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BRAIN TARGETING NASAL DRUG DELIVERY SYSTEM

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ABSTRACT
Present review highlights the nasal mucosa as an administration route for targeting the central nervous system, in specific, the brain. Thus, since last few decades, nasal route has attracted a broad observation of researcher, as a convenient, non- invasive, reliable and safe pathway to reached faster and higher levels of drug in the brain. The nasal mucosa when differentiate to other mucous membrane is easily accessible and gives a practice entrance portal for small and large molecule. The brain and central nervous system both have limited availability to blood chamber due to number of barriers. Intranasal drug delivery is one of the attensive delivery options for the brain targeting, as the brain and nose chamber are linked to each other through the olfactory route and through peripheral circulation. This review will discuss factor affecting brain targeted nasal delivery system.

KEYWORDS: Nasal Delivery, Brain Targeting, Blood Brain Barrier, Central Nervous System, Cerebrospinal Fluid (CSF).

INTRODUCTION

Drug delivery through nasal route has been practiced since ancient times for systemic effect. Nasal drug delivery has now been acknowledge as an superlative route for delivery of therapeutic compounds including biopharmaceuticals. Disfavour of the tremendous development in drug delivery system for treatment of central nervous system disorders like Schizophrenia, Migraine, Parkinson's, Alzheimer's disease and brain tumours, remain there is require of novel brain targeted drug delivery system. The major obstacle for targeting the drug to brain is presence of blood brain barrier. The major issue in drug delivery to brain is the presence of blood brain barrier, which boundary the access of most drugs to the brain. It is well accepted that blood brain barrier is a hurdle that segregates the brain from circulating blood. Nasal route has been investigate as the correct route, for local delivery of drugs for treatment of local diseases like, nasal allergy, nasal congestion, nasal infection, rhinitis. Because last few decades, nasal route had enticed a wide attention for researcher as a suitable, good and a protective route carry out faster and higher level of drug absorption. The concentration time profiles achieved after nasal administration are the same to those after intravenous administration, resulting fast onset of pharmacological activity. The interval from nasal to brain is shorten, penetration via brain is easy. Most of the therapeutic agents have been abandoned since required amount of drug level in brain have not been reach by the drugs through the systemic circulation. Macromolecular drugs like peptides and proteins known as 'Biologics' are to large and to hydrophilic to pass through the blood brain barrier from the systemic circulation.[1][3][6]

Advantages of Nasal drug delivery system

-Drug deterioration in the GI tract is avoiding.
-Prevent the hepatic first pass metabolism.
-Fast drug absorption and rapid onset of action can be reached.
-Perfect route for systemic delivery of drug that indicate poor absorption via oral route.
-Improved patient observance.
-Polar compounds showing poor oral absorption may be specifically suited for this route of delivery.
-Serves as an another route for parenteral administration, particularly for protein and peptides drugs.
-Shows better bioavailability for small and low molecular weight drugs.
-Bioavailability of larger molecules can be better using absorption enhancers.

Limitations of Nasal drug delivery system

-Fast elimination of drug substances from nasal cavity due to mucocilliary clearance poses a extensive difficulties in nasal drug delivery system.
-Nasal cavity gives smaller absorption surface area as compared to GI tract.

-Absorption enhancers used in formulation may generates mucosal toxicity.
-Mechanical lost of the dosage form could occur due to inappropriate way of administration.
-Low bioavailability may conclusion from enzymatic degradation and metabolism at mucosal surface.
-Self medication is also probable with this route of drug administration.

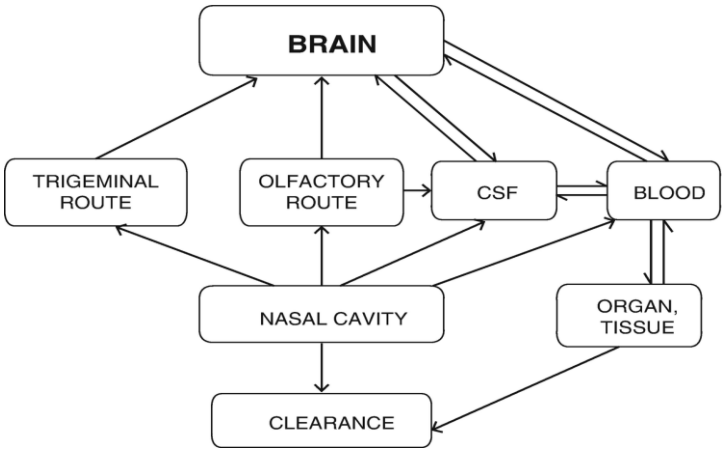

Figure 1: Different pathways for reaching the brain after transnasal administration.

Brain Targeting through nasal route

From time to time the blood brain barrier has impleted the development of many prospectively interesting central nervous system drug candidates due to their low distribution into the CNS. Owing to the special relation of the nose and the CNS, the intranasal route can neglet the blood brain barrier. Absorption of drug across the olfactory region of the nose supply a unique characteristics and superior choice to target drug to brain. Recently multiple nasal formulations, such as Ergotamine (Novartis), Sumatriptan (Glaxo smithkline) and Zolmitriptan (Astra Zeneca) have been marketed to therapy of migraine. Scientist have also concentrated their research achieve intranasal administration for drug delivery to brain. Mostly for the treatment of disease, such as epilepsy, migraine, emesis, depression, and erectile dysfunction.[7]

Nasal cavity Anatomy and Physiology

In human the activity of the nasal cavity are breathing and olfaction. It also provide an important protective action once it filters, heat and humidity the inhaled air before arrive at the lowest airways. Nasal is covered with mucus layer and hairs which are elaborate in those activity are trapping inhaled particles and pathogens. The nasal cavity is a space located above the oral cavity and hard palate and below the skull base and intracranial chamber. The nasal septum be made up of cartilage in its front end and bone towards the back of the nose. The left and right nasal cavities turn into continuous in the back of the nose through the opening to the nasopharynx is called the choana. In this area, the nasal cavity transformation into the nasopharynx. The human nasal cavity has a total capacity of 15-20ml and a total surface area of 150 $cm^{2.}$ It is separated by middle septum into two symmetrical halves, each one opening at the face via nostrils and extending posterior to the nasopharynx.[4][8][9]

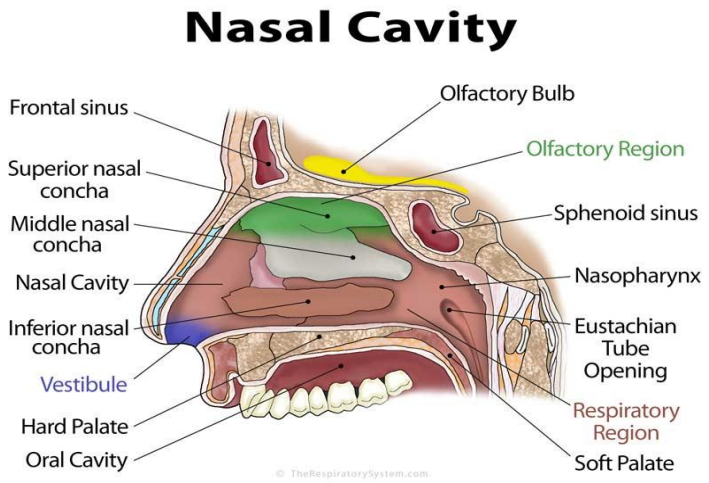

Figure 2: Anatomy and physiology of Human nasal cavity.

Respiratory Region

The respiratory epithelium is composed of with four type of cells are non- ciliated and ciliated columnar cells, basal cells and goblet cells. These cells promote active transport processes such as the change of water and ions between cells and motility of cilia and also to avoid drying of the mucosa by trapping moisture in order to assist mucociliary clearance. The frequency of 1000 strokes per min of the cilia beat. Hence the mucus moves only one way from the anterior to the posterior part of the nasal cavity to the nasopharyn.[4][5]

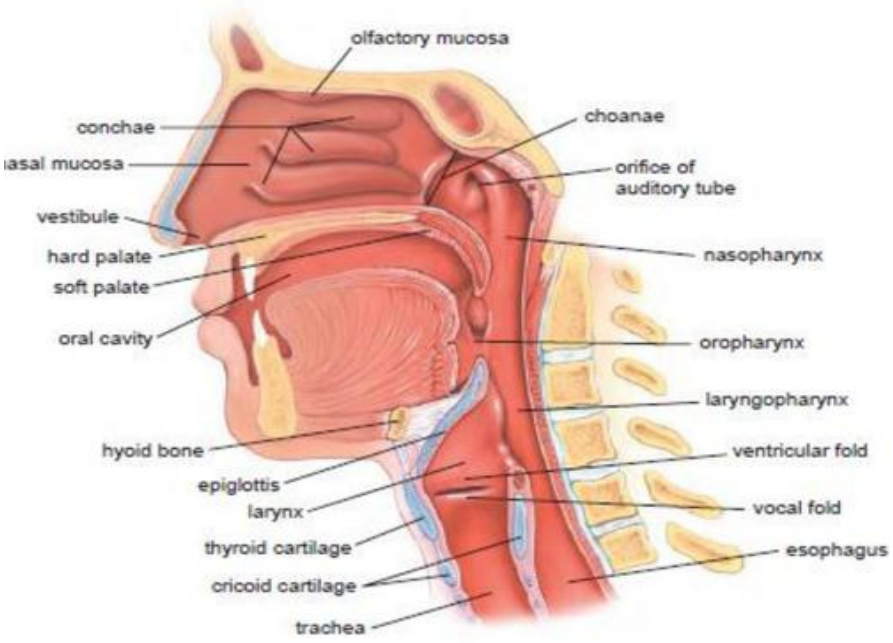

Figure 3: The Respiratory region.

Olfactory region

Odour allows human and animals with olfactory receptor to recognize food, mates, predators, and gives both sensual pleasure as well as warning of danger. The olfactory region made up of cilia projecting down out of the olfactory epithelium into a layer of mucous which is nearby 60 microns thick. The mucous layer is generated by the Bowman's glands which residue in olfactory epithelium. In the region there are some small serous glands (glands of Bowman) which lead to secretions acting as a solvent for odorous substances.[3][4][10]

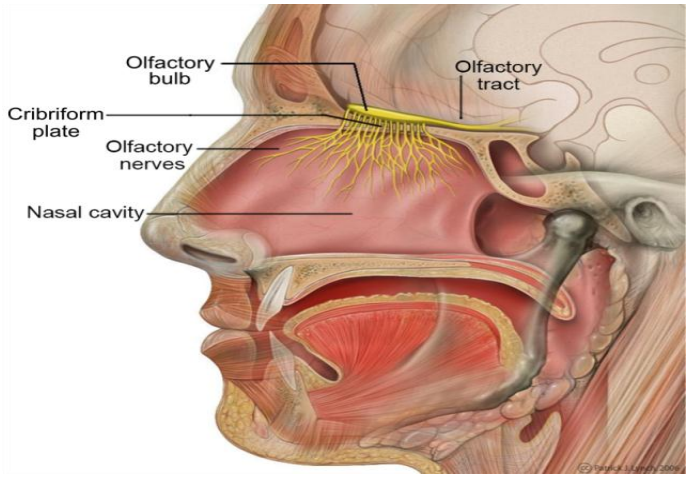

Figure 4: The Olfactory region.

Mechanism of Nasal absorption

The absorbed drug from the nasal cavity passes via mucus layer. It is the first process in absorption. Small unchanged drug simply passed via this layer but large, charged drug find problems to cross it. It has the susceptibility to bind to the solutes and hinders diffusion of drug molecules. Structural changes in the mucus layer are feasible as a result of environmental changes in pH, temperature.[1][11][13]

a) First mechanism: It is also called as the para cellular transport. It included an aqueous route of transport but slow and passive. There is an opposite link between intranasal absorption and the molecular weight of water soluble compound drug having molecular weight larger than 1000 Daltons indicates poor bioavailability.

b) Second mechanism: It transport via lipoidal route. It is also called as the Trans cellular process. It is liable for the transport of lipophilic drug that indicate a frequency dependency on their lopophilicity.

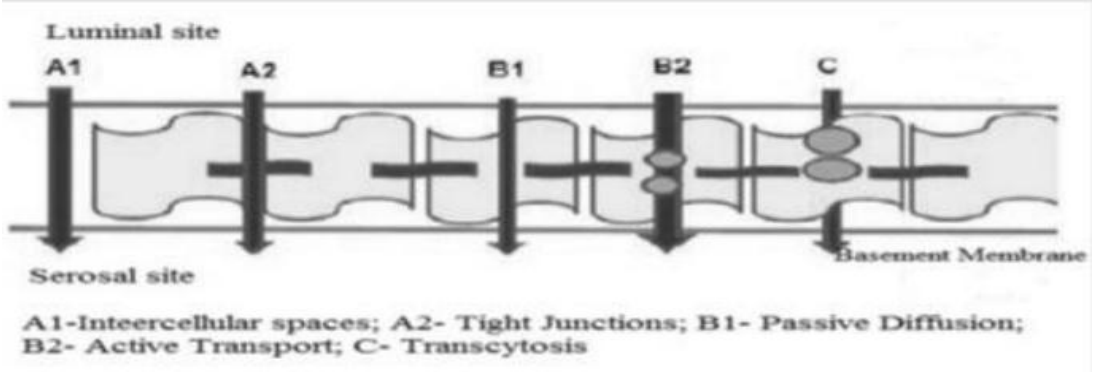

Figure 5: Transport through the opening of tight junctions.

Factor affecting Brain- Targeted nasal delivery system

- **Physiochemical properties of drug**

1) **Chemical form**: The chemical form of a drug is an essential factor in determining absorption. For example, transformation of the drug into a salt forms can also change its absorption.[3]
2) **Polymorphism:** Polymorphic character of drug molecules is known to affect the dissolution rate and solubility of drugs and thus their absorption via biological membranes.[1]
3) **Molecular weight**: A linear inverse connection exists between the absorption of drugs and molecular weight up till 300 Daltons. Shape is also important that impact the absorption of drugs. Linear molecules have reduced absorption whereas the cyclic-shaped molecules indicate higher absorption.[1][12]
4) **Particle size**: It has been described that particle size larger than 10µm are placed in the nasal cavity. Too fine particles i.e. below 5µm should be preventing for nasal administrationas there are possibility of inhalation directly into the lungs.[3]
5) **Solubility and Dissolution Rate**: Drug solubility and dissolution rate are the main factors that governs nasal absorption from powder and suspensions. The particle placed in the nasal cavity should be diffused prior to absorption.[3][14]

- **Formulation factor**

1) **Viscocity**: In nasal mucosa the contact time of the drug enhanced with use of viscocity increasing agent in the formulationwhich enhanced the nasal permeation of drug.[5]
2) **pH of formulation**: The pH of development and nasal surface influence a drug permeation. Nasal irritation is prevented by using nasal development of pH ranges from 4.5-6.5. The volume of dosage based on the area of the nasal cavity.

The significance of maintaining the pH of the nasal formulation are as follows:-
-To Avoided the irritation in nasal mucosa.
- It allows the absorption of drug in unionised form.
- To Avoided bacterial growth in the nasal passage.[5][15]

3) **Buffer capacity**: Nasal formulations are mostly administered in small volume ranging from 25-200µl. Hence nasal secreation may changes the pH of administered dose.[1]
4) **Role of absorption enhancers**: Absorption enhancers are application when a drug suggest decreased membrane permeability, huge molecular lenght, insufficiency of lipophilicity and enzymatic deterioration through way of amino peptidases.[1][16]

Nasal Formulations

The selection of delivery systembased on the drug being used.

Nasal Drops

Nasal drops are one of the most easy and convenient system established foe nasal delivery. The quanitity of drug delivery is not known. The main limitations of this is the accuracy of dosage. Nasal drops capably placed serum albumin of human in the nostrils compared to nasal sprays.[4][5][17]

Nasal Sprays

The Nasal sprays are developed as nasal solution and suspension. An exact dose can be delivered via nasal sprays by applications of metered dose pump and actuators. About 25-200µl are delivered via the nasal drug delivery. The powder sprays are change as nasal

spraya because dry powder generates nasal irritations.[5][18]

Nasal Gels

Nasal gels are large viscocity thickened solutions or suspensions. The benefits of a nasal gel contain the reduction of post nasal drip due to decreased swallowing, reduction of anterior leakage of the formulations, reduction of irritation by using soothing excipients and target delivery to mucosa for great absorption.[4]

Nasal Powder

This dosage form may be formulated if solution and suspension dosage forms cannot be formulated due to lack of drug stability. The benefits to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. The powder formulation be dependent on solubility, particle size, aerodynamic properties and nasal irritancy of Active drug and excipients.[4]

CONCLUSION

Many advanced and effective approaches to cental nervous system drug delivery have developed in recent years. The nasal drug delivery system is an perfect route for delivery of drugs to the brain directly and the passage of drug to blood brain barrier via nasal route. This pathway has exhibited better potential to directly target the brain with reduced systemic side effects. The nasal cavity well developed for better absorption and patience compliance. The identification of ways to enhanced the bioavailabilty of drugs in the brain open chances for the casual treatment of disease related with a dificiency in neurosteroids and neurotransmitters in the brain. It decreases systemic exposure and thus decreases the side effects.

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