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Review Article

Review Article on Pulmonary Drug Delivery Systems

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Chronic respiratory diseases present a significant global health challenge, necessitating advanced therapeutic approaches for effective management. Pulmonary drug delivery systems offer a targeted, non-invasive, and efficient means of administering medication directly to the lungs, maximizing therapeutic effects while minimizing systemic side effects. This review comprehensively examines contemporary pulmonary drug delivery technologies, including metered-dose inhalers, dry powder inhalers, and nebulizers, alongside emerging nanoparticulate carriers and controlled-release formulations. Key physiological and pharmaceutical factors influencing drug deposition, absorption, and efficacy in the respiratory tract are explored. Additionally, the review highlights current applications spanning asthma, chronic obstructive pulmonary disease, cystic fibrosis, and emerging areas such as pulmonary gene therapy and vaccination. Challenges such as device usage complexities, drug stability, and local toxicity are discussed. Future perspectives emphasize the need for multidisciplinary research to bridge technological advances with clinical practice to improve patient outcomes in respiratory medicine.

Keywords: Pulmonary drug delivery, inhalation therapy, chronic respiratory diseases, metered-dose inhalers, dry powder inhalers, nebulizers, nanoparticulate carriers, controlled-release formulations, respiratory drug absorption, targeted lung therapy.

INTRODUCTION

Chronic respiratory disorders (CRDs) encompass a range of diseases affecting the lungs, airways, and related structures. The World Health Organization (WHO) identifies CRDs as major contributors to global mortality and disability, impacting individuals across all socioeconomic backgrounds. The five most prevalent diseases causing respiratory impairment and illness are asthma, chronic obstructive pulmonary disease (COPD), tuberculosis (TB), lung cancer, and acute respiratory tract infections.[1] According to the WHO Report 2017, lung disease-related deaths in India account for approximately 10.9% of total deaths, placing it fourth among respiratory disease-related fatalities.[2] This significant global health burden has driven the need for advanced delivery systems and tools designed to effectively prevent and treat these respiratory conditions. Pulmonary drug delivery systems focus on administering aerosols directly to the respiratory epithelium through inhalation. These systems are designed to achieve either prolonged drug retention or rapid absorption, depending on the intended therapeutic effect.[3] Inhaled drugs serve three primary purposes: prophylactic treatment, localised or systemic disease management, and ongoing therapy. Devices such as nebulizers, metered-dose inhalers, dry powder inhalers, and other aerosol technologies are utilised for drug delivery.[3] Inhalation provides a targeted approach that requires smaller drug doses compared to systemic delivery methods like oral medications and injections, thus minimising systemic side effects and enhancing the therapeutic effect by delivering medication directly to the affected area. Furthermore, inhalation can facilitate systemic drug absorption through the alveoli due to the large surface area of the lungs. Although drug absorption via the lungs is generally faster than other non-invasive methods, rapid drug clearance and metabolic degradation, especially for small molecules and peptide-based drugs, can reduce the overall effectiveness of inhaled therapies.[4]

Advantages:

- **Non-invasive Delivery**: Pulmonary drug delivery offers a non-invasive alternative for administering drugs that traditionally require injections, such as peptides and proteins (e.g., insulin for diabetes, Interferon beta for multiple sclerosis, and many recent biotech drugs).

- **Efficient Targeting**: It allows for targeted drug delivery directly to the lungs, making it effective for treating common respiratory conditions like asthma, emphysema, and chronic bronchitis.

- **Rapid Onset**: Inhaled medications can act as quickly as intravenous (i.v.) drugs and faster than oral or subcutaneous injections.

- **Avoids Gastrointestinal Issues**: Inhalation bypasses problems related to the gastrointestinal tract, such as poor solubility, low bioavailability, gut irritation, unwanted metabolites, food interactions, and dosing variability.

- **Low Dose Requirement**: Inhaled drugs typically require a smaller dose compared to oral medications; for example, one 4 mg tablet of salbutamol is equivalent to about 40 doses from a metered-dose inhaler.

- **Minimal Side Effects**: Because the medication is delivered directly to the lungs, there is minimal exposure to the rest of the body, resulting in very few systemic side effects.

- **Safety for Long-term Use**: For chronic conditions like asthma and diabetes, pulmonary delivery is safer for long-term use as the medication primarily affects the lungs, minimising systemic exposure.

Disadvantages:

- **Local Side Effects**: Medications can cause local side effects in the oropharyngeal region.

- **Device Usage Challenges**: Patients might struggle with the correct use of inhalation devices.

- **Mucus Barrier**: The presence of mucus in the lungs can limit drug absorption.

- **Reproducibility Issues**: Various factors, including physiological and pharmaceutical barriers, can affect the consistency of drug delivery to the lungs.

- **Device and Drug Stability**: Ensuring that drug delivery devices effectively target the drug to the lungs and that the drug remains stable in vivo can be challenging.

- **Targeting Specificity**: Achieving precise targeting of the drug to the intended lung area can be difficult.

- **Irritation and Toxicity**: Drugs may cause irritation or toxicity to the lung tissue.

- **Immunogenicity**: Proteins administered via inhalation can potentially trigger immune responses.

- **Short Duration of Action**: The effects of inhaled drugs can be short-lived due to rapid drug clearance from the lungs or drug metabolism.

Pulmonary delivery systems can be classified into immediate-release, controlled-release, and sustained-release categories, each differing in polymeric composition and excipients used. Controlled- and sustained-release systems offer several benefits, including lower drug doses, improved therapeutic efficacy, better patient compatibility, rapid onset of action, avoidance of liver metabolism, localised treatment, reduced systemic side effects, extended duration of action, and cost-effectiveness. These systems employ particle-based technologies such as microparticles, nanoparticles, micelles, liposomes, and protein nanoparticles.[3-5] This chapter will explore how drugs are processed and absorbed in the lungs and describe the ideal characteristics of particle-based pulmonary delivery systems. It will also provide an overview of innovative systems developed for controlled and targeted delivery to specific sites of respiratory diseases.

Anatomy and Physiology of Pulmonary Drug Delivery

The respiratory system collaborates with the circulatory system to transport oxygen from the lungs to the body's cells, remove carbon dioxide, and return it to the lungs for exhalation. This process of exchanging carbon dioxide and oxygen between the air, blood, and body tissues is known as respiration. Healthy lungs typically inhale about a pint of air 12–15 times per minute, and the entire blood supply in the body passes through the lungs every minute.[2]

The human respiratory system is divided into two main regions:

1. **Conducting Airways**: This includes the nasal cavity, sinuses, nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles.

2. **Respiratory Region**: This area comprises the respiratory bronchioles, alveolar ducts, and alveolar sacs.

The respiratory tract functions as a branching network of air channels. The primary role of the lungs is to facilitate gas exchange by delivering oxygen to and removing carbon dioxide from the blood as it flows through the pulmonary capillaries.[2]

Mechanisms for pulmonary drug administration

Drugs can be delivered to the lungs through two main approaches using pulmonary delivery systems[3]:

(a) Intranasal Delivery

(b) Oral Inhalative Delivery, which includes Intratracheal Inhalation and Intratracheal Instillation

Intranasal Delivery involves administering drugs through the nasal passages to reach the lungs, a method often referred to as nose-to-lungs aerosol delivery. This approach is advantageous for situations requiring frequent dosing because it is non-invasive and allows patients to self-administer without disrupting their daily routines. However, the nasal passages act as a filter, which can reduce the effectiveness of delivering conventional aerosols, especially those sized between 3 to 7 µm, with potential concentration losses up to 85% for small particles.[3]

Oral Inhalative Delivery is generally more effective than intranasal delivery for administering small-sized particles, with concentration losses as low as 20%. This method includes[3]:

- **Intratracheal Instillation**: Commonly used in laboratory settings for assessing the effectiveness of pulmonary delivery systems in preclinical animal studies. It involves delivering a drug solution or dispersion directly into the trachea via syringe. This method is simple, cost-effective, and allows for precise drug measurement. However, it is not suitable for human use due to physiological limitations and is therefore restricted to animal studies.[3]

- **Intratracheal Inhalation**: Utilises aerosol technology to deliver drug particles directly to the lungs, offering improved penetration and more uniform drug distribution compared to intratracheal instillation.[3]

Factors affecting pulmonary drug delivery:

- Mechanisms of Particle Deposition in the Airways
- Physiological Factors Affecting Particle Deposition in The Airways
- Pharmaceutical factors affecting aerosol deposition

- **Mechanisms involved in deposition of particles in lungs:**

The deposition of inhaled particles in various parts of the respiratory system is a complex process influenced by several factors, including[6]:

- Breathing rate
- Breathing through the mouth or nose
- Lung volume
- Volume of each breath
- Overall health of the individual
- Bifurcations in the airways, which create a constantly changing flow pattern.

Particle deposition in the respiratory system occurs through several key mechanisms, depending on particle size, airflow, and the specific location within the respiratory tract:

- **Impaction**: This is the primary mechanism for depositing particles larger than 1 µm, especially in the upper airways at branching points. This occurs when particles are trapped in the respiratory system due to their inertia. The likelihood of deposition by impaction depends on the particle's mass (size and density) and its velocity, which is influenced by the flow velocity of the air in the airways. Impaction commonly occurs at bifurcations, and particles from tobacco smoke, for instance, may impact these areas, potentially contributing to the development of lung tumours at these sites.[6,7]

- **Sedimentation**: This mechanism involves gravitational settling of particles in the smaller airways, such as the bronchioles and alveoli, where the airflow is slower and the airway dimensions are smaller.[6]

- **Interception**: Particles are deposited by interception when they physically contact the surface of the airways due to their size or shape. Unlike impaction, particles deposited by interception do not deviate from their airflow streamlines.[6]

- **Brownian diffusion**: This mechanism is predominant for particles less than 0.5 microns in diameter. Deposition by diffusion is based on geometric size rather than aerodynamic properties, with the highest likelihood of deposition occurring in the lung periphery, where the airways are very small. For smaller particles, diffusion occurs due to random bombardment by gas molecules, which can lead to collisions with airway walls.[8]

- **Absorption**: The pulmonary membrane naturally allows the passage of small molecule drugs as well as various therapeutic peptides and proteins. The lung's epithelial layer, which acts as a key barrier to the absorption of inhaled medications, is relatively thick (50–60 µm) in the trachea. However, this thickness significantly reduces to just 0.2 µm in the alveoli.[7]

- **Physiological Factors Affecting Particle Deposition in the Airways:[6]**

Lung Morphology: The structure of the tracheobronchial tree, with its progressively narrowing and lengthening airways, influences where particles are deposited.

Inspiratory Flow Rate: Higher inspiratory flow rates can increase particle deposition by impaction, especially in the initial generations of the tracheobronchial tree.

Coordination of Aerosol Generation with Inspiration: The energy of aerosol particles from pressurised metered-dose inhalers (pMDIs) is primarily determined by the pMDI formulation rather than the subject's inspiratory flow rate (IFR). Aerosol droplets from pMDIs travel at velocities of 2,500–3,000 cm/s.

Tidal Volume: A higher inspiratory flow rate usually results in a larger volume of air inhaled per breath, known as tidal volume. Increased tidal volume allows aerosol particles to penetrate deeper into the tracheobronchial and alveolar regions, enhancing the chance of deposition.

Breath Holding: Extending the time between inhalation and exhalation increases the duration for sedimentation of particles, optimising pulmonary drug delivery. Breath-holding is commonly used to improve the effectiveness of inhaled medications.

Disease States: Conditions like bronchial obstruction can lead to larger local airflows and turbulence, resulting in localised particle deposition in the larger airways of the tracheobronchial region.

- **Pharmaceutical Factors Affecting Aerosol Deposition:[6]**

Aerosol Velocity: pMDIs produce aerosol droplets with velocities higher than the inspiratory airflow, causing the particles to impact the oropharyngeal region more frequently.

Size: Commercially available devices often produce aerosols with a wide range of particle sizes and shapes, leading to a broad size distribution rather than a uniform one.

Density: Particles with densities below 1 g/cm³ may have a larger mean physical diameter than the aerodynamic limit, affecting their deposition.

Physical Stability: High humidity in the airways can cause particles to expand, increasing the likelihood of premature deposition. It should not be assumed that water vapour uptake will always occur.[9]

Drug Delivery Carriers for Pulmonary Delivery

To ensure effective pulmonary drug delivery and minimise side effects, various carriers are employed to aid in targeting the lungs. These carriers include[10]:

Liposomes: Liposomes are vesicles composed of one or more phospholipid bilayers. Their polar core can encapsulate polar drugs, while amphiphilic and lipophilic substances dissolve within the phospholipid layers based on their affinity for the lipids.[11] Liposomes can be unilamellar (with a single bilayer) or multilamellar (with multiple bilayers).[12]

Biodegradable Polymers: Research is focused on biodegradable polymers for environmental waste management. Biodegradation involves the breakdown of materials by microorganisms like bacteria, fungi, and algae. Common biodegradable polymers include aliphatic polyesters such as polylactide, poly(ε-caprolactone), polyethylene oxide, poly(3-hydroxybutyrate), and polyglycolic acid, along with thermoplastic proteins.[13]

Large Porous Particles: Pulmospheres are large, porous, hollow particles with low density and excellent dispersibility, suitable for use in metered-dose inhalers (MDIs) and dry powder inhalers (DPIs). They can be made from polymeric or non-polymeric materials using techniques like solvent evaporation and spray-drying. Pulmospheres often contain phosphatidylcholine, a major component of lung surfactant.[6]

Nanoparticles and Nano Suspensions: Nano formulations, typically ranging from 100 to 700 nm, are increasingly used in liquid nebulizers for both topical and systemic lung delivery. These nano particulate formulations provide higher bioavailability due to improved drug delivery efficiency, faster dissolution, and increased residence time in the lungs, compared to traditional micro suspensions.[14]

Lactose Carrier System: Lactose is widely used as a carrier in DPI formulations. Various grades of inhalation-grade lactose are available, with α-lactose monohydrate being the most common. Lactose is favoured for its well-documented safety profile, stability, compatibility with drugs, availability, and affordability.[15]

Dendrimers: Dendrimers, or dendritic polymers, are nanoparticles with a central core surrounded by tree-like branches. These highly branched structures feature functional groups on their surfaces and cavities in their interiors, which facilitate the conjugation or encapsulation of drug molecules.[3,6]

Polymeric Micelles: Polymeric micelles are potential nano carriers for delivering anticancer agents. They form when the hydrophobic segments of a block copolymer aggregate in the centre, encapsulating poorly soluble drugs, while the hydrophilic segments face outward, forming the micelle's shell. Commonly used amphiphilic polymers, such as polyethylene glycol (PEG) and polyethylene oxide (PEO), are FDA-approved and widely used in micelle formulations. For example, PEG5000–DSPE micelles containing paclitaxel have been produced using solvent evaporation techniques.[12]

Technologies for Producing Pulmonary Drug Particles

Recent advancements have introduced several technologies that are effective for creating drug particles in the respirable range (1-5 μm). These technologies include[2]:

- **Micronization**: A process that reduces drug particle size to the micron scale, making them suitable for pulmonary delivery.
- **Spray Freeze-Drying**: A technique where drug solutions are rapidly frozen and then dried to produce fine particles ideal for inhalation.
- **Supercritical Fluid Crystallisation**: This method uses supercritical fluids to precipitate drug particles, achieving the desired size for effective pulmonary delivery.

General types of pulmonary drug delivery devices

The choice of delivery device is crucial for effective pulmonary drug administration. Significant advancements have been made in developing sophisticated systems for this purpose. Selecting the right device is a key factor in formulation design and depends on where in the respiratory tract the drug needs to be administered. The device must be able to produce particles with the correct aerodynamic diameter to reach the intended lung regions.[3] The three most widely used delivery devices for pulmonary administration are:

- **Pressurised Metered-Dose Inhalers (pMDIs)**
- **Dry Powder Inhalers (DPIs)**
- **Nebulizers**

Metered-Dose Inhaler (MDI)

A metered-dose inhaler (MDI) is a pressurised device that delivers medication via a propellant spray. It comprises four main components: the formulation (which includes the drug, propellant, and excipients), the container, the metering valve, and the actuator (or mouthpiece). The MDI releases fine droplets of medication with a particle size of less than 5 micrometres, making it suitable for treating respiratory conditions such as asthma and COPD.[2] MDIs can deliver medication in two forms: suspension or solution. In suspension formulations, drugs that are insoluble in the propellant and solvent are dispersed within the propellant. For solution formulations, the active ingredient is dissolved in a pure propellant or a mixture of propellants. Solution aerosols are easier to prepare if the ingredients dissolve well in the propellant-solvent system.[2] MDIs typically use propellants such as chlorofluorocarbons or hydro fluoroalkanes, and they often contain micronized drug particles mixed with surfactants to prevent clumping. Other components may include lubricants for the valve mechanism and additional solvents. When the MDI is used, the propellant is exposed to atmospheric pressure, causing the drug to aerosolize. As the aerosol travels, the propellant evaporates, reducing the particle size to the desired range.[2] MDIs can be classified into two types:[6]

1. **Accurately Metering Devices**: These include spray pumps, pMDIs, and unit/bi-dose devices.

2. **Non- or Poorly Metering Devices**.

Advantages of MDIs:

1. Delivers a precise dose of medication.
2. Compact, portable, and user-friendly.
3. Generally, less expensive than dry powder inhalers and nebulizers.
4. Quick to use.
5. Protects contents from contamination.
6. Can provide more than 100 doses per device.

Disadvantages of MDIs:

1. High doses are difficult to administer through an MDI.
2. Requires precise coordination between actuation and inhalation.
3. Drug delivery effectiveness relies on the patient's technique.

Dry Powder Inhalers (DPIs)

Dry powder inhalers (DPIs) are devices designed for pulmonary drug delivery that simplify the process of inhalation by requiring minimal coordination between actuation and breathing. Unlike metered-dose inhalers (MDIs), which use suspensions or solutions, DPIs contain drugs in a dried powder form, offering better chemical stability. However, formulating and manufacturing these dry powders to ensure they are suitable for aerosolization and effective delivery to the lungs can be complex.[16,17] Typically, DPI formulations include micronized drug particles mixed with larger excipients such as lactose, sucrose, or glucose. The energy needed for drug delivery is provided by the patient's inhalation. DPIs have structural components like a mesh, cyclone, manifold, and spiral chamber, which work to deaggregate the drug-excipient mix using the force of inhalation. Depending on the product, the required inspiratory force ranges from 30 to 60 L/min.[18] DPIs are known for their stability, ease of use, and lower cost compared to MDIs. They do not require propellants like chlorofluorocarbons (CFCs), making them a cleaner alternative. There are different types of DPIs:[6]

- **Unit-Dose Devices**: These involve placing a powder-filled capsule into the inhaler. The capsule is opened within the device, and the powder is inhaled. Example: Rotahaler.

- **Multi-Dose Devices**: These devices contain a circular disk with multiple doses of powder. The doses are stored in separate aluminium blisters until they are needed. Example: Turbohaler.

Advantages of Dry Powder Inhalers (DPIs):

- Provides a larger amount of drug per puff.
- No need for blending with other substances.
- Allows for the use of small, flow-rate-independent inhalers.
- Particles readily disaggregate, despite their small size.
- Improves lung deposition, reduces dose variability, and enhances dispersibility.

Disadvantages of Dry Powder Inhalers (DPIs):

- Requires sufficient inspiratory effort: The effectiveness of DPIs depends on the patient’s ability to generate a strong inhalation flow rate, which may be challenging for some individuals, particularly those with severe respiratory conditions.
- Limited dose accuracy: Variability in inspiratory flow can affect the dose accuracy and delivery efficiency.
- Potential for powder aggregation: If the powder absorbs moisture or is not properly handled, it may clump together, affecting the consistency of drug delivery.
- Device complexity: Some DPIs may have complex mechanisms that can be difficult for patients to operate correctly.
- Inhalation technique: Proper use and inhalation technique are crucial for effective drug delivery, which may require patient training and practice.

Nebulizer

Nebulizers are devices designed to convert liquid medication into a fine mist or aerosol, with particle sizes typically ranging from 1 to 5 micrometres. This mist can be easily inhaled to deliver medication directly to the deeper parts of the respiratory tract via a face mask or mouthpiece. Unlike metered-dose inhalers (MDIs) and dry powder inhalers (DPIs), nebulizers do not require the patient to coordinate their inhalation with the device's actuation, making them suitable for a broader range of patients, including those who may struggle with other inhalation devices. Nebulizers also have the advantage of delivering larger doses of medication.[19] Key factors for optimising nebulizer performance include the volume and viscosity of the drug solution, the air pressure, and the design of the mouthpiece. Nebulizer solutions are relatively straightforward and cost-effective to prepare compared to those required for MDIs and DPIs. However, a significant drawback of nebulizers is that they need to be assembled and loaded before each use and thoroughly cleaned and disassembled after each use by the patient.

The formulation of nebulizer solutions typically involves:[2]

- Pharmaceutical solution technology, including parenteral products.
- Solutions prepared in water.
- Use of co-solvents.
- Maintaining a pH above 5.

Nebulizers can be characterised by:

1. Jet Nebulizers

Description: Jet nebulizers, also known as pneumatic nebulizers, use compressed air to create a fine mist of medication. They consist of a chamber where the medication is placed and an air compressor that delivers a stream of air through the medication, converting it into an aerosol.[2]

Advantages:

- Widely used and effective for a variety of medications.
- Can handle a range of medication viscosities.

Disadvantages:

- Relatively bulky and noisy.
- Requires a power source (usually plugged into an outlet).

Common Uses: Often used in hospitals and clinics, but also available for home use.

2. Ultrasonic Nebulizers

Description: Ultrasonic nebulizers use high-frequency sound waves to generate an aerosol. These sound waves vibrate a piezoelectric crystal or plate to break up the medication into fine droplets.[2]

Advantages:

- Quieter and smaller compared to jet nebulizers.
- More efficient at nebulizing certain medications.
- Portable and can be battery-operated.

Disadvantages:

- Can be more expensive.
- Not suitable for all medications, especially those with high viscosity or suspensions.

Common Uses: Often used for home treatments and in settings where noise reduction is important.

3. Mesh Nebulizers

Description: Mesh nebulizers use a vibrating mesh or membrane with small holes to create an aerosol. The medication is pushed through the mesh by a small motor, breaking it into fine droplets.[6,20]

Advantages:

- Compact and portable.
- Quiet operation.
- Efficient and precise medication delivery.
- Suitable for a wide range of medications, including those with high viscosity.

Disadvantages:

- Can be more expensive.
- Mesh devices may require more maintenance and cleaning.

Common Uses: Ideal for home use and for patients who need a portable, efficient nebulizer.

Current Applications of Pulmonary Drug Delivery Systems [6,21]

- **Asthma and COPD:** Utilising pulmonary drug delivery for managing and treating chronic respiratory conditions like asthma and chronic obstructive pulmonary disease (COPD).
- **Patients on Ventilators:** Exploring the use of pulmonary delivery systems for patients who are mechanically ventilated.
- **Cystic Fibrosis:** Applying pulmonary drug delivery methods to treat cystic fibrosis, a genetic disorder that affects the respiratory system.
- **Diabetes:** Investigating the novel application of pulmonary drug delivery for managing diabetes.
- **Migraine:** Exploring the potential of pulmonary delivery for treating migraines.
- **Angina Pectoris:** Utilising pulmonary drug delivery systems for the treatment of angina pectoris, a condition characterised by chest pain.
- **Vaccination:** Implementing pulmonary delivery methods for administering vaccines.
- **Pirfenidone:** Delivering pirfenidone, a drug used for treating idiopathic pulmonary fibrosis, via the pulmonary route.
- **Transplantation:** Recent advancements in using pulmonary drug delivery for post-transplant care.
- **Pulmonary Arterial Hypertension:** Applying pulmonary drug delivery systems to manage pulmonary arterial hypertension.
- **Acute Lung Injury:** Utilising pulmonary delivery techniques for treating acute lung injury.
- **Surfactant Aerosol:** Using pulmonary drug delivery systems to administer surfactant aerosols for lung health.
- **Gene Therapy:** Exploring the use of pulmonary routes for delivering gene therapy.
- **Cancer Chemotherapy:** Applying pulmonary drug delivery systems for administering chemotherapy in cancer treatment.
- **Pentamidine:** Delivering pentamidine, a medication used for treating pneumocystis pneumonia, via the pulmonary route.

- **Amphotericin:** Utilising pulmonary drug delivery for administering amphotericin, an antifungal medication.

- **Smoking Cessation:** Using nicotine aerosols for aiding smoking cessation.

- **Tuberculosis Therapy:** Implementing inhaled drug delivery methods for the treatment of tuberculosis.

FUTURE PROSPECTS

Recent advancements in the evaluation and characterization of pulmonary drug delivery systems have been significant. These evaluation methods are categorised into in vitro, in vivo, and ex vivo approaches.[2] **In vitro** methods include the physicochemical characterization of particles, assessment of aerosol performance, particle dissolution studies, and cell culture experiments. **In vivo** research focuses on drug administration systems, drug deposition, and pharmacokinetic studies. **Ex vivo** methods are employed to evaluate drug efficacy and safety. Techniques such as transmission electron microscopy (TEM) are used to study the morphology of nanoparticles, including various methods like cryogenic transmission, negative staining, and freeze-fracture to analyse particle shape, structure, and arrangement.[2] Current research in pulmonary drug delivery is extensive but still has considerable areas for development, particularly in inhaler devices and formulation innovations for dry powder and colloidal systems. A major challenge in this field is the limited number of excipients approved by the FDA/EMA for inhalation use.[3] Recent interest has grown in the topical delivery of antibiotics, which holds promise for enhancing treatment of pulmonary infections. Additionally, the delivery of antivirals via inhalation is being explored as a potential strategy for addressing viral lung diseases, including COVID-19. Research is also ongoing into the use of inhalation drug delivery for conditions such as lung cancer and mucosal vaccination against bacterial or viral infections.[3]

CONCLUSION

The use of the lungs as a route for drug administration has a long history and continues to be a preferred method for delivering various medications. Today, pulmonary drug delivery remains a crucial area of research, significantly impacting the treatment of conditions such as asthma, chronic obstructive pulmonary disease (COPD), and other respiratory illnesses. Inhalation offers the most direct access to drug targets within the lungs, allowing for rapid therapeutic effects, reduced systemic side effects, and lower required doses by delivering medication directly to the lungs' conducting zones. Additionally, it provides a needle-free alternative. Recent advancements have led to the development of various techniques aimed at enhancing the quality of pulmonary drug delivery systems while maintaining their effectiveness. These improvements make pulmonary delivery a superior option compared to other methods. Innovative pulmonary delivery technologies have notably improved the efficiency and precision of drug delivery to the lungs for respiratory conditions. The rise in FDA-approved nanoparticulate delivery systems for diagnostic and therapeutic applications has spurred further research and development. A deeper understanding of lung physiology and clearance mechanisms will contribute to the creation of more effective and safer nanoparticulate delivery systems. Nevertheless, extensive research is needed to bridge the gap between laboratory developments and industrial production, ensuring that advanced pulmonary drug delivery systems are successfully brought to market to address ongoing respiratory health challenges.

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