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Revolutionizing Parkinson's Disease Treatment with Nanotechnology: A Focus on Lipid Nanoparticles

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to motor and non-motor impairments. Despite advancements in treatment, current therapies remain largely palliative, failing to address disease progression. A major challenge in PD treatment is the restricted delivery of therapeutics across the blood-brain barrier (BBB). Nanotechnology, particularly lipid nanoparticles (LNPs), offers a promising drug delivery approach due to their biocompatibility, controlled release, and ability to enhance BBB penetration. LNPs can encapsulate various therapeutic agents, including small molecules, proteins, and RNA-based therapies, offering potential disease-modifying effects. Preclinical studies demonstrate that LNPs improve drug bioavailability, target specificity, and therapeutic efficacy. Additionally, modifications such as PEGylation and ligand conjugation (e.g., transferrin, angiopep-2) further enhance brain-targeted delivery. While LNPs have been successfully applied in vaccine and gene therapy development, their potential in PD treatment remains underexplored, with limited clinical trials. Future research should focus on optimizing LNP formulations for brain-specific delivery, leveraging genetic therapies like RNA interference, and translating preclinical findings into clinical applications. This review highlights the transformative potential of LNP-based nanomedicine in PD treatment, paving the way for more effective and targeted therapeutic strategies.

Keywords: *Parkinson 's Disease, Neurological Disorders, BBB, LNPs.*

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I. INTRODUCTION

Neurological conditions are a diverse group various disorders affecting the brain, spinal cord, and peripheral nerves, which are all parts of the nervous system. These conditions may be brought on by infections, genetic anomalies, lifestyle factors, environmental influences, injuries, or degenerative changes in the nervous system. They often manifest through a range of physical, cognitive, emotional, and behavioural symptoms, significantly impacting an individual's quality of life [1].

Neurological disorders comprise a wide spectrum, including conditions like epilepsy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke, and migraines. Some disorders are acute and reversible, such as transient ischemic attacks, while others are chronic and progressive, like amyotrophic lateral sclerosis (ALS) or Huntington's disease [2].

The complexity of neurological disorders arises from the intricate structure and function of the nervous system. The brain, as the control centre of the body, and the spinal cord, which transmits signals to and from the brain, coordinate essential processes such as movement, sensation, memory, thought, and emotion. Any disruption in these systems can lead to neurological impairments [2]

Developments in the fields of neurology and medical technology have substantially improved the understanding, diagnosis, and treatment of neurological disorders. However, many challenges remain, including the need for early detection, effective therapies, and comprehensive care for individuals and their families [3].

Recognizing the reasons, symptoms, and treatment options for neurological disorders is crucial for enhancing patient outcomes, advancing research, and fostering greater awareness and support for those affected by these conditions.

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II. EPIDEMIOLOGY OF NEUROLOGICAL DISORDERS

Neurological disorders are a major global health issue that millions of people face, and contributing to substantial morbidity, disability, and mortality. They account for approximately 6.3% of the global disease burden and 16.8% of global deaths, making them one of the leading causes of disability-adjusted life years (DALYs) and mortality. Conditions such as stroke, dementia, epilepsy, Parkinson's disease, multiple sclerosis, and migraines are among the most prevalent neurological disorders, with stroke alone affecting 15 million people resulting in 5 million fatalities and 5 million cases of long-term impairment each year. Dementia affects over 55 million individuals worldwide, with numbers expected to triple by 2050. While these disorders are more common in older populations, conditions like epilepsy mostly impact low- and middle-income nations, where around 80% of instances take place. Risk factors include aging, genetic predisposition, infections, trauma, and modifiable lifestyle factors such as smoking and poor diet. The economic and social burden is immense, with conditions like dementia costing the global economy over $1.3 trillion annually. With the Population aging and shifting lifestyles, the prevalence of neurodegenerative disorders is projected to rise, underscoring the need for preventive strategies, equitable healthcare access, and advancements in research and treatment [4].

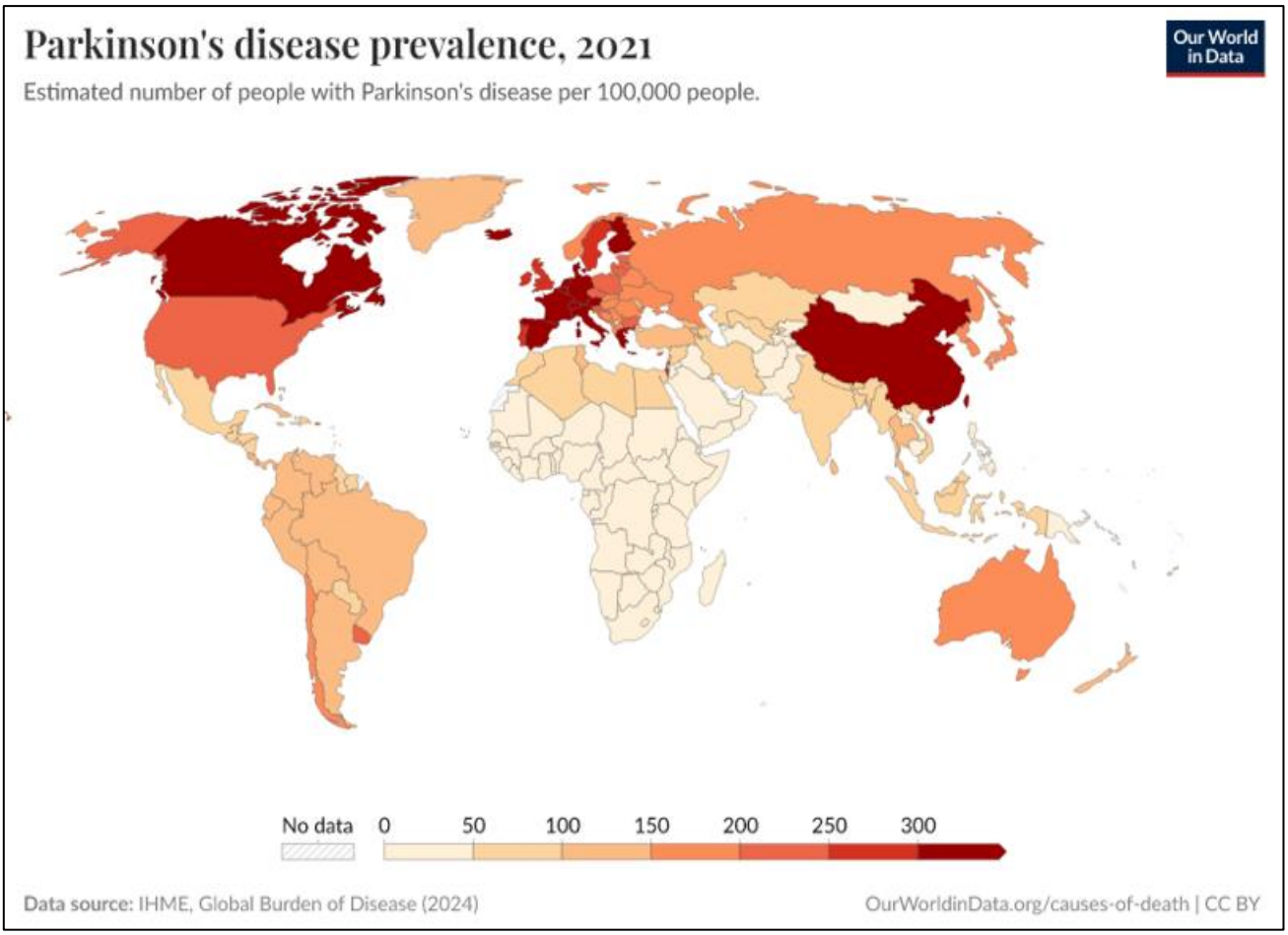

Fig 1: Epidemiology of Parkinson's Disease Prevalence

III. CHALLENGES TO DELIVERY OF DRUGS TO BRAIN

Delivering drugs and accessing the brain is extremely difficult because of the presence of the blood-brain barrier (BBB), a selective, semipermeable membrane that restricts most therapeutic agents, especially hydrophilic and large molecules, while allowing only small, lipophilic ones or those utilizing specific transport systems [5]. Efflux transporters like P-glycoprotein further limit drug accumulation by actively removing substances from the brain. Enzymatic barriers and rapid clearance mechanisms reduce the drug's stability and half-life, while poor solubility and permeability often hinder effective delivery. Additionally, the brain's complex structure, potential immune responses to advanced delivery systems, and the risk of off-target effects make precise targeting difficult. These challenges necessitate innovative strategies such as nanotechnology, receptor-mediated transport, intranasal delivery, and momentary disruption of the BBB to improve the efficacy of CNS drug delivery [6].

Increased parenchymal medication concentrations would result from disrupting or weakening the BBB in order to improve CNS drug delivery. BBB is opened using techniques that include the infusion of metals like aluminium,

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solvents like ethanol or dimethyl sulfoxide, and X-ray radiation. The synthetic bradykinin homolog RMP-7 (receptor-mediated permeabilizer), histamine, and bradykinin are infused into certain animal models to help open the blood-brain barrier. These treatments frequently cause toxicity and injury to neurons, and doxorubicin, loperamide, and tubocerarine have all been transported between the blood and brain via nanoparticles (NPs) utilizing the endocytosis transport mechanism [7].

Table 1: Surface Tailoring of Nanoparticles to Improve their Ability to Cross the Blood-Brain Barrier.

LIGAND	FAVOURABLE PROPERTIES
Transferrin	Transferrin receptors (Tfr) are often employed targeting ligands because of their high expression in BCECs. They facilitate the effective build-up of medications within the brain.
Lactoferrin	A glycoprotein found within the brain called lactoferrin functions as a BBB receptor. It has been determined that this method improves the drug's pharmacological characteristics.
Glucose	Glucose transporters (GLUTs), which are present in the blood-brain barrier, actively transfer glucose into the brain to meet the brain's high energy needs. Through this transport mechanism, glucose-coated NPs could be able to effectively traverse the BBB.
Glutathione PEGylation	The sodium-dependent transporter allows PEGylated lipids with glutathione conjugates to cross the blood-brain barrier.
Angiopep-2	possesses strong BBB transcytosis capabilities and is conjugable to LNPs.

IV. LIPID-BASED DELIVERY SYSTEMS FOR NEUROLOGICAL DISEASES CREATED USING NANOTECHNOLOGY

Lipid-based delivery systems using nanotechnology are emerging as a promising approach for treating neurological diseases by overcoming the challenges of drug delivery to the brain, particularly crossing the blood-brain barrier (BBB). These systems, such as liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and exosomes, offer unique advantages like biocompatibility, controlled drug release, and the ability to encapsulate various therapeutic agents, including small molecules, proteins, and nucleic acids. By employing surface modifications, such as PEGylation or targeting ligands, these nanoparticles can achieve enhanced BBB penetration and targeted delivery to affected brain regions. Applications include delivering anti-amyloid agents for Alzheimer's disease, neuroprotective compounds for Parkinson's disease, antiepileptic drugs for epilepsy, chemotherapeutics for brain tumors, and anti-inflammatory agents for stroke. Despite these advancements, challenges such as stability, immunogenicity, and scalability remain, necessitating further research and clinical trials to optimize these systems for widespread clinical use [8].

PARKINSON 'S DISEASE

1817 saw the publication of An Essay on the Shaking Palsy, is the publication that first detailed that how Parkinson's illness manifests (PD), which bears the name of its English physician, James Parkinson. PD is a neurological condition that affects both motor and non-motor functions. It is sometimes referred to as shaking palsy and paralysis agitans. Postural instability, tremor, stiffness, and bradykinesia are uncontrolled movements known as motor symptoms which are the hallmarks of Parkinson's disease (PD), a degenerative neurological condition [9].Among the signs of Parkinson's disease, the non-motor signs of Parkinson's disease are hysteria, melancholy, constipation, and sleeplessness. It results from DA levels falling and the neural circuitry governing movement becoming disrupted due to the degeneration of substantia nigra neurons in the mesencephalon, a part of the midbrain. Disruptions in sub corticocortical connections are caused by imbalances in striatal relay functions.

Parkinson's disease (PD) is a devastating and life-altering state that mostly impacts the brain's neural composition. It is classified as a neurodegenerative illness. Between 7 and 10 million people are thought to be affected by this illness globally [10].

NEUROPATHOLOGY – PARKINSONS'S DISEASE

Developing a suitable treatment plan requires an understanding of the neuropathological characteristics of a disease. The disease starts with dopaminergic neuron degeneration in the substantia nigra (SN) pars compacta in the midbrain. Lewy bodies are protein aggregates and neurons. These protein aggregates are identified as insoluble alpha-synuclein aggregates and cytoplasmic inclusions [11]

PD. and can be either sporadic or hereditary. Two cell groups within the SN are impacted: the ventrolateral cell groups (A9 or nigrostriatal route) are susceptible, but the medial and dorsal cell groups (A10 or mesolimbic pathway) are tough. Transients in calcium are associated with this susceptible state, where a lack of the former dopaminergic neurons are nevertheless susceptible to cellular stress since calcium buffering is present in A9 neurons as opposed to A10 neurons. The most frequent causes of autopsies of PD patients have been identified as corticobasal degeneration (CBD), tauopathies and synucleinopathies, and progressive supranuclear palsy (PSP) [12]

The existence of accumulating blood RNA biomarkers in Parkinson's disease was examined in an intriguing early patient-based investigation. According to reports, mRNA is degraded by the nonsense-mediated decay (NMD) mechanism, which also has a regulatory function in the brain. The writers suggested modifying NMD of RNA in Parkinson's patients' leukocytes by deep brain stimulation surgery to alleviate the disease's motor symptoms [13]

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The excessive production and incapacity to efficiently detoxify reactive oxygen species (ROS) and reactive nitrogen species (RNS) is another important sign of Parkinson's disease (PD) progression.

Dopaminergic neuron degeneration is facilitated by oxidative and nitrative stress in PD. This leads to cellular death by interfering with vital biological functions. Dysregulation of iron and calcium metabolism, a rise in neuroinflammatory cells, aging, and mitochondrial dysfunction are all likely to occur once these important elements in the PD substantia nigra are disrupted [14]

PARKINSON'S DISEASE- LNPS

There are several benefits to using nanomedicine in drug administration, such as longer resistance time in the body (i.e., longer half-life for clearance), better bioavailability because of improved aqueous solubility, and more specificity when it comes to addressing disorders like Parkinson's disease0[15].

The use of lipid-based NPs in medicine and vaccination has been emphasized. It is more appealing as a treatment for neurological disorders due to its innate capacity to enter the brain. These LNPs' advantageous size, surface charge, programmable surface area, and shape have made them suitable nanocarriers. Several parameters must be taken into account when building an LNP for drug delivery in order to increase therapeutic indices. A few of these elements are compiled in Figure below [16]

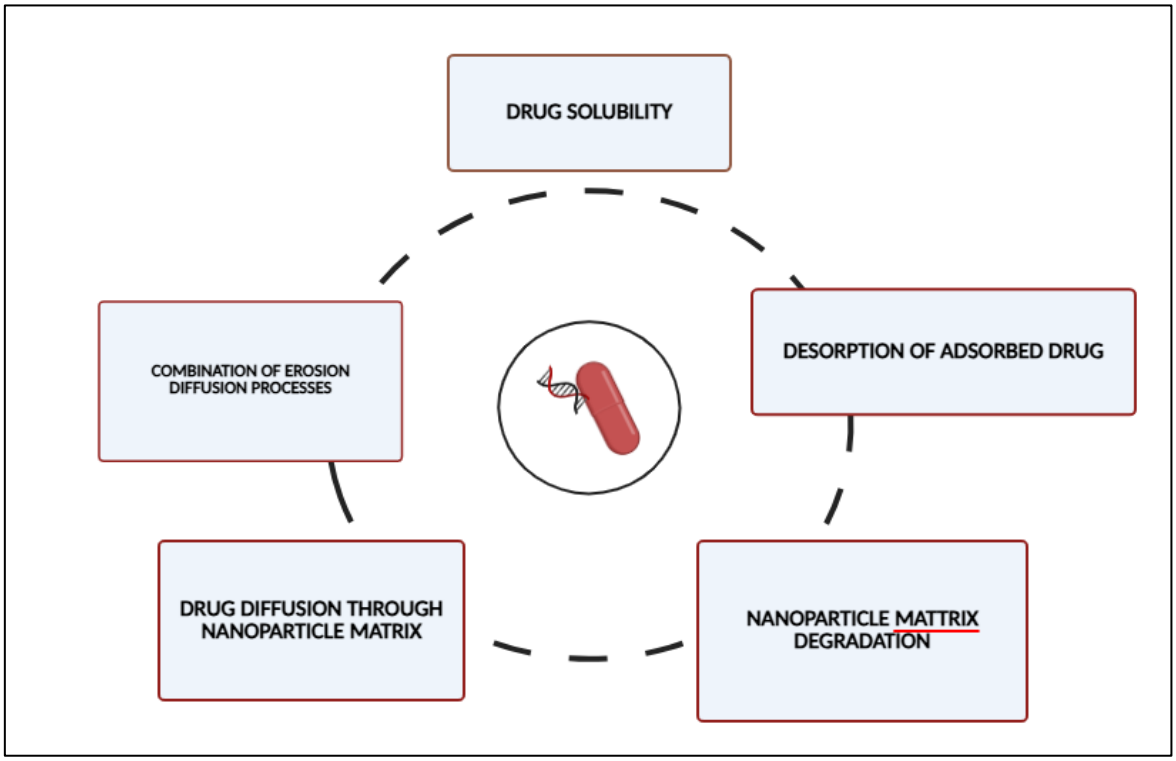

Fig.2 Parameters to Evaluate When Formulating Lipid Nanoparticles for Effective Drug Delivery

CURRENT TREATMENT STRATEGIES IN PD

Dopamine supplementation is required to make up for the loss of dopaminergic neurons in PD patients, according to currently known treatments. An albumin/PLGA NP conjugated to dopamine was used in a recent study. The presented nanocomplexes successful permeability to the brain by successful BBB crossing. This was explained by the fact that the albumin-coated NP improved its interactions with particular cell membrane receptors. Additionally, in a mouse model comparing NPs lacking dopamine and mice with L-DOPA, the administration of dopamine rather than L-DOPA—a medication that is frequently converted to dopamine in vivo—reduced symptoms. Restored balance, motor coordination, and sensorimotor performance were among the improvements [17].

In addition to a system of delivery that targets the brain composed of 29 amino acid peptides (RVG29) generated from the rabies virus glycoprotein, functionalized liposomes carrying the dopamine derivative N-3,4-bis (pivaloyloxy) dopamine were also investigated. Crucially Dopaminergic and endothelial cells were both visible and enhanced cellular absorption, with better BBB penetration. Additionally, the selective drive of RVG29-LNPs to the substantia nigra and striatum was observed to result in improved therapeutic effectiveness [18].

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Dudhipala and Gorre's (2020) study further highlights the effectiveness of drug therapy and nanomedicine by using LNPs conjugated with the dopamine agonist ropinirole (RP). Research on pharmacodynamics has shown elevated dopamine, glutathione, and catalase levels with a decrease in lipid peroxidation levels. Increased pharmacokinetics were observed considering the medicine in the host, oral delivery increases the drug's effectiveness by more than two times, topical administration increases it by three times, and one-fold increase in the SLN and 3NLC complexes' topical bioavailability [20].

V. NEW REFORMS ON PD CLINICAL TRIALS USING LIPID NANOPARTICLES

LNPs have not yet been used as nanocarriers for treatments to treat Parkinson's disease, according to a recent NIH search database for clinical studies conducted in the previous ten years. Liposome-based Phase 1 research started in 2021 and is expected to be finished in December 2022. The trial merely assesses the Talineuren's safety, a medication that combines a novel liposomal formulation with GM1, a monosialotetrahexosylganglioside, as the treatment [21].

Nonetheless, a study with gold nanocrystals has been finished. The findings, which are anticipated, may mark a turning point in nanomedicine and a new avenue for nano-based treatments [22].Transdermal patches are one of the approved therapy methods for Parkinson's disease symptoms. Selegiline (Emsam®) is used to treat depression, while rotigotine (Neupro®) is used as transdermal patches to alleviate PD symptoms of restless legs syndrome.[23] These do, however, have a few known adverse consequences. Interestingly, these formulations do not make use of LNPs. LNPs are used to deliver a therapeutic siRNA in the treatment patisiran administered intravenously (ONPATTRO®), which has been authorized for the treatment of polyneuropathy. However, more investigation is needed to completely explore the potential of LNPs in the development of a gene or medication delivery system for Parkinson's disease [24].

VI. CONCLUSIONS AND PROSPECTS FOR THE FUTURE

Parkinson’s disease (PD) remains a significant health challenge, with current therapies focused mainly on palliative care rather than curing the disease. While symptom reduction is essential, the associated side effects often compromise patients' quality of life. Due to the incomplete understanding of PD’s mechanisms and causative factors, greater emphasis on research is needed.

Nanomedicine has emerged as a promising avenue, addressing treatment challenges through advanced drug and gene delivery systems. RNA interference (RNAi) holds potential in order to suppress genetic alterations associated with PD, such as LRRK2, PARK7, PINK1, PRKN, and SNCA. Lipid nanoparticle (LNP)-based systems have demonstrated safety, scalability, and efficiency, enabled tissue-specific drug delivery and facilitating commercial production. LNP formulations can be further optimized to target neurological conditions like PD effectively [25].

Future advancements should focus on brain-specific LNP formulations by integrating ligands like angiopep-2 or transferrin, which improve blood-brain barrier (BBB) navigation. Additionally, polymers like polyethylene glycol can enhance stability and in vivo efficacy. Personalized therapies, tailored to specific molecular targets, represent the next frontier in PD treatment. Expanded basic research and clinical translation of innovative LNP-based strategies are critical to achieving transformative outcomes.

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