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Next-generation lipid nanocarriers for Parkinson's therapy: nose-to-brain innovations and clinical prospects

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Parkinson's disease (PD) remains one of the most formidable challenges in central nervous system (CNS) drug delivery due to the restrictive blood–brain barrier (BBB) and limited efficacy of current dopaminergic therapies. Lipid-based nanocarriers, including liposomes, cubosomes, and nanostructured lipid carriers, have emerged as versatile nose-to-brain platforms offering rapid CNS access, dual encapsulation of synthetic and plant-derived neuroprotective agents, and tunable release kinetics. This review bridges nanoscale material design (*e.g.*, lipid crystallinity, phase transitions, hybridization with plant exosomes) with intranasal transport pathways and therapeutic outcomes in PD. We highlight multifunctional innovations such as stimuli-responsive lipid systems, exosome–cubosome hybrids, and AI-guided formulation modeling coupled with microfluidic manufacturing. By linking mechanistic insights with translational hurdles—including safety and regulatory challenges—we provide a forward-looking roadmap for next-generation nanotherapies poised to redefine PD management and accelerate clinical translation.

1. Introduction: challenges in Parkinson's therapy and rationale for lipid nanocarriers

According to the World Health Organization (WHO), neurological diseases pose one of the most significant threats to public health; central nervous system (CNS) diseases are responsible for an average of 1% of global casualties.[1] PD is frequently described as a debilitating neurodegenerative disorder that affects the human brain, resulting in the deterioration of its functions. It is a prevalent neurodegenerative condition that progressively manifests due to the death of a small set of neurons that govern body motions and the depletion of dopamine in the substantia nigra area of the brain.[2–4] The clinical manifestations of PD are characterized by motor and non-motor symptoms. Motor symptoms include rest tremor, muscular rigidity, postural instability, and bradykinesia.[5] While sleep disturbances, anosmia, constipation, speech changes, and cognitive and behavioral or neuropsychiatric alterations are all non-motor symptoms observed in PD.[6] Two primary hallmarks define the pathophysiology of PD. The first is the loss of dopaminergic neurons in the substantia nigra pars compacta, which is mainly triggered by the formation of free radicals, resulting in oxidative stress-induced neurodegeneration (Fig. 1).[7] Additionally, α-synuclein (α-syn) protein aggregates into Lewy bodies, which in turn disrupt microtubule-based subcellular transport, resulting in synaptic dysfunction and destabilization of neuronal homeostasis.[8]

Parkinson's disease is still regarded as incurable. Despite the advancements in medicine, current treatments remain palliative, as the prospect of a cure depends on addressing root causes, such as genetic defects or mutations. The four major strategies are pharmacologic treatment, physical therapy for motor and non-motor symptoms, rehabilitation therapy, and surgery (Fig. 2).[6]

Thus far, dopaminergic therapies have shown short-term effectiveness in managing movement disorders, while antipsychotic medications address the psychosomatic symptoms. Table 1 summarizes the medications currently used for PD treatment and their mechanisms of action.[10] A major draw-

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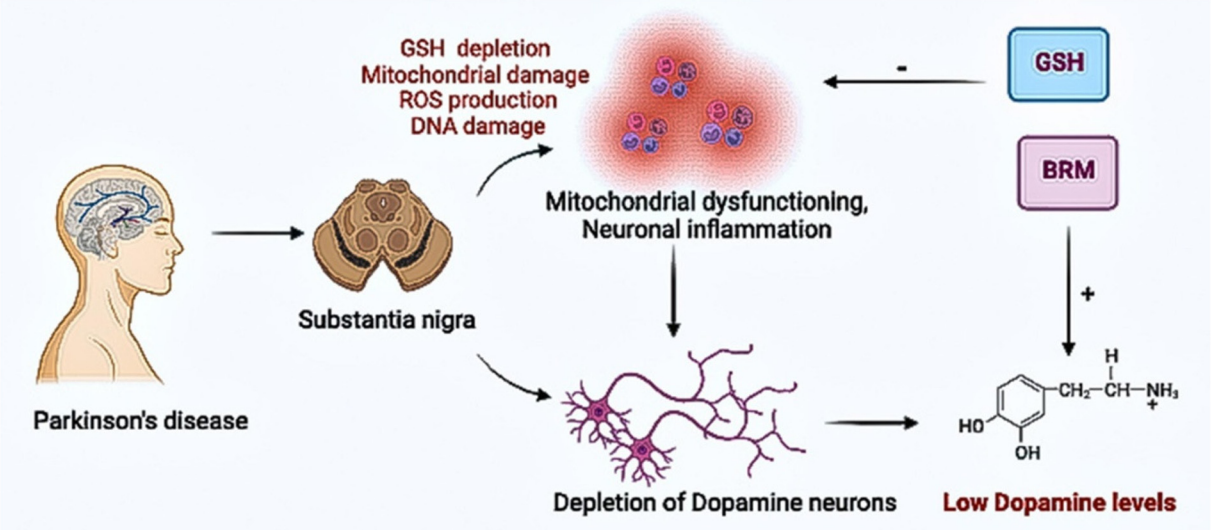

Fig. 1 Mechanistic depiction of PD pathogenesis: glutathione depletion, mitochondrial dysfunction, and ROS accumulation converge to trigger dopaminergic neuronal loss in the substantia nigra. This figure has been adapted from ref. 9 permission from Elsevier, copyright (2022).

Fig. 2 Outline of existing medical treatment for PD: pharmacological, physical, rehabilitation, and surgical therapies should be developed, along with new strategies that also focus on palliation beyond currently available treatment modalities, such as nanocarrier-based nose-to-brain delivery. This illustration has been created by Biorender. https://www.biorender.com/.

back of both synthetic and plant-derived anti-PD agents is their poor ability to cross the blood–brain barrier (BBB), which limits their CNS penetration and often necessitates low doses. Given the challenges associated with the current drugs in use, it is imperative to explore alternative avenues to bridge the gap between palliative treatment and a cure. One promising approach is the integration of nanomedicine into therapeutic delivery systems targeting the brain.[11]

Despite multiple reviews on nanocarriers for neurological disorders, few have systematically dissected lipid-based systems optimized explicitly for nose-to-brain delivery in PD. In this regard, the so-called "next-generation lipid nanocarriers" refer to a newer generation of lipid-based designs that surpass classical liposomes and solid lipid nanoparticles. These carriers integrate structural plasticity (*e.g.*, cubic or hexagonal phases), surface functionalization with peptides or exosomal membranes, and stimuli-responsive or hybrid lipid domains, alongside computational or microfluidic design paradigms that promote greater precision and scale. It is not just their small size but also programmable constructs and tunable bio-interaction that set them apart for targeted and individualized brain delivery beyond what can be accomplished with traditional formulations.

Table 1 Summary of the popular drug categories currently utilized for PD treatments and their mechanisms

Drug category	Examples	Mechanism	Ref.
Dopamine decarboxylase inhibitor/ Dopamine precursor	Carbidopa-levodopa	Levodopa is a prodrug of dopamine and is considered its replacement treatment. It is frequently administered with Carbidopa to prevent its peripheral breakdown and avoid its side effects.	12
Dopamine agonist	Apomorphine	Activates D1-like and D2 like receptors	13 and 14
	Pramipexole (non-ergolinic dopamine agonist)	Complete stimulation of the D2 subfamily of dopamine receptors.	15
	Ropinirole (non-ergoline)	Acts as a selective D2 agonist.	16
	Rotigotine (RTG) (non-ergoline)	Acts as a dopamine (D1-D5) and 5-HT1A agonist and an α-2 adrenergic receptor antagonist.	17
	Bromocriptine mesylate	Acts as a selective agonist on D2 and a partial antagonist for D1 dopamine receptors.	18
Monoamine oxidase-B (MAO-B) inhibitors (inhibit the breakdown of dopamine)	Selegiline, Rasagiline, Safinamide.	Inhibit dopamine degradation.	19 and 20
N-Methyl-D-aspartate (NMDA) receptor antagonism	Amantadine	Since an imbalance in dopamine levels is associated with increased extracellular glutamate, Amantadine helps regulate glutamate levels, thereby minimizing motor fluctuations associated with Parkinson's disease.	21
Catechol-*O*-methyltransferase (COMT) inhibitors	Entacapone, Tolcapone, Opicapone.	Inhibit dopamine and epinephrine metabolism.	22
Anticholinergics	Trihexyphenidyl	It blocks central cholinergic receptors and inhibits the reuptake and storage of dopamine, thus treating the motor symptoms.	23
	Benztropine	It reduces the central cholinergic effect and inhibits the reuptake and storage of dopamine.	24 and 25

This work distinguishes itself by linking carrier design (composition, flexibility, surface functionalization) with therapeutic outcomes and by incorporating emerging plant-derived systems, offering a more holistic view of translational opportunities.

Although several reviews focus on nanocarriers for neurological diseases, few systematically correlate the lipidic material properties (*e.g.*, cubic *vs.* lamellar phase behavior, interfacial charge, and crystallinity) to nose-to-brain transport mechanisms in PD. Furthermore, bioinspired hybrids are rarely demonstrated, although much could be borrowed from plant exosomes. This review aims to fill these gaps by demonstrating fundamental structure–property-function relationships, dual-drug and multifunctional designs for new paradigms in treating CNS diseases, and a rational direction for translation with the aid of AI-facilitated optimization and microfluidic fabrication.

2. Nose-to-brain drug delivery: pathways, barriers, and opportunities

In the wide landscape of developed approaches aimed at bypassing the BBB, the intranasal (IN) route has been considered one of the most promising non-invasive routes for delivering drugs to the CNS (in particular when combined with nanotechnology-based carrier systems).[26,27] Ease of self-administration for inhalation can potentially lead to enhanced patient compliance and provides direct entry to the brain *via* olfactory and trigeminal nerve pathways, escaping hepatic first-pass metabolism and systemic dilution as occurs with oral or parenteral exposure.[28] This direct targeting provides superior bioavailability and quicker onset of action for the treatment of neurodegenerative diseases, specifically PD (Fig. 3).[29,30] Although the IN route has these advantages, several physiological and anatomical barriers interfere with efficient intranasal drug uptake:

- The small available volume of the nasal cavity (100–200 μL) limits dosing.
- Formulations cleared by mucociliary transport are often rapidly removed, resulting in a short residence time.
- Other diffusion barriers include the nasal epithelium and mucosa, leading to suboptimal CNS penetration and a lack of therapeutic response.

These challenges demonstrate the need for novel carrier systems that can promote drug retention, improve mucosal permeation, and protect payloads from enzymatic degradation.[31] Among the various nanocarriers for drug delivery, lipid-based nanoparticles have demonstrated high efficiency in encapsulating hydrophobic and hydrophilic drugs, with adjustable surface properties and low or no cytotoxicity. Their ability to integrate mucoadhesive polymers, surface ligands, or stimuli-responsive lipids allows fine control over transport dynamics and brain bioavailability.[11]

Although the intranasal route bypasses first-pass metabolism and is well-suited for direct CNS delivery, its efficacy depends on the carrier design. Mucociliary clearance, small dosing volumes, and enzymatic degradation continue to limit bioavailability, requiring lipid-based delivery systems designed for mucoadhesion, sustained release, and epithelial permeation.

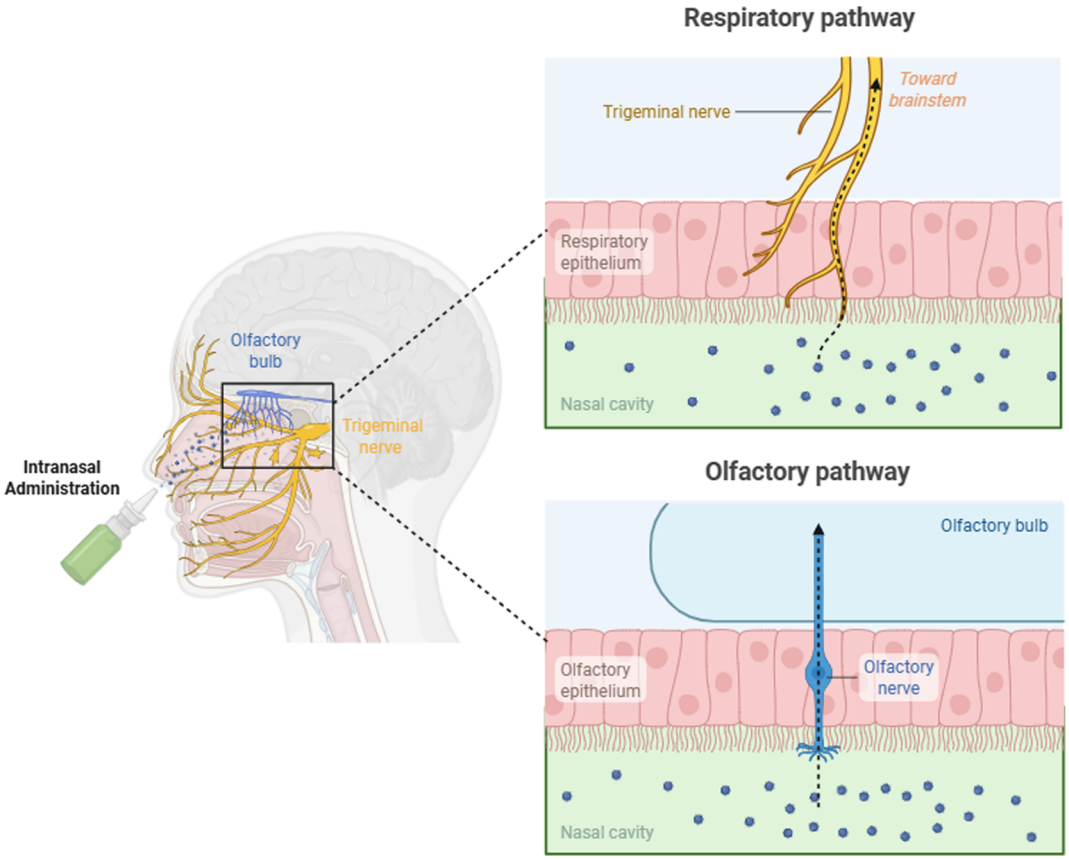

Fig. 3 Nasal-to-brain transport mechanisms: drugs traverse the olfactory epithelium to the olfactory bulb or the trigeminal pathway to the brainstem, bypassing the BBB and enabling rapid CNS drug delivery. This illustration has been created by Biorender. https://www.biorender.com/.

3. Lipid-based nanocarriers: design principles and emerging innovations

Lipidic nanocarriers, with biocompatibility and structural tunability, and the potential to encapsulate hydrophilic and lipophilic drugs, have become a backbone of drug delivery to the brain *via* the nasal route. Their proposed therapeutic benefit in PD is derived from circumventing the BBB, maintaining dopaminergic tone, and reducing oxidative stress. Crucial design variables—lipid crystallinity, interfacial charge, and phase transitions- dictate drug loading, mucosal retention, and release kinetics. For instance, lipid NP crystallinity governs drug release rates, as they are influenced by drug molecule diffusion rates through the lipid matrix and by matrix degradation by enzymes such as lipases and esterases. The molecular mobility of drugs immobilized in a solid, crystalline lipid matrix will be lower than that of compounds in liquid lipids or supercooled melts, leading to slower diffusion and drug release. Furthermore, lipase activity is limited in highly ordered lipid matrices due to decreased accessible surface area, leading to lower enzymatic degradation and contributing to improved stability and sustained release.[32]

In contrast, lipid bilayers can have multiple phases as a function of temperature. A lipid bilayer can, basically, assume two different physical conditions, which depend on temperature: a solid-ordered (gel) phase at low temperatures, where lipids are closely packed and ordered, and a liquid-disordered (fluid) phase at higher temperatures with increased molecular movement leading to an enhanced mobility of the lipid molecules and less order. Melting of the bilayer from the rippled phase to the liquid phase occurs at the main transition temperature (T_m), which is characteristic for each type of lipid. Lipid vesicles possess a spheroidal morphology at temperatures above the T_m, whereas nonspheroidal aggregates grow below the T_m upon lipid crystallization.[33] Thus, phase transitions are key processes in the preparation of stimuli-responsive delivery vehicles, as the manipulation of T_m or of the transition behavior (occurrence of a plateau region) in the carrier matrix allows for induction of drug release to occur only when a well-selected physiological condition is met or when an external trigger like temperature, pH, or light irradiation is applied.

Advanced analytical tools (*e.g.*, dynamic light scattering, small-angle X-ray scattering, cryo-TEM) are now indispensable for correlating nanoscale architecture with pharmacokinetic outcomes. They should be standardized to enable regulatory comparability. Recent innovations, including stimuli-respon-

sive lipids, AI-predicted lipid–drug interactions, and exosome–lipid hybrids, are reshaping this field. Meanwhile, microfluidic continuous production offers a scalable/reproducible manufacturing for clinical translation.[34,35]

3.1. Stimuli-responsive lipids

An emerging topic is the use of stimuli-sensitive lipid systems, which can enable precise control over drug release at specific pathological sites, improve dosing accuracy, enhance efficacy, and reduce off-target effects. They generally consist of a variety of environment-responsive functionalities incorporated into their structures, which respond to either physiological stimuli (*e.g.*, pH, certain enzymes) or exogenous stimuli (*e.g.*, temperature, light).[34,36,37] In addition, by modifying surface-targeting ligands (*e.g.*, folic acid (FA), peptides, antibodies, and so on) on the surface of stimuli-sensitive release systems, nanocarriers can exhibit a stronger ability to carry the loading agents and transfer them more effectively.[38] Yet, synthesizing stimuli-responsive NPs is very tedious due to their complex structures, which limit production to small-scale and are insufficient for clinical applications. Moreover, although multi-stimuli-responsive nanocarriers appear very promising due to their ability to respond to multiple triggers simultaneously, it remains uncertain whether the additional complexity they introduce results in delivery improvements significant enough to justify the extra design and development effort.[39]

3.2. AI-design of experiments and predictive modeling

The integration of AI-driven models can significantly improve the prediction of lipid-based nanocarriers' biodistribution and efficacy. Such a model increases efficiency and prevents extensive synthetic overhead of large chemical libraries and reliance on *in vivo* experiments by accurately predicting *in vivo* results.[40] Additionally, AI and machine learning (ML) have provided computational tools that enhance simulation and modeling in nanotoxicology and nanotherapeutics, particularly by improving the correlation between *in vitro* pharmacokinetic and pharmacodynamic data and *in vivo* biological outcomes.[41] For example, the lipid NP formulation and design machine learning approach consists of four key steps:

1. Synthesis of lipid NPs: It begins with the experimental formulation of various lipid structures and NP formulations to build a large dataset. This phase focuses on the high-throughput synthesis of a large library of structurally diverse lipids to generate sufficient data for training the ML model.

2. Data transformation: It refers to the conversion of chemical structures into machine-readable formats, such as molecular descriptors or fingerprints. The structural and physicochemical characteristics are calculated using tools such as PaDEL-descriptor and RDKit, which account for each lipid in ML input.

3. ML model selection and training: It involves applying suitable algorithms to correlate input descriptors with desired lipid NP properties, such as size and pK_a. This involves supervised learning using pre-labeled datasets.

4. Model evaluation and improvement: Accuracy, precision, recall, bias, and variance are used to evaluate the model's performance. Overfitting is addressed through data splitting, hyperparameter tuning, and regularization. And finally, promising predictions are validated experimentally to improve reliability.[42]

More than simply optimizing prediction accuracy, AI-informed formulation also redefines the nature of nanocarrier design away from mass-empirical, access-based (*i.e.*, high-throughput) optimization. Unlike traditional empirical optimization methods, AI-guided formulation modeling involves multivariate learning from historical data and *in silico* (simulated) physical/chemical properties to predict the optimal lipid ratios, surfactant types, and processing conditions required for target particle size and release kinetics. There are nonlinear dependencies that are not apparent to common design of experiments (DoE) tools, which can be detected by predictive modeling, thereby reducing the number of learning iterations in wet-lab experiments. *In silico* models developed from pharmacokinetic and toxicological endpoints even facilitate virtual screening of excipient safety before synthesis, thereby accelerating the translation of adherence to green chemistry and animal-reduction principles. Ultimately, AI transforms formulation development from a trial-and-error process into a rational, data-driven workflow that accelerates discovery and increases the likelihood of clinical success.[42]

3.3. Microfluidic continuous manufacturing technologies

Despite recent advances in lipid-based nanocarriers, this technology remains hindered by manufacturing challenges. Accordingly, it is found that its polydispersity is high, and variability between batches thereof is dependent on the workers in the experiment and manufacturing. It has the drawback of limiting production capacity. Microfluidics avoids many of the drawbacks associated with bulk methods, enabling the production of lipid-based nanocarriers at lower cost and with higher productivity. Its principle relies on manipulating liquid flow at the microscale using a microfluidic device containing a micromixer to produce nanocarriers encapsulating drug cargoes, providing a continuous system for generating large numbers of nanocarriers with high reproducibility, tunable size, and easy parameter adjustment. These include the ability to accurately manipulate fluids, highly effective mixing, rapid heat and mass transfer, applicability for online analysis, and the stable production of NPs with a narrow particle size distribution.[43]

The introduction of monodispersed droplets as single reaction units in a microfluidic reactor expanded the potential of microreactors for preparing NPs by enabling various complex synthetic procedures under harsh conditions (*e.g.*, high temperature and pressure, strong reagents), thereby enhancing the variety of NPs that could be synthesized as nanostructures.[44] The combination of microfluidic reactors with additional externally applied physical fields (electrical, magnetic, and acoustic) has enabled the specific design and development of nanoparticles with varied architectures and functionalities.[45] As a

result, microfluidic systems provide an effective technology for generating functional NPs in a well-controlled manner with less batch-to-batch variation in feature size.[46] Crucially, lipid nanocarrier production can be more easily scaled *via* device parallelization, enhanced by using commercially available microfluidic platforms (*e.g.*, the NanoAssemblr platform from Precision Nanosystems), and enables controlled, reproducible manufacturing at a clinical scale.[43] Practical examples from recent findings demonstrate such advances. Vendors, such as NanoAssemblr, offer commercial microfluidic mixing systems, such as the Ignite and Blaze systems, that have been used to generate clinical-grade LNPs with reproducible particle size and encapsulation efficiency, which have long been approved for mRNA vaccine production. Similarly, researchers applied AI-aided optimization tools, such as Bayesian optimization algorithms combined with high-throughput microfluidic screening, to calibrate lipid ratios and flow parameters to achieve consistent nanocarrier lots. Together, these technologies connect academic formulation design and industrial pharmaceutical processing, enabling next-generation lipid systems for regulatory approval and patient benefit. More recently, lipid-based nanocarriers have emerged as a pioneering discovery, revealing their great potential to improve the oral bioavailability and blood–brain barrier penetration of CNS-active drugs.[47] Thus, they provide potential for the treatment of PD, especially in the case of drugs with inadequate aqueous solubility, as an efficient carrier system.[48] Lipid-based nanocarriers include several types of nanoparticles and nanovesicles, such as liposomes, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), nanoemulsions (NEs), cubosomes, exosomes, transferosomes, rhamnosomes, *etc.* (Fig. 4).

Design and optimization of lipid carriers require fine-tuning of lipid constituents, their arrangement, crystallinity, and interfacial properties, to optimize drug encapsulation and release profiles and mucosal compatibility. Formulation decisions, such as the addition of edge activators to enhance deformability or PEGylation to evade the blood–brain barrier, strongly determine nose-to-brain transport kinetics. Understanding these structure–property–function relationships is of significant importance for translating preclinical

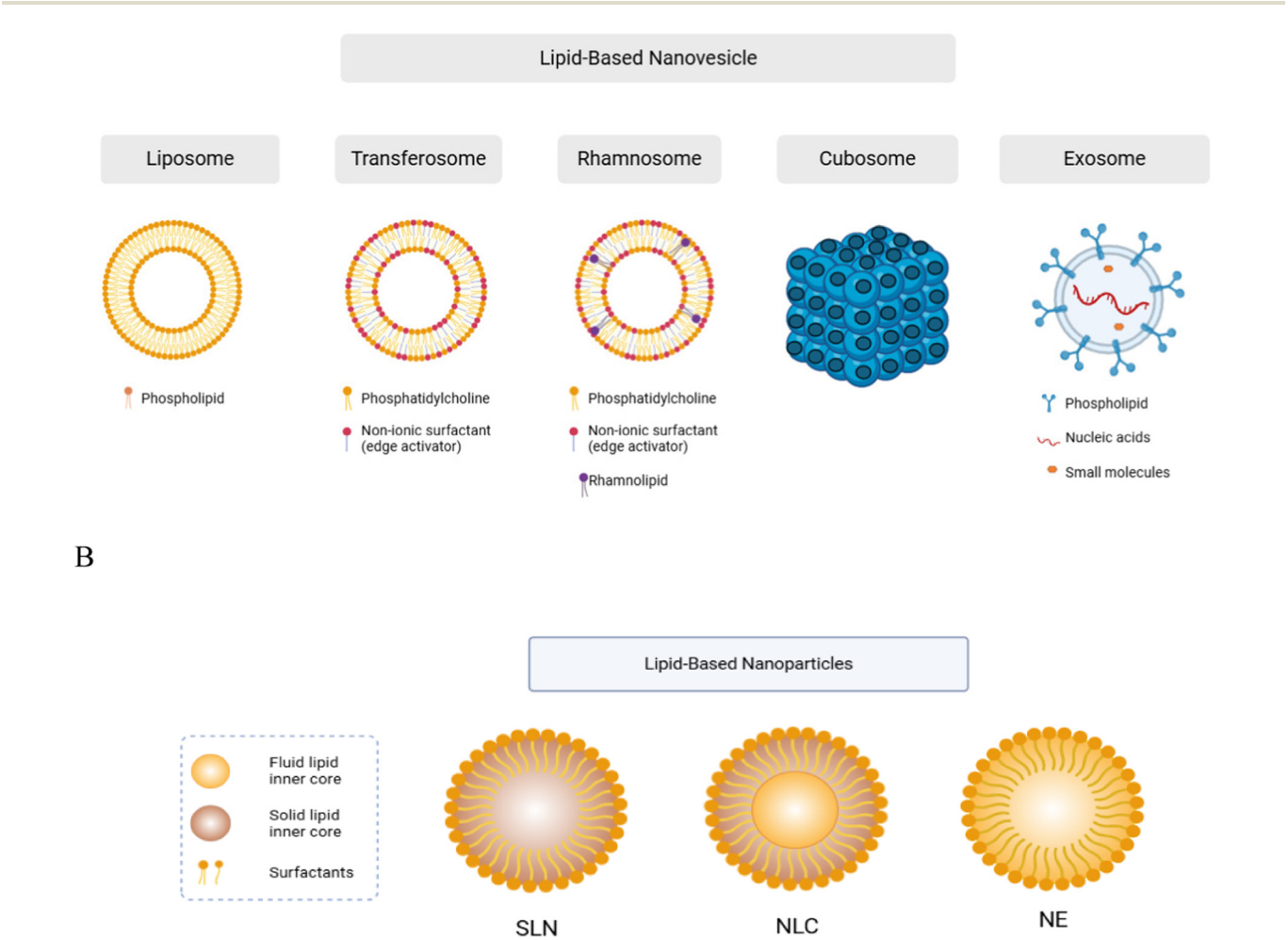

Fig. 4 Classification of lipid-based nanocarriers for nose-to-brain drug delivery: (A) nanovesicles (liposomes, transferosomes, rhamnosomes, cubosomes, exosomes) and (B) solid and hybrid lipid nanoparticles (NEs, SLNs, NLCs), each offering distinct encapsulation and release profiles. This illustration has been created by Biorender. https://www.biorender.com/.

progress into clinically relevant formulations. To develop lipid-based nanocarriers for nose-to-brain delivery, the encapsulation efficiency, mucosal adhesion, and release kinetics must be balanced. The structural diversity, ranging from lamellar liposomes to bicontinuous cubosomes and biomimetic exosomes, enables a customized release profile for diverse anti-Parkinson drugs. Recent advances involve stimulus-responsive formulations, hybrid lipid–polymer architectures for stabilization, and mathematical modeling to forecast lipid–drug interactions. These developments, along with the microfluidic fabrication process, make resulting systems more reproducible and scalable, fitting for clinical translation.

3.4. Liposomes: classical platforms and functional modifications

Liposomes are small (usually 50–500 nm) spherical vesicles composed of a phospholipid bilayer surrounding an aqueous core. Hydrophobic drugs adhere to the bilayer, whereas hydrophilic compounds localize in the core. The combination of their easy preparation, biocompatibility, and the possibility of surface functionalization makes them a broadly applicable platform for neurotherapeutic delivery.

Advantages of PD therapy:

• Facilitate the encapsulation of both levodopa analogues and antioxidant phytochemicals.

• Functionalization with ligands (lactoferrin, transferrin) for uptake by nasal epithelium and olfactory neurons.

Limitations:

• Susceptible to drug leach-out and oxidative degradation of unsaturated lipids during storage.

• Stabilization (PEGylation or stabilizers) is necessary to increase shelf life and avoid aggregation.

Liposomes have been extensively studied, although newer systems (cubosomes, NLCs) may offer greater long-term stability and drug loading for the chronic management of PD.[49–51]

3.5. Transferosomes and rhamnosomes: deformable vesicles

Transferosomes are ultradeformable liposomes containing edge activators (EAs), usually single-chain surfactants such as sodium cholate or Span 80, which perturb bilayer packing and increase flexibility. This deformability enables tight-junction penetration and enhanced mucosal penetration.

Rhamnosomes are also a new concept, in which biosurfactants (rhamnolipids) replaced EAs to generate vesicles that were as flexible but biocompatible and less irritating to mucosal tissue.

Pros:

• High permeability across the nasal mucosa and possible evasion of efflux transporter.

• Rhamnosomes offer a green reprieve, as they are 17-fold less toxic.

Cons:

• Transferosomes can cause irritation when surfactant levels are high.

• Limited long-term stability; the lipid-to-surfactant ratio has to be carefully tuned.

Emerging trend: A combination of transferosomal deformability with targeted ligands (such as mannose and peptides) can bring two advantages: improved penetration and receptor-mediated uptake in the PD-related brain regions.[52–54]

3.6. Cubosomes and exosomes: advanced bicontinuous and bioinspired systems

Cubosomes are bicontinuous cubic-phase lipid nanocarriers with a honeycomb-like structure. With their highly porous structure, these architectures possess a large surface area and interior aqueous channels, which are beneficial for high drug loading and controlled release.

In contrast, exosomes are endogenously secreted extracellular vesicles with proteins, lipids, and nucleic acids. The above-mentioned characteristics, such as natural biocompatibility, immunological safety, and intrinsic targeting, make them more suitable for bioinspired nose-to-brain delivery.

Recently, hybrid exosomes have been developed. They are engineered extracellular vesicles created by combining natural exosomes with synthetic or semi-synthetic vesicular systems or by using hybrid cell sources. They comprise different configurations, for example, liposome–exosome fusion compositions, inorganic NP–exosome core/shell, or NP-conjugated exosomes. Their primary benefit is that, by combining the best attributes of exosomes (*e.g.*, biocompatibility and the ability to cross biological barriers) with improved drug loading, stability, tunable membrane properties, or ascribed functionalities, they can harness synergistic advantages across a wide range of treatment and theranostic applications. Hybrid systems can be generated *via* extrusion, sonication, and the freeze–thaw process. Mechanistically, the advantage of exosome–cubosome hybrids lies in their bimodal transport and targeting. The cubic lipid phase provides large internal channels that can be readily loaded with both hydrophilic and lipophilic drugs and support a diffusion-based controlled release along bicontinuous domains. Upon fusion with exosomal membranes, these nanostructures acquire surface proteins such as tetraspanins (CD9, CD63) and integrins, whose functions involve interactions with neuronal and olfactory receptors to facilitate cell uptake and retrograde axonal transport. In addition, the hybrid membrane also prevents endosomal capture and enhances intracellular delivery of neuroprotective agents. Furthermore, the cooperation of these mechanisms accounts for their enhanced brain uptake and therapeutic effects compared with conventional liposomes.[55]

Comparative insight:

• **Cubosomes** are structurally robust and offer strong release modulation, but are complex to produce (requiring high-energy methods and a stabilizer).

• **Exosomes** have intrinsic targeting but with **batch variability** and **non-scalable** processes (isolation and purification being the major bottleneck again).

Future outlook: Hybrid systems, such as the synthetic lipid cubosome incorporating an exosomal membrane, have the potential to enhance structural stability and biological targeting (a promising area of PD treatment[56–59]).

3.7. SLNs, NLCs, and nanoemulsions: solid and hybrid nanoparticles

Solid Lipid Nanoparticles (SLNs) are lipid nanoparticles composed of a solid lipid core stabilized by surfactants that provide high stability and well-controlled release; however, their applicability can be compromised by drug expulsion during storage due to lipid crystallization.

Nanostructured Lipid Carriers (NLCs) overcome some of the SLNs' limitations by combining solid and liquid lipids, reducing crystallinity to enable higher drug loading and reduced expulsion, and being especially suited for long-term storage of chronic PD therapies.

Nanoemulsions (NEs) are submicron oil-in-water dispersions with droplet sizes usually <200 nm that offer good mucosal penetration and industrial-scale production, yet lower controlled release properties compared to SLNs/NLCs.

Comparative insight:

• NLCs have attracted attention for dual-drug loading (synthetic + phytochemical) and for improving stability.

• NEs could be the optimal choice for rapid-onset intranasal delivery but need to be reformulated for chronic therapy (*e.g.*, by using gelling agents to prolong retention).[4,60,61]

Table 2 summarizes the types of lipid-based nanocarriers, their advantages, and disadvantages.

4. Formulations of anti-Parkinson's drugs: advances in synthetic therapeutics

Generally, there are several design principles for intranasal lipid-based nanocarriers:

1 The aerodynamic diameter is one of the most important factors to be considered to prevent inspiratory flow from diffusing into the lower airways and to ensure particle packing on the nasal mucosa. Optimally, the emitted particle size (PS) from the spray device must be 10 μm or greater. Particles measuring between 1 and 10 μm tend to be deposited and retained in the lungs, while those smaller than 1 μm are usually exhaled.

2 The molecular weight of the nanocarrier also affects drug absorption, as substances with molecular weights above 1000 Da are less absorbed than those with molecular weights below 300 Da.

3 Lipophilic drugs are insoluble in mucus, so they are not cleared by mucociliary clearance, thereby promoting better nasal absorption. Contrarily, hydrophilic drugs tend to dissolve in the mucus before absorption, as the mucus layer exhibits a low diffusion rate that limits their permeation.[64]

4 The administered formulation volume should be at least 200 μl. Smaller volumes are inadequately retained by the nasal mucosa's low surface area, risking elimination by mucociliary clearance.[64]

Table 2 Comparison of lipid-based nanocarriers used for nose-to-brain delivery in Parkinson's therapy

	Composition	Advantages	Disadvantages	Ref.
Liposomes	Spherical vesicles consisting of a phospholipid bilayer enclosing an aqueous core.	- Facilitate the encapsulation of both levodopa analogues and antioxidant phytochemicals. - Can be functionalized with ligands to enhance their uptake.	Prone to drug leakage and are unstable, thus requiring stabilizers to prevent aggregation.	49, 50, 51, 62 and 63
Transferosomes	Ultradeformable liposomes incorporating EAs.	High permeation through the nasal mucosa and potential to bypass efflux transporters.	• May irritate due to high surfactant content. • Limited long-term stability.	52, 53 and 54
Rhamnosomes	Flexible vesicles incorporating biosurfactants.	- High permeation - Rhamnosomes offer a greener alternative with reduced toxicity compared to transferosomes.	• Limited long-term stability.	52, 53 and 54
Cubosomes	Lipid nanocarriers with a bicontinuous cubic phase structure with high surface area and internal aqueous channels.	Characterised by structural robustness and tunable release.	Usually face manufacturing complexity.	56, 57, 58 and 59
Exosomes	Naturally secreted extracellular vesicles containing proteins, lipids, and nucleic acids.	They provide intrinsic targeting.	Exosomes suffer from batch variability and scalability challenges.	56, 57, 58 and 59
SLNs	They consist of a solid lipid core stabilized by surfactants.	High stability and controlled release.	Their use is often limited by drug expulsion during storage due to lipid crystallization.	4, 60 and 61
NLCs	They improve upon SLNs by mixing solid and liquid lipids, reducing crystallinity, and thereby increasing drug loading and preventing expulsion.	Characterized by reduced crystallinity, increased drug loading, and decreased expulsion.	Expensive.	4, 60 and 61
NEs	Oil-in-water dispersions with droplet sizes typically <200 nm.	They provide excellent mucosal permeation and scalable manufacturing.	Limited sustained-release capability compared to SLNs/NLCs.	4, 60 and 61

Furthermore, the physical and chemical properties of drugs, such as solubility and surface groups, determine the type of nanocarrier used. For instance, hydrophobic drugs are usually incorporated into the outer layer of liposomes, while hydrophilic ones are located in the aqueous core.[62]

In the subsequent section, we will present lipid-based nanoformulations for anti-PD agents, including dopamine agonists, MAO-B inhibitors, and NMDA antagonists.

4.1. Dopamine agonists

Piribedil, a non-ergot dopamine agonist, has attracted considerable attention in recent years as a promising anti-Parkinson's drug. However, clinical use has been very limited due to poor bioavailability *via* oral administration, multiple daily drug administrations (up to 5 tablets), and serious gastrointestinal (GI) toxicity. Hence, Uppuluri *et al.*[65] prepared SLNs containing Piribedil and loaded them in a thermoresponsive methylcellulose *in situ* gel for reaching the nose-to-brain pathways, aiming at direct drug uptake as well as retarding mucociliary clearance upon nasal delivery to rats. SLNs were prepared with palmitic acid, and they possessed a mean particle size (PS) of 358 nm, a drug loading capacity (DLC%) of 15%, a polydispersity index (PDI), a zeta potential (ZP), and an encapsulation efficiency (EE%) from 0.092 to 0.226, −12 to −19 mV, and 65.86 to 92.64%, respectively. Pharmacokinetic investigations reveal that the nanoformulation enhanced brain delivery of Piribedil, with a 4-fold higher area under the curve (AUC) and a direct transport percentage (DTP) of 27%, whereas the maximal plasma concentration (C_{max}) was reduced by ~2.3-fold compared to plain IN suspension.[65]

Prajapati *et al.*[17] formulated Rotigotine-loaded SLNs for nose-to-brain delivery to enhance their low oral bioavailability, which ranges from 1 to 5% due to extensive gut clearance and limited brain barrier penetration. SLNs were synthesized from Dynasan 118 by the hot-melt emulsification method and had a PS of 129 nm, an EE% of 83%, a PDI of 0.285, a ZP of −23.1, a DLC% of 87%, and *in vitro* drug release in phosphate buffer (pH 7.4) for 30 hours of 99%. *Ex vivo* permeation studies and CLSM analysis of cellular uptake, along with histopathological studies, showed that Rotigotine-SLNs effectively penetrated the goat nasal mucosa. The reviewed formulation was highly compatible with the mucosa, and no oral toxic effects or structural changes in the coculture were observed. This data underscores the capacity of this method for a safe and effective way of transporting drugs to the brain.[17]

To mitigate oxidative stress and facilitate efficient PD management, Ashhar *et al.*[9] employed intranasal delivery of Bromocriptine and GSH-loaded NE. The latter were synthesized from Capmul PG-8 NF by a high-energy ultrasonication method. They had a PS, a PDI, and a ZP of 80.71 ± 2.75 nm, 0.217 ± 0.009, and −12.60 ± 0.10 mV, respectively. CLSM confirmed enhanced NE permeation compared to suspension. Furthermore, biochemical estimation studies in haloperidol-induced PD Wistar rats showed a significant increase in the levels of GSH (9.53 ± 1.40 mol per mg protein), superoxide dismutase (SOD) (6.85 ± 0.70 mg protein), and catalase (CAT) (139.51 ± 19.42 nmol H_2O_2 per min per mg protein), along with a reduction in the level of thiobarbituric acid reactive substances (TBARS) (2.10 ± 0.47 nmol per mg protein). Additionally, the levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were also significantly reduced after NE administration. Following intranasal administration, the pharmacokinetic study revealed higher concentrations of Bromocriptine (10.37 ± 2.59 μg mL^{-1}) and GSH (120.10 ± 29.98 μg mL^{-1}) in rat brains than in plasma. These compounds also persisted in the brain for a longer duration due to sustained release from the NE.[9]

Another attempt to reduce Rotigotine's extensive first-pass metabolism was made by Zafar *et al.*,[66] who prepared, optimized, and evaluated Rotigotine-loaded chitosan-coated NLCs for nose-to-brain delivery. Following their synthesis from the solid lipid Compritol 888 ATO and Caproyl 90, the optimized Rotigotine-loaded chitosan-coated NLCs formulation showed a PS of 170.48 ± 8.37 nm, a PDI of 0.19 ± 0.03, a ZP of +26.73 mV, an EE% of 82.37 ± 2.48%, and an *in vitro* sustained drug release pattern (86.73 ± 8.58% in 24 hours) compared to Rotigotine dispersion (Dis). Moreover, it exhibited significantly enhanced bioavailability and brain targeting. Its relative bioavailability was 3.2 times that of Dis, and the absolute bioavailability following intranasal administration was twice as high as the intravenous route. In addition, intranasal administration showed better brain targeting, with DTE and DTP of 422.03 and 76.03, respectively, as compared to rotigotine-Dis (173.91% and 59.97%). CLSM further confirmed improved brain targeting.[66]

To reduce free radical damage and impede the biochemical changes associated with PD, Kumar *et al.*[4] loaded Lisuride, an ergot derivative, into NEs targeting the brain *via* the intranasal route. Oil-in-water NEs were prepared from almond oil, olive oil, and grape seed oil using high-energy emulsification. The NE droplet size ranged from 45.60 to 147.00 nm, with a PDI of 0.19, and a ZP of around −26.8 mV. After 24 hours, the NEs showed a release of 90.87 ± 4.10% of Lisuride during the *in vitro* release study, with a permeation profile through the nasal mucosa of 95.61 ± 4.15 g cm^{-2}. Meanwhile, compared with haloperidol-challenged rat models, the *in vivo* assessment of the antioxidant effect of Lisuride NEs revealed increased expression of antioxidant enzymes, including SOD and GSH, following intravenous administration. Moreover, intranasal NEs effectively increased dopamine concentrations to 17.48 ± 0.05 ng mL^{-1}, compared with haloperidol-treated rats (7.28 ± 0.02 ng mL^{-1}). Furthermore, treatment with NEs restored dopamine levels to normal and significantly improved behavioral function.[4]

Since the utilization of lipid nanoparticles can be a promising approach to overcome Bromocriptine's bioavailability limitations, KM *et al.*[48] developed Bromocriptine-loaded SLNs and NLCs from Compritol 888 ATO using the high-pressure homogenization method and employing the Box–Behnken design. The PS, PDI, and EE of optimized SLN and NLC formulations were found to be 219.21 ± 1.3 nm and 182.87 ± 2.2 nm, 0.22 ± 0.02 and 0.16 ± 0.004, and 72.2 ± 0.5% and

83.57 ± 1.8%, respectively. The *in vitro* release profiles of both nanoparticle formulations exhibited a biphasic pattern, with an initial rapid release followed by a sustained release phase, while the pharmacokinetic study revealed enhanced plasma and brain bioavailability of the drug compared to the Bromocriptine solution.[48]

4.2. MAO-B inhibitors

Since transferosomes can easily squeeze through the nasal mucosa due to their elastic nature, ElShagea *et al.*[19] directed Rasagiline mesylate directly to the brain through its inclusion within a transferosomal *in situ* gel administered intranasally. Transferosomes were synthesized by the thin-film hydration method using Phosphatidylcholine and Cholesterol. They displayed a PS of 198.63 ± 34.98 nm, a PDI of 0.45 ± 0.079, a ZP of −33.45 ± 4.73 mV, and an EE% of 95.73 ± 0.09%. Compared to intravenous aqueous solution, intranasal transferosomal *in situ* gel showed safety and biocompatibility in rats' nasal mucosa, with enhanced brain bioavailability (131.17%), along with high drug targeting efficiency and direct transport percentage indices of 304.53% and 67.16%, respectively.[19]

Recently, several studies have focused on increasing the brain bioavailability of Selegiline and improving patient compliance. For instance, Alsamarrai *et al.*[54] loaded Selegiline into deformable rhamnosomes, prepared from Rhamnolipid and Lecithin soybean by lipid-film hydration method, and decorated with lactoferrin for brain targeting (Fig. 5). Lactoferrin is a biological brain-targeting ligand that eliminates non-specific binding because its receptors are overexpressed in CNS diseases. After lactoferrin conjugation *via* polyelectrolyte complexation, the optimized rhamnosomes had a PS of 107 nm, a PDI of 0.23, a ZP of −41 mV, and an EE% of 78%. *Ex vivo* nasal mucosa skin permeation showed a superimposed pattern with the drug release profile, reaching 60% after 24 hours, due to the incorporation of rhamnolipids, which enabled the rhamnosomes to squeeze through the nasal mucosa. Pharmacokinetic studies confirmed their potential to target the brain non-invasively, as the optimized rhamnosomes exhibited 7 times higher absolute bioavailability than the market product and more than double the brain drug-targeting efficiency, with a DTE% of 328.41% and a DTP% of 69.55%.[54]

Instead of rhamnosomes, Kakulade *et al.*[67] loaded Selegiline into a thermoreversible cubosomal gel formulated into a mucoadhesive *in situ* nasal gel. The cubosomes were synthesized from Glycerol monooleate using high-shear homogenization followed by High-pressure homogenization. An optimized formulation showed PS, EE%, and drug release at 6 h at 166.8 ± 3.12 nm, 72.85 ± 1.50%, and 89.15 ± 1.04%, respectively. The PDI values range from 0.081 ± 0.028 to 0.257 ± 0.015, and the ZP values range from −8.52 ± 1.12 to −29.1 ± 2.25 mV. A sustained-release pattern was observed *in vitro* drug release, while *in vivo* pharmacokinetic studies in Swiss Albino mice showed a 1.90-fold increase in C_{max} and a 36.92 ± 0.41 ng min mL^{-1} AUC in the brain after intranasal administration. A stability study was carried out for shelf-life estimation, yielding 20.64 months, indicating that the formulation is stable over the long term.[67]

4.3. NMDA antagonists (Amantadine)

In 2023, Farag *et al.*[68] presented a novel paradigm for controlled release of the polar drug Amantadine in the course of PD management. This work discussed the most essential limitation of oral amantadine therapy, poor bioavailability, which is particularly aggravated in PD patients with comorbid pathologies, including dysphagia and gastroparesis. Their study focused on the development of a novel formulation of Amantadine nano-emulsified organogel. They selected *N*-palmitoyl L-serine methyl derivatives as organogelators for two reasons. First, because these derivatives have strong gelation ability, and second, because they possess a low critical concentration, enabling efficient and sustainable gel formation. The NE was prepared from sesame oil and Plurol Oleique CC 497. The final organogel had a PS of 162.58 nm, a PDI of 0.373, and a ZP of −22.24 mV, and exhibited controlled release, with 81.31% ± 2.47% of Amantadine released over

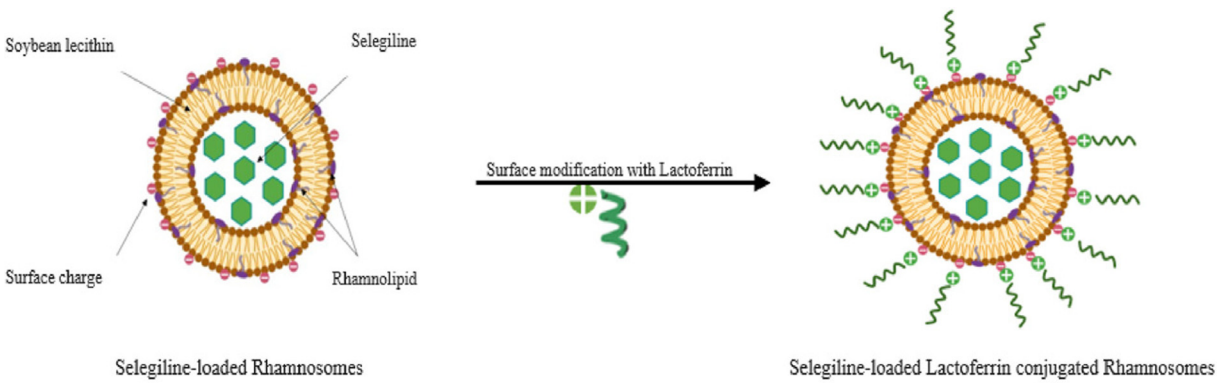

Fig. 5 Design of lactoferrin-decorated rhamnosomes for nose-to-brain Selegiline delivery: biosurfactant-based flexible vesicles exploit lactoferrin receptor-mediated transport, improving brain targeting and reducing off-target effects. This figure has been adapted from ref. 54 permission from Elsevier, copyright (2024).

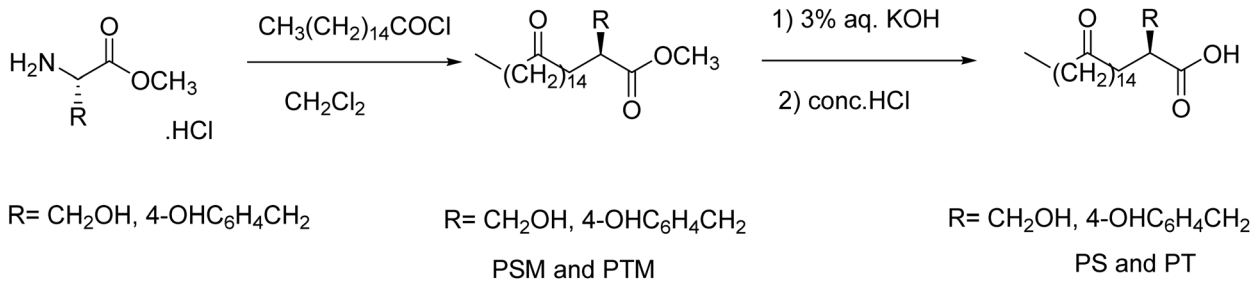

Fig. 6 Synthetic pathway for *N*-palmitoyl L-serine and L-tyrosine derivatives used as organogelators in amantadine nanoemulsified gels, enabling controlled release and enhanced nasal permeation.

8 hours. The pharmacodynamic study of intranasal administration of the nanoemulsified organogel in rotenone-induced PD rat models demonstrated the superiority of the nasal route over the transdermal route. It neutralized the harmful effects of rotenone on motor behavior, including prominent increases in ambulation frequency and fall-off latency, without altering histopathological morphology of the nasal vestibules. These tremendous improvements were attributed to a substantial elevation in striatal contents of dopamine, brain-derived neurotrophic factor, and messenger RNA (mRNA) expression of aromatic L-amino acid decarboxylase, which collectively led to intact dopaminergic neurons (Fig. 6).[68]

All data regarding the type of nanocarrier, loaded drug, size, PDI, ZP, EE%, DLC%, and advantages of nose-to-brain delivery of lipid-based nano vehicles encapsulating anti-Parkinson's drugs are summarized in Table 3.

Across synthetic drug nanoformulations, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) dominate due to high encapsulation efficiency and ease of lipid selection. Chitosan-coated systems consistently outperform uncoated formulations in mucosal adhesion and brain targeting, suggesting that surface charge modulation is pivotal for intranasal transport. Best-performing trends occur at particle sizes less than 200 nm and with either slightly negative or a more mild positive zeta potential, though dissimilar study designs and imprecise detailing of crucial parameters (*e.g.*, drug-to-lipid ratio, crystallinity) prevent valid cross-comparison analysis. Proper manufacturing practices (GMP) for physicochemical and pharmacokinetic assays are urgently needed for translation readiness.

5. Plant-derived compounds and hybrid phyto-nanoformulations: emerging paradigms

The FDA stated that conventional anti-Parkinsonian drugs effectively resolve the symptoms initially for several years but become less and less effective and induce motor fluctuations, DOPA-induced dyskinesia, and agonist-induced sleep attacks. In addition, dopaminergic medications have been shown to induce or worsen various neuropsychiatric complications, such as delirium, hallucinations, delusions, paranoia, psychosis, compulsive behaviors, and impulse control disorders.[69] As a result, growing attention has been directed toward the neuroprotective and antioxidant properties of natural compounds. Phytochemicals are being studied as mainstream therapeutics for PD and ageing-related symptoms and are likely to be beneficial for chronic diseases with fewer side effects.[70] Most of these compounds exert their effects by providing antioxidant and neuroprotective benefits. In the following sections, examples of nano-formulated plant-derived anti-PD agents and their congeners are described.

Curcumin is well-established for its antioxidant, anti-inflammatory, and neuroprotective benefits. Therefore, extensive research has been conducted to improve its poor bioavailability and sustained release by developing various nanocarrier systems. In 2022, Peng *et al.*[71] developed therapeutic self-oriented mesenchymal stem cell-derived exosomes loaded with curcumin. They showed a PS of ~130–197 nm, a ZP of −7.23 mV, and a curcumin loading efficiency of 75.53%. These exosomes navigate multiple membrane barriers and directly release drugs into the cytoplasm of target cells following intranasal administration. This targeted delivery enhances drug accumulation at the action site and achieves a three-pronged synergistic treatment. It reduces α-synuclein aggregation, restores neuronal function, and reduces neuroinflammation, thereby improving movement and coordination in PD model mice. *In vitro*, the improved exosomes increased miR-133b levels by 48.31%. *In vivo*, they observed high brain targeting of curcumin (67.26 μg g^{-1} in the substantia nigra) and decreased levels of neuroinflammation markers, accompanied by increased interleukin-10 (IL-10) and regulatory T cells (Fig. 7).[71]

Silymarin is a polyphenolic flavonoid derived from the seeds of milk thistle that has been widely used for various neurological disorders due to its neuroprotective effects and safety. Consequently, a mucoadhesive microemulsion of lipophilic silymarin, coated with chitosan for intranasal delivery, has been developed *via* spontaneous nanoemulsification using Labrafil M 1944 CS to manage PD. The particle size, ZP, and DLC% were 72.34 ± 4.32 nm, −24.26 ± 0.2 mV, and 96.31 ± 5.22%, respectively. *In vitro* release studies showed higher drug release from the

Table 3 Overview of lipid-based nanoformulations incorporating anti-Parkinson's drugs, detailing nanocarrier type, physicochemical characteristics (size, PDI, ZP, EE%, and DLC%), and reported therapeutic advantages

Type of lipid-based nanocarrier	Loaded drug	Lipid composition	Size (nm)	PDI	ZP (mV)	EE%	DLC%	Advantages	Ref.
SLN	Piribedil	Palmitic acid	358	0.092 to 0.226	−12 to −19	65.86 to 92.64	15	The nanoformulation improved Piribedil's brain delivery, increasing the AUC by 4-fold and achieving a DTP of 27%, while also reducing plasma C_{max} by approximately 2.3-fold compared to the plain intranasal suspension.	65
SLN	Rotigotine	Dynasan 118	129	0.285	−23.1	83	87	Rotigotine-SLNs could effectively permeate through the goat nasal mucosa. The formulation demonstrated high mucosal compatibility, with no toxic effects or structural damage observed.	17
NE	Bromocriptine and GSH	Capmul PG-8 NF	80.71 ± 2.75	0.217 ± 0.009	−12.60 ± 0.10	N/A	N/A	Following intranasal administration, NE increased the levels of GSH (9.53 ± 1.40 mol per mg protein), SOD (6.85 ± 0.70 mg protein), and CAT (139.51 ± 19.42 nmol H_2O_2 per min per mg protein), and decreased the levels of TBARS (2.10 ± 0.47 nmol per mg protein), IL-6, and TNF-α. Additionally, a pharmacokinetic study revealed higher concentrations of Bromocriptine (10.37 ± 2.59 μg mL^{-1}) and GSH (120.10 ± 29.98 μg mL^{-1}) in rat brains compared to their levels in plasma, and a longer persistence due to sustained release from the NE.	9
NLC	Rotigotine	Compritol 888 ATO and Caproyl 90	170.48 ± 8.37	0.19 ± 0.03	+26.73	82.37 ± 2.48	N/A	Rotigotine-loaded chitosan-coated NLCs enhanced bioavailability and brain targeting, with relative bioavailability 3.2-fold higher than the Dis, and absolute bioavailability 2.1-fold greater than intravenous administration. Intranasal delivery also demonstrated superior brain targeting, with DTE at 422.03% and DTP at 76.03%, compared to 173.91% and 59.97% for Rotigotine-Dis	66
NE	Lisuride	Almond oil, olive oil, and grape seed oil.	45.60 to 147.00	0.19	−26.8	N/A	N/A	The *in vivo* assessment of the antioxidant effect of Lisuride NEs revealed increased expression of antioxidant enzymes, including SOD and GSH, compared with intravenous administration. This was accompanied by elevated dopamine concentrations of 17.48 ± 0.05 ng mL^{-1}, compared with those in rats receiving haloperidol (7.28 ± 0.02 ng mL^{-1}). Furthermore, treatment with NEs restored dopamine levels to normal and significantly improved behavioral performance.	4
Transferosome	Rasagiline	Phosphatidylcholine and Cholesterol.	198.63 ± 34.98	0.45 ± 0.079	−33.45 ± 4.73	95.73 ± 0.09	N/A	The transferosomal *in situ* gel demonstrated safety and biocompatibility on rats' nasal mucosa, with enhanced brain bioavailability (131.17%), along with high drug targeting efficiency and direct transport percentage indices of 304.53% and 67.16%, respectively.	19
Nano-emulsified organogel	Amantadine	Sesame oil and Plurol Oleique CC 497.	162.8	0.373	−22.24	N/A	N/A	The nanoemulsified organogel neutralized the harmful effects of rotenone on motor behavior without altering histopathological morphology in the nasal vestibules. This was attributed to a substantial elevation in striatal dopamine, brain-derived neurotrophic factor, and mRNA expression of aromatic L-amino acid decarboxylase, which collectively support intact dopaminergic neurons.	68
SLN and NLC	Bromocriptine	Compritol 888 ATO	SLN: 219.21 ± 1.3; NLC: 182.87 ± 2.2, 0.22 ± 0.02	SLN: 0.22 ± 0.02; NLC: 0.16 ± 0.004	N/A	SLN: 72.2 ± 0.5; NLC: 83.57 ± 1.8%	N/A	The *in vitro* release profiles of both nanoparticle formulations exhibited a biphasic pattern, with an initial rapid release followed by a sustained release phase, while the pharmacokinetic study revealed enhanced plasma and brain bioavailability of the drug compared to the Bromocriptine solution	48

Table 3 *(Contd.)*

Type of lipid-based nanocarrier	Loaded drug	Lipid composition	Size (nm)	PDI	ZP (mV)	EE%	DLC%	Advantages	Ref.
Rhamnosome	Selegiline	Rhamnolipid and Lecithin soybean.	107	0.23	−41	78	N/A	*Ex vivo* nasal mucosa skin permeation reached 60% after 24 hours. Pharmacokinetic studies confirmed their potential to target the brain non-invasively, as the optimized rhamnosomes exhibited 7 times higher absolute bioavailability than the market product and more than double the brain drug-targeting efficiency, with a DTE% of 328.41% and a DTP% of 69.55%.	54
Cubosome	Selegiline	Glycerol monooleate	166.8 ± 3.12	0.081 ± 0.028 to 0.257 ± 0.015	−8.52 ± 1.12 to −29.1 ± 2.25	72.85 ± 1.50	N/A	*In vivo* pharmacokinetic studies revealed a 1.90-fold increase in C_{max} and AUC in the brain after intranasal administration, with values of 11.77 ± 0.32 ng mL^{-1} and 36.92 ± 0.41 ng min mL^{-1}, respectively. The stability study found a duration of 20.64 months, demonstrating the formulation's long-term stability.	67

microemulsion (66.28% after 12 h) as compared to the control, plain silymarin solution (28.345%). In addition, *ex vivo* results revealed that drug permeation and diffusion from the microemulsion were markedly improved across the nasal mucosa. Trials conducted *in vivo* in rotenone-induced Parkinson's disease (PD) rats demonstrated improved motor function and mobility, and reduced latency to falls. Additionally, they significantly reduced oxidative stress and inflammation, with increased levels of GSH, SOD, and CAT, along with a decrease in levels of α-synuclein, TNF-α, and IL-6.[72]

Chrysin is a flavone (5,7-dihydroxyflavone) that can alleviate age-related neurodegeneration and prevent dopaminergic neuronal death by suppressing pro-apoptotic genes and down-regulating anti-apoptotic proteins. It is generally found in honey, propolis, mushrooms, and the blue passion flower. Hence, an intranasal chrysin ME was developed using Capryol 90 by the phase titration method to yield spherical globules with a PS, a PDI, a ZP, and *in vitro* and *ex vivo* drug release (at 24 hours) of 365.03 ± 6.8 nm, 0.107 ± 0.0316, −24.86 ± 2.286 mV, and 90.52% and 68.67%, respectively. The *in vivo* study showed significantly improved locomotor activity and catalepsy score, elevated dopamine levels, and enhanced oxidative stress markers, including SOD, GSH, and CAT levels, compared to oral or nasal chrysin suspension groups in PD rat models. A brain distribution study showed that the ME formulation administered nasally achieved a 2-fold higher chrysin concentration than the oral formulation.[73]

Esculin hydrate is an active coumarin derivative found in a wide range of fruits, vegetables, and herbs, exhibiting a significant anti-PD effect due to its free radical scavenging potential. In 2024, Ansari *et al.*[74] prepared nanoliposomes loaded with Esculin using the solvent evaporation method for nose-to-brain delivery. The liposomes were made from Phospholipid 90G and Cholesterol and had a PS of 88.36 nm, a PDI of 0.06, a ZP of −30 mV, an EE% of 94.22 ± 0.93%, and a sustained drug release of 76.776 ± 1.127% over 48 hours. Compared to standard ascorbic acid, the liposomes demonstrated enhanced antioxidant activity (78.52% DPPH inhibition) and deeper tissue penetration. *Ex vivo* permeation across the nasal mucosa was also significantly better. Studies revealed that Esculin nanoliposomes had markedly enhanced permeation (79.484 ± 0.754%) compared to Esculin suspension (38.326 ± 1.279%), showing over 2-fold higher drug flux. The pharmacokinetic study showed much higher brain uptake with intranasal nanoliposomes (C_{max} 3347.15 ng mL^{-1}) than with oral delivery (901.20 ng mL^{-1}), confirming efficient brain targeting.[74]

Both 7,8-dihydroxyflavone (7,8-DHF), a compound previously shown to exert therapeutic effects in alleviating PD, and its chemically modified derivative, 6,7-DHF methyl ester, were encapsulated in liposomes and delivered intranasally (Fig. 8). The liposomal formulations were made using DSPC and DPPC. They aimed to treat PD and its common side effect, L-DOPA-induced dyskinesia (LID), which arises from prolonged L-DOPA therapy. The liposomes showed a PS of ~100–250 nm, a PDI of ~0.205, an EE% of 92–94%, and a drug release of ~50% within 3 hours and ~90% within 24 hours. The intranasal route led to

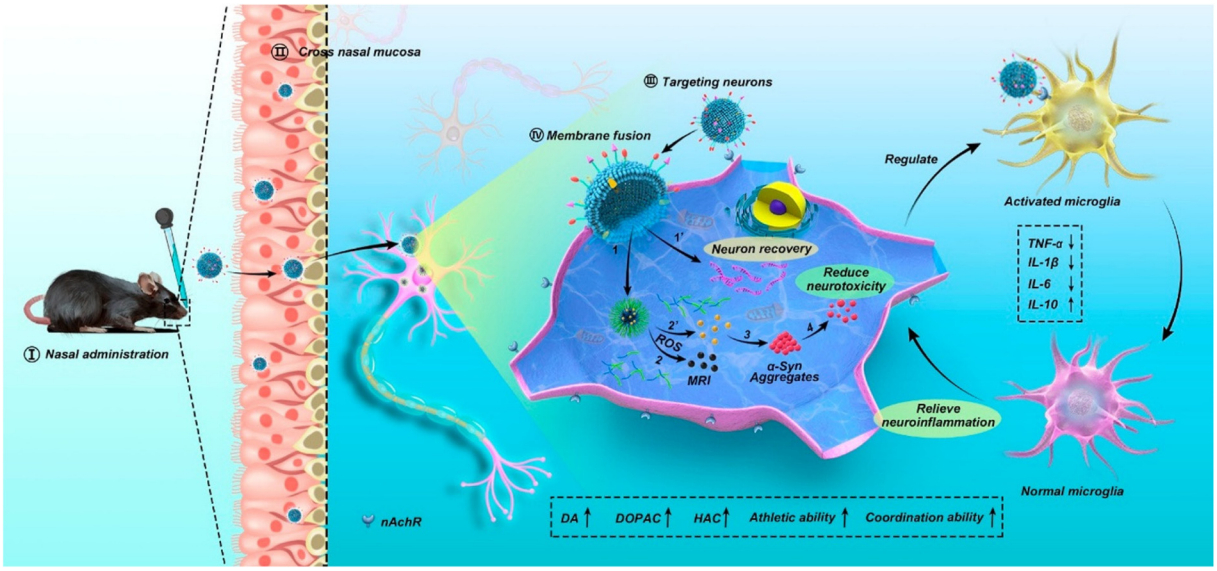

Fig. 7 Curcumin-loaded mesenchymal stem cell-derived exosomes for synergistic PD therapy: intranasal delivery reduces α-synuclein aggregation, enhances neuronal recovery, and modulates neuroinflammation. This figure has been adapted from ref. 71 permission from ACS, copyright (2022).

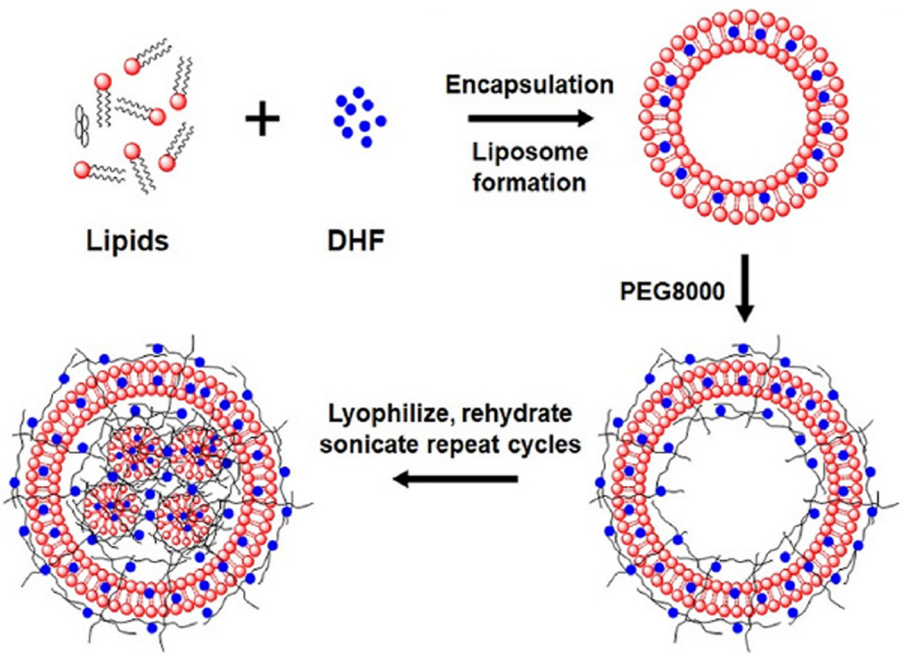

Fig. 8 Liposomal encapsulation of 7,8-DHF and derivatives for PD therapy: PEG-stabilized liposomes provide controlled release and restore motor function while reducing L-DOPA-induced dyskinesia. This figure has been adapted from ref. 75 permission from Elsevier, copyright (2024).

high brain concentrations at 1-hour post-dose and corrected some long-term signaling adaptations. Behaviorally, the liposomes restored ~90% of motor function, reduced abnormal involuntary movements, decreased the level of ΔFosB and α-synuclein, and improved LID in the PD mice model.[75]

Plant-derived exosomes are considered the future of cell-homogeneous nanoplatforms characterized by high efficacy and safety for brain drug delivery. On the other hand, *Pueraria lobata* is a medicinal plant used to treat CNS diseases, whose exosomes incorporate multiple active compounds targeting mitochondrial dysfunction. Consequently, Xu *et al.*[58] demonstrated that the exosomes derived from the medicinal plant *Pueraria lobata* (Pu-Exos) (Fig. 9) have an outstanding capability to pass through cellular membranes and endosomal barriers for efficient delivery of loaded biomacromolecules to target cells. Lipidomic analysis confirmed that the present

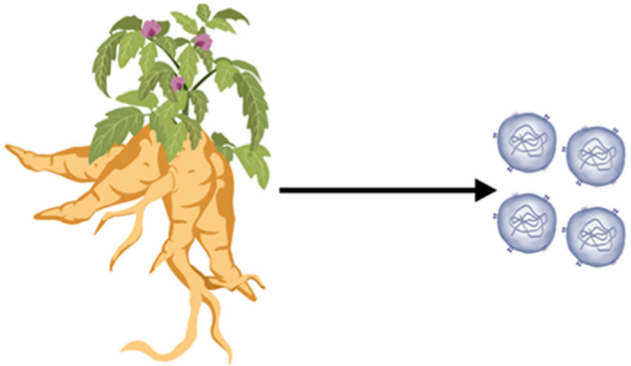

Fig. 9 Illustration showing the preparation process of Pu-Exos from the medicinal plant *Pueraria lobata*. This figure has been adapted from ref. 58 permission from Elsevier, copyright (2024).

lipids consisted of sphingosine, triglycerides, ceramides, monohexosylceramide, and diglycerides. Pu-Exos had a PS of 125.0 ± 9.7 nm and a ZP of −5.0 ± 0.7 mV. They promoted PINK1-Parkin-mediated mitophagy, cleared dysfunctional mitochondria, and restored ATP levels. A ternary ligand, DSPE-PEG-RVG, was then added to form Pu-Exos-PR. *In vivo*, Pu-Exos-PR demonstrated outstanding biocompatibility and exceptional penetration into both nasal tissue and the BBB. They promoted the survival of dopaminergic neurons and decreased cellular degeneration. They also increased tyrosine hydroxylase expression and improved motor and non-motor symptoms.[58]

In 2024, Castellani *et al.*[76] co-loaded dopamine and the antioxidant grape seed-derived pro-anthocyanidins into SLNs and used slightly viscous dispersions (SVDs) as vehicles for the SLNs' nasal delivery. SLNs were prepared by the melt homogenization method using Gelucire® 50/13. For SVDs, two polymeric blends, Poloxamer/Carbopol (PF-127/Carb) and oxidized alginate/Hydroxypropylmethyl cellulose (AlgOX/HPMC), were investigated. Both had a PS of ~131.4 nm, pH values within the normal range for nasal fluid, minimal osmotic effect, and minimal cytotoxicity in human nasal RPMI 2650 cells, yet the PF-127/Carb blend showed better penetration capability. Cell viability studies using RPMI 2650 cells showed that both SVDs enhanced cell viability at intermediate dopamine concentrations (50–75 μM) after 6 and 12 hours of treatment. Flow cytometry studies demonstrated time-dependent uptake of SLNs by human nasal RPMI 2650 cells, with no difference between the two SVD formulations.[76]

Recently, Nematalla *et al.*[77] loaded Carbenoxolone, the succinyl ester of glycyrrhetinic acid, previously shown to inhibit neuroinflammation and mitochondrial damage, into chitosan-coated SLNs to enhance its brain targeting. The nanoparticles were synthesized from Compritol ATO and exhibited a PS of 164 ± 0.12 nm, a PDI of less than 0.3, a ZP of 18 ± 0.89 mV, an EE% of 97.98 ± 0.98%, and a sustained drug release profile. Compared with the Carbenoxolone suspension, *in vivo* evaluations in a rotenone-induced rat model demonstrated that intranasally delivered SLNs significantly improved motor function, coordination, and balance, and modulated neurotransmitter levels. Additionally, they increased total antioxidant capacity (TAC) by 92%. They also restored dopamine levels by approximately 54–56% and reduced α-synuclein by 51–52% compared to the control group. Furthermore, reductions in neuroinflammation, oxidative stress, and apoptosis markers, and the restoration of neuronal architecture were also observed.[77]

All data regarding the type of nanocarrier, loaded compound, size, PDI, ZP, EE%, DLC%, and advantages of nose-to-brain delivery of lipid-based nano vehicles encapsulating anti-Parkinson's drugs are summarized in Table 4.

Phytochemicals, especially polyphenols such as curcumin, silymarin, and chrysin, possess antioxidant and dopamine-enhancing potential when delivered in combination *via* lipid-based nanocarriers. Among all exosome-based formulations, those consisting of a biocompatible nature and capable of penetrating the BBB without specific surface modifications are more prominent. However, isolation of exosomes, compositional heterogeneity, and scaling up are challenges that need to be addressed and can be obstacles to clinical applications. Future approaches could potentially center on mixed systems, in which plant exosomes are hybridized with synthetic lipid scaffolds, uniting bioactivity and structural stability to engender strong translational efficacy.

6. Emerging therapeutic modalities in PD therapy: nucleic acid therapy

Nucleic acid therapy, in particular small interfering RNA (siRNA), is considered an innovative therapeutic approach that silences the SNCA gene encoding α-synuclein, reducing its expression and alleviating neurotoxicity, thereby slowing disease progression.[78] Nevertheless, translation to the clinic is severely impeded by the protein's rapid degradation, low cellular internalization, and ineffective targeting of specific tissues that limit its therapeutic efficacy. Nanobiotechnology has changed the landscape of nucleic acid therapeutics, enabling their specific and safe delivery.

In 2025, Katamesh *et al.*[79] developed dual-acting nanoplatforms that combine siRNA gene silencing and MAO-B inhibition to mitigate dopamine degradation and α-synuclein aggregation in PD. Albumin-coated liposomal systems were prepared by the ethanol injection method and were loaded with Selegiline and α-synuclein-targeting siRNA. DSPC, DOTAP, Cholesterol, and C16-PEG2000 Ceramide were used for the synthesis of the liposomes. The albumin-coated optimized liposomes had a PS of 136.5 ± 10.3 nm, a PDI of less than 2, a ZP of −13.5 ± 1.4 mV, and an EE% of 85.12 ± 4.3% for Selegiline and 71.36 ± 7.5% for siRNA. Intranasal administration achieved a 3-fold increase in brain AUC compared to intravenous delivery, with a DTE% of 507.43% and a DTP% of 80.29%, and improved motor and non-motor functions in rotenone-induced PD rat models. Furthermore, it substantially

Table 4 Overview of lipid-based nanoformulations incorporating anti-Parkinson's compounds, detailing nanocarrier type, physicochemical characteristics (size, PDI, ZP, EE%, and DLC%), and reported therapeutic advantages

Type of lipid-based nanocarrier	Loaded natural anti-PD compounds or their derivatives	Lipid composition	Size (nm)	PDI	ZP (mV)	EE%	DLC%	Advantages	Ref.
Exosomes	Curcumin	N/A	~130–197	N/A	−7.23	N/A	75.53	Exosome administration resulted in enhanced drug accumulation at the action site, reduced α-synuclein aggregates, promoted neuronal function recovery, and alleviated neuroinflammation, leading to improved movement and coordination in PD model mice. *In vitro*, they enhanced miR-133b expression by 48.31%. *In vivo*, they achieved high brain targeting with curcumin levels of 67.26 μg g^{-1} in the substantia nigra, reduced neuroinflammatory markers, and increased IL-10 and regulatory T cells.	71
Microemulsion	Silymarin	Labrafil M 1944 CS	72.34 ± 4.32	N/A	−24.26 ± 0.2	N/A	96.31 5.22	*In vitro* drug release studies showed that more drug was released from the microemulsion, reaching 66.28% after 12 hours, compared with the plain silymarin solution (28.345%). *Ex vivo* studies demonstrated markedly enhanced drug permeation and diffusion from the microemulsion across the nasal mucosa. *In vivo* tests improved motor functions with better locomotor activity and longer latency to fall. They also increased the levels of GSH, SOD, and CAT and reduced the levels of α-synuclein, TNF-α, and IL-6.	72
NE	Chrysin	Capryol 90	365.03 ± 6.8	0.107 ± 0.0316	−24.86 ± 2.286	N/A	N/A	The *in vivo* study showed significantly improved locomotor activity and catalepsy score, elevated dopamine levels, and enhanced oxidative stress markers, including SOD, GSH, and CAT levels, compared to oral or nasal chrysin suspension groups in PD rat models. A brain distribution study showed that the ME formulation administered nasally achieved a 2-fold higher chrysin concentration than the oral formulation.	73
Nanoliposomes	Esculin	Phospholipid 90G and Cholesterol.	88.6	0.06	−30	94.22 ± 0.93	N/A	NE demonstrated enhanced antioxidant activity (78.52% DPPH inhibition) and deep tissue penetration. They also showed markedly enhanced permeation (79.484 ± 0.754%) compared to Esculin suspension (38.326 ± 1.279%), resulting in over 2-fold higher drug flux. The pharmacokinetic study showed much higher brain uptake with intranasal NEs (C_{max} 3347.15 ng mL^{-1}) than with oral delivery (901.20 ng mL^{-1}), confirming efficient brain targeting.	74
Liposome	7,8-DHF and 7,8-DHF methyl ester	DSPC and DPPC	~100–250	~0.205	N/A	92–94	N/A	The liposomes restored ~90% of motor function, reduced abnormal involuntary movements, decreased levels of ΔFosB and α-synuclein, and improved LID in the PD mouse model.	75
Exosomes	*Pueraria lobata*'s multiple active substances.	Sphingosine, triglycerides, ceramides, monohexosylceramide, diglycerides, and DSPE.	125.0 ± 9.7	N/A	−5.0 ± 0.7	N/A	N/A	*In vivo*, Pu-Exos-PR demonstrated biocompatibility and penetration into both nasal tissue and the BBB. They promoted the survival of dopaminergic neurons and decreased cellular degeneration. They also increased tyrosine hydroxylase expression and improved motor and non-motor symptoms.	58

Table 4 *(Contd.)*

Type of lipid-based nanocarrier	Loaded natural anti-PD compounds or their derivatives	Lipid composition	Size (nm)	PDI	ZP (mV)	EE%	DLC%	Advantages	Ref.
SLN	Dopamine and grape seed-derived pro-anthocyanidins into	Gelucire® 50/13	~131.4	N/A	N/A	N/A	N/A	Cell viability studies using RPMI 2650 cells showed that both SVDs enhanced cell viability at intermediate dopamine concentrations (50–75 μM) after 6 and 12 hours of treatment. Flow cytometry studies demonstrated time-dependent uptake of SLNs by human nasal RPMI 2650 cells with no difference between the two SVD formulations.	76
SLN	Carbenoxolone	Compritol ATO	164 ± 0.12	Less than 0.3	18 ± 0.89	97.98 ± 0.98	N/A	Intranasally delivered SLNs significantly improved motor function, coordination, and balance, as well as modulated neurotransmitter levels. Additionally, they increased TAC by 92%. They also restored dopamine levels by approximately 54–56% and reduced α-synuclein by 51–52% compared to the control group. Furthermore, reductions in neuroinflammation, oxidative stress, and markers of apoptosis, as well as the restoration of neuronal architecture, were observed.	77

restored dopamine levels significantly ($p < 0.05$), enhanced catalase activity, and reduced MAO-B levels.[79]

Another recent study designed intranasal tyrosine-modified polyethylenimines (PEIs) and polypropylenimine dendrimers (PPIs) complexed with siRNA targeting the α-synuclein-encoding gene SNCA and combined with liposomes. The liposomes were synthesized using DPPC by the thin-film hydration and extrusion method. Both PS and ZP varied dramatically across polymers and buffers used for complexation. NPs efficiently transfected SH-SY5Y neuroblastoma cells with up to 86% SNCA mRNA knockdown and minimal cytotoxicity (<10% LDH release). *In vivo*, intranasally administered labeled NPs distributed widely across the brain, especially in the olfactory bulb, substantia nigra, and prefrontal cortex, and were taken up by dopaminergic neurons. Following 4 days of treatment, the loaded NPs significantly reduced α-synuclein protein by 72% and dropped the level of SNCA mRNA by up to 74%. Mice showed neither overt adverse behavioral effects nor increased reactive microglia, and there was no sign of neuroinflammation or cytokine activation.[80]

In parallel, peptide-, antibody-, and mRNA-based therapies are rapidly progressing in PD research through alternative delivery routes, and lipid nanocarriers are increasingly being explored to improve their stability and targeting. Monoclonal antibodies against α-synuclein have reached clinical trials, and peptide-based neurotrophic factors show promise in halting neurodegeneration, although their intranasal lipid-based delivery remains largely unexplored.

All data regarding the type of nanocarrier, loaded drug, size, PDI, ZP, EE%, DLC%, and the advantages of nose-to-brain delivery of lipid-based nanovehicles encapsulating nucleic acid therapy are summarized in Table 5.

In parallel, mRNA-loaded lipid nanoparticles (LNPs)—validated in the clinic for vaccination—have demonstrated CNS transfection and therapeutic protein expression in preclinical models, offering a modular platform that could be adapted for nose-to-brain administration. Thus, while current nasal lipid-based studies focus mainly on siRNA, integrating peptides, antibodies, and mRNA into next-generation LNPs represents a logical and highly promising future direction for disease-modifying PD nanotherapies.

7. Safety, regulatory, and translational challenges

However, preclinical studies have reported difficulties in translating lipid-based IN nanocarriers to the clinic, and so far, no lipid NCs are in clinical development or being tested in humans. Chronic nasal administration requires detailed assessment of the mucosal integrity, immunogenicity, and olfactory function, which are in general, overlooked in rodent studies and do not consistently predict human responses. Manufacturing scale-up compounds these challenges: achieving GMP-compliant processes that preserve particle size, crystallinity, drug loading, and sterility, especially for hybrid exosome–lipid systems, remains non-trivial. Regulatory agencies (*e.g.*, EMA, FDA) now require

Table 5 Overview of lipid-based nanoformulations incorporating anti-Parkinson's nucleic acid therapy, detailing nanocarrier type, physicochemical characteristics (size, PDI, ZP, EE%, and DLC%), and reported therapeutic advantages

Type of lipid-based nanocarriers	Loaded nucleic acid therapy	Lipid composition	Size (nm)	PDI	ZP (mV)	EE%	DLC%	Advantages	Ref.
Liposomes	siRNA	DSPC, DOTAP, Cholesterol, and C16-PEG2000 Ceramide	136.5 ± 10.3	Less than 2	−13.5 ± 1.4	85.12 ± 4.3	N/A	Intranasal administration achieved a 3-fold increase in brain AUC compared to intravenous delivery, with a DTE% of 507.43% and a DTP% of 80.29%, and improved motor and non-motor functions in rotenone-induced PD rat models. Also, it restored dopamine levels and enhanced catalase activity.	79
Liposomes	siRNA	DPPC	—	—	—	—	—	NPs efficiently transfected SH-SY5Y neuroblastoma cells with up to 86% SNCA mRNA knockdown and minimal cytotoxicity (<10% LDH release).	80

nanomaterial-specific safety assessments that encompass biodistribution, mucociliary clearance, reproductive toxicity, and long-term immunogenicity. Furthermore, patient-centric factors such as nasal tolerability and dosing frequency must be addressed to ensure adherence.

Moreover, multiple anatomical limitations might limit the efficacy or reproducibility of intranasal nanocarrier-mediated CNS targeting for PD, including factors that restrict drug entry or cause it to be pumped back into the nasal lumen. Besides, drugs undergo nasal metabolism and degradation by Cytochrome P450 enzymes, exopeptidases, and endopeptidases in the respiratory and olfactory mucosa, potentially limiting drug absorption. To address each of those limitations, several pathways might be explored. For instance, incorporating permeation enhancers increases membrane fluidity and opens tight junctions to improve the absorption of large drugs, while mucoadhesive agents slow mucociliary clearance and extend nasal residence for better uptake. Furthermore, nanocarriers can overcome drug efflux, providing some protection for long-term delivery. Enzyme inhibitors, particularly bestatin and fusidic acid, can also prevent enzymatic degradation in the nasal cavity and further stabilize the peptide.[81]

New solutions are changing the scenery: AI-based toxicity prediction models facilitate early safety assessment; nasal-on-chip and brain organoid platforms offer physiologically relevant, non-animal approaches; and microfluidic manufacturing guarantees reproducibility and scalability of advanced lipid architectures. Developing benchmarks for physicochemical characterization and bioavailability will be exploratory, with intense interest in such studies, which must be standardized across laboratories to achieve regulatory acceptance. Together, the developments described here clear the path toward the clinical translation of intranasal lipid nanocarriers (iLNCs) that are safe, scalable, and patient-friendly. Multifunction or AI-enhanced nanocarriers are increasingly under regulatory review. Adaptive or continuously learning models that direct formulation optimization need to adhere to new EMA and FDA guidelines for "Software as a Medical Device", including versioning, algorithmic transparency, and post-market performance tracking. Likewise, hybrid vesicles containing natural and synthetic components create ambiguity in classification as biologic, combination, or advanced therapy medicinal products, each of which requires different toxicology-related and stability evaluations. To obtain clinical approval, researchers will need to engage early with regulatory bodies, ensure harmonized characterization (*e.g.*, assessing particle heterogeneity and residual solvents), and maintain data traceability throughout an AI pipeline.

8. Conclusion and future perspectives: roadmap for clinical translation

Lipid-based nanocarriers have revolutionized the concept of intranasal drug delivery for PD, providing brain-targeting

benefits *via* a non-invasive route and thereby facilitating the co-delivery of antiparkinsonian vehicular agents and neuroprotective phytochemicals. The next wave will be a combination of hybrid systems, especially lipid-exosome hybrids, which integrate bioinspired targeting and structural stability. Further developments in AI-guided molecular modeling will perfect predictions of lipid–drug compatibility, and microfluidic continuous manufacturing will ensure reproducibility and scalability. When combined with patient-derived organoid and nasal-on-chip validation platforms, these advances pave the way for personalized, multifunctional nanocarriers that can be readily translated to the clinic. By integrating materials science and neurotherapeutics approaches, nose-to-brain lipid carriers have the potential to transform PD treatment in the upcoming decade.

In the future, the convergence of nanomedicine, artificial intelligence, and precision neurotherapeutics will expedite the translation of preclinical promise into clinical reality. Lipid-based hybrid systems comprising synthetic lipids, plant exosomes, and stimuli-responsive polymeric materials enable bidirectional approaches, *i.e.*, normalizing the tone of dopaminergic control and attenuating loss due to oxidative insult. AI and machine learning will direct the rational design, long-term safety prediction, and release kinetics optimization; apart from that, organoid-based platforms will facilitate high-throughput ethical preclinical screening. Regulatory science must also adapt to include nanomaterial-specific endpoints, including mucociliary clearance and long-term and immune modulation studies. This progress will pave the way for custom-designed nanotherapies for PD based on genetic and pathogenetic profiles, promising transformative effects in disease modification and symptom relief. In the future, harmonizing AI-enabled predictive toxicology with real-patient-derived organoid data will be critical for regulatory translation. In addition, the incorporation of digital twins of nasal structure and disease evolution might enable *in silico* treatment personalization prior to clinical trials. Adoption of agreed global guidelines for the characterization of nanocarriers and the incorporation of multi-omic biomarkers in early-phase trials will enable the rapid clinical deployment of the next generation of hybrid lipid–exosome therapeutics.

Conflicts of interest

There are no conflicts to declare.

Data availability

This manuscript does not involve any experimental work

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