Next Nanotechnology 9 (2026) 100466

Contents lists available at ScienceDirect

Next Nanotechnology

journal homepage: www.sciencedirect.com/journal/next-nanotechnology

Review article

Nanotechnology-enabled nose-to-brain delivery: Promising strategies for targeting neurological disorders

Ritika Saxena [a], Alka Lohani [b,*]

[a] Pharmacy Academy, Faculty of Pharmacy, IFTM University, Moradabad, Uttar Pradesh 244102, India
[b] Amity Institute of Pharmacy, Amity University Uttar Pradesh, Noida, 201313, India

ARTICLE INFO

Keywords:
Nanotechnology
Nose to brain delivery
CNS, Blood brain barrier
Neurodegenerative disorders

ABSTRACT

Despite the expanding global occurrence of neurological disorders, achieving the effective and sufficient delivery of therapeutic drug molecules to the central nervous system (CNS) continues to pose a considerable impediment. The brain's protective mechanisms, including the cerebrospinal fluid (CSF) and blood-brain barrier (BBB), hinder the passage of large lipophilic and hydrophilic molecules, thereby reducing the efficiency of conventional drug delivery approaches. As a non-invasive alternative, intranasal delivery has gained attention for its capability to evade the BBB and transport medications efficiently to the brain, though its efficacy remains reliant on the unique physiological characteristics of the nasal cavity. This review puts emphasis on nanotechnology-based nose-to-brain drug delivery techniques, which have shown significant potential in addressing these challenges. Various approaches, including the application of nano-carriers like liposomes, polymeric nanoparticles, lipid nanoparticles and nanoemulsions, are discussed for their ability to enhance bioavailability, improve permeability, facilitate BBB traversal, extend drug retention in the body, and enable targeted delivery to the brain, offering promising advancements in the therapy of neurological disorders.

1. Introduction

Any kind of anomalous medical condition affecting the nerve system is referred to as a neurological disorder. In recent times, there has been an increasingly prevalent observation that neurological ailments are the foremost reason of infirmity and mortality universally. Some of the common prevailing neurological illnesses are Alzheimer's disease, Migraine, Parkinson's disease, Strokes, Epilepsy, Multiple Sclerosis and so on [1]. The difficulties of the brain in neurological diseases are often characterized by Cognitive disorders and also impacts impact a person's capacity for speech, mobility, learning, and walking. A brain injury can be fatal since the brain regulates all of the body's nerves. 10.2% of the cases might be attributed to the worldwide prevalence of these illnesses. Moreover, the relative causation rates of these disorders are significant at 16.8% annually [2]. These statistics show that compared to other human conditions, neurological disorders have higher rates of disability [3].

Drugs that are intended to treat neurological illnesses must pass through or get past a numerous obstruction, including the BBB and blood CSF barrier to access the CNS. In current years, interest in nose-to-brain drug delivery has grown significantly as an approach for transporting therapeutic medications directly to the brain [4]. Hence, any therapeutic agent's clinical potency depends on both its bioavailability and its capacity to pierce the BBB and CSF, two layers of protection, because they prevent massive lipophilic and hydrophilic molecules from entering the brain. The physicochemical features of active therapeutic compounds and formulations for brain medication delivery are taken into account while forging or developing any drug delivery mechanism. The nasal passageway is the sole site that has close association with the brain; therapeutic drugs that target the central nervous system demonstrate a possible effect with an inadequate metabolic environment and an elevated rate of absorption by bypassing the BBB.

Intranasal drug delivery methods absorb drug molecules via nasal mucosa and reach the epithelial cells of the olfactory system, allowing for non-invasive access into the brain to provide therapeutic effects. The intranasal method of administering drugs provides benefits including circumventing the intestine, escaping first pass metabolism, and minimizing systemic adverse effects [5]. Many APIs now have a potential to reach the brain directly through the nose, but this is tricky to do because of issues like clearance of the mucociliary tract, which decreases the

* Corresponding author.
E-mail addresses: alohani@amity.edu, alkalohani06@gmail.com (A. Lohani).

https://doi.org/10.1016/j.nxnano.2026.100466
Received 8 May 2025; Received in revised form 22 February 2026; Accepted 14 April 2026
Available online 21 April 2026

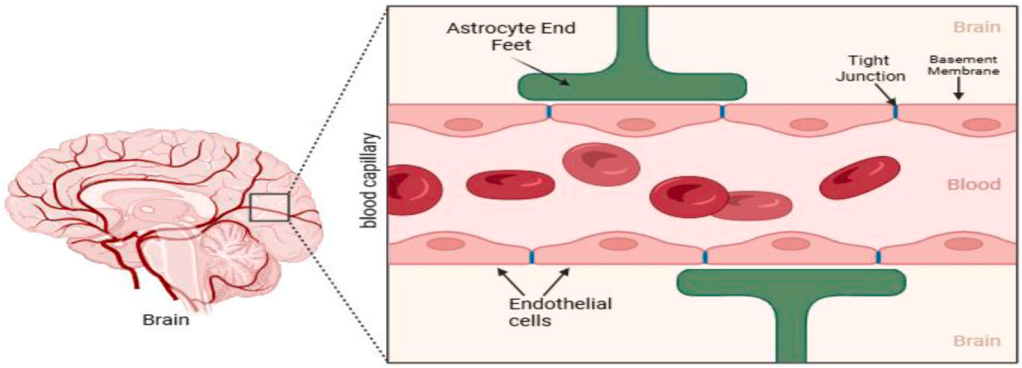

Fig. 1. Blood Brain Barrier.

amount of time the drug is present at the administration site and can interfere with nasal administration because of nasal absorption [6]. Nanomedicines are able to penetrate impaired brain tissue and breach the BBB. Additionally, nanomedicines are associated with improved surface area, strength, stability, and sensitivity. In this review the focus is drawn at Nanotechnology based nose-to-brain drug delivery in the management of neurological disorders as a viable drug delivery to brain overcoming the major impediments in CNS drug delivery.

2. Blood brain barrier (BBB): hurdle in CNS drug delivery

The brain is a highly sensitive and complex neuronal organ that relies on a continuous supply of fuel, gases, and nutrients to maintain homeostasis and support vital functions. However, the BBB, a specialized structure of the central nervous system vasculature, acts as a protective barrier, restricting the passage of various substances. It prevents therapeutic medications from reaching the CNS and obstructs the administration of a wide range of pharmaceuticals through endothelial capillaries to the brain. Because of its selective permeability, which also varies under certain health conditions, the BBB is unique in nature [7]. In terms of structure, The BBB comprises endothelial cells of capillaries, astrocytic end-feet encircling the exterior of brain capillary endothelial cells, and pericytes integrated into the capillary basement membrane (Fig. 1). The capillaries are non-fenestrated channels characterized by tight junctions, which restrict the paracellular transport of these therapeutic compounds [8].Furthermore, P-glycoprotein and other ATP-binding cassette transporters inhibit the accumulation of therapeutic medicines and extrude these molecules from the brain [9,10]. Considering the tight junctions that restrict the paracellular pathway for drug delivery, the primary routes for drug transport to the CNS are the transcellular route (requiring the drug molecule to be highly lipophilic and have a molecular weight of less than 500 Da), receptor-mediated endocytosis, and carrier-mediated transport. To utilize these routes for medication entrance into the brain, a drug or delivery vehicle must satisfy specified conditions [11–14].The BBB restricts the entry of therapeutic molecules into the brain following oral or parenteral administration [15]. This, coupled with hepatic metabolism and the elimination and inactivation of drugs during systemic circulation, diminishes treatment efficacy, necessitates elevated drug dosages, and frequently leads to adverse side effects [16]. Additionally, researchers have devised several other techniques to address this physiological barrier, including chemical modification of medicines, intracerebroventricular injection, and intrathecal injection. Although intracerebroventricular and intrathecal injections allow neurotherapeutic molecules to reach high concentrations in the brain, these approaches have several limitations. The drugs and injections must meet specific conditions such as suitable pH, appropriate diluents, and controlled volume to be safely administered into the brain [17]. In addition, these strategies are invasive and associated with high surgical risk, which makes their clinical use difficult and limits their applicability [18]. Since all of the procedures described above are invasive and costly, the intranasal delivery system has attracted attention as a route for potential drug delivery to the brain, it circumvents the BBB by utilizing the direct physical link between the nasal cavity and the brain. This non-invasive method facilitates the fast and effective administration of many therapeutic agents, including as peptides, proteins, and macromolecules, without requiring drug modification or carriers, rendering it a potential technique for central nervous system drug delivery [19].

3. Overview of neurological disorders

3.1. Alzheimer's disorder

Alzheimer's disease (AD), the most prevalent form of dementia, is characterized by progressive cognitive, behavioral, and functional decline and is primarily associated with the accumulation of toxic amyloid-β (Aβ) peptides in the brain [20]. The pathological cascade begins with the cleavage of amyloid precursor protein (APP) by β- and γ-secretases, generating aggregation-prone Aβ peptides, particularly $A\beta_{1-42}$ [21]. These peptides misfold and form soluble oligomers, which are considered the most neurotoxic species in AD [22]. Aβ oligomers disrupt synaptic function, compromise cell membranes, induce oxidative stress, trigger neuroinflammation, and cause mitochondrial dysfunction, ultimately leading to neuronal death [23]. Over time, oligomers further assemble into fibrils and extracellular amyloid plaques, especially in the medial temporal lobe and neocortex, driving disease progression [24].

Current therapeutic strategies for AD are largely symptomatic. Cholinesterase inhibitors donepezil, rivastigmine, and galantamine remain the first-line treatment, enhancing cholinergic neurotransmission by inhibiting acetylcholine degradation [25]. While tacrine was the first FDA-approved acetylcholinesterase inhibitor, its hepatotoxicity led to withdrawal, prompting the development of safer analogues [26]. Rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase, whereas donepezil and galantamine are more selective for acetylcholinesterase [27]. Other therapeutic approaches targeting Aβ production and aggregation include γ-secretase and β-secretase inhibitors, NSAIDs, aggregation modulators, and immunotherapy, though safety and efficacy concerns limit their clinical utility [28]. Additionally, memantine, a noncompetitive NMDA receptor antagonist, is approved for moderate-to-severe AD and provides neuroprotection against glutamate-induced excitotoxicity, particularly when used in combination with cholinesterase inhibitors [29].

3.2. Parkinson's disorder

Parkinson's disease (PD) is a common neurodegenerative disorder first described by James Parkinson in 1817 [30]. It is clinically characterized by hypokinesia, rigidity, resting tremor, postural instability,

and progressive loss of balance, primarily resulting from the degeneration of nigrostriatal dopaminergic neurons [31]. The hallmark pathological feature of PD is the presence of Lewy bodies, composed mainly of aggregated α-synuclein [32]. Progressive neuronal loss within the nigrostriatal pathway leads to dopamine depletion in the striatum, giving rise to the characteristic motor symptoms [33]. Multiple interconnected mechanisms contribute to PD progression, including α-synuclein misfolding and aggregation, impaired protein clearance, mitochondrial dysfunction, dysregulation of the ubiquitin–proteasome and autophagy–lysosomal systems, and neuroinflammation [34].

Levodopa remains the gold-standard therapy for PD, providing significant symptomatic relief and improving quality of life; however, long-term use is associated with motor fluctuations and dyskinesias [35]. Dopamine agonists such as ropinirole and pramipexole serve as alternative or adjunct therapies, particularly in younger patients, though their use is limited by adverse effects including somnolence, edema, and hallucinations [36]. Anticholinergic agents are generally avoided due to poor tolerability. In contrast, monoamine oxidase-B (MAO-B) inhibitors and amantadine exhibit favourable safety profiles and require minimal dose titration [37] MAO-B inhibitors, including selegiline and rasagiline, enhance dopaminergic transmission by preventing dopamine degradation and have demonstrated efficacy in improving motor function, reducing motor fluctuations, and delaying the need for long-term levodopa therapy [38]. Clinical studies, including the MOTION and ANDANTE trials, support the combined use of dopamine agonists and MAO-B inhibitors to further alleviate motor symptoms, although real-world treatment strategies often favour dopamine agonists as initial therapy, with MAO-B inhibitors introduced later alongside levodopa [39,40].

3.3. Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease or Lou Gehrig's disease, is a progressive neurodegenerative disorder affecting motor neurons in the brain and spinal cord, leading to muscle weakness, paralysis, and eventual respiratory failure [41,42]. Motor neuron degeneration in ALS is driven by multiple pathogenic mechanisms, including glutamate-mediated excitotoxicity, oxidative stress, toxic protein aggregation, genetic mutations producing aberrant proteins, and astrocyte-mediated neurotoxicity [43]. These converging processes result in the progressive loss of motor neurons, disrupting nerve impulse transmission and causing severe motor dysfunction [44,45].

Clinically, ALS is characterized by muscle weakness, atrophy, spasticity, and hyperreflexia, supported by electrophysiological evidence from electromyography and nerve conduction studies, as well as neuropathological findings such as protein aggregates and neuronal degeneration. In addition to motor impairment, ALS is frequently associated with frontotemporal dementia, behavioral changes, and cognitive decline. The disease typically progresses rapidly, with most patients succumbing within 3–5 years of symptom onset. Currently, therapeutic options are limited to riluzole, which modestly extends survival, and edaravone, which slows disease progression; however, no disease-modifying treatments are available, and management remains largely symptomatic [46].

3.4. Huntington's disease

Huntington's disease (HD) is a hereditary neurodegenerative disorder with midlife onset, caused by an unstable expansion of CAG repeats in the huntingtin gene, resulting in an elongated polyglutamine tract [47]. The disease is characterized by motor, cognitive, and psychiatric disturbances, with chorea being a prominent motor feature, often preceded by mood disorders such as depression and cognitive impairment [48]. Additional manifestations include dementia, behavioral abnormalities, involuntary weight loss, sleep and circadian rhythm

Table 1
Comparative study of other drug delivery system to Intranasal system.

Parameter	Intranasal	Intravenous	Oral	Intracerebral injection	References
BBB Penetration	Direct BBB bypass via olfactory & trigeminal pathways, bypassing systemic circulation, non-invasive	Limited, most drug poorly cross BBB	Very poor BBB penetration	Direct access to brain parenchyma, best BBB penetration but highly invasive	[147]
Brain Bioavailability	Intranasal often achieves significantly higher brain concentration than Oral or IV	Moderate systemic bioavailability but insufficient brain uptake due to BBB	Low for CNS drugs due to first pass metabolism, many therapeutic molecules fails to reach CNS	Very high local brain concentration	[148]
First Pass metabolism	Bypassed, yielding greater systemic and CNS availability	No first pass metabolism	High first- pass in liver/GI tract	Not Applicable	[149]
Onset of Action	Fast, especially beneficial for acute CNS needs	Immediate systemic action but limited CNS action without BBB crossing strategies	Slow (variable absorption)	Immediate onset of action at local site	[150]
Patient Compliance	High, non-invasive, self-administrable	Moderate requires technical skills/setting	Very high, easy to take, but ineffective for CNS targets	Low, clinical setting required	[151]
Side effects	Lower systemic side effects. Potential local nasal irritation	Systemic toxicity	Gastrointestinal side effects, poor CNs targeting	High surgical risk	[152]
Practical Limitations	Limited dose volume, mucociliary clearance can reduce residence time	Systemic exposure and potential toxicity	Limited CNS efficacy, large molecules degrade	Invasive, costly	[56,150]

disturbances, and autonomic dysfunction. Although the typical age of onset is between 30 and 50 years, it can range widely, and disease duration averages 17–20 years, with progressive dependency and eventual death [49].

Tetrabenazine (TBZ) is commonly used to manage chorea in HD by inhibiting monoamine uptake into presynaptic neurons, leading to depletion of dopamine, serotonin, and norepinephrine. Clinical trials have shown that TBZ significantly reduces chorea severity but is associated with adverse effects, including somnolence, parkinsonism, depression, and anxiety [50]. Deutetrabenazine (DBZ), a newer alternative, has a shorter half-life, requires less frequent dosing, and is associated with a lower incidence of neuropsychiatric and motor adverse events, as well as fewer treatment interruptions, making it a better-tolerated option for HD-associated chorea [51].

AD, PD, ALS, and HD are distinct clinical and pathological entities but share the same types of difficulties in their therapy, namely progressive loss of neurons and poor penetration of drugs through the blood-brain barrier [52]. One of the biggest challenges in treating these disorders is that the BBB prevents the effective delivery of neuroprotective, disease-modifying, and symptomatic agents to specific areas in the brain [53]. In general, most pharmacotherapeutic approaches to treating neurodegenerative diseases including cholinesterase inhibitors and anti-amyloid agents for AD dopaminergic and MAO-B inhibitors for PD riluzole and edaravone for ALS and monoamine-depleting agents such as tetrabenazine for HD are hindered by low bioavailability to the brain, systemic side effects, and dose-limiting toxicity [54].

Intranasal drug delivery has emerged as a promising CNS-targeted strategy capable of bypassing the BBB and enabling direct nose-to-brain transport via the olfactory and trigeminal neural pathways [55]. The intranasal route is a quick way to administer drugs to the brain while allowing for accumulation of a drug at the site and minimizing the systemic exposure of drug, providing increased effectiveness of the therapeutic treatment of a disorder once it reaches the brain [56]. Because of this and the importance of long-term treatment and reduced toxicity to the rest of the body in treating chronic neurodegenerative diseases, the use of the intranasal method will also be helpful in delivering many different types of therapeutic agents (including small molecules, peptides, proteins, nucleic acids, and nanocarrier systems) to parts of the brain that are involved in AD, PD, ALS, and HD [57]. As shown in Table 1, intranasal drug delivery offers significant advantages over intravenous, oral, and intracerebral routes.

4. Nose to brain pathway: an earmarked drug delivery to CNS

The brain has a remarkable level of resistance to the penetration of foreign constituents, such as harmful compounds and drugs. This protective function is maintained by some cell types at key primary barriers: the BBB, the CSF, and the arachnoid barrier. For a drug agent to gain access to the brain, it must meet some requirements maintaining a non-ionized form, lipophilic nature, molecular weight under 400 Da, and lesser than eight H- bonds [58]. BBB limits several biologicals from accessing the CNS.As a result, researchers have investigated other ways to the brain, notably intranasal delivery, which has several advantages over intravenous or oral treatment [59]. The nasal route of administration has seen increased adoption over the past few years owing to its lack of invasiveness and simple delivery system, where first-pass metabolism is evaded and rapid absorption is ensured. The technique allows direct pharmacologic delivery to the brain through two different pathways: intracellular and extracellular. Within the intracellular pathway, sensory olfactory cells undergo endocytosis and are subsequently transported via axons to the synaptic clefts. Drug molecules are subsequently exocytosed to the olfactory bulb, where nerve cell transmit signals to various areas of the brain. The extracellular pathway, on the other hand, allows drug diffusion across the epithelial junction of the nasal mucosa, ultimately targeting the compounds to the cerebrospinal fluid. Once in the CSF, the drug molecules move via neuronal conduits

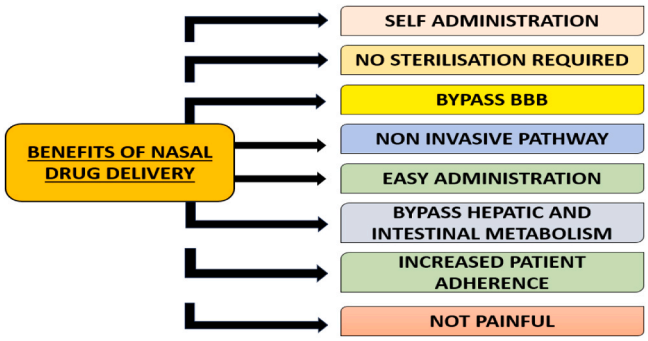

Fig. 2. Advantages of Intranasal drug delivery system.

extending into the subarachnoid space of the brain. Although both pathways aid drug transportation, the intracellular route is slower and cannot efficiently deliver intranasal markers to brain regions beyond the olfactory bulb's projections [60]. Some of its advantages include increased patient compliance, bypassing BBB and disadvantages such as mucosal damage,nasal congestion and rapid elimination are shown in Figs. 2 & 3 respectively.

4.1. Factors affecting nasal drug delivery

It is important to take into account certain physicochemical, formulation, and physiological aspects before developing intranasal administration. Few of them are mentioned below in Fig. 4

4.2. Mechanism for absorption of drugs

There are two major pathways for Intranasal drug delivery depicted in Fig. 5

4.2.1. Olfactory nerve pathway

The foremost route for intranasally delivered drugs to traverse the brain relies on olfactory receptor neurons in the nasal olfactory region, aided by supporting cells [61]. In olfactory nerve tracts, drug substances pass through the nasal olfactory epithelium, Arising from olfactory mucosa of the nasal cavity to the brain parenchyma or CSF. During this process, the arachnoid layer overlying the subarachnoid space offers three distinct pathways through the olfactory lining. The first is the intracellular route, which takes place primarily within sustentacular cells. n this process, lipophilic drugs are rapidly and effectively transported through targeted vesicular uptake, fluid phase endocytosis, or passive diffusion. The rate of transport in this pathway is influenced by the lipophilicity of the drug molecules. Secondly, the paracellular circuit involves the tight connections between olfactory neurons and sustentacular cells, which have clefts between them. Hydrophilic drugs are absorbed via diffusion through water pores or channels. The molecular mass of the drug material plays a key role in regulating the pace of this pathway. Drugs with molecular weights between 300 and 1000 Dalton exhibit good bioavailability without absorption enhancers, while drugs with molecular weights up to 6000 Dalton require absorption enhancers. In the last stage of the olfactory nerve route, medicines enter neuronal cells by endocytosis or pinocytosis and travel to the olfactory bulb via intracellular axonal transport. Therefore, transcellular passive diffusion, paracellular passive diffusion, and efflux transport are important pathways for drug transportation via the nose olfactory epithelium [62].

4.2.2. Trigeminal nerve pathway

The trigeminal nerve transmits neurological impulses from the mouth and nasal cavities, eyelids, and cornea to the brain via its ophthalmic, the maxillary, and mandible branches. The respiratory and olfactory epithelia can also communicate with the CNS via the trigeminal nerve [63]. Since it is the largest cranial nerve tract, trigeminal

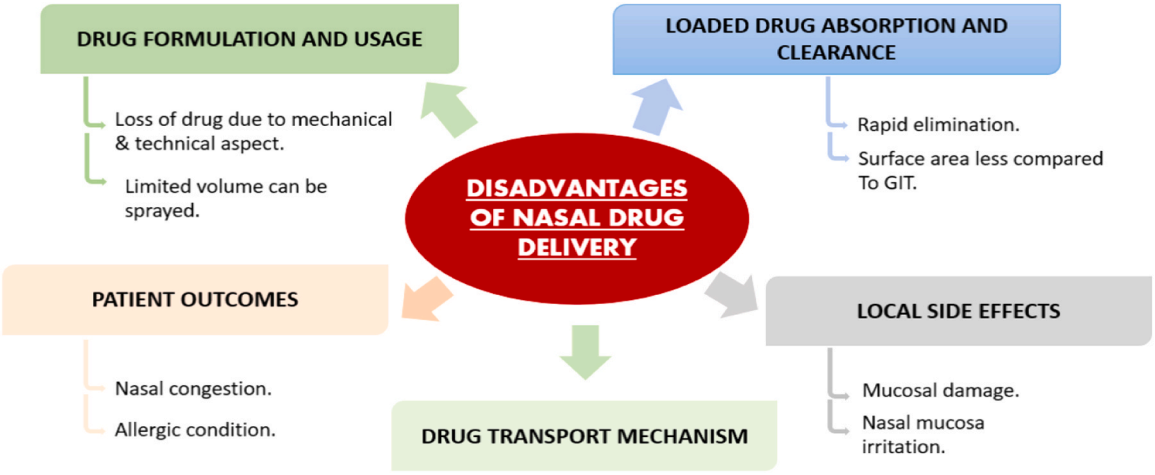

Fig. 3. Disadvantages of Intranasal drug delivery system.

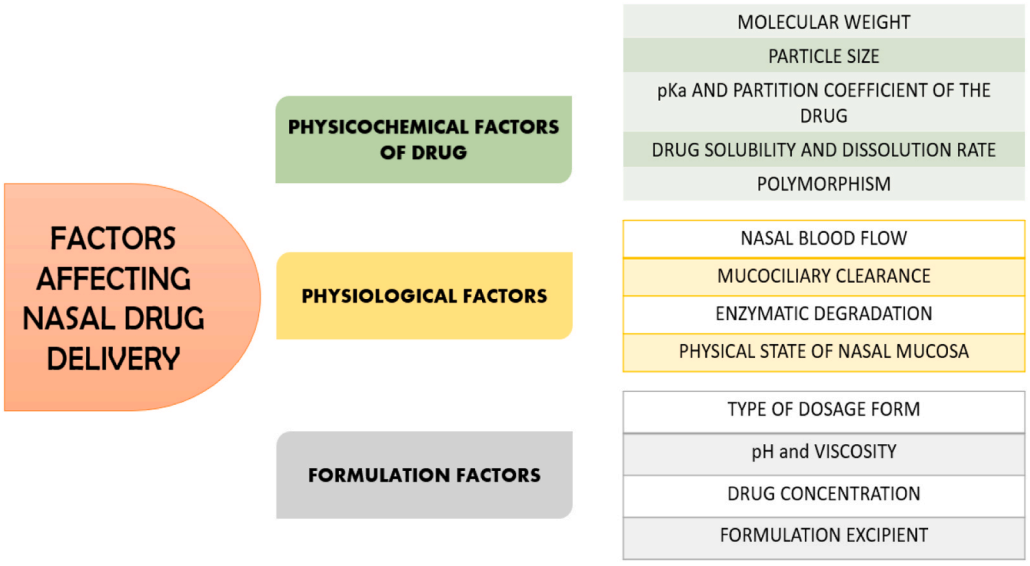

Fig. 4. Factors affecting nasal drug delivery.

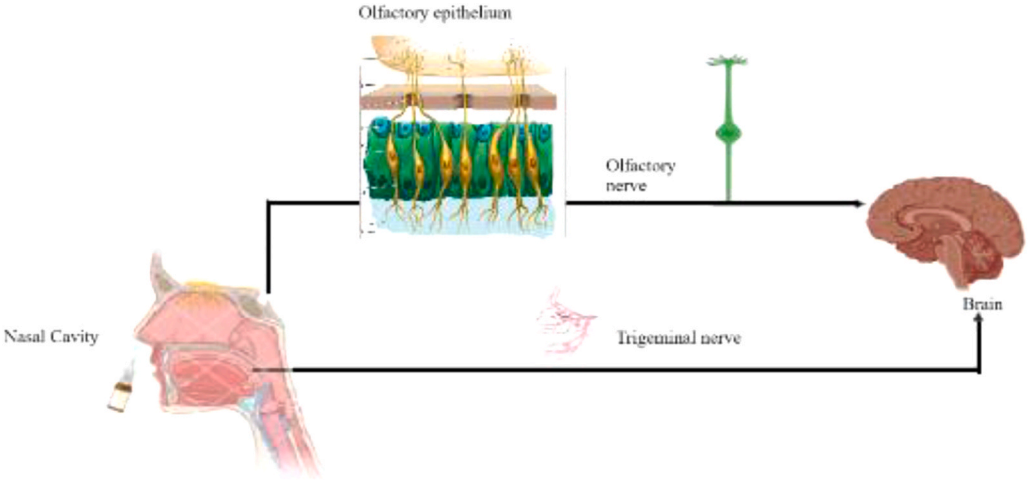

Fig. 5. Pathways of Intranasal Drug Delivery System.

nerve plays a vital role in nasal drug delivery through its maxillary and ocular branches crossing through the nasal mucosa. The two critical

Fig. 6. Nanotechnology based Intranasal drug delivery system.

points of access are the cribriform plate at the olfactory bulb and the anterior lacerated foramen around the pons lead to various areas of the brain following intranasal drug delivery, with the cribriform plate being the dominant route of transport through trigeminal nerves [64].

4.2.3. Respiratory mucosa pathway

The respiratory mucosa pathway is a significant indirect method of delivering drugs intranasally to the CNS. The nasal respiratory area has a ciliated pseudostratified epithelium lined with sufficient vascularity to allow rapid delivery of drugs to the systemic circulation by circumventing hepatic first-pass metabolism [65]. Drugs are transported across the epithelium via either a transcellular (intracellular) or paracellular route. Lipophilic compounds can freely diffuse across epithelial membranes, whereas hydrophilic substances and macromolecules must utilize tight junction modulation or endocytosis-based transport depending on molecular size. Drug molecules are thereafter absorbed into circulation systemically and enter the CNS through the BBB with limitations imposed on this route by the selective nature of the BBB and efflux transporters located therein [66]. With regard to nanosystems, nanocarriers and absorption enhancers can be utilized to enhance permeability through the mucosal compartment, protect ineffective drugs against degradation, and improve bioavailability in order for an increased probability that therapeutic levels of drug reach the brain. Therefore, relative to olfactory or trigeminal pathways, the respiratory mucosal route is complementary relative to the CNS drug delivery strategies [67].

4.3. Nanotechnology for nose-to-brain drug delivery

The rising prevalence of CNS ailments and dementia poses a significant obstacle in managing human well-being, affecting approximately 1.5 million individuals. While various drugs and therapeutic agents are effective, their limitations stem from the unique profiles of individual patients. The BBB impede the site-specific delivery of treatments, reducing their effectiveness in combating targeted conditions [68]. As a result, there is a growing need for the advancement of nano-enabled drug delivery systems for treating CNS diseases [69].

A range of nano-enabled pharmacological methods has been investigated, including carriers such as nanoparticles, nanocomposite hydrogels, dendrimers, nanospheres, and liposomal drug delivery systems (Fig. 6). Nonetheless, these methods face challenges in clinical application, particularly in CNS therapy [70]. Some of them are as follows-

4.3.1. Nanoparticles

4.3.1.1. Inorganic nanoparticles. The exploration of inorganic nanoparticles (NPs) is an exciting field with a multitude of applications, especially in the healthcare sector. Metals including gold and silver, metal oxides like iron oxide, along with ceramics, are employed in the development of these NPs [71]. They are noted for their stability, distinctive optical, magnetic, and electronic characteristics, and the simplicity of modifying ligands to target particular locations within the body. In the realm of biomedicine, inorganic nanoparticles are utilized for treatment, diagnostic imaging, and the delivery of drugs [72].

Gold Nanoparticles: Gold NPs (AuNPs), because of their exclusive properties and capability to cross the BBB, are emerging as promising therapeutic agents for NDs. These NPs exhibit neuroprotective qualities by reducing oxidative stress and immune responses, common in NDs such as AD and PD [73]. Functionalized AuNPs, targeting harmful proteins like Tau and α-synuclein, can boost the delivery of therapeutic drugs to the affected regions, increasing their effectiveness and minimizing side effects [74]. Additionally, AuNPs can modulate the immune system to reduce neuroinflammation, a critical factor in the progression of various NDs. Their diminutive size and surface characteristics contribute to a more effective penetration of the BBB, ensuing in better drug distribution in the brain [75]. Experimental research has also indicated that AuNPs can improve cognitive and antioxidant functions, suggesting potential advantages in the treatment of conditions like AD. Affrald and colleagues explored a novel delivery method for 4-aminopyridine using AuNPs and chitosan-based nasal drug delivery systems to enhance its effectiveness and reduce toxicity. They evaluated the neuroprotective potential through various characterization techniques and *ex vivo* brain models. Their findings suggested improved brain permeability and reduced toxicity, offering a promising strategy for treating neurodegenerative diseases [76]. The research assessed the efficacy of intranasal delivery in the delivery of AuNPs to the CNS. Scientists compared gold nanospheres and nanoprisms modified with polyethylene glycol and D1 peptide and validated their biocompatibility. Intranasal delivery was also superior, wherein nanospheres provided greater brain levels compared to nanoprisms. Pharmacokinetic investigation revealed maximal gold levels in the brain at 0.75 h after administration, where intranasal delivery is a viable option for targeted drug and nanoparticle delivery with decreased systemic exposure. [77]. Salem and colleagues utilized resveratrol-incorporated transferosomal carriers and nanoemulsion systems tagged with AuNPs for drug delivery. Their goal was to amplify resveratrol's neuroprotective properties against AD and optimize its transport to the brain through intranasal administration. The study depicted that transferosomes provided greater permeation and fluorescence intensity compared to nanoemulsions, significantly enhancing cognitive learning and spatial recall in amnesic rodents. Moreover, transferosomes led to a higher accumulation of AuNPs in the rat brains. The results suggested that transferosomes could be an effective brain-targeting system for delivering drugs to treat CNS diseases. The research highlighted the potential application of these transferosomes in treating various central nervous system disorders, including AD, PD, schizophrenia, and sleep disorders [78].

Iron oxide Nanoparticles: Iron oxide NPs (IONPs) are pivotal in treating NDs because of their exceptional properties like magnetic capabilities, small size, biological compatibility and minimal adverse effects [79]. They can be directed to specific brain areas by means of external magnetic fields, enhancing the accuracy of drug delivery, crucial for managing conditions like AD and PD [80]. Furthermore, IONPs mitigate inflammation and oxidative stress, which are two major

characteristics of NDs, by neutralizing reactive oxygen species and reactive nitrogen species, protecting neurons in the process [81]. Their magnetic characteristics enable them to function as visual markers in magnetic resonance imaging, supporting early detection and tracking of NDs. Additionally, IONPs can penetrate the BBB, elevating the localized delivery of pharmacological compounds to the brain [82].They integrate both therapeutic and diagnostic capabilities into a unified platform, termed theranostic, enabling concurrent disease treatment and progression tracking [83]. The research investigates the potency of nasal delivery for transporting magnetic IONPs into the brain, with the goal of enhancing magnetic particle imaging of specific regions. Researchers explored various surface modification techniques to facilitate the nasal introduction of these NPs and confirmed their efficacy through live assessments. By combining magnetic nanoparticles with gold, they achieved additional surface modifications without compromising the magnetic properties. The study demonstrated that specially designed PEGylated magnetic NPs migrated into the brain after nasal delivery and accumulated at specific target sites, as indicated by tracking agents attached to the PEG ends [84]. This research examines the application of magnetically targeted cell delivery to strengthen the transplantation of olfactory ecto-mesenchymal stem cells for the management of PD. Intranasal delivery of SPIONs (superparamagnetic iron oxide nanoparticles) labeled olfactory ecto-mesenchymal stem cells yielded improved therapeutic effects in PD models through the mechanism of neuronal replacement and improvement of dopaminergic markers in the damaged striatum. As a less invasive procedure, this method offers a promising alternative to traditional treatments with potential advantages in neuroregenration and disease management [85]. Abbas and colleagues developed chitosan-coated bilosomes containing resveratrol and SPIONs, which were embedded into wafers made of sodium alginate and polyvinylpyrrolidone. These bilosomes facilitated a sustained release of resveratrol over 24 h and were administered intranasally to mice with inflammation-induced neurodegeneration. The results demonstrated that these specialized bilosomes better cognitive and memory functions, reduced inflammatory markers, and suppressed the activation of key cellular regulatory proteins associated with neuroinflammation. This enhancement is likely attributed to the combined therapeutic advantages of nanoencapsulation, nasal administration, and externally applied magnetics targeting [86].

Cerium Oxide Nanoparticles: Cerium oxide NPs (CONPs), hold substantial potential in treating NDs owing to their distinctive properties [87]. They exhibit strong antioxidant capabilities by mimicking the role of enzymes like catalase and superoxide dismutase, helping to reduce oxidative stress and neutralize ROS, which are crucial in the advancement of NDs like PD [88]. These NPs can also act as therapeutic agents to halt neuronal death and promote recovery in neurodegenerative conditions by affecting signal transduction pathways related to neuronal survival and neuroprotection. They further reduce brain inflammation, which is vital in treating NDs, by modulating the immune system and mitigating damage caused by chronic inflammation [89]. Moreover, because of their capability to penetrate through BBB, CONPs can directly deliver drugs to the brain, enhancing the proficiency of ND treatments by guaranteeing that therapeutic agents more effectively target their intended sites. Additionally, they prevent the accumulation of harmful proteins associated with AD, such as tau and amyloid-beta, reducing neurotoxicity and preserving cognitive function. Overall, the multifunctional properties of CONPs present a promising approach for Creating innovative therapies for neurological conditions, underscoring their capability to improve patient responses in NDs [90]. In one study, CONPs were utilized to mitigate oxidative stress in rats induced by haloperidol, a drug acknowledged to subsidize knowingly to the pathogenesis of PD. The effectiveness of intranasal CONPs was evaluated through assessments of antioxidant activity, biochemical estimations, and experiments. The study proved that CONPs significantly minimized oxidative stress markers encompassing thiobarbituric acid reactive substances, catalase, superoxide dismutase, and glutathione, while elevating interleukin-6 and TNF-α. Furthermore, treatment with intranasal CONPs and oral levodopa resulted in a notable rise in dopamine levels compared to the disease group. Behavioral assessments, including locomoter activity and coordination tests, indicated that intranasal CONPs provided a neuroprotective benefit against haloperidol triggered PD [91]. SM et al. developed intranasal CONPs to evaluate their effectiveness in experimental AD. The CONPs were synthesized via a homogeneous precipitation method and optimized using Box-Behnken Design. Their synthesis was verified by Ultraviolet-Visible analysis and FTIR, and elemental composition analysis validated their presence. The DPPH assay indicated a $95.40 \pm 0.006\%$ radical scavenging at a 50 μg/mL concentration. In vivo cognitive assessments on scopolamine-induced Alzheimer's rats demonstrated that intranasal CONPs dose-dependently restored cognitive abilities. Biochemical estimations revealed that intranasal CONPs increased SOD and Glutathione levels in the brain. Hence, intranasal CONPs, with their robust antioxidant activity, may offer a promising technique to managing signs associated with AD [92].

4.3.1.2. Polymeric nanoparticles. Polymeric NPs are consists of a polymeric matrix that entraps, encapsulates, or chemically conjugates therapeutic molecules. Polymeric NPs are often larger than micelles (100–200 nm) and have a higher Polydispersity Index. The carrier system is sustainable, biodegradable, stable, and cost-effective, allowing for regulated or sustained medication release. The polymer employed in NPs might be natural (such as albumin,chitosan, gelatin, alginate, collagen) or artificial (like polycaprolactones or polyacrylates) [93].This affects the nanoparticle's biological compatibility, drug loading, toxicity, and stability. Synthetic polymers can outperform natural polymers due of their flexibility [94].

Polymeric NPs are highly versatile due to their safety, excellent drug encapsulation capacity, and the ability to modify their composition and structure [95]. This allows them to adhere to mucosal surfaces, minimizing mucociliary clearance, and extend their retention time in the nasal mucosa [96]. Additionally, they enhance permeation by temporarily opening tight junctions, thereby increasing paracellular permeability across the nasal epithelium. Different polymeric NPs have been investigated for intranasal delivery, demonstrating diverse levels of success in preclinical studies [95]. The study aimed the formulation of chitosan NPs for targeted intranasal delivery of donepezil hydrochloride to the brain. The optimized nanoparticles demonstrated favourable particle size, zeta potential, and drug release, achieving over 90% drug release and 70% permeation within 24 h. Intranasal administration resulted in a 2.6-fold upsurge in brain drug levels relative to oral delivery. Confocal microscopy confirmed successful brain transport, highlighting the viability of chitosan NPs as an efficient strategy for improving donepezil hydrochloride delivery in AD treatment [97]. Sonawane et al. prepared polymeric nanoparticles by ionic gelation technique for intranasal delivery of ropinirole HCl to the brain. Box-Behnken design was applied to fine-tune the formulation using encapsulation efficiency and mucoadhesion. Compatibility studies were carried out to ensure drug-polymer interaction stability, and in vitro release analysis depicted prolonged release of the drug with 65–81% release in five hours. With growing curiosity in intranasal delivery of therapeutics for aiming the CNS, the study suggested polymeric NPs is an excellent technique for effective brain targeting of ropinirole HCl [98]. Another research explored the formulation of polymeric NPs for intranasal administration of Levodopa (L-Dopa) in the intervention of PD. Employing PLGA and chitosan as polymeric matrices, scientists optimized the nanoparticles using solvent evaporation and ionic gelation methods. Among the developed formulations, chitosan-based NPs exhibited the most desirable characteristics, such as enhanced encapsulation efficiency and stable drug loading. In vivo experiments confirmed that intranasal administration considerably improved L-Dopa's pharmacokinetic profile, resulting in increased brain

concentrations of the drug and sustained release over conventional oral delivery. These findings identified intranasal L-Dopa-loaded chitosan NPs as a prospective substitute for the enhancement of therapeutic effects in PD patients [99].

4.3.1.3. Lipid nanoparticles. Lipid nanoparticles (LNPs) are particles ranging in size from 50 to 1000 nm that are composed of biocompatible solid or liquid lipids. They are favoured over other colloidal systems for their superior carrier properties. Solid lipid nanoparticles or SLNs are the most efficient lipid-based colloidal carriers, comprising a solid lipid matrix encased by surfactants in an aqueous dispersion. A group of LNPs called as nanostructured lipid carriers or NLCs include a solid lipid core composed of both liquid and solid lipids, which increases drug loading capacity while reducing burst release and drug ejection. Lipid-drug conjugates (LDCs) NPs have been introduced to address the restricted hydrophilic drug loading capacity of LNPs. LNP production is scalable and yields physico-chemically stable formulations. LNPs are employed intensively for intranasal delivery of drugs because of their stability, biocompatibility, and surface modification simplicity as well as scalability. Intranasal administration is beneficial due to fast onset of therapeutic action, evasion of intestinal and liver first-pass metabolism, minimized systemic exposure and associated side effects, direct entry into the CSF and brain, simplicity of application, and enhanced patient compliance with therapy regimens [100]. One such study explored the use of NLCs to boost the delivery of doxepin to the brain via intranasal delivery. The developed formulation yielded smaller particle sizes, showed high entrapment efficiency, and controlled drug release. In vivo studies in rats exposed significantly high brain concentrations upon intranasal delivery compared to intravenous delivery, hence showing the efficient targeting of the drug via olfactory and trigeminal routes. These findings highlight the promise of NLCs as a realistic strategy for increasing the absorption and pharmacological effect of doxepin in the treatment of NDs [101]. Researchers investigated the preparation of chitosan-coated NLCs for improving cerebral delivery of Tanshinone IIA to treat PD. The optimized formulation was more stable, had improved drug entrapment efficiency, and prolonged release for 24 h. In vivo experiments conducted in a PD rat model revealed more effective antiparkinsonian and antidepressant activities than uncoated Tanshinone IIA -NLCs and free TAN. Biochemical analysis proved improved brain targeting and therapeutic efficacy, with the chitosan-coated system being more effective. These results identify chitosan-coated -NLCs as a promising intranasal delivery system to improve TAN bioavailability in the treatment of PD. [102].

4.3.2. Liposomes

These phospholipid vesicles composed of lipid bilayers that encase an aqueous compartment. Reliant on their solubility, drugs are incorporated into either the lipid or water layer. This system effectively accommodates molecules of different sizes, hydrophilicity levels, and pKa values [103]. Liposomes are gaining prominence as impactful drug delivery systems for the CNS because of their capability to encapsulate water loving or hydrophilic, lipophilic, and amphiphilic molecules [104]. The incorporation of biocompatible and biodegradable lipids makes this vesicular system well-suited for therapeutic use. Researchers worldwide have explored and documented nose-to-brain delivery techniques utilizing liposomes to manage various CNS disorders. To optimize drug delivery to brain tissues, both passive and active targeting approaches have been implemented. Passive targeting leverages physiological mechanisms driven by the body's hormones and neurotransmitters, while active targeting involves attaching a ligand to the liposomal surface, enabling selective binding to specific brain cells. Additionally, stimuli-responsive liposomal formulations are designed to react to environmental factors such as pH fluctuations, temperature variations, and other external conditions [105]. A study evaluated the effectiveness of intranasal liposomal formulations containing donepezil, Beta-site amyloid precursor protein cleaving enzyme 1 siRNA and memantine for AD treatment. Using genetically engineered mice with APP/PS1 mutations as an AD model, researchers found that intranasally administered drugs led to greater short-term memory improvements compared to oral delivery. This triple-drug approach not only enhanced memory function but also lowered beta-amyloid levels and reduced BACE-1 mRNA expression. Furthermore, it contributed to a decline in inflammatory cytokine mRNA expression. This pioneering method introduces new opportunities for AD therapy and direct transnasal drug delivery. Findings highlight the capability of this delivery system for AD management and its broader applications in other CNS conditions, including NDs and brain tumors [106] A study investigated the development of +vely charged liposomes containing selegiline hcl for intranasal delivery as a potential treatment for PD. Using the Box Behnken design for optimization, the liposomes underwent coating with stearylamine to introduce a positive charge. The resulting Selegiline Hydrochloride-Liposome Preparation 3 (SH-LP3) liposomes exhibited a minimal size of 173 ± 2.13 nm, an optimal surface charge of $+16 \pm 1.98$, and a highest entrapment efficiency of $40.14 \pm 1.83\%$. Morphological study confirmed their spherical shape within the 100–200 nm range. In vitro cytotoxicity assays on Subclone Human-SY5Y (SHSY5Y) cell lines demonstrated a significant reduction in toxicity, nearly tenfold lower than that of sheer selegiline hydrochloride. Additionally, animal studies utilizing a rotenone-lesioned C57BL6 mouse model of PD showed that intranasal administration of SH-LP3 liposomes effectively alleviated PD symptoms. These findings highlight SH-LP3 liposomes as a promising candidate for PD treatment via intranasal delivery, offering controlled drug release, augmented safety, and improved efficacy, paving the direction for forthcoming developments in PD therapeutics [107].

4.3.3. Nanogels

Nanogels, which are biocompatible three-dimensional polymeric networks, are utilized for CNS drug delivery because of their straightforward synthesis, customizable functionality, adjustable structure and porosity, suitability with biomolecule loading, biodegradability, and responsiveness to stimuli. However, traditional bulk hydrogels face challenges in crossing the BBB owing to their micron-scale structures, leading to suboptimal drug delivery efficiency [108]. Nanogel-based drug delivery systems hold promise for maximum drug loading capacity, higher drug stability, controlled or dynamic drug release, and precise aiming of CNS disorders [109].

Nanogels are promising as drug nanocarriers due to their small size, which permits them to invade tissues through transcellular pathways [110]. They provide enhanced encapsulation and can be delivered through multiple pathways, including pulmonary, nasal, oral and intraocular routes. The nanogels' size significantly affects their circulation time in the blood and bioavailability [111]. Their ability to permeate body barriers results in enhanced permeability and retention effects, leading to stable and responsive therapeutic applications. Nanogels also adapt to external factors including temperature, magnetic fields, pH, and ionic strength [112]. In this study, researchers formulated an in situ nasal nanogel loaded with nanosuspension of nortriptyline HCl to increase nasal drug delivery. This approach facilitates brain targeting via olfactory and trigeminal nerves, improving therapeutic efficacy. The nanosuspension was synthesized using a nanoprecipitation–ultrasonication process, subsequently subjected to high-pressure homogenization, and then integrated into an in situ gelling polymer system. The improved nanogels, composed of gellan gum, featured a particle size ranges from 10 to 100 nm, an advantageous PDI value, improved solubility, effective gelation behavior, and the optimal viscosity needed for nasal mucosal adhesion via ionic interactions. In vitro, the drug release exceeded that of a drug solution within 60 min. Studies on spreadability and viscosity confirmed prolonged residence time, establishing in situ nanogels as a potent technique for brain-localized drug delivery at the nanoscale. [113]. Chen et al.

conducted a study to develop a novel glycyrrhizic acid-zinc alginate nanogel, reinforced by hydrogen bonds to enhance drug loading capacity and stability. The H- bond interaction amid glycyrrhizic acid and the carrier effectively encapsulated albiflorin, minimizing leakage. The release of albiflorin occurs when the H-bond among glycyrrhizic acid and sodium alginate dissociates. Furthermore, glycyrrhizic acid serves not only as a nanogel component but also as a therapeutic agent due to its pharmacological benefits. A thermosensitive hydrogel was incorporated to load albiflorin-glycyrrhizic acid nanogel, ensuring adhesion to the nasal cavity and facilitating PD treatment via intranasal administration. The findings revealed that albiflorin and glycyrrhizic acid encapsulated within the heatsensitive nanogel exhibited potent antioxidant and anti-inflammatory effects upon intranasal delivery. This study highlighted the potential of hydrogen bond interactions between small molecules and carriers in improving drug loading efficiency and system stability for PD treatment [114].

4.3.4. Nanoemulsions

Nano emulsions are nano-sized emulsions formulated to elevate drug delivery to the intended location, reduce undesired outcomes, and limit harmful responses [115]. These biphasic dispersions systems consist of two immiscible liquids, with particles of nanometric size ranging from 10 nm to 1000 nm [116]. NEs are biocompatible, physically stable, easily manufactured, and biodegradable. They are beneficial for intravenous administration due to their droplet size and nasal drug delivery systems through mucoadhesive agents. The review explores the implementation of NE in NDs including AD, PD, and prion's disease, focusing on their molecular aspects and the significance of nano emulsions in treating these diseases [117].

NEs are tiny dispersed particles utilized in pharmaceuticals for delivering drugs to treat NDs. Nano formulations, including NEs, have been crafted for enhanced drug delivery in PD. NEs based on palm oil, combined with Levodopa, offer advantages due to their efficiency, superior thermal characteristics, and resistance to oxidation [118]. Additionally, NEs have been adapted with mucoadhesive properties for PD treatment [119]. This research aimed to enhance trans nasal drug delivery by optimizing nasal NEs of Iloperidone applying Design Expert (Version 11) and incorporating chitosan for surface modification. The chitosan-functionalized nanoemulsions were formulated through ultrasonication using oleic acid as a charge regulator, along with appropriate excipients. Characterization studies exposed a droplet size of 146.4 $\pm$ 0.5 nm, a PDI of 0.291 $\pm$ 0.02, and a zeta potential of + 23.6 $\pm$ 0.3 mV. Surface functionalization was validated through Ninhydrin assay, TEM, and FTIR analysis. In vitro drug release analysis indicated that Iloperidone release from the NEs and chitosan-functionalized formulations were 90.41 $\pm$ 2.1% and 72.02 $\pm$ 0.21%, respectively. After eight hours, ex vivo permeation experiments over goat nasal mucosa showed Iloperidone penetration values of 1270.58 $\pm$ 0.023 μg/cm^2 and 1096.13 $\pm$ 0.043 μg/cm^2. Studies employing Neuro2A brain cell lines and RPMI 2650 nasal cells validated the chitosan-functionalized nanoemulsions' safety profile. Furthermore, experiments in Wistar rats revealed enhanced cataleptic effects, improved cognitive function, and reduced anxiety-related behavior, along with increased brain aggregation, highlighting the promise of this technique for efficient nasal drug delivery [120]. In a recent study,scholars designed a mucoadhesive microemulsion incorporating lipophilic silymarin for PD treatment. Using Central Composite Design, they optimized the microemulsion to achieve favourable droplet size, zeta potential, and drug loading efficiency. The refined formulation exhibited a droplet size of 61.26 $\pm$ 3.65 nm, a surface charges of $-$24.26 $\pm$ 0.2 mV, and an impressive drug loading efficiency of 97.28 $\pm$ 4.87%. Chitosan incorporation notably enhanced droplet size and zeta potential. In vitro cell toxicity assessments confirmed the formulation's safety and non-toxicity. The mucoadhesive microemulsion demonstrated superior permeability across sheep nasal mucosa collated to a conventional microemulsion and drug solution, highlighting its potential for transnasal delivery of sparingly soluble silymarin. In vitro release studies revealed substantially greater drug diffusion and release from microemulsions compared to silymarin solutions. Moreover, behavioral and biochemical analyses in a rotenone-triggered rat model demonstrated substantial neuroprotective effects, reinforcing the formulation's therapeutic promise for PD management [121].

4.3.5. Nisosomes

Nisosomes are nanoscale vesicular systems having a robust bilayer structure, composed primarily of non-ionic emulsifiers and cholesterol. The vesicles are extremely biologically suitable and biodegradable [122]. The vesicles are noted for enhanced chemical inertness, good shelf life, low adversity, and low production price. Nisosomes are capable of entrapping lipophilic as well as hydrophilic drugs and releasing them at localized sites in a controlled manner [123]. Besides, Nisosomes are reported to possess the ability to affect organ distribution and metabolic stability of drugs. This study analyses the capability of dual drug-loaded niosomes in the intranasal delivery of Rivastigmine and N-Acetyl Cysteine to the CNS. The preparation achieved a nanoscale size of 162.4 nm, along with high drug entrapment efficiencies, and proved to be stable in liquid form for six months. The niosomes were able to endorse sustained release of the drug for two days, showing enhanced therapeutic effects compared to conventional free drug solutions. Pharmacokinetic and biodistribution analyses showed greater retention in the brain, which suggested that the self-assembled lipidic nanoscale structure of niosomes can efficiently enable nasal drug delivery, hence circumventing the BBB through the intranasal route [124]. The research assessed the use of niosomes for intranasal delivery of Bromocriptine Mesylate for improved brain targeting through the olfactory route for better treatment of PD. The best formulation showed effective encapsulation, improved permeation through nasal mucosa, and enhanced brain bioavailability in comparison to conventional approaches. In vivo studies justified its efficacy in reducing PD symptoms with an excellent safety profile, without any toxicity observed within 28 days. The results underscore intranasal niosomal delivery as a viable strategy for delivering drugs of therapy to the brain, providing improved efficacy at reduced doses with fewer systemic side effects [125].

4.3.6. Dendrimers

Dendrimer is a term Professor Donald Tomalia coined by uniting the two Greek words δέντρο (dendro) for "tree" and μέροσ (meros) for "part." Dendrimers (DDs) are highly branched three-dimensional synthetic macromolecules with the highly controlled size, shape, and functionality of terminal groups on synthesis [126]. Their typical design consists of a central core, which can be a single atom or a cluster of atoms, as well as multiple identical chemical activities, outwards expanding branches replicated from the core, and terminal groups on the nanoparticle's surface. DDs are considered prospective drug delivery methods since they can traverse the BBB and increase the absorption rate of conventional medicines in the brain [127]. They have been found to be useful in gene delivery by suppressing the expression of certain target proteins. Additionally, DDs are promising as anti-inflammatory, anti--amyloidogenic agents and facilitate cellular uptake in certain cell types. They can also be used as very potent diagnostic tools for NDs. Additionally, DDs possess higher water solubility, biocompatibility, polyvalence, and well-defined molecular weight compared to conventional polymers and thus can be employed for targeted delivery of drugs to the brain [128]. This research assessed dendrimers as a possible nanocarrier for siRNA gene targeting of the apolipoprotein E gene through the BBB for treating NDs. Researchers compared complexation stability, mechanism of interaction, and cytotoxicity against brain endothelial cells. Amongst the dendrimers tested, third-generation silicon-based dendrimer with polyethylene glycol 6000 conjugation) showed the greatest potential, with attractive characteristics for drug delivery. On the other hand, fourth-generation oxygen-based dendrimer with polyethylene glycol 6000 conjugation was found to be extremely cytotoxic, while

Table 2
Comparison of different nanosystems in intranasal drug delivery system.

Delivery System	Particle size	Loading Efficiency	Limitations	References
Liposomes	50–500 nm	Moderate	Stability issues. Leakage	[130]
Polymer Nanoparticles	50–300 nm	High	Toxicity concern, complex synthesis	[131]
Inorganic Nanoparticles	1–100 nm	Variable	Poor biodegradability, toxicity	[132]
Lipid Nanoparticles	50–300 nm	Moderate-High	Surfactant irritation	[133]
Nanoemulsions	10–200 nm	High	Instability	[134]
Niosomes	100–1000 nm	High	Aggregation, size variability	[135]
Dendrimers	1–100 nm	Very high	Cost, cationic toxicity.	[136]

Table 3
An overview of intranasal nano delivery system studied for neurological disorders.

Drug	Nano formulation	Route	Bioavailability	Advantage	Limitation	Toxicity	References
Levodopa	Polymeric nanoparticle	Intranasal	↑Bioavailability (from 26.56% to 45.20%)	↑Solubility, ↑nasal residence time, ↑CNS absorption	↓entrapment efficiency (~40%) - Mucociliary clearance ↑Polymer-induced aggregation ↑particle size - Delayed Tmax due to larger nanoparticle size	NA	[137]
Riluzole	nanoparticle	Intranasal	↑bioavailability ↑Absorption	↑therapeutic effects by reaching CSF directly, ↓oxidative stress, improved memory impairment	NA	mitigated haloperidol-induced memory impairment and toxicity in rats.	[138]
Buspirone	solid lipid nanoparticles	Nasal	↑brain targeting ↑ease of administration, ↑drug distribution	self-medication better patient compliance Rapid absorption -fast onset of action	↓entrapment efficiency	low toxicity of solid lipid nanoparticles.	[139]
hydroxy-α-sanshoo	Liposomes	Nasal	↑bioavailability	↑Brain-Targeting, ↑Stability, ↑Safety Profile,	Despite high stability therapeutic efficacy in AD remain insufficiently validated.	Caused slight nasal mucosa damage.	[140]
donepezil, memantine, and BACE-1 siRNA	Liposomes	Intranasal	NA	-Intranasal liposomal delivery offers a non-invasive route that bypasses the BBB, protects siRNA from degradation, ↑drug efficacy and safety ↓systemic side effects	↓inherent stability, ↓cellular uptake	-free(non-encapsulated) donepezil and memantine exhibit measurable cytotoxicity, indicating the need for a protective delivery system to reduce drug-induced cell damage.	[141]
magnolol	Thermosensi-tive hydrogel	Intranasal	↑bioavailability, Prolonged plasma release	Bypassed BBB for direct brain transport. ↑nasal residence time ↑drug release ↓mucociliary clearance	Poor solubility and aggregation. inability to effectively cross the BBB.	↓Toxicity -Biocompatibility	[142]
Osthole	Nano-emulsion	Nasal	↑bioavailability ↑drug release ↑therapeutic efficacy	↑nasal drug delivery ↑Transport, ↑mucoadhesion, ↑stability ↑solubility ↑,	NA	-toxicity profile was not evaluated, leaving safety unconfirmed.	[143]
Dolutegravir	Nano-emulsion	Nasal	↑ Dolutegravir's brain bioavailability, ↓Systemic exposure	once-daily dosing regimen. High genetic barrier to drug resistance. good safety profile. ↑brain targeting	potential patient variability, unassessed clinical scalability.	NA	[144]
Lacosamide	Niosomes	Intranasal	↑brain bioavailability, Showed 4.5–7 times higher brain uptake	↑transcellular transport ↑mucoadhesion ↑stability	NA	safe and non-toxic, minimal nasal inflammation, no mucosal damage	[145]
Bromo-criptine	Niosomes	Nasal	↑brain bioavailability,	↑brain uptake and distribution of drugs, lower doses, bypassed hepatic first-pass metabolism	uncertain human safety, unassessed long-term toxicity, restricted intranasal dosing	No organ toxicity, minimal nasal inflammation	[146]

*NA – Not Addressed

third-generation oxygen-based dendrimer with polyethylene glycol 6000 conjugation was characterized by balanced complexation competence and thus had promise as an siRNA carrier. The results revealed the promise of dendrimer-based delivery systems to improve

ND treatments [129]. Another study investigated a DDs supported drug delivery system to improve the brain-targeting activity of tacrine with reduced systemic side effects. Researchers functionalized poly(propylene imine) G5.0 DDs with oleic acid as a brain-targeting ligand and assured successful binding using spectroscopic techniques. Tacrine hydrochloride was physically entrapped in these dendrimers without loss of its AChE inhibitory activity, a key enzyme in AD. Safety tests confirmed the biocompatibility of the formulation, thus warranting subsequent in vivo studies as a potentially useful approach to treat AD. Comparison of different nanosystems is depicted in Table 2.

An overview of intranasal nano delivery system studied for neurological disorders is represented in Table 3.

5. Conclusion

Nasal delivery of drugs has become an exciting non-invasive way to overcome the limitations of the BBB when treating neurological disorders. In this review, we discussed how different types of nanocarrier systems such as liposome, niosome, polymeric nanoparticle, and nanogel have varying drug characteristics related to particle size, delivery performance, drug loading efficiencies, mucoadhesion properties, but also differences in other areas like limitations associated with that particular carrier. While liposomes and niosomes offer biocompatibility and efficient encapsulation, issues related to stability and rapid clearance persist. On the other hand, polymeric nanoparticles provide controlled release of drugs and improved stability due to crosslinking and appeasement via chemical reactions. However, Polymer neurotoxicity and difficulties for scaling up production remain concerns. While nanogels provide superior mucoadhesion and have high drug loading capacity, long-term safety data is incomplete.

Despite having preclinical evidences demonstrating an ability to achieve better targeting to the brain and decreased systemic exposure using intranasal nanocarriers, there are still numerous issues that will impact clinical translation of these products including variability between patients due to differences in nasal anatomy and physiology, the reproducibility of formulation composition, the unknown impact of long-term use with respect to neurotoxicity as well as the regulatory hurdles needed for approval.

In this view, future studies should focus on further standardizing comparative data comparing carriers through thorough mechanistic investigation on olfactory and trigeminal transport mechanisms and develop biodegradable, scalable and pharmaceutically optimized nanocarriers. Additionally, well-designed preclinical and clinical studies specifically evaluating nose-to-brain targeting efficiency, safety, and long-term neurological outcomes are necessary to facilitate successful clinical translation.

CRediT authorship contribution statement

Ritika Saxena: Writing – original draft, Investigation, Conceptualization. **Alka Lohani:** Writing – review & editing, Supervision, Conceptualization.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M. Sharma, T. Dube, S. Chibh, A. Kour, J. Mishra, J.J. Panda, Nanotheranostics, a future remedy of neurological disorders, Expert Opin. Drug Deliv. 16 (2) (2019 Feb 1) 113–128.
[2] R. Gautam, M. Sharma, Prevalence and diagnosis of neurological disorders using different deep learning techniques: a meta-analysis, J. Med. Syst. 44 (2) (2020 Feb) 49.
[3] A.A. Lima, M.F. Mridha, S.C. Das, M.M. Kabir, M.R. Islam, Y. Watanobe, A comprehensive survey on the detection, classification, and challenges of neurological disorders, Biology 11 (3) (2022 Mar 18) 469.
[4] S. Md, S.K. Bhattmisra, F. Zeeshan, N. Shahzad, M.A. Mujtaba, V.S. Meka, A. Radhakrishnan, P. Kesharwani, S. Baboota, J. Ali, Nano-carrier enabled drug delivery systems for nose to brain targeting for the treatment of neurodegenerative disorders, J. Drug Deliv. Sci. Technol. 43 (2018 Feb 1) 295–310.
[5] R.K. Verma, S. Garg, Drug delivery technologies and future directions, Pharm. Technol. 25 (2) (2001 Feb) 1–4.
[6] T.P. Crowe, W.H. Hsu, Evaluation of recent intranasal drug delivery systems to the central nervous system, Pharmaceutics 14 (3) (2022 Mar 12) 629.
[7] R.K. Upadhyay, Drug delivery systems, CNS protection, and the blood brain barrier, BioMed. Res. Int. 2014 (1) (2014) 869269.
[8] R. Daneman, A. Prat, The blood–brain barrier, Cold Spring Harb. Perspect. Biol. 7 (1) (2015 Jan 1) a020412.
[9] D.S. Miller, Regulation of P-glycoprotein and other ABC drug transporters at the blood–brain barrier, Trends Pharmacol. Sci. 31 (6) (2010 Jun 1) 246–254.
[10] W. Löscher, H. Potschka, Blood-brain barrier active efflux transporters: ATP-binding cassette gene family, NeuroRx 2 (1) (2005 Jan 1) 86–98.
[11] W.M. Pardridge, The blood-brain barrier: bottleneck in brain drug development, NeuroRx 2 (1) (2005 Jan) 3–14.
[12] S. Ohtsuki, T. Terasaki, Contribution of carrier-mediated transport systems to the blood–brain barrier as a supporting and protecting interface for the brain; importance for CNS drug discovery and development, Pharm. Res. 24 (9) (2007 Sep) 1745–1758.
[13] D. S Hersh, A. S Wadajkar, N. B Roberts, J. G Perez, N. P Connolly, V. Frenkel, J. A Winkles, G. F Woodworth, A. J Kim, Evolving drug delivery strategies to overcome the blood brain barrier, Curr. Pharm. Des. 22 (9) (2016) 1177–1193.
[14] J. Barar, M.A. Rafi, M.M. Pourseif, Y. Omidi, Blood-brain barrier transport machineries and targeted therapy of brain diseases, BioImpacts BI 6 (4) (2016 Dec 5) 225.
[15] Begley D.J., Bradbury M.W., Kreuter J. Blood–Brain Barrier and Drug Delivery.
[16] L. Illum, Nasal drug delivery—possibilities, problems and solutions, J. Control. Release 87 (1-3) (2003 Feb 21) 187–198.
[17] A.M. Cook, K.D. Mieure, R.D. Owen, A.B. Pesaturo, J. Hatton, Intracerebroventricular administration of drugs, Pharmacother. J. Hum. Pharmacol. Drug Ther. 29 (7) (2009 Jul) 832–845.
[18] A.M. Cook, K.D. Mieure, R.D. Owen, A.B. Pesaturo, J. Hatton, Intracerebroventricular administration of drugs, Pharmacother. J. Hum. Pharmacol. Drug Ther. 29 (7) (2009 Jul) 832–845.
[19] X.C. Yu, J.J. Yang, B.H. Jin, H.L. Xu, H.Y. Zhang, J. Xiao, C.T. Lu, Y.Z. Zhao, W. Yang, A strategy for bypassing the blood-brain barrier: facial intradermal brain-targeted delivery via the trigeminal nerve, J. Control. Release 258 (2017 Jul 28) 22–33.
[20] S. Dá Mesquita, A.C. Ferreira, J.C. Sousa, M. Correia-Neves, N. Sousa, F. Marques, Insights on the pathophysiology of Alzheimer's disease: the crosstalk between amyloid pathology, neuroinflammation and the peripheral immune system, Neurosci. Biobehav. Rev. 68 (2016 Sep 1) 547–562.
[21] Z. Breijyeh, R. Karaman, Comprehensive review on Alzheimer's disease: causes and treatment, Molecules 25 (24) (2020 Dec 8) 5789.
[22] R. Brookmeyer, E. Johnson, K. Ziegler-Graham, H.M. Arrighi, Forecasting the global burden of Alzheimer's disease, Alzheimer's. Dement. 3 (3) (2007 Jul 1) 186–191.
[23] H. Hillen, The beta amyloid dysfunction (BAD) hypothesis for Alzheimer's disease, Front. Neurosci. 13 (2019 Nov 7) 1154.
[24] G. Forloni, V. Artuso, P. La Vitola, C. Balducci, Oligomeropathies and pathogenesis of Alzheimer and Parkinson's diseases, Mov. Disord. 31 (6) (2016 Jun) 771–781.
[25] W.J. Deardorff, E. Feen, G.T. Grossberg, The use of cholinesterase inhibitors across all stages of Alzheimer's disease, Drugs Aging 32 (2015 Jul) 537–547.
[26] T.J. Eckroat, D.L. Manross, S.C. Cowan, Merged tacrine-based, multitarget-directed acetylcholinesterase inhibitors 2015–present: synthesis and biological activity, Int. J. Mol. Sci. 21 (17) (2020 Aug 19) 5965.
[27] M. Weinstock, Selectivity of cholinesterase inhibition: clinical implications for the treatment of Alzheimer's disease, CNS Drugs 12 (4) (1999 Oct) 307–323.
[28] M. Weinstock, Selectivity of cholinesterase inhibition: clinical implications for the treatment of Alzheimer's disease, CNS Drugs 12 (4) (1999 Oct) 307–323.
[29] M. Asai, C. Hattori, N. Iwata, T.C. Saido, N. Sasagawa, B. Szabó, Y. Hashimoto, K. Maruyama, S.I. Tanuma, Y. Kiso, S. Ishiura, The novel β-secretase inhibitor KMI-429 reduces amyloid β peptide production in amyloid precursor protein transgenic and wild-type mice, J. Neurochem. 96 (2) (2006 Jan) 533–540.
[30] K. Wirdefeldt, H.O. Adami, P. Cole, D. Trichopoulos, J. Mandel, Epidemiology and etiology of Parkinson's disease: a review of the evidence, Eur. J. Epidemiol. 26 (1) (2011 Jun) 1.
[31] K. Wirdefeldt, H.O. Adami, P. Cole, D. Trichopoulos, J. Mandel, Epidemiology and etiology of Parkinson's disease: a review of the evidence, Eur. J. Epidemiol. 26 (2011 Jun) 1–58.

[32] B.S. Shastry, Parkinson disease: etiology, pathogenesis and future of gene therapy, Neurosci. Res. 41 (1) (2001 Sep 1) 5–12.
[33] A.L. Bartels, K.L. Leenders, Parkinson's disease: the syndrome, the pathogenesis and pathophysiology, Cortex 45 (8) (2009 Sep 1) 915–921.
[34] D.J. Moore, A.B. West, V.L. Dawson, T.M. Dawson, Molecular pathophysiology of Parkinson's disease, Annu. Rev. Neurosci. 28 (1) (2005 Jul 21) 57–87.
[35] J.E. Ahlskog, M.D. Muenter, Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Movement disorders: official journal of the, Mov. Disord. Soc. 16 (3) (2001 May) 448–458.
[36] F. Stocchi, Optimising levodopa therapy for the management of Parkinson's disease, J. Neurol. 252 (2005 Oct) iv43-8.
[37] H. Iwase, J.I. Sudo, J. Terui, K. Kakuno, T. Watanabe, K. Takayama, T. Nagai, Transdermal absorption of L-dopa from a new system composed of two separate layers of L-dopa and hydrogel in rats, Drug Dev. Ind. Pharm. 26 (7) (2000 Jan 1) 755–759.
[38] D. Robakis, S. Fahn, Defining the role of the monoamine oxidase-B inhibitors for Parkinson's disease, CNS Drugs 29 (2015 Jun) 433–441.
[39] Parkinson Study Group, A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease, Arch. Neurol. 61 (4) (2004 Apr 1) 561–566.
[40] W.H. Jost, A critical appraisal of MAO-B inhibitors in the treatment of Parkinson's disease, J. Neural Transm. 129 (5) (2022 Jun) 723–736.
[41] V.A. Cwik, 2001, What is amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis: A guide for patients and families. 2001;4:1-6.
[42] A.E. Renton, A. Chiò, B.J. Traynor, State of play in amyotrophic lateral sclerosis genetics, Nat. Neurosci. 17 (1) (2014 Jan) 17–23.
[43] S.C. Barber, P.J. Shaw, Oxidative stress in ALS: key role in motor neuron injury and therapeutic target, Free Radic. Biol. Med. 48 (5) (2010 Mar 1) 629–641.
[44] G.Y. Wang, S.L. Rayner, R. Chung, B.Y. Shi, X.J. Liang, Advances in nanotechnology-based strategies for the treatments of amyotrophic lateral sclerosis, Mater. Today Bio 6 (2020 Mar 1) 100055.
[45] M. Strong, J. Rosenfeld, Amyotrophic lateral sclerosis: a review of current concepts, Amyotroph. Lateral Scler. Other Mot. Neuron Disord. 4 (3) (2003 Sep 1) 136–143.
[46] V. Kumar, T. Kashav, M.I. Hassan, Amyotrophic lateral sclerosis: current therapeutic perspectives, Pathol. Prev. Ther. Neurodegener. Dis. (2019) 207–224.
[47] L.A. Raymond, V.M. André, C. Cepeda, C.M. Gladding, A.J. Milnerwood, M. S. Levine, Pathophysiology of Huntington's disease: time-dependent alterations in synaptic and receptor function, Neuroscience 198 (2011 Dec 15) 252–273.
[48.] Bruyn G.W.. Handbook of clinical neurology (Vol. 4). Amsterdam: North. 1968.
[49] R.A. Roos, Huntington's disease: a clinical review, Orphanet J. rare Dis. 5 (2010 Dec) 1–8.
[50] J.D. Lane, J.E. Smith, P.A. Shea, W.J. McBride, Neurochemical changes following the administration of depleters of biogenic monoamines, Life Sci. 19 (11) (1976 Dec 1) 1663–1667.
[51] S.J. Pearson, G.P. Reynolds, Depletion of monoamine transmitters by tetrabenazine in brain tissue in Huntington's disease, Neuropharmacology 27 (7) (1988 Jul 1) 717–719.
[52] A. Patel, N. Surti, A. Mahajan, Intranasal drug delivery: Novel delivery route for effective management of neurological disorders, J. Drug Deliv. Sci. Technol. 52 (2019 Aug 1) 130–137.
[53] K. Greish, Enhanced permeability and retention (EPR) effect for anticancer nanomedicine drug targeting. InCancer nanotechnology: Methods and protocols, Humana Press, Totowa, NJ, 2010 Jan 25, pp. 25–37.
[54] W.H. De Jong, P.J. Borm, Drug delivery and nanoparticles: applications and hazards, Int. J. Nanomed. 3 (2) (2008 Dec 1) 133–149.
[55] W. Ying, The nose may help the brain: Intranasal drug delivery for treating neurological diseases. Future, Neurology 3 (1) (2007 Dec 13) 1–4.
[56] Y. Fan, M. Chen, J. Zhang, P. Maincent, X. Xia, W. Wu, Updated progress of nanocarrier-based intranasal drug delivery systems for treatment of brain diseases, Crit. Rev. ™ Ther. Drug Carr. Syst. 35 (2018) 5.
[57] S. Dighe, S. Jog, M. Momin, S. Sawarkar, A. Omri, Intranasal drug delivery by nanotechnology: advances in and challenges for Alzheimer's disease management, Pharmaceutics 16 (1) (2023 Dec 29) 58.
[58] W.M. Pardridge, Drug transport across the blood–brain barrier, J. Cereb. blood Flow. & Metab. 32 (11) (2012 Nov) 1959–1972.
[59] M.E. Meredith, T.S. Salameh, W.A. Banks, Intranasal delivery of proteins and peptides in the treatment of neurodegenerative diseases, AAPS J. 17 (2015 Jul) 780–787.
[60] R. Boyuklieva, B. Pilicheva, Micro-and nanosized carriers for nose-to-brain drug delivery in neurodegenerative disorders, Biomedicines 10 (7) (2022 Jul 14) 1706.
[61] R.G. Thorne, G.J. Pronk, V. Padmanabhan, W.H. Frey Ii, 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) (2004 Jan 1) 481–496.
[62] T.P. Crowe, M.H. Greenlee, A.G. Kanthasamy, W.H. Hsu, Mechanism of intranasal drug delivery directly to the brain, Life Sci. 195 (2018 Feb 15) 44–52.
[63] S. Soni, R.K. Ruhela, B. Medhi, Nanomedicine in central nervous system (CNS) disorders: a present and future prospective, Adv. Pharm. Bull. 6 (3) (2016 Sep) 319.
[64] S.V. Dhuria, L.R. Hanson, W.H. Frey II, Intranasal delivery to the central nervous system: mechanisms and experimental considerations, J. Pharm. Sci. 99 (4) (2010 Apr 1) 1654–1673.
[65] K. Kashyap, R. Shukla, Drug delivery and targeting to the brain through nasal route: mechanisms, applications and challenges, Curr. Drug Deliv. 16 (10) (2019 Dec 1) 887–901.
[66] Y.B. Zhang, D. Xu, L. Bai, Y.M. Zhou, H. Zhang, Y.L. Cui, A review of non-invasive drug delivery through respiratory routes, Pharmaceutics 14 (9) (2022 Sep 19) 1974.
[67] T.P. Crowe, M.H. Greenlee, A.G. Kanthasamy, W.H. Hsu, Mechanism of intranasal drug delivery directly to the brain, Life Sci. 195 (2018 Feb 15) 44–52.
[68] M. Nair, R.D. Jayant, A. Kaushik, V. Sagar, Getting into the brain: Potential of nanotechnology in the management of NeuroAIDS, Adv. Drug Deliv. Rev. 103 (2016 Aug 1) 202–217.
[69] G.A. Silva, Nanotechnology approaches for the regeneration and neuroprotection of the central nervous system, Surg. Neurol. 63 (4) (2005 Apr 1) 301–306.
[70] G. Unnikrishnan, A. Joy, M. Megha, E. Kolanthai, M. Senthilkumar, Exploration of inorganic nanoparticles for revolutionary drug delivery applications: a critical review, Discov. Nano 18 (1) (2023 Dec 19) 157.
[71] S. Narayana, B.J. Gowda, U. Hani, S.S. Shimu, K. Paul, A. Das, S. Ashique, M. G. Ahmed, M.A. Tarighat, G. Abdi, Inorganic nanoparticle-based treatment approaches for colorectal cancer: recent advancements and challenges, J. Nanobiotechnol. 22 (1) (2024 Jul 19) 427.0.
[72] M.C. Chiang, Y.P. Yang, C.J. Nicol, C.J. Wang, Gold nanoparticles in neurological diseases: A review of neuroprotection, Int. J. Mol. Sci. 25 (4) (2024 Feb 17) 2360.
[73] P.C. Silveira, M.S. Rodrigues, D.P. Gelain, J. de Oliveira, Gold nanoparticles application to the treatment of brain dysfunctions related to metabolic diseases: Evidence from experimental studies, Metab. Brain Dis. 38 (1) (2023 Jan) 123–135.
[74] C. Paviolo, P.R. Stoddart, Gold nanoparticles for modulating neuronal behavior, Nanomaterials 7 (4) (2017 Apr 24) 92.
[75] J. Affrald, S. Narayan, Gold/4-aminopyridine mucoadhesive chitosan nanocomposites as promising nasal drug delivery system for neuroprotection–An ex vivo investigation. Emergent, Materials (2024 Jun 25) 1–25.
[76] E. Gallardo-Toledo, A. Tapia-Arellano, F. Celis, T. Sinai, M. Campos, M.J. Kogan, A.C. Sintov, Intranasal administration of gold nanoparticles designed to target the central nervous system: fabrication and comparison between nanospheres and nanoprisms, Int. J. Pharm. 590 (2020 Nov 30) 119957.
[77] H.F. Salem, R.M. Kharshoum, H.A. Abou-Taleb, D.M. Naguib, Brain targeting of resveratrol through intranasal lipid vesicles labelled with gold nanoparticles: in vivo evaluation and bioaccumulation investigation using computed tomography and histopathological examination, J. Drug Target. 27 (10) (2019 Nov 26) 1127–1134.
[78] A. Vashist, P. Manickam, A.D. Raymond, A.Y. Arias, N. Kolishetti, A. Vashist, E. Arias, M. Nair, Recent advances in nanotherapeutics for neurological disorders, ACS Appl. Bio Mater. 6 (7) (2023 Jun 27) 2614–2621.
[79] Z. Asefy, S. Hoseinnejhad, Z. Ceferov, Nanoparticles approaches in neurodegenerative diseases diagnosis and treatment, Neurol. Sci. 42 (7) (2021 Jul) 2653–2660.
[80] A. Waris, A. Ali, A.U. Khan, M. Asim, D. Zamel, K. Fatima, A. Raziq, M.A. Khan, N. Akbar, A. Baset, M.A. Abourehab, Applications of various types of nanomaterials for the treatment of neurological disorders, Nanomaterials 12 (13) (2022 Jun 22) 2140.
[81] D.E. Nayab, F.U. Din, H. Ali, W.A. Kausar, S. Urooj, M. Zafar, I. Khan, K. Shabbir, G.M. Khan, Nano biomaterials based strategies for enhanced brain targeting in the treatment of neurodegenerative diseases: an up-to-date perspective, J. Nanobiotechnol. 21 (1) (2023 Dec 13) 477.
[82] S. Seino, H. Ikehata, M. Tanabe, T. Umeda, T. Tomiyama, A. Tanaka, T. Furubayashi, T. Sakane, T. Kiwa, M. Washino, K. Nomura, Investigating the efficacy of nasal administration for delivering magnetic nanoparticles into the brain for magnetic particle imaging, J. Control. Release 367 (2024 Mar 1) 515–521.
[83] S. Simorgh, Z. Bagher, M. Farhadi, S.K. Kamrava, M.E. Boroujeni, Z. Namjoo, F. Q. Hour, S. Moradi, R. Alizadeh, Magnetic targeting of human olfactory mucosa stem cells following intranasal administration: a novel approach to Parkinson's disease treatment, Mol. Neurobiol. 58 (2021 Aug) 3835–3847.
[84] H. Abbas, H. Refai, N. El Sayed, L.A. Rashed, M.R. Mousa, M. Zewail, Superparamagnetic iron oxide loaded chitosan coated bilosomes for magnetic nose to brain targeting of resveratrol, Int. J. Pharm. 610 (2021 Dec 15) 121244.
[85] J. Aparicio-Blanco, C. Pucci, D. De Pasquale, A. Marino, D. Debellis, G. Ciofani, Development and characterization of lipid nanocapsules loaded with iron oxide nanoparticles for magnetic targeting to the blood–brain barrier, Drug Deliv. Transl. Res. (2024 May 13) 1–8.
[86] A.Y. Estevez, J.S. Erlichman, The potential of cerium oxide nanoparticles (nanoceria) for neurodegenerative disease therapy, Nanomedicine 9 (10) (2014 Jul 1) 1437–1440.
[87] A. Vashist, P. Manickam, A.D. Raymond, A.Y. Arias, N. Kolishetti, A. Vashist, E. Arias, M. Nair, Recent advances in nanotherapeutics for neurological disorders, ACS Appl. Bio Mater. 6 (7) (2023 Jun 27) 2614–2621.
[88] Mohammad, U.A. Khan, M.H. Warsi, H.M. Alkreathy, S. Karim, G.K. Jain, A. Ali, Intranasal cerium oxide nanoparticles improves locomotor activity and reduces oxidative stress and neuroinflammation in haloperidol-induced parkinsonism in rats, Front. Pharmacol. 14 (2023 May 30) 1188470.
[89] S.M. Danish, A. Gupta, U.A. Khan, N. Hasan, F.J. Ahmad, M.H. Warsi, A.M. Ali, A. Zafar, G.K. Jain, Intranasal cerium oxide nanoparticles ameliorate cognitive function in rats with Alzheimer's via anti-oxidative pathway, Pharmaceutics 14 (4) (2022 Mar 30) 756.
[90] S. Naahidi, M. Jafari, F. Edalat, K. Raymond, A. Khademhosseini, P. Chen, Biocompatibility of engineered nanoparticles for drug delivery, J. Control. Release 166 (2) (2013 Mar 10) 182–194.

[91] D. Vllasaliu, R. Exposito-Harris, A. Heras, L. Casettari, M. Garnett, L. Illum, S. Stolnik, Tight junction modulation by chitosan nanoparticles: comparison with chitosan solution, Int. J. Pharm. 400 (1-2) (2010 Nov 15) 183–193.
[92] L. Jiang, L. Gao, X. Wang, L. Tang, J. Ma, The application of mucoadhesive polymers in nasal drug delivery, Drug Dev. Ind. Pharm. 36 (3) (2010 Mar 1) 323–336.
[93] M.J. Mitchell, M.M. Billingsley, R.M. Haley, M.E. Wechsler, N.A. Peppas, R. Langer, Engineering precision nanoparticles for drug delivery, Nat. Rev. Drug Discov. 20 (2) (2021 Feb) 101–124.
[94] Y. Garg, M. Kumar, G. Sharma, O.P. Katare, S. Chopra, A. Bhatia, Systematic designing and optimization of polymeric nanoparticles using central composite design: a novel approach for nose-to-brain delivery of donepezil hydrochloride, J. Clust. Sci. 35 (4) (2024 Apr) 1007–1019.
[95] A. Sonawane, G. Jawale, N. Devhadrao, A. Bansode, J. Lokhande, D. Kherade, P. Sathe, N. Deshmukh, G. Dama, H. Tare, Formulation And Development Of Mucoadhesive Nasal Drug Delivery Of Ropinirol Hcl For Brain Targeting, Int J. Appl. Pharm. 15 (5) (2023) 325–332.
[96] M.Z. Ahmad, A.H. Sabri, Q.K. Anjani, J. Domínguez-Robles, N. Abdul Latip, K. A. Hamid, Design and development of levodopa loaded polymeric nanoparticles for intranasal delivery, Pharmaceuticals 15 (3) (2022 Mar 18) 370.
[97] L. Battaglia, P.P. Panciani, E. Muntoni, M.T. Capucchio, E. Biasibetti, P. De Bonis, S. Mioletti, M. Fontanella, S. Swaminathan, Lipid nanoparticles for intranasal administration: application to nose-to-brain delivery, Expert Opin. Drug Deliv. 15 (4) (2018 Apr 3) 369–378.
[98] H.P. Patel, A.V. Vasandia, R. Jha, B.V. Desai, D.T. Desai, P.P. Dedhiya, B.A. Vyas, F.A. Maulvi, Intranasal delivery of doxepin: enhancing brain targeting efficiency utilizing nanostructured lipid carriers for a biopharmaceutics drug disposition classification system class-I drug, Pharm. Dev. Technol. 29 (6) (2024 Jul 2) 639–647.
[99] D.M. Hassan, A.H. El-Kamel, E.A. Allam, B.A. Bakr, A.A. Ashour, Chitosan-coated nanostructured lipid carriers for effective brain delivery of Tanshinone IIA in Parkinson's disease: interplay between nuclear factor-kappa β and cathepsin B, Drug Deliv. Transl. Res. 14 (2) (2024 Feb) 400–417.
[100] A. Ganeshpurkar, A. Ganeshpurkar, A. Agnihotri, V. Pandey, N. Vishwakarma, D. Bansal, N. Dubey, Chondroitin Sulfate Surface Engineered Docetaxel-Loaded Liposomes for Tumor Targeting: Design, Development, and Characterization. InProceedings of All India Seminar on Biomedical Engineering 2012 (AISOBE 2012), Springer, India, 2013, pp. 77–82.
[101] M.R. Micheli, R. Bova, A. Magini, M. Polidoro, C. Emiliani, Lipid-based nanocarriers for CNS-targeted drug delivery, Recent Pat. CNS Drug Discov. (Discontin.) 7 (1) (2012 Apr 1) 71–86.
[102] J. Xie, Z. Shen, Y. Anraku, K. Kataoka, X. Chen, Nanomaterial-based blood-brain-barrier (BBB) crossing strategies, Biomaterials 224 (2019 Dec 1) 119491.
[103] D. Lee, A.M. Shen, M. Shah, O.B. Garbuzenko, T. Minko, Vivo Evaluation of Nose-to-Brain Delivery of Liposomal Donepezil, Memantine, and BACE-1 siRNA for Alzheimer's Disease Therapy, Int. J. Mol. Sci. 25 (19) (2024 Sep 26) 10357.
[104] K.B. Khot, S. DS, G. Gopan, N.S. Deshpande, P. Shastry, A. Bandiwadekar, J. Jose, Enhancing selegiline hydrochloride efficacy: Box Behnken-optimized liposomal delivery via intranasal route for Parkinson's disease intervention, J. Liposome Res. (2024 Apr 8) 1–8.
[105] R.D. Jayant, V.S. Atluri, M. Agudelo, V. Sagar, A. Kaushik, M. Nair, Sustained-release nanoART formulation for the treatment of neuroAIDS, Int. J. Nanomed. (2015 Feb 4) 1077–1093.
[106] A. Kaushik, R.D. Jayant, M. Nair, Advancements in nano-enabled therapeutics for neuroHIV management, Int. J. Nanomed. (2016 Sep 1) 4317–4325.
[107] I. Neamtu, A.G. Rusu, A. Diaconu, L.E. Nita, A.P. Chiriac, Basic concepts and recent advances in nanogels as carriers for medical applications, Drug Deliv. 24 (1) (2017 Jan 1) 539–557.
[108] K.S. Soni, S.S. Desale, T.K. Bronich, Nanogels: An overview of properties, biomedical applications and obstacles to clinical translation, J. Control. Release 240 (2016 Oct 28) 109–126.
[109] Y. Kim, M. Thapa, D.H. Hua, K.O. Chang, Biodegradable nanogels for oral delivery of interferon for norovirus infection, Antivir. Res. 89 (2) (2011 Feb 1) 165–173.
[110] A.J. Amkar, B.R. Rane, A.S. Jain, Development and Evaluation of Nanosuspension Loaded Nanogel of Nortriptyline HCl for Brain Delivery, Eng. Proc. 56 (1) (2023 Oct 26) 58.
[111] Y.B. Chen, T. Qiao, Y.Q. Wang, Y.L. Cui, Q.S. Wang, Hydrogen bond-enhanced nanogel delivery system for potential intranasal therapy of Parkinson's disease, Mater. Des. 219 (2022 Jul 1) 110741.
[112] M. Jaiswal, R. Dudhe, P.K. Sharma, Nanoemulsion: an advanced mode of drug delivery system, 3 Biotech 5 (2015 Apr) 123–127.
[113] M. Jaiswal, R. Dudhe, P.K. Sharma, Nanoemulsion: an advanced mode of drug delivery system, 3 Biotech 5 (2015 Apr) 123–127.
[114] B. Chatterjee, B. Gorain, K. Mohananaidu, P. Sengupta, U.K. Mandal, H. Choudhury, Targeted drug delivery to the brain via intranasal nanoemulsion: Available proof of concept and existing challenges, Int. J. Pharm. 565 (2019 Jun 30) 258–268.
[115] M. Kosicek, S. Kirsch, R. Bene, Z. Trkanjec, M. Titlic, L. Bindila, J. Peter-Katalinic, S. Hecimovic, Nano-HPLC–MS analysis of phospholipids in cerebrospinal fluid of Alzheimer's disease patients—a pilot study, Anal. Bioanal. Chem. 398 (2010 Dec) 2929–2937.
[116] S. Zainol, M. Basri, H.B. Basri, A.F. Shamsuddin, S.S. Abdul-Gani, R.A. Karjiban, E. Abdul-Malek, Formulation optimization of a palm-based nanoemulsion system containing levodopa, Int. J. Mol. Sci. 13 (10) (2012 Oct 11) 13049–13064.
[117] A. Azeem, S. Talegaonkar, L.M. Negi, F.J. Ahmad, R.K. Khar, Z. Iqbal, Oil based nanocarrier system for transdermal delivery of ropinirole: a mechanistic, pharmacokinetic and biochemical investigation, Int. J. Pharm. 422 (1-2) (2012 Jan 17) 436–444.
[118] N.D. Sawant, P.A. Tatke, N.D. Desai, Systematic approach in the development of chitosan functionalized iloperidone nanoemulsions for transnasal delivery, in vitro and in vivo studies, AAPS PharmSciTech 25 (8) (2024 Oct 21) 247.
[119] M. Imran, M. Almehmadi, A.A. Alsaiari, M. Kamal, M.K. Alshammari, M. O. Alzahrani, F.K. Almaysari, A.O. Alzahrani, A.F. Elkerdasy, S.K. Singh, Intranasal delivery of a silymarin loaded microemulsion for the effective treatment of Parkinson's disease in rats: formulation, optimization, characterization, and in vivo evaluation, Pharmaceutics 15 (2) (2023 Feb 12) 618.
[120] D. Ag Seleci, M. Seleci, J.-G. Walter, F. Stahl, T. Scheper, Niosomes as nanoparticular drug carriers: fundamentals and recent applications, J. Nanomater 2016 (2016) 7372306.
[121] A.R. Al Jayoush, H.A. Hassan, H. Asiri, M. Jafar, R. Saeed, R. Harati, M. Haider, Niosomes for nose-to-brain delivery: a non-invasive versatile carrier system for drug delivery in neurodegenerative diseases, J. Drug Deliv. Sci. Technol. 89 (2023 Nov 1) 105007.
[122] P. Kulkarni, D. Rawtani, T. Barot, Design, development and in-vitro/in-vivo evaluation of intranasally delivered Rivastigmine and N-Acetyl Cysteine loaded bifunctional niosomes for applications in combinative treatment of Alzheimer's disease, Eur. J. Pharm. Biopharm. 163 (2021 Jun 1) 1–5.
[123] V.G. Sita, D. Jadhav, P. Vavia, Niosomes for nose-to-brain delivery of bromocriptine: Formulation development, efficacy evaluation and toxicity profiling, J. Drug Deliv. Sci. Technol. 58 (2020 Aug 1) 101791.
[124] D.A. Tomalia, H. Baker, J. Dewald, A new class of polymers: starburst-dendritic macromolecules, Polym. J. Soc. Polym. Sci. 34 (5-2) (2002) 132–147.
[125] D.A. Tomalia, The dendritic state, Mater. Today 8 (3) (2005 Mar 1) 34–46.
[126] S. Bayda, M. Adeel, T. Tuccinardi, M. Cordani, F. Rizzolio, The history of nanoscience and nanotechnology: from chemical–physical applications to nanomedicine, Molecules 25 (1) (2019 Dec 27) 112.
[127] D.A. Bölükbas, S. Datz, C. Meyer-Schwickerath, C. Morrone, A. Doryab, D. Gößl, M. Vreka, L. Yang, C. Argyo, S.H. van Rijt, M. Lindner, Organ-restricted vascular delivery of nanoparticles for lung cancer therapy, Adv. Ther. 3 (7) (2020 Jul) 2000017.
[128] S. Zawadzki, Á. Martín-Serrano, E. Okła, M. Kędzierska, S. Garcia-Gallego, P. O. López, F.J. de la Mata, S. Michlewska, T. Makowski, M. Ionov, E. Pędziwiatr-Werbicka, Synthesis and biophysical evaluation of carbosilane dendrimers as therapeutic siRNA carriers, Sci. Rep. 14 (1) (2024 Jan 18) 1615.
[129] R.C. Sahu, T. Suthar, D. Kumar, P. Singh, A.K. Datusalia, K. Jain, Novel ligand conjugated poly (propylene imine) dendrimers for brain targeted delivery of tacrine hydrochloride, J. Drug Deliv. Sci. Technol. 92 (2024 Feb 1) 105336.
[130] V.A. Duong, T.T. Nguyen, H.J. Maeng, Recent advances in intranasal liposomes for drug, gene, and vaccine delivery, Pharmaceutics 15 (1) (2023 Jan 6) 207.
[131] S.U. Islam, A. Shehzad, M.B. Ahmed, Y.S. Lee, Intranasal delivery of nanoformulations: a potential way of treatment for neurological disorders, Molecules 25 (8) (2020 Apr 21) 1929.
[132] J.K. Patra, G. Das, L.F. Fraceto, E.V. Campos, M.D. Rodriguez-Torres, L.S. Acosta-Torres, L.A. Diaz-Torres, R. Grillo, M.K. Swamy, S. Sharma, S. Habtemariam, Nano based drug delivery systems: recent developments and future prospects, J. Nanobiotechnol. 16 (1) (2018 Sep 19) 71.
[133] H.M. Aboud, M.H. El Komy, A.A. Ali, S.F. El Menshawe, A. Abd Elbary, Development, optimization, and evaluation of carvedilol-loaded solid lipid nanoparticles for intranasal drug delivery, AAPS pharmscitech 17 (6) (2016 Dec) 1353–1365.
[134] A.K. Lorenzett, V.A. Lima, C.O. Fonseca, R.M. Mainardes, Nanoemulsions and microemulsions for intranasal drug delivery: a bibliometric analysis and emerging trends (2004–2024), Pharmaceutics 17 (9) (2025 Aug 25) 1104.
[135] S.U. Islam, A. Shehzad, M.B. Ahmed, Y.S. Lee, Intranasal delivery of nanoformulations: a potential way of treatment for neurological disorders, Molecules 25 (8) (2020 Apr 21) 1929.
[136] S. Mignani, X. Shi, A. Karpus, J.P. Majoral, Non-invasive intranasal administration route directly to the brain using dendrimer nanoplatforms: an opportunity to develop new CNS drugs, Eur. J. Med. Chem. 209 (2021 Jan 1) 112905.
[137] M.Z. Ahmad, A.H. Sabri, Q.K. Anjani, J. Domínguez-Robles, N. Abdul Latip, K. A. Hamid, Design and development of levodopa loaded polymeric nanoparticles for intranasal delivery, Pharmaceuticals 15 (3) (2022 Mar 18) 370.
[138] B. Nabi, S. Rehman, M. Fazil, S. Khan, S. Baboota, J. Ali, Riluzole-loaded nanoparticles to alleviate the symptoms of neurological disorders by attenuating oxidative stress, Drug Dev. Ind. Pharm. 46 (3) (2020 Mar 3) 471–483.
[139] M. Yasir, I. Chauhan, A. Zafar, M. Verma, K.M. Noorulla, A.J. Tura, N. K. Alruwaili, M.J. Haji, D. Puri, W.G. Gobena, D.D. Dalecha, Buspirone loaded solid lipid nanoparticles for amplification of nose to brain efficacy: formulation development, optimization by Box-Behnken design, in-vitro characterization and in-vivo biological evaluation, J. Drug Deliv. Sci. Technol. 61 (2021 Feb 1) 102164.
[140] R. Li, F. Lu, X. Sun, L. He, H. Duan, W. Peng, C. Wu, Development and in vivo evaluation of hydroxy-α-sanshool intranasal liposomes as a potential remedial treatment for Alzheimer's disease, Int. J. Nanomed. (2022 Jan 11) 185–201.
[141] D. Lee, A.M. Shen, O.B. Garbuzenko, T. Minko, Liposomal formulations of anti-Alzheimer drugs and siRNA for nose-to-brain delivery: design, safety and efficacy in vitro. The, AAPS J. 26 (5) (2024 Sep 4) 99.

[142] Y. Tan, Y. Liu, Y. Liu, R. Ma, J. Luo, H. Hong, X. Chen, S. Wang, C. Liu, Y. Zhang, T. Chen, Rational design of thermosensitive hydrogel to deliver nanocrystals with intranasal administration for brain targeting in Parkinson's disease, Research (2021 Nov 19).
[143] Y. Song, X. Wang, X. Wang, J. Wang, Q. Hao, J. Hao, X. Hou, Osthole-loaded nanoemulsion enhances brain target in the treatment of Alzheimer's disease via intranasal administration, Oxid. Med. Cell. Longev. 2021 (1) (2021) 8844455.
[144] A.B. Nair, S. Chaudhary, S. Jacob, D. Patel, P. Shinu, H. Shah, A. Chaudhary, B. Aldhubiab, R.M. Almuqbil, A.S. Alnaim, F. Alqattan, Intranasal administration of dolutegravir-loaded nanoemulsion-based in situ gel for enhanced bioavailability and direct brain targeting, Gels 9 (2) (2023 Feb 3) 130.
[145] A.S. Tulbah, M.H. Elkomy, R.M. Zaki, H.M. Eid, E.M. Eissa, A.A. Ali, H.A. Yassin, B.N. Aldosari, I.A. Naguib, A.H. Hassan, Novel nasal niosomes loaded with lacosamide and coated with chitosan: a possible pathway to target the brain to control partial-onset seizures, Int. J. Pharm. X 6 (2023 Dec 15) 100206.
[146] V.G. Sita, D. Jadhav, P. Vavia, Niosomes for nose-to-brain delivery of bromocriptine: formulation development, efficacy evaluation and toxicity profiling, J. Drug Deliv. Sci. Technol. 58 (2020 Aug 1) 101791.
[147] H. Li, X. Shen, B. Zhang, Y. Li, C. Alexander, P. Harvey, Z. Zhu, Brain-targeted intranasal delivery of biologics: a perspective for Alzheimer's disease treatment, RSC Pharm. (2025).
[148] M.M. Miyake, B.S. Bleier, The blood-brain barrier and nasal drug delivery to the central nervous system, Am. J. Rhinol. Allergy 29 (2) (2015 Mar) 124–127.
[149] Y.B. Zhang, D. Xu, L. Bai, Y.M. Zhou, H. Zhang, Y.L. Cui, A review of non-invasive drug delivery through respiratory routes, Pharmaceutics 14 (9) (2022 Sep 19) 1974.
[150] M.J. Ruigrok, E.C. de Lange, Emerging insights for translational pharmacokinetic and pharmacokinetic-pharmacodynamic studies: towards prediction of nose-to-brain transport in humans, AAPS J. 17 (3) (2015 May) 493–505.
[151] S.H. Jeong, J.H. Jang, Y.B. Lee, Drug delivery to the brain via the nasal route of administration: exploration of key targets and major consideration factors, J. Pharm. Investig. 53 (1) (2023 Jan) 119–152.
[152] K. Mitusova, O.O. Peltek, T.E. Karpov, A.R. Muslimov, M.V. Zyuzin, A.S. Timin, Overcoming the blood–brain barrier for the therapy of malignant brain tumor: current status and prospects of drug delivery approaches, J. Nanobiotechnol. 20 (1) (2022 Sep 15) 412.