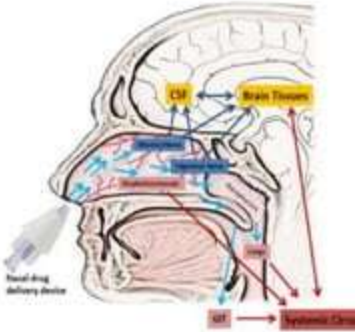
INTRANASAL DRUG DELIVERY SYSTEM



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INTRODUCTION

✓ Nasal Drug Delivery System is administration of drug through Nasal route.

✓ Nasal mucosa has been considered as a potential route of administration to achieve faster & higher level of drug absorption.

✓ Ideal & non-invasive alternative to the parenteral route for systemic drug delivery; since it offers a truly "Needleless" drug delivery.

✓ This route has been a convenient and reliable route.

✓ Several new formulations are used to deliver drugs to the brain by olfactory, neuronal, and trigeminal pathways.

ANATOMY OF NASAL CAVITY

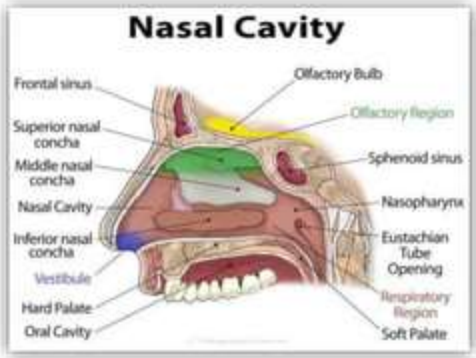
✓ It is divided into 2 halves big nasal septum.

✓ It contains 3 regions:

a) Nasal vestibule

b) Olfactory region

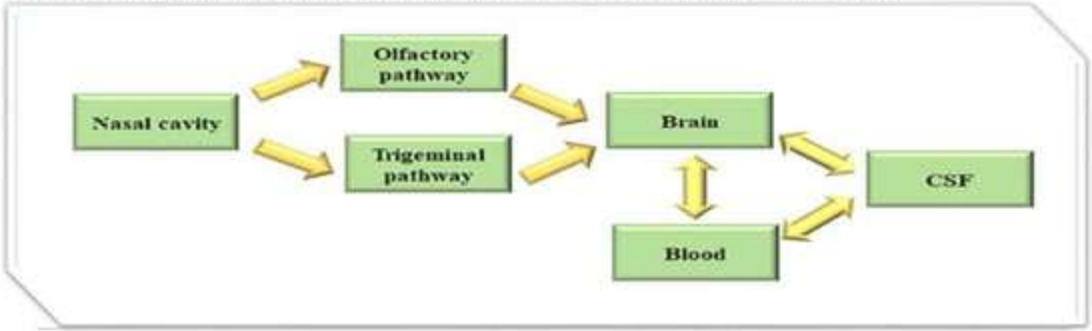
c) Respiratory region



Nasal cavity is covered with mucous membrane which contains goblet cells that secrets mucous.

NOSE BRAIN PATHWAY

The **olfactory mucosa** (smelling area in nose) is in direct contact with the brain & CSF.



✓ Medications absorbed across the olfactory mucosa directly enter the brain.

✓ This is termed as nose brain pathway which offers a rapid, direct route for drug delivery to the brain.

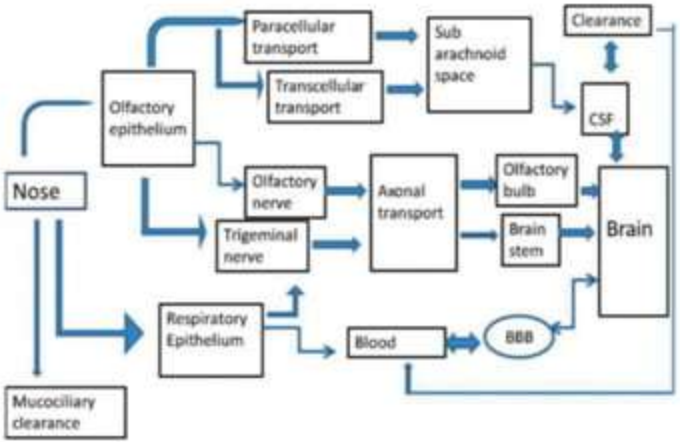


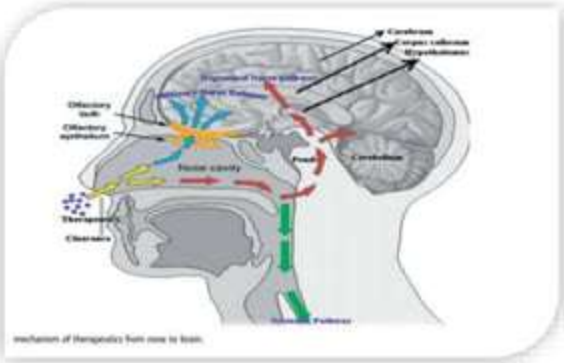
Figure 1. Overview of three different pathways after nasal administration.

NOSE BRAIN PATHWAY.

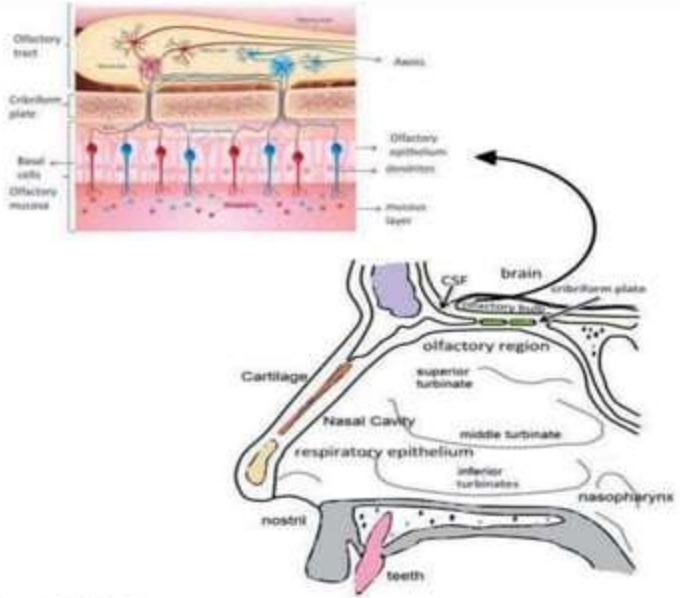
✓ Another way of drug absorption is through **Trigeminal Nerve Pathway with the help of Pons.**

✓ Besides the direct nose-to-brain pathways, there are other routes for the drugs to penetrate the brain.

✓ Such as from the **respiratory route**, drug can be transported partially to the circulation & reach the brain by the "nose-to-blood-to- brain" pathway.



mechanism of therapeutics from nose to brain.



Olfactory pathway after nasal administration.

MECHANISM OF DRUG ABSORPTION

✓ The 1st step in absorption is passage of absorbed drug through the mucus layer.

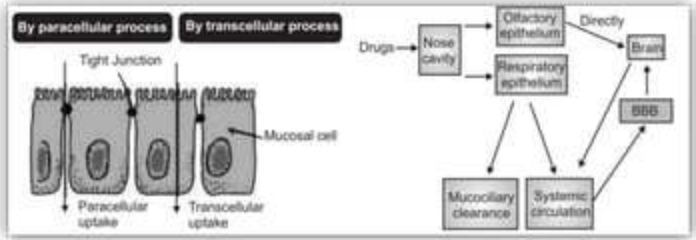
✓ 2 mechanisms have been primarily used-

1) PARACELLULAR TRANSPORT

- ❖ Aqueous Route of Transport
- ❖ Slow and Passive

2) TRANSCELLULAR TRANSPORT

- ❖ Transport through lipoidal membrane
- ❖ Active transport via carrier mediated means



Advantages of Nasal Drug Delivery System

1. Drug degradation that is observed in the gastrointestinal tract is absent.
2. Hepatic first-pass metabolism is avoided.
3. Rapid drug absorption and quick onset of action can be achieved.
4. The bioavailability of larger drug molecules can be improved using an absorption enhancer or other approach.
5. The nasal bioavailability for smaller drug molecules is good.
6. Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
7. Studies so far carried out indicate that the nasal route is an alternative to the parenteral route, especially, for protein and peptide drugs.
8. Convenient for the patients, especially for those on long-term therapy, when compared with parenteral medication.
9. Drugs possessing poor stability in G.I.T. fluids are given by nasal route.
10. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.

Disadvantages of Nasal Drug Delivery System

1. The histological toxicity of absorption enhancers used in the nasal drug delivery system is not yet clearly established.
2. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3. The nasal cavity provides a smaller absorption surface area when compared to GIT.
4. 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.
5. Certain surfactants used as chemical enhancers may disrupt and even dissolve membranes in high concentrations.
6. 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.

VARIOUS APPROACHES:

1. Prodrug Approach:

The absorption of peptides like angiotensin II, Bradykinin, Vasopressin, and Calcitonin is improved when prepared into enamine derivatives.

2. Structural Modification:

Chemical modification of Salmon Calcitonin to elcatonin (C-N bond replaces the S-S bond) showed better bioavailability.

3. Particulate drug Delivery:

1. Microspheres, Nanoparticles, and Liposomes.
2. Nasal Enzyme Inhibitors.
   - ✓ Peptides and Proteases.
   - ✓ Trippin Aprotinin, Borovaline, Amastatin, Betaststin, and Boroleucin inhibitors.

The Components of the Nasal Formulations:

- Drug component :- Turbutaline sulphate ,Budesonide, ipratropium bromide, Sod. Chromoglycate
- Viscosifying Agents – Hydroxypropyl cellulose.
- Solubilizers – Glycol, Alcohol, Cyclodextrins.
- Surfactants – SLS, Polyacrylic acid.
- Bio-adhesive Polymers – Methylcellulose, Carboxymethylcellulose.
- Preservatives – Parabens, Benzalkonium chloride.
- Antioxidants – Sodium metabisulphite.

Nasal Formulations

1. Nasal Gels: These are highly viscous, thickened solutions or suspensions. These have the following advantages:

- Reduction of post-nasal drip due to high viscosity.
- Reduction of taste impact due to reduced swallowing.
- Reduction of anterior leakage of the formulation. These are useful as there is the reduction of irritation by using emollient excipients.

2. Nasal Drops: These are simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit Human Serum albumin in the nostrils more efficiently than nasal sprays.

3. Nasal Ointments: These are translucent, homogenous, viscous, semi-solid preparations intended to be instilled in the nose. Due to their viscosity, they will not ooze out of the nose.

4. Nasal Sprays: Solution and Suspension formulations can be formulated into nasal sprays. Due to the availability of metered-dose pumps and actuators, a nasal spray can deliver an exact dose from 25-200 µm. The particle size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

5. Nasal Powder: This dosage form may be developed if solution and suspension dosage forms cannot be developed. E.g. due to lack of drug stability.

The advantages of the nasal powder dosage form are the absence of preservatives and superior stability of the formulation. However, the suitability of powder formulation is dependent on the solubility, particle size, aerodynamic properties, and nasal irritancy of the active drug and/or excipients. Local application of the drug is another advantage of this system.

6. Liposomes: Liposomal nasal solutions can be formulated as a drug alone or in combination with pharmaceutically acceptable excipients. They are administered to the respiratory tract as an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, above or in combination with an inert carrier such as; lactose, the particles of the formulation have diameters of less than 50 microns.

7. Microspheres: The main usefulness of a specialized system in designed nasal products is that it prolongs the contact with the nasal mucosa. The microspheres in their powder form swell in contact with nasal mucosa to form a gel and control the rate of clearance from the nasal cavity. Thus, increases the absorption and bioavailability by adhering to the nasal mucosa and increases the nasal residence time of the drug. The ideal microsphere particle size requirement for nasal delivery should range from 10-50 µm as smaller particles.

Nasal Gels

Nasal Drops

Nasal Sprays

Nasal Ointments

Nasal Powder

RECENT ADVANCES IN INTRANASAL DRUG DELIVERY

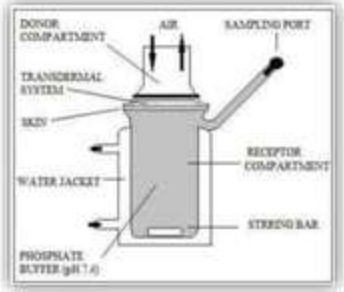
Desmopressin Insulin Nasal Spray

Antivomiting Nasal Spray

Nasal Vaccine (Covid 19)

Influenza Vaccine (Nasal use only)

IN VITRO NASAL PERMEATION STUDIES (DIFFUSION):



The nasal diffusion cell is fabricated in glass.

The lid has 3 opening, each for

1.Sampling,

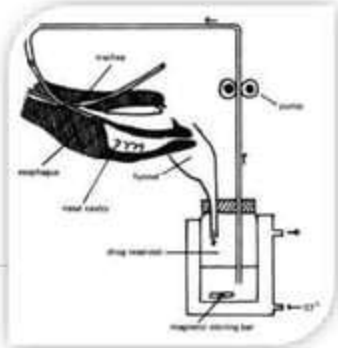
2.Thermometer, and

3.Donor tube chamber.

1. The nasal mucosa of sheep was separated & stoned in distilled water containing few drops at gentamycin injection.
2. Mucosal surface is attached to donor chamber tube.
3. The donor chamber tube is placed such a way that it just touches the diffusion medium in recipient chamber.
4. At predetermined intervals, samples (0.5 ml) from recipient chamber are with draw and transferred to amber colored ampoules.
5. The samples are estimated for drug content by suitable analytical technique.

The rat Model

1. The rat is anaesthetized.
2. An incision is made in the neck and the trachea is cannulated with a polyethylene tube.
3. Another tube is inserted through the oesophagus towards the posterior region of the nasal cavity..
4. The drug solution is delivered to the nasal cavity through the nostril or through the cannulation tubing.
5. The blood samples are collected from the femoral vein.



The Rabbit Model

1. The rabbit is anaesthetized by an intramuscular injection of a combination of ketamine and xylazine.
2. The rabbit's head is held in an upright position and the drug solution is administered by nasal spray into each nostril.
3. During the experiment the body temperature of the rabbit is maintained at 37°C with the help of a heating pad.
4. The blood samples are collected by an catheter in the marginal ear vein or artery.

Applications of Nasal Drug Delivery System

1. Delivery of non-peptide pharmaceuticals. E.g. Adrenal corticosteroids, Hormones like Progesterone, Vitamin, Cardiovascular drugs, etc.
2. Delivery of peptide-based pharmaceuticals. E.g. Insulin, Calcitonin, Pituitary hormones.
3. Delivery of diagnostic agents. E.g. Phenolsulfonphthalein is used to diagnose kidney function.
4. Delivery of vaccines through nasal route. E.g. Anthrax and Influenza are treated by using nasal vaccines.
5. Delivery of drugs to the brain through the nasal cavity. E.g. Parkinson's disease, Alzheimer's disease.

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