Naso pulmonary drug delivery system

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Abstract- **Nasal drug delivery has received a great deal of attention as a convenient, reliable and promising method for the systemic administration of drugs. It is especially for those molecules which are ineffective orally and only effective if administered by injection. This is due to high vascularity, large surface area, the avoidance of hepatic first pass metabolism, gut wall metabolism and/or destruction in gastrointestinal tract. Since nasal mucosa offer several benefits for target delivery, a wide variety of therapeutic compounds may be administered intranasally for topical, systemic and central nervous system action. Many drug delivery devices for nasal application of liquid, semisolid and solid formulation are investigated to deliver the drugs to the treat most crisis CNS diseases (I . e. Parkinson's disease, Alzheimer's disease) because it requires rapid and/or specific targeting of drugs to the brain. It is well suitable for the delivery of biotechnological products like proteins, peptides, hormones, DNA plasmids for DNA vaccines to give enhanced bioavailability. Pulmonary drug delivery has attracted tremendous scientific and biomedical interest in recent years and has progress considerably within the context of local treatment for lung diseases, by virtue of enhanced local targeting and reduced systemic side effects with the administration of minute drug dosages. The present review is an attempt to provide some information concerning naso-pulmonary drug delivery system such as advantages, disadvantages, mechanism of drug absorption, anatomy of nasal cavity and respiratory tract, factors affecting nasal drug absorption, dosage form, novel drug formulations and recent advancement of nasal delivery system.**

Keywords: **Naso-Pulmonary drug delivery, peptides and proteins, nose, nasal pulmonary, respiratory tract.**

INTRODUCTION:

Chronic respiratory disorders (CRDs) comprise the group of diseases that affect the lungs, airways, and other associated structures. The World Health Organization (WHO) has categorized CRDs among the leading causes of global death and disability burden affecting people of all socioeconomic classes. The five most common diseases responsible for respiratory impairment and illness are asthma, chronic obstructive pulmonary disorder (COPD), tuberculosis (TB), lung cancer, and acute respiratory tract infections . According to the WHO estimate, about 235 million people around the world currently have asthma, and more than 3 million people die every year from COPDs. This global disease burden has given rise to the clinical need for developments of delivery systems and tools aimed at the efficient prevention and treatment of these respiratory diseases.(1)

The most common and ancient method of drug delivery to the lungs and airways has been through inhalation. The drugs delivered by inhalation have either of the three main purposes: prophylaxis, topical or systemic disease treatment, and therapy management. Inhaler devices like nebulizers, metered-dose inhalers, dry powder inhalers, and other aerosol-based device technologies are used for delivering drugs.

In the end the currently marketed systems and novel patented systems would be summarized, thereby giving an insight into the required delivery systems and the future research prospects.(2)

Anatomy and physiology of nose and pulmonary system:

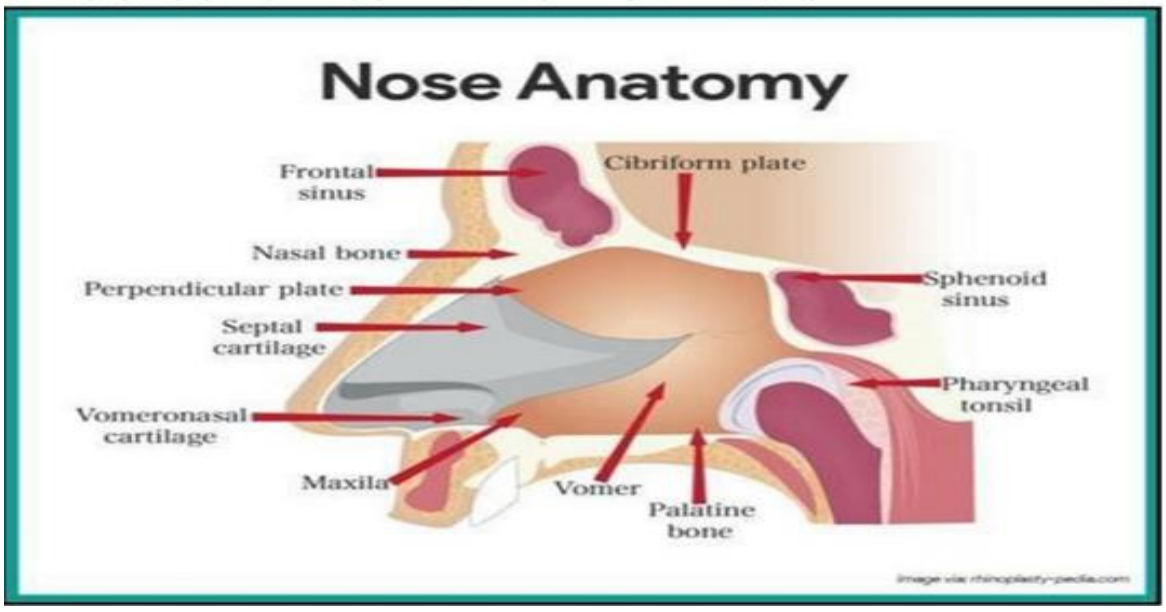

Fig:1. Nose Anatomy.

Nose:

The nose is the complex multifunctional organ. The nose is the primary entrance of the respiratory track.

External Nose:

The external nose is a pyramidal structure, situated in the mid face, with its base on the facial skeleton and its apex projecting anterior. The paired nasal bones form the external nose superiorly and two sets of paired cartilage inferiorly. The upper lateral cartilages provide the shape of the middle third of the nose and support for the underlying nasal valve. During periods of increased nasal breathing, such as during exercise, an increase in the activity of the dilating muscles occurs and aids in increasing the nasal airway patency.

Vestibule:

The first part of the respiratory tract to contact the external environment is the vestibule. Unlike the remaining nasal cavity, the vestibule is lined with stratified squamous epithelium. The epithelium of the nasal vestibule changes into pseudo stratified columnar epithelium. The vestibule also contains thermo receptors that are not found in the portion of the nasal cavity lined by respiratory epithelium. The vestibule is the most important area for sensing nasal airflow.

Nasal Valve and Airflow:

The nasal valve lies just posterior to the nasal vestibule. It is bounded laterally by the caudal end of the upper lateral cartilage, medially by the septum, and inferiorly by the lower rim of the pyriform aperture. A widened area of the septum in this region, called the nasal septal swell body or septal turbinate, is considered part of the expansile vascular tissues of the nose. The nasal septal swell body mucosa is a highly glandular structure with moderate proportion of venous sinusoids that appears to contribute functionally to the area of the valve

Nasal Septum:

The nasal septum divides the nasal cavity into two separate compartments, increasing the total mucosal surface area. It consists of an anterior the percentage of nasal septal deformities changes with age. A multinational study has shown that septal deformities are present in approximately 90% of adult patients. A straight septum is twice more frequent in females than in males.

Turbinates:

The turbinate's are three, rarely four, scroll like projections from the lateral nasal wall. The lower two, referred to as the inferior and middle turbinates, are functionally the most significant. Each turbinate consists of a bony frame with overlying respiratory epithelium. Like the nasal septum, this aid in increasing the mucosal surface area of the nasal cavity to approximately 100 to 200 cm.[3]

Mechanisms for pulmonary drug administration:

The drugs can be primarily delivered by pulmonary delivery systems using two approaches:

1. Intranasal delivery
2. Oral inhalative delivery:

- intratracheal inhalation
- intratracheal instillation

Intranasal delivery refers to the administration of drugs to lungs through the nasal passage, that is, nose-to-lungs aerosol delivery. The intranasal delivery can prove to be advantageous in cases where frequent dosing is required. The method

being noninvasive can be used by the patients without external assistance while not interfering with the daily routine of the patients. Intranasal delivery has often observed to be employed for gas delivery with techniques like nasal high flow therapy, and low flow therapy.(4)

Oral inhalative delivery is found to be far more effective when compared with intranasal administration in the delivery of small-sized particles with concentration loss as less as 20% . Intratracheal instillation is the method of pulmonary delivery most commonly employed in laboratories for evaluating the pulmonary and systemic effectiveness of delivery systems in preclinical animal studies. In this method, drug solution or dispersion is delivered by means of a syringe, make the delivery device plays a major role in the successful pulmonary administration. There has been remarkable research and development in the field of advanced systems for pulmonary administration. The selection of the delivery device is a very significant parameter in formulation design and is based on the desired site of administration in the respiratory tract. The device selected must have suitable characteristics enabling it to generate particles of appropriate aerodynamic diameter so as to deliver them to the desired locations in the lungs. The three most commonly used delivery devices for pulmonary administration are as following the method simple, inexpensive, and fast while delivering quantifiable drug amounts. Despite the advantages, intratracheal instillation cannot be practically used in humans physiologically, hence limiting its application to animal studies only. Contrary to this, intratracheal inhalation uses aerosol technology to deliver drug-carrying particles to the lungs with better penetration and uniform drug distribution.(5)

Mechanism of drug absorption in nasal drug delivery:

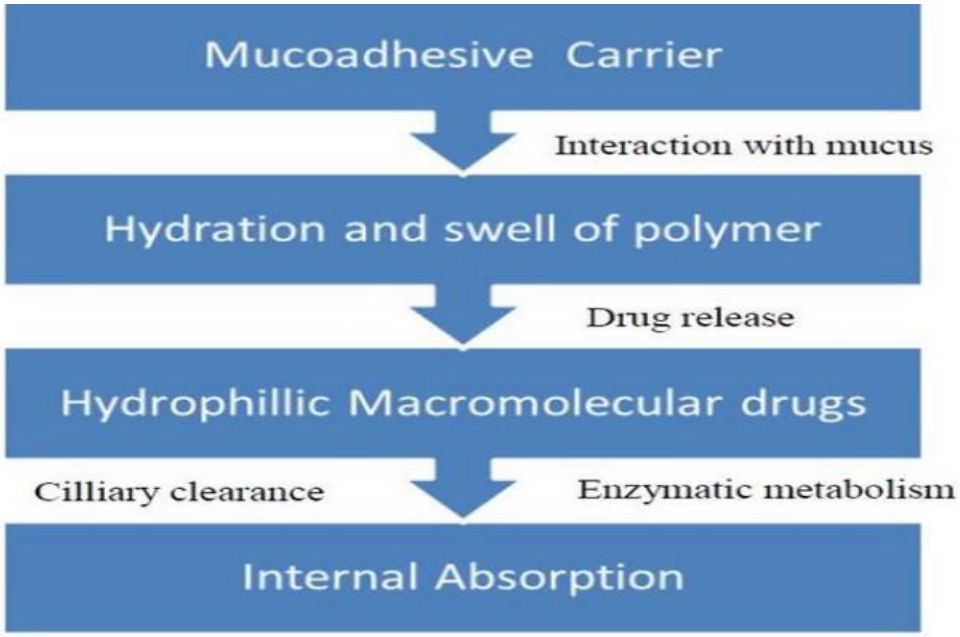

Fig: 2. Absorption of nasal drug delivery.

General types of pulmonary drug delivery devices

The delivery device plays a major role in the successful pulmonary administration. There has been remarkable research and development in the field of advanced systems for pulmonary administration. The selection of the delivery device is a very significant parameter in formulation design and is based on the desired site of administration in the respiratory tract. The device selected must have suitable characteristics enabling it to generate particles of appropriate aerodynamic diameter so as to deliver them to the desired locations in the lungs. The three most commonly used delivery devices for pulmonary administration are as follows:

- Pressurized metered-dose inhalers.
- Dry powdered inhaler
- Nebulizers.

Pressurized metered-dose inhalers:

Pressurized metered-dose inhalers (pMDIs) are the most common delivery device employed for the treatment of respiratory tract diseases like chronic obstructive pulmonary disorder and asthma. All the inhalable drug classes are available for administration in the form of pMDIs either as a single formulation or combination of two or more drugs. When the drug particles reach the air, the difference between the boiling temperature of the formulation and the room temperature leads to the formation of aerosolized droplets due to evaporation. The aerosolized particle size varies from product to product.(6)

Dry powdered inhalers:

Dry powdered inhalers (DPIs) are another class of devices used for pulmonary delivery that require minimum coordination between the process of actuation and breathing for delivery of powdered drugs to respiratory tracts. DPIs have greater chemical stability as they consist of a dried form of the medications as compared with that of suspensions or solutions in the case of pMDIs. However, the formulation and manufacturing of dried powder particles with appropriate characteristics to enable aerosolization and pulmonary delivery is complex.

The structural components of DPIs include mesh, cyclone, manifold, and a spiral chamber. These components must be able to deaggregate the drug-excipient aggregates by utilizing the inhalation force. The inspiratory force required varies from product to product, but a minimum effort of 30–60 L/min is recommended. [(7)]

Nebulizers:

Nebulizers are the devices used to generate aerosol droplets ranging from 1 to 5 µm aimed at inhalation-based pulmonary delivery. Two different kinds of nebulizers are generally used: jet and ultrasonic nebulizers. These two types of nebulizers differ in the type of force that they utilize to generate aerosols from liquid suspension/solution. Nebulizers do not require coordination between inspiration and actuation and thus can be used for a variety of patients who are unable to use pMDIs and DPIs. Moreover, nebulizers have the ability to administer large doses. The formulation of solutions used for nebulizers is easy and cheap as compared with that required for pMDIs and DPIs. One of the major disadvantages associated with the use of nebulizers is that they require to be assembled and loaded before each use and disassembled and cleaned again after every use by the patient, which might be difficult for an untrained patient.[(8)]

Novel delivery systems targeting respiratory diseases:

The potential of pulmonary delivery for the treatment of respiratory diseases has been acknowledged and utilized for more than 3500 years in the form of different technologies. The other routes that are used for lung diseases include oral and parenteral delivery. The concept of repurposing the established drugs for the treatment of respiratory diseases by developing novel pulmonary drug delivery systems has attracted the interest of the biomedical scientific community and the pharmaceutical companies owing to the drug absorption capacity of lungs. Different drug absorption mechanisms in the case of pulmonary delivery have been discussed in Several advantages of the pulmonary delivery systems that have intrigued the attention of researchers toward the development of novel pulmonary systems are as follows:

- Lungs have been found to have a high absorptive surface area of about 70–140 m^2 for an adult human covered with a thin layer of mucosa, which allows easy absorption.
- Lungs also exhibit high permeability
- Peroral and systemic delivery leads to drug delivery throughout the body, thereby a small fraction of drugs reaching the lungs. Targeted delivery using the pulmonary route would enable the delivery of the required amount of drug locally to respiratory tract regions.
- The unwanted systemic side effects caused due to the drug reaching every part of the body can be avoided or reduced.[(9)]

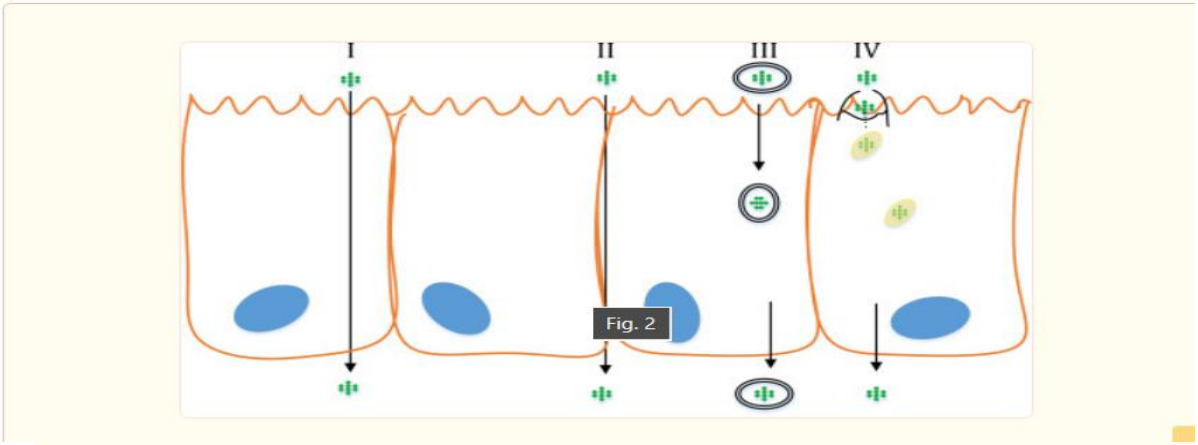

Fig3: Drug absorption mechanisms through pulmonary route includes (I) transcellular diffusion, (II) paracellular diffusion, (III) vesicle-based transport, and (IV) carrier-mediated transport.

The development of controlled drug delivery systems for pulmonary delivery has been an area of interest for researchers for long. Many systems have been developed for targeting specific respiratory diseases. The structure of different particle-based pulmonary systems and the factors influencing pulmonary delivery are demonstrated in. However, in spite of increased investigations in this area, not many systems have translated to the market. Some of the most popularly developed systems and their significance for various respiratory diseases would be discussed in this section.[(9)]

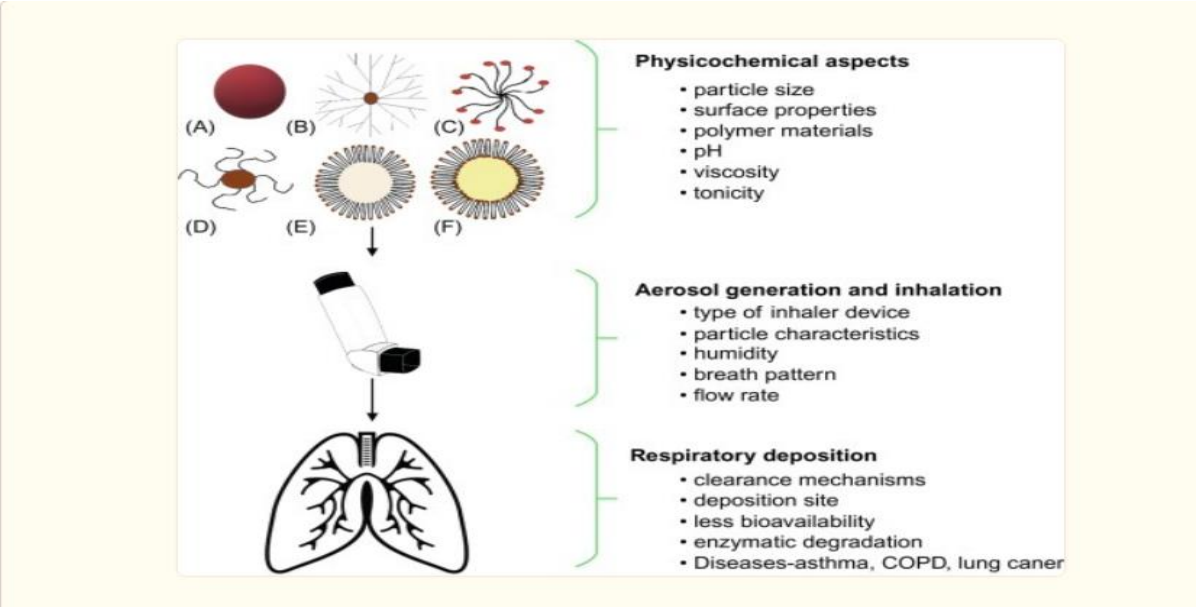

Fig:4 Types of particle-based pulmonary systems and the factors influencing pulmonary drug delivery: (A) polymeric nanoparticles, (B) dendrimers, (C) micelles, (D) functionalized nanoparticles, (E) solid lipid nanoparticles, and (F) liposomes

Factors influencing nasal drug absorption:

Several factors affect the systemic bioavailability of drugs which are administered through the nasal route. The factors can be affecting to the physiochemical properties of the drugs, the anatomical and physiological properties of the nasal cavity and the type and characteristics of selected nasal drugs delivery system. These factors play key role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. The factors influencing nasal drug absorption are described as :

A. Physiochemical properties of drug

1. Molecular size.
2. Lipophilic-hydrophilic balance.
3. Enzymatic degradation in nasal cavity.

B. Nasal Effect:

1) Membrane permeability.
2) Environmental pH.
3) Mucociliary clearance.
4) Cold, rhinitis

C. Delivery Effect

1) Formulation (Concentration, pH, osmolarity)
2) Delivery effects
3) Drugs distribution and deposition.
4) Viscosity.[10]

Advantages of pulmonary drug delivery:

1. It is needling free pulmonary delivery.
2. It requires small and fraction of oral dose.
3. Low concentration in the systemic circulation is associated with reduced systemic side effects.
4. Rapid Onset of action
5. Avoidance of gastrointestinal upset
6. Degradation of drug by liver is avoided in pulmonary drug delivery.
7. Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs
8. Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
9. Drugs possessing poor stability in G.I.T. fluids are given by nasal route.
10. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.[11]

Disadvantages of pulmonary drug delivery:

1. Oropharyngeal deposition gives local side effect.

2. Patient may have difficulty using the pulmonary drug devices correctly.
3. Drug absorption may be limited by the physical barrier of the mucus layer.
4. Various factors affect the reproducibility on drug delivery on the lungs, including physiological and pharmaceutical barrier.
5. The lungs are not only accessible surface for drug delivery complex but also delivery devices are required to target drug delivery.
6. There is a risk of local side effects and irreversible damage of the cilia on the nasal ucosa, both from the substance and from constituents added to the dosage form.
7. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
8. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.[12]

CONCLUSION:

The nasal cavity has a large surface area and a highly vascularized mucosa. Drugs absorbed by the rich network of blood vessels pass directly into the systemic circulation, thereby avoiding the first pass metabolism. A growing body of evidence relating to nasal drug delivery suggests it might use for challenging drugs which can facilitate the pharmaceutical manufacturing and drug delivery challenges.

The pulmonary route has been found to be promising for the delivery of drugs locally to lungs and rapid systemic delivery for several diseases. The pulmonary delivery offers advantages like the rapid onset of delivery, self-administrable noninvasive delivery, enhanced efficiency, localized action, and reduced side effects. The inherent properties offered by lungs such as high surface area and low enzymatic environment further make pulmonary delivery even more desirable. However, there are several challenges that are required to be tackled for successful pulmonary delivery, which includes rapid drug degradation, clearance mechanism by the alveolar macrophages, limited control over the particle deposition, and site of deposition of inhaled formulations.

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