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# Nose - Brain Drug Delivery System: A review

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**ABSTRACT:** The treatment of brain disorders is challenging due to the presence of a variety of obstacles to deliver drugs to the brain. The blood brain barrier is the major obstacle to the uptake of drugs into the brain following systemic administration. Nasal to brain rout is a great deal which is a very convenient, reliable, and promising method for the systemic administration of drugs as discovered. The present review describes nasal drug delivery systems in recognizing their potential and limits. This review is an effort to provide some information about nasal to brain drug delivery system on its advantages, limitations, anatomy of nasal cavity, mechanism of drug transport, strategies to enhance nasal absorption, different approaches of nasal drug delivery.

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## INTRODUCTION:

The blood-brain barrier (BBB) represents a stringent barrier for delivery of neurotherapeutics *in vivo*. An attempt to overcome this barrier is represented by the direct transport of drugs from the nose to the brain along the olfactory and trigeminal nerve pathways [1]. Nasal delivery of drugs is taken as the convenient route of administration for delivery of drugs which is used for curing nasal congestion, nasal allergy and nasal infection. In the last few decades, the nasal route has attracted wide attention as a reliable, safe, non-invasive and convenient route to accomplish faster and higher levels of drug absorption [2]. When direct drug transport to systemic circulation and to the brain, thereby avoiding first-pass hepatic metabolism and enhancing bioavailability.

In Nasal route, the delivery of drugs from nose to the brain in sufficient quantities to achieve therapeutic levels is required for the treatment of CNS diseases [3,4]. On the other hand, there are several barriers restricting the delivery of therapeutics to the brain, such as the BBB and the Blood-Cerebrospinal Fluid Barrier [4]. The BBB is located at the cerebral microvasculature level and is critical for maintaining the CNS homeostasis, by allowing the efficient nutrient exchange between the blood and the brain tissue, while precluding the entry of xenobiotics that could impair neurological functions. It prevents both the paracellular and transcellular transport of hydrophilic, ionized and high molecular weight molecules in the circulating blood due to the complex network of tight junctions between adjacent cells, the non-fenestrated capillaries, as well as the diminished pinocytotic activity [3]. Inevitably, a number of aggressive strategies like intraparenchymal, intraventricular and intrathecal delivery (BBB disruption) and non-invasive techniques like chemical modifications, prodrug approach and conjugation of drugs with antibodies or ligands have been utilized to increase the CNS targeting of drugs. Thus, better targeting action can be achieved due to direct movement of drug from the submucosal space of the nose into the cerebrospinal fluid (CSF) compartment of the brain.

The intranasal route exploits the unique neural connection that the olfactory and the trigeminal nerves provide between the nose and CSF to deliver drugs to the brain. This route can be exploited as a potential alternative drug delivery route for efficient delivery of challenging drugs such as low molecular weight polar compounds, peptides, proteins and large proteins and polysaccharides like vaccines or DNA plasmids. Evidence of nose-to-brain transport has been reported by many scientists round the globe with Illum Lisbeth thoroughly reviewing the possibilities, problems, and solutions of nasal drug delivery [5]. Also, drug absorption across the olfactory region of the nasal mucosa provides a distinctive feature and better option to preferentially target the drugs to the brain although there are some studies that are contrary. Many potent centrally acting drugs promise to become successful therapeutic agents via the intranasal route [6].

**Advantages of Nasal drug delivery [6,7]:**

- By passing Hepatic first pass metabolism.
- Better patient compliance.
- It avoids drug degradation in the GI tract.
- It facilitates rapid drug absorption & quick onset of action.
- It improves the absorption of drugs that shows poor absorption through oral route.
- Polar compounds exhibiting poor oral absorption may be mainly suitable for this route of delivery.
- Serves as an alternative route for parenteral administration especially for protein & peptide drugs.
- Improved therapeutic efficacy and Bioavailability of drugs.
- Shows excellent bioavailability for small and low molecular weight drugs.
- Bioavailability of larger molecules can be improved using absorption enhancers.

**Limitations [7]:**

- Nasal administration is primarily suitable only for potent drugs.
- Nasal irritation.
- Drugs for continuous frequent administration may be less suitable because of harmful long-term effects.
- Rapid elimination of drug substances from nasal cavity due to mucociliary clearance poses a major problem in nasal drug delivery systems.
- Nasal cavity provides a smaller absorption surface area as compared to the gastrointestinal tract.
- Absorption enhancers used in formulation may create mucosal toxicity.
- Self-medication is also possible with this route of drug administration.

## ANATOMY OF NASAL CAVITY AND PHYSIOLOGY:

### *Nasal Cavity:*

Structurally, the nose is divided into two nasal cavities via a midline septum. The nasal cavity is extended to 12 to 14 cm long and 5 cm in height, while its total surface area and total volume are reported to range between 150 and 200 $cm^2$ and 13 to 25 ml respectively. Each cavity consists of three different regions, namely the vestibule, the olfactory region and the respiratory region. The nasal vestibule consists of the region just inside the nostrils with an area of about 0.6 $cm^2$. The respiratory region contains three nasal turbinates, the superior, the middle and the inferior turbinate. These turbinates produce turbulent airflow through the nasal passages which ensure a better contact between inhaled air and mucosal surface. The olfactory region is situated at the roof of the nasal cavity in humans and covers about 10 % of the total surface area of the nasal cavity (Fig 1).

Functionally, the nasal cavity plays an important protective role to filter, warm and humidify the inhaled air before it reaches the lower airways. It provides a supply and conditioning of air to lungs. Any inhaled particles or microorganisms are trapped by the hair of the nasal vestibule or by the mucus layer covering the respiratory area of the nasal cavity. The mucociliary clearance mechanism of the mucus layer gradually carries such particulates to the back of the throat, down the oesophagus and further into the gastrointestinal tract. Nasal mucosa also has the metabolic capability of converting endogenous materials into compounds that are eliminated more readily [5].

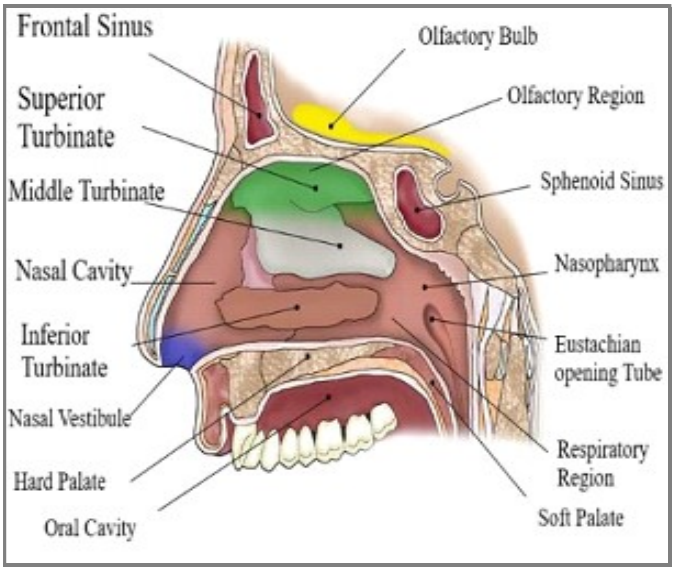


**Fig 1. The Anatomy of Nose.**

### *Respiratory Epithelium:*

The respiratory epithelium consists mainly of four types of cells, namely ciliated and non-ciliated columnar cells, mucus-containing goblet cells and basal cells. These cells facilitate active transport processes and also play a role in the prevention of drying of mucosa by trapping moisture. Additionally, respiratory epithelium is covered by 300 microvilli per cell.The respiratory mucus is a viscoelastic gel, composed of a network of high molecular weight glycoproteins called mucins, water, salts, other proteins and a small fraction of lipids, and it serves as a protective barrier due to its viscoelastic and adhesive properties and represents the first line of defence against inhaled particulates and irritants.

### *Olfactory Epithelium:*

The olfactory epithelium is a specialized epithelial tissue inside the nasal cavity that is involved in smell. In humans, it measures 9 $cm^2$ and lies on the roof of the nasal cavity about 7 cm above and behind the nostrils [8].

The olfactory epithelium is the part of the olfactory system directly responsible for detecting odours. Olfactory epithelium consists of four distinct cell types namely Olfactory sensory neurons, Supporting cells, Basal cells, Brush cells [9,10].

Olfactory sensory neurons: The olfactory receptor neurons are sensory neurons of the olfactory epithelium. They are bipolar neurons and their apical poles express odorant receptors on non-motile cilia at the ends of the dendritic knob, which extend out into the airspace to interact with odorants. The axons of the olfactory sensory neurons congregate to form the olfactory nerve. Once the axons pass through the cribriform plate, they terminate and synapse with the dendrites of mitral cells in the glomeruli of the olfactory bulb.

Supporting cells: Analogous to neural glial cells, the supporting cells are non-neural cells in the olfactory epithelium that are located in the apical layer of the pseudostratified ciliated columnar epithelium. There are two types of supporting cells in the olfactory epithelium: sustentacular cells and microvillar cells. The sustentacular cells function as metabolic and physical support for the olfactory epithelium. Microvillar cells are another class of supporting cells that are morphologically and biochemically distinct from the sustentacular cells, and arise from a basal cell population that expresses the c-KIT cell surface protein.

Basal cells: Resting on or near the basal lamina of the olfactory epithelium, basal cells are stem cells capable of division and differentiation into either supporting or olfactory cells. While some of these basal cells divide rapidly, a significant proportion remains relatively quiescent and replenishes olfactory epithelial cells as needed. This leads to the olfactory epithelium being replaced every 6 to 8 weeks [11].

Olfactory (Bowman's) glands: Tubuloalveolar serous secreting glands lying in the lamina propria of the olfactory mucosa. These glands deliver a proteinaceous secretion via ducts onto the surface of the mucosa. The role of the secretions is to trap and dissolve odiferous substances for the bipolar neurons. Constant flow from the olfactory glands allows old odours to be constantly washed away (Fig 2) [9].

### *Mucociliary Clearance:*

The mucociliary clearance mechanism is a very efficient defence mechanism in humans protecting the lungs against inhaled particulates, droplets and microorganisms. Mucus is present in two layers on the

epithelium in order to facilitate the mucociliary clearance. A viscous gel layer, the 'mucus blanket' (2 to 4 µm in thickness), floats on the serous fluid layer called the sole layer (3 to 5 µm in thickness).

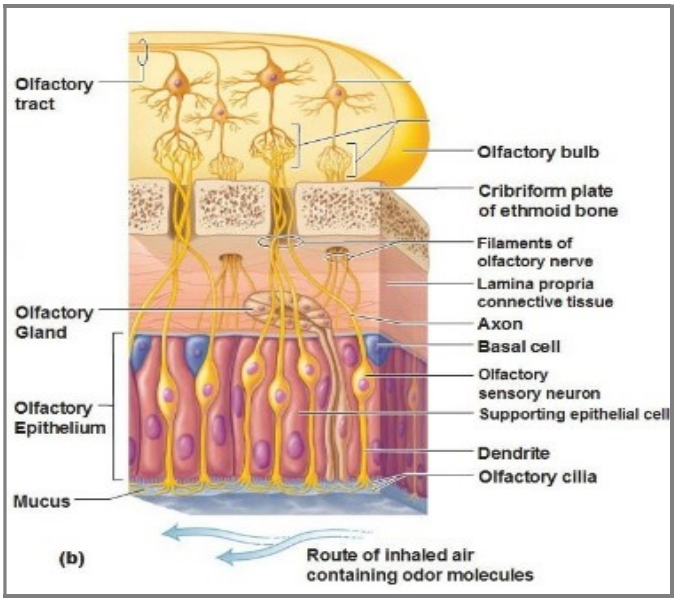


**Fig 2. Olfactory epithelium.**

The viscous gel layer is moved along by the hook shaped cilia termini during the energy-dependent 'effective stroke' phase of the ciliary motion. Cilia are up to 7 µm in length when fully extended but can fold to half this length during the recovery stroke where the hook terminus detaches from the gel layer and moves immersed in the sol layer in the opposite direction to the gel layer movement (Fig 3).

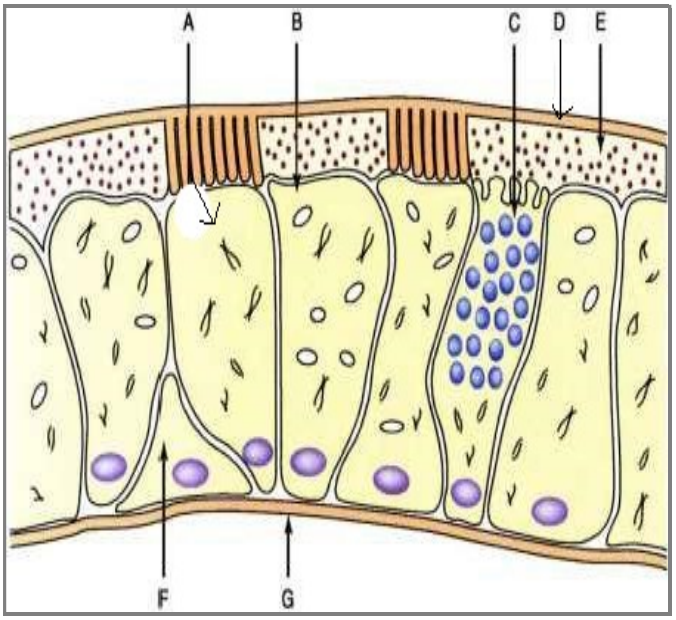


**Fig 3. Mucociliary Clearance.**
**A -Ciliated cells, B- Non-ciliated cells, C- Goblet cells, D- Gel layer, E- Sol layer, F- Basal cells, G- Basement membrane.**

Cilia are up to 7 µm in length when fully extended but can fold to half this length during the recovery stroke (return beat). During the recovery stroke, the hook terminus disengages from the gel layer and moves, immersed in the sol layer, in the opposite direction to the movement of the gel layer. The cilia beat with a frequency of 1000 strokes/min. These coordinated strokes of cilia result in the movement of mucus in one direction only from the anterior to the posterior part of the nasal cavity up to the nasopharynx. Therefore, particles applied on the nasal respiratory mucosa will be transported on the mucus to the back of the throat. The mucus flow rate is 5 mm/min (with a range of 0.5 to 23.6 mm/min) and hence the mucus layer is renewed every 15 to 20 min. In humans, mucociliary flow can be measured by means of gamma scintigraphy or the saccharine clearance test [1].

## PATHWAYS OF NOSE TO BRAIN:

Although the direct transport of several therapeutic entities to the brain through the nasal cavity has been the topic of numerous research studies, only a small fraction of the initial medication dose can in fact reach the brain, which suggests that the exact pathways and mechanisms still remain elusive. Additionally, pathways involving the vasculature, CSF and lymphatic system have been employed in transport of molecules from nasal cavity to the CNS. In order for a drug to travel from the olfactory region in the nasal cavity to the CSF or brain parenchyma, it has to cross the nasal olfactory epithelium and, depending on the pathway followed, also the arachnoid membrane surrounding the subarachnoid space (Fig 4).

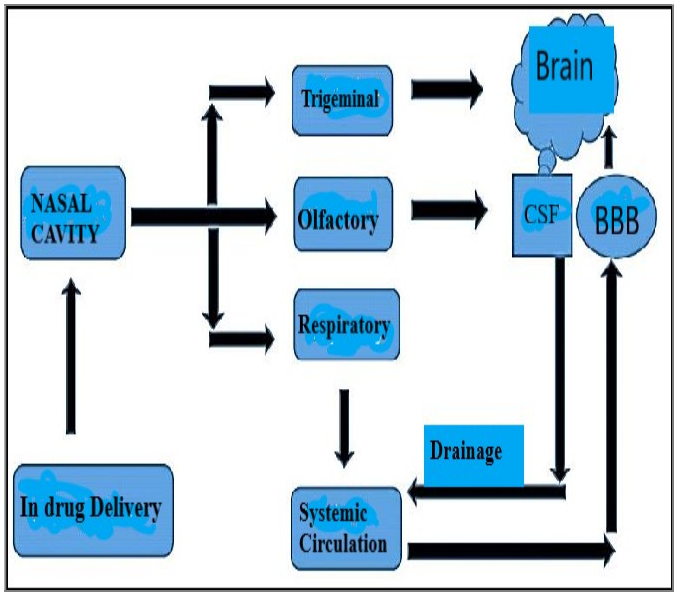


**Fig 1. Pathways of Nose to Brain drug delivery.**

In principle, one can envisage three different pathways across the olfactory epithelium:

- Transcellular pathway; especially across the sustentacular cells, most likely by receptor-mediated endocytosis, fluid phase endocytosis or by passive diffusion.
- Paracellular pathway; through tight junctions between sustentacular cells or the clefts between sustentacular cells and olfactory neurons. Nasal absorption of hydrophilic drugs most probably occurs by diffusion through aqueous channels or pores. This route is responsible for transport of hydrophilic drugs and it shows rate dependency on the molecular weight of a drug. Drugs with a molecular weight up to 1000 Da without absorption enhancer shows good bioavailability which can be extended to drugs with molecular weight up to 6000 Da with absorption enhancer.
- Olfactory nerve pathway; where drug is taken up into the neuronal cell by endocytosis or pinocytosis mechanisms and transported by intracellular axonal transport to the olfactory bulb [12].

Thus, the different modes of drug transport across the nasal olfactory epithelium are shown in Fig 5.

Various pathways have been reported to justify nose to brain drug delivery Fig 4. However, a combination of these pathways is responsible for the delivery of therapeutics to the brain following intranasal administration.

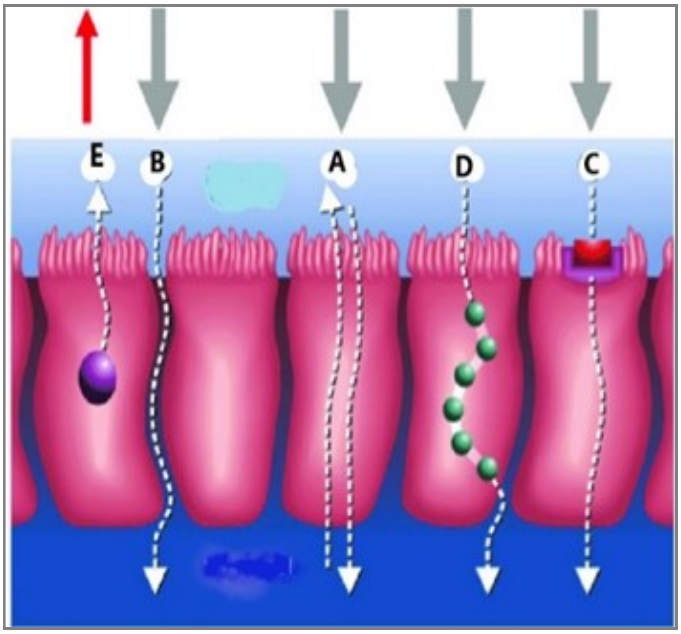


**Fig 2. Mechanisms of drug transport across nasal olfactory epithelium.**

**A: transcellular passive diffusion, B: Pore transport, C: Efflux transport D: Transcytosis and E: Carrier-mediated transport.**

***Systemic Pathway:***

Drug uptake into the brain from nasal cavity involves the direct absorption of the drug from the highly vascular nasal respiratory epithelium, lymphatic system, and its subsequent transport into the systemic circulation. Due to the rich vasculature of the respiratory epithelium than olfactory mucosa fraction of the drug was absorbed into the systemic circulation [13]. The respiratory segment comprises of combination of the continuous and fenestrated endothelium which allows the passage of drug into the blood circulation subsequently transport across the BBB to the CNS [3]. The systemic circulation does not necessarily correspond to the successive direction of the drug towards the BBB, regardless of its ability to cross it. Drug transfer from blood to the brain can alternatively occur across the choroid plexus, where the drug will initially enter the cerebrospinal fluid (CSF) at a rate inversely related to its molecular weight, and may subsequently diffuse into the brain tissue, although in minor quantities, due to a slow, diffusion-driven permeation process [14,15]. The transport to the CSF from the bloodstream is unidirectional, since the CSF is subsequently drained into the peripheral bloodstream, approximately every 5 h [16].

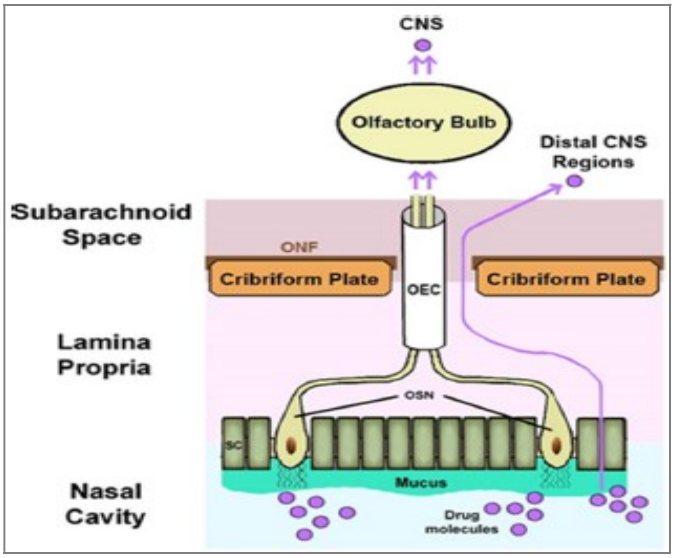


**Fig 6. Intranasal drug transport through the olfactory route to the CNS by intracellular and extracellular pathways.**

***Olfactory Pathway:***

In order for a drug to transport through the olfactory region has been widely explored as a promising approach to efficiently deliver therapeutic entities from the nasal cavity to the CSF or brain tissue, while simultaneously allowing for the prompt onset of action, reduced systemic exposure and ability to bypass the

BBB. Indeed, the absorption of the drugs along the olfactory region accounts primarily for their high exposure in the CNS, CSF and olfactory bulb [17]. Olfactory mucosa contains olfactory receptor neurons that are responsible for the transduction.

Transduction happens in olfactory receptors on the cilia. Molecules reach the olfactory receptor neurons by paracellular or transcellular mechanism. The integrity of nasal epithelium, along with the tight junctions, desmosomes, adherens junctions and space between the epithelial cells allows the entry of compounds by paracellular transport [18]. The neuronal pathway is considered to be the determining step of the nose to brain route. Drug moieties travel along axons and via nerve bundles cross the cribriform plate and reach the olfactory bulb which actually appears on the surface of the brain. From the olfactory nerves, the therapeutic moiety can enter the cerebrospinal fluid (CSF) and olfactory bulb [19]. The drug can be distributed from the CSF to the brain by mixing with interstitial fluid in the brain.

After a nasal administration of a drug, it takes only a few minutes to reach the brain via olfactory transport. Intraneuronal pathway and extra-neuronal pathway are the two different pathways of the olfactory neuronal pathway into the brain. Intra-neuronal pathway involves axonal transport and it requires hours to days for active moiety to reach different regions of the brain. In the case of an extra-neuronal pathway which involves transport through perineural channels; it takes only a few minutes to reach active moiety directly to the brain [19]. The olfactory neural pathway innervates to the deeper areas of the brain such as cortex, cerebrum and cerebellum.

### *Trigeminal Nerve Pathway:*

An important pathway connecting nasal passages to the CNS involves the trigeminal nerve pathway connecting to the tail part of the brain such as the spinal cord, the medulla and the pons. Drugs transported through the nose via trigeminal nerve pathway by intracellular transport (axonal transport) or by endocytosis. The trigeminal nerve is the largest cranial nerve and its main function lies in the conveying of chemosensory and thermosensory information to the oral, ocular and nasal mucosa [3,20]. Although the trigeminal nerve is the largest and fifth cranial nerve fibre endings are not directly exposed in the nasal cavity, it is assumed that the initial point of entry is likely from three branches (e.g., ophthalmic and maxillary and mandibular).Out of these three mainly ophthalmic and maxillary branches plays an important role in nose to brain drug delivery, the neurons from these branches pass directly through the nasal mucosa. Some segments of the trigeminal nerve also end in the olfactory bulbs [21].

Branches from the ophthalmic part of the trigeminal nerve innervate to the dorsal part of the nasal mucosa and the anterior nose but considering maxillary branch innervate to the turbinates of the nasal mucosa. Once the compounds diffuse through the mucosa of the nasal cavity, it reaches the branches of trigeminal nerves in olfactory and respiratory regions, and via brain stem transported to the axonal route.

A part of the trigeminal nerve that passes through the cribriform plate that may also involve in the delivery of therapeutics from nasal cavity to the forebrain]. Intranasally administered drug/nanoparticles absorbed from nasal cavity is passage through the mucus, this is the first step involved in absorption. After passing through the mucus, there are several mechanisms involved in the transportation through mucosa. There are para-celular, transcellular, carrier-mediated transport, receptor-mediated transport and transcytosis [22]. Paracellular route is the transport of molecules between the cells. Transcellular route refers to the transport of drugs across the cells this may occur by carrier-mediated transport by endocytosis. In transcellular route, adsorptive transcytosis mechanism involves transport of macromolecules. This Process involves interaction between the ligand in bloodstream and cell surface. This type of interaction may be due to electrostatic interaction between the positively charged ligands such as protein or macromolecules and negatively charged membrane. Nanoparticles and some compounds undergo transcytosis for the permeation.

## FORMULATIONS APPROACHES FOR NOSE TO BRAIN DRUG DELIVERY:

### *Nanoparticles:*

Nanoparticles are colloidal systems with closed structure where the therapeutic agent is either trapped within a colloidal matrix or covered the particle surface by conjugation or adsorption. They can offer sustained and controlled release of drug, and are made of polymer, lipid or combination of both. The use of nanoparticles increases the drug absorption in the brain and the nanoparticles are also used in administration to conjugate bio-recongnitive lectins to the surface of poly ethylene glycol through nasal route [23]. Based on the

generations of lipid nanoparticles evolved, they are categorized in following types [24].

- Solid lipid nanoparticles (SLN).
- Nanostructured lipid carriers (NLC).
- Polymer-lipid hybrid nanoparticles (PLN).
- Lipid-drug conjugate (LDC).

### *Polymeric Micelles:*

Advances in the syntheses of block copolymers have led to the formation of polymeric micelles that may serve as nanoscopic drug carriers. They are known as self-assemblies of block copolymers, and promising nanocarriers for drug and gene delivery. For drug delivery, polymeric micelles have been prepared from biodegradable and biocompatible block copolymers [25].

### *Liposomes:*

Liposomes are lyotropic liquid crystals composed of relatively biocompatible and biodegradable materials and consist of an aqueous core entrapped by one or more bilayers of natural and/or synthetic lipids. Liposomes have been widely investigated since 1970 as drug carriers for improving the delivery of therapeutic agents to specific sites in the body. The success of liposomes as drug carriers has been reflected in a number of liposome-based formulations, which are commercially available [24]. Liposomes can be used for targeting and introduction of therapeutic agents to specific sites by conjugation or cross linking of targeting moiety to the native liposome or by surface modification of the fabricated liposomal formulation [26].

### *Nasal Drops:*

They are the most convenient and simple system developed for nasal drug delivery. Nose drops can be delivered with a squeezy bottle. These pharmaceutical formulations are often recommended for treating local conditions, which include suffering some challenges such as microbial growth, mucosal dysfunction, and non-specific loss of the nose or lower back. The featured disadvantage of this system is the lack of the dose precision, and therefore, nasal drops may not be useful for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays [27].

### *Nasal Inserts:*

Nasal inserts are solid dosage forms which are unique and bioadhesive used for extended systemic delivery of drugs through the nasal cavity. The principle involved in this is to absorb nasal secretion from the mucosa after administration and to avoid foreign body sense by forming gel in the nasal cavity [27].

### *Nasal Gels:*

Until the recent development of precise dosing devices, there was not a lot of interest during this system. Nasal gels are high viscosity thickened solutions or suspensions(27).The benefits of a nasal gel include the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation using emollient excipients, and target to mucosa for higher absorption [28].

## CONCLUSION:

Direct nose to brain drug delivery system is a potential strategy to overcome the obstacles presented by the BBB. Intranasal delivery bypasses the BBB to target CNS, reducing systemic exposure of the drug, thereby reducing the systemic side effects. It is an attractive option of drug delivery due to its non-invasiveness. A successful drug delivery system is one which offers commercial applicability to pharmaceutical industries for large-scale production.

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## REFERENCES:

1. Pardeshi CV, Veena SB. Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood brain barrier an excellent platform for brain targeting. Expert Opin. Drug Deliv, 2013; 10(7): 957-972.
2. Pardeshi CV, Rajput PV, Belgamwar VS, Tekade AR. Formulation optimization and evaluation of spray-dried mucoadhesive microspheres as intranasal carriers for Valsartan. J Microencapsul, 2011; 29: 103-14.
3. Kozlovskaya L, Abou-Kaoud M, Stepensky D. Quantitative analysis of drug deliver to the brain via nasal route. J Controll Rel, 2014; 198: 133-140.
4. Warnken Z, Smyth C, Watts A, Weitman S, Kuhn J. Formulation and device design to increase nose to brain drug delivery. J Drug Deliv Sci Technol, 2016; 35: 213-222.
5. Illum L. Nasal drug delivery-possibilities, problems and solutions. J Control Rel, 2003; 87(1-3): 187-198.

6. Misra A, kher G. Drug Delivery Systems from Nose to Brain. Curr Pharm Biotechnol, 2012; 13: 2355-2379.
7. Moran, David T, Rowley JC, Jafek BW, Lovell MA. The fine structure of the olfactory mucosa in man. J of Neurocytol, 1982; 11(5): 721-746.
8. Mistry A, Stolnik S, Illum L. Nanoparticles for direct nose-to-brain delivery of drugs. Int J Pharm, 2009; 379: 146-157.
9. Mistry A, Stolnik S, Illum L. Nanoparticles for direct nose-to-brain delivery of drugs. Int J Pharm, 2009; 379: 146-157.
10. Garcia E, Andrieux K, Gil S. Colloidal carriers and blood-brain barrier (BBB) translocation a way to deliver drugs to the brain. Int J Pharm, 2005; 298: 274-292.
11. Selvaraj K, Gowthamarajan K, VV, Reddy S. Nose to brain transport pathways an overview: potential of nanostructured lipid carriers in nose to brain targeting. Int J Artificial Cells, Nanomed Biotechnol, 2018; 46(8): 2008-2095.
12. Dhuria SV, Hanson LR, Frey WHI. Novel Vasoconstrictor Formulation to Enhance Intranasal Targeting of Neuropeptide Therapeutics to the Central Nervous System. J Pharmacol Exp Ther, 2009; 328: 312-320.
13. Pardridge WM. Drug transport in brain via the cerebrospinal fluid, Fluids Barrier CNS, 2011; 8:. 8-12.
14. Bourganis V, Kammona O, Alexopoulos A, Kiparissides C. Recent advances in carrier mediated nose-to-brain delivery of pharmaceutics. Eur J Pharm Biopharm, 2018; 128: 337-362.
15. Medina C, Santos-Martinez MJ, Radomski A. Nanoparticles: Pharmacological and toxicological significance. J Pharmacol, 2009; 150: 552-558.
16. Dhuria SV, Hanson LR, Frey WH. Novel vasoconstrictor formulation to enhance intranasal targeting of neuropeptide therapeutics to the central nervous system. J Pharmacol Exp Ther, 2009; 328: 312-320.
17. Cometto-Muñiz JE, Simons C. Trigeminal chemesthesis. In: Doty RL, editor. Handbook of Olfaction and Gustation. 3rd ed. US: Wiley-Blackwell; 2015. pp. 1091-1112.
18. Dhuria SV, Hanson LR, Frey WH. Intranasal delivery to the central nervous system mechanisms and experimental considerations. J Pharm Sci, 2010; 99: 1654-1673.
19. Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drug Deliv Tech, 2002; 7(18): 967- 975.
20. Alam MI, Beg S, Samad A, Baboota S, Ali AA, Akbar M. Strategy for effective brain drug delivery. Euro J Pharm Sci. 2010; 40(5): 385-403.
21. Goyal P, Goyal K, Kumar SGV, Singh A, Katare OP, Mishra DN. Liposomal drug delivery systems – Clinical applications. J Acta Pharma, 2005; 55: 1-25.
22. Patel Z, Patel B, Patel S, Pardeshi C. Nose to Brain Targeted Drug Delivery bypassing the Blood-Brain Barrier: An overview. Drug Invention Today, 2012; 12: 601-615.
23. Prajapati J, Patel K, Agrawal YK. Targeted drug delivery for central nervous system: a review. Int J Pharm Pharm Sci, 2012; 3: 32-38.
24. Alnasser S. A Review On Nasal Drug Delivery System And Its Contribution In Therapeutic Management. Asian J Pharm Clin Res, 2019; 12(1): 40-45.
25. Hardy JG, Lee SW, Wilson CG. Intranasal drug delivery by spray and drops. J Pharm Pharmacol, 1985; 37: 294-297.
26. Jyothi SL, Gowda DV, Gupta NV, Osmani R, Ali MO. Nose to Brain Drug Delivery: New Perspectives for Old Problems -An Enlightening Review. J Chem Pharm Res, 2017; 9(7): 111-122.
27. Schaefer ML BBSWea. Trigeminal collaterals in the nasal epithelium and olfactory bulb: a potential route for direct modulation of olfactory information by trigeminal stimuli. J Comp Neurol, 2002; 444: 221-226.
28. Kwon GS. Polymeric micelles as new drug carriers. Adv Drug Deliv Rev, 1996: 21(2): 107-116.


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