NOSE TO BRAIN DRUG DELIVERY SYSTEM

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ABSTRACT

Nose-to-brain conveyance addresses a major context in Novel drug delivery systems. There are an enormous number of neurological illnesses that require treatments in which the medication should reach the cerebrum and cranial cavity keeping away the obstruction because of the blood-brain barrier (BBB) and the issues associated with the fundamental organization for example, drug bioavailability and toxicity. Consequently, the improvement of nasal delivery ready to convey the medication into the cranial cavity is of expanding significance. The blood-brain barrier (BBB) is frequently a restricting variable for drugs arriving at the cerebrum. Bypassing the BBB intranasally (IN), or additionally called the nose to the brain, is an intriguing and oftentimes explored idea for conveying medications to the brain. The goal was to study the attainability and estimation of a normalized IN assessment of direct brain conveyance. The IN course contrasted with the parenteral course to choose if there is a potential direct cerebrum transport. The study showed that the focuses and extents in blood and tissue are exceptional factors and not generally reproducible. The blood-brain barrier and the blood-cerebrospinal fluid barrier are significant barriers to drug delivery in the central nervous system (CNS) since they prevent most molecules from accessing the brain. Alternative drug delivery methods, such as intraparenchymal or intrathecal, are invasive and bear the risk of infection. Nose-to-brain delivery, on the other hand, is a minimally invasive drug delivery method. The drug is delivered from the nasal cavity to the brain through an administration pathway that bypasses the blood-brain barrier. The CNS is especially close to the skull base, which is situated at the roof of the nasal cavity. The olfactory mucosa covers this region. The architecture, structure, and physicochemical characteristics of nose-to-brain drug delivery formulations are used to design and customize them. The mucosa is a crucial criterion. As a result, we'll go through
the most up-to-date information on the properties of the nasal and, in particular, the olfactory mucosa, which will help us design rational intranasal formulations and dosage types. In addition, the data may be used to improve systemic or local intranasal drug delivery systems, as well.

**KEYWORDS:** Olfactory Pathway, Trigeminal Pathway, Blood-Brain Barrier, Alzheimer's Disease, Parkinson’s Disease, Migraine, Neurotherapeutic Delivery.

**INTRODUCTION**

Novel Drug Delivery System has negotiated a role in assisting target site-specific delivery for well-controlled and effective delivery and to associate risk ratio of drugs. Ideally, a drug intended for clinical use should fall under the therapeutic window. The etiology of the disease or a disorder is responsible to target the site-specific delivery. The main aim of NDDS is to restrict access to non-target normal cellular linings, thus minimizing toxic effects and maximizing the therapeutic index. To understand the site-specific target delivery, the pathogenesis of a drug-disease / disorder must be well known. Blood-Brain Barrier and Blood Cerebrospinal Fluid Barrier are barriers that restrict molecules to pass through them when a drug is delivered systematically to target the central nervous system. To overcome the barrier restriction for CNS delivery of a drug, nasal cavity and cranial cavity tissues make a bridge to feasibly deliver a drug.

Brain-related health disorders or neurological diseases or diseases of diverse etiology are major causes of debilitation, agony, and death. Though, the highly lipophilic nature of BBB is a limitation of systemic CNS delivery, physiological functions, and anatomy of the nasal cavity is considered a preferable route to administer drugs to surpass BBB. Nose to brain delivery of a drug is an emerging strategy for selective delivery to the brain and arise from physiological function and mechanism.\[2-3\]
Neurologic issues are the biggest reason for disability-adjusted life years and the subsequent driving reason for death universally. The weight of neurologic illnesses is ascending with unipolar and burdensome issues anticipated to turn into the second biggest reason. Conditions like dementia, uneasiness, and compulsion cause the best expenses on wellbeing spending plans. There is a squeezing need for new focal sensory system medications. The improvement of CNS drugs is as of now hampered by the way that these medications need to cross the blood-brain barrier (BBB) in helpful amounts. For medications to cross the BBB, they should be under 400 Daltons in sub-atomic weight, be to a great extent unipolar, and not multi-cyclic. In case, an enormous number of mixtures don't fit inside these boundaries, granting genuine imperative to the advancement of CNS activities. An elective strategy for conveying atoms to the cranial area is the nose-to-brain course. This course sidesteps the BBB.[4] The nose-to-brain course is acquiring prominence, as shown by both preclinical and human investigations.

Nose to brain drug route is used to deliver substance to the brain by olfactory and trigeminal nerve. The drug is delivered to the nasal cavity which is transported to the cranial cavity of humans and rodents. The transportation is mediated via trigeminal and olfactory pathways. Olfactory bulb is targeted by olfactory pathway and brain stem is targeted by trigeminal pathway. Administration of drug through nose via nasal mucosa is considered faster and higher level of drug absorption site. Many low molecular weight, nonpolar drugs [<300Daltons] in solution can in filtrate nasal epithelium. Drugs with poor stability in Gastrointestinal fluids, poor intestinal absorption are preferable to deliver via the intranasal route.
Intranasal route delivery to the brain circumvents the obstacle for BBB and surpasses pre-systemic metabolism, thus increasing/enhancing the drug bioavailability with that of systemic delivery.

Nose-to-Brain conveyance may address a non-intrusive technique that empowers the conveyance of complex medications to the CNS while staying away from the BBB. This course depends on the rule that medications can get to the CNS following an “alternate way” from the nose straightforwardly to the cranial cavity along the trigeminal or olfactory nerves, situated at the upper piece of the nasal depression. The expanding quantities of peptide and protein drugs that might bear some significance in treating ongoing CNS infections have invigorated exploration in the nose-to-brain conveyance field.

**History and Development**

The nasal depression is separated into the respiratory region and the olfactory zone, with the last arranged high up in the nares and the previous nearer to the nostrils\(^5\). The nasal epithelium is all around vascularized, and inside the olfactory zone, olfactory neurons are uncovered\(^6\) empowering the vehicle of medication compounds straight to into the cerebrum through the olfactory neurons. The specific instrument by which mixtures move from the nasal mucosa to the cerebrum isn't completely perceived. In any case, it is realized that ingestion of atoms happens at the olfactory and respiratory epithelia\(^7\). The courses of compound exchange through the olfactory zone, of the nares, to the olfactory bulb are transcellular through either the sustentacular cells or the uncovered olfactory tactile neurons. The course of movement of mixtures through the nasal respiratory epithelium to the brain is using the trigeminal nerves. Transport to other brain territories after section to the cerebrum (e.g., to the mid cerebrum from the olfactory bulb or to the mind come from the trigeminal nerve) is believed to be principally either by extracellular convective mass stream or by means of perivascular courses.\(^8\) The paracellular course isn't believed to be critical. Intranasally dosed nanoparticles have been seen in the olfactory bulb only 5 minutes in the wake of dosing\(^9\) demonstrating this to be the course of passage for nanoparticle conveyance frameworks. Medicated compounds, having crossed the olfactory epithelium, may likewise be taken up into the overall course through the nasal vasculature.

In any case, the nasal vasculature is without fenestrations and communicates the tight intersection proteins (e.g., zonula occludens 1, occludin, and claudin 5) subsequently, critical vehicle to the overall flow by means of this course will be restricted to low atomic weight
polar compounds. A vital benefit of the nose-to-brain course is the chance of decreasing plasma openness,\(^\text{[10]}\) in this manner taking out fringe results. The normal volume of the human nasal cavity has been estimated utilizing attractive reverberation imaging as 16,449.81 ± 4288.42 mm\(^3\), with the region of the nostril opening being 357.83 ± 108.09 mm\(^2\).\(^\text{[11]}\) Nostril opening connects emphatically with nasal cavity volume. No contrast between the normal volume of the nasal cavity was seen among people. In human examinations, intranasal insulin has been situated inside the cerebrospinal liquid (CSF) of human subjects\(^\text{[12]}\) and found to improve psychological execution in Alzheimer's sickness (AD) patients. Studies with intranasal insulin show that there is no increment in blood insulin levels, demonstrating that particular cerebrum conveyance of peptides in people is conceivable using this course. These investigations exhibit the utility of the nose-to-cerebrum course in people, particularly if fringe drug action ought to be kept away from.

**Drug Formulations**

Albeit clinical investigations prevalently elaborate the utilization of medications in arrangement, in preclinical examinations an assortment of plan types have been tried, like the two arrangements and particulate scatterings. Most creature contemplations have been directed in rodents, and clinical examinations have typically elaborate the utilization of a nasal medication conveyance.\(^\text{[13]}\)

**Solutions**

Just dissolving the medication particle in a fluid stage has been utilized to oversee atoms through the nose-to-brain course. By far most of clinical investigations, which report pharmacological impacts, have included an answer of the medication in fluid media conveyed utilizing a nasal conveyance. One of the primary reports on the conveyance of peptides to the cranial cavity included the intranasal conveyance of insulin to the cerebrum in an insulin arrangement. Pharmacological movement has been seen in clinical examinations, yet preclinical investigations uncover exactly how little of the applied portion is really conveyed to the brain. Thorne et al. (2008) conveyed a C-max of 0.0064% of the portion of radio-labelled interferon-β1b to a monkey’s mind utilizing a fluid arrangement of the medication and guessed that conveyance would be improved with the expansion of ingestion enhancers in the definition.

**Nanoparticles**

To address the low medication levels seen with customary arrangement nasal definitions,
drug conveyance tests have been led with nanoparticulate details (nanoemulsions, lipids, or polymer particles). Basically, these details offer the chance of infiltration upgrade or a more drawn out nasal cavity home time with great proof that nanoparticulates bring about improved conveyance of the cargoes, however restricted quantitative proof of conveyance of the real nanosystems. In reality, Ahmad et al. (2017) found that nanoemulsion particles of 100 nm entered the olfactory bulb and could be found in the cerebrum to a little degree, while particles of 900 nm didn’t infiltrate the mind by any means. The nano-emulsion freight was circulated all through the brain with the 100 nm emulsion beads. These information show that a molecule size cut-off might be operational for the conveyance of nano-formulations past the olfactory bulb.

Lipid Nanoparticles
Lipid nanoparticles, otherwise called strong lipid nanoparticles, comprise of a lipid center settled by a surfactant, and they vary from oil-in-water emulsions in that the lipids are solids at room temperature and the plan is set up by dissolving the lipid, trailed by a type of size decrease and afterward surfactant adjustment of the subsequent particles in a watery scatter stage. These details might be stacked with hydrophobic medications, and on application through the nasal course have appeared to convey medications to the cerebrum. Valproic corrosive lipid nanoparticles when directed intranasally conveyed altogether more medication to the brain, when contrasted and the medication in arrangement, and secured creatures against seizures in a maximal electric stun seizure model, with the insurance being to a comparative degree as that seen on organization of intraperitoneal phenytoin. The model utilized summed up tonic–clonic fractional seizures. It is hypothesized that these lipid plans shield the medication from corruption in the nasal cavity and may surely advance medication transport by vague components. The lipid definition was set up from octyldodecanol, soy lecithin S100, cetyl palmitate, and the nanoparticles settled with Poloxamer 188.

Other Delivery System
Actual mediations pointed toward expanding drug confinement specifically regions are an arising zone. Centered ultrasound with the organization of microbubbles has been utilized to convey gold nanoclusters to explicit brain districts[14] 64Cu-marked or Texas Red–named gold nanoclusters were conveyed to the brain stem utilizing centered ultrasound and microbubbles to confine the nanoclusters to the cerebrum stem. The engaged ultrasound causes restricted microbubble cavitation at the objective district and subsequently empowers
cell take-up, with negligible conveyance to the fringe flow No histologic-level tissue harm was identified in the nose, trigeminal nerve, and brain.

**Importance of Cns Drug Delivery System**

Owing to the poor CNS bioavailability of novel drugs like antibodies, the treatment of CNS diseases such as neurodegenerative, demyelinating, or psychiatric diseases, as well as brain tumours, remains an unmet medical need. Cancer is also one of the diseases with the highest mortality rate. A big issue of drug delivery to the tumor site through the blood-brain barrier is used in the treatment of brain tumours. As a result, the procedure involves invasive intracerebroventricular or intraparenchymal injections.[15] Targeting receptors like transferrin to induce transcytosis in the blood-brain barrier is one alternative currently being researched: Targeting ligands may be attached to biopharmaceuticals or can be found on the surface of the nanoparticles however, the disadvantages of using transferrin for targeting must be considered. Targeting techniques for the blood-brain barrier should be improved to include cell-specific targeting. Since the drug also needs to be guided to the tumor, ligated nanoparticles that directly target the tumor site would be of great interest. The use of dual targeting delivery systems in conjunction with intranasal delivery drugs would have a better chance of meeting their target sites if they were applied. Several viruses have been discovered. Antiviral medications, on the other hand, are effectively blocked from passing across the blood-brain barrier by efflux transporters.

**DISEASE PROFILE**

**Alzheimer's Disease**

A Progressive neurodegenerative problem that influences more seasoned people and is the most well-known reason for dementia. It might advance to an absolutely vegetative state.

Alzheimer's disease is a progressive brain disease that wreaks havoc on a person's memory, intellect, and personality.[16]

Atrophy of cortical and subcortical areas is associated with deposition of Beta-amyloid protein in the form of extracellular senile (amyloid) plaques and formation of intracellular neurofibrillary tangles made up of ‘tau’ protein. These abnormal proteins accumulate mostly due to reduced clearance, but in some cases, due to overproduction, and cause neuronal damage followed by neuron loss. There is marked cholinergic deficiency in the brain, though other neurotransmitter systems, especially Glutamate and neuropeptide, are also affected.
Consequences of Alzheimer’s Disease
1. Alzheimer’s disease (AD) and multi-infarct dementia (MID)
2. Mild cognitive impairment (MCI) Or ‘Common Symptoms’ of the elderly; dizziness and episodic memory lapses
3. Mental retardation in children, learning defects, attention deficit disorder.
4. Transient ischaemic attacks (TIAs), Cerebrovascular accidents, stroke.

Cause of Alzheimer’s Disease
Alzheimer's is believed to be brought about by the strange development of proteins in and around synapses. One of the proteins included is called amyloid, stores of which structure plaques around synapses. The other protein is called tau, stores of which structure tangles inside synapses.

Even though it’s not known precisely what makes this cycle start, researchers presently realize that numerous prior year’s indications show up. As synapses become influenced, there’s likewise an abatement in compound couriers (called synapses) engaged with sending messages, or signals, between synapses. Levels of one synapse, acetylcholine, are especially low in the cerebrums of individuals with Alzheimer's illness. Over the long haul, various territories of the cerebrum contract. The principal regions generally influenced are liable for recollections. In more uncommon types of Alzheimer's sickness, various regions of the cerebrum are influenced. The main side effects might be issues with vision or language as opposed to memory.

Depression
A mental illness due to mood suppression, energy reduction, loss of interest, irregular eating and appetite, improper sleep and insomnia and lack of concentration while working and mind disturbance while listening. Depression is linked to stress, poor self -esteem, adverse events occurring due to long time medication, increased mortality and suicidal risk. [17]

According to clinical psychology, depression is characterized as a disorder instead of a disease which is caused due to emotional, physical, behavioural, imbalance and leads to difficulty in functioning of the body.
According to the World Health Organisation (WHO) depression would become the second largest cause of illness leading to morbidity.

**Consequences of Depression**

A person may feel the isolated and feel the following:

- Sleep disruption and amnesia
- Neglecting work
- Loss of concentration
- Dis-orientation towards intellectual or creative work
- Emotionally weak
- Excessive aggression
- Drug and alcohol abuse.

**Migraine**

Headache frequently starts at adolescence and most influences those matured somewhere in the range of 35 and 45 years. It is more normal in ladies, ordinarily by a factor of about 2:1, in light of hormonal impacts. It is brought about by the actuation of a component somewhere down in the mind that prompts the arrival of agony delivering provocative substances around the nerves and veins of the head. Headache is intermittent, frequently deep-rooted, and portrayed by repeating assaults. Assaults regularly include migraine, which is: of moderate or extreme power uneven throbbing in quality disturbed by routine actual work with term of hours to 2-3 days queasiness (the most trademark related component); assault recurrence is anyplace between once every year and once per week; and in youngsters, assaults will in general be of more limited length and stomach side effects more conspicuous.\(^{[18]}\)

**Parkinson’s Disease**

Parkinson's disease (PD) is a progressive degenerative disorder that primarily affects the elderly. It was first described in 1817 by James Parkinson. The majority of cases are idiopathic, while some are arteriosclerotic and postencephalitic. Wilson's disease (Hepatolenticular Degeneration) is a rare condition caused by chronic copper poisoning.\(^{[19]}\)

An extrapyramidal motor disorder is characterized by rigidity, tremor, and hypokinesia, A progressive degenerative disorder that majorly affects the elderly. There is a progressive degeneration of dopamine-releasing neurons in the extrapyramidal system, especially at the basal ganglia.
Consequences
- The slowness of movement (Bradykinesia) and difficulty initiating movements
- Fixed muscle tone causing expressionless facial features, the rigidity of voluntary muscles causing the slow and characteristic, stiff shuffling gait and stooping posture
- Muscle Tremor extremities that usually begins in one hand, e.g. ‘pill rolling’ movement of the fingers.
- Speech Problems, excessive salivation, and, in advanced disease, dysphasia.

Causes of Parkinson's Disease
- Degeneration of neurons in the substantia nigra pars compacta (SN-PC) and the nigrostriatal (Dopaminergic) tract
- Deficiency of dopamine (DA) in the striatum which controls muscle tone and coordinates movements. An imbalance between dopaminergic (inhibitory) and cholinergic (excitatory) systems in the striatum occurs giving rise to the motor defect.
- Ageing
- Genetic predisposition
- Oxidative generation of free radicals

Anatomy
The human nasal cavity reaches from the nostrils to the 12-14 cm long nasopharynx and is separated by the nasal septum. Three turbinates - the lower turbinate, the middle turbinate, and the upper turbinate with a total surface area of around 160 cm of mucosal filter, warm and humidify the inhaled air. There are four distinct types of epithelia and the underlying mucosa in the nasal cavity: squamous, Olfactory, transitional and respiratory. The frontal parts of the nasal vestibule contain squamous mucosa. From the nostrils, the nasal vestibule stretches to the inferior turbinate. The squamous epithelium is stratified and has feathers, sebaceous glands, and sweat glands in its mucosa. There are no cilia in the transitional epithelium and the one separating the squamous from the respiratory epithelium, epithelium, and the respiratory tract of the olfactory epithelium. The respiratory and olfactory mucosa are of particular concern concerning drug absorption. The lymphoid tissue associated with the nasopharynx (NALT) comprises immune cells and is closely related to local lymph nodes and tonsils in humans.
Respiratory Region
Nasal respiratory mucosa is an important section which helps in delivering drugs systemically. It is also known as conchae and this is the largest part of the nasal cavity. It is divided into three turbinates which are superior, middle and inferior turbinates. Nasal respiratory region is useful for delivering drugs systemically. It is constituted by epithelium, basement membrane and lamina propria. Nasal respiratory epithelium consists of pseudostratified columnar epithelial cells, goblet cells, basal cells and mucous and serous glands.

Olfactory Region
Olfactory region located on the roof of the nasal cavity. As the respiratory region is also pseudostratified but for small perception it contains specialised olfactory receptor cells. Neuroepithelium of the olfactory region is only a part of CNS which is exposed directly to the external environment.

Blood-Brain Barrier
The blood-brain barrier was first recognized by Lewandowsky in 1900 while he was studying the limited permeation of potassium ferrocyanide into the brain. BBB is a highly dense protective layer that only allows the passage of selective molecules into the brain. BBB is divided into two components which are the Endothelial or capillary barrier and the Ependymal carrier. BBB is formed by a complex cellular system that consists of endothelial cells, astroglia, pericytes, perivascular macrophages, and basal lamina. The brain is highly restricted by BBB. Human brain receives about 20% of cardiac output. BBB segregates brains from the circulating blood. In brain targeting, permeability through the BBB is a major problem. Blood capillaries which are present in CNS are different in their structure from the other tissue’s blood capillaries. These structural differences in blood capillaries and are responsible for permeability barriers within the extracellular fluid in brain tissue and blood within brain capillaries. Capillaries of the vertebrate brain and spinal cord allow rapid movement of solute within the organs, with a special layer of endothelial cells tightly sealed in the capillaries, the surface area of BBB is greater than blood-cerebrospinal fluid barrier approximately 5000 folds. BBB acts as a rate-limiting factor for the permeation of the drug into the brain. BBB is only permeable for the transportation of nutrients such as blood glucose, proteins, peptides, and peptide drugs. Practically, it is shown that if drugs are soluble and used in brain disorders can easily cross BBB by oral administration.
The pericytes embedded in the basal lamina are claw-like appendices twisted together to intertwine the capillaries. Pericytes have their important functional properties such as intervening in a dispute to bring about the inflammatory process, regulation for the activities of endothelial cells of the brain, and for associate rapidly they include capillary-structure.

Small lipophilic molecules are easily diffused by BBB is a common misconception because some small lipophilic molecules do not penetrate the brain, this is due to the presence of some active transport in BBB. Several ATP-binding cassettes (ABC) are present in BBB. These ABC transporters are responsible to expel the multiplicity of drugs from the CNS. On the surface of BBB, some natural transport systems are also present which helps in the transport of some special large polar compounds into the brain. So, these also work the same as pseudo transporters, by carrier-mediated transcytosis transport small molecules by receptor-mediated transcytosis transport large molecules.

**Marketed Nasal Formulations**[^24]

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Vaccine</th>
<th>Dosage form</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Nasal FluBerna</td>
<td>Human influenza vaccine</td>
<td>Virosomes spray</td>
<td>Berna Biotech</td>
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<td>Flu Avert</td>
<td>Equine influenza vaccine</td>
<td>Drops</td>
<td>Heska</td>
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<td>Flu Mist</td>
<td>Human influenza vaccine</td>
<td>Spray</td>
<td>MedImmune</td>
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<tr>
<td>StrepAvax</td>
<td>Human streptococcus- a vaccine</td>
<td>Proteosomes nanoparticulate</td>
<td>ID Biomedical</td>
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<tr>
<td>MaxiGuard Nasal Vac</td>
<td>Porcine Bordetella bronchiseptica vaccine</td>
<td>Drops</td>
<td>Addison Biological Laboratory</td>
</tr>
</tbody>
</table>

**Mechanism of Action**

Olfactory Mucosa is Suitable for delivery of nasal gel. Drugs reach the CNS by transportation via neuronal connection.[^25-26] Pathway through which drug uptake Commences

1) Intracellular

2) Extracellular

**Intracellular Pathway**

- In olfactory or trigeminal axons endocytosis of a drug takes place, the mechanism of uptake of a drug via axons is transported in nervous tissue and reaches the synaptic cleft in the olfactory bulb or brain stem.
- The transportation of a drug takes place along the nerve in endocytic vesicles.
- Exocytosis occurs when drug reaching the Brain distribution occurs throughout CNS via this pathway treatment of CNS disorder or infection can be treated.
Endocytosis of particles with large size is done in the olfactory nerve. Internalizing smell molecules like aluminium lactate (294Da) as well as Wheat-Germ agglutinin horseradish peroxidase [LGA-HRP, 80 KDA].

Ophthalmic maxillary branches are involved in trigeminal nerve endocytosis to apply drugs.

Transport from olfactory nerve takes 1.5-6 Hours on the other hand trigeminal takes 17-56 hours to reach CNS.

Trigeminal nerve pathway takes longer time to reach & act on CNS as that of olfactory nerve Pathway.

**Extracellular Pathway**

- The Bulk Flow process along with Olfactory & Trigeminal nerves is descriptive in this pathway.
- Drug Penetrates the epithelial layer & Reaches Lamina propria, the drug is switched in cleft between axons & ensheathing layer crossing of tight epithelial junctions takes place & drug reaches the nerves.
- The lamina propria passage doesn’t imply that it will reach CNS rather can be absorbed by blood vessels & enter systemic circulation.
- Entering into glands or lymphatic vessels connected to deep cervical lymph nodes can also take place.
- The subarachnoid spare in the cranial cavity which is adjacent to the trigeminal or olfactory bulb can receive some amount of drug.
- The Bulk flow of CSF in cranial cavity Distribution.
- Intracellular route is size dependent on the other hand endocytosis is process dependent or molecular weighing Substance.

**Key Considerations For Successful Formulation Development**

Water-based, hydroalcoholic, nonaqueous, suspensions, and emulsions are all options for nasal spray compositions. Excipients in a formulation can comprise solvents, mucoadhesive agents, buffers, antioxidants, preservatives, and penetration enhancers, among others (i.e., compounds to improve absorption or penetration). The excipients chosen are determined by the API's solubility as well as the concentration required to provide the required dose in each spray. The formulation should be designed to increase contact with the nasal mucosa, delay clearance as much as possible, and absorb quickly.\(^{[27]}\)
Although most nasal medications are in spray form, dry powders have some advantages. Chemical stability is improved, as is the danger of microbiological deterioration (which requires less preservatives) and the possibility to provide bigger doses of API.

During the creation of a nasal formulation, there are numerous problems to address, including:

- Overcoming poor solubility of the API
- Minimizing clearance
- Increasing bioavailability
- Ensuring compatibility with the delivery device
- Improving patient acceptance

### Marketed Products of Nasal Delivery Devices

<table>
<thead>
<tr>
<th>Devices</th>
<th>Drug</th>
<th>Stage</th>
<th>Indication</th>
<th>Product Name</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Mechanical powder sprayers</td>
<td>Zolmitriptan</td>
<td>Marketed</td>
<td>Migraine</td>
<td>Zomig</td>
<td>AstraZeneca</td>
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<td>Phase 2 trial</td>
<td>Parkinson’s disease</td>
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<td>-</td>
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<td>Sumatriptan Powder</td>
<td>Marketed</td>
<td>Migraine</td>
<td>Imitrex</td>
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<td>Nicotine</td>
<td>Marketed</td>
<td>Smoking cessation</td>
<td>Nicotrol NS</td>
<td>Pfizer</td>
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<td>Powder sprayers (Nasal spray)</td>
<td>Dihydroergotamine mesylate</td>
<td>Marketed</td>
<td>Migraine</td>
<td>Migranal</td>
<td>Valeant Pharma</td>
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<tr>
<td>Spray pumps (Nasal spray)</td>
<td>Nafarelin acetate</td>
<td>Marketed</td>
<td>Endometriosis</td>
<td>Synarel</td>
<td>Pfizer</td>
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<td>Multi-dose metered dose spray pumps</td>
<td>Calcitonin</td>
<td>Marketed</td>
<td>Osteoporosis</td>
<td>Miacalcin</td>
<td>Novartis</td>
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<tr>
<td>Multi-dose metered dose spray pumps</td>
<td>Oxytocin</td>
<td>Marketed</td>
<td>Induction of lactation and labor</td>
<td>Syntocinon</td>
<td>Novartis</td>
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### BARRIERS TO NASAL ABSORPTION

#### Physiological barrier

- Nasal mucosa
- Nasal epithelial barrier
- Mucociliary clearance
- Pathophysiological factor
- Nasal metabolism
- Efflux transport system
Physicochemical barrier
❖ Drug solubility and dissolution
❖ Molecular weight and size
❖ Compound lipophilicity
❖ pH and pKa

Formulation factor
❖ Site of disposition
❖ Osmolarity
❖ Dose and volume
❖ Drug concentration

Brain Targeted Intranasal Formulations of Cns Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Formulations[24]</th>
<th>Disease</th>
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<tbody>
<tr>
<td>Bromocriptine</td>
<td>Dopamine D₂ agonist</td>
<td>Chitosan -loaded nanoparticles CS -BRC -NPs</td>
<td>Parkinson’s disease</td>
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<td>Busprione HCL</td>
<td>Anxiolytic agent</td>
<td>Bus-chitosan nanoparticles</td>
<td>Anxiety</td>
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<td>Clonazepam</td>
<td>Benzodiazepine derivative</td>
<td>Mucoadhesive microemulsion</td>
<td>Status epilepticus</td>
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<td>Deferoxamine</td>
<td>High affinity iron chelator</td>
<td>Nasal solution</td>
<td>Cerebral ischemia</td>
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<td>Duloxetine</td>
<td>Serotonin and norepinephrine reuptake inhibitor [SNRI]</td>
<td>Nanostructured lipid carrier [NLC]</td>
<td>Depression</td>
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<td>Steroid Hormone</td>
<td>E₂ loaded chitosan nanoparticle</td>
<td>Alzheimer’s disease</td>
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<td>Growth hormone – releasing neuropeptide</td>
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<td>Stimulate GH secretion</td>
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<td>Dopamine agonist</td>
<td>Mucoadhesive nanoemulsion and solid lipid nanoparticles [SLNs]</td>
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<td>Acetylcholinesterase [AChE]inhibitor</td>
<td>Chitosan-loaded nanoparticles CS-RHT-NPs</td>
<td>Alzheimer’s disease</td>
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<td>Ropinirole</td>
<td>Dopamine D₂ agonist</td>
<td>Mucoadhesive formulation</td>
<td>Parkinson’s disease</td>
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<td>Sumatriptan</td>
<td>Selective 5-HT ID agonist</td>
<td>Micellar nanocarrier &amp; microemulsion</td>
<td>Migraine</td>
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<td>Venlafaxine</td>
<td>Serotonin and norepinephrine reuptake</td>
<td>Chitosan-loaded nanoparticles VLF-CS-NPs</td>
<td>Depression</td>
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Future Perspective of Intranasal Delivery of Intranasal Delivery To Cns

The effective non-invasive treatment of neurological diseases is often limited due to the presence of biochemical dynamics barriers: blood-brain barrier and cerebrospinal fluid. BBB represents a hurdle for a large number of drugs, including antibiotics, antineoplastic agents, and various CNS active medications such as neuropeptides. This creates a considerable threat for the therapy of brain diseases.\textsuperscript{[24]} It is becoming increasingly clear that the crossover of the BBB and drug delivery CNS is a complex and challenging task that requires close collaboration and common efforts between researchers from various scientific areas, including pharmaceutical sciences, chemistry, physiology and pharmacology. Therefore, the treatment of neurological diseases has become one of the most important challenges. Recent advances in nanotechnology have provided promising solutions to this challenge. Of the work done in recent years, nanotechnology is receiving more and more attention efficiently. Various nanocarriers, for example, polymeric nanoparticles, solid lipid nanoparticles, liposomes, micelles, dendrimers, nanogels, nano emulsions and nano suspensions have been studied for the administration of CNS therapies. It is very likely that in near future more drugs intended for CNS disorders in nasal formulation form will come on the market. But this functional mechanism of drug delivery to the brain is a potential investigation area. There are some challenging tasks that must be faced during intranasal delivery, especially of High molecular weight polar drugs such as peptides and proteins, low membrane permeability, possibility of enzymatic degradation of the molecule in the lumen of the nasal cavity and mucociliary clearance. These challenges should be improved by focusing on bioadhesive excipients and absorption enhancers in the formulation to overcome rapid mucociliary clearance, enzymatic degradation and low permeability of the membrane, thus improving the bioavailability of the incorporated drugs. Nanoparticle-based drug delivery technology that currently exists should be improved in addition, so that it can be safe, effective, goal-oriented and also profitable. Future development of CNS nanomedicines should focus on increasing their drug trafficking. Performance and specificity for brain tissue using novel targeting halves, improving their BBB permeability and reducing its neurotoxicity. Drug delivery mechanisms to target the brain are also unclear, so attention should be paid to clear up the confusion about how exactly the drug passes through the nose to specific areas of the brain for the treatment of neurological and psychiatric diseases and focus on formulation

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<th>Talwar et al.</th>
<th>World Journal of Pharmacy and Pharmaceutical Sciences</th>
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<td>inhibitor [SNRI]</td>
<td>Serotonin receptor agonist [IB AND ID]</td>
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<tr>
<td>Zolmitriptan</td>
<td>Micellar nanocarrier</td>
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<td>Migraine</td>
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strategies, drug delivery devices, invention of new excipients to improve the nose bioavailability, study of the mucoadhesive property of polymers to prevent the expulsion of drugs so they can be withheld by longer periods and show maximum effects. Apart from this, Toxicodynamic studies of drugs and excipients and the nanotoxicity of nanocarriers also need to be extensively evaluated.

Challenges
For quite a while intranasal organisation is credited as a viable course to convey drugs into the fundamental dissemination, bringing about quick beginning and higher medication bioavailability than old style extravascular organisation courses. All the more as of late, intranasal delivery began to acquire consideration as a potential conveyance course to the cerebrum because of the remarkable association between the focal sensory system and the outside climate, which is made by the olfactory nasal neuroepithelium. Both restorative uses have been (and stay) testing, not just because of anatomic and physiological attributes of the nasal pit and the basic components of medication assimilation and medication conveyance, yet additionally due to the in vitro models. Right now accessible models to foresee nasal pervasion remain ineffectively prescient of nose-to-brain conveyance and of medication retention in people.

The extent of this Research Topic remembers the new advances for intranasal drug conveyance frameworks, innovations and gadgets that have been created to elevate nose-to-blood, nose-to-lung and nose-to-mind conveyance of medications, peptides, proteins and biologics.[28-29]

Explanation and updates on the components that underlie and bargain these kinds of transport in a nose that is in solid or neurotic state, are specifically compelling to endeavor to build the achievement of novel intranasal systems. Translational examinations of direct nose-to-cerebrum and nose-to-lung transport[30] from cell models to creatures and creatures to people would be of extraordinary importance for the advancement of intranasal conveyed therapeutics.

CONCLUSION
The blood–brain barrier (BBB) is an impenetrable barrier to neurotherapeutic delivery in vivo. The direct transport of drugs from the nose to the brain through the olfactory and
trigeminal nerve pathways represents an attempt to overcome this barrier. These nerve pathways begin in the olfactory neuroepithelium of the nasal cavity and end in the brain.

This path provides a wide range of neurotherapeutics to the central nervous system (CNS), including macromolecules and low molecular weight medicines. The current review focuses on the anatomy and physiology of the nasal cavity, as well as the pathways.

Mechanisms of neurotherapeutic transport across the nasal epithelium and various strategies to improve direct drug delivery from the nose to the brain.

Therapeutic drug delivery through Nose to brain is a promising potential treatment option for neurological diseases. To successfully build Nose to brain delivery systems, one must first comprehend the olfactory region's specific structure. When compared to methods that attempt to cross the blood-brain barrier, using the Nose to brain delivery system in drug delivery has several advantages. Since the transport is guided specifically from the nose to the brain and does not have to overcome blood-brain barrier barriers or systemic clearance, it is likely that a lower dose of the applied drug is needed while using Nose to brain. The exact targeting results in reduces the possibility of systemic toxicity as well. The relatively high patient compliance is a key feature of Nose to Brain. Some obstacles must be overcome in order to develop suitable intranasal formulations, as well as medical delivery devices. Avoiding immunogenicity in biopharmaceutical proteins, in particular, is a challenge that can only be overcome with a clever formulation strategy. Medical devices that specifically target this site are still unavailable. As a result, more research is needed to advance intranasal Nose to Brain delivery and pave the way for its safe and reliable clinical use.

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