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Research

A Comprehensive Review on Current Progress and Future Perspectives in Pulmonary Drug Delivery Technologies

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Abstract

Pulmonary drug delivery has gained substantial attention as a targeted and efficient method for administering therapeutic agents. This route is particularly valuable in the treatment of respiratory illnesses such as asthma, chronic obstructive pulmonary disease (COPD), and pulmonary infections, offering rapid onset of action and reduced systemic exposure. Despite its advantages, pulmonary delivery faces formulation and device-related challenges, including inconsistent drug deposition, mucosal barriers, and the need for proper inhalation techniques. Various delivery systems have been developed to address these challenges, including pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), nebulizers, and soft mist inhalers (SMIs). Each device offers unique benefits and limitations depending on the formulation and intended therapeutic outcome. Moreover, the pulmonary route shows potential for the administration of biopharmaceuticals and vaccines, offering an alterna

tive to invasive delivery methods. This review discusses the fundamental anatomy and physiology of the respiratory system, evaluates drug delivery technologies, and outlines recent advances in pulmonary therapeutics. A comprehensive understanding of these factors is essential to optimize treatment strategies and enhance the effectiveness of inhalation-based therapies.

Keywords: Pulmonary Drug Delivery

INTRODUCTION

For centuries, the respiratory system has served as a pathway for introducing biologically active substances into the human body. Historically, ancient civilizations inhaled volatile oils and herbal smoke, including tobacco, for medicinal and recreational purposes. This reflects the lungs' exceptional ability to absorb drugs and efficiently transport them into the bloodstream Because of their vast surface area and abundant blood flow, the lungs receive the full cardiac output, making them the most highly perfused organs in the body. In contemporary medicine, inhaled therapeutic proteins such as growth hormone and insulin have shown effectiveness in treating systemic diseases. Inhalation is considered the most effective route for the management of localized respiratory disorders, including lung infections, asthma, and chronic obstructive pulmonary disease (COPD). This technique facilitates the swift transport of drug particles to the target site with a relatively low dosage, minimizing systemic side effects. However, developing pharmaceutical aerosols is often more complex and less efficient compared to traditional administration routes like oral or parenteral methods. The complex architecture and physiology of the lungs present challenges in optimizing pulmonary drug delivery. Despite these difficulties, significant progress continues to be made, justifying the growing research focus on this area. [1].

The bronchial circulation is primarily drained by the bronchial veins. Blood supply to the walls of the bronchi and the smaller airway passages comes from branches of both the right and left bronchial arteries. Venous blood is returned via the superior intercostal vein on the left and the Azygos vein on the right. As recipients of the entire cardiac output, the lungs are the most thoroughly perfused organs in the human body. Pulmonary circulation mainly supports the alveoli and respiratory bronchioles, while the systemic circulation supplies the larger airways—from the trachea to the terminal bronchioles—accounting for roughly 1% of the total cardiac output. The exact function of bronchial circulation in transporting inhaled medications to non-ventilated lung areas or remote deposition sites is still not fully understood. Blood from the endobronchial circulation supplies blood to the lung parenchyma and the distal airways through the bronchial veins, ultimately reaching the right atrium (figure 1). In conditions such as bronchiectasis, bronchial blood flow can surge from 1% to 30% of cardiac output. [2].

For inhalation therapy to be effective, it is vital to understand how inhaled aerosols are transported and deposited in the lungs. This review addresses the technical, physiological, and efficacy-related challenges of pulmonary drug delivery systems. Key focus areas include transepithelial transport and pulmonary administration pathways. Additionally, the review presents a compilation of polymer dosage options and various types of delivery devices. [3].

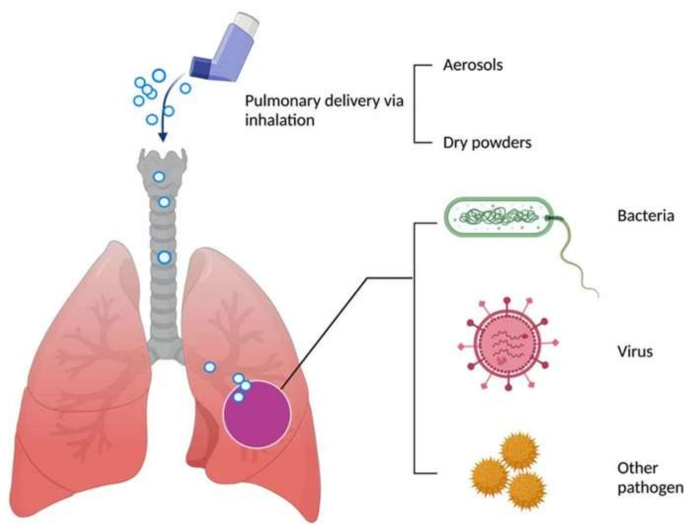

Fig 1: Anatomy and Physiology of the Human Respiratory Tract

The respiratory and cardiovascular systems collaborate to deliver oxygen to cells and remove carbon dioxide from the body, which is transported back to the lungs for elimination. This gas exchange process—occurring in the air passages, bloodstream, and surrounding tissues is referred to as a respiration. In a healthy individual, the lungs typically intake around one pint of air. 12 to 15 times each minute, and the entire blood volume circulates through the lungs approximately once per minute. The respiratory system is divided into two main parts: the upper respiratory tract, which comprises the nose, nasal cavity, and pharynx, and the lower respiratory tract, which includes the larynx, trachea, bronchi, and lungs. Beginning at the larynx, the trachea divides into two bronchi that lead to each lung, providing a pathway for air. Inside the lungs, these bronchi further divide into smaller bronchioles, eventually ending in alveoli—tiny air sacs where the actual exchange of gases takes place.

The respiratory system is particularly prone to a range of illnesses, with the lungs being especially sensitive to conditions triggered by genetic predispositions, environmental toxins, infectious agents, and other harmful substances. Some of the most common respiratory conditions include:

- Asthma
- Bronchiolitis
- Chronic obstructive pulmonary disease (COPD).[4]

Benefits of administering drugs through the pulmonary route

Pulmonary delivery is an innovative and increasingly explored method for administering certain classes of drugs known as "inhalables," which includes both respiratory and systemic therapies administered through inhalation. Inhalable drugs offer several advantages over traditional delivery methods such as injectables, transdermal patches, or oral medications.

- **Ensures Effective Targeting for Lung Diseases:** Inhaled medications are especially effective in managing common respiratory disorders such as asthma, emphysema, bronchitis, and chronic bronchitis.
- **Quick initiation of drug action:** They provide a faster therapeutic effect comparable to the intravenous (IV) route and act more quickly than oral or subcutaneous injections.
- **Dose Reduction:** Inhalation allows for lower drug dosages while maintaining efficacy. For example, a 4 mg compressed dose of salbutamol can be delivered in 40 metered doses.[5]
- **Minimal Side Effects:** Pulmonary drug delivery offers the advantage of reduced systemic side effects, as the medication primarily targets the lungs with minimal exposure to the rest of the body. This needle-free approach also requires a significantly lower dose compared to oral administration.
- **Rapid Onset of Action:** The therapeutic effects of pulmonary drug administration appear relatively quickly.
- **Bypassing Liver Metabolism:** This method prevents the drug from being metabolized by the liver, ensuring higher bioavailability and improved efficacy.

Disadvantage

- **Local Side Effects:** Oropharyngeal deposition can lead to local side effects, and some patients may struggle to use pulmonary drug delivery devices effectively.
- **Mucus Barrier:** The physical barrier created by the mucus layer can hinder drug absorption in the lungs.
- **Variability in Drug Distribution:** The consistency of drug distribution within the lungs is affected by various pharmacological and physiological factors.
- **In Vivo Drug Stability:** Ensuring the stability of drugs within the body remains a significant challenge.
- **Targeting Accuracy:** Precise targeting of the drug to the intended lung regions is crucial for optimal efficacy.
- **Drug Toxicity and Inflammation:** Some pulmonary drugs may cause toxicity or trigger inflammatory responses.
- **Immunogenicity of Proteins:** The immune response to inhaled proteins can impact the safety and effectiveness of pulmonary therapies.[6] [7]

Pulmonary Delivery of Biopharmaceuticals

Vaccines can directly reduce the need for antibiotics by lowering the prevalence of bacterial infections. Consequently, vaccination may help minimize antibiotic usage. Delivering vaccines through mucosal surfaces presents an interesting alternative to parenteral immunization, as it often mimics the natural route by which microbes enter the body. In this review, Hell Fritsch and Scherließ provide an overview of respiratory vaccination, focusing on formulation strategies and application methods. [8].

Aerosols

Aerosol preparations are characterized as stable systems in which solid particles or liquid droplets are uniformly dispersed or suspended within a gaseous medium. (figure 2) Aerosol delivery and deposition of medications in the airways occur through diffusion, inertial impaction, and gravitational sedimentation. Inertial impaction and gravitational sedimentation primarily deposit larger drug particles in the airways, while diffusion enables smaller particles to reach the peripheral regions of the lungs.

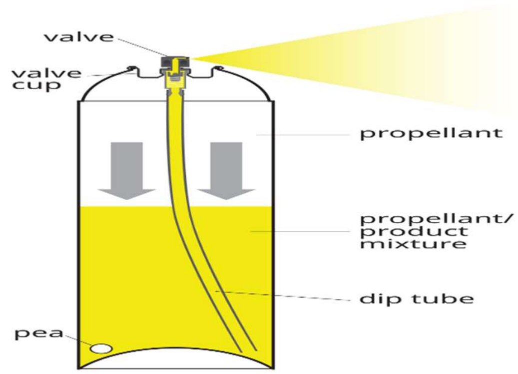

Fig 2: Basic structure and mechanism of aerosols

Drug Delivery Devices

Drug delivery devices are just as important as the formulation itself for effective pulmonary drug administration. Without suitable delivery systems, delivering medications through the pulmonary route becomes challenging. [9][10][11][12].The main types of medication delivery devices for pulmonary drug administration include: Pressurized-Metered dose inhaler, Dry powder inhaler, Nebulizers Jet nebulizers & Ultrasonic nebulizers Table 1 summarizing the Pulmonary Drug Delivery Systems, including key features, advantages, disadvantages, and examples.

Table 1: summarizing the Pulmonary Drug Delivery Systems, including key features, advantages, disadvantages, and examples

Device Type	Mechanism of Drug Delivery	Formulation Type	Advantages	Disadvantages	Examples
Metered Dose Inhaler (MDI)	Propellant-driven aerosol spray	Solution or suspension in propellant (e.g., HFA)	Portable, quick onset, dose consistency	Requires coordination, low lung deposition	Salbutamol, Fluticasone
Dry Powder Inhaler (DPI)	Breath-actuated powder dispersion	Dry powder (micronized API with carrier like lactose)	Breath-actuated, no propellant	Dependent on inspiratory flow, humidity sensitive	Budesonide, Salmeterol
Nebulizer	Compressed air or ultrasonic waves generate mist	Aqueous solution or suspension	Good for elderly/children, no coordination needed	Bulky, longer administration time, costly	Ipratropium, Tobramycin
Soft Mist Inhaler (SMI)	Mechanical energy creates slow-moving mist	Aqueous solution	High lung deposition, coordination less critical	Expensive, device complexity	Tiotropium (Respimat®)

Pressurized-Metered Dose Inhaler

A pressurized-metered-dose inhaler (MDI) device that utilizes a pressurized propellant to dispense the medication. It comprises four main components: the formulation—which includes the active drug, propellant, and necessary excipients—the container that holds the formulation, a metering valve to ensure precise dosing, and the actuator or mouthpiece through which the aerosol is released. This system delivers medication in the form of tiny droplets with a particle size of less than five micrometers, thereby making it well-suited for treating respiratory conditions like asthma and chronic obstructive pulmonary disease (COPD).

MDIs are capable of delivering medications in the form of either solutions or suspensions. In suspension formulations, insoluble materials are dispersed within the propellant vehicle, making particle size and the solubility of active ingredients, surfactants, and dispersing agents critical considerations. In solution formulations, the active substance is dissolved in a pure or mixed propellant. As long as the components are soluble in the propellant-solvent mixture, creating a solution aerosol is relatively straightforward. Common propellants in MDIs include hydrofluoroalkanes (HFAs) and chlorofluorocarbons (CFCs). The medication is micronized to prevent drug crystals from clumping, aided by surfactants, while alternative solvents and lubricants support the valve mechanism.

Upon activation, the propellant is released into ambient pressure, resulting in the aerosolization of the medication for inhalation. As the aerosol travels through the atmosphere, the propellant evaporates, reducing particle size to the ideal range. Inhalation therapy remains the preferred treatment method for lung-related disorders such as asthma, cystic fibrosis, (COPD), it allows for smaller doses and minimizes systemic side effects.

Pulmonary drug delivery has garnered significant scientific interest over the past two decades due to the lungs' Capability to serve as a channel for systemic drug delivery. This is attributed to rapid drug absorption over a large surface area, the thin air-blood barrier, an extensive vascular network, and the ability to bypass first-pass metabolism in the alveolar region. The effectiveness of aerosol therapy heavily depends on the amount of medication that reaches the intended site.[13-15]

Steps to use the pMDIs

Steps for Proper Use of a pressurized-Metered-Dose Inhaler (pMDIs)

1. Shake the inhaler thoroughly typically 3 to 4 times before each use.
2. Remove the protective cap from the mouthpiece.
3. Exhale gently, directing your breath away from the inhaler.
4. Position the inhaler between your teeth and seal your lips tightly around the mouthpiece.
5. Begin to inhale slowly and deeply through your mouth. As you start inhaling, press down on the inhaler to release one dose of medication.
6. Continue to inhale fully, then take the inhaler out of your mouth and hold your breath for about 10 seconds, then exhale gently.

One of the main challenges with MDIs is that users need proper training to operate the device effectively. Another limitation is that MDIs can only deliver a relatively small amount of medication to lungs.

Pressurized metered-dose inhaler (pMDI) consists of several key components, including:

- **Canister** — Holds the medication and propellant.
- **Metering Valve** — Releases a specific, measured dose.
- **Actuator (Mouthpiece)** — Directs the aerosol into the mouth.
- **Propellant** — Helps disperse the medication in fine particles.

DRY POWER INHALER

This flexible delivery method requires a certain level of dexterity. As the name implies, the formulation is in solid form. The dry powder mixture contains the medication, which becomes fluidized when the patient inhales, functioning as a bolus drug delivery system. The the formulation can include the active ingredient alone or be combined with a carrier powder to enhance flow properties. Compared to metered-dose inhalers (MDIs), dry powder inhalers (DPIs) offer better stability, easier handling, and greater cost-effectiveness.

Advantages of Dry Powder Inhalers (DPIs)

- For payloads per puff, a greater medication is accessible.
- It doesn't require blending.
- It permits the use of compact inhalers that are independent of flow rate.
- Despite their small size, the particles easily disintegrate better lung deposition, reduced dosage variability, and the possibility of a condensed dose due to better dispersibility are made possible.[16] [17] [18]

Unit dose devices

In single-dose dry powder inhalers, a capsule containing the powdered drug is inserted into a designated chamber. Once the capsule is punctured in the device, the powder is released and inhaled by the patient.
Types of single-dose powder inhalers include:

Spinhaler

This device operates similarly to a rotahaler, but with an outer sleeve that slides down to puncture the capsule, allowing the propellant to disperse the medication.

Rotahaler

In this device, the capsule is inserted and rotated with the colored end first to break it. The user inhales deeply to draw the powder into the airway. Synchronization with breathing is not required, although multiple breaths may be needed to ensure full dosage delivery[19] [20].

Multi-dose device

Multi-dose dry powder inhalers are designed with a circular disk that holds four or eight individual doses of medication. Each dose is sealed within a separate aluminum blister reservoir, maintaining stability and protection until the moment of inhalation.

One example of a multi-dose device is:

- **Turbohaler:**
  The Turbohaler is a user-friendly dry powder inhaler designed to eliminate the need for loading individual doses or using a carrier powder. Its intuitive design simplifies the drug delivery process, making it more convenient for patients [21] [22].

Nebulizer

Nebulizers are commonly used to aerosolize medication suspensions or solutions for delivery to the respiratory system. They are especially beneficial for managing hospitalized patients with respiratory disorders like asthma and cystic fibrosis.

Nebulizer Formulation

Utilizes pharmaceutical solution technology comparable to that used in parenteral formulations. the formulation is primarily water-based. Co-solvents may be incorporated to enhance solubility or stability. The pH is generally maintained above 5 to ensure drug compatibility and patient comfort.

Nebulizers

- **Jet nebulizer:** Uses compressed gas to create a fine mist of medication.
- **Ultrasonic nebulizer:** Uses high-frequency vibrations to aerosolize the medication solution.

Jet nebulizer

A jet nebulizer uses pressurized gas to convert liquid medication into a fine mist of tiny droplets for inhalation. It includes baffles that help prevent larger droplets from escaping the device, ensuring that only fine particles reach the respiratory system for effective treatment..

Disadvantages

- consumption of time.
- wastage of drug.

Ultrasonic nebulizer

Ultrasonic nebulizers produce aerosol droplets through high-frequency vibrations generated by a piezoelectric crystal, which creates ultrasonic waves that convert the liquid medication into a fine mist. Ultrasonic nebulizers have significantly enhanced drug delivery to the lungs, providing effective treatment for various respiratory conditions. [23] [24] [25]. Ultrasonic nebulizers theoretically offer the potential to adjust the dosage instantly based on a patient's specific needs, considering factors such as breathing patterns, physiological profile, and disease state. This is possible because the generation of aerosol droplets is independent and does not rely on breath actuation. However, the effectiveness of this adaptability is limited by the challenges and constraints associated with traditional designs and technologies. [26]

Drugs for nebulization

Common Medications Used in Nebulizers

- **Diluent Solutions:** Distilled water or normal saline.
- **Mucolytics:** (Help break down mucus)
  - Mesna.
  - Acetylcysteine.
- **Beta-2 Agonists:** (Bronchodilators to relax airway muscles)
  - Salbutamol.
  - Terbutaline.
  - Formoterol.
  - Salmeterol.
- **Antimuscarinics:** (Reduce bronchospasm)
  - Ipratropium bromide.
- **Steroids:** (Reduce inflammation)

- Budesonide.

Advantages

- Propellant-free, reducing environmental concerns and complexity.
- Require less patient coordination compared to metered-dose inhalers (MDIs).
- Fewer formulation issues due to the solid-state nature of the medication.
- Dry powders exist in a lower energy state, which reduces the rate of chemical degradation, thereby improves the formulation's shelf life.

Disadvantage

- Performance is highly dependent on the patient's inspiratory flow rate and breathing pattern.
- Device resistance and design limitations can impact the efficiency of drug delivery.

Soft mist inhalers

SMIs are often multi-dose devices that could compete with pMDIs and DPIs in the portable inhaler market. Soft Mist Inhalers utilize Liquid formulations comparable to those used in nebulizer devices. The device is powered by a compressed spring mechanism, which generates the energy needed to produce a slow-moving, fine mist for inhalation; propellants are not needed.[27] Currently, there is just one human-use gadget that represents SMIs: the Respimat. The Respimat uses water to dissolve its active components instead of propellant or batteries.[28]

CONCLUSION

Pulmonary drug delivery represents a powerful and evolving approach for treating both respiratory and systemic conditions. Its ability to deliver drugs directly to the lungs allows for rapid onset of action, targeted therapy, and minimized systemic side effects. Advances in inhalation devices such as MDIs, DPIs, nebulizers, and SMIs have significantly improved the precision and effectiveness of aerosol therapy. However, challenges like formulation stability, device handling, and patient coordination still need to be addressed. With ongoing research and innovation, pulmonary delivery systems hold great promise in enhancing therapeutic outcomes and broadening the scope of drug administration beyond traditional methods.

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