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A Mini Review on Pulmonary Drug Delivery System

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ABSTRACT

Respiratory drug delivery has emerged as an attractive, non-invasive route for drug administration due to its large surface area, rich vasculature, and rapid onset of action. In addition to drugs intended for local therapeutic effects within the lungs, this route is increasingly explored for the systemic delivery of molecules, offering advantages such as avoidance of first-pass metabolism and improved bioavailability. However, successful pulmonary drug delivery depends on several critical factors. Beyond the physicochemical properties of the drug, formulation into a stable and effective inhalable dosage form is essential to ensure consistent performance and shelf life. The formulation must be compatible with an appropriate inhaler device capable of generating an aerosol with an optimal particle or droplet size to achieve deposition in the targeted region of the respiratory tract, whether the upper airways, bronchi, or deep alveolar regions. Furthermore, patient-related factors play a significant role in therapeutic outcomes. Variations in lung anatomy, respiratory diseases, breathing patterns, and inspiratory flow rates can markedly influence aerosol deposition and drug absorption. Therefore, an integrated approach considering drug characteristics, formulation design, inhaler technology, and patient (patho-)physiology is crucial for the effective development and clinical success of respiratory drug delivery systems.

1. INTRODUCTION

Pulmonary drug delivery is an emerging and rapidly developing drug delivery technology in which medication is administered through inhalation and absorbed into the bloodstream via the alveolar epithelium. Owing to the extensive surface area of the lungs, high permeability of the alveolar membrane, and dense capillary network, this route enables rapid drug absorption and onset of action. Pulmonary drug delivery offers a non-invasive and patient-friendly alternative to conventional routes such as subcutaneous and intravenous injections, thereby improving patient compliance and reducing discomfort and associated risks [1]. In addition, this route bypasses hepatic first-pass metabolism, which can enhance bioavailability and reduce dose requirements.

Targeting drug delivery to the lungs has become one of the most significant strategies for achieving both local and systemic therapeutic effects. As a result, extensive research efforts over recent years have focused on the development of advanced pulmonary drug delivery techniques and innovative inhalation devices designed to improve drug deposition and therapeutic efficiency. Currently, the predominant drug targeting approaches involve the direct administration of drugs into the lungs, primarily through inhalation therapy. This is commonly achieved using pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs), which are widely used due to their convenience, portability, and effectiveness.

In addition to inhalation-based methods, intratracheal administration is frequently employed as an initial experimental approach in in vivo lung drug delivery studies. To ensure effective delivery of a sufficient drug dose to the lungs, the use of appropriate drug carriers is essential. These carriers may consist of solid, liquid, or gaseous excipients, which play a crucial role in improving drug stability, aerosolization, lung deposition, and overall therapeutic performance.

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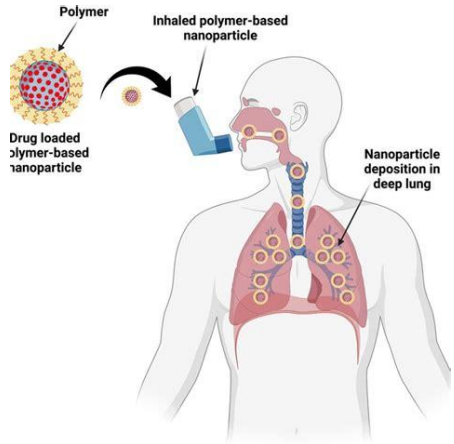

Fig.1 Pulmonary drug delivery schematic with inhaler and lung deposition

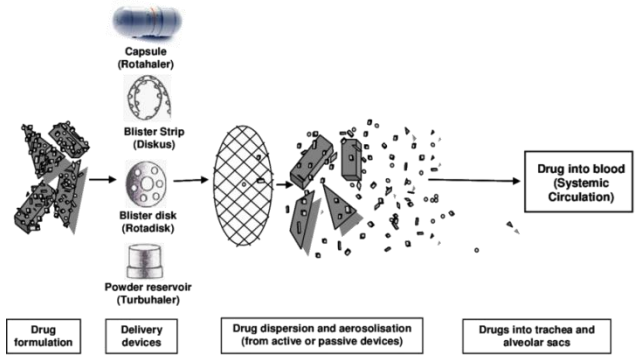

Fig.2 Dry powder inhaler (DPI) drug delivery diagram

The use of micro reservoir type systems offers clear advantages, such as high loading capacity and possibility of controlling size and permeability, and thus of controlling there lease kinetics of the drugs from the carrier systems. These systems make it possible to use relatively small numbers of vector molecules to deliver substantial amounts of a drug to the target.

- ✓ The respiratory tract is one of the oldest routes used for the administration of Drugs Over the past decade inhalation therapy has established itself as a valuable tool in the local therapy of pulmonary diseases such as asthma or COPD (Chronic Obstructive Pulmonary Disease).
- ✓ This type of drug application in the therapy of these diseases is a clear form of targeted drug delivery.
- ✓ Pulmonary delivery of drug has become an attractive target and of tremendous scientific and biomedical interest in the health care research area as the lung is capable of absorbing pharmaceuticals either for local deposition or for systemic delivery. The respiratory epithelial cells have a prominent role in the regulation of airway tone and the production of airway lining fluid.
- ✓ Pulmonary drug delivery system refers to a device, technology or formulation of a drug meant for infusion into the body via the pulmonary route.
- ✓ Pulmonary route used to treat different respiratory diseases from last decade
- ✓ Pulmonary drug delivery is primarily used to treat conditions of the airways, delivering locally acting drugs directly to their site of action.
- ✓ In recent years, the possibility of utilizing the pulmonary route for the systemic delivery of peptides and other molecules which are not absorbed through the gastrointestinal tract has also been explored [2-10].

2. GROSS ANATOMY OF THE LUNGS

The lungs are major organs of the respiratory system, and each lung contains structures belonging to both the conducting zone and the respiratory zone. Their primary function is to facilitate the exchange of oxygen and carbon dioxide between the atmospheric air and the blood. This vital gas exchange occurs across an exceptionally large epithelial surface area of approximately 70 square meters, which is thin, highly permeable to gases, and richly supplied with capillaries, thereby enabling efficient diffusion of respiratory gases.

Anatomically, the lungs are paired, pyramid-shaped organs located within the thoracic cavity and are connected to the trachea through the right and left primary bronchi. Inferiorly, the lungs rest on and are bordered by the diaphragm, a flat, dome-shaped skeletal muscle that separates the thoracic cavity from the abdominal cavity and plays a crucial role in respiration by altering thoracic volume during breathing. The lungs are enclosed and protected by a double-layered serous membrane known as the pleurae, which are also attached to the mediastinum and reduce friction during lung movement.

Structurally, the right lung is shorter and wider than the left lung, while the left lung is smaller in volume to accommodate the position of the heart. The presence of the cardiac notch on the surface of the left lung provides space for the heart. The apex of each lung refers to the superior pointed region extending above the clavicle, whereas the base is the broad inferior region adjacent to the diaphragm. The costal surface lies against the ribs, and the mediastinal surface faces the midline and contains the hilum for passage of bronchi, blood vessels, and nerves [12].

2.1 Absorption Of Drugs

- ✓ Through intercellular junctions.
- ✓ Vesicle mediated transport (Figure4).
- ✓ Transcellular diffusion.
- ✓ Transport mediate Absorption.

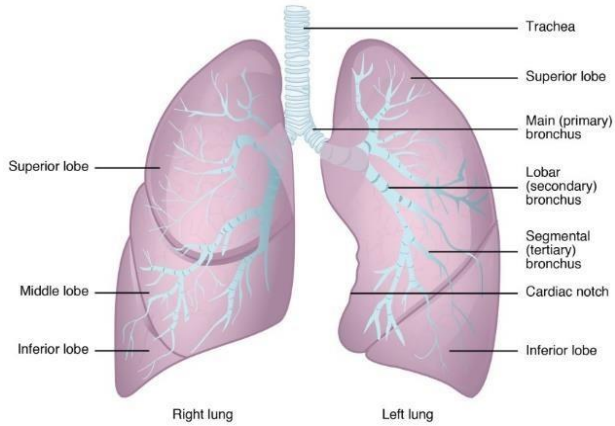

Figure3: Gross anatomy of lungs.

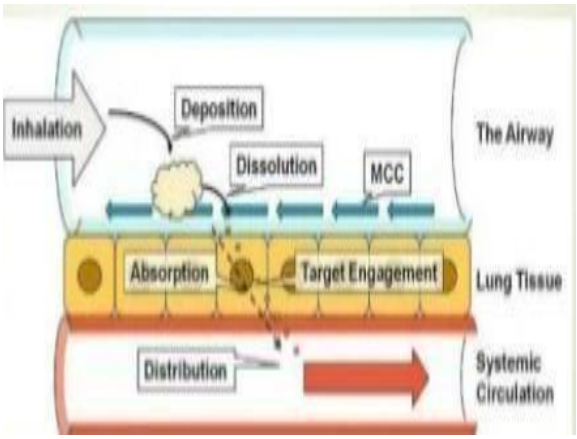

Figure4: Absorption of drugs.

3. DISEASES OR DISORDERS OF THE PULMONARY TRACT

Lung disease refers to any condition that interferes with the normal functioning of the lungs and impairs effective respiration. Pulmonary diseases can broadly be classified into three major categories based on the region of the lung affected: airway diseases, lung tissue diseases, and lung circulation diseases. In clinical practice, many lung disorders involve overlapping features of more than one category.

3 1. Airway Diseases

Airway diseases are among the most prevalent respiratory disorders worldwide; however, their actual prevalence is often underestimated. These diseases primarily affect the airways responsible for conducting air to and from the lungs. Common airway diseases include asthma, chronic obstructive pulmonary disease (COPD), and bronchiectasis. Although these conditions share similar symptoms such as coughing, wheezing, and shortness of breath, they differ significantly in disease progression and clinical outcomes. Early differentiation between these diseases is crucial for initiating appropriate therapeutic strategies. Due to shared pathophysiological mechanisms, patients with different airway diseases may present with overlapping clinical symptoms, complicating diagnosis and treatment [13].

3.2. Lung Tissue Diseases

Lung tissue diseases affect the structure and elasticity of the lung parenchyma. These conditions are often characterized by inflammation or fibrosis, leading to restrictive lung disease in which the lungs are unable to expand fully. As a result, oxygen uptake and carbon dioxide elimination are impaired. Patients frequently describe a sensation of chest tightness or difficulty taking deep breaths, often compared to wearing a tight garment. Pulmonary fibrosis and sarcoidosis are common examples of lung tissue diseases.

3.3. Lung Circulation Diseases

Diseases of lung circulation affect the pulmonary blood vessels and are commonly caused by clot formation, inflammation, or scarring. These conditions reduce the efficiency of gas exchange and may place additional strain on the heart. Pulmonary hypertension is a notable example, and affected individuals typically experience severe breathlessness during physical exertion.

4. COMMON PULMONARY DISEASES

The most frequently encountered lung diseases include:

- Asthma
- Partial or complete lung collapse (pneumothorax or atelectasis)
- Bronchitis (inflammation of bronchial tubes)
- Lung cancer
- Pneumonia
- Pulmonary edema (abnormal fluid accumulation in the lungs)

5. FACTORS AFFECTING PULMONARY DRUG DELIVERY SYSTEMS

5.1. Physiological Factors

- Lung morphology and surface area
- Oral versus nasal breathing patterns
- Breath-holding capacity
- Disease state of the lungs
- Tidal volume and inspiratory flow rate

5.2. Pharmaceutical Factors

- Particle size and shape
- Particle density and velocity
- Aerosol velocity
- Physical and chemical stability of the formulation

5.3. Factors Affecting Absorption and Metabolism

- Thickness of the absorption barrier

- Pulmonary blood supply
- Enzymatic activity within the lungs
- Membrane permeability

6.CHALLENGES IN PULMONARY DRUG DELIVERY

6.1 Low Efficiency of Inhalation Systems

An effective aerosol system must generate particles of optimal size. Very small particles are exhaled before deposition, while large particles tend to deposit in the oropharyngeal region rather than reaching the lower respiratory tract.

6.2 Limited Drug Mass per Puff

Many drugs require milligram doses for therapeutic efficacy; however, most inhalation systems deliver less than 1000 µg per puff to the lungs, limiting their effectiveness.

6.3 Poor Formulation Stability

Several drugs, particularly corticosteroids and moisture-sensitive compounds, exhibit instability due to their crystalline nature and sensitivity to environmental conditions.

6.4 Poor Dose Reproducibility

Variability in patient technique, device malfunction, disease severity, and formulation instability can lead to inconsistent dosing and reduced therapeutic outcomes [2–10].

7. ADVANTAGES OF PULMONARY DRUG DELIVERY

Pulmonary drug delivery offers numerous advantages, including:

- Rapid absorption and onset of action
- Reduced systemic side effects
- Direct delivery to the target site
- Improved stability of labile drugs
- Ease and convenience of administration
- Reduced irritation compared to topical application
- Ability to nebulize protein-based drugs
- Improved solubility using lipid or emulsion-based carriers
- Dose titration capability
- High patient compliance in respiratory disorders

8. DISADVANTAGES OF PULMONARY DRUG DELIVERY

Despite its benefits, pulmonary drug delivery has certain limitations:

- Uncertain drug transport to the target site
- Risk of irritation and local toxicity
- Rapid drug clearance from the lungs
- Limited targeting specificity
- Potential for drug abuse due to rapid brain entry
- Difficulty in dose regulation for some patients
- Improper inhaler usage by elderly or pediatric patients [14]

9. RECENT ADVANCES IN PULMONARY DRUG DELIVERY SYSTEMS

The pulmonary route offers significant advantages due to its large surface area, high vascularization, and thin blood–alveolar barrier. However, most marketed inhalable formulations are short-acting and require frequent dosing, which reduces patient compliance. Recent research has focused on developing controlled pulmonary drug delivery systems while overcoming airway clearance mechanisms.

Key advancements include:

- Development of controlled-release pulmonary formulations
- Novel strategies to bypass mucociliary clearance
- Use of large porous particles for improved aerosolization
- Swellable microparticles for sustained drug release
- Porous nanoparticle–aggregate particles (PNAPs) for prolonged therapeutic action [15]

10.CONCLUSION

1. Pulmonary drug delivery has become a preferred route for administering both local and systemic drugs due to its non-invasive and needle-free nature, leading to improved patient compliance.
2. This route is effectively used in the treatment of respiratory and systemic conditions such as asthma, migraine, angina pectoris, and vaccination, while also minimizing systemic side effects.
3. The lungs offer a unique physiological advantage, including a large absorptive surface area, an extremely thin alveolar membrane, and rich blood supply, which enables rapid drug absorption and onset of action.
4. Pulmonary delivery systems provide a promising alternative to oral and intravenous routes by reducing high serum drug concentrations and associated adverse effects.
5. Recent advances in particle engineering, formulation strategies, and inhalation devices have enabled controlled drug release, targeted lung delivery, and improved deep lung deposition.
6. The overall success of pulmonary drug delivery depends on the combined performance of the drug, formulation, and inhaler device, emphasizing the need for integrated system design to achieve optimal therapeutic outcomes.

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