Nasal topical therapeutics

A reality

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By

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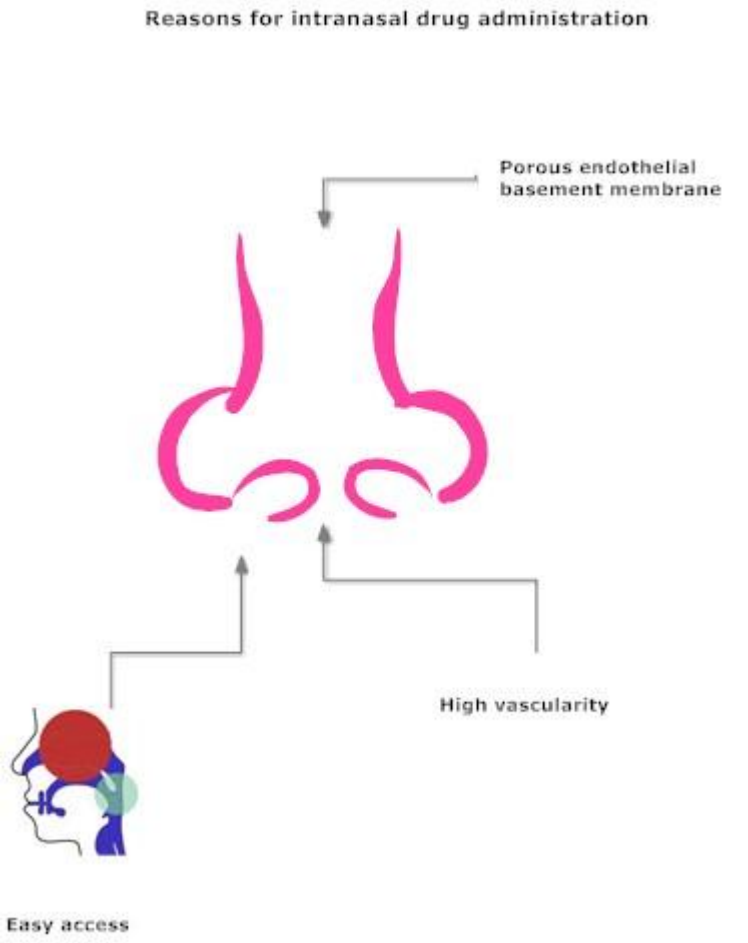
Introduction:

Intranasal drug delivery systems for the management of local and systemic ailments have caught up recently. Initially this route of drug administration was attempted for the management of allergic rhinosinusitis. Now inflammatory sinusitis is also managed by intranasally administered drugs. The reasons for interest in this route of drug administration because of its high vascularity, porous endothelial basement membrane and a high total blood flow per volume of tissue.

Since first pass metabolism is avoided in this drug delivery method the drug is metabolized slowly thus helping in reducing the dosage of the drug. This also goes a long way in reducing the potential toxicity of the administered drug even if it has a very low therapeutic index.

The complex nasal anatomy and the varying dynamics of nasal air flow make this drug delivery modality a little bit unpredictable. This is more so especially in patients with nasal cold which is associated with congestion of nasal mucosa and turbinates.



Variables that have a significant bearing on intranasal drug absorption:

1. Particle size of the drug
2. Flow volume
3. Pressure
4. Spray angle
5. Complex anatomy
6. Nasal airflow dynamics

Role of particle size of the drug:

Primary nasal drug delivery system works on the inertial impaction while the drug is deposited and secondarily gravitational sedimentation and Brownian

diffusion play their roles. Hence the particle size and its density affect the degree and site of deposition. Drug particles greater than 10 µm tends to remain inside the nasal vault while drug particles with size less than 5 µm remain aerosolised and get absorbed from the lower airway. Experiments have shown that by reducing the size of the molecule and by increasing the flow rate of the drug administered the efficacy of intranasally administered drug can be improved.

Significant amount of intranasally administered drug gets deposited in the anterior nares to be cleared during the next expiratory effort thus reducing the efficacy of the drug administered.

Physiologic obstacles that prevent optimal absorption of intranasally administered drugs:

Mucous barrier and mucociliary clearance mechanism:

The nasal cavity can be divided into:

1. Vestibule (about 0.5 – 1 cm^2) – is lined by stratified squamous epithelium. This epithelium is highly resistant to dehydration and penetration by noxious chemicals. It also is also poorly permeable to nasally administered drugs.
2. Respiratory epithelium (about 130 – 150 cm^2) – covers the maximum surface area of the nasal cavity. It is lined by pseudostratified columnar epithelium with cilia, goblet cells, basal cells and seromucinous glands. The cilia present over the columnar epithelium serves to increase the absorptive surface area more.
3. Olfactory epithelium (20 – 50 cm^2).

Following deposition into the nasal cavity the mucous blanket is the first obstacle encountered by the drug administered. This mucous blanket is roughly 5 µm thick. Each day about 1.5 – 2 litres of mucous is secreted. This mucous blanket not only increases the thickness the drug needs to penetrate to reach the blood stream, it also washes out the drug. For optimal absorption of the drug this mucosal barrier should be penetrated. Several strategies have

been developed to enable a drug to breach this mucosal barrier. These include:

1. Lipid solubility of the drug. If the drug is lipid soluble then it breaches the mucosal barrier easily.
2. Smaller molecules penetrate mucosal barrier better than larger ones.
3. Combining the active drug with a mucolytic like N – acetyl cysteine or Dornase alpha increases the chances of the drug penetrating the nasal mucosa.

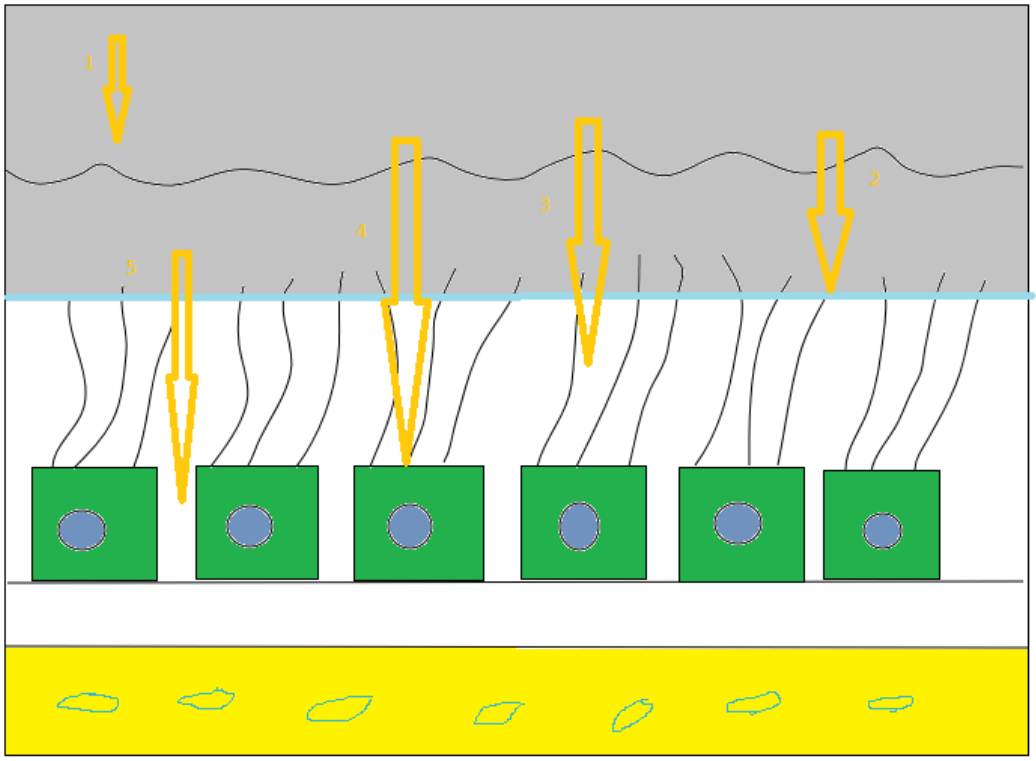


Figure showing various physiological barriers for intranasal drug absorption.

1. Deposition of the drug
2. Distribution to the mucosal surface
3. Ciliary beat clearing the drug
4. Cellular lipid bilayer (barrier to water soluble molecules)
5. Intercellular skeleton constituting the intracellular barrier

The mucous blanket which plays a vital role in drug clearance does its job virtually in 20 minutes flat. This mucous blanket can be circumvented by using bio adhesive drug carriers which would stick to this mucous barrier there by prolonging the exposure of mucosa to the drug administered.

Enzymes present in the mucous secretions:

Various degrading enzymes have been identified in the mucous blanket of nasal mucosa. These enzymes act on the drugs deposited in the nasal mucosa and degrades them by any of the following chemical reactions:

1. Hydrolysis
2. Oxidation
3. Isomerization
4. Photochemical decomposition
5. Polymerization

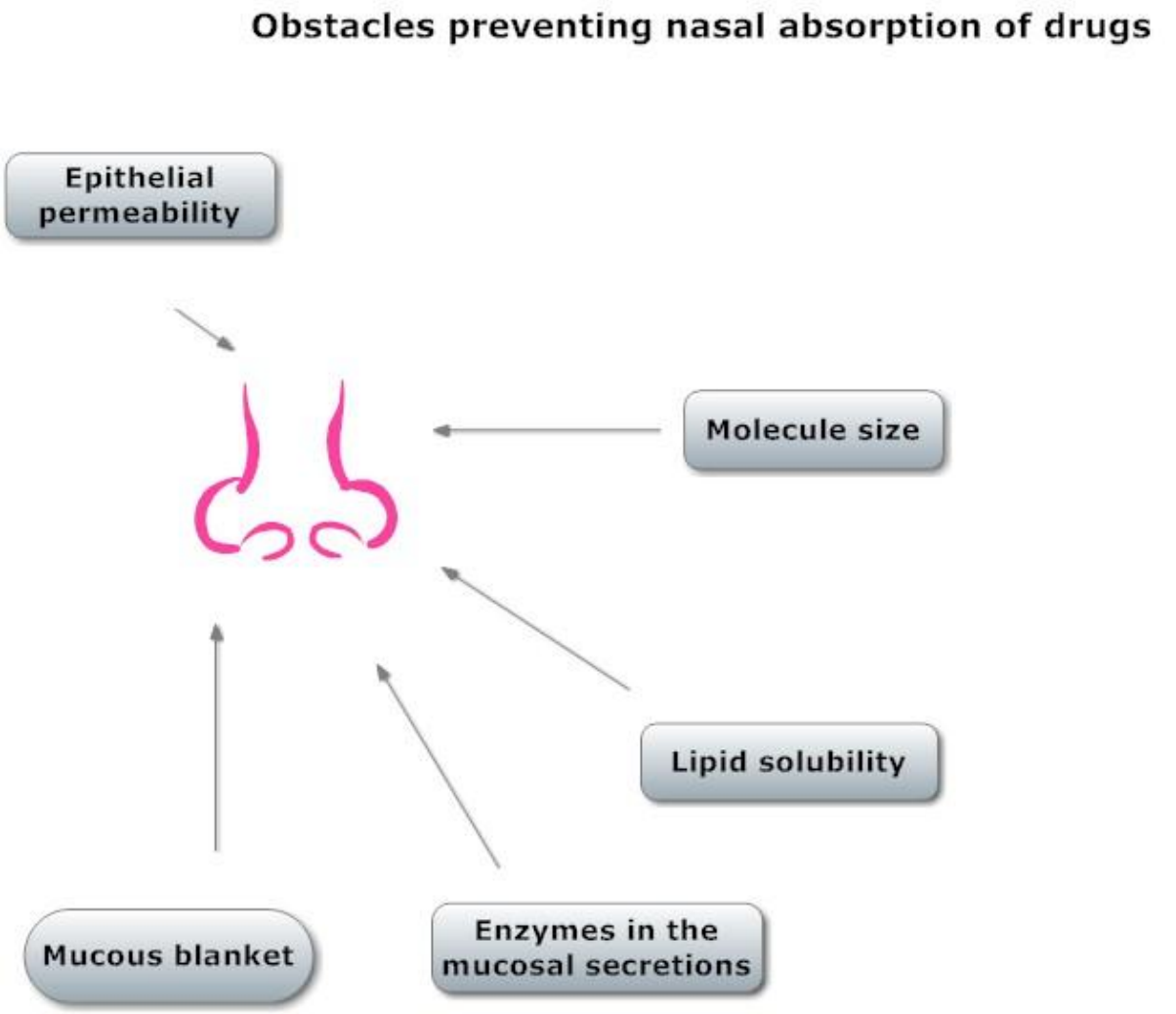
The effect of enzymes can be countered by simultaneous administration or co administration of protease inhibitors like bestatin or L-aspertase.

Epithelial permeability:

After successfully traversing the mucosal blanket, the drug must then be absorbed through the intact epithelial surface. The epithelial barrier is composed of two components i.e. cell wall and intercellular tight junctions.

Cell wall: Is composed of phospholipid bilayered wall which favours penetration by lipophilic low molecular weight molecules (less than 1000 Da). Hence if the drug is lipophilic and of low molecular weight then it will easily penetrate this barrier.

Tight junctions: Binds the cells together. These junctions are responsible for dynamic regulation of paracellular transport of substances. These junctions are composed of membrane proteins that connect directly to the actin cytoskeleton. Claudins represent a major component of tight junctions.



In order to by-pass these inherent obstacles the drug administered into the nasal cavity as prodrugs. This drug is inactive till it gets absorbed through the cell wall and gets metabolized into its active component by the enzymes present in the system i.e. either in blood or liver. Example of such prodrug is testosterone 17b-N, N-dimethylglycinate hydrochloride.

The second strategy to deliver optimal doses of drug through nasal mucous membrane is to increase the permeability of the lipid bilayered cell wall by using permeability enhancers like sodium glycocholate, sodium lauryl sulphate. Drugs combined with these permeability enhancers will easily penetrate the cell wall. These enhancers should be used with caution as they can cause irreparable damage to the cell wall if used in high concentrations. These enhancers belong to the amphipathic group of molecules which are capable of

dissolving both in water and lipid. Chemicals belonging to this group have been classified as:

1. Cationic
2. Anionic
3. Zwitterionic – possessing both anionic and cationic components

Johnson and Johnson baby shampoo can be used in 1% concentration to serve this very purpose of breaching the nasal mucosal barrier.

The third strategy to deliver optimal doses of drug through nasal mucosa is to make use of the tight junction transport system. This method focuses on enhanced drug delivery system rather than causing any changes in the cellular layers. The poor water solubility of lipophilic drugs results in suboptimal drug absorption. If the drugs are dissolved in cyclodextrins which act as aqueous vehicle for the drug then its penetration via tight junctions is improved.

Development of mucoadhesive drug eluting polymers:

In order to overcome the challenges confronting nasal route of drug administration a new frontier in drug dispersion has been thrown up. It is known as biocompatible drug eluting polymer. These polymers can be theoretically loaded with the pharmaceutical agent and implanted in any location. The active agent will be released into the circulation periodically from these polymers which adhere to the nasal mucosa. One such polymer is the Chitosan. The advantages of this polymer are multifold:

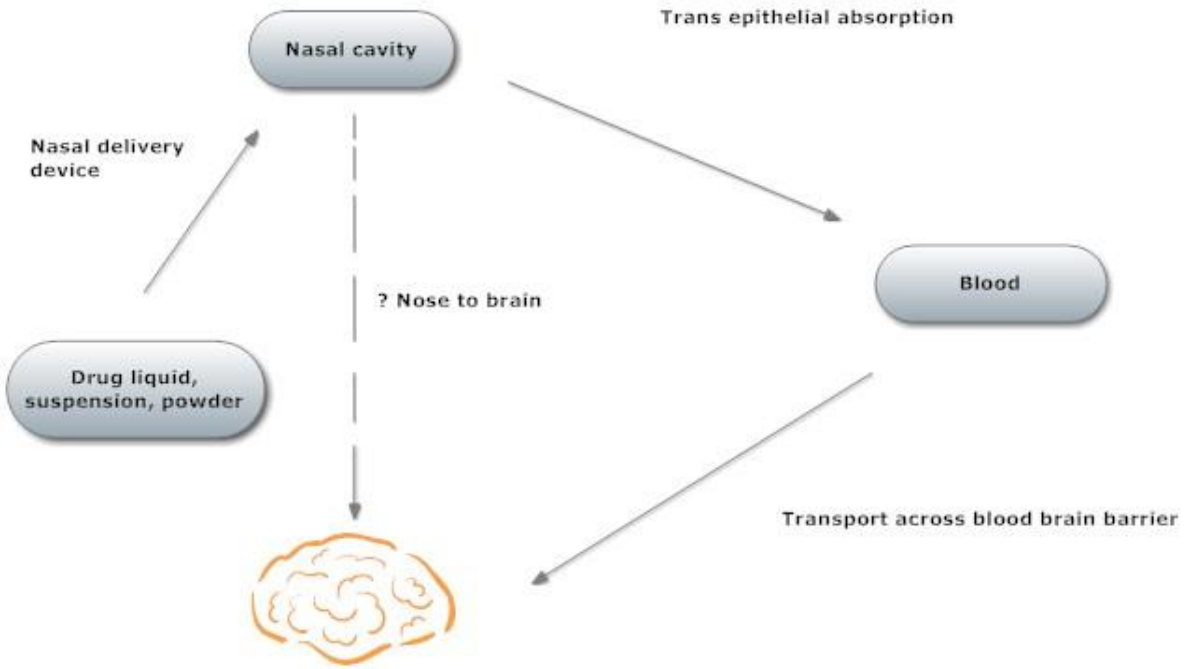
1. It has excellent mucoadherent property
2. It is a hemostatic agent
3. It has antimicrobial properties
4. It is a viable tool in transferring adequate quantities of steroids into the nasal mucosa

Nano particulate drug carriers:

This is an alternative approach to enhance the drug delivery into the nasal cavity. This method involves complexing pharmacologically active agents to particulate carriers capable of selectively binding to cell surface proteins or mucous blanket. These carriers can be manufactured in sizes as small as 200 Nano meters. This small size allows the drug to readily diffuse into the cell of nasal mucosa. These nano particles enter the nasal mucosal cell by an active process known as endocytosis.

Advantages of nasal drug delivery system include:

1. Large mucosal surface area making efficient drug absorption possible
2. Porous endothelium facilitates better drug absorption
3. High total blood flow enabling efficient transportation of the absorbed drug
4. Decreased enzymatic degradation
5. Avoidance of first pass metabolism
6. Non invasive
7. Painless
8. Does not require sterile preparation
9. Improved delivery route for non-Lipinski group of drugs
10. Nasally administered drugs have been shown to reach brain in adequate concentrations



Use of topical agents in the management of chronic sinusitis:

Two factors must be borne in mind while using topical agents in managing chronic sinusitis i.e. mechanical lavage and pharmaceutical intervention. These two factors are potentially conflicting and hence an optimal balance must be struck whenever topical application of drug is desired in managing rhinosinusitis.

Role of mechanical lavage: Lavage facilitates mechanical removal of mucous, antigen, pollutants, inflammatory products, bacteria, bacterial products and biofilms. Lavage should be performed using high volume positive pressure irrigation of the nasal cavity in order to provide the necessary shearing force for clearing these substances. Administration of drugs into the nasal cavity cannot be done using the high volume positive pressure route because prolonged mucosal contact time is necessary for optimal absorption of the drug from nasal cavity.

Delivery devices:

Nebulizers – Drugs delivered using nebulizers does not adequately penetrate the sinus cavity.

Large volume squeeze bottles – This group of device is very useful in administering drugs after endoscopic sinus surgery.

Netipots – Drug administration using Netipots can be used in non-operated sinuses because of the head position and retrograde flow which facilitates better drug permeation into the nasal cavity.

Figure showing a Netipot

Simple low volume sprays and drops – Distribution of drugs when low volume sprays and drops is highly erratic and suboptimal and hence should be used for nasal cavity treatment only.

Enhancement of drug delivery sans mucosal blanket: The presence of mucous blanket significantly affects intranasal drug delivery. Removal of this mucosal blanket will augment intranasal drug delivery. This mucous blanket is excessive in patients with rhinitis. Irrigation of nasal cavity with hypertonic saline before administration of nasal steroids enhances its absorption.

Drugs that can be administered through the nose:

1. Steroids
2. Insulin
3. Vasopressin

4. Oxytocin

Intranasal topical steroids: are commonly used to treat patients with seasonal allergic rhinitis, perennial allergic rhinitis and non-allergic rhinitis. It has been demonstrated that fluticasone propionate resides in the nasal mucosa for 24 hours. While applying intranasal steroid spray the nozzle of the bottle should be directed towards the lateral nasal wall. This ensures that the drug reaches the portion of the nose which is maximally affected by allergic reaction. The nasal cavity should be cleared of mucous before spraying the nasal cavity with the drug.

Vaccine delivery through nose: The ability of nose associated lymphoid tissue to generate cell mediated as well as humoral immunity has kindled interest in using this route for vaccine administration. This route will be very useful in undertaking mass immunization programmes. One classic example of vaccine which can be administered through nose is Flumist (live influenza virus vaccine). Vaccine administered through the nose should contain antigen coupled with a mucosal adjuvant or carrier.

Advantages of using this route for immunization include:

1. It is painless
2. The vaccine administered need not be sterile
3. Since nose happens to be a potential portal of entry for infections this route can increase local immunity

Intranasal morphine for management of intractable cancer pain:

Morphine administered orally has very poor bioavailability due to extensive first pass metabolism hence intranasal route is preferred. Morphine administered via nose is rapidly absorbed, avoids first pass metabolism and is non-invasive.

Intranasal acetyl cholinesterase inhibitors in treating Alzheimer's disease: Galantamine an acetyl cholinesterase inhibitor has been administered with reasonable degree of success in managing patients with Alzheimer's disease.

Antinausea and motion sickness medications: Treatment of nausea and motion sickness is ideally performed using intranasal route of administration. Intranasal metoclopramide has been used intranasally with reasonable degree of success in managing post-operative nausea. Scopolamine an antimuscarininc drug used for managing motion sickness is another drug that can ideally be administered through the nose.