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NOSE TO BRAIN DELIVERY FOR TREATMENT OF NEUROLOGICAL DISORDERS: A POTENTIAL ROUTE FOR BRAIN TARGETING

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ABSTRACT
Delivery of drug to the brain is Major challenge due to Presence of two Physiological barriers that restricts the delivery of drug to the Central Nervous System **[CNS]**, The Blood Brain Barrier **[BBB]** and Blood Cerebrospinal Fluid Barrier **[BCSFB]**. The **BBB** is present in most organisms in which the **CNS** is well-developed and it protects the brain from the foreign matter and maintains the cerebral homeostasis. The drug has to be delivered to the brain for treating **CNS** diseases like Alzheimer's, Meningitis, Schizophrenia, Migraine and Parkinson's diseases. These nerve pathways initiate in the nasal cavity at olfactory neuroepithelium and terminate in the brain. The drug is administered for the treatment of **CNS** issues for treating **CNS** disorders and systemic administration for sedatives, analgesics, corticosteroid hormones, hormones, vaccines and cardiovascular drugs through the nasal mucosa. The BBB, which is present at the capillary level regulates and monitors the entry of all small and large molecules entering into the brain. Excitotoxicity and apoptosis are other reasons for neurodegeneration. Hyperactivity of glutamate receptors leads to deleterious effects on neurons, which can be attributed to the over production of free radicals.

KEYWORDS: Nose to brain delivery, Blood Brain Barrier, Central Nervous System, Blood Cerebrospinal Fluid Barrier, Drug Transport and nasal devices.

INTRODUCTION
Nose to brain drug delivery System is a targeted approach in which drug is targeted in nasal route for systemic effect. Nasal drug delivery system is recognized as an excellent route of therapeutic compounds including in Pharmaceuticals and Biopharmaceuticals. Nasal Mucosa is considered as potential administration route to achieve rapid and higher level of drug absorption. Nasal cavity having a Larger surface area, porous endothelial membrane, high total blood flow and avoidance of problem of first pass metabolism are this few reasons. Researchers are interested in nasal route for the systemic delivery of medications due to their high degree of permeability of nasal mucosa. Delivery of drug to the brain is Major challenge due to Presence of two Physiological barriers that restricts the delivery of drug to the Central Nervous System **[CNS]**, The Blood Brain Barrier **[BBB]** and Blood Cerebrospinal Fluid Barrier **[BCSFB]**.[1]

Nasal delivery of drug is taken as the convenient route of administration for delivery of drugs which is used for curing nasal congestion, nasal allergy and nasal infection. The drug has to be delivered to the brain for treating **CNS** diseases like Alzheimer's, Meningitis, Schizophrenia, Migraine and Parkinson's diseases. Over 36 million people in the world have **CNS** related diseases and disorders, by 2030 about 66 million the numbers will continue to rise to about 66 million by 2030 and projected to be around 115 million by 2050. The study conducting experiments on animal through nasal drug delivery route shows that 35-40 substances reach the central nervous system examples, carbamazepine, dopamine, neurotoxic metals, local anaesthetics, carboxylic acids and the nerve growth factor. The nasal cavity and brain are connected from peripheral circulation by olfactory or trigeminal or respiratory pathway.

The drug is administered for the treatment of **CNS** issues for treating **CNS** disorders and systemic administration for sedatives, analgesics, corticosteroid hormones, hormones, vaccines and cardiovascular drugs through the nasal mucosa. The choroid plexus epithelium, cerebral capillary endothelium and the arachnoid membranes consists of layers of cell called blood brain barrier. These epithelium membranes are connected by tight junctions. The blood separates the cerebrospinal fluid and brain. These endothelium tight junctions are 100 times tighter compare to other capillary endothelium junction. The quercetin liposomes are delivered through intranasal route, a non-invasive delivery system has high

bioavailability than oral route owing to decreased hepatic metabolism. The distance from nasal to brain is shorter, penetration through brain is easy. Quercetin liposomes improve memory impairment.[2]

The nasal cavity has been employed not only as a portal for the local, but also for the systemic delivery of certain therapeutic agents [examples, peptides, proteins, stem cells, etc.], due to its large surface area and high degree of vascularisation. Compared to conventional drug delivery approaches, which fall short in overcoming the BBB, intranasal delivery can provide an unprecedented opportunity to administer drugs to the **CNS** in a targeted and non-invasive manner compared to intra-cerebroventricular or intra-parenchymal injections. This can be achieved by granting direct access to the brain via the olfactory and trigeminal nerve pathways, circumventing this way the **BBB** and the pre-systemic gastrointestinal and hepatic elimination.

This drug administration pathway is also associated with enhanced safety, increased patient compliance, ease of administration, rapid onset of action, as well as with minimized systemic exposure. However, despite its numerous advantages, the direct nose-to-brain delivery of therapeutic entities is severely hampered by insufficient bio-availabilities, cytochrome P450-mediated degradation, short retention times, restrictions imposed by the geometry of the nasal cavity [examples, small volume, limited surface area of the olfactory region, etc.], as well as lack of targeting specificity to the affected area of the brain. Therefore, the direct Nose-to-Brain delivery has mostly been restricted to the administration of extremely potent molecules.[3]

Advantages of Intranasal Drug Delivery

- Rapid drug absorption via highly vascularised mucosa
- Ease of administration, non-invasive
- Improved bioavailability
- Improved convenience and compliance
- Self-administration
- Large nasal mucosal surface area for dose absorption
- Avoidance of the gastrointestinal tract and first-pass metabolism
- Rapid onset of action
- Lower side effects
- Drugs which cannot be absorbed orally may be delivered to the Systemic circulation through nasal drug delivery system.

Disadvantages of Intranasal Drug Delivery

- Some drugs may cause irritation to the nasal mucosa
- Nasal congestion due to cold or allergies may interfere with absorption of drug.
- Drug delivery is expected to decrease with increasing molecular weight.
- Frequent use of this route leads to mucosal damage
- The amount of drug reaches to different regions of the brain and spinal cord varies with each agent.[4]

Limitations of Nasal Drug Delivery

- There is a risk of both of irreversible damage of the cilia of the nasal mucosa and local side effects from both constituents and substances additional to the dosage form.
- There can be a mechanical loss of the dosage form in other parts of the respiratory system, for example, lungs due to the inappropriate technique of administration.
- Some of the surfactants used as a chemical catalyst and may cause or even dissolve the membrane at high concentrations.[5]

Neurological Disorders

It has been estimated that approximately 35.6 million individuals are suffering with dementia worldwide. The researchers speculate that these numbers will double almost every 20 years and may reach up to 65.7 million in 2030 and 115.4 million in 2050. The neurological diseases, which affect the brain and **CNS**, are generally caused due to two major reasons: neurodegeneration and neuroinflammation. The cause and exact mechanism of neurodegeneration is still unknown but it can be well associated with the age. Individuals who have a family history of any neurodegenerative disease are more prone to such diseases.

Excitotoxicity and apoptosis are other reasons for neurodegeneration. Hyperactivity of glutamate receptors leads to deleterious effects on neurons, which can be attributed to the over production of free radicals. It is believed that p53 apoptotic pathway is activated at the time of stress, which further leads to programmed cell death. The mutant Cu, Zn-Superoxide Dismutase 1 **[SOD1]** has been shown to exert toxic effect on motor neurons in C. elegans's Amyotrophic Lateral Sclerosis **[ALS]** model. When human wild type or G93A **SOD1** was specifically expressed in motor neurons of C. elegans, it caused defects related to locomotion, which recapitulates some of the characteristic features of **ALS**, which include age-associated motor neuron dysfunction and motor neurons degeneration with respect to **SOD1** aggregation.

The Bristrol strain of N2 worms was used in this study and standard C elegans techniques were employed. Five different mutant strains were used in the study and the gene expression analysis was done by real time Polymerase Chain Reaction **[PCR]** using respective forward and reverse primers. The locomotory analysis was done in the growth media. It was calculated as the distance travelled in 30 seconds, which was divided by the length of the body.[6]

Configurational Parameters Pertinent To Intranasal Administration[3]

The main morphological and structural properties of the nasal cavity are discussed below in order to gain an insight into its elaborate geometry and distinct characteristics related to the Nose-to-Brain delivery of drugs. Thorough understanding of these crucial configurational aspects is essential for the identification of the exact mechanism governing the administration of medications across this pathway, which would in turn take the formulation development to a whole new level by achieving increased therapeutic efficacies and enable the development of successful clinical formulation candidates.

The Nasal Cavity[3]

Alongside with the oral cavity, the nasal cavity comprises an external opening for the respiratory system, providing a portal for the entry of air before its subsequent flow to the lower airways. The nasal cavity plays a pivotal role in essential physiological functions, such as humidity and temperature regulation of the inhaled air, particulate and dust filtration and olfaction processes. From a structural perspective, the nasal septum divides the nose longitudinally into two identical halves, each of which is comprised by three different regions, namely the vestibule [with a surface area of ~0.6 cm^2], the olfactory [with a reported surface area of 2–12.5 cm^2], and the respiratory regions.

During the inhalation process, the air enters through the nostrils into the nasal vestibule and is then directed through the flexible nasal valve [the narrowest aperture of the respiratory tract], into the main nasal chamber. Cumulative evidence has suggested that only [15–20%] of the inhaled air reaches the olfactory region, due to the anatomic configuration of the nasal cavity.

The Respiratory Epitheliuma[3]

A ciliated pseudostratified columnar epithelium, called respiratory epithelium or Schneiderian membrane, lines the respiratory region, which occupies the greatest part of the nasal cavity [~80–90%] of the total surface area. The respiratory epithelium [Figure 1] is the major site for systemic drug absorption, primarily due to its large microvilli-covered surface area and its high degree of vascularisation. In fact, it receives its blood supply from an arterial branch of the maxillary artery. The respiratory epithelium is covered by a double-layered mucus gel, consisted of the low viscocity pericilliary layer, which extends 3–5 μm in thickness and surrounds the motile cilia [2–4 μm in length] and the overlying viscous gel layer, which extends 2–4 μm in thickness.

This particular ability of the cilia to perform a coordinated sweeping movement with a frequency of approximately 1000 S/min, translates into mucus shedding by vectorial propulsion towards the pharynx, which, along with the continuous mucus secretion process, results to mucociliary clearance, that exerts its protective effect by entrapping and removing inhaled particulates, irritants and microbes, which are transported posteriorly with an approximate rate of 1–30 mm/min until they get inactivated by acid- and enzyme-mediated lysis in the stomach. This can lead to the rough estimation that the respiratory mucus layer is renewed every 10–20 min.

The Olfactory Epithelium[3]

The olfactory system has attracted significant scientific interest among the components of the nasal cavity, due not only to the ability of its neurons to detect odorants and provide the sense of smell, but also for its ubiquitous ability to provide a portal for direct delivery of medications to the brain. From a structural perspective, the olfactory mucosa **[Figure 1]** consists of a ciliated chemosensory pseudostratified columnar epithelium and is situated on the superior turbinate and bilaterally on the nasal septum, while it is completely surrounded by respiratory epithelium.

The olfactory mucosa also involves the lamina propria, which is located beneath the epithelial basement membrane and apart from a dense capillary network, contains lymphatic vessels, olfactory axon bundles, autonomic nerve fibers, the maxillary branch of the trigeminal nerve and the mucus-secreting Bowman's glands, which account for the secretion of the overlying mucus gel layer. In contrast to the respiratory epithelium, the olfactory mucosa receives its blood supply from ophthalmic artery branches, and the cilia of the olfactory epithelium are longer [i.e., over 50 μm and non- motile]. Although there exist significant variations in the reported values, the olfactory region in humans occupies [2–12.5 cm^2], which represents a minor fraction of the total surface area of the nasal cavity [approximately 1.25–10%], while it is around 60 μm thick. It should be noted that the exact morphology and structure [examples, olfactory surface area, cellular composition] of the olfactory system and related structures may vary significantly among species, which reflects the major differences in the sensing ability and olfaction between human subjects and other species.

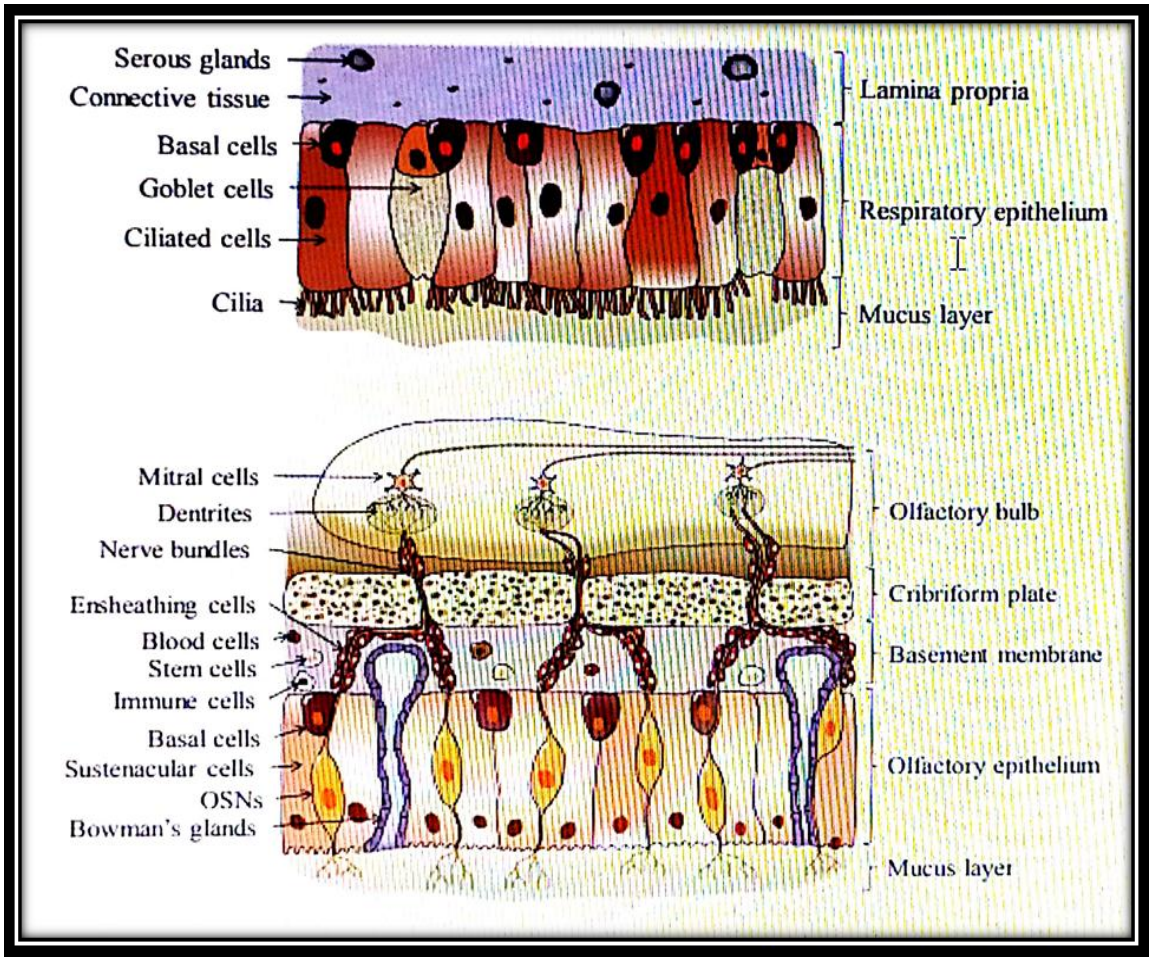

Figure No. 1: Two distinct types of pseudostratidfied epithelia located in the nasal cavity: [a] the respiratory epithelium, which lines the upper airways and is mainly comprised by goblet, basal and ciliated cells and [b] the olfactory epithelium located on the roof of the nasal cavity, which mainly containing the ciliated receptor neurons, the basal and the sustenacular cells.[3]

Anatomical and Physiological Consideration for Intranasal Delivery[5]

Nasal cavity can anatomically be segregated into five different regions: The nasal vestibule, atrium, respiratory area, olfactory region, and the nasopharynx **Table No. 1.** The nasal cavity is divided into two symmetrical halves by the nasal septum [comprised bone and cartilage], each cavity has volume up to approximately 7.5 mL and a surface area around 75 cm^2. The nasal cavity extends posteriorly to the nasopharynx. The most anterior part of the nasal cavity, the nasal vestibule opens at the face through the nostrils.

The atrium is an intermediate region between the vestibule and the respiratory region. The respiratory region occupies the major part of the nasal cavity which possesses lateral walls dividing it into three sections: Inferior **[C1]**, middle **[C2]**, and superior **[C3]** nasal turbinate's. These folds provide the nasal cavity with a very high surface area of about 150 cm2 in humans compared to its small volume. The respiratory region is richly supplied with blood, and receives the maximum amount of nasal secretions, rendering it most suitable for the permeation of compounds. The olfactory region situated above the superior nasal turbinate which possesses ciliated olfactory nerve cells for smell perception. The total surface area of the olfactory epithelium is about 200–400 mm^2.

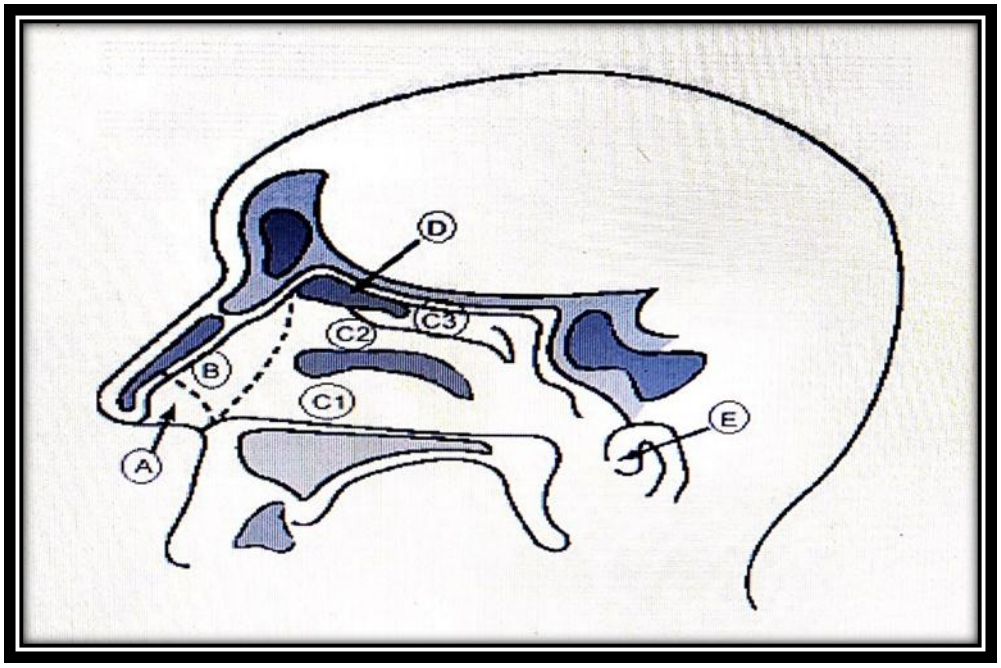

Figure No. 2: Sagittal section of human nasal cavity showing the [A] Nasal Vestibule, [B] Atrium, [C] Respiratory Region [C1] Inferior Turbinate, [C2] Middle Turbinate [C3] Superior Turbinate [D] Olfactory Region and [E] Nasopharynx.[7]

Table No. 1: Structural features of various regions and their impact on the permeability of nasal cavity.[5]

Sr. No.	Region	Structural features	Permeability
1	Nasal vestibule	Nasal hairs [vibrissae] Epithelial cells are stratified, squamous, and keratinized Sebaceous glands present.	Least permeable due to the presence of keratinized cells, very resistant to hydration and can withstand insults from noxious substances of the environment.
2	Atrium	Transepithelial region Stratified squamous cells present anteriorly and pseudostratified cells with microvilli present posteriorly The narrowest region of the nasal cavity.	Less permeable as it has small surface area and stratified cells are present anteriorly.
3	Respiratory region [inferior turbinate middle turbinate superior turbinate]	Pseudostratified ciliated columnar cells with microvilli [300 per cell], large surface area receives maximum nasal secretions due to the presence of seromucous glands, nasolacrimal duct, and goblet cells Richly supplied with blood for heating and humidification of inspired air, the presence of paranasal sinuses.	Most permeable region due to large surface area and rich vasculature.
4	Olfactory region	Specialized ciliated olfactory nerve cells for smell perception Receives ophthalmic and maxillary divisions of the trigeminal nerve.	Direct access to cerebrospinal fluid.
5	Nasopharynx	The upper part contains ciliated cells, and the lower part contains squamous epithelium.	Receives nasal cavity drainage.

Nasal drug delivery system Comparision between Oral, Parenteral and Transdermal drug delivery system [DDS][1]

Nasal drug delivery system is a novel approach of drug delivery system in which, drug is targeted in nose to brain. It is a unique approach to target the drug direct from nose to brain bypassing the BBB. The nasal drug delivery system comparison with oral, parenteral and transdermal drug delivery system is reported in **Table No. 2.**

Table No. 2: Nasal DDS Comparision between Oral, Parenteral and Transdermal DDS.

Sr. No.	Parameters	Nasal	Oral	Parenteral	Transdermal
1	Higher Plasma drug levels	Yes	No	Yes	Yes
2	BBB and CSF bypass	Yes	No	No	No
3	Rapid onset	Yes	No	Yes	Yes
4	Pain at the site of administration	No	No	Yes	No
5	Mucosal irritation	No	Yes	No	Yes
6	Systemic activity	Yes	No	Yes	Yes
7	Self-administration	Yes	Yes	No	Yes
8	Patient compliance	High	High	Low	Low
9	Drug degradation	No	High	No	Low
10	Hepatic first pass metabolism	No	Yes	No	No
11	Targeted delivery	Yes	No	Yes	Yes

Variable Factors Affecting the Permeability of Drugs through the Nasal Mucosa[7]

Biological

Structural Features

The structural features of the regions those are responsible for the permeability of the nasal cavity. Three tubinates: inferior **[C1]**, middle **[C2]** and superior **[C3]** tubinate, are mainly responsible for heating and humidification of the cavity. The presence of microvilli on cells greatly increases the area available for permeation of drugs.

Biochemical Changes

Nasal mucus acts as an enzymatic barrier to the delivery of drugs because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, and also peptidases and proteases. These enzymes are responsible for the degradation of drugs in the nasal mucosa.

Physiological Factors

Blood Supply and Neuronal Regulation

Nasal cycles of congestion [increased blood supply resulting from parasympathetic stimulation] and relaxation [decreased supply resulting from sympathetic stimulation] regulate the rise and fall in the amounts of drug permeated, respectively. The increased permeability of a compound results from parasympathetic stimulation.

Nasal Secretions-[Solubility of Drug in Nasal Secretions]

A drug needs to be solubilized before it permeates. In addition to almost 90% water, nasal secretions also contain mucin [2%], salts [1%], proteins [1%; mainly albumin, immunoglobulins, lysozyme, lactoferrin, and so on] and lipids. Thus, a drug needs to have appropriate physicochemical characteristics for dissolution in nasal secretions. This can best be studied in the case of levodopa, where the use of water-soluble prodrugs of L-dopa via the nasal route has been shown to increase absorption.

pH of the Nasal Cavity

Greater drug permeation is usually achieved at a nasal pH that is lower than the drug's pKa. This is because; under such conditions the penetrating molecules exist as unionized species. A change in the pH of mucus can affect the ionization and thus increase or decrease the permeation of drug, the ideal pH of a formulation should be within 4.5-6.5 and if possible the formulation should also have buffering capacity.

Mucociliary Clearance and Ciliary Beat Frequency

Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min by **MCC**. Reduced **MCC** increases the time of contact between a drug and the mucus membrane and subsequently enhances drug permeation; whereas, increased **MCC** decreases drug permeation.

Formulation

Physicochemical Properties of Drug

Molecular Weight and Size

Molecular weight and lipophilicity/hydrophilicity act together to determine the drug permeation. Bioavailability ranges from 0.5% to 5% for compounds with molecular weight around 1 kDa. E.g, proteins and peptides. In the case of lipophilic compounds, a direct relationship exists between the MW and drug permeation whereas, water soluble compounds depict an inverse relationship. Drugs with molecular weight less than 300 Da mostly permeate through aqueous channels of the membrane regardless of physicochemical properties of the drug.

Solubility

As nasal secretions are more watery in nature; a drug should have appropriate aqueous solubility for increased dissolution.

Lipophilicity

On increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. In one study on intranasally administered corticosteroids, a high degree of lipophilicity diminished the water solubility of corticosteroids in the nasal mucosa and, therefore, the amount of drug swept away by mucociliary clearance increased considerably. However, excess hydrophilicity is also known to decrease the systemic bioavailability. So balance between both the factors is necessary.

pKa and Partition Coefficient
As per the pH partition theory, unionized species are absorbed better as compared with ionized species and the same holds true in the case of nasal absorption.

Physicochemical Properties of Formulation
pH and Mucosal
Irritancy to avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5-6.5 which also results in efficient drug permeation and prevents the growth of bacteria.

Viscosity/Density
A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. Highly viscous formulations interfere with the normal functions and thus alter the permeability of drugs.

Area of Nasal Membrane Exposed
Increased bioavailability was observed when ointment was applied in both the nostrils which resulted in the conclusion that, as the area of mucus membrane exposed increases, it results in increased permeation.

Dosage Form
Nasal drops are the simplest and most convenient dosage form but, the exact amount that can be delivered is not an easy task to maintain. Also the, rapid nasal drainage is a problem with drops. Solution and suspension sprays are preferred over powder sprays because powder results in mucosal irritation. Metered-dose gel devices have been developed that accurately deliver drug. Gels reduce the postnasal drip and anterior leakage, and localize the formulation in mucosa. Lipid emulsions, microspheres [using chitosan, carbopol 934P and lactose], liposomes, proliposomes, films and niosomes have already been developed as efficient carriers in case of nasal delivery.

Lipophilic drugs are transported transcellularly by an efficient concentration-dependent passive diffusion process, by receptor or carrier mediation and by vesicular transport mechanisms as in case of propanolol, progesterone, pentazocine and fentanyl etc. These drugs are reported to be absorbed rapidly and efficiently when given intra- nasally. For such drugs, it is possible to obtain pharmacokinetic profiles similar to those obtained after an intravenous injection, where in case bioavailability for some drugs approaching up to 100%. Polar drugs are believed to pass through the epithelium via the gaps or pores between the cells (the tight junctions). The size of these channels is less than 10 Å. The nasal absorption of more polar compounds is poor, with bioavailability not exceeding 10% for small molecular weight drugs [examples, alniditan, morphine, sumatriptan] and even less than 1% for peptides such as insulin, calcitonin and leuprolide.

The Major Factors Governing Nasal Absorption Include

- Low membrane permeability, especially for the larger molecular weight drugs.
- A rapid clearance of the drug formulation from the nasal cavity as a result of the mucociliary clearance mechanism.
- Enzymatic degradation of the drug in the nasal cavity.[7]

Blood Brain Barrier [BBB][6]
The brain is a well-protected organ. There are numerous gateways to enter brain parenchyma and the two most important gateways are blood circulation, that is the systemic route and **CSF**. The **BBB** is present in most organisms in which the **CNS** is well-developed and it protects the brain from the foreign matter and maintains the cerebral homeostasis. The **BBB** is formed by the endothelial cells, which are the basic structural unit of the capillary walls. In human brain, there exist about 100 billion capillaries corresponding to total length of approximately 650 km and total surface area of approximately 20 m^2. Thus, the brain endothelium forms the anatomical and functional site of **BBB [Figure 3].**

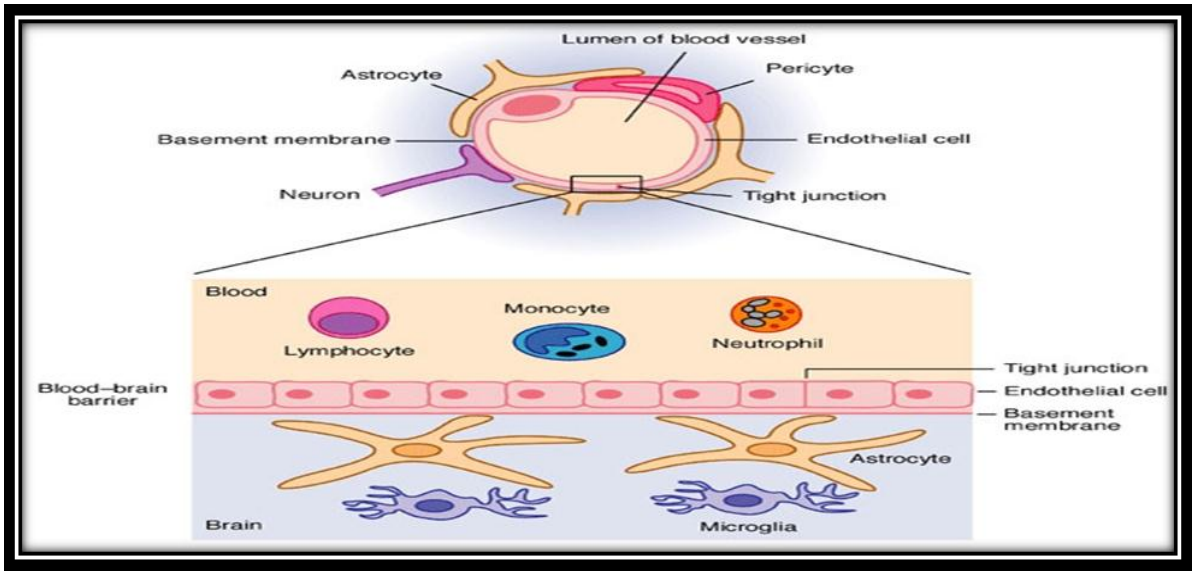

Figure No. 3: The Blood Brain Barrier.

The characteristics features of the BBB are as follows: **[i]** the lack of fenestrations with very few pinocytic vesicles, **[ii]** existence of Tight Junctions **[TJ]** between adjoining endothelial cells and associated complex of transmembrane proteins like Junctional Adhesion Molecule 1 **[JAM 1]**, claudin, occludin, zona occludens etc. [Figure **4**] and **[iii]** limited passage of the immune cells due to paucity of lymphatic drainage and major histocompatibility complex **[MHC]** antigens. Apart from the brain capillary endothelial cells, the extracellular base membrane, astrocytes, adjoining pericytes, microglia, and the cerebral microvasculature endothelium are integral part of **BBB** support system. The **BBB** thus acts as a barrier and prevents the entry of molecules in the brain parenchyma from the blood capillary network. The **BBB** restricts the entry of almost all of the large molecules and 98% of the small sized molecules.

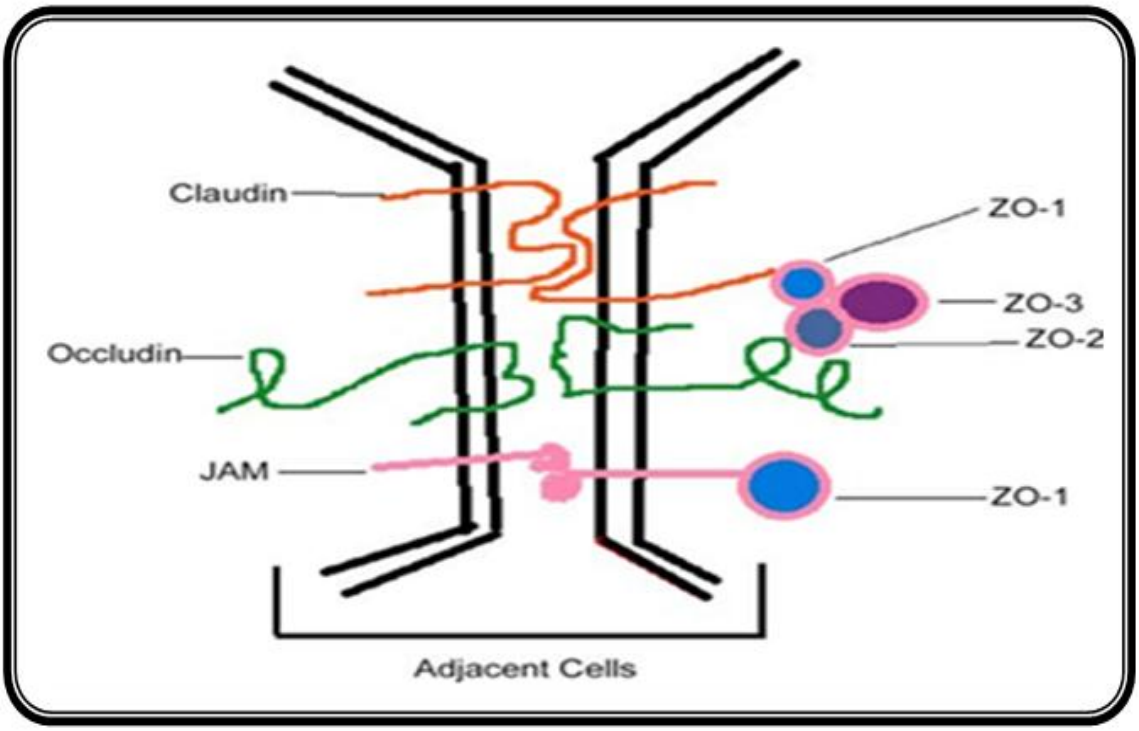

Figure No. 4: The tight junctions [TJ] between the adjacent endothelial cells formed by the assembly of trans-membrane proteins.

A second barrier to the brain is also present, which is established by the epithelial cells of the choroid plexus that are in direct contact with the cerebrospinal fluid and it is known as blood cerebrospinal fluid barrier

[BCSFB]. It is secreted across the choroid plexus epithelial cells into the brain ventricular system. The third barrier to the brain is constituted by the avascular arachnoids epithelium, underlying the dura and it completely encloses the **CNS**, which in turn accomplishes the segregation between the extracellular fluids of **CNS** and the rest of the body. The contribution of this barrier is less significant in comparison to the BBB and **BCSFB**.[6]

Routes of Drug Administration to CNS[6]

The routes of drug administration to **CNS** can be broadly grouped into two categories: systemic administration and direct **CNS** administration **[Table No. 3]**

Table No. 3: Different routes of drug administration to CNS.

Sr. No.	Systemic	Direct to CNS
1	Intravenous	Intra-cerebral
2	Intra-arterial	Intra-ventricular
3	Intranasal	Intra-thecal

Systemic Administration

For **CNS** drug delivery, systemic administration is achieved by following three methods: intra-venous, intra-arterial, and intra-nasal administration.

Intravenous

The drugs, which are administered intravenously, are generally in the form of injectable. For **CNS** and brain drug delivery, intravenous route is the most widely used route of drug administration. Most of the polymeric and liposomal based drug formulations are delivered intravenously. For example, **PLGA** nanoparticles conjugated with cationized albumin and **PEG-PLGA** nanoparticles decorated with a peptide, comprising of 12 amino acids, have been administered by the intravenous route. Other examples of intravenously administered polymeric formulations include polymeric nanoparticles conjugated with transferring, PLGA nanoparticles modified with trimethylated chitosan and tempol-loaded nanoparticles made using **PLGA**. These nanoparticles are aimed at treating the Alzheimer's and Parkinson's diseases.

Intra-arterial

It is similar to the intravenous route but not as widely used because it is easy to locate the veins in comparison to arteries. Intra-arterial administration is mainly used for the disruption of the **BBB**. Doolittle et al. used the intraarterial route to deliver methotrexate to **CNS** in conjunction with **BBB** disruption. The intra-arterial route has been used to deliver stem cells to treat cerebral ischemia. To study the effect on uptake of the hemispheres, a radiotracer was delivered intra-arterially.

Intranasal

Intranasal route of drug administration is used for drug delivery to brain because the intranasal route can sidestep the **BBB** and the drug can be delivered to brain with the help of cellular processes of the olfactory pathway. Administration through intranasal route requires expertise and specialized equipment to control the dosage. The advantage of this system is that it is a painless method and hence patient friendly.

Microemulsions and nanogels are administered preferably through the intranasal route. Patel and coworkers administered paliperidone-loaded microemulsions via intranasal route to deliver drug to the brain. The intranasal drug delivery is primarily dependent on the interaction of the drug molecule with the olfactory epithelial cells. Chitosan, **PLA** and **PLGA** nanoparticles were investigated for the direct olfactory uptake in the olfactory ensheathing cell line. Human acidic fibroblast growth factor fused with **TAT** peptide was also administered intranasally. This study also aimed at evaluation of safety issues of the intranasal delivery. The results confirmed the safety and efficacy of the system delivered via the intranasal route.

Direct Administration to CNS

The advantage of directly administering the drugs to **CNS** is that the availability of drug to the affected area it highly enhanced. It is a painful route as the patient has to go through a surgical intervention but the advantage is that the drug is not exposed to any of the cellular and physiological barriers. The bioavailability of drug is at maximum. This route is so robust that it can not only be used to administer drugs and therapeutics but also the diagnostics and imaging moieties. For instance, this route can be used to incorporate array of microelectrodes and optoelectronics. Optoelectronics, in particular, are combination of optical fibers, photodetectors, and light emitting diodes, and used to study, monitor and control brain activities.

Intracerebral

The intracerebral delivery of the drug into the brain involves the administration of drugs directly into the parenchymal space of the brain and it involves the use of various catheters and matrices. The problem with the intracerebral administration is that the brain microenvironment is tightly packed. Because of this, the diffusion coefficient is quite limited, which leads to slow movement of the drug. Therefore, to maintain constant drug concentration, a large amount of drug is required. In one study, drug delivery catheters were used to infuse carboplatin to the pons of cynomoglus monkeys. The pumps, which infused the drug or saline, were placed in high thoracic/low cervical region.

The cynomoglus monkeys [n=5] were subjected to midline incision for placing the catheters. A 2.5 cm hole was made, through which a catheter was inserted into cerebellum, which further led the catheter to the pons. The saline infusing and carboplatin infusing pumps were placed in separate groups of animals. The study was used to carry out radiographic imaging and assess the neurotoxicity. Animals were assessed using the

computed tomography scanning, histopathology, magnetic resonance imaging, and various neurological examinations. Similar studies were done by Bernal et al., who used convection enhanced delivery to increase the bioavailability. This type of delivery makes use of hydrostatic pressure gradient to distribute drug in the brain tissue, through the implanted catheters.

Intraventricular

Similar to the intracerebral route of administration, this route of administration is used to deliver drug directly into the brain, especially in the ventricles of the brain as well as the sub arachnoids' space. Since there is no tight packing as in the intracerebral route of administration, the drug moves at a higher pace and smaller amount of drug suffices the need, it is used intracerebroventricular route to deliver the drug to brain and investigated the anti-inflammatory capacity of Dapsone loaded-chitosan nanoparticle in mouse model of dementia induced by streptozotocin. The chitosan nanoparticles were prepared by using the nano precipitation method with some modifications. Briefly, chitosan was used in an aqueous solution of acetic acid and polysorbate 80 was used as the surfactant. The nanoparticles were obtained by centrifugation.

The morphology was studied by Transmission Electron Microscopy **[TEM]** analysis, and size, polydispersity index, and surface charge were analyzed on a Zetasizer. The in vitro release studies were done in Phosphate Buffered Saline **[PBS]** and the in vivo studies were carried out in Swiss Albino mice. The dapsone-loaded chitosan nanoparticles were successful in reversing the dementia. In a case of subarachnoid hemorrhage, nicardipine releasing implants were placed intraventricularly in human subjects. The intraventricular delivery of the drug proved to be effective and well tolerate. Recently, in a study of multiple sclerosis in an animal model of autoimmune encephalomyelitis, Neural Stem Cells **[NSC]** was administered intraventricularly. The data proved the efficacy of the intraventricularly administered **NSC** in preventing remitting relapses.

Intrathecal

The intrathecal administration delivers the drug into the **CSF** through the intrathecal route. This method is relatively less invasive as compared to the other two methods of direct **CNS** administration. The disadvantage of this method is that the drug is unable to penetrate the deeper tissues of brain and therefore, it is mainly used in diseases related to spine. The intrathecal route has been used to deliver arylsulfatase, a therapeutic enzyme, for the treatment of metachromatic leukodystrophy. The enzyme even though effective is unable to reach the brain due to the **BBB** and, therefore, was administered directly into the **CSF** via the intrathecal route.

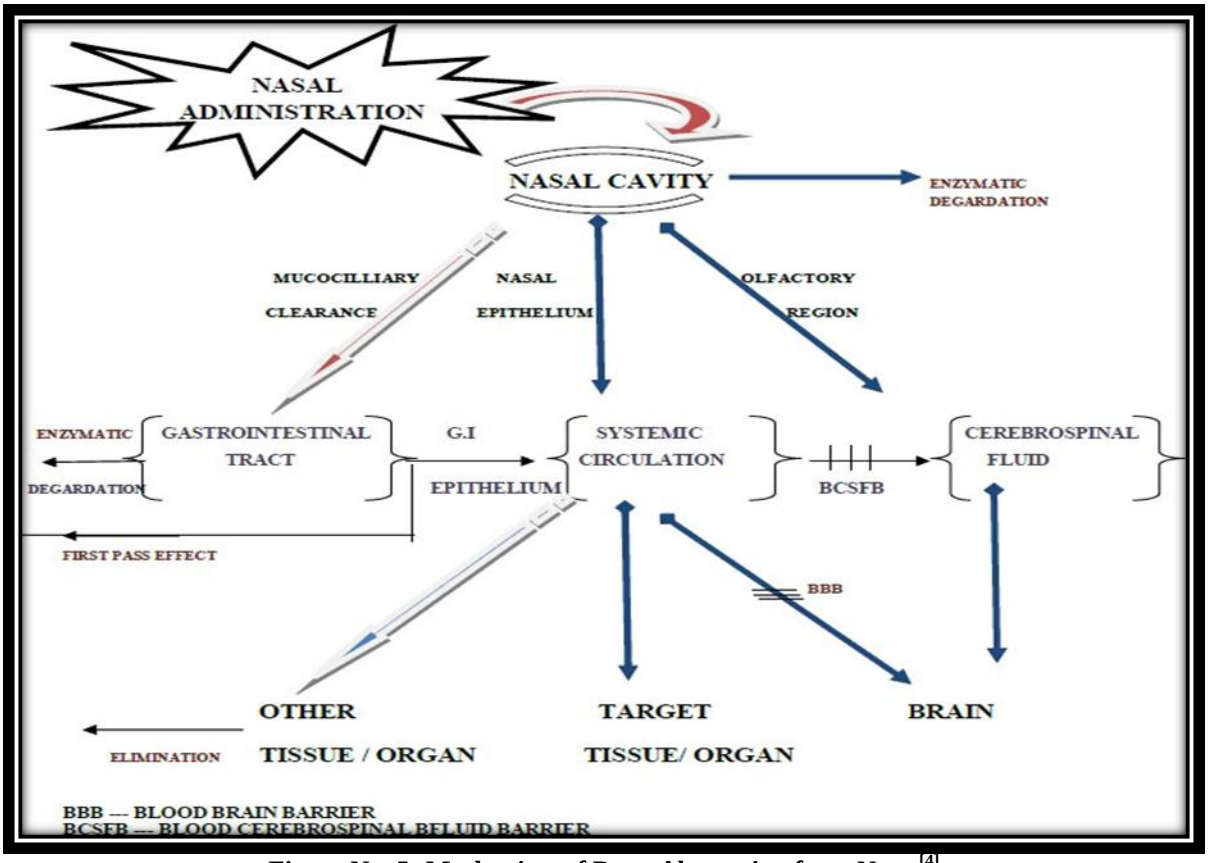

Figure No. 5: Mechanism of Drug Absorption from Nose.[4]

Drug Transport across the BBB

As discussed above, **BBB** regulates the entry and exit of molecules across the **BBB**. Transport of molecules across the **BBB** is possible by following three mechanisms: **[i]** passive diffusion; **[ii]** carrier-mediated transport; and **[iii]** receptor-mediated endocytosis/transcytosis **[Figure]**. These transport mechanisms can be exploited to deliver drug across the **BBB**.

Passive Diffusion

Due to the existence of tight junction between the endothelial cells, the passive diffusion takes place by trans-cellular route and not paracellular route. In passive diffusion, molecules move across the membrane from a region of high concentration to that of low concentration without the input of energy, following Fick's law. However, due to the presence of tight junctions, only lipid soluble molecules with molecular weight of <500 Da are able to diffuse across the BBB passively. A high polar surface area, tendency to form hydrogen bonds (more than six), presence of rotatable bonds, and high affinity for plasma proteins will greatly reduce the ability to diffuse passively across the **BBB**. Usually, molecules with positive charge will have advantage over neutral or anionic molecules. Example of molecules that cross the **BBB** by passive diffusion includes alcohol, steroidal hormones, blood oxygen etc.

Carrier-mediated Transport

Carrier-mediated transport is used for the polar molecules, which cannot passively diffuse across the **BBB**. It is achieved by either facilitated diffusion or active transport. In facilitated diffusion, transport proteins forming the membrane channel undergo conformational change, which allows specific molecules to pass through the membrane down the electrochemical gradient, without the input of energy. Examples include glucose and equilibrative nucleoside transporters.

Receptor-mediated Endocytosis/Transcytosis

Transcytosis via endocytic route is used for the transport of macromolecules across the **BBB**. In Receptor Mediated Transcytosis **[RMT]**, the macromolecule ligand binds to the specific receptor on the cell surface [luminal membrane] and internalized into endocytic vesicles. Transcytosis is achieved, if the endocytic vesicle containing the macromolecule reaches the other end of the cell (basal membrane) without fusing with the lysosome, which may degrade the contents of endocytic vesicle. The macromolecules are finally exocytosed and released into the brain. In Adsorptive-Mediated Transcytosis **[AMT]**, the cationic macromolecule ligand interacts (electrostatic interactions) with anionic cell membrane and induces endocytosis and subsequent transcytosis. Peptides like albumin, insulin, insulin growth factor, low density lipoprotein, ceruloplasmin, transferrin, etc. are transported across the **BBB** by receptor mediated endocytosis/transcytosis.[6]

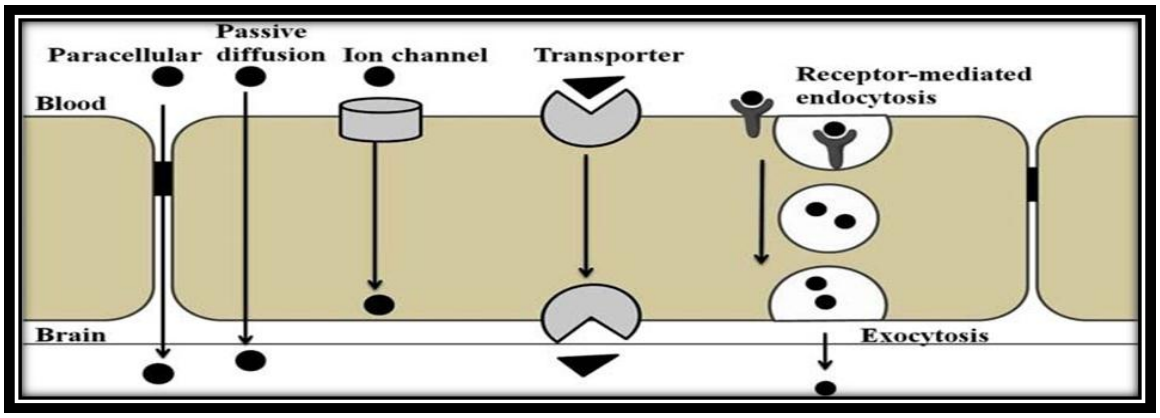

Figure No. 6: Major routes of drug transport across the blood brain barrier.

Barriers for nasal drug absorption[8-9]

Enzymatic Barrier

The nasal mucosa contains enzymes such as cytochrome P450-dependent monooxygenase, carboxyl esterase and amino peptidase. Nasal delivery avoids hepatic first-pass metabolism to some extent, the enzymes present in nasal mucosa provides a pseudo-first-pass effect.[8] The role of the enzymatic barrier is to protect the lower respiratory airways from toxic agents. In addition, there are various barriers in the nasal membrane for protection from the microorganisms, allergens and irritating substances from the environment that must be overcome by drugs before they can be absorbed into the systemic circulation.[9]

Mucociliary clearance[10-11]

Particles entrapped in the mucus layer are transported and cleared from the nasal cavity. The combined action of the mucus layer and cilia is called mucociliaryclearance.[10] This is andefence mechanism of the respiratory tract to protect against noxious inhaled materials. Mucus traps the particles of dust, bacteria and drug substances and is transported towards the nasopharynx at a speed of 5 - 8 mm/min where it is

swallowed. The normal mucociliary transit time in humans has been reported to be 13 to 15 min.[11]

Protective barriers[13]

Small molecular weight and uncharged substances can easily pass through this layer. But larger or charged particles are difficult to cross. Mucin, the protein in the mucus, has the potential to bind to solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes such as pH, temperature etc.[12] The nasal membrane is a physical barrier and the mucociliary clearance is a temporal barrier to drug absorption across the nasal epithelium.[13]

Polymers Used In Nasal Drug Delivery[14]

Cellulose Derivatives

Different cellulose derivatives are seen to be effective on enhancing the intranasal absorption of drugs such as Hydroxypropyl Methylcellulose **[HPMC]**, Hydroxypropyl Cellulose **[HPC]**, Methylcellulose **[MC]**, and Carboxymethyl Cellulose **[CMC]**, and insoluble cellulose derivatives such as Ethylcellulose **[EC]** and Microcrystalline Cellulose **[MCC]**. Cellulose derivatives can markedly prolong the residence time of drugs in the nasal cavity due to their desirable mucoadhesive property.

Additionally, due to their high viscosity following hydration in the nasal cavity, the celluloses can sustain the release of drugs. For these reasons, using celluloses as an absorption enhancer can lead to improved intranasal absorption and increased bioavailability. Many references show that the celluloses are effective in increasing the intranasal bioavailability of small hydrophobic as well as hydrophilic macromolecular drugs. For example, administered nasally with **CMC**, apomorphine can obtain a relative bioavailability of 102% compared with subcutaneous injection in rabbits. The peptide drugs, leuprolide and **FD-4**, when dosed with **MCC/HPC** through nasal route, turned over an absolute bioavailability of 34.9% and 35.5% in rabbits, respectively.[14]

Polyacrylates[15,14]

Polyacrylates have been investigated very frequently in many drug administration routes, like nasal drug delivery systems, due to their excellent mucoadhesive and gel-forming capability. Among the pharmaceutical polyacrylates, carbomers, and polycarbophil, which differ in the cross-linking condition and viscosity, are widely used in the nasal mucoadhesive drug delivery systems. Polyacrylates, capable of attaching to mucosal surfaces, can offer the prospects of prolonging the residence time of drugs at the sites of drug absorption, and ensure intimate contact between the formulation and membrane surface. Studies by Ugwoke in rabbits reported that the use of Carbopol 971P in nasal dosage forms increases their residence time in the nasal cavity. The percentage of the formulations cleared from the nasal cavity at 3 hours was 24% for Carbopol 971P, while it was 70% for lactose. Prolonged release of drugs can also be obtained by using polyacrylates in nasal formulation, which result in a more stable blood concentration-time curve.[15,14]

Chitosan[16]

Chitosan is a linear polysaccharide biopolymer produced by deacetylation of chitin, the main component of crustacean's exoskeleton. Due to its biodegradability, biocompatibility and bio adhesive properties associated to a low toxicity, Chitosan is widely used in intranasal formulations. It is believed that it interacts with the protein kinase C system and opens the tight junctions between epithelial cells increasing Para cellular transport of polar drugs. Moreover, it interacts strongly with nasal mucus layer enhancing the contact time for the transfer of the drug across the membrane. Finally; Chitosan also enhances the dissolution rate of low water soluble drugs. Consequently, Chitosan is used in several intranasal pharmaceutical forms, including powders, liquids, gels, microparticles and microspheres. For some drugs, it is well documented that the addition of Chitosan to nasal formulation increases drug bioavailability.[16]

Cyclodextrins[17,15,14]

Cyclodextrins are cyclic oligosaccharides composed of glucose units joined trough α-1, 4-glycosidic bonds resulted from bacterial digestion of cellulose. Structurally, they take in a hydrophilic counter surface and a lipophilic central cavity where polar drugs can be included. Cyclodextrins are used as complexing agents to improve nasal drug absorption by increasing the drug solubility and stability.

They can work as absorption enhancers, since they interact with the lipophilic components of biological membrane changing their permeability. Although widely used in intranasal medicinal preparations; Cyclodextrins present some local and systemic toxicity. Moreover, alterations of nasal morphology, ciliary beat frequency, erythrocyte haemolysis and cytotoxic effects have also been reported.[17,15,14]

Lectins[17]

Lectins are classified as a group of structurally diverse proteins that are found in plants as well as in the animal kingdom. Lectins have the capacity to identify and bind to specific sugar moieties. The sugarbinding moiety of most lectins is only a small part of the lectin, i.e., a major portion of lectin is not involved in the recognition and binding to the receptor. Lectins also cause agglutination due to their ability to cross link sugar containing macromolecules.

The various lectins which have shown specific binding to the mucosa include lectins extracted from Ulex europaeus I, soybean, peanut and Lens culinarius. Lectins have the ability to stay on the cell surface or become internalized via a process called endocytosis if

the adhesion is receptor mediated. Lectins have potential to be used in Nasal Drug Delivery; especially where internalization of the drug encapsulated nanoparticles is of particular importance such as **DNA** delivery.[17]

Thiomers[18]

Thiomers are mucoadhesive polymers that have side chains carrying thiols which lead to the formation of covalent bonds between the cystiene groups in the mucus and the polymer by thiol/disulphide exchange reactions or simple oxidation process. These adhesions are also known as disulphide bridges. These bridges sometimes improve mucoadhesion by 100 congregations. They also have a permeability enhancing effect and the ability to control the rate at which drugs are released.

This property and increased mucoadhesion lead to higher residence time of the drugs administered in combination with thiomers hence improving their bioavailability. Thiolated polymers display in situ gelling properties due to the oxidation of thiol groups at physiological pH-values, which results in the formation of inter- and intramolecular disulfide bonds. This increases the viscosity of the formulation coupled with extensive crosslinking due to formation of disulphide bonds with the nasal mucosa, which increases the residence time of the formulation tremendously.[18]

Alginate poly-ethylene glycol acrylate[15,18]

Alginate Polyethylene glycol Acrylate is also recognized by the acronym Alginate-**PEGAc**. It has an alginate backbone with acrylated polyethylenglycol groups attached to it. This polymer meshes the properties of alginates [strength, simplicity and gelation] with characteristics specific to the acrylate functionality of **PEG** like mucoadhesion. **PEG's** have the ability to penetrate the mucus surface while the acrylate group of the polymer reacts with the sulphide group of glycoproteins present in the mucus.

This solution in a potent interaction between the mucus and the polymer. It is expected to be cross-linkable by two different paths: chemically via the acrylate end groups and physically through the alginate backbone. Alginate is a mucoadhesive polysaccharide of 1 → 4 linked α-l-glucuronic acid and β-d mannuronic acid which binds to the glycoproteins in the mucus through carboxyl–hydroxyl interactions. It is anionic in nature. It is known to undergo ionic sol to gel transition [gelation] upon interaction with multivalent ions such as Ca2+, Fe2+, thus reducing its adhesion to mucosal tissues.[15,18]

Poloxamer [Pluronics]

Poloxamers are made up of non-ionic difunctional triblock copolymers containing a centrally located hydrophobic polypropylene oxide between hydrophilic polyethylene oxides. Aqueous solutions of poloxamers are extremely stable in the presence of acids, alkalis and metal ions. These polymers are readily soluble in aqueous, polar and non-polar organic solvents. Hence, they are widely preferred choice as excipients in formulations. Poloxamers are said to contain thermo reversible property and will convert from a liquid to a gel at body temperature, thus, causing in situ gelation at the site of interest preventing the drug to be removed from the nasal cavity due to mucociliary clearance. This vastly improves the bioavailability of the drug administered.[15-16]

Formulation Strategies for Nose to Brain Drug Delivery System[19-20]

The Nasal route is efficient for **CNS** and systemic delivery of wide range of drugs, most of the drugs exhibit low bioavailability even when administered by this route. The low bioavailability may be due to the low solubility of drugs, rapid enzymatic degradation in nasal cavity, poor membrane permeability and rapid mucociliary clearance. Several strategies is employed to overcome these limitations include, **[Figure No. 7].** Pro-drug approach, enzymatic inhibitor, structural modifications, absorption enhancers and mucoadhesive drug delivery system.

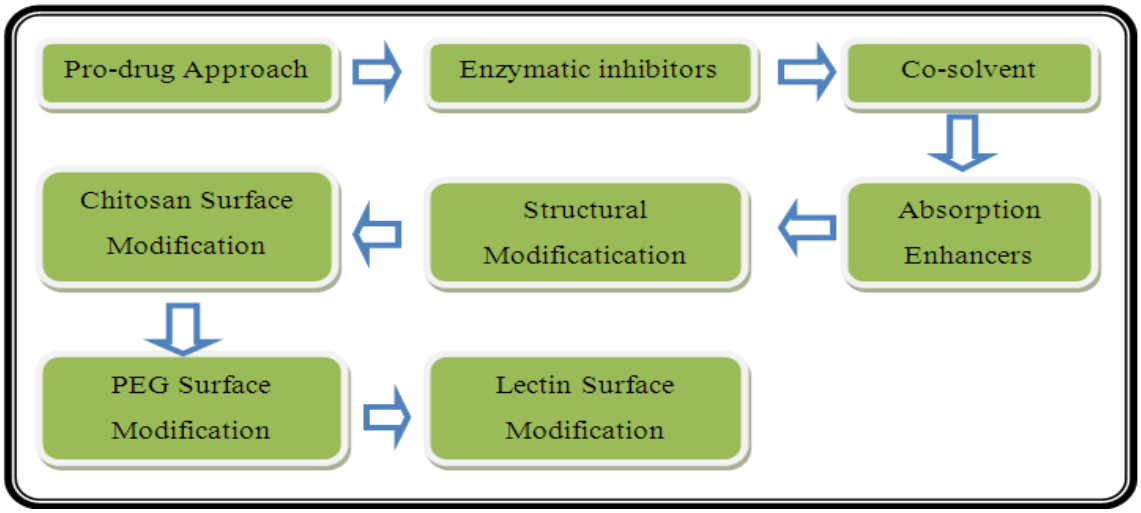

Figure No. 7: Formulation Strategies for Nose to Brain Drug Delivery System.

Pro-drug Approach

In Pro-drug approach, the drugs that administered in the form of solution undergo dissolution prior to absorption. Lipophilic drugs get easily absorbed through nasal membrane, However they are poorly water soluble drugs. So the Pro-drug approach may be utilized to get of higher hydrophilic character that can make as aqueous formulation of hydrophobic drugs. It should be also focused, when that formulation reaches to systemic circulation, Pro-drug must be converted to the parent drug molecule. L-dopa is a poorly water soluble drug, but when administered as Pro-drug its solubility is increases significantly in Comparision with parent drug molecules. Similar results were obtained with testosterone, which is a poor water-soluble drug but in the Pro-drug form with higher lipophilic nature, Permeation increases through the membrane.

This approach is applicable to inhibit the enzymatic degradation of drugs in nasal mucosa and to render the formulation for maintaining the enzymatic stability. Laspartate--b-ester Pro-drug of acyclovir is more permeable and more stable toward enzymatic degradation [it is an example of Pro-drug approach]. Pro-drug approach is a powerful approach for enhancement of bioavailability of large molecular weight compounds such as protein and peptides drugs by this drug delivery.[19-20]

Enzymatic inhibitors[21-22]

Nasal mucus layer and nasal mucosa is act as enzymatic barriers for nasal drug delivery system [they have a wide variety of enzymes]. Several approaches were used to avoid the enzymatic degradation, including the use of protease and peptidases inhibitors. Bestatin and comostate amylose were used as amino-peptidases inhibitor and leupeptine, Aprotinin as tyrosine inhibitors is probably involved in the degradation of calcitonin. The bacitracin, amastatin, boroleucin and puromycin are used to avoid the enzymatic degradations of drugs such as leucine, encephalin and human growth harmone. Finally enzymatic inhibition can be achieved by using certain absorption enhancers such as bile salts and fusidic acid. Di-sodium ethylene diamine-tetra acetic acid, an absorption enhancer that reduces enzymatic degradation of beta sheet peptide, used for the treatment of Alzheimer's disease.[21-22]

Co-solvent[21]

This approach is used to increases the solubility of the drugs. Mostly used co-solvent includes glycerol, ethanol, propylene glycol and ethylene glycol, since these are nontoxic, non-irritant to nasal mucosa and pharmaceutical acceptable. [21]

Absorption enhancer[23-25]

Absorption enhancer, in which the poor permeability of hydrophilic drugs may be overcome by the used of absorption enhancers that induces reversible modification of epithelial barrier. The absorption enhancer is used in nasal delivery were surfactant [SLS, Poloxamer, tweens, spans], bile salts [sodium glycodeoxycholate, sodium taurodeoxycholate], fatty acids [taurodihydrofusidate, oleic acid, ethyl oleate], Chelators [EDTA, citric acid], peppermint oil and polymers. Some examples of polymers such as cyclodextrines and methylated cyclodextrines, chitosan and trimethyl chitosan, carbopol, starch and animated gelatine. This is responsible to changes the permeability of epithelial layers of nasal mucosa by modifying phospholipids bilayer and also changes fluidity or reversible openings of tight junctions between epithelial cells and increases paracellular transport of drug molecule.[23]

The high molecule weight polymeric absorption enhancers were not absorbed and reduced the systemic toxicity in comparison with low molecular weight. Chitosan can interact with protein kinase C and its open tight junctions between epithelial cells to increases the paracellular transport of polar drugs, its strongly interact with the nasal mucous layer and increases the contact time to overcome mucociliary clearance, thus it can widely used in intranasal dosage forms.[24] Cyclodextrines complexes interact with the lipophilic components of natural biological membrane and increase the permeability of drugs to increase the absorption. Although cyclodextrines are widely used for nasal drug delivery, some local and systemic toxicity was reported. The Novel formulations such as mucoadhesive, micro and nanoemulsion, microspheres and nanoparticles containing absorption enhancers are demonstrated to better for bypassing the BBB.[25]

Structural Modification[26-27]

Modification of structure of drug without altering pharmacological activity, it is one of the important factor to improve the Nasal drug absorption. On structural modification of drug molecule, the physicochemical characteristics that are commonly modified, the molecular weight, molecular size, partition coefficient and solubility, all favourable for nasal drug absorption. Examples of structural modification in which, the chemical modification of salmon calcitonin into ecatonin [C-N bond replaced by an S-S bond] was help to improved bioavailability when compared with parent drug molecule.

Chitosan surface modification[28]

Chitosan surface modification is one of the important formulations Strategy for improving the solubility profile of pharmaceutical molecules. Chitosan molecules are the alkaline hydrolytic derivative of the chitin molecules. Chitosan molecules having an ability to enhance the solubility profile of pharmaceutical molecules. They having a minimum crystallinity and particular from of the chemical structural modifications due to its chemically highly reactive functional group such as acetamide, hydroxyl and amines functional groups.

The chemical structural modifications are not affecting the fundamental structure of chitosan molecules. The chemical structural modifications are included carboxylation, Biochemical or Enzymatic modifications and copolymerization or graft copolymerization. Chitosan surface modification is an excellent approach for pharmaceutical, biochemical, biotechnological and biopharmaceutical field.

PEG surface modification[28]

It is a surface modification approach to improve the solubility of pharmaceutical molecules. The kDa monopolymeric **PEG** surface modification system having a surface 110-200 nm particle size of the nanoparticles and the diffusion coefficient of the nanoparticulate system having 20 and the 380 times. This approach is maximum relevant, in which the low molecular mass of **PEG** molecule and the high surface modification of **PEG** molecules are responsible for high penetration capacity to that mucus **PEG** molecule is rapidly absorbed in the surface of the particle.

The longer chins of **PEG** molecules are having a maximum ability to interact the mucus fibers to reducing the mucosal movements of nanoparticulate system. The surface charge of nanoparticulate system responsible for composition of core of nanoparticulate system. **PEG** surface modification is applicable for transport of proteins and peptides in nanoparticulate systems.

Lectin Surface Modification[28]

It is class of surface modification is important to improve the solubility of pharmaceutical molecules. Lectin is a class of proteins and glycoproteins polymeric system and other purified sources of plants include jack bean, tomatoes. Lectin is obtained from the sugar residue on the biological surfaces and it is applicable for the intranasal drug delivery.

Colloidal Carriers in Nose to Brain Drug Delivery Systems[29]

Colloidal drug carriers include microemulsion, nanoemulsion, nanoparticle, polymeric micelles, liposomes, mucoadhesive solutions and microspheres. The intent behind use of colloidal drug carriers for nose to brain drug delivery was to increases the specifically towards cell or tissue to increases bioavailability of drugs by increasing their diffusion through the biological membranes and protect against enzymatic degradations.

Microemulsion[30-31]

Microemulsion is a clear, stable, isotropic mixture of oil; water and surfactant are frequently in the combination with cosurfactants this approach is interested to the pharmaceutical scientist because of their considerable potential to act as drug delivery vehicle by incorporating of wide range drug molecules. They offer the advantages of spontaneous formation, easy manufacturing and scale up, thermodynamic stability and it's important to improve the solubilization and bioavailability. Preparing a pharmaceutically acceptable dosage from demands a clear understanding of the microemulsion structure, phase behaviour, factor leading to its thermodynamic stability, factors associated drug release from the formulation and potential uses and limitation of microemulsion system.

Nanoemulsion[29,32]

Nanoemulsion is an isotropic mixture of oil, surfactant: cosurfactant [Smix] and drug is known as nanoemulsion. The colloidal size ranges from 50-100 nm are often referred to as Miniemulsion, nanoemulsion, ultrafine emulsion or the multiple emulsions. These nanoemulsion appear transparent and translucent to the necked eyes and the possess stability against sedimentation or creaming. These properties make nanoemulsion as carriers of vast interest for fundamental studies and practical applications in various fields like chemical, cosmetic and pharmaceutical and Biopharmaceutical fields.

Polymeric micelles[33-34]

Polymeric micelles that may serve as nanoscopic drug carriers. Polymeric micelles are the self-assemblies of block of co-polymers and promising nanocarriers for drug and gene delivery, for drug delivery, polymeric micelles have been prepared from biodegradable and biocompatible blocks of copolymers. Polymeric micelles are characterized by core shell structure. It has reported that mixed micelles of bile salts and fatty acid have a synergistic effect on the nasal absorption of peptides.

Nanoparticles[35-39]

Nanoparticle is a nanosized particle range size range of 1-1000 nm. It is applicable to improve the solubility of poorly soluble drugs and permeability of drug molecules.[35] This nanoparticulate system is based on biodegradable polymers, have been extensive exploited in targeting drug delivery as they offer excellent improvement in nose to brain delivery by protecting the encapsulated drug from biological and chemical degradation, the extracellular transport by P-gp efflux system is increases the **CNS** availability of drugs. The poly-lactic acid **[PLA]**, polyglycolic acid **[PGA]**, poly-lactide-co-glycolic acid **[PLGA]**, poly-g-caprolactone **[PCL]**, polymethyl methacrylate, are the polymers known to be biodegradable, biocompatible and nontoxic.[36-37] Illum is demonstrated that chitosan based nanoparticles can enhance nose-to-brain delivery of drugs compared to equivalent drug solutions formulations due to the protection of the drug from degradation and/or efflux back into the nasal cavity.[38] Seju has reported olanzapine-loaded **PLGA** nanoparticles for the treatment of psychotic illness, schizophrenia, via nose to brain drug delivery platform.[39]

Liposomes and Proliposomes[40-43]

Liposomes and Proliposomes is a novel approach of drug delivery system is important to deliver the various routes. Liposomes can be used for targeting and introduction of

therapeutic agents to specific site by conjugation or cross linking of targeting moiety to the native liposome or by surface modification of the fabricated liposomal formulation. Positively charged liposomes possessed maximum bioadhesion prolonging the residence time within the nasal cavity thereby improving the bioavailability.[40]

Free flowing Proliposomes containing propranolol hydrochloride were prepared by Shim et al. and evaluated their potential for transnasal delivery of propranolol to sustain its plasma concentration.[41] In a study on rats by Wattanathorn et al. intranasal liposomes containing quercetin decreased anxiety like behavior and increased spatial memory. US Patent 6342478 describes a nasal micellar or liposomal preparation for the delivery of fibroblast growth factor to the brain.[42] Vyas et al. have reported multilamellar liposomes for intranasal delivery of nifedipine.[43]

Nasal Delivery Devices[44]

Nasal drug delivery devices are versatile tool for direct drug delivery in nasal cavity by using various nasal devices. The nasal devices include Powder formulation devices and liquid Formulation devices. Liquid formulations currently completely dominate the nasal drug Market, but nasal powder formulations and devices do exist, and more are in development.

Powder formulation devices[44]

The powder nasal devices are more convenient and it is having a maximum stability than liquid nasal devices. In powder nasal devices preservatives are not required for preparation. It is having a larger dose of drug and they improve stability of formulation. They can be free from microbial growth. The nasal powder administration is increases the patient compliances and patient acceptance. Nasal powder devices are applicable for the number of proteins, peptides and non-peptide pharmaceutical molecules. Powder-polymer complex formulation allows easy or convenient approach to nasal delivery of drugs.

Insufflators[44]

In this nasal devices shown in [**Figure No. 8]** to deliver the pharmaceutical molecules for inhalation. This device is mainly constructed in the straw or tubes which contains the pharmaceutical molecules. It is a pre-dose powder capsules.

Dry powder inhaler[44]

Dry powder inhalers **[DPIs] [Figure No. 8]** are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and **COPD** and have also been used in the treatment of diabetes mellitus.[44] The medication is commonly held either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are a variety of such devices. The dose that can be delivered is typically less than a few tens of milligrams in a single breath since larger powder doses may lead to provocation of cough.[45]

Pressurized Metered-Dose Inhale [PMDI][46]

The pressurized metered dose inhaler is a nasal device **[Figure No. 8]** to deliver optimum amount of drug to the lungs, this is a short burst aerosolized drug that inhaled the patient. It is used for treatment of asthma, **COPD** and other pulmonary disorders. A **PMDI** device is important to deliver the optimum amount of medication to the lungs.

Breath-powered Bi-Directional technology[46]

The Breath-powered Bi-Directional technology **[Figure No. 8]** is a new concept for delivering the drug molecule to direct nose to brain administration. It is novel approach for delivering the powder and liquid formulation to intranasal administration.

Liquid Formulation Devices[46]

Liquid nasal devices are delivering the aqueous or watery solutions to nasal cavity. The suspension and emulsions are also transported to nasal cavity for intranasal delivery. Liquid formulation devices are useful for chronic nasal disorders.

Sprays and Solution[46]

The solutions of drug molecule are administered in nasal cavity is act as a nasal sprays **[Figure No. 8]** and nasal solutions. The optimum dose of **API** is based on the amount of drug molecule or volume of drug in pharmaceutical formulations. It is most convenient approach for delivering the drug formulation for nose to brain delivery bypassing the BBB.

Instillation and Rhinyle Catheter[46]

Rhinyle catheter **[Figure No. 8]** is a liquid formulation device is important to deliver the formulation by drop by drop in appropriate region of nasal cavity. Catheter dosing is measured by the filling prior to admin-istration. This system is applicable for the experimental studies only.

Compressed Air Nebulizers[46]

Nebulizers **[Figure No. 8]** are the nasal administration devices in which the drug loaded formulation in the gases state deliver to the lungs. It is a compressed air filling devices for delivering the drug formulation to nasal cavity. This device is more applicable for targeting the drug formulation to respiratory tract to give rapid on-set of action and reduces the toxic effects. This device is not applicable for drug delivering into systemic pathways.

Squeezed Bottle[46]

In this devices **[Figure No. 8]** are important for delivering the decongestants. They are smooth plastic bottles with simple jet outlet by pressing the bottle air passes in inside the container is pressed out of the small nozzle, having the optimum volume. After minimizing the pressure the air again passes to inside the bottles. Dose concentration and deposition of liquid phase delivering via Squeezed bottles they are strongly dependent on mode of administration. Dose and droplet size of that formulation is mainly dependent on pressed application of that container.

Metered-dose Pump Sprays[46]

Marketed nasal formulations such as suspension, emulsion, solution are directly delivered to intranasal pathway by using metered dose pump sprays **[Figure No. 8].** It is applicable for treatment of nasal hypersensitivity and other nasal disorders. It is based on hand operated pump mechanism. It is important to give local effect such as topical decongestants, antihistamines. These containers can be containing the pump, valve and the actuator. Dose of metered dose pump sprays depends upon the viscosity and surface tension of those formulations.

Single and Duo Dose Spray Devices[46]

Single dose devices **[Figure No. 8]** are administered single dose of drug formulation to the intranasal pathway and duo dose device administered more than one dose of different or same drug formulation intranasal cavity. It is simple convenient and non-invasive mode for delivering the drug into nasal cavity. It is used for treatment of chronic rhinosinusitis and in a vaccine study.

ViaNase Atomizer[46]

A handheld battery-driven atomizer **[Figure No. 8]** intended for nasal drug delivery has been introduced [Via Nase by Kurve Technology Inc., Lynnwood, WA, USA]. This device atomizes liquids by producing a vortical flow on the droplets as they exit the device. The induced vortical flow characteristics can be altered in circular velocity and direction to achieve different droplet trajectories. As discussed above, it is not clear that vortex flow is desirable for penetration past the nasal valve; however, it has been suggested that this technology is capable of targeting the sinuses, and some gamma-deposition images suggesting delivery to the sinuses have been published. However, no information related to impact of prior surgery or numerical quantification of nasal or sinus deposition verifying the claimed improved deposition to the upper parts of the nose has been published.

The ViaNase device has been used to deliver nasal insulin in patients with early Alzheimer's disease **[AD]**, and clinical benefit has been demonstrated. In these studies, delivery of insulin was performed over a 2-min period by nasal inhalation. However, when insulin is delivered with this device, lung deposition is likely to occur, and some concerns related to airway irritation and reduction in pulmonary function have been raised in relation to longterm exposure to inhaled insulin when Exubera was marketed for a short period as a treatment for diabetes. This example highlights the issue of unintended lung delivery, one important potential clinical problem associated with using nebulizers and atomizers producing respirable particles for nasal drug delivery.

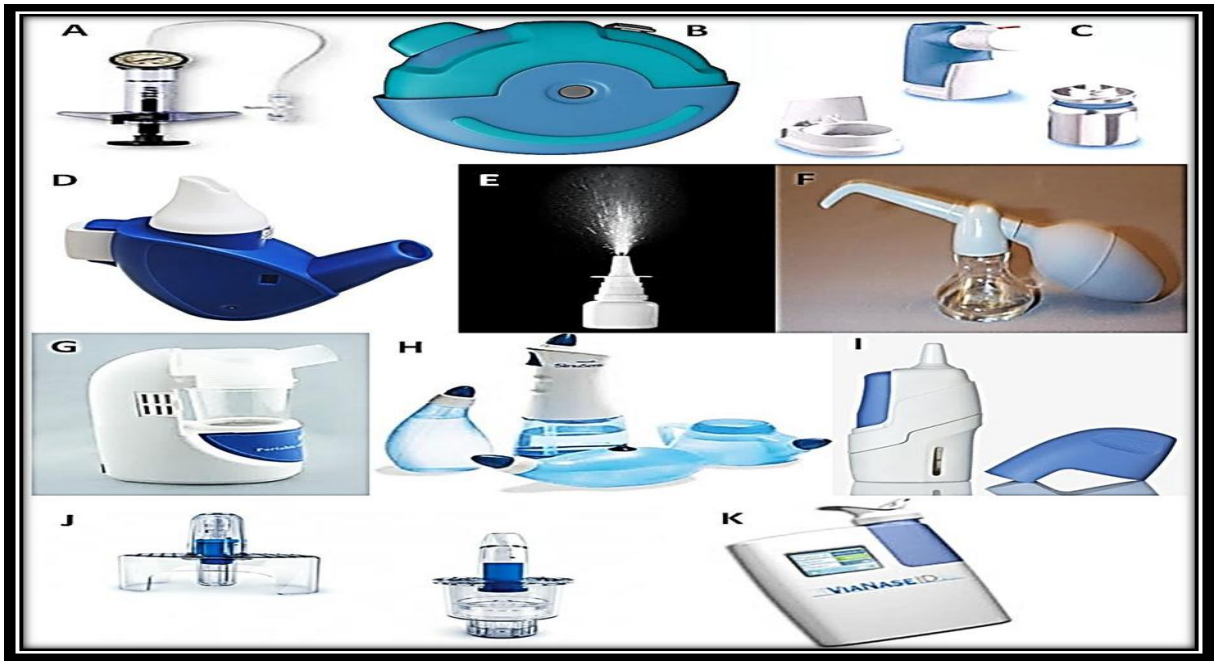

Figure No. 8: Nasal delivery devices: [A] Insufflators, [B] Dry powder inhaler, [C] Pressurized Metered Dose Inhale, [D] Breath-powered Bi-Directional technology, [E] Sprays and Solution, [F] Instillation and rhinyle catheter, [G] Compressed air nebulizers, [H] Squeezed bottle, [I] Metered-dose pump sprays, [J] Single and duo dose spray devices, [K] ViaNase atomizer.

CONCLUSIONS

Brain is a complex organ and more complex are its diseases. The conventional drugs are either inefficacious or efficacious but hindered by various physiological and cellular barriers like the BBB and the BCSFB. These barriers greatly reduce the bioavailability of the drug. To increase the therapeutic dose, the patient is compelled to take the drug time and again, which adds to his discomfort. The mucosa is well supplied with both vascular and lymphatic drainage. Nose to brain drug delivery bypasses the BBB to target CNS, reducing systemic exposure of drug, thereby reducing the systemic side effects. It is an attractive option of drug delivery due to its non-invasiveness.

The drug delivery targeting the brain should be evaluated for their safety and risk-benefit ratio for the patients. A variety of neurotherapeutic agents including small drug molecules, proteins, peptides, hormones and biological cells such as stem cells can be delivered by this route, thereby yielding new insights into prevention and management of different neurological disorders. In parallel, rapid advancement has been made in the field of diagnostics through implantation of, for instance, optoelectronics. MRI contrast agents have been developed, which target CNS with high efficiency.

All these drug delivery systems have the advantages of reduced drug intake, reduced toxicity, reduced side effects, and controlled and sustained drug delivery. The intranasal route is an accessible alternative to parenteral routes. The need for safe and effective nasal permeation and absorption enhancers is a major component for a promising future in the area of nasal drug delivery. Despite the enormous progress, still there is a need for a device for selective delivery of the product at the olfactory region in the nasal cavity. The drug delivery targeting the brain should be evaluated for their safety and risk-benefit ratio for the patients.

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