***Review Paper:***

# Containers on the micro- and nanoscale for neurodegenerative diseases: nose-to-brain drug transportation

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## *Abstract*

*The ever-increasing elderly population and the prevalence of harmful lifestyle choices have combined to make neurodegenerative illnesses as a major concern in global health. Numerous studies have investigated the best ways to treat the most prevalent neurological illnesses such as Alzheimer's, Parkinson's and migraine. But the blood-brain barrier means that conventional treatments for neurological diseases are often unsuccessful. A number of therapeutic medications face a formidable challenge when trying to reach the brain across the blood-brain barrier. One new approach to drug administration is the nasal route, which bypasses the digestive system and goes straight to the brain via the olfactory and trigeminal neurones. Fast absorption via the nasal route allows for immediate therapeutic impact by avoiding first-pass metabolism. Peptides, proteins and polar medicines with modest molecular weights may enter the nasal passage with relative ease. These medications need rapid onset of action otherwise they are difficult to administer by other means.*

*To increase the likelihood of drug absorption, MSs are mostly used for nose-to-brain delivery. This is because MSs prolong the time the medication interacts with the mucosal barrier. When microspheres touch the nasal mucosa, they enlarge and then solidify into a gel, making it impossible to expel them from the nose. As a novel approach to treating neurodegenerative illnesses, this study offers a comprehensive analysis of MS in nose-to-brain drug delivery.*

**Keywords:** Neurodegenerative illnesses, Alzheimer, Parkinsons, Migraine, Microspheres.

## Introduction

With an ageing population and a sharp rise in the number of cases in recent decades, neurodegenerative diseases have emerged as a major public healthcare problem on a worldwide scale[1]. Neurodegenerative diseases have far greater direct and indirect treatment costs compared to cancer[2,3]. The majority of neurodegenerative disorders (NDs) include neuroinflammation, the accumulation of intracellular α-synuclein (α-Syn), increased oxidative stress, oxidative damage to lipids and so on. The most common NDs are Alzheimer's disease and Parkinson's disease[4]. All of these things cause harm to neurones, which in turn affect our ability to move, control our muscles, feel and think clearly[5,6]. There have been a lot of efforts to find dependable and successful ways to treat NDs.

The majority of therapies, however, only halt the disease's course and do not eliminate it entirely. BBB and other limiting factors make it harder for many APIs to do their job. So, for NDs treatment to work, it is very important to make sure that the active molecules get to the brain safely and effectively[7]. Avoiding first-pass metabolism, gastrointestinal and systemic adverse effects are some of the benefits of nasal medication. After that, it crosses the BBB and reaches the brain via the olfactory and trigeminal nerves. Many APIs can already reach the brain via nose-to-brain delivery, but it is complicated. Mucociliary clearance lowers drug residence time and absorption in the nasal cavity[8].

Researchers often used micro and nanotechnology to increase brain tissue drug availability and to circumvent these limits. Micro and nanoparticulate carriers comprised of natural and manmade materials are a unique ND treatment. These carriers interact with biological structures molecularly. Engagement between target places may lessen negative impacts. For Alzheimer's and Parkinson's patients, this study will summarise micro and nanoscale nose-to-brain medicine delivery systems' advancements.

## Barrier to Brain

There are many ways for substances to get from the blood to the brain such as transmembrane diffusion, extracellular routes, saturable transporters and adsorptive endocytosis[9,10]. Transmembrane diffusion and transporters are the most important processes in drug delivery. The study found that transmembrane diffusion is not saturable because of the physicochemical properties of the substance[11].

In the brain, there are three barriers: the blood-cerebrospinal fluid barrier, the cerebrospinal fluid-brain barrier and the blood-cerebrospinal fluid barrier[12,13]. It is possible for the

interstitial fluid in the brain parenchyma and the cerebrospinal fluid (CSF) to exchange molecules.

The CSF can also very precisely control which chemicals from the blood enter it[14].When it comes to the metabolic activity and neuronal function of the brain, the BBB is crucial in controlling the biological chemicals needed [15]. The blood vessels that bring blood to the brain and the central nervous system have a unique property called the blood-brain barrier (BBB). This barrier helps to control the flow of chemicals, ions and cells from the bloodstream to the brain. Controlling the homeostasis of the central nervous system is important for keeping neurones working properly and keeping the body safe from poisons and infections. Alterations in these barrier properties significantly affect pathology and the onset of certain neurological diseases[16].

The astrocytes and pia mater that make up the CBB have properties of selective permeabilization[17,18] that make it easier for chemicals to move from cerebrospinal fluid into the brain parenchyma. BBB breakdown can be caused by changes in the flow of chemicals from the blood to the brain, inflammatory responses, abnormal angiogenesis, vascular regression, low blood flow and the breaking of tight junctions[19]. These factors may start or worsen a "vicious cycle" of health problems that lead to the death or failure of synapses and neurones[20].

**Influence on nasal-to-brain administration:** The nasal mucosa is an ideal delivery method for biopharmaceuticals and small-molecule medications due to its high absorption rate and exceptional permeability[26]. By going straight to the central nervous system (CNS) without going through the BBB, intravenous (IV) injection makes it possible to deliver therapeutic drugs without any harm [27]. One great advantage of nose-to-brain delivery is the potential for rapid and patient-compliant pharmaceutical administration[28]. Previous research has demonstrated strong evidence that targeting the olfactory mucosa increases the likelihood of drug transport to the central nervous system[29]. The olfactory region and the olfactory cleft in particular are challenges that must be overcome before the medicine can be effectively administered; the gap is located deep within the nasal cavity and is hence difficult to reach.

Given that the olfactory cleft is at the very top of the nasal canal, it is very important that formulations have excellent adhesion properties to stay attached to the mucosa [30]. It is hard for hydrophilic and macromolecular substances to get through the nasal mucosa because the membrane permeability is low where the epithelial cells attach. The primary controllers of paracellular transport are tight junctions, which form a robust link between cells [31]. When it comes to liquids and powders, the dose volume limits are 100–250 µl and 20–50 miligram, depending on the bulk density of the powder[32]. This means that only strong drugs can be given this way. Powerful pharmaceuticals must be shielded against nasal enzyme breakdown. Formulations should not irritate nasal passages. Nose-to-brain medicine delivery requires a nasal administration device[33].

New IN drug delivery methods have been developed due to improved systemic bioavailability. Nano and micro technologies enable brain tissue medication delivery. The way NDs are treated can be changed by the way molecules interact with carriers of micro and nanoparticles. These carriers can be made of natural or man-made materials[34]. Using microspheres (MSs) in a nose-to-brain approach to treat NDs has been the subject of manyinvestigation[35-40].

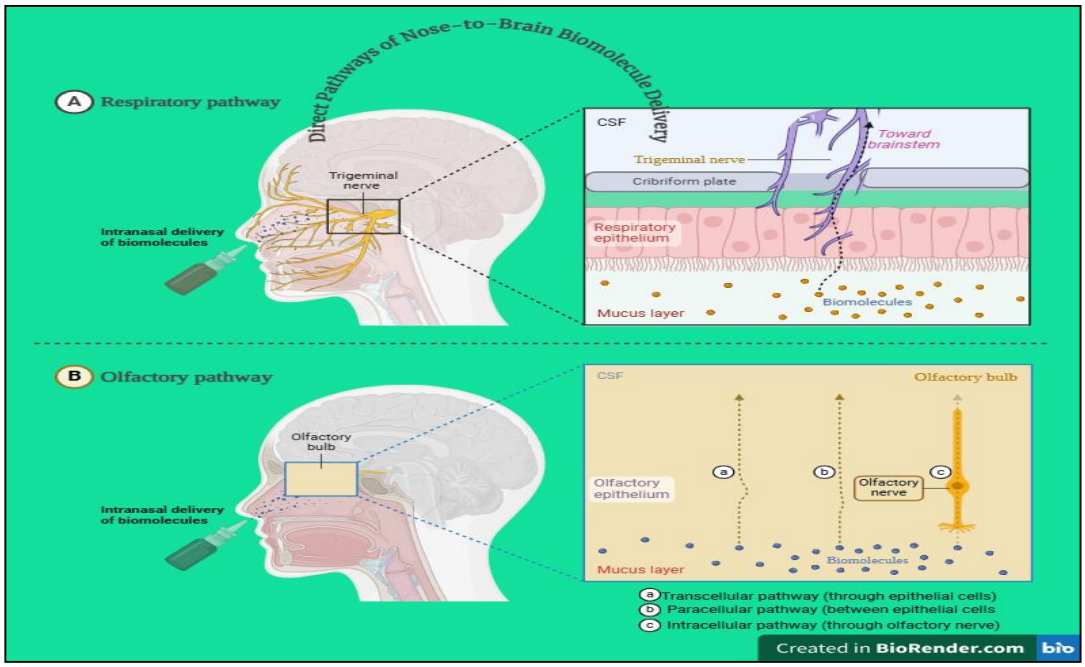


**Figure 1: Drugs enter the brain via the nose. Diagram of olfactory and trigeminal neurons in the nasal cavity: limestone-olfactory, whitish-trigeminal.**

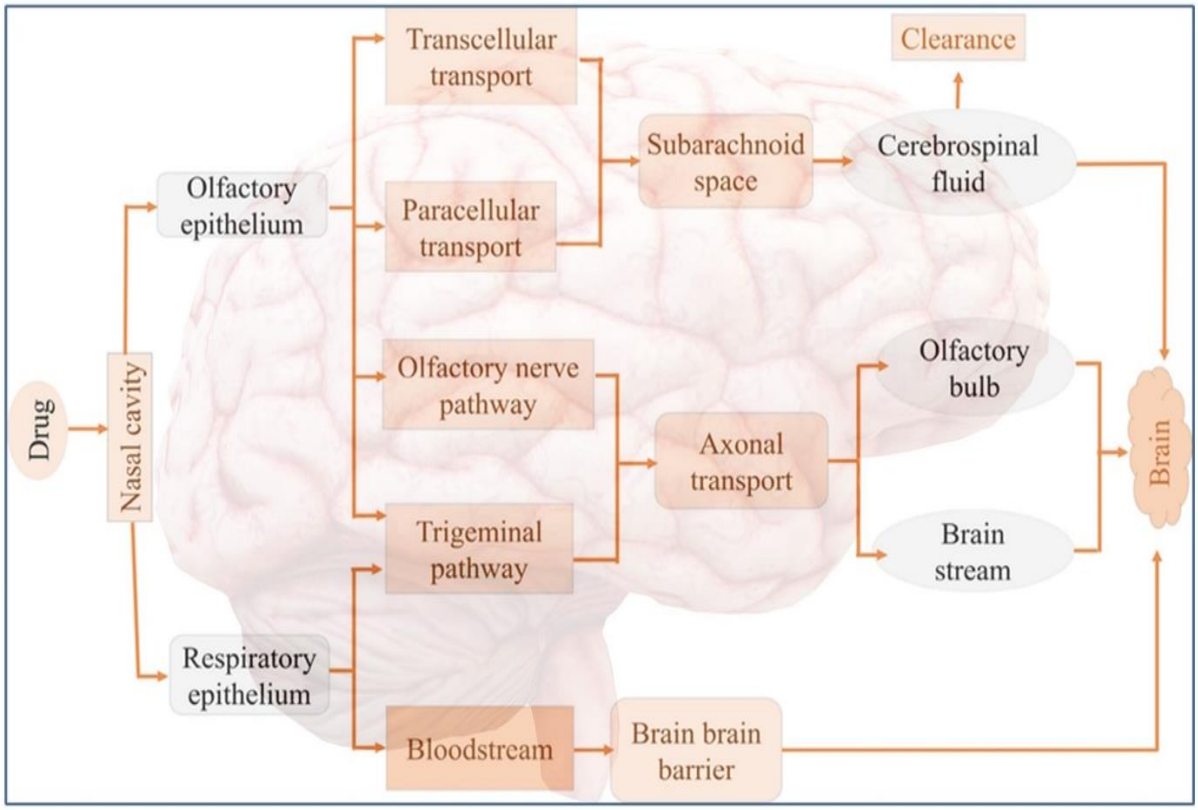


**Figure 2: Drug molecules can reach the brain via olfactory, systemic and trigeminal routes after nasal delivery. Through transcellular and paracellular transport, olfactory and trigeminal routes circumvent BBB and deliver medicines straight to the brain without first-pass processing.**

**Active Pharmaceutical ingredients suited for Nose-to-Brain Drug Delivery:** Most effective nose-to-brain drugs have a high first-pass impact, several adverse effects and do not reach therapeutic brain tissue concentrations when taken orally[35,36]. Drug transport from the nasal cavity to brain tissue depends on molecular weight, lipophilicity and dissociation[37]. Dopamine cannot penetrate the BBB, rendering it unsuitable for Parkinson's disease treatment. In an experiment to determine whether medication administered by the nose reached the brain, animals' blood and cerebrospinal fluid dopamine levels were measured. Administer the medication either nasally or intravenously. There was a noticeable difference in brain dopamine levels 30 minutes after nasal treatment vs intravenous administration. What these findings mean is that the olfactory pathway in rats is responsible for the transport of unaltered dopamine to the olfactory bulb[38].

Studies on humans[39] show that peptides like insulin, melanocortin and vasopressin build up in brain tissue after an intranasal injection. These peptides have been found to influence brain processes like learning, memory and cognition. Despite no change in peripheral blood levels, intranasal insulin improved cognitive functioning in Alzheimer's disease-patients[40-44].

**Criteria for optimal micro- and nanoparticle properties for nasal-to-brain transport:** There are a number of dosage forms that have been developed for delivery to the brain through the nasal passages including solutions, suspensions, microemulsions, gels and more. Traditional formulations sometimes fail to offer targeted administration and do not allow for the regulated release of medicinal compounds[45]. In most of the cases, the active molecules are absorbed and released quickly after delivery and the plasma concentration spikes sharply, which may cause harmful side effects. This concentration goes below therapeutic levels quickly, which may increase dosage or utilisation. Particulate formulations may exceed standard formulations in stability, mobility and nasal cavity residence[46,47].

To provide medication to the brain via the nose, the formulation must be deposited in the olfactory region. The correct liquid and solid devices can do this[48,49]. The nasal dose form must also have a lengthy residence duration and must maintain a high medicine concentration for diffusion[50].

Particle size is considered while designing a nose-to-brain injection system. Small nanoparticles may pass through phospholipid membranes more readily than microparticles. The tight connections in the nasal epithelium are less than 15 nm. Passive diffusion absorbs medications from larger particles that cannot penetrate the epithelium and enter mucosal tissue. Surface charge helps carriers stay in touch with mucosa longer. Because mucin is net negative, positively charged microparticles may stick to it.

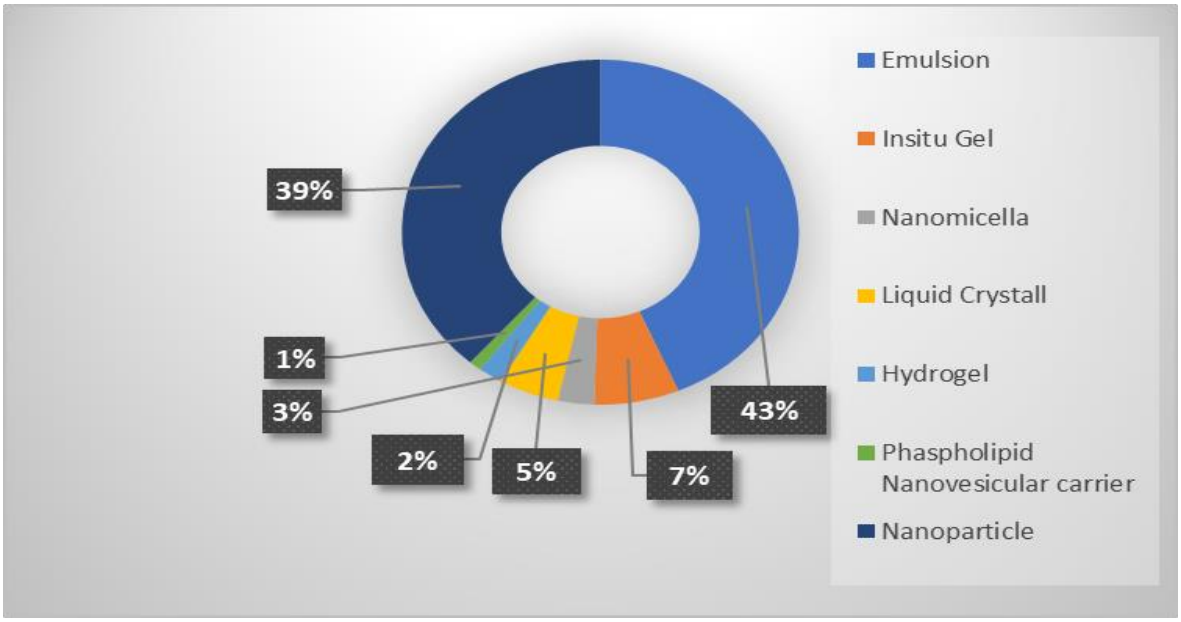


**Figure 3: Summary of the type of formulations investigated in the collected publications**

**Treatment of Neurodegenerative Diseases using Microparticles:** Microparticles, which can carry drugs, are found in the size range of 1-1000 µm. Their structural and functional abilities give them therapeutic and technological advantages. Some of these are the ability to deliver and release drugs in a targeted and modified way, to keep the encapsulated active agent from breaking down, to reduce systemic side effects, to make dose titration easier with less dose dumping, to make distribution more uniform and to make pharmacokinetics more predictable with fewer variables.

Microparticles can be homogeneous or heterogeneous systems, depending on their manufacturing process and constituents. All sorts of liquids, semisolids and solids (such as gels, creams, pastes and tablets) can include them in various dose forms. Both the geometry of the nasal cavity and the qualities of the particles including their size, shape and density. They also influence the deposition of particles in the human nasal cavity. If you inhale particles bigger than 20 µm, they tend to settle at the front of your nose because of the strong inertial impaction, according to the literature.

Particles smaller than 5 µm, on the other hand, follow the airways and go out of your nose. According to research, when particles of 10 µm in size are given intranasally at typical inhalation rates, they are more likely to settle in the olfactory area. Table 1 suggests that micron-sized carrier drug particles may assist the drug in settling in the nasal olfactory region. In drug carrier formulation, mucoadhesive polymers are often used to help get drugs to the olfactory epithelium more effectively. Because they cling to mucus, drug-loaded particles linger in the nasal cavity longer[61].

**Nose-to-brain delivery of microspheres for migraine:** Migraine, an episodic headache disorder, is characterised by recurrent episodes of severe, undulating pain, often on one side of the head, accompanied by nausea, vomiting, photophobia and phonophobia. A sensory processing dysfunction in the brain, likely hereditary and influenced by environmental factors, causes migraine attacks. When it comes to impairments experienced by those in their twenties and thirties, migraines rank second.

Migraine headaches are a hallmark of many mental and psychiatric disorders including depression and anxiety. Migraine headaches are caused by non-specific inflammation of the trigeminal nerve within the dura mater of the skull. These central stimuli have the potential to activate and sensitise trigeminal neurones. As shown in table 1, the IN route is renowned for its ability to deliver a high concentration of the medicine to the brain and a rapid onset of action for treating severe migraines[62].

**The cerebral delivery of MSs used for Alzheimer's disease:** Alzheimer's disease (AD) disproportionately affects the elderly globally. Alzheimer's disease causes cognitive deterioration owing to brain cell loss, especially neurones. Alzheimer's disease (AD) symptoms grow with time, making everyday tasks harder and causing a considerable cognitive and functional loss. Contemporary living choices may trigger younger-stage AD, which appears earlier in life. Traditional oral medicines account for most FDA-licensed AD treatments. Alzheimer's disease is linked to brain protein deposits called beta-amyloid plaques and tau tangles[60].

These deposits impair neural transmission and kill cells. New methods are being developed to increase therapy efficacy and brain area targeting. Gene therapy, stem cell treatment and MS-mediated nose-to-brain medication delivery are examples. Table 1 summarises MS's nose-to-brain. The research on Alzheimer's disease therapy is summarised in the table 1[63].

**Table 1**
**Microspheres in nose to brain delivery for different disease[50-63]**

| **Nose-to-brain delivery of microspheres for migraine** | | | |
|---|---|---|---|
| **Medicines** | **Polymers** | **Preparation technique** | **Important results** |
| Sumatriptan succinate | HPMC-K4M and K15M | Spray drying | The nasal mucosa was unaffected by the HPMC-based MS's adequate mucoadhesion[50]. |
| Zolmitriptan | Chitosan glutamate, HPMC | Spray drying | The highest zolmitriptan efficacy was shown by CG microparticles within an hour[51]. |
| Sumatriptan succinate | Polylactic-co-glycolic acid | Spray drying | We observed that the particle size ranged from 12-30 µm and that the entrapment efficacy was between 94% and 100%[52]. |
| Almo triptan | Gellan gum | Water-in-oil (w/o) emulsification cross-linking technique | Round, smooth microspheres encasing a medication with a 71.65% efficacy ± 1.09%–91.65% ± 1.13%[53]. |
| Rizatriptan benzoate | Polysaccharide (Trigonella Foenum-Graecum) | Emulsification | Results showed that the particle size ranged from 40.82 + 12 µm-62.48 + 0.41 µm and the encapsulation efficiency was 60.7% + 0.2%-79.22% + 0.2%[54]. |
| Rizatriptan mucoadhesive microparticle | Carbopol, chitosan | Spray drying | Both chitosan and carbopol have drug permeabilities ranging from 76.53% to 91.09%[55]. |
| **Microspheres in the nose to brain delivery for Alzheimer** | | | |
| Rivastigmine | Ethylcellulose, chitosan | Solvent emulsion method | It was discovered that after 7.3 hours, the particle size was 19.9µm, the entrapment efficiency was 77.8% and the drug release qualities were 80%. 4.4% in each case[56]. |
| Flurbiprofen sodium | - | Spray drying | Absolute bioavailability was 33% for microparticles and 58% for pellets. Since almost 60% of the intranasal dose reached the brain, it is worth it to administer FS as nose powder. This is according to the Direct Transport Percentage Index[57]. |
| Rivastigmine (microemulsion, mucoadhesive microemulsions) | Cetyl trimethyl ammonium bromide and chitosan | Titration method | There is a wide range for zeta potential (2.73 Mv-6.52 mV), drug content (53.8 nm-55.4 nm) and globule size (98.59%-99.43%)[58]. |
| Curcumin (microemulsion) | Deacetylated gellan gum (DGG), Capryol 90 | Emulsification | After intravenous administration, the AUC increases thrice compared to an intravenous solution. The IN delivery had a far higher brain targeting index (6.50) than the IV solution[59]. |
| **Nose-to-brain delivery of microspheres for Parkinsonism** | | | |
| Levodopa | Glycol chitosan | Spray-drying | Over time, brain DA (dopamine) concentrations rose to values significantly higher than those in a crystalline L-DOPA solution. After nasal administration of GCPQ-LDOPA, plasma L-DOPA availability was shown to be higher[60]. |
| Ropinirole hydrochloride | Chitosan | Spray drying method | The range of entrapment effectiveness for RH is 91% to 99%. Amorphous drug release was delayed with a 90:10 (w/w) drug-polymer ratio[61]. |
| Ropinirole hydrochloride (microparticle) | Sodium Alginate | Spray drying method | Encapsulation effectiveness ranges from 101% to 106% and spray-dried particle size falls between 2.5 and 4.37µm[62]. |
| Ropinirole hydrochoride | Chitosan, Carbopol, guar gum | Emulsion evaporation technique | For F1–F21, the in-vitro drug release experiments were carried out for 12 hours in 250 cc of phosphate buffer with a pH of 6.6. Over a 12-hour period, F21 showed a drug release of 81.2% while F15 showed 82.7% ± 0.23%[63]. |

**Nose-to-brain delivery of microspheres for Parkinsonism:** The neurological disorder known as PD is both common and complex. This disease develops when a handful of susceptible types of nerve cells undergo alterations to their cytoskeleton.

In the long run, injured neurones in the periphery and neurones themselves form Lewy bodies and Lewy neurites, which affect movement. It develops over time and symptoms, which often start out modest and tend to worsen. Some of the most common symptoms of Parkinson's disease include: tremors, which start in one hand and progress to the others; a generalised slowing of movement that makes even the most mundane tasks difficult; stiffness in the trunk or limbs that can cause pain and limit movement; and impaired coordination and balance that increase the risk of falling. Possible supplementary symptoms include cognitive decline, emotional problems and changes in verbal and nonverbal communication as well as facial expressions.

When people with PD lose neurones that produce dopamine, it affects a specific area of the brain called the substantia nigra. Medications like levodopa increase brain dopamine levels which help with movement problems. Ongoing research into the underlying mechanisms of PD and innovative medications aims to improve management and, eventually, finds a cure as shown in the table 1[62].

**Nose-to-brain delivery of microspheres for Miscellaneous:** Small pieces made of chitosan or methyl-β-cyclodextrin were used to help deferoxamine mesylate (DFO) to get from the nose to the brain more quickly. DFO is a neuroprotector that cannot cross the blood-brain barrier (BBB) and has bad effects on the body's edges. Cyclic oligosaccharide beta-cyclodextrin is hydrophobic inside and hydrophilic outside. This amphiphilic structure forms inclusion complexes with medicines, enhancing solubility and stability. Beta-cyclodextrin's improved medication bioavailability is especially important in nose-to-brain transport. Beta-cyclodextrin keeps lipophilic medicines from being broken down by enzymes in the nose by enclosing them in its hydrophobic core. This improves drug delivery to the brain.

The hydrophilic coating makes it compatible with the nasal mucosa, increasing medicine transfer across the nasal epithelium. Natural polysaccharide chitosan is mucoadhesive and biocompatible. Chitosan's amino group-charged positive charge is necessary for nose-to-brain transfer. Chitosan stays in the body longer because its positive charge sticks to the nasal mucosa's negatively charged cell membranes. Chitosan temporarily opens epithelial cell connections, making paracellular transport and nasal drug absorption simpler.

This helps to transfer larger molecules like peptides and proteins to the brain. DFO brain transfer may increase with solid microparticle nasal drug administration. We created spherical chitosan chloride and methyl-cyclodextrin microparticles by spray drying with DFO, DCH and MCD.

The microparticles had aerodynamic dimensions of 1.1 µm and volume-surface diameters of 1.77 ± 0.06 µm DCH to 3.47 ± 0.05 µm MCD. Scientists found that MCD helped DFO flows through lipophilic membranes better than DCH in pig nasal mucosa. Neurone-like PC 12 cell monolayers may increase DFO permeability with MCD. Unlike DCH, it did not affect DFO penetration across epithelial Caco-2 monolayers. In rats, 200 µg DFO microparticles were nasally administered and absorbed into the CSF. Peak DCH and MCD values were 3.83 ± 0.68 and 14.37 ± 1.69 µg/ml respectively, 30 minutes post-insufflation. The absolute bioavailability of DFO was 6% with DCH and 15% with MCD nasal delivery. Quercetin's oral absorption and solubility restrict its advantages.

Complexation with hydroxypropyl-CD and methyl-CD cyclodextrin derivatives through neutralization or lyophilization improved Que's physicochemical characteristics. We also advised the IN administration of mixed lyophilised powders containing mannitol/lecithin microparticles (MLMPs) after *in vitro* and *ex vivo* testing. In a PK investigation of Wistar rats, we compared orally lyophilized Que powders with MLMPs (75:25 w/w). We achieved brain targeting or bloodstream penetration using IN. Both sites produced substantial amounts of the chemical, unlike oral delivery. These findings suggest that systemic and nose-to-brain Que nasal powders may prevent and cure neuroinflammatory degenerative diseases like Parkinson's and AD. Brains received DSP via sprayable powder. After quality-by-design optimisation, we combined DSP-loaded MSs with lactose monohydrate, or mannitol.

Lactose made powder mix flows worse than mannitol. When MSs are mixed with mannitol, DSP can pass through epithelial model barriers and can keep or improve mucoadhesion. The recommended powder platform may provide specific olfactory stimuli due to the 17.0% DSP dosage ratio. Nasal cavity asymmetry influenced olfactory targeting, requiring a unique method. To absorb water and generate a gel-like nasal coating, we suggested egg whites, starch and DEAE dextran MSs. Three hours after delivery, half of the egg whites, starch MSs and 60% of dextran MSs were at the testimonial site. The study on degradable starch MS showed that the amount of human growth hormone that was bioavailable in sheep rose from 0.1 to 2.7%[63].

## Conclusion

This study aims to provide an overview of the unconventional methods used for nasal delivery to the brain. These methods circumvent the blood-brain barrier, thereby establishing a direct channel to the brain. Neurodegenerative disorders (NDs) such as Parkinson's disease, Alzheimer's disease and migraines are all examples of conditions that might possibly benefit from the deployment of these treatments.

## Future Perspectives

Several reports have shown that particulate carriers are useful for delivering drugs through different routes of administration. Many studies in the medical literature show that nose-to-brain delivery has a lot of potential for treating a wide range of illnesses affecting the central nervous system (CNS). Because of the olfactory and trigeminal nerve routes, medicines can be given through the nose instead of the mouth. This gets around the blood-brain barrier (BBB) and other possible issues with ingesting medications such as enzyme breakdown and first-pass metabolism.

As a consequence, there is less systemic exposure and far fewer systemic side effects, while brain bioavailability is increased. Due to nasal delivery constraints, micro- and nanosized drug carriers have been studied extensively.

The goals of these drug delivery systems are to keep the medicine safe from the environment, make it stay in the body longer, help it absorb better through the nasal mucosa, make it more bioavailable and improve its therapeutic effectiveness. Neurodegenerative illnesses are being investigated for potential therapy using an increasing number of biomolecules such as RNA, proteins, peptides and monoclonal antibodies. However, their therapeutic effectiveness is limited due to certain constraints including crucial physicochemical and pharmacokinetic properties.

The nose-to-brain transfer is a possible way to directly move complex macromolecules from the nasal cavity to the brain. Crucial to this field of study is optimising drug carriers' physicochemical characteristics. Adding cell-penetrating peptides or targeted ligands to the carriers is another way to make them more effective. To guarantee a tailored treatment approach, future research should primarily concentrate on the use of tailored, multi-targeted techniques. More innovative delivery techniques should make it into clinical trials and eventually into practice if new technologies that use the nose-to-brain route are developed.

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