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FORMULATION STRATEGIES & CHALLENGES IN PULMONRY DRUG DELIVERY

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Abstract
Pulmonary drug delivery systems (PDDS) have emerged as an effective and non-invasive approach for both local and systemic drug administration, owing to the unique anatomical and physiological features of the lungs. The large alveolar surface area, thin epithelial barrier, rich vasculature, and avoidance of hepatic first-pass metabolism enable rapid onset of action, improved bioavailability, and reduced systemic side effects. Advances in particle engineering technologies-such as micronization, spray freeze-drying, and supercritical fluid techniques-have enabled the production of reparable particles with enhanced deposition in the deep lung regions. However, challenges including mucociliary clearance, enzymatic degradation, limited drug stability, and patient-dependent device handling remain critical barriers. Overall, the collective findings emphasize that continued innovations in formulation design, delivery devices, and targeting strategies are essential to fully realize the therapeutic potential of pulmonary drug delivery systems in modern drug therapy.
***Keywords**: Inhalation therapy, Lung targeting, Aerosol formulations, Inhaler devices.*

INTRODUCTION

Pulmonary disorders afflict millions of people, and their numbers are steadily rising globally. These encompass a number of complex human airway conditions, such as asthma, pulmonary hypertension, cystic fibrosis, lung cancer, TB, chronic obstructive pulmonary disease (COPD), and others. 1 The pulmonary administration provides an alternate method of systemic drug distribution because of the distinct physiological characteristics of the lungs. These distinct physiological characteristics include 2, 3. The alveolar surface area for medication absorption is vast and highly vascularized. lungs, the pulmonary administration serves as an alternative route for systemic drug delivery. These unique physiological features involve [1].

As of Dec. 14, 2021, the World Health Organization (WHO) reported that the ongoing pandemic caused by SARS-CoV-2 had spread to at least 223 countries worldwide and killed over 5,301,714 people. Regretfully, as new coronavirus strains emerge, as the Delta strain that was initially identified in India in October 2020, the numbers keep rising. Vital organs like the kidney, liver, heart, and brain are damaged when the SARS-CoV-2 virus infects the lung, creating a shortage of oxygen and systemic inflammation that leads to acute respiratory distress syndrome [2].

ANATOMY AND PHYSIOLOGY OF PULMONARY DRUG DELIVERY SYSTEM

Together with the circulatory system, the respiratory system transports oxygen from the lungs to the cells, extracts carbon dioxide, and then returns it to the lungs for exhalation. Respiration is the process by which carbon dioxide and oxygen are exchanged between the blood, air, and bodily tissues [3].

PULMONARY DRUG DELIVERY

For many years, pulmonary medication administration has proven to be highly effective in treating chronic obstructive pulmonary disease (COPD) and asthma. Since it targets the medicine directly in the lungs and has a quick onset of action, it provides patients with the maximum therapeutic efficacy, making it one of the most crucial areas for research and development. In comparison to oral formulation, this lowers the overall dosage; for example, salbutamol dosages are lowered by a factor of 10 to 20 [4].

1DRY POWDER INHALERS

Bell and colleagues were introducing in 1971 the first inhaler device which used in DPI technology [14]. Then, advanced DPI devices has been developed for patients with COPD and Asthma. the dose delivered into the patient's deep lungs. DPI broadly classified into three different categories such as single dose DPIs, multiple dose DPI, and active or power assisted DPIs [5]. Once more, multiple doe devices are multi-dose and multi-unit DPI devices. Power-assisted DPI devices were created to address the problem of COPD patients' inadequate inhalation.

2. Nebulizers

Bell and colleagues were introducing in 1971 the first inhaler device which used in DPI technology. Then, advanced DPI devices have been developed for patients with COPD and Asthma. Single dosage DPIs, multiple dose DPIs, and active or power aided DPIs are the three general categories into which DPIs fall.

3. Soft mist inhaler

Microelectronic dosimetry devices are used in soft mist inhalers (SMI, such as the Respirator). A fixed volume of medication solution is pulled up into the dosing system through a nozzle with two tiny outlet channels carved using microchip technology when a SMI is manually primed. The SMI aerosol has a high fine particle fraction, a low velocity, and more sustained duration than a pie. The SMI form two or three times more pulmonary deposition than a pie.

4. Metered Dose Inhalers

Among the various pulmonary drug delivery devices, metered dose inhalers are most promising technique. Recent progress in material sciences, nanotechnology, biotechnology, particle engineering and allied sciences open a door for improving the use of metered dose inhalation therapy.

5. Polymeric Nano carriers

Polymeric Nano carriers are one of the widely studied Nano carriers for various drug delivery applications including cancer, HIV, COVID-19, and inflammatory bowel diseases. Polymeric nanoparticles extensively explored for their excellent potential as a carrier for delivery of drug to treat various diseases. Functional polymeric nanoparticles can be design through modification and fictionalization of polymer before making nanoparticles.

At present, common treatments for lung cancer include surgery, radiation, immunotherapy, and chemotherapy or a combination. The pH-sensitive mPEG-1 K DOX conjugated NPs were fabricated using the precipitation method and Schiff base re-arrangement technique. The NPs showed mean particle size and DOX loading of 104 nm and 32.7%, respectively. During in-vitro aerodynamic analysis, NPs showed FPF and MMAD of 63.5% and 1.6µm, respectively [6].

- Dendrimers

Dendrimers are branched macromolecules with monodispersed architectures. The dendrimers can synthesize through click chemistry, multicomponent reactions, and cycloaddition methods. Drug delivery and targeting using dendrimers made significant progress in last few years.

Among the various dendrimers, polyester based dendrimers are alleviating toxicity issues, that associated with non-biodegradable dendrimers. Generation three (G3) and four (G4) polyester dendrimers were primarily conjugated to FITC. FITC conjugated G3 (0.8 nm) and G4 (1.3 nm) polyester dendrimers showed zeta potential of −2.3 and −1.3 mV, respectively. PEGylated generation G4 polyester dendrimers did not show any significant degradation until day 5 and after 30 days' dendrimer showed a degradation profile similar to the unmodified dendrimer Small interfering RNA (siRNA)-based therapies have great potential in treating respiratory diseases such as asthma, cystic fibrosis, and lung cancer. Accordingly, Tiny, uniform dendriplexes showed mean particle size 285 nm in scanning electron microscopy with 96.2% siRNA complexation efficiency [7].

Lipid Based Nano carriers

Among the various Nano carrier's system, lipid-based Nano particles have their own unique features. There are different lipid nanoparticles such as liposome, solid lipid nanoparticles, nanostructures lipid carriers, and self-emulsifying drug delivery systems. Liposomes shows up to 24 hr. of retention time in lungs.

CLASSIFICATION

Targeting pulmonary drugs involves inhaling aerosols that are delivered straight to the respiratory epithelium and epithelial cells (macrophages). In order to encourage retention or clearance from the lung, it is crucial to take into account the design of molecules or formulations. Pulmonary drug delivery methods are generally divided into three main categories based on the way the drug releases.

- Immediate release systems (excipient drug mixture such as lactose-drug mixtures)
- Controlled release systems (liposomes, micelles, Nano- and micro particles based on polymers)
- Sustained release systems (microspheres based on polymers)
- The advantages of controlled and sustained release pulmonary drug delivery systems include:
- Extended duration of action
- Reduction in dose size
- Improved therapeutic management
- Improved patient compliance
- Reduction in side effects
- Potential cost savings that exist for sustained release therapy

These delivery systems involve particulate drug carriers such as liposomes, nanoparticles, Nano suspensions, micro- spheres, genetic engineered particles, etc. Thorough under- standing of ethology of pulmonary diseases along with physiology of lung forms the basis of design of such drug delivery systems. Additionally, right choice of the carrier materials, delivery devices and production process leads to successful pulmonary targeted drug delivery [8].

1. Liposomes

Lipids and phospholipids are examples of amphiphilic substances that spontaneously form unilamellar or multi-lamellar concentric bilayers separated by water compartments to create liposomes, which are vesicles of the micro or nanometres range. They come in a variety of sizes and can be made using lung endogenous phospholipids as surfactants.

2. Nanoparticles
Drug-loaded nanoparticles are the particulate systems possessing certain characteristics to be used for pulmonary delivery of therapeutics for various lung diseases like lung cancer. The Nano- particles can be airborne and easily delivered to the alveoli due to their small size and hence can be suitable for pulmonary drug delivery. A wide range of polymers helps in delivery of peptides and proteins through the pulmonary route.

3. Nanosuspensions
Nanosuspensions, which have an average particle size of 300–700 nm, are colloidal dispersions containing pure drug particles in the submicron range stabilized by surfactants. Targeted pulmonary medication delivery has made extensive use of nanosuspension. They have several significant advantages over solution formulations, such as:

4. Microspheres
Microspheres are uniform, monolithic, spherical, colloidal particles made of one or more polymer types that have a size of less than 200µm. According to certain research, microspheres may be one of the dose forms used to treat pulmonary conditions. Recent Trends in Applications of Pulmonary Drug Delivery. Apart from asthma and COPD pulmonary drug delivery is employed for the following indication.

- Insulin by Aerosol
- Therapy of Migraine
- Nicotine Aerosol for Smoking Cessation
- Aerosols for Angina.
- Aerosol Vaccination.
- Alpha 1 Antitrypsin
- Aerosols in Transplantation

Merits of Pulmonary Drug Delivery

- Extremely large surface area of a lung (approximately 100 m2) and the ease of mucosal permeation of drug substances due to well developed vascular system and extremely thin alveolar wall.
- Bypass the barriers such as hepatic first-pass metabolism and poor gastrointestinal absorption due to relatively low activity of drug-metabolizing enzymes in intracellular or extracellular compartment. For example, various proteins and peptides act as ideal candidates for pulmonary delivery.
- Improves efficacy and potentially minimizes adverse effects, especially for local therapies due to localized drug deposition and reduced systemic and generalized exposure and lower dosage regimens may provide considerable cost saving especially with expensive therapeutic agents.
- Less invasive and shows increased patient compliance.
- Site-specific drug delivery at high concentrations within the diseased lung thereby reducing the overall amount of drug given to patients (10–20 % of per oral quantity).
- Improved bioavailability of drugs.
- Reproducible absorption kinetics. Tong, H. H., & Chow, A. H. (2006). Control of physical forms of drug particles for pulmonary delivery by spray drying and supercritical fluid processing. *KONA Powder and Particle Journal*, *24*, 27-40.

❖ **Demerits of Pulmonary Drug Delivery**

- Oropharyngeal deposition gives local side effects.
- Patients may have difficulty using the pulmonary drug devices correctly.
- Drug absorption may be limited by the physical barrier of the mucus layer.
- Various factors affect the reproducibility of drug delivery in the lungs, including Physiological and pharmaceutical barriers.
- Stability of drug in vivo.
- Targeting specificity.
- Drug irritation and toxicity.
- Immunogenicity of proteins.

Factors Influencing Pulmonary Drug Delivery System

Various factors affect pulmonary drug delivery, including both drug-related and formulation-related factors.
1. Drug Related Factors
These factors relate to the various properties of the drug molecules, which are discussed in Table 2:
2. Formulation Related Factors
These factors refer to the various physicochemical and dosage form characteristics of the drug candidate.
A). Physicochemical Properties of Formulation
The physicochemical properties are concerned with the pH, tonicity and viscosity that individually affect the physical and chemical behaviour of the drug.
B). Dosage Form Characteristics
Different dosage forms have different characteristics that govern its action inside the body. The nature of the drug, its proposed indications and overall its marketing preferences determine the selection of dosage form.

Technologies for Producing Pulmonary Drug Particles

Currently, various newer technologies have been developed that are potentially useful for generating drug particles within the respirable range (1-5 μm). These include [9]:

1. Micronization
2. Spray freeze drying
3. Supercritical Fluid Crystallization

8. ANTIVIRAL APPROACHES

Additionally, COVID-19 led to a renewed interest in the local administration of antiviral medications. These included a variety of strategies, including biologics, novel decoy-based techniques, and nebulized delivery of well-known antivirals like remdesivir and NA-831 (National Clinical Trial number NCT02408874) Respiratory infections encompass much more than SARS-CoV-2, and efforts to improve treatment strategies through local delivery must continue [10].

DRUG DELIVERY DEVICES

There are many commercially available devices on the market, and a key element influencing how well drugs are delivered to the intended location is their design. The two most widely used methods for pulmonary medication administration are aerosol inhalation and intratracheal instillation.

The drug delivery devices are given below:

- Metered dose inhaler
- Dry powder inhaler
- Nebulizer
- Jet nebulizers
- Ultrasonic nebulizers

1. Metered dose inhaler

A pressurized inhaler that uses a propellant spray to deliver medication is known as a metered-dose inhaler, or MDI for short [11]. From suspension or solution, they will tend. The materials that are insoluble in the propellant and solvent are distributed throughout the appropriate propellant vehicle only in the event of suspension formulations. The active substance is dissolved in a pure or mixed propellant in an MDI solution formulation.

2. Dry powder inhaler

It's a flexible system that needs a point of dexterity. The name itself indicates that the formulation is in solid form. It contains the active drug alone or features a carrier powder mixed with the drug to extend the flow properties of a drug. Dry powder inhaler features greater stability, and simple handling, and are comparatively cheap in comparison to metered dose inhaler.

3. Unit-Dose Devices

Single-dose powder inhalers are devices in which a powder-containing capsule is placed in a holder. The capsule is opened within the device and powder is inhaled.

4. Nebulizer

In order to administer medication to the respiratory system, the nebulizer is frequently employed as an aerosolizing drug solution or suspension. It is especially useful for treating hospitalized patients. Asthma, cystic fibrosis, and other respiratory conditions are frequently treated with it.

CURRENT TRENDS IN PULMONARY DRUG DELIVERY

For many years, pulmonary drug administration has been utilized to treat conditions locally, such as COPD, asthma, allergic rhinitis, and nasal congestion. It is also well-established for systemic therapy.

a. Current trends in pulmonary drug delivery technology
b. Current trends in pulmonary drug delivery devices
c. Current trends in pulmonary drug delivery formulation [12-17].

1. Particle Engineering for Pulmonary Drug Delivery

Particle engineering is a science that combines the principles of microbiology, chemistry, formulation science, aerosol and powder science, nanotechnology, etc.

2. Agglomerated Vesicle Technology for Pulmonary Drug Delivery

3. Liposomes

Several studies on anti tubercular (ATD) loaded liposomal formulation have revealed their sustained and targeted release in the lungs with minimum bio distribution throughout the systemic circulation.

4. Lactose carrier

Systems Recent advances in inhalation therapy have introduced lactose as an efficient carrier for respiratory drug formulation. Lactose carrier system consists of smaller sub units of lactose which must be evaluated for drug-carrier adhesion, variation in drug-carrier forces and influence on drug aerosol performance prior to their use [18-20].

CONCLUSION

It can be concluded from the whole literature that pulmonary drug targeting offers several advantages which can improve drug's efficacy and reduce unwanted systemic side effects Continued commitment to this field is needed to overcome the many unique challenges faced by this delivery route to translate these efforts into successful products Various new technologies for pulmonary drug delivery as well as novel targeting methodologies have directed researchers to focus upon this route as a more preferred one for targeting various pulmonary disorders.

FUTURE OUTLOOK

By creating tiny particles with an aerodynamic particle size of less than 5 microns, a metered dose inhaler delivers medication straight into the airways. Asthma and other respiratory disorders like COPD are treated with it. These devices can be divided into two groups: accurately metering devices (such unit/bi-doses, pressurized metered dose inhalers (pies), and spray pumps) and non-metering or poorly metering devices.

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DECLARATION OF COMPETING INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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