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INSIGHTS OF NOSE TO BRAIN DELIVERY IN TREATING PARKINSON'S DISEASE: A SYSTEMATIC REVIEW

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ABSTRACT
Background: In Parkinson's disease (PD), a complicated neurodegenerative ailment, neurons in the substantia nigra that produce dopamine are lost, resulting in an insufficiency of the neurotransmitter that is essential for the regulation of voluntary and smooth muscular movements. This review focuses on the obstacle triggering the effectiveness of traditional PD treatments, which is the blood-brain barrier (BBB), which prevents some therapeutic medicines from reaching the brain. It encompasses the potential strategy of nose-to-brain administration by innovative approaches, including nanoparticles, liposomes, dendrimers, and cell-based carriers, directly delivering the drugs from nose to brain. **Methods:** The methodology involved examining the characteristics, advantages, applications, and challenges of various nanoparticles like SLNs, Nanoliposomes, Quantum dots, dendrimers, etc., through meticulous analysis of articles including from PubMed (5), ScienceDirect (5), Bentham Science (4) and Scopus databases (5). **Conclusion:** The review concludes by emphasizing the potential applications of nanoparticles in circumventing the problems encountered with traditional methods of drug administration in treating PD. This detailed study brings to light the applications and the challenges that need to be faced in utilizing nanoparticles for nose-to-brain delivery. Attention is directed towards the enlightenment of advanced carriers that target specific brain regions via the olfactory and trigeminal routes. The drug directly reaches the brain, bypassing BBB.

INTRODUCTION

The progressive neurological ailment known as Parkinson's disease (PD) affects the nervous system's ability to control movement [1]. Due to injury to or death of nerve cells (neurons) in certain brain regions, a person may experience difficulties with movement, tremors, stiffness in the body's limbs or trunk, or decreased balance [2]. People may find moving, speaking, or

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performing other basic duties more difficult as their symptoms worsen [3].

Types of Parkinson's disease

There are two main types:

a. **Idiopathic Parkinson's disease:** It typically occurs at later periods in life and progresses slowly [4].

b. **Secondary parkinsonism/Parkinson-plus syndrome:** It is a complex disorder caused by underlying conditions such as brain injuries and neurological disorders [5].

Pathophysiology of Parkinson's disease

- Dopaminergic neuronal degeneration [6].
- Alpha-synuclein aggregation [7].
- Mitochondrial dysfunction [8].
- Inflammation and immune response [9].
- Neurotransmitter imbalance [10].
- Impaired brain circuitry [11].
- Non-motor symptoms [12].
- Clinical manifestation [13].
- Impaired protein degradation [14].
- Genetic factors [15].

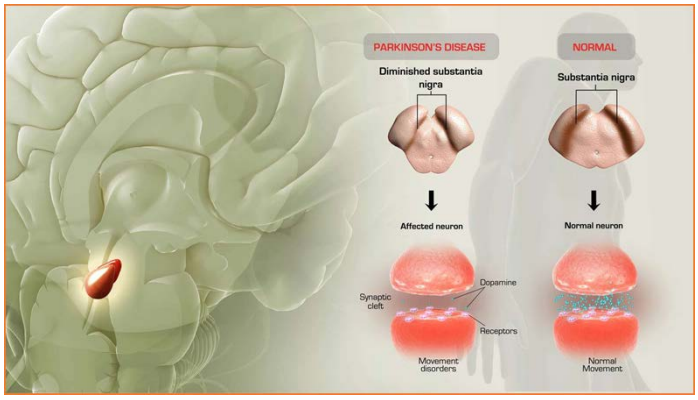

Figure 1: Schematic illustration of neuron degeneration in PD

The degeneration of neurons is seen in Figure 1. Nerve cell death and the loss of norepinephrine-producing nerve terminals occur in this condition in the substantia nigra, a region in the center of the brain that supplies the basal ganglia with dopamine, an important chemical messenger of the sympathetic nervous system (SNS), which regulates several bodily processes including heart rate and blood pressure and, as a result, can impair a wide variety of motor and non-motor actions [16]. This degeneration causes a significant reduction in dopamine levels in the striatum, leading to motor symptoms of Parkinson's disease (PD), such as tremors, rigidity, and bradykinesia. The underlying mechanisms include oxidative stress, mitochondrial dysfunction, and the accumulation of misfolded proteins like alpha-synuclein, which form Lewy bodies. Genetic mutations in genes such as LRRK2, PINK1, and Parkin also contribute to the vulnerability of dopaminergic neurons. Additionally, neuroinflammation and impaired protein clearance further exacerbate neuronal damage. [17].

Generally, α-synuclein is a protein crucial for synaptic function. However, its misfolding and aggregation result in the formation of Lewy bodies and Lewy neurites, which are toxic to neurons. This aggregation disrupts various cellular processes, including mitochondrial function, protein degradation pathways, and synaptic transmission [18].

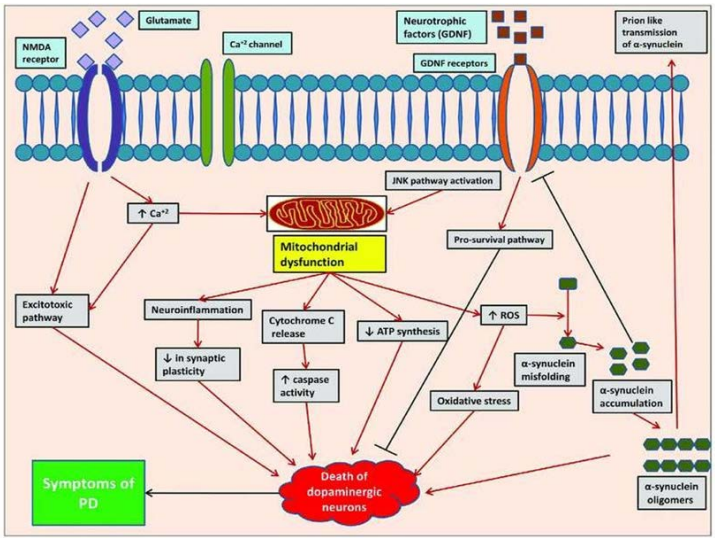

Figure 2: The causes of PD

Figure 2 describes the most prominent pathological features of PD. Degeneration of basal ganglia cells impacts neurons in the substantia nigra area that secrete dopamine, resulting in Parkinson's disease. In PD, an alpha-synuclein protein molecule becomes misfolded and clumped into each other. These clumps cannot be removed by the cell, leading to Lewy bodies forming that become cytotoxic and damage the neurons [19-20]. When astrocytes (star-shaped cells) die, and microglia (another kind of glial cell) proliferate in the substantia nigra, neurons are lost [21]. The medulla and olfactory bulb are the first sites of PD, which then spreads to the midbrain and the substantia nigra [22]. When injury or degeneration to neurons spreads from the medullary area to the substantia nigra region, movement problems usually become apparent [23].

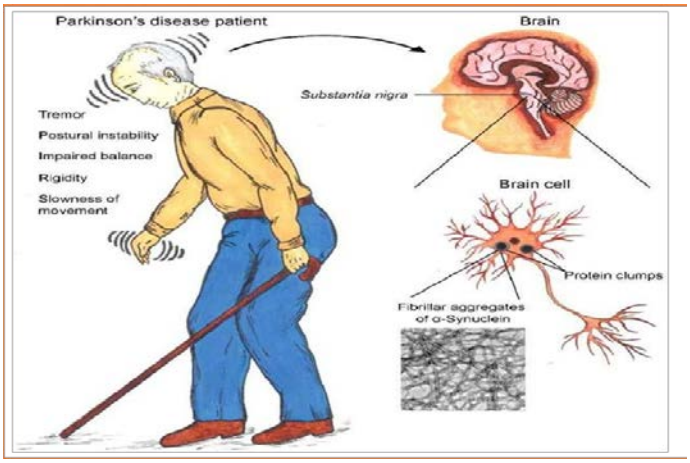

Figure 3: Schematic representations of symptoms of PD

Figure 3 depicts some of the symptoms of PD. One of the hallmarks of this disorder is a Parkinsonian gait, which manifests itself in a variety of ways, including a diminished ability to swing one or both arms, a propensity to lean forward, and short, quick steps that resemble a sprint (a phenomenon known as festination) [24-25]. They also cannot get moving (start reluctance) or stop moving altogether when walking [26].

Indeed, here are some common symptoms [27-35]:

Tremors: Involuntary movements of the body [27].

Bradykinesia: Slowness of movement [28].

Rigidity: Increased muscle stiffness and resistance to passive movement [29].

Postural instability: Impaired ability to maintain an upright and balance [30].

Akinesia and freezing: Loss of the ability to initiate voluntary movements [31].

Micrographia: Abnormally small and cramped handwriting [32].

Dysarthria: Speech difficulty [33].

Dysphagia: Swallowing difficulty [34].

Symptoms that do not involve movement include emotional distress, nervousness, changes in cognition (such as memory and reasoning issues), insomnia, constipation, and a loss of smell (anosmia), among others [35].

Risk factors of Parkinson's disease

Age	Genetics
Family history	Gender
Pesticide and herbicide exposure	Industrial chemicals
Head trauma	Smoking
Poor gut health	Lifestyle

Current treatment options for PD

- Levodopa (in combination with carbidopa) is the most effectively used drug; in addition to this, dopamine agonists like Pramipexole, MAO-B inhibitors like Selegiline, COMT inhibitors like Entecapone, NMDA receptor antagonists like Memantine are used in treating PD [36-38].
- **Deep brain stimulation (DBS):** This has shown benefits in individuals who have advanced PD and do not well respond to medication; physical and occupational therapy, which focuses on improving mobility, balance, and coordination; speech therapy, which manages speech and swallowing difficulties that often arise in PD [39].

Routes of Drug Administration for an Existing Therapy and Their Limitations

Oral/traditional route

The first choice of treatment for PD is the combination of levodopa and carbidopa tablets [40].

Limitations

It includes Drug passage by BBB, Low bioavailability, First-pass effect, and Limited targeting.

Non-traditional oral and buccal route

Compared to conventional oral formulations, extended-release formulations possess numerous advantages, such as reduced dosing frequency, smooth plasma drug concentrations, uniform drug release, reduced toxicity, and increased patient compliance [41]. The following are various unconventional formulations administered orally to treat PD.

- Orally disintegrating tablets (i.e., neuroactiva) [45].
- Buccal film containing levodopa [46].
- Others like lozenges (i.e., dopaguard) & sublingual drops (i.e., levostabil) [47].

Limitations

× Hydrophilic and large molecular drugs are not suitable.
× Enzymatic degradation & first-pass metabolism.
× Reduced degree of precision and targeting.

Transdermal route

In addition to advantages such as avoiding first-pass metabolism and improving patient adherence, this route also allows for easy dose retrieval by removing the patch at any time [48-49]. Rotigotine and selegline transdermal patches were used as alternatives [50].

Limitations

× Permeation of drugs through BBB might be restricted.
× Absorption & penetration capacity of drugs may be altered.

Injectable depot forming route

Biodegradable polymers and their matrices were employed in this route, encapsulating the drug in nanoparticles. The entire depot is injected into the body and releases the drug gradually over a prolonged time [51]. In contrast, non-invasive routes such as intranasal, buccal, sublingual, pulmonary, and transdermal delivery provide painless alternatives that bypass the gastrointestinal tract and first-pass metabolism, resulting in faster onset of action and improved patient compliance.

However, these methods face challenges such as limited absorption, variability in drug delivery due to individual anatomical differences, degradation by salivary enzymes, and potential irritation or damage to mucosal surfaces.

Limitations:

× Crossing of depot formulations through BBB may be challenging.
× Issues related to patient compliance and acceptance may be raised.
× Risk of tissue damage and infections may be propagated.

To overcome the limitations encountered by the above-mentioned existing routes and to enhance the site-specific activity of drugs used to treat PD [52]. Intranasal (IN) route has been chosen as it offers a direct path for certain drugs to reach the central nervous system and the brain, bypassing the BBB and potentially improving the treatment of neurodegenerative disorders [53]. Lipid-based nanoparticles, such as liposomes and solid lipid nanoparticles, encapsulate drugs to shield them from enzymatic degradation in the nasal cavity and liver.

These nanoparticles can cross the nasal mucosa and directly reach the brain, bypassing the blood-brain barrier (BBB) and avoiding first-pass hepatic metabolism. Similarly, nanoemulsions enhance drug solubility and stability, promoting efficient drug transport via the nasal route to the brain. This targeted delivery method improves therapeutic efficacy and minimizes systemic side effects, making it a promising approach for treating neurological disorders.

Intranasal route

It's a highway for nose-to-brain delivery. IN route is an excellent alternative for the drugs that possess the least oral bioavailability, for those drugs that get degraded in GIT or that irritate the gastric mucosa [54]. As it bypasses the hepatic metabolism, enhanced bioavailability with rapid onset of action can be achieved [55]. The drugs whose transportation into the brain and CSF is restricted due to the protective function of BBB can be administered in this route as it offers direct transport of drugs to the brain and escalating the drug transportation through olfactory, trigeminal pathways and mechanisms of these pathways shown in Figure 4 [56].

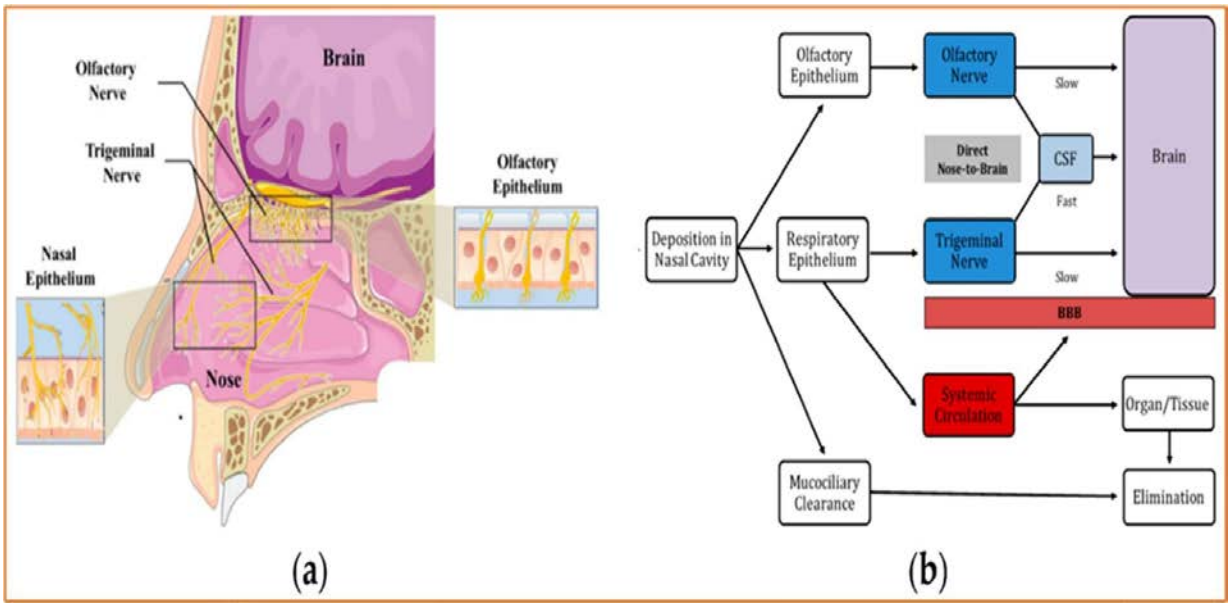

Figure 4: (a) Mechanism of drug transportation through nasal cavity; (b) Pathways of drug absorption

Pathways of drug delivery through IN route: IN delivery is a method of administering medications through the nasal cavity, and they are expected to be absorbed by four different routes [57-61].

1. An extra-neuronal route through olfactory neurons [58].
2. An intra-neuronal route by olfactory neuron endocytosis [59].
3. Through the supporting cells [60]
4. Through the tight junctions [61]

1. **An extra neuronal route through olfactory neurons:** An extra neuronal route through olfactory neurons allows drugs to bypass the typical neural signaling process and enter the central nervous system (CNS) or other parts of the brain via the olfactory system. This is the major pathway through which the drug is transported directly from the nose to the brain within approximately 30 minutes [63].
2. **An intraneuronal route by olfactory neuron endocytosis:** The intraneuronal route involves drug molecules being engulfed by olfactory neurons(endocytosis) and released into the olfactory bulb [64]. From there, the drug gets distributed to the various regions of the brain, and it may take several hours or days [65].
3. **Through the supporting cells:** It includes:
   a. **Olfactory pathway:** It is the primary route for nose-to-brain delivery and involves the following steps [66].
      i. **Drug reception**: In the nasal cavity, specialized olfactory sensory neurons detect drug molecules administered through the intranasal route. These neurons are equipped with olfactory receptors [67].
      ii. **Axonal projection**: Once stimulated, olfactory sensory neurons send drug molecules through the cribriform plate (a thin bony structure separating the nasal cavity from the brain), from which they enter the olfactory bulb in the brain [68].
      iii. **Olfactory bulb to brain**: The olfactory bulb provides direct access to the brain. Drug molecules reach brain regions, such as the olfactory cortex, hippocampus, and basal forebrain, without passing through the BBB [69].
   b. **Trigeminal Pathway:** The trigeminal nerve pathway is a secondary route for nose-to-brain delivery, and it involves the following steps [70].
      i. **Nerve activation**: The IN route activates the trigeminal nerve endings in the nasal mucosa [71].
      ii. **Intranasal transport**: Upon activation, signals are transmitted through the trigeminal nerve to the brainstem and regions such as the spinal trigeminal nucleus [72].
      iii. **Central nervous system penetration**: The trigeminal pathway allows molecules to reach the central nervous system, including the brainstem, thalamus, and cerebellum [73].
   c. **Systemic pathway:** Due to its rich vasculature, the nasal mucosa receives blood from maxillary, ophthalmic, and facial arteries [74].

Nose-to-brain delivery has gained attention as a potential strategy to overcome BBB and improve drug delivery to the brain. Upon intranasal administration, nanoparticles can traverse the nasal epithelium via transcellular or paracellular routes. Olfactory neurons in the olfactory epithelium provide a direct route to the brain by transporting nanoparticles along the olfactory nerve to the olfactory bulb. Similarly, the trigeminal nerve, which innervates the nasal cavity's respiratory region, can carry nanoparticles to the brainstem and other brain areas. These pathways bypass the blood-brain barrier, enabling direct delivery of therapeutic agents to the central nervous system. Cellular uptake mechanisms, including endocytosis and receptor-mediated transport, facilitate the internalization of nanoparticles into neurons and glial cells, thereby enhancing drug delivery efficiency and targeting specificity. While this approach is still under research and development, it holds promise for enhancing the treatment of PD and shown in Figure 5[75].

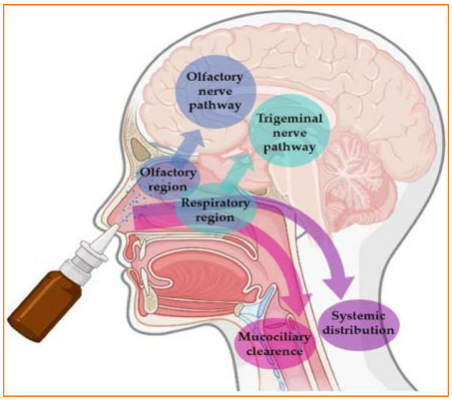

Figure 5: Schematic diagram of nose-to-brain delivery formulation

The nose provides a non-invasive and direct route, allowing the drugs to be targeted directly to the brain regions by olfactory and trigeminal routes without crossing the BBB. This route stands

beneficial to the drugs whose passage is inhibited by BBB and shows immediate action [76].

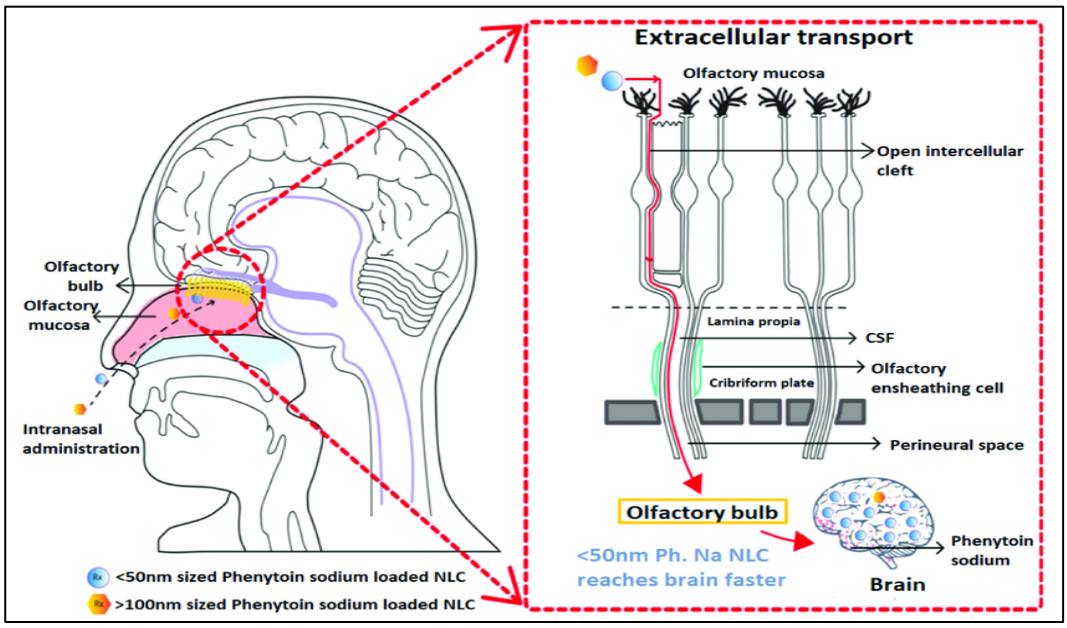

Figure 6: Illustration of nanoparticles reaching the brain via olfactory pathway

Nanoparticles reaching the brain through this pathway are a fascinating area of research in drug delivery. They offer a highway for therapeutic agents to bypass the BBB. Hence, these drug-enclosed nanoparticles reach the damaged regions of the brain directly and elucidate the necessary action, as shown in Figure 6 [77-78].

Advantages of nose-to-brain delivery

Précised targeting	Non-invasive
Minimized systemic exposure	Drug encapsulation
Targeted delivery	Increased bioavailability
Reduced side effects.	Continuous release
Combination therapies	Neuroprotective activity

Challenges encountered with nose-to-brain delivery

Despite gaining extensive attention towards novel drug delivery, nanoparticles often trigger some challenges for researchers, which need to be sorted out. Some of those are:

Limited drug absorption	Enzymatic degradation
Nasal toxicity	Mucociliary clearance.
Dose limitation	
Immune activation & inflammatory mediation	

The novel approach of nose-to-brain delivery has gained significant attention because it precisely delivers the therapeutic agents directly from the nasal cavity to the brain [79-80]. Advanced nanomaterials are used as potential carriers for nose-to-brain delivery due to their ability to enhance drug stability, improve bioavailability, and target specificity towards the brain regions [81]. Intranasal delivery has significantly improved the bioavailability of various drugs, especially those targeting the central nervous system. For instance, intranasal administration of sumatriptan for migraine treatment achieves a bioavailability of approximately 15-20%, compared to just 1-2% with oral administration. This enhancement is due to direct absorption through the nasal mucosa, bypassing the gastrointestinal tract and first-pass hepatic metabolism. Pharmacokinetic studies indicate that intranasal delivery can result in a faster onset of action and higher peak plasma concentrations than oral routes. For example, intranasal administration of diazepam for acute seizure clusters reaches peak plasma concentration within 10-15 minutes, significantly quicker than the 30-60 minutes observed with oral administration.

Nanoparticles have demonstrated significant potential in clinical settings, especially oncology and neurology. For instance, nanoparticle-based therapies like liposomal doxorubicin (Doxil) are approved and actively used in cancer treatment, offering improved targeting and reduced side effects. In neurology, nanoparticles employed in glioblastoma treatment have shown the capability to cross the blood-brain barrier and deliver drugs

directly to the brain, thereby enhancing therapeutic outcomes. Despite these promising developments, further data from ongoing human trials are essential to comprehend their long-term safety and efficacy fully

Table 1: Current status of animal and human trials conducted for nose-to-brain delivery of nanoparticles

Aspect	Animal Trials	Human Trials	Conducting Agency
Aim	Testing efficacy and safety in animal models (e.g., mice)	Evaluating safety and effectiveness in human patients with CNS-TB.	INST, Mohali
Method	Employing chitosan nano-aggregates to deliver TB drugs directly to the brain	Employing chitosan nano-aggregates to deliver TB drugs directly to the brain	INST, Mohali
Results	Marked decrease in bacterial counts and brain inflammation.	In the initial phases, aiming to validate animal trial results in a clinical setting.	INST, Mohali
Potential Applications	Addressing CNS-TB, brain infections, neurodegenerative diseases, brain tumors, and epilepsy.	Treating CNS-TB, with potential applications for other brain conditions in the future.	INST, Mohali
Challenges	Ensuring the method's safety and efficacy in animals.	Verifying the method's safety and efficacy in humans while navigating regulatory and ethical considerations.	INST, Mohali

Here are some of the nanomaterials utilized.

Lipid-based nanoparticles

LNPs are a class of nanoparticles containing lipids (fats) that can encapsulate various therapeutic agents, including drugs, nucleic acids, and proteins [82].

Solid lipid nanoparticles (SLNs): These comprise biocompatible lipids and can encapsulate hydrophobic and hydrophilic drugs [83].

Advantages

- ✓ Biodegradable and compatible
- ✓ Controlled drug release
- ✓ Targeted drug delivery

Safety profile: They exhibit good biocompatibility and low toxicity; however, long-term safety data remain limited.

Nanostructured lipid carriers (NLCs): Like SLNs, NLCs Comprise a lipid matrix and incorporate liquid lipids. This increases drug-loading capacity and enhances drug-release kinetics [84].

Advantages

Enhanced Solubility Protection BBB Penetration

Safety profile: They are generally well-tolerated with minimal toxicity. However, some studies have reported mild nasal irritation and inflammation.

Hybrid nanoparticles

Silica-coated nanoparticles: Core-shell structures with a silica outer layer provide stability and allow for drug loading [85].

Advantages

Improved stability Personalized therapeutics

Polymeric nanoparticles: They have gained significant interest for their ability to encapsulate various types of drugs and their capacity to overcome the obstacles posed by the BBB [86].

Examples like PLGA, PEG, nano gels, micelles, nanospheres, nanocapsules, and dendrimers exhibit remarkable potential in enhancing drug delivery to the brain. Due to their surface modification properties, these nanoparticles offer benefits like improved drug stability, prolonged action, and high drug loading capacity. Their applications extend to targeted therapies for neurological disorders and other medical conditions [87].

Advantages

Dose precision Multi-functionality

Carbon Nanotubes (CNTs): Multi-walled (MW) CNTs and single-walled (SW) CNTs have been investigated for intranasal approach for their remarkable properties [88].

Advantages

High drug-loading Nasal uptake

Safety profile: They have the potential for significant toxicity and inflammation, making them less favorable for clinical use.

Nanoliposomes are lipid vesicles that can encapsulate hydrophilic drugs within their aqueous core and hydrophobic drugs within their lipid bilayers [89]. There are different types of nanoliposomes, such as PEGylated, surface modified, stealth, gene loaded, and temperature & pH-responsive types, which are meant for incorporating the drug within the polymeric membrane to exhibit potential characteristics like extending the drug's circulation time in the brain, recognizing the receptors present in the nasal mucosa, and delivering genetic material, such as RNA or DNA, to modulate gene expression in the brain [90].

Advantages

Enhanced drug bioavailability Targeted delivery
Reduced systemic exposure Minimal side effects.

Safety profile: The safety profile of nanoliposomes largely depends on the dosage and formulation used.

Metal Nanoparticles: Gold and silver nanoparticles have been utilized to carry drugs and target specific brain regions. Their distinct optical characteristics can also serve imaging purposes. The distinct types include gold, silver, and magnetic nanoparticles, expected to exhibit discrete functionalities, such as targeted drug delivery, antimicrobial activity, and excellent biocompatibility, as shown in Figure 7 [91].

Advantages

Enhanced drug transport Targeted delivery
Imaging and tracking BBB modulation

Safety profile: Renowned for their antimicrobial properties, they can, however, induce cytotoxicity and oxidative stress at higher concentrations.

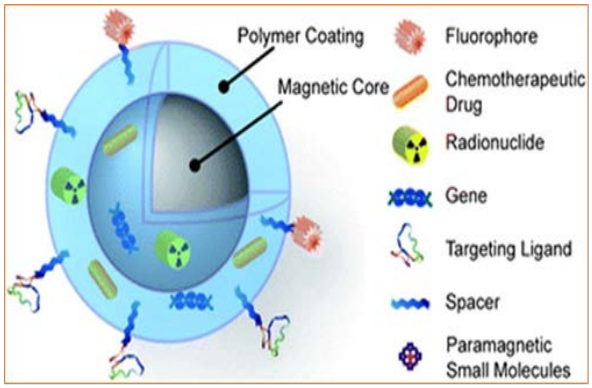

Figure 7: Structure of magnetic nanoparticles

Quantum Dots: Quantum dots (QDs) are a unique class of nanoparticles with distinctive optical and electronic properties. They are semiconductor nanocrystals, typically made from materials such as cadmium selenide (CdSe) or cadmium telluride (CdTe), that exhibit size-dependent fluorescence [92].

Safety profile: Cadmium ions are highly toxic, primarily due to their ability to induce significant oxidative stress and cytotoxicity

Theranostic Approach: Quantum dots have dual functionality as therapeutic carriers and imaging agents, enabling a theranostic approach to simultaneously monitor and regulate drug delivery and its effects, as shown in Figure 8 [93].

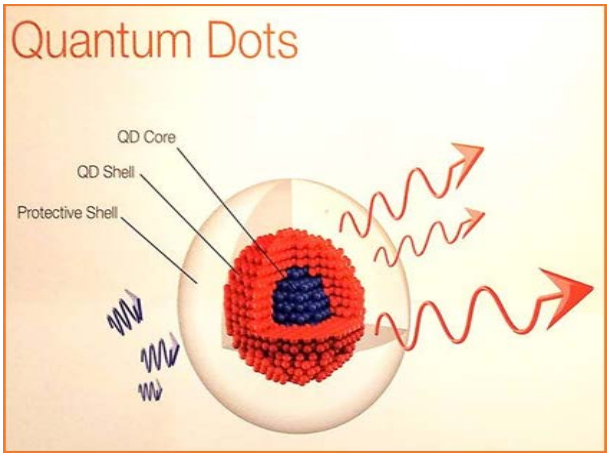

Figure 8: Quantum dots

Nanocrystals: Nanocrystals are submicron-sized crystalline particles that can be used as drug delivery carriers; they are extremely small, typically in the nanometre range [94].

Advantages:

High drug load Safety and efficiency

Safety profile: The neurotoxicity may be influenced by the nanocrystals' material composition and surface characteristics.

Olfactory Ensheathing Cells (OECs):

OECs are specialized cells found in the olfactory system responsible for our sense of smell. They are known for their unique ability to support the growth and regeneration of nerve fibers (axons) in the olfactory system.

Due to this regenerative property, OECs have gained attention as potential tools for facilitating nose-to-brain delivery, especially for promoting nerve regeneration and drug delivery to the brain [95].

Safety profile: OECs are typically deemed safe because of their natural function in the olfactory system, which aids in ongoing neurogenesis.

Advantages

Regeneration support Migration Barrier crossings

Exosomes and Nanovesicles: Natural carriers like exosomes and nanovesicles derived from cells can be loaded with drugs and functionalized for targeted delivery to the brain. Due to their capability to navigate the olfactory nerve pathways linking the nasal cavity to the brain, they show potential for facilitating nose-to-brain drug delivery [96].

Advantages

Biocompatibility Cell mediation
Targeting capabilities Stability

Safety profile: Exosomes and nanovesicles are generally considered safe due to their natural origin and intrinsic biocompatibility

Chitosan-based carriers: Chitosan, a natural polymer extracted from chitin found in crustacean shells, is recognized as a promising avenue for nose-to-brain drug delivery. Its mucoadhesive properties, biocompatibility, and capacity to enhance drug transport from the nasal cavity to the brain underscore its potential [97].

Advantages:

Mucoadhesive properties Opening tight junctions

Safety profile: The safety profile of chitosan-based carriers largely depends on the dosage and formulation used.

Cell-penetrating peptides (CPPs): CPPs, as they contain positively charged amino acids, interact with negatively charged cell membranes. This interaction can result in endocytosis, a process by which the cell engulfs the CPP and its cargo, allowing them to enter the cell [98].

Advantages

Highly specific Versatile cargo delivery Well tolerated

Safety profile: CPPs are typically considered safe because they can effectively deliver therapeutic agents across the blood-brain barrier (BBB) with minimal toxicity.

Nanowires: These are tiny, nanoscale structures typically made from materials like silicon or polymers. Because of their specific properties, such as size, surface chemistry, and conductivity, researchers are investigating using nanowires as carriers in nose-to-brain delivery.

Though these nanowires are expected to show various advantages like précised drug delivery, enhanced penetration, and rapid action, there are a lot of key challenges associated, which include [99]:

- Biocompatibility issues
- Toxicity related problems
- Difficulties in size and shape optimization
- Lack of ensured drug loading
- Nasal irritation
- Lack of efficacy due to nasal clearance

Nanobots: Nanobots are even smaller robotic devices, often at the nanometre scale, which can be remotely controlled or programmed to perform specific tasks, like precise drug delivery, monitoring the activity of drug molecules in the brain regions, imaging the targeted site with fully equipped sensors, monitoring the brain's condition and provide feedback to healthcare providers, which makes the treatment more convenient by enabling personalized adjustments etc [100].

Though these nanobots offer the above-mentioned valuable applications, there are still many practical challenges associated with them as carriers, which include:

- Risk of potential toxicity.
- Technical challenges associated with integration of sensors and biological membranes.
- Monitoring of nanobot activities within the body is even more difficult.
- Power source utilization to operate nanobots for extended periods may be lethal to the body.
- Difficulty in permeation of nanobots through narrow and complex nasal pathways.
- Ensuring nanobots accurately navigate the nasal cavity to the brain without deviating from their path.
- Designing nanobots that are biocompatible and do not trigger adverse immune responses
- Developing scalable and cost-effective manufacturing processes for producing nanobots.

Table 2 lists details of some nanoparticles used for intranasal delivery and their clinical investigations. Table 3 tabulates the novel carriers currently used to treat PD and their recent research findings.

Nanoparticles enhance drug delivery by offering tailored release rates, targeting specificity, and half-lives. Lipid nanoparticles provide moderate, sustained drug release with high brain targeting but have shorter half-lives. Polymeric nanoparticles offer customizable, controlled release, moderate to high brain targeting, and longer half-lives. Gold nanoparticles deliver drugs rapidly with potential for controlled release, moderate brain targeting, and variable half-lives. Silica nanoparticles ensure controlled or burst release, moderate brain targeting, and long half-lives. Magnetic nanoparticles enable controlled release via magnetic fields, high brain targeting, and variable half-lives. These diverse properties optimize therapeutic efficacy and safety across various medical applications.

Table 2: Few recently used nanoparticles and their clinical investigations [101].

Carrier Type	Drug Name	Clinical Investigations	Adverse Effects	Bioavailability Improvements	Patient Outcomes
Nanoparticles	L-DOPA	Improved bioavailability and targeted delivery	Mild inflammation at the administration site	Enhanced BBB penetration	Improved motor function, reduced “off” periods
	Ropinirole	Enhanced therapeutic efficacy and reduced side effects	Potential immune response activation	Sustained release, targeted delivery	Improved quality of life
	Pramipexole	Enhanced cell-to-cell communication and neuroprotection.	Minimal toxicity, long-term effects	High drug loading	Slowed disease progression
Liposomes	Rotigotine	Enhanced drug stability and SR	Potential oxidative stress at high concentrations	Improved stability	Reduced neuroinflammation
	Apomorphine	Improved brain targeting	Mild irritation	Improved BBB penetration	Better overall symptom control
	Selegiline	CDR and reduced dose frequency	Nausea	Enhanced bioavailability	Improved quality of life
Exosomes	GDNF	Enhanced cell-to-cell communication	Loss of appetite, low sodium levels	Improved BBB penetration	Improved dopamine levels
	siRNA	Effective gene silencing and potential disease modification	Activation of immune responses, improper gene targeting, cell toxicity	Protection from enzymatic degradation	Reduced tumor growth, suppression of viral replication
Dendrimers	Rasagiline	Improved BBB penetration	Upset stomach, episodes of vomiting	Improved BBB penetration	Improved motor function
	Pramipexol	Enhanced drug transport	Toxic on long term use	High drug loading	Slowed disease progression
Cell-Penetrating Peptides	Levodopa	Increased cellular uptake and potential for enhanced brain delivery.	Mild inflammation	Enhanced BBB penetration	Improved motor function, reduced “off” periods
Chitosan-Based Carriers	Rotigotine	Improved solubility and CDR.	Oxidative stress at high doses	Improved stability	Reduced neuroinflammation

Table 3: Various novel carriers used in the treatment of PD and their research findings [102]

Novel Carriers and Drugs	Research Findings
Nanoparticles	Nanoparticles exhibit potential for transporting neuroprotective agents to the brain.
Gold	Gold nanoparticles loaded with nerve growth factor (NGF) enhanced neuron survival and improved motor function in PD models
Silver	Silver nanoparticles combined with dopamine receptor agonists demonstrated enhanced drug delivery and therapeutic effects
PEGylated liposomes	In animal models, PEGylated liposomes loaded with dopamine agonists improved drug stability and prolonged therapeutic effect.
Targeted liposomes	Targeted liposomes functionalized with ligands enhanced brain targeting and drug delivery.
Exosomes and nanovesicles	Exosomes derived from stem cells can potentially promote neuroprotection and regenerative effects. In PD models, Stem cell-derived exosomes improved motor function and reduced dopaminergic neuron loss.
Cell-penetrating Peptides	CPPs have been explored to enhance brain penetration of therapeutic agents. Peptide-modified drugs have demonstrated improved uptake and therapeutic efficacy in PD models.
Chitosan based carriers	They can be loaded with neuroprotective agents enhanced drug delivery across the BBB. Chitosan nanoparticles containing glial cell line-derived neurotrophic factor (GDNF) showed improved neuroprotection in PD models.

Table 4: Comparison of different nanoparticle systems [103]

Nanoparticle type	Drug release rates	Brain targeting capacity	Half-life
SLNs	0.5%/h	60-70%	12-24h
NLCs	1.5%/h	80-90%	8-16h
Liposomes	1.0%/h	85%	6-12h
Polymeric Nanoparticles	1.2%/h	70-80%	24-48h

Various statistical tests were employed to compare and validate different nanoparticles:

ANOVA (Analysis of Variance): Compares the means of different groups, such as drug release rates or brain targeting efficiency across various nanoparticle formulations.

t-test: Compare the means between two groups, such as treated vs. control groups, to assess the efficacy of the nanoparticle delivery system.

Chi-square test: Evaluate categorical data, such as the presence or absence of adverse effects in different treatment groups.

Kaplan-Meier survival analysis: Assesses time-dependent outcomes, such as the duration of therapeutic effects or survival rates in preclinical studies**.**

Regression analysis: Examines the relationship between nanoparticle characteristics (e.g., size, surface charge) and their delivery efficiency or bioavailability [104].

CONCLUSION

Among these novel options, nose-to-brain administration improves the patient's quality of life. Enhanced intranasal drug delivery techniques have several uses in treating brain illnesses. This comprehensive analysis shows that the intranasal approach may cross the BBB, delivering drugs to the brain more directly and efficiently. Current challenges in nose-to-brain nanoparticle delivery involve addressing limitations in drug release profiles and stability and mitigating the potential for immunogenic reactions that may cause adverse immune responses. Ongoing clinical trials investigate various nanoparticle formulations for intranasal delivery in Parkinson's disease to enhance drug bioavailability and patient outcomes. Expected advancements include improved targeting specificity, reduced systemic side effects, and increased therapeutic efficacy. Implementing nose-to-brain delivery requires balancing cost-effectiveness with patient compliance by providing user-friendly administration methods and ensuring treatments are affordable. Continued research is crucial to optimize these systems for safe and effective clinical applications that could significantly improve patient outcomes and advance treatment strategies in neurodegenerative diseases.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Pranay Renukuntla (PR) wrote the draft, revised, and answered to all reviewer comments. Ravi Kumar Tatikayala (RT) and Sujatha Damera (SD) helped in conceptualization and bibliography. Pranay Renukuntla (PR) and Naveen Pathakala (NP) created graphical abstract. Rajendra Kumar Jadi (RKJ) communicated and guided in the journey from the draft preparation to publication. All authors reviewed and consented to the final version of the manuscript.

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