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Review: Nose to Brain Drug Delivery System

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ABSTRACT

The aim of the present review transport drug in the nose to the brain through olfactory and trigeminal nerve pathways bypassing blood-brain barrier (BBB). These route gives many advantages over the oral and parenteral route and has shown potential for targeting the drug to the brain for treating various central nervous system disease such as psychosis, Parkinson's, and Alzheimer's disease. The use of the nasal route for the delivery of challenging drug such as some small polar molecules vaccine, hormones as well as peptides and also protein have to produce much more interest in present situation. Because of high permeability, vascular low enzymatic condition of nasal cavity and mucosa, and also avoidance of hepatic first-pass metabolism and are well susceptible to systematic delivery of the drug. Various formulation strategies for help in enhancing drug delivery from nose to brain are discussed. The success of small nanocarrier for direct targeted drug delivery depends on its ability to the incorporated drug in particular dosage form or different kinds of therapeutic agents penetrate through several anatomical barriers, sustained release of incorporated drug and stability in the nanometric size range. Drug delivery systems such as liposomes, microspore, microemulsion, nanoemulsion, and hydrogels have been showing that it has good bioadhesive to a biological system and are briefly discussed in the present review.

INTRODUCTION

The acute & chronic drug treatment for various neurodegenerative as well as a psychiatric disorder is challenging from several aspects. The poor bioavailability, limited brain exposure of oral drug, fast metabolism & elimination. Drug delivery through nasal route has been the practice from ancient times for systemic effect. The Nasal mucosa is considered as a potential administration route to get a fast and higher level of drug absorption due to the larger surface area, porous endothelial cell membrane, high blood flow, the avoidance of liver metabolism and ready accessibility are the major reason for drug delivery across the nasal mucosa.

The concept of designing a specified delivery system to the achievement of selective targeting drug has been originated from the perception of the scientist Paul Ehrlich, who has proposed drug delivery & named to be the 'magic bullet'. Several essential aspects that need to be considered while designing targeted drug delivery systems include a carrier, target, and targeting ligand carrier are drug vectors that sequesters transport & retain drug in route while delivering it within vicinity of target. The targeting ligand bound to carrier Proteins to negotiate its exclusive delivery to the specific identified site. The brain is a delicate organ to isolate from general circulation and characterized by the presence of relatively impermeable endothelial cells within the target cell junction, enzymatic activity, & active efflux transporter mechanism like p-glycoprotein efflux. The interests in nasal route for therapeutic purposes arise from an anatomical, physiological, and histological characterization of the nasal cavity that provides rapid systemic drug absorption and quick onset of action. [1]

Reason:

The disorder of central nervous system required delivery of drugs for a particular treatment. Hydrophilic and large molecular weight drugs usually face problems so then being transport to the brain because of the permeability issues of the endothelial membrane which separate systemic circulation and central interstitial fluid as well as Blood-brain barrier.

Nasal anatomy and physiology:[3, 4]

The nose is a complex organ from a kinetic point of view because of three different process takes place inside the nose.

1. Deposition

2. Clearance or translocation

3. Absorption

Nose is structurally divided into two parts external nose and internal nose.

- **External Nose-**

1. Supporting bone (frontal bone, nasal bone, maxillae)

2. Hyaline cartilage (Septal cartilage, lateral nasal cartilage and hyaline cartilage)

- **Internal Nose-**

It is a large cavity situated in inferior to the nasal and superior to the mouth. Nasal passage runs from nasal vestibule that is a nasal valve to the nasopharynx and has a depth of nearly 12-15cm. The lining is highly vascular and rich in mucous gland goblet cells.

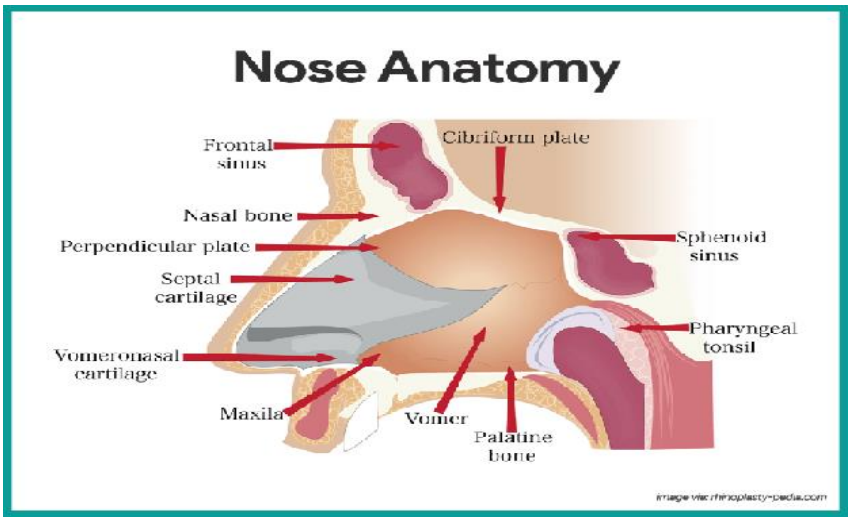

Figure No. 1: Anatomy of nose

Nasal vestibules

This is the most anterior portion of the nasal cavity inside the nostril and surrounded by the cartilage.

The stratified squamous cells covered the nasal portion.

Nasal conchae [5,6]

The lateral wall convoluted to strategically place turbinate that contain the air stream to their configuration and changing dimension. These structures are responsible for maintaining humidification and temperature regulation inhaled air.

Nasal Meatuses

The conchae septum is subdivided into each side of the nasal cavity into a groove like passage as superior, middle, and inferior meatuses. The meatuses increase the surface area in the internal nose.

Olfactory epithelium

The olfactory receptors are situated in the membrane lining the superior nasal conchae and adjacent septum and such region are called olfactory epithelium it consists of a specialized olfactory cell (for smell), supporting cells well as both serous and mucous glands.

Nasal secretion-

Nasal secretions are made up of a mixture of secretory material from goblet and the nasal lacrimal glands. The PH of nasal secretion is 5.3 to 6.3 and it containing protein such as lysozyme, enzyme, albumin, glycoprotein, etc.

- **Mechanism of drug transport across Nasal Mucosa**

The absorbed drug from the nasal cavity must pass through the mucous layer it is the first step in absorption. Small molecule and uncharge drug easily pass through this layer, but large, charged drugs find it difficult to cross it .the principle protein of the mucous is mucin it has tendency to bind the solute molecule, hindering diffusion. Additionally, structural change in a mucous is possible as a result of environmental change. Various mechanisms have been proposed for nasal drug absorption as follows.

Mechanism-1 – Paracellular route-

In that involve the aqueous route of transport mechanism which is the passive diffusion. The drug having a molecular weight above 1000 daltons shows poor bioavailability.

Mechanism-2- Transcellular route-

It involves the transport of drugs through the lipoidal route and it is called a transcellular process. The drug cross cell membrane by the active transport through carrier-mediated that is transported via the opening of tight junction.

Mechanism-3- Transcytosis route-

In this mechanism, particles are internalized by vesicle that is transcytosis.

- **The following pathways are involved in the absorption and distribution for nasal administration**-

1) In the case of hormones that are estradiol which is absorbed in the nasal membrane and directly goes in olfactory neurons after that, it distributed in the brain and cerebrospinal fluid.

2) When penicillin is administered through the nasal route then it absorbs in nasal membrane and distributes in the bloodstream.

3) If albumin is taken through nasal route it will be absorbed in the nasal mucosa, they go toward sensory nerve cells of olfactory epithelium then they are distributed in the bloodstream through subarachnoid space.

4) After the administration of egg albumin directly distribute in the lymphatic system through nasal mucosa. [7].

- **Metabolism of drug in nasal cavity**-

Enzymes are called to exit in nasal cavity, but they can't appear to have a significant effect in the extent absorption of the maximum of the compound other than protein and peptide. The drug has been shown maximum absorption and higher bioavailability in nasal cavity.

1) The rate of absorption is fast and short exposure time of drug delivered to the enzymes.

2) Enzyme level within the nasal tissue which is very low may be easily saturated to drug.

Materials and Methods

Formulation

During the process of formulation of nasal doss, its various factor is considered for the absorption such as stability and their Molecular weight, chemical form, polymorphism, partition coefficient of drug, solubility and dissolution rate of drug. Physical factors including the blood flow in nasal mucosa, enzymatic degradation, volume of administration also in that involve biological factor including effect of perfusion rate, effect of perfusion volume, effect of solution PH, effect of drug lipophilicity and MCC.

Table No. 1: Formulation components

Sr. No.	Formulation excipient	Examples
1.	Buffer capacity	Citrate buffer and acetate buffer
2.	Osmolarity	Sodium sulfite or sodium acid phosphate.
3.	Viscofying agent	Carbopol, cellulose, starch.
4.	Solubilizer	Cyclodextrins such as hydroxypropyl beta-cyclodextrin.
5.	Preservative	EDTA, benzyl alcohol, phenyl ethyl alcohol.
6.	Antioxidant	Tocopherol, sodium bisulfite.
7.	Humectant	Glycerin, sorbitol, mannitol.

[8]

For the administration of nasal drug the various dosage form are available they are as follows;

1) Nasal drop

2) Nasal spray

3) Nasal gel

4) Nasal powder

5) Nasal microemulsion

6) Mucoadhesive microspheres[9]

Pharmacological effect of nasal drug-

A) Insulin in the form of solution which administered by nasal route that helps to improve memory in Alzheimer disease patient also increase cognition in pediatric patient and also decrease nicotine craving syndrome.

B) Likewise, oxytocin administered in solution form, give pharmacological effect decreasing the post-traumatic stress disorder response in human and also improve ability emotionally rate faces inpatient with an autistic spectrum disorder.

C) Valproic acid shows it's effect against seizures in rat model.

D) Pramipexole in chitosan nanoparticle helps in increasing the pharmacological response for Parkinson's disease.

E) In the form of chitosan nanoparticle, the plasmid encoding for red fluorescent protein effect on gene expression in the striatal region of mice brain.

F) The propofol is formulated by molecular envelope technology nanoparticle, they help production of sedation in the rate which already healthy situation.

G) Oxcarbazepine in the form of nanoparticle they decrease the seizure of rat.

H) Huperzine A which formulated in PLGA nanoparticle coated with trimethyl chitosan help to increase brain exposure during comparison with uncoated PLGA nanoparticle.

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