergized with a third-generation cytotoxic drug . There are FDA-sanctioned treatments for NSCLCs exhibiting EGFR mutations, including compounds like gefitinib, erlotinib, and others . Moreover, Bevacizumab, a compound targeting VEGF, has been approved for the first-line treatment of non-squamous NSCLC, especially when paired with chemotherapy. Lung carcinoid tumors, although rare, are categorized as either typical or atypical carcinoids, both originating from neuroendocrine cells. Central carcinoids emerge within the central regions of the lungs, while peripheral carcinoids evolve toward the lungs' extremities.[29,30]

For patients with metastatic lung carcinoids, a variety of treatments is available, which range from surgical procedures to chemotherapy. Subcutaneous administrations of drugs like octreotide are commonly the go-to treatments, while targeted drugs like everolimus also show efficacy. To treat stage III atypical carcinoids, a mix of cisplatin and etoposide is typically used and is occasionally augmented with radiation sessions.[31,32,33]

3. Lung Barriers and Aerodynamic Considerations When Designing Nanoparticles for Pulmonary Drug Delivery

Several factors need to be explored in order to guarantee the efficient pulmonary transport of nanoparticles. These include the different biological and anatomical obstacles that the nanoparticles must overcome as they travel through the respiratory system to get to their destination. Furthermore, designing nanoparticles with the right size, dispersibility, and distribution requires careful consideration of aerodynamics. This section covers the fundamental aerodynamic factors for efficient pulmonary medication delivery as well as the main pulmonary barriers influencing nanoparticle drug delivery.[34]

3.1. Pulmonary Barriers Affecting Drug Delivery of Nanoparticles

The lungs have intricate defense mechanisms that help stop the spread of nanoparticles and micro-sized particles because of their ongoing vulnerability to foreign infections and particles. The task of providing appropriate therapy to the lungs is extremely difficult due to the respiratory system's intricate anatomy. There are four primary defense systems that make up the lungs' barrier system. The first is an uninterrupted layer of epithelial cells that divides the body from the outside world. The second is mucociliary clearance, which includes the formation of mucus and the ciliated cells' synchronized movement. Research has demonstrated that, irrespective of their size, zeta potential, or protein composition, nanoparticles containing agglutinated proteins have a tendency to accumulate in inflammatory lungs. As a chemical barrier, the lung surfactant's proteins and antimicrobial peptides make up the third barrier. It has been demonstrated that lung surfactant affects the destiny of inhaled nanoparticles by interacting with them in diverse ways depending on their distinct physicochemical characteristics (such as hydrophobicity, particle size, and surface charge). Last but not least are the various immune and non-immune cells that cooperate to form the barrier of immunity. Accessing the alveolar region after avoiding the upper airways is difficult due to the lung branching structure and all of its bifurcations.[35,36,37,37,39]

3.2. Aerodynamic Considerations for Effective Pulmonary Drug Delivery

Nanoparticles' aerodynamic behavior in the respiratory tract must be carefully considered in order to deliver drugs to the lungs effectively. Inertial impaction, Brownian diffusion, and gravity sedimentation are the three main processes that lead to particle deposition in the lungs. To increase the likelihood of deep lung deposition, nanoparticles should ideally be "respirable" and form inhalable aggregates or be integrated into carriers with an aerodynamic diameter between 1 and 5 μm. The

proper design and optimization of the device's settings are also necessary to protect the nanoparticles from harm and encourage efficient deposition. These factors are crucial for optimizing therapeutic efficacy and reducing inhaled nanomedicine's off-target negative effects.[40,41]

4.Inhalation drug delivery system

Drug delivery in the lungs includes a wide range of formulations and aerosol-producing equipment. We will look at the most popular and recent varieties, as well as the particular drawbacks of each. Pressurized metered dosage inhalers (pMDIs), dry powder inhalers (DPIs), soft mist inhalers (SMIs), and medical nebulizers are the four pulmonary medication delivery devices now on the market. Intelligent digital technologies have recently become a potent substitute for traditional inhalation equipment. These devices primarily provide inhalation formulations as aerosolized liquids or powders. [42,43,44]

4.1. Pressurized Metered Dose Inhalers (pMDIs)

The most often used inhalation device is a pressurized metered dosage inhaler (pMDI). A canister, retention cup, metering valve, metering chamber, expansion chamber, actuator, and actuator nozzle make up a typical pMDI device. To withstand pressure and corrosion that may be brought on by the liquefied propellant gas, the canister's interior body is composed of inert materials. One of the most crucial parts of pMDIs is the propellant, which includes either a drug in solution or a colloidal suspension of a micronized drug. This is because it regulates a number of factors that impact the medication's effectiveness and delivery. The propellant evaporation time, for example, can impact the dosage since it causes changes in the aerosolized particle's physicochemical properties and performance (i.e., size distribution, aerodynamic diameter, speed, and oropharyngeal deposition). The benefits of pMDIs include easy mobility and predetermined dosages. However, lack of coordination during delivery of pMDI aerosol commonly results in oropharyngeal deposition, especially when utilized by youngsters.[45,46,47,48]

4.2 Dry Powder Inhalers (DPIs)

Dry powder inhalers are portable devices that carry dry pharmaceutical preparations that have been micronized and can be inhaled either by itself or in combination with a carrier. DPIs are specifically made to allow patients to actively inhale the drugs for deposition into their lungs, and they have greater chemical stability. However, it is difficult to construct these kinds of inhalation devices. As a result, several PDI designs were put forth, and as a result, several classifications were offered according to the aerosolization method. The two primary categories of DPI devices are active (powered by a mechanism) and passive (breath-activated). The only source of power that propels the movement and direction of particles from the device to the respiratory tract in passive DPIs is the airflow produced by breathing. On the other hand, the active DPIs use an internal energy source to produce the aerosol, such as a spring, battery, or compressed gas. According to reports, the requirement for a high inspiratory flow rate is the primary cause of DPI restrictions. With a DPI, a pressure decrease of one Kilopascal or more was the cutoff point beyond which the patient might receive a dose that was adequate for inhaling. Additionally, the DPI powder may be sensitive to humidity and heat, which could have an impact on pulmonary deposition and aerosol function.[49,50,51,52]

4.3 Soft Mist Inhalers (SMIs)

A gentle mist of the medication is released by soft mist inhalers (SMIs), which are propellant-free metered dose inhalers that use slow-moving micro-sized droplets that contain the medication. One type of SMI pushes the liquid medication through a tiny nozzle using a spring-loaded mechanism that provides compression power at the device's base (also known as a uniblock system). The nozzle produces small, slow-moving aerosol droplets with optimal droplet size and velocity by creating an angle that permits particle convergence. A mouthpiece, capillary tube, dosage chamber, nozzle outlet, and double-walled plastic bag make up a standard soft mist inhaler. SMIs assist patients in

overcoming the barriers experienced with DPIs and pMDIs through their capacity to produce slow-moving aerosols with lower drug deposition in the oropharyngeal region, allowing simple and consistent aerosol delivery . The soft mist produced can last for roughly 7–10 times longer than usual aerosols generated from pMDIs, due to the decreased velocity of the aerosol particles generated by SMIs . Additionally, it helps the patient exert less effort to stay in sync with the device.[53,54]

4.4 Medical Nebulizers

In order to transport the medication to the lower respiratory tract, medical nebulizers—also known as nebulizers—transform the drug suspension or solution into a fine mist of micro-sized droplets suitable for deep lung deposition. Without the requirement for a propellant, as with pMDIs, or complex formulation techniques, as with DPIs, nebulizers can give large dosages of several medications at once from easily prepared solutions or suspensions. Nebulizers are also appropriate for a broader spectrum of patients, such as youngsters, the elderly, people who have trouble using pMDIs and DPIs, and patients in critical condition. The medication can be administered via nebulizers while the patient is breathing normally. Air-jet (pneumatic), mesh, and ultrasonic nebulizers are the three primary categories based on their aerosol generation mechanisms. They also depend on their own power source to generate and propel the movement of the aerosolized medications into the deep lung.[55,56,57]

4.5 Air-Jet Nebulizers

The first nebulizer type to hit the market was an air-jet nebulizer, also known as a jet nebulizer. They work by using a compressor to create a high-velocity gas stream. The gas transforms the liquid medication into atomized droplets as it goes through a tiny "venturi" nozzle at the bottom of the nebulizer cup. The nebulizer baffles play a part in the formation of those particles, which come in a range of sizes. By serving as a filter, the baffle regulates the particle size by letting tiny droplets of inhalable secondary aerosol reach the patient while larger droplets of primary aerosol crash with the baffles and return to the reservoir for more fragmentation.[58,59]

5. Inhaled Nanomedicine Formulations in Inflammatory Lung Diseases

"Nanomedicines" refers to the use of carefully designed structures, typically ranging in size from 1 to 100 nm, for the diagnosis and treatment of illnesses. With the goal of achieving efficient distribution with few systemic adverse effects, nanotechnology has emerged as a ground-breaking technique for overcoming the lung obstacles associated with traditional treatments in the context of pulmonary medication administration. In addition to having a great localized effect in the lung, formulations based on nanotechnology offer longer therapeutic effects and improved target ability. They can also be used to improve drug penetration through the pulmonary tissue, which will allow the drug to be delivered to organs that are far from the lung through systemic circulation.

A variety of nanoparticulate-based formulations, including liposomes, nanoliposomes, nano-polymersomes, and microspheres, have demonstrated enhanced lung-targeting therapy recently, particularly when surface-modified with various functional groups. Because of their superior capacity to be incorporated into bigger microparticles (1–5 μm), like nebulized droplets, which increases their aerosolization effectiveness, nanoparticle-based formulations provide advantages in deep lung administration when it comes to inflammatory lung illnesses. Their large surface area, however, might encourage aggregation, frequently necessitating the employment of stabilizers or formulation techniques to preserve the nanoparticles' colloidal stability. Additionally, some inhaled nanoparticle formulations have unpredictable clearance profiles, such as a lack of biodegradability, which can result in accumulation and toxicity. For this reason, it is crucial to use materials that are both effective and biocompatible and biodegradable when creating nanoparticles. Liposomes, polymer nanoparticles, nanocrystals, exosomes, dendritic macromolecules, inorganic nanoparticles, virus-like particles, and nanogels are among the nanoparticle formulations being studied for administration through the respiratory system.[58,59,60,61,62,63,64]

6. Lung anatomy and microenvironment

The surface area of human lungs is big (>100 m2), thin (0.1–0.2 μm), and extensively vascularized for absorption. Particle impaction is encouraged by the airways' progressive branching and narrowing. The relative humidity of the lung is about 99.5%. Drug particles are known to be hygroscopic, meaning that high humidity can cause them to enlarge or contract. The amount of drug deposited and, in particular, the distribution of the aerosolized drug within the lung should be impacted by the increase in particle size beyond the initial size. Additional medication absorption may take place through the lymphatic system.[65,66,]

The lungs get the entire cardiac output and are the organ with the highest blood flow. But only the alveolar region is supplied by the pulmonary circulation. About 1% of cardiac output is delivered to the larger airways (trachea, bronchi) by the systemic circulation. The endobronchial circulation is returned to the lung parenchyma and peripheral airways via the right atrium and bronchial veins. Bronchial blood flow rises from 1% to 30% of cardiac output in diseases such as bronchiectasis. The possibility of downstream and peripheral redistribution of inhaled drugs that are absorbed into the circulation from the tracheobronchial areas into otherwise inaccessible lung regions may improve drug effectiveness.[67,68]

Nanomedicine is a rapidly growing field that use nanotechnology to treat and prevent illnesses. Nanomedicine, which uses materials at the nanoscale, may improve the distribution and effectiveness of anticancer medications. Nanoparticles can be efficient drug carriers due to their unique properties. They improve drug solubility, prolong circulation half-life, and allow targeted drug delivery to tumor locations. For instance, anticancer medications like cisplatin have been encapsulated in lipid-based liposomes; these nanoparticles preferentially gather in lung tumor tissues, enhancing drug delivery and lowering toxicity in healthy cells. For example, patients with stage IIIB and IV NSCLC who have not responded to prior platinum-based treatments may benefit from liposomal cisplatin.[69,70]

Nanoparticle engineering allows for both passive targeting based on enhanced permeability and retention effects and active targeting utilizing specific ligands. The process by which ligands or compounds locate specific receptors or markers on cancer cells is known as active targeting. Reference 26 The goal of both active and passive targeting is to deliver therapeutic drugs to cancer cells specifically while causing the least amount of harm to healthy areas. Using certain ligands or chemicals that are able to identify and attach to distinct markers or receptors found on the surface of cancer cells is known as active targeting. One significant example of active lung cancer targeting is the selective targeting of the protein Epidermal Growth Factor Receptor (EGFR), which is typically overexpressed in non-small cell lung cancer (NSCLC). This method makes use of a ligand, such as the antibody cetuximab, that has been specifically designed to bind to EGFR.[71,72,73]

6.1 Use of Nanoparticle Delivery Systems

Non-small-cell lung cancer (NSCLC) is a challenging disease to treat due to its complex molecular heterogeneity and resistance to conventional medications. However, drug delivery strategies utilizing nanoparticles have demonstrated potential in the battle against non-small cell lung cancer. Among the many advantages of these minuscule particles are their ability to precisely target cancer cells, enhance the effectiveness of medications, and reduce toxicity. Inhalable self-assembled albumin nanoparticles conjugated with doxorubicin and octyl aldehyde and adsorbed with the apoptotic TRAIL protein constitute a novel inhalation-based combination therapy method for the treatment of resistant lung cancer. A study found that mice's lungs have a preferred concentration of mesoporous silica nanoparticles (MSNs) following inhalation. This reduced the MSNs' capacity to concentrate in other organs and stopped them from escaping into the systemic circulation. The experimental results revealed that the recommended DDS satisfies the fundamental parameters for a successful treatment of non-small-cell lung cancer.[74,75,76]

6.2 Lipid-Based Nanoparticle Delivery Systems (LNPs)

Lipid-drug conjugate nanoparticles are one type of drug delivery technique that shows great potential for accurately delivering drugs to cancer cells, especially non-small cell lung cancer. The drug core

of these nanoparticles, which is composed of drug molecules covalently bonded to lipid molecules, is encased in a protective shell. Because the lipid shells of these nanoparticles may be either hydrophilic or hydrophobic, they can interact with different human tissues and cell types and provide a platform for efficient drug delivery. The covalent link between pharmaceuticals and lipid molecules allows the drugs to self-assemble into nanoparticles, which can provide better stability and circulation times than previous lipid nanoparticle formulations. Because the coupling of the medications to lipids also enhances biocompatibility, these nanoparticles are safe and effective drug transporters. These nanoparticles have a protective shell around their drug core, which is made up of drug molecules covalently bound to lipid molecules. These nanoparticles can interact with various human tissues and cell types and offer a platform for effective drug delivery since their lipid coats can be either hydrophilic or hydrophobic. Drugs can self-assemble into nanoparticles thanks to the covalent bond between lipid molecules and pharmaceuticals, which can improve stability and circulation times over earlier lipid nanoparticle formulations. These nanoparticles are secure and efficient drug carriers since the coupling of the drugs to lipids also improves biocompatibility.[77,78,79,80]

7. Aerosol Drug Delivery Systems

Drug delivery in the lungs includes a wide range of formulations and aerosol-producing equipment. We will look at the most popular and recent varieties, as well as the particular drawbacks of each. Metered dosage inhalers (MDIs), Inhalation Powder and medical nebulizers are pulmonary medication delivery devices now on the market. Intelligent digital technologies have recently become a potent substitute for traditional inhalation equipment. These devices primarily administer inhalational formulations as aerosolized liquids or powders.[81,82]

7.1 Metered Dose Inhalers (MDIs)

The most common type of inhaler people use is the Metered-dose inhaler (MDI). It's made up of several key parts: a canister, retention cup, metering valve, metering chamber, expansion chamber, actuator, and nozzle. The inside of the canister is built with special, non-reactive materials so it can handle both the pressure and the potential corrosion caused by the liquefied propellant gas. The propellant is one of the most important components of a MDI because it carries the medication either dissolved in the propellant or suspended as tiny particles. How the propellant behaves affects how well the medicine works. For example, the speed at which it evaporates influences the size and movement of the aerosol particles, which in turn affects how much of the medicine actually reaches the lungs versus getting stuck in the mouth or throat. MDIs are popular because they're portable and deliver a set dose each time. However, using them properly can be tricky if the timing between pressing the inhaler and breathing in isn't right, much of the medicine ends up in the throat instead of the lungs. This is especially common in children. [83,84,85,86]

7.2 Inhalation Powder

Inhalation Powders are small, portable devices that deliver medication in the form of a fine dry powder. The medicine inside is micronized made into very tiny particles so it can be inhaled directly, either alone or mixed with a carrier substance. Inhalation Powders are designed to let patients actively breathe the drug into their lungs, and one of their advantages is that the medicine tends to stay chemically stable for longer.

That said, designing Inhalation Powders is more complicated than it sounds. Over time, many different designs have been developed, and they're usually classified by how the powder is released into the air. There are two main types: passive DPIs and active DPIs. Passive DPIs rely entirely on the patient's own breath—the airflow created by inhaling is what carries the particles into the lungs. Active DPIs, on the other hand, use some kind of built-in energy source, like a spring, battery, or compressed gas, to help generate the aerosol.

One of the main challenges with Inhalation Powders is that they require patients to inhale strongly enough to get an effective dose. Research shows that a pressure drop of at least 1 kilopascal when inhaling is needed to deliver enough medication. Another drawback is that the powder can be sensitive

to humidity and heat, which may affect how well the medicine is dispersed and deposited in the lungs. [83,84,85]

8. Challenges for the Delivery of Inhaled Chemotherapy

Inhaled therapy is a popular method for treating respiratory disorders like asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. This method delivers medication straight to the lungs through inhalation. Nevertheless, various challenges come with inhaled chemotherapy that can affect its safety and effectiveness.

8.1 Uniform Drug Deposition

It is difficult to achieve the homogenous deposition of the chemotherapeutic medication in the lungs. Inhaled medications may not be distributed equally throughout the respiratory system, resulting in drug concentration differences at distinct lung areas.

8.2 Patient Variability

Variability in patient anatomy, respiratory rates, and inhalation patterns can all have an impact on inhaled chemotherapeutic deposition. It is difficult to provide consistent and effective drug distribution across a heterogeneous patient group.

8.3 Device Design and Performance

Inhalation device design and function are critical for medicine delivery. Issues such as device blockage, poor aerosolization, or insufficient patient breathing techniques can all have an impact on inhaled anti-lung-cancer agents' delivery efficiency

8.4 Disease-Specific Challenges

Inhaled chemotherapy may bring distinct complications for certain lung conditions. Conditions such as chronic obstructive pulmonary disease (COPD) or cystic fibrosis, for example, may change lung physiology, which in turn impacts drug deposition and effectiveness.

8.5 Toxicity and Side Effects

Chemotherapy inhalation may induce local irritation or systemic side effects. The continuous difficulty of designing inhaled chemotherapy formulations involves balancing therapeutic efficacy with minimizing side effects.

8.6 Drug Stability

Some chemotherapy medications could be affected by environmental conditions such as temperature and humidity. It is critical to ensure a drug's stability during storage and inhalation in order to preserve its effectiveness.[85,86,87]

9. Challenges in the Treatment of Inflammatory Lung Diseases

A critical need for more sophisticated and efficient treatments is highlighted by the frequent emergence of new respiratory illnesses, the most recent of which being COVID 19. An inventive approach that offers opportunities to overcome the drawbacks of traditional treatments and improve efficacy against inflammatory lung disorders is nanotechnology. The true effectiveness of all these rapidly evolving nanoparticle-based medicines in clinical settings is, however, doubtful due to the information gaps that exist between inhalation devices and formulations based on nanoparticles. The fact that there is now only one FDA-approved inhalable nano-formulation product serves as evidence of this (Table 1). The primary obstacles to the clinical translation of nanoparticles and guaranteeing their best use in respiratory delivery studies are covered in this section.[88]

9.1 Transition from Preclinical Studies to Clinical Trials

Inhalable nanoparticle-based formulations have recently been extensively studied at the fundamental research level; yet, there has been a noticeable delay in their transition from basic research to clinical

use. The formulation methods and preclinical testing of inhalable nanoparticle-based formulations for the delivery of anti-tuberculosis medications were recently compiled in a systematic review. None have advanced to clinical trials, despite a sizable number of preclinical research showing that inhalable nanoparticles had improved efficacy and decreased negative effects. The high expenses of creating and describing inhaled regimens, the requirement for inhalation devices to administer the formulation, and the low level of medical adoption were among the justifications put out by the systematic review. Notably, only a small number of clinical trials have been carried out on nanoparticle-based treatments for inflammatory lung conditions in general, and Arikayce® is the only one that has managed to reach the market.[87,88]

9.2 Toxicity of the Different Types of Inhalable Nanoparticles

Numerous types of nanoparticles have been shown to have harmful effects on the lungs, despite the fact that they represent an efficient way to load and distribute drugs, either locally or systemically. This involves lung structural and functional alterations as well as the induction of cytotoxic consequences. For example, in vitro toxicity to immortalized human epithelial cells has been observed for nano-Ag, Si3N4, Fe2O3, ZrO2, Al2O3, TiO2, and Chrysotile. Additionally, silica nanoparticles have been shown to harm mitochondria, alveolar structures, and collagen when inhaled. The harmful effects of quantum dots on the respiratory system in both in vitro and in vivo investigations have also been compiled by Wu et al. While in vivo toxicities included long-term negative effects, inflammation, lung injuries, and the buildup of quantum dots in lung tissues, the toxicity was demonstrated in vitro by immune cell reactions that were disordered, genetic material damage, and decreased cell viability. In contrast, biodegradable nanoparticles such as polymeric, lipid-based, protein-based, and biodegradable inorganic nanoparticles all have minimal or no toxicity in vitro and in vivo Another favorable safety profile was seen with exosomes, which were shown to have only minimal toxicity and high stability and managed to attenuate the side effects of the drug incorporated . Because of their diverse structural, physical, chemical, optical, and magnetic features, nanoparticles' combined toxicity characteristics vary greatly. Additionally, the surface charge, size, and composition of nanoparticles affect their potential toxicity; for instance, smaller particles have been shown to be more biodegradable (i.e., less poisonous) than bigger ones. In chronic inflammatory lung diseases, patients with stiffened alveolar walls commonly have higher deposition and preservation of nanoparticles due to reduced clearance and changes in airflow. More particle composition is transferred to the systemic circulation along with this, which could be harmful to other organs. The total toxicity of nanoparticles on the respiratory system, as suggested by earlier studies, may include genetic alterations, fibrosis, respiratory epithelium damage, inflammation, and oxidative stress.[89,90,91]

10. Lung Surfactants and Impact on Drug Deposition

The alveolar lining of the lung contains a mixture of lipids and proteins called lung surfactants, or endogenous surfactants. By creating a single layer at the alveolar air-liquid interface, they primarily reduce surface tension. Lung surfactants increase aerosol movement between lung locations and help medications administered to the lungs distribute efficiently across mucus surfaces, which leads to more consistent drug dosage in the deeper lung regions. When a surfactant shortage occurs, exogenous surfactants are used as a stand-in treatment for respiratory distress syndromes. These can be made artificially or naturally. The main components of natural surfactants are proteins, neutral fats (mostly cholesterol), and phospholipids, particularly dipalmitoylphosphatidylcholine (DPPC). Common natural surfactants are derived from cows, pigs, humans, and other animals. Conversely, synthetic exogenous lung surfactants, such as lucinactant and colfosceril, are completely synthetic and frequently derived from DPPC.

The surfactant layer is essential for the deposition of drugs in the lungs. To reach the underlying tissue, inhaled medications must first pass through this layer. Lung surfactants have a variety of effects on drug deposition, including:

• Diffusion limitation: The surfactant layer might act as a barrier, hindering drugs from reaching deeper tissues. This can lead to reduced drug concentrations in the lungs and diminished treatment effectiveness.

• Extended residence time: The surfactant layer can prolong the duration of time that the drugs linger in the lungs. This is beneficial for drugs that are rapidly expelled, as it allows for extended exposure to lung tissue, which enhances their potency.

• Drug particle dimensions: The size of the drug particles affects their deposition depth in the lungs. Larger particles might be trapped atop the surfactant layer, which limits their penetration, while smaller particles might navigate past the layer to access the deeper lung regions.

In essence, lung surfactants can enhance deposition by ensuring even alveolar expan sion during inhalation and enhancing alveolar resistance to collapse upon exhalation . Additionally, lung surfactants quickly adhere and redistribute effectively at the air–water boundary, facilitating the even spread of inhaled drugs across the mucus-covered lung surfaces, optimizing drug deposition . Thus, the surfactant quantity present can consid erably influence the drug amounts deposited in the lungs.[90,91,92,93]

CONCLUSION

The uniform and prolonged drug distribution provided by nanoparticles, along with their capacity to get beyond the challenges presented by the complex lung anatomy, make their application in the treatment of respiratory illnesses a promising one. There is a definite correlation between the aerosol performance and formulation properties for every kind of device. Therefore, the suitable inhalation device should be chosen for the right formulation in order to achieve appropriate deep lung deposition and maximize the therapeutic efficacy of the medicine. We maintain that every inhalation device has unique characteristics that can interact differently with different formulations, despite the literature's obvious preference for mesh nebulizers as the most promising devices for delivering nanoparticle formulations. Therefore, before deciding if nanoparticles and the kind of inhalation device are compatible, a number of parameters need to be considered. These include how the inhalation device affects the drug's stability, trapping effectiveness, physicochemical characteristics, and aerosol deposition in the lungs. Additionally, the device's impact on the stability, size, agglomeration, concentration, viscosity, fine particle fraction, and—above all—the formulation's resistance to shearing forces should be taken into account. It's important to highlight, finally, that we had trouble finding research on the compatibility of nanoparticles with inhalation devices. This is because, while it is important to first develop a solid understanding of the mechanism by which the drug is delivered efficiently to the target site, a significant portion of the literature that is currently available concentrated more on the therapeutic outcomes than on the formulation's suitability with the inhalation device.

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