Review Paper:

Nasal Drug Delivery System for Brain Targeting: A Potential Route

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Abstract

Targeted drug delivery aims to concentrate medication in the target tissues while lowering the relative concentration in the remainder of the body. As a result, the drug's efficacy and adverse effects are improved. The Blood brain barrier prevents possible therapeutic molecules from reaching the brain. Approximately 1.5 billion people suffer from CNS illnesses which must be treated with effective drug delivery to the brain. Alzheimer's disease, Parkinson's disease, Huntington's disease, depression, anxiety, seizures, epilepsy, migraine and other CNS illnesses can now be efficiently treated using intranasal medication delivery to the brain. The intranasal route of administration allows for direct medication delivery to the brain without the need for systemic absorption, improving efficacy and reducing side effects in neurotherapeutics.

The olfactory and trigeminal neural pathways allow direct drug delivery to the brain over the BBB and this has become a popular method for delivering a wide spectrum of therapeutic molecules to the brain. When compared to other mucous membranes, the nasal mucosa is highly accessible and serves as a convenient entry point for tiny and big molecules. Intranasal administration has a quick beginning of action, no first-pass effect, no gastrointestinal or pulmonary toxicity and is non-invasive. It also increases bioavailability. This review will give ways for improving drug delivery to the brain via the nasal mucosa as well as recent clinical trials in this area.

Keyword: Nasal Delivery, Brain targeting, Blood-Brain barrier (BBB), Cerebrospinal fluid (CSF), Olfactory and trigeminal pathways.

Introduction

Nasal vestibule, respiratory area and olfactory region make up the nasal cavity. The olfactory area, which is placed high in the nasal cavity and partly overlies the cribriform plate, is one of these. The cribriform plate is a bony structure with pores that allow neuronal bundles from the olfactory area to pass through to the CNS. The olfactory epithelium is located partly on the nasal septum and partly on the superior turbinate, above the normal direction of airflow. Both nasal canals have a surface area of 150-200 cm^2. The respiratory epithelium (large inferior turbinate) covers around 130 cm^2 and the olfactory region covers about 2-10 cm^2 (superior conchae). The exterior naris (nasal valve) is roughly 1.5 cm distant from the internal naris (nasal valve).

Approximately half of the overall resistance to respiratory airflow from the nostril to the alveoli is created by the nasal valve. Breathing and olfaction are the two primary activities of the nasal cavity. Aside from them, the paranasal sinuses and nasal cavity play a function in voice resonance.[1-4]

Physiology of Nasal Cavity

Nasal vestibule: The nasal vestibule, located immediately inside the nostrils and covering roughly 0.6 cm^2, is the most anterior section of the nasal cavity. Nasal hairs, also known as vibrissae, are present in this area and filter inhaled pollutants.[5-6]

Atrium: The atrium is a space between the nasal vestibule and the respiratory region. The anterior section is made up of stratified squamous epithelium whereas the posterior section is made up of pseudostratified columnar cells with microvilli.

Respiratory region: The respiratory region, also known as the conchae, is the largest section of the nasal cavity and it is separated into superior, middle and inferior turbinates that protrude from the lateral wall. Pseudostratified columnar epithelial cells, globet cells, basal cells and mucous and serous glands make up the nasal respiratory epithelium.

Olfactory region: The olfactory area is located on the roof of the nasal cavity and extends down the septum and lateral wall a short distance. The neuro-epithelium of the CNS is the only portion of the brain that is directly exposed to the outside world. The olfactory epithelium, like the respiratory epithelium, is pseudostratified but contains specific olfactory receptor cells that are critical for scent perception.

Mucus membrane of nose and its composition: The nasal mucus layer is only 5 m thick and is divided into two layers: one that is viscous and dense on the outside and another that is fluid and serous on the inside. In all, the nasal mucus layer contains 95% water, 2.5-35% mucin and 2% electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products.

Epithelial cells: These cells have two primary functions: 1. Provide a physical barrier against the entry of infectious germs and allergy particles; and 2. Produce and remove

mucus and foreign particles from the nasal cavity in collaboration with mucus glands and cilia.[7-9]

Ideal Drug Characteristics for Nasal Delivery: The following characteristics should be present in an ideal nasal medication candidate:

• Appropriate aqueous solubility to provide the necessary dose in a 25–150 ml volume of formulation administration per nostril.
• Nasal absorption qualities that are appropriate.
• There was no nose irritation as a result of the medication.
• A clinical justification for nasal dose forms such as quick beginning of action.
• Use a low dose. In most cases, less than 25 mg each dose.
• There are no harmful metabolites in the nose.
• There are no objectionable scents or aromas linked with the medication.
• Stability properties that are appropriate.[10-11]

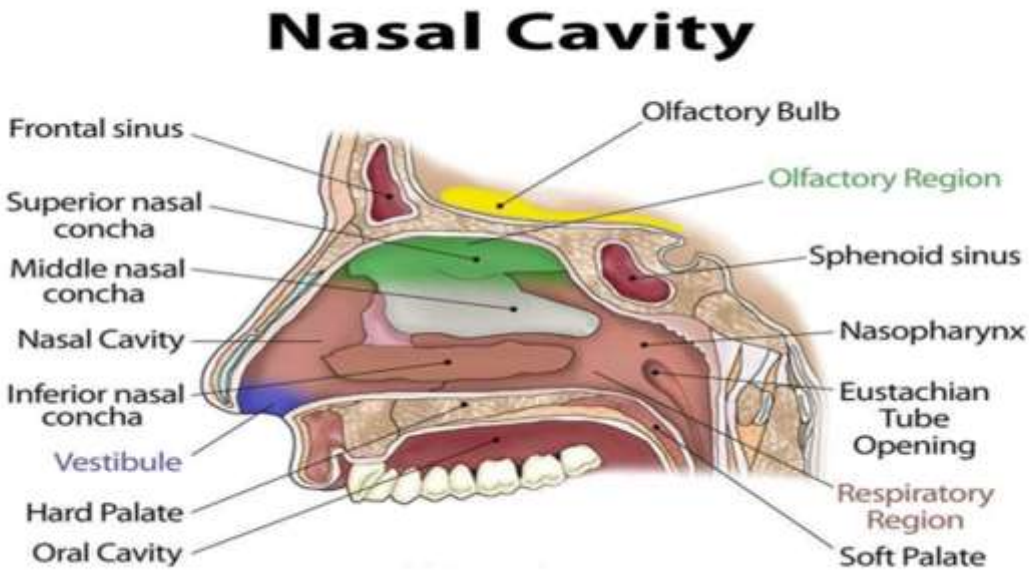

Fig. 1: Physiology of Nasal Cavity

Fig. 2: Ideal Drug Characteristics for Nasal Delivery

Importance of Nasal system:

➢ It provides high permeability of drug, especially for lipophilic and low relative molecular mass drugs.

➢ It provides the direct contact site with lymphatic tissues for vaccines.

➢ Drug degradation within the alimentary canal is absent and drugs with poor stability in G.I.T. fluids are given by nasal route.

➢ Hepatic first pass metabolism is avoided and it provides large area for the absorption of a drug. Rapid drug absorption at the site of the action with quick onset of action will be achieved.

➢ It prevents the risk of overdose of medicaments, avoidance to polluted environment and gastrointestinal conditions.

➢ As it is a non-invasive it reduces the risk of communicable disease transmission.

➢ Convenient for the patients, especially for those on long run therapy, in comparison with parenteral medication.

➢ Hydrophilic compounds exhibit poor oral absorption and could also be particularly fitted to this route of delivery.[12]

Mechanism of drug absorption from nose: The initial step in drug absorption from the nasal cavity is passing through the mucus; large/charged particles may find it more difficult to pass through. Small, unaltered particles, on the other hand, easily pass through this layer. Paracellular transport via cell-to-cell migration or simple diffusion across the membrane are two mechanisms for absorption through the nasal mucosa.[13,14]

1. The watery route of transport, also known as the paracellular pathway, is the initial mechanism. This is a sluggish and undemanding path. Because there is an inverse link between molecular weight and absorption, medicines having a molecular weight larger than 1000 Daltons have poor bioavailability.

2. The second mode of transport via a lipoidal pathway is the transcellular process, which is responsible for the transport of lipophilic medicines with a rate dependence on their lipophilicity. Drugs can also be transported through cell membranes by carrier-mediated transport or through the opening of tight junctions. Chitosan, a natural biopolymer, for example, facilitates medication delivery by opening tight junctions between epithelial cells.[15]

Nasal drug delivery to brain: The nasal route has been studied for decades for systemic administration of medications that cannot be administered orally, but it has recently gained popularity and potential for direct IN delivery of neurotherapeutics to the brain by bypassing the bloodstream, lowering systemic exposure and hepatic/renal clearance. This pathway, which involves the olfactory and trigeminal nerves, has become a significant concern for the safe and effective delivery of a wide range of medicinal compounds including plasmids to the brain.[16]

Pathways of nasal drug delivery

Olfactory pathway: This pathway is made up of the olfactory epithelium, lamina propria and olfactory bulb. The olfactory epithelium is made up of neuronal cells, progenitor cells and supporting cells that are connected by tight junctions. From the olfactory bulb in the CNS to the olfactory epithelium in the nasal cavity, neuronal cells transfer information to the brain. Basal cells and neural cells constantly replace each other and the nasal mucosa becomes permeable as a result of this ongoing motility and replacement, resulting in improved drug transport to the brain.

The nasal epithelium shields the brain from hazardous compounds that are trapped by the mucus layer on the epithelium and removed by the cilia. Blood arteries, mucus-secreting glands, olfactory axons and the maxillary branch of the trigeminal nerve are all found in the lamina propria which lies on the nasal epithelium. Olfactory axons are divided into groups of 20 and enclosed by the Schwann cell sheath, which restricts perineural movement by reducing the space between axons. The ensheathing of the axons is known as filia olfactoria. The olfactory bulb projects to several parts of the brain, including the piriform cortex, amygdale and hypothalamus, making it possible to transport medications directly to the brain through the nose.[17]

Trigeminal pathway: The trigeminal route is also significant in medication delivery IN. Trigeminal nerves innervate the respiratory area which takes up the majority of the nose cavity. The ophthalmic nerve, maxillary nerve and mandibular nerve are all branches of the trigeminal nerve which is responsible for feeling in the nasal cavity. The nasal mucosa is innervated by the ophthalmic and maxillary nerves, which convey information from the nasal cavity to the CNS. Various DDSs target these two branches for medication delivery to various areas of the brain. The trigeminal nerve, which innervates the nasal cavity, reaches the brainstem via the pons and the forebrain via the cribriform plate, boosting drug entry to the caudal and rostral portions of the brain and serving as the main point for IN drug transport to the brain.

Need of nasal drug delivery system for brain targeting: Despite significant progress in drug delivery systems (DDSs) for the treatment of central nervous system illnesses such as schizophrenia, migraine, Parkinson's disease, Alzheimer's disease and brain tumours, novel brain-targeted DDSs are still needed.

The presence of the blood brain barrier is a major impediment to directing the medicine to the brain (BBB). The BBB, which divides the brain from the circulatory system, is a delicate network of blood arteries with tightly packed endothelial cells. It keeps hazardous elements like poison and germs out of the brain. Chronic treatment was required for patients with neurological problems which resulted in side effects in non-targeted organs.

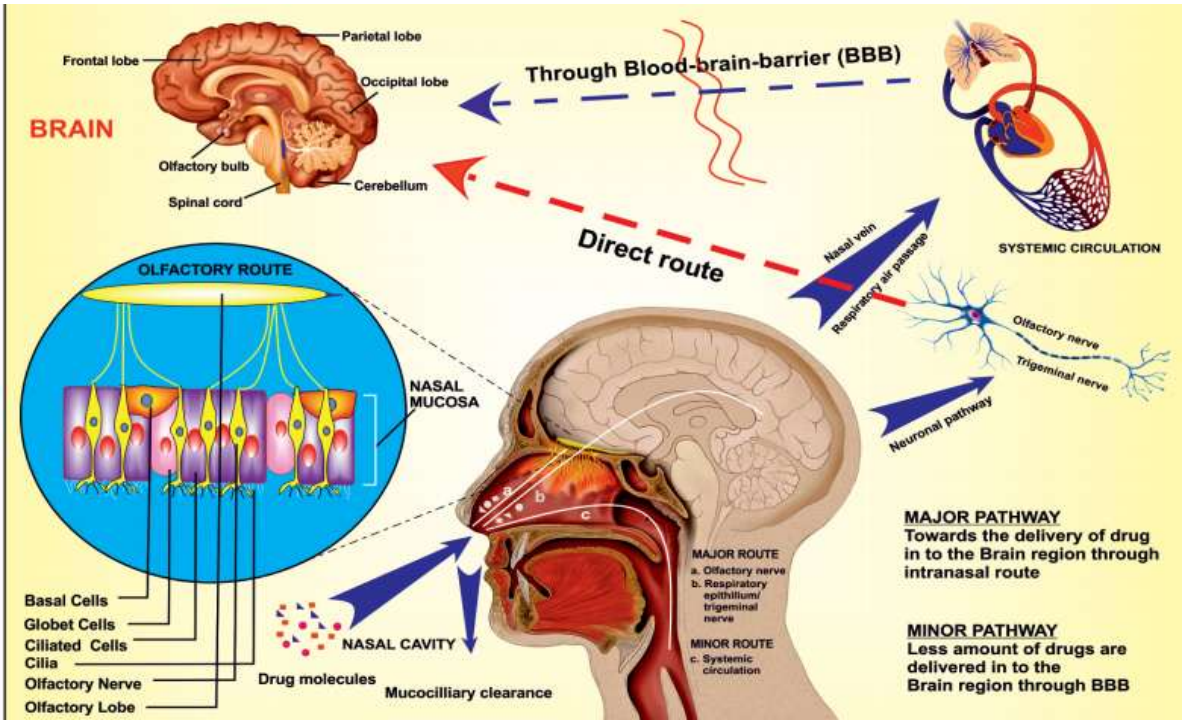

Fig. 3: Drug transport from the nasal cavity to the brain

Because of the BBB, it is thought that the majority of medications used to treat neurological disorders have lost their effectiveness, leaving patients with neurodegenerative diseases and brain tumours with limited therapeutic options.[18] As a result, non-invasive drug delivery to the brain is critical for neurological illnesses and brain cancers that require long-term treatment. The olfactory route is a solid approach for achieving desired therapeutic results at lower doses while reducing negative effects in the treatment of chronic disorders. Direct IN drug transportation to brain refers to the transmucosal delivery of a drug to the brain via the olfactory or trigeminal pathways while passing through the BBB. This is the sole way for the brain to communicate with the rest of the world.[19]

This neural connection has gained attention for delivering a wide range of drug molecules to the brain via formulations ranging from small molecules to large molecules such as nucleotides, peptides and proteins without systemic absorption or toxicity to the major peripheral organs by preventing enzymatic degradation and enhancing pharmacological effects without systemic absorption and toxicity. Different DDSs were studied in animal and human research to see if boosting nasal permeability, increasing mucoadhesion, providing steady or regulated drug release, or increasing deposition at the olfactory epithelium resulted in successful drug delivery from the direct nose to the brain.

Drug delivery strategies for brain targeting: Different DDSs were studied in animal and human research to see if boosting nasal permeability, increasing mucoadhesion, providing steady or regulated drug release, or increasing deposition at the olfactory epithelium resulted in successful drug delivery from the direct nose to the brain.[20]

Invasive strategies

Chemical disruption of BBB: To disrupt the BBB and improve drug delivery to the brain, a variety of invasive procedures are performed. One of the invasive procedures requiring temporary shrinkage of endothelial cells, opening of tight junctions and drug leaking into the CNS is osmotic disruption of the BBB. Tight connections were opened by infusing a hypotonic mannitol solution intracarotidally which facilitated the delivery of chemotherapeutic drugs to the brain. Transport of plasma protein to the CNS, impaired glucose absorption, micro embolism, neurotoxicity of cerebral tissues, altered brain functions and technicality concerns are all important downsides of this technology.[21]

Vasoactive substances like bradykinin and histamine disrupt the BBB and increase medication delivery to the CNS. The activation of B2 receptors, leaking of endothelial cells based on caveolin-1 and caveolin-2 regulation and permeability increase of brain tumour micro capillaries via (KATP) channels are all purpose mechanisms involved in bradykinin's BBB opening actions.

Chemotherapeutic drugs were poorly distributed in the brain due to the transient action and unequal distribution of receptors in the brain. Vasoactive agents' efficacy could be maintained by conjugating them to the surface of NPs. The combination of methylmethacrylate-sulfopropylmethacrylate (MMA-SPM) NPs with RMP-7 resulted in effective antiretroviral medication transport across the BBB, according to a study. This method of mixing drug-encapsulating liposomes or nanoparticles with hyperosmotic agents has proved to improve drug delivery to the brain while lowering systemic side effects.[22,23]

Focus ultrasound enhanced delivery: Another adaptable method for improving medication transport to the CNS is to employ ultrasonic waves to reversibly and transiently open the BBB. Microbubbles (MBs) were used as a contrast agent in ultrasound-based medication administration. These bubbles were given intravenously and acted on the basis of acoustic energy to apply pressure on endothelial cells and open tight junctions, resulting in greater BBB permeability and improved medication delivery to the brain. MBs are made up of semi-rigid lipid and albumin shells encased in perfluorocarbon and have a diameter of 1–10 m. These MBs work in tandem with low-intensity Focus Ultrasound (FUS) and the resulting system is referred to as MB assisted FUS.

The MB-FUS technology reduces the amount of acoustic energy required by focusing it within blood arteries. FUS has been used to successfully deliver anticancer medicines such as trastuzumab, temozolomide, methotrexate, nucleotides such as siRNA and stem cells. For brain targeted delivery, the FUS-MB system works well with other DDSs. This approach could be used in conjunction with PEGylated NPs to disrupt the BBB and boost penetration as well as to target the malignant cell. FUS-grafted gold NPs were given to a brain tumour model through MRI guidance. The FUS system could be useful in brain tumour gene therapy.[24]

Craniotomy-based drug delivery: Intracerebral or intraventricular medication distribution by cranialotomy is a direct technique of addressing a specific portion of the brain without exposing peripheral organs. In intraventricular delivery, a drug reservoir implanted in the scalp allows for regulated medication release and is connected to the brain's ventricles through a catheter. Drug concentrations are increased without the need for delivery to the brain's interstitial fluid. The intraventricular system delivers drugs directly to the ventricles and subarachnoid region of the brain, making it ideal for the treatment of meningioma and CSF metastatic cells. Because diffusion slows with increasing distance, this device relies on the diffusion process to achieve gradual medication distribution inside the brain. As a result, intracerebral administration necessitates high medication doses to obtain the desired therapeutic response.[25]

Convection-enhanced delivery (CED): The difficulties of the intracerebral delivery approach are overcome by convection-enhanced delivery (CED). This intracranial catheter-based diffusion system uses a continuous infusion approach and a pressure gradient to transport a large volume of medicines to target tissues. Drug exposure to adjacent tissue, difficulties in designing optimal formulations, drug instability and subtherapeutic drug levels in the target location are all disadvantages of CED. The efficacy of CED for brain tumour targeting was increased by combining it with liposomes.[26,27]

Polymeric wafers and microchip technology: Polymeric devices for targeted and regulated administration of therapeutic moieties have been developed as a result of advancements in polymer technology. Polyanhydride-based wafers were implanted in the tumour resection area, passed the BBB and slowly released and dispersed the medicine into the brain and targeted site. The first clinically employed local method to cross the BBB was the polymeric wafer which delivered prolonged carmustine release at the tumor's target site. Gliadel® has been shown to be effective in treating newly diagnosed glioblastomas in clinical trials.

Gliadel® wafers have become increasingly important in preserving the therapeutic potential of medications that have been rendered ineffective due to systemic toxicity or BBB impermeability. Due to systemic side effects, camptothecin failed in clinical studies. Wafers have some drawbacks including decreased penetration into deep brain tissue, the production of cysts, meningitis, impaired wound healing and the formation of abscesses. Intracranial implants called programmable microchips are implanted to control drug release at a specific location. Microelectromechanical systems (MEMS) and passive chips are two types of chips. Chip technology could be used to administer single and numerous doses.

MEMS-based active microchips have a drug-filled reservoir on a silicon chip and offer highly programmable drug release at the desired location. Multiple reservoirs carrying various medications could be discharged at the same or different time intervals by active chip technology. The medicine is released by passive chips as the polymeric layer around the microreservoir degrades over time. These chips can also supply several medications in response to a therapy's need. Compared to polymeric drug delivery, these active and passive devices have significant advantages. These devices outperformed polymer delivery due to higher drug loading, drug remaining in touch with microchip, no drug interaction with polymer and programmed controlled drug release.[28]

Non-invasive strategies: For drug transport across the BBB, non-invasive techniques rely on endogenous processes. Prodrug approach, chemical modification of BBB, efflux pump inhibition and different route of administration are some of these techniques.

Efflux pump inhibition: The existence of an efflux pump in the BBB is another impediment to successful medication delivery to the brain. The active P-glycoprotein (P-gp) found on the apical membrane of BBB endothelial cells causes low drug availability in the targeted brain regions. P-gp has a stronger affinity for lipophilic and cationic substances. The majority of low molecular weight medicines, such as nitrosoureas, are P-gp substrates and cannot enter the brain. P-gp efflux inhibition is a good strategy for preserving the therapeutic efficacy of powerful medicines. Pazopanib is a P-gp efflux inhibitor candidate. Verapamil and cyclosporine A are first-generation P-gp inhibitors that cause cytochrome P450 3A (CYP3A) enzyme inhibition and are toxic. Valspodar is a second-generation P-gp inhibitor that has

fewer toxicity concerns. Elacridar, zosuquidar and tariquidar are third-generation inhibitors that have been shown to be safe and do not block CYP3A enzymes.

Dual therapy of efflux inhibitors with NPs was investigated to avoid major side effects associated with efflux inhibitors. To evaluate paclitaxel toxicity in multidrug resistant (MDR) cancer cells, researchers used verapamil in conjunction with paclitaxel micelles. In MDR tumour cells, combination therapy showed paclitaxel toxicity. Patil et al published a study in which they found that paclitaxel-encapsulated NPs had no anticancer effect in a drug-resistant tumour model. In a mouse model, NPs encapsulated with tariquidar and paclitaxel showed an anticancer impact.[29-31]

Pro-drug approach: The chemical alteration of an active molecule to modulate its lipophilic behaviour, enhance permeability and water solubility is known as the pro-drug method. The capacity of a medication to permeate the BBB is aided by increasing its lipophilic properties. Targeted pro-drugs are made up of chemical entities and parent drugs that are designed to approach enzymes or transport systems at the target site, convert them to active moiety. To preserve the chemotherapeutic potential of mustard alkylating agents, a targeted pro-drug strategy based on redox chemical delivery was used.

Alkylating agent redox derivatives passed the BBB and stayed in the brain for longer. Alkylating drugs' lipophilicity and efficacy were found to be improved in pharmacokinetic investigations. This customized pro-drug technology allowed the pro-drug to stay in the brain for longer. The delivery of neurotherapeutics to treat neurological problems has been successful using the pro-drug method. Dopamine, which is used to treat Parkinson's disease pharmacologically, is unable to cross the BBB. L-dopa is carried across the BBB and transformed to dopamine in the brain by the L-amino acid transporter.[32]

Cell based therapy: The use of cell-based treatment to deliver a variety of medications to treat neurological diseases and brain tumours has gained popularity. As transporters for delivery to the brain, macrophages and several types of stem cells are used in this therapy, paracellular and transcellular transport pathways deliver macrophages to the brain. They have phagocytosis as a natural capacity, which allows them to penetrate the brain as Trojan horses. Macrophages are drawn to and infiltrated into the brain during brain tumour and inflammatory situations. Macrophages are a good option for delivering NPs as well as diagnostic and imaging chemicals to brain tumours and neurodegenerative disorders. Gold nanoshells containing macrophages for photothermal therapy invaded glioblastoma spheroids in *in vitro* tests.

Exosomes are nanovesicles that carry a variety of medications and biological compounds in their cargo. Exosomes' protein and lipidic makeup makes it easier for them to merge with recipient cells and deliver therapeutic substances. Exosomes and macrophages are targeted at specific sites in the brain using ligands such as peptides. Exosomes brain targeted delivery ligands include rabies virus glycopeptides, tet-1 peptide and EGFRvIII-specific antibodies for glioblastomas. Stem cells could be employed as a vehicle for cytokines, oncolytic viruses and suicide genes to be delivered to the brain.[33,34]

Intranasal drug delivery: The drug is absorbed into the systemic circulation via the nasal mode of delivery. Transcellular and paracellular absorption, carrier-mediated transport and trancytosis absorption are all followed by drug absorption through the nasal respiratory epithelium. When a medication was injected deep into the nasal cavity, it reached the nasal mucosa, resulting in direct drug transmission to the brain via the olfactory route.[35] The olfactory pathway is made up of olfactory neurons that transport medicines from the olfactory mucosa to the brain in a gradual process. The olfactory epithelium route transports drugs more quickly. The drug is transported directly to the brain after passing via the olfactory epithelium through a paracellular route.

Comparison of current approaches for CNS drug delivery

BBB is a significant obstacle in brain targeting. For effective treatment of neurological diseases, invasive and noninvasive ways to disrupting the protecting BBB were investigated. Hyperosmotic and vasoactive substances break the BBB transiently in invasive techniques. This rupture causes the tight connection between endothelial cells to open, allowing medicines to be transported to the brain. Chemical disruption, on the other hand, has the disadvantages of neurotoxicity and disruption of brain functioning. FUS delivery using MBs to improve BBB permeability is an alternative invasive technique. FUS in combination with NPs and liposomal delivery for direct brain tumour targeting. HIFU improves chemotherapeutic agent delivery to the brain tumour.

Through a catheter, intracerebral and intraventricular injections deliver drugs directly to the brain parenchyma. To ensure maximal drug targeting to the tumour, this method necessitates very detailed mapping of the injection or insertion site. Traditional improved delivery relied on a catheter-linked reservoir to distribute chemotherapeutic drugs slowly and reduce toxicity. One study found that paclitaxel toxicity was increased when CED was used and that this administration approach was no better than other options for increasing survival rates.

Wafers and microchips are polymeric devices that are implanted in the brain to offer regulated drug delivery. Glioblastoma wafers are an effective treatment for both recurrent and freshly diagnosed glioblastoma.[36] Wafer technology is unable to deliver drugs deep into the brain and brain traumas involving poor wound healing and abscess formation have limited its potential. Invasive procedures are confined to well-defined brain tumours despite their

therapeutic value in brain illnesses. These methods entail surgical procedures and are associated with the risk of brain infections. Mechanical equipment has the potential to cause thrombosis and other brain damage. Non-invasive ways to treating life-threatening brain illnesses were developed in light of the risks involved with invasive strategies.

Lipophilic and low molecular weight medicines cannot reach the brain because of P-gp efflux. P-gp efflux is inhibited by cyclosporine A, valspodar, elacridar and zosuquidar, which make brain delivery easier. Toxicity has been recorded with efflux inhibitors, particularly those of the first generation.

Pro-drugs were created to control the lipophilic properties of drugs. The pro-drug strategy involves lowering the number of polar groups in hydrophobic medications or combining them with a lipophilic moiety. This conversion necessitates difficult engineering skills and is ineffective. Stem cells could be used as a delivery vehicle for brain cells. Multiple stem cell types have been found to have a natural affinity for brain malignancies. Suicidal genes, cytokines and oncolytic viruses have all been delivered via stem cells. Clinical investigations of stem cell-based brain delivery failed to achieve positive outcomes. The lack of a defined technique made it difficult to interpret *in vivo* results based on *in vitro* data and a lack of expertise in building oncolytic virus-loaded stem cells limited stem cell-based delivery.

The conveyance of therapeutic components for neurological illnesses is aided by colloidal carriers.[37] The use of nanoparticles in conjunction with other tactics yielded positive outcomes. Scientists are increasingly interested in biligand-targeted nanocarriers for dual targeting of the BBB and the brain parenchyma. Nanocarrier diffusion to the parenchyma is unknown and is dependent on their surface properties. In the case of brain targeting, all invasive and non-invasive techniques have limits. The majority of techniques disrupt or increase BBB delivery rather than bypassing it. IN delivery is non-invasive, as it bypasses the BBB without causing blood absorption and goes straight to the brain.

Intranasal delivery is a valuable and dependable CNS delivery method. The IN neural route for brain delivery has been successfully studied by a variety of colloidal carriers. This method keeps medications out of the peripheral organs and keeps them safe. To produce a therapeutic response via the IN pathway, only a small amount of medication is required. Patients-operated nasal drug delivery devices have recently been introduced to administer pharmaceuticals deep into the nasal cavity.

Formulations Approaches for Nose to Brain Drug Delivery

Nanoparticles: Nanoparticles are closed colloidal systems in which the therapeutic substance is either retained within the colloidal matrix or coated via conjugation or adsorption on the particle surface. They are constructed of polymer, lipid, or a combination of both and can provide prolonged and controlled medication release. Nanoparticles are utilised in administration to attach biorecongnitive lectins to the surface of polyethylene glycol via the nasal route and nanoparticles are also employed in administration to improve drug absorption in the brain. Lectin is a surface-modifying nonimmunological biorecongnitive ligand. Nasal adsorption of nanoparticles can be boosted using this strategy. Lectins are molecules that are used to identify molecules on the surface. The targeting of the brain Conjugated Ulexcuropeus agglutinins I improves the efficiency of nanoparticles (UEAI).

The nasal mucosa is more attracted to UAE-I altered nanoparticles than the pulmonary mucosa. It becomes a possible brain medication carrier. Odorranolectin is the smallest lecithin and has a lower immunogenicity than other members of the lectin family. Nano Odorranolectin, a macromolecular medicine, could be used to deliver medications to the brain in the treatment of CNS illnesses. Polymeric nanoparticles used in the development of nano drug delivery to treat CNS disorders include nanospheres, nanosuspensions, nanoemulsions, nanogels, nano-micelles and nano-liposomes, carbon nanotubes, nanofibers and nanorobots, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and lipid drug conjugates (LDC).

The mechanism of nanoparticles is not fully understood. However, after injection, nanoparticles breach the BBB via numerous endocytotic processes, allowing them to enter the brain. Polymeric nanoparticles consisting of albumin or poly (butyl cyanoacrylate) reach the brain via facilitated endocytosis due to their smaller size. These nanoparticles clump together and release the medicine straight into the brain milieu, where it is then biodegraded due to endocytotic absorption by the BBB.[38-40]

Solid lipid nanoparticles: Colloidal lipid nanoparticles are solid lipid nanoparticles. It is made out of a biocompatible/biodegradable lipid medium that is solid at body temperature and has a size range of 100 to 400 nanometers. It has a number of advantages including targeted distribution, controlled drug release, enhanced drug stability, low biotoxicity, large-scale production and ease of sterilizing. SLN are utilised for hydrophilic and lipophilic drug(s) that are locked in a biocompatible lipid core made of lipids or their combination form such as precirol ATO 5, Compritol 888 ATO, palmitic acid, glyceryl monostearate, stearic acid are supported by surfactant at the outer shell. SLNs outperform traditional drug transport from the nose to the brain.

Because of the occlusive action, adhesion and good application qualities of SLNs to mucosal membranes, they can protect compressed drugs from chemical or biological degradation while also increasing nasal retention time.[41]

Micelles: The micelles are made in an aqueous solution and the hydrophilic head area is connected to the adjacent solvent, while the hydrophobic single tail region is presumed in the micelle centre. This phase is caused by the stuffing behaviour of single-tail lipids in a bilayer. Micelles are approximately spherical in shape; however, they can also take on different shapes such as cylinders, ellipsoids and double layers. Micelle form and size are crucial in the molecular geometry of its surfactant particles and in circumstances of solutions such as temperature, surfactant concentration, ionic strength and pH.[42] As colloidal transporters for drugs, polymeric micelles derived from block copolymers are used. Because of its larger drug-loading capability, gene targeting draws more attention in the field of drug delivery and targeting.

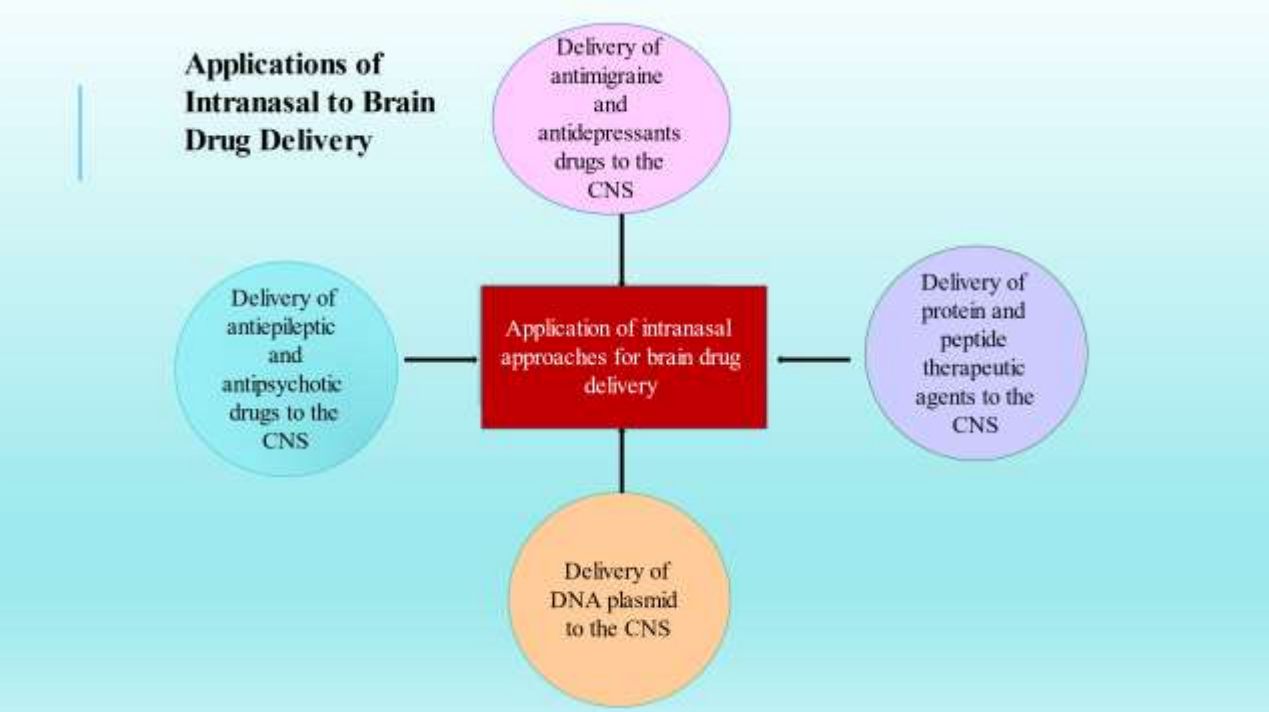

Fig. 4: Applications of Intranasal to Brain Drug Delivery

Recent Clinical Trials on Delivering Drug Molecules to The Brain via Nasal Route[44]

Title	Status	Conditions	Locations
Treatment of Parkinson Disease and Multiple System Atrophy using Intranasal Insulin.	Completed	Parkinson Disease, Multiple System Atrophy	University of Massachusetts Medical School, Worcester, Massachusetts, United States
Chordate System Prophylactic Migraine Clinical Investigation	Unknown status	Migraine	Helsingborg, Sweden Linköping, Sweden
CNS Uptake of Intranasal Glutathione	Completed	Parkinson's Disease	University of Washington, Seattle, Washington, United States
A Study of Diazepam after Intranasal and Intravenous Administration to Healthy Volunteers	Completed	Epilepsy	Prism Clinical Research Unit, Saint Paul, Minnesota, United States
Study of Intranasal Clonazepam in Adult Subjects with Epileptic Seizures	Completed	Epilepsy	Clinical Trials. inc., Little Rock, Arkansas, United States Tampere University Hospital, Tampere, Finland
Effects of Intranasal Nerve Growth Factor for Traumatic Brain Injury	Completed	Traumatic Brain Injury	Department of Neurology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, Jiangsu, China
Effect of Intranasal Oxytocin on Headache in Chronic Daily Headache	Completed	Chronic Daily Headache	MedVadis Research Corporation, Wellesley Hills, Massachusetts, United States
Nasal Versus Venous Lorazepam for Control of Acute Seizures in Children	Completed	Status Epilepticus Seizures	All India Institute of Medical Sciences, New Delhi, Delhi, India

Chitosan loaded nanoparticles: Because the fundamental properties such as noxious substances are less, biocompatibility of the substance is brilliant. Greater filling and entrapment efficacy and capability of delivering hydrophilic particles are obtained from cationic polysaccharides. The chitosan shows favorable outcomes in the delivery of drugs to the brain through the nose.[43]

Conclusion

Drug delivery via the nasal route is a practical, non-invasive method of delivering therapeutic substances to the brain by bypassing the blood-brain barrier (BBB). This technology allows non-crossing BBB drug to be delivered to the central system in a flash, bypassing both the olfactory and trigeminus neuronal pathways. This delivery technique has clinical advantages such as reduced drug dose and overall exposure, resulting in fewer side effects. Furthermore, it provides noninvasiveness, self-medication, patient comfort and patient compliance, all of which are obstacles in endogenous drug medical care. Drug-related issues and pathophysiological conditions of the nose confirm nasal drug absorption.

Enhancing the length of the drug in the nasal cavity, using absorption or penetration enhancers and lowering mucociliary clearance are all popular methods for increasing the bioavailability of nasally given drugs. Because of the successful administration of vaccines and biomolecules like proteins, peptides and non-peptide medicines, which are prone to rapid or acidic degradation and first-pass internal organ metabolism, the intranasal route is seen to be an alternative to the oral and canal routes.

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