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A REVIEW ARTICL ON NASOPULMONARY 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. 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. 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.

The intranasal route has become one of the most explored areas in the field of pharmaceutical research for the delivery of small polar molecules, vaccines, hormones, peptides, and proteins. Due to its high membrane permeability, high vasculature, low enzymatic environment, and avoidance of hepatic first-pass metabolism, this route has been chosen for the systemic distribution of medicines. The enormous surface area of the nasal mucosa promotes non-invasiveness, direct medication transport to the central nervous system (CNS), and rapid commencement of therapeutic impact. The intranasal route can enhance patient convenience, comfort, and compliance because it is practically painless and simple for doctors or patients to administer. This page seeks to provide information about the nasal cavity, its benefits and drawbacks, factors affecting nasal drug absorption, methods to enhance drug absorption, dosage forms, and delivery systems for pharmaceuticals, and some of their applications.

Nasal route of drug delivery 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, neutral pH of the nasal mucus and less dilution by gastrointestinal contents.

It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides. 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 muco-ciliary clearance mechanism.

Keywords: *Naso-Pulmonary drug delivery, mucociliary clearance, nasal, pulmonary, respiratory tract.*

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INTRODUCTION:

In ancient times the Indian Ayurvedic system of medicines used nasal route for administration of drug and the process is called as “Nasya”.

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For many years, drugs have been administered nasally for both topical and systemic action.

Topical administration includes the treatment of congestion, rhinitis, sinusitis and related allergic or chronic conditions. Prominent therapeutic classes of drugs delivered are decongestants for cold nasal symptoms and antihistamines and corticosteroids for allergic rhinitis

The intranasal administration of drugs is an effective way for the systemic availability of drugs as compared to oral and intravascular routes of administration. It provided fast and extended drug absorption than oral and parenteral administration. Therapeutic classes of drugs delivered include analgesics (morphine), cardiovascular drugs as propranolol and carvedilol, hormones such as levonorgestrel, progesterone, and insulin, anti-inflammatory agents as indomethacin and ketorolac, and antiviral drugs (acyclovir).

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Anatomy and Physiology of nose and pulmonary system:

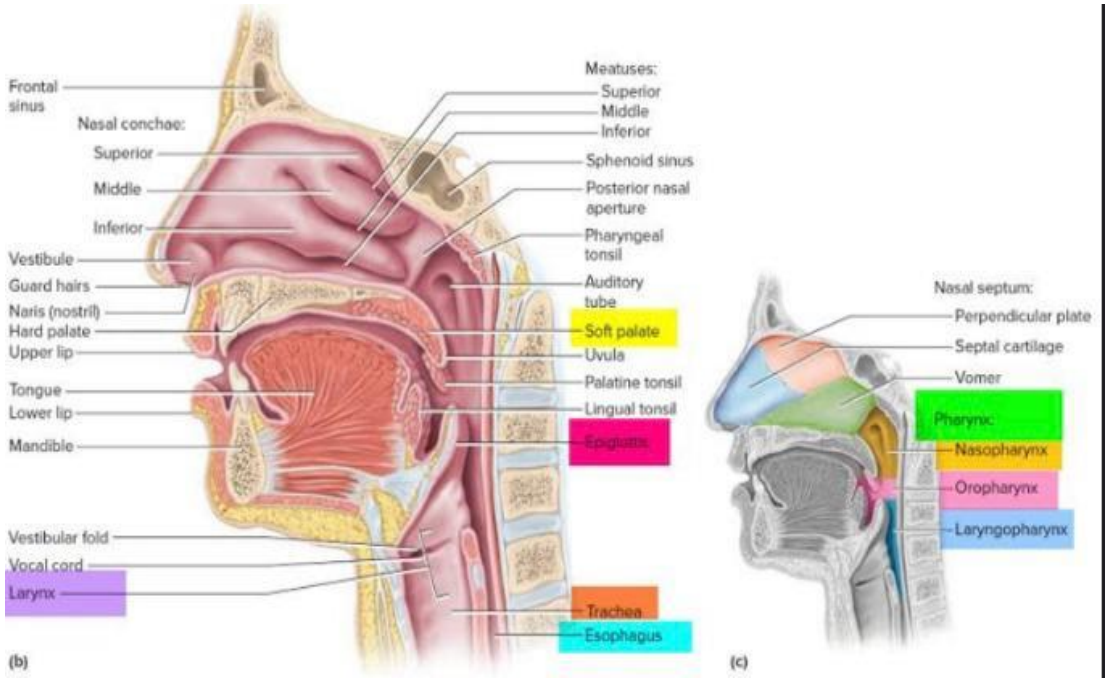


Fig:1 Anatomy of nose and pulmonary system

The nasal cavity consists three main regions:

1. Nasal vestibule

2. Respiratory region

- Major drug absorption.
- 15-20 % of the respiratory cells covered by layer of long
- Cilia size 2-4 µm

3. Olfactory region.

- Small area in the roof of the nasal cavity of about 10 cm2
- Drug is exposed to neurons thus facilitate it across the cerebro-spinal fluid.
- Normal pH of the nasal secretions in adult 5.5-6.5.
- Infants and young children 5.0-6.7.
- Nasal cavity is covered with a mucous membrane Mucus secretion is
- composed of 95%-water,2%-mucin,1%-salts,1%-of other proteins
- Such as albumin, lysozyme and lactoferrin and 1%-lipids.

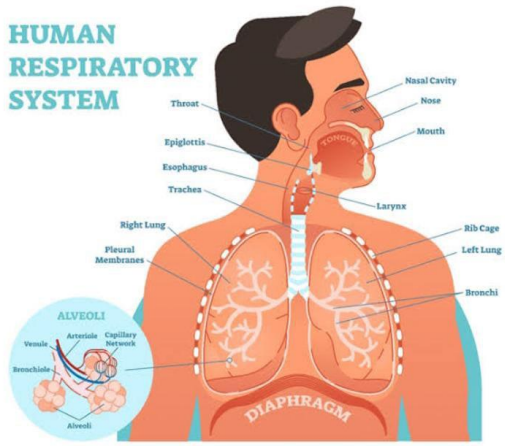


Fig:2 Human respiratory system

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.

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.

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.

Turbinate's: - 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 turbinate's, 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

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.

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

Trachea-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.

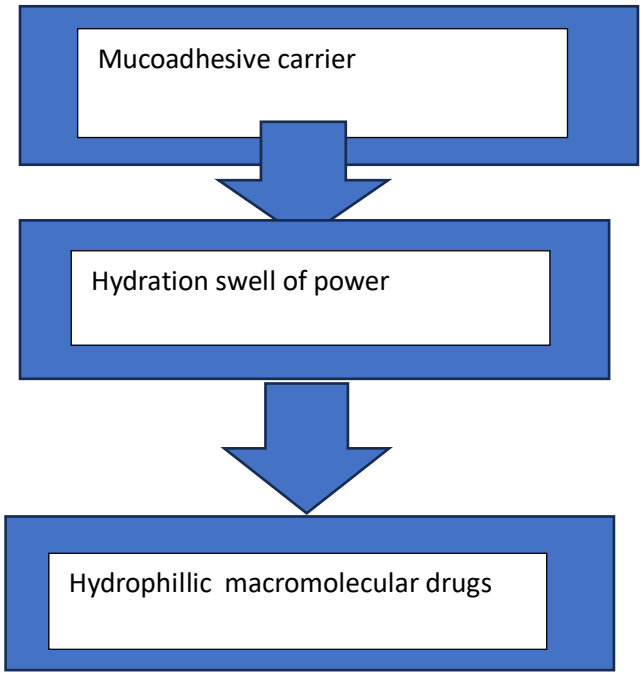
Pulmonary epithelium: - The lung contains more than 40 different cell types, of which more than six line the airways. The diversity of pulmonary epithelia can be illustrated by examining its structure at three principal levels.

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.

Mechanism of drug absorption in nasal drug delivery:



Two mechanisms have been considered predominantly out of several mechanisms that have been proposed.

The first involves an aqueous route of transport, which is also known as the paracellular route. Key feature of this mechanism involves.

- This route is slow and passive.
- There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds.
- Poor bioavailability was observed for a drug with a molecular weight greater than 1000 Daltons.

The second involves transport through a lipoidal route is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. For examples, chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport.

Dosage forms in naso-pulmonary drug delivery system:

1.Nasal drops.

They are the most convenient and simple system developed for nasal drug delivery. Nose drops can be delivered with a squeezy or by a pipette a bottle. These pharmaceuticals formulations are often recommended for treating local conditions, which include suffering some challenges such as microbial growth, mucosal dysfunction, and non-specific loss of the nose or lower back. The featured disadvantage of this system is the lack of the dose precision, and therefore, nasal drops may not be useful for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

2.Nasal sprays

Solution and suspension are formulated into nasal sprays. Availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 µm. The morphology particles size (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

3.Nasal gels

Until the recent development of precise dosing device, there was not a lot of interest during this system. Nasal gels are high viscosity thickened solutions or suspensions. The benefits of a nasal gel include the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation using soothing/emollient excipients, and target to mucosa for higher absorption.

4.Nasal powder.

This dosage form may be formulated if solution and suspension dosage forms cannot be formulated, for example, due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of superior stability and preservative of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particles size, aerodynamic properties, and nasal irritancy of the active drug and excipients. Local application of the drug is another advantage of this system.

5.Liposomes.

These are phospholipid vesicles composed by bilayer enclosing one or more aqueous compartments, in these compartments drug can be entrapped or adsorbed.

6.Microspheres

Microsphere has an important role in nasal drug delivery with enhancing absorption, sustained release, and also has great importance because it protects the drug from enzymatic degradation.

7.Instillation and rhinyle catheter.

Catheters are used to deliver the drops to a specified region of nasal cavity easily. Place the formulation in the tube and kept tube one end was positioned in the nose, and the solution was delivered into the nasal cavity by blowing through the other end by mouth. Dosing of catheters is determined by the filling prior to administration and accuracy of the system and this is mainly used for experimental studies only.

8.Compressed air nebulizers.

Nebulizer is a device used to administer medication in the form of a mist inhaled into the lungs. The compressed air is filling into the device, so it is called compressed air nebulizers. The common technical principal for all nebulizers, is to either use oxygen, compressed air or ultrasonic power, as means to break up medical solutions/ suspensions into small aerosol droplets, for direct inhalation from the mouthpiece of the device. Nebulizers accept their medicine in the form of a liquid solution, which is often loaded into the device upon use. Corticosteroids and Bronchodilators such as salbutamol (Albuterol USAN) are often used, and sometimes in combination with ipratropium. The reason these pharmaceuticals are inhaled instead of ingested is in order to target their effect to the respiratory tract, which speeds onset of action of the medicine and reduces side effects, compared to other alternative intake routes This device is not suitable for the systemic delivery of drug by patient himself.

9. Squeezed bottle:

Squeezed nasal bottles are mainly used as delivery de-vice for decongestants. They include a smooth plastic bottle with a simple jet outlet. While pressing the plastic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle. This procedure often results in contamination of the liquid by microorganisms and nasal secretion sucked inside. Dose accuracy and deposition of liquids delivered via squeezed nasal bottles are strongly dependent on the mode of administration. The differences between vigorously and smoothly pressed applications influence the dose as well as the droplet size of the formulation. Thus, the dose is hard to control. Therefore, squeezed bottles with vasoconstrictors are not recommended to be used by children.

10. Insufflators.

Insufflators are the devices to deliver the drug sub-stance for inhalation; it can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also. The achieved particle size of these systems is often increased compared to the particle size of the powder particles due to insufficient disaggregation of the particles and results in a high coefficient of variation for initial deposition areas. Many insufflator systems work with pre-dosed powder doses in capsules.

11. Dry powder inhaler.

Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus. The medication is commonly held either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are a variety of such devices. The dose that can be delivered is typically less than a few tens of milligrams in a single breath since larger powder doses may lead to provocation of cough.

12. Pressurised MDIs:

A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases. The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD. Other medications less commonly used but also administered by MDI are mast cell stabilizers, such as (cromoglicate or nedocromil). The advantages of MDIs are their portability and small size, availability over a wide do-sage range per actuation, dose consistency, dose accuracy, protection of the contents and that they are quickly ready for use.

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 follows.

1. Physiochemical properties of drug.
    - Molecular nature
    - Hydrophilic and lipophilic balance
    - Enzymatic dehydration in nasal cavity
    - Stability
    - Solubility
    - Physical state od drug
    - Chemical state of drug

    2. Nasal Effect:

    - Membrane permeability
    - Environmental PH.
    - Muco-ciliary clearance.
    - Cold, rhinitis.
    - Blood flow
2. Effect of drug formulation:
    - Formulation (concentration, PH, osmolarity)
    - Delivery effects
    - Drug distribution and deposition.
    - Viscosity
    - Pharmaceutical excipients.

Nasal Sprays:

Most of the pharmaceutical nasal preparations on the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to generally alleviate cold or allergy symptoms such as nasal congestion or systemically, see nasal administration. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by action of a hand-operated pump mechanism. The three main types available for local effect are: antihistamines, corticosteroids, and topical decongestants Metered- dose pump sprays include the container, the pump with the valve and the actuator. The dose accuracy of metered-dose pump sprays is dependent on the sur-face tension and viscosity of the formulation. For solutions with higher viscosity, special pump and valve combinations are on the market.

Excipients Used in Nasal Spray Formulations:

There are various types of excipients used in nasal formulations. Commonly used and frequently added excipients are as follows:

a. Buffers: Nasal secretions may alter the pH of the administrated dose, which can affect the concentration of un-ionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ. Examples of buffer used in nasal spray sodium phosphate, Sodium citrate and citric acid.

b. Solubilizers: Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transductal (diethylene glycol monomethyl ether), medium chain glycerides and Labra sol (saturated polyglycol zed C8-C10 glyceride) can be used to enhance the solubility of drugs. Other compounds can be used like, the use of surfactants or cyclodextrins such as HP–cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers. In these cases, their impact on nasal irritancy should be considered.

c. Preservatives: Most nasal formulations are aqueous based so needs preservatives to prevent microbial growth. Parabens, phenyl ethyl alcohol, benzalkonium chloride, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations.

d. Antioxidants: A small quantity of antioxidants may be required to prevent drug oxidation. Commonly used antioxidants are

sodium bisulfited, butylated hydroxytoluene, sodium metabisulfite and tocopherol. Usually, antioxidants do not affect drug absorption or cause nasal irritation.

e. Humectants; Because of allergic and chronic diseases there can be crusts and drying of mucous membrane. Certain preservatives/ antioxidants are also likely to cause nasal irritation especially when used in higher quantities. Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and do not affect drug absorption. Common examples include glycerine, sorbitol and mannitol.

f. Surfactants: Surfactant incorporation into nasal dosage forms can modify the permeability of nasal membranes, which may facilitate the nasal absorption of drug. It also increases stability of suspension. Common examples include Polysorbate.

g. Bio adhesive polymers: Compound that is capable of interacting with biological material through interfacial forces and being retained on such material for prolonged periods is called as bio adhesive polymer. They are also called as mucoadhesive if biological material is mucus membrane. The bio adhesive force of a polymer material is dependent on the nature of the polymer, the surrounding medium (pH), swelling and physiological factors (mucin turnover, disease state). From a safety (nasal irritancy) point of view use of a combination of carriers is often recommended.

h. Penetration enhancer: Chemical penetration enhancers are widely used in the nasal drug delivery.

Characterization of Nasal Spray:

- pH
- Osmolality
- Viscosity
- Impurities and Degradation Products
- Preservatives and Stabilizing Excipients Assay
- Pump Delivery
- Spray Content Uniformity (SCU)
- Spray Pattern and Plume Geometry
- Droplet Size Distribution
- Particle Size Distribution

Pulmonary routes of drug delivery

Introduction:

Pulmonary drug delivery (PDD) systems were recently introduced into the pharmaceutical field to treat both the local and the systemic type of lung diseases. PDD systems are known to be able to simply deliver the drug to the required site in the body directly or to other distant sites through the bloodstream. The lungs provide a huge surface area of alveoli with rich capillary network, which acts as an excellent absorbing surface for administration of drugs.

Throughout the past several years, rapid onset of action and higher efficiency has been responsible for the success of pulmonary delivery system for symptomatic relief in treatment of asthma and chronic obstructive pulmonary disease (COPD). The efficacy of a treatment mostly depends on the techniques by which the drug is delivered and optimum concentration of the drug, above or below this range can be toxic or produce no therapeutic benefit at all. The slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutic agents to targets in tissues. The efficacy of the drug and its treatment can be achieved from the new ideas on controlling the pharmacokinetics, pharmaco-dynamics, immunogenicity, and bio-recognition. These new strategies based on interdisciplinary approaches such as polymer science, pharmaceutical technology, bio-conjugate chemistry, and molecular biology, are often called novel/advanced drug delivery systems. Different drug delivery/drug targeting systems already exist and currently under development can be efficiently used to minimize the drug degradation and loss, to prevent harmful side effects and to increase drug bioavailability. For over 20 years, the potential benefit of nanotechnology is appreciated by most of the researchers and it is providing vast improvements in drug delivery and drug targeting. New advancements in the drug delivery strategies are minimizing the unwanted toxicities and improving the efficacy of the treatments.

Pulmonary delivery of drug has become an attractive target and of tremendous scientific and biomedical interest in the health care research area as the lung is capable of absorbing pharmaceuticals either for local deposition or for systemic delivery. The respiratory epithelial cells have a prominent role in the regulation of airway tone and the production of airway lining fluid. In this respect, growing attention has been given to the potential of a pulmonary route as a non-invasive administration for systemic and local delivery of therapeutic agents, because the high permeability and large absorptive surface area of lungs, (approximately 70-140 m2 in adult humans having extremely thin absorptive mucosal membrane) and good blood supply.

Advantages:

1. Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug.

2. Onset of action is very quick with pulmonary drug delivery.

3. Degradation of drug by liver is avoided in pulmonary drug delivery.

4. The ability to nebulize viscous drug formulations for pulmonary delivery, thereby overcoming drug solubility issues with the ability to use lipid, water or lipid/water emulsions as drug carriers.

5. Increased drug delivery efficacy due to size-stable aerosol droplets with reduced hygroscopic growth and evaporative shrinkage.

6. Liposomal drug formulations remain stable, when nebulized.

7. Ability to nebulizer protein-containing solutions.

8. Inhaled drug delivery puts drug where it is needed.

Limitations:

1. The oropharyngeal settlement may give local adverse effects.

2. Patients may have trouble using the delivery devices correctly.

3. Various aspects affect the reproducibility of drug delivery to the lungs, including physiological (respiratory scheme) and pharmaceutical (tool, formulation) variables. For the systemic delivery of drugs with a small therapeutic index, such deviations may be undesirable.

4. Drug absorption may be limited due to the barrier action of the mucus and the drug–mucus interactions.

5. Mucociliary clearance diminishes the retention time of drugs within the lungs that may affect the pharmacological efficacy of the slowly absorbed drugs.

6. The lungs are not an easily reachable surface for drug delivery, and complex delivery devices are required for targeted drug delivery.

Mechanisms of Respiratory Deposition:

The respiratory tract deposition of inhaled aerosol particles is due to three principal mechanisms: inertia impaction, Brownian diffusion and gravitational settling. A theory is developed to predict the particle deposition and its distribution in human respiratory tract for any breathing condition.

- Once the particle enters the respiratory tract via either the nose or mouth, it may be deposited in different regions of the respiratory tract. During breathing, the airflow undergoes several direction changes in the nasal/mouth, pharynx, larynx regions, and airway bifurcations.
- Larger particles (>0.5 μm) may deposit by impaction in these regions because they could not follow the air streamline. In fact, deposition by impaction in the Oro-pharyngeal region remains a major portion of the emitted dose for pMDI and DPI devices.
- In the small airways and alveolar region, deposition by sedimentation is the major deposition mechanism of inhaled particles.
- Small particles (0.2μm) may be deposited by diffusion in all regions of the respiratory tract. Diffusion deposition is important for nano-particles<100nm.
- Interception deposition is important for elongated particles such as fibrous aerosols when the long particle dimension is comparable with the pulmonary airway dimension.

Formulation of Inhalers:

1. **Dry power inhalers:**
   The dry-powder-inhalers are designed to deliver drug/excipients powder to the lungs. Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus. The dry powder platform comprises devices that generate an aerosol directly from 1 to 5 μm size drug powder, or mixtures with excipients. Excipients used in DPI are used as carrier for Active Pharmaceutical Ingredient (API). Most commonly used carrier is Lactose Monohydrate.

Formulation of DPI mainly includes following three steps:

a. API Production

The important requirement of API in case of DPI is particle size. Particle size of drug should be less than 5 µm. It should be in the range of 2-5 µm. There is various sort of mills used for size reduction of drugs but few of them are appropriate for DPI to reduce the size in the range of 2-5 µm such as fluid-energy mills, such as the jet mill; high-peripheral-speed mills, such as the pin-mill; and the ball mill.

b. Formulation of API with or without carriers. The part of carrier in DPI is enhancing the flow property of powder and also aerosol performance of the cohesive drugs and fine lactose. After drug and carrier (s) have separately been brought to their desired forms, they are combined in the blending process.

c. Integration of the formulation into device

After the formulation has been blended, it is filled into capsules, multi-dose blisters, or reservoirs for use with the inhaler device. The filling process is automated and depends on the nature of the metering system.

The primary inhaler parts are same for all type of devices on the market and many in development. Dry Powder Inhaler device consists of; powder formulation, dose measuring system, powder de-agglomeration principle and mouthpiece.

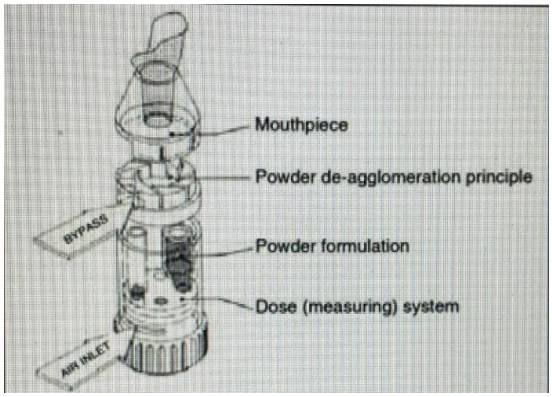


Fig:3 Inhaler device

Currently there are two types:

- Unit dose devices: In a single-unit dose device, the drug is formulated as a micronized drug powder and carrier system and supplied in individual gelatine capsules, which are then embedded into the device for a single dose.
- Multi dose Devices: The multi-unit dose device utilizes factory metered and sealed doses packaged in a way that the device can hold multiple doses without having to reload. Commonly, the packaging comprises of replaceable disks or cartridges, or strips of foil polymer blister packaging that may or may not be reloadable.

2. Formulation of Pressurized Metered Dose Inhalers:

A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases. The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD.

- Pressurized metered aerosols may be formulated as either solutions or suspensions of drug in the liquefied propellant. MDIs can be formulated with the drug completely dissolved in the formulation, rendering a solution formulation, or with the drug practically insoluble in the formulation, rendering a suspension formulation. Compared with suspension formulations, solution MDIs offer the benefits of homogenous formulation (i.e., patients do not need to shake the vial immediately prior to use and there is no concern related to sampling homogeneity), a finer residual aerosol.
- When formulating solution MDIs, the total amount of fine particle drug delivered cannot simply be increased by increasing the drug concentration in a formulation. Many drugs are not readily soluble in HFA propellants, which frequently limits the amount of drug that can be dosed using MDIs. Previously, surfactants or complexation aids were used in MDIs to increase drug solubility in CFC systems. However, many of the conventional excipients used in CFC formulations and approved for human use, are insoluble in HFA system.
- The method for preparing drug particles for MDI formulations needs to be selected based on the chemical stability of the drug. Proteins, for instance, require additional care when micronizing, due to being heat-labile and need to preserve any three-dimensional conformation. Frequently, spray-drying with another agent (i.e., sodium carboxymethylcellulose, polyvinyl alcohol, and/or polyvinylpyrrolidone (PVP)) is utilized for protein drugs due to the need to preserve the three-dimensional conformation and biological activity of the protein.
- The basic requirements for formulation of MDIs are containers, propellants, and metering valve.

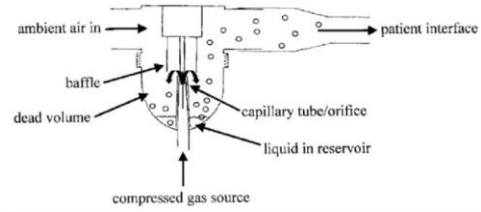
3. Nebulizers:

A device converts liquids into aerosols that can be inhaled into the lower respiratory tract. Nebulizers are used in aerosol drug delivery produce a poly-disperse aerosol where the drug delivered in the particles size range 1–5 µm in diameter. Most Nebulizers use compressed air for atomization, but some use ultrasonic energy. Nebulizers are generally used for the treatment of cystic fibrosis, asthma, COPD and other respiratory diseases or

disorders. There are following three main types of nebulizers commercially available.

• **Jet Nebulizer:**

This uses compressed gas to make an aerosol (tiny particles of medication in the air). Jet nebulizers are applicable for acute and domiciliary treatment of various respiratory diseases, paediatric and adult medical practices. These types of nebulizers required 2-10 L\min withdraw medication a capillary tube from the reservoir of the nebulizer. It may cause generate a wider range of particles which blasted into one or more baffles (to convert larger particles to smaller particles) out of suspension and return them to nebulizer.



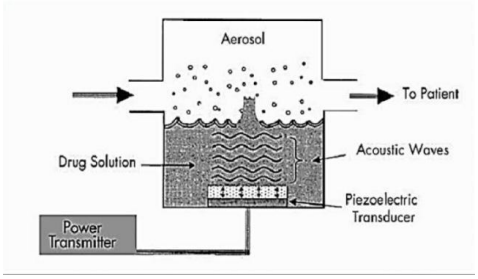


Fig:4(a) Jet nebulizer
Fig4(b) ultrasonic nebulizer

• **Ultrasonic Nebulizer:**

nebulizer. Ultrasonic nebulizers incorporate a piezoelectric crystal vibrating at high frequencies (1-3 MHz) This makes an aerosol through high-frequency vibrations. The particles are larger than with a jet to produce an aerosol. Ultrasonic nebulizers work on the principle that converts electrical energy to high frequency vibrations using a transducer. This nebulizer generates vibrations, which are transferred to solution surface that would create waves, and those waves produce aerosol; we can say that these types of nebulizers are large volume nebulizers to deliver hypertonic saline for sputum inductions.

• **Mesh Nebulizer**:

Mesh nebulizers contain apertures or aperture plate; when we applied force, it will generate aerosol. They force liquid medications through multiple apertures in a mesh or aperture plate to generate aerosol. Comparisons of mesh and ultrasonic nebulizers demonstrated similar drug delivery in simulated ventilator-dependent patients. Mesh nebulizers are more efficient than jet nebulizers and can provide higher drug doses to patients. The efficiency of mesh nebulizers is affected by various factors like size of the pore, aerosol chamber, and reservoir.

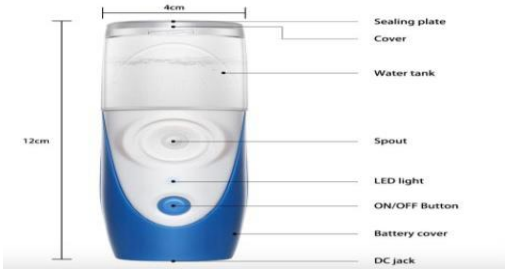


Fig:5 Mesh nebulizer

Formulating Nebulizer Fluids:

Nebulizer fluids are formulated in water, occasionally with the addition of co-solvents such as Ethanol or propylene glycol and with the addition of surfactants for suspension formulations. Because hypo-osmotic and hyper-osmotic solutions may cause bronchoconstriction, as may high hydrogen ion concentrations, iso-osmotic solutions of PH greater than 5 are usually employed. Stabilizers such as antioxidants and preservatives may also be included, although these may also cause bronchospasm and for this reason sulphites in particular are generally avoided as antioxidant in such formulations.

Whilst most nebulizer formulations are solutions, suspensions of micronized drug are also available for delivery from nebulizers. In general, suspensions are poorly delivered from ultrasonic nebulizers, whereas with jet nebulizer the efficiency of drug delivery increases as the size of suspended drug is decreased, with little or no release of particles when they exceed the droplet size of the nebulizer aerosol.

APPLICATIONS:

1. Delivery of non-peptide pharmaceuticals:

Low molecular weight (below 1000 daltons) small non-peptide lipophilic drugs are well absorbed through the nasal mucosa even though absence of permeation en-hancer. Nasal membrane containing epithelium is highly vascularized and it contains large surface area it is readily accessible for drug absorption because presence of nasal turbinates. Drugs with extensive pre-systemic metabolism, such as progesterone, estradiol, propranolol, nitroglycerin, sodium chromoglyate can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of approximately 100% (Ramaprasad YV et al., 1996; Hus-sain AA et al., 1980). These drugs can reach widespread circulation within few minutes after dosing, as the

venous blood passes from the nose directly into the systemic circulation. In fact, many drugs that are administered intranasally are often absorbed faster and more efficiently than hose from oral administration translating into a quick uptake Some of non-peptide drugs being studied for nasal delivery and have shown good bioavailability by this route includes:

1) Adrenal corticosteroids

2) Sex hormonses: 17B-estradiol, progesterone, norethinarone, and testosterone.

3) Vitamins: vitamin B

4) Cardiovascular drugs: hydralazine, Angiotensin Il antagonist, nitroglycerine, isosobide dinitrate, propanolol, and colifilium tosylate.

5) Autonomic nervous system:

a. Sympathomimetics: Ephedrine, epinephrine, phenylephrine,

Xylometazoline, dopamine and dobutamine.

b.Parasympathomimetics: nicotine, methacholine

c.Parasympatholytics: scopolamine, atropine, walogium "rostagianoins

6) Central nervous systems stimulants: cocaine, lidocaine

7) Narcotics and antagonists: bupemorphine, naloxone Histamine and antihistamines: disodium cromoglycate, meclizine Antimigrane drugs: dierogotamine, ergotamine, Tanacie

8) Phenicillin, cephalosporins, gentamycin

9) Antivirals: Phenyl-p-guanidine benzoate, enviroxime

10) Inorganic compounds: Inorganis salts, colloidal gold, colloidal carbon, colloidal silver.

2. Delivery of peptide-based pharmaceuticals:

Peptides & proteins have a generally low oral bioavailability because of their physico-chemical instability and susceptibility to hepato-gastrointestinal first-pass elimination. examples are insulin, calcitonin, pituitary hormones etc (O'Hagan DT et al., 1990). These peptides and proteins are hydrophilic polar molecules of relatively high molecular weight, are poorly absorbed across biological membranes with bioavailability's because of their physico-chemical instability and susceptibility to hepato-gastrointestinal first-pass elimination.

examples are insulin, calcitonin, pituitary hormones etc (O'Hagan DT et al., 1990). These peptides and proteins are hydrophilic polar molecules of relatively high molecular weight, are poorly absorbed across biological membranes with bioavailabilities obtained in the region of 1-2% concentrations when administered as simple solutions. To overcome this problem mainly we are using the absorption enhancers like sufactants, glycosides, cyclodextrin and glycols to increase the bioavailability. Nasal route is proving to be the best route for such biotechnological products.

3. Delivery of Drugs to Brain through Nasal Cavity:

This delivery system is beneficial in conditions like Par-kinson's disease, Alzheimer's disease or pain because it requires rapid and/or specific targeting of drugs to the brain. The development of nasal delivery system to brain will increase the fraction of drug that reach the

CNS after nasal delivery. The olfactory region located at the upper remote parts of the nasal passages offers the potential for certain compounds to circumvent the blood-brain barrier and enter into the brain. The recent studies express neurotrophic factors such as NGF, IGF

1, FGF and ADNF have been intranasally delivered to the CNS shows good results to increase the bioavailability of drug in the brain. Studies in humans, with proteins such as AVP, CCK analog, MSH/ACTH and insulin have revealed that they are delivered directly to the ordin trom the nasal cavity.

4. Delivery of Vaccines through Nasal Route:

Mucosal sites gives first line of defense against the microorganisms entered into the body, nasal mucosa act by filtering the pathogens from the inspired air by compaction and mucociliary clearance. Nose with nose associated lymphoid tissue (NALT) acts as an efreave ste or immune sustem. lis caleo waldevers Ring in human beings and nasal secretions mainly contains immunoglobulins (IgA, IgG, IgM, IgE), protective proteins such as complement as well as neutrophil sane monoc tes nine mucosa vesteck et ol.1997; Kuper CF et al., 1992; Durrani Z et al 1998). Main reasons for exploiting the nasal route for vaccine delivery are

1) the nasal mucosa is the first site of contacts with inhaled pathogens,

2) The nasal passages are rich in lymphoid tissue,

3) Creation of both mucosal and systemic immune responses,

4) Low cost, patient friendly, non-injectable, safe. Nasal delivery of vaccines has been reported to not only produce systemic immune response, but also local immune response in the nasal lining, providing addi-tional barrier of protection (Mestecky Jet al., 1997). Delivering the vaccine to the nasal cavity itself stimulates the production of local secretory IgA antibodies as well as IgG, providing an additional first line of defense, which helps to eliminate the pathogen before it becomes established (Durrani Z et al 1998). Recently, for the diseases like anthrax and influenza are treated by using the nasal vaccines prepared by using the recombinant Bacillus anthracis protective antigen (rPA) and chitosan respectively (Read RC et al.2005; Soane RJ et al., 2001). The common diseases like measles, pertussis, meningitis, and influenza causing pathogens are mainly enter into the body through the nasal mucosal surfaces and hence good candidates for nasal vaccines

5. Delivery of diagnostic drugs:

Nasal drug delivery system also play very important role in the delivery of diagnostic agents for the diagnosis of various diseases and disorders in the body. Because the intranasal route better for systemic release of medicament into blood circulation, so can get quick results with less toxicity. Phenolsulfonphthalein is a diagnostic agent used to the diagnose the kidney function of the patients. Pancreatic disorders of the diabetic patients were diagnosed by using the 'Secretin'. And the secretory function of gastric acid was determined by Pentagastrin, diagnostic agent.

Future scope:

The intranasal route is an accessible alternative route for drug administration. This route provides future potential for several drugs through the development of safe and efficacious formulations for simple, painless and longterm therapy. Despites the various challenges faced by pulmonary drug delivery system, several peptide and protein drugs are currently investigated for potential systemic absorption through pulmonary system, which includes insulin, calcitonin, luteinizing-hormone-releasing hormone (LHRH) analogs, granulocyte colony-stimulating factor (rhG-CSF), and human somatotropin (hGH).

Despite considerable clinical experience with aerosolized macromolecules, there have been no serious safety issues to date, nor have there been significant problems with throat irritation or cough. Much has been investigated and far more are to be investigated for the recent advancement of nasal drug delivery system.

CONCLUSION:

Nasal drug delivery system is a promising alternative route of administration for the several systemically acting drugs with poor bioavailability and it has advantages in terms of improved patient acceptability and compliance compared to parenteral administration of drugs.

REFERENCES:

1. A J. Hickev. Pharmaceutical Inhalation Aerosol Technology, 2nd edition, Marcel Dekker, NY, 2004 Alagusundaram M., Deepthi N., Ramkanth S., Angala-parameswari S., Mohamed Saleem T.S., Gnanapra-kash K.. Thiruvengadarajan V. S, Madhusudhana Chetty C, Dry Powder Inhalers - An Overview,Int. J. Res. Pharm. Sci. 2010, 1;1: 34-42
2. Armengot,M., Basterra, Macro,.Rev. Larngol.Octol. Rhinol. 1990, 111,219-226 Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drug Discov Today 2002; 7,18, 967-975.
3. Aulton M.E. " Pharmaceutics - The science of dosage form design" Churchill Livingston., 494, 2002 Aurora J. Development of Nasal Delivery Systems: A Review.Drug Deliv Technol 2002; 2,7, 1-8.
4. Buri P. Hydrogels destines a la muqueuse nasale. Controle physiologique, Pharm. Acta Helv. 1966,41, 88-101.
5. Chien Y.W., Su K.S.E., Chang S.F., Nasal Systemic Drug Delivery, Ch. 1, Marcel-Dekker, New York, 1-77, 1989
6. Chien YW, Chang SF. Intranasal drug delivery for systemic medications. Crit Rev Ther Drug Carr- Syst 1487401-194.
7. Edman P, Bjork E, Ryden L. Microspheres as a nasal delivery system for peptidedrugs j controlled release, 1992;21:165-72
8. Finlay, Warren Hither mechanics of inhaled pharmaceutical aerosols: an introduction. Boston: Academic Press. ISBN 0-12-256971-7,2001.
9. Franz, M.R., Oth, M.P., U.S patent, 5232704, 1993. Gikuriro S, Bechgaard E. Intranasal administration of insulin to humans. Diabetes kes Clin Prad 1991;12:71-84.
10. Hardy J.C., Lee S.W., Wilson C.G., Intranasal drug delivery by spray and drops, J. Pharm. Pharmacol. 1985, 37, 294-297.
11. Harris A.S., Nilsson I.M, Wagner Z.G, Alkner U., Intranase aommstaton o peotdes, rasa ceooston. biological response and absorption of desmopressin, J. Pharm. Sci. 1986,75, 1085-1088.
12. Hirai, S., Yoshiki, T., Mima, H., Effect of surfactants on nasal absorption of insulin in rats, Int. J. Pharm., 1981,9, 165-171.
13. Hofstee BH. Specificity of esterase. Il.Behavior of pancreatic esterase I and Il toward a

homologous series of N-fatty acid esters. J Biol Chem 1952; 199:365-71
14. Hughes B.L., Allen D.L., Dorato M.A., Wolff R.K., Effect of devices on nasal deposition and mucociliary clearance in rhesus monkeys, Aerosol Sci. Technol. 1993,18, 241-249.
15. Hussain A, Hamadi S, Kagoshima M, Iseki K, Dittert L. Does increasing the lipophilicity of peptides enhance their nasal absorption. J Pharm Sci 1991; 80: 1180-1181.
16. Hussain A.A., Hirai S., Bawarshi R., Nasal absorption of natural contraceptive steroids in rats-progesterone absorption, of insulin in rats, Int. J. Pharm., 1981,9, 165-171.
17. Hofstee BH. Specificity of esterase. Il.Behavior of pancreatic esterase I and Il toward a homologous series of N-fatty acid esters. J Biol Chem 1952; 199:365-71
18. Hughes B.L., Allen D.L., Dorato M.A., Wolff R.K., Effect of devices on nasal deposition and mucociliary clearance in rhesus monkeys, Aerosol Sci. Technol. 1993,18, 241-249.
19. Hussain A, Hamadi S, Kagoshima M, Iseki K, Dittert L. Does increasing the lipophilicity of peptides enhance their nasal absorption. J Pharm Sci 1991; 80: 1180-1181.
20. Hussain A.A., Hirai S., Bawarshi R., Nasal absorption of natural contraceptive steroids in rats-progesterone absorption,
russanza.rosen.alas. resthad.batennorsuk Jone M. Nasal absorption of propranolol in humans. J Pharm Sci 1980; 69:1240-1243.
21. Hussain MA, Koval CA, Shenvi AB, Aungst BJ, Recovery of rat nasal mucosa from the effects of aminopepti-dase inhibitors. J Pharm Sci 1990;79:398-400
22. Illum L. In: Mathiowitz E, Chickering DE, Lehr CM Ed, Bioadhe- sive formulations for nasal peptide deli-very: Fundamentals, Novel Approaches and Devel-opment. Marcel Dekker. New York; 507-539,1999.
23. Illum L., Drug delivery systems for nasal application, S.T.P. Pharma 1987, 3, 594-598.
24. Illum L., Jorgensen H., Bisgaard H., Krogsgaard O., Ross-ing N., Bioadhesive microspheres as a potential nasal drug delivery system, Int. J. Pharm.,1987,39, 189-199.
25. Inagaki M, Sakakura Y, Itoh H, Ukai K, Miyoshi Y. Ma-cromolecu- lar permeability of the tight junction of human nasal mucosa. Rhinology 1985; 23: 213-221.
26. Inagaki M, Sakakura Y, Itoh H, Ukai K, Miyoshi Y. Ma-cromolecu- lar permeability of the tight junction of human nasal mucosa. Rhinology 1985; 23: 213-221.
27. Jorissen,M., AND Bessems, A., Eur.Arch.Otorhinolar ngol, 1995.252,451-454.
28. Junginger HE. Mucoadhesive hydrogels. Pharmazeu-tische Industrie 1956; 53: 1056-1065.
29. Kadam, S.S., Mahadik, K.R., Pawar, A.P., Paradkar, A.R., Transnasal delivery of peptides - a review, The East.Pharm. July 1993. 47 - 49
30. Kaliner M., Marom Z., Patow C., Shelhamer J, Human respiratory mucus, J. Allergy Clin. Immunol. 1984,73, 318 - 323.
31. Kisan R. Jadhav,Manoj N. Gambhire, Ishaque M. Shaikh, Vilarsrao J. Kadam and Sambjahi S. Pisal, Nasal Drug Delivery System-Factors Aftecting and Applications, Current Drug Therapy, 2007, 2, 27-38
32. M.Alagusundara et al. | Int. J. Res. Pharm. Sci. Vol-1, Issue-4, 454-465, 2010 Kuper CF, Koornstra PJ, Hameleers DM, et al. The role of naso- pharyngeal lymphoid tissue. Immunol Today 1992; 13: 219-224.
33. Lee V.H.L., Enzymatic barriers to peptide and protein absorption, CRC Crit. Rev. Ther. Drug Carrier Syst. Knoch, M. & Finlay, W. H. "Nebulizer Technologies", Chapter 71 in Modified-Release Drug Delivery Technology, ed. Rathbone/Hadgraft/Roberts, Marcel Dekker, pp. 849-856, 2002
34. Mahalaxmi rathananand, D. S. Kumar, A. Shirwaikar, Ravi kumar, D. Sampath kumar, Preparation of Mu-coadhesive Microspheres for Nasal Delivery by Spray Drying, Indian Journal of Pharmaceutical Sciences, 2007,652.
35.Martin E, Nicolaas GM, Schipper J, Coos V,Frans WH. Nasal mucociliary clearance as a factor in nasal drug delivery. Adv Drug Del Rev 1997;29:13-38
36. McMartin C, Hutchinson LE, Hyde R, Peters GE. Analysis of structural requirements for the absorption of drugs and macromole- cules from the nasal cavity. J Pharm Sci 1907; 76: 935-540.
37.Mestecky J, Moldoveanu Z, Michalek SM, et al. Current options for vaccine delivery systems by mucosal routes. I Control Release 1997; 48: 243-257.
38. Michael I. Ugwoke, Remigius U. Agu, Norbert Verbeke, Renaat Kinget, Nasal mucoadhesive drug delivery:Background, applications, trends and future perspec-tives, Advanced Drug Delivery Reviews, 2005, 57, 1640-1665
39. Morimoto K, Miyazaki M, Kakemi M. Effects of proteo-lytic en- zyme inhibition on nasal absorption of salmon calcitonin in rats. Int J Pharm 1995; 133: 1-8.
40. Mygind N., Vesterhauge S., Aerosol distribution in the nose, Rhinology 1978,16, 79-88. Newhouse M.T., Advantages of pressured canister metered dose inhalers, J. Aerosol Med. 1991,4, 139-150.

41. O'Hagan DT, Illum L. Absorption of peptides and proteins from the respiratory tract and the potential for development of locally administered vaccine. Crit Rev Ther Drug Carrier Syst 1990; 7(1): 35-97.
42. Ohwaki K, Ando H, Watanabe S, Miyake Y, Effects of dose, p" and osmolarity on nasal absorption of secretin in rats, J Pharm Sci 1985;74:550-2
43. Mygind N., Vesterhauge S., Aerosol distribution in the nose, Rhinology, 1978; 16: 79-88.
44. Hughes B.L., Allen D.L., Dorato M.A., Wolff R.K., Effect of devices on nasal deposition and mucociliary clearance in rhesus monkeys, Aerosol Sci. Technol, 1993; 18: 241-249.
45. Alagusundaram M., Deepthi N., Ramkanth S., Angala-parameswari S., Mohamed Saleem T.S., Gnanapra-kash K.. Thiruvengadarajan V. S, Madhusudhana Chetty C, Dry Powder Inhalers - An Overview Int. J. Res. Pharm. Sci, 2010; 1(1): 34-42.
46. Finlay, Warren H.The mechanics of inhaled pharmaceutical aerosols: an introduction. Boston: Academic Press, 2001; ISBN 0-12-256971-7.
48. Newhouse M.T., Advantages of pressured canister me-tered dose inhalers, J. Aerosol Med, 1991; 4: 139-150.
49. Coro DC, Liu JC, Chien YW. Characterization of the barrier properties of mucosal membranes. J Pharm Sci, 1990; 79: 202-206.
50. Bawarshi RN, Hussain A, Crooks PA. Nasal absorption of 17a- ethinyloestradiol in the rat. J Pharm Pharmacol, 1989; 41: 214-215.
51. Lee V.H.L., Enzymatic barriers to peptide and protein absorption, CRC Crit. Rev. Ther. Drug Carrier Syst, 1988; 5: 69-97.
52. Inagaki M, Sakakura Y, Itoh H, Ukai K, Miyoshi Y. Ma-cromolecu- lar permeability of the tight junction of human nasal mucosa. Rhinology, 1985; 23: 213-221.
53. Franz, M.R., Oth, M.P., U.S patent, 1993; 5232704.
54. Jorissen, M., AND Bessems, A., Eur. Arch. Otorhinolar ngol, 1995; 252: 451-454.
55. Arora P, Sharma S, Garg S. Permeability issues in nasal drug deliv- ery. Drug Discov Today, 2002; 7(18): 967-975.
56. Satish BB, adhikrao VY, Amelia MA, Rajkumar M, Bio availability of intranasal drug delivery system, Asian I of Pharmaceutics, 2008; 201-15.
57. Ohwaki K, Ando H, Watanabe S, Miyake Y, Effects of dose, pH and osmolarity on nasal absorption of se-cretin in rats, J Pharm Sci, 1985; 74: 550-2.
58. Gizurarson S, Bechgaard E. Intranasal administration of insulin to humans. Diabetes Res Clin Prac, 1991; 12: 71-84.