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INTRANASAL DRUG DELIVERY: A NON INVASIVE APPROACH IN BRAIN TARGETED NDDS

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ABSTRACT

By partially avoiding the blood–brain barrier (BBB), intranasal medication delivery is a new and promising method of delivering therapeutic medicines directly to the brain. The architectural and physiological features of the nasal cavity, the pathways and mechanisms of nose-to-brain medication transport, and the key elements affecting drug absorption and brain targeting are all covered in this review. To enhance drug stability, nasal retention, bioavailability, and targeted distribution, a number of formulation techniques have been studied, including nanoparticles, liposomes, nanoemulsions, microemulsions, exosomes, mucoadhesive systems, and thermoresponsive in-situ gels. To improve medication deposition in the olfactory area, specialized nasal administration devices have also been created. Clinical translation is still significantly hampered by issues such mucociliary clearance, enzymatic degradation, restricted nasal absorption, formulation stability, and possible toxicity. To determine the long-term effectiveness and safety of these technologies, more investigation, thorough safety evaluations, standardized assessment techniques, and carefully planned clinical studies are required. As a result, administering drugs intranasal is a practical method of treating central nervous system disorders.

KEYWORDS: Intranasal drug delivery, Nose-to-brain drug delivery, Blood–brain barrier, Central nervous system, Brain targeting, olfactory pathway, Neurological disorders.

1. INTRODUCTION

The medication is delivered specifically to the site of action in a targeted drug delivery system, avoiding non-target organs. which is a highly semi permeable membrane. Any disorder (or) diseases related to brain are difficult to control because it is covered by the blood brain barrier. Which doesn't allow the 100% of large molecules and 98% of small molecules. The blood brain barrier consists of tight junctions around the capillaries and actively transport the metabolic products such as glucose crosses the barrier with specific protein. There are different factors responsible for crossing the blood brain barrier like binding of the drug to a transporter, opening and closing of ion channels, lipophilicity, enzymatic degradation of drugs, higher molecular weight of drugs and the presence of functional groups. The blood-brain barrier permeability of any medication is determined by these parameters.[1]

The quick absorption and distribution of medications in the brain is one of the main advantages of nasal administration. The Nasal mucosa allows for quick access to several brain Regions, including the olfactory bulb, cortex, Hippocampus, and hypothalamus. This direct path It is perfect for treating acute neurological diseases since it guaranties that therapeutic medicines can work quickly on their designated targets within the brain. Furthermore, intranasal delivery reduces the risk of Systemic side effects by limiting the exposure of the Drug to the rest of the body.[2]

This review synthesises current knowledge on nasal anatomy and Physiological determinants of absorption and deposition, the Formulation approaches for intranasal drug delivery systems, and Device technologies designed to improve targeting especially in the direction of the olfactory region for possible transport from the nose to the brain.
By integrating These aspects, the review aims to provide a comprehensive under-Standing of how intranasal delivery can optimise therapeutic outcomes, Especially for CNS therapist.[3]

In this study, we aim to analyse the current status and trends in nasal drug delivery and N2BD technologies based on a survey of researchers and an analysis of patents. By Understanding the advantages, disadvantages, and challenges of these technologies, we Hope to provide insights into the development of novel drug delivery systems and the Treatment of neurological disorders.[4]

2. Previous Development of NBDD Systems

Controlling material flow, preserving a stable neuronal environment, and safeguarding the brain all depend on the BBB. The BBB has active efflux transporters, closely packed endothelial cells, and major facilitator superfamily domain-containing protein (MFSD2A), in contrast to peripheral capillaries. Transmembrane tight junction proteins (TJs) such as occludin, claudins, and junctional adhesion molecules are linked to the intracellular actin cytoskeleton by proteins like zonula occludens-1. While MFSD2A controls transcytosis, these TJs prevent paracellular diffusion, forming a physical barrier with poor permeability reinforcing the transcellular barrier. Neurovascular units are made up of endothelial cells, pericytes, and astrocytes that interact through secreted proteins to control the growth and function of BBB microcirculation. The blood-brain barrier (BBB) strictly regulates the flow of various substances from the blood to the brain via the paracellular and transcellular pathways. Ions and solutes can passively diffuse according to concentration gradients thanks to the paracellular route.

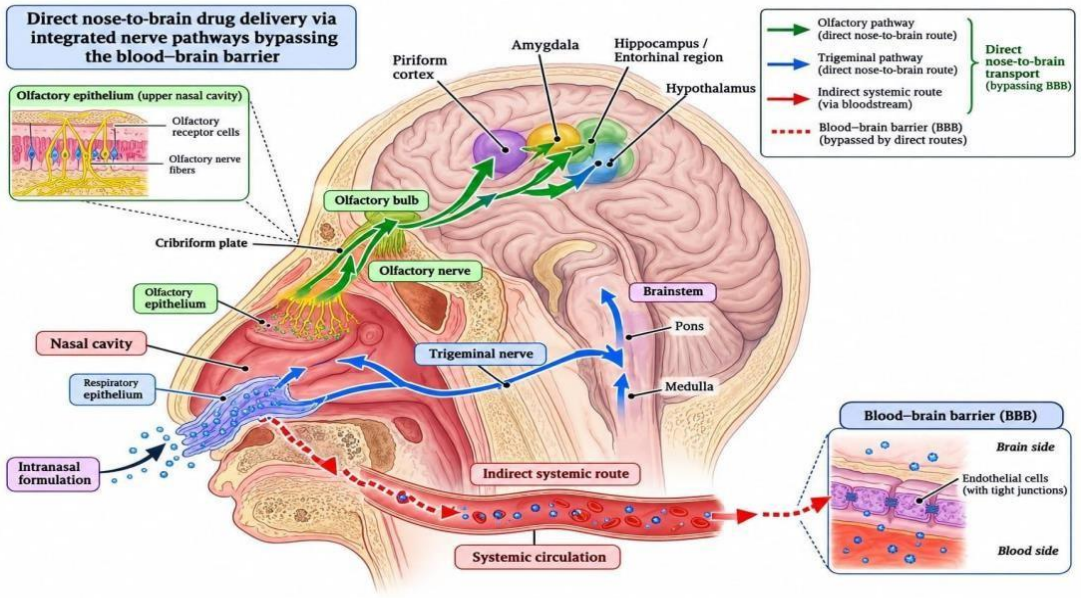

Fig. 1: Direct drug delivery from the nose to the brain using integrated neural pathways that avoid the blood-brain barrier.[5]

Passive diffusion, absorptive transcytosis, receptor-mediated transcytosis (RMT), and carrier-mediated transport (CMT) are all components of the transcellular route. Only tiny molecules under 400 Da or those with strong lipid solubility are allowed by passive diffusion. By controlling the composition of the interstitial fluid in the brain, these transport mechanisms preserve synaptic function, information processing, and neural connections, safeguarding the brain. As a result, the BBB prevents most medication molecules, blood cells, viruses, and neurotoxic plasma components from entering.[6]

Higher permeability from TJ loss and higher transcytosis from MFSD2A deficiency or more caveolin-1, which affect CMT and RMT functioning, are BBB dysfunctions that are crucial to brain and CNS disorders. For instance, after an ischaemic stroke (IS), the BBB becomes excessively permeable to macromolecules. However, due to a number of constraints, the extent and timing of BBB disruption in each disease remain poorly understood. For example, BBB permeability decrease in MS is frequently and reliably found to be either transitory or chronic.

Cerebrovascular degeneration, neuropathological alterations, and cognitive impairment linked to AD can be made worse by early degeneration of the cerebral microvasculature, decreased cerebral blood flow, and eventual BBB disintegration. destruction from pathological disorders linked to traumatic brain injury (TBI) goes beyond simple blood vessel destruction; bleeding and edema worsen the rupture of the blood-brain barrier at the lesion site and in surrounding areas. Current research on BBB disruption in a variety of disorders is still in its infancy due to the intricacy of CNS pathologies. Recognising that drug distribution through a damaged BBB poses considerably more difficulties than through an intact BBB is crucial. Changes in the blood-brain barrier can impact medication accumulation and intracranial distribution by either promoting or obstructing their passage, which might complicate the development and research of therapeutic-tic agents. Consequently, understanding the key proteins and structures involved in the formation and regulation of the BBB is essential for advancing IN drug delivery strategies for a range of diseases. Furthermore, the administration of drugs via various nanocarriers represents a promising therapeutic approach for addressing BBB injury and dysfunction.[6]

3. The nasal cavity's anatomical and physiological aspects

A direct pathway to the brain is provided by the highly vascularized nasal cavity. The rich lined with respiratory and olfactory mucosa, playing vascularization facilitates rapid systemic and brain a vital role in air filtration, humidification, and drug absorption of drugs, while the mucociliary clearance absorption. Its close connection to the olfactory and mechanism helps in protecting against pathogens and trigeminal pathways enables direct nose-to-brain foreign particles, transport, bypassing the blood–brain barrier for rapid and targeted drug delivery.[2]

The nasal mucosa serves as the main interface for intranasal medication deposition and absorption, and the nasal cavity facilitates speech, breathing, air filtering, and smell. Adults have a cavity volume of about 15 mL and a mucosal surface area of about 1 cm^2, which is somewhat increased by the turbinate structures. The nasal cavity's anatomy can be separated into the olfactory, respiratory, and vestibular regions.

The vestibular region encompasses an area of around 0.6 cm^2 and is situated in the anterior part of the nasal cavity. The area is distinguished by a strong squamous epithelial lining, a large amount of mucus production, and an abundance of hair follicles known as vibrissae. Its main function is to act as a barrier of defense against dangerous environmental elements by filtering breathed air and capturing particulate debris. Intranasal absorption in this area is modest and pharmacologically negligible due to these anatomical characteristics and the squamous epithelium's restricted permeability.[3]

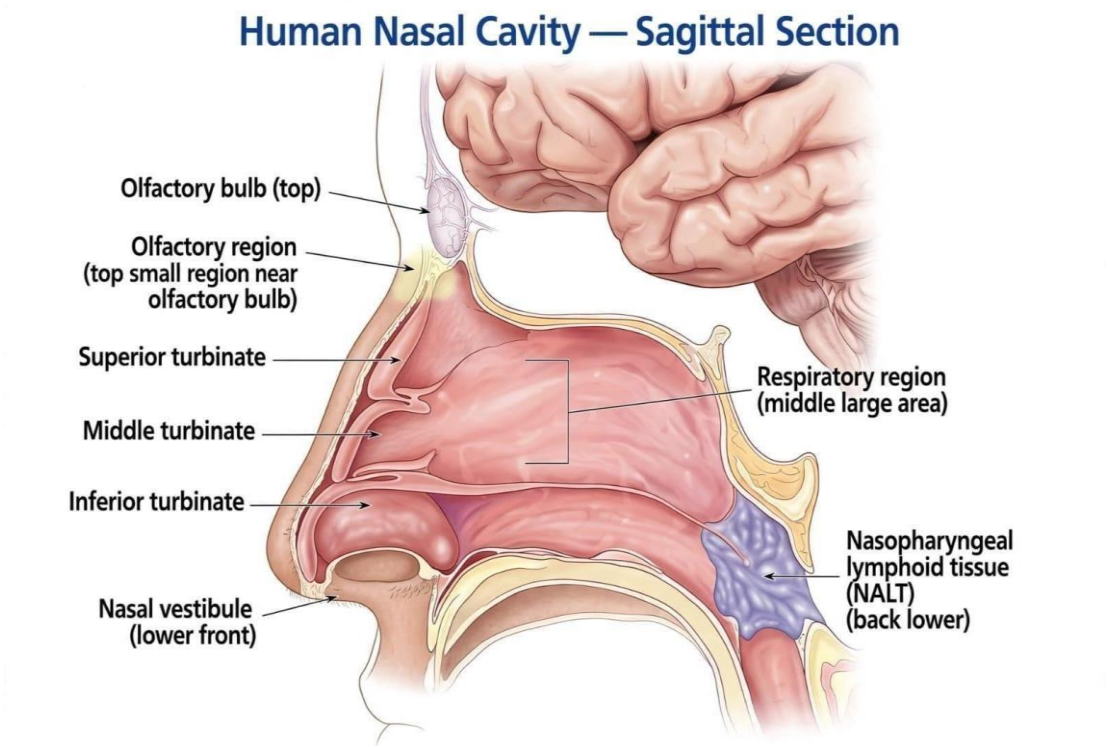

Fig. 2: Schematic anatomy of the human nasal cavity.[3]

The respiratory region, commonly referred to as the respiratory mucosa, includes the turbinates (conchae). At about 130 cm^2, it makes up the greatest portion of the nasal cavity. It extends from the lateral wall and is divided into superior, intermediate, and inferior turbinates. The humidification and thermoregulation of air absorbed into the respiratory system depend on these specialized anatomical components. Meatuses, which are pathways that facilitate airflow and

guaranty substantial interaction between the breathed air and the respiratory mucosal lining, are positioned in between these structures. Goblet cells and pseudo stratified, ciliated columnar epithelial cells, which are essential for intranasal medication administration, line the nasal respiratory mucosa. Under normal physiological conditions, the nasal epithelium is covered in a thin layer of mucus produced by glandular tissues and goblet cells. The nasal mucus layer is only 5 µm thick and is made up of two separate layers, an inner layer and a thick, viscous outer layer that exhibits a more liquid and serous consistency.[3]

Water makes up the majority of this mucus layer's makeup (95%), with mucin (2.5–3%) and a combination of electrolytes, proteins, lipids, enzymes, antibodies, and bacterial byproducts making up the remaining 2%. The olfactory region, located in the superior portion of the nasal canal, is characterised by a lining of specialised olfactory epithelium that includes Bowman's glands and olfactory sensory neurones (OSNs). Because it is the sole part of the central nervous system that is directly exposed to the outside world, this neuroepithelium is special. This unique anatomical characteristic makes it possible for medications given intranasally to get beyond the blood-brain barrier and enter the brain. Therefore, the olfactory region is a useful pathway for administering CNS-targeted treatments, especially when treating neurological conditions like epilepsy, Parkinson's disease, and Alzheimer's disease, migraine, and multiple sclerosis. Although the olfactory epithelium and the respiratory epithelium share a pseudostratified structure, the olfactory epithelium has specialized receptor cells that are necessary for detecting odours.[3] The unique anatomical structure of olfactory nerves connecting the olfactory bulb through the cribriform suggests the possibility of direct drug delivery into the brain.[7]

However, the nasal cavity also contains inductive immunological tissues, which makes it a desirable location for immunization. Similar to Waldeyer's ring in humans (adenoids and tonsils), NALT is a crucial site for immunological surveillance. It has dendritic cells, organized lymphoid follicles with B- and T-cell regions, and other antigen-presenting cells that effectively analyse antigens administered intranasally. By producing secretory IgA at mucosal surfaces and circulating IgG, intranasal immunization can prime both mucosal and systemic immunity, offering multilayer protection.

The nasal cavity's anatomical structure offers many benefits for medication distribution from a pharmaceutical standpoint. For example, the presence of turbinates enhances the surface area of the nasal mucosa, enabling drug deposition and absorption, while the highly vascularized nasal mucosa allows a direct pathway for absorption into the systemic circulation. While the nasopharynx aids in the subsequent transfer of inhaled or deposited substances, the nasal septum facilitates targeted local medication administration.

While the nasal cavity's physical features greatly increase medication absorption and speed up therapeutic responses, intranasal drug delivery formulation features are just as important for attaining the best possible therapeutic results. To improve intranasal absorption, key physicochemical characteristics of the medication, such as particle size and solubility, must be carefully evaluated. The bioavailability of medications given intra-nasally can be further increased by adding appropriate excipients and carriers, such as permeation enhancers.[7]

The respiratory area, which makes up the majority of the nose cavity, is mostly used as a protective surface and is covered in respiratory ciliated epithelium. In addition to removing particles and allergens, it warms and humidifies the air that is inhaled. Trigeminal nerve branches supply innervation to the respiratory mucosa.[8]

4. The routes and methods of delivery from the nose to the Brain

4.1. Routes

4.1.1. Pathway of the olfactory nerve

According to certain research, the olfactory nerve pathway is how the majority of neurophilic viruses (including rabies, herpetic stomatitis, and horse encephalomyelitis viruses), steroid hormones, metal ions (like nickel and cadmium), and proteins enter the brain. These materials are taken up by pinocytosis, endocytosis, or simple diffusion at the axon terminals of olfactory neurons after passing through the olfactory mucosa. They then travel straight to the olfactory bulb via the sieve plates after passing through the axonal plasma of neurons and arriving at the rhinencephalon. The olfactory nerve pathway is thought to be the most significant route for medications to enter the brain from the nose and the most straightforward approach to get beyond the blood-brain barrier.[9,10,11]

4.1.2. The route of olfactory mucosal epithelium

Drugs enter the central nervous system (CNS) directly through the mucosal epithelial channel, also known as the nose-brain pathway, after reaching the olfactory mucosal epithelium through cytosolic action or diffusion. This pathway allows the brain to absorb the majority of small-molecule medications, including insulin, lidocaine, dopamine, 5fluorouracil, and dihydroergotamine. This pathway is further subdivided into two parts: a transcellular transport pathway and a paracellular pathway. In the former, drug molecules are transported into supporting and glandular cells surrounding the olfactory nerve via mechanisms involving carrier transport or cytosolic or passive diffusion across mucosal epithelia other than olfactory neuron receptor cells.[9]

4.1.3. Pathway of the trigeminal nerve

The trigeminal nerve's ophthalmic and maxillary nerve branches can reach epithelial cells in the nasal cavity's respiratory and olfactory regions, while the opposite end enters the central nervous system either passes via the ethmoid plate and terminates at the olfactory bulb region or begins at the pons and ends at the brainstem's spinal nucleus of the trigeminal nerve. Strong radioactivity was found in the trigeminal nerve, trigeminal branch ganglia, and olfactory bulb after iodine-125-conjugated insulin-like growth factor 1 was administered intranasally. The concentration of radioactivity in the trigeminal nerve was ten times higher than in the olfactory bulb, indicating that the trigeminal nerve may occasionally act as a conduit for drugs to enter the brain after intranasal administration.[9,10,11]

4.1.4 The route of blood circulation

The extensive capillary network in the lamina propria of the respiratory region is the primary route by which low-molecular-weight lipophilic medicines enter the brain after being absorbed into the general circulation. However, pharmaceuticals must pass the blood-brain barrier (BBB) after entering the general circulation in order to reach the central nervous system (CNS). As a result, this pathway limits the therapeutic use of many medications. A medication will eventually enter the central nervous system (CNS) through one or more of the previously stated channels after nasal administration; the dominant pathway of a drug delivery system is determined by variations in drug characteristics, formulations, and administration methods.[9]

4.2. MECHANISMS OF DRUG TRANSPORT FROM THE NOSE TO THE BRAIN

IN order to get across the constrictive blood-brain barrier (BBB), nose-to-brain drug administration takes advantage of special anatomical and physiological connections between the nasal cavity and the central nervous system (CNS). Direct neuronal transport, extracellular diffusion, perivascular and perineural bulk flow, and supplementary indirect pathways

via lymphatics or systemic circulation are the main mechanisms. The proportional contributions of these pathways vary depending on the drug's qualities, the formulation's features, and the nasal deposition site; they are not mutually exclusive.[12]

The nose's nasal cavity, which is lined with a mucosal layer and consists of two small chambers that are 12–14 cm long, is crucial for breathing and smelling. It has a surface area of about 150 cm². The vestibule, respiratory, and olfactory areas make up each nasal cavity. Due to its small surface area (about 0.6 cm^2) and restricted circulation, the vestibule most anterior portion absorbs drugs very little. The nose cavity receives sensory input from the ophthalmic and maxillary branches of the trigeminal nerve, which innervates the respiratory region, which has the greatest surface area and extensive capillaries.

The semilunar ganglion contains trigeminal nerve neurons, whose axons travel through the pons to the brainstem. Lateral branches create a route for drugs to enter the brain by passing through the cribriform plate to the olfactory bulb. Nevertheless, drug transport is not facilitated by the trigeminal nerve terminals located beneath the mucosal epithelium. The mucosa of the respiratory region is essential for systemic medication distribution because of its large surface area and rich blood flow. Despite having a lesser mucosal area, the olfactory region of the upper nasal cavity is important for IN drug delivery. Neurons, supporting cells, basal cells, and Bowman's gland cells are among the cells found in the olfactory epithelium. Direct medication delivery to the brain is made possible via the olfactory bulb's connections to the piriform cortex, amygdala, and hypothalamus. In general, the olfactory nerve, trigeminal nerve, and respiratory pathway are the three pathways that contribute to the NBDD.[6]

Drug molecules are mostly transported into the brain via the olfactory and trigeminal pathways, which make it easier for the medications to reach different parts of the brain and distribute throughout the entire organ. There are two main ways that drug molecules are transported. The internalization of olfactory or trigeminal neurons through nonspecific mechanisms or receptor-mediated endocytosis is the main mechanism of intraneuronal trafficking. Once inside, drug molecules are enclosed in vesicles and carried to nerve terminals via the axon. From there, they are released into the synaptic cleft, attach to postsynaptic cells in the olfactory bulb, and eventually travel to different parts of the brain. Furthermore, a key route for IN delivery is the extra-neuronal pathway, which comprises paracellular and transcellular transport.[6]

4.3. Pharmacokinetics of drug delivery from the nose to the brain

Developing the best medication formulation, figuring out dosage schedules, and learning about drug interactions are the objectives of pharmacokinetic research for nose-to-brain drug administration. According to earlier pharmacokinetic research, drugs like donepezil liposomes, dantrolene, and clomipramine nanoparticles can reach their peak concentrations in rodent brains as soon as 20 to 30 minutes after intranasal administration.

The highest concentration of intranasally delivered nanoparticles containing fibroblast growth factor, however, was only measured in the olfactory bulb after 30 minutes in another investigation; the peak concentration in the rest of the rat brain was achieved four hours after application. The trigeminal nerve, optic nerve, and olfactory bulb had the highest drug concentrations, followed by the cerebrum and hippocampus, according to pharmacokinetic profiles of intranasal vascular endothelial growth factor in rats and intranasal allopregnanolone in mice. Rats given fibroblast growth factor intranasally showed the lowest quantities in the cerebellum and even lower values in the serum.

Drugs are getting into the systemic circulation because the nasal mucosa is well vascularized. Methotrexate, for example, reaches rats' cervical lymph nodes with peak concentrations an hour after intranasal delivery, in addition to several brain regions. Humans and experimental animals clearly have different pharmacokinetic characteristics. Both humans and dogs received insulin lispro intra-nasally; although the amount in the human CSF was below the measurement limit, it was found in the of dogs. For additional pharmacokinetic research, a computational model that compares the intranasal delivery patterns of humans and mice has been created. The model indicates that the amount of nanomaterials delivered nasally to the mouse brain is two orders of magnitude lower than that of the human brain. This implies that extrapolating pharmacokinetic research from lab animals to people has limited value and should always be done carefully.[8]

5. Systems for Drug Delivery

The IN route has benefits, but it also has drawbacks, such as a short absorption time, the need for modest dosages (25–200 µL) because of the narrow surface area, quick mucociliary clearance, and enzymatic degradation. Furthermore, the physical Additionally, a drug's molecular size, solubility, and lipophilicity can affect how well it absorbs in the nasal cavity and accumulates in the brain. Several delivery strategies have been used in CNS disease studies to improve the therapeutic results of medications. Recently developed nano carriers, viral vectors, EV carriers, and intelligent responsive drug delivery systems can efficiently encapsulate medicines, guaranty prolonged drug release, boost drug stability, and enhance drug penetration. Patients with neurological diseases can now receive genes via viral vectors.

However, manufacturing difficulties, high production costs, and serious safety issues, such as patient deaths in clinical trials limit their use. Despite these problems, viral vectors are still a promising field for further study. Exosomes have also been utilized to move proteins, nucleic acids, and tiny compounds across the blood-brain barrier. For instance, an exosome connected to RAGE-binding peptide was created as a hypoxiaspecific carrier for NBDD of anti-microRNA oligonucleotide. In recent decades, nanocarrier systems have played a crucial role in the advancement of drug delivery technology. Numerous nanocarriers have been successfully used to improve CNS drug delivery via IN, including lipid nanoparticulate systems, liposomes, nanoemulsions, microemulsions, polymeric micelles, dendrimers, transforsomes, and nanosuspensions. These carriers have several advantages, such as better drug solubility and higher bioavailability due to improved absorption.

They are regarded as biodegradable and biocompatible carriers and can include ligands for specific organ delivery. Surface targeting is a crucial method for brain targeting. modified nanocarriers functionalized with monoclonal antibodies, proteins, and peptides. For instance, RVG29 peptide-modified polyethylene glycol-polylactic acid-co Glycolic acid nanoparticles (NPs) have stable and prolonged drug release characteristics and have been shown to be effective in targeting the brain in a rat model of cerebral ischemia (CI). Another strategy to improve bioavailability and absorption is the application of nasal formulations that are mucoadhesive and improve retention at the application location. Quercetin, for instance, has been developed into a mucoadhesive nanoemulsion that may pass the blood-brain barrier and preferentially accumulate in the brain, thereby minimizing systemic side effects.

However, advancements have been made in the realm of intelligent responsive drug delivery systems. For example, the thermosensitive hydrogel system (THS) has shown potential smart response and controlled release properties. THS-loaded resveratrol was used as a model medication in a study by Zhou et al. It showed features including slow release, temperature sensitivity, cytocompatibility, and a notable rise in neurotransmitter levels after low-dose IN

administration. The completion of quality assessments, process optimization, and preclinical research, including toxicological analyzes of excipients, permeation enhancers, and polymers, will determine these delivery systems' viability for clinical drug formulation. The development of innovative drug delivery methods has greatly expanded the therapeutic uses of medications for the treatment of CNS disorders.[6]

5.1. IN CNS Treatment Drug Administration

Intranasal administration of vaccines

According to recent research, IN administration is important in the treatment of CNS disorders, especially neurodegenerative diseases like Parkinson's and Alzheimer's. This technique improves therapeutic efficacy by facilitating the efficient delivery of large-molecule medicines to the brain. For IN delivery, a variety of chemical medications and biological agents, including as peptides, proteins, and RNA, have been produced. This section examines current studies on the use of IN drugs to treat CNS diseases. The limitations of the current vectors present a significant clinical hurdle for gene delivery to the central nervous system. The majority of viral vectors must be injected straight into brain tissues because they are too large.

Because nasal administration is non-invasive, it is becoming more popular as a substitute technique for delivering plasmid DNA expressing therapeutic or antigenic genes. Calcitoningene-related peptide (CGRP), a powerful vasodilator, was administered intranasally to the brain in one research. According to the research, intranasal CGRP greatly reduced cortical and endothelial cell death, enhanced cerebral blood flow, and alleviated vasospasm. It has been demonstrated that the intranasal route is a successful method of delivering CGRP for brain targeting. After intranasal treatment, brain tissues showed a considerable expression of the beta-galactosidase protein produced by the recombinant plasmids. The brain targeting efficiencies of intranasally delivered plasmid DNA were continuously higher than those of intravenously administered plasmid DNA more than an hour after dosage.

The scientists came to the conclusion that the nasal route might be an alternate way to transport plasmid DNA to the brain, and that intranasally applied plasmid DNA may reach the brain directly, perhaps through the olfactory bulb. The neurotropic nature of the herpes simplex virus-based vectors is an advantage. However, prior research has shown that type 1 herpes simplex virus (HSV-1)-based vectors caused CNS neurons to undergo apoptosis, resulting in severe and frequently fatal encephalitis in immunocompetent patients. However, compared to HSV-1, vectors based on the herpes simplex type 2 virus, ΔRR, are less pathogenic in the central nervous system and do not cause CNS neurons to undergo apoptosis.

According to a study, ΔRR administered intranasally prevented seizures and neuronal death in rats and mice, making it a suitable therapeutic platform for the treatment of chronic neurodegenerative illnesses.[6,13]

5.2. Nasal Drug Delivery System Applications

Intranasal administration of vaccines

Intranasal administration of vaccines Nasal injection of vaccines is utilized for both local and systemic immune responses in the nasal route. Furthermore, it offers a protective barrier. The mucosal surface is where most foreign antigens enter the body. Because of mucociliary clearance, the nasal mucosa serves as both a filter for pathogens and a first barrier or protective layer against microbes. Vaccines increase the development of antibodies, or immunoglobulins (IgA, IgG, IgM, and IgE), which make up nasal secretion and are the first line of defence.[11]

Targeting the brain via nasal medication administration

The main obstacle to medication distribution to the brain Tissue is the creation of appropriate dose forms that have the potential to cross the blood-brain barrier. The drug's ability to penetrate the blood-brain barrier depends on a number of material characteristics, including molecular size, lipophilicity, and selectivity. The direct olfactory link between the brain and the nose at the start of the 20th century. The discovery of neurons and the movement of CSF from olfactory Observing neurons led to the creation of new concepts. The nasal cavity can provide access to brain tissues, and that transport can occur in the other direction.[11]

Medication delivery using proteins and peptides

The majority of proteins and peptides have large molecular weights and are hydrophilic in nature. At concentrations between 1% and 2%, these polar compounds have low bioavailability and poor absorption. For medications like desmopressin and calcitonin, poor bioavailability is not seen as a significant issue due to their broad therapeutic index; nevertheless, in certain situations where the therapeutic index is restricted, other approaches must be used. Numerous studies have used absorption enhancers and bio-adhesive compounds to increase the bioavailability of these medications. Glycols, cyclodextrin, and surfactants are a few types of absorption enhancers.[11]

6. Elements to Take Into Account When Developing a Nasal Drug Delivery System.[11]

When developing a nasal drug delivery system, several elements are deemed crucial. These are regarded as such because minor adjustments to these variables could the dose types increased therapeutic efficacy. The following table lists these factors. The nasal epithelium without being considerably impacted by physiochemical variables.

Key factors involved in the formulation of nasal drug delivery system

Category	Key factors
Physicochemical factors	• Chemical structure of the drug • Molecular size and weight • Polymorphism (different crystalline forms) • Lipophilicity (fat solubility)
Formulation-related factors	• pH of the formulation • Osmolarity (tonicity) • Type of gelling agent used for in-situ systems • Solubilizers (surfactants and co-solvents) • Drug dose and concentration
Physiological factors	• Nasal blood circulation and flow rate • Mucociliary clearance mechanism • Enzymatic degradation (nasal enzymes) • Pathological conditions (e.g., inflammation, infection)

The drug's chemical form

When creating intranasal dosage forms, the drug's chemical form is more crucial. It has an impact on both stability and medication absorption.[11] For instance, the drug's absorption may change if it is transformed into a salt form. In-situ nasal absorption of L-tyrosine carboxylic acid esters was shown to be substantially higher than that of tyrosine.[14]

Molecular Weight

Since only compounds with lower molecular weight can be employed for brain targeting, molecular weight is one of the most crucial criteria. Drugs up to a molecular weight of 1000 Da can be administered when discussing brain targeting with intranasal medication administration.[11]

In order to facilitate the transport of bigger molecules across the nasal barrier, sophisticated formulation techniques such the use of permeation enhancers, carrier systems (such as emulsions, liposomes, and NPs), or mucoadhesive agents are frequently used.[15] Absorption diminishes dramatically as the molecular weight exceeds 1000 Daltons. Absorption enhancers can be used to improve absorption.[14]

Polymorphism

Many chemical substances can be found in nature in several forms. They exist in several states, including stable, metastable, and unstable.[11] It is well recognized that the polymorphic character of drug molecules influences the solubility and rate of drug dissolution, and consequently, the absorption of medications through the biological member tyrosine.[14]

Lipophilicity

The drug's ability to be absorbed from the mucosal surface is determined by its lipophilic nature. In general, it depends on the drug's hydrophilic lipophilic balance (HLB).[11] However, the lipid-rich nasal membrane makes it difficult for highly hydrophilic medications, which favor watery conditions, to pass through, leading to decreased absorption rates. Hydrophilic drug delivery can be improved by formulation techniques including encapsulation in lipid-based NPs or the addition of lipophilic excipients.[14]

pH of formulation

The nasal mucosa has a pH between 5.5 and 6.5. This pH range should be covered by the formulations created for intranasal delivery. The nasal mucosa contains an enzyme called lysozyme, which is responsible for getting rid of a variety of microbes.[11] For example, a formulation including a pH much lower than 4.5. However, the mucosal barrier may be compromised by a pH that is extremely alkaline. In order to maintain pH compatibility and guaranty both patient comfort and efficient drug delivery, buffering agents are frequently used.[15]

Tonicity

The concentration of a solution in relation to bodily fluids is called its tonicity. The nasal mucosa’s ability to absorb drugs can be impacted by tonality. It has been noted in earlier research that the drug’s hypertonic solutions constrict the nasal mucosa and improve absorption. Additionally, hypertonic solutions prolong the duration of drug occupancy and reduce the normal ciliary activity.

Gelling agent

The materials that increase a formulation's viscosity are called gelling agents. The more the gelling capacity, the greater the how long a medication stays in the nasal cavity. Research indicates that drugs with high molecular weight do not exhibit a substantial increase in absorption, while dosage forms with high viscosity and less molecular weight that are meant to be taken through the intranasal route are better absorbed from the nasal mucosa.[11]

Solubilizers

High aqueous solubility of pharmaceuticals is undesirable, yet the soluble form of the medication is ideal for absorption. When the medications are meant to be absorbed through the nasal cavity, they should be sufficiently fat soluble. Alcohol, glycerol, medium chain glycerides, and labrasol are examples of aqueous solvents and cosolvents that can be used for this. Cyclodextrin complexation and the use of non ionic surfactants are two more methods to solve this issue. Nasal irritation must be taken into account when taking these substances.[11]

Drug concentration

While this wasn't always the case, some research indicated that drug absorption increased as drug concentration increased. When drug absorption occurs in accordance with a concentration gradient, drug absorption increases as concentration rises; however, when absorption is carrier mediated, there is no discernible increase in absorption as concentration rises.[11]

Nasal blood flow

There are a lot of blood vessels in the nasal mucosa. It is crucial to the humification of breathed air. Fast drug molecule absorption from the nasal mucosa is facilitated by the presence of blood vessels.[11]

Pharmacological substances like vasoconstrictors (like phenylephrine) or vasodilators, or physiological factors like stress or exercise, might alter nasal blood flow and affect the effectiveness of delivery.[15]

Mucociliary clearance

The natural process of clearing dust, allergies, and other foreign objects from the nasal passages is known as mucociliary clearance. This clearance and absorption process has an indirect impact on the residence time of dose forms. Chitosan, carbopol, and HPMC are examples of bio-adhesive polymers that are employed in formulations to get around this.[11]

Enzymatic degradation

Numerous enzymes found in the nasal route can break down medications when they are administered through the nasal cavity. The protease enzyme is primarily responsible for breaking down proteins into peptones. Endopeptidases like serine and cysteine proteases disrupt the peptide molecule's internal structure, making the medication ineffective, while exopeptidases like mono and diamino peptidases break the protein molecule from the C- and N-terminal.[11]

Pathological conditions

Drug absorption and mucociliary clearance are impacted by pathological diseases include nasal allergies, allergic rhinitis, nasal infections, and nasal surgery. During a cold or the flu, the intranasal route cannot be used due to increased nasal cavity outflow. Drug absorption may be impacted by pathological disorders that may change the pH of the nose.[11]

6.1 Intranasal Medication Administration

Treating disorders of the central nervous system (CNS), such as Parkinson's disease, Alzheimer's disease, and other neurodegenerative or psychiatric conditions, remains a significant therapeutic challenge. Despite medical advancements, the majority of treatments are symptomatic and do not stop the course of the disease. The blood-brain barrier (BBB), a highly selective membrane that keeps almost all large biomolecules and 98% of small molecule medications from entering the brain, is one of the main obstacles to treating CNS illnesses. As a result, there is still a gap in the availability of efficient, focused treatments for CNS disorders.

Because the nasal cavity provides a highly vascularized surface and direct access to the brain via the olfactory and trigeminal neural pathways, intranasal drug delivery is becoming more and more popular as a non-invasive, quick, and direct method of delivering drugs to the brain, avoiding the restrictive nature of the BBB. Furthermore, the potential of nose-to-brain delivery has been further enhanced by breakthroughs including breath-powered bi-directional devices, magnetophoretic systems, nanocarrier-based formulations, and mucoadhesive technologies.[2]

6.1.1. Methods for Nose-to-Brain Medication Administration

For the treatment of illnesses of the central nervous system, nose-to-brain medication administration presents a possible alternative to the blood brain barrier. Numerous cutting-edge methods have been developed, such as iontophoresis, magnetophoretic systems, breath-powered bi-directional delivery, and formulations based on nanocarriers. These methods minimize systemic side effects while improving drug targeting to the brain. Because they are non-invasive, they enable quick action and better patient compliance. Enhancing formulation parameters Additionally, distribution methods are essential for enhancing therapeutic results in neurological disorders.[11]

6.1.2. A comparative analysis of nasal drug delivery methods for central nervous system targeting

Recent years have witnessed a great deal of innovation in the development of nasal medication delivery systems for brain targeting, with several methods showing promise in getting past the blood-brain barrier. Depending on the therapeutic need, drug characteristics, and intended targeting point within the central nervous system, each method offers distinct benefits. Iontophoresis improves penetration for medications with limited permeability by driving charged molecules over the nasal mucosa with a modest electric current. This method is effective and non-invasive, but it is constrained by the requirement for specific electrical equipment, improving drug absorption, lowering systemic exposure, and providing non-invasive substitutes for conventional methods.

An emerging approach to neuro-regeneration for the treatment of neurodegenerative diseases is nasal stem cell delivery. In order to promote tissue healing and repair, it offers a non-invasive method of delivering viable stem cells into the central nervous system. Nonetheless, preserving stem cell viability, preventing immunological rejection, and reducing tumor formation continue to be major obstacles. All things considered, these cutting-edge nasal delivery methods show a great deal of promise for brain targeting; yet, their clinical application necessitates resolving obstacles pertaining to device design, safety, and drug or cell stability.[11]

7. Factors Affecting Nasal Drug Delivery and Brain Targetting

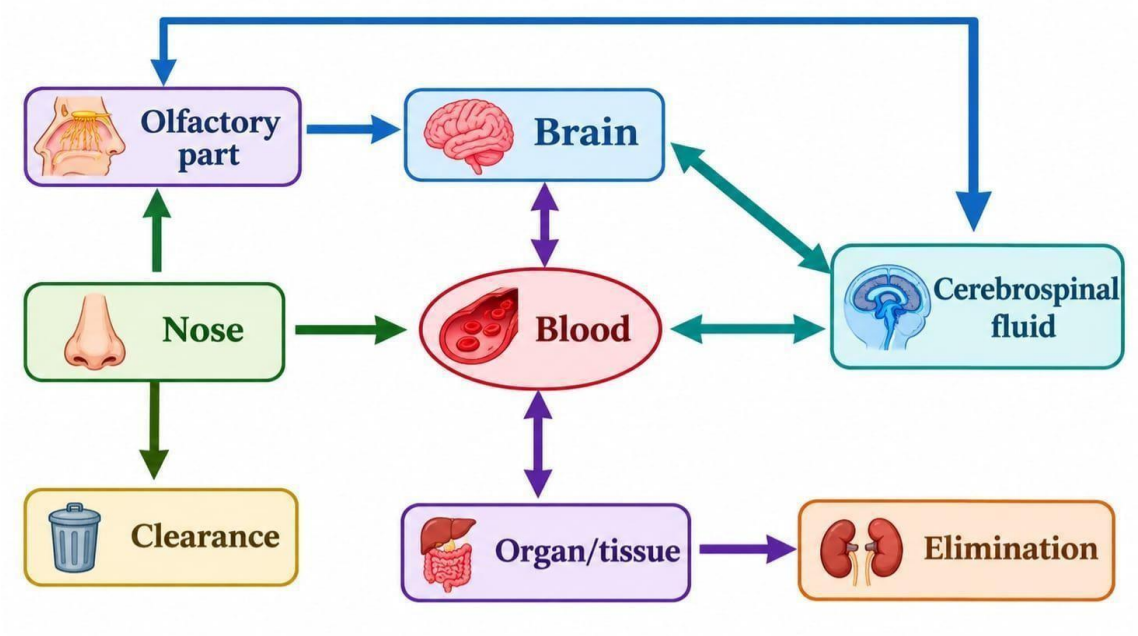

Fig. 3: Various routes of drug transport from nose to the brain.[16]

The physicochemical characteristics of the drug (such as molecular weight, lipophilicity, and charge), formulation features (particle size, pH, and viscosity) and biological elements (mucociliary clearance and enzymatic activity) all affect brain targeting and nasal drug delivery. These establish the drug's overall targeting effectiveness, retention period, and absorption.[2]

7.1. The drug's physicochemical characteristics

A drug's nasal absorption and brain targeting effectiveness are significantly influenced by its physicochemical characteristics. While highly lipophilic compounds exhibit improved membrane permeability and increased brain uptake, drugs with low molecular weight typically diffuse more readily across the nasal mucosa. On the other hand, carrier systems can be necessary for the effective distribution of big or hydrophilic substances. Additionally, the surface charge affects mucosal interaction. While negatively charged molecules may experience electrostatic repulsion, positively charged molecules adhere to the negatively charged mucosa more strongly, enhancing retention and absorption.[2]

7.2. Formulation factors

Mucoadhesive systems

Mucoadhesive systems are sophisticated formulations that stick to the mucosal surface to extend the duration of medication residence in the nasal cavity. They decrease medication clearance brought on by mucociliary action, increase bioavailability, and improve absorption. Chitosan, carbopol, and hyaluronic acid are common mucoadhesive compounds that promote close contact between the formulation and nasal epithelium. This guaranties continuous release and improves medication penetration for effective brain targeting. Mucoadhesive devices are especially useful for medications, proteins, and peptides that have low nasal mucosal permeability.[2]

7.3. Biological factors

Brain targeting and nasal medication absorption are significantly influenced by biological variables. Drug residence duration and absorption may be shortened by mucociliary clearance, which quickly eliminates foreign particles and formulations from the nasal cavity. Sensitive medications, especially peptides and proteins, may be broken down by enzymatic activity in the nasal mucosa, reducing their efficacy. Drug absorption patterns are impacted by interspecies differences in nasal anatomy, physiology, and enzyme expression, which makes extrapolating animal results to humans difficult. In order to optimize formulation design and guaranty consistent therapeutic results in nasal medication administration, it is imperative to comprehend these biological aspects.[2]

8. Formulation Till Now…

8.1 Intranasal Delivery Devices

Intranasal delivery devices can be classified by therapeutic objective (local nasal therapy or systemic or nose-to-brain transport) and dose form (e.g., drops, sprays, nebulizers, gels, and powders). They are frequently used to give local drugs including corticosteroids, antihistamines, and antibiotics as well as for nasal irrigation (e.g., isotonic or hypertonic saline).

Formulations are mostly deposited by conventional devices in the front and middle portions of the nasal cavity, with little deposition occurring in the posterior or superior areas. Specialized device designs have been developed to improve delivery to posterior-superior locations, such as the olfactory region and upper nasal space, in order to get around this restriction. These methods use mechanisms like optimized plume geometry or nozzle orientation and regulated airflow (such as breath-powered bidirectional flow) to facilitate passage past the nasal valve and reduce anterior Losses from deposits.[3]

Using an inert liquid (hydrofluoalkane) that forms a gas propellant, the Precision Olfactory Device delivers liquids and powders to the olfactory region of the nasal cavity. The powder is propelled via the nares by Alchemy Pharmatech's Naltos device, which employs Noseto-Brain Delivery 599 of an inert gas that the device activates. Lastly, Options takes advantage of the patient's own expiration, which isolates the nasal and oral cavities and drives the dose deep into the nose. To present, human nose-to-brain research have only employed the Options, Precision Olfactory Delivery, and Vianase devices.[1]

8.1.1 Powder Devices

Powder particles can stay in the nasal mucosa for a longer period of time than liquid (solution or suspension) and gel medication formulations because they are stable and difficult to dissolve. Additionally, powder dosages might be administered in high doses and prevent microbial contamination due to the free preservatives. Many parameters, such as the size and shape of the powder particles, flow properties, and solubility as demonstrated in an insufflator made of straw or tube with medications could directly affect the deposition and absorption of a powder formulation of drugs for nasal delivery. Deliver medications to the olfactory region; however, prior to insufflation, local anaesthetics or decongestants are typically required.[14]

8.1.2 Sprays and Solution

Drug molecule solutions are injected into the nasal cavity as nasal sprays and nasal solutions. Bypassing the blood-brain barrier is the most practical method of transporting the drug formulation from the nose to the brain.[14]



Fig.:- Sprays and Solution.

8.1.3 Instillation and Rhinylecather

To administer the formulation drop by drop in the proper area of the nasal cavity, a liquid formulation device is essential. The filler is used to measure catheter dosage before administration.[14]



Fig:- Nasal Aspirator.

8.1.4 Liquid-Based Devices

To provide the fluids, this method is typically used in conjunction with anaesthesia or a sedative. Due to the sensitivity of mucosa It is a significant problem with this medication delivery strategy for the deposition site. Blowing with the mouth allows the solution inside the catheter to enter the nostril through the nose cavity's opposite end. Due to their affordability and ease of production, drops have been a significant nasal medication administration method for liquid formulations for many years.[14]

8.2. Intranasal delivery formulation considerations

Choosing the right dosage form—dry powder or liquid (solution or suspension)—is essential when giving medication

intranasally. Numerous formulation techniques have been thoroughly studied, such as dry powders, in situ gels, polymeric nanoparticles, and lipid nanocapsules. the methods of formulation and related medications. In general, powder formulations are more stable than liquid ones. However, each form poses particular optimal delivery and efficacy considerations and requires different formulation methodologies. A number of crucial elements, such as particle size, viscosity, pH, volume of therapeutic agents, osmolarity, and the thoughtful addition of excipients, must be assessed in order to develop the optimal formulation for intranasal drug administration in order to guaranty efficacy and patient comfort.[3]

Particle size for deposition

The effectiveness of intranasal delivery is greatly impacted by the size of the medications that are delivered. The ideal particle size for intranasal deposition, according to research, is between 8 to 18 μm, albeit this may vary depending on the delivery mechanism and individual anatomical variances. Smaller particles (< 10 mm) tend to deposit in the anterior region and, to a greater extent, in the middle and posterior nasal regions, whereas particles with a volume The anterior section of the nasal canal is where mean diameters greater than 50 μm are mostly deposited.[3]

Osmolarity

Intranasal absorption and tolerability are significantly influenced by osmolarity. To lessen stinging and mucosal irritation, intranasal formulations are typically adjusted to physiological isotonicity (~270–330 mOsm/kg), which is typically accomplished using 0.9% NaCl (≈0.154 M). Certain hypertonic NaCl concentrations (e.g., ~0.462 M) can temporarily increase paracellular permeability and enhance uptake, according to preclinical studies, such as those carried out in rats. However, hypertonicity can also cause mediator release and should be balanced against epithelial integrity and comfort. In general, tonicity should be optimized on an individual basis, taking into account the drug's characteristics and dosage form, while remaining close to isotonicity for long-term use.[3]

8.2.1. Conventional Formulations for Nose-to-Brain Delivery

Using the nasal cavity's anatomical and physiological linkages to the central nervous system, a number of medicines have been developed and authorized for therapeutic purposes that benefit from nose-to-brain administration. The approved formulations with clinical indications in line with the nose-to-brain route. These include therapies for mental and neurological disorders like depression, epilepsy, migraines, and opioid overdoses. For instance, sumatriptan nasal sprays with a quick onset of action, such as Imitrex®, OnzetraXsail®, and Tosymra®, were licensed for use in treating acute migraine attacks. Naloxone nasal spray (Narcan®), which is used to counteract an opioid overdose, is another noteworthy example. For depression, esketamine nasal spray (Spravato®) was authorized.

A major breakthrough in treatment, nose-to-brain administration enables quick brain access and quick-acting antidepressant effects. A non-invasive treatment for seizure clusters is diazepam nasal spray (Valtoco®). The possibility of nose-to-brain medicine delivery for a variety of CNS illnesses has also been the subject of multiple clinical investigations. Diazepam (NRL1) successfully finished a Phase 3 trial for epilepsy (NCT02721069). A number of medications have been tested for migraine, including lidocaine (NCT03806595—Phase 1), zolmitriptan (NCT03275922—Phase 3), zavegepant (NCT04571060—Phase 3), and dihydroergotamine administered using a Precision Olfactory Delivery (POD) device (NCT03874832—Phase 1 and NCT03557333—Phase 3).

Ketamine has been thoroughly investigated for depression in Phase 3 trials (NCT04338321 and NCT03039192) and a

Phase 2 study in conjunction with midazolam NCT03185819). A Phase 1 safety study for intranasal olanzapine administered using a POD device for bipolar disorder and schizophrenia was finished (NCT03624322). Together, these studies highlight nose-to-brain delivery's quick development and potential for quick, focused therapies of a variety of CNS disorders.[15]

Examples of FDA-approved formulations for intranasal delivery and nose-to-brain applications.

Active substance	Product	Manufacturer	FDA approval	Delivery format	Main indication
Butorphanol tartrate	Stadol NS	Bristol-Myers Squibb	1991 (discontinued in 2004)	Nasal spray	Pain
Diazepam	Valtoco®	Neurelis	2020	Nasal spray	Epilepsy
Dihydroergotamine mesylate	Migranal®	Bausch Health US	1997	Nasal spray	Migraine
Dihydroergotamine mesylate	Trudhesa®	Impel	2021	POD® system	Migraine
Esketamine hydrochloride	Spravato®	Janssen	2019	Nasal spray	Depression
Midazolam	Nayzilam®	UCB Inc.	2019	Nasal spray	Epilepsy
Naloxone hydrochloride	Narcan®	Emergent Operations Ireland	2015	Nasal spray	Opioid overdose
Naloxone hydrochloride	Kloxxado®	Hikma	2021	Nasal spray	Opioid overdose
Naloxone hydrochloride	Naloxone hydrochloride	Amphastar Pharmaceuticals	2023	Nasal spray	Opioid overdose
Sumatriptan	Imitrex®	GlaxoSmithKline	1997	Nasal spray	Migraine
Sumatriptan	Onzetra Xsail®	Currax	2016	Xsail® system	Migraine
Sumatriptan	Tosymra®	Upsher-Smith Laboratories	2019	Nasal spray	Migraine
Varenicline	Tyrvaya®	Oyster Point Pharma	2021	Nasal spray	Dry eye disease
Zavegepant	Zavzpret®	Pfizer	2023	Nasal spray	Migraine
Zolmitriptan	Zomig®	Amneal	2003	Nasal spray	Migraine

9. New Developments in Nasal Formulation Technologies.

Enhancing drug stability, absorption, and targeted brain delivery are the main goals of recent developments in nasal formulation technologies. Mucoadhesive formulations, thermoresponsive gels, lipid and polymeric nanoparticles, exosomes, and cell-based carriers are examples of innovative systems that enhance retention time, prevent drug degradation, and facilitate effective nose-to-brain transport. These innovations present viable approaches to the management of intricate neurological conditions.[2]

9.1. Technologies for formulation

9.1.1. Gels that respond to heat

Thermoresponsive gels are novel nasal medication delivery methods that, when exposed to the temperature of the nasal cavity, change from a liquid to a gel. This sol-gel transition offers sustained drug release, decreases mucociliary clearance, and improves drug retention. These systems are frequently developed using polymers including carbopol, poloxamers, and chitosan derivatives. Better contact with the nasal mucosa is ensured by their gelling property, which enhances absorption and brain targeting. They are especially useful for peptides, proteins, and controlled-release therapies.[2]

9.1.2. Polymeric and lipid nanoparticles

Advanced carriers that improve stability, bioavailability, and brain targeting in nasal medication administration are lipid and polymeric nanoparticles. High drug loading, controlled release, and protection against enzymatic

degradation are offered by lipid-based systems such as solid lipid nanoparticles and nanostructured lipid carriers [B]. Polymeric nanoparticles made from biocompatible polymers like PLGA and chitosan enhance mucoadhesion and permeability across nasal mucosa. These nanosystems are useful for delivering tiny chemicals, peptides, proteins, and nucleic acid-based treatments. They also reduce systemic adverse effects and enable effective nose-to-brain transit.[2]

9.1.3. Cell-based carriers and exosomes

Emerging nasal medication delivery methods with exceptional promise for brain targeting include exosomes and cell-based carriers. Exosomes are naturally occurring nanovesicles that can transport proteins, peptides, RNA, and medications across the nasal mucosa due to their inherent biocompatibility, low immunogenicity, and effective cellular absorption. Delivery vehicles that can penetrate biological barriers and release therapeutic drugs at specific brain areas are cell-based carriers, such as stem cells and modified immune cells. These systems present intriguing approaches to the treatment of inflammatory or hereditary brain problems as well as neurodegenerative diseases.[2]

9.2. Nasal Administration Devices

Optimizing medication deposition on the olfactory epithelium is essential for optimal treatment efficacy because drug deposition in the nasal epithelium plays a critical role in affecting the nose-to-brain route. Due to their placement in the upper section of the nose and the limitations imposed by the nasal turbinate, traditional intranasal devices of liquid formulations, like droppers and spray pumps, have difficulty delivering medications to the olfactory epithelium. For instance, a dropper necessitates a specific patient posture, and a spray pump delivers less than 3% of the medication to the olfactory region. As a result, the medication may be eliminated by mucociliary clearance or absorbed systemically by blood vessels.

Researchers have created devices that can administer medications in various forms (liquids or powders) in order to address the drawbacks of traditional devices. Impel NeuroPharma (Seattle, WA, USA) developed a precise olfactory delivery system that uses a tank, compressed air or nitrogen, and a chlorofluorocarbon (or hydrofluoroalkane) to deliver medications to the olfactory area.41 Spinose (Yokne'am Illit, Israel) invented a nasal device that allows aerosol administration and is activated by drinking action. The patient must exhale force in order to administer OptiNoseTM (OptiNose, Yardley, PA, USA), a bi-directional administration device.[7]

9.3 Formulation Approaches for Nose to Brain Drug Delivery

9.3.1. Non-Invasive Techniques

The BBB can be crossed using either invasive or non-invasive methods. Direct injection into the brain parenchyma, cerebrospinal fluid, or the therapeutic opening of the blood-brain barrier are examples of invasive methods. In order to treat neurological and mental diseases as well as stroke, direct medication injection or implantation into the brain parenchyma has been investigated. However, because there is little diffusion between the extracellular and intracranial fluids, direct injection may be less effective. Significant variations in intracranial pressure and possible dangers of brain tissue damage are also present. The other invasive method, which involves temporarily breaking the blood-brain barrier, requires cooperation with highly skilled neurosurgeons and may result in negative consequences from BBB disruption, including inflammation, brain injury, and bleeding.8Non-invasive techniques use endogenous cellular processes to help medications enter the central nervous system via the transcellular pathway.[7]

9.3.2. Nanoemulsions

With droplet sizes usually in the nanometer range, nanoemulsions are thermodynamically and kinetically stable dispersions of water and oil stabilized by surfactants. They increase absorption through the nasal mucosa and improve drug solubility, particularly for medications that are poorly soluble in water. In addition to increasing drug permeability and bioavailability, nanoemulsions offer a vast surface area for quick drug delivery to the brain.[19,20,10]

Gel System in Situ

ISGs have recently surfaced as a viable strategy to improve drug uptake and overcome the difficulties associated with intranasal drug delivery from the nose to the brain. Before being administered, ISGs are clear or low-viscosity liquids; nevertheless, in response to nasal physiological circumstances (pH, temperature, and ionic shift), they transform into a thick gel. This lowers the frequency of doses, prolongs the duration of drug retention in the nasal cavity, and slows the drug's quick excretion.[7]

10. Clinical Studies and Translational Challenges

Numerous clinical trials on intranasal drug delivery have demonstrated encouraging effects in terms of improving therapeutic outcomes and brain targeting. Smooth clinical translation is hampered by issues such as interspecies variability, formulation stability, large-scale production, safety, and regulatory approval. For wider use, long-term efficacy and patient compliance are still essential.[2]

1. Finished or ongoing clinical research

Intranasal administration has been investigated in several clinical studies for CNS conditions such as multiple sclerosis, depression, Parkinson's disease, and Alzheimer's. While interferon-β showed improved brain targeting, intranasal insulin and oxytocin have been found to improve cognition and social behaviour. Mucoadhesive compositions based on nanoparticles are being tested for safer, more potent treatments. These findings show that nasal medication delivery has translational promise, but they also highlight the need for bigger patient populations, long-term safety data, and standardised methodologies for clinical validation.[2]

2. Safety, effectiveness, and legal standing

The safety and efficacy of intranasal pharmaceutical administration are influenced by long-term tolerance, excipients, and formulations. When compared to traditional methods, numerous studies show improved treatment outcomes and decreased systemic toxicity. Variability in mucociliary clearance and absorption, however, is still an issue. Only a small number of intranasal products have been approved by regulators. Establishing clear regulatory criteria for the general clinical deployment of these advanced technologies requires rigorous investigation of pharmacokinetics, toxicity, scalability, and patient compliance.[2]

Safety considerations for nose-to-brain delivery

When creating medications for regulatory approval, safety is an essential factor that must be taken into consideration. When developing intranasal medications, it is crucial that both the medication and its excipients such as mucoadhesives or nanoparticles are safe and do not have any negative side effects. It's crucial to take into account both local nasal mucosa and CNS toxicity in addition to systemic adverse effects when it comes to nose-to-brain administration. The small amount of medication that enters the systemic circulation and the liver, which lowers the risk of systemic side effects and quick metabolization, is a significant benefit of intranasal delivery over systemic delivery. Numerous studies

have demonstrated that intranasal medications are generally safe or perhaps safer than other methods of administration.

For example, only minor adverse events were reported in clinical investigations testing intranasal recombinant erythropoietin; no serious adverse events were reported. Furthermore, there was no difference in the number of adverse events between the treatment group and the placebo group. Additionally, rats' blood parameters did not change when paliperidone palmitate, a medication that causes severe side effects when taken orally, was administered intranasally. This suggests that intranasal delivery is a promising method of reducing systemic side effects. Because the medication comes into direct contact with the nasal mucosa, it is crucial to screen for local harmful effects and take into account several elements that affect nasal conditions, such as temperature, humidity, or disorders like rhinitis.

Prior assessments of cytotoxicity to the nasal mucosa were conducted in nasal mucosa cell culture models, mostly using primary cells taken from the rat olfactory area and the immortalized cell line RPMI 2650 obtained from a squamous cell carcinoma of the nasal septum These models can be used for cytotoxicity testing and permeation investigations, such as measuring transepithelial electrical resistance. Mucociliary activity is one of the protective roles of the nasal tissue that keeps foreign particles from entering the upper airways. Therefore, it is crucial to make sure the medication has no negative effects on ciliary movement.

In order to do this, ciliotoxicity ex vivo investigations were carried out on sheep nasal mucosa, keeping an eye out for ciliary or epithelial damage, necrosis, or bleeding in reaction to drug administration using nanoparticles. It's interesting to note that, at appropriate dosages, nanoparticle composition may improve safety and reduce local nasal toxicity. Rats were given free-diazepam solution intranasally, and mucosal irritation was assessed in comparison to an aqua-triggered in-situ gelling microemulsion containing diazepam. The gelling microemulsion preserved the mucosa while the free-diazepam caused mild to moderate histological mucosal lesions.

Therefore, it might be conceivable to find carriers that can carry a medication without causing local adverse effects if it is known to induce local mucosal irritation. It is important to make sure that the olfactory nerve and the central nervous system are unaffected in addition to the negative effects on cilia and mucosa. In vitro tests utilizing primary neuronal cells or neuroblastoma cell lines like SH-SY5Y cells can be used to anticipate effects on neuronal cells. Assays such as lactate dehydrogenase, MTS (3-(4,5dimeth-ylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2Htetrazolium, or MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2Htetrazolium bromide) can be used to evaluate cells.[8]

11. Future Perspective

In order to treat CNS illnesses, researchers have recently concentrated on creating innovative medication delivery methods to get across the blood-brain barrier (BBB). Numerous carriers, including liposomes, micelles, polymeric nanoparticles, and nanoemulsions, have demonstrated promise for brain medication delivery. However, many CNS medications are hydrophilic, which makes it challenging for them to pass through the BBB. Promising methods to enhance drug transport to the brain include nasal drug delivery and surface modification of drug carriers. As a result, nose-to-brain drug delivery is a promising non-invasive method that could enhance patient compliance and aid in the creation of new pharmaceuticals in the future.[5]

Nose-to-brain medication delivery is one potential non-invasive way to deliver therapeutic drugs to the central nervous system (CNS). Nose-to-brain medication delivery is one potential non-invasive way to deliver therapeutic drugs to the central nervous system (CNS). But there are issues like mucociliary. Its efficacy is restricted by limited drug permeability, enzymatic degradation, and clearance. Microemulsions, stimuli-responsive systems, and surface-functionalized nanoparticles are examples of advanced techniques that may enhance drug targeting and delivery effectiveness. To determine the effectiveness and safety of these systems, more investigation, clinical studies, and long-term safety evaluations are necessary. Neurological conditions like Alzheimer's disease, Parkinson's disease, epilepsy, and brain tumours may have better therapy choices with further developments in nose-to-brain drug administration.[18,10]

Examples of drugs investigated for delivery from the nose to the brain (12)

Selected Drugs Explored for Nose-to-Brain Delivery

Drug / Prodrug	Potential Therapeutic Use	Intranasal Formulation	Proposed Transport Route	Reported Finding	Company / Development Status
Insulin	Alzheimer's disease and cognitive impairment	Nasal solution or spray	Olfactory and trigeminal pathways	May enable central nervous system effects with limited changes in peripheral glucose	Novo Nordisk
Oxytocin	Autism-related social difficulties and social anxiety	Nasal spray	Olfactory neuronal transport	May rapidly reach limbic regions linked with social behavior	Ferring Pharmaceuticals
Rivastigmine	Alzheimer's disease and Parkinson's-related dementia	Nasal gel or nanoscale formulation	Olfactory-associated extracellular transport	May increase brain availability and reduce systemic cholinergic effects	Novartis
Donepezil	Alzheimer's disease	Nasal nanoparticle formulation	Trigeminal nerve route	May improve brain targeting and lessen gastrointestinal adverse effects	Eisai Co., Ltd.
Levodopa	Parkinson's disease	Nasal nanoparticles or powder	Trigeminal and perivascular transport	May act faster while bypassing hepatic first-pass metabolism	AbbVie
Desmopressin	Central diabetes insipidus	Nasal spray	Direct olfactory transport	Nasal dosing can support uptake into the central nervous system	Ferring Pharmaceuticals
Naloxone	Opioid overdose	Nasal spray	Trigeminal nerve route	Enables rapid emergency treatment of opioid toxicity	Emergent BioSolutions
Midazolam	Acute seizures and status epilepticus	Nasal solution	Trigeminal transport and systemic absorption	Can provide prompt seizure control without intravenous delivery	Pfizer
Sumatriptan	Migraine	Nasal spray	Trigeminal nerve transport	May provide faster relief than oral administration	GlaxoSmithKline
Selegiline	Parkinson's disease and depression	Intranasal formulation	Olfactory and trigeminal routes	May support CNS delivery and reduce extensive hepatic metabolism	Teva Pharmaceuticals
Dopamine (prodrug-based systems)	Parkinson's disease	Nasal nanoparticles or prodrug strategy	Olfactory neuronal transport	Investigational approaches aim to address dopamine's BBB limitations	Research-stage academic/industry development

CONCLUSION

A promising non-invasive method for treating problems of the central nervous system and delivering drugs specifically to the brain is intranasal medication administration. This strategy can reduce systemic exposure and related side effects while facilitating medication delivery to the brain through the olfactory and trigeminal nerve routes. Nanoparticles, nanoemulsions, liposomes, exosomes, mucoadhesive formulations, and thermoresponsive gels are examples of formulation technologies that have shown promise for enhancing drug stability, nasal residence time, absorption, and brain-targeting efficacy.

Drug deposition in the olfactory area may be further enhanced by specialized nasal delivery systems. Mucociliary clearance, enzymatic degradation, restricted drug permeability, absorption variability, and worries about local and neurological toxicity are some of the difficulties that still exist. The direct use of preclinical results in clinical practice is further restricted by the differences between human and animal models. In order to improve formulations, determine suitable dosage regimens, assess long term safety, and verify therapeutic efficacy through carefully planned clinical studies, more research is necessary.

All things considered, nose-to-brain drug administration has a great deal of promise for improving the treatment of neurological illnesses, such as epilepsy, Parkinson's disease, Alzheimer's disease, and other CNS disorders. Transforming this promising concept into safe and effective medicinal applications would require ongoing technological progress and thorough clinical evaluation.

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