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IFTM University, Moradabad, Uttar Pradesh

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INTRA NASAL DRUG DELIVERY SYSTEM

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CONTENT

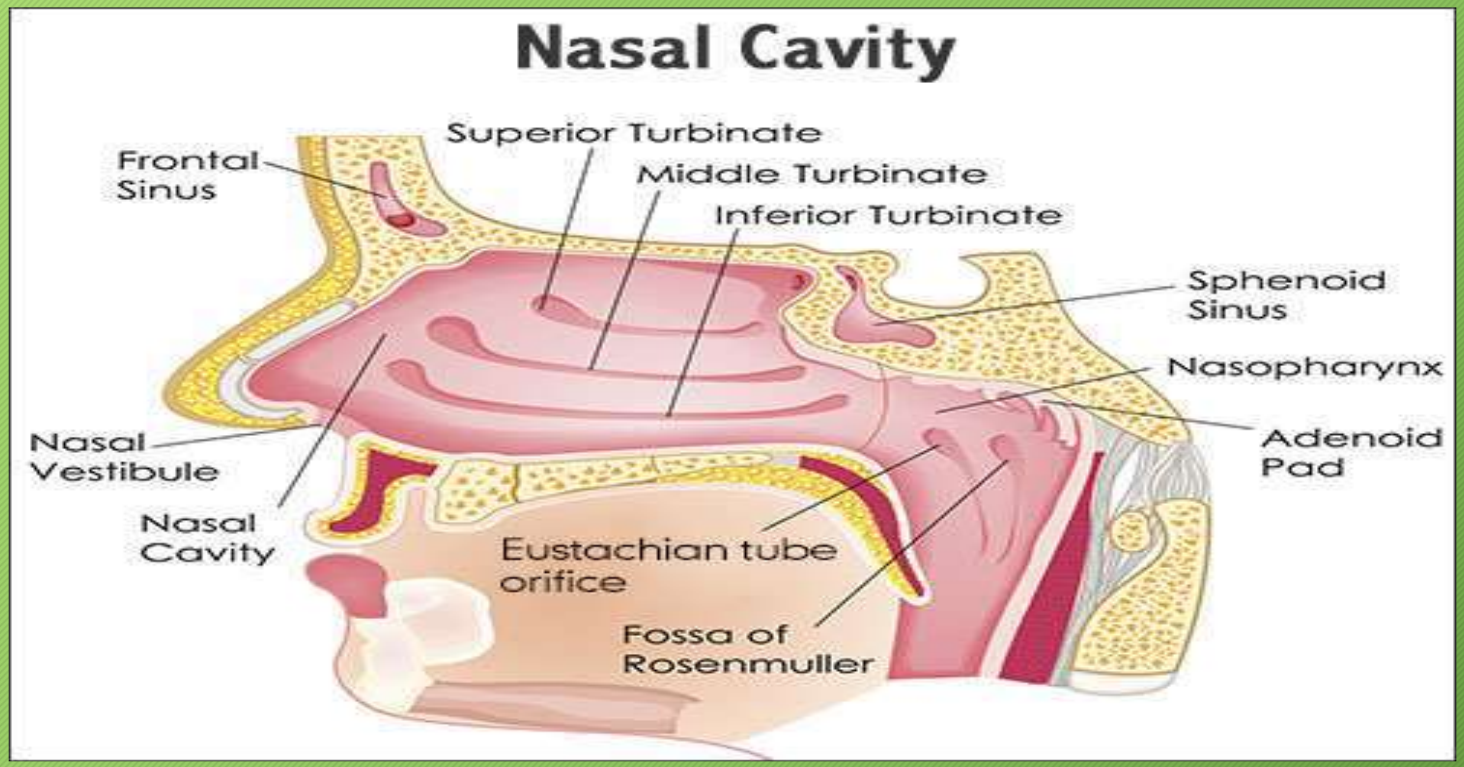
INTRODUCTION:

Nasal drug delivery is receiving much attention from the pharmaceutical industry.

About 2% of the overall drug delivery is administered via the nasal route.

Topical decongestants or anti-inflammatory drugs used to treat a rhinitis or allergy related indications are well-known drug products.

The nasal route is an attractive alternative to invasive administrations, and provides a direct access to the systemic circulation.



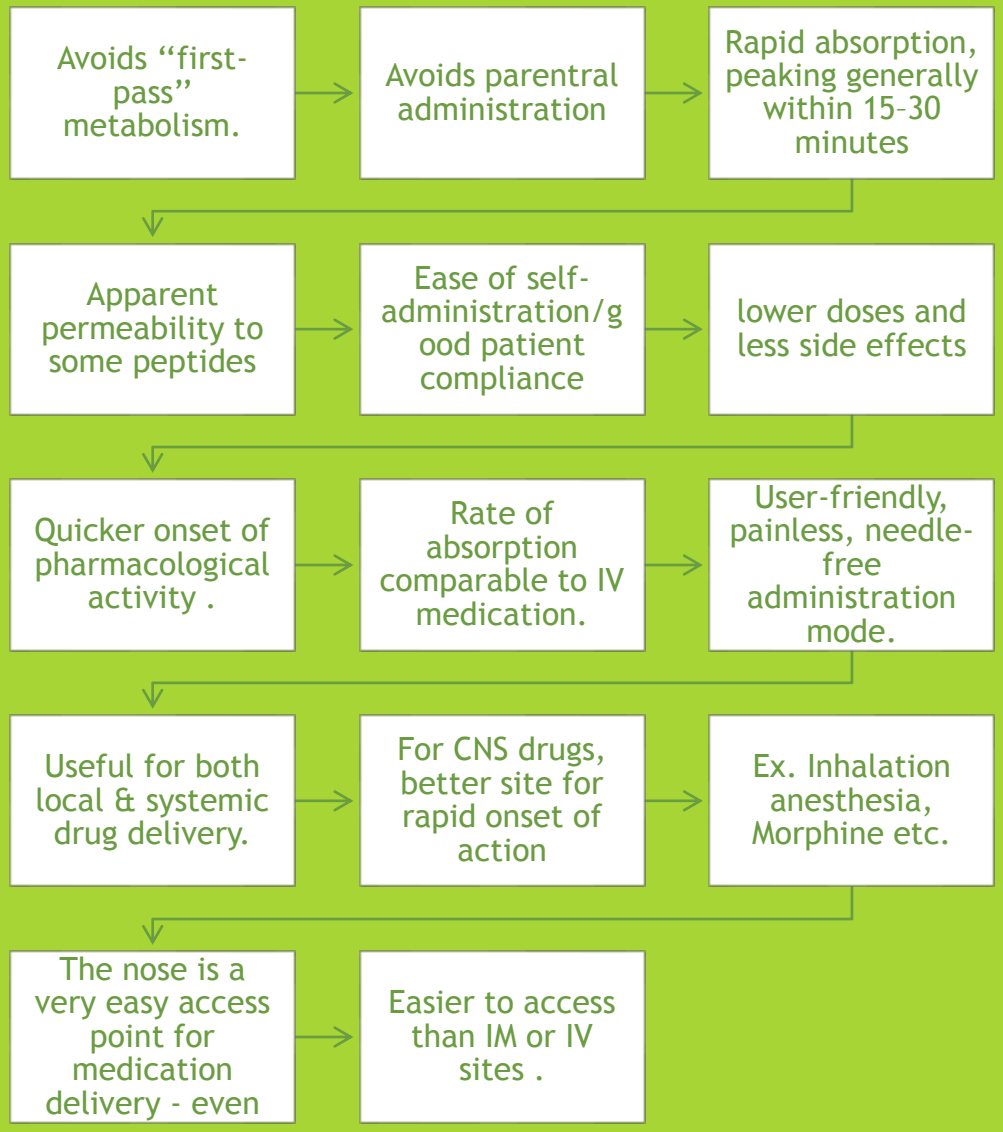
ANATOMY AND PHYSIOLOGY OF NOSE

- The nasal cavity is run from the nasal vestibule to the nasopharynx which has depth of approximately 12-14cm.
- The nasal vestibule, the respiratory region and the olfactory region are the three main regions of the nasal cavity.
- The submucosal zone of the nasal mucosa directly connects to the systemic circulation, thus avoids first pass metabolism.
- The lateral walls of the nasal cavity includes a folded structure which enlarges the surface area in the nose to about 150cm2 .
- This folded structure includes three turbinates: the superior, the median and the inferior.
- These turbinates increases the area of absorption.
- Nasal cavity is about 60mm in length.
- The nasal cavity is covered with a mucous membrane which can be divided into nonolfactory and olfactory epithelium areas. The nonolfactory area includes the nasal vestibule and respiratory region.

- Nasal blood flow external & internal carotid arteries.
- Nasal secretions (1500-2000ml/day):- Goblet cell, nasal glands, lacrimal glands
- Composition:- 95% water, 1-2% salt, 2-3% mucin. In trace amount Na, K, Ca, Albumin also present.
- Nasal enzymes:- Monooxygenase, lactate dehydrogenase, oxidoreductase, phosphates , hydrolases, esterases, etc.
- Nasal pH:- 5.5-6.5(adults)

  5.0-6.7(infants & child)

MERITS


Avoids "first-pass" metabolism.
Avoids parentral administration
Rapid absorption, peaking generally within 15-30 minutes
Apparent permeability to some peptides
Ease of self-administration/good patient compliance
lower doses and less side effects
Quicker onset of pharmacological activity .
Rate of absorption comparable to IV medication.
User-friendly, painless, needle-free administration mode.
Useful for both local & systemic drug delivery.
For CNS drugs, better site for rapid onset of action
Ex. Inhalation anesthesia, Morphine etc.
The nose is a very easy access point for medication delivery - even
Easier to access than IM or IV sites .

DEMERITS

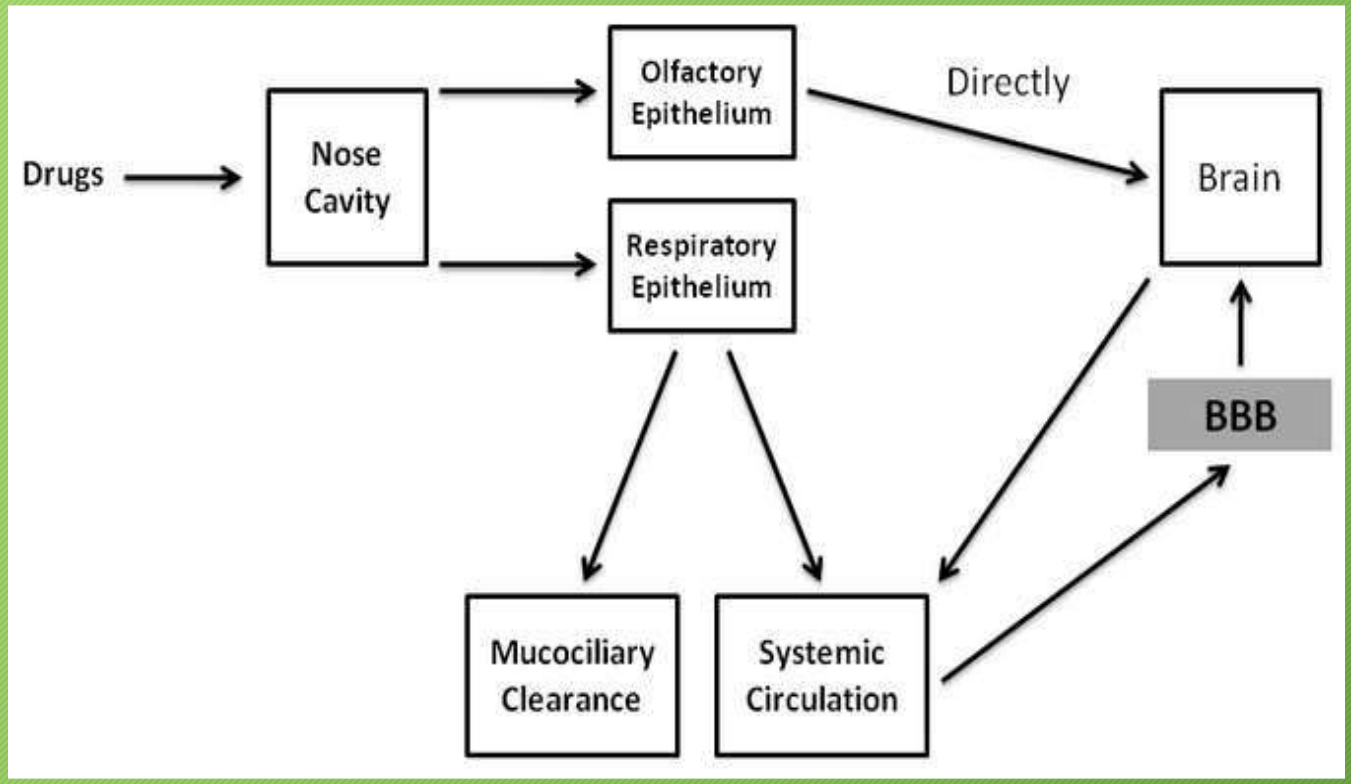
- Environmental conditions, infection, and inter-subject variability can lead to inconsistent absorption.
- Short time span is available for absorption due to rapid clearance.
- Local metabolism in the nose and instability of compound (especially for peptide drugs) occur.
- Once administered, removal of the therapeutic agent from the site of absorption is difficult.
- The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
- Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
- Nasal cavity provides smaller absorption surface area when compared to GIT.
- 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.
- Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
- 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.

MECHANISM OF ABSORPTION

- Majority of Drugs are absorbed by passive diffusion.
- Some may be by active transport, such as amino acids.
- Literature shows that upto 1000dalton drug get easily absorbed without help of penetration enhancers.
- Two mechanisms are found:

Transcellular process:
Transport of lipophillic drugs through cell membrane by active transport or transport through opening of tight junction.
Example: Levodopa,Carbidopa

Paracellular process:
It involves aqueous route of transport. It is slow and passive. Water soluble drugs which have molecular weight greater than 1000 dalton shows poor bioavailability.
Example: Insulin,MSH,ACTH

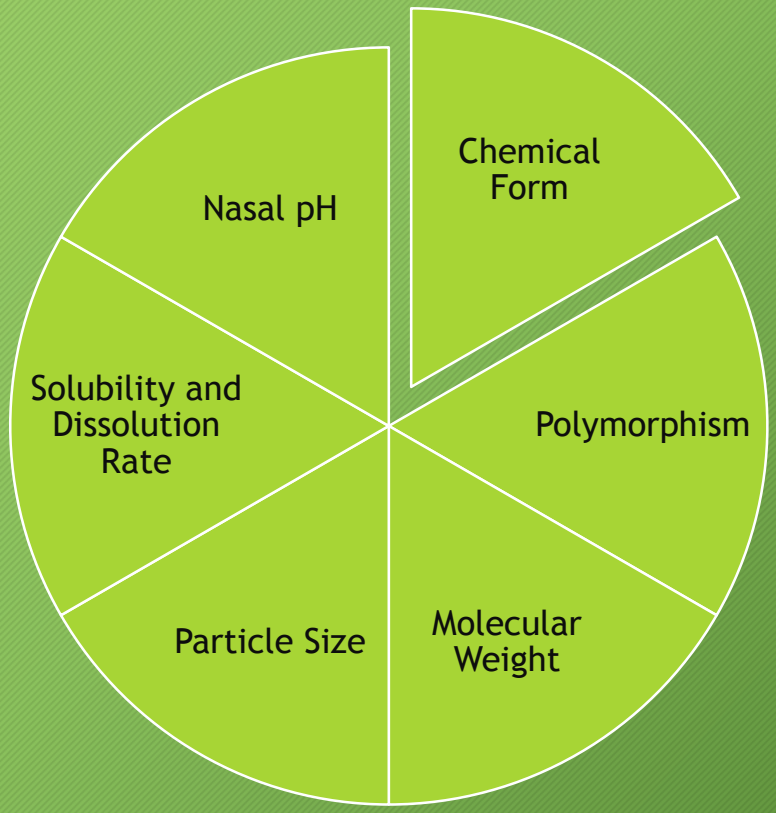


PATHWAY OF ABSORPTION

BARRIERS TO NASAL ABSORPTION

Low Bioavailability	Low Membrane Transport	Enzymatic Degradation
It is due to Low membrane permeability (limiting factor for high mol.weight polar drugs like protein and peptides)	Rapid clearance of administered formulation due to MCC. Ex: Liquid and powder formulation shows rapid clearance	Degradation of protein and peptides by Exopeptidase and Endopeptidase

FACTORS AFFECTING DRUG ABSORPTION

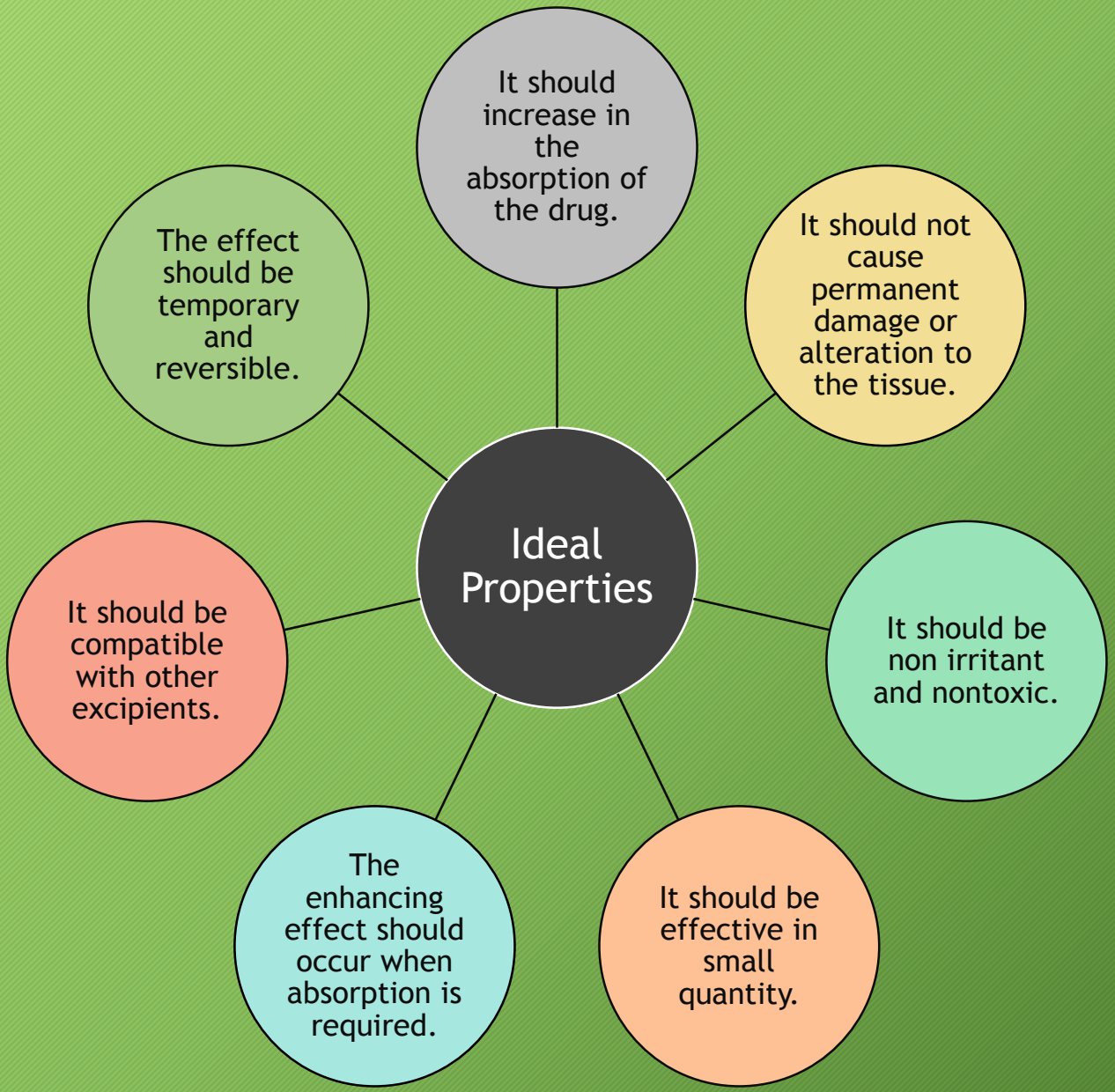


Strategies To Improve Nasal Absorption

1. Nasal Enzymes Inhibitors
2. Formulation Design
3. Modifying drug structure
4. Prodrug approach
5. Particulate drug delivery
6. Absorption Enhancers

Mechanism of Penetration Enhancers:

1. Inhibit enzymatic activity
2. Reduce mucus viscosity
3. Reduce MCC
4. Open tight junctions
5. Solubilize the drug


Ideal Properties
It should increase in the absorption of the drug.
The effect should be temporary and reversible.
It should not cause permanent damage or alteration to the tissue.
It should be compatible with other excipients.
It should be non irritant and nontoxic.
The enhancing effect should occur when absorption is required.
It should be effective in small quantity.

Classification of Penetration Enhancers

Type	Examples
Surfactants	Sodium dodecyl sulphate, Polyoxyethylene-9-lauryl ether, Saponin
Complexing and chelating agents	EDTA, Salicylates
Cyclodextrins and derivatives	α-, ß-, γ-cyclodextrin, DMß-cyclodextrin, HPß-cyclodextrin
Bile salts	Sodium taurocholate Sodium glycocholate Sodium deoxycholat Fusidic acid derivatives
Fatty acid salts	Oleic acid, Caprylate (C8), Caprate (C10), Laurate (C12)
Dry microspheres	Degradable starch microsphere Dextran microsphere

FORMULATION CONSIDERATION

- pH of the formulation
  - It is important as..
    - To avoid irritation of nasal mucosa.
    - To allow drug to be available in unionised form for absorption.
    - To prevent growth of the bacteria in nasal passage.
    - To sustain normal physiological ciliary moments.
- Humectants
  - To prevent dehydration adequate intranasal moisture is required and therefore humectants are added.
  - Prevent nasal irritation.
  - The commonly used humectants are

    Glycerin, Sorbitol, Mannitol

- Osmotic Agent
  - The osmolarity of the dosage form affect the nasal absorption of the drug.
  - The higher concentration of drug not only causes increased bioavailability but also leads to the toxicity to the nasal epithelium.
  - The commonly used osmotic agents are-
    Sodium Chloride, Sodium Sulfite, Sodium Acid Phosphate

- Solubilizers
  - Aqueous solubility of drug is always a limitation for nasal drug delivery of dosage form.
  - Commonly used solubilizers are glycols, surfactants, etc.

- Gelling/Viscosifying Agents/Gel Forming Carrier
  - Increasing solution viscosity may provide means of prolonging the therapeutic effect of nasal preparations.
  - Highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drug.
  - Commonly used gelling agents are…
    Carbopol, Cellulose agents, Starch, Dextran, Chitosan, etc.

- ABSORPTION ENHANCERS
  - Unlike the most small drug molecules, some drugs and peptides do no cross the nasal membrane efficiently.
  - The nasal mucosa is almost impermeable to molecular size greater than 1000 Dalton.
  - The low nasal membrane permeability is due to Molecular Size, Lack Of Lipophilicity & Enzymatic Degradation.
- ANTIOXIDANT
  - Usually antioxidants do not affect drug absorption or cause nasal irritation.
  - Chemical / Physical interaction of antioxidant with drug and excipients should be considered during formulation development
  - Commonly used antioxidants are Sodium Metabisulfite, Sodium Bisulfite, Butylated Hydroxytoluene.
- PRESERVATIVE
  - Commonly Used Preservatives are Parabens, Benzolkonium Chloride, Phenyl Ethyl Alcohol, Benzoyl alcohol.

DELIVERY SYSTEM

- Liquid drop
- Liquid spray/nebulizers
- Aerosol
- Suspension spray/nebulizers
- Gel
- Sustained release

APPLICATION OF NASAL DRUG DELIVERY SYSTEMS

1. Delivery of non-peptide pharmaceuticals
   Eg. Progesterone, estradiol, propranolol, nitroglycerin, sodium chromoglyate, etc.

2. Delivery of peptide-based pharmaceuticals
   Eg. Insulin, Calcitonin, Pituitary hormones etc.

3. Delivery of Diagnostic Drugs
   - Phenolsulfonphthaline-For diagnosis of kidney functions
   - Secretin-For diagnosis of pancreatic disorders
   - Pentagastrin-For diagnosis of secretory functions of gastric acid.
   - Cerulin-For diagnosis of Gallbladder function
   - Vital dyes-Trypan blue and Evans blue (it can not enter in cranium because they can not pass through sheath)

4. Delivery of drugs to Brain:
   - For Treatment of Parkinson'sdisease,Alzheimer disease.
   - For Delivery of MSH,ACTH,Insulin to brain

5. Delivery of Vaccines :
   - Nasal mucosa is the first site of contacts with inhaled pathogens
   - Nasal passages are rich in lymphoid tissue
   - Creation of both mucosal and systemic immune responses
   - Non injectable

Examples:

Nasal Vaccines are Prepared for Measels, pertussis, meningitis and Influenza virus because these pathogens enter into the body through nasal mucosa.

- Nasal delivery of vaccines produces both local and systemic immune response.

CONCLUSION

Nasal route is attractive for the delivery of the many drugs and vaccines.

Studies are going on improving the efficiency of the nasal route.

Outcome of these studies is that we can utilise it for treatment of diabetes, osteoporosis, infertility.

Nasal drug delivery offers such benefits as Rapid onset of action with lower dose & minimal side effects

It has an advantage of site-specific delivery with improved therapeutic effects.

Allowing systemic administration without significant degradation.

Nasal drug delivery system offers flexibility for multiple formulations ranging from nasal drop to suspension spray

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