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Innovations in Pulmonary Drug Delivery: A Comprehensive Guide to Inhalation Devices

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Abstract

Pulmonary drug delivery systems (PDDS) are essential in the targeted treatment of respiratory conditions such as asthma, COPD, cystic fibrosis, and lung cancer. By delivering medications directly to the lungs, these systems enhance therapeutic efficiency and minimize systemic side effects. The primary modes of drug delivery via the pulmonary route include nebulizers, metered dose inhalers (MDIs), and dry powder inhalers (DPIs). Each device has unique mechanisms and characteristics that influence drug deposition in the respiratory tract. This article provides an in-depth review of the anatomy and physiology of the respiratory system, mechanisms of drug deposition, and the advantages and limitations of each delivery device. The discussion emphasizes the evolution of inhalation therapy and highlights the critical role of PDDS in improving the management of pulmonary diseases. Advances in technology and formulation strategies continue to drive the development of more efficient and patient-friendly inhalation devices, reinforcing the pulmonary route as a preferred method for respiratory drug delivery.

Introduction:

The respiratory tract is one of the oldest routes used for the administration of drugs. Over the past decades inhalation therapy has established itself as a valuable tool in the local therapy of pulmonary diseases such as asthma or COPD.This drug application showcases targeted delivery, effectively treating pulmonary diseases with precision and accuracy. [1] Pulmonary drug delivery system refers to a device, technology or formulation of a drug meant for infusion into their body via the pulmonary route. Pulmonary drug delivery is

mainly used to treat conditions of airways, delivering locally acting drugs directly to their site of action. Delivery of drugs directly to their site of action reduces the dose needed to produce a pharmacological effect. Pulmonary route of administration is used to treat various pulmonary diseases such as lung cancer, cystic fibrosis, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis and pulmonary hypertension. The primary goal of inhalation therapy for local treatment is to reduce pulmonary symptoms through the alleviation or prevention of airway inflammation and constriction. Examples of inhaled drugs are β_2 agonists {salbutamol, terbutaline, and formoterol}, corticosteroids {beclomethasone}, and mast cell stabilizers {sodium cromoglycate}. [2]

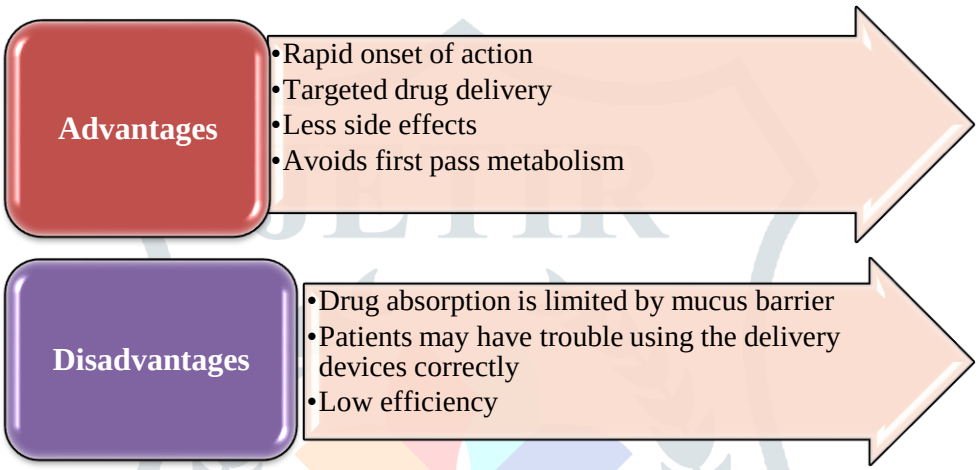

Figure 1: advantages & disadvantages of PDDS

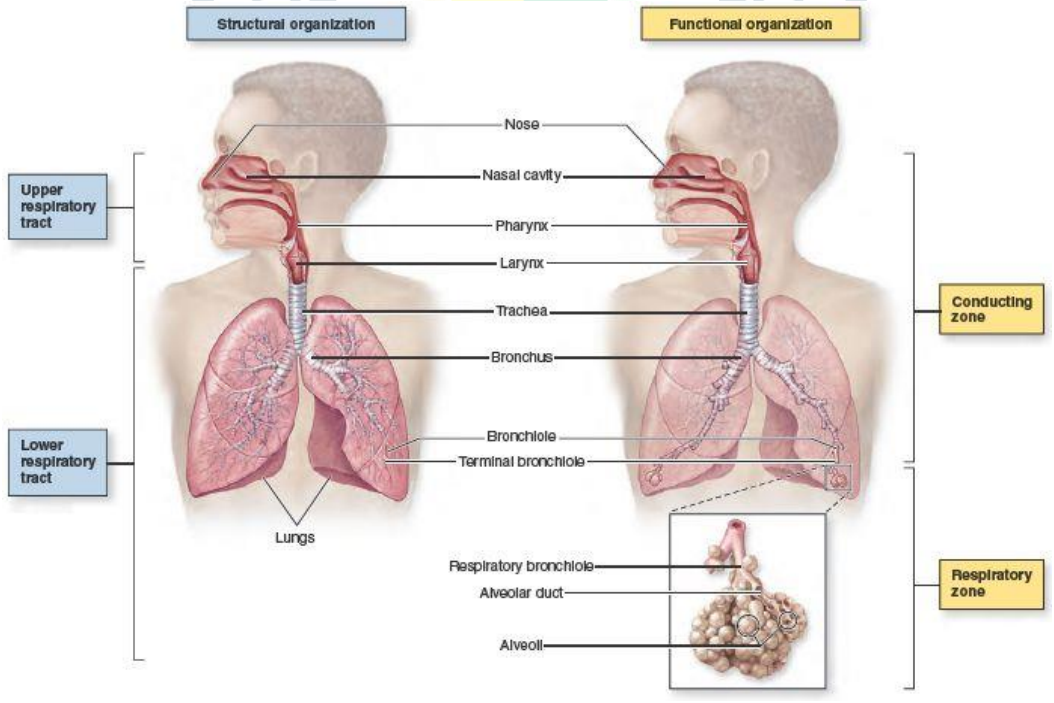

Figure 2: General anatomy of the respiratory system

Anatomy & Physiology of Respiratory Tract

The human respiratory system is a very complicated organ system. It mainly consists of two main regions:

1} the conducting airways

2} the respiratory region

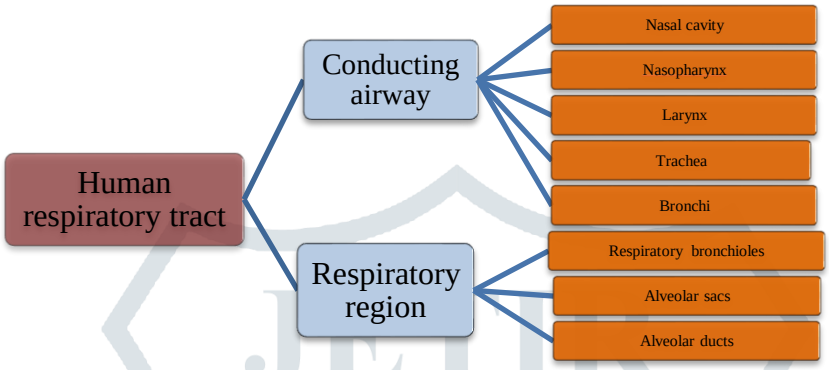

Figure3: Divisions of respiratory tract

Functionally, the respiratory system can be divided into a conducting zone & a respiratory zone. [3] The conducting zone consists of airways that transport gases into and out of the lungs which includes from nose to bronchioles. The respiratory zone corresponds to the lung parenchyma and includes alveolar ducts, alveolar sacs and alveoli where gaseous exchange takes place. [4]

Mechanism of respiratory deposition:

The deposition of the drug into the lungs and airways using aerosol inhalation technique generally occurs by three mechanisms: Inertial impaction, Sedimentation, Brownian diffusion. The deposition of drug particles in different regions of the respiratory tract is a complex phenomenon and depends on factors like particle size, air flow, and respiratory region. [5] During breathing, the airflow undergoes several direction changes in the nasal/mouth, pharynx, larynx regions and airway bifurcations. Larger particles >0.5µm may deposit by impaction in these regions because they could not follow the air streamline. Infact, deposition by impaction in oropharyngeal region remains a major portion of the emitted dose for pMDI or DPI devices. In the small airways and alveolar regions, deposition by sedimentation is the major deposition mechanism of inhaled particles. Small particles <0.2µm may be deposited by diffusion in all regions of respiratory tract. Diffusion deposition is important for nanoparticles <100nm. Interception deposition is important for elongated

particles such as fibrous aerosols when the long particle dimension is comparable with pulmonary airway dimensions. Pharmaceutical aerosol may carry electrostatic charges during the generation and transportation of aerosol, especially for DPI & pMDI devices. [6]

Pulmonary drug delivery devices:

The lung has served as a route of drug administration for thousands of years. The origin of inhaled therapies can be traced back 4000 years ago to India, where people smoked the leaves of the *Atropa belladona* plant to suppress the cough. In the 19th & early 20th centuries, asthmatics smoked asthma cigarettes that contained stramonium powder mixed with tobacco to treat the symptoms of their diseases. [7] The drug can be administered by pulmonary route utilizing two techniques: aerosol inhalation and intratracheal instillation. By applying aerosol technique we could achieve more uniform distribution with greater extent of penetration into the peripheral or the alveolar region of the lung. Following are the types of inhalation devices:

1) Nebulizer
2) Metered dose inhaler (MDI)
3) Dry powder inhaler (DPI) [8]

Nebulizers:

Nebulizers are medical devices that convert liquid drug into aerosols or fine mist of minimal size which can be easily inhaled so that it directly reaches the inferior part of the respiratory tract, through a facemask or mouth piece. A nebulizer can be used with an electrical compressor, which vaporizes drugs so that they can be inhaled to open out the airways, or it can use an ultrasound crystal that vibrates. [9] Nebulizers have been used for many years to treat asthma & other respiratory diseases. There are two basic types of nebulizers: jet nebulizers and ultrasonic nebulizers.

A) Jet nebulizer: The jet nebulizer functions by the Bernoulli principle by which compressed gas (air or oxygen) passes through a narrow orifice creating an area of low pressure at the outlet of the adjacent liquid feed tube. This results in drug solution being drawn up from the fluid reservoir and shattered into droplets in the gas stream.

B) Ultrasonic nebulizer: The ultrasonic nebulizer uses a piezoelectric crystal vibrating a high frequency (usually 1-3MHz) to generate a fountain of liquid in the nebulizer chamber, the higher the frequency, the smaller the droplets produced. [10]

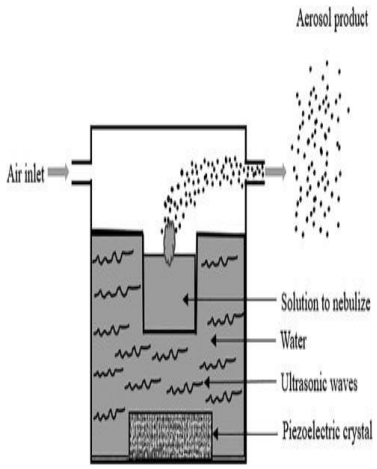

Figure 3: Ultrasonic nebulizer

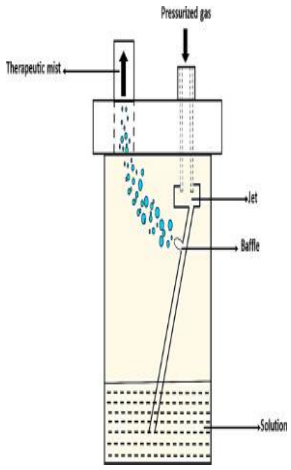

Figure 4: Airjet nebulizer

The nebulizers are mostly formulated with aqueous solution. Water is normally used to make nebulizer solution. In addition glycerin, ethanol, propylene glycol may also be used as solvent. While developing the nebulizer solution, physicochemical properties such as solubility, isoelectric pH, pKa, logP are important parameters to be considered. [11]

Advantages:

i. No specific inhalation technique or coordination is required.
ii. Aerosolizes most drug solutions
iii. Delivers large doses
iv. Suitable for infants and people too sick or physically unable to use other devices

Disadvantages:

i. Time consuming
ii. Expensive
iii. Non portable [12]

Metered dose inhalers (MDI):

A metered dose inhaler is a drug delivery system that produces a medicament in the form of fine aerodynamic particle size of less than 5 microns for direct inhalation to the airways. It is used for the treatment of respiratory diseases such as asthma and COPD. These devices can be categorized into two types: accurately metering pumps (such as pMDIs, spray pumps) and non or poorly metering devices. [13] The pMDI comprises several components each of which is important to the success of the whole container, propellant, drug formulation, metering valve and actuator.

- Container - The pMDI container must be able to withstand the high pressure generated by the propellant. Stainless steel, aluminum is used to make containers.
- Propellant – propellants in pMDIs are liquefied compressed gases that are in the gaseous phase at atmospheric pressure, but form liquid when compressed. They are required to be non-toxic, non-flammable, and compatible with drugs formulated either as suspensions or solutions.
- Metering valve- metering valve crimped onto the container is the most critical component of the pMDI and has a volume ranging from 25 to 100µL.
- Actuator- complete pMDI canister is fitted into a plastic actuator for use by the patient. The actuator nozzle is critical to spray formation. [14]

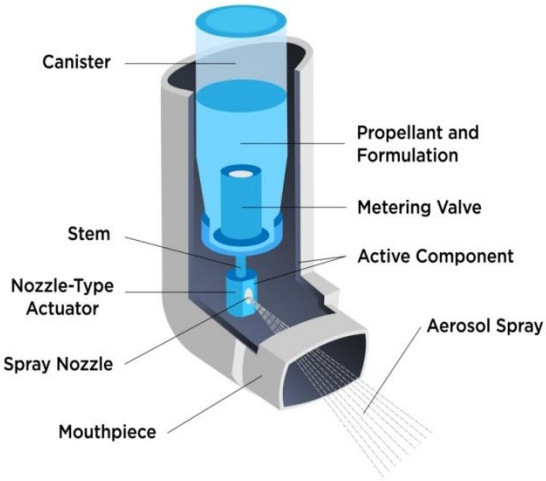

Figure 5: Metered dose inhaler

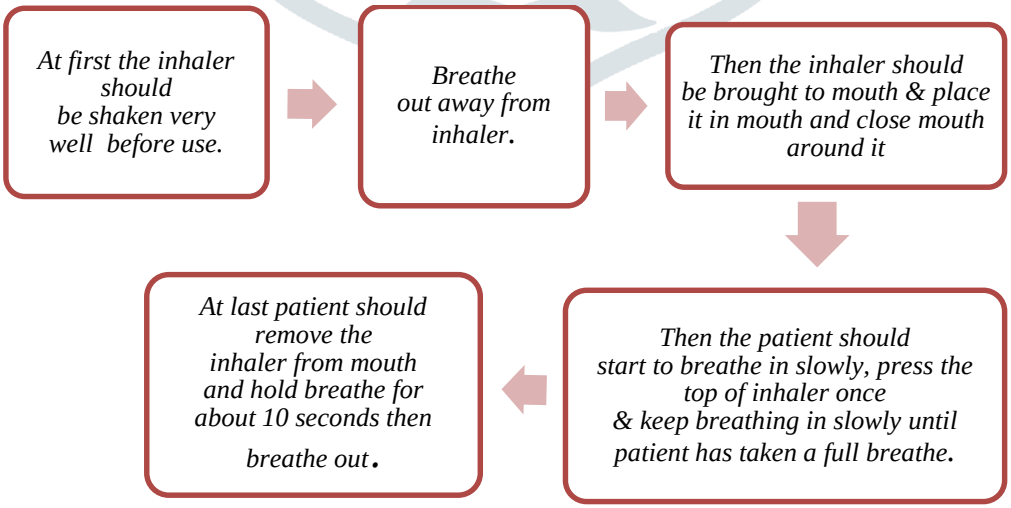

Figure 6: how to use MDI

Advantages:

i. It delivers a specified amount of dose.

ii. It is small in size, portable and convenient for use.

iii. It is usually less expensive as compared to dry powder inhaler and nebulizers.

iv. The contents are protected from contamination by pathogens.

v. Quick to use

Disadvantages:

i. It is difficult to deliver high doses through PMDI.

ii. Accurate coordination between actuation of a dose and inhalation is required.

iii. Drug delivery is dependent on patient technique. [15]

Dry powder inhalers (DPI):

Dry powder inhalers (DPIs) are devices through which a drug powder formulation of an active drug is delivered for local and systemic effect via pulmonary route. Dry powder devices which operate at low inspiratory flow rate e.g.: Diskhaler, turbohaler. The formulation of DPI can be classified into three categories:

- API production
- Formulation of API with or without carrier
- Integration of formulation into device

API production – To introduce the drug particle into the lungs, they must be <5µm in aerodynamic diameter. This is achieved by milling the powder prior to formulation.

Formulation of API with or without carrier – In carrier free system, the drug particle which is to be inhaled must have aerodynamic diameter less than 5µm and present either in the form of single compound or as an encapsulated particles. In carrier based system, lactose is most commonly & frequently used carrier in DPI formulations. It offers several advantages like improve drug particle flow ability, improving dosing accuracy, minimum dose variability, inhalation efficiency increases etc.

Integration of formulation into a DPI device - In the development of a new DPI formulation, DPI device is the primary factor of concern. It is essential to have knowledge about computational fluid dynamics (CFD) while designing DPI devices. Particle flow, shear stress and potential particle impaction within the

device is analysed by CFD. Consequently this data may be utilized to estimate the in-vitro aerosolisation efficiency of a model drug.

Figure 7: Dry powder inhaler

Advantages:

i. Propellant free device.
ii. Less need for patient coordination.
iii. Less potential for formulation problems.
iv. Formulation stability.

Disadvantages:

i. Depends on patients inspiratory flow rate and profile.
ii. Device resistance.
iii. More expensive than pMDI.
iv. Less protection from environmental effects. [16]

Types of DPIs: Three general types of DPIs are available in the market depending upon the dose size.

1) **Unit dose devices:** single-dose powder inhaler consists of a powder containing capsule placed in a holder which gets open within the device and the powder is inhaled. The used capsule residue shall be replaced by a next dose.
2) **Multi dose devices**: multi dose device uses a single circular disk of either four or eight powder doses maintained in separate aluminium blister reservoirs to serve the treatment schedule for one to two days.
3) **Multi unit dose devices:** multi unit dose devices utilize individually prepared and sealed drug doses. [17]

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. Pulmonary drug delivery is an important research area which impacts the treatment of illness including asthma, chronic obstructive pulmonary disease and various diseases. Inhalation gives the most direct access to drug target. 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. So, pulmonary drug delivery is best route of administration as compared to other routes.

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