INTRANASAL ROUTE-AN INNOVATIVE TECHNIQUE FOR BRAIN TARGETTING

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ABSTRACT

The complex arrangement of Blood-Brain Barrier (BBB) restricts the entry of drugs into the brain. The intranasal route is widely accepted route for the delivery of many therapeutic agents due to a reason it bypasses BBB. Direct nose to brain drug delivery has been proved to be an excellent platform for brain targeting through surface engineering of neurotherapeutic-loaded carrier systems resulting in enhanced product performance. There is a unique pathway through nasal mucosa to brain by which many upcoming therapeutic agents will also delivered through this route to brain which have brain as target site. Nowadays, macromolecules, stem cells, DNA plasmids, chemotherapeutic agents etc are delivered by intranasal route.

KEYWORDS: Noninvasiveness, Intranasal drug delivery, Brain targeting, Blood Brain Barrier, Central nervous system.

INTRODUCTION

Intranasal therapy has been an accepted form of treatment in the Ayurveda system of Indian medicine since early. Nasal therapy also called “NASYA KARMA”. It is one of the PANCHAKARMA mentioned in Ayurveda. It is the process by which drug is administered through the nostrils. If ‘Nasyakarma’ is done properly and regularly alleviate disease like cervical spondylitis, headache, facial paralysis, hemiplegia, diseases of nose frozen shoulder, mental disorder and skin complaints. Nasyakarma will enhance the activity of sense organs and prevent the disease of head (URDHWANGA).1 The early 1980s saw the introduction of nasal route as a promising systemic delivery alternative to other conventional drug delivery system. Nasal mucosa has been considered as potential co-administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds then
the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucous and less dilution by gastrointestinal contents.[2] It is useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides.[3]

ADVANTAGES[4][5][6][7]
1. Rapid absorption, higher bioavailability, therefore, lower dose.
2. Fast onset of therapeutic action.
3. Avoidance of liver first pass metabolism & metabolism by GIT.
4. Minimum irritation to the gastrointestinal membrane.
5. Reduced risk of overdose.
6. Non-invasive, ease of convenience along with self medication.
7. Improved patient compliance.
8. It can be a beneficial adjunct product to an existing product.

DISADVANTAGES[8][9]
1. Concentration achievable in different regions of the brain and spinal cord varies with each agent.
2. Delivery is expected to decrease with increasing molecular weight of drug.
3. Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa or may cause irritation to the mucosa.
4. The absorption enhancers used to improve nasal drug delivery system may have histological toxicity which is not yet clearly established.
5. Absorption surface area is less when compared to GIT.
6. Once the drug administered can not be removed.
7. Nasal irritation.

NASAL ANATOMY & PHYSIOLOGY
Externally, nose consist of paired nasal bones and upper and lower lateral cartilages. Nasal cavity is divided by nasal septum. The lateral nasal wall consists of inferior and middle turbinates and occasionally a superior or supreme turbinate bone. The nasal membrane composed of ciliated pseudostratified glandular columnar epithelium. Mucociliary transport relies on mucus production and ciliary function.[10] The level of congestion & nasal membrane is controlled by Blood and autonomic nerve supply. Contributions of nerve supply are from the facial nerve originating at the inferior salivatory nucleus and following along the
distribution of the facial nerve through the sphenopalatine ganglion. internal and external carotid artery systems supplies blood to the nose.\textsuperscript{[11]} ophthalmic artery of the internal carotid artery system supply the posterior aspect of the nasal cavity. Olfactory nerve endings originate in the olfactory bulb under the frontal lobe and pass directly through the cribiform plate as second-order neurons entering the nasal cavity. Olfactory nerves are found on the superior portion of the septum, superior turbinates, and cribiform region.\textsuperscript{[12]}\textsuperscript{[13]}

![Figure 1: Anatomy of nose.](image)

**NASAL VESTIBULE**
The nasal vestibule is a small dilated space just internal to the naris, that is lined by skin and contains hair follicles.

**RESPIRATORY SECTION**
The respiratory section of the nasal cavity refers to the passages through which air travels into the respiratory system. The respiratory section of each nostril contains four conchae (protrusions or bumps) which are also referred to as turbinate bones or lobes and are covered by the nasal mucosa. conchae (also named turbinates) are the curved bony projections pointed downwards and medially. Below and lateral to every concha is a
corresponding meatus. Superior and middle nasal conchae are the projections from the medial surface of the ethmoidal labyrinth. Inferior concha is a separate bone, The superior concha is smallest and inferior concha is largest in size. Meatuses are the passages (recesses) below the overhanging conchae.\textsuperscript{14} They’re visualized once conchae are removed. Inferior meatus is the largest and is located underneath the inferior nasal concha. Middle meatus is located underneath the middle concha. The meatuses of the nasal cavity connect to the paranasal sinuses.\textsuperscript{15}

**OLFAC TORY REGION**

The olfactory receptors (receptors for smell sensations) are found in this section of the nasal cavity. Bowman’s glands are also found in this section of the nasal cavity.

Three types of cells constitute olfactory epithelium i.e basal, supporting, and olfactory receptor cells. Stem cells are the basal cells that give rise to olfactory receptor cells. The continuous turnover and new supply of these neurons are unique to the olfactory system. Supporting cells are scattered over the receptor cells and have numerous microvilli and secretory granules, which empty their contents onto the mucosal surface\textsuperscript{16}\textsuperscript{17}. The receptor cells are actually bipolar neurons contains specialized cilia which provide the transduction surface for odorous stimuli.

The conchae (turbinate bones) of the nasal mucosa expand the total surface area of the mucosa and create turbulence in air entering the respiratory passage. This causes air to swirl as it moves through the nasal cavity and increases contact between infiltrating air and the nasal mucosa, allowing particles in the air to be trapped before entering other parts of the respiratory system (e.g. the lungs).\textsuperscript{18}

The olfactory system functions to process sensory information related to smell.

BOWMAN’S GLAND-Bowman’s glands secrete the majority of the mucus which overlies the nerves of the olfactory system. They also secrete the pigment which gives this mucus its yellow colour. Mucus secreted by these glands dissolves odours as they enter the nose, enabling them to interact with the olfactory receptors.
PATHWAYS OF NASAL DRUG DELIVERY

Olfactory pathway: The possible mechanism by which drugs are transported from nose to brain has not yet clear but olfactory pathway contributes a vital role. Basal cells and neural cells replace each other during their constant motion and due to this constant motion and replacement nasal mucosa becomes permeable resulting in enhanced delivery of drug to brain. Three different pathways across the olfactory epithelium includes:

Paracellular pathway: Through the tight junctions between between sustentacular cells and olfactory neurons. Hydrophillic drugs most probably absorbed by diffusion through aqueous channels (pores). This pathway is slow and passive. This route is responsible for transport of hydrophilic drugs and it shows rate dependency on the molecular weight of a drug.\(^\text{[19]}\) 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.\(^\text{[20]}\)

Transcellular pathway: Across the sustentacular cells most likely by receptor-mediated endocytosis, fluid phase endocytosis or by passive diffusion. Passive diffusion is a common transport pathway for lipophilic drugs.

Olfactory nerve pathway: In this drug is taken up into the neuronal cell by endocytosis or pinocytosis mechanisms and transported by intracellular axonal transport to the olfactory bulb.\(^\text{[21]}\)

Figure 2: Olfactory & Trigeminal pathway.
**Trigeminal pathway**: Trigeminal nerve which connects the nasal passages to the brain plays an important role in IN delivery of drug. Respiratory region occupies major portion of nasal cavity and innervated by trigeminal nerves.[22][23] Trigeminal nerve is fifth (V) cranial nerve having three branches; ophthalmic nerve, maxillary nerve and mandibular nerve and is responsible for sensation in nasal cavity. Olfactory pathway delivers drug to rostral area of brain, whereas trigeminal pathway not only targets rostral but also caudal area of brain, making it difficult to differentiate whether intranasally administered drug is translocated to rostral area by olfactory or trigeminal pathway. A unique feature of the trigeminal nerve is that it enters the brain from the respiratory epithelium of the nasal passages at two sites: i) through anterior lacerated foramen near the pons and ii) through the cribriform plate near olfactory bulb, creating entry points into both caudal and rostral brain areas following intranasal administration.[24][25]

![Figure 3: Nose to brain transport.](image)

**BRAIN TARGETTING STRATEGIES**

There are various techniques which are used to disrupt the BBB & helps in the transport of drug molecules across this barrier to the CNS have been studied. These includes:-
Figure 4: Drug delivery strategies to brain.

INVASIVE STRATEGIES

Distruption of BBB by chemicals: Various invasive techniques are used for the disruption of the BBB and enhance the delivery of drug to Brain. Osmotic disruption of BBB is one of the invasive techniques in which shrinkage of endothelial cells takes place for a short period of time & leakage of drug to the CNS through opening of tight junctions. On injecting intracarotid hypotonic solution of mannitol, tight junctions were opened and subsequently promoted the delivery of chemotherapeutic agents to the brain. This technique is less specific.
and inefficient and major drawbacks are transport of plasma protein to CNS, disturbed glucose uptake, neurotoxicity of cerebral tissues, altered brain functions and technicality related issues. Bradykinin and histamine act as vasoactive agents which disturb the BBB & improve the transportation of drugs to CNS. Role of bradykinin are the activation of B2 receptors, leakage of endothelial cells based on modulation of caveolin-1 and caveolin-2 and permeability enhancement of brain tumor microvessels via (KATP) channels.\[^{27}\]

**Focus Ultrasound enhanced Delivery:** Another versatile approach for enhancing of drug transportation to the CNS by the use of ultrasound waves which reversibly and transiently open the BBB. In this type of drug delivery microbubbles (MBs) is used as a contrast agent. These bubbles were administered systemically and worked on acoustic energy principle to exert pressure on endothelial cells and open the tight junctions, resulted in increased permeability of BBB and improved delivery of drug to the brain. These MBs operate in collaboration with low intensity Focus Ultrasound (FUS) and this combined system is called MB facilitated FUS.

MB-FUS system decreases the acoustic energy requirement, focusing the acoustic energy within blood vessels. Different antitumor agents such as trastuzumab\[^{28}\], temozolomide\[^{29}\], methotrexate\[^{30}\], nucleotides i.e. siRNA\[^{31}\] and stem cells\[^{32}\] have been successfully delivered with the help of FUS. FUS-MB system is effectively used with other DDSs for brain targeted delivery.

**Craniotomy-based drug delivery:** Craniotomy-based drug delivery is the direct way of targeting the specific part of the brain without exposure to peripheral organs via Intracerebral or intraventricular injection. In intraventricular delivery, drug reservoir implanted in the scalp provided the controlled release of a drug and is connected to the ventricles in the brain through catheter\[^{33, 34}\]. Higher concentration of drugs is achieved without distribution to the interstitial fluid of brain. Intraventricular system directly delivers the drug to the ventricles and subarachnoidal part of the brain and is suitable for therapy of meningioma and metastatic cells of CSF\[^{35}\]. Intracerebral system directly injects or infuses the drug into brain parenchyma through catheter\[^{36}\] and controlled devices maintain the delivery\[^{37}\]. This system depends on the diffusion mechanism and provides slow distribution of drugs within the brain, as diffusion decreases with the increase of distance. Hence, intracerebral delivery requires large doses of a drug to achieve desired therapeutic response\[^{38}\].
**Convection-enhanced Delivery:** This system involves continuous infusion method and pressure gradient to distribute large volume of drugs at target tissues via intracranial catheter. This delivery overcomes the disadvantages of intracerebral delivery system. It has certain limitations of drug entry to surrounding tissue, difficult to design, instability of drug and low therapeutic level of drug in the target area. Coupling of CED with liposomes improved the efficiency of CED for brain tumor targeting. Liposomal delivery, significantly, inhibited tumor volume and increased the survival rate.

**Polymeric wafers based delivery systems:** Development of polymeric devices for targeted and controlled delivery of therapeutic moieties lead to advancement in polymer technology. This involves the controlled release of drug at targeted site. Wafers based on polyanhydride were implanted in tumor resection area, crossed the BBB, gradually released and distributed the drug into the brain and targeted site. Polyhydride based polymer shows effective results in animals with minimum toxicity. Wafers have certain limitations of less penetration into deep brain tissue, cyst formation, meningitis, impaired wound healing and abscess formation.

**NON-INVASIVE STRATEGIES**
These strategies utilizes the endogenous mechanism for transport of drug across the BBB.

**Prodrug approach:** With increase in lipophilic characters in drug molecule, it facilitates better permeation. This approach based on chemical modifications in the drug molecule to modulate its lipophilic behavior, increase permeability & water solubility. Targeted prodrugs contain chemical entity along with parent drugs designed to approach enzymes or transport system at the targeted site to be converted to active moiety. Peptidase enzymes in the brain removed the spacer and released the active drug. Prodrug approach has been successfully utilized for delivery of neurotherapeutics to treat neurological disorders. This approach retains the drug at brain for longer period of time.

**Efflux Pump inhibition:** The presence of efflux pump in the BBB which is another barrier for effective drug transportation to the brain. Efflux by the active P-glycoprotein (P-gp) presents on the apical membrane of the endothelial cells of BBB results in poor drug availability at the targeted brain tissues. P-gp has more affinity for lipophillic and cationic drugs. Most of the low molecular weight drugs such as nitrosoureas are substrate for P-gp and are restricted to enter the brain. Inhibition of P-gp efflux is the useful approach to save
the therapeutic efficacy of potent drugs. Dopamine, pharmacologically effective for the treatment of Parkinson's disease, is unable to cross BBB disease. L-dopa is transported through L-amino acid transporter crossed BBB and converted to dopamine in the brain.

**Cell based therapy:** This therapy utilizes macrophages and many types of stem cells as carriers for delivery to brain. An effective delivery for neurological disorders and brain tumors. In this macrophages with phagocytosis property migrated towards to brain by transcellular or paracellular transport. During brain tumor and inflammatory conditions macrophages are attracted and infiltrated towards brain. Macrophages are suitable candidates for targeted delivery of NPs and diagnostic and imaging agents to the brain tumor and neurodegenerative diseases. Stem cells could be used as vector for delivery of cytokines, oncolytic viruses, and suicide genes to brain. Stem cells could be effective cargo for oncolytic virus to treat the glioma. In a study, Mesenchymal Stem Cells carrying oncolytic herpes simplex virus exhibited efficacious results in glioma-bearing mice.

**Intranasal drug delivery:** Drug administered through nasal route of administration is absorbed into the systemic circulation. Drug absorption through nasal respiratory epithelium follows transcellular and paracellular absorption, carrier-mediated transport, and absorption through transcytosis mechanism. Nasal drug delivery to the brain posed a big challenge of BBB-mediated restriction. Administration of drug deep into the nasal cavity approached nasal mucosa, led to direct transmission of drug into brain via olfactory pathway. Olfactory pathway consists of olfactory neurons that carry drugs from olfactory mucosa to the brain and is slow process of drug transmission. Olfactory epithelium pathway is faster way of drug transportation. Drug is passed through olfactory epithelium via paracellular mechanism into perineural space and transferred directly to the brain.

**RECENT ADVANCEMENTS IN BRAIN TARGETED DRUG DELIVERY SYSTEM**

**Antibodies mediated drug delivery:** Restriction posed by the BBB and low brain permeability of the antibodies limited the potential of antibody mediated therapy for neurological diseases. mAbs are much large in size and unlike small molecules, unable to cross BBB and approach target sites in the brain. Although, no mAb has been approved for brain targeted therapy but several mAbs are under clinical trials especially for the treatment of Alzheimer’s disease.
Bispecific antibody (bsAb) is newly designed Ab with two different binding specificities. bsAbs are introduced for chemotherapy with one binding specificity targets the tumor cell and other targets the antigen on immune cells. Recent application of bsAbs is the targeted delivery across BBB. bsAbs constructed with one specificity to promote transportation across BBB via receptor mediated transport and second specificity to target the specific site in the brain for desired therapeutic effect. Several BBB crossing bsAbs were formulated and evaluated for brain targeted delivery such as bsAb with transferrin receptor (TfR) binding domain to cross BBB and single-chain variable region fragments (scFv) specificity against amyloid beta peptide.

**Laser light based technology:** This technology is beneficial in disruption of BBB & helpful in glioma targeted delivery. Due to this laser light defects are created in endothelial cells & it becomes leaky, allow transport of therapeutic agents to parenchymal tissues. Combination therapy of 5-aminolevulinic acid (5-ALA) with laser light opened the tight junctions between the endothelial cells for longer period of time. Laser could be combined with other strategies to potentiate BBB disruption. Ultrashort laser pulses are successfully transport nanoparticles, genetically engineered viruses and numerous therapeutic agents to the brain.

**APPLICATION**

**Delivery of macromolecules:** Large molecular size and susceptibility to enzymatic degradation is the prime reason behind low bioavailability of such compounds. Proteins and peptides are generally administered parenterally owing to their physicochemical instability and susceptibility to hepatogastrointestinal first-pass elimination. IN delivery of large number of protein based molecules to brain, such as corticotropin-releasing hormone (CRH), neurotrophic factors, insulin and MSH/ACTH.

**Delivery of stem cell & DNA plasmids:** By nasal administration of DNA plasmids, the level of plasmid in brain was 3.9 -- 4.8 times higher than the plasmid concentration in lungs and spleen & reaches the brain within 15 min following intranasal administration. IN delivery of Neural stem/progenitor cells (NSPC) rapidly migrate to malignant glioma via olfactory pathway. IN delivery of NSPC provides non-invasive and chronic therapy for treating gliomas and other CNS disorders.

**Delivery of chemotherapeutic agents:** Anticancer drugs when administrated by parenteral or oral route to target the brain tumors not only limited the efficacy of these agents by BBB
but also caused serious side effects on other organs; therefore, the nasal route of drug delivery has been explored by researchers. Chemotherapeutic agents such as Perillyl alcohol (POH)\textsuperscript{[53]}, NSPCs\textsuperscript{[54]}, glioma-adapted vesicular stomatitis virus strain (VSVrp30)\textsuperscript{[55]}, methotrexate\textsuperscript{[56]} and telomerase inhibitors (GRN163)\textsuperscript{[57]} have been successfully delivered to target brain tumors by nasal route.

**CONCLUSION**

An innovative drug delivery system is one which delivers the desired concentration of drug at the required site. Intranasal delivery bypasses the BBB to target CNS, reducing systemic exposure of drug, thereby reducing the systemic side effects & target the particular area. Direct nose to brain drug delivery system is a potential strategy to overcome the obstacles presented by the BBB. It is an attractive option of drug delivery due to its non-invasiveness. 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. It is uncertain, however, whether the drug is being released from the carrier system in the nasal cavity and transported to CNS, or the carrier system is transported along olfactory and/or trigeminal nerve pathways into the CNS where the drug is released. Thus, more basic research is required to determine the possible transport pathway of therapeutic carrier to the CNS and their further fate into the biological system.

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