A REVIEW ON NOSE TO BRAIN DRUG DELIVERY SYSTEM

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ABSTRACT

The nose- to- brain pathway has gained attention because it transports direct targeting drug patch bypassing Blood Brain hedge and systemic effect into the brain. This system demonstrated an important lower expression distribution rate in the olfactory as compared to that in other nasal drug delivery systems. The end of this review is to make easy vacuity of the information about nasal drug delivery system to the people who are busy in doing the study of nose to brain drug delivery system. The Central nervous system is the main system in mortal body, and due to BBB, it come a complex system. So multitudinous condition of central nervous system which is veritably delicate to treat, because of one chain and the name is Blood Brain hedge which is present in brain. BBB blocks the entry of mixes like macromolecules into the brain. For avoiding this problem during the treatment of condition, the various advanced approaches are used. From that nose to brain delivery system is a good approach for brain targeting. Brain relates to nose through the olfactory route and supplemental gyration. A variety of internal ails which include Parkinson's complaints, multiple sclerosis, Alzheimer's complaints, epilepsy, and psychiatric conditions are the big problem on the earth. For reducing this problem, the advanced ways are used for the treatment of this complaints.

KEYWORDS *Nose to brain drug delivery, Blood brain barrier, Olfactory and trigeminal nerve, Bioavailability, Mucociliary clearance, Passive diffusion, Lipid carrier.*

INTRODUCTION

Nose to brain medicine delivery system is used for original as well as systemic effect. The most fashionable exemplification square measure nasal sprays and nasal drops that the medicine is developed as a solution or suspension.[1] The crucial advantages are easy available, the prospect of good to moderate bioavailability of medicine, which are considerably metabolized following oral administration. More lately, nasal drug delivery (NDD) has been proven as a useful gateway in hormone relief remedy using small peptides[2],In Epilepsy, Psychiatric issues,[3] In Parkinson's complaint[4], In Glioblastoma Multiforme (GBM)[5] also in Alzheimer's complaint which is considered to be the most common in world, presently affecting more than 35 million people.[6,7] one of the most important issues that could ameliorate neurological complaint treatments includes developing effective brain medicine delivery systems. One of these approaches is to take advantage of the nasal route which is a channel for medicine delivery directly into the brain.[8] The hydrophobic (lipid dissolvable) particles is quickly enter to the circulatory system from nasal mucosa and in this manner arrive at the CNS by crossing the BBB.[3]

NASAL ANATOMY AND PHYSIOLOGY

The primary function of the nose is considered to be olfaction, although the region involved in the sense of smelling is fairly small.[2] Positionally, the nasal vestibules refer to the anterior part of the nasal cavity and mainly play a role related to the removal of drugs and foreign substances.[9] The nasal cavity is divided into two halves by the middle nose blade. The respiratory region forms a major part of the nasal cavity conforming of three corridors: upper, middle, and lower.[8] The metabolic exertion in the nose is lower than the digestive tract, which contains enzymes, proteins, and peptides. This is another factor that makes this route more seductive than the oral route. Compared with the oral route, the nasal pathway prevents the destruction of the medicine in the stomach, bowel, or liver, before it reaches the circulatory system. [10,11] The largest part of the nasal cavity is the respiratory region, which is divided into three thin projections known as conchae. The conchae, or turbinate, are thin, bony plates covered by a spongy mucosa and are located just behind the entrance way the inferior, middle and superior turbinate.[2] The epithelium in the olfactory region is non-ciliated and contains olfactory nerve endings. The remaining face of the nasal cavity is covered with a mucosal epithelium conforming of basal cells, goblet cells, and columnar cells that all can either be ciliated or non-ciliated.[10]

1. Nasal vestibule:

During this space of nasal cavity there are nasal hairs additionally known as vibrissae, which filter the gobbled air.[1] The nasal vestibules refer to the anterior part of the nasal cavity and mainly play a role related to the removal of drugs and foreign substances.[9]

2. Olfactory Region:

The olfactory region route is the essential pathway for intranasal medicine delivery. The olfactory mucosa is located within the skull, at the top of the nasal cavity about 7cm from the nostril.[12] The intracellular pathway, also known as the olfactory nerve pathway.[13] The olfactory epithelium consists of three types of cells: nerve cells, progenitor cells, and supporting cells, all of which are attached to each other via tight junctions. The neurons begin in the olfactory bulge and end in the olfactory epithelium.[14] Olfactory mucosa contains olfactory receptor neurons that are responsible for the transduction.[15]

3. Respiratory Region:

The respiratory region is the largest having a total surface area of about 130 cm^2 and is mainly responsible for systemic drug absorption across nasal mucosa.[16] It includes three folded structures namely the superior turbinate, the middle turbinate and the inferior turbinate which causes humidification and temperature regulation of the inhaled air.[12] The respiratory epithelium is made of with four types of cells are non-ciliated and ciliated columnar cells, basal cells and goblet cells. These cells prevent drying of the mucosa by Trapping moisture for mucociliary clearance. [17] One of the pathways for the drug to reach the brain via the nasal cavity includes the trigeminal nerve. The mean residence time for the respiratory region is only 15–20 min. while in the olfactory region it can be as long as a few days.[8]

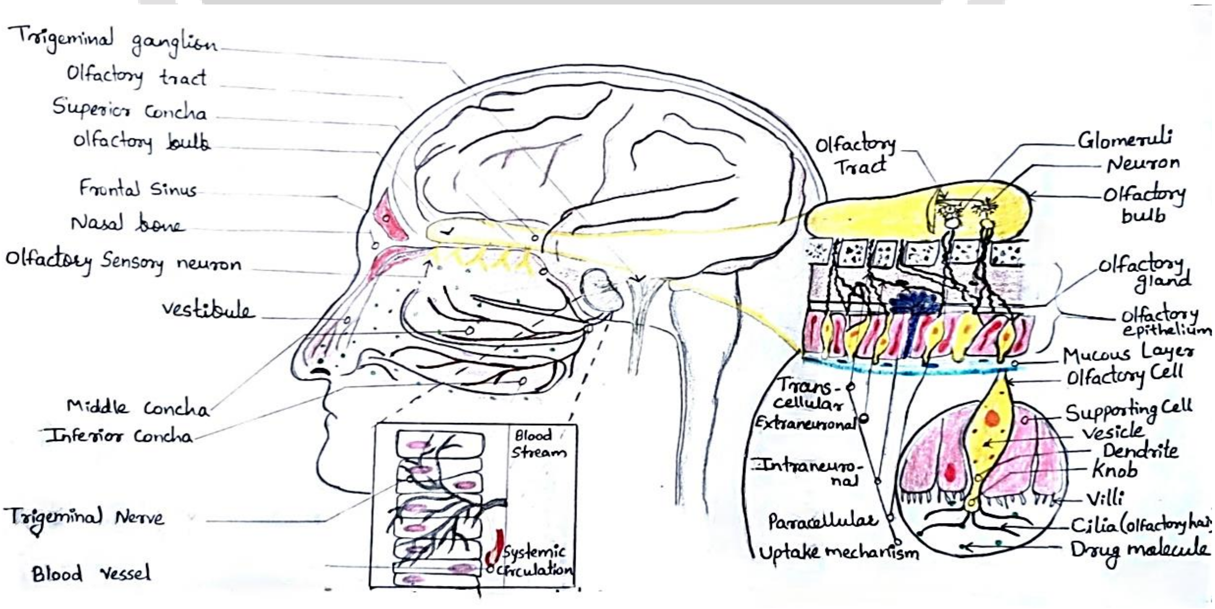

Fig-1: Schematic figure of olfactory and trigeminal nerve pathways to the brain.

4. Airflow:

An adult respires about 105 liters of air per day, which must be heated and humidified before it enters the lungs. The humidification provided by the nasal mucosa raises the relative humidity (RH) to 95% before the air reaches the nasopharynx & it maintains an air temperature of 31–37 °C. [18]

5. Nasal Secretions:

Mucous membranes constantly secrete mucus, which is a watery fluid rich in silylated proteins. The glands secreting the fluids are of a mixed type comprising serous and mucous types. The system can be stimulated by cold dry air.[2]

6. Mucociliary Clearance:

Goblet cells and mucus glands within the nasal epithelium are responsible for the production of the nasal mucus.[2] The most important natural obstacle to drug delivery via the nasal cavity is mucociliary clearance.[8] Mucociliary clearance is an important defense mechanism of the upper respiratory system and is responsible for clearing the surface of the airways of any inhaled pathogens, pollutants and allergens.[2]

ADVANTAGES OF NASAL TO BRAIN DRUG DELIVERY SYSTEM: -

1. Case can Self-administer the drug without the help of professional person.[19]
2. It Improves patient convenience and compliance.[20]
3. The formulation with polymeric nanoparticles minimizes systemic side effects of drug.[21]
4. In this nasal route of medicines administration, first – pass metabolism is absent.[22]
5. It allows direct delivery to the brain and spinal cord while reducing systemic drug exposure and its side effects.[19]
6. Rapid attainment of therapeutic drug levels in the blood.[23]

LIMITATIONS OF NASAL TO BRAIN DRUG DELIVERY SYSTEM: -

1. Dose is restricted due to comparatively tiny space offered for the absorption of drug.[19]
2. The Time offered for medicines absorption is confined.[24]
4. There is possibility of Nasal irritation after the administration of medicines.[16]
5. The Surfactants used as chemical enhancers could disrupt and indeed dissolve Membrane in high concentration.[1]
6. The nasal cavity gives a lower surface area for absorption as a compared to the gastrointestinal tract. [25,26]

APPROACHES TO OVERCOME ABOVE LIMITATAION: -

1. The olfactory mucosa has a wide variety of enzymes. Hence, enzymatic inhibitors like protease and peptidase inhibitors are used to prevent enzymatic degradation of drug and enhances its activity.[12]
2. Some absorption enhancers also act as enzyme inhibitors like disodium ethylene diamine tetraacetate prevents the enzymatic degradation of beta sheet breaker peptide which is used for treating Alzheimer's disease.[27]
3. A mucoadhesive formulation can be made using a polymer like chitosan to extend the formulation's residence time and increase nasal cavity permeability.[19]
4. Co-solvents increase the drug solubility and hence, increase the drug absorption.[28]
5. Permeation enhancers have been developed as a potential formulation that improves the permeability of therapeutic agents across membranes.[8]

MECHANISM: -

There is different drug transportation pathway along the nasal epithelium. The most important natural obstacle to drug delivery via the nasal cavity is mucociliary clearance.[2] This process is not very efficient for rapidly absorbed drugs, but for those drugs that are more slowly absorbed due to their physicochemical properties, it can be limiting.[8] absorption of molecules takes place at the olfactory and respiratory epithelia.[29] The forward movement in the respiratory region is much faster than in the olfactory region. The residence time for the respiratory region is 15–20 min, whereas in olfactory region it can be as long as a few days. [30,31] Absorption of drug substance mainly takes place at the respiratory & olfactory epithelia.[32]

There are two main pathways, transcellular and paracellular pathway. The routes of compound transfer through the olfactory area to the olfactory bulb are transcellular through either the sustentacular cells or the exposed olfactory sensory neurons.[33]

Transport Across the Nasal Membrane: Although some compounds, such as hydroxyzine and triprolidine can diffuse freely across nasal epithelia, this passive route is only accessible by highly lipophilic compounds.[2] There are two pathways: a) In direct pathway, drug is going through olfactory and trigeminal nerve and goes into the CNS. b) In indirect pathway, drug is going into lymphatic system and after that passes into blood circulation, crosses the BBB and reaches to brain.[1]

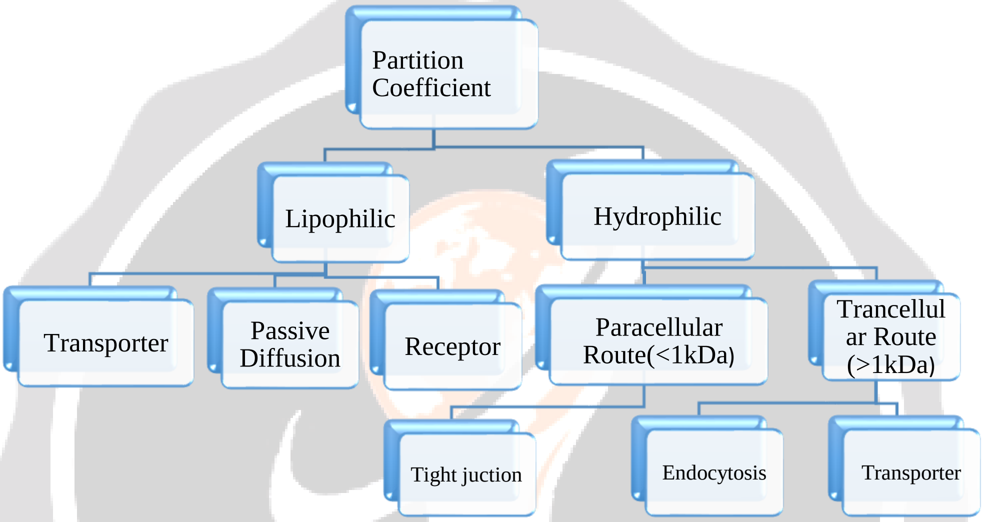

Chart-1: Routes of transport across the nasal respiratory epithelium.

Pathways of medicine movement from the nasal depression to the brain-

A) Olfactory pathway-

Three different pathways across the olfactory epithelium

i) Paracellular pathway This is involvement of waterless route of transport through tight junctions. Nasal immersion of hydrophilic medicines most presumably occurs by prolixity through Waterless channels (pores). It shows rate reliance on the molecular weight of a medicine up to 1000 Da without immersion enhancer shows good bioavailability.[20]

ii) Transcellular pathway- It involves lipoidal route of transport. Passive prolixity is most likely for further lipophilic medicines. It's intermediated fleetly and at a high rate. This route is responsible for the transport of lipophilic medicines.[34]

iii) The olfactory nerve pathway where medicine is taken up into the neuronal cell by endocytosis or pinocytosis mechanisms and transported by intracellular axonal transport to the olfactory bulb. [35,36]

B) Trigeminal pathway-

The trigeminal nerve with three branches, including the ophthalmic, maxillary and mandibular nerve control the respiratory region and sensation of the nasal depression.[37] The ophthalmic and maxillary branches are important for medicine delivery as neurons from these branches pass directly through the nasal mucosa. numerous intranasally applied neurotherapeutics fleetly enter the CSF and this transport is dependent on the lipophilicity, molecular weight.[34] The medicine is being released in the nasal depression it would be absorbed either transcellularly or paracellularly in the epithelium and transported to CNS. [38,39]

C) Vascular pathway-

The nasal mucosa is largely vascularized for entering blood force from branches of both the internal and external carotid roadway, including the facial roadway and maxillary roadway.[40] The mucosa of the nose has a lot of blood vessels. As the vasculature are rich the respiratory epithelium than olfactory mucosa bit of the medicine gets absorbed into the systemic rotation[24] and receives blood from the anterior and posterior ethmoidal highways, which are the lowest highways in the optical depression.[19] Medicines delivered in this way can be absorbed either by the epithelium of the respiratory tract or by the epithelium of the olfactory region.[8] The CNS actually consists of two abstract walls with different parcels the blood – cerebrospinal fluid hedge(BCSFB) and the blood – brain hedge(BBB).[41]

THE BLOOD-CEREBROSPINAL FLUID BARRIER: -

The BCSFB The first component of the BCSFB separates the blood from the CSF and is formed by the choroid plexus, a complex neuroendocrine structure where the CSF is produced and which provides passive transport, active transport and the second component of the BCSFB separates the CSF from the neurons and brain extracellular fluid and is formed by the arachnoid membrane.[41]

THE BLOOD BRAIN BARRIER: -

The blood–brain barrier (BBB), formed by the endothelial cells lining the cerebral micro vessels, has a pivotal role in protecting the brain parenchyma from blood-borne agents.[42] It is difficult for drugs to penetrate the BBB and the amount of drugs that can reach the brain is limited due to extensive metabolism and excretion during systemic circulation.[9] The endothelial cells forming the BBB are characterized by tight intercellular junctions, minimal pinocytotic activity.[42] Compounds with a value of greater than 1 freely cross the BBB, whereas compounds with a brain/plasma ratio of smaller than 0.1 may be unable to enter the CNS.[43] The amount of drugs indirectly delivered is probably less than that delivered directly from the nasal cavity to the brain due to the tightness of the BBB and extensive drug metabolism and/or elimination in the body.[9]

FACTOR AFFECTING NASAL DRUG ABSORPTION: -

Physicochemical factors

1. Molecular weight
2. Solubility & dissolution rate
3. Lipophilicity & hydrophilicity
4. Size
5. Partition coefficient

Formulation Factor

1. pH
2. Concentration
3. Excipients
4. Dosage forms

Biological factors

1. Blood flow through nose
2. Mucociliary clearance
3. Enzymatic degradation

Delivery device related factors

1.Particle size of powders. [17,24,34,40,44]

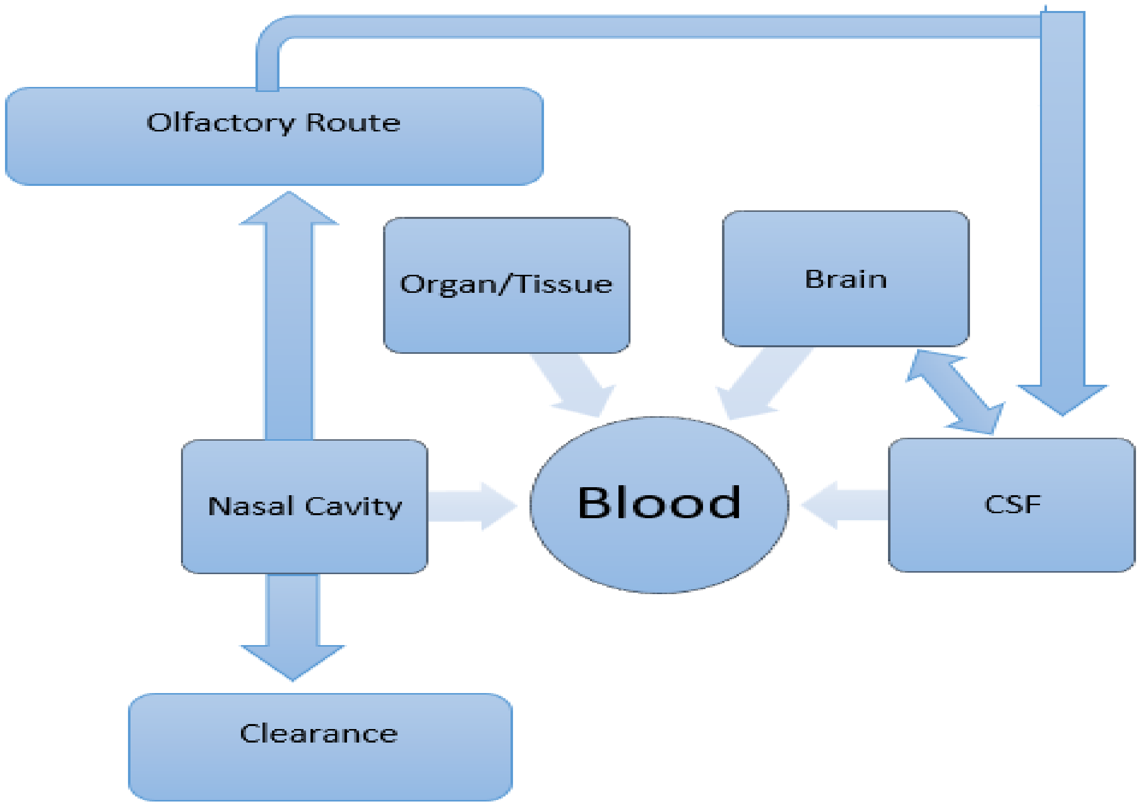

Chart-2: DRUG TRANSPORTATION

FACTORS THAT ENHANCE THE NASAL DRUG DELIVERY: -

1. Density Enhancers –

   The substances used in the expression enhances the retention time that leads to the lesser immersion of the medicine.[45]

2. Mucoadhesive Substances-

   These can be used to increase the continuance of medicines within the nasal depression to ameliorate medicine immersion.[8]

3. Ciliary Movement -

   In addition, other factors may intrude with cilia movement or the rheological parcels of the mucus, similar as the common cold wave also affect immersion.[46]

4. Saturation Enhancers –

The Saturation boosters are extensively used in the provision of medicines for increased membrane saturation.[47] The most common saturation enhancers include tight junction modulators, surfactants, cationic polymers, and cyclodextrins. The tight junctions between endothelial cells in the brain produce an effective hedge to trans- endothelial prolixity, therefore, saturation of medicine substance is largely defined.[48]

Table-:1 Comparative Study of The Different Drugs Used in Nasal Route of Drug Delivery

Disease/Condition	Drug & Carrier System	Conclusion
1.Migraine Headaches [49,58,59]	Sumatriptan loaded nanostructured lipid carriers	Nano structured formulation led to rapid absorption & bioavailability.so, provide quick relief of migraine attacks.
2.Drug targeted to Brain [50]	Domperidone	It can Quickly take up in the respiratory epithelial cells located in the lamina propria of the respiratory region.
3.Alzheimer's Disease [8]	Polymeric Nano Particles	These delivery systems can improve efficiency of drug delivery and reduction in drug side effects.
4.Microcontainers based on calcium carbonate microparticles were developed for the encapsulation of anxiolytic drug zolpidem [51]	Mucoadhesive Polymer for Zolpidem drug	The use of mucoadhesive polymer coating improve retention of drugs within the nasal cavity and thereby, improves the resultant bioavailability.
5.Alzheimer's Disease [44]	Rivastigmine Hydrogen Tartrate (RHT)	Poor penetration and lesser concentration in the brain hence requiring frequent oral dosing.
6.Brain Cancer [5]	Nano Emulsion Technology Formulation of Lomustine.	It reduces the drug toxicity and potentially increase targeting to the brain.
7.Huntington's Disease [52]	Tetrabenazine Nano Emulsion	The preparation increases in permeation rate compared to the tetrabenazine suspension.
8.Parkinson's Disease [53]	Rotigotine (RTG) solid lipid nanoparticles (SLN)	The RTG-SLNs had a particle size 129nm & In vitro drug release (99%) in phosphate buffer 7.4 for 30 h.
9.Schizophrenia [13]	Risperidone solid lipid nanoparticles.	IV SLN implies less risperidone to enter the body circulation and reduce its systemic side effects.
10.Depression [54,55]	Duloxetine Nanostructured lipid carrier (NLC)	DLX possess therapeutic effect for a longer period & 2.5 times more permeable than drug solution.

Table-2: Marketed Formulations Available for Nasal Route Administration: -

Brand name	Drug	Dosage form	Manufacture
Zicam	Multi ingredients	Spray	Church& Dwight, Inc

Atridox	Doxycycline hyclate	Spray	Tolmar Therapeutics Inc [56,51]

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