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NASO PULMONARY DRUG DELIVERY SYSTEM -A NOVEL APPROACH

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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.

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

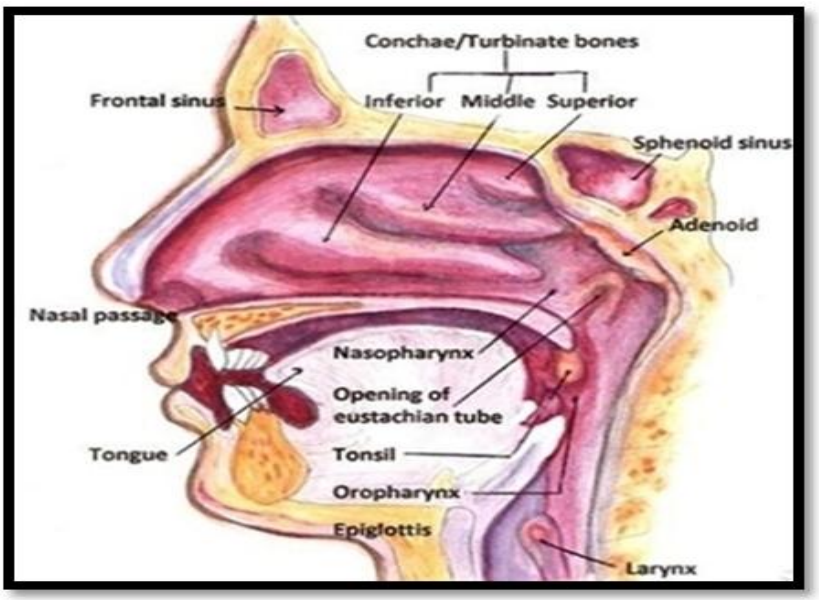
INTRODUCTION

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

Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. Undoubtedly, the intranasal administration of medicines for the

symptomatic relief and prevention or treatment of topical nasal conditions has been widely used for a long period of time.[1,2] Nasal administration is a route of administration in which drugs are insufflated through the nose .It can be a form of either topical administration or systemic administration, as the drugs thus locally delivered can go on to have either pirely local or systemic effects. In general, among the primary targets for intranasal administration are pharmacologically active compounds with poor stability in gastrointestinal fluids, poor intestinal absorption and/or extensive hepatic first-pass elimination, such as peptides, proteins and polar drugs. The nasal delivery seems to be a favourable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the bio phase of central nervous system (CNS)-active compounds. It has also been considered to the administration of vaccines. Pulmonary drug delivery is the inhalation of drug formulation through mouth and the further deposition of inhaled pharmacological agents in lower airways. Pulmonary delivered drugs are rapidly absorbed except large macromolecules drugs, which may yield low bioavailability due to enzymatic degradation and/or low mucosal permeability. Pulmonary bioavailability of drugs could be improved by including various permeation enhancers such as surfactants, fatty acids, and saccharides, chelating agents and enzyme inhibitors such as protease inhibitors. The most important issue is the protein stability in the formulation: the dry powder formulation may need buffers to maintain the pH, and surfactants such as Tween to reduce any chance of protein aggregation. The stabilizers such as sucrose are also added in the formulation to prevent denaturation during prolonged storage. The pulmonary route has gained increasing importance in the recent times due to its unique properties such as large absorptive area of up to 100m[2] extremely thin 0.1 μm absorptive mucosal membranes and good blood supply. The respiratory tract is one of the oldest routes used for the administration of drugs. Over the past decades inhalation therapy as established itself as a valuable tool in the local therapy of pulmonary diseases such as asthma or COPD (Chronic Obstructive Pulmonary Disease).[3,4]

Anatomy and Physiology of nose and pulmonary system



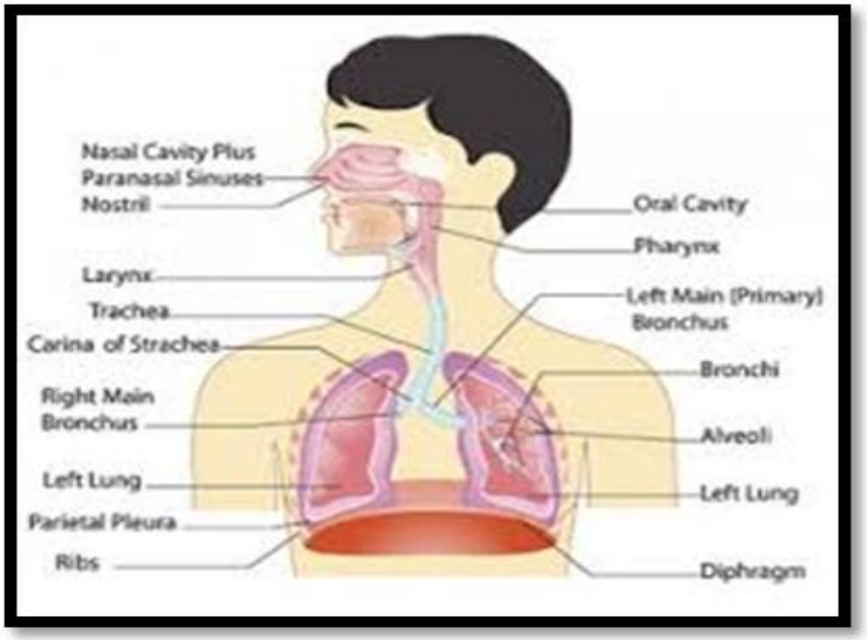
The nasal cavity consists three main regions

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. Mucussecretion is
- composed of 95%-water,2%-mucin,1%-salts,1%-of other proteins
- Such as albumin, lysozyme and lactoferrinand 1%-lipids.



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.

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

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.

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.

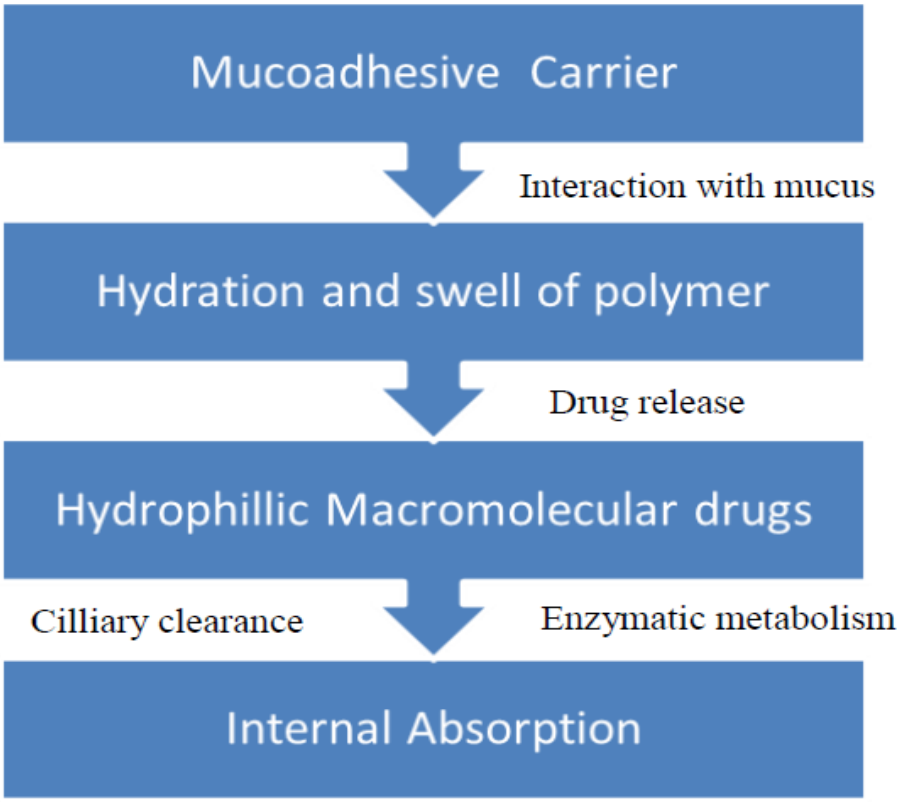
Pulmonary epithelium:- The lung contains more than 40 different cell types, of which more than six line the airways. The diversity of pulmonary epithelia can be illustrated by examining its structure at three principal levels.

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.[5]

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.[6,7,8]

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.[9-14]

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.[9,10,13,15]

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.[9,13,15,16,17]

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.[9,13,15,18,19,20]

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.[21]

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.[22]

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.[23,24]

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 de-pendent 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.[25]

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 deaggregation 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.[26]

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.[27,28]

12. Presurised 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.[24,29]

Factors influencing nasal drug absorption

- Several factors have an effect on the general bioavailability of medication that square measure administered through the nasal route. The factors may be touching to the physiochemical properties of the medication, the anatomical and physiological properties of the cavum and therefore the sort and characteristics of chosen nasal medication delivery system. These factors play key role for many of the medication so as to achieve therapeutically effective blood levels once nasal administration. The factors influencing nasal drug absorption square measure represented as follows.

1. Physiochemical properties of drug.

¬ Molecular size.

¬ Lipophilic-hydrophilic balance.

¬ Enzymatic degradation in cavum.

2. Nasal result

¬ Membrane porosity.

¬ Environmental pH

¬ Mucociliary clearance

¬ Cold, rhinitis.

3. Delivery result

¬ Formulation (Concentration, pH, osmolality) Delivery effects

¬ Drugs distribution and deposition.

¬ Viscosity

1) Physiochemical properties of drug

Molecular size

The molecular size of the drug influence absorption of the drug through the nasal route. The oleophilic medication have direct relationship between the MW associated drug permeation whereas water- soluble compounds depict an inverse relationship. The speed of permeation is high-ly sensitive to molecular size for compounds with MW ≥ three hundred Daltons.[30]

Lipophilic-hydrophilic balance

The deliquescent and oleophilic nature of the drug additionally affects the method of absorption. By increasing lipophilicity, the permeation of the compound usually in-creases through nasal mucous membrane. though the nasal mu-cosa was found to possess some deliquescent character, it seems that these mucosae are primarily oleophilic in nature and also the lipid domain plays a very important role within the barrier operate of those membranes. Oleophilic medication like Narcan, buprenorphine, androgen and 17a-ethinyl- estrogen are nearly utterly absorbed once administered intranasal route.[31]

Enzymatic degradation in cavum

In case of peptides and proteins are having low bio-availability across the cavum, thus these medication might have chance to bear catalyst degradation of the drug molecule within the lumen of the cavum or throughout passage through the animal tissue barrier. These each sites are having exo-peptidases and endopeptidases, exo-peptidases are mono-amino peptidases and di-amino peptidases. These are having capability to cleave peptides at their N and C termini and endopeptidases like aminoalkanoic acid and aminoalkanoic acid, which may attack internal amide bonds.[32]

2) Nasal effect factors

Membrane permeability

Nasal membrane porousness is that the most significant issue, that have an effect on the absorption of the drug through the nasal route. The water soluble medication and particularly massive mass medication like peptides and proteins area unit having the low membrane porousness. That the compounds like peptides and proteins area unit main-ly absorbed through the endocytotic transport method in low amounts. Soluble high mass medication cross the nasal membrane principally by passive diffusion through the liquid pores (i.e. tight junctions).[33]

Environmental pH

Hydrogen ion concentration

The environmental hydrogen ion concentration plays a crucial role within the potency of nasal drug absorption. little soluble compounds like carboxylic acid, 2-hydroxybenzoic acid, and organic compound acid show that their nasal absorption in rat occurred to the best extent at those hydrogen ion concentration values wherever these compounds area unit within the unionized kind. However, at hydrogen ion concentration values wherever these compounds area unit partly ionized, substantial absorption was found. This implies that the unionized oleophilic kind crosses the nasal animal tissue barrier via transcellular route, whereas the additional oleophilic ionized kind passes through the liquid paracellular route.[34]

Mucociliary clearance

Mucociliary clearance may be a one among the functions of the higher tract is to forestall baneful sub-stances (allergens, bacteria, viruses, toxins etc.) from reaching the lungs. Once such materials adhere to, or dissolve in, the secretion lining of the cavum, they're transported towards the cavity for ultimate discharge into the epithelial duct. Clearance of this secretion and therefore the adsorbed/dissolved substances into the bum is named the MCC. This clearance mechanism influence the absorption method thanks to the dissolved medicine within the cavum square measure discharge by the each the secretion and therefore the cilia, that is that the motor of the MCC and therefore the secretion transport rate is half dozen mm/min. it's of utmost importance that the MCC isn't impaired so as to forestall lower tract infections.[35]

Cold, rhinitis Rhinitis may be a most often associated common malady, it influence the bioavailability of the drug. It’s chiefly classified into coryza and customary, the symptoms square measure hyper secretion, skin sensation and physiological reaction chiefly caused by the viruses, microorganism or irritants. coryza is that the allergic airway malady, that affects 100 percent of population. It’s caused by chronic or acute inflammation of the mucosa of the nose. These conditions have an effect on the absorption of drug through the secretion membrane due the inflammation.

3) Delivery effect factors

Factors that have an effect on the delivery of drug across nasal membrane like surfactants, dose pH, osmolarity, viscosity, particle size and nasal clearance, drug structure will be wont to advantage to boost absorption.

Formulation (Concentration, pH, Osmolarity)

The pH of the formulation and nasal surface, will have an effect on a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation ought to be adjusted to four.5–6.5 as a result of muramidase is found in nasal secretions that is answerable for destroying sure microorganism at acidic pH. Below basic conditions, muramidase is inactivated and therefore the tissue is liable to microorganism infection. In addition to avoiding irritation, it ends up in getting efficient drug permeation and prevents the expansion of bacteria.[36]

Concentration gradient plays important role within the absorption / permeation method of drug through the nasal membrane thanks to nasal tissue layer injury. Examples for this are nasal absorption of L-Tyrosine was shown to extend with drug concentration in nasal introduction experiments. Another is absorption of hydroxy acid was found to say no with concentration. This decline is probably going thanks to nasal tissue layer injury by the permanent.[37]

The osmolarity of the indefinite quantity type affects the nasal absorption of the drug; it absolutely was studied within the rats by victimization model drug. The binary compound concentration of the formulation affects the nasal absorption. The maximum absorption was achieved by zero.462 M binary compound concentration; the upper concentration not solely causes augmented bioavailability however conjointly ends up in the toxicity to the nasal epithelial tissue.[38]

Drugs distribution and deposition

The drug distribution within the cavity is one among the important factors, which affect the efficiency of nasal absorption. The mode of drug administration could effect the distribution of drug in cavity, which successively will determine the absorption efficiency of a drug. The absorption and bioavailability of the nasal dosage forms mainly depends on the location of disposition. The anterior portion of the nose provides a protracted nasal residential time for disposition of formulation, it enhances the absorption of the drug. And the posterior chamber of cavity will use for the deposition of dosage form; it's eliminated by the mucociliary clearance process and hence shows low bioavailability. The site of disposition and distribution of the dosage forms are mainly depends on delivery device, mode of administration, physicochemical properties of drug molecule.[39]

Viscosity

A higher viscosity of the formulation increases contact time between the drug and therefore the nasal mucosa thereby increasing the time for permeation. At an equivalent time, highly viscous formulations interfere with the traditional functions like ciliary beating or mucociliary clearance and thus alter the permeability of medicine.

Advantages and disadvantages of naso-pulmonary drug delivery system

Advantages

1. Drug degradation that's observed within the alimentary canal is absent.
2. Hepatic first pass metabolism is avoided.
3. Rapid drug absorption and quick onset of action are often achieved.
4. The bioavailability of larger drug molecules are often improved by means of absorption enhancer or other approach.
5. The nasal bioavailability for smaller drug molecules is sweet .
6. Drugs that are orally not absorbed are often delivered to the circulation by nasal drug delivery.
7. Studies thus far administered 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 future therapy, in comparison 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 could also be particularly fitted to this route of deli-very.

Disadvantages

1. There's a risk of native facet effects and irreversible injury of the cilia of nasal mucous membrane, each from substances and from constituents accessorial to the indefinite quantity type.
2. Sure surfactants used as chemical attention could disrupt and even dissolve membrane in high concentration.
3. There might be a mechanical loss of the indefinite quantity type into the opposite components of the tract like lungs due to the improper technique of administration.
4. The length of activity is usually transient because of the rapid removal of drug from the lungs or because of drug metabolism. Necessitates frequent dosing.

5. Pathologic conditions like cold or allergies could alter considerably the nasal bioavailabilty.
6. The microscopic anatomy toxicity of absorption enhancers utilized in nasal drug delivery system isn't nevertheless clearly established.
7. Comparatively inconvenient to patients in comparison to oral delivery systems since there's an opening of nasal irritation.
8. Bodily cavity provides smaller absorption area in comparison to bum.

Recent formulations of pulmonary drug delivery[40,41]

- Insulin by aerosol
- Nicotine aerosol for Smoking cessation
- Alpha 1 Antitrypsin
- Aerosols for Angina
- Gene therapy via aerosol
- In cancer chromatography
- Pentamicine aerosol
- Gentamycin aerosol
- Ribavirin aerosol
- Pulmonary delivery of lower molecular weight heparin
- Controlled delivery of drugs to lungs
- Pulmonary delivery of drugs for bone disorders

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 long term 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

Considering the wide unfold interest in nasal drug delivery and also the potential advantages of intranasal administration, it's expected that novel nasal merchandise can still reach the market. They'll embrace not solely medicine for acute and long run diseases, however conjointly novel nasal vaccines with higher native or general protection against infections. Within the treatment of preventative metabolism diseases, respiratory organ delivery will minimize general facet effects, offer fast response and minimize the desired dose since the drug is delivered on to the conducting zone of the lungs. Within the treatment of preventative metabolism diseases, respiratory organ delivery will minimize general facet effects, offer fast response and minimize the desired dose since the drug is delivered on to the conducting zone of the lungs.

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