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Nose-to-brain delivery of microcarrier in the treatment of neurodegenerative diseases

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ABSTRACT

Neurodegenerative diseases (NDs) have emerged as a major global health concern due to the perpetually aging population and unhealthy lifestyle. The most prevalent NDs such as Alzheimer's, Parkinson's, and Migraine, have seen a great deal of research into dependable and efficient treatment approaches. However, the conventional approach to treating NDs is not very effective due to the presence of the blood–brain barrier (BBB). BBB is a major hurdle for the delivery of various therapeutic agents to the brain. Nasal drug delivery is a novel approach providing direct delivery of drugs to the brain through the olfactory and trigeminal neurons. The nasal route also guarantees quick absorption, avoiding first-pass metabolism and early action of therapeutic activity. The nasal cavity has excellent permeability and effective absorption of drugs including peptides, proteins, and tiny molecular weight polar medicines, which are difficult to administer by anything other than injection or where a fast onset of action is necessary. Microspheres (MSs) are micron-sized particles that can be used in nose-to-brain delivery. The main justification for using MSs for nose-to-brain delivery is to increase the likelihood that the medication will be absorbed by enabling closer and longer contact between the medication and the mucosal barrier. MSs swell on contact with nasal mucosa and solidify into a gel to prevent its clearance from the nasal cavity. This article made a comprehensive review of the application of MS in nose-to-brain drug delivery as a unique approach to treating NDs.

INTRODUCTION

Progressive illnesses known as neurodegenerative diseases (NDs) weaken and eventually kill neurons in the central nervous system (CNS). Disruption of critical neurodevelopmental processes results in neurodevelopmental disorders like autism spectrum disorder, attention-deficit/hyperactivity disorder, and intellectual impairment. The blood–cerebrospinal fluid barrier and the blood–brain barrier (BBB), which block medications from entering the CNS from the systemic circulation, present challenges to the management of illnesses related to neurodevelopment and NDs, which collectively impact 120 million people globally [1]. The nose-to-brain channel can bypass the BBB. It increases the bioavailability of medications taken orally promising to better the management of CNS disorders [2]. Nervous system dysfunction is the end outcome of neurodegenerative illnesses, which are characterized by the progressive and slow death of neural cells [3]. Individual NDs have different aetiologies and manifest in different brain areas. They may act on comparable cellular and molecular pathways. There is still a great need for effective medicines with therapeutic benefits. Although attempts to discover suitable therapeutics for neurodegenerative illnesses are growing, there are still numerous obstacles to overcome [4]. The majority of therapies aim to delay the course of the illness but do not result in a full recovery. Many limiting constraints, such as BBB prevent many active pharmaceutical agents from having the intended therapeutic impact. Therefore, for the successful treatment of NDs, it is imperative to guarantee the delivery of active molecules to the brain securely and effectively [5]. The use of polymers in nose-to-brain microcarrier delivery systems represents an innovative approach to neurotherapeutics. It helps

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to overcome some of the major limitations of conventional drug delivery methods, offering new possibilities for treating a wide range of neurological conditions. Their ability to enhance drug targeting, stability, and controlled release, combined with their capacity to bypass the BBB, positions them as key players in the advancement of effective and innovative treatments for neurological disorders. Polymers offer immense versatility in the design of microcarriers, allowing them to be customized for specific therapeutic applications. Polymers can be functionalized with various ligands or targeting molecules that enhance their ability to reach and treat the affected brain regions. Polymeric microcarriers are generally biocompatible and can be designed to minimize toxicity. By selecting appropriate polymer materials and optimizing their properties, these microcarriers can safely deliver drugs without causing adverse reactions or triggering immune responses, making them suitable for long-term therapeutic use [6,7]. While various NDs—such as amyotrophic lateral sclerosis, multiple system atrophy, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and others—occur in different brain regions and have distinct aetiologies, accumulating evidence suggests that they share cellular and molecular mechanism [8,9].

BARRIER TO BRAIN

Substances can penetrate the BBB by adsorptive endocytosis, saturable transporters, extracellular pathways, and transmembrane diffusion [10]. The key mechanisms that are particularly significant in drug delivery are transmembrane diffusion and transporters. Transmembrane diffusion is non-saturable and is dependent upon the substance's physicochemical properties as determined by the first analysis [11]. The blood–cerebrospinal fluid barrier, and the BBB. The cerebrospinal fluid-brain barrier (CBB) are the three barriers that develop between the cerebral vasculature and the brain parenchyma [12,13]. Cerebrospinal fluid (CSF) can exchange molecules with the brain parenchyma's interstitial fluid and precisely control the entry of blood-borne molecules into the CSF [14]. The BBB plays a major role in regulating biological substances required for the brain's metabolic activity and neuronal function [15]. The blood vessels that vascularize the CNS have a unique property called the BBB that allows them to precisely regulate the passage of ions, chemicals, and cells between the blood and the brain. Appropriate neuronal activity and protection from toxins and pathogens are made possible by the exact regulation of CNS homeostasis. Changes in these barrier qualities have a substantial impact on pathology and the development of several neurological disorders [16]. The pia mater and astrocytes that make up the CBB show signs of selective permeabilization and aid in the passage of chemicals from the CSF into the brain parenchyma [17,18]. The breakdown of the BBB can be caused by abnormal angiogenesis, vascular regression, hypoperfusion of the brain, rupturing of tight junctions, changes in the way that chemicals are transported from the blood to the brain, and inflammatory reactions [19]. These elements have the potential to initiate or exacerbate a "vicious circle" of medical conditions that eventually cause synapses and neurons to die and malfunction [20].

NOSE-TO-BRAIN DELIVERY

One of the many benefits of administering drugs intranasally is that they can enter the brain directly through the olfactory and trigeminal neurons, avoiding the BBB [21]. Due to its huge surface area (150 cm^2) and high blood vascularity, the nasal cavity can be used to administer drugs because it allows for improved drug absorption through the nasal epithelium [22,23]. Since the medication enters the systemic circulation by the nose rather than the portal vein, it is especially well-suited for medicines that experience considerable first-pass hepatic inactivation [24] Transport via the trigeminal and olfactory nerve branches that supply the respiratory and olfactory epithelia, respectively, is the mechanism of nose-to-brain delivery. Intranasal (IN) routes are divided into extracellular and intracellular. The olfactory sensory cells initiate the intracellular route by engulfing the medication, which is subsequently transported to their synaptic clefts in the olfactory bulb by axonal transport. Olfactory neurons replicate this transynaptic process, which spreads the drug to other parts of the brain. Under the extracellular pathway, medications enter the cerebral spinal fluid directly after first traversing the nasal epithelium's paracellular space and then the perineural space, leading to the subarachnoid space of the brain [25].

Factor affecting nose-to-brain delivery

The nasal mucosa has excellent permeability and effective absorption that make, the nasal cavity an ideal site for administering biopharmaceuticals and small-molecule medicines [26]. Therapeutic drugs may be administered noninvasively by IN administration, which circumvents the BBB to give immediate access to the CNS [27]. A fantastic possibility for quick and patient-compliant medication administration is presented by nose-to-brain delivery [28]. As previously shown, there are solid grounds to believe that pharmacological delivery to the CNS would be more likely if the olfactory mucosa were the target [29]. However, there are still certain obstacles to be addressed in terms of the drug's application, such as the olfactory area, and particularly the olfactory cleft, which is well concealed within the nasal cavity. Also, formulations must have excellent adhesion to stay on the mucosa since the olfactory cleft is located at the top of the nasal cavity [30]. The poor membrane permeability where the epithelial cells are positioned in the nasal mucosa is the main barrier to the absorption of hydrophilic molecules and macromolecules. Tight junctions establish a strong connection between cells and are the main regulators of paracellular transport [31]. Only potent medications may be administered using this route due to the dosage volume limitations for liquids (100–250 µl) and powders (20–50 mg, depending on the powder's bulk density) [32]. Potent medications that are degraded by the enzymes in the nasal cavity must be shielded from deterioration. Nasal formulations must not irritate the nasal cavity. Furthermore, the administration of medications via the nose-to-brain pathway requires a nasal administration device [33]. Novel IN drug delivery methods have been developed to boost the systemic bioavailability of medications taken via the IN route. Nano- and micro-technologies have become available to improve medication access in brain tissue. Natural or artificial

materials make up micro- and nanoparticulate carriers, which interact molecularly with biological structures to change the way NDs are treated [34]. Several studies have looked at the application of microspheres (MSs) to treat NDs via the nose-to-brain route [35].

Microspheres in nose-to-brain delivery

MSs are microscopic solid particles that are spherical and have dimensions between 1 and 1,000 micrometers (μm) [36]. Therapeutic molecules are dissolved, encapsulated, or entrapped into the polymeric matrix of MS. A variety of natural, semi-synthetic, and synthetic materials can be used to produce MSs [37]. Starch, dextran, albumin, and hyaluronic acid are the building blocks to create the MSs [38]. Despite being water-insoluble, every kind of MS that has been employed for nasal delivery absorbs water into its matrix, causing the spheres to inflate and form gel. This gives the formulation more time to stay in the nasal cavity, improves drug-mucosa contact, and increases drug concentration at the deposition site. MSs produce sustained drug release which may help achieve the desired concentration of the drug at the absorption site [39]. Figure 1 depicts the delivery of drug-loaded MSs from the nose to the brain. In several animal models, the bioavailability of various peptides and proteins was enhanced using MSs. Additionally, the delivery of some low-molecular-weight medications in microsphere formulations has been beneficial [40]. MSs have a significantly longer residence duration in the cavity than solutions. They can also improve the absorption of large hydrophilic medicines. Additionally, MSs directly affect the mucosa, causing the epithelial cells' tight connections to open. Given their recurrent use, starch, and dextran MSs are considered safe dose forms [41]. Animal models are chosen based on anatomical similarities to the human nasal cavity, ease of handling, and established protocols for neurological studies. The most frequently used animals include rats, mice, rabbits, pigs, dogs, and monkeys. These animal models offer unique advantages, helping researchers to optimize nasal drug delivery systems and assess their potential for effective nose-to-brain transport. Sheep are one of the favored animal models for pharmacokinetic (PK) and formulation research in nasal medication administration; therefore, *in vivo* experiments were conducted on them [42].

MSs in the nose-to-brain delivery for migraine

Migraine, an episodic headache condition, is characterized by recurring episodes of intense, usually unilateral, undulating pain that are typically accompanied by nausea, vomiting, photophobia, and phonophobia [43]. Dysfunction of the brain's sensory processing that is likely cyclical and impacted by both heredity and environment gives rise to migraine attacks [44]. Migraine is the second most typical reason for impairment in young and middle-aged people [45,46]. One of the main indicators of several psychiatric and mental illnesses, such as anxiety and sadness, is migraine [47].

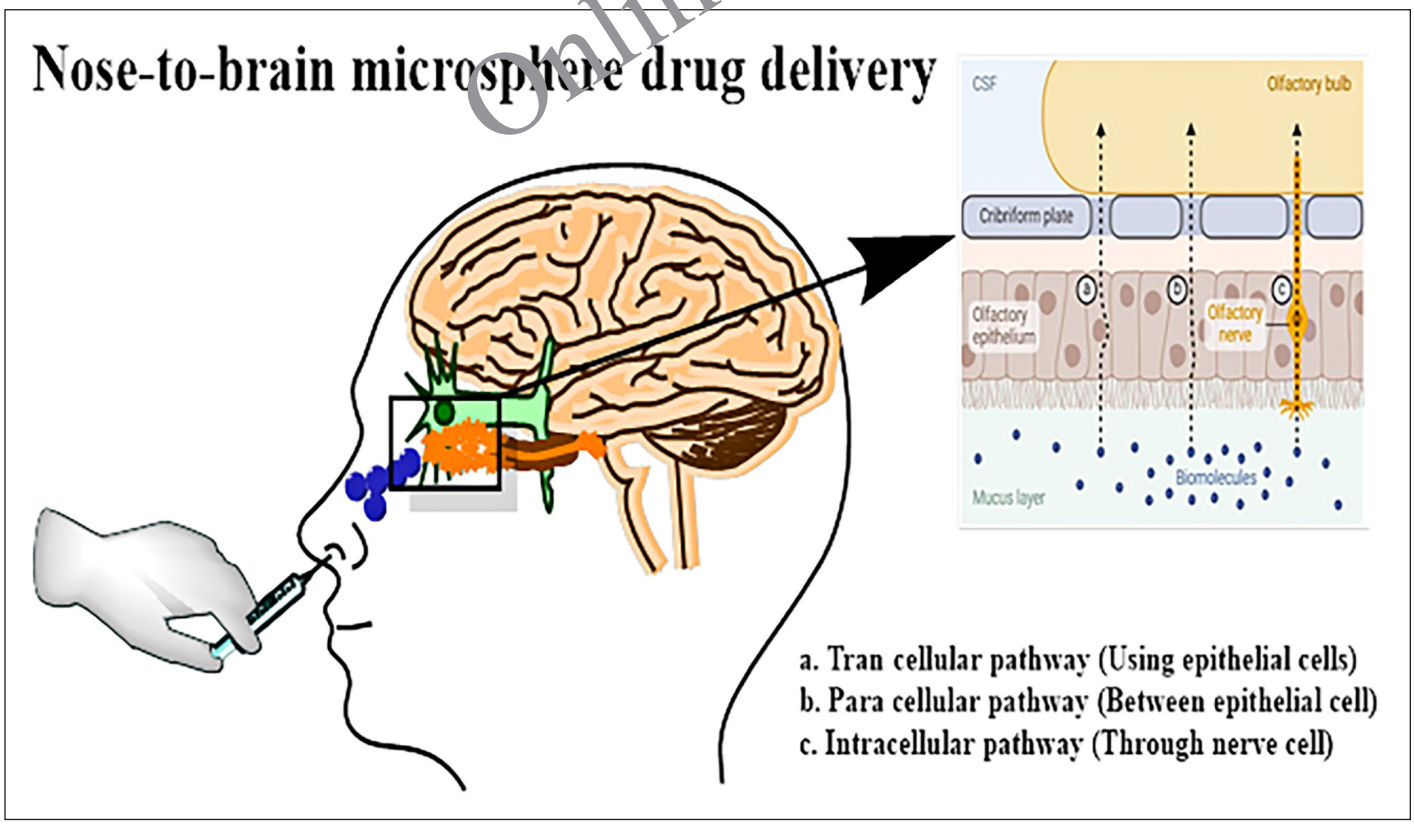

Figure 1. Drug-loaded MSs delivered from the nose to the brain.

Table 1. MSs in nose to brain delivery for Migraine.

Drug	Polymer	Method of preparation	Key findings	References
Sumatriptan succinate	HPMC-K4M, and K15M	Spray drying	The mucoadhesion of HPMC-based MS was sufficient, without any negative effects on the nasal mucosa.	[50]
Zolmitriptan	Chitosan glutamate (CG), HPMC	Spray drying	Within an hour, CG microparticles demonstrated the maximum zolmitriptan effectiveness.	[51]
Sumatriptan succinate	Polylactic-co-glycolic acid (PLGA)	Spray drying	Particle size and entrapment efficiency were found to be 12–30 µm and 94%–100% respectively.	[52]
Almo triptan	Gellan gum	Water-in-oil (w/o) emulsification cross-linking technique	Spherical and smooth microspheres with drug entrapment efficiency of 71.65% ± 1.09%–91.65% ± 1.13%.	[53]
Rizatriptan benzoate	Polysaccharide (Trigonella Foenum-Graecum)	Emulsification	Particle size and encapsulation efficiency were found to be 40.82 + 12 µm–62.48 + 0.41 µm &60.7% + 0.2%–79.22% + 0.2% respectively.	[54]
Rizatriptan mucoadhesive microparticle	Carbopol, chitosan	Spray drying	Drug permeability was found to be 76.53–91.09 and 78.49%–92.25 % for chitosan and Carbopol respectively.	[55]

Neurogenic inflammation of the trigeminal nerve in the cranial dura mater is the cause of migraine headaches. Trigeminal neurons may be activated and sensitized by these central stimulations [48]. For the treatment of acute migraines, the IN route is known to provide a high brain drug concentration and a quick beginning of action as given in Table 1 [49].

MSs in nose to brain delivery for Alzheimer

AD is a major global cause of dementia or memory loss that primarily affects older folks. The hallmark of AD is the progressive deterioration and loss of brain cells, especially neurons, which results in a reduction in cognitive ability [56]. AD symptoms progressively get worse over time, making it harder for a person to do everyday tasks and ultimately resulting in a serious deterioration in cognitive and functional abilities. However, with today's lifestyle, it appears to affect people at a younger age, a condition called as younger-stage AD [57]. Most of the FDA-approved pharmaceuticals for treating AD symptomatology are sold as traditional oral medications [58,59]. AD is linked to the buildup of aberrant protein deposits in the brain, such as tau tangles and beta-amyloid plaques, which obstruct neuronal transmission and promote cell death [60]. Gene therapy, stem cell treatment, and innovative drug delivery methods like nose-to-brain distribution using MSs are examples of emerging techniques meant to increase therapeutic efficacy and more precisely target certain brain areas [61]. Table 2 highlights some research based on nose-to-brain delivery of MS for the treatment of Alzheimer's.

MSs in nose-to-brain delivery for Parkinsonism

PD is a prevalent and intricate neurological condition [66]. Changes in the neuronal cytoskeleton that occur in a small number of vulnerable kinds of nerve cells cause this illness. Lewy bodies and Lewy neurites are eventually produced by damaged neurons in their perikaryal and neuronal processes have an impact on mobility [67]. It happens gradually, with symptoms that frequently begin mildly and get worse with time. Among the main signs and symptoms of PD are involuntary shaking, which often begins in one hand, slowness of motion, which makes basic things challenging, Stiffness in the trunk or limbs, which can hurt and restrict range of motion, decreased coordination and balance, which raises the possibility of falls. Cognitive impairment, emotional issues, and alterations in speech, writing, and facial expressions are possible additional symptoms [68]. The substantia nigra, a part of the brain, is where dopamine-producing neurons are lost in PD [69]. Levodopa and other medications raise dopamine levels in the brain, which helps with movement issues [70]. With the goal of better management and, perhaps, a cure, research on novel medicines and the underlying processes of PD is still ongoing [71,72]. The role of MS in the treatment of PD has been discussed in Table 3.

Miscellaneous application of MSs for nose-to-brain

Solid microparticles based on chitosan or methyl-β-cyclodextrin were used to increase the nose-to-brain transport of deferoxamine mesylate (DFO), a neuroprotector that is unable to pass through the BBB and has detrimental peripheral effects. Beta-cyclodextrin is a cyclic oligosaccharide with a hydrophobic interior and a hydrophilic exterior. This amphiphilic structure allows it to form inclusion complexes with various drugs, improving their solubility and stability. In nose-to-brain delivery, the most crucial feature of beta-cyclodextrin is its ability to enhance drug bioavailability. By encapsulating lipophilic drugs within its hydrophobic core, beta-cyclodextrin can protect the drugs from enzymatic degradation in the nasal cavity, thereby increasing the amount of drug that reaches the brain. Additionally, its hydrophilic exterior ensures good compatibility with the nasal mucosa, facilitating efficient drug transport across the nasal epithelium. Chitosan is a natural polysaccharide known for its biocompatibility and mucoadhesive properties. The primary chemical feature that makes chitosan crucial for nose-to-brain delivery is its positive

Table 2. MSs in the nose to brain delivery for Alzheimer.

Drug	Polymer	Method of preparation	Key findings	References
Rivastigmine	Ethylcellulose, chitosan	Solvent emulsion method	Particle size, entrapment efficiency, and drug release properties were found to be 19.9µm, 77.8% and 80% in 7.3 hours. 4.4% respectively.	[62]
Flurbiprofen sodium (FS)	-	Spray drying	For pellets and microparticles, the absolute bioavailability was 58% and 33%, respectively. FS administration as nose powder is worth it since the Direct Transport Percentage Index showed that more than 60% of the intranasal dosage reached the brain.	[63]
Rivastigmine (microemulsion, mucoadhesive microemulsions)	Cetyl trimethyl ammonium bromide, and chitosan	Titration method	Zeta potential, drug content, and globule size range from 2.73 Mv–6.52 mV, 53.8 nm–55.4 nm, and 98.59%–99.43%, respectively.	[64]
Curcumin (microemulsion)	Deacetylated gellan gum (DGG), Capryol 90	Emulsification	In comparison to an IV solution, the AUC increases three times following IN delivery.Compared to IV solution, brain targeting index was found to be significantly greater at 6.50 in IN delivery.	[65]

Table 3. MSs in the nose to brain delivery for Parkinsonism.

Drug	Polymer	Method of preparation	Key findings	References
Levodopa(microparticulate)	n N-palmitoyl-N-monomethyl-N, N-dimethyl-N, N, N-trimethyl-6-O-glycolchitosan (GCPQ)	spray-drying	DA (Dopamine) concentrations in the brain increased with time, reaching far greater levels than those found in a crystalline L-DOPA dispersion. Plasma L-DOPA availability increased when GCPQ-LDOPA was administered nasally.	[73]
Ropinirole hydrochloride (RH)	Chitosan	Spray drying method	Entrapment efficacy of RH is in the range of 91%–99%. A drug-polymer ratio of 90:10 (w/w) showed prolonged drug release with an amorphous form	[74]
Ropinirole hydrochloride (microparticle)	Sodium Alginate	Spray drying method	Spray-dried particle size and encapsulation efficiency within the range of 2.5–4.37µm & 101%–106% respectively.	[75]
Ropinirole hydrochoride	Chitosan, Carbopol 974P and guar gum	Emulsion solvent evaporation technique	The *in-vitro* drug release studies were performed for F1-F21 in 250 ml phosphate buffer at pH6.6 for 12 hours. F21 demonstrated 81.2% drug release over 12 hours, while F15 demonstrated 82.7% ± 0.23%.	[76]

charge, which arises from its amino groups. This positive charge allows chitosan to interact with the negatively charged cell membranes in the nasal mucosa, enhancing adhesion and prolonging the residence time of the drug at the absorption site. Furthermore, chitosan can transiently open tight junctions between epithelial cells, promoting paracellular transport and improving drug permeation across the nasal barrier. This property is particularly valuable for delivering larger molecules, such as peptides and proteins, directly to the brain [77,78]. Solid microparticle formulations as nasal drug delivery vehicles could augment the transfer of DFO from the nose to the brain. Spray drying was used to create spherical chitosan chloride microparticles loaded with DFO DCH and methyl-βcyclodextrin microparticles loaded with DFO MCD. The aerodynamic diameters of microparticles were approximately 1.1 µm and the volume-surface diameters varied from 1.77 ± 0.06 µm DCH to 3.47 ± 0.05 µm MCD. As demonstrated by *ex vivo* permeation investigations across pig nasal mucosa, MCD improved DFO permeability across lipophilic membranes in comparison to DCH. Additionally, MCD may increase DFO permeability via PC 12 cell monolayers (which are like neurons). However, unlike DCH, it was unable to alter the DFO permeation pattern through Caco-2 monolayers (which are similar to epithelium). When 200 µg of DFO encapsulated in microparticles was administered nasally to rats, the microparticles' absorption into the CSF was observed. Thirty minutes after insufflation, peak values ranged from 3.83 ± 0.68 µg/ml DCH to 14.37 ± 1.69 µg/ml MCD. DCH and MCD nasal delivery produced DFO systemic absolute bio availabilities of 6% and 15%, respectively [79].Quercetin (Que), a potent antioxidant, has limited absorption upon oral treatment and poor solubility restricts its beneficial effects. It has been discovered that the physicochemical characteristics of Que were improved by complexation with two distinct cyclodextrin

(CD) derivatives (hydroxypropyl-β-CD and methyl-β-CD) using the neutralization/lyophilization process. Additionally, following *in vitro* and *ex vivo* testing, mixes of the lyophilized powders with mannitol/lecithin microparticles (MLMPs) have been suggested as candidates for IN administration. Wistar rats were used in a comparative PK investigation comparing the IN versus. oral administration of Que lyophilized powders and their mixes with MLMPs (75:25 w/w). The results demonstrated the efficacy of IN administration in either brain targeting or bloodstream penetration. At both locations, significant amounts of the chemical were obtained, in contrast to negligible levels following oral delivery. These findings support the possible systemic and nose-to-brain distribution of the produced Que nasal powders for the prevention and/or therapy of neuroinflammatory degenerative diseases including Parkinson's and AD [80]. A sprayable powder delivery system for of dexamethasone sodium phosphate (DSP) was developed to target the brain. DSP-loaded MSs were combined with soluble inert carriers (lactose monohydrate or mannitol) after being optimized using the Quality-by-Design technique. Compared to lactose, mannitol offered superior powder mix flow characteristics. Mannitol-blended MSs improved DSP permeability across epithelial model barriers and maintained or expanded their mucoadhesive characteristics. The proposed powder platform can provide specific olfactory stimuli, as evidenced by the 17.0% DSP dosage fraction deposited in the olfactory area. The influence of nasal cavity asymmetry was shown to be significant, indicating the need for an individual strategy when targeting the olfactory area [81]. The use of egg whites, starch, and DEAE dextran (diethyl aminoethyl dextran) MSs was advised to help the nasal cavity gradually absorb water and produce a gel-like coating. Half of the delivered egg whites and starch MSs and 60% of the dextran MSs had been present at the testimonial site for 3 hours after the organization. As indicated, the degradable starch MS program increased the virtual IN bioavailability of human growth hormone in sheep from 0.1 % for explanation to 2.7 % [82].

CONCLUSION

Nose-to-brain delivery avoids the BBB and gives a direct path to the brain, the unique methodologies based on lipid-based microsize spherical carriers to target the brain through the nasal cavity were summarised in this review paper, along with its applicability in treating NDs including PD, AD, and migraines, avoiding the BBB and giving a direct path to the brain.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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