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Formulation Strategies for Nose-to-Brain Drug Delivery

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ABSTRACT

Background: Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, Dementia, and others are becoming more common globally due to people's changing lifestyles. Furthermore, the presence of the Blood-Brain barrier and other limitations of oral and other routes of administration makes drug delivery to the brain somewhat tricky. As a result, numerous novel drug delivery systems are being developed for drug administration to the brain. However, nose-to-brain administration is one of the most effective, safe, and non-invasive methods.

Purpose: To discuss nose-to-brain delivery as a novel drug delivery system in the treatment of various brain disorders and to provide information about various formulation strategies designed to deliver the drug to the brain effectively.

Methods: A preliminary search was conducted in the PubMed, OVID Medline, Embase, ScienceDirect, Web of Science, and Google Scholar databases using keywords such as "Intranasal delivery, nose-to-brain drug transport, formulations for intranasal delivery."

Results: Various marketed formulations for nose-to-brain drug delivery are listed in this review, like naringenin, donepezil, pentamidine, rivastigmine, efavirenz, desvenlafaxine, lamotrigine, haloperidol, nimodipine, olanzapine, valproic acid, ovalbumin, clonazepam, fentanyl citrate, nifedipine in the form of poloxamer chitosan-based nano-formulation, nano-emulsion, chitosan niosomes, chitosan containing emulsion, solid-lipid nanoparticles, PLGA-chitosan nanoparticles, solution, mucoadhesive microemulsion, nanostructured lipid carriers, cationic liposomes, peptide-attached liposomes, multimellar liposomes with their research findings in treating various brain disorders.

Conclusion: This review discusses nose-to-brain drug delivery processes, the pathway for its action, advantages over other delivery routes, barriers to this system, and current formulation strategies for nose-to-brain transport.

1. Introduction

Neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, Multiple sclerosis, Dementia, etc., are increasing day by day globally due to the lifestyle of individuals. These brain disorders require a targeted delivery of the drug for their treatment. However, drug delivery is quite tricky to the brain because of the existence of the Blood-Brain barrier, Blood-Cerebrospinal fluid barrier, and various limitations of oral and other routes of drug delivery like low bioavailability, rapid metabolism, and fast elimination of the drugs. In addition, the impermeable nature of the Blood-brain barrier restricts the entry of pharmaceutical agents into the brain, especially for hydrophilic drugs with high molecular weight (Pandey *et al.*, 2018), (Gajbhiye *et al.*, 2015).

For targeting the brain, drugs must bypass the Blood-Brain barrier for effective therapeutic action. Alternative drug delivery routes like intraparenchymal or intrathecal are invasive methods with a remaining risk of infections (Gänger & Schindowski, 2018). Therefore, various novel drug delivery systems are being developed for the delivery of drugs to the brain. Nose to brain drug delivery system is one of the most effective, safe, and non-invasive types of administration, as it bypasses the Blood-Brain barrier. Many novel drug delivery systems, like in-situ gelling, solid-lipid nanoparticles, chitosan-based delivery, nano-emulsions, nano-suspensions, etc., are widely used for the treatment of various brain diseases effectively by avoiding the Blood-Brain barrier. The drug administered intranasal route is transported to the brain primarily through the olfactory and trigeminal nerves. This review contains information

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about the nose to brain drug delivery, its mechanisms, its advantages over other delivery systems, the barriers to this system, andcurrent formulation strategies of nose-to-brain delivery.

1.1. Neurological Disorders for Nose-to-Brain Delivery

There are various central nervous system disorders in which nose to brain drug delivery route is preferred.

1.1.1. Parkinson's disease

It is a progressive neurodegenerative disorder resulting from oxidative stress, aging, and neuroinflammation (Gao *et al.*, 2003), (Takahashi & Wakabayashi, 2005). Tremors, muscular rigidity, slow movement, etc., mark it. This disease is mainly associated with the degradation of the brain's basal ganglia and dopamine deficiency.

Clinical features of Parkinson's disease are bradykinesia, tremor, rigidity, postural deformities, and freezing (Jankovic, 2018), (Berardelli *et al.*, 2001).

Treatment of Parkinson's disease through the intranasal route- It has been reported that if mesenchymal stem cells are given through the intranasal route, it enhances the behaviors of 6-hydroxydopamine-lesioned Parkinson's disease rats. Mesenchymal stem cells administered through the intranasal route accumulate in the olfactory bulbs, cerebellum cortex, striatum, brain stems, hippocampus region, and spinal cord (Pandey *et al.*, 2018), (Danielyan *et al.*, 2011). In addition, more ovalbumin (OVAL)-containing cationic liposomes are found in the substantia nigra and striatum when administered through the intranasal route, which is essential in the pathophysiology of Parkinson's disease. Therefore, nose-to-brain delivery holds potential in the transportation of drugs or biologics to treat this disorder (Fine *et al.*, 2014).

1.1.2. Alzheimer's disease

It is also a neurodegenerative disease affecting memory and other vital physiological functions in diseased individuals. This disease process is characterized by two pathologies: β-amyloid plaque deposition and neurofibrillary tangles of hyper-phosphorylated tau (Weller & Budson2018).

Treatment of Alzheimer's disease through the nose to brain delivery(Pandey *et al.*, 2018).

In the treatment of Alzheimer's disease, insulin is directly delivered through the intranasal route to the brain through the olfactory route (Benedict *et al.*, 2011), and it was found that there is a profound improvement in memory and mood in healthy volunteers when insulin is delivered through this route. Furthermore, to increase the bioavailability of rivastigmine in the brain, its encapsulated chitosan nanoparticles are delivered through the intranasal route and increase the targeting potency of rivastigmine in the brain when compared to intravenous administrationof the drug (Fazil *et al.*, 2012).

1.1.3. Multiple sclerosis

It is a complex neurodegenerative disease mainly affecting the central nervous system (CNS) (Huang *et al.*, 2017). In multiple sclerosis, the immune system attacks the myelin (protective sheath) that covers nerve fibers and creates communication issues between the brain and the rest of the body.

1.1.4. Ischemic stroke

Ischemic stroke is caused by the blockage of an artery that carries blood to the brain, and the blockage decreases the blood flow and oxygen in the brain, resulting in damage or death of the brain's cells. Insulin-like growth factors (IGF) are being used for the treatment, but they cannot cross the blood-brain barrier. Therefore IGF-1 is given intranasally, improving neurological functions and resulting in the effective treatment of ischemic stroke(Liu *et al.*, 2001). In addition, N6-cyclopentyladenosine (CPA) (i.e., polar drug) is entrapped with a chitosan micro-particulate system, leading to effective drug delivery to CNS. Furthermore, CPA is aneffective and tranquilizing agonist of adenosine A1 receptors (Dalpiaz *et al.*, 2008).

1.1.5. Brain tumors

It is an abnormal cell growth in the brain. Brain tumors can be of two types malignant or benign. The intranasal route can also be used for chemotherapeutic drugs by providing a practical, non-invasive method and bypassingthe blood-brain barrier.

1.2. Anatomy of the Nose

In humans, the nose serves three functions: it serves as a resonating cavity for the voice, it contains olfactory organelles that detect odors, and it is the top section of the respiratory system, filtering, warming, and moistening the air before it reaches the lungs. The overall capacity of the human nasal cavity is 15-20 mL, with a surface area of 150-160 cm^2 (Hong *et al.*, 2019).

The nasal cavity consists of two extensive chambers and various sinuses. The main two chambers are separated by a midline wall called the septum.

1.2.1. Vestibular region

The entry of nose, known as the nares or nostrils, has long hairs that prevent the entry of large airborne objects

like insects and smaller particles like pollen and dust that flow past the hairs. Moreover, they get entrapped in the sticky layer of mucous that covers the internal lining of the nose and then drawn to the nasopharynx by cilia activity, resulting in the removal of hazardous compounds from the nasal cavity every 15 to 20 minutes. (Thakur *et al.*, 2020).
The nasal septum is relatively featureless but profoundin its mucous membrane, it is an extensive network of blood vessels that brings warm blood to the surface to enable the mucosal layer to warm the inhaled air, and in addition, it keeps the mucosa well-supplied with the nutrients.

1.2.2. Arteries of the medial wall

The branches from the posterior ethmoid artery and anterior ethmoid artery, the superior labial artery, the greater palatine artery,and the sphenopalatine artery form network in the vassal septum. The interior portion of the nasal septum, where all the artery meets, creates an area of dense vascularity called Kiesselbach's area. It is prone to drying and trauma, leading to nose bleeding (Vaskovic, 2022), (Jones, 2019).

1.2.3. Skelton of Nasal septum

Itis partly bone and cartilage; the bony portion of the nasal septum is made through the perpendicular plate of the ethmoid bone, vomer bone, and smaller particular regions from the superior surface of the palatine bone and maxilla bone (Vaskovic, 2022). Anteriorly, the nasal septum is built majorly through the septal cartilage, added by the two smaller cartilages- vomerine cartilage and alar cartilage (Jones, 2019)**.**

1.2.4. The lateral wall of the nasal cavity has a much more complex structure than the septum. Three prominent elevations- superior, middle, and inferior concha- increase the air's surface area.

1.2.5. Nerve supply to the lateral wall of the nasal cavity

The lateral nasal branches of the anterior ethmoidal nerve and maxillary nerve supply sensory innervation of the nasal cavity's lateral wall. The nasal branches from the maxillary nerve enter the nasal cavity into the palatine foreman, deep into the mucosa (Vaskovic, 2022).

1.2.6. Olfactory region

The sensory receptors for smell are located in the olfactory epithelium at the superior aspects of the nasal cavity; odor in inhaled air is bound to the receptor cells, which signal the olfactory bulb and the olfactory regions of the brain (Thakur *et al.*, 2020).

1.3. Challenges in Brain Drug Delivery

The major hurdle in the targeted brain delivery of the drug is the blood-brain barrier and blood-cerebrospinal fluid barrier, which have tight junctions and are impermeable for various substances except for nutrients, electrolytes, etc. Due to these barriers, most drugs cannot cross them, which results in decreased therapeutic effects of the particular drug. The next factor that challengesdrug administration to the brain is the high molecular weight of the drugs (more than 1000 Daltons).

Furthermore, the blood-brain barrier is highly lipophilic, which creates a significant problem for hydrophilic drugs, i.e., drugs containing –OH, -COOH groups, etc., to cross it easily. Ionized drugs can also not penetrate the brain as they cannot mimic the properties of the blood-brain barrier. To overcome all these significant issues, the drugs are given through the intranasal route, proven to be very effective, safe, and non-invasive for the drugs to be given directly to the brain.

1.4. The Blood-Brain Barrier (Bros & Erdő, 2019)

The brain's capillaries consist of endothelial cells, joined together by continuous tight intercellular tight junctions, forming the blood-brain barrier. The tight and adhered junctions prevent paracellular transport, but limited transcellular transport occurs (Abbott *et al.*, 2010) and has low pinocytotic activity (Sedlakova *et al.*, 1999), (Redzic, 2011).In addition, the presence of special cells known as astrocytes and pericytes, which supports the tissue found at the base of the endothelial membrane, forms a solid envelope around the brain's capillaries.

A solute may get entry to the brain via two pathways:

- Passive diffusion through the lipoidal barrier is restricted only to small molecules witha molecular weight of less than 700 Daltons and drugs with high lipophilicity.
- Active transport takes place for essential nutrients like sugars and amino acids. Thus, the drugs which mimic the essential nutrients can also penetrate through the blood-brain barrier.

1.5. Cerebrospinal Fluid Barrier

The interface between the brain and cerebrospinal fluid at the surface of cerebral ventricles is known as B-CSF-B, and this barrier inhibits transit between the fluid (CSF) and the brain parenchyma. Molecular diffusion bypasses these barriers in the nasal cavity, directing medications directly to the brain (Erdő *et al.*, 2018).

2. Intranasal Route: Nose to Brain Delivery (Pandey *et al.,* 2018)

Administration of drugs through this mode is suitable for drugs with limited or nearly no oral bioavailability. Furthermore, the intranasal route has many advantages over conventional drug administration systems. It also provides a direct transport route to the CNS; hence, it overcomes the disadvantages ofthe blood-brain barrier, thus offering aneffective mode for delivering neurotherapeutic agents (Erdő *et al.*, 2018).

3. Why is the Nasal Route Preferred? (Pardeshi & Belgamwar, 2013)

- *Bypasses the blood-brain barrier: The drugs are given through the intranasal route as they are directly* transported to the brain and CSF viathe olfactory region of the nose.
- *Safe, convenient, and non-invasive:* Administration of drugs through this route is easy and convenient for patients.
- *Prevents drug degradation in the GIT:* Many drugs get degraded in the GIT because of acid and various enzymes. Therefore, the intranasal route is helpful in the prevention of drug degradation.
- *Bypasses the first-pass metabolism:* The drug given through the nasal route does not undergo hepatic first-pass metabolism; hence, less drug dose can treat the particular condition effectively.
- *Enhanced bioavailability for drugs having a low molecular weight.*
- *Large surface area:* Nasal mucosa has a large surface area, due to which drug absorption occurs at a higher rate.
- *Highly vascularized mucosa:* Nasal mucosa is highly rich with blood vessels, leading to significant drug uptake.
- *Rapid onset of action:* Dueto the high vascularity and larger surface area, drugs get absorbed rapidly and show their action quickly.

4. Barriers to Drug Absorption Via Nasal Route (Pandey *et al.,* 2018)

4.1. Nasal Blood Flow

Vasoconstriction and vasodilation determine the absorption of the drug. Therefore, the more the blood flows during the dilation of vessels, the more drug absorption,and vice versa. In addition, due to thehighlyvascular nature of nasal mucosa, it plays a vital role in the thermo-regulation of inhaled air (Agu, 2016), (Kushwaha *et al.*, 2011).

4.2. Nasal Cycle

The normal physiological cycle, including decongestion and congestion, is regulated by the highly vascular "erectile" tissues of the nasal cavity. The nitric oxide agglomeration in the congested pathway is because ofan autonomic cycle. It is required for the defense mechanism against microbes by either increasing mucociliary clearance,directly showing antimicrobial action, or both (Agu, 2016), (Djupesland *et al.*, 2001).

4.3. Nasal Valve and its Aerodynamics

Itprovides a powerful filtration and air conditioning system for the inspired air, enhancing olfaction. It has a significant role in maintaining and protectingthe air temperature. Active nasal inhalation through the nasal mucosa may generate a negative pressure inside the nasal cavity; hence, it may be accountable for active contraction andbreak the nasal valve (Hsu & Suh, 2018), (Nigro *et al.*, 2009).

4.4. Mucociliary Clearance

It is an essential factor for the delivery of drugs and vaccines through the intranasal route. The mucosal layer should be a lipid bilayer or tri-layer. The outermost layer, which has a gel-like consistency, is the "periciliary liquid layer," which tends to float over the lower layer. The free movement of cilia between each effective stroke occurs because of sodium and chloride ions (Gizurarson, 2015). Mucociliary clearance protects the lungs from foreign particles, pathogens, and inhaled materials from the air and acts as a protective mechanism for the respiratory tract (Hersh *et al.*, 2016), (Pires *et al.*, 2009). Drug absorption is mainly affected by the contact time of the drug molecules and tissue of the epithelium. Hence, by increasing the contact time of the drug with the epithelial membrane, mucociliary clearance decreases, increasing drug absorption (Kushwaha *et al.*, 2011), (Hersh *et al.*, 2016).

4.5. Efflux System and Transporter

In nasal respiratory tract and olfactory tract have a large numberof transports that causes resistance to various drugs and play an essential role in the transportation of the many hydrophobicsubstances having amphiphilic nature(Oliveira *et al.*, 2016), (Costantino *et al.*, 2007). Permeability glycoprotein (P-gp) is an example of an efflux transporter present in the epithelium's apex region containing ciliated cells. Moreover,it is also present in the submucosal vessels of the olfactory region.Therefore, it inhibits active transport via the nasal mucosal membrane.

4.6. Enzymatic Degradation

Various enzymes like aldehyde dehydrogenases, glutathione S-transferases, carboxylesterases, and epoxide hydrolases are found in this system and provide its contribute to the metabolic pathway of drugs (Oliveira *et al.*, 2016). For the metabolism of various drugs such as cocaine, nicotine, alcohol, progesterone, and decongestants, isoenzyme Cytochrome P450 is responsible (Dimova *et al.*, 2005). The peptide drugs, such as calcitonin, desmopressin, and insulin, also suffer from the same drug absorption problem due to proteolytic enzymes. Although various carrier systems and mucoadhesive systems can prevent enzyme degradation of the drugs, they also boost the drug's dissolution rate and uptake by epithelium and increase the contact time between the drug and nasal mucosa.

Various novel drug delivery systems like liposomes, gels, and microspheres have excellent mucoadhesive properties anda high swelling index (Clementino *et al.*, 2016), (Türker *et al.*, 2004), (Chaturvedi *et al.*, 2011).

5. Major Pathways for Drug Delivery Through Intranasal Route

There are two major possible pathways to target the brain via the intranasal route, one is absorption through the systemic route from the respiratory region, or the second way is for direct delivery throughthe olfactory region of the nose to the CNS (Crowe *et al.*, 2018), (Thorne *et al.*, 2004). The olfactory region comprises olfactory cells, which are connected directly to the cranial cavity. Therefore, when a formulation is administered intranasally, it comes into touch with the nasal mucosa, resulting in rapid delivery of the drug molecule into the brain by breaching the BBB (Miyake & Bleier, 2015).

The highly lipophilic drugs show great targeting ability to CNS due to their high partition coefficient value. Furthermore, earlier research has shown that hydrophilic drugs can penetrate via the nasal mucosal barrier (Borlongan & Emerich, 2003).

Some recent research has examined the importance of the trigeminal nerve pathway in the brain-specific delivery of the drug, with particular emphasis on the caudal area of the brain and the spinal cord (Crowe *et al.*, 2018), (Ross *et al.*, 2008), (Thorne *et al.*, 2008).

5.1. Systemic Pathways

The capillary blood vessels in the nasal mucosa absorb the drugs administered through the intranasal route and directly reach the systemic circulation. The nasal mucosa is extensively vascularized, receiving blood from carotid artery branches in the form of maxillary, ophthalmic, and facial arteries (Clerico *et al.*, 2003). The segments of the ophthalmic artery provide blood to the olfactory epithelium, while the maxillary artery delivers blood to the respiratory epithelium. The respiratory mucosa contains more blood capillaries than the olfactory mucosa; thus, the respiratory epithelial membrane is an excellent spot for drug absorption. Therefore, particles of any size can penetrate the systemic circulation from the blood vessels into the respiratory area. In addition, drugs can exhibit counter-current transfer, in which the drug molecule enters the veins of the nasal tube and is swiftly transmitted to the brain and spinal cord via the carotid artery (Stefanczyk-Krzymowska *et al.*, 2000), (Skipor *et al.*, 2003), (Einer-Jensen & Hunter, 2005). However, numerous issues are related tosystemic drug circulation, such as drug elimination by hepatic first-pass metabolism, renal mechanism, enzyme degradation, drug plasma protein binding, peripheral side effects, and restricted entrance through BBB.

The intranasal route administration also follows the perivascular transportation of the drugs to the CNS (Lochhead *et al.*, 2015). Perivascular spaces exist between the basal lamina of nearby tissues and the blood vessel's outermost layer. These gaps function as a lymphatic system, preventing and restricting the entry of neuron-derived substances into the brain interstitial fluid. The "perivascular pump" exhibits a bulk flow mechanism that can aid in the quick delivery of drugs throughout the brain (Hadaczek *et al.*, 2006), (Schley *et al.*, 2006). According to several studies, even after the drug has been removed from the subsequent saline perfusion, the intranasal route of administration could benefit from access to perivascular regions when there are elevated drug levels within the cerebral blood vessels and carotid artery (Thorne *et al.*, 2004), (Skipor *et al.*, 2003), (Hadaczek *et al.*, 2006), (Savale & Mahajan, 2017).

5.2. Olfactory nerve pathway (Abbott et al., 2010)

The olfactory nerve pathway is the main pathway followed by the drugs when given through the intranasal route for delivery to the brain. This channel can be found in the upper part of the nasal passage. Olfactory receptor neurons (ORNs) and supporting cells are found in the olfactory area of the nose. These olfactory receptor neurons are in charge of transmitting sensory information from the peripheral environment to the brain. It includes the bowman's gland, axons, lymphatic vessels, blood vessels, and connective tissue beneath the epithelial layer. Drugs are transported across the olfactory epithelium via three distinct mechanisms, which include the transcellular pathway, paracellular pathway, and endocytosis.

5.3. Trigeminal Nerve Pathway (Abbott et al., 2010)

Trigeminal nerves pass through the olfactory and respiratory epithelium region and penetrate the brain at the pons region. The vital function of the trigeminal nerve is to convey sensory information from the oral cavity, nasal cavity, eyelids, and cornea to the brain through ophthalmic division, maxillary division, and mandibular region of the trigeminal nerve.

6. Drug Absorption Mechanisms from the Nose to the Brain

The absorption of the drug through the nasal cavity is governed by the extent of penetration of drug molecules through the mucosal layer. The larger drug molecules or those with charges on their surface face problems during penetration, whereas smaller or neutral molecules cross the mucosal membrane easily.

6.1. Paracellular Transport

No energy is involved in the slow absorption during this transit between the sustentacular cells. The hydrophilic route of absorption is another name for it. As it accounts for the transport of hydrophilic drugs, the extent of this depends on the drug's molecular weight. The molecules possessing molecular weight less than 1000 Dalton exhibit good bioavailability. Nasal permeation enhancers are used widely to increase the bioavailability and absorption of molecules with high molecular weight.

6.2. Transcellular Transport

Only lipophilic drugs are transported during this process, which takes place across sustentacular cells. Better nasal absorption is made possible by the molecule's enhanced lipophilicity (Bhise *et al.*, 2018).

7. Factors affecting Drug Delivery by the Intranasal Route

Drugs must pass through the mucus layer in the nasal cavity to be absorbed, and the mucus' protein, mucin, attaches to the drug's molecule and prevents absorption from the layer.

7.1. Physiochemical Properties of the Drugs (Upadhyay et al., 2011)

7.1.1. Molecular size

It is the critical factor influencing drug absorption through the intranasal route. Lipophilic drugs have a direct relationship between molecular weight and drug penetration, whereas water-loving drugs have the opposite relationship. For drugs with molecular weights of more than 300 Daltons, the permeation rate is vulnerable (Corbo *et al.*, 1990).

7.1.2. Partition coefficient of the drug

Increasing lipophilicity, the permeation of the drug molecules usually increases through the nasal mucosa. However, hydrophilic drugs face some problems in permeation through the mucosal barrier because to reach the systemic circulation or brain; the drug must go across the phospholipid bilayer membrane (Frey *et al.*, 1997).

7.1.3. Polymorphism

Many chemical substances exist in more than one form in nature. These are present in various forms, like unstable, metastable, and stable. The metastable form of the drug is used for the formulation of dosage form because of its maximum solubilityand suitable stability (Garg *et al.*, 2013).

7.1.4. Enzymatic degradation of the drug in the nasal cavity

Drug decomposition by enzymes reduces drug absorption and, as a result, impacts drug bioavailability. Using various approaches like prodrugs, enzyme inhibitors, and drugs should be protected from nasal enzymes.

7.2. Formulation-Related Factors

7.2.1. The pH of the pharmaceutical formulation

The drug absorption is controlled by the pH of the nasal passage, the drug's pKa value, and drug ionization with pH alteration. The difference in pH between the formulation and the nasal mucosa (5.0-6.0) can irritate the nasal epithelium (Washington *et al.*, 2000). As a result, the formulation's pH should be kept within the range. In addition, the nasal epithelium contains lysozyme, which is responsible for destroying various microbes. This enzyme remains active only at the acidic pH of the nasal passage, and if the nasal cavity's pH gets altered, it may cause an infection in the nasal passage.

7.2.2. Viscosity

The time a drug molecule is in contact with the epithelial membrane of the nasal passage is an essential factor in how well it is absorbed. The nasal mucosal membrane absorbs less drug because of the nose's ability to discharge mucus. Therefore, to enhance the drug's contact time with the mucous membrane and raise the viscosity of the pharmaceutical formulation, different mucoadhesives, such as sodium alginate and hydroxypropyl cellulose, are utilized.

7.2.3. Osmolarity

Osmolarity/Tonicity measuresthe concentration of a solution concerning body fluids. It can affect drug absorption through the nasal mucosa. Nasal formulations with Tonicity between 0.6% and 1.8% NaCl equivalent are well tolerated, whereas 0.9% NaCl equivalent is isotonic. Drug hypertonic solutions cause nasal mucosa atrophy. As a result, isotonic solutions are used for administration (Dhakar, 2011).

7.2.4. Absorption enhancers

There are various processes by which the absorption enhancers may improve drug absorption-

- By enhancing the membrane's fluidity
- By improving the blood flow of the nasal passage
- By reducing the viscosity of nasal mucus
- By blocking the enzyme present in the nasal cavity

8. Limitations of Conventional Formulations

The drugs are presently delivered into the brain using several conventional methods, but they have many limitations, so nowadays, advanced and novel drug delivery systems are being used.

Various conventional methods include (Sandhu, 2011).

8.1. Invasive Methods for Brain Targeting

One of the invasive methods of brain drug delivery is temporary physiological disruption of the endothelial integrity of the brain.

8.1.1. Disruption of Blood-brain barrier

This is done with the help of injecting 25% mannitol solution into the carotid artery, resulting in the break out of the barrier momentarily. The effect of injected mannitol lasts for around 20-30 minutes, during which the drug quickly diffuses into the brain and shows its therapeutic action. This method delivers chemotherapeutic agents for treating cerebral lymphoma, malignant glioma, and CNS germ cell tumors.

8.1.2. Intracerebral Implants

In this method, the drug is added to the polymer pellets implant through the intracranial route, bypassing the blood-brain barrier and releasing the drug locally in the brain sustainably.

8.1.3. Intrathecal route

Intraventricular infusions or intra-lumbar injections are administered directly into the CSF via the Ommaya reservoir, a plastic reservoir implanted subcutaneously in the scalp and connected to the ventricles in the brain through an output catheter.

8.1.4. Injections, Catheters, and Pumps

As discussed above, Ommaya reservoirs or implantable pumps deliverthe drug to the brain. Various types of pumps are currently being used, following different mechanisms. For example, a pump that uses the vapor pressure of compressed Freon to deliver a drug solution is known as an Infusaid pump; the MiniMed PIMS system uses a solenoid pumping mechanism, and the Medtronic SynchroMed system delivers through the peristaltic mechanism.

Limitations of Invasive methods:

- Hazardous approach for brain targeting
- Very painful
- It is not a safe method
- The highly skilled person should only administer the drug

8.2. Non-Invasive Methods for Brain Targeting (Marx et al., 2015)

As it is a non-invasive drug delivery technique, no skin rupturing is done due to the insertion of the needles, and it is a safe method compared to invasive techniques for brain targeting.

8.2.1. Oral route

This is the safest drug administration method, butit has various limitations. Nevertheless, this pathway is used majorly for drug delivery. Dosage forms like tablets, capsules, solutions, suspensions, and many more are given orally.

Limitations of the oral route for targeting brain:

- Hepatic first-pass metabolism of drugs occurs in the liver
- Blood-brain barrier
- Decreased bioavailability of drugs
- Drug degradation by gastric juices and enzymes

8.2.2. Intranasal route

The intranasal route is a safer and potential technique for the delivery of drugs to the brain because it directly transports the drug through the olfactory nerve into the brain, bypassing the blood-brain barrier.

8.2.2.1. Dry powder system

For enhancing the storage conditions of some drugs and vaccines, dry powder formulations are being used nowadays, but developing powders with the correct particle size is very

challenging. The particles must be designed to allow rapid disintegration, excellent deposition, and safe administration within the nasal mucous layer. For dry powder formulations, electrostatic charge and moisture admission must also be considered.

8.2.2.2. Multidose solutions

These are the most popular packaged solutions. Simple squeeze bottles are commonly used; however, they are regarded as outmoded since precise dosing is not achievable, and mucus may be drawn back into the bottle when using them. Therefore, metering nasal spray pumps linked to bottles are currently utilized as multidose standards.

8.2.2.3. Droppers

This is the cost-effective and most straightforward way of drug delivery into the nose. The most used technology is blow-fill-seal (BFS), and the BFS droppers are made of polyethylene or polypropylene.

8.2.2.4. Nasal sprays and drops

This system can be used for liquid or dry powder dosage forms. The drug should not be irritating and should not have an unpleasant smell for drug delivery through this system.

All the conventional or currently used systems discussed above have some limitations also due to which scientists are moving towards advanced and novel drug delivery systems. Limitations of conventional systems are:

- Mucociliary clearance
- Low absorption rate
- Low bioavailability

9. Recent Formulation Strategies

Various novel drug delivery systems are being developed to overcome the limitations of alternative and conventional drug delivery systems to facilitate drug delivery.

9.1. Solutions

The solutions administered directly to the brain through the intranasal route is the novel approach. To administer drug molecules via the nose-to-brain pathway, the drug has been dissolved in an aqueous solution (Wang *et al.*, 2019). Usually, the solutions are delivered through nasal delivery devices. One of the first studies on peptide delivery to the brain was the intranasal delivery of insulin to the brain(Sigurdsson *et al.*, 1997). Oxytocin has also been administered to the brain in solution form via the nasal route, having a Cmax of 0.003% of a 10g dose in the brain (Tanaka *et al.*, 2018).

9.2. Nanoparticles

The size range of nanoparticles between 1-1000 nmis colloidal solid particles. The nanoparticles offer different advantages over other delivery techniques because of their tiny size. Furthermore, only the tiniest nanoparticles can pass through the mucosal membrane via paracellular transport via tight junctions. As a result, they are regarded as the optimum technique for administering nasal immunizations.

9.2.1. Polymer-based nanoparticles

Chitosan is produced via the deacetylation of chitin in crustacean shells. Chitosan is a polymer utilized in intranasal delivery due to its bio-adhesive qualities, which increase the drug's nasal residence length by slowing nasal evacuation (Soane *et al.*, 2001). In addition, chitosan has the unique virtue of opening up the tight junctions of the mucosal epithelium of the nasal cavity, increasing the membrane permeability of bioactive-like drug molecules, peptides, and proteins (Sonaje *et al.*, 2011), (Amidi *et al.*, 2010).

Polyethylene glycol (PEG) is one of the widely used polymers due to its low toxicity. In addition, surface modification of nanoparticles using PEG enhances transport and uptake across the mucus membrane (Lai *et al.*, 2007).

Poly (lactic-co-glycolic acid) (PLGA) is also used to deliver drug nanoparticles through the intranasal nasal route. For example, olanzapine-loaded PLGA nanoparticles are delivered intranasally for better drug uptake (Seju *et al.*, 2011).

9.2.2. Lipid-based nanoparticles

These are also adaptable carrier systems for loaded bioactive brain targeting, and this system has several advantages due to its excellent biocompatibility and biodegradability due to its lipid nature (Rai *et al.*, 2015). Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers are two examples of lipid-based nanoparticles. Intranasal administration of haloperidol-loaded solid lipid nanoparticles and valproic acid-based NLCs is used.

9.2.3. Liposomes

These are phospholipid vesicles composed of a phospholipid bilayer enclosing one or more aqueous regions, with medicinal substances enclosed in either a lipid or a water layer based on their hydrophilic nature and lipophilicity (Ganeshpurkar *et al.*, 2013). This system effectively encapsulates smaller and larger molecules with the overall range of hydrophilic nature and pKa value (Alsarra *et al.*, 2008), (Bansal *et al.*, 2016). Cationic liposomes can increase the therapeutic efficacy of proteins like ovalbumin when administered intranasally by increasing brain transport and residence time.

9.2.4. Nanogels

These are dense suspensions or solutions with high viscosity. Nanogels provide various advantages over other systems:

- It candecrease the viscosity of postnasal drip
- It reduces the anterior leakage of the pharmaceutical formulation
- Reduces irritation by providing a soothing and emollient effect
  For example, insulin-loaded nanogels are delivered through the intranasal route to enhance brain insulin delivery.

9.3. Microemulsions

Intranasally administered microemulsions are also better for targeting the brain through the nasal route. The therapeutic technique in epilepsy that provides a rapid start of action followed by a prolonged duration of action by combining clonazepam as a microemulsion formulation with mucoadhesive substancesis suggested by Vyas *et al.* (2006) in their studies (Vyas *et al.*, 2006).

9.4. Microspheres

This delivery method delivers prolonged medication release while protecting against enzymatic metabolism (Kushwaha *et al.*, 2011).

9.5. In-Situ Gelling Systems

These systems show sol-to-gel transitions at the administered site. They are fluid before administration and go through a sol-to-gel transition triggered by environmental stimuli such as temperature, pH, ion shift, magnetic field, or in a biological context (Aderibigbe, 2018), (Sosnik & Seremeta, 2017). Therefore, they are highly compatible with various medications, including soluble, insoluble, low or high molecular weight, etc. For example, various drugs like amantadine, levodopa, ropinirole, etc., are delivered using an in-situ-based gelling system and administered via the intranasal route (Singh *et al.*, 2018).

Table 1: Various novel drug delivery systems developed for intranasal drug delivery to the brain.

S. No.	Drug	Delivery system	Research findings	References
1.	Levodopa	Levodopa-loaded nanoparticles	• Increased bioavailability in the brain	Dimiou *et al.*, 2022
2.	Naringenin	Poloxamer chitosan-based nano-formulation	• Improved bioavailability in the brain	(Ahmad *et al.*, 2020)
3.	Donepezil	Nano-emulsions	• Increases in permeability • Increases bioavailability • Bypasses First-pass metabolism • Reduced GIT adverse effects	(Espinoza *et al.*, 2019)
4.	Pentamidine	Chitosan niosomes	• Enhanced bioavailability • Elimination of hepatotoxicity • Bypasses First-pass metabolism • Reduced side effects	(Rinaldi *et al.*, 2018)
5.	Rivastigmine	Chitosan containing emulsion	• Increased brain exposure 5-folds	(Shah *et al.*, 2018)
6.	Efavirenz	Solid lipid nanoparticles	• Improved bioavailability and brain uptake	(Dong, 2018)
7.	Desvenlafaxine	PLGA-chitosan nanoparticles	• Improved pharmacokinetic and pharmacodynamics profile of the desvenlafaxine	(Tong *et al.*, 2017)
8.	Lamotrigine	Solution	• Increased bioavailability	(Serralheiro *et al.*, 2015)
9.	Haloperidol	Solid lipid nanoparticles	• Better brain targeting efficiency • Bypasses blood-brain barrier	(Yasir & Sara, 2014)
10.	Nimodipine	Mucoadhesive microemulsion	• Decreased mucociliary clearance • Enhanced bioavailability of nimodipine in the brain	(Pathak *et al.*, 2014)

11.	Olanzapine	PLGA nanoparticles	• Enhanced brain uptake of drug	(Seju *et al.*, 2011)
12.	Valproic acid	Nanostructured lipid carriers (NLCs)	• Increased concentration of drugs in the brain	(Eskandari *et al.*, 2011)
13.	Ovalbumin	Cationic liposomes	• Improved therapeutic efficacy	(Migliore *et al.*, 2010)
14.	Clonazepam	Microemulsion with mucoadhesive agents	• The quick onset of action • Extended duration of action	(Vyas *et al.*, 2006)
15.	Fentanyl citrate	Peptide-attached liposomes	• Lower C_{max}, slower T_{max}, decreased AUC0–120min compared to solutions. • Liposomal encapsulation reduces the systemic absorption of fentanyl and slows brain uptake.	(Sedlakova *et al.*, 1999)
16.	Nifedipine	Multimellar liposomes	• Increased mucociliary clearance • Does not cause nasal obstruction • Provide constant plasma drug profile	(Vyas *et al.*, 1995)

10. Future Prospective of Novel Strategies for Nose-to-Brain Delivery

For compelling nose-to-brain delivery, there are still several obstacles to be solved. As a result, it is anticipated that research to remove constraints and clarify the mechanics of the relevant pathways will continue.To ensure that formulations can effectively transfer drugs from the nasal passage to the brain, efforts must be made to understand the mechanisms of drug delivery of it. Additionally, a formulation must be designed to have the sufficient physical strength to prevent removal by physicochemical forces once it has reached critical areas of the nasal cavity and to maintain the required bonding strength.Till now, nasal-brain drug delivery research has primarily concentrated on delivering drugs to the brain, with little knowledge of mechanistic approaches that allow medications (delivered to the cranial nerve system) to operate on specific parts of brain tissue (Jeong *et al.*, 2022). As a result, it is predicted that focused research, which allows pharmaceuticals to work exclusively on specific components to minimize side effects and boost therapeutic outcomes, will be aggressively applied to the nose-to-brain delivery pathway. By targeting only particular aspects within the cranial nerve system, the findings of studies on target factors that are crucial to the beginning and treatment of various cranial neural illnesses can be used to limit side effects in areas unrelated to lesions.

Conclusion

The therapy for CNS illnesses is still a significant effort with many challenges for the delivery of therapeutic moieties to the brain, which has several physiological, metabolic, and biochemical barriers that all work together as a portion of the BBB. As a result, there is a need to create an alternative route for drug delivery, and distribution via the nose to the target brain is being investigated. The nose-to-brain route is advantageous since it is a non-invasive method to circumvent the BBB, removing the limitation for therapeutic drug delivery to the brain. The nasal-to-brain route through a novel drug delivery system is beneficial in treating several neurological disorders. The targeting directly into the brain bypasses the BBB, providing better efficacy, effective permeability, improved retention, absorption, and bioavailability, and lower risk of side effects related to conventional treatment options.

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Authors Contributions

Ms. Manisha Vohra is the major contributor to the writing, literature, and drafting of the manuscript; Dr. Sheetu Wadhwa, Dr. Amit Sharma, and Mr. Mohammad Amir is the major contributor in editing and drafting the manuscript; all authors read and approved the final manuscript.

Conflict of Interest Statement

The authors have declared that no competinginterests exist.

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References

Pandey, V., Gadeval, A., Asati, S., Jain, P., Jain, N., Roy, R. K., & Tekade, R. K. (2020). Formulation strategies for nose-to-brain delivery of therapeutic molecules. In *Drug Delivery Systems* (291-332). Academic Press.
https://doi.org/10.1016/B978-0-12-814487-9.00007-7

Gajbhiye, K. R., Gajbhiye, V., & Soni, V. (2015). Targeted brain delivery of bioactive molecules using nanocarriers. *Journal of Bioequivalence & Bioavailability*, *7*(3), 112.
http://doi.org/10.4172/jbb.1000224

Gänger, S., & Schindowski, K. (2018). Tailoring formulations for intranasal nose-to-brain delivery: a review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal olfactory mucosa. *Pharmaceutics*, *10*(3), 116.
https://doi.org/10.3390/pharmaceutics10030116

Gao, H. M., Liu, B., Zhang, W., & Hong, J. S. (2003). Novel anti-inflammatory therapy for Parkinson's disease. *Trends in Pharmacological Sciences*, *24*(8), 395-401.
https://doi.org/10.1016/S0165-6147(03)00176-7

Takahashi, H., & Wakabayashi, K. (2005). Controversy: is Parkinson's disease a single disease entity? Yes. *Parkinsonism & Related Disorders*, *11*, S31-S37.
https://doi.org/10.1016/j.parkreldis.2005.02.011

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *Journal of Neurology, Neurosurgery & Psychiatry*, *79*(4), 368-376.
http://dx.doi.org/10.1136/jnnp.2007.131045

Berardelli, A., Rothwell, J. C., Thompson, P. D., & Hallett, M. (2001). Pathophysiology of bradykinesia in Parkinson's disease. *Brain*, *124*(11), 2131-2146.
https://doi.org/10.1093/brain/124.11.2131

Danielyan, L., Schäfer, R., von Ameln-Mayerhofer, A., Bernhard, F., Verleysdonk, S., Buadze, M., ... & Frey, W. H. (2011). Therapeutic efficacy of intranasally delivered mesenchymal stem cells in a rat model of Parkinson disease. *Rejuvenation Research*, *14*(1), 3-16.
https://doi.org/10.1089/rej.2010.1130

Fine, J. M., Forsberg, A. C., Renner, D. B., Faltesek, K. A., Mohan, K. G., Wong, J. C., & Hanson, L. R. (2014). Intranasally-administered deferoxamine mitigates toxicity of 6-OHDA in a rat model of Parkinson's disease. *Brain Research*, *1574*, 96-104.
https://doi.org/10.1016/j.brainres.2014.05.048

Weller, J., & Budson, A. (2018). Current understanding of Alzheimer's disease diagnosis and treatment. *F1000Research*, *7*.
http://doi.org/10.12688/f1000research.14506.1

Benedict, C., Frey II, W. H., Schiöth, H. B., Schultes, B., Born, J., & Hallschmid, M. (2011). Intranasal insulin as a therapeutic option in the treatment of cognitive impairments. *Experimental Gerontology*, *46*(2-3), 112-115.
https://doi.org/10.1016/j.exger.2010.08.026

Fazil, M., Md, S., Haque, S., Kumar, M., Baboota, S., kaurSahni, J., & Ali, J. (2012). Development and evaluation of rivastigmine loaded chitosan nanoparticles for brain targeting. *European Journal of Pharmaceutical Sciences*, *47*(1), 6-15.
https://doi.org/10.1016/j.ejps.2012.04.013

Huang, W. J., Chen, W. W., & Zhang, X. (2017). Multiple sclerosis: Pathology, diagnosis and treatments. *Experimental and Therapeutic Medicine*, *13*(6), 3163-3166.
https://doi.org/10.3892/etm.2017.4410

Liu, X. F., Fawcett, J. R., Thorne, R. G., DeFor, T. A., & Frey II, W. H. (2001). Intranasal administration of insulin-like growth factor-I bypasses the blood–brain barrier and protects against focal cerebral ischemic damage. *Journal of the Neurological Sciences*, *187*(1-2), 91-97.
https://doi.org/10.1016/S0022-510X(01)00532-9

Dalpiaz, A., Gavini, E., Colombo, G., Russo, P., Bortolotti, F., Ferraro, L., & Giunchedi, P. (2008). Brain uptake of an anti-ischemic agent by nasal administration of microparticles. *Journal of Pharmaceutical Sciences*, *97*(11), 4889-4903.
https://doi.org/10.1002/jps.21335

Hong, S. S., Oh, K. T., Choi, H. G., & Lim, S. J. (2019). Liposomal formulations for nose-to-brain delivery: recent advances and future perspectives. *Pharmaceutics*, *11*(10), 540.
https://doi.org/10.3390/pharmaceutics11100540

Thakur, A., Singh, P. K., Biswal, S. S., Kumar, N., Jha, C. B., Singh, G., ... & Kumar, R. (2020). Drug delivery through nose: A non-invasive technique for brain targeting. *Journal of Reports in Pharmaceutical Sciences*, *9*(1), 168.
http://doi.org/10.4103/jrptps.JRPTPS_59_19

Nasal cavity. (2022). Ken Hub [Internet]. Available from: https://www.kenhub.com/en/library/anatomy/nasal-cavity

The nasal cavity. (2019). TeachMe Anatomy [Internet]. Available from: https://teachmeanatomy.info/head/organs/the-nose/nasal-cavity/

The nasal skeleton. (2019). TeachMe Anatomy [Internet]. Available from: https://teachmeanatomy.info/head/osteology/nasal-skeleton/

Bors, L. A., & Erdő, F. (2019). Overcoming the blood–brain barrier. challenges and tricks for CNS drug delivery. *Scientia Pharmaceutica*, *87*(1), 6. https://doi.org/10.3390/scipharm87010006

Abbott, N. J., Patabendige, A. A., Dolman, D. E., Yusof, S. R., & Begley, D. J. (2010). Structure and function of the blood–brain barrier. *Neurobiology of Disease*, *37*(1), 13-25. https://doi.org/10.1016/j.nbd.2009.07.030

Sedlakova, R., Shivers, R. R., & Del Maestro, R. F. (1999). Ultrastructure of the blood-brain barrier in the rabbit. *Journal of Submicroscopic Cytology and Pathology*, *31*(1), 149-161. PMID: 10363362.

Redzic, Z. (2011). Molecular biology of the blood-brain and the blood-cerebrospinal fluid barriers: similarities and differences. *Fluids and Barriers of the CNS*, *8*(1), 1-25. https://doi.org/10.1186/2045-8118-8-3

Erdő, F., Bors, L. A., Farkas, D., Bajza, Á., & Gizurarson, S. (2018). Evaluation of intranasal delivery route of drug administration for brain targeting. *Brain Research Bulletin*, *143*, 155-170. https://doi.org/10.1016/j.brainresbull.2018.10.009

Pardeshi, C. V., & Belgamwar, V. S. (2013). Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood–brain barrier: an excellent platform for brain targeting. *Expert Opinion on Drug Delivery*, *10*(7), 957-972. https://doi.org/10.1517/17425247.2013.790887

Agu, R. U. (2016). Challenges in nasal drug absorption: how far have we come?. *Therapeutic Delivery*, *7*(7), 495-510. https://doi.org/10.4155/tde-2016-0022

Kushwaha, S. K., Keshari, R. K., & Rai, A. K. (2011). Advances in nasal trans-mucosal drug delivery. *Journal of Applied Pharmaceutical Science*, 21-28.

Djupesland, P. G., Chatkin, J. M., Qian, W., & Haight, J. S. (2001). Nitric oxide in the nasal airway: a new dimension in otorhinolaryngology. *American Journal of Otolaryngology*, *22*(1), 19-32. https://doi.org/10.1053/ajot.2001.20700

Hsu, D. W., & Suh, J. D. (2018). Anatomy and physiology of nasal obstruction. *Otolaryngologic Clinics of North America*, *51*(5), 853-865. http://doi.org/10.16/j.otc.2018.05.001

Nigro, C. E. N., de Aguiar Nigro, J. F., Mion, O., & Mello Jr, J. F. (2009). Nasal valve: anatomy and physiology. *Brazilian Journal of Otorhinolaryngology*, *75*(2), 305-310. https://doi.org/10.1016/S1808-8694(15)30795-3

Gizurarson, S. (2015). The effect of cilia and the mucociliary clearance on successful drug delivery. *Biological and Pharmaceutical Bulletin*, b14-00398. https://doi.org/10.1248/bpb.b14-00398

S Hersh, D., S Wadajkar, A., B Roberts, N., G Perez, J., P Connolly, N., Frenkel, V., ... & J Kim, A. (2016). Evolving drug delivery strategies to overcome the blood brain barrier. *Current Pharmaceutical Design*, *22*(9), 1177-1193.

Pires, A., Fortuna, A., Alves, G., & Falcão, A. (2009). Intranasal drug delivery: how, why and what for?. *Journal of Pharmacy & Pharmaceutical Sciences*, *12*(3), 288-311. https://doi.org/10.18433/J3NC79

Oliveira, P., Fortuna, A., Alves, G., & Falcao, A. (2016). Drug-metabolizing enzymes and efflux transporters in nasal epithelium: influence on the bioavailability of intranasally administered drugs. *Current Drug Metabolism*, *17*(7), 628-647.

Costantino, H. R., Illum, L., Brandt, G., Johnson, P. H., & Quay, S. C. (2007). Intranasal delivery: physicochemical and therapeutic aspects. *International Journal of Pharmaceutics*, *337*(1-2), 1-24. https://doi.org/10.1016/j.ijpharm.2007.03.025

Dimova, S., Brewster, M. E., Noppe, M., Jorissen, M., & Augustijns, P. (2005). The use of human nasal in vitro cell systems during drug discovery and development. *Toxicology in Vitro*, *19*(1), 107-122. https://doi.org/10.1016/j.tiv.2004.07.003

Clementino, A., Batger, M., Garrastazu, G., Pozzoli, M., Del Favero, E., Rondelli, V., & Sonvico, F. (2016). The nasal delivery of nanoencapsulated statins–an approach for brain delivery. *International Journal of Nanomedicine*, *11*, 6575. http://doi.org/10.2147/IJN.S119033

Türker, S., Onur, E., & Özer, Y. (2004). Nasal route and drug delivery systems. *Pharmacy world and Science*, *26*(3), 137-142. https://doi.org/10.1023/B:PHAR.0000026823.82950.ff

Chaturvedi, M., Kumar, M., & Pathak, K. (2011). A review on mucoadhesive polymer used in nasal drug delivery system. *Journal of Advanced Pharmaceutical Technology & Research*, *2*(4), 215. http://doi.org/10.4103/2231-4040.90876

Crowe, T. P., Greenlee, M. H. W., Kanthasamy, A. G., & Hsu, W. H. (2018). Mechanism of intranasal drug delivery directly to the brain. *Life Sciences*, *195*, 44-52. https://doi.org/10.1016/j.lfs.2017.12.025

Thorne, R. G., Pronk, G. J., Padmanabhan, V., & Frey Ii, W. H. (2004). Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. *Neuroscience*, *127*(2), 481-496. https://doi.org/10.1016/j.neuroscience.2004.05.029

Miyake, M. M., & Bleier, B. S. (2015). The blood-brain barrier and nasal drug delivery to the central nervous system. *American Journal of Rhinology & Allergy*, *29*(2), 124-127. https://doi.org/10.2500/ajra.2015.29.4149

Borlongan, C. V., & Emerich, D. F. (2003). Facilitation of drug entry into the CNS via transient permeation of blood brain barrier: laboratory and preliminary clinical evidence from bradykinin receptor agonist, Cereport. *Brain Research Bulletin*, *60*(3), 297-306. https://doi.org/10.1016/S0361-9230(03)00043-1

Ross, T. M., Martinez, P. M., Renner, J. C., Thorne, R. G., Hanson, L. R., & Frey Ii, W. H. (2004). Intranasal administration of interferon beta bypasses the blood–brain barrier to target the central nervous system and cervical lymph nodes: a non-invasive treatment strategy for multiple sclerosis. *Journal of Neuroimmunology*, *151*(1-2), 66-77. https://doi.org/10.1016/j.jneuroim.2004.02.011

Thorne, R. G., Hanson, L. R., Ross, T. M., Tung, D., & Frey Ii, W. H. (2008). Delivery of interferon-β to the monkey nervous system following intranasal administration. *Neuroscience*, *152*(3), 785-797. https://doi.org/10.1016/j.neuroscience.2008.01.013

Clerico, D. M., To, W. C., & Lanza, D. C. (2003). Anatomy of the human nasal passages. *Neurological Disease and Therapy*, *57*, 1-16.

Stefanczyk-Krzymowska, S., Krzymowski, T., Grzegorzewski, W., Wasowska, B., & Skipor, J. (2000). Humoral pathway for local transfer of the priming pheromone androstenol from the nasal cavity to the brain and hypophysis in anaesthetized gilts. *Experimental Physiology*, *85*(6), 801-809. https://doi.org/10.1111/j.1469-445X.2000.02056.x

Skipor, J., Grzegorzewski, W., Einer-Jensen, N., & Wasowska, B. (2003). Local vascular pathway for progesterone transfer to the brain after nasal administration in gilts. *Reprod Biol*, *3*(2), 143-59.

Einer-Jensen, N., & Hunter, R. H. F. (2005). Counter-current transfer in reproductive biology. *Reproduction*, *129*(1), 9-18. https://doi.org/10.1530/rep.1.00278

Lochhead, J. J., Wolak, D. J., Pizzo, M. E., & Thorne, R. G. (2015). Rapid transport within cerebral perivascular spaces underlies widespread tracer distribution in the brain after intranasal administration. *Journal of Cerebral Blood Flow & Metabolism*, *35*(3), 371-381. https://doi.org/10.1038/jcbfm.2014.215

Hadaczek, P., Yamashita, Y., Mirek, H., Tamas, L., Bohn, M. C., Noble, C., & Bankiewicz, K. (2006). The "perivascular pump" driven by arterial pulsation is a powerful mechanism for the distribution of therapeutic molecules within the brain. *Molecular Therapy*, *14*(1), 69-78. https://doi.org/10.1016/j.ymthe.2006.02.018

Schley, D., Carare-Nnadi, R., Please, C. P., Perry, V. H., & Weller, R. O. (2006). Mechanisms to explain the reverse perivascular transport of solutes out of the brain. *Journal of Theoretical Biology*, *238*(4), 962-974. https://doi.org/10.1016/j.jtbi.2005.07.005

Dhuria, S. V., Hanson, L. R., & Frey, W. H. (2009). Novel vasoconstrictor formulation to enhance intranasal targeting of neuropeptide therapeutics to the central nervous system. *Journal of Pharmacology and Experimental Therapeutics*, *328*(1), 312-320. https://doi.org/10.1124/jpet.108.145565

Savale, S., & Mahajan, H. (2017). Nose to brain: A versatile mode of drug delivery system. *Asian J. Biomater. Res*, *3*, 16-38.

Bhise, S. B., Yadav, A. V., Avachat, A. M., & Malayandi, R. (2008). Bioavailability of intranasal drug delivery system. *Asian Journal of Pharmaceutics (AJP)*, *2*(4). https://doi.org/10.22377/ajp.v2i4.203

Upadhyay, S., Parikh, A., Joshi, P., Upadhyay, U. M., & Chotai, N. P. (2011). Intranasal drug delivery system-A glimpse to become maestro. *Journal of Applied Pharmaceutical Science*, 1(3), 34-44.

Corbo, D. C., Liu, J. C., & Chien, Y. W. (1990). Characterization of the barrier properties of mucosal membranes. *Journal of Pharmaceutical Sciences*, *79*(3), 202-206. https://doi.org/10.1002/jps.2600790304

Frey, W. H., Liu, J., Chen, X., Thorne, R. G., Fawcett, J. R., Ala, T. A., & Rahman, Y. E. (1997). Delivery of 125I-NGF to the brain via the olfactory route. *Drug Delivery*, *4*(2), 87-92. https://doi.org/10.3109/10717549709051878

Garg, T., Singh, S., & Goyal, A. (2013). Stimuli-sensitive hydrogels: an excellent carrier for drug and cell delivery. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, *30*(5).
http://doi.org/10.1615/CritRevTherDrugCarrierSyst.2013007259

Washington, N., Steele, R. J. C., Jackson, S. J., Bush, D., Mason, J., Gill, D. A., & Rawlins, D. A. (2000). Determination of baseline human nasal pH and the effect of intranasally administered buffers. *International Journal of Pharmaceutics*, *198*(2), 139-146.
https://doi.org/10.1016/S0378-5173(99)00442-1

Dhakar, R. C. (2011). Nasal drug delivery: success through integrated device development. *Journal of Drug Delivery and Therapeutics*, *1*(1).
https://doi.org/10.22270/jddt.v1i1.3

Sandhu, P., Rathore, D., Kataria, S., Middha, A., Brain targeting noval approaches: a comprehensive review [Internet]. Available from: https://www.pharmatutor.org/articles/brain-targeting-novel-approches-a-comprehensive-review

Marx, D., Williams, G., & Birkhoff, M. (2015). Intranasal drug administration—an attractive delivery route for some drugs. *Drug Discov Dev*, 299-320.
http://dx.doi.org/10.5772/59468

Wang, Z., Xiong, G., Tsang, W. C., Schätzlein, A. G., & Uchegbu, I. F. (2019). Nose-to-brain delivery. *Journal of Pharmacology and Experimental Therapeutics*, *370*(3), 593-601.
https://doi.org/10.1124/jpet.119.258152

Sigurdsson, P., Thorvaldsson, T., Gizurarson, S., & Gunnarsson, E. (1997). Olfactoryabsorption of insulin to the brain. *Drug Delivery*, *4*(3), 195-200.
https://doi.org/10.3109/10717549709051892

Tanaka, A., Furubayashi, T., Arai, M., Inoue, D., Kimura, S., Kiriyama, A., & Yamamoto, A. (2018). Delivery of oxytocin to the brain for the treatment of autism spectrum disorder by nasal application. *Molecular Pharmaceutics*, *15*(3), 1105-1111.
https://doi.org/10.1021/acs.molpharmaceut.7b00991

Soane, R. J., Hinchcliffe, M., Davis, S. S., & Illum, L. (2001). Clearance characteristics of chitosan-based formulations in the sheep nasal cavity. *International Journal of Pharmaceutics*, *217*(1-2), 183-191.
https://doi.org/10.1016/S0378-5173(01)00602-0

Sonaje, K., Lin, K. J., Tseng, M. T., Wey, S. P., Su, F. Y., Chuang, E. Y., & Sung, H. W. (2011). Effects of chitosan-nanoparticle-mediated tight junction opening on the oral absorption of endotoxins. *Biomaterials*, *32*(33), 8712-8721.
https://doi.org/10.1016/j.biomaterials.2011.07.086

Amidi, M., Mastrobattista, E., Jiskoot, W., & Hennink, W. E. (2010). Chitosan-based delivery systems for protein therapeutics and antigens. *Advanced Drug Delivery Reviews*, *62*(1), 59-82.
https://doi.org/10.1016/j.addr.2009.11.009

Lai, S. K., O'Hanlon, D. E., Harrold, S., Man, S. T., Wang, Y. Y., Cone, R., & Hanes, J. (2007). Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus. *Proceedings of the National Academy of Sciences*, *104*(5), 1482-1487.
https://doi.org/10.1073/pnas.0608611104

Seju, U., Kumar, A., & Sawant, K. K. (2011). Development and evaluation of olanzapine-loaded PLGA nanoparticles for nose-to-brain delivery: in vitro and in vivo studies. *Acta Biomaterialia*, *7*(12), 4169-4176.
https://doi.org/10.1016/j.actbio.2011.07.025

Rai, A., Jain, A., Jain, A., Jain, A., Pandey, V., Chashoo, G., & Sharma, P. R. (2015). Targeted SLNs for management of HIV-1 associated dementia. *Drug Development and Industrial Pharmacy*, *41*(8), 1321-1327.
https://doi.org/10.3109/03639045.2014.948453

Ganeshpurkar, A., Ganeshpurkar, A., Agnihotri, A., Pandey, V., Vishwakarma, N., Bansal, D., & Dubey, N. (2013). Chondroitin Sulfate Surface Engineered Docetaxel-Loaded Liposomes for Tumor Targeting: Design, Development, and Characterization. In *Proceedings of All India Seminar on Biomedical Engineering*, 77-82.

Alsarra, I. A., Hamed, A. Y., & Alanazi, F. K. (2008). Acyclovir liposomes for intranasal systemic delivery: development and pharmacokinetics evaluation. *Drug Delivery*, *15*(5), 313-321.
https://doi.org/10.1080/10717540802035251

Bansal, D., Yadav, K., Pandey, V., Ganeshpurkar, A., Agnihotri, A., & Dubey, N. (2016). Lactobionic acid coupled liposomes: an innovative strategy for targeting hepatocellular carcinoma. *Drug Delivery*, *23*(1), 140-146.
https://doi.org/10.3109/10717544.2014.907373

Vyas, T. K., Babbar, A. K., Sharma, R. K., Singh, S., & Misra, A. (2006). Intranasal mucoadhesive microemulsions of clonazepam: preliminary studies on brain targeting. *Journal of Pharmaceutical Sciences*, *95*(3), 570-580.
https://doi.org/10.1002/jps.20480

Aderibigbe B. A. (2018). In Situ-Based Gels for Nose to Brain Delivery for the Treatment of Neurological Diseases. *Pharmaceutics*, *10*(2), 40.
https://doi.org/10.3390/pharmaceutics10020040

Sosnik, A., & Seremeta, K. P. (2017). Polymeric hydrogels as technology platform for drug delivery applications. *Gels*, *3*(3), 25.
https://doi.org/10.3390/gels3030025

Singh, M., Thakur, V., Deshmukh, R., Sharma, A., Rathore, M. S., Kumar, A., & Mishra, N. (2018). Development and characterization of morin hydrate-loaded micellar nanocarriers for the effective management of Alzheimer's disease. *Journal of Microencapsulation*, *35*(2), 137-148.
https://doi.org/10.1080/02652048.2018.1441916

Dimiou, S., Lopes, R. M., Kubajewska, I., Mellor, R. D., Schlosser, C. S., Shet, M. S., Huang, H., Akcan, O., Whiteside, G. T., Schätzlein, A. G., & Uchegbu, I. F. (2022). Particulate levodopa nose-to-brain delivery targets dopamine to the brain with no plasma exposure. *International Journal of Pharmaceutics*, *618*, 121658.
https://doi.org/10.1016/j.ijpharm.2022.121658

Ahmad, N., Ahmad, R., Ahmad, F. J., Ahmad, W., Alam, M. A., Amir, M., & Ali, A. (2020). Poloxamer-chitosan-based Naringenin nano-formulation used in brain targeting for the treatment of cerebral ischemia. *Saudi Journal of Biological Sciences*, *27*(1), 500-517.
https://doi.org/10.1016/j.sjbs.2019.11.008

Espinoza, L. C., Silva-Abreu, M., Clares, B., Rodríguez-Lagunas, M. J., Halbaut, L., Cañas, M. A., & Calpena, A. C. (2019). Formulation strategies to improve nose-to-brain delivery of donepezil. *Pharmaceutics*, *11*(2), 64.
https://doi.org/10.3390/pharmaceutics11020064

Rinaldi, F., Hanieh, P. N., Chan, L. K. N., Angeloni, L., Passeri, D., Rossi, M., & Marianecci, C. (2018). Chitosan glutamate-coated niosomes: a proposal for nose-to-brain delivery. *Pharmaceutics*, *10*(2), 38.
https://doi.org/10.3390/pharmaceutics10020038

Shah, B., Khunt, D., Misra, M., & Padh, H. (2018). Formulation and in-vivo pharmacokinetic consideration of intranasal microemulsion and mucoadhesive microemulsion of rivastigmine for brain targeting. *Pharmaceutical Research*, *35*(1), 1-10.
https://doi.org/10.1007/s11095-017-2279-z

Dong, X. (2018). Current strategies for brain drug delivery. *Theranostics*, *8*(6), 1481.
http://doi.org/10.7150/thno.21254

Tong, G. F., Qin, N., & Sun, L. W. (2017). Development and evaluation of Desvenlafaxine loaded PLGA-chitosan nanoparticles for brain delivery. *Saudi Pharmaceutical Journal*, *25*(6), 844-851.
https://doi.org/10.1016/j.jsps.2016.12.003

Serralheiro, A., Alves, G., Fortuna, A., & Falcão, A. (2015). Direct nose-to-brain delivery of lamotrigine following intranasal administration to mice. *International Journal of Pharmaceutics*, *490*(1-2), 39-46.
https://doi.org/10.1016/j.ijpharm.2015.05.021

Yasir, M., & Sara, U. V. S. (2014). Solid lipid nanoparticles for nose to brain delivery of haloperidol: in vitro drug release and pharmacokinetics evaluation. *Acta Pharmaceutica Sinica B*, *4*(6), 454-463.
https://doi.org/10.1016/j.apsb.2014.10.005

Pathak, R., Dash, R. P., Misra, M., & Nivsarkar, M. (2014). Role of mucoadhesive polymers in enhancing delivery of nimodipine microemulsion to brain via intranasal route. *Acta Pharmaceutica Sinica B*, *4*(2), 151-160.
https://doi.org/10.1016/j.apsb.2014.02.002

Eskandari, S., Varshosaz, J., Minaiyan, M., & Tabbakhian, M. (2011). Brain delivery of valproic acid via intranasal administration of nanostructured lipid carriers: in vivo pharmacodynamic studies using rat electroshock model. *International Journal of Nanomedicine*, *6*, 363.
http://doi.org/10.2147/IJN.S15881

Migliore, M. M., Vyas, T. K., Campbell, R. B., Amiji, M. M., & Waszczak, B. L. (2010). Brain delivery of proteins by the intranasal route of administration: a comparison of cationic liposomes versus aqueous solution formulations. *Journal of Pharmaceutical Sciences*, *99*(4), 1745-1761.
https://doi.org/10.1002/jps.21939

Vyas, S. P., Goswami, S. K., & Singh, R. (1995). Liposomes based nasal delivery system of nifedipine: Development and characterization. *International Journal of Pharmaceutics*, *118*(1), 23-30.
https://doi.org/10.1016/0378-5173(94)00296-H

Jeong, SH., Jang, JH. & Lee, YB. (2022). Drug delivery to the brain via the nasal route of administration: exploration of key targets and major consideration factors. *J. Pharm. Investig.*
https://doi.org/10.1007/s40005-022-00589-5

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