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NASOPULMONARY DRUG DELIVERY SYSTEM: A REVIEW ARTICLE

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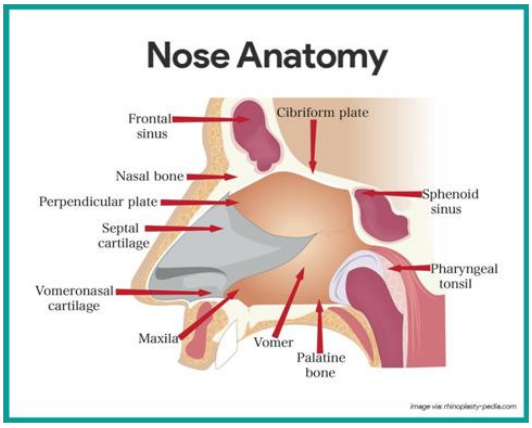
ABSTRACT

The pulmonary drug delivery system offers several merits over other drug delivery systems and therefore, this delivery route has been in prime focus for various applications like local and systemic therapeutics delivery. The overall development of drug delivery system depends on its efficacy, quality and safety and to achieve such attributes there is a need of reliable evaluation methods to test them. This review provides an in-depth analysis of the development in the evaluation of pulmonary drug delivery systems.

INTRODUCTION

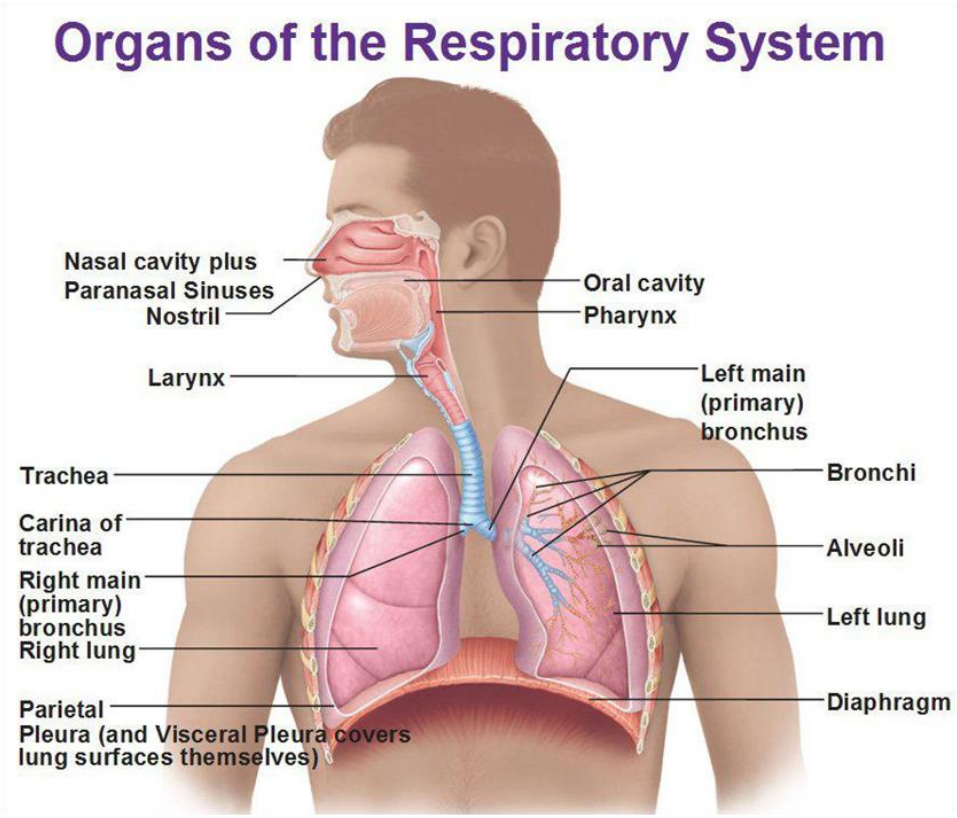
The respiratory tract is one of the oldest route of administration of the drugs. In ancient times the Indian Ayurvedic system of medicines used nasal and pulmonary route for administration of drug and the process is called as "NASYA KARMA". Intranasal administration is an attractive routes for local and systemic delivery of many therapeutic agents. Nowadays the development of inhalation therapy and investigation of nasal routes has established itself as a valuable tool focused on the local therapy of pulmonary diseasesand nasal application for systemic drug delivery.The nasal mucosa is easily accessible and provides a practical entrance portal for small and large molecule of drugs compared to other mucosal routes. Intranasal drug administration is noninvasive, essentially painless and particularly suited for children. Application can be performed easily by patients or by physicians in emergency situation.Systemic delivery of drug molecule via nose and pulmonary track is more suitable becauseof the high permeability, high vasculature, low enzymatic environment of nasal cavity and avoidance of hepatic first pass metabolism in respiratory track .Nasal and Pulmonary route has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity.It may found that certain drugs taken by pulmonary route are readily absorbed by the alveolar region direct in to blood circulation. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism. The nasal route circumvents hepatic first pass elimination associated with the oral delivery, it is easily accessible and suitable for self-medication.



Anatomy and physiology of Nose and pulmonary system:-

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 midface, 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 pseudostratified columnar epithelium. The vestibule also contains thermoreceptors 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 cartilaginous portion, which provides support for the nasal tip, and a posterior bony portion formed by the perpendicular plate of the ethmoid and the vomer. 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 as frequent in females than in males.

Turbinates :-The turbinates 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, these aid in increasing the mucosal surface area of the nasal cavity to approximately 100 to 200 cm .The inferior turbinate has an important role in the defence of the lungs and the physiology of the nose. Trimming of the anterior portion of the inferior turbinate can lead to a decrease in the total nasal resistance to airflow (42) by enlarging the nasal valve, but this should be considered only after potential causes for its enlargement have been investigated.

Histology :-The nasal lining has a mucosal epithelial layer with an underlying sub mucosal layer. The mucosa consists of pseudostratified columnar epithelium containing goblet cells, ciliated and nonciliated columnar cells with microvilli, and, occasionally, intraepithelial mast cells, eosinophils, and lymphocytes. The epithelial cells provide a protective barrier, and they produce inflammatory substances and the secretory portion of immunoglobulin IgA. The seromucous glands account for the largest proportion of nasal secretions. These glands are located throughout the nasal cavity, but the greatest concentration resides in the anterior nasal cavity. Depending on the cell type, these glands secrete either a serous or a mucous secretion.

Mucociliary Clearance:- Mucociliary transport is the mechanism by which the nasal cavity clears itself of secretions and trapped particulates. The two major components of this system are the mucous blanket and the ciliated epithelial cells.(12.np [https://en.m.wikipedia.org/wiki/Lung])

Lungs:- The lungs are the primary organs of the respiratory system in humans. In mammals and most other vertebrates, two lungs are located near the backbone on either side of the heart. Their function in the respiratory system is to extract oxygen from the atmosphere and transfer it into the bloodstream, and to release carbon dioxide from the bloodstream into the atmosphere, in a process of gas exchange. They are conical in shape with a narrow rounded apex at the top, and a broad concave base that rests on the convex surface of the diaphragm. The apex of the lung extends into the root of the neck, reaching shortly above the level of the sternal end of the first rib. The lungs stretch from close to the backbone in the rib cage to the front of the chest and downwards from the lower part of the trachea to the diaphragm. The left lung shares space with the heart, and has an indentation in its border called the cardiac notch of the left lung to accommodate this. The cardiac impression is an indentation formed on the surfaces of the lungs where they rest against the heart. Both lungs have a central recession called the hilum at the root of the lung, where the blood vessels and airways pass into the lungs. There are also bronchopulmonary lymph nodes on the hilum.

Lung regions:-The respiratory tract starts at the nose and terminates deep in the lung at an alveolar sac. There are a number of schemes for categorizing the various regions of the respiratory tract.

Right lung :-The right lung has both more lobes and segments than the left. It is divided into three lobes, an upper, middle, and a lower lobe by two fissures, one oblique and one horizontal.

Left lung :-The left lung is divided into two lobes, an upper and a lower lobe, by the oblique fissure, which extends from the costal to the mediastinal surface of the lung both above and below the hilum.

Nasopharyngeal region:- This is also referred to as the “upper airways”, which involves the respiratory airways from the nose down to the larynx.

Tracheo-bronchial region:- This is also referred to as the “central” or “conducting airways”, which starts at the larynx and extends via the trachea, bronchi, and bronchioles and ends at the terminal bronchioles.

Alveolar region:- This is also referred to as the "respiratory airways", "peripheral airways" or "pulmonary region", Comprising the respiratory bronchioles, alveolar ducts and alveoli.

Pulmonary epithelium:- The lung contains more than 40 different cell types, of which more than six line the airways. The diversity of pulmonary epithelia can be illustrated by examining its structure at three principal levels.

The bronchi:- These are lined predominantly with ciliated and goblet cells. Some serous cells, brush cells and Clara cells are also present with few Kulchitsky cells.

The bronchioles:- These are primarily lined with ciliated cuboidal cells. The frequency of goblet and serous cells decreases with progression along the airways while the number of Clara cells increases.

The alveolar region:-This is devoid of mucus and has a much flatter epithelium, which becomes the simple squamous type, 0.1–0.5 μm thick.

Ciliated cells:- In the trachea bronchial region, a high proportion of the epithelial cells are ciliated such that there is a near complete covering of the central airways by cilia. Towards the periphery of the tracheobronchial region, the cilia are less abundant and are absent in the alveolar region. The ciliated cells each have about 200 cilia with numerous interspersed microvilli, of about 1–2 μm in length. The cilia are hair-like projections about 0.25 μm in diameter and 5 μm in length.[7.np,https://en.m.wikipedia.org/wiki/Lung)]

Major Functions of the Respiratory System:-

1. Maintaining hemostasis (acid-base balance) of arterial blood
2. Maintaing heat exchange
3. Removing waste (carbob dioxide) from body tissues
4. Supplying oxygen to the body.(13.np)

Advantages of pulmonary drug delivery

1) It is needle free pulmonary delivery.

2) It requires small and fraction of oral dose.

3) Low concentration in the systemic circulation are 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.

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 mucosa, 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.

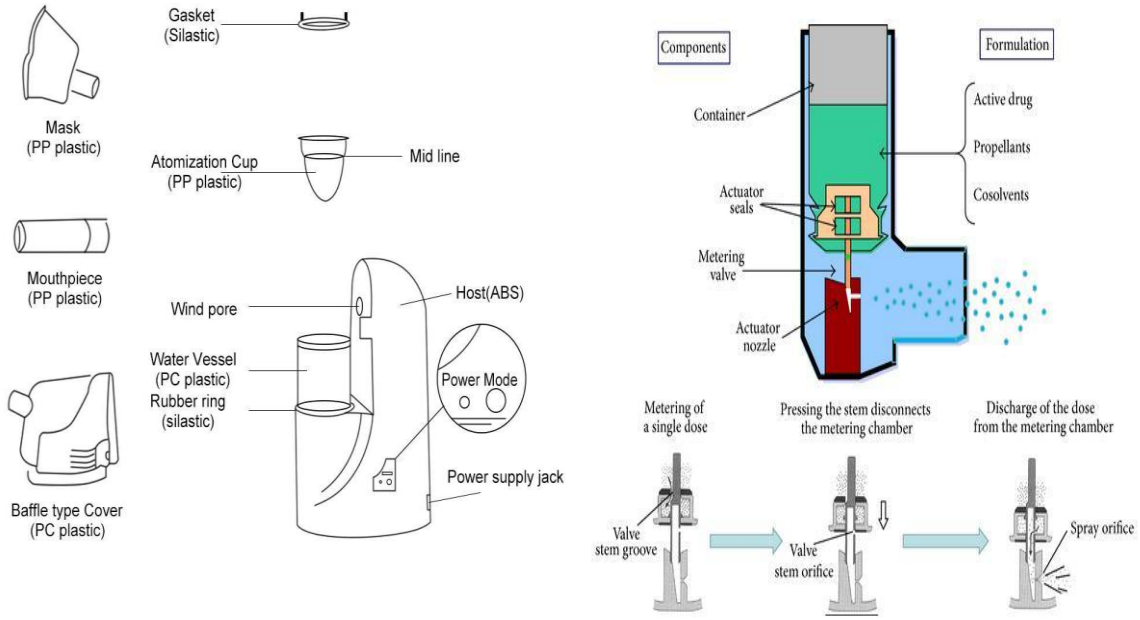
8) There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

Recent technologies of pulmonary

Drug delivery:-

Nebulizer: Nowadays the many physicians are mostly use nebulizer for the treatment of acute asthma in an emergency care unit or for treating patients with severe asthma at home. In jet nebulizers, an aerosol is prepared by a high velocity air stream from a pressurized source directed against a thin layer of liquid solution. Ultrasonic nebulizers include the vibration of a piezoelectric crystal aerosolizing the solution. The nebulizer can transport more drugs to the lungs than MDI or DPI, the most common disadvantage of nebulizer are lack of possibility, higher costs of drug delivery as a result of the larger need for assistance from healthcare professionals, and the need for higher drug doses to achieve a therapeutic result.

Metered Dose Inhaler (MDI): These are the most common device for administration of aerosolized drugs. In this technique, a medication is mixed in a canister with a propellant, and the preformed mixture is expelled in exact measured amounts upon actuation of the device. Correct use of MDIs requires that patients learn how to organize exhalation and inhalation with actuation of the device. By using the spacer device it may solve the problem moderately the bulky size of the device can be prevention for patients who have need of use of MDIs outside their homes. In near the beginning 1990, attempts were actively made to reformulate MDIs as a result of the mandatory ban on the use of propellant chlorofluorocarbons (CFCs), which have been concerned in the depletion of the Earth's ozone layer.



Dry powder inhalers:-

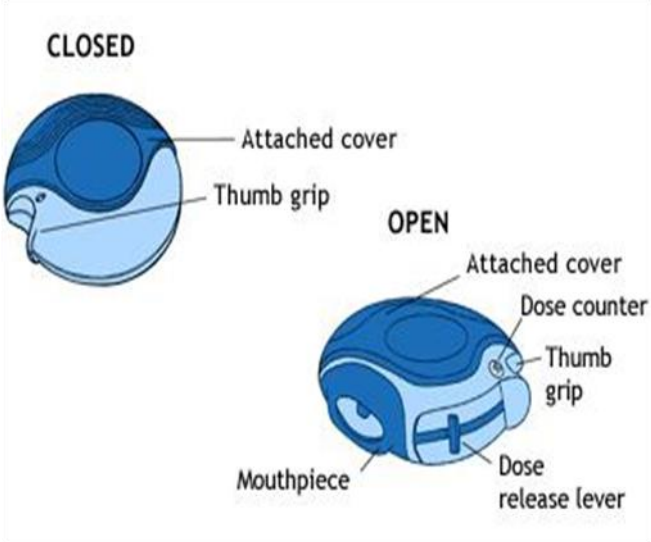
Interest in DPIs as an effective, efficient and environmentally friendly way of delivering drugs to the lung has accelerated in recent years. A fundamental difficulty with developing solid state aerosols, or DPIs, is managing both the ubiquitous and the transient forces contained in powder beds. Indeed, managing such particulate forces, for example via particle engineering techniques, is now considered central to successful DPI formulation and production. With DPIs, the drug aerosol is created by directing air through loose powder. Most particles from DPIs are too large to penetrate into the lungs due to large powder agglomerates or the presence of large carrier particles (e.g. lactose).

Evaluation of pulmonary drug delivery devices:-

1. **In vitro**:-

In this respect, in vitro models for pulmonary drug delivery studies propose another as it convey up fewer moral questions but also because they allow a fast screening of drugs. In both cellular models, it is significant that epithelial cells form a tense monolayer in order to characterize the natural epithelial barrier. Monolayer tension and reliability are classically assessed by measuring Tran's epithelial electrical resistance (TEER) and potential difference crosswise the monolayer. Monolayers of lung epithelial cells permit the categorization of drug transport and evaluation of potential drug and formulation toxicity.

In –vivo :- Guinea-pigs have been generally used as an animal form of allergic asthma and infectious diseases (e.g., tuberculosis) since the airway anatomy and the respond to inflammatory stimuli are similar to the human case. In large mammals, the rate of mucus permission in millimetres per minute is elevated compared with small rodents. Though, huge mammals also have longer airways than minute rodents and thus, worldwide, the bronchial permission of inhaled particles is comparatively slow in humans.



Principal mechanisms of respiratory deposition

The deposition of inhaled particles in the different regions of the respiratory system is very complex, and depends on many factors. Some of the factors influencing respiratory deposition include:

• Breathing rate • Mouth or nose breathing • Lung volume • Respiration volume • Health of the individual • Bifurcations in the airways result in a constantly changing hydrodynamic flow field. Depending on the particle size, airflow, and location in the respiratory system, particle deposition occurs via on of the following principal mechanisms: 1.Absorption

Indication	Active pharmaceutical ingredient	Formulation
Analgesia	Diamorphine hydrochloride Fentanyl citrate	Powder and diluent for reconstitution-aqueous spray Nasal spray, solution
Acute treatment of migraine	Sumatriptan Zolmitriptan	Nasal spray, solution Nasal spray, solution
Endometriosis Ovarian stimulation	Nafarelin acetate	Nasal spray, solution
Nasal congestion (associated with sinusitis, common cold, rhinitis and other UTIs) Symptomatic relief of rhinorrhoea	Xylometazoline hydrochloride Oxymetazoline hydrochloride Azelastine Hydrochloride Ephedrine Ipatropium bromide	Nasal spray, solution, nasal drops Nasal spray, solution Nasal spray, solution Nasal drops Nasal spray, solution
Prophylaxis and treatment of perennial and seasonal allergic rhinitis	Budesonide, beclometasone dipropionate (and monohydrate (micronized), Mometasone furoate Triamcinolone acetonide Fluticasone propionate Fluticasone furoate Fluticasone with azelastine HCl Sodium cromoglicate	Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension, spray solution
Prostatic carcinoma (hormone -dependent)	Buserelin acetate	Nasal spray, solution
Nasal congestion	Levomenthol	Nasal ointment
Nasal infection	Neomycin sulfate and Chlorhexidine dihydrochoride	Nasal cream
Nicotine withdrawal symptoms	Nicotine	Nasal Spray Solution
Nocturia associated with multiple sclerosis The diagnosis and treatment of vasopressin-sensitive cranial diabetes insipidus. Establishing renal concentration capacity.	Desmopressin acetate	Nasal Spray Solution
Vaccinations	Influenza vaccine	Nasal spray suspension

The development of nasal products .Therapeutic Considerations Answers to key questions whether the drug is intended for (a) local or systemic delivery or for (b) single or repetitive administration and (c) patient- related issues (e.g. adults, children) define the development strategy for the nasal product. An idea of the clinically effective drug concentration in the target site should exist in order to estimate the feasibility of the nasal application route.

Local Delivery:- Prominent examples for locally acting intranasally administered drugs are decongestants for nasal cold symptom relief, antihistamines and corticosteroids for allergic rhinitis. Due to the fact that relatively low doses are effective when administered topically,

the intranasal administration of antihistamines and corticosteroids has a weak potential for systemic adverse effects as opposed to systemic therapy. Intranasal administration is therefore a logical delivery choice for the topical (local) treatment of nasal symptoms.

Systemic Delivery: - The nasal mucosa provides a practical entrance portal for systemically acting molecules. Intranasal administration offers a rapid onset of therapeutic effects, avoids the first- pass effect or gastrointestinal degradation of drugs, is noninvasive, essentially painless and finally easily administered by patients or by physicians in emergency settings. The intranasal administration provides a true alternative route for systemic drugs presently delivered more conventionally by oral or parenteral routes

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 .

1) Physiochemical properties of drug.
1. Molecular size.
2. Lipophilic-hydrophilic balance.
3. Enzymatic degradation in nasal cavity.

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

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

CONCLUSION:

The general expansion of drug delivery system depends on its efficiency, superiority and protection and to attain such characteristic there is a requirement of reliable evaluation methods to test them. This review provides an in-depth investigation of the growth in the evaluation of pulmonary drug delivery systems.

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